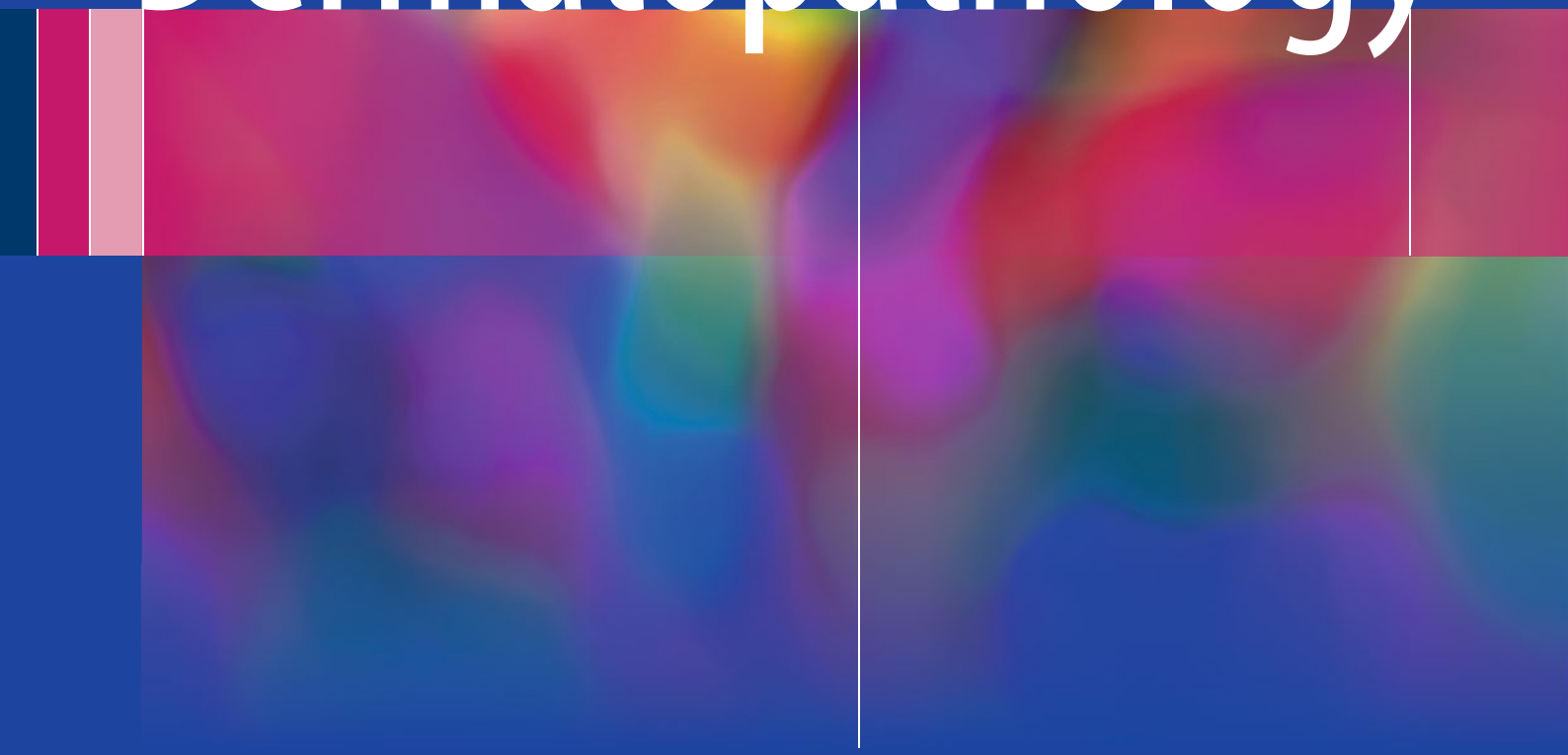
Thuy L. Phung
Teresa S. Wright
Crystal Y. Pourciau
Bruce R. Smoller

Pediatric Dermatopathology



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Preface

This project was undertaken in hopes of filling a need for pathologists and dermatologists who review skin biopsies in their practice of medicine. While pediatric dermatopathology is a small niche, it is an important one, and one that slips through the cracks of the curriculum in both pathology and dermatology training programs. The nomenclature in diagnostic dermatopathology presents great problems for pathologists who do not have specialized training in dermatopathology. The problem is even more dramatic when one attempts to master dermatologic diseases that are seen largely in children with their own unique set of histologic changes. It is the authors' sincere hope that with the concerted efforts of our team of clinical pediatric dermatologists and pathology-trained dermatopathologists, we were able to put together a compendium of dermatologic diseases that is readily accessible and contains useful up-to-date information regarding the diagnostic clinical and histologic features, useful discussion of histologic mimics to be differentiated, and current knowledge of the molecular basis of diseases and their pathogenesis. We have attempted to concentrate our efforts on diseases that affect children, recognizing that some dermatologic conditions are seen in adults as well, and therefore, are not included in this volume. In situations where patients of any age may develop a dermatologic problem, we have highlighted the features that are more commonly encountered in children. We have also attempted to keep abreast with currently accepted disease classifications, particularly related to the rapidly evolving field of vascular anomalies.

We have assembled into a single book many representative clinical and histologic photographs that serve to highlight the major diagnostic features required to establish diagnoses. We received the generous support of many clinical colleagues, who helped us to accumulate clinical and histologic photographs of some of the diseases, and these contributors are acknowledged throughout the volume. The authors would also like to publicly acknowledge others whose contributions may not be obvious from the text.

Thuy L. Phung
Teresa S. Wright
Crystal Y. Pourciau
Bruce R. Smoller

Acknowledgment

This book is the combined efforts of many dedicated individuals. First and foremost, I would like to deeply thank Drs. Teresa Wright, Crystal Pourciau, and Bruce Smoller, my coauthors of this voluminous work. We have labored together shoulder-to-shoulder, with much patience and forbearance for one another, for over two years to make this book happen. I want to sincerely thank the members of my research lab, Sriram Ayyaswamy, Wa Du and Tommy Nguyen for their valuable help with many aspects of the book. I would like to thank all my current and former mentors, teachers and colleagues, who have guided and supported my path in science and medicine. Many thanks to the wonderful staff at Springer International Publishing for patiently working with us on this book. On a more personal note, I am deeply appreciative of my dear family—my parents and sisters—for their love and support. I am eternally grateful to my parents, Thach and Thai, for their strong love and selfless sacrifice in order to give me a better life and better future as a young child when we left Vietnam as boat refugees. This book is a tribute to them. - Thuy L. Phung, MD, PhD

I would like to thank my wonderful husband, Kyle, and daughters, Evangeline and Savannah, who have provided boundless love and support throughout this endeavor. I also would like to thank my parents, Drs. Thomas Brooks III and Willie Mae Hubbard, who initially fostered my interest in medicine. Lastly, I would like to express my sincerest gratitude for the amazing mentors and patients with whom I have had the privilege to work; they are a constant inspiration to me.- Crystal Y. Pourciau, MD

To Dr. Karen Wiss, for inspiring me to become a pediatric dermatologist; to Drs. Amy Nopper, Kim Horii, and Brandon Newell, for teaching me (almost) everything I know about pediatric dermatology; and to my dear husband, Patrick, for his tremendous love and support.- Teresa S. Wright, MD

In addition to my loving wife, Laura, who provides constant support and encouragement for these types of projects, I would like to acknowledge and thank our coauthor, Dr. Thuy Phung, who provided the initial idea, the motivation, and the inspiration for this work. Her enthusiasm, her drive, and her idealistic spirit provided me with the energy to undertake and bring to completion my portion of this enormous project. Her attention to detail raised the bar for all of us. Thank you, Thuy!- Bruce R. Smoller, MD

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Spongiotic Dermatitis

1

1.1 Atopic Dermatitis

1.1.1 Clinical Features

Atopic dermatitis is a multifactorial, primarily type 2 T-helper cell immune-mediated, inflammatory disorder characterized by chronicity, xerosis, and pruritus. Sixty percent of cases present within the first year of life, with 90 % of patients demonstrating clinical disease by 5 years old [1]. The estimated prevalence in industrialized nations, such as Europe and the USA, is 15–30 %, affecting about 25 % of children and 3 % of adults [1]. There is a strong genetic predisposition with 70 % of patients having a positive family history of atopy.

Clinical examination shows erythematous, xerotic, scaled patches and plaques with or without weeping crust and overlying excoriations. Lichenification and exaggerated skin markings highlight disease chronicity. In infants, eczematous lesions are found on the face and extensor surfaces with sparing of the diaper area, owing to pronounced humidity at that site. In contrast, older children and adults usually have skin findings localized to the flexural skin of the neck, antecubital fossae, wrists, popliteal fossae, dorsum of the feet and ankles (Fig. 1.1).

Atopic dermatitis is described as the first "step" of the atopic march with 40–60 % of patients later developing allergic rhinoconjunctivitis and/or asthma [2]. Although atopic dermatitis has a relapsing course, most patients have resolution of disease by puberty with only 30 % having persistence into adulthood [1].

1.1.2 Histology

Histologic changes in acute atopic dermatitis are quite subtle. Scant wispy parakeratosis overlies an epidermis that demonstrates slight spongiosis and small collections of Langerhans cells [3] (Fig. 1.2). Scattered eosinophils may be present in the superficial dermis, admixed with increased numbers of lymphocytes [4] (Fig. 1.3). Degranulated mast cells may be present but are rarely observed on routine histologic sections. A folliculocentric pattern with spongiosis concentrated within follicular infundibula has been described, and is more common in darker skinned individuals [5].

In the chronic phase, changes are nonspecific and are those of a chronic spongiotic dermatitis, often with superimposed lichen simplex chronicus-like changes. Hyperkeratosis is present diffusely overlying an acanthotic epidermis with elongated rete ridges and hypergranulosis. Spongiosis is only minimally present and there is a sparse perivascular lymphocytic infiltrate. Eosinophils are minimally increased in number. A specific diagnosis of chronic atopic dermatitis is not possible based solely upon histologic changes.

1.1.3 Pathogenesis

Genetics studies have revealed a strong association between atopic dermatitis and the epidermal barrier protein filaggrin, particularly in Northern Europeans [6–8]. Depending on the population, between 10 and 50 % of patients with atopic dermatitis carry filaggrin gene mutations [7, 9, 10]. In particular, two loss-of-function genetic variants of filaggrin (R510X and 2282del4) are strong predisposing factors for atopic dermatitis [7, 8, 11]. These variants also show significant association with asthma in the setting of atopic dermatitis.

The filaggrin gene is located within the epidermal differentiation complex, which is a large cluster of genes (including filaggrin, loricrin, and involucrin) that are important in keratinocyte terminal differentiation [8, 11]. The gene product is profilaggrin, which is a major component of the keratohyaline granules in keratinocytes. Profilaggrin is proteolyzed to produce functional filaggrin monomers. These monomers coalesce to form a dense protein–lipid

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Fig. 1.1 Atopic dermatitis presents as erythematous, scaly plaques over the face of a toddler

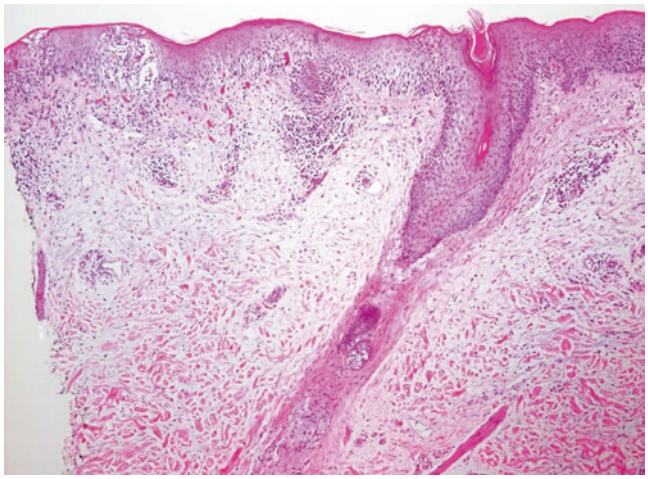

Fig. 1.2 Atopic dermatitis presents with a mild spongiotic dermatitis and a mild lymphocytic infiltrate in the superficial dermis

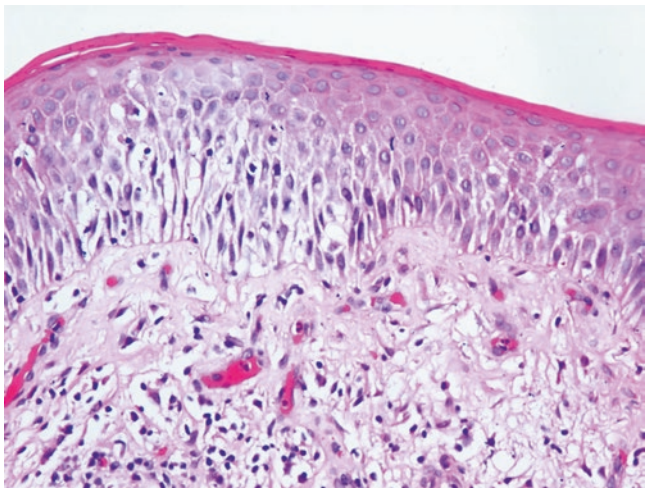

Fig. 1.3 A spongiotic dermatitis with scant exocytosis of lymphocytes is seen in atopic dermatitis

matrix of the cornified cell envelope. This structure serves an epithelial barrier function that prevents epidermal water loss and impedes the entry of allergens, chemicals, and microorganisms across the skin barrier [12, 13]. Although filaggrin mutation is a major predisposing factor for classic atopic dermatitis, many patients with atopic dermatitis do not have defects in filaggrin. Thus, other genetic factors that influence skin barrier function may also be important. Potential candidate molecules are proteins that are involved in the processing of profilaggrin, such as retroviral-like aspartic protease (SASPase), caspase-14 and bleomycin hydrolase [14].

The antimicrobial skin barrier is compromised in atopic dermatitis, leading to secondary bacterial infection, such as *Staphylococcus aureus* colonization that can exacerbate inflammation in the disease process [15]. This is consistent with the clinical findings of impetiginization, folliculitis, and even skin abscesses as complications of infection in atopic dermatitis. The microbial exacerbation may be due to the augmentation of IgE production that is directed towards staphylococcal exotoxins [6]. Toll-like receptors (TLRs) are important in the detection of invading pathogens. There is evidence of impairment of toll-like receptor-2 (TLR2) expression and function in monocytes and macrophages in atopic dermatitis [16, 17]. TLR2 polymorphism (R753Q) has been reported in patients with severe form of atopic dermatitis, but the role of this polymorphism remains controversial [18, 19].

T lymphocytes play important roles in the pathogenesis of atopic dermatitis. The important T lymphocyte subsets in this disorder are type 2 T-helper cells (Th2), type 17 T-helper cells (Th17), and type 22 T-helper cells (Th22) [20–22]. The immune infiltrates in chronic atopic dermatitis skin are mainly composed of Th2 and Th22 cells, and some Th17 cells [22]. Cytokines produced by Th2 cells, particularly IL-4, IL-13, and IL-31, regulate important functions in the epidermal barrier, including epidermal cornification and the production of antimicrobial peptides [9]. Th2 cells also produce cytokines and interferon-gamma (IFN-gamma) that can affect filaggrin expression and epidermal differentiation [23]. Th17 cells produce IL-17 and some IL-22, and they regulate the production of antimicrobial peptides in keratinocytes as well as chemotaxis of neutrophils. IL-17 levels are decreased in atopic dermatitis skin, and that may contribute to the decreased production of antimicrobial peptides. Regulatory T cells (Tregs) are important in suppressing T-cell mediated immune response [24]. Loss of Treg function has been reported in atopic dermatitis [25].

Vascular changes and angiogenesis are other key features in atopic dermatitis. High levels of vascular endothelial

growth factor-A (VEGF-A) are present in the skin of atopic dermatitis patients and appear to correlate with disease activity [26–28]. Activated macrophages can induce VEGF expression and angiogenesis during inflammation and contribute to the disease process.

Atopic dermatitis can occur as part of a syndrome, such as Netherton syndrome which is characterized by ichthyosis, chronic dermatitis, asthma, and allergic rhinitis [29]. Netherton syndrome is caused by mutations in the SPINK5 (serine protease inhibitor Kazal-type 5) gene, which encodes the protease inhibitor lymphoepithelial Kazal-type-related inhibitor (LEKTI) [30, 31]. Genetic studies have demonstrated linkage between polymorphisms in SPINK5 gene in Netherton syndrome and atopic dermatitis, asthma, and high levels of serum IgE [31, 32].

1.2 Dyshidrotic Eczema

1.2.1 Clinical Features

Dyshidrotic eczema, also known as pompholyx, is a chronic relapsing, vesiculobullous disorder of the palms and soles (Fig. 1.4). It is seen worldwide, though perhaps less frequently in Asian populations [33]. Associated conditions include both atopic dermatitis and contact dermatitis, with contact sensitivity noted in approximately one-third of affected individuals [33].

On physical exam, there are tense, deep-seated, "tapioca-like" vesicles as well as larger bullae on the palms, soles, and lateral fingers. Erythema and scaling may or may not be present. Involvement is usually bilateral. Patients may complain of pruritus or a burning sensation, and hyperhidrosis is a frequent feature, typically with increased occurrence during warmer seasons and climates [33]. Management hinges on avoidance of identifiable triggers and treatment of relapses of eczematous flares.

1.2.2 Histology

Histologic features of dyshidrotic eczema are nonspecific. The only distinguishing feature from other spongiotic processes is the acral location for this eruption (Fig. 1.5). Parakeratosis is present (except in very acute lesions) overlying an irregularly acanthotic epidermis with focal spongiosis that can range from slight to marked changes [34]. Collections of Langerhans cell microabscesses are seen in most cases (Fig. 1.6). Within the dermis, there is an infiltrate of

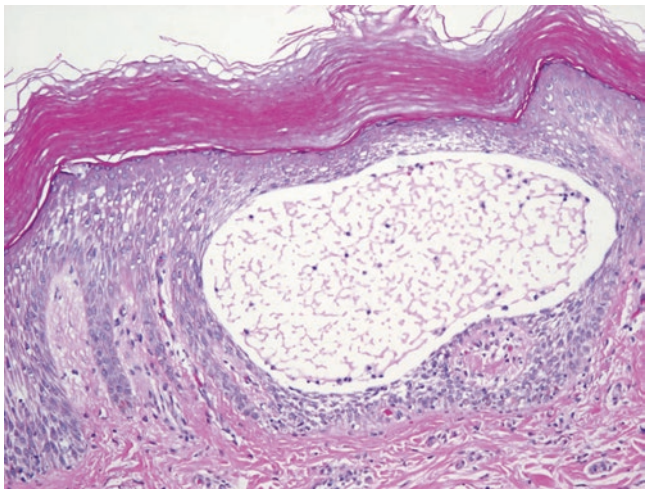

Fig. 1.5 Acral skin demonstrating spongiotic dermatitis with microvesiculation is present in dyshidrotic eczema

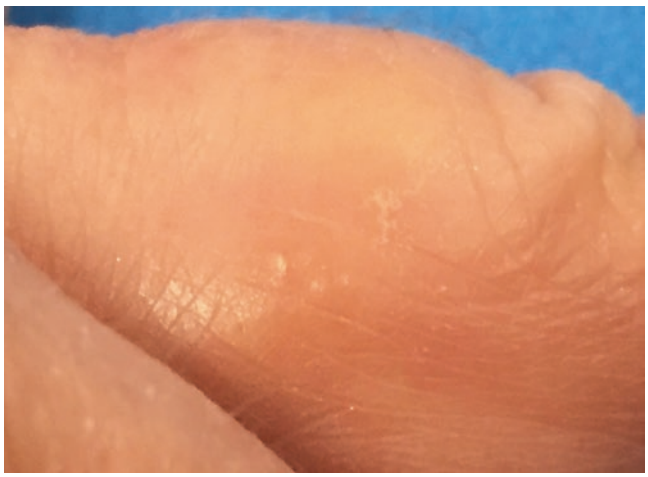

Fig. 1.4 Dyshidrotic eczema presents as scaly papules and deep-seated vesicles on the lateral finger

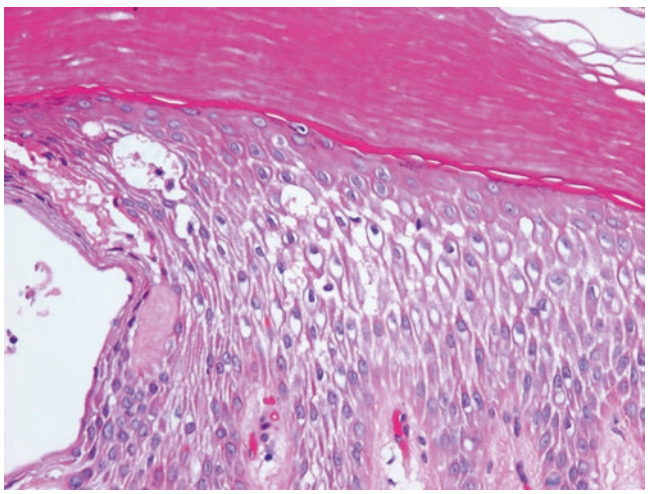

Fig. 1.6 Dyshidrotic eczema reveals a spongiotic dermatitis on acral skin

lymphocytes and eosinophils may be present. Late lesions may demonstrate only minimal spongiosis and are indistinguishable from lichen simplex chronicus. In most cases, a PAS stain is recommended to exclude acral fungal infection, as the histologic changes may be identical.

1.2.3 Pathogenesis

The pathogenesis of dyshidrotic eczema is not known. A number of factors, such as atopy, contact allergy, dermatophyte infection and drug eruption, can influence the development of dyshidrotic eczema in predisposed individuals. Studies of a large Chinese family with a rare autosomal dominant form of dyshidrotic eczema have identified a locus on chromosome 18q22.1–18q22.3 that may contain the responsible gene(s) [35]. There are 17 genes within this locus, some of which are calcium-dependent adhesion molecules, such as cadherins, which are important in maintaining the structural integrity of epithelial tissues including the skin.

1.3 Nummular Eczema

1.3.1 Clinical Features

The specific etiology of nummular eczema is unknown in children, but associations include xerosis and exposure to various contact allergens in adult patients [36]. It occurs with increased frequency in children with atopic dermatitis but can be seen independently as well [36]. Nummular eczema is characterized by well-circumscribed, erythematous, scaled to exudative pruritic plaques (Fig. 1.7). It typically presents with a relapsing course, although it may abate after puberty.

1.3.2 Histology

Nummular eczema demonstrates the classic histologic features of spongiotic dermatitis with no specific distinguishing characteristics (Fig. 1.8). Acute lesions demonstrate marked spongiosis, Langerhans cell abscesses within the epidermis and a brisk lymphocytic infiltrate around the superficial vascular plexus, often with associated eosinophils [37]. Fully developed lesions contain parakeratosis and serum within the stratum corneum, slightly less intraepidermal spongiosis and fewer Langherans cell microabscesses (Fig. 1.9). The dermal inflammatory infiltrate is less intense in chronic lesions than in acute lesions. Well-established chronic lesions are indistinguishable from lichen simplex chronicus.

Fig. 1.7 Nummular eczema presents as erythematous scaly circular plaques on the back of an infant

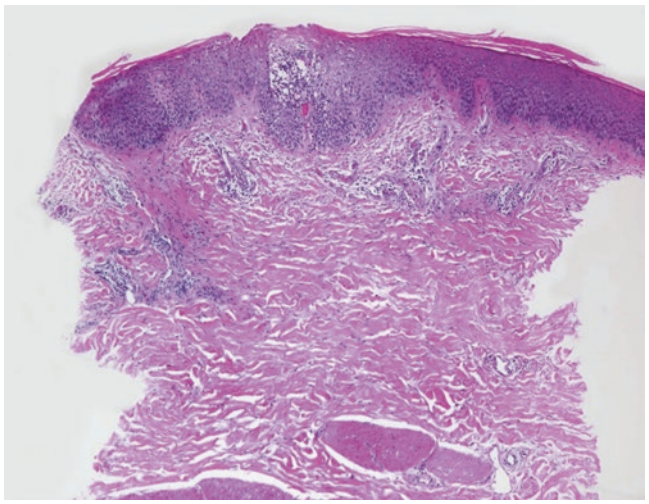

Fig. 1.8 Nummular eczema is a spongiotic dermatitis that displays only a mild superficial perivascular lymphocytic inflammatory infiltrate

1.3.3 Pathogenesis

A number of factors have been implicated in the pathogenesis of nummular eczema, including the state of hydration of the skin, infections by house dust mites and *Candida albicans*, isotretinoin and gold therapy, mercury in dental amalgams, and internal infections of the teeth and respiratory tract [36]. Nummular eczema is likely to be caused by a

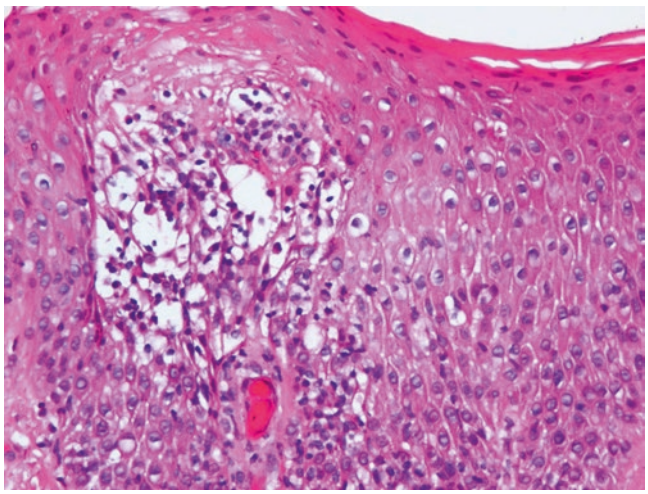

Fig. 1.9 Parakeratosis, spongiosis, and microvesiculation are present in most cases of nummular eczema

Fig. 1.10 Allergic contact dermatitis presents as an erythematous scaly plaque on the lower abdomen of a toddler due to contact with nickel

combination of skin lipid barrier dysfunction and dysregulated immunologic response. Hypersensitivity to metals in the mouth may drive an immune response that results in nummular eczema. Drugs, such as interferon, ribavirin, and inhibitors of tumor necrosis factor (TNF), can induce generalized nummular lesions [38, 39]. Nummular eczema is pruritic, and mast cells, which are increased in number in this disorder, play a role in pruritus [40–42]. Contributing molecular factors to pruritus include the release of histamine and other inflammatory mediators from mast cells that interact with nerve fibers, and the presence of substance P and calcitonin gene-related peptide, which are increased in eczema skin [41].

1.4 Contact Dermatitis

1.4.1 Clinical Features

Allergic contact dermatitis is a delayed type IV hypersensitivity reaction with apparent increased occurrence in children with incidence rates of 14–70 %, mimicking or exceeding those of adults [43]. Patch testing is the gold standard for diagnosis of allergic contact dermatitis with the top ten allergens in children being nickel (metal in jewelry, belt buckles, buttons), neomycin (topical antibiotic), balsam of peru/fragrance mix (fragrance), thimerosal (preservative), cobalt (metal), chromate (metal in tanned leathers, paints), thiuram (rubber accelerant in elastic bands, shoes, gloves), lanolin (wool wax alcohol found in emollients), formaldehyde (preservative in cosmetic and hygiene products), and paraphenylenediamine (oxidative chemical in hair dye, black henna tattoos) [43].

Fig. 1.11 Allergic contact dermatitis shows diffuse erythema, edema, vesicles, and bullae on the legs of a child

Disease presentation is characterized by pruritic, erythematous patches and plaques localized to the site of contact with the suspected allergen (Figs. 1.10 and 1.11). In more acute variants, erythematous, edematous plaques are

present that may or may not vesiculate with secondary serous drainage. In contrast, chronic allergic contact dermatitis is typified by a more insidious onset of lichenified plaques or a generalized eczematous response (namely, auto-sensitization or id reaction). The prognosis is good with resolution of dermatitis if the offending agent is avoided.

Irritant contact dermatitis is the most common subtype of contact dermatitis [44]. It requires no prior sensitization and can be seen in any person exposed to the offending agent given the appropriate clinical scenario. Patients present with eczematous dermatitis at the point of contact, with sparing at areas where the skin is protected or not exposed (Fig. 1.12). Resolution with or without secondary dyschromia is seen once the eliciting agent is eliminated.

1.4.2 Histology

Contact dermatitis can be divided into allergic contact dermatitis and irritant contact dermatitis and there are subtle histologic differences that may allow for distinction on biopsy.

Allergic contact dermatitis is a spongiotic process, characterized by parakeratosis (except in the acute state), marked intraepidermal edema and abundant Langerhans cell microabscesses [45] (Fig. 1.13). In florid cases, the spongiosis results in microvesiculation. Eosinophils are abundant within the dermis and may extend into the epidermis (Fig. 1.14). A brisk lymphohistiocytic inflammatory infiltrate is present surrounding vessels of the superficial vascular plexus. Ordinarily, the inflammation does not extend into the lower portions of the dermis [46, 47].

Irritant contact dermatitis has similar changes; however, eosinophils are much less common and may be absent in many cases. Occasional dying keratinocytes may be present as a result of direct cytotoxicity in some cases. As a result of severe toxicity, extensive epidermal necrosis may be present [47, 48].

In chronic stages, both allergic and contact dermatitis demonstrate hyperkeratosis with less parakeratosis, less prominent spongiosis, less intense inflammatory infiltrates and elongation of rete ridges, which are changes reminiscent of lichen simplex chronicus.

1.4.3 Pathogenesis

Allergic contact dermatitis is a T-lymphocyte mediated, delayed-type hypersensitivity reaction elicited by the contact of the skin with a chemical in an individual who has been previously sensi-

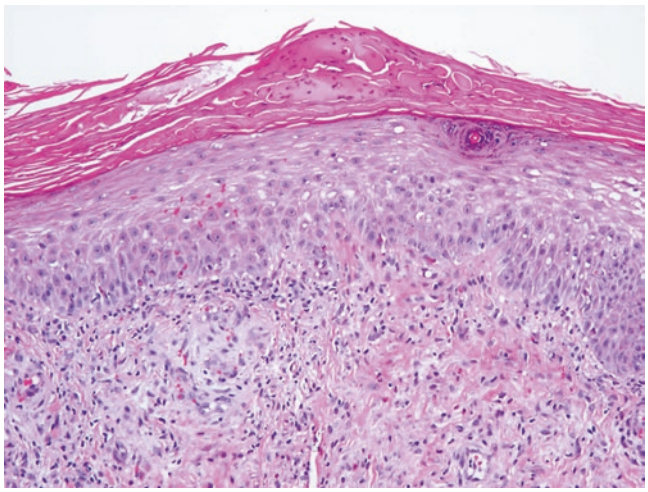

Fig. 1.13 A serum and neutrophil crust overlies a spongiotic epidermis in allergic contact dermatitis

Fig. 1.12 Irritant contact dermatitis presents as erythematous patches over skin surfaces in the diaper area due to fecal soilage

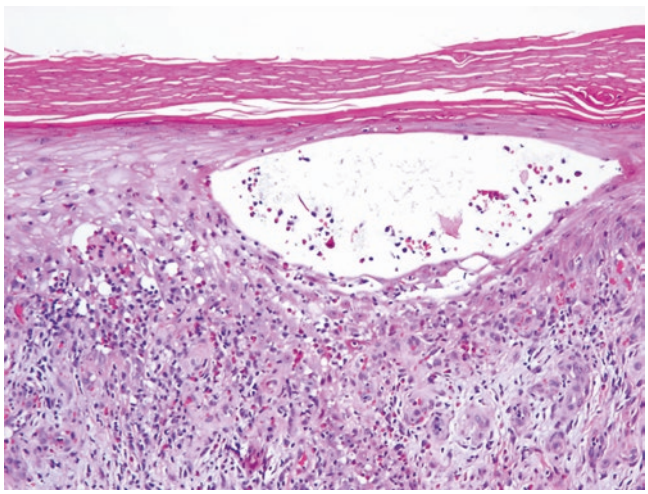

Fig. 1.14 Allergic contact dermatitis frequently displays spongiotic microvesicles that contain eosinophils. Abundant eosinophils are characteristic of this disease

tized to the same chemical [49]. The initial sensitization phase involves innate immune response to skin contact with small chemicals. These chemicals are haptens, which are low molecular weight molecules that can penetrate the skin. They can be naturally occurring substances, such as urushiol found in poison ivy, synthetic compounds, dyes, fragrances, drugs, and metal cations (such as nickel and chromium which are common allergic contact dermatitis-associated haptens) [50]. By themselves, haptens are not immunogenic, but when bound to a protein carrier, they can be recognized by the immune system.

The sensitization phase in allergic contact dermatitis requires skin Langerhans cells and dendritic cells that act as antigen presenting cells to present contact allergens to naïve T lymphocytes in the draining lymph nodes [51]. Dendritic cells in the skin interact with keratinocytes, migrate to the local draining lymph nodes and act as antigen-presenting cells to prime naive T lymphocytes. This results in the priming of CD8+ cytotoxic T lymphocytes and type 1 T-helper lymphocytes (Th1) to generate chemical-specific, skin-homing T cell repertoire [52]. There is increased number of allergen-specific circulating T lymphocytes in the blood of patients with allergic contact dermatitis [53–55]. Upon re-exposure to the same chemical, CD8+ T lymphocytes home in and infiltrate the skin, inducing keratinocyte apoptosis via the perforin/granzyme and Fas/Fas ligand pathways [56, 57]. CD4+ CD25+ regulatory T cells (Tregs), which regulate antigen sensitization process, are also important. Allergic contact dermatitis has been found to be associated with defects in Treg cells [58–60].

Small chemicals act as haptens to induce the release of damage-associated molecular pattern (DAMP) molecules and toll-like receptor (TLR) stimulation with the release of pro-inflammatory cytokines, such as interleukin-1β and tumor necrosis factor-α, as well as the recruitment Th1 and IL-17-producing T helper cells (Th17) [53, 54]. TLR2 and TLR4 in particular are important in ACD, and they are activated by DAMP molecules. TLR2 and TLR4 activation leads to the production of interleukins, IFN-γ and TNF-α, which are potent activators of keratinocytes and promote the recruitment of effector T lymphocytes and the inflammatory response [61, 62].

1.5 Autosensitization Dermatitis/Id Reaction

1.5.1 Clinical Features

Auto-sensitization dermatitis or "id reaction" is a cutaneous hypersensitivity mediated by host T-cell lymphocytes to a number of stimuli including infectious insults and primary inflammatory skin conditions [63]. Disease onset may follow initiation of antimicrobial therapy or may occur subsequent to flare of the responsible dermatitis.

Fig. 1.15 Autosensitization/Id reaction presents as monomorphous scaly papules over the extensor arm

Patients typically present with the acute onset of generalized, symmetric, pruritic, edematous papules and papulovesicles. Clinical features vary and are dependent upon the inciting agent and the secondary host response [63]. Diagnosis is suggested by resolution of acute eruption following appropriate treatment of the primary inciting event (Figs. 1.15 and 1.16). The prognosis is good but recurrence is common if the primary source is not appropriately eliminated.

1.5.2 Histology

Histologic features of autosensitization dermatitis include parakeratosis admixed with serum in the stratum corneum, intraepidermal spongiosis with occasional microvesiculation, and a lymphohistiocytic infiltrate surrounding vessels within the superficial vascular plexus (Figs. 1.17, 1.18 and 1.19). Eosinophils are generally not abundant, in contrast to allergic contact dermatitis. The deep dermis is usually not involved [63, 64]. As lesions become more chronic, there is a tendency for diminution of spongiosis and inflammation, and increased acanthosis of the epidermis.

Fig. 1.16 Autosensitization/Id reaction may present as monomorphous scaly papules coalescing into a plaque as seen here over the dorsal hand and wrist of a child

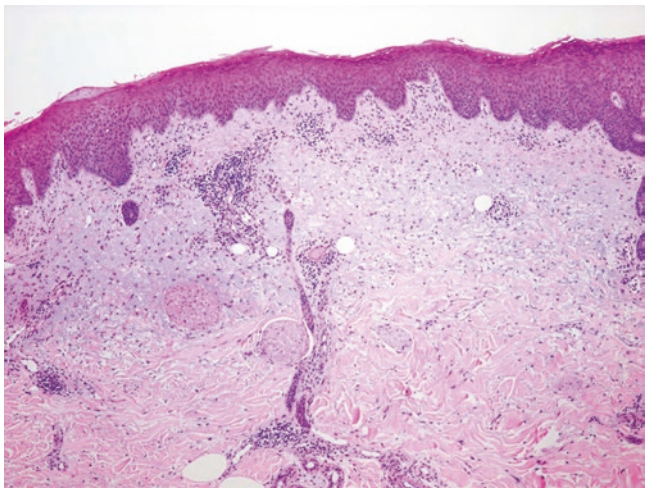

Fig. 1.17 An id reaction is characterized by a mild spongiotic dermatitis and a superficial perivascular lymphocytic inflammatory infiltrate

1.5.3 Pathogenesis

Autosensitization (id reaction) is a delayed hypersensitivity reaction to prior antigen exposure [65]. It is a secondary immunologic response to circulating antibodies and activated T lymphocytes directed against a sensitizing antigen. For example, an id reaction to fungal organisms may be due to a chain reaction induced by fungal antigens at the site of infection, opsonization of antigens by host antibodies, development of memory T lymphocytes and dissemination of these cells systemically [66]. Id reaction can present as localized vesicular lesions in tinea pedis, erythema nodosum in bacterial and deep fungal infections, and erythema multiforme in herpetic infections [63].

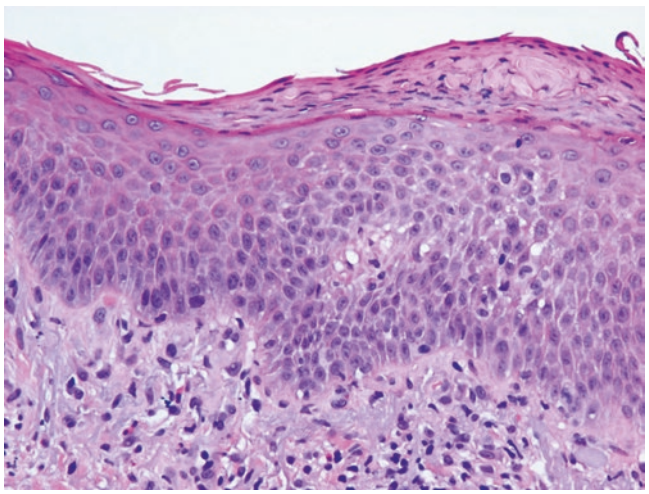

Fig. 1.18 Parakeratosis is present overlying a spongiotic epidermis in an id reaction

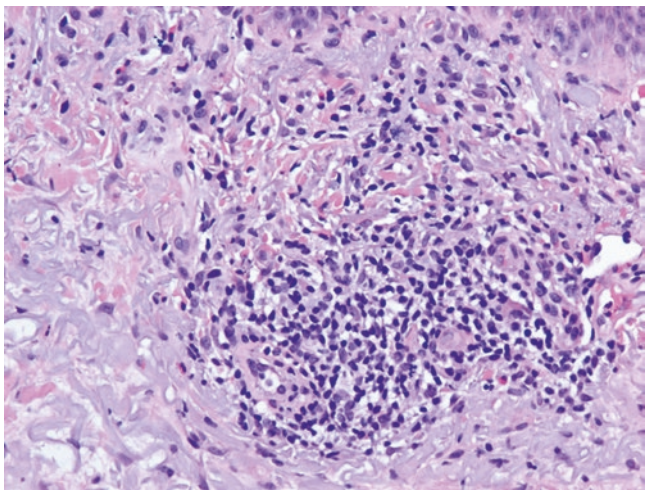

Fig. 1.19 An id reaction demonstrates a perivascular lymphocytic infiltrate with scattered eosinophils

1.6 Photoallergic Dermatitis

1.6.1 Clinical Features

Photoallergic dermatitis is thought to represent a cell-mediated delayed hypersensitivity reaction, requiring prior sensitization to an exogenous photoallergen and subsequent ultraviolet light (UV) radiation, namely UVA [67]. Initial sensitization and development of skin changes may occur 1–2 days after exposure to the allergen and sunlight [67].

On subsequent exposures, cutaneous reaction typically occurs within 24 hours even with minimal sun exposure.

Urticarial and eczematous lesions have been described with the physical exam mimicking that of allergic contact dermatitis, although skin changes are most obvious in areas that are more heavily exposed to the sun. Secondary post-inflammatory hyperpigmentation is rare [67]. The prognosis is good when the causative agent is avoided and photoprotection is employed.

1.6.2 Histology

Photoallergic dermatitis is histologically indistinguishable from acute contact dermatitis. Histologic sections demonstrate a stratum corneum that may be unremarkable in the acute state, or contain parakeratotic nuclei and serum in the subacute phase. The epidermis is markedly spongiotic with occasional microvesicles [68, 69] (Fig. 1.20). Clusters of Langerhans cells and scattered intraepidermal eosinophils and lymphocytes are present. Dying keratinocytes are not prominent. Within the papillary dermis, there is edema and a moderately intense collection of lymphocytes and eosinophils surrounding the superficial vascular plexus (Fig. 1.21). In late stages, the epidermis becomes more acanthotic and spongiosis dissipates.

1.6.3 Pathogenesis

Photoallergic dermatitis to allergens, such as plant materials (phytophotodermatitis), results from skin exposure to sap from a plant that reacts with long wavelength ultraviolet light (UV) [70]. Photoallergens may form from haptens that become covalently coupled to a carrier protein via UV irradiation [71]. UVA, but not UVB, is the UV spectrum of this photoreactivity. Cells that are modified by photoallergens are capable of inducing the proliferation of sensitized T lymphocytes and eliciting an immune response [72, 73]. In addition to T lymphocytes, skin Langerhans cells are important in the pathogenesis of photodermatitis and function as antigen-presenting cells of photoallergens to sensitized T lymphocytes [71].

1.7 Pityriasis Alba

1.7.1 Clinical Features

Pityriasis alba most commonly affects children between 3 and 16 years of age with an incidence of 2 to 5 % in pediatric populations [74]. Prevalence is higher in darker-skin individuals. No gender predilection exists.

Pityriasis alba is characterized by hypopigmented patches with subtle scaling, most commonly on the face but also occurring on the neck, upper trunk, and proximal extremities (Fig. 1.22). Skin changes typically are most prominent after sun exposure, as affected areas do not darken with ultraviolet light exposure. Although pityriasis alba is a chronic condition with a relapsing course, it has a good prognosis with eventual spontaneous resolution.

1.7.2 Histology

Histologic changes in pityriasis alba are nonspecific. They include hyperkeratosis and parakeratosis, mild spongiosis, and plugging of follicles in some cases [75]. Atrophic sebaceous glands have been described in some patients [76].

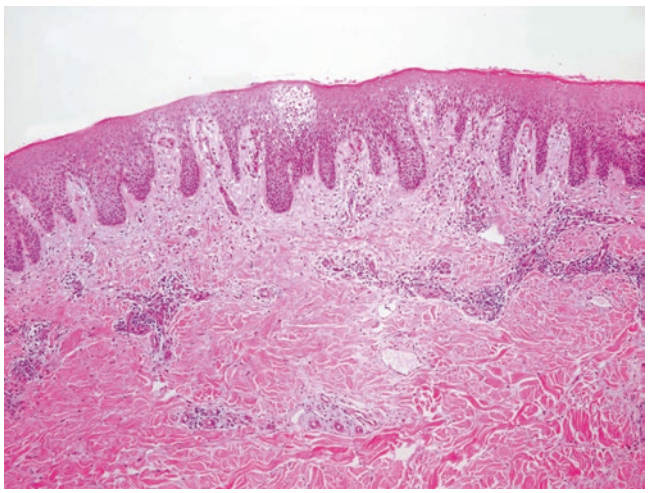

Fig. 1.20 Photoallergic dermatitis is a spongiotic dermatitis that results in intraepidermal edema, exocytosis of lymphocytes into the epidermis, and microvesiculation when severe

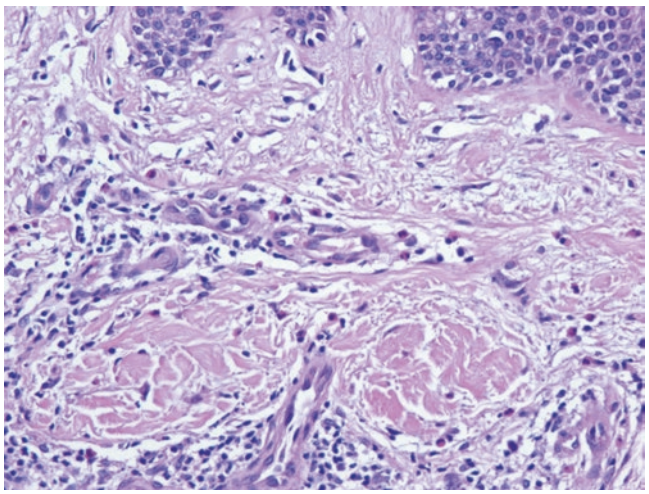

Fig. 1.21 The inflammatory infiltrate in photoallergic dermatitis includes lymphocytes and abundant eosinophils within the dermis and sometimes extending into the epidermis

Fig. 1.22 Pityrisis alba shows scattered, poorly defined hypopigmented macules and patches over the cheeks

There is a superficial perivascular lymphocytic infiltrate with focal exocytosis. The most specific changes are those of decreased numbers of melanocytes in the epidermis [77]. However, use of melanocyte-specific markers suggest that there is no significant decrease in numbers of melanocytes, but there is diminished melanin production [78]. Residual melanocytes within affected areas demonstrate decreased numbers of melanosomes on ultrastructural analysis [77, 78].

1.8 Gianotti–Crosti Syndrome

1.8.1 Clinical Features

Gianotti–Crosti syndrome is a dermatitis almost exclusively seen in children, with peak incidence between 1 and 6 years of age (range of 3 months old to 15 years old) [79]. It is thought to be a cutaneous response to a viral insult and may be seen following vaccinations, although reports of similar eruptions following a bacterial infection have been reported [79–81].

The syndrome is characterized by multiple symmetric, monomorphic and erythematous (pink–reddish brown) 1–5 mm papules or papulovesicles on the face, buttocks, and extremities (Figs. 1.23, 1.24, and 1.25). Distinct lesions may coalesce in some areas. A preceding prodrome may be present and includes malaise, fever, diarrhea, and concomitant lymphadenopathy [79]. Skin lesions resolve spontaneously

Fig. 1.23 Diffuse small monomorphic papules on the face of a child with Gianotti–Crosti syndrome

Fig. 1.24 Diffuse small papules present on the extensor arm and hand in the same child with Gianotti–Crosti syndrome

within weeks to months without secondary dyschromia or scarring. Hepatitis and other visceral involvement are rare with no reports of long-term sequelae or morbidity [79].

1.8.2 Histology

Gianotti–Crosti syndrome is characterized by a mild spongiotic process, often with pronounced papillary dermal edema (Fig. 1.26). Focal parakeratosis is variably present. A superficial perivascular lymphohistiocytic infiltrate demonstrates

Fig. 1.25 This same child with Gianotti–Crosti syndrome had similar diffuse monomorphic papules on the legs and buttocks

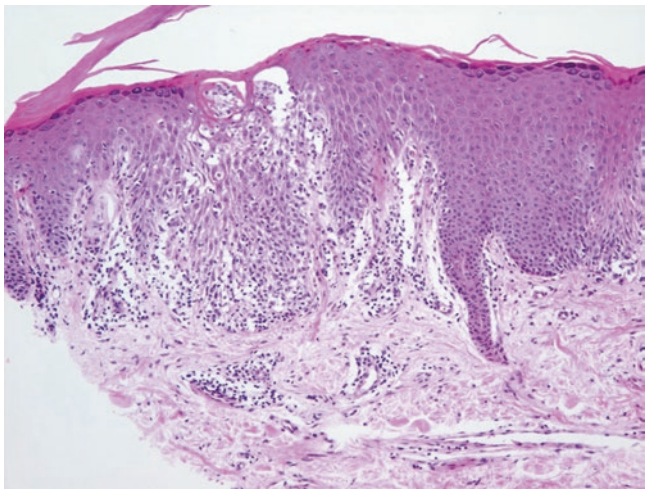

Fig. 1.26 Gianotti–Crosti disease demonstrates nonspecific spongiotic dermatitis with a lymphocytic infiltrate and scattered exocytosis

only rare eosinophils. In rare cases, spongiotic microvesicles containing Langerhans cells may be present adjacent to areas of epidermal acanthosis. Some authors have suggested that papillary dermal edema is most prominent in cases associated with Epstein–Barr virus infection [82]. Extravasated erythrocytes have been described in some cases. In rare cases, an interface dermatitis with scattered basal vacuolization has been described [83].

1.8.3 Pathogenesis

Viral infection is an important contributing factor in the pathogenesis of Gianotti–Crosti Syndrome. Epstein–Barr virus (EBV) is a common viral infection associated with the disease [84, 85]. Viral antigens and antiviral antibodies have been found in the serum of patients. Hepatitis B virus (HBV) is another common viral infection associated with Gianotti–Crosti syndrome, although there has been a decline in HBV-associated disease due to anti-HBV immunizations [86, 87]. Atopic dermatitis has also been implicated in disease pathogenesis. In a case–control study, children with Gianotti–Crosti syndrome were more likely to have atopic dermatitis or a family history of atopy than children without disease, who were being evaluated for recurrent infections (24.1 % versus 6.8 % for atopic dermatitis, and 51.7 % versus 31 % for family history of atopy) [88]. Gianotti–Crosti syndrome commonly occurs in children, and the disease is less severe in children than in adults. A possible explanation for the higher frequency of disease in children is that EBV infection is more common in children. The immature immune system of infants and children, and the resulting differences in response to viral infections in children may be a basis for different disease severity in children as compared to adults.

1.9 Intertrigo

1.9.1 Clinical Features

Intertrigo is a frictional dermatitis caused by persistent rubbing of adjacent skin surfaces. The condition is frequently exacerbated by excess moisture within the deep skin folds of the affected areas. Secondary infection may be seen, most commonly with candida fungal species, although reports of infection by group A β-hemolytic streptococcus, Staphylococcus aureus and mixed bacterial species have been documented as well [89].

Intertrigo is characterized by macerated, erythematous patches at the skin folds. Candidal intertrigo may be distinguished by presence of satellite papules and pustules. Bacterial intertrigo, on the other hand, has circumscribed, weeping or moist, “fiery red” erythema, possibly with associated malodor and tenderness (Fig. 1.27). Clearance can be achieved with measures to minimize friction and treatment of any secondary infections.

1.9.2 Histology

Intertrigo has no characteristic histologic changes [90]. Mild spongiosis may be present in the epidermis in some cases. In many cases, there is superimposed infection with bacteria and fungi (Fig. 1.28). In those cases, changes suggestive of impetigo or dermatophyte infection may be present.

1.9.3 Pathogenesis

Intertrigo is precipitated by moisture trapped in deep skin folds [90, 91]. Hyper-hydration and friction between skin folds can lead to maceration of the stratum corneum and

Fig. 1.27 Bacterial intertrigo presents in this infant as an erythematous erosion in the axillary crease

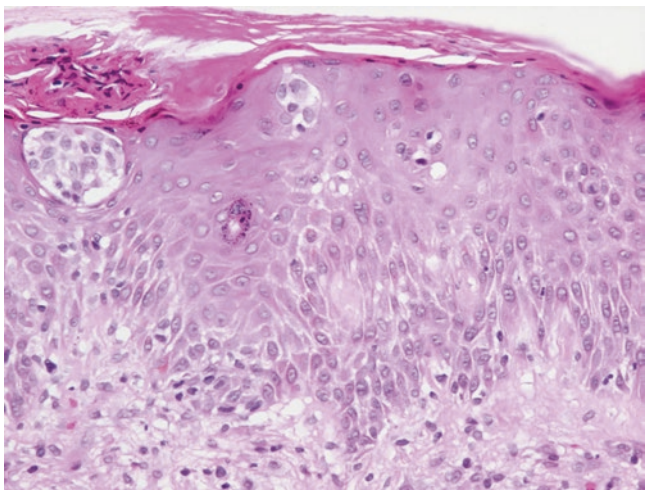

Fig. 1.28 The findings in intertrigo include a nonspecific spongiotic dermatitis, here seen containing Langerhans cell abscess within the epidermis

damages to the epidermis. The condition can progress to severe inflammation and erosion of the skin barrier, thus facilitating the growth of microorganisms, such as *Staphylococcus aureus*, group A β-hemolytic streptococcus, and fungi.

Candida albicans is a fungus that has predilection to colonize macerated folds of skin and is often associated with intertrigo. Candida infection and intertrigo occur more frequently in patients with diabetes mellitus because these patients have a higher pH in intertriginous areas, which may be a factor that promotes the susceptibility of these patients to Candida infection [92, 93]. Other dermatophytes, namely Trichophyton rubrum, Trichophyton mentagrophytes and Epidermophyton floccosum, are often found in interdigital intertrigo in the hands and feet [90].

1.10 Periorificial Dermatitis

1.10.1 Clinical Features

Periorificial dermatitis is an eczematous and acneiform eruption of unknown etiology seen across a spectrum of pediatric patients from infants to older adolescents, although most cases are reported in those less than 5 years old [94]. A majority of children with disease have a history of steroid exposure, whether it is topical, inhaled or by systemic administration [95]. Sub-variants of the disorder include granulomatous periorificial dermatitis and facial Afro-Caribbean childhood eruption (FACE), both of which are seen more commonly in persons with darker skin. Isolated perioral lesions are more commonly seen, although lesions can be more generalized with skin changes around the nose, eyes, and mouth and even at the genital orifices [95].

On clinical examination, erythema and scaling are frequently seen interspersed with papules, pustules, plaques, and patches (Figs. 1.29 and 1.30). There usually is sparing of the upper lip and vermillion border, distinguishing it from a lip licking eczema [94]. Periorificial dermatitis has a relapsing course with eventual remission.

1.10.2 Histology

Periorificial dermatitis displays many of the same histologic features as rosacea. Early lesions are characterized by parakeratosis overlying a spongiotic and mildly acanthotic epidermis (Figs. 1.31 and 1.32). Papillary dermal edema and vasodilatation are common findings. There is some accen-

Fig. 1.29 Erythematous papules and scaly plaques are seen around the mouth, nose, and eyelids of a child with periorificial dermatitis

Fig. 1.30 Periorificial dermatitis typically presents as small erythematous papules around the mouth, nose, and eyes of a child

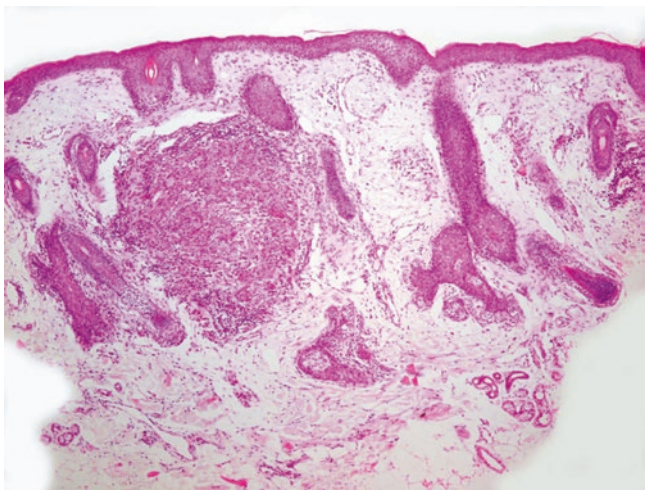

Fig. 1.31 Periorificial dermatitis characteristically demonstrates a spongiotic dermatitis. In florid cases such as the one depicted here, perifollicular granulomas are present in the dermis

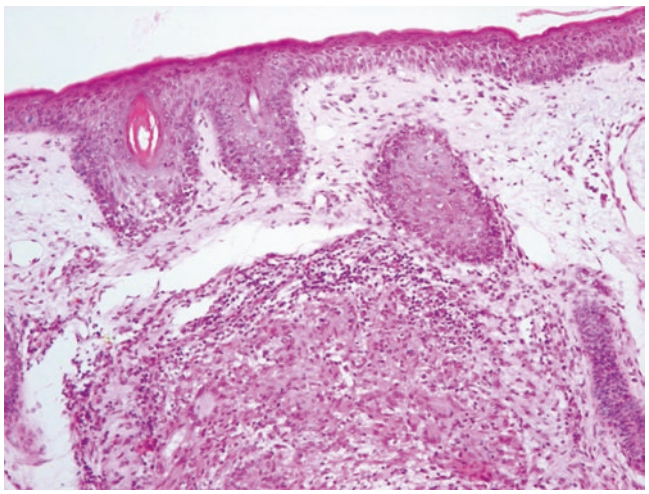

Fig. 1.32 Perifollicular granulomas are seen only in florid cases of periorificial dermatitis, although a spongiotic epidermis is seen in all cases of this entity

tuation of the spongiotic pattern in the region of pilosebaceous units with follicular hyperkeratosis. Abscesses containing neutrophils may be identified within the affected hair follicles. In some patients, sebaceous hyperplasia may be prominent. A pronounced lymphohistiocytic infiltrate is present, and scattered neutrophils can be seen. In the most florid cases, perifollicular non-caseating granulomas may be present [96].

1.11 Juvenile Plantar Dermatosis

1.11.1 Clinical Features

Juvenile plantar dermatosis is a dermatitis of the foot, typically occurring in school-age children during the winter months [97]. In some studies, atopy is seen with greater prevalence in the affected population. The clinical exam is characterized by a scaling, fissured eruption along the weight-bearing areas of the forefoot with associated pruritus and burning (Fig. 1.33) [97]. The eruption typically clears spontaneously sometime during early adolescence.

Fig. 1.33 Juvenile plantar dermatosis shows mild erythema and patchy superficial desquamation over the plantar forefoot and toes

1.11.2 Histology

Juvenile plantar dermatosis demonstrates psoriasiform epidermal hyperplasia with focal loss of the granular layer. Confluent parakeratosis overlies the epidermis. A perieccrine lymphocytic infiltrate is present with the densest infiltrate located just beneath the acrosyringial portion of the eccrine apparatus [98, 99]. Spongiosis is present surrounding the acrosyringia and may result in microvesiculation.

1.11.3 Pathogenesis

Juvenile plantar dermatosis is a type of frictional dermatitis caused by excessive moisture of the feet [100]. It is mainly seen in the fall and winter seasons when children wear heavy socks and footwear that result in excessive foot moisture [101]. Nonbreathable, occlusive footwear, such as heavy socks, can lead to higher foot temperature, resulting in transepidermal water loss and disruption of the skin barrier [102]. Impaired epidermal barrier can lead to drying of the epidermis, and defects in keratinocyte adhesion, all of which can cause fissure formation. Thus far, there is no evidence for fungal infection or irritants in the etiology of the disease. However, bacterial colonization may be a contributing factor [99]. Juvenile plantar dermatosis has also been associated with eczema [103].

1.12 Hyperimmunoglobulin E Syndrome

1.12.1 Clinical Features

Hyperimmunoglobulin IgE Syndrome (HIES) can be inherited in either an autosomal dominant or autosomal recessive manner. Both subtypes are exceedingly rare with no known racial or gender predilection.

Fig. 1.34 Hyperimmunoglobulinemia E syndrome patient presents with diffuse erythematous lichenified papules and plaques of atopic dermatitis complicated by numerous small waxy papules of widespread molluscum over the face and neck

Both subtypes are associated with increased IgE levels, moderate to severe atopic dermatitis as well as recurrent cutaneous and sinopulmonary infections, beginning soon after birth [104, 105] (Fig. 1.34). In autosomal dominant HIES, a prominent scalp folliculitis may be seen in infancy as well as coarse facies and bony defects, thus predisposing patients to fractures, scoliosis and dental abnormalities, including retention of primary teeth [105]. Autosomal recessive HIES, in contrast, lacks bony abnormalities and infantile rashes, but has higher rates of asthma, environmental and food allergies and a predisposition to severe viral infections, namely warts and molluscum contagiosum [104].

Patients with autosomal recessive HIES have higher rates of malignancy and overall mortality in comparison to their counterparts with the autosomal dominant variant [106]. Reported malignancies in autosomal recessive disease include aggressive cutaneous T-cell lymphoma, squamous cell carcinoma and diffuse large B-cell lymphoma [106].

1.12.2 Histology

The most common histologic changes seen in hyperimmunoglobulin E syndrome are those of a spongiotic dermatitis. In addition, at the time of birth, patients with this syndrome often have a pustular eruption, most pronounced on the face that demonstrates abundant eosinophils on biopsy [107] (Fig. 1.35). However, in most cases, this eruption rapidly abates and gives rise to typical changes of spongiotic derma-

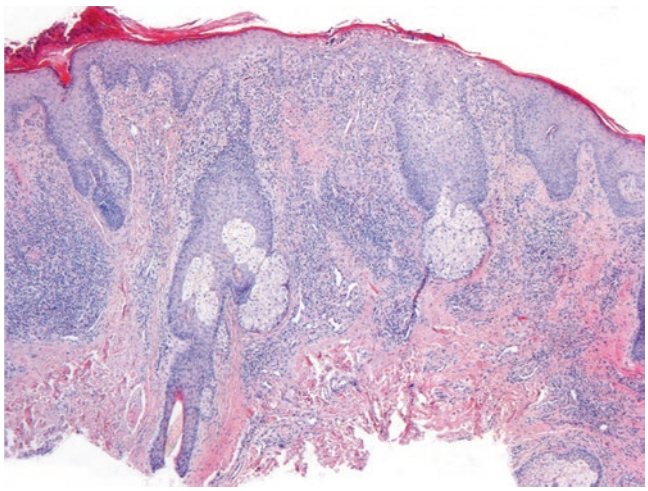

Fig. 1.35 A spongiotic dermatitis with overlying parakeratosis and pustules can be seen in hyperimmunoglobulinemia E syndrome (figure courtesy of Irina Margaritescu, MD, Bucharest, Romania)

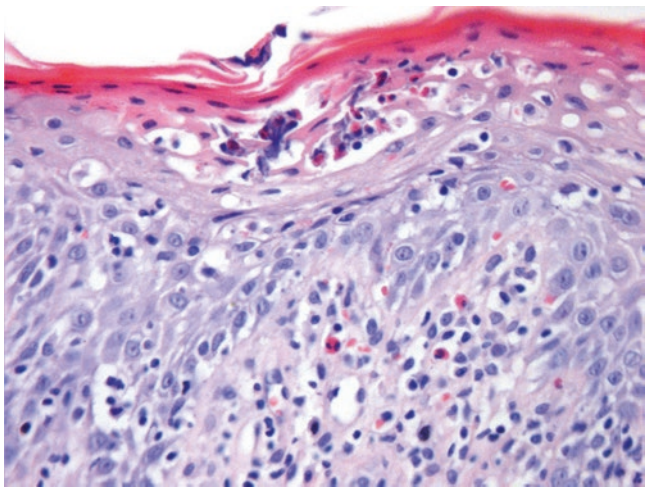

Fig. 1.36 Abundant eosinophils within the epidermis and dermis are seen in most cases of hyperimmunoglobulinemia E syndrome (figure courtesy of Irina Margaritescu, MD, Bucharest, Romania)

titis. The stratum corneum has parakeratosis and small amounts of serum. The epidermis is mildly spongiotic and acanthotic, and lymphocytes are present in the superficial dermis, focally extending into the epidermis. Eosinophils are present in most cases (Fig. 1.36). In some cases, an eosinophilic pustular folliculitis (resembling changes commonly seen in neonates with this syndrome) is seen on biopsies taken during childhood [108].

1.12.3 Pathogenesis

Familial HIES is a primary immune deficiency characterized by high levels of circulating immunoglobulin E (IgE) and abnormal susceptibility to infections, most commonly *Staphylococcus aureus* and *Candida albicans* [109, 110]. HIES has both autosomal dominant and recessive inheritance patterns [111]. However, most cases of HIES are sporadic.

A landmark discovery of the cause of HIES is the finding of dominant-negative mutations in STAT3 (signal transducer and activator of transcription 3) in classical multisystem HIES. In a key study, de novo heterozygous mutations in the DNA-binding domain of STAT3 were found in 8 out of 15 unrelated nonfamilial HIES patients [112]. Other missense and deletion mutations in STAT3 have been identified in 50 familial and sporadic cases of HIES [113]. Many of the mutations are located in the DNA-binding domain and the SRC homology 2 (SH2) domain of STAT3, resulting in the impairment of the DNA-binding activity of STAT3.

The identification of STAT3 mutations, together with the previous finding of a mutation in TYK2 (tyrosine kinase 2) in HIES [114], underlines the critical involvement of cytokine signaling in the pathogenesis of HIES. Deficiency in STAT3 leads to the upregulation of cytokines secreted by type 1 T helper cells (such as interferon-γ and TNF-α) and the downregulation of the inflammatory and anti-inflammatory responses governed by interleukin-6 and interleukin-10 [115]. High levels of circulating IgE in patients with HIES may reflect a role for STAT3 in IgE production. In an experimental animal model with conditional loss of STAT3 in hematopoietic cells, there is eosinophilia and accumulation of mature granulocytes in the bone marrow [116].

Another key understanding of the pathogenesis of HIES is the finding that patients with autosomal dominant HIES have impaired differentiation of IL-17-producing T helper cells (Th17) [117]. Th17 cells are an important subset of helper T cells that are critical in the clearance of fungal and bacterial infections. Naive T cells from these patients fail to differentiate into Th17 cells upon stimulation with staphylococcal enterotoxin B, Candida albicans and streptokinase. Importantly, deficiency in the differentiation of these cells is due to mutations in STAT3, which lead to a reduction in the expression of retinoid-related orphan receptor (ROR) [118]. ROR is a key transcriptional regulator in Th17 cells. Thus, the inability to produce Th17 cells due to STAT3 mutations is a mechanism underlying the susceptibility to recurrent infections commonly seen in patients with HIES [117].

1.13 Wiskott–Aldrich Syndrome

1.13.1 Clinical Features

Wiskott–Aldrich Syndrome is an X-linked immunodeficiency, affecting 1 in 100,000 individuals with the gene mutations [119]. Clinical symptoms of petechiae, bruising and bloody diarrhea frequently are present at birth with moderate to severe atopic dermatitis developing in early infancy [119]. Almost three quarters of affected individu-

als have an autoimmune or inflammatory complication with hemolytic anemia being most common [120]. Patients also have recurrent bacterial infections from encapsulated bacteria [119]. The syndrome has a progressive course with premature death from infection, hemorrhage and malignancy in approximately 10 % of affected individuals [119, 120].

1.13.2 Histology

Skin biopsies from patients with Wiskott–Aldrich syndrome demonstrate histologic changes of spongiotic dermatitis. The changes are indistinguishable from atopic dermatitis. Due to the abnormalities in platelets, extravasated erythrocytes are frequently seen in biopsies taken from petechiae and ecchymoses in affected patients. Leukocytoclastic vasculitis has been reported as part of the constellation of findings in some patients [121].

1.13.2.1 Pathogenesis

Wiskott–Aldrich syndrome (WAS) is caused by dysregulated activity of the WAS protein, which functions as a scaffolding protein to transduce signals from the cell surface to the actin cytoskeleton [122, 123]. Defects in WAS protein cause abnormal actin polymerization in cells and consequently affect cell adhesion and migration [124, 125]. Mutations that result in complete loss of WAS protein result in classic Wiskott–Aldrich syndrome phenotype [126, 127]. Decreased expression of WAS protein result in a milder variant of the disease known as X-linked thrombocytopenia [128, 129]. Conversely, constitutive activation of WAS protein leads to X-linked congenital neutropenia [130, 131].

WAS protein expression is restricted to hematopoietic cells. In particular, WAS protein-deficient B and T lymphocytes and natural killer (NK) cells are morphologically abnormal with defective migration and adhesion [132–134]. Defects in T lymphocytes are a major cause of the immunodeficiency in Wiskott–Aldrich syndrome. Reduction in T lymphocytes is due to abnormal development and reduced thymic output [133, 135–137]. WAS protein-deficient T lymphocytes fail to polymerize actin and rearrange the actin cytoskeleton in response to CD3 co-receptor ligation [138]. NK cells have reduced cytotoxic activity and fail to form stable conjugates with target cells [132, 139]. Monocytes and macrophages are also affected with defects in podosome formation and failure to migrate to a chemokine gradient [140]. Wiskott–Aldrich syndrome patients have micro-thrombocytopenia associated with a bleeding diathesis. This is likely due to the absence of WAS protein in platelets.

1.14 Lichen Simplex Chronicus/Prurigo Nodularis

1.14.1 Clinical Features

Both prurigo nodularis and lichen simplex chronicus fall under a broader category of psychosomatic dermatoses as lesions can develop de novo, be associated with underlying systemic disease, or occur at sites of preexisting dermatitis [141]. Prurigo nodularis is a dermatosis triggered by an intense underlying pruritus that fuels persistent scratching [141]. Prurigo nodularis is characterized by firm and hyperpigmented papulonodules and nodules, ranging in size from 1–5 cm at sites that are easily reached by the patient, such as the limbs, face, and peripheral trunk (Fig. 1.37). Many of the affected areas are excoriated with overlying hemorrhagic crust.

Lichen simplex chronicus (circumscribed neurodermatitis) is a chronic pruritic dermatitis characterized by localized lichenification and hyperpigmentation at previous sites of repeated scratching and rubbing [141]. Lichen simplex chronicus presents with ill-defined, erythematous, edematous plaques with exaggerated skin markings that evolve to

Fig. 1.37 Prurigo nodularis presents as multiple hyperpigmented lichenified papules and nodules over the legs

Fig. 1.38 Lichen simplex chronicus presents as lichenified hyperpigmented plaques over the dorsal hands, fingers, and knees

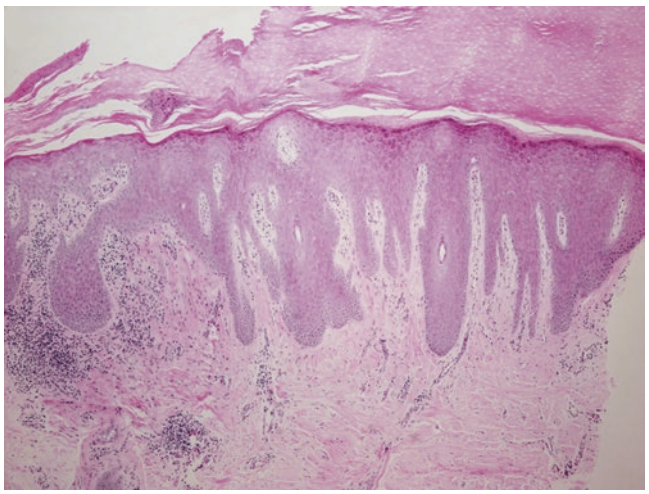

Fig. 1.39 Lichen simplex chronicus demonstrates a markedly hyperkeratotic stratum corneum and an acanthotic epidermis with elongated rete ridges and hypergranulosis. Papillary dermal fibrosis is frequently present

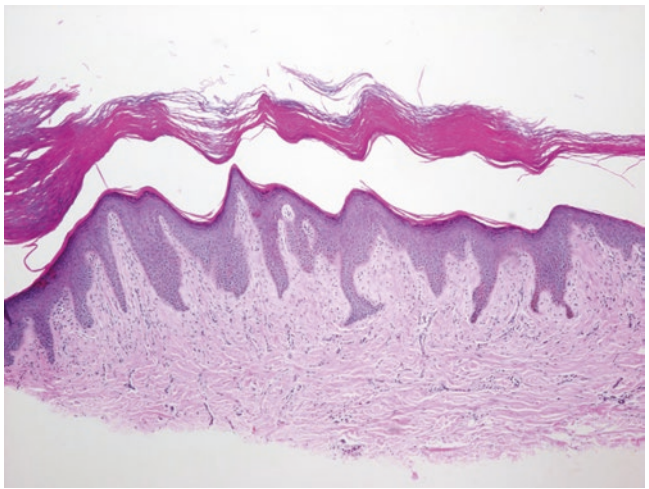

Fig. 1.40 Prurigo nodularis demonstrates marked hyperkeratosis overlying an acanthotic epidermis with hypergranulosis. Psoriasiform elongation of rete ridges is seen in most cases

the more classic presentation of well-demarcated, dry-scaled, hyperpigmented plaques (Fig. 1.38).

Disease resolution requires that the underlying pruritus and scratching behavior be addressed and appropriately modified, which frequently proves difficult for patients. If left undisturbed, lesions typically resolve with scarring and hyperpigmentation.

1.14.2 Histology

Lichen simplex chronicus and prurigo nodularis are best considered as two ends of a spectrum that range from a plaque-like lesion (lichen simplex chronicus) to an isolated nodule (prurigo nodularis) [142]. Both of these processes represent late stages of cutaneous lesions that have undergone extensive secondary development. In both entities, extensive superficial irritation caused by exogenous sources or by rubbing results in very similar histologic changes. Late stages of spongiotic dermatitis invariably result in these changes and often obscure the underlying etiology of the primary dermatologic process [143].

Histologic sections demonstrate marked compact hyperkeratosis, often with no or minimal residual parakeratosis. Serum is usually no longer present within the stratum corneum. The epidermis is acanthotic, with irregular elongation of the rete ridges (Figs. 1.39 and 1.40). In some cases, small amounts of intraepidermal edema may be present, but in most cases, this is absent. The granular layer is markedly and diffusely increased [142]. In cases with continued exogenous trauma, scattered dying keratinocytes may be seen in the epidermis. The papillary dermis is characterized by dense fibrosis, with vertically oriented collagen bundles extending from the superficial vascular plexus up to the epidermis (Fig. 1.41). A slight perivascular lymphohistiocytic infiltrate is present, and depending upon the antecedent cause of the process, scattered eosinophils may be seen within the dermis [142]. Neural hypertrophy has been described in these entities, but observation of this criterion is not necessary to make the diagnosis [144–146]. Other authors have failed to identify neural hyperplasia [143]. Lichen simplex chronicus has a flat surface while in prurigo nodularis, a "crescendo/decrescendo" type of nodularity is present and aids in the diagnosis. As the changes seen in these entities are secondary to mechanical trauma, evidence of acute excoriation is often seen in the same biopsies.

The histologic differential diagnosis includes psoriasis, lichen planus, and verruca vulgaris. Psoriasis shares the pat-

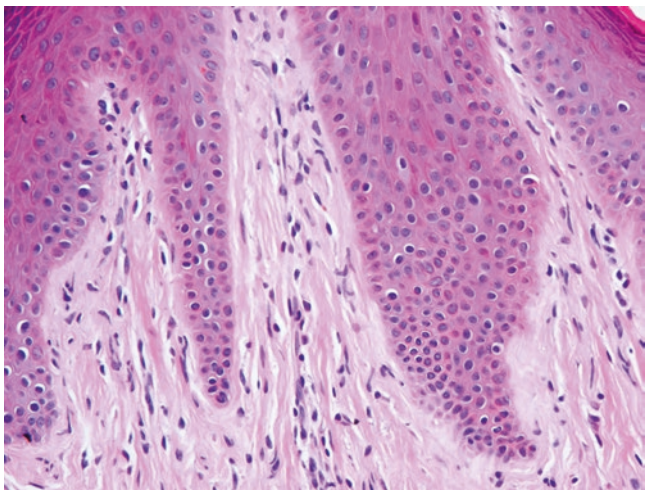

Fig. 1.41 Vertically oriented fibrotic collagen is present within the papillary dermal projections in prurigo nodularis

tern of epidermal elongation; however, the granular layer in psoriasis is diminished or absent, whereas it is greatly thickened in lichen simplex chronicus and prurigo nodularis. Furthermore, psoriasis is characterized by thick, diffuse parakeratosis, and neutrophilic abscesses within the stratum corneum and the epidermis, which are findings not characteristic of lichen simplex chronicus or prurigo nodularis. Lichen planus shares the histologic findings of compact hyperkeratosis and thickened granular layer; however, in lichen planus, the epidermis does not have psoriasiform elongation of rete ridges. In addition, the presence of a dense bandlike infiltrate of lymphocytes with basal vacuolization and dying keratinocytes are characteristic features of lichen planus. These features are not seen in lichen simplex chronicus and prurigo nodularis. Verruca vulgaris frequently demonstrates focal columns of parakeratosis, a feature that may help to distinguish it from lichen simplex chronicus or prurigo nodularis. Punctate thrombi in the stratum corneum are often seen in verruca vulgaris but not in the other two entities. Alternating hypergranulosis and hypogranulosis, the presence of clumped keratohyaline granules and widely dilated venules in the papillary tips of the dermis also would help to support a diagnosis of verruca vulgaris. Either of these two entities can sometimes be superimposed upon verruca vulgaris, making precise distinction impossible at times.

1.14.3 Pathogenesis

Inflammatory responses mediated by type 2 T-helper cells (Th2) play a major role in the pathogenesis of lichen simplex chronicus and prurigo nodularis. Most epidermal keratinocytes in prurigo nodularis express high levels of activated (phosphorylated) STAT6 and STAT3 and show intercellular hyaluronan deposition [147]. Activated STAT6 is expressed in response to Th2 cytokines, and high levels of phosphorylated STAT6 suggest the dominant effects of Th2 cytokines in the epidermis in prurigo nodularis. Hyaluronan deposition has been detected in the epidermis of prurigo nodularis and may be involved in spongiotic changes [148]. Hyaluronan is a major extracellular glucosamine that retains aqueous liquids in the intercellular spaces. Hyaluronan production is induced by STAT6 and by other Th2 cytokines, such as IL-4/IL-13, and by Th1 cytokines, such as IFN-γ, which increase the expression of hyaluronan synthase in epidermal keratinocytes and induce intracellular hyaluronan deposition. Epidermal acanthosis in prurigo nodularis may be due to STAT3 activation, although the functional significance of STAT3 remains to be further elucidated.

Nerve hyperplasia can be seen in prurigo nodularis and may be caused by the overexpression of nerve growth factor (NGF) [149]. Lesions have a high number of mast cells around nerves. Mast cells may be a source of NGF and contribute to the pathogenesis of prurigo nodularis [150]. Eosinophils are another cell type present in the lesions, and they are in close proximity to sensory nerves and may contribute to neurohyperplasia [151].

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Papulosquamous Diseases

2

2.1 Ichthyosis Vulgaris

2.1.1 Clinical Features

Ichthyosis vulgaris is a non-syndromic ichthyosis and is the most commonly seen variant of disease with a reported incidence of 1 in 250 to 1 in 1000 individuals [1]. It appears to be exacerbated by cold, dry climates and is seen in association with atopic dermatitis in 50–60 % of the cases.

Ichthyosis vulgaris is characterized by fine, light gray, fish-like scaling, most notably along the lower extremities, sparing the face and skin folds. As previously mentioned, it frequently is seen in the setting of atopy with other clinical findings of xerosis, hyperlinear palms and soles, hypohidrosis, pruritus, and keratosis pilaris [1]. Skin involvement is usually quite mild and may be managed with aggressive use of moisturizers, emollients, and mild keratolytics.

2.1.2 Histology

Ichthyosis vulgaris shows orthokeratotic hyperkeratosis and loss of the granular layer [2] (Fig. 2.1). The epidermis is usually of normal thickness, although it may be slightly thinned. A rare variant limited to acral surfaces demonstrates similar epidermal changes associated with the loss of eccrine structures [3]. Acquired ichthyosis associated with HIV, lupus erythematosus, sarcoidosis, and other systemic illnesses has identical histologic features to ichthyosis vulgaris [4].

2.1.3 Pathogenesis

Ichthyosis vulgaris is caused by loss-of-function mutations in the gene filaggrin (FLG) [5–7]. FLG mutations at positions R501X and 2282del4 account for about 80 % of the mutations in northern Europeans [8]. Mutations in FLG gene result in a truncated profilaggrin (filaggrin precursor) protein that cannot be correctly processed into functional filaggrin [9]. Subsequently, filaggrin is significantly reduced or absent in ichthyosis vulgaris [10].

The severity of ichthyosis vulgaris phenotype depends on the extent of loss of filaggrin expression. Patients heterozygous for the mutations have a mild phenotype, whereas those who are homozygous for the mutations exhibit a more severe phenotype [11]. A major characteristic of ichthyosis vulgaris is the absence of the granular layer and abnormal or missing keratohyalin granules [10, 12]. Similar to the mutational genotype and the correlative severity of the disease phenotype, patients with heterozygous mutations in FLG have a reduced granular layer, whereas those with homozygous mutations have a complete loss of the granular layer.

At the molecular level, profilaggrin and filaggrin deficiency has multiple consequences. Profilaggrin is a major protein component of keratohyalin granules in the stratum granulosum [13]. Profilaggrin is proteolytically processed to produce filaggrin, which aggregates keratin filaments to form the cornified cell envelope [13, 14]. Filaggrin protein is essential for epidermal differentiation, lipid metabolism and barrier function [15]. Mature filaggrin is proteolyzed into its constituent amino acids and small peptides with hygroscopic properties that underlie hydration in the stratum corneum [16, 17]. The loss of filaggrin reduces the ability of keratinocytes to remain hydrated, resulting in excessive scale [18]. Defects in filaggrin also cause cytoskeletal disorganization, and impaired organization and maturation of the lamellar bilayers, thus affecting the lipid contents in the stratum corneum. There is also increased permeability of chemicals and allergens in filaggrin-defective skin, leading to increased sensitization to these irritants in ichthyosis vulgaris [15, 19]. Importantly, there is a strong association of ichthyosis vulgaris with atopic dermatitis in the context of FLG null alleles [6, 20].

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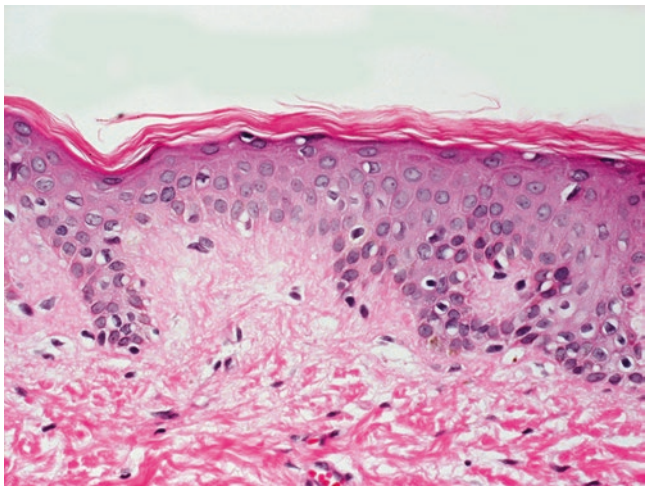

Fig. 2.1 Histologic changes seen in ichthyosis vulgaris include acanthosis and loss of the granular layer with overlying orthokeratotic hyperkeratosis

Fig. 2.2 Sex-linked ichthyosis demonstrates brown, adherent and polygonal scales on the lower extremity

2.2 Sex-Lined Ichthyosis

2.2.1 Clinical Features

Sex-linked ichthyosis (or X-linked ichthyosis) is the second most common ichthyosis subtype [21]. It is transmitted in an X-linked recessive manner and affects 1:2000 to 1:6000 males with no racial prevalence [22].

Patients often present with generalized xerosis and scaling with progression to larger, polygonal, adherent, "dirty brown" scales along the extensor surfaces of the extremities and symmetrically along the sides of the trunk. Involvement at the scalp, preauricular cheeks, and neck resolve over childhood (Fig. 2.2) [21]. Comma-shaped corneal opacities are pathognomonic, appearing during adolescence with no apparent effect on visual acuity, although they may predispose affected individuals to corneal erosions. Cryptorchidism is seen in 20 % of individuals with X-linked ichthyosis. The associated deficiency of steroid sulfatase in the fetal placenta may present with failed labor initiation or delayed progression [21, 22].

In individuals with X-linked ichthyosis, there is an increased risk of testicular germ cell cancer [21]. However, patients generally do very well and follow a benign clinical course with improvement in cutaneous findings over time. Hydration, lubrication, and keratolytics (for thicker areas of scale) are key to disease management.

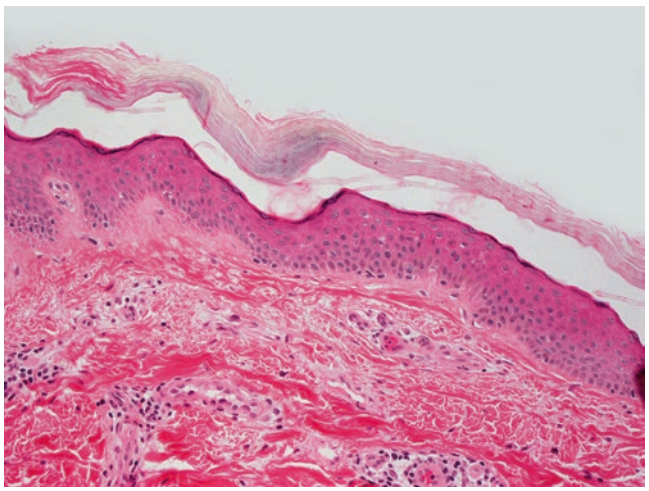

Fig. 2.3 Histologic changes in X-linked ichthyosis include subtle orthokeratotic hyperkeratosis and preserved granular layer. The epidermis usually has normal thickness

2.2.2 Histology

Sex-linked ichthyosis shows little histologic change and skin biopsies often resemble normal skin. Some authors have suggested that diagnosis is not possible on biopsy and that enzyme analysis is required to establish the diagnosis [23]. There is slight orthokeratotic hyperkeratosis and the basket-weave pattern is usually preserved (Fig. 2.3). The granular layer is preserved and the epidermis has normal thickness. In one series, a diminished granular layer was reported in some patients with X-linked ichthyosis [2]. Hyperkeratosis overlying eccrine and follicular orifices has been described in some patients with this type of ichthyosis [24]. Some authors believe sex-linked ichthyosis to be identical to steroid sulfatase deficiency and its associated ichthyosis [25, 26]. Others believe the diseases to be similar, but the sex-linked disease to be associated with more severe ichthyosis [27]. On ultrastructural examination, keratohyalin granules are larger and have a spongy appearance [28]. A banding pattern has been described in polarized hair microscopic examination in some of these patients [29].

2.2.3 Pathogenesis

Sex-linked ichthyosis is a recessive X-linked keratinization disorder that affects males [30]. Female carriers generally do not manifest the disease. Sex-linked ichthyosis is caused by loss-of-function mutations in the steroid sulfatase (STS) gene [31–33]. About 90 % of patients with X-linked ichthyosis have complete or partial deletions of *STS* [34]. STS is located on chromosome Xp22.3 and encodes an enzyme that is involved in lipid metabolism by catalyzing the hydrolysis of 3-beta-sulfate esters [35]. Loss of STS activity leads to the accumulation of cholesterol sulfate in the stratum corneum, perturbs the cell membrane integrity and increases intercellular cohesion, inducing scale formation [33, 34, 36, 37]. Excess cholesterol sulfate can also lead to separation between corneocytes and impaired skin barrier function in the epidermis. In addition, there is increased calcium in the stratum corneum, which may contribute to corneocyte retention by increasing intercellular cohesion [36].

2.3 Lamellar Ichthyosis

2.3.1 Clinical Features

Autosomal recessive congenital ichthyosis encompasses a wide spectrum of non-syndromic ichthyoses, often presenting with collodion membrane and eventual progression to a number of varied phenotypes including harlequin ichthyosis, lamellar ichthyosis, non-bullous congenital ichthyosiform erythroderma, self-healing collodion baby, acral self-healing collodion baby, and bathing suit ichthyosis [1, 38].

Lamellar ichthyosis is the most common subtype of autosomal recessive congenital ichthyosis with reported prevalence of 1 in 200,000–300,000 neonates [38]. It usually presents at birth with collodion membrane (Fig. 2.4), which is a tight, shiny membrane encasing the entire body with periorificial tightening, causing ectropion and eclabium. Although the membrane is shed within the first few weeks of life, patients later develop generalized, dark-colored, plate-like scales, occasionally with persistence of ectropion. Patients may develop scarring alopecia on the scalp as well as palmoplantar keratoderma (Fig. 2.5).

Disease expression is varied, but most individuals have skin changes that are persistent throughout life [1]. Hyperkeratotic plaques may interfere with sweat gland functioning and predispose patients to hyperthermia [39, 40]. Ectropion places the patient at risk for keratitis and corneal abrasions [39, 40]. Conductive hearing loss may occur secondary to external auditory canal stenosis by cerumen impaction [39]. Collodion membrane has an overall mortality rate of 10–20 % with morbidity secondary to temperature dysregulation, fluid and electrolyte imbalance, infection secondary to impaired skin barrier function and failure to thrive [1]. Management necessitates admission to an intensive care unit.

2.3.2 Histology

Lamellar ichthyosis, renamed ichthyosis congenital type II by some authors [41], is the most prominent variant of ichthyosis congenita and is characterized by compact orthokeratotic hyperkeratosis (Figs. 2.6 and 2.7). Cholesterol clefts are noted within the stratum corneum on electron microscopy.

Fig. 2.4 Lamellar ichthyosis baby presents at birth with collodion membrane

Fig. 2.5 Lamellar ichthyosis shows dark-colored scaling in the setting of pronounced keratoderma on the soles of an infant (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

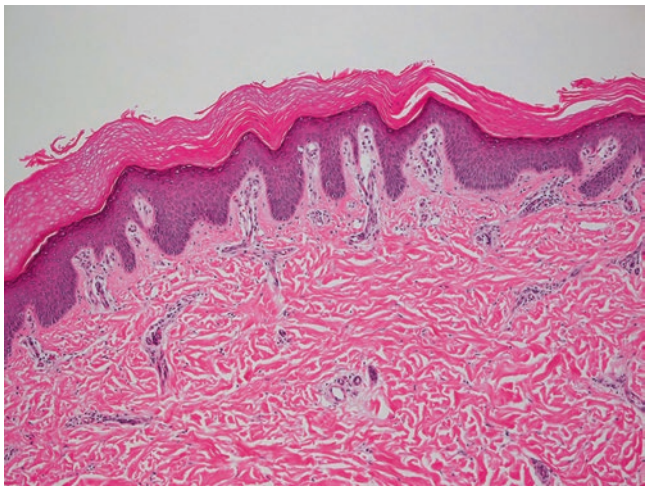

Fig. 2.6 Lamellar ichthyosis is characterized by dense, compact orthokeratotic hyperkeratosis, preservation of the granular layer and an acanthotic epidermis

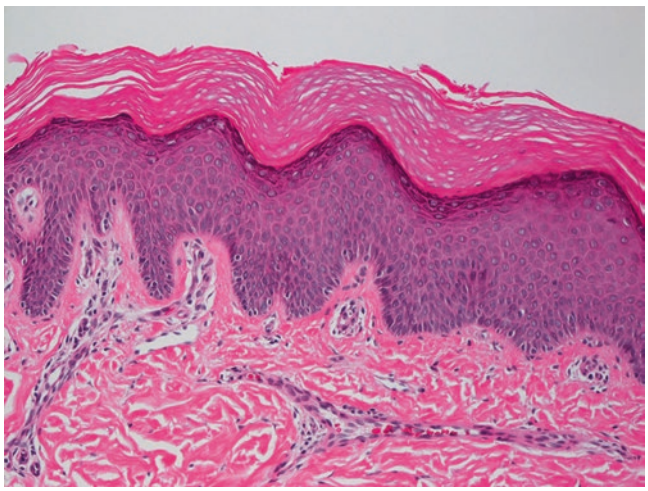

Fig. 2.7 Hyperkeratosis and hypergranulosis are present in lamellar ichthyosis

Harlequin fetus demonstrates massive, confluent hyperkeratosis. Focal parakeratosis is present in some cases and is accompanied with a diminished granular layer [42]. Large concentric lamellar bodies and giant mitochondria are seen on electron microscopy [43–45]. As there are many histologic similarities between patients with lamellar ichthyosis and those with Harlequin fetus phenotype, electron microscopy is the preferred method in distinguishing between the two entities [46].

2.3.3 Pathogenesis

Lamellar ichthyosis is a type of autosomal recessive congenital ichthyosis that is caused by mutations in the transglutaminase-1 (TGM1) gene [47–50]. Over 50 different mutations in TGM1 have been identified. Some mutations result in disruption of the active site of the enzyme, leading to loss of enzyme activity [11, 51, 52]. Patients with lamellar ichthyosis can be homozygous for single mutations or heterozygous for two different mutations in the same gene.

The function of TGM1 is to crosslink proteins and sphingolipids to the cornified cell envelope [53, 54]. The cornified envelope is an essential scaffold for the intercellular lipid layer formation in the stratum corneum. Defects in TGM1 activity can impair the formation of the lipid layers, leading to defective barrier function and the proliferative hyperkeratosis seen in lamellar ichthyosis. As noted in their clinical presentation, patients with lamellar ichthyosis have increased epidermal turnover and proliferative hyperkeratosis.

As a group of autosomal recessive congenital ichthyoses (ARCI), several causative genes associated with ARCI have been identified. These genes include transglutaminase 1, adenosine triphosphate binding cassette 12 (ABCA12), and the lipoxygenases ALOXE3 and ALOX12B [47, 50, 55–59]. In particular, ABCA12 mutations have been report in lamellar ichthyosis [60]. Other studies, however, have reported ABCA12 mutations in non-bullous congenital ichthyosiform erythroderma, but not in lamellar ichthyosis in Japanese population, noting that these findings may be different among Asian and European populations [61].

2.4 Epidermolytic Hyperkeratosis/Bullous Congenital Ichthyosiform Erythroderma

2.4.1 Clinical Features

Epidermolytic hyperkeratosis (also known as bullous congenital ichthyosiform erythroderma and epidermolytic ichthyosis) is an autosomal dominant disorder with six distinct clinical phenotypes [22]. Patients may present with generalized blistering in the neonatal period, infancy, and early childhood with eventual development of malodorous, corrugated plaques along the flexural folds (Figs. 2.8, 2.9, and 2.10).

Skin changes are persistent. As in other ichthyoses, hydration, lubrication and keratolysis are key to disease management [22]. Although the skin appears quite thick, the skin barrier is significantly impaired, predisposing affected individuals to greater bacterial colonization and recurrent infection. High rates of dermatophytosis are seen as well.

2.4.2 Histology

Epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythroderma) is characterized by orthokeratotic hyperkeratosis overlying the epidermis with marked alterations in the upper layers. The keratinocytes have marked clumping of keratohyalin granules and ballooning vacuolization. There is

Fig. 2.8 Epidermolytic hyperkeratosis presents with hyperpigmented hyperkeratosis along the extensor surface of the distal lower extremity with multiple erythematous erosions and ruptured bullae

Fig. 2.9 Corrugated plaques along the flexural folds are key features of epidermolytic hyperkeratosis in older patients

slight epidermal acanthosis (Figs. 2.11 and 2.12). There is continuous involvement of the epidermis unlike the situation in some epidermal nevi, in which focal epidermolytic hyperkeratosis occurs as an incidental finding [62]. A mild dermal inflammatory reaction is seen in some patients. Due to its

Fig. 2.10 Characteristic features of hyperpigmented thickening of the extensor knee with surrounding healing erosions are seen in this example of epidermolytic hyperkeratosis

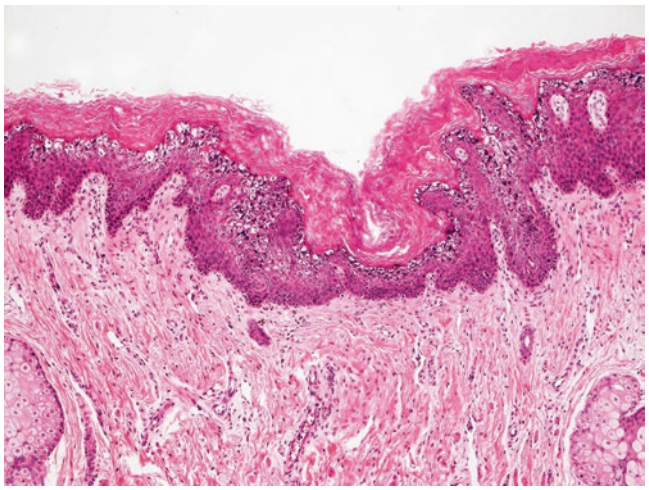

Fig. 2.11 Epidermolytic hyperkeratosis features marked clumping of keratohyaline granules in the granular layer of the epidermis

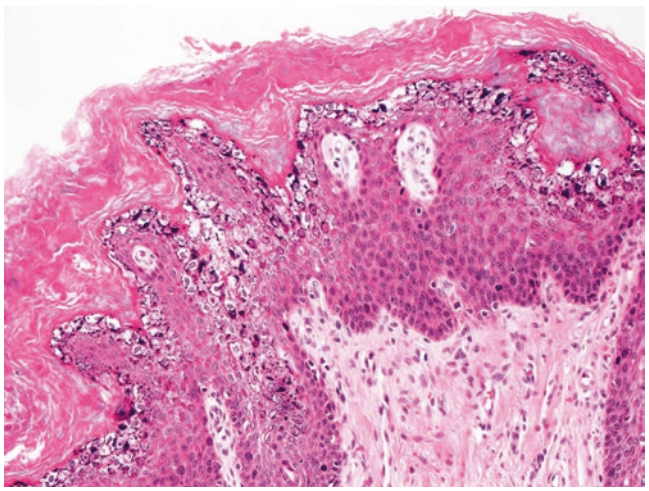

Fig. 2.12 Epidermolytic hyperkeratosis demonstrates marked hyperkeratosis, keratohyaline clumping and vacuolization of the superficial layers of the epidermis

striking and characteristic histologic findings, this is one type of ichthyosis that is readily diagnosed based upon routine microscopic examination.

Ichthyosis bullosa of Siemens is quite similar to bullous congenital ichthyosiform erythroderma, but clinically lacks the erythroderma [62]. Histologically, mild epidermolytic hyperkeratosis is detected and there is minimal dermal inflammatory reaction [63, 64]. Altered tonofilaments are present as seen by electron microscopy [64].

2.4.3 Pathogenesis

Bullous epidermolytic hyperkeratosis has an autosomal dominant pattern of inheritance. The classic generalized form of epidermolytic hyperkeratosis is caused by mutations in keratin 1 and keratin 10 [65–68]. Keratins 1 and 10 are parts of the keratin intermediate filament [11, 69, 70]. Mutations in either keratins disrupt keratin filaments, causing skin fragility with impaired skin barrier function. Localized forms of epidermolytic hyperkeratosis are due to genetic mosaicism in the affected tissue [11, 71].

2.5 Non-bullous Epidermolytic Hyperkeratosis/Congenital Ichthyosiform Erythroderma

2.5.1 Clinical Features

Congenital ichthyosiform erythroderma is a rare autosomal recessive non-syndromic ichthyosis [1]. Babies may present with a collodion membrane with subsequent development of generalized redness and fine white scales once the membrane is shed. Frequency of blistering improves after childhood, although subtle erythema and fine scaling may persist over an affected individual's lifetime [72]. The degree of palmoplantar keratoderma varies with some individuals with no acral hyperkeratosis.

2.5.2 Histology

Congenital ichthyosiform erythroderma, also known as ichthyosis congenita type 1, demonstrates marked hyperkeratosis and focally prominent parakeratosis, in contrast to the lamellar variant [73] (Fig. 2.13). Psoriasiform epidermal hyperplasia is present (Fig. 2.14). A mild superficial perivascular lymphocytic infiltrate is seen in some cases.

2.5.3 Pathogenesis

The best characterized genetic defect in congenital ichthyosiform erythroderma is the transglutaminase-1 gene [47, 50]. Mutations in the ATP-binding cassette transporter ABCA12 have also been found in a small number of cases [61, 74, 75]. Other mutated genes implicated in this disorder are 12R-lipoxygenase (ALOX12B) and arachidonate lipoxygenase-3 (ALOXE3) [57]. These mutations which completely eliminate the enzyme function have been found in a small number of families in the Mediterranean and Germany [57, 76]. Functional studies have provided evidence that the lipoxygenases ALOX12B and ALOXE3 are important in skin differentiation, permeability barrier function, and the biological actions of essential fatty acids [77, 78].

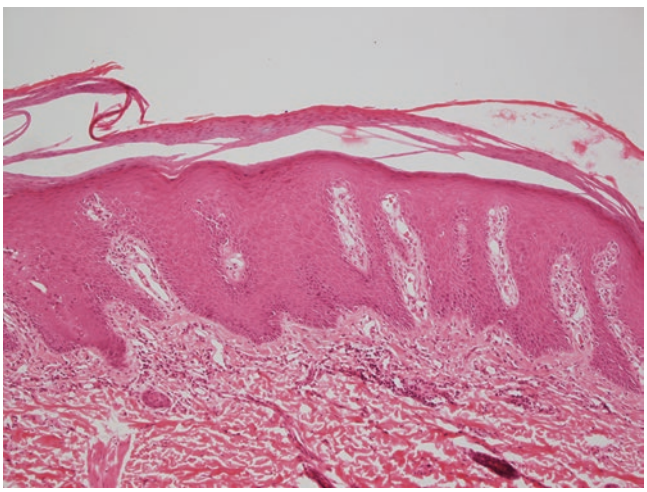

Fig. 2.13 Congenital ichthyosiform erythroderma is characterized by acanthosis with overlying confluent parakeratosis

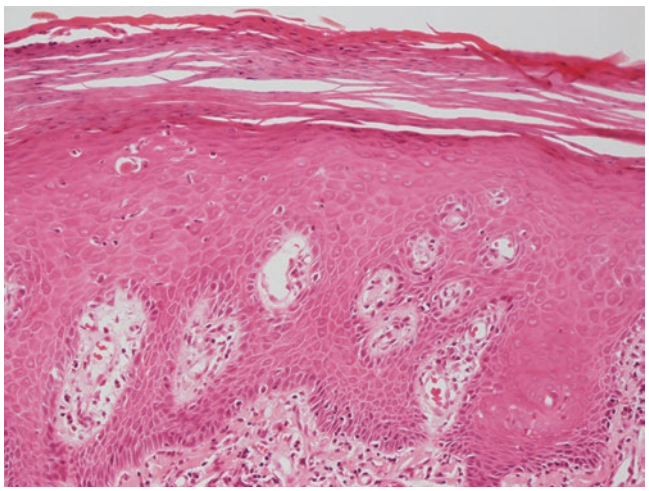

Fig. 2.14 Congenital ichthyosiform erythroderma demonstrates confluent and thick parakeratosis overlying acanthotic epidermis with focal presence of a granular layer

2.6 Erythrokeratoderma Variabilis

2.6.1 Clinical Features

Erythrokeratoderma variabilis is an autosomal dominant disease that presents at birth or within the first year of life [22]. Patients have generalized fixed brown hyperkeratotic plaques with migratory erythematous, well-circumscribed patches and plaques that may be triggered by trauma or temperature variation. The hyperkeratotic plaques tend to persist and worsen during childhood, but stabilize later in life. Migratory lesions may resolve in adulthood following stabilization of the plaques [79].

2.6.2 Histology

Erythrokeratoderma variabilis has a nonspecific histologic pattern. Orthokeratotic hyperkeratosis is present with an acanthotic epidermis and prominent granular layer. Focal parakeratosis may be present. Follicular hyperkeratosis is described in some patients, while others demonstrate dyskeratosis [45, 80]. A mild lymphohistiocytic infiltrate permeates the superficial dermis in most cases. Immunohistochemistry shows a marked reduction in epidermal Langerhans cells [81]. Electron microscopic examination reveals membrane clefts resembling those seen in harlequin fetus [45].

2.6.3 Pathogenesis

Erythrokeratoderma variabilis is primarily an autosomal dominant disorder that is caused by de novo missense mutations in connexin 31 (encoded by GJB3 gene) [82]. Mutations in connexin 30.3 (encoded by GJB4 gene) and connexin 43 (encoded by GJA1) have also been reported in this disorder [83–85]. Connexins form important intercellular gap junctions that mediate the exchange of ions and metabolites between adjacent cells. They are important for the development and maintenance of the epidermis [86]. Mutations in connexins result in abnormal localization of the proteins and their aggregation within the Golgi, resulting in defects in gap junction formation [87].

2.7 Netherton Syndrome

2.7.1 Clinical Features

Netherton Syndrome is a rare autosomal recessive condition with no gender and ethnic predilection. It has a reported incidence of 1 in 200,000 newborns, accounting for approximately 18 % of all cases of congenital erythroderma [88]. Netherton Syndrome is characterized by ichthyosis, hair shaft abnormalities (specifically, trichorrhexis invaginata or "bamboo hairs") and atopy with elevated serum levels of immunoglobulin E [90–92]. Patients may present at birth with erythroderma or collodion membrane [22]. Ichthyosis varies from generalized fine scaling to plate-like lesions mimicking lamellar ichthyosis. Ichthyosis linearis circumflexa is pathognomonic in Netherton syndrome and is characterized by polycyclic, erythematous plaques with double-edged scale along the lesion edge. Some authors allow for the presence of congenital ichthyosiform erythroderma as a component of this syndrome as opposed to ichthyosis linearis circumflexa [89].

During the neonatal period, patients are at increased risk of hypernatremic dehydration, temperature dysregulation, failure to thrive, and infection. Patients also are at increased risk for systemic absorption of applied topical therapies [22]. Associated atopy may be more pronounced and persistent. Lastly, early onset of cutaneous neoplasms can be seen in some patients with Netherton syndrome, which demonstrate the same characteristics as similar neoplasms occurring in patients without the syndrome [93].

2.7.2 Histology

Ichthyosis linearis circumflexa shows focal parakeratosis alternating with orthokeratosis. Parakeratosis may be the dominant pattern in severe cases. The granular layer is markedly diminished or completely absent underlying the areas with parakeratosis, and slightly thickened in other regions [92]. Psoriasiform epidermal hyperplasia overlies a mild superficial perivascular lymphocytic infiltrate [94, 95] (Figs. 2.15, 2.16 and 2.17). The presence of neutrophils, even forming abscesses in some cases, results is a microscopic appearance quite similar to that seen in psoriasis [96]. However, suprapapillary thinning is not seen in most cases [97]. Round lipid bodies are seen within the parakeratotic cells in electron microscopy [98].

A subset of patients with Netherton syndrome has other histologic changes in skin biopsies. Prominent dermal eosinophils are seen in up to one third of patients with Netherton syndrome. Rarely, the histologic pattern is one of compact orthohyperkeratosis and a thickened granular layer [97].

2.7.3 Pathogenesis

Ichthyosis linearis circumflexa is inherited as an autosomal recessive trait. The disorder can present in isolation or, more commonly, as part of Netherton syndrome, an autosomal recessive disorder caused by mutations in the SPINK5 (serine protease inhibitor Kazal-type 5) gene that encodes for LEKTI (lymphoepithelial-Kazal-type 5 inhibitor), a serine

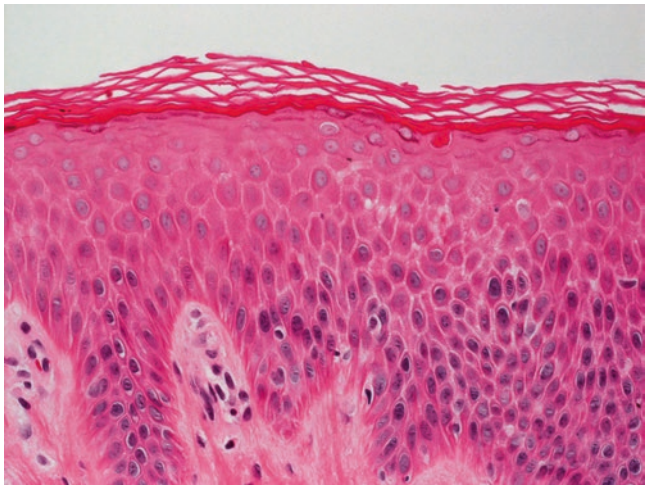

Fig. 2.15 Skin biopsies from patients with Netherton's syndrome demonstrate ichthyosis linearis circumflexa with the characteristic psoriasiform and mildly spongiotic epidermis

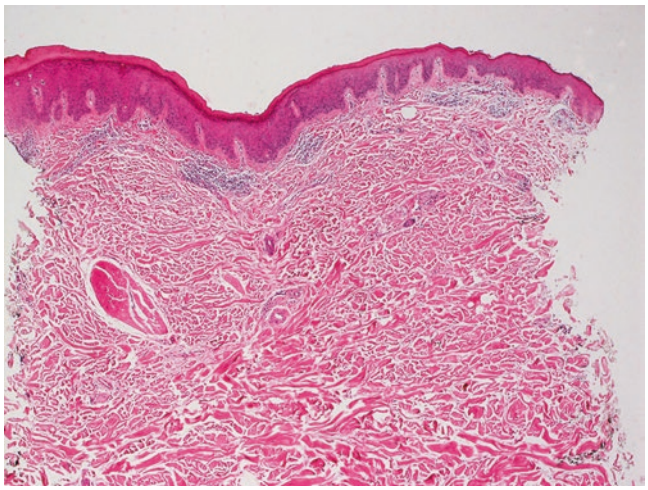

Fig. 2.16 Ichthyosis linearis circumflexa demonstrates psoriasiform epidermal hyperplasia with overlying hyperkeratotic orthokeratosis and a variable dermal inflammatory infiltrate

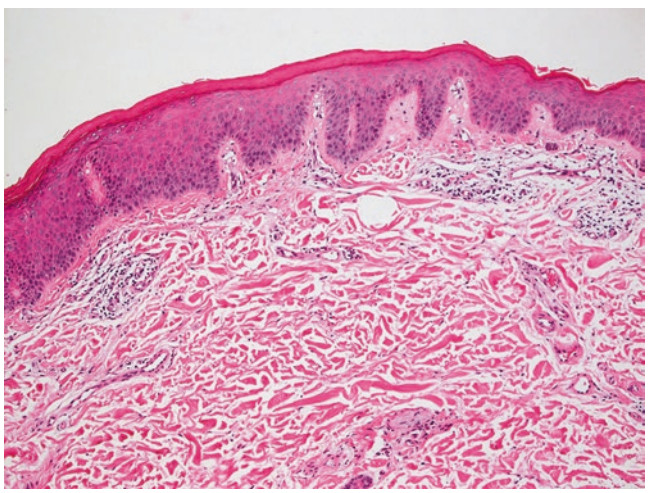

Fig. 2.17 Psoriasiform epidermal hyperplasia with focal preservation of the granular layer and orthokeratotic hyperkeratosis is seen in ichthyosis linearis circumflexa

protease inhibitor [11, 88, 99]. Several cases of ichthyosis linearis circumflexa that carry SPINK5 mutations have been reported, suggesting that isolated ichthyosis can be a part of the Netherton syndrome phenotypic spectrum [100, 101].

LEKTI is normally expressed in the epidermis, within the stratum corneum and stratum granulosum [102, 103]. Mutations in LEKTI can result in unopposed serine protease activity, leading to desmosome degradation and premature desquamation of the epidermis. LEKTI functions by inhibiting serine proteases via regulation of activities of kallikrein 5 and kallikrein 7 in the epidermis, both of which degrade desmosomes in the skin [104–106]. Mutations in SPINK5 gene result in a truncated, nonfunctional LEKTI protein. Due to loss of functional LEKTI, there is increased activities of kallikrein 5, kallikrein 7 and epidermal elastase 2, resulting in loss of stratum corneum skin barrier function [99, 107, 108]. Some studies have provided evidence that elastase 2 is an epidermal protease important in the pathogenesis of Netherton syndrome [107]. Elastase 2 is constitutively expressed and active in the stratum corneum and stratum granulosum. It is involved in the processing of filaggrin and the formation of lipid lamellae, thus affecting skin barrier function.

In addition to inhibiting kallikreins, LEKTI has diverse inhibitory activities towards a number of other proteases, including trypsin, plasmin, subtilisin A, cathepsin G, and human neutrophil elastase [109, 110]. Taken together, it appears that the balance between proteases and protease inhibitors, such as LEKTI, is essential for normal skin desquamation and skin barrier function [111].

Different patients with Netherton syndrome can have different truncation mutations in SPINK5 [88, 111]. There might be a correlation between genotype and phenotype in Netherton syndrome, depending on the location of the mutations. It has been shown that the severity of the skin phenotype in this disorder correlates *inversely* with the levels of functional LEKTI protein and its serine protease inhibitory activity [112].

2.8 Refsum Disease

2.8.1 Clinical Features

Refsum disease is an uncommon, autosomal recessive disorder of lipid metabolism, typically affecting Scandinavians and Northern European populations [22]. Extracutaneous features include retinitis pigmentosa, polyneuropathy, cranial nerve disease, and cerebellar symptoms [22]. Following onset of neurologic and ophthalmologic disease, patients typically present with fine scales along the lower trunk and extremities that may progress to thicker, plate-like scaling if left untreated [113]. Clinical improvement may be achieved by eliminating chlorophyll, phytol, phytanic acid and their precursors from the diet.

2.8.2 Histology

Refsum syndrome demonstrates skin with orthokeratotic hyperkeratosis and acanthosis. Additionally, vacuolization is present within keratinocytes [114]. However, despite these histologic features, the diagnosis is more readily established with plasma phytanic acid studies than by skin biopsy [26, 115].

2.8.3 Pathogenesis

Refsum disease is a biochemical disorder caused by deficiency in the breakdown of phytanic acid. This is due to mutations in PHYH (peroxisomal enzyme phytanoyl-CoA hydroxylase) gene or PEX7 (peroxisomal biogenesis factor 7) gene that are involved in various aspects of phytanic acid metabolism [116–118].

In healthy individuals, phytanic acid undergoes oxidative decarboxylation by alpha-oxidation in the peroxisome to form formyl-CoA and pristanic acid. In Refsum disease, the alpha-oxidation of phytanic acid is impaired by mutations in either the PHYH gene that catalyzes this process or in PEX7 that is required for the correctly targeting of PHYH to the peroxisome [116–118]. As a consequence, phytanic acid fails to be properly metabolized and accumulates in the blood and tissues of the patients. High levels of phytanic acid can interfere with protein prenylation and impair the correct targeting of prenylated proteins to cellular membranes [119]. Phytanic acid is also a ligand for several members of the nuclear hormone family, including the retinoid X receptors (RXRs) and the peroxisome proliferator-activated receptors (PPARs), which are involved in the regulation of lipid and glucose metabolism. Thus, defects in phytanic acid metabolism can result in a wide range of phenotypic abnormalities.

Infantile Refsum disease is distinct from classical Refsum disease. It is an autosomal recessive disorder of peroxisome biogenesis [120–122]. Biochemical derangements in this condition include increased levels of phytanic acid, pipecolic acid and very-long-chain fatty acids, as well as abnormalities in the synthesis of plasmalogen lipids [122]. Two of the genes implicated in infantile Refsum disease are PEX1 (peroxisomal biogenesis factor 1) and PEX6 (peroxisomal biogenesis factor 6), which are ATPases and function in the import of peroxisomal proteins [123].

2.9 Sjogren–Larsson Syndrome

2.9.1 Clinical Features

Sjogren–Larsson syndrome is a rare disorder, characterized by progressive neurologic impairment with spastic paralysis and mental retardation in the setting of generalized fine, fish-like scaling and refractory pruritus [22]. Newborns may present with collodion membrane. Glistening white dots in the retina is pathognomonic of the disorder [22]. The disease course is progressive with most morbidity and mortality secondary to the associated neurologic disease.

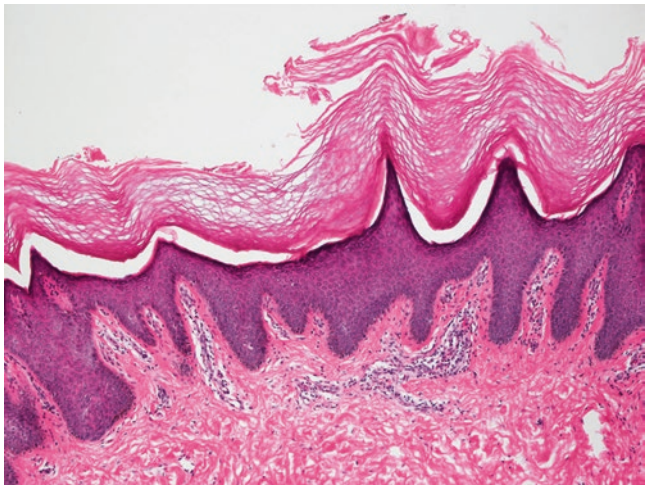

Fig. 2.18 Histologic findings include orthokeratotic hyperkeratosis, focal papillomatosis, and acanthosis in patients with Sjogren–Larsson syndrome

2.9.2 Histology

In Sjogren–Larsson syndrome, the epidermis shows pronounced hyperkeratosis with only rare parakeratotic foci (Fig. 2.18). It is acanthotic and the granular layer is increased in thickness [124]. A papillomatosis growth pattern has been described [125]. There is a modest inflammatory infiltrate in the superficial dermis. Lamellar inclusions and increased numbers of mitochondria are seen in keratinocytes on electron microscopy [124, 126].

2.9.3 Pathogenesis

Sjogren–Larsson syndrome is an autosomal recessive disorder of lipid metabolism, caused by mutations in ALDH3A2, a gene that encodes for the microsomal enzyme fatty aldehyde dehydrogenase (FALDH), resulting in a deficiency of FALDH [127]. Over 70 mutations in ALDH3A2 gene have been identified in Sjogren–Larsson syndrome patients including amino acid substitutions, deletions, insertions, and splicing errors [128]. The function of FALDH is to catalyze NAD-dependent oxidation of medium- and long-chain fatty aldehydes to fatty acids [129, 130]. The pathogenesis of Sjogren–Larsson syndrome is a result of abnormal lipid accumulation in the membranes of skin and brain cells, the formation of aldehyde Schiff base adducts, and impaired

eicosanoid metabolism [128]. Defects in the metabolism of leukotriene B4, which is a pro-inflammatory mediator, also appears to play an important role in the disease [131].

Ultrastructural analysis of Sjogren–Larsson syndrome skin shows misshapen lamellar bodies and abnormal lipid inclusions in the cytoplasm of cells in the granular layer in the epidermis, indicating that affected keratinocyte membranes have an altered lipid composition as well as abnormal water barrier function that can cause reactive hyperkeratosis in the epidermis [124, 128, 132].

2.10 Conradi–Hunermann–Happle Syndrome/X-Linked Dominant Chondrodysplasia Punctata Type 2

2.10.1 Clinical Features

Conradi–Hunermann–Happle Syndrome is the X-linked dominant subtype of chondrodysplasia punctata, a varied mix of skeletal dysplasias arising from deficiencies in cholesterol biosynthesis. It is a rare genodermatosis, primarily affecting females [133]. Erythroderma may present soon after birth, followed by development of hyperkeratotic blaschkoid plaques [133]. These plaques evolve to form linear and whorled, atrophic and hypopigmented patches. Scalp alopecia is a frequent clinical feature as well. Additional clinical findings include cataracts, short stature, rhizomelic limb shortening, and vertebral anomalies with stippled epiphyses on X-ray. Overall, skin changes may improve with persistence of blaschkoid follicular atrophoderma and scarring alopecia.

2.10.2 Histology

Conradi–Hunermann–Happle syndrome associated with chondrodysplasia punctata demonstrates skin with thick laminated orthokeratosis. Prominent keratotic follicular plugs are present and give rise to dystrophic calcification, a finding that appears to be specific for this syndrome [134].

2.10.3 Pathogenesis

This syndrome is an X-linked dominant disease caused by mutations in emopamil binding protein (EBP, also called 3-beta-hydroxysteroid-delta8, delta7-isomerase) located on the X chromosome [135, 136]. To date, over 70 different mutations in EBP have been reported.

EBP has dual functions. It serves as a binding protein for the calcium blocker emopamil, and also functions as a delta8–delta7 sterol isomerase [137, 138]. Defects in EBP result in increased levels of the sterol precursors 8(9)-cholesterol and 8-dehydrocholesterol. Measuring plasma sterol profiles is a useful test in the diagnostic work-up for Conradi–Hunermann–Happle syndrome, and there is a relationship between sterol levels and the disease phenotype [135, 136, 139, 140].

2.11 Other Syndromes with Ichthyosis

CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb dysplasia) syndrome is an X-linked disorder with a remarkable feature of an inflammatory nevus with unique lateralization and midline demarcation. Histologic features of the nevus show alternating areas of orthokeratotic hyperkeratosis and parakeratosis. In the areas with parakeratosis, ghost cells and other keratinocytes demonstrating large granular cells are seen. Vacuoles are present within the cytoplasm of these cells. Ultrastructural analysis reveals many cytoplasmic lamellar bodies [141]. Similar structures are seen in an extracellular location [142]. Verruciform xanthoma has been described in association with this type of ichthyosis [143–145].

IBIDS syndrome is a syndrome with *i*chthyosis, *b*rittle hair (trichothiodystrophy), *i*mpaired intelligence, *d*ecreased fertility and *s*hort stature [146]. The ichthyosis is the lamellar type and can range from mild to severe.

MAUIE syndrome is comprised of *m*icropinnae, *a*lopecia *u*niversalis, *i*chthyosis and *e*ctropion [147]. The histologic findings include orthokeratosis alternating with parakeratosis. The granular layer is diminished or absent and the epidermis is acanthotic. Focal vacuolization of superficial keratinocytes may be present. Dilated capillaries are surrounded by a mild perivascular lymphohistiocytic inflammatory infiltrate. Clinical areas of skin sparing demonstrate mild orthokeratosis but no other histologic changes. There is a suggestion that patients with MAUIE syndrome are predisposed to developing skin cancers at a young age, although there is no good explanation for this observation [147].

2.12 Seborrheic Dermatitis

2.12.1 Clinical Features

Seborrheic dermatitis is a multifactorial disorder affecting cutaneous surfaces with the highest density of sebaceous glands, namely the scalp, face (nasolabial folds, ears, eyebrows, and glabella), upper chest/presternal area, and intertriginous areas. It is seen more commonly in males, and across various ethnic and racial backgrounds [148]. Current opinion suggests that excessive colonization by malassezia species, a lipophilic yeast, may play a significant role in the development and chronicity of the disease. It affects 1–3 % of immunocompetent adults, but prevalence rates are as high

Fig. 2.19 Seborrheic dermatitis presents as rough, erythematous thin plaques with overlying adherent, greasy scales involving the scalp and face of an infant (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

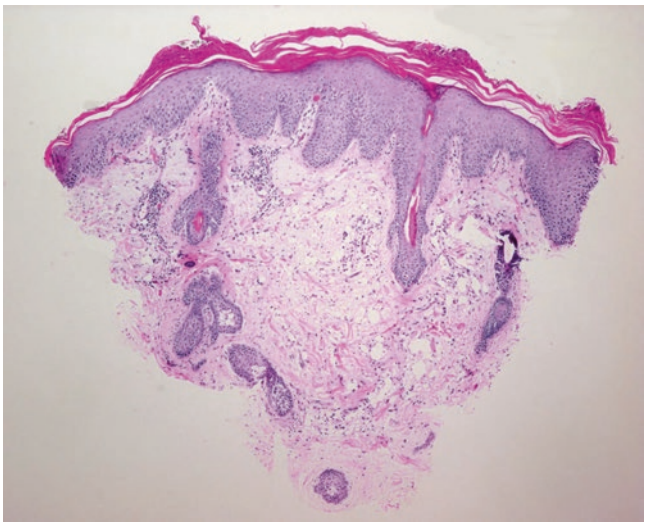

Fig. 2.20 Seborrheic dermatitis demonstrates tufts of parakeratosis at the outflow tracts of hair follicles and psoriasiform epidermal hyperplasia

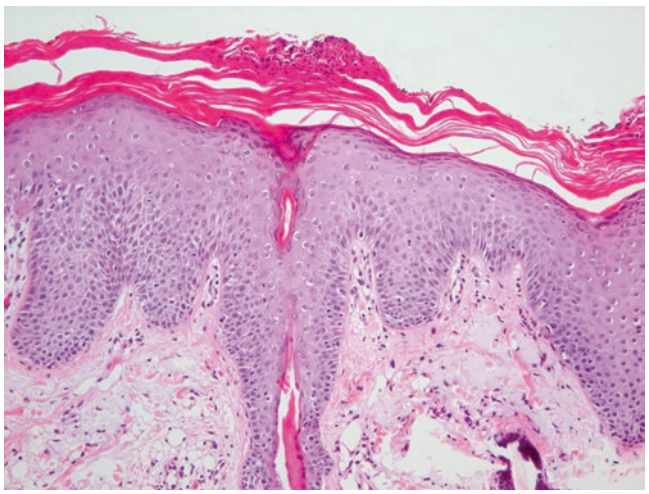

Fig. 2.21 Clusters of neutrophils are seen overlying follicular orifices in some cases of seborrheic dermatitis

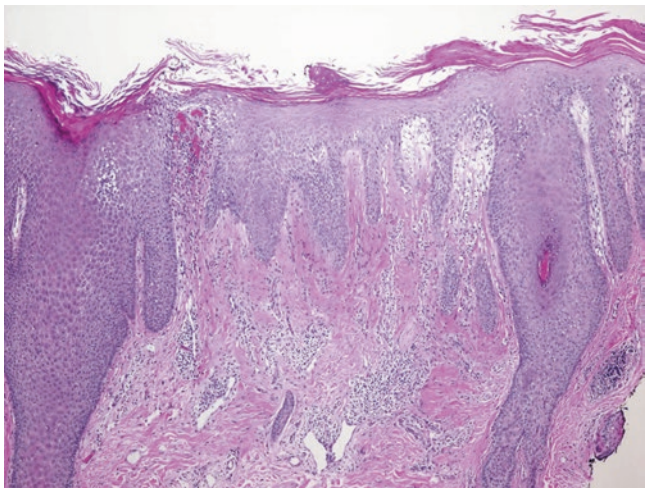

Fig. 2.22 Spongiosis, especially within follicular epithelium, and psoriasiform epidermal hyperplasia are seen along with a mild lymphocytic infiltrate in seborrheic dermatitis

as 83 % in persons with immunodeficiency, implicating immune dysregulation as a potential pathogenic factor [148]. In children, there is a bimodal distribution with incidence highest in infants less than 3 months old and in adolescents, suggesting an androgenic hormonal influence as well.

On physical exam, patients present with erythematous plaques and patches with overlying greasy, yellow scale in any of the above mentioned sebaceous gland-rich body areas (Fig. 2.19). Additional clinical findings may include erythematous folliculitis. Pruritus is typically minimal, distinguishing it from atopic dermatitis. The disorder is amenable to a number of topical therapies, but it has a chronic and relapsing course.

2.12.2 Histology

Seborrheic dermatitis has parakeratosis that is often most prominent in the outflow tracts of hair follicles (Fig. 2.20). Small clusters of neutrophils may be present in this location (Fig. 2.21). The epidermis demonstrates psoriasiform hyperplasia with bulbous elongation of rete ridges. There is focal hypogranulosis in most cases [149]. Some intraepidermal spongiosis is present, especially in regions surrounding and within the follicular epithelium (Fig. 2.22). Classically, this

is most pronounced in regions of the follicular ostia and/or infundibula. Papillary dermal edema may be observed in conjunction with vascular dilation. The dermis is characterized by an infiltrate of lymphocytes, histiocytes and rare neutrophils concentrated around pilosebaceous units. Commonly, colonization with *Pityrosporum (Malassezia)* yeast forms is present, especially within the follicular keratin and stratum corneum.

It is often quite difficult to distinguish seborrheic dermatitis from psoriasis. The perifollicular nature of the infiltrate, small amounts of spongiosis and partial retention of the granular layer are features in favor of seborrheic dermatitis, although these can all be seen in some cases of psoriasis as well.

2.12.3 Pathogenesis

Pathologic features in seborrheic dermatitis include androgenic hormones, fungal colonization and immunologic regulation. In fact, there is a strong correlation between yeast density on the skin and the severity of seborrheic dermatitis, a concept supported by the fact that antifungal agents are routinely used effectively in the treatment of seborrheic dermatitis [150, 151]. A reaction between Malassezia, cells in the stratum corneum where the yeasts reside, and the immune system may be a primary trigger factor [152]. Moreover, the presence of host susceptibility factors associated with Malassezia infection and the host immune response may predispose certain individuals to developing seborrheic dermatitis. How Malassezia yeasts initiate inflammation in seborrheic dermatitis is not clear. The yeasts may cause inflammation by inducing cytokine production by keratinocytes or Langerhans cells with subsequent T-lymphocyte activation [153]. Another factor that may cause inflammation is the lipase activity of Pityrosporum ovale, which generates inflammatory fatty acids from skin lipids [154].

Scalp hyperkeratosis in seborrheic dermatitis, commonly known as dandruff, is believed to be mediated by Malassezia metabolites, particularly irritating free fatty acids released from sebaceous glands [155]. Transcriptome microarray analysis of dandruff lesional scalp skin as compared with non-dandruff scalp skin shows that genes involved in lipid metabolism are strongly reduced, and genes involved in the immune response defense against pathogens are increased in dandruff lesional skin as compared with normal skin [156]. Interestingly, treatment of scalp dandruff with a shampoo containing potentiated zinc pyrithione (ZPT) shows that the treatment induces a transcriptomic profile resembling that of normal scalp skin.

Fig. 2.23 Psoriasis presents as a well demarcated erythematous plaque with micaceous scale along the gluteal fold (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

2.13 Psoriasis

2.13.1 Clinical Features

Psoriasis is a systemic inflammatory condition that is seen across the pediatric spectrum from infancy to adolescence. It is thought to represent a Type 1 T-helper cell predominant hyperactivity in response to environmental stimuli in genetically susceptible individuals. Psoriasis is estimated to affect 1 % of the general population with a mean age of onset between 8 and 11 years old when seen in children [157]. A family history of psoriasis appears to convey a significant risk for development of the disease in children with 68 % of children having an affected family member in one study [158].

Erythematous plaques with overlying micaceous scale at the extensor extremities and scalp characterize chronic plaque type psoriasis, although any cutaneous surface can be involved (Fig. 2.23). Plaque type psoriasis is the most common subtype seen in children [157]. The scalp is the most frequently affected area, and it is the site of initial presentation in more than 50 % of pediatric patients [159]. Guttate psoriasis is seen in children as well with rates as high as 40 %. In this variant, the physical exam is noted for smaller erythematous, scaled papules and plaques in a generalized distribution, including the face. Skin changes often follow Group A β-hemolytic streptococcal infection. In infants, psoriatic diaper dermatitis (napkin dermatitis) may occur with circumscribed, erythematous plaques at the lower abdomen, groin, and buttocks. Other subtypes include intertriginous psoriasis (minimally scaled, erythematous patches and

Fig. 2.24 Erythrodermic psoriasis may present as generalized erythema with desquamation as seen in this teenage girl

plaques at the flexural folds), pustular psoriasis (superficial sterile pustules overlying erythematous patches and plaques possibly with accompanying fever, arthralgia), palmoplantar psoriasis, anogenital psoriasis (eroded patches or hyperkeratotic plaques at the groin and perianal skin), erythrodermic psoriasis (generalized erythema with secondary desquamation) (Fig. 2.24), and even isolated nail psoriasis.

For most patients, psoriasis is a chronic disease with periodic episodes of remission and relapse [159]. The relationship between the cutaneous disease and systemic inflammation has long been evidenced by the presence of psoriatic arthritis. Data now also link psoriasis with metabolic syndrome and cardiovascular disease with increased incidence of hyperlipidemia, obesity, hypertension, and diabetes mellitus even in affected children [157].

2.13.2 Histology

The histologic features of psoriasis are manifold depending upon the type and the duration of the lesions biopsied [160]. Classic *plaque psoriasis* is characterized by confluent parakeratosis that contains clusters of neutrophils (Munro's microabscesses) (Figs. 2.25 and 2.26). The underlying epidermis displays marked hypogranulosis and regular acanthosis with "psoriasiform" elongation of the rete ridges. Neutrophilic clusters (spongioform pustules of Kogoj) are also present within the epidermis. The most prominent dermal changes include suprapapillary thinning with marked

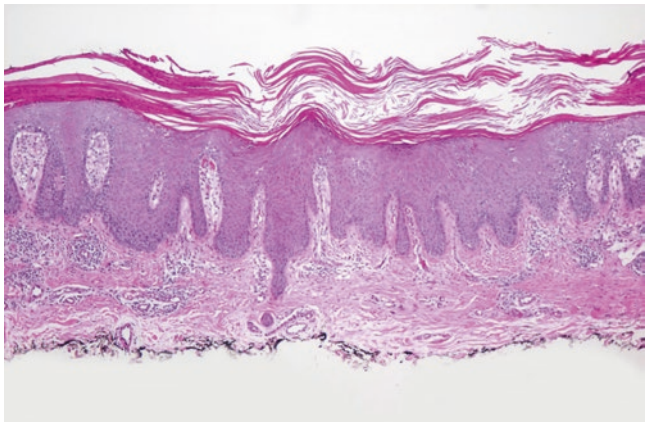

Fig. 2.25 Thick parakeratosis overlies an acanthotic epidermis with psoriasiform epidermal hyperplasia in psoriasis

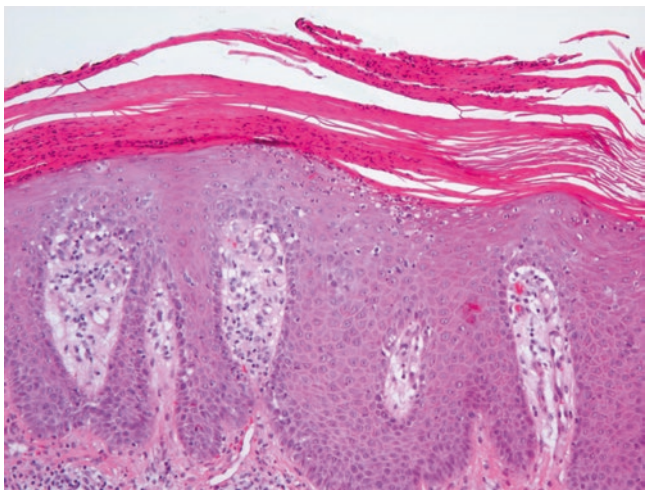

Fig. 2.26 Neutrophilic clusters within the stratum corneum and in the uppermost epidermis that lacks the granular layer characterize psoriasis

dilatation of post-capillary venules. A modest superficial perivascular infiltrate of lymphocytes and histiocytes is present, and eosinophils are uncommon in psoriasis [161]. Sebaceous gland atrophy has been described in a series of patients with psoriasis involving the scalp [162].

Large neutrophilic abscesses within the stratum corneum as well as within the epidermis characterize pustular psoriasis. The other histologic changes as described above may or may not be present since these lesions are often quite acute. In contrast to plaque lesions, focal spongiosis may be present, acanthosis is rarely pronounced and elongation of the rete ridges is not usually regular or prominent. The dermal infiltrate may include neutrophils. Vascular dilation is usually present in these cases [163].

Guttate psoriasis demonstrates yet another constellation of histologic findings. Parakeratosis is present, yet it is often focal and relatively sparse. It may be difficult to find neutrophils in the stratum corneum and they are most often not

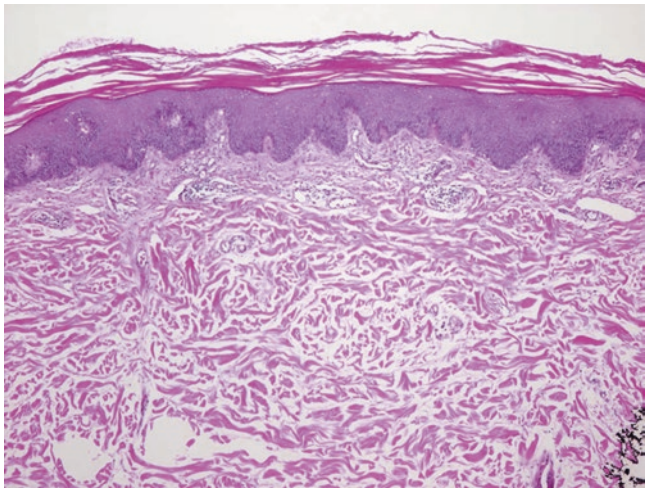

Fig. 2.27 Guttate psoriasis demonstrates an acanthotic epidermis with focal parakeratosis. The rete ridges are not as elongates as they are seen in plaque psoriasis

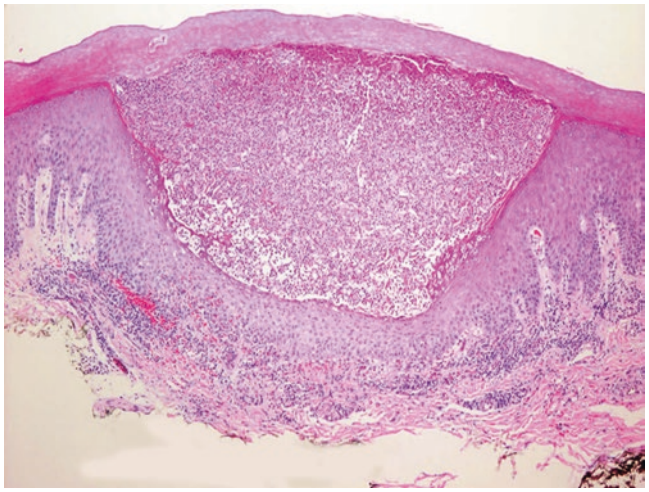

Fig. 2.29 A subcorneal neutrophilic abscess in pustular psoriasis. Other changes associated with psoriasis may not be present in this acute process

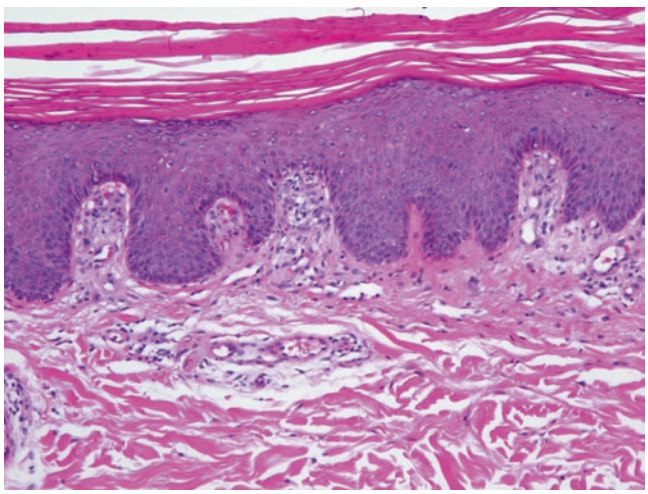

Fig. 2.28 Focal parakeratosis, focal preservation of the granular layer and ectatic blood vessels within papillary dermal tips characterize guttate psoriasis

seen within the epidermis. The epidermis is only minimally acanthotic and elongation of rete ridges is not normally present (Fig. 2.27). Vascular dilation is invariably present and is often a significant clue to establishing this diagnosis (Fig. 2.28).

The differential diagnosis depends upon the type of psoriatic lesion biopsied. Classic plaque type psoriasis can be difficult to distinguish from a chronic spongiotic dermatitis, though the presence of confluent parakeratosis, neutrophils and vascular dilation and the absence of a granular layer and spongiosis may help one to make a diagnosis of psoriasis. If lesions of psoriasis are secondarily traumatized, this distinction can be very difficult, if not impossible. Pityriasis rubra pilaris shares some histologic features with plaque psoriasis. However, the parakeratosis is less confluent and is restricted to the outflow tracts of hair follicles in most cases. The epidermis is less acanthotic with less elongation of the rete ridges. The granular layer is preserved in much of the epidermis and the inflammatory infiltrate within the dermis tends to be less pronounced [164].

Pustular psoriasis closely resembles the histologic changes seen in acute generalized exanthematous pustulosis. The presence of eosinophils and spongiosis would favor acute generalized exanthematous pustulosis, but the distinction can be difficult without clinical history (Fig. 2.29). Subcorneal pustular dermatosis may demonstrate similar if not identical features to that of psoriasis. In some cases, IgA pemphigus can display clusters of intraepidermal neutrophils, but the presence of focal acantholysis will help with this distinction. Also in the differential diagnosis is dyshidrotic eczema, although it is usually characterized by a greater degree of spongiosis [163].

Guttate psoriasis raises the differential diagnoses of pityriasis rosea and small plaque parapsoriasis (guttate parapsoriasis, digitate dermatosis). The presence of neutrophils and focal loss of the granular layer favor psoriasis. The presence of tufts of parakeratosis and focal hemorrhage within the epidermis and dermis favors pityriasis rosea. The changes in small plaque parapsoriasis are less intense than those seen in psoriasis, and there may be slightly more exocytosis of lymphocytes into the epidermis; however, these changes can be very subtle and it may be difficult to distinguish this entity from psoriasis without clinical history and follow-up.

2.13.3 Pathogenesis

Psoriasis is a complex disease whose pathogenesis is multifactorial with genetic, microbial and immunologic components. Studies of the genetic basis of psoriasis have shown that the psoriasis susceptibility locus 2 (PSORS2) is located on chromosomal region 17q25-qter in a large family of European ancestry [165]. Sequencing of the locus revealed a mutation in CARD14 (caspase recruitment domain family, member 14) that segregates with psoriasis [166]. As shown in the study, psoriasis skin has reduced levels of CARD14 in the basal layer, but increased levels in the upper layers of the epidermis as compared with normal skin [166]. It has been suggested that mutations in CARD14 can upregulate an inflammatory response via the nuclear factor-κB (NF-κB) pathway.

Homozygous missense mutation in IL36RN (interleukin-36 receptor antagonist) gene has been identified in generalized pustular psoriasis [167, 168]. IL36RN encodes for an anti-inflammatory cytokine, and substitution of a proline residue for leucine (L27P) has been predicted to affect the stability of IL-36RN and its interaction with its receptor (IL-1 receptor–related protein 2). The result of the mutation is reduced anti-inflammatory response and enhanced production of pro-inflammatory cytokines in the IL-1 family [167, 169].

Psoriasis is strongly associated with streptococcal infection, and patients have increased occurrence of the disease after such infections. It has been suggested that streptococcal association in psoriasis may reflect the co-occurrence of streptococcal determinants and superantigen production promoting skin homing of T lymphocytes in the immunopathogenesis of psoriasis [170].

The immunological basis of psoriasis involves mainly type 1 T-helper cells (Th1) and type 17 T-helper cells (Th17). Macrophages and dendritic cells produce interleukin-12 (IL-12), which is important in inducing the differentiation of naïve CD4+ T lymphocytes into Th1 cells [171, 172]. Th1 cells produce Th1-type cytokines, including interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-2 (IL-2), in psoriatic skin lesions [173–175]. Serum levels of these cytokines have been shown to correlate with the severity of psoriasis [173, 176]. IFN-γ is important in the development of Th1-mediated immune response. TNF-α affects the proliferation and activation of keratinocytes and T lymphocytes in psoriasis [174, 177].

Th17 cells play a crucial role in T cell-mediated adaptive immunity in psoriasis [178, 179]. Naïve CD4+ T lymphocytes are stimulated to differentiate into activated Th17 cells by IL-1, IL-6, and transforming growth factor-beta (TGF-beta). Th17 cells in turn produce IL-17 and IL-22, which are key cytokines that affect keratinocyte differentiation and induce chemokine expression in keratinocytes [180–182]. IL-17 and IL-22 contribute to the inflammatory process in psoriasis by inducing the accumulation of T lymphocytes and neutrophils in psoriatic lesions [183–185]. Dendritic cells and macrophages produce a key cytokine IL-23 that induces the proliferation and activation of Th17 cells [186]. High levels of IL-23 also stimulate the production of TNF-α and IL-22, which can induce the onset of psoriasis [174, 187]. Thus, the IL-23–Th17 axis appears to be crucial in the pathogenesis of psoriasis.

A number of other factors have been implicated in the pathogenesis of psoriasis. Studies have indicated a causal role of TGF-β in psoriasis [188]. TGF-β inhibitors (such as Etanercept) have been used to treat psoriasis and other autoimmune diseases. NF-κB is another crucial mediator in psoriasis by modulating inflammation [189]. NF-κB may be involved in altered keratinocyte and immune cell behavior seen in psoriasis. Proangiogenic factors, namely angiopoietin and vascular endothelial growth factor (VEGF), are involved in the induction of epidermal hyperplasia and angiogenesis in psoriasis [190, 191].

Biologics therapies with inhibitors of TNF-α, IL-12, IL-17, and IL-23 that block Th1 (IL-12) and Th17 (IL-23) inflammatory pathways have greatly improved the symptoms in severe psoriasis with excellent control of disease as measured by Psoriasis Area and Severity Index (PASI) score [192–194].

2.14 Reactive Arthritis (Reiter's Disease)

2.14.1 Clinical Features

Reactive arthritis is defined by the triad of conjunctivitis, urethritis and arthritis. It most frequently occurs in young males within 4 weeks of an infection of the urogenital or gastrointestinal system. Approximately half of patients with reactive arthritis have mucocutaneous symptoms, most commonly circinate balanitis of the penis (50 %) and keratoderma blennorrhagicum in the skin (10 %) [195]. Findings of nail dystrophy (pustules along the nail folds, subungual debris, nail plate thickening, nail pitting, onycholysis, and leukonychia), ulcerative vulvitis (similar in appearance to circinate balanitis in males) and painless oral mucosal erosions have been reported as well [195]. Additional systemic manifestations include fever, fatigue, weight loss and visceral disease.

Keratoderma blennorrhagicum typically begins as erythematous, vesiculopustules with eventual evolution to hyperkeratotic plaques on the palms and soles [195]. These lesions also can be seen on the scalp, trunk and dorsal aspect of the extremities, mimicking pustular psoriasis. A similar process occurs on the penis (circinate balanitis) with uncircumcised males developing small fragile vesicles and pustules that evolve into painless, serpiginous erosions. Circumscribed males, in contrast, more commonly develop thick plaques on the glans penis. The clinical course is variable, either resolv-

ing spontaneously or progressing to a more chronic variant with intermittent flares. Reports suggest that children tend to have milder disease with fewer episodes of recurrence [195].

2.14.2 Histology

The histologic changes seen in Reiter's disease are indistinguishable from those seen in pustular psoriasis [196]. Subcorneal and intraepidermal neutrophilic abscesses are seen in great abundance. Confluent parakeratosis overlies a variably acanthotic epidermis that has psoriasiform hyperplasia. Suprapapillary thinning and vascular ectasia are present along with a dermal infiltrate of lymphocytes, histiocytes and neutrophils [197, 198].

2.14.3 Pathogenesis

Reactive arthritis is thought to be secondary to an autoimmune immunologic response to an infectious insult in genetically predisposed individuals [195]. There is a strong association between disease presence and HLA-B27 haplotype, which is a MHC class I molecule involved in T-cell antigen presentation [199, 200]. On average, about 70–80 % of patients with the disease carry HLA-B27 [201]. In a study of Tunisian patients, other HLA alleles, namely HLA-B51 and HLA-DRB1, also were found to be associated with reactive arthritis [202].

Pathogens such as group A streptococci, Shigella, Salmonella, Yersinia, and Campylobacter as well as Chlamydia trachomatis have been implicated as triggering agents in reactive arthritis [203–205]. Group A streptococcal infection with elevated anti-streptolysin O antibodies can cause post-streptococcal reactive arthritis [204]. How the interaction of the inciting microorganism with an HLA-B27-positive host leads to disease development is not known. It has been suggested that molecular similarities (molecular mimicry) between the inciting microorganism antigen and HLA-B27 molecule may trigger an immune response that results in reactive arthritis [199]. Microbial antigens may also utilize toll-like receptors (TLRs) of the innate immune system to incite the disease process [206, 207]. Synovitis in reactive arthritis is induced by proinflammatory cytokines, including interleukin-17 (IL-17), IL-6, IL-1β, and IL-21. IL-17, which is produced by type 17 T-helper cells, is elevated in the synovial fluid of patients with the disease [208, 209].

2.15 Pityriasis Rubra Pilaris

2.15.1 Clinical Features

Pityriasis rubra pilaris is seen infrequently in children. It is divided into four categories with types III-V listed as juvenile variants. There is no gender predilection, and most pediatric cases are sporadic [210]. Pityriasis rubra pilaris is characterized by the cephalocaudal spread of coalescing, hyperkeratotic, follicular, salmon–colored papules with the eventual development of "islands of sparing" and the potential for generalization to erythroderma (Figs. 2.30, 2.31, and 2.32). A waxy, orange-yellow colored palmoplantar keratoderma may be present as well (considered a hallmark of juvenile disease by some experts) with or without associated nail dystrophy [211]. Many reports suggest an excellent response to retinoid therapy, but recurrence rates may be 20 % [210].

Fig. 2.30 Pityriasis rubra pilaris is characterized by coalescing hyperkeratotic, follicular, salmon-colored papules

Fig. 2.31 Pityriasis rubra pilaris may be widespread with cephalocaudal spread

Fig. 2.32 Islands of sparing are a key feature of pityriasis rubra pilaris

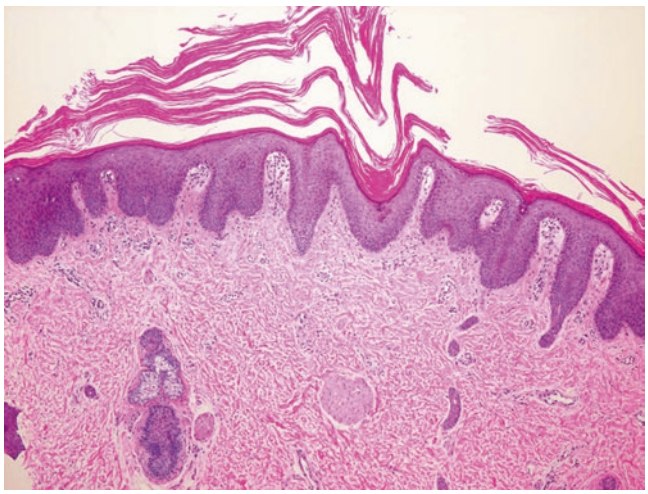

Fig. 2.33 Pityriasis rubra pilaris is characterized by psoriasiform epidermal hyperplasia, alternating parakeratosis and hyperkeratosis, and follicular dilatation

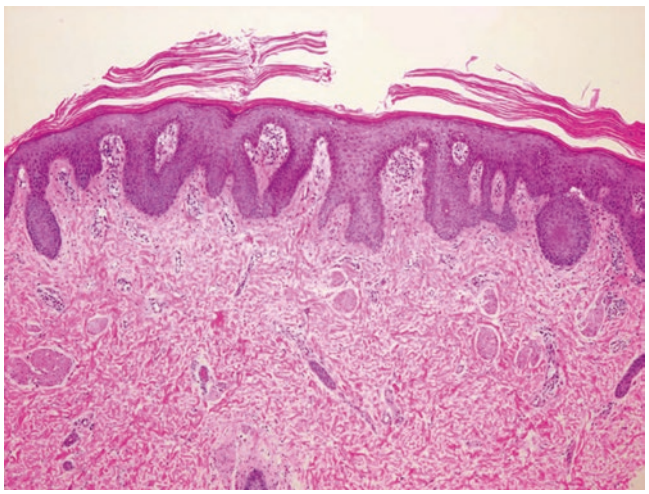

Fig. 2.34 Parakeratosis is not confluent in pityriasis rubra pilaris and psoriasiform epidermal hyperplasia coexists with a focally persistent granular layer

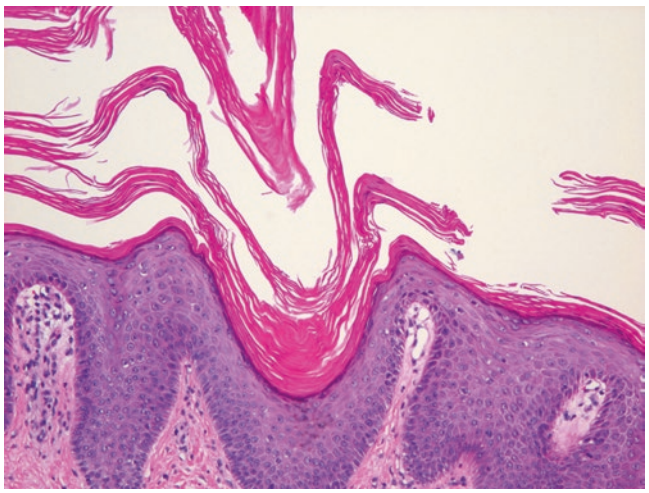

Fig. 2.35 Pityriasis rubra pilaris demonstrates parakeratosis at the outflow tract of dilated hair follicles

2.15.2 Histology

Pityriasis rubra pilaris is characterized by a distinct pattern of alternating parakeratosis and orthokeratosis. Some authors describe this pattern as occurring in a horizontal, as well as a vertical manner, giving rise to a "checkerboard" appearance. The areas of parakeratosis correlate with the follicular ostia, though this is not always seen on routine sectioning (Figs. 2.33, 2.34 and 2.35). The granular layer is present throughout, though focally diminished and in some areas may actually be of increased thickness. The epidermis is diffusely acanthotic [164], including in the areas of the suprapapillary plates and demonstrates psoriasiform epidermal hyperplasia. Focal acantholysis has been described in up to 70 % of lesions. The dermis shows a very sparse lymphohistiocytic inflammatory response. There is slight dilation of post-capillary venules in the papillary dermal tips. Hypertrophy of the arrector pili muscles is seen in some cases.

The main histologic differential diagnosis is psoriasis. Psoriasis differs by demonstrating confluent parakeratosis, neutrophils within the stratum corneum and epidermis, and more prominent elongation of rete ridges with suprapapillary thinning. Psoriasis also has a more intense lymphohistiocytic infiltrate in the dermis, often admixed with neutrophils.

Mycosis fungoides may also enter into the histologic differential diagnosis. This epidermotrophic lymphoma shows more invasion of the epidermis by atypical, enlarged and hyperchromatic lymphocytes than would be expected in pityriasis rubra pilaris [212]. In addition, the patterned parakeratosis is not a feature seen in mycosis fungoides.

2.15.3 Pathogenesis

Pityriasis rubra pilaris is often sporadic, but rare familial cases with autosomal dominant inheritance have been reported [213, 214]. Familial pityriasis rubra pilaris is caused by gain-of function mutations in CARD14 (caspase recruitment domain family, member 14) gene with increased expression of CARD14 in the epidermis of patients [215, 216]. CARD14 is an activator of nuclear factor (NF)-κB signaling, leading to the activation of the inflammatory response [217]. CARD14 does not appear to be involved in sporadic cases, as no mutations in CARD14 were found in a study of 61 patients with sporadic disease [218]. Another postulation of the etiology of pityriasis rubra pilaris is an abnormal immune response to an antigenic trigger. There are case reports of the disease occurring after streptococcal infections in children [219].

2.16 Pityriasis Lichenoides

2.16.1 Clinical Features

Pityriasis lichenoides is a disorder of unknown etiology currently thought to be a reactive T-cell lymphoproliferative disorder secondary to an antigenic stimulus [220]. In pediatric populations, disease before 2 years of age is exceedingly rare with bimodal peak incidence around 5 and 10 years of age [220]. In a retrospective cohort study by Ersoy-Evans et al., [220] patients with pityriasis lichenoides et varioliformis acuta (PLEVA) were slightly younger than those with pityriasis lichenoides chronica (PLC). Outbreaks occurred most often in the winter and fall, with one third of patients reporting a history of preceding infection, primarily viral. No gender, ethnic, or geographic predilection has been identified in adults [221], but a male predominance is seen in children [220].

PLEVA is characterized by the acute onset of papulovesicles with secondary necrosis, focal ulceration, and development of overlying hemorrhagic crust (Fig. 2.36). Lesions tend to heal with scarring and post-inflammatory dyschromia. Patients with PLEVA frequently have associated fever and arthralgias [220].

PLC has a more indolent course of flares and remission with recurrent crops of polymorphic scaly papules and thin plaques. Active lesions resolve with hypopigmentation (Fig. 2.37). In both disorders, most patients have generalized eruptions with involvement of the trunk and extremities [220].

Fig. 2.36 Pityriasis lichenoides et varioliformis acuta (PLEVA) shows papulovesicles with secondary necrosis and overlying hemorrhagic crust

Fig. 2.37 Pityriasis lichenoides chronica (PLC) often presents as crops of polymorphic, hypopigmented papules and thin plaques

Overall, pediatric pityriasis lichenoides is recognized as a benign disorder with spontaneous resolution within years. However, as there are reports of malignant transformation to cutaneous T-cell lymphoma, long-term surveillance is recommended [221].

2.16.2 Histology

PLEVA is characterized by a thick parakeratotic stratum corneum (Fig. 2.38). The epidermis is variably atrophic and acanthotic, depending upon the developmental stage of the lesion sampled. Secondarily rubbed lesions may demonstrate psoriasiform epidermal hyperplasia. Dying keratinocytes are present within the epidermis, and marked basal

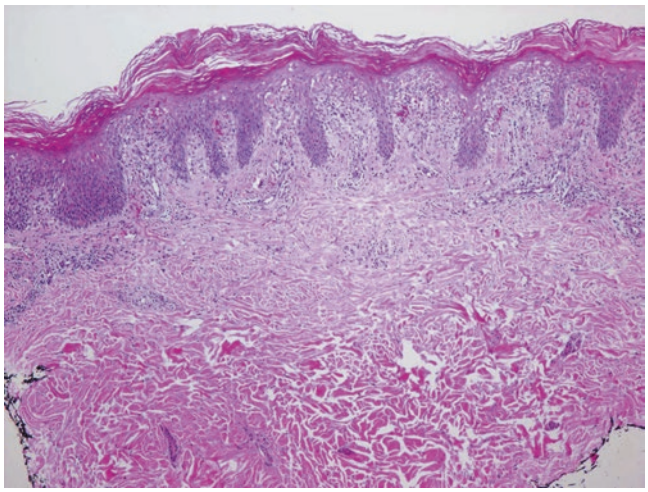

Fig. 2.38 Confluent parakeratosis overlies a brisk interface dermatitis in well-developed lesions of PLEVA

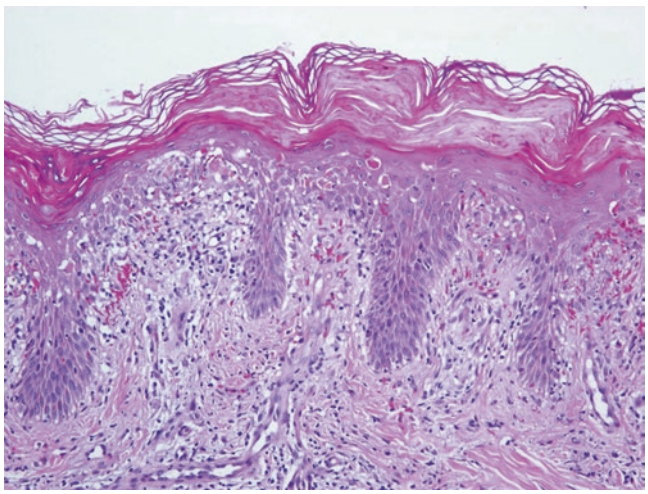

Fig. 2.39 PLEVA shows an intense interface dermatitis with abundant dying keratinocytes

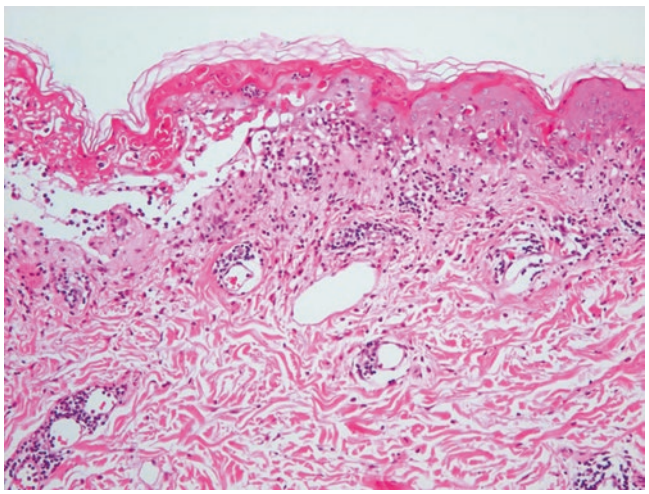

Fig. 2.40 Dying keratinocytes and dermal hemorrhage are constant features in PLEVA

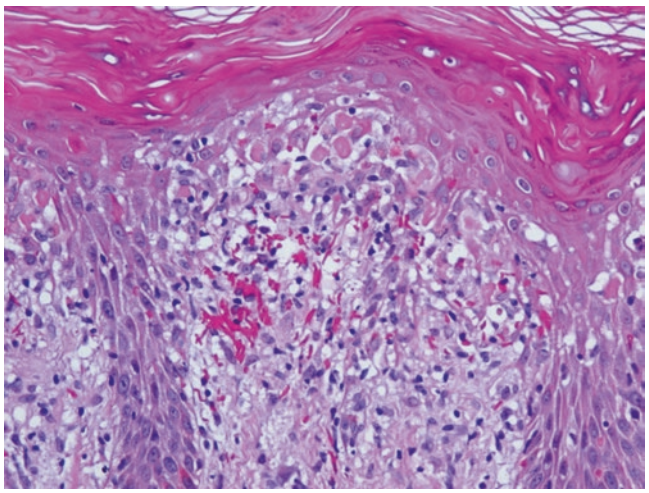

Fig. 2.41 Abundant dying keratinocytes may give rise to subepidermal blisters in PLEVA. Hemorrhage within the dermis and extending into the epidermis is almost always present

vacuolization is present in florid cases (Figs. 2.39 and 2.40). In some cases, there is extensive epidermal necrosis that may result in ulceration. A superficial and occasionally deep infiltrate of lymphocytes is present with marked exocytosis into the epidermis and follicular epithelium. There is extravasation of erythrocytes within the papillary dermis, often extending into the epidermis (Fig. 2.41). Eosinophils are not frequently encountered.

The histologic differential diagnosis of PLEVA includes pityriasis lichenoides chronica, pityriasis rosea, guttate psoriasis, digitate dermatosis (small plaque parapsoriasis), arthropod bite reaction, and lymphomatoid papulosis [222]. Pityriasis lichenoides chronica differs from PLEVA mainly in degree of inflammation. Similar histologic changes are present, but with much less intensity such that there is only focal parakeratosis, dying keratinocytes are rare, lymphocytes within the epidermis are sparse and hemorrhage is not often present within the dermis [223, 224]. Pityriasis rosea demonstrates only focal mounds of parakeratosis. In general, there is more prominent spongiosis (though only focally) in pityriasis rosea than is the case with PLEVA and dying keratinocytes are quite unusual. The dermal inflammatory infiltrate is less intense, though extravasated erythrocytes are commonly seen. Lesions of guttate psoriasis frequently demonstrate ectatic vessels located along the dermal epidermal junction, a characteristic feature that is helpful in making the distinction. Also, the presence of neutrophilic abscesses encountered in psoriasis, if present, will help in this differential diagnosis. The changes of digitate dermatosis are nonspecific and generally relatively mild. Delicate parakeratosis is present focally overlying small regions of mild spongiosis with a scant exo-

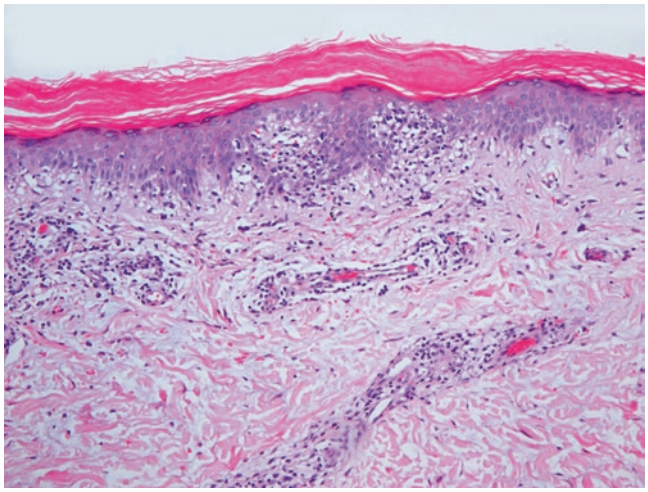

Fig. 2.42 PLC demonstrates parakeratosis, pityriasiform dermatitis, and slight amounts of dermal hemorrhage in some cases

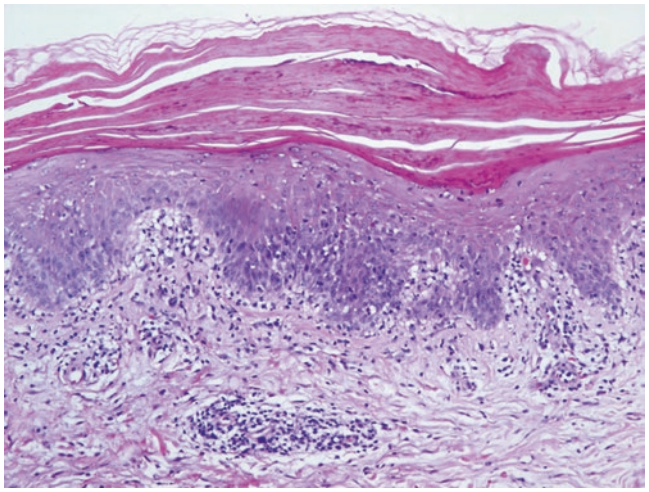

Fig. 2.43 Exocytosis of lymphocytes into the epidermis with overlying parakeratosis is seen in PLC

cytosis of lymphocytes into the epidermis. The dermal infiltrate is superficial and of lesser intensity than that seen in PLEVA. Arthropod bite reactions may also have extensive histologic overlap with PLEVA. Parakeratosis is usually more focal in these lesions. Dermal hemorrhage is present in the region of the puncture wound and eosinophils are commonly encountered around dermal blood vessels as well as within the interstitial collagen. Lymphomatoid papulosis has virtually all of the features seen in PLEVA, and is differentiated mainly based upon the cytologic features of the lymphoid infiltrate. A minority population of dermal lymphocytes has cytologic atypia, resembling either the cells seen in Hodgkin's disease or those seen in mycosis fungoides. CD30 immunostain may be helpful in highlighting these cells, and when they are present in clusters or in large numbers, this favors a diagnosis of lymphomatoid papulosis over that of PLEVA [225].

PLC has histologic changes that suggest a milder form of PLEVA [224]. Focal and delicate parakeratosis is present overlying an epidermis that contains minimal spongiosis and very rare dying keratinocytes [226] (Figs. 2.42 and 2.43). Scattered lymphocytes extend from the dermis into the epidermis. Basal vacuolization may be present but is relatively inconspicuous in most cases. Within the dermis, there is a mild lymphohistiocytic inflammatory infiltrate surrounding the superficial vascular plexus. In most cases, extravasated erythrocytes are minimally present or not seen. Eosinophils are not ordinarily encountered. The majority of the T cells are helper T cells. It has been suggested that the etiology for this eruption may be diverse, including reactions to viral infections [223, 227].

The histologic differential diagnosis of PLC includes PLEVA, in which all of the same histologic changes are present much more extensively [224]. Also included is guttate psoriasis that has papillary dermal vascular ectasia and a more regularly acanthotic epidermis. Digitate dermatosis can be very difficult to distinguish from PLC and clinical correlation is essential to definitively separate these two entities. Pityriasis rosea demonstrates more spongiosis that is focal with mounds of parakeratosis limited to the areas of spongiosis and intraepidermal hemorrhage. Increased spongiosis is also seen in small plaque or guttate parapsoriasis [226].

2.16.3 Pathogenesis

PLEVA has been proposed to be part of a spectrum of clonal T-cell lymphoproliferative disorders. Studies of PLEVA patients have reported the presence of a dominant T-cell clone and monoclonal TCR-γ gene rearrangements [228–230]. CD8+ cytotoxic suppressor T lymphocytes are the main cell type in the inflammatory infiltrate in PLEVA unlike PLC, which has more CD4+ lymphocytes and FOXP3+ regulatory T-cells [223, 225, 231, 232]. Lymphoma has been reported in children following PLEVA eruption [233]. However, it remains controversial whether PLEVA has some malignant potential with possible progression to lymphoma.

Immune complex-mediated vasculitis has been proposed to be a possible etiology of pityriasis lichenoides. Immunofluorescence stains in biopsy specimens of fresh purpuric lesions obtained from patients with pityriasis lichenoides showed circulating C3 immune complex deposition in the basement membrane in some patients [234, 235].

Another proposed etiology of PLEVA is viral infection. Parvovirus B19 DNA was detected in some patients, and the incorporation of viral DNA into the host cell may result in keratinocyte antigenicity [236]. Another viral agent implicated in PLEVA is human herpesvirus-8 [223].

The inflammatory infiltrate in PLC is mainly composed of CD4+ T lymphocytes [237, 238]. Some studies have suggested

that PLC is a form of indolent cutaneous T-cell dyscrasia with limited propensity for progression to mycosis fungoides as shown by the presence of monoclonal T-cell population in a restricted T-cell profile by TCR-β gene analysis [239]. However, other studies have shown that T lymphocytes in PLC are polyclonal [229]. Immunohistochemical studies demonstrated that PLEVA is a disorder of cytotoxic T lymphocytes. The cytotoxic T cell population often presents in close proximity to epidermal keratinocytes, suggesting that the primary event is epidermal damage induced by CD8+ cytotoxic T cells [236].

Although PLC is believed to be a T-cell disorder, it may also be a manifestation of a hypersensitive reaction to bacterial or viral infectious agent similar to PLEVA. Parvovirus B19 has been suggested as a causative infectious agent [236, 240]. Other infectious agents have been implicated as evident by sporadic outbreaks of the disease in patients with a history of previous upper respiratory tract infection, mononucleosis, or infections with Toxoplasma gondii and human immunodeficiency virus [236, 241, 242].

2.17 Pityriasis Rosea

2.17.1 Clinical Features

Pityriasis rosea is a self-limiting dermatitis of uncertain etiology. Approximately one-third of patients recall an upper respiratory tract infection preceding the onset of skin eruption [243]. Physical exam is characterized by presence of a “herald lesion” (large, fine-scaled patch or thin plaque) followed by generalized erythematous to hyperpigmented, scaly papules and plaques parallel to the lines of cleavage on the proximal extremities and trunk, giving a "Christmas tree" appearance (Fig. 2.44). Less common variants of pityriasis rosea include diffuse (trunk and extremities), inverse (intertriginous areas) and peripheral (extremities only). In one series of pediatric cases, pruritus was a prominent feature noted by 69 % of affected patients [243]. The skin changes usually resolve within 6–8 weeks without long-term dyschromia.

2.17.2 Histology

In its classic manifestation, pityriasis rosea demonstrates delicate mounds of parakeratosis interspersed with areas of normal orthokeratosis (Figs. 2.45 and 2.46). The epidermis displays mild acanthosis with elongation of the rete ridges in some cases. In areas subjacent to the parakeratosis, foci of mild spongiosis, exocytosis of lymphocytes into the epidermis and focal intraepidermal hemorrhage are apparent. There is a superficial perivascular lymphohistiocytic infiltrate usually lacking in eosinophils or neutrophils (Fig. 2.46).

Fig. 2.44 Pityriasis rosea is characterized by hyperpigmented, scaly papules and plaques on the trunk

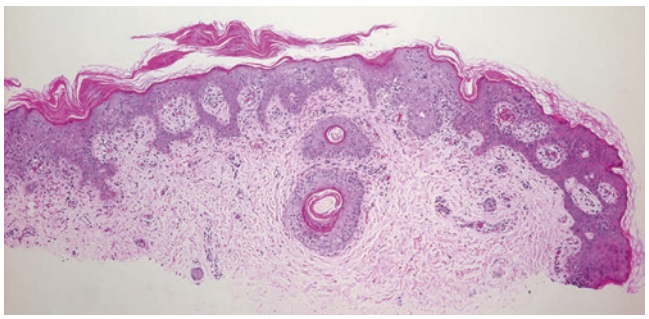

Fig. 2.45 Pityriasis rosea demonstrates delicate mounds of parakeratosis interspersed with areas of normal orthokeratosis

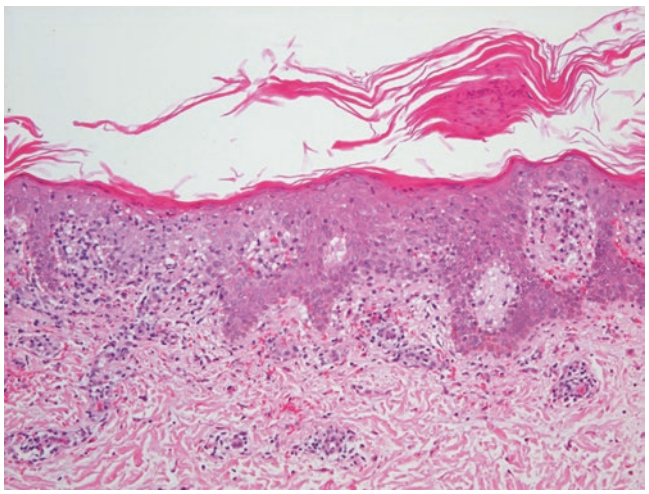

Fig. 2.46 There is a superficial perivascular lymphohistiocytic infiltrate usually lacking in eosinophils or neutrophils in pityriasis rosea

Atypical pityriasis rosea is characterized by a slightly more intense dermal inflammatory infiltrate with papillary dermal edema, more exocytosis and more extensive basal vacuolization. Dyskeratotic cells are present within the epidermis. A vesicular form characterized by foci of more extensive spongiosis is rare, but occurs with increased frequency in children, especially those with darker skin color [244, 245].

The main histologic differential diagnosis of pityriasis rosea is secondary syphilis. The major histologic difference is the presence of scattered plasma cells in secondary syphilis that are not seen in pityriasis rosea. The use of anti-spirochetal antibody immunostains or a Warthin–Starry stain may be helpful in detecting microorganisms in secondary syphilis. Also in the differential diagnosis is a pityriasis rosea-like drug reaction that occurs most commonly in patients undergoing therapy with gold [246]. A similar eruption has been described in a child with nephrotic syndrome secondary to receiving pneumococcal vaccine [247].

2.17.3 Pathogenesis

Pityriasis rosea is an exanthem suspected to be caused by a viral infection. Intra-nuclear and intra-cytoplasmic virus-like particles have been observed in pityriasis rosea lesions by electron microscopy [248, 249]. Some studies suggested that human herpesvirus 6 and 7 (HHV-6 and HHV-7) may be causally related to the disorder [250, 251]. However, other publications refuted that HHV-7 infection is causally related [252, 253]. It has been difficult to assess the causative role of HHV due to the high prevalence of such viral infections in the general population.

An autoimmune process has been suggested to link to the development of pityriasis rosea. A positive anti-nuclear antibody (ANA) test is commonly observed in patients even without clinical evidence of autoimmune disease [254–256]. It has been postulated that pityriasis rosea patients already are genetically predisposed to developing the disease, which manifests itself when triggered by a viral infection. Other triggers include many drugs that cause a pityriasis rosea-like eruption in some individuals. In one study, the stage and severity of the disease appeared to correlate with the number of Langerhans cells and CD4+ T-helper lymphocytes in the lesions [256, 257].

2.18 Keratosis Lichenoides Chronica

2.18.1 Clinical Features

Keratosis lichenoides chronica (KLC) is a rare condition with only 60 reported cases, 25 % of which involve pediatric patients [258]. KLC in children is most frequently reported in infants less than 1 year old, including incidents of congenital disease. In one case series, familial disease was reported in 57 % of affected persons [258].

Lesions first appear on the face as erythematous to purpuric macules that later darken. On the body, lesions are most pronounced along the dorsal aspects of the limbs and buttocks with three primary clinical features: (1) violaceous keratotic papules in linear parallel distribution, (2) discrete follicular papules with a keratotic plug, and (3) keratotic papules in retiform plaques [258]. Lesions may be distinguished clinically from lichen planus by lack of Wikham's striae. Painful ulcerations may be found in the oral mucosa. Prognosis is guarded with reports of poor response to topical steroids and a chronic progressive clinical course.

2.18.2 Histology

The few scattered reports of pediatric keratosis lichenoides chronica suggest the histologic features are similar to those in adults [258, 259]. Foci of parakeratosis are interspersed with hyperkeratosis. Neutrophils may be present in the stratum corneum. The epidermis has basal vacuolization and multiple dyskeratotic cells. There is a lichenoid inflammatory infiltrate comprised of lymphocytes [260]. The differential diagnosis includes lupus erythematosus, although parakeratosis is unusual in lupus and the inflammatory infiltrate extends deeper into the dermis and surrounds appendages in lupus but not usually seen in keratosis lichenoides chronica. Lichen planus may be difficult to distinguish from KLC, although parakeratosis is not ordinarily seen in lichen planus.

2.18.3 Pathogenesis

The pathogenesis of KLC is not known. It has been associated with a number of conditions, including drug-induced erythroderma, hypothyroidism, lymphoma, multiple sclerosis and chronic hepatitis [261].

2.19 Infantile Granular Parakeratosis

2.19.1 Clinical Features

Infantile granular parakeratosis is a rare frictional diaper dermatitis with a reported age range between 9 and 22 months old [262]. Moisture and occlusion appear to be contributing factors. There is no demonstrated race or sex predilection. Two clinical patterns have been described. The first is characterized by well-demarcated, erythematous, scaled plaques where the diaper rests along sites of pressure and friction [262]. The second is described as hyperkeratotic verrucous plaques at the inguinal folds with minimal associated erythema. While many

cases show poor response to standard topical interventions, all eventually clear within 4 weeks to 12 months of disease onset.

2.19.2 Histology

Histologic changes in infantile granular parakeratosis are identical to those seen in axillary granular parakeratosis in adults. There is a markedly thickened stratum corneum that is diffusely parakeratotic. The basket weave pattern is replaced by a compact appearance that overlies a pronounced granular layer. The epidermis has normal thickness with a disproportionately thickened granular layer and stratum corneum [262, 263]. Cytologic examination of skin scrapings can be used to establish the diagnosis through observation of nucleated keratinocytes within the flakes of stratum corneum [263].

2.19.3 Pathogenesis

The cause of infantile granular parakeratosis is not known, but chemical and mechanical irritation in a humid and occlusive environment with increased sweating (such as diaper areas) may compromise the epidermal barrier. This environmental irritation could lead to abnormal proliferation and dysmaturation within the epidermis, as seen by the presence of parakeratosis with retention of cell nuclei and keratohyaline granules in the lesion [263–265]. Other studies have proposed that defects in the processing of profilaggrin to filaggrin can result in a failure to degrade keratohyaline granules and cause the aggregation of keratin filaments during cornification [266, 267].

2.20 Porokeratosis

2.20.1 Clinical Features

Porokeratosis is a rare group of inherited and acquired keratinization disorders. Inherited cases have an autosomal dominant transmission [268]. The exact prevalence and incidence are not known. No racial predilection exists, but there are differences in incidence between males and females depending on the presenting subtype. Variants more commonly seen in children include porokeratosis of Mibelli and disseminated superficial actinic porokeratosis (DSAP, usually appearing between 5 and 10 years of age) [268]. Similarly, linear porokeratosis can be seen earlier in life with reports of congenital lesions. Overall, the most commonly seen variant is DSAP, which typically occurs in adults over 30 years old in areas with high sun exposure.

Porokeratosis is classically described as keratotic papules with centrifugal spread and progress to well-demarcated, annular plaques with atrophic, slightly hyperpigmented centers and hyperkeratotic borders (Fig. 2.47) [268].

Fig. 2.47 Porokeratosis presents as well-demarcated annular plaques with erythematous center and raised hyperkeratotic border

Clinical variants of porokeratosis include:

- *Porokeratosis of Mibelli* is solitary or multiple erythematous plaques of varying sizes usually along the limbs, presenting in childhood and most often in males with a male to female ratio of 2:1 [268].
- *Linear porokeratosis* exists in two primary forms: (1) localized subtype with Blaschkoid distribution of papules and plaques, most frequently occurring along the distal extremity, and (2) generalized subtype with multiple lesions on the trunk and extremities. Nail changes of pterygium and longitudinal fissures can be seen in cases involving the extremity.
- *Disseminated superficial actinic porokeratosis* (DSAP) appears to be associated with UV exposure with lesions most frequently seen on the extensor limbs, shoulders, back, and face. DSAP presents with erythematous to hyperpigmented hyperkeratotic papules with central atrophy on the trunk, genitalia, palms and soles that evolve into annular plaques [268]. Oral lesions can occur. The disease has a slowly progressive course.
- *Punctate porokeratosis* is characterized by monomorphic pin-point pitted keratotic papules at the palms and soles that are tender to palpation [268].
- *Porokeratosis palmaris, plantaris and disseminata* is described as symmetric, reddish brown hyperkeratotic 1–2 mm papules on the palms and soles, beginning in adolescence with progression to generalized lesions on the trunk and extremities over time [268]. Males are more often affected with a positive family history.

While some cases of porokeratosis will resolve spontaneously, most have an indolent and progressive course with an increase in the number and size of lesions over time [269]. All variants of porokeratosis have the potential for malignant degeneration with malignancy reported in approximately

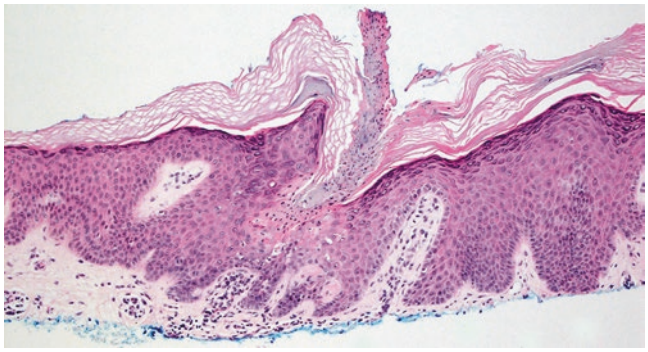

Fig. 2.48 Porokeratosis is characterized by columns of angulated parakeratosis arising from invaginated foci of epidermis (cornoid lamella)

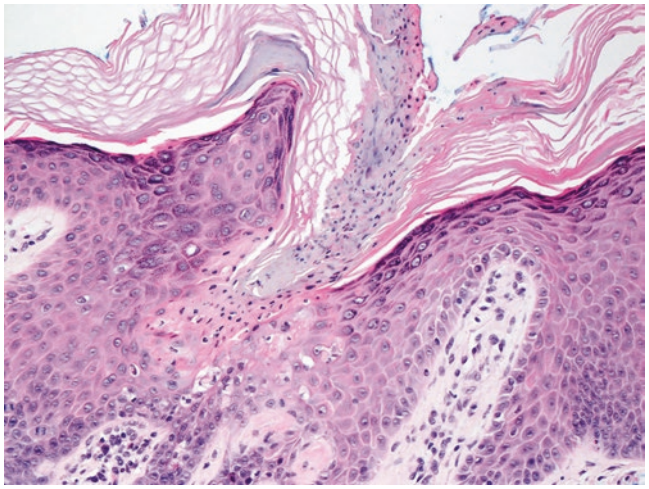

Fig. 2.49 Loss of the granular layer and scattered dyskeratotic cells are present beneath a cornoid lamellae in porokeratosis

7.5 % of cases [268]. Linear porokeratosis and giant type porokeratosis carry the greatest risk of malignancy. Other risk factors include older lesions, distribution on the limbs, and Japanese ancestry in whom the reported risk of malignant transformation is greater than 11 % [268]. Invasive squamous cell carcinoma is the most commonly reported cancer, although association with Bowen's disease and basal cell carcinoma have also been reported.

2.20.2 Histology

Biopsy findings of different clinical variants of porokeratosis share many histologic similarities despite a wide range of clinical presentations. Multiple clinical variants may coexist within a single patient [270–273]. The defining characteristic includes a column of parakeratotic cells extending upwards from the stratum corneum known as a cornoid lamella (Fig. 2.48). In the ideal specimen, two cornoid lamellae, representing the peripheral margins of the lesion are seen, angling inwards towards each other with ascent from the top of the epidermis. In most biopsy specimens, however, both margins are not simultaneously apparent in a single biopsy specimen. Deep to the cornoid lamella, the epidermis shows a focal loss of the granular layer with scattered dyskeratotic cells (Fig. 2.49). There is no increase in the mitotic rate within the epidermis [274].

In some cases, the epidermis in the center of the porokeratotic lesion between two cornoid lamellae appears atrophic. Occasionally, the epidermis may be paradoxically acanthotic. The stratum corneum between the cornoid lamella is often hyperkeratotic. Dilated capillaries are present in the superficial papillary dermis. A variably intense lymphocytic infiltrate that ranges from lichenoid to virtually nonexistent is present in the papillary dermis. The lichenoid infiltrate is most common in the disseminated superficial actinic porokeratosis variant. Amyloid deposits in the papillary dermis have been described underlying some cases of porokeratosis [275].

Porokeratotic eccrine ostial and dermal duct nevus has cornoid lamella in the outflow tracts of eccrine ducts, the explanation for the name of the entity. However, most authors see this as a distinct and pathogenetically unrelated entity that shares a single common histologic finding [276, 277].

Cornoid lamellae are not specific for porokeratosis and have been described in conditions ranging from pachyonychia congenital to verruca vulgaris [278]. It is important to correlate the presence of cornoid lamella with the other histologic findings and the clinical presentation.

2.20.3 Pathogenesis

Porokeratosis is a heterogeneous group of keratinization disorders that appear to have different genetic basis. DSAP is a common type and has an autosomal dominant pattern of inheritance. It begins in adolescents and reaches near-complete penetrance in adulthood. A genetic locus for DSAP has been mapped to chromosome 18p11.3 [279, 280]. Other genetic loci that may be linked to DSAP include DSAP1 (chromosome 12q24.1-24.2), DSAP2 (on chromosome 15q25.1-26.1), and DSAP3 (on chromosome 1p31.3-p31.1) [281, 282].

Mutations in MVK (mevalonate kinase) gene have been identified as causative in DSAP [283]. MVK encodes an enzyme involved in the synthesis of isoprenoids. Functional studies of MVK in human keratinocytes indicate that MVK is important in regulating calcium-induced keratinocyte differentiation and could protect keratinocytes from apoptosis induced by ultraviolet radiation [283]. Other studies involving DNA sequencing and copy number variation screen of exons of patients with familial and sporadic forms of porokeratosis revealed additional mutations in three genes in the mevalonate pathway that are linked to porokeratosis, namely

phosphomevalonate kinase, mevalonate decarboxylase, and farnesyl diphosphate synthase [284].

Porokeratosis of Mibelli and linear porokeratosis are subtypes of porokeratosis that primarily present in infancy and childhood. Molecular studies of porokeratosis of Mibelli show that there is increased expression of hyperproliferative keratins (such as keratin 17), S100 family of calcium binding proteins, and the gap junction proteins connexin 26 and connexin 30 in the cornoid lamella [285]. These molecules are important in cytoskeleton structure, epidermal hyperproliferation, and cell–cell communication.

2.21 Palmoplantar Keratodermas

2.21.1 Clinical Features

Palmoplantar keratoderma (PPK) is a highly heterogeneous group of disorders defined by significant thickening of the epidermis at the palms and soles (Figs. 2.50, 2.51, and 2.52). The condition may be inherited or acquired. Acquired PPK may be secondary to medications, chemical exposure, metabolic disease, and other underlying dermatoses such as psoriasis [286]. Malignancy should be excluded in cases of spontaneous onset of PPK with no identifiable etiology. Inherited PPK usually presents once the child begins to walk, and shows symmetrically distributed lesions. In contrast, acquired PPK may be asymmetric, and typically appearing later in life [286].

There are three primary clinical morphologies seen in both of the broader categories of PPK: diffuse, focal, and punctate [286, 287]. In cases associated with hyperhidrosis, malodorous maceration may occur with subsequent superimposed bacterial and fungal infections. Treatment primarily is supportive in the inherited form as skin changes tend to be persistent. However, improvement may be seen in acquired types if the underlying issue is addressed.

Fig. 2.50 There is significant thickening of the sole in palmoplantar keratoderma

Fig. 2.51 Skip areas of hyperkeratosis most notably along pressure points of the sole as seen in palmoplantar keratoderma

Fig. 2.52 Palmoplantar keratoderma was seen concomitantly in an adolescent girl presenting with truncal rash consistent with pityriasis rosea

2.21.2 Histology

There are many different clinical variants of keratodermas, some of which are syndromic and others are isolated findings. The histologic findings vary dependent upon the type, although the findings are often relatively nonspecific. Fortunately, genetic testing is useful in further delineating these conditions with overlapping histologic changes.

The histologic finding in *Olmsted syndrome* is epidermal hyperproliferation that manifests itself by an acanthotic epidermis with overlying compact hyperkeratosis [288]. The epidermis has a psoriasiform pattern with elongated rete ridges [289]. The epidermis may also display a papillomatous surface appearance [290]. A mild lymphohistiocytic infiltrate is present in the dermis in some cases [291]. Defective keratinization is seen on electron microscopic examination [289]. Ki-67 immunostain confirms the markedly increased proliferation rate seen in the epidermis in this type of keratoderma [290].

Greither's disease shows nonspecific histologic changes. There is focal orthokeratosis that overlies depressed areas of epidermis [292]. Tonofilaments aggregate around the nucleus, but do not form actual clumps as seen on electron microscopy [293].

Huriez syndrome demonstrates orthokeratotic hyperkeratosis. Although not readily apparent on routine staining, use of CD1a immunostain demonstrates a marked reduction in intraepidermal Langerhans cells [294, 295]. Predisposition to cutaneous squamous cell carcinoma is the major concern with this type of keratoderma [296].

Punctate keratoderma is characterized by circumscribed areas of dense orthokeratotic hyperkeratosis overlying the epidermis with pronounced hypergranulosis [297] (Fig. 2.53 and Fig. 2.54). In one case study, a patient with punctate keratoderma showed lentigo-like lesions with increased basilar melanin adjacent to the keratodermatous foci [298]. It is not clear if it represents a variant of this keratoderma subtype.

Punctate porokeratotic keratoderma demonstrates columns of parakeratosis, cornoid lamellae, and overlying epidermis that shows loss of the granular layer beneath the areas with parakeratosis [299].

The *Unna Thost* variant of keratoderma shows changes of epidermolytic hyperkeratosis. Keratinocytes in the upper layers of the epidermis show marked clumping of the keratohyaline granules, resulting in dissolution of the epidermis. Prominent vacuolization is present in keratinocytes within the spinous and granular layers. There is pronounced overlying hyperkeratosis [300, 301].

The histologic findings in Unna Thost keratoderma are identical to those described in the *Vorner* type [300, 302]. A single patient with these histologic changes and woolly hair is reported as a variant of this syndrome [303–305].

Vohwinkel syndrome demonstrates pronounced orthokeratotic hyperkeratosis [306].

Fig. 2.53 Markedly thickened stratum corneum is present in punctate keratoderma

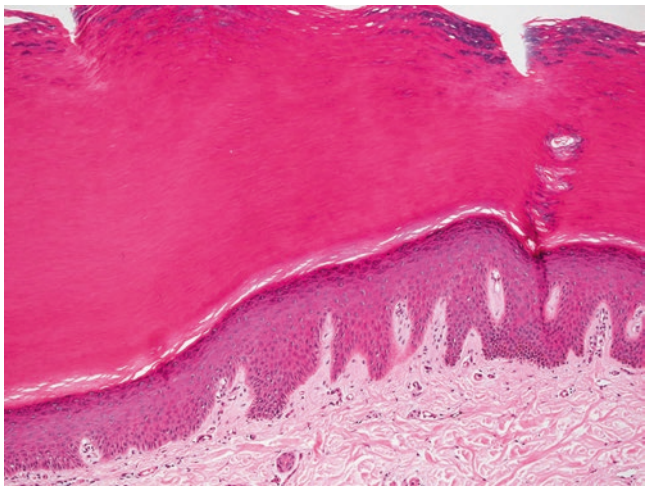

Fig. 2.54 Acral skin with massive compact orthokeratosis is seen in punctate keratoderma

Papillon–Lefevre syndrome has pronounced orthokeratotic hyperkeratosis with no other specific distinguishing features. One study suggests a predisposition for the development of secondary cutaneous malignancies, including melanoma, in these patients [307].

Mal de meleda and *Howel-Evans* syndromes have marked orthokeratotic hyperkeratosis and minimal inflammation. The histologic changes are not specific and the syndrome can be diagnosed based upon the clinical constellation of findings and genetic testing.

Gamborg Nielsen syndrome is described as a milder variant of *mal de meleda* with similar histologic changes [308]. The distinction is made based upon subtle changes in keratinocyte maturation as detected on electron microscopic examination.

Acrokeratoeolastoidosis is a punctate keratoderma that has additional histologic changes of marked degeneration of dermal elastic tissue fibers [309]. The stratum corneum displays orthokeratotic hyperkeratosis and has an undulating appearance [310].

2.21.3 Pathogenesis

Palmoplantar keratoderma is a heterogeneous group of keratin disorders that primarily have an autosomal dominant pattern of inheritance [311]. Given the diverse nature of the disorders, the molecular defects underlying palmoplantar keratoderma are diverse and cannot be explained by a single pathogenic mechanism. Over the years, we have gained important insights into the molecular basis of some forms of palmoplantar keratoderma. It is noteworthy that the nature and location of the gene mutation correlates with the disease phenotype.

A causative gene of palmoplantar keratoderma is keratin 9 (KRT9) gene, which is expressed primarily in the skin of the palms and soles [312–314]. Mutations in keratin 9 affect the helical rod domain that is important for keratin heterodimerization [315]. Mutations in keratin 1 (KRT1) gene have also been reported in palmoplantar keratoderma [316, 317].

A type of palmoplantar keratoderma, called diffuse non-epidermolytic palmoplantar keratoderma, is caused by missense mutations in aquaporin 5 (AQP5) gene [318, 319]. Aquaporins are proteins that form water channels, which are primarily responsible for osmotic water movement across the plasma membrane in the cell. It is important for fluid secretion, such as sweat in eccrine glands. Another form of palmoplantar keratoderma associated with pachyonychia congenita has been linked to deletions in keratin 6C (KRT6C) and keratin 16 (KRT16) genes [320–322]. Palmoplantar keratoderma associated with deafness has an autosomal dominant inheritance and is caused by mutations in connexin 26 (GJB2) gene [323]. Connexin 26 is a gap junction protein expressed in cochlear cells and in the epidermis.

2.22 Acanthosis Nigricans

2.22.1 Clinical Features

Acanthosis nigricans most commonly is associated with obesity, with increasing prevalence rates mirroring that of obesity. Two-thirds of adolescents with body weight greater than 200 % of ideal body weight have acanthosis nigricans [324]. No sex predilection exists. It occurs most commonly in Native Americans, Blacks and Hispanics with lower incidence in Caucasians. Juvenile acanthosis nigricans is subcategorized into eight groups: benign, obesity-related, syndromic, malignant, unilateral, acral, drug-induced and mixed types [324]. Benign acanthosis nigricans may be present at birth or occur during childhood or adolescence and is thought to represent a rare autosomal dominant disorder with incomplete penetrance. Obesity is the most common cause of acanthosis nigricans worldwide, typically presenting after puberty. Malignant acanthosis nigricans is rare in children and occurs in the setting of an underlying malignancy, such as Wilms' tumor, osteogenic sarcoma, gastric carcinoma, adrenocortical carcinoma, and papillary thyroid carcinoma.

Acanthosis nigricans is characterized by symmetrically distributed, velvety, hyperpigmented, hyperkeratotic to verrucous plaques most prominently along the intertriginous folds (axillae, neck, inframammary breasts, and groin) (Fig. 2.55). The most commonly cited location is the neck. Full resolution of the lesions may occur with management of the underlying causative condition, such as weight loss, chemotherapy for malignancy, or elimination of the precipitating medication. The benign variant tends to be more persistent and is refractory to therapy [324].

2.22.2 Histology

Acanthosis nigricans has orthokeratotic hyperkeratosis overlying a papillomatous epidermis (Figs. 2.56 and 2.57). The epidermis is acanthotic with slight basilar hyperpigmentation. There is no increase in the number of melanocytes. The dermis is unremarkable, and there is no significant inflammatory infiltrate [325–328].

The histologic differential diagnosis includes epidermal nevus, seborrheic keratosis, and confluent and reticulated papillomatosis of Gougerot and Carteaud [329]. Clinical pre-

Fig. 2.55 Acanthosis nigricans shows velvety, hyperpigmented, hyperkeratotic to verrucous plaques in the axilla (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

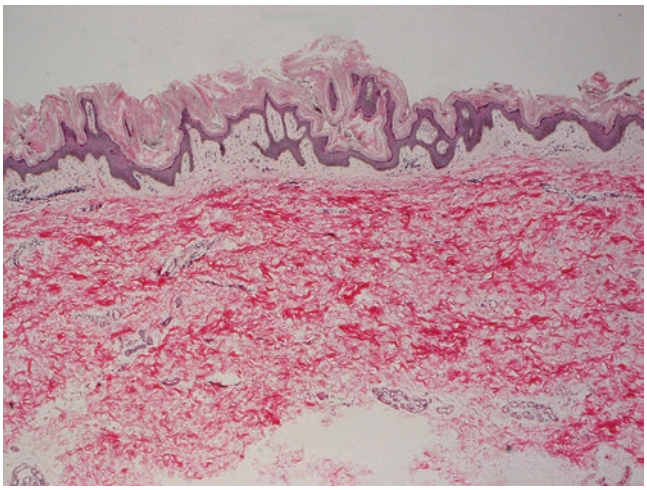

Fig. 2.56 Acanthosis nigricans shows hyperkeratosis overlying a papillomatous and mildly acanthotic epidermis

Fig. 2.57 Marked hyperkeratosis is present in acanthosis nigricans. While sometimes present (as in this example), increased basilar melanin pigments is not a major contributor to the clinical appearance of hyperpigmentation

sentation will serve to differentiate all of these entities. Confluent and reticulated papillomatosis may also have yeast forms in the stratum corneum, which are not seen in acanthosis nigricans [330].

2.22.3 Pathogenesis

Acanthosis nigricans is associated with insulin resistance and hyperinsulinemia [331, 332]. Hyperinsulinemia may stimulate epidermal proliferation through growth factors, such as the insulin-like growth factor receptor-1 [331]. Acanthosis nigricans is also associated with malignancies, and this may be related to increased serum levels of growth factors, such as transforming growth factor-α, which stimulates skin growth [333, 334]. Lastly, it may also have a genetic basis since an autosomal dominant mutation in fibroblast growth factor receptor-3 (K650T mutation) has been reported in a familial case [335, 336].

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Vesiculobullous Diseases

3

3.1 Acropustulosis of Infancy

3.1.1 Clinical Features

Acropustulosis of infancy typically affects young children, with onset between birth and 1 year of age. It is more common in African American infants [1]. Recurrent crops of pruritic vesiculopustules in an acral distribution are characteristic (Figs. 3.1 and 3.2). Lesions typically last up to 2 weeks, clear, and then recur within a few weeks. Severity of outbreaks tends to diminish over time. Spontaneous resolution generally occurs by 2–3 years of age.

3.1.2 Histology

The histologic findings of acropustulosis of infancy are not specific, but characteristic of this entity. The epidermis has foci of spongiosis with microvesiculation [2] (Fig. 3.3). Neutrophilic abscesses are present within the vesicles (Fig. 3.4). Acute lesions do not have parakeratosis, although this is a common finding in more established lesions. Less commonly, eosinophils may be present within the microvesicles [3].

The differential diagnosis includes candidiasis and impetigo, each of which can be further delineated with use of special stains and microbiological tissue cultures. Pustular psoriasis may present a more difficult diagnostic dilemma in that the usual changes of plaque psoriasis are often not present in acute pustular lesions. The presence of ectatic vessels within the papillary dermis may be some evidence in favor of psoriasis, but in most cases clinical correlation is the best way to make this distinction. In rare cases with eosinophils in the inflammatory infiltrate, erythema toxicum neonatorum enters the differential diagnosis, but it should be easily distinguished based upon the clinical presentation. Similarly, incontinentia pigmenti might show similar histologic features. The presence of dyskeratotic cells favors the diagnosis of incontinentia pigmenti, and the clinical appearance makes for a relatively straightforward distinction.

3.1.3 Pathogenesis

Acropustulosis of infancy is seen in children with scabies infestation, and this may represent an allergic or id reaction to scabies [2, 4–7].

3.2 Transient Neonatal Pustular Melanosis

3.2.1 Clinical Features

The overall incidence of transient neonatal pustular melanosis is estimated at 0.2–0.6 % [8]. It is more common in African American infants, where incidence is 4.4 % [8]. The disorder is characterized by vesiculopustules on a non-erythematous background. Lesions are typically present at birth or within the first few days of life. Pustules tend to rupture easily leaving hyperpigmented macules behind. These macules usually fade within a few weeks. Although lesions may appear anywhere (including the palms and soles), they tend to favor the chin, neck, upper chest, lower back, buttocks, and thighs [8]. Pustules resolve spontaneously within approximately 1 week. Residual hyperpigmented macules resolve over a few weeks.

3.2.2 Histology

Histologic features include neutrophilic abscesses within the stratum corneum and in the upper portions of the epidermis (Fig. 3.5). Dermal melanin appears in later lesions secondary to post-inflammatory pigmentation. Special stains for fungi

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Fig. 3.1 Vesiculopapules and pustules as well as hyperpigmented macules at sites of previously active lesions on the distal legs and feet in acropustulosis of infancy

Fig. 3.2 Acropustulosis of infancy, closer image of the same patient in Fig. 3.1

and bacteria are negative but are usually required to exclude an infectious etiology. There is only a minimal inflammatory infiltrate within the dermis [9, 10].

The histologic differential diagnosis includes pustular psoriasis. This is quite unusual in neonates and can usually be distinguished based upon clinical findings. Vascular ectasia that characterizes psoriasis may be of some use in making

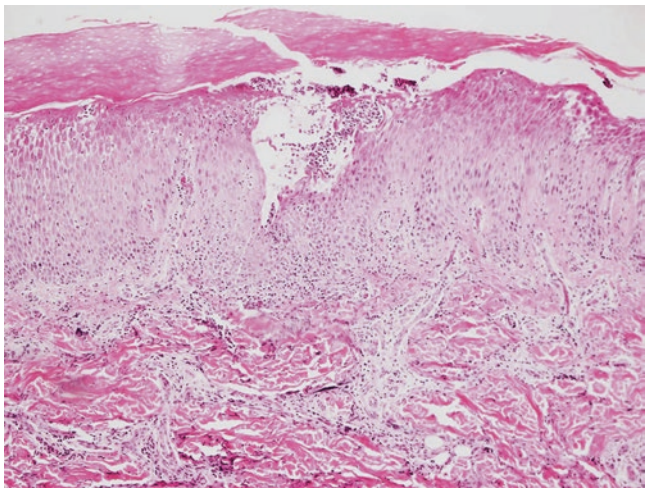

Fig. 3.3 Histologic features of acropustulosis of infancy include intraepidermal spongiosis and clusters of neutrophils within the stratum corneum

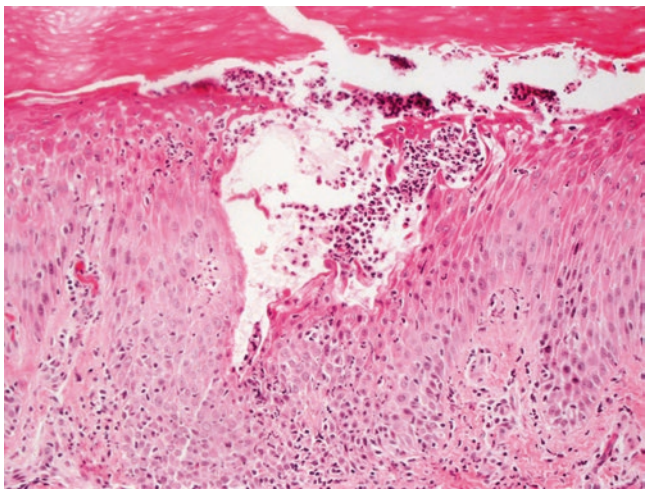

Fig. 3.4 Subcorneal neutrophilic clusters are present in acropustulosis of infancy

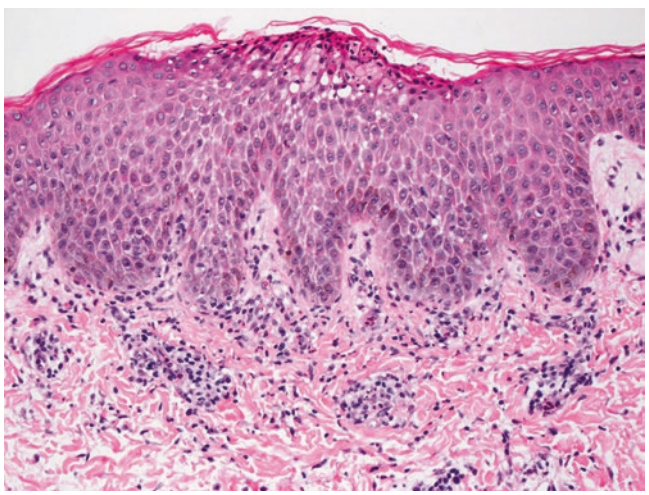

Fig. 3.5 A subcorneal neutrophilic abscess is seen with surrounding spongiosis in transient neonatal pustular melanosis. The basal layer of the epidermis is generally pigmented in patients with this disorder

this distinction histologically. Subcorneal pustulosis of Sneddon–Wilkinson is also extremely rare in neonates. Erythema toxicum neonatorum occurs in the same population. Histologically, this entity has eosinophils in the pustules in contrast to the neutrophils present in transient neonatal pustular melanosis. This difference allows some authors to consider these two entities to be unrelated [10, 11]. Other authors believe transient neonatal pustular melanosis represents precursor lesions to what rapidly evolves into erythema toxicum neonatorum [9, 12].

3.3 Staphylococcal Scalded Skin Syndrome

3.3.1 Clinical Features

Staphylococcal scalded skin syndrome affects primarily infants and young children, although it has been reported in adults [13]. The primary infection typically involves the conjunctivae, nares, perioral region, perineum and umbilicus [14].

Erythema of the skin progresses to superficial fragile blisters that rupture easily, leaving tender eroded areas behind (Fig. 3.6). Involvement is often most prominent in the flexural creases. Patients may be mildly or severely affected. With extensive desquamation of the skin, there are secondary risks of fluid and electrolyte loss, thermoregulatory instability, and infection. With proper management, the skin is expected to heal without permanent scarring.

Fig. 3.6 Staphylococcal scalded skin syndrome often presents as tender, dusky red patches at the intertriginous skin with flaccid bullae and superficial erosions on the trunk

3.3.2 Histology

Histologic changes consist of a non-inflammatory subcorneal blister at the level of the granular layer (Fig. 3.7). In many cases, the stratum corneum, which is the blister roof, is desquamated and not present in the biopsy specimen. Its absence is often overlooked, making the diagnosis difficult. Rare acantholytic cells may be observed within the granular layer (Fig. 3.8). There is virtually no underlying inflammation within the dermis. Special stains for bacteria are negative [15].

The major differential diagnosis based on histologic grounds is a superficial variant of pemphigus such as pemphigus foliaceus or pemphigus erythematosus. However, these entities have markedly different clinical presentations and are not common in children. Frequently, the pathologist is asked to differentiate staphylococcal scalded skin syndrome from toxic epidermal necrolysis. The histologic distinction is made based upon the level of the blister. In toxic epidermal necrolysis, the blister occurs at the dermal epidermal junction. Abundant dying keratinocytes are present throughout the epidermis, all of which is on the roof of the blister. In contrast, in staphylococcal scalded skin syndrome, all nucleated keratinocytes are on the floor of the blister, with the roof comprised solely of stratum corneum. Impetigo, when caused by staphylococcus, is characterized by neutrophilic abscesses and dermal inflammatory infiltrate. Tissue gram stains demonstrate abundant gram-positive cocci.

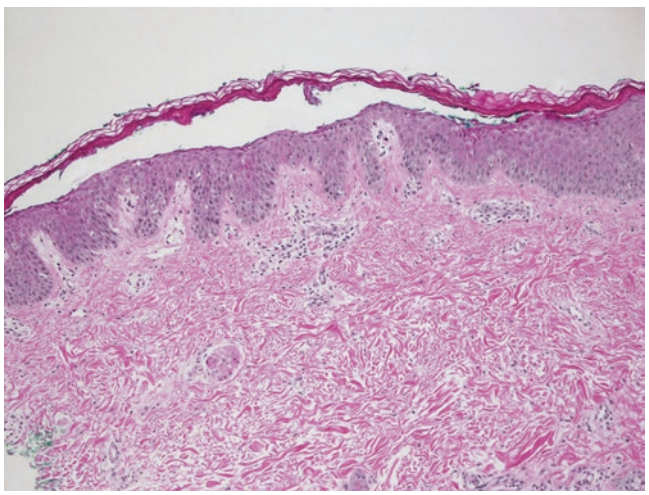

Fig. 3.7 Staphylococcal scalded skin syndrome features a subcorneal blister in the absence of any inflammatory infiltrate

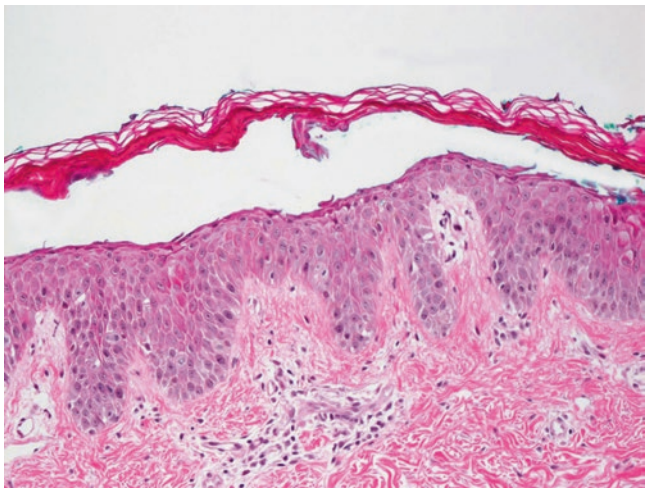

Fig. 3.8 Rare acantholytic cells can be seen at the base of the separation in Staphylococcal scalded skin syndrome

3.3.3 Pathogenesis

Staphylococcal scalded skin syndrome is caused by exfoliative toxin produced by *Staphylococcus aureus* [16–21]. About 5 % of *S. aureus* human isolates produce exfoliative toxins A and B that cause the disease. Exfoliative toxin disseminates throughout the circulation from a localized site of infection and causes widespread skin involvement at distant sites. Therefore, microbiological cultures of the bullous material in staphylococcal scalded skin syndrome lesions are often sterile.

S. aureus exfoliative toxin is a trypsin-like serine protease [19]. As it accumulates in the skin, the toxin digests desmoglein-1, which is a component of desmosome adhesion between keratinocytes [22–24]. Loss of desmoglein-1 disrupts keratinocyte-to-keratinocyte adhesion in the stratum granulosum, resulting in bullae formation [22, 25]. The relative amount of desmoglein-1 in the skin differs with age group and location in the epidermis. This may partially explain the increased frequency of staphylococcal scalded skin syndrome in young children, and the preferential involvement of the upper layer of the epidermis.

3.4 Subcorneal Pustular Dermatosis of Sneddon–Wilkinson/IgA Pemphigus

3.4.1 Clinical Features

Subcorneal pustular dermatosis is most common in 40–50-year-old women [26]. It is rare in children, although it has been reported in a 7-week-old infant [14]. Subcorneal pustular dermatosis begins with small vesicles or pustules on a normal to slightly erythematous base. Patients experience mild pruritus. The pustules tend to coalesce, forming annular and serpiginous patterns (Fig. 3.9). Lesions tend to occur on the trunk, intertriginous, and flexural areas. The face and mucous membranes are spared. Lesions can rupture, leaving superficial erosions and crusts that heal with blotchy hyperpigmentation. Although benign, subcorneal pustular dermatosis is characterized by remissions and exacerbations that may last for several years. In adults, patients require long-term follow-up, as there is a reported association with possible development of monoclonal gammopathy and multiple myeloma.

3.4.2 Histology

IgA pemphigus, likely identical to Sneddon–Wilkinson syndrome, has two predominant histologic patterns. In one pattern, neutrophils aggregate as subcorneal pustules, while in the other, they are deeper within the epidermis and accompanied by slight acantholysis [27]. Even less commonly, epidermal acanthosis resulting in a pattern resembling pemphigus vegetans has been reported [28]. Direct immunofluorescence examination reveals intercellular staining throughout the epidermis with anti-IgA antibodies (Fig. 3.10).

The histologic differential diagnosis is dependent upon the histologic pattern. In the subcorneal form of the disease, a wide range of subcorneal blistering processes occurring in the pediatric population must be considered. Special stains can help to exclude the infectious processes such as candidiasis and impetigo. Clinical history might help with transient neonatal pustular melanosis and acral pustulosis of infancy. The variant with intraepidermal abscesses must be distinguished from infectious etiologies. As with all of the pemphigus subtypes, resolution of the differential diagnosis is simplified by direct immunofluorescence stains. Other types of pemphigus are quite rare in children. Pemphigus foliaceus, demonstrating blister formation within the granular layer of the epidermis, has been described in children [29].

3.4.3 Pathogenesis

The etiology of subcorneal pustular dermatosis is not known. Infection does not appear to be a cause, since microbiological cultures of the pustules in this disorder do not show growth of microorganisms [30]. Subcorneal pustular dermatosis may have immunologic mechanisms. Some patients with the disorder have circulating IgA antibodies to desmocollins-1, 2, and 3, which have been described as auto-

Fig. 3.9 Subcorneal pustular dermatosis of Sneddon–Wilkinson (IgA pemphigus) presents as erythematous, serpiginous plaques at the anterior neck and superior trunk

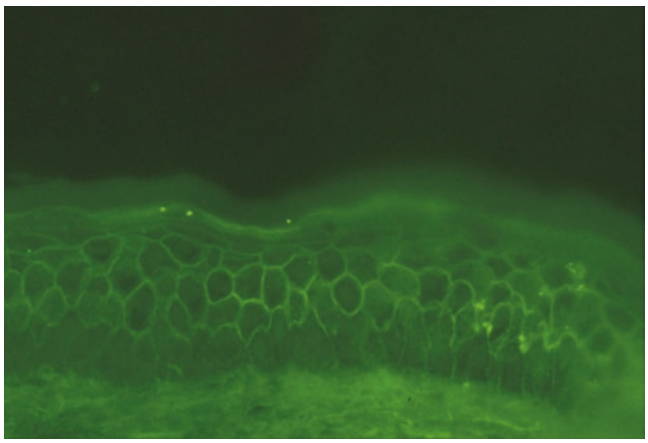

Fig. 3.10 Intercellular staining throughout the epidermis with anti-IgA antibodies characterizes IgA pemphigus

antigens in some cases [31–33]. However, the exact role of these antibodies in the pathogenesis of the disease remains to be determined.

3.5 Acute Generalized Exanthematous Pustulosis

3.5.1 Clinical Features

Acute generalized exanthematous pustulosis (AGEP) is most common in adults, although it has been reported in some children [34]. Mortality rate is 2 %. AGEP is characterized by the acute onset of an eruption composed of generalized erythroderma and non-follicular, sterile pustules (Fig. 3.11).

Fig. 3.11 Generalized, non-follicular based erythematous papules and pustules as seen on the trunk of an adolescent patient with AGEP (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

This typically occurs in the setting of fever. It generally resolves spontaneously with patchy superficial desquamation within 4–10 days. Recurrences are expected to occur with reexposure to the offending trigger and are typically faster in onset.

3.5.2 Histology

AGEP is uncommon in children, but when it occurs, shows the same histologic changes as have been reported in adults [35]. Subcorneal pustules comprised of neutrophils are present within a slightly spongiotic epidermis (Fig. 3.12). Parakeratosis is infrequent, except in older lesions. The granular layer persists and acanthosis is not a common finding. Within the dermis, there is a mixed inflammatory infiltrate that consists of neutrophils, eosinophils, and histiocytes [36] (Fig. 3.13).

The major histologic differential diagnosis is pustular psoriasis that can be distinguished by the absence of eosinophils, occasional acanthosis and suprapapillary thinning. However, in many acute cases, these changes may not be well developed and distinction may be quite difficult without the aid of clinical history [37]. Infectious etiologies such as impetigo and candidiasis might present some diagnostic difficulties, but this can usually be resolved with the use of special stains for microorganisms. Transient neonatal pustular melanosis can be distinguished most easily based upon clinical presentation. The inflammatory infiltrate in erythema toxicum neonatorum is predominantly eosinophilic with only a minority population of neutrophils unlike in AGEP.

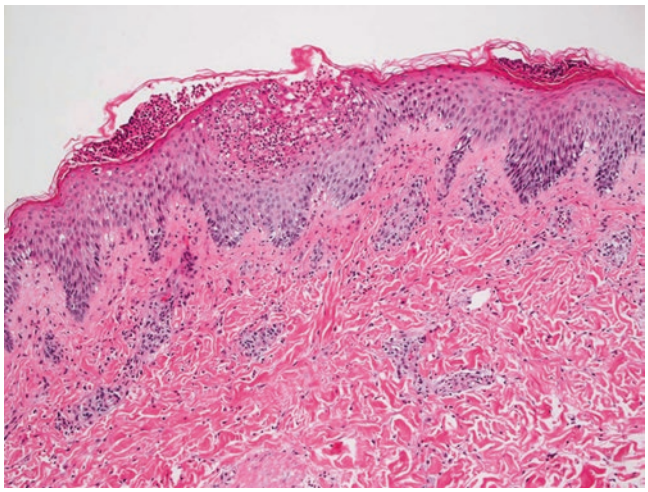

Fig. 3.12 AGEP demonstrates subcorneal and intraepidermal neutrophilic abscesses. There is focal spongiosis and a mild, mixed superficial dermal perivascular infiltrate

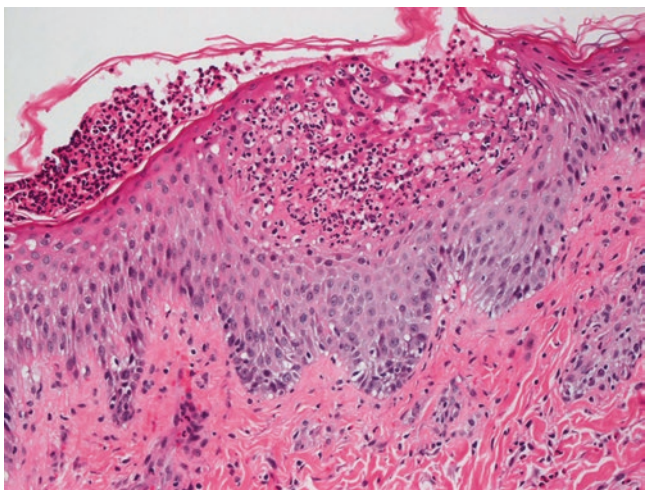

Fig. 3.13 In addition to the neutrophilic abscesses in the epidermis, AGEP has neutrophils and eosinophils within the dermal infiltrate

3.5.3 Pathogenesis

AGEP is caused by drugs in most cases. Common drugs associated with AGEP are pristinamycin, aminopenicillins, quinolones, hydroxychloroquine, sulfonamides, terbinafine, and diltiazem [38–40]. Infectious agents, such as coxsackie virus, cytomegalovirus, parvovirus B19, *Chlamydia pneumoniae*, and *Escherichia coli*, are also associated with this disorder [41].

AGEP may have a genetic basis. Mutation frequency in IL-36 receptor antagonist (IL36RN) is higher in patients with AGEP than in control population (1.6 % vs. 0.4 %) [42]. It has been suggested that IL36RN gene mutation may be a predisposing genetic factor to developing AGEP.

AGEP is a T lymphocyte-mediated reaction. Exposure to the causative agent results in the presentation of the inciting antigen by antigen-presenting cells to T lymphocytes. Activation, proliferation and migration of drug-specific CD4+ and CD8+ T lymphocytes are observed in AGEP [40, 43]. Infiltrating CD4+ T lymphocytes and keratinocytes release CXCL-8 (a potent neutrophilic cytokine) and granulocyte macrophage-colony stimulating factor (GM-CSF), which result in the recruitment of neutrophils and the formation of neutrophilic pustules [43]. Drug-specific CD4+ T lymphocytes from patients with AGEP are predominantly type 1 T helper cells (Th1) with Th1-type cytokine profile and the production of interferon-γ (IFN-γ) and GM-CSF [44, 45]. IFN-γ and GM-CSF augment neutrophil survival. There is also increased IL-15 production, which is a potent stimulator of eosinophil proliferation and differentiation. Type 17 T helper cells (Th17) also play a role in AGEP [46, 47]. Th17 cells produce IL-17 and IL-22, which increase the production of CXCL8 by keratinocytes. Apoptosis of keratinocytes is mediated by CD8+ cytotoxic T lymphocytes via perforin/granzyme B and Fas ligand mechanisms, leading to epidermal necrosis and vesicle formation as observed in this disorder [43, 48].

3.6 Friction Blister

3.6.1 Clinical Features

Friction blisters are very common, especially in active individuals. Blisters result from frictional forces that mechanically induce cleavage of the epidermis at the level of the stratum spinosum. The area of separation fills with fluid secondary to hydrostatic pressure. Blisters are more common in areas with a thick horny layer that is tightly adherent to underlying tissues (e.g., palms and soles) [49]. If the bulla is de-roofed, there is a tender erosion. With adequate wound care and protection from additional trauma, friction blisters typically heal spontaneously within several days.

3.6.2 Histology

Blisters caused by friction can occur at any level of the epidermis or commonly at the dermal-epidermal junction. The blisters are non-inflammatory unless there is secondary infection and inflammation as a reaction to the injury (Fig. 3.14). Epidermal necrosis is only present after a period of time during which the keratinocytes on the roof of the blister are devoid of blood flow.

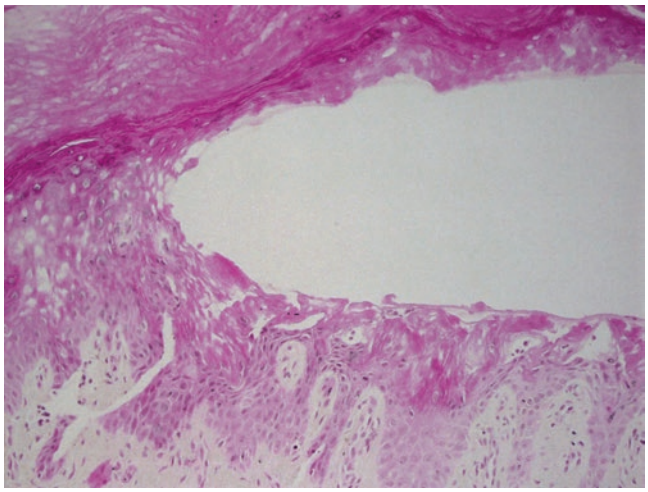

Fig. 3.14 A mid-epidermal blister without any immune response is characteristic of a friction blister

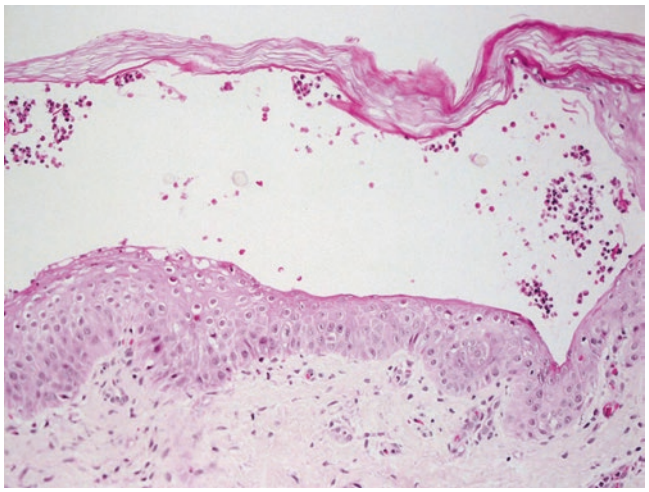

Fig. 3.15 Erythema toxicum neonatorum shows a subcorneal eosinophilic abscess

The histologic differential diagnosis is small. Epidermolysis bullosa is the closest histologic mimic and in fact, this family of diseases results in mechanically induced blisters identical to friction blisters. However, clinical history easily resolves the diagnostic dilemma.

3.7 Erythema Toxicum Neonatorum

3.7.1 Clinical Features

Erythema toxicum neonatorum is a benign skin eruption of the newborn that typically appears 24–48 hours after birth. Up to 70 % of newborns are affected. Although it does not appear to have a gender or racial predilection, it is more common with increasing gestational age and birth weight.

Clinically, lesions appear as small white papules or pustules on an erythematous base (similar to a "flea bite"). They are usually most numerous on the trunk, but may also occur on the face, arms, and legs. Palms and soles are typically not affected. Lesions clear within 5–7 days without discoloration or permanent scarring.

3.7.2 Histology

Histologic sections demonstrate skin with subcorneal abscesses containing a predominance of eosinophils (Fig. 3.15). Parakeratosis is variably present depending upon the age of the lesion. Within the dermis, there is a relatively slight inflammatory infiltrate that consists of lymphocytes, histiocytes, and scattered eosinophils. Increased numbers of Langerhans cells are also present within lesions [50].

The differential diagnosis includes incontinentia pigmenti, which is differentiated based upon the presence of dying keratinocytes and is not a feature of erythema toxicum neonatorum. Eosinophilic abscesses may also be encountered in IgA pemphigus, although the clinical history and age of the patient will help to make this distinction. Other subcorneal pustular processes are easily distinguished by the predominance of neutrophils as opposed to the eosinophils that characterize erythema toxicum neonatorum. Some authors have suggested that neutrophilic abscesses may be present in erythema toxicum neonatorum and that differentiation from transient neonatal pustular melanosis is not always possible [12].

3.8 Hydroa Vacciniforme

3.8.1 Clinical Features

Hydroa vacciniforme is common in children with disease onset typically between the ages of 1 and 15 years old. Prevalence of hydroa vacciniforme has been reported at 0.34 cases per 100,000 individuals [51]. Hydroa vacciniforme is a photodermatosis. The primary skin lesions are edematous papules, vesicles or bullae that appear within hours to days after sun exposure. Lesions tend to favor exposed areas, such as the face, neck, and extensor arms and hands. Patients report itching and burning of the skin within hours of sun exposure,

Fig. 3.16 Hydroa vacciniforme presents as photodistributed, crusted, erythematous papules and vesicles (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

and may also have mild constitutional symptoms. Vesicles and bullae tend to crust over within a few days and heal with varioliform scarring (Fig. 3.16). The course of hydroa vacciniforme tends to be relapsing and remitting, although it typically improves or resolves after puberty [14]. Children with hydroa vacciniforme in the setting of chronic Epstein–Barr virus infection appear to have an increased risk of lymphoproliferative disease and should be monitored closely [51].

3.8.2 Histology

The histologic findings in hydroa vacciniforme are not specific. The epidermis is markedly spongiotic in early lesions, progressing to reticular degeneration and ultimately necrosis in later stage lesions (Fig. 3.17). Within the dermis, there is a brisk infiltrate that consists predominantly of lymphocytes and histiocytes (Figs. 3.18 and 3.19). Eosinophils are not abundant. Neutrophils may be observed in ulcerated lesions, but this is likely a secondary phenomenon.

The histologic differential diagnosis in early lesions or mild cases includes spongiotic processes, such as atopic dermatitis and nummular eczema. As the degree of epidermal edema increases, other entities, such as polymorphous light eruption and herpetic dermatitis, enter the differential diagnosis. Polymorphous light eruption does not ordinarily result in epidermal necrosis, and the inflammatory infiltrate is often deeper and not quite as intense as that seen in hydroa vacciniforme. The marked papillary dermal edema seen in some

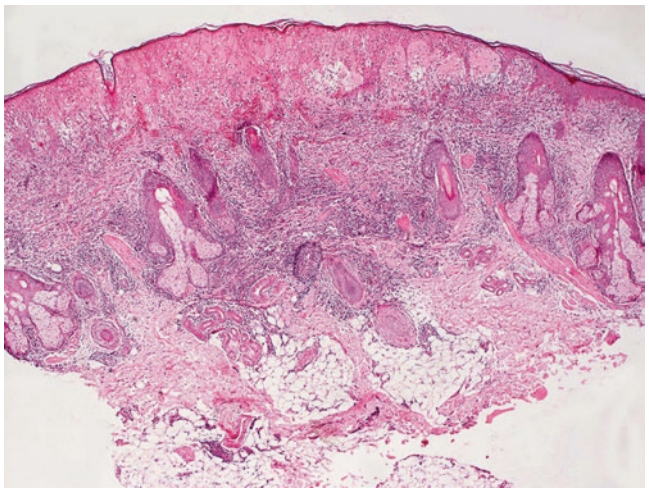

Fig. 3.17 Hydroa vacciniforme demonstrates a subepidermal blister with abundant dermal edema and a brisk inflammatory infiltrate

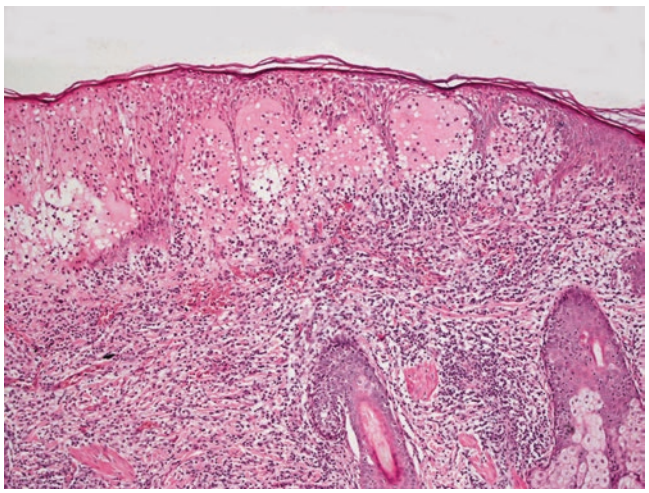

Fig. 3.18 A brisk inflammatory infiltrate in the dermis extends into the overlying epidermis in hydroa vacciniforme. Blister formation is due to spongiosis and can be at any level

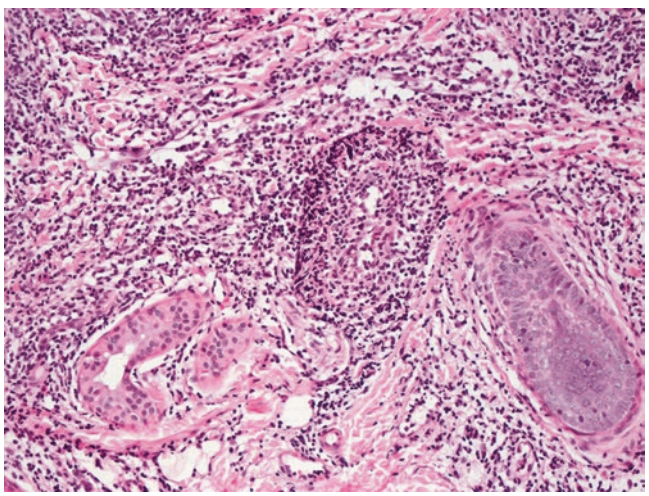

Fig. 3.19 Hydroa vacciniforme is characterized by a brisk superficial and often deep dermal inflammatory infiltrate

cases of polymorphous light eruption might also help with this distinction. Herpetic infection demonstrates the same reticular degeneration that characterizes florid cases of hydroa vacciniforme, but keratinocyte multinucleation, nuclear molding, and viral inclusions seen with herpes infections are not present in hydroa vacciniforme. There have been several reports of cutaneous T cell and natural killer cell lymphomas that have similar clinical findings [52–55]. In these cases, the cytologic features of the inflammatory infiltrate should help to elucidate the true nature of the process.

3.8.3 Pathogenesis

The cause of hydroa vacciniforme is not known. However, ultraviolet A (UVA) appears to have an important role in the disease [56–58]. Lesions characteristic of hydroa vacciniforme can be reproduced with artificial UVA exposure. Infections with Epstein–Barr virus (EBV) may also be causative. Increased levels of EBV DNA have been found in the peripheral blood of patients, and EBV-encoded small nuclear ribonucleic acid (EBER) is present in skin lesions in classic hydroa vacciniforme and hydroa vacciniforme-like cutaneous eruptions [59–61].

3.9 Hailey–Hailey Disease

3.9.1 Clinical Features

Skin manifestations of Hailey–Hailey disease usually begin in the late teens or early twenties [14]. Hailey–Hailey disease is characterized by vesiculobullous lesions, crusted erosions, and vegetative plaques, occurring mainly at the neck, axillae, groin, and perineum (Fig. 3.20). Patients may have significant burning, pruritus, and tenderness in the affected areas. The course of Hailey–Hailey disease is chronic and unremitting. Heat, humidity, friction, and secondary infection tend to exacerbate the disease [62].

3.9.2 Histology

Histologic features of Hailey–Hailey disease show an epidermis with varying degrees of spongiosis and acantholysis. The stratum corneum has normal thickness. The roof of the intraepidermal blister is often fragmented with single keratinocytes separating from other keratinocytes, the so-called "dilapidated brick wall" appearance (Figs. 3.21 and 3.22). Dyskeratotic cells are not abundant. An inflammatory infiltrate that is predominantly lymphohistiocytic with scattered eosinophils is present and may extend into the epidermis [63, 64].

Fig. 3.20 Crusted and eroded vegetative plaques at the axilla and anterior trunk characterize Hailey–Hailey disease (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

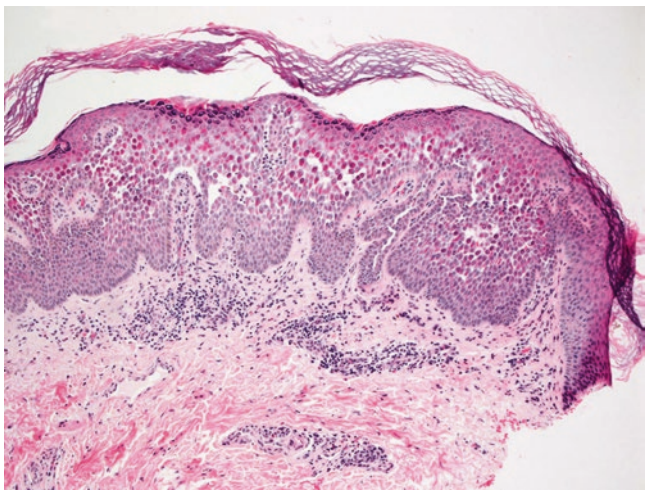

Fig. 3.21 Hailey–Hailey disease shows a mid-epidermal or suprabasilar blistering process within a spongiotic epidermis

The histologic differential diagnosis includes other vesiculobullous disorders, such as Darier's disease and Grover's disease. Darier's disease is easily distinguished based upon the presence of marked hyperkeratosis, acanthosis, corps ronds, and grains. Grover's disease may display an identical histologic appearance but the disorder is usually not seen in the pediatric population. Herpetic dermatitis may also represent a diagnostic dilemma, but the presence of viral changes, as well as the clinical presentation, easily distinguishes these diseases from Hailey–Hailey disease. A florid spongiotic dermatitis might enter into the differential diagnosis. The clinical history may be the best way to make the distinction. While intertrigo may demonstrate spongiosis and share some clinical features, the histologic changes are quite mild in intertrigo when compared with the changes seen in Hailey–Hailey disease.

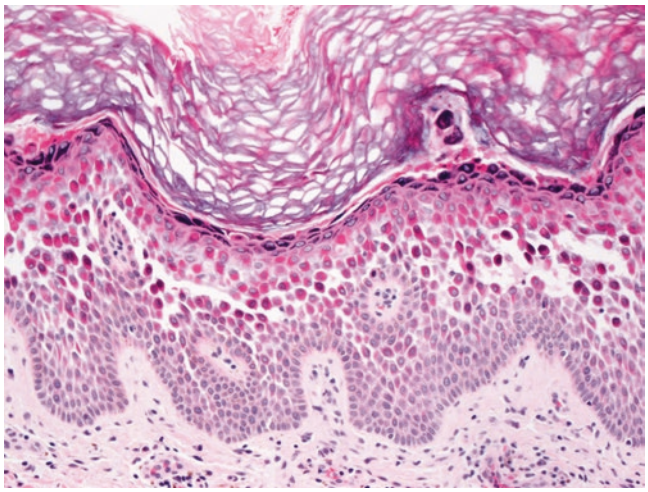

Fig. 3.22 The roof of the blister in Hailey–Hailey disease appears to be disintegrating as individual keratinocytes separate into the blister cavity from above

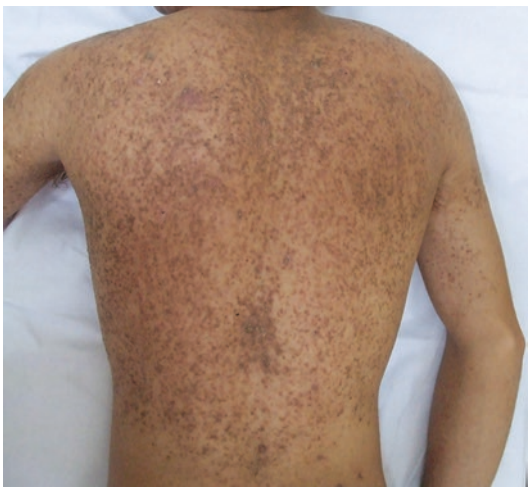

Fig. 3.23 Lesions in Darier's disease are hyperkeratotic, malodorous, hyperpigmented papules coalescing into plaques in a somewhat seborrheic distribution at the trunk (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

3.9.3 Pathogenesis

Hailey–Hailey disease is caused by mutations in the ATP2C1 (ATPase, Ca^{2+} transporting, type 2C, member 1) gene, which encodes the secretory pathway Ca^{2+}/Mn2 ATPase (hSPCA1) [65, 66]. Over 100 different mutations in ATP2C1 have been found in patients with Hailey–Hailey disease, many of which lead to haploinsufficiency in the protein product hSPCA1 [67, 68]. hSPCA1 is a magnesium-dependent enzyme that catalyzes the hydrolysis of ATP coupled with the transport of calcium ions [69]. hSPCA1 functions as a calcium pump that regulates the sequestration of calcium in the Golgi apparatus [70, 71]. Desmosomes and adherens junctions between keratinocytes consist of calcium-binding transmembrane glycoproteins. Perturbations in calcium homeostasis can result in impairment in these junctions, and consequently cause acantholysis of the epidermis. The calcium content of basal keratinocytes in Hailey–Hailey disease is lower than that in normal skin, consistent with perturbations in calcium regulation in the disease [65, 68, 72].

Fig. 3.24 Hyperkeratosis with pitting along pressure points of both soles in Darier disease (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

3.10 Darier Disease

3.10.1 Clinical Features

Classic skin findings of Darier disease typically appear between 8 and 15 years of age [14]. The disease prevalence is estimated at 1 in 50,000 individuals [73]. Males and females are equally affected. Skin lesions are hyperkeratotic papules with waxy scale occur mainly in a "seborrheic" distribution, favoring the scalp, forehead, ears, nasolabial creases, upper chest, and upper back. Papules coalesce into crusted plaques that often become malodorous. Punctate keratoses and pits may occur on the palms and soles (Figs. 3.23 and 3.24). Thin keratoses resembling flat warts appear on the dorsal hands and are known as acrokeratosis verruciformis. Nails tend to be fragile with characteristic V-shaped nicking at the edges and longitudinal alternating

red and white streaks. Darier disease has a chronic and unremitting clinical course. Sun and heat exposure tend to exacerbate the disease.

3.10.2 Histology

Histologic sections show skin with marked hyperkeratosis and focal parakeratosis (Fig. 3.25). The epidermis is acanthotic with elongation of the rete ridges. Dyskeratotic keratinocytes are frequent with corps ronds and grains that are easy to find in most cases (Fig. 3.26). Spongiosis is present focally, but it is not a prominent feature. There is no significant underlying inflammatory response in most cases.

The histologic differential diagnosis includes other acantholytic processes and intraepidermal blistering disorders. Hailey–Hailey disease can be distinguished based upon clinical presentation, as well as histologic differences. Dyskeratosis and hyperkeratosis are not significant features of Hailey–Hailey disease, which is characterized more by extensive spongiosis. Herpetic dermatitis also demonstrates acantholysis, but viral changes such as nuclear molding, multinucleation and nuclear inclusions are also observed in addition to a far more intense inflammatory response in most cases. Pemphigus vulgaris, another acantholytic process, is uncommon in children and does not ordinarily feature prominent dyskeratosis or hyperkeratosis. (The pemphigus vegetans variant may be hyperkeratotic, but has acantholysis without dyskeratosis.) A warty dyskeratoma may demonstrate identical features to Darier disease, although its architecture is that of a cup-shaped lesion. These are extremely uncommon in children. Similarly, dyskeratotic acanthoma and some variants of Grover's disease (transient acantholytic dermatosis) may appear identical to Darier disease microscopically, but they do not enter into the differential diagnosis in the pediatric population.

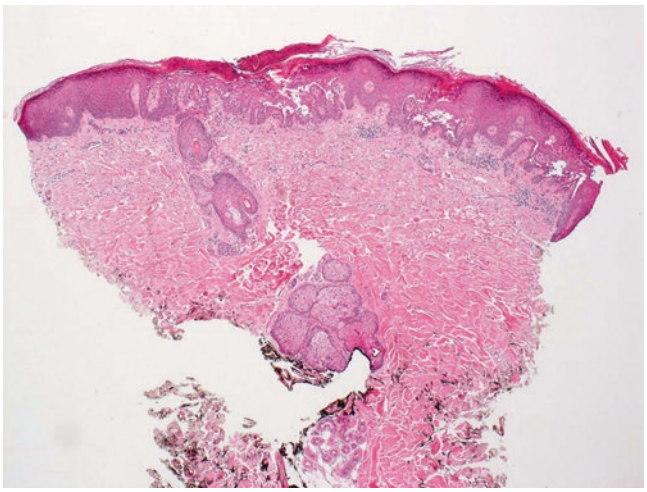

Fig. 3.25 Hyperkeratosis and hypergranulosis are present in Darier disease. Foci of intra-epidermal acantholysis are present resulting in suprabasilar blister formation

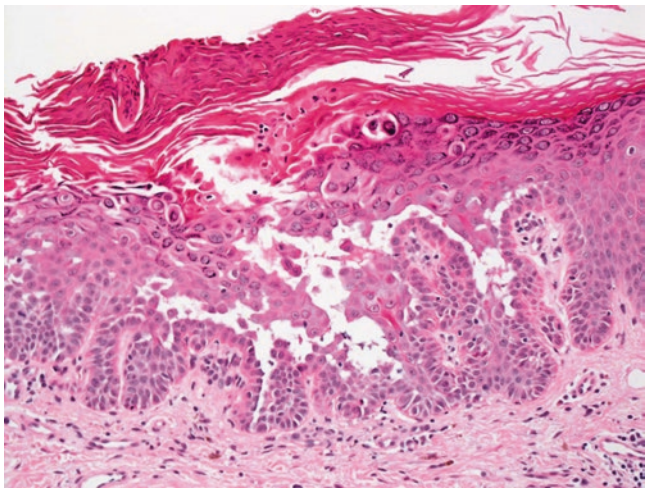

Fig. 3.26 Abundant corps ronds and grains are present in the setting of a suprabasilar acantholytic blister in Darier disease

3.10.3 Pathogenesis

Darier disease is an autosomal dominant disease with high penetrance (95 %) [74, 75]. The gene implicated in Darier disease is ATP2A2 (ATPase, calcium-transporting, cardiac muscle, slow twitch 2), which encodes SERCA-2 protein [76, 77]. SERCA-2 is a calcium ATPase that transports calcium from the cytosol back to the endoplasmic reticulum (ER) lumen, and facilitates the sequestration of cytosolic calcium in the ER [78–80]. Abnormalities in SERCA-2 can deplete calcium stores in the ER in keratinocytes and disrupt the assembly of the desmosomal complex. In fact, electron microscopic studies have shown loss of desmosomes, breakdown of desmosome–keratin intermediate filament attachment, and perinuclear aggregates of keratin intermediate filaments in Darier disease [81, 82]. Thus, SERCA-2 is important for proper cell-to-cell adhesion. Depletion of calcium ER stores in the cell can have other negative consequences. It can impair posttranslational modifications of newly synthesized proteins and trigger the ER stress response [80, 83]. In fact, the trafficking of desmoplakin, which is a protein component of desmosomes, is defective in Darier keratinocytes [84]. Activation of apoptosis in keratinocytes in Darier disease is another consequence of perturbations in calcium regulation [85].

In Darier disease, there are over 130 mutations that disrupt critical functional domains of SERCA-2 with mutations rendering SERCA2 haploinsufficiency in which mutations in one allele are sufficient to cause the disease phenotype [76, 86, 87]. These mutations lead to a reduction in the expression and activity of SERCA-2 by enhancing proteasome-mediated degradation [88]. There is decreased expression of SERCA2 in the epidermis in Darier disease skin as compared with normal skin [89]. Mosaicism in ATP2A2 mutations can result in segmental Darier disease [90].

3.11 Epidermolysis Bullosa Simplex

3.11.1 Clinical Features

The prevalence of epidermolysis bullosa simplex is estimated at 4.6 per million, and the incidence is approximately 10.8 per million [91]. All forms of epidermolysis bullosa are caused by mutations in a variety of structural genes in the skin, resulting in increased fragility of the skin and blister formation. Most forms of epidermolysis bullosa simplex are inherited in an autosomal dominant manner.

Localized epidermolysis bullosa simplex (the most common variant) typically presents in childhood or adolescence with trauma-induced blisters, primarily located on acral surfaces. As blistering occurs within the epidermis, lesions typically heal rapidly without residual scarring. Nails and mucous membranes are generally not affected. The more severe forms of epidermolysis bullosa simplex, generalized and Dowling–Meara forms, typically present with blistering at birth. They are also unlikely to cause scarring, although patients are more likely to have nail dystrophy and oral involvement. Overall, patients with epidermolysis bullosa simplex have a relatively good prognosis. Many patients show improvement over time. Patients with the less common subtypes of epidermolysis bullosa simplex tend to have more complications and a poorer prognosis.

3.11.2 Histology

The blistering in epidermolysis bullosa simplex occurs within basal keratinocytes. This separation is within the cytoplasm, beneath the nuclei. Thus, the histologic appearance is that of a blister that is above the basement membrane zone, located within the basal layer of the epidermis (Fig. 3.27). In many cases, however, it is difficult to detect the small residual fragments of basal keratinocytes that remain attached to the floor of the blister, giving rise to the appearance of a subepidermal blistering process. The small fragments of basal keratinocytes tend to retract and lie flat along the basement membrane and may not be easily detected on H&E stains [92]. Ultrastructural analysis will easily resolve

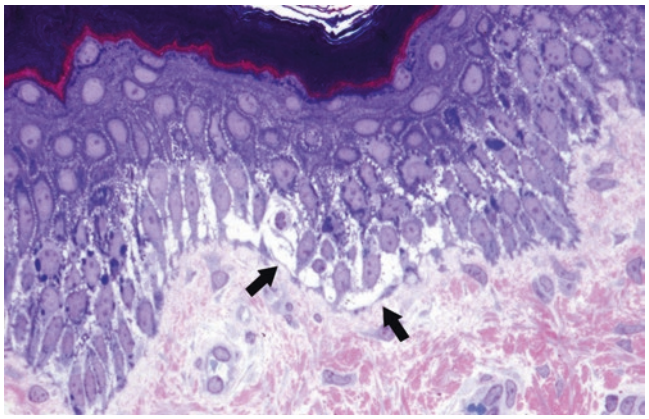

Fig. 3.27 Epidermolysis bullosa simplex has an intraepidermal split within the lower half of basal keratinocytes (photo courtesy of Dr. John Hicks, Texas Children's Hospital, Houston, TX)

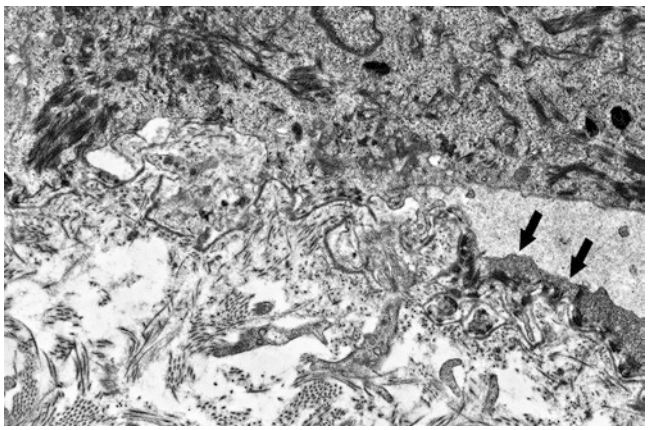

Fig. 3.28 A blister is seen above the basement membrane zone with arrows indicating keratinocyte cytoplasm at the base of the blister cavity in epidermolysis bullosa simplex (photo courtesy of Dr. John Hicks, Texas Children's Hospital, Houston, TX)

the level of the blistering (Fig. 3.28) [93]. Since this is a mechanically induced blistering disorder, an inflammatory infiltrate is not ordinarily part of the process, except as a secondary phenomenon that is seen in older lesions. Histologic scarring is not seen in epidermolysis bullosa simplex.

The histologic differential diagnosis includes all cell-poor, non-inflammatory subepidermal blistering disorders, despite the fact that the blister is not actually subepidermal in epidermolysis bullosa simplex. Entities such as porphyria can be differentiated based upon the PAS positive, thick-walled blood vessels in the papillary dermis.

3.11.3 Pathogenesis

There are three major subtypes of epidermolysis bullosa simplex—the severe (Dowling–Meara) type, the moderate and generalized (Koebner) type, and the mild localized (Weber–Cockayne) type [94, 95]. Epidermolysis bullosa simplex is

caused by mutations in keratin 5 and keratin 14, resulting in abnormal keratin network in the epidermis and blister formation within the cytoplasm of basal epidermal keratinocytes [96–101]. The position of mutations in keratin 5 and keratin 14 genes correlate closely with the resulting phenotype. For example, the severe (Dowling–Meara) type is often caused by mutations in the initiation or termination peptides of the rod domain of keratin [100, 102]. The mild localized (Weber–Cockayne) type is caused by mutations in other parts of the rod domain or in the linker region of keratin. There are other rare forms of epidermolysis bullosa simplex that are recessively inherited, namely epidermolysis bullosa simplex with muscular dystrophy and pyloric atresia that are caused by mutations in the plectin gene [103–106].

3.12 Epidermolysis Bullosa, Junctional Type

3.12.1 Clinical Features

Junctional epidermolysis bullosa presents in infancy. Blistering is nearly always present at birth. Children typically have generalized blistering and large erosions (Fig. 3.29). Nail dystrophy and nail loss are common. Exuberant perioral granulation tissue is common in the Herlitz subtype. The mucous membranes are frequently affected. The teeth tend to have hypoplastic enamel and are prone to decay. Blisters tend to heal with atrophic scarring. Malnutrition and growth failure may occur.

The Herlitz form is associated with high mortality in the first 2 years of life (Fig. 3.30). Death occurs in 40 % of the cases by 1 year of age, and 50 % by 2 years of age [91]. Common causes of death are failure to thrive, sepsis, and respiratory failure. Patients with the non-Herlitz subtype are more likely to survive into adulthood.

Fig. 3.29 An erosion involving the nasal ala and upper cutaneous lip with distinctive periorifical granulation tissue is seen in a boy with junctional epidermolysis bullosa. Irregular tooth enamel is seen as well

3.12.2 Histology

Histologic changes of junctional epidermolysis bullosa are those of a non-inflammatory subepidermal blister (Fig. 3.31). The epidermis is unremarkable and there is a clean separation from the dermis beneath the basal keratinocytes. Within the underlying dermis, the only inflammatory response is a secondary one in long-standing lesions. There is no keratinocyte necrosis except in older lesions [92]. The absence of necrosis and inflammation helps to distinguish epidermolysis bullosa of the junctional and dystrophic types from other types of subepidermal blistering disorders.

Fig. 3.30 Multiple tense bullae and large erosions in an infant with LAMB-3-associated junctional epidermolysis bullosa (Herlitz variant)

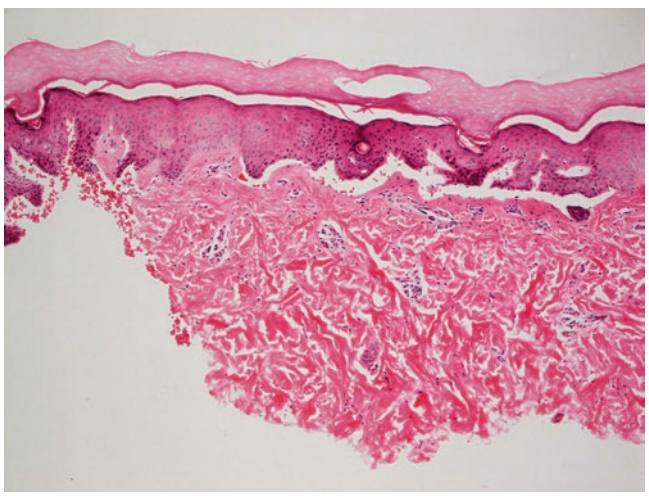

Fig. 3.31 Junctional epidermolysis bullosa is histologically identical to the dystrophic variant, demonstrating a non-inflammatory subepidermal blister

The histologic differential diagnosis includes other non-inflammatory subepidermal blistering processes. The dystrophic variant of epidermolysis bullosa can be distinguished from the junctional variant with the use of immunomapping and ultrastructural studies as well as on their different clinical presentations. The presence of underlying dermal scarring is more apparent in the dystrophic variant than in junctional types of epidermolysis bullosa.

3.12.3 Pathogenesis

Junctional epidermolysis bullosa (JEB) is divided into two main types—the lethal Herlitz type with extreme fragility of the skin and mucous membranes, usually leading to death early in life, and the milder non-Herlitz type [95, 107]. JEB-Herlitz type is caused by loss-of-function mutations in LAMA3, LAMB3, and LAMC2, which are protein components of laminin 332, resulting in the complete loss of laminin 332 [108–111]. Laminin 332 is a major extracellular matrix component in the basement membrane. The absence of laminin 332 causes tissue separation along the lamina lucida of the epidermal basement membrane, so that the intact epidermis separates into the roof of the blister and the basement membrane is on the floor of the blister [112]. The presence of any of the three laminin 332 chains (LAMA3, LAMB3 and LAMC2) can be detected by immunofluorescence stains. Absence of signals for these chains indicates JEB-Herlitz type [108]. LAMB3 is the main gene affected in about 80 % of the cases of JEB-Herlitz, and it is usually the first gene to be screened [113]. The most frequent mutation in LAMB3 is R635X, a mutational hot spot, which accounts for over 60 % of all mutated LAMB3 alleles in JEB-Herlitz [111].

JEB-non Herlitz type is caused by mutations in LAMA3, LAMB3 and LAMC2 that result in reduced amounts of functional laminin 332, but not complete loss of laminin 332 as seen in JEB-Herlitz type [109, 114, 115]. JEB-non Herlitz can also be caused by mutations in COL17A1 gene, which encodes collagen XVII, a binding ligand of laminin 332 [116]. Collagen XVII can be detected by immunofluorescence stains, and absence of collagen XVII signal indicates JEB-non Herlitz type. There are also rare cases of JEB with pyloric atresia that is caused by loss of integrin α6 or β4 subunits, which are the main receptor for laminin 332 [117, 118].

3.13 Epidermolysis Bullosa Dystrophica

3.13.1 Clinical Features

Dystrophic epidermolysis bullosa is divided into two major subtypes, recessive dystrophic epidermolysis (RDEB) and dominant dystrophic epidermolysis bullosa (DDEB). RDEB has a prevalence of 0.9 per million, and an incidence of 2 per million [91].

In general, patients with DDEB have a relatively mild phenotype due to partial reduction in the expression of collagen VII as compared to the more severe RDEB where patients have a complete absence of collagen VII. Blistering is limited to areas of pressure and friction, such as the hands, feet, elbows, and knees. Nail dystrophy is common, especially the great toenails. Patients with DDEB tend to have a relatively good prognosis, showing improvement in blistering after early childhood.

RDEB is the most severe form of epidermolysis bullosa. Patients tend to have a progressive course with poor quality of life and shortened life span. RDEB patients typically have widespread blistering at birth (Fig. 3.32). Severe mucosal involvement affecting the eyes, the gastrointestinal tract, and the genitourinary tract is common. Wounds are deeper and tend to heal with scarring. Over time, this leads to syndactyly of the fingers and toes. Patients are also susceptible to development of aggressive squamous cell carcinoma, which is the most common cause of early death [91].

3.13.2 Histology

The histologic changes in dystrophic epidermolysis bullosa are largely indistinguishable from those seen in the junctional variant. A non-inflammatory subepidermal blister is

Fig. 3.32 Wide spread erosions and hyperplastic granulation tissue may represent malignancy in later stages of recessive dystrophic epidermolysis bullosa

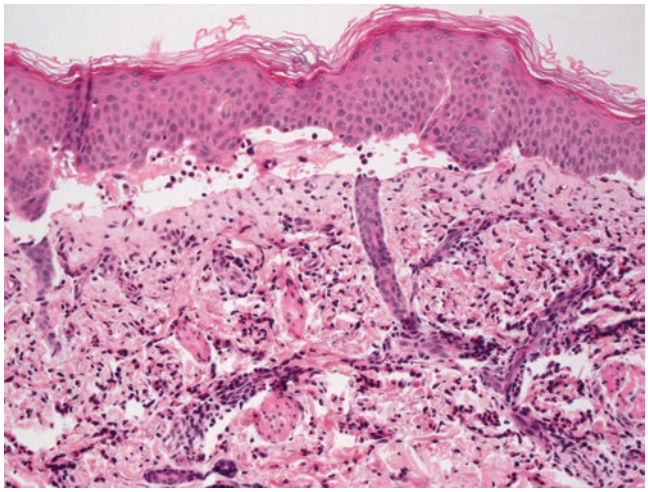

Fig. 3.33 Recessive dystrophic epidermolysis bullosa demonstrates a subepidermal blister with some lymphocytic inflammation

present with no other alterations in the epidermis [92]. In contrast to the junctional form of epidermolysis bullosa, prominent dermal scarring may be present, especially if the biopsy is taken from an area of repeated blistering. In these cases, there may be a slight inflammatory response within the dermis secondary to repeated ulceration and healing; however, the inflammation is reactive and not part of the primary disease process (Fig. 3.33). Ultrastructural studies demonstrate the presence of blister formation deep to the lamina densa due to reduction (dominant forms) or absence (recessive forms) of anchoring fibrils comprised of type VII collagen [119–122].

3.13.3 Pathogenesis

Dystrophic epidermolysis bullosa is caused by mutations in COL7A1 gene, which encodes collagen VII [123]. To date, several hundred mutations in COL7A1 have identified in both recessive and dominant forms of the disease [124, 125]. Mutational analysis of COL7A1 gene can be performed by PCR amplification of all 118 exons and exon–intron boundaries as well as by direct DNA sequencing [126]. The blisters in dystrophic epidermolysis bullosa are caused by structural and functional abnormalities in the anchoring fibrils that serve to anchor the epidermal basement membrane to the dermis. Type VII collagen is a major component of anchoring fibrils [112]. Reduction or absence of collagen VII results in the loss of anchoring fibrils and blister formation.

Dystrophic epidermolysis bullosa has the three common variants—generalized, generalized intermediate, and generalized severe [127–129]. The severity of the disease is dependent on the extent of loss of collagen VII. Generalized variant is the mildest form, and is caused by reduced type VII collagen expression. Generalized severe variant is the most severe form, and is caused by complete loss of collagen VII production. Collagen VII is not produced in this variant due to a premature stop codon and truncation of newly synthesized collagen VII protein, which is subsequently degraded in the cell [127]. Generalized intermediate variant has some residual collagen VII present.

3.14 Kindler Syndrome

3.14.1 Clinical Features

Kindler syndrome is a rare subtype of hereditary blistering epidermolysis bullosa. It is an autosomal recessive condition. Patients present with increased skin fragility from birth, and are prone to blistering with minor trauma. They also have skin atrophy, poikiloderma, photosensitivity, and hyperkeratosis of the palms and soles (Fig. 3.34). Mucosal involvement is common, and patients are susceptible to corneal erosions with conjunctival scarring, severe gingivitis and periodontal disease, esophageal stenosis, colitis, vaginal stenosis, urethral stenosis and strictures, as well as phimosis [130]. Disease management is focused on close surveillance, treatment of complications, and supportive care.

3.14.2 Histology

Histologic examination reveals a non-inflammatory blister that can occur at multiple cleavage planes. Most cases demonstrate intraepidermal blisters. Some of these are relatively high in the epidermis, while others are suprabasilar. In some

Fig. 3.34 Poikiloderma is seen on the dorsum of the hand of a child with Kindler syndrome

cases, non-inflammatory subepidermal blisters have been described. In most cases, the cleavage plane is close to the dermal-epidermal junction [131, 132].

Electron microscopy reveals the presence of anchoring filaments, differentiating Kindler syndrome from some subtypes of epidermolysis bullosa, which is the entities it most closely resembles [133]. Abundant apoptotic basal keratinocytes are seen in some patients with Kindler syndrome [134]. It has been suggested that Kindler syndrome may be closely related to or even identical to hereditary sclerosing poikiloderma [135] or a variant of epidermolysis bullosa [91].

3.14.3 Pathogenesis

Kindler syndrome has an autosomal recessive pattern of inheritance. It is caused by mutations in FERMT1 (fermitin family member 1) gene, which encodes for kindlin-1 [136, 137]. FERMT1 mutations have been identified in the majority of patients with Kindler syndrome [138, 139]. Over 70 pathologic variants in FERMT1 have been reported, most of which are nonsense mutations that often lead to reduced expression and loss of function of kindlin-1 [140–143].

Kindlin-1 is expressed mainly in basal keratinocytes in the skin [141, 142]. Kindlin1 is important in cell–cell adhesion with essential roles in integrin binding and activation. It is a key component of focal adhesions in basal epidermal keratinocytes [139, 141, 142, 144]. Loss of kindlin-1 impairs the attachment of the cell actin cytoskeleton to focal adhesion junctions at the dermal–epidermal junction, leading to blister formation.

3.15 Epidermolysis Bullosa Acquisita

3.15.1 Clinical Features

Epidermolysis bullosa acquisita (EBA) is much more common in adults than children. Only about 40 cases of EBA have been reported in children [14]. EBA is divided into inflammatory and non-inflammatory (mechanobullous) subtypes. While the inflammatory type is characterized by generalized blistering, the non-inflammatory type features more acral blistering at sites of pressure/trauma. Erosions of the oropharyngeal membranes, nail dystrophy, and scarring alopecia can occur. EBA tends to have a chronic course with intermittent flares, although children appear to have an overall better prognosis than adults [14].

3.15.2 Histology

While unusual in children, this autoimmune blistering disease is occasionally encountered, and demonstrates similar findings to those described in the adult population [145–148]. In most cases, there is a non-inflammatory, cell-poor subepidermal blister [149] (Figs. 3.35 and 3.36). Less commonly, a neutrophil-rich dermal inflammatory infiltrate occurs. Dermal scarring is seen in cases in which the biopsies are taken from areas of repeated blistering and ulceration. Direct immunofluorescence examination demonstrates

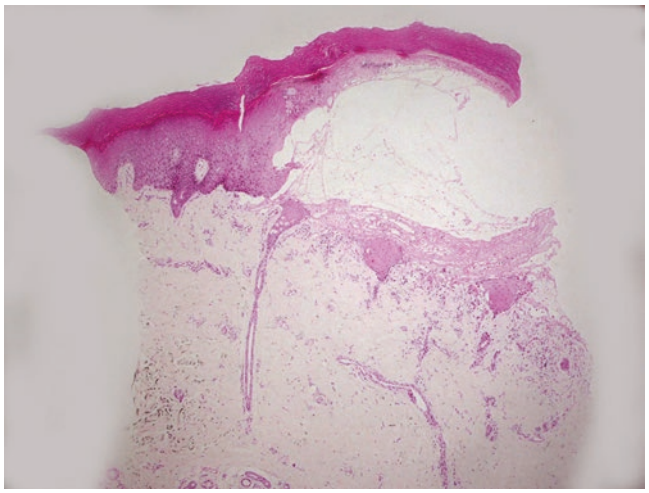

Fig. 3.35 A subepidermal blister with little to no dermal inflammation is characteristic of epidermolysis bullosa acquisita

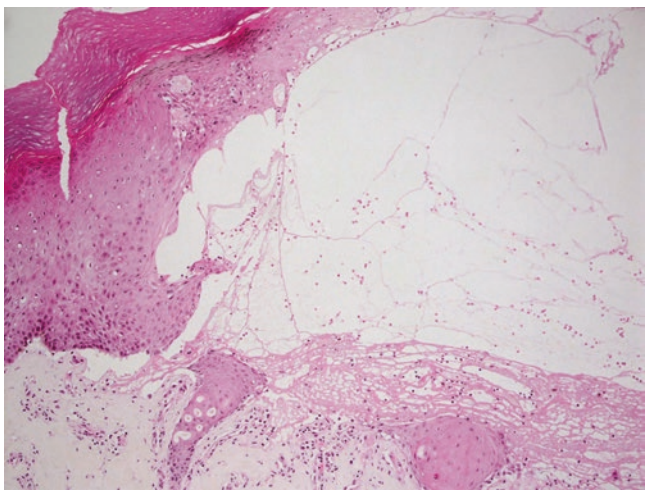

Fig. 3.36 Epidermolysis bullosa acquisita shows a subepidermal blister with no epidermal necrosis and a mild dermal inflammatory infiltrate

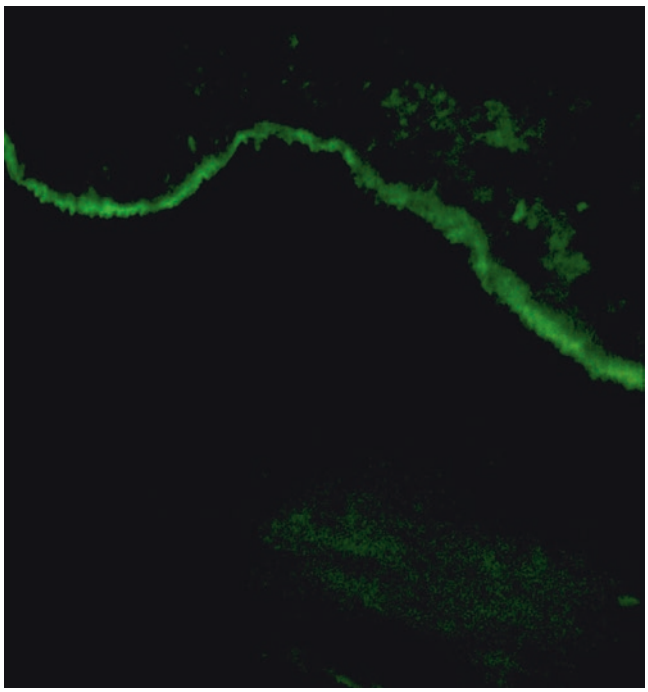

Fig. 3.37 Linear staining along the dermal-epidermal junction with anti-IgG antibodies is seen in epidermolysis bullosa acquisita

linear staining along the dermal epidermal junction with antibodies directed against IgG and C3 (Fig. 3.37).

The histologic differential diagnosis of EBA includes other subepidermal blistering disorders, especially those that may result in underlying scar formation. The dystrophic type of epidermolysis bullosa may present a diagnostic challenge based purely upon histologic changes; however, in most cases, clinical course can make this distinction [146]. Immunofluorescence studies, including those performed on salt-split skin, can easily separate the acquired form from the inherited forms of epidermolysis bullosa, since they are not autoimmune-induced processes. Another subepidermal blistering process that enters into the differential diagnosis is cicatricial pemphigoid. While also unusual, this disorder can occur in children and also demonstrates dermal scarring underlying a subepidermal blister. In most cases, a neutrophilic or mixed inflammatory infiltrate is present within the blister cavity and in the underlying dermis, but this can be relatively scant, resulting in histologic similarity to EBA. Immunofluorescence studies may be helpful in resolving this diagnostic dilemma [150]. Bullous dermatosis of childhood may also enter into the differential diagnosis based upon the presence of subepidermal blisters. In most cases, the clinical history and the presence of a dense neutrophilic infiltrate will help to distinguish these entities [151].

3.15.3 Pathogenesis

EBA is characterized by subepidermal blisters caused by circulating auto-antibodies to collagen VII [152, 153]. Collagen VII is encoded by COL7A1 gene [154]. It is a major component of anchoring fibrils that link the lamina densa in the basement membrane to the dermis. The major antigenic epitopes in collagen VII are located within the non-collagenous-1 (NC1) domain [155–157]. It has been shown that titers of anti-collagen VII auto-antibodies correlate with disease activity [158].

EBA has two major clinical subtypes: non-inflammatory (mechanobullous) and inflammatory subtypes [159]. Blisters in the mechanobullous subtype form where the adhesive function of the basement membrane is impaired. Blisters in the inflammatory subtype are due to complement activation and neutrophil recruitment that result in damages to the basement membrane. IgG auto-antibodies can activate complements and induce dermal–epidermal separation [160–162]. EBA is associated with class II major histocompatibility complex, particularly with human leukocyte antigen (HLA)-DR2 as well as with HLA-DRB1*15:03 in people of African descent and DRB1*13 in Koreans [163–165].

3.16 Dermatitis Herpetiformis

3.16.1 Clinical Features

Dermatitis herpetiformis is rare in children, and typically presents between early adulthood and the fifth decade of life. In children, it most often presents between the second and seventh year of life. It is more common in individuals of Northern European descent and rarer in African American population. In adults, it is more common in males than females [166].

Characteristic lesions are small, tense vesicles, often grouped together and tend to favor the extensor surfaces, particularly the elbows, knees, sacrum, buttocks, and shoulders. Vesicles tend to rupture easily, leaving crusted papules and erosions. Patients often complain of intense pruritus and a burning sensation in the skin [14]. Dermatitis herpetiformis tends to follow a relapsing and remitting chronic course. However, strict adherence to a gluten-free diet typically results in complete remission. Most children will remit in about a year on a gluten-free diet.

3.16.2 Histology

Histologic sections of dermatitis herpetiformis demonstrate skin with an intact epidermis overlying small subepidermal splits (Fig. 3.38). Within the papillary dermal tips, clusters of neutrophils form microabscesses. These microabscesses are

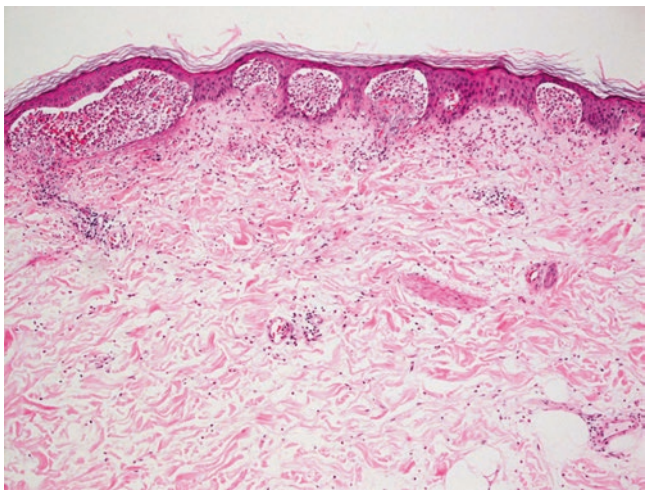

Fig. 3.38 Multiple small subepidermal blisters that contain many neutrophils in the blister space characterize dermatitis herpetiformis

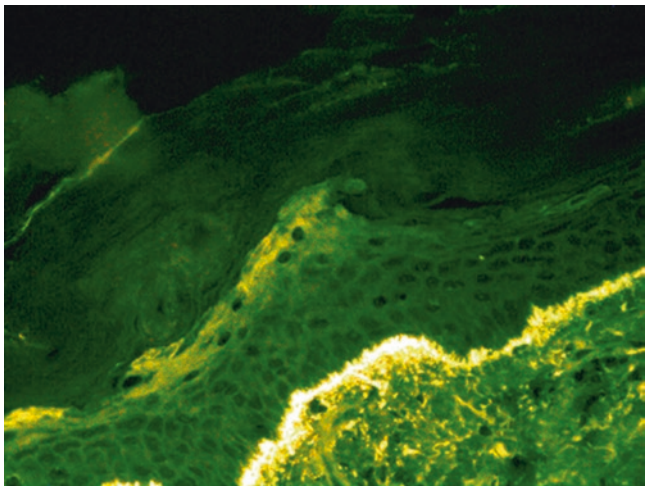

Fig. 3.40 Granular staining with anti-IgA antibodies in papillary dermal tips is seen in dermatitis herpetiformis

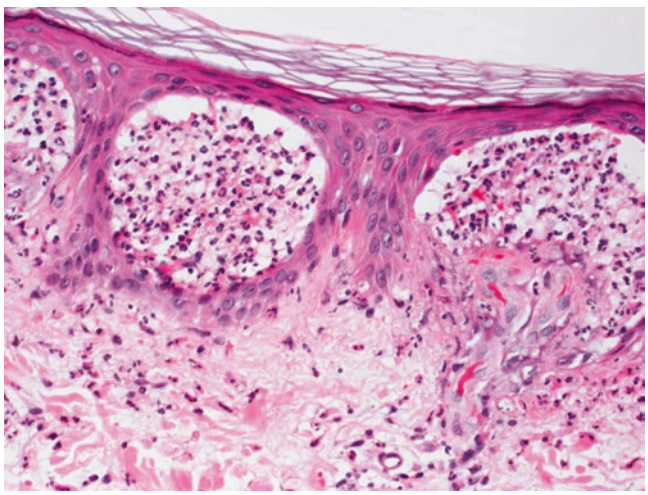

Fig. 3.39 Clusters of neutrophils are seen in the papillary dermal spaces in dermatitis herpetiformis. The overlying epidermis has small separations

quite small and commonly involving only one or two papillary dermal tips (Fig. 3.39). Scattered eosinophils may be present. There is a lymphocytic infiltrate around vessels of the superficial vascular plexus, but the infiltrate does not extend into the reticular dermis [167]. It is important that the neutrophilic abscesses be detected in areas away from any superficial excoriations in order to prevent over diagnosis. Excoriations are very frequently seen in biopsies of this entity and a dense, mixed inflammatory infiltrate is expected beneath such disruptions of the epidermis. The diagnosis of dermatitis herpetiformis is often confirmed with a direct immunofluorescence examination of peri-lesional skin that demonstrates granular IgA staining within papillary dermal tips (Fig. 3.40).

The histologic differential diagnosis of dermatitis herpetiformis includes other neutrophil-rich subepidermal blistering disorders, such as bullous dermatosis of childhood, bullous lupus erythematosus, and less commonly, cicatricial pemphigoid [168, 169]. In bullous dermatosis of childhood, the subepidermal blisters are much larger, extending over many rete ridges and there is an extensive neutrophilic infiltrate. Clinical presentation also helps with this distinction. Similarly, the blister cavities in bullous lupus erythematosus are larger than those in dermatitis herpetiformis, and most commonly, other histologic changes of lupus erythematosus such as a superficial and deep perivascular and periappendageal lymphocytic infiltrate are also present. Cicatricial pemphigoid demonstrates dermal scar formation in many cases, and often involves mucosal surfaces, which are features not associated with dermatitis herpetiformis.

3.16.3 Pathogenesis

The pathogenesis of dermatitis herpetiformis is multifactorial with contributing genetic, environmental and autoimmune factors. Many patients with the disorder have HLA DR3, HLA DQ2, or HLA DQ8 haplotypes [170, 171]. Myosin IXB (MYO9B) gene polymorphism has been associated with dermatitis herpetiformis [172–174]. Myosin IXB is involved in cell signaling and the regulation of actin cytoskeleton dynamics, which are important in cell integrity and permeability of the gut barrier. In patients with dermatitis herpetiformis and myosin IXB mutations, there may be increased permeability of the intestinal mucosa to gluten and subsequent immunologic events leading to the disease phenotype [173].

Dermatitis herpetiformis can be triggered by dietary factors, particularly gluten, which is a glycosylated storage protein in cereals such as wheat, barley, and rye [175]. Alpha-gliadin in gluten can trigger a mucosal immune response and gastrointestinal alterations in celiac disease associated with dermatitis herpetiformis [176–178]. A strict gluten-free diet can resolve the skin and intestinal manifestations of dermatitis herpetiformis and celiac disease [179, 180]. Anti-tissue transglutaminase (tTG) IgA antibodies are a diagnostic marker for enteropathy in patients [181–183]. The levels of anti-tTG IgA antibodies correlate with the extent of intestinal damage and decrease with a gluten-free diet [183]. Patients with dermatitis herpetiformis also have high serum levels of IL-8, which is important in neutrophil inflammatory responses seen in the disease [184].

3.17 Chronic Bullous Dermatosis of Childhood

3.17.1 Clinical Features

The onset of chronic bullous dermatosis of childhood is typically in the first decade of life, with a mean age at presentation of 4.5 years old [185]. The characteristic lesions are large, tense, clear or hemorrhagic bullae, often in an annular arrangement that has been described as a "rosette," a "string of pearls," or a "cluster of jewels" (Figs. 3.41 and 3.42). These appear on the face, trunk, and extremities, but tend to favor the lower trunk, genitalia, and medial thighs. Lesions tend to heal with dyspigmentation, but no permanent scarring. The mucous membranes may or may not be affected. Patients may complain of pruritus or burning of the skin. The disease typically remits with a few months to a few years after onset, but it can sometimes persist beyond puberty [14].

Fig. 3.41 Large tense bullae in an annular arrangement, described as a "string of pearls," are characteristic of childhood bullous dermatosis

Fig. 3.42 Tense, clear and hemorrhagic bullae on the legs of an infant with childhood bullous dermatosis

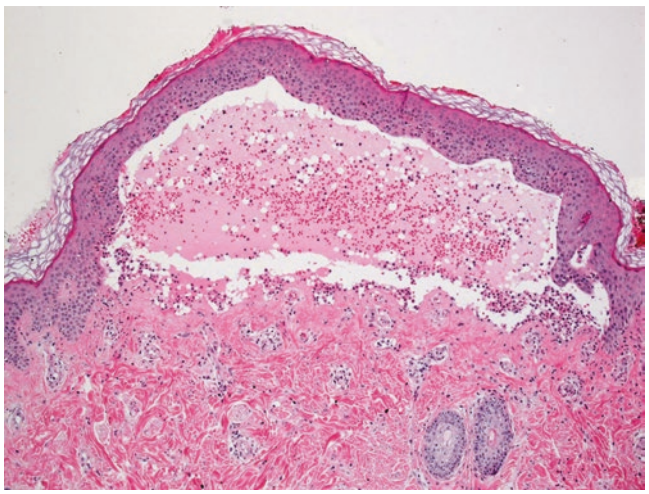

Fig. 3.43 Chronic bullous dermatosis of childhood demonstrates a subepidermal blister with a dense neutrophilic infiltrate within the blister cavity. Epidermal necrosis is not seen

3.17.2 Histology

Histologic sections of chronic bullous dermatosis of childhood demonstrate skin with an intact epidermis overlying a subepidermal blister (Fig. 3.43). The blister cavity is relatively large and contains an abundance of neutrophils and scattered eosinophils (Fig. 3.44). The papillary dermis contains many neutrophils, and there is a mixed infiltrate of neutrophils, occasional eosinophils and lymphocytes surrounding the superficial blood vessels. A deep inflammatory infiltrate is not a characteristic finding [169, 186, 187]. Similar changes can be seen in biopsies from oral mucosa, usually with severe disease [188, 189]. In cases where histology does not provide an unequivocal diagnosis, direct immunofluorescence studies are diagnostic showing linear IgA along the dermal-epidermal junction (Fig. 3.45).

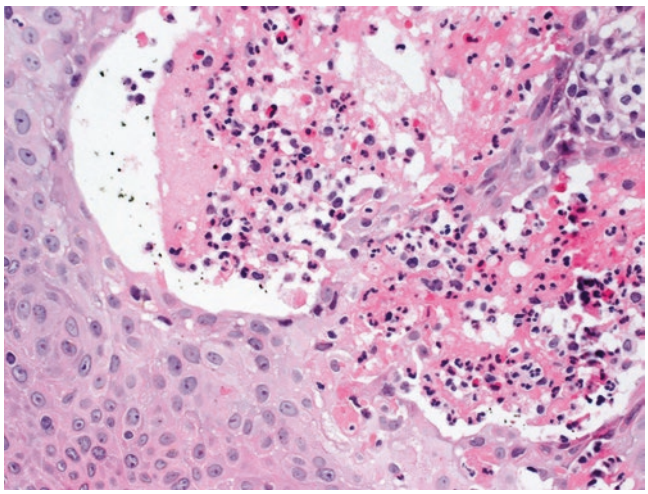

Fig. 3.44 Scattered eosinophils are present admixed with many neutrophils in the blister cavity in chronic bullous dermatosis of childhood

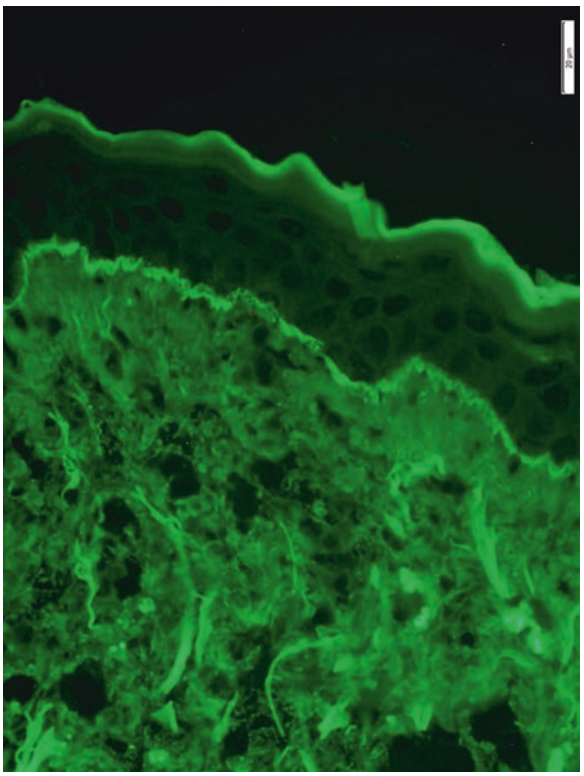

Fig. 3.45 Linear staining along the dermal-epidermal junction with anti-IgA antibodies is seen in chronic bullous dermatosis of childhood

The differential diagnosis includes bullous pemphigoid, cicatricial pemphigoid, dermatitis herpetiformis, and epidermolysis bullosa acquisita. Bullous pemphigoid is rare in children, but can occur. It is characterized by a predominantly eosinophilic infiltrate within the subepidermal blister cavities and linear deposits of IgG and C3 along the dermal-epidermal junction [190]. Cicatricial pemphigoid also has a subepidermal blistering process and in most cases, neutrophils are the main cell type within the inflammatory infiltrate. Scarring is invariably present, while it is only present in severe cases of chronic bullous dermatosis of childhood. Immunofluorescence studies most commonly demonstrate IgG and C3 along the dermal-epidermal junction; however, linear IgA deposition has been described in some cases and when present, makes the distinction from chronic bullous dermatosis of childhood quite difficult. Small, subepidermal blisters with neutrophilic microabscesses characterize dermatitis herpetiformis. In most cases, the size of the blisters can easily separate the two entities, as can the clinical presentation. When there is still some dilemma, immunofluorescence examination shows granular deposition of IgA along the dermal-epidermal junction in dermatitis herpetiformis, which is in contrast to the linear deposition seen in chronic bullous dermatosis of childhood.

It has been postulated by some that linear IgA disease in adults and cicatricial pemphigoid are identical diseases to chronic bullous dermatosis of childhood [191, 192]. However, this view is not shared and most authors believe them to be distinct entities.

3.17.3 Pathogenesis

Chronic bullous dermatosis of childhood is a nonhereditary and autoimmune bullous disease that often occurs in prepubertal children. Genetic analysis indicates that HLA-B8, DR3, DQ2, and Cw7 may confer susceptibility to early disease onset [193].

Chronic bullous dermatosis of childhood is caused by IgA auto-antibodies to the antigens LABD97 (97 kDa) and LAD-1 (120 kDa linear IgA-disease antigen), which are fragments of the extracellular domain of BP180 [194–196]. The full length BP180 is also a target of IgA antibodies but less efficiently than the 97-kDa and 120-kDa protein fragments. BP180 localizes in the lamina lucida of the basement membrane of the epidermis. It is a transmembrane protein that serves to maintain the linkage between intracellular and the extracellular structural elements in epidermal adhesion [195]. There is a small subset of patients with auto-antibodies directed against collagen VII antigens in both the lamina lucida and lamina densa [197]. Immunoelectron microscopy has shown antibody labeling of multiple components of the basement membrane, including the hemidesmosomes, lamina lucida, lamina densa, and sublamina densa. Thus, there are heterogeneous auto-antibodies targeting different antigens localized in various components of the basement membrane in chronic bullous dermatosis of childhood [185].

Besides the humoral antibody-mediated immune response, a cellular immune response is also present in chronic bullous dermatosis of childhood with complement activation and recruitment of inflammatory cells [198, 199]. Bullae formation in this disease results from plasmin production and the

release of matrix metalloproteinase-9 and neutrophil elastase. Plasmin is able to cleave BP180 to generate antigenic peptides [200, 201]. The action of metalloproteinase-9 leads to chemoattraction of neutrophils and the release of neutrophil elastase to cause epidermal detachment.

Linear IgA dermatosis in children does not appear to be associated with precipitating factors, such as hematologic malignancies, bladder cancer, ulcerative colitis, and systemic lupus erythematosus, which are associated with linear IgA dermatosis in adults [185, 202]. Drugs can also induce chronic bullous dermatosis of childhood. Such drugs include amoxicillin with clavulanic acid, vancomycin, and nonsteroidal inflammatory agents [191, 192, 203]. These drugs can serve as haptens to elicit an autoimmune response. Infections, such as Epstein–Barr virus infection, have also been associated with this disorder [204].

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Interface Dermatoses

4

4.1 Lichen Planus

4.1.1 Clinical Features

Lichen planus most commonly occurs in individuals between 30 and 60 years old with children only accounting for 1–4 % of all cases [1]. Familial disease accounts for anywhere between 1 % and 50 % of cases, and may be seen more frequently in children [1]. Patients with a positive family history tend to present with disease at a younger age (median age at diagnosis of 26 years in familial disease versus 46 years in non-familial disease), and there is a greater likelihood of generalized involvement and oral mucosal findings as well as relapsing and prolonged disease course.

The physical exam findings of lichen planus are classically described as polygonal, purple (violaceous), flat-topped papules with overlying white reticulate scale (Wickham striae) (Fig. 4.1). Although nail involvement can be seen in up to 10 % of adult cases, it is an infrequent feature in children. Nail changes are characterized by thinning of the nail plate, longitudinal ridging, fragility, onycholysis, and pterygium formation [1]. Oral lesions are seen in 30–70 % of adult cases, and may be erosive with reticulate white patterning on the buccal and lingual mucosa. The incidence of oral disease in children is much less common with a prevalence between 4 % and 30 %. On the contrary, hypertrophic variants with hyperkeratotic plaques and adherent scale localized to the distal legs and ankles most often occur in children. Most active lesions resolve within 1 year, although post-inflammatory hyperpigmentation is noted in almost all cases. Hypertrophic lesions are more likely to resolve with residual dyschromia, atrophy, and scarring.

4.1.2 Histology

Lichen planus occurring in children has similar histologic features to the same disease in adults. The stratum corneum is hyperkeratotic without acanthosis. The epidermis is acanthotic with hypergranulosis (Fig. 4.2). The rete ridges demonstrate a saw-toothed alteration in appearance. The basal layer is disrupted and in some places obscured by a dense, band-like infiltrate of lymphocytes along the dermal epidermal junction (Fig. 4.3). Dying keratinocytes are present either focally or extensively, resulting in separation of the epidermis from the dermis. In some cases, this may present with clinically apparent bullae (bullous lichen planus) [2]. In older lesions, especially in patients with darker skin tones, post-inflammatory pigment incontinence is detected in the presence of papillary dermal melanophages (lichen planus pigmentosus in its most extensive form). The inflammatory infiltrate consists of lymphocytes and histiocytes. Eosinophils and plasma cells are not common. The infiltrate is restricted to the papillary dermis, and does not ordinarily extend into the reticular dermis [3–5].

Actinic lichen planus consists of lesions with similar histology in a photo-distributed area. As this variant of the disease is more common in darker skinned individuals, dermal melanophages are frequently part of the histologic constellation of findings [6].

Oral lichen planus demonstrates similar histologic features with several differences [7]. These changes are more site-specific than anything about the disease itself. Parakeratosis is often present, since this is the normal finding in mucosal surfaces and not a feature of cutaneous lichen planus. The inflammatory infiltrate may contain plasma cells, again more a feature of the normal inflammatory response within the oral mucosa rather than lichen planus itself.

The histologic differential diagnosis is quite broad. Lupus erythematosus is characterized by epidermal atrophy and not acanthosis in most cases. The inflammatory infiltrate centers

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Fig. 4.1 Lichen planus is characterized by polygonal violaceous papules with overlying white reticulations often at the distal extremities

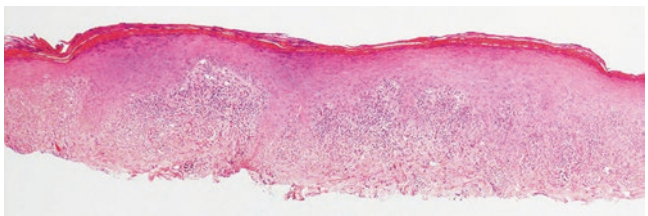

Fig. 4.2 Lichen planus has orthokeratotic hyperkeratosis, hypergranulosis, acanthosis and a bandlike lymphocytic infiltrate in the papillary dermis

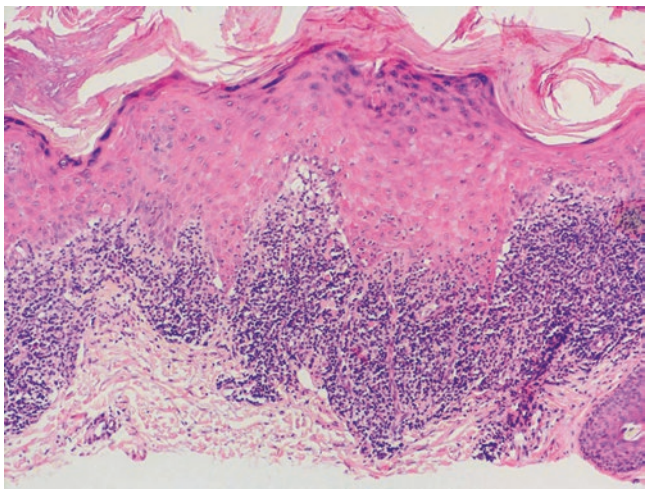

Fig. 4.3 In some cases of lichen planus, the epidermis appear papillomatous and hypergranulotic. Scattered dying keratinocytes are seen along with a dense band-like infiltrate and focal exocytosis of lymphocytes into the epidermis

on cutaneous appendages and extends deep into the dermis, features not associated with lichen planus. Plasma cells may be present in the infiltrate, and dermal mucin is a helpful finding in lupus erythematosus. Lichen striatus may also present some diagnostic difficulty, but as with lupus erythematosus, the inflammatory infiltrate extends deep into the dermis and is commonly peri-eccrine. Moreover, the inflammatory response along the epidermal junction is often not quite as intense as is the case with lichen planus. Pityriasis lichenoides, both the acute and chronic variants, demonstrate overlying parakeratosis, which is not a feature of lichen planus. Additionally, in most cases of pityriasis lichenoides, the infiltrate is less band-like, extending deeper into the dermis in most cases, and hemorrhage is frequently encountered. Lichenoid drug eruptions may be histologically indistinguishable from lichen planus and require history to make the correct diagnosis in some situations. The presence of a deeper infiltrate, and eosinophils and plasma cells in the dermis would favor drug-induced lichenoid dermatitis over lichen planus.

Lichen planus pemphigoides is generally believed to be a heterogeneous group of disorders that share histologic features of lichen planus and bullous pemphigoid with linear deposition of IgG and C3 along the dermal-epidermal junction [4, 8]. Whether this entity is related to lichen planus remains controversial, but it remains in the histologic differential diagnosis on account of its similarities to lichen planus.

4.1.3 Pathogenesis

Lichen planus is a T cell-mediated autoimmune response. Both CD4+ and CD8+ T lymphocytes are present in the dermis, while CD8+ T lymphocytes infiltrate the epidermis in lichen planus lesions [9]. Most of the lymphocytes in the infiltrate are CD8+ and CD45RO+ cells and express the α-β T cell receptor (TCR). These cells are believed to trigger apoptosis of basal keratinocytes in the epidermis that is often observed in a lichenoid inflammatory reaction [10]. Possible mediators of keratinocyte cell death include perforin and granzyme B [11].

Several cytokines important for lymphocyte homing are involved in lichen planus, including TNF-α, IL-1, IL-6, IL-8, and IFN-γ [12, 13]. These cytokines are derived from resident macrophages, lymphocytes, and keratinocytes. The chemokine RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted) is thought to be important in oral lichen planus [14]. RANTES can induce mast cell degranulation, releasing pro-inflammatory mediators to induce an inflammatory reaction in lichen planus.

Lichen planus may have a genetic susceptibility factor as some patients have a positive family history of disease [15, 16]. HLA A-3 and HLA-A5 have been documented to occur at a higher prevalence in patients with lichen planus [17].

Lichen planus may be associated with viral infections, specifically hepatitis C virus (HCV) [18, 19]. In a meta-analysis, 16 % of patients with lichen planus had hepatitis C virus infection [19], suggesting a need for infectious workup

in patients with widespread or unusual presentations of lichen planus. Of note, this association was primarily seen in adult patients and not in children with lichen planus, mitigating the need for screening in this population. Hepatitis C virus infection and lichen planus in the oral mucosa could be related to immunogenetic factors, such as the HLA-DR6 [20, 21]. Oral lichen planus occurs less frequently in children than in adults, possibly because adults more often undergo dental procedures that utilize dental amalgam, which is associated with oral lichen planus. Although the amalgam material itself does not cause lichen planus, the corrosion of amalgam and the continuous contact of corroded amalgam with the oral mucosa are associated with increased risk of oral lesions [22, 23].

4.2 Lichen Striatus

4.2.1 Clinical Features

Lichen striatus is an acquired asymptomatic lichenoid dermatosis, most frequently occurring in children between 4 months old and 15 years old, although many report median age to be closer to 2–3 years old [1]. There is no racial or gender predilection.

The physical exam is characterized by skin-colored to slightly erythematous, flat-topped 1–2 mm papules in blaschkoid distribution along the affected area (Fig. 4.4). Multiple bands may be seen with bilateral involvement described, although this is uncommon [1]. Skin changes are most often seen on the limbs but may occur on the face or trunk as well. It often progresses linearly with possible nail dystrophy if it involves the distal digits. As skin changes progress, lesions flatten and hypopigmentation becomes a more prominent feature. Vesicular variants have been reported [1]. Lichen striatus is characterized by spontaneous resolution of active dermatitis within 1 year, but residual hypopigmentation may persist for years.

Fig. 4.4 Lichen striatus presents as a Blaschkoid erythematous papular plaque extending distally from the right posterior shoulder down the arm of a boy

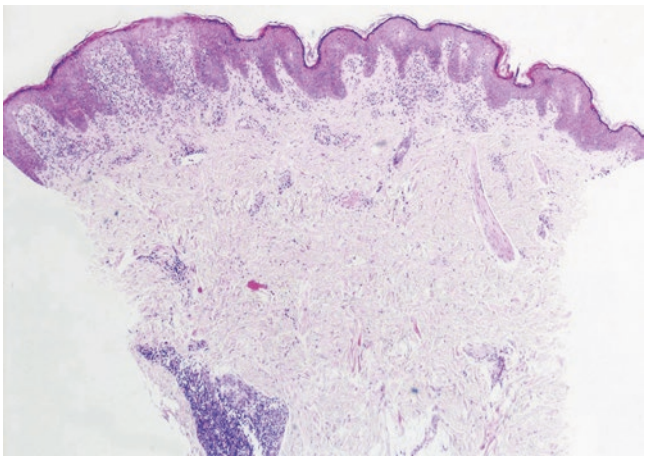

Fig. 4.5 A papillomatous epidermis with an underlying band-like infiltrate is characteristic of lichen striatus. A dense inflammatory infiltrate is also seen surrounding eccrine ducts

4.2.2 Histology

The diagnosis of lichen striatus requires careful clinicopathologic correlation. The epidermis is generally either unremarkable or displays focal spongiosis that some authors have described as occurring within the lower portions of the epidermis [24]. Parakeratosis is present in many cases. Acanthosis may be seen with elongation of the rete ridges [25]. An interface dermatitis is present, although often there is only a focal lymphocytic infiltrate of the basal layer leading to keratinocyte vacuolization and destruction (Figs. 4.5 and 4.6). Earlier lesions tend to have a more confluent and band-like infiltrate along the epidermal junction, and this diminishes in intensity with progressive age of the lesions. The dermis contains a superficial and deep perivascular infiltrate of lymphocytes and histiocytes. A similar infiltrate is seen around hair follicles and especially around eccrine coils [26]. Eosinophils and plasma cells are not part of the reactive process in most cases. While there are histologic features for lichen striatus as described, for the most part these are not specific and can be seen in a variety of lesions.

The histologic differential diagnosis includes lichen planus, lupus erythematosus, lichen aureus and arthropod bite

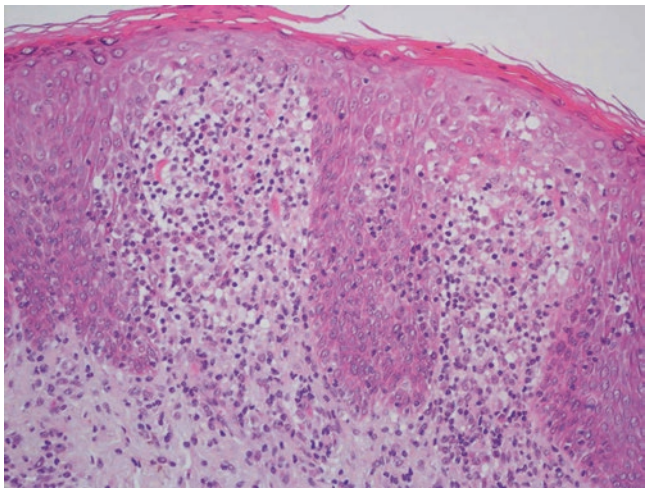

Fig. 4.6 An intense interface dermatitis with abundant exocytosis and focal spongiosis within an acanthotic epidermis is seen in some cases of lichen striatus

reactions. Lichen planus may present the greatest diagnostic dilemma, especially the linear variant [27]. Early lesions of lichen striatus will demonstrate a similar band-like infiltrate along the epidermal junction; however, in lichen striatus, there is typically a deep component to the infiltrate and a noticeable peri-appendageal infiltrate that is not present in most cases of lichen planus. In addition, the focal hyperkeratosis that characterized lichen planus is not a common feature in lichen striatus, which often shows parakeratosis that is not seen in lichen planus. Lupus erythematosus presents a diagnostic challenge due to the interface reaction pattern superimpose upon the superficial and deep perivascular and peri-appendageal infiltrate similar to the pattern seen in classic lichen striatus. In most cases, this does not present a clinical diagnostic dilemma and can easily be resolved. The lack of epidermal atrophy, basement membrane thickening and dermal mucin in lichen striatus further helps in making this distinction. Lichen aureus shows a lichenoid inflammatory infiltrate similar to lichen striatus, but this is accompanied by extravasation of erythrocytes and the presence of papillary dermal hemosiderin, which are features not seen in lichen striatus. Arthropod bite reactions may have a similar inflammatory reaction pattern, but in most cases, eosinophils and neutrophils are also present within the infiltrate. In addition, while cutaneous appendages may be involved, there is no apparent predilection for them as typically seen in lichen striatus.

4.2.3 Pathogenesis

The pathogenesis of lichen striatus involves a combination of environmental and inherent genetic factors. The fact that lichen striatus occurs along the lines of Blaschko (Blaschkitis) suggests that a somatic mutation occurring during embryogenesis may be involved in its etiology [1, 28, 29]. Blaschko's lines have an embryologic origin and correspond to the direction of growth of skin cells. Somatic mutations occurring during embryogenesis may produce an aberrant skin cell clone that is predisposed to give rise to lichen striatus [29]. This is further supported by reports of recurrent lesions in the same location [28]. Lichen striatus has also been considered to be a consequence of an acquired stimulus that induces the loss of immune tolerance resulting in a T-cell-mediated inflammatory reaction [29, 30]. It may also have an infectious etiology. Viruses have been implicated due to reports of multiple simultaneous cases in siblings, outbreaks among unrelated children in shared living quarters, and seasonal variation [31]. However, viral particles have not been identified in lesional skin [26]. Other possible precipitating factors include skin injury and trauma [32].

4.3 Lichen Aureus

4.3.1 Clinical Features

Lichen aureus is uncommon in children and more frequently presents in young adults [33]. No consistent sex predilection has been established, although some studies of pediatric populations suggest higher prevalence in females [1].

The appearance of lichen aureus is similar to that of a bruise, characterized by a gold to "rust-colored" patch or plaque of grouped lichenoid papules [1, 33] (Fig. 4.7). Lesions appear suddenly with slow expansion usually along the lower extremities, although any cutaneous surface can be affected. Multiple lesions may occur and occasionally coalesce into larger patches or plaques. Distribution is

Fig. 4.7 Lichen aureus is characterized by a "rust-colored" circumscribed, non-blanching plaque on the lower extremity

typically unilateral with involvement at the trunk and arms more frequently seen in children [33]. Patients may complain of mild pruritus, but lesions are most commonly asymptomatic. Lichen aureus has a self-limiting course, recurring in crops or persisting unchanged for years. Lesions occurring in children resolve more readily with an approximate duration of 2.5 to 3 years [1, 34].

4.3.2 Histology

Lichen aureus demonstrates a lichenoid inflammatory infiltrate along the epidermal junction, usually characterized by little destruction of the epidermal basal layer, similar to the histologic changes that have been described in adults with the same condition [33] (Figs. 4.8 and 4.9). The epidermis is unremarkable except for focal basal vacuolization and exocytosis of lymphocytes. Within the dermis, there is a dense lymphohistiocytic infiltrate usually confined to the papillary dermis [35]. The distinguishing diagnostic feature is the presence of erythrocyte extravasation with hemosiderin deposition, often accumulating within dermal macrophages. The gold brown pigment may be readily apparent on routine histologic sections, but can be better visualized on iron stains.

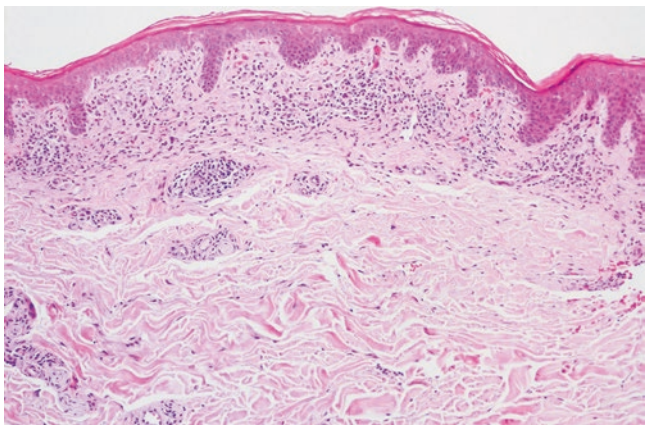

Fig. 4.8 Lichen aureus demonstrates a band-like infiltrate along the papillary dermis with focal hemorrhage

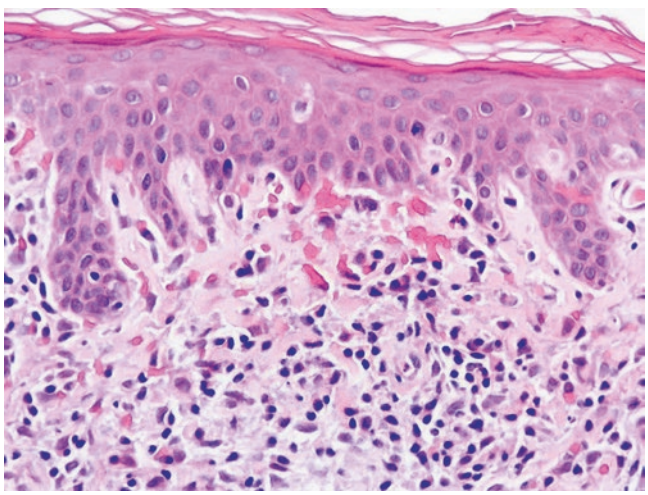

Fig. 4.9 Papillary dermal hemorrhage and a lymphocytic infiltrate without obvious vascular destruction are features of lichen aureus

The differential diagnosis includes other entities with dermal hemorrhage such as pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis rosea. PLEVA is characterized by thick, usually confluent parakeratosis, which is not a feature of lichen aureus. In addition, the inflammatory infiltrate in PLEVA tends to extend deeper into the dermis than is usually seen in lichen aureus. Pityriasis rosea does not demonstrate the hemosiderin, has focal spongiosis, focal parakeratosis and a less intense inflammatory infiltrate than that seen in lichen aureus. Other types of pigmented purpuric eruptions may enter into the differential diagnosis, but the lichenoid pattern of inflammation is the defining feature of this subtype. The distinctions have no clinical or prognostic significance. Stasis dermatitis could be confused with lichen aureus in adults, but it would not be expected to enter the differential diagnosis in children. Leukocytoclastic vasculitis is often the major clinical differential diagnosis but is easily separated from lichen aureus based upon the findings of a neutrophilic infiltrate, vascular destruction, thrombosis and in more florid cases, epidermal necrosis. The major histologic differential diagnosis of clinical significance is mycosis fungoides. Rare cases of mycosis fungoides have been reported in children. Mycosis fungoides has more infiltration of the epidermis by lymphocytes, some of which may show cytologic atypia. Dying keratinocytes are not seen in most cases, and the infiltrate is rarely a confluent band within the papillary dermis. Dermal hemorrhage is unusual in mycosis fungoides. While clonality has been described in some cases of lichen aureus, most authors do not believe that it has the propensity for progression to mycosis fungoides [35, 36].

4.3.3 Pathogenesis

Several mechanisms of pathogenesis of lichen aureus have been suggested, including capillary fragility, benign chronic capillaritis, and possible exogenous factors such as infections, drugs, and contact allergens [37–39].

There are reports describing clonal T lymphocyte infiltrates in lichen aureus lesions with some suggestions of progression to mycosis fungoides [36, 40, 41]. However, malignant transformation to mycosis fungoides is not the typical course. A study showed no observed progression to mycosis fungoides in 23 patients with conventional lichen aureus [42]. It has been suggested that lichen aureus may be

a type of dermatoses with clonal T cell expansion, in which the clone is kept under control by immune surveillance, but in a few patients, the clone may escape surveillance and become a dominant clone, predisposing the individual to cutaneous lymphoma.

4.4 Lichen Nitidus

4.4.1 Clinical Features

Lichen nitidus is an asymptomatic dermatosis of early childhood with most cases presenting before 10 years of age [1]. There is no gender or racial predilection. Physical exam is notable for generalized pinpoint (1–2 mm), monomorphic, skin-colored to slightly hypopigmented, flat-topped papules clustered at the trunk (abdomen, chest) and upper extremities (Fig. 4.10). Koebnerization is a key feature and is seen almost universally in affected persons. Fine scale or hyperkeratotic plug may overlie some papules. Generalized disease has been reported, presenting as fine hyperkeratosis with palmar involvement as well as ridging and pits of the nail plates [1]. Lichen nitidus eventually regresses, but it may persist for years.

4.4.2 Histology

Lichen nitidus is characterized by what has been described as a "ball and claw" pattern. The epidermis demonstrates focal parakeratosis overlying areas of epidermal thinning. On either side of the thinned epidermis, there is a classic elongation of rete ridges with an inward turn, creating the "claw" pattern that surrounds the "ball" (Figs. 4.11 and 4.12). Within the papillary dermis, there is a focally dense inflammatory infiltrate that consists primarily of lymphocytes and histiocytes that comprises the "ball." The infiltrate may extend into the lower portion of the epidermis, resulting in basal vacuolization and keratinocyte necrosis [43]. Extension around cutaneous appendages has been described in rare cases [44]. In some cases, there is an extensive histiocytic component that creates a granulomatous appearance, while in other cases the histiocytic infiltrate is relatively scant. Eosinophils and plasma cells are not prominent, although they may be seen in some cases [45]. The infiltrate is usually confined to the region subjacent to the flattened

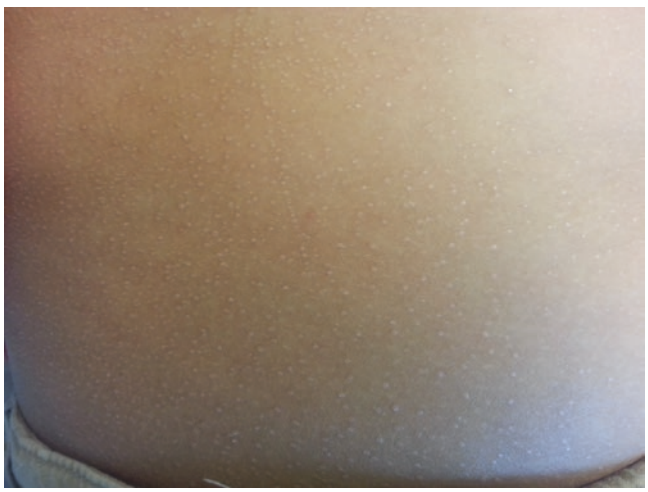

Fig. 4.10 Lichen nitidus frequently presents as monomorphic, flat-topped, skin-colored to hypopigmented papules with evidence of koebnerization on the abdomen of a child (photo courtesy of Audrey Chan, MD, Baylor College of Medicine, Houston, TX)

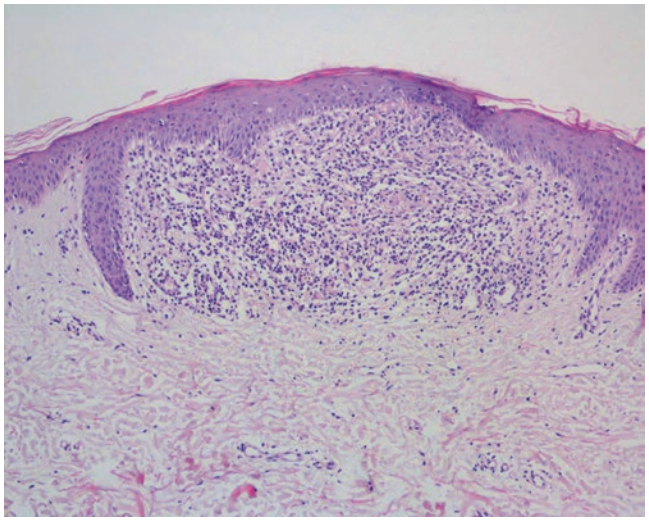

Fig. 4.11 Lichen nitidus demonstrates the classic "ball and claw" configuration with a small, circumscribed granulomatous inflammatory infiltrate enveloped by elongated rete ridges

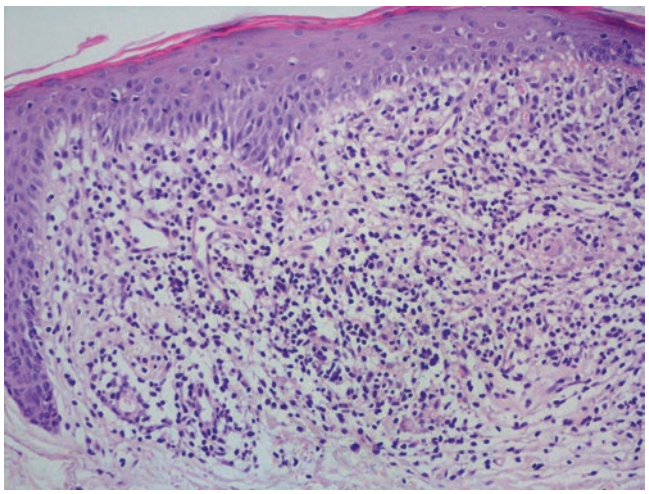

Fig. 4.12 The inflammation in lichen nitidus consists of lymphocytes and abundant histiocytes largely within the dermis with some extension into the overlying epidermis

epidermis. Outside of this region, the dermis is relatively devoid of inflammation [43]. Rare cases of transepidermal elimination and perforation have been described [46, 47].

The histologic differential diagnosis includes lichen planus and granulomatous processes. Lichen planus has a more diffuse dermal infiltrate along the epidermal junction. The wedge-shaped hypergranulosis and altered shape of the rete ridges that characterize lichen planus are not present in lichen nitidus. In most cases, the histiocytic infiltrate in lichen nitidus is relatively scant, and infectious processes would not enter into the differential diagnosis. However, in rare cases with an abundance of histiocytes, a granulomatous appearance may suggest sarcoidosis, histoplasmosis and tuberculosis [48]. Special stains for microorganisms and clinical history will easily resolve this dilemma. Another differential consideration is lichen striatus, which has a more diffuse inflammatory infiltrate along the epidermal junction, and also has lymphocytes deeper within the dermis and around eccrine structures, which are features not associated with lichen nitidus.

4.4.3 Pathogenesis

Lichen nitidus is associated with immune dysfunction, particularly in cases of generalized disease [1]. It may be closely related to lichen planus. This is supported by the coexistence of both diseases in some patients, overlapping histomorphologic features, and similar infiltrates of CD4+ T lymphocytes [49, 50]. Lichen nitidus can occur in patients with atopic dermatitis, advanced HIV, and Crohn's disease [51–53]. Some cases occurring in families have been reported [54, 55].

4.5 Lichenoid Drug Eruptions

4.5.1 Clinical Features

Incidence of lichenoid drug eruption in children is rare, since many of the causative agents are infrequently used in this patient population [1, 56]. The time of onset of skin changes in lichenoid drug eruption typically is longer than that seen in other drug reactions, with latency of approximately 12 months [56]. The associated skin lesions may mimic those of lichen planus, or may have a more eczematous appearance with larger discrete papules, more pronounced erythema, lichenification and scale [1]. Additionally, lichenoid drug eruption often spares the flexural wrist, genitals, and mucosal surfaces with rare reports of photodistribution. Skin eruption typically resolves after discontinuing the causative agent, although it may demonstrate slower resolution in comparison to other types of drug eruptions [56].

4.5.2 Histology

Drug eruptions manifest with many histologic patterns, one of which is a histologic mimic of lichen planus. In these cases, the epidermis may be slightly acanthotic with variable hyperkeratosis. Parakeratosis is present in some cases. The papillary dermis demonstrates a band-like inflammatory infiltrate that invades the lower portion of the epidermis, resulting in basal vacuolization, dying keratinocytes, and even small subepidermal blister formation (Figs. 4.13 and 4.14). In most cases, eosinophils and/or plasma cells will be present in addition to lymphocytes and histiocytes [1]. Their presence helps to make this distinction, along with a good

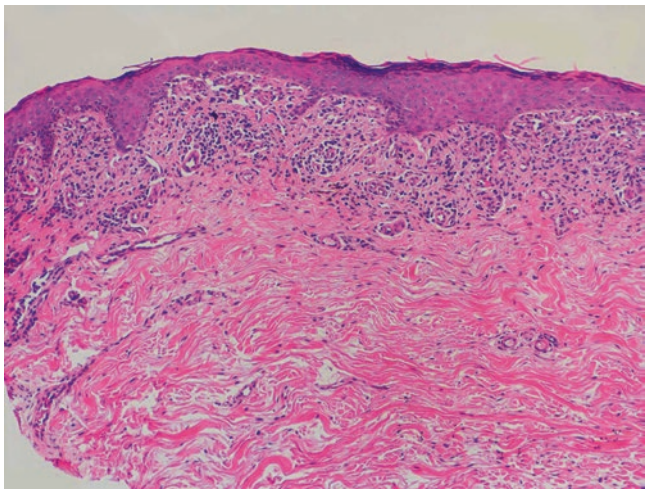

Fig. 4.13 Lichenoid drug eruption demonstrates a band-like infiltrate of lymphocytes in the papillary dermis with focal exocytosis into the epidermis. Hypergranulosis and rare dying keratinocytes may be present

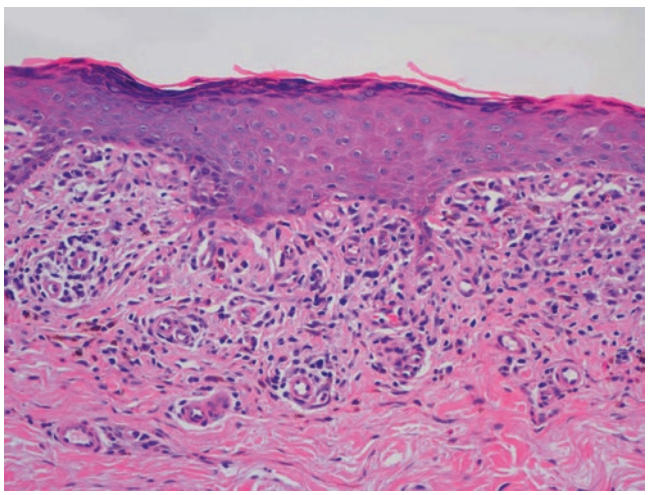

Fig. 4.14 Hypergranulosis, a band-like lymphocytic infiltrate and pigment-laden macrophages are present in lichenoid drug eruption

clinical history. Further more, lichenoid drug eruptions often display involvement of the deeper dermis, which is not usually seen in lichen planus. Another differential diagnosis is an arthropod bite reaction. Arthropod bite reactions have a different clinical presentation from a lichenoid drug eruption. The presence of a punctum, dermal hemorrhage, and frequent eosinophils extending between reticular dermal collagen bundles all favor an insect bite reaction over a lichenoid drug eruption.

4.5.3 Pathogenesis

Many clinically heterogeneous inflammatory dermatoses ranging from lupus erythematosus to fixed drug eruption share overlapping elements of a lichenoid inflammatory reaction [57]. Autoimmune attack by T lymphocytes in the epidermis is the primary pathological event in lichenoid dermatitis [57]. CD8+ T lymphocytes that are primed and activated by an infection, such as viruses, could evolve into long-lived effector memory T cells, and become effectors of epidermal damage seen in a lichenoid tissue reaction when they are exposed to stimuli, such as drugs or self-antigens. The severity of damages in the epidermis is dependent on the relative balance between the intensity and duration of T lymphocyte-mediated inflammatory reaction, as well as the capacity of epidermal cells to be protected from the immune response.

4.6 Lupus Erythematosus

4.6.1 Clinical Features

Juvenile systemic lupus erythematosus (JSLE) is a systemic autoimmune connective tissue disorder. It is estimated that approximately 10–20 % of patients with systemic lupus erythematosus develop signs and symptoms of disease during childhood and adolescence [58, 59]. Thirty-five percent of pediatric patients present between 5 and 10 years of age, and 5 % occur in children under 5 years of age. The overwhelming majority of cases are diagnosed in postpubertal children between the ages of 11 and 15 years old (60 %) with median age of onset of 12.1 years old [58, 60–62].

The incidence of JSLE is between 0.3 and 0.9 per 100,000 per year while prevalence ranges from 0.3 to 8.8 per 100,000 [58]. It is more common in females with a female to male ratio of 3–5 to 1. Children and adolescents often present with more acute and severe disease than those with adult onset lupus, including more significant organ involvement [59].

A variety of mucocutaneous manifestations are seen in JSLE (Figs. 4.15, 4.16 and 4.17). The lesions of acute cutaneous lupus erythematosus (ACLE) include localized and generalized lesions that are photosensitive. The most common localized lesion is a malar ("butterfly") rash, characterized by a well-defined erythematous, edematous plaque over the nasal bridge (Fig. 4.15). In one study, the malar rash was reported in approximately 80 % of children with systemic lupus [60]. A more diffuse erythematous rash affecting non-sun exposed areas can also occur. Subacute cutaneous lupus (SCLE) is extremely rare. It is characterized by widespread annular and psoriasiform lesions.

Fig. 4.15 Multiple violaceous atrophic plaques with an erythematous rim are on the face, most notably in a malar distribution across the nose and cheeks in a girl with lupus erythematosus (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

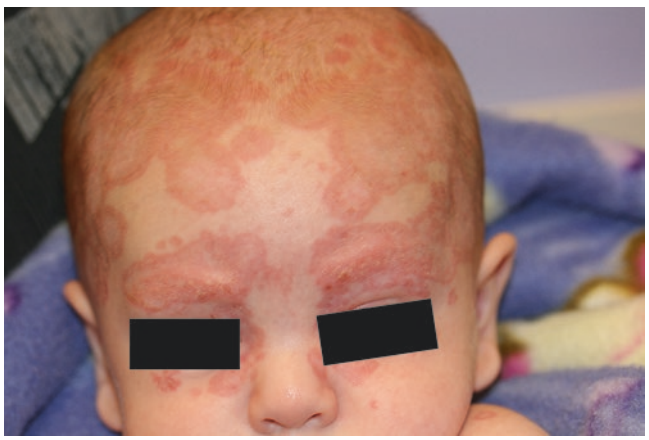

Fig. 4.16 Neonatal lupus erythematosus presents with annular scaled, erythematous thin plaques and patches scattered on the scalp and face an infant

Fig. 4.17 Tumid lupus erythematosus is characterized by smooth, indurated erythematous plaques on the head and neck with minimal epidermal change (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

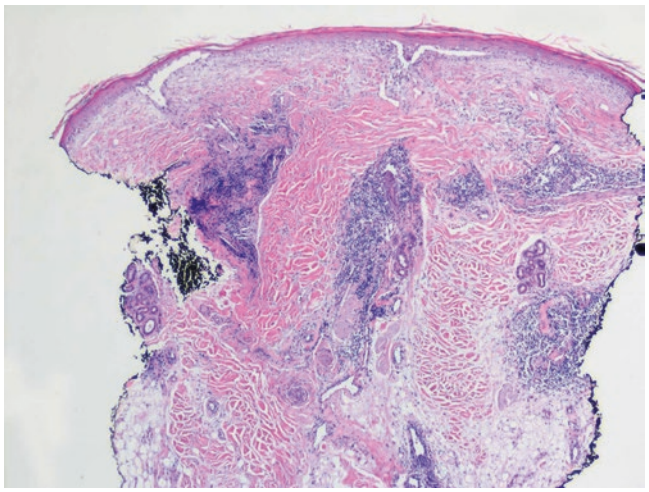

Fig. 4.18 Hyperkeratosis, atrophic epidermis with interface dermatitis, and a superficial and deep perivascular and peri-appendageal lymphocytic infiltrate characterize lupus erythematosus

Discoid lesions of chronic cutaneous lupus (CCLE) are unusual in children under 10 years old. They are most common on the scalp, face and ears, and present as well-circumscribed, indurated, red-violaceous papules and plaques with adherent, keratotic scale or fine telangiectasia that cause atrophic scarring. Only approximately 25 % of children with discoid lupus go on to develop systemic disease [63]. Other forms of CCLE, such as lupus panniculitis and tumid lupus, are also rare in children (Fig. 4.17).

A variety of nonspecific skin lesions and changes can also be seen in JSLE. These include oral ulcers, non-scarring alopecia, photosensitivity, leukocytoclastic vasculitis, livedo reticularis, Raynaud's phenomenon, and bullae, to name a few.

Management of JSLE is tailored to severity and presence of organ involvement. Systemic steroids and other immunosuppressants are mainstays of therapy for systemic disease. Aggressive photoprotection is of paramount importance. Disease prognosis varies widely depending on disease severity, patient compliance, and response to therapy.

Neonatal lupus is a special subtype of lupus erythematosus, and is a relatively rare disease that affects 1 in 10,000–20,000 newborns [64]. It is more commonly seen in females. Cutaneous manifestations are present in 50 % of cases with only 10 % of patients having coexistence of both cutaneous disease and complete atrioventricular block (the most severe variant) [64]. Approximately 25 % of patients have hepatobiliary or hematologic abnormalities with transient thrombocytopenia [62].

The skin eruption in neonatal lupus typically appears within the first few weeks of life, although congenital lesions have been reported. Patients most commonly present with erythematous annular plaques with predilection for the face and scalp (Fig. 4.16). Periocular erythema or "raccoon eyes" is a frequently described clinical finding. Post-inflammatory dyschromia may occur, but lesions tend to resolve without scarring [64]. Almost all subtypes of neonatal lupus have a good prognosis with disease manifestations subsiding by about 1 year of life, which corresponds to the clearance of maternal autoantibodies. The one exception is disease associated with complete atrioventricular block, which is frequently more chronic and requires a pacemaker [64].

4.6.2 Histology

There are many clinical subtypes of lupus erythematosus, some of which can be differentiated on routine histologic sections. The most common subtype encountered is *discoid lupus erythematosus* and it demonstrates the most classic features of cutaneous involvement by lupus erythematosus. Histologic changes include orthokeratotic hyperkeratosis with follicular plugging and dilatation (Figs. 4.18 and 4.19). In well-developed lesions, the epidermis is atrophic, but in early lesions, the epidermis may have normal thickness. There is an interface dermatitis with scattered dying keratinocytes and lymphocytes extending into the lower portions of the epidermis (Figs. 4.20 and 4.21). In long-standing lesions, basement membrane thickening may be apparent on routine sections or on PAS stains. The dermis is characterized by a superficial and deep perivascular and peri-appendageal inflammatory infiltrate consisting primarily of lymphocytes. Scattered plasma cells are seen in some cases, but the presence of eosinophils is unusual. Dermal mucin may be present but usually in relatively small amounts. H&E sections may show mucin, which can be highlighted with colloidal iron or alcian blue stains.

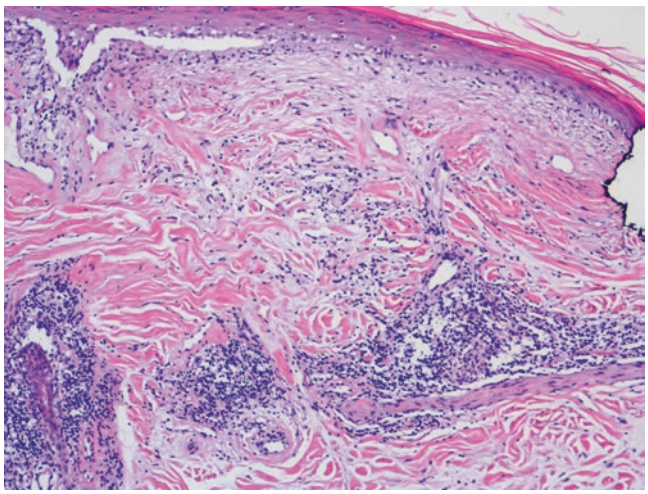

Fig. 4.19 Interface dermatitis resulting in epidermal atrophy and a perivascular lymphocytic infiltrate along with dermal mucin are seen in lupus erythematosus

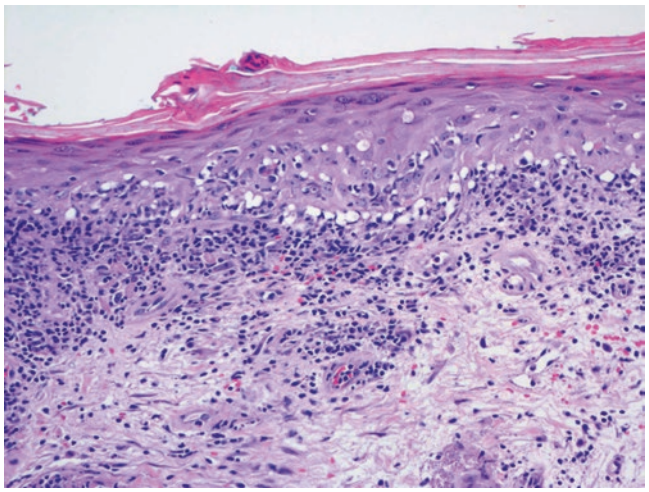

Fig. 4.21 Interface dermatitis with scattered dying keratinocytes in lupus erythematosus

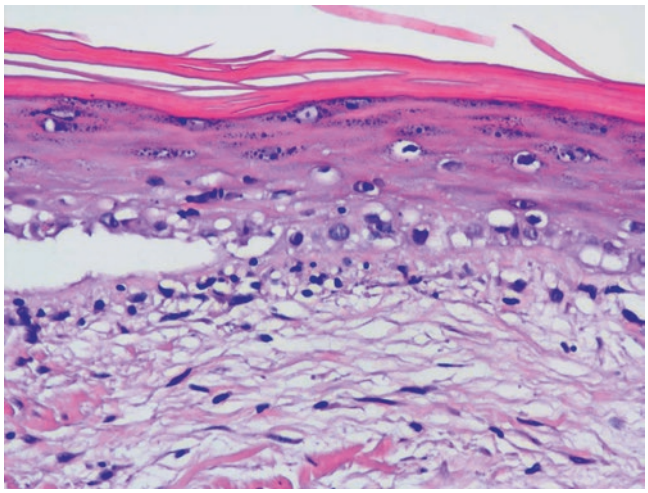

Fig. 4.20 Diffuse basal vacuolization is present in lupus erythematosus

The histologic features seen in *subacute cutaneous lupus erythematosus* are identical to those described in discoid lesions. While some authors have attempted to distinguish these subtypes based upon biopsy findings [65], others have not been able to replicate the findings [66].

Systemic lupus erythematosus demonstrates similar histologic changes to those described in discoid lupus erythematosus. However, in most cases, the changes are paradoxically less intense. This generalization is not significant enough, however, to make the distinction based purely on biopsy results. Direct immunofluorescence stains and serologic studies are warranted to make a precise diagnosis.

Tumid lupus erythematosus is a less common variant of cutaneous lupus erythematosus in which the changes are restricted to the dermis and the epidermis remains histologically normal. Within the dermis the characteristic features of lupus erythematosus are seen with a superficial and deep perivascular and peri-appendageal infiltrate of lymphocytes and occasional plasma cells [67]. In tumid lupus, mucin deposition is often more pronounced than in other subtypes [68]. Tumid lupus is generally considered to be identical to what has previously been called *reticular erythematous mucinosis* [69].

Bullous lupus erythematosus is a rare subtype of lupus erythematosus that presents with clinically apparent blisters [70–73]. This is reflected in the histologic changes wherein a subepidermal blister is present. The underlying papillary dermis displays a pronounced infiltrate of neutrophils. The remainder of the dermis typically demonstrates the more classic findings of lupus erythematosus with a superficial and deep perivascular and peri-appendageal infiltrate.

Lupus profundus is primarily a panniculitis and is described in details in the chapter on panniculitides. Some cases may show changes of cutaneous lupus erythematosus, but in many cases the changes are restricted either entirely or largely to the subcutaneous fat.

Neonatal lupus erythematosus is a rare condition caused by the transplacental passage of maternal autoantibodies. In most cases, the clinical and histologic features resemble those seen in subacute cutaneous lupus erythematosus [74–77]. There is an interface dermatitis with vacuolar degeneration of basal keratinocytes. A superficial and deep perivascular and peri-appendageal lymphocytic infiltrate is present. Epidermal atrophy and melanophage deposition are seen in some cases. More recently, several cases of neonatal lupus erythematosus have been descried that display a neutrophilic dermal infiltrate [78, 79]. In rare cases, the neutrophilic infiltrate may be admixed with large histiocytoid cells

that express CD68, CD33, and myeloperoxidase [80]. Vascular ectasia has also been described in some patients with neonatal lupus and a resemblance to cutis marmorata telangiectatica congenita has been reported [74, 81].

Direct immunofluorescence examination is helpful in establishing the diagnosis in some cases; however, the sensitivity varies greatly depending upon the subtype of lupus erythematosus. A granular staining pattern with antibodies directed against IgG, IgA, IgM, and C3 is found in most lesional biopsies taken from patients with discoid lupus erythematosus. The sensitivity is much lower for those with subacute lupus, tumid lupus, and lupus profundus. Nonlesional skin will show similar immunodeposits in patients with systemic lupus erythematosus and in some patients with subacute lupus, but it is otherwise usually negative.

The histologic differential diagnosis includes many entities, but the most commonly encountered ones are polymorphous light eruption, Jessner's lymphocytic infiltrate, dermatomyositis, lymphoma, and cutaneous lymphoid hyperplasia. Polymorphous light eruptions do not demonstrate an interface dermatitis and peri-adnexal inflammation. Similarly, Jessner's lymphocytic infiltrate would not be expected to show an interface process; however, this entity is poorly defined and many authors believe some cases to be on the spectrum of cutaneous lupus erythematosus.

4.6.3 Pathogenesis

Lupus erythematosus is an autoimmune disease characterized by the production of self-antibodies to cell nuclear components. Genetic and experimental animal studies have provided important insights into toll-like receptor (TLR) and type I interferon (IFN) signaling in lupus erythematosus . An IFN-induced gene signature has been identified in children and adults with active systemic lupus erythematosus (SLE) [82–84]. There is a unique pattern of 14 upregulated gene targets of type I IFN, some of which are related to known autoantigens in SLE [82, 83, 85, 86]. Immune complexes of DNA and anti-double-stranded DNA antibodies that are normally found in the serum of patients with SLE can induce plasmacytoid dendritic cells (pDC) to secrete IFN-α [87]. pDC and IFN gene activation have been observed in skin lesions and nephritic glomeruli from SLE patients [88]. About 25 % of SLE patients have endogenous anti-IFN-α antibodies in the serum [89]. These patients also have reduced serum IFN levels as well as decreased IFN-pathway and disease activity. These findings indicate that inhibition of IFN activity may ameliorate disease condition in SLE. In fact, anti-IFN therapies are being developed for lupus [90]. Some of the therapies are humanized monoclonal antibodies to IFN-α and IFNα/β receptor. IFN-α blockade significantly reduces the IFN-gene signature in patients, although ultimately there have been no significant effects on disease activity thus far.

Experimental animal models of lupus erythematosus have shed important insights into the role of IFN and interleukin-1 pathways in the disease. IRAK1 (interleukin-1 receptor associated kinase-1) has been identified as a risk gene in the pathogenesis of SLE [91]. Deficiency of type I IFN receptor or IRAK1 in lupus-susceptible mice results in improvement in lupus disease phenotype [91, 92]. Moreover, chronic type I IFN production due to mutations in IFIH1 (a gene that encodes the cytoplasmic double stranded RNA sensor MDA5) results in aggressive disease in lupus-susceptible mice [93].

Dendritic cells are important in the pathogenesis of lupus erythematosus. In addition to its role in producing IFN, dendritic cells are necessary for B cell activation and tolerance [94, 95]. Lupus serum can induce dendritic cells to promote the differentiation of naive and memory B lymphocytes into IgG- and IgA-secreting plasma cells.

Neutrophils also play an important role in lupus erythematosus by contributing to the dysregulation of IFN in this disease. Anti-ribonucleoprotein antibodies found in SLE can stimulate neutrophils to release neutrophil extracellular traps (NETs), which are composed of DNA and protein complexes [96]. NET can activate pDCs to increase levels of IFN-α in a DNA- and TLR-dependent manner. Another mechanism of neutrophil involvement is that neutrophils can undergo accelerated spontaneous apoptosis in vitro. Serum from lupus patients can induce neutrophil apoptosis and the release of neutrophil nuclear antigens, such as double stranded DNA, leading to the production of autoantibodies [97, 98].

There are familial cases of lupus erythematosus with pediatric onset that have a Mendelian pattern of inheritance. Genetic defects of the early complement components, namely homozygous C1q (90 % of cases), C4 (60 %), or C2 (30 %) deficiency, confer a high genetic risk of developing lupus [99]. DNA sequencing of affected siblings in a family with SLE identified a homozygous missense mutation in PRKCD gene, which encodes protein kinase C-δ (PKC-δ) [100]. Mutations in PKC-δ result in increased B lymphocyte survival and proliferation. Affected individuals have increased immature B lymphocytes and a developmental shift towards an immature phenotype of naive B lymphocytes. Experimental animal model with deficiency in PKC-δ develops SLE-like features, and has defects in the negative selection of self-reactive B cells [101, 102].

A rare autosomal recessive form of SLE with a fully penetrant pattern of Mendelian inheritance has been identified, in which there is a null mutation in the DNASE1L3 gene [103]. The onset of SLE related to DNASE1L3 occurs in children at 5 years of age. Additionally, a gene linked to a rare autosomal dominant form of SLE is heterozygous null allele in DNASE1, which encodes for a deoxyribonuclease enzyme [104]. These genetic findings raise a hypothesis that

the inability to clear DNA materials released from apoptotic cells can trigger an autoimmune response, and the formation of anti-DNA antibodies with disease manifestations of lupus erythematosus.

4.7 Juvenile Dermatomyositis

4.7.1 Clinical Features

Juvenile dermatomyositis (JDM) accounts for more than 80 % of the cases of idiopathic inflammatory myopathies seen in children [105]. The annual incidence of disease is approximately 3 per million children per year in both the USA and the UK [106]. Girls are more commonly affected than boys with a mean age of onset of 7 years old, although a quarter will be diagnosed by 4 years old [106]. Non-Hispanic whites represent the overwhelming majority of those affected.

The vasculopathy of JDM affects the skin, skeletal muscles, gastrointestinal tract, lungs, kidneys, eyes, and heart [106]. The majority of children with dermatomyositis will have cutaneous findings at the time of diagnosis. The most frequently seen pathognomonic features are the heliotrope rash, Gottron's papules and periungal changes of erythema, telangiectasia, hyperkeratosis, and fraying of the proximal nail fold. Sun-protected areas are frequently spared, suggesting photosensitivity.

The heliotrope rash is described as a violaceous to red erythematous eruption with discrete telangiectasia around the eyes and potential extension to the upper cheeks, forehead, temples, and ear. Similarly scaled dermatitis at the scalp, nape of the neck, extensor surfaces of the arms, shoulders, and upper trunk are qualified as the "shawl sign". Gottron's papules are violaceous, flat-topped papules along the dorsal interphalangeal joints with subsequent evolution to poikiloderma (which may also be seen at other sites as a feature of more chronic disease) (Fig. 4.22).

Additional clinical features may include oral telangiectasia with concomitant erosions and ulcerations along the gums, buccal mucosa, and palate. Also present are palmar erythema and hyperkeratosis with fissuring (mechanic's hands). Acquired lipodystrophy and associated metabolic derangements are seen in 10–40 % of children with longstanding and poorly controlled disease [105, 106]. Tender panniculitis also may occur at the arms, thigh, and buttocks. Lastly, firm, irregular nodules of cutaneous calcinosis that extrude whitish, chalky material can be seen in 30 % of pediatric cases, most commonly along pressure points or sites of trauma [106].

One-third of pediatric patients will enter complete remission within 3 years of disease onset, while the remainder will experience more persistent disease with polycyclic relapses [105]. Cutaneous ulceration may be seen in up to 10 % of patients and portends a more severe disease course. Overall, cutaneous disease typically responds well to immunosuppressive therapy, and children fare better than their adult counterparts with a lower associated mortality rate of less than 2 % [105].

Fig. 4.22 Erythematous, scaled patches and thin plaques present on the dorsum of the hand and interphalangeal joints of a boy with dermatomyositis

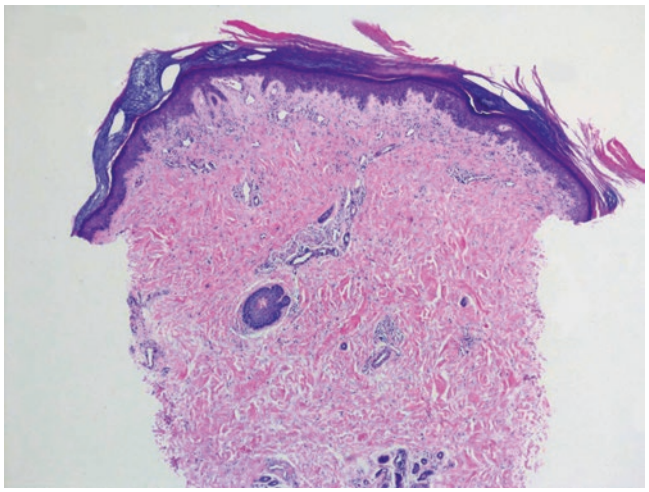

Fig. 4.23 Dermatomyositis demonstrates only a slight superficial interface dermatitis without deep or peri-appendageal inflammatory infiltrate

4.7.2 Histology

Histologic findings in JDM are similar to those seen in lupus erythematosus. The epidermis is either normal or slightly atrophic with basal vacuolization (Figs. 4.23 and 4.24). Lymphocytes are present within the epidermis, papillary dermis and surrounding the vessels of the superficial vascular plexus. The inflammatory infiltrate does not usually extend deep into the reticular dermis, and does not involve cutane-

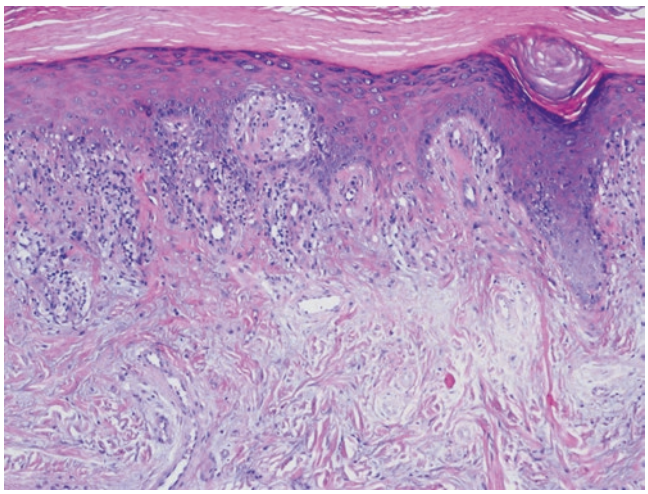

Fig. 4.24 Dermatomyositis has interface dermatitis with mucin present in the superficial dermis

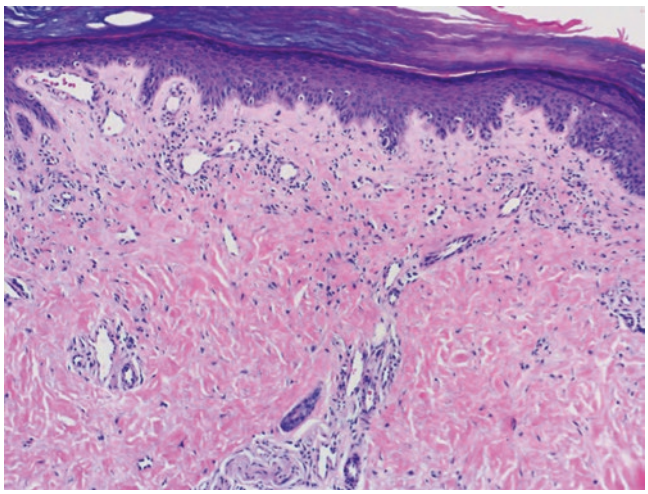

Fig. 4.25 A Gottron's papule has the same histologic features as dermatomyositis affecting other areas of the skin but is present on acral skin

ous appendages. Occasional plasma cells may be encountered, but eosinophils are extremely uncommon in this condition. Dermal mucin is readily apparent on routine sections in most cases of dermatomyositis, but can be highlighted on colloidal iron or alcian blue stains [107–109]. Some authors have emphasized the finding of thickened blood vessels and sclerotic collagen in late stage lesions, which are features that may raise the question of scleroderma in some cases [110].

Gottron's papules have very similar histologic changes to those seen in biopsies taken from the poikilodermatous or erythematous lesions of dermatomyositis (Fig. 4.25). The major difference is that the epidermis is acanthotic and papillomatous with overlying hyperkeratosis rather than being atrophic [111]. An interface dermatitis with basal vacuolization, superficial lymphocytic infiltrate, and extensive dermal mucin characterizes the major histologic alterations in Gottron's papules.

A consequence of long-standing dermatomyositis in children is the presence of diffuse dermal calcinosis, known as *calcinosis universalis*. Histologic changes may or may not show features consistent with active lesions of dermatomyositis. In most cases, scattered lymphocytes and plasma cells are present along with increased numbers of fibroblasts. Elastic tissue fibers within the reticular dermis demonstrate a granular blue appearance, consistent with calcium deposition [112, 113].

4.7.3 Pathogenesis

The pathogenesis of juvenile dermatomyositis is believed to involve a combination of environmental triggers and dysfunction of the adaptive immune system in genetically susceptible individuals. Certain HLA alleles that may be important in JDM susceptibility, including HLA-DQA1*0501, HLA-DQA*0301, HLA-DRB1*0301, and HLA-B8, have been found more frequently in patients with JDM [105]. Some studies suggest that HLA-dependent chimeric cells play a direct role in disease pathogenesis, and that the mother's HLA genotype facilitates the transfer and persistence of maternal cells in the fetal circulation [114].

The immune system contributes to the pathogenesis of JDM. Myositis-associated antibodies and myositis-specific autoantibodies (MSAs) have been identified in about 40 % of JDM patients [115]. These autoantibodies are directed against cytoplasmic and nuclear components of myocytes. Vasculitis and vessel injury occur in JDM through activated complement components that induce cytokine release and the formation of the membrane attack complex [105, 115, 116]. In children with dermatomyositis, MHC-I heavy chain and β2-microglobulin are overexpressed in affected muscle tissues [117]. Type 1 interferons (IFNα and IFNβ) and tumor necrosis factor-α (TNF-α) play a central role in dermatomyositis by upregulating MHC class I in muscle fibers and causing activation of the endoplasmic reticulum stress response, leading to muscle injury and resulting myositis [117–119]. Dermatomyositis in children and adults seem to correlate with the type 1 IFN gene signature [120]. In addition, IL-6 production and type 1 IFN gene signature are potential biomarkers for disease activity in dermatomyositis [120].

An abnormal response to a foreign antigen that is homologous to a self-antigen (molecular mimicry) may be another mechanism for the aberrant immune response seen in JDM. For example, the amino acid sequence of the M5 protein of group A β-hemolytic streptococci is homologous to human skeletal myosin heavy chain [121]. Moreover, myosin heavy chain epitope may be a target autoantigen in JDM with

cytotoxic T lymphocytes contributing to muscle fiber damage. Other possible triggers include infectious agents (such as coxsackievirus, toxoplasma, echovirus, and parvovirus), sun exposure, medications, and vaccines [105, 122].

4.8 Erythema Multiforme and Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis

4.8.1 Clinical Features

Erythema multiforme is relatively rare in children, accounting for 20 % of reported cases [123]. It is slightly more common in boys. Erythema multiforme typically is thought to represent a reactive process to an exogenous stimulus, most commonly drugs (such as penicillins) or infection (such as herpes simplex virus, mycoplasma pneumoniae, Epstein B virus, and group A streptococcus) [123, 124]. In pediatric cases, the most common cause is infection, and mycoplasma pneumoniae and herpes simplex virus are most frequently associated with disease onset [125].

"Classic" erythema multiforme is described as the acute onset of symmetrically distributed, dusky-colored, targetoid, erythematous macules and papules with acral accentuation, including the palms and soles (Fig. 4.26). Central vesiculation and erosions may be seen. Mucosal involvement may occur as well (coined by some as erythema multiforme major). Skin changes typically resolve within 2 weeks, but secondary dyschromia and scarring may persist for longer periods of time. Relapses do occur, especially in the setting of recurrent mucocutaneous herpes simplex virus infection [126].

Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a delayed-type hypersensitivity reaction that causes widespread apoptosis of keratinocytes. In contrast to erythema multiforme, SJS/TEN is more commonly caused by drug exposure [125]. The main causative agents include anti-infective sulfonamides and anticonvulsants, specifically carbamazepine, followed by penicillins and nonsteroidal anti-inflammatory drugs [125, 127]. Mycoplasma pneumoniae is the leading infectious cause of disease seen in children, although cases following infections by viruses (such as coxsackievirus, influenza virus, Epstein–Barr virus, human herpes virus 6 and 7, cytomegalovirus, and parvovirus), bacteria (streptococcus β-haemolyticum group A), mycobacterium, and rickettsia have been described as well [128].

Fig. 4.26 Erythema multiforme shows targetoid erythematous papules and plaques with central vesiculation

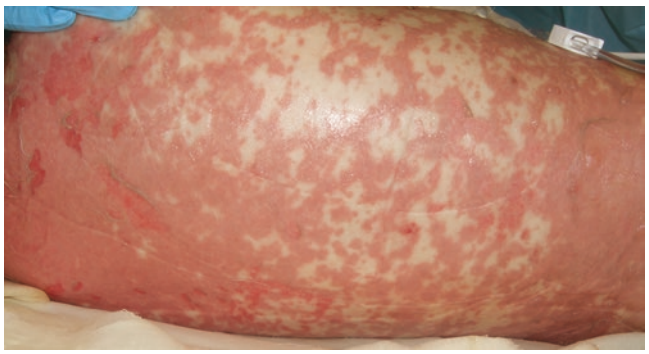

Fig. 4.27 Toxic epidermal necrolysis is characterized by dusky-colored, erythematous macules, papules and bullae with widespread necrotic desquamation

When skin detachment is limited to less than 10 % of body surface area involvement, patient is said to have SJS, while patient with more than 30 % of body surface area involvement is qualified as TEN. The skin exam of SJS/TEN is characterized by dusky-colored, erythematous macules and papules with eventual evolution to vesicles and bullae that coalesce into large areas of widespread necrotic desquamation (Figs. 4.27 and 4.28). Pain is a prominent feature as well as a positive Nikolsky sign (bulla formation when the skin is gently rubbed). The cutaneous presentation may be preceded by fever, malaise, ocular symptoms, and dysphagia [126, 128]. Almost all patients have involvement of at least two mucosal surfaces with similar vesicles, erosions, and overlying hemorrhagic crust. Children appear to have a better prognosis than adults when the offending drug is eliminated, or the underlying infection is treated [128]. Morbidity and mortality rates appear to improve with admission to a specialized burn unit or a pediatric intensive care unit. Long-term sequelae may include dyschromia, scarring (with hair loss or anonychia), mucosal strictures, and impaired vision.

4.8.2 Histology

The histologic changes in erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis are quite similar and are described together. The stratum corneum is

Fig. 4.28 Toxic epidermal necrolysis invariably involves mucosal surfaces with hemorrhagic crust overlying erosions at the mouth, cheeks, nose and eye lids

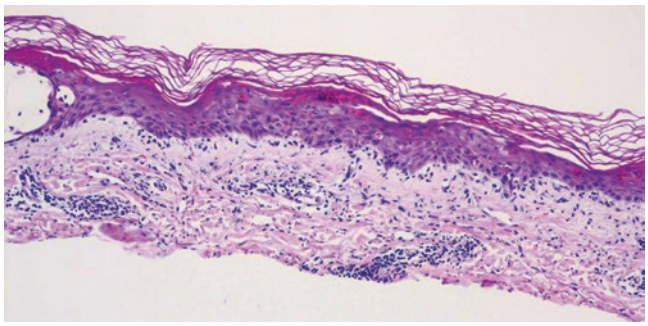

Fig. 4.29 Erythema multiforme is characterized by interface dermatitis and multiple dying keratinocytes, frequently giving rise to blisters

unremarkable. Specifically, except in old lesions, parakeratosis is not an expected finding, although mucosal biopsies in patients with Stevens–Johnson syndrome may demonstrate site-specific parakeratosis. This is important in distinguishing erythema multiforme from other inflammatory dermatoses with an interface pattern of inflammation. The epidermis has normal thickness, and it is characterized by varying amounts of basal vacuolization, keratinocyte necrosis, and lymphocytic exocytosis into the epidermis (Figs. 4.29 and 4.30). In TEN, full thickness epidermal necrosis is a common finding, often resulting in a subepidermal blister. In these cases, there is paradoxically a relatively scant inflammatory infiltrate. In the minor form of the disease, lymphocytes are present within the epidermis, along the dermal-epidermal junction and surrounding the superficial vessels [129]. In some cases, eosinophils may be present, but in many cases they are absent or inconspicuous. It has been suggested that there is preferential keratinocyte necrosis within acrosyringia in drug-induced erythema multiforme, likely due to accumulation of toxic levels of the drug within these structures [130]. A macrophage predominant pattern of exocytosis has

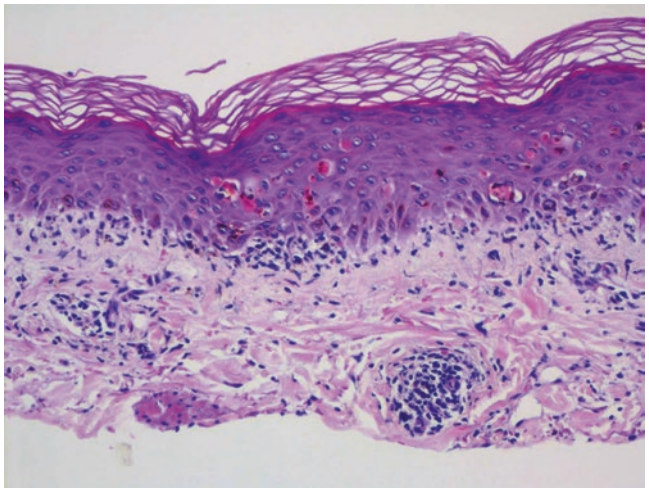

Fig. 4.30 Orthokeratotic keratin, exocytosis of lymphocytes into the epidermis and dying keratinocytes are the hallmark features of erythema multiforme

been observed in some cases of erythema multiforme [131, 132]. An overlap syndrome with lupus erythematosus has been described (Rowell syndrome) that demonstrates histologic features of both entities [133].

The differential diagnosis includes lupus erythematosus, dermatomyositis, graft vs. host disease, and pityriasis lichenoides. Lupus erythematosus can be distinguished based upon the presence of hyperkeratosis, a deep and peri-appendageal inflammatory infiltrate and dermal mucin, which are features not seen in erythema multiforme. Dermatomyositis similarly has abundant dermal mucin not seen in erythema multiforme. Graft vs. host disease can be very difficult to distinguish from erythema multiforme. The presence of eosinophils and a predilection for acrosyringeal necrosis might favor erythema multiforme, but often the clinical history is the best or only way to make this distinction. Pityriasis lichenoides demonstrates parakeratosis and hemorrhage, which are features not seen in erythema multiforme. TEN may be clinically confused with staphylococcal scalded skin syndrome. However, TEN results in a subepidermal blister, while a very superficial blister within the stratum corneum or uppermost portion of the granular layer characterizes staphylococcal scalded skin syndrome.

4.8.3 Pathogenesis

Erythema multiforme is a delayed-type hypersensitivity reaction that results in widespread apoptosis of epidermal keratinocytes. The pathogenesis is multifactorial and includes genetic and immune predispositions together with an inciting event, such as infection or medications [134]. In children, infectious causes that can induce erythema multiforme

include bacteria (Mycoplasma pneumoniae, streptococcus, and rickettsiae) and viruses (herpesvirus and parvovirus) [128]. In most cases, the precipitating event is infection with herpes simplex virus (HSV) being involved in 70–80 % of cases [134–136]. Drugs, particularly sulfonamides, nonsteroidal anti-inflammatory drugs (NSAIDs) and anticonvulsants, are other key triggering factors. Although less common, the disease can also be associated with malignancies, autoimmune diseases, radiation, and food additives [134, 137].

Genetic factors, particularly human leukocyte antigens (HLAs), predispose patients to develop erythema multiforme in response to stimuli. HLA-DQw3 has been found to be associated with HSV-associated erythema multiforme and may be a helpful marker to distinguish this entity from other erythema multiforme-like disorders [138]. Recurrent disease has been found to be associated with a number of HLAs, including HLA-B15 (B62), HLA-B35, HLA-A33, HLA-DR53, and HLADQB1*0301 [139, 140].

Studies of HSV-associated erythema multiforme have provided some insights into the mechanism of disease. Disease development starts with HSV infection of skin keratinocytes and mononuclear cells, such as macrophages and CD34+ Langerhans cell progenitors [141, 142]. Mononuclear cells carry HSV antigens (such as viral DNA fragments) to distant sites, leading to the recruitment of HSV-specific CD4+ type 1 T helper cells (Th1) [141, 143]. Th1 cells respond to viral antigens by producing interferon-γ (IFN-γ), which induces a robust immunologic response, causing epidermal damage. T-lymphocyte-mediated immune reaction results in cytotoxic immunological attacks on keratinocytes that express foreign viral antigens.

In drug-induced erythema multiforme, reactive drug metabolites trigger the disease process. Tumor necrosis factor-α (TNF-α), perforin, and granzyme B as well as cytotoxic CD8+ T lymphocytes cause keratinocyte apoptosis and epidermal damage [140]. Antibody-mediated immune response may also be involved in the disease.

Infection, vaccination, systemic diseases and drugs all have been implicated as the causes of *Stevens–Johnson syndrome and toxic epidermal necrolysis*. Among these potential sources, drugs are the most common inciting agents with antibiotics identified as the most frequent cause, followed by analgesics, anticonvulsants, and (NSAIDs) [144, 145]. The development of SJS/TEN is significantly higher in patients with immunosuppression, such as those with human immunodeficiency virus (HIV) infection and bone marrow transplantation [146, 147]. Mycoplasma pneumoniae leads to SJS predominantly in children and adolescents, the age group in which infections by this agent is most frequently seen [128, 148].

There is a strong genetic association between SJS/TEN and HLA allotypes, particularly in the Han Chinese population. In particular, HLA-B*1502 and HLA-B*5801 are associated with adverse drug reactions to carbamazepine and allopurinol [149, 150]. These findings are significant in that the FDA recommends genotyping all Asian patients for these HLAs before administration of drugs. These findings, however, have not been found in white Caucasian population [151]. An association between HLA-B*5801 and allopurinol-induced SJS/TEN has been found in the Japanese population [152]. Other HLA allotypes associated with adverse drug reactions have emerged, including HLA-A*3101 and HLA-B*1511 with carbamazepine, HLA-B*1502 with phenytoin, HLA-B*5801 with allopurinol, HLA-B*38 with sulfamethoxazole, and HLA-B*73 with NSAIDs [153]. Thus, an accurate knowledge of the risks associated with various HLAs would allow drugs to be tailored to an individual's genetic risk.

A major pathological finding in SJS/TEN is widespread keratinocyte apoptosis. T lymphocytes are involved in epidermal destruction in this disease. This process involves Fas–Fas ligand interaction, CD8+ cytotoxic T lymphocytes and natural killer-cells, and TNF-α and IFN-γ [154, 155]. Keratinocytes undergo apoptosis mediated by Fas-Fas ligand [156, 157]. Keratinocytes in lesional skin of patients with TEN have high levels of Fas and FasL that interact with Fas and FasL on adjacent keratinocytes. Skin-infiltrating lymphocytes have also been found to express Fas ligand. Interaction of Fas and FasL leads to the activation of caspase enzymes and cell apoptosis [158]. CD8+ T lymphocytes and natural killer cells are present in high number in blister fluid of patients with TEN. These cells express granzyme B and perforin, and can trigger keratinocyte apoptosis by the perforin, granzyme B, and granulysin pathway [155]. Drug-specific CD8+ T lymphocyte clones have been found in the skin of patients with drug eruptions which may serve as a mediator of apoptosis in TEN [159, 160]. Fluid from blisters in TEN patients has high concentrations of IFN-γ, TNF-α, and interleukins 6, 13, and 18 [161]. These cytokines can increase the expression of Fas ligand on keratinocytes, upregulate adhesion molecules and induce T lymphocyte recruitment to the skin, thus further enhancing keratinocyte apoptosis. The discovery of the roles of Fas-Fas ligand and CD8+ cytotoxic T lymphocytes in SJS/TEN has led to improved therapy for this disorder, including IVIG containing anti-Fas antibodies that can block Fas–FasL interactions, and cyclosporine which inhibits cytotoxic T lymphocytes [154].

4.9 Phototoxic Dermatitis

4.9.1 Clinical Features

Phototoxic dermatitis is a non-immunologic skin reaction occurring minutes to hours after concomitant exposure to a photosensitizing substance and UV radiation. Reaction is

dose dependent and universal in any person exposed to the substance in high enough quantities to elicit the photo-induced skin response [162].

Phytophotodermatitis (plant-induced photosensitivity) is the most common variant of phototoxic dermatitis seen in children, with plant-derived furocomarin compounds serving as the sensitizing agent. These naturally occurring psoralens may be found in a variety of plants, although the most frequently implicated families are Umbelliferae (celery, parsley, parsnip), Rutaceae (lemons, limes), and Moraceae (figs) [163]. Skin changes may mimic a sunburn with redness and occasional edema or appear in geometric patches and plaques with or without vesiculation. Pain may be reported at the site while pruritus occurs less frequently [163]. The acute dermatitis eventually evolves to hyperpigmentation and desquamation at the affected area.

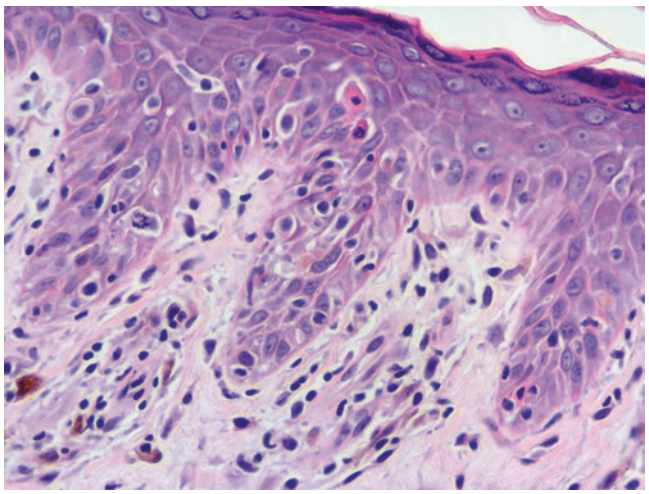

Fig. 4.32 Dying keratinocytes adjacent to intraepidermal lymphocytes are features of phototoxic dermatitis

4.9.2 Histology

Histologic sections of a phototoxic dermatitis show an epidermis of normal thickness with overlying orthokeratotic keratin. Within the epidermis, scant spongiosis is present along with scattered dying keratinocytes (Figs. 4.31 and 4.32). There is a mild lymphohistiocytic inflammatory infiltrate. Lymphocytes demonstrate exocytosis into the epidermis and are otherwise largely confined to the papillary dermis and around the superficial vessels. Eosinophils are infrequently seen in this type of drug eruption [164–166].

The histologic differential diagnosis includes graft vs. host disease, erythema multiforme and other interface dermatoses such as lupus erythematosus, dermatomyositis, and pityriasis lichenoides. A polymorphous light eruption might also enter the differential diagnosis. Graft vs. host disease and erythema multiforme might only be differentiated from phototoxic dermatitis based upon clinical history and presentation, as the histologic changes are quite similar. Lupus erythematosus shows a deep and peri-appendageal infiltrate, and dermatomyositis has dermal mucin not seen in a phototoxic drug eruption. The parakeratosis that is common in pityriasis lichenoides would not be an expected finding in phototoxic drug eruptions. Polymorphous light eruption does not feature dying keratinocytes, and the papillary dermal edema and reticular dermal inflammatory infiltrate in polymorphous light eruption are not seen in phototoxic drug eruptions. A photoallergic drug eruption demonstrates abundant spongiosis and a significant eosinophilic component in the inflammatory infiltrate.

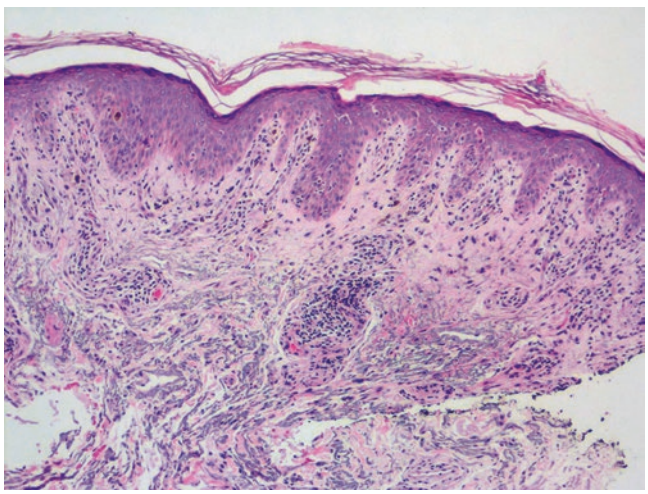

Fig. 4.31 Interface dermatitis with lymphocyte exocytosis and scattered dying keratinocytes characterize a phototoxic dermatitis

4.9.3 Pathogenesis

Phototoxic dermatitis is caused by concomitant exposure to sun and photosensitizing agents that increase the reactivity of the skin to ultraviolet (UV) light. A specific type of phototoxic dermatitis often seen in children is phytophotodermatitis [167, 168]. This is caused by chemicals in certain plants, such as lemons, celery, and parsley, that react with sunlight. Chemical furocoumarins (e.g., psoralens) in these plants react with UVA light, leading to a chemical reaction that causes local skin reaction in area of the body that comes into contact with the plant material [169]. When furocoumarins are photoactivated, they form covalent bonds with pyrimidine bases on DNA, resulting in DNA modifications and cell death [170].

Phototoxic reactions can be either oxygen dependent (photodynamic) or oxygen independent (non-photodynamic) [171, 172]. In oxygen-dependent reactions, radiation energy

excites the photosensitizer, resulting in tissue damage [173–175]. In oxygen-independent reactions, the photosensitizer, such as psoralen molecules, can cause direct tissue damage by binding to nuclear DNA, causing inflammation and inducing apoptosis of epidermal keratinocytes [171, 172, 176].

4.10 Fixed Drug Eruption

4.10.1 Clinical Features

Fixed drug eruption is relatively common with an incidence as high as 22 % in one case series of children with cutaneous drug eruptions [177]. The most frequently cited offending agent is co-trimoxazole in children and adults [177]. Other frequently cited drugs include dapsone, aspirin, NSAIDs, ampicillin, metronidazole, tetracycline, oral contraceptives, and phenolphthalein.

Fixed drug eruption is characterized by the development of solitary or multiple, round, circumscribed erythematous (pink to red) plaques on the skin following exposure to a specific drug (Fig. 4.33). The skin changes recur at the exact same location with reexposure, and resolve with a greyish brown, hyperpigmented patch. Mucocutaneous lesions can occur anywhere, but are most commonly seen on the trunk, extremities, lips, and genitalia. Lesions typically are noted within minutes to hours after drug exposure with more pronounced inflammation if exposure persists. Associated symptoms include burning and pruritus [177]. Subsequent dyschromia may persist for months to years, but should resolve with avoidance of the triggering agent.

Fig. 4.33 Fixed drug eruption may present as a round, circumscribed dusky colored thin plaque with a flaccid bulla centrally (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

4.10.2 Histology

Histologic changes are quite similar to those seen in erythema multiforme. The epidermis generally demonstrates overlying orthokeratosis with focal spongiosis and exocytosis of lymphocytes (Figs. 4.34, 4.35 and 4.36). Dying keratinocytes are seen largely within the basal layer and this may result in a subepidermal blister (bullous fixed drug eruption). The dermis shows a lymphohistiocytic inflammatory infiltrate along the dermal-epidermal junction, within the papillary dermis and around superficial vessels [178]. In many

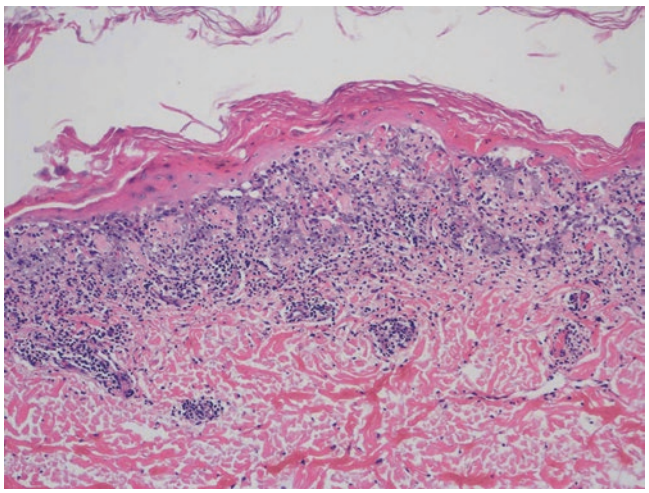

Fig. 4.34 Fixed drug eruption demonstrates brisk interface dermatitis with abundant dying keratinocytes

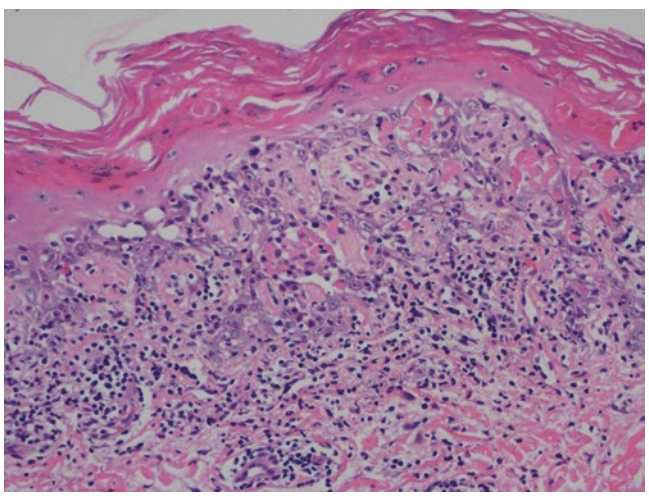

Fig. 4.35 Extensive exocytosis of lymphocytes into the epidermis and keratinocyte necrosis are features of fixed drug eruption

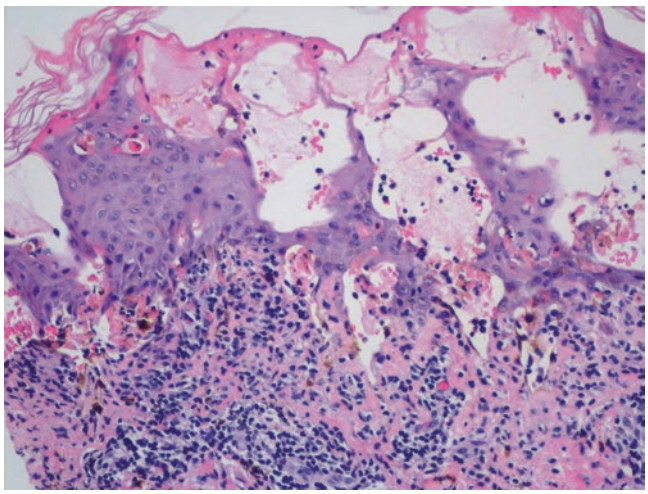

Fig. 4.36 Abundant keratinocyte necrosis results in dissolution of the epidermis and blister formation in fixed drug eruption

cases, neutrophils and scattered eosinophils may be encountered. Likely due to the locally recurrent nature of the process, pigment-laden macrophages often populate the papillary dermis, giving rise to the clinically apparent pigmented lesions (post-inflammatory pigmentary alterations).

The differential diagnosis includes erythema multiforme. It may be difficult to make this distinction purely on histologic grounds, although the presence of neutrophils and pigment-laden macrophages would favor a fixed drug eruption. Other interface processes such as lupus erythematosus, pityriasis lichenoides, and lichen planus (especially late stage lesions) might enter into the differential diagnosis, but these entities all have varying epidermal changes that are not seen in fixed drug eruptions. Post-inflammatory pigmentary alterations have many of the same histologic changes, but this is a reaction pattern that occurs as a consequence of many interface dermatoses and is nonspecific.

4.10.3 Pathogenesis

Fixed drug eruption is a delayed-type hypersensitivity reaction mediated by CD8+ T lymphocytes [179]. Skin-resident T lymphocytes that are abundant in resting lesions may originally have evolved to protect tissue integrity from invading pathogens. However, excessive activation of these cells by drugs could result in localized tissue injury. CD8+ T lymphocytes, which are normal resident cells in the epidermis, have an effector-memory phenotype and play a major role in the development of recurrent and localized tissue damage [180]. Additional recruitment of CD4+ and CD8+ T lymphocytes to a specific tissue site would also contribute to the late stage of fixed drug eruption. Direct action of activated CD8+ T lymphocytes as well as the release of cytokines into the local environment can result in the destruction of local keratinocytes [180]. Drugs can also induce the expression of intercellular adhesion molecule-1 (ICAM-1) on lesional keratinocytes and provide a localized initiating stimulus to activate T lymphocytes [181]. Thus, CD8+ T lymphocytes in the epidermis are critical in the initiation of destructive immune responses in fixed drug eruption.

4.11 Erythema Dyschromicum Perstans

4.11.1 Clinical Features

In adult populations, there appears to be a preponderance of erythema dyschromicum perstans in Hispanic individuals, but in children, most affected individuals are Caucasians [182]. Males and females are affected similarly.

The physical exam is characterized by lightly scaled, gray to blue oval macules, patches and thin plaques, occasionally with erythematous borders, beginning on the trunk and later spread to the extremities (Fig. 4.37). In adults, dyschromia appears to be persistent, while children can expect spontaneous resolution over months to years [182].

4.11.2 Histology

Depending upon the age of the lesion biopsied, the changes seen in erythema dyschromicum perstans resemble those seen in an interface dermatitis (acute) or those of post-inflammatory pigmentary alteration (chronic) (Fig. 4.38). Early lesions demonstrate skin with a normal epidermis infiltrated by lymphocytes. The basal layer has vacuolization with scattered keratinocyte necrosis. Mild spongiosis may be present. Lymphocytes are present along the dermal-epidermal junction and in the papillary dermis in either a lichenoid or

Fig. 4.37 Erythema dyschromicum perstans presents as bluish brown, hyperpigmented patches on the posterior neck of a young boy

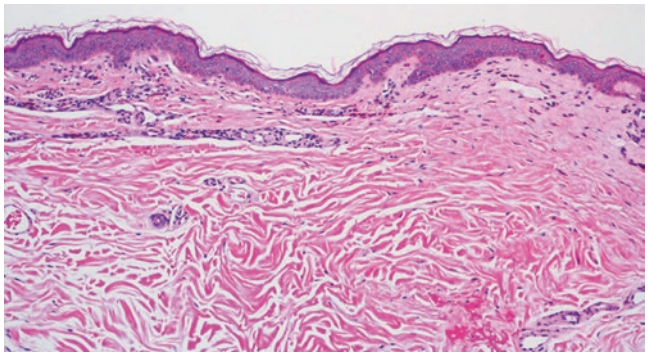

Fig. 4.38 Erythema dyschromicum perstan demonstrates interface dermatitis with melanophages in the papillary dermis

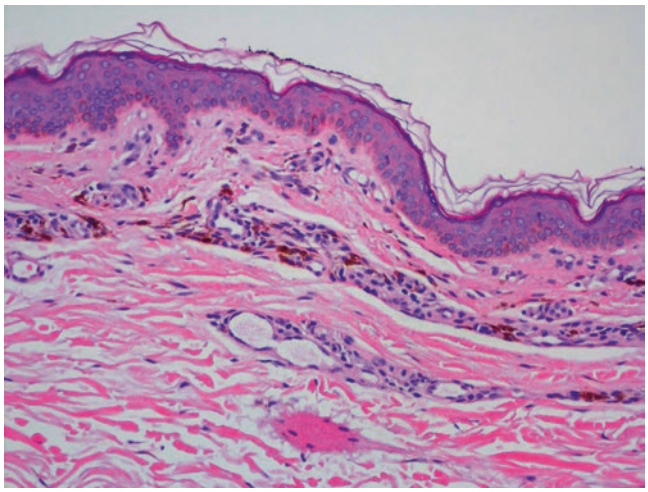

Fig. 4.39 A mild perivascular lymphocytic infiltrate and perivascular melanophages are the most common findings in erythema dyschromicum perstans

superficial perivascular distribution (Fig. 4.39). Eosinophils are not commonly seen [183–186]. Later lesions have less lymphocytic infiltrate and lesser amounts of exocytosis. Within the dermis, there is often slight papillary dermal fibrosis and abundant melanin-laden macrophages. Epidermal atrophy may be present. Late lesions have more extensive atrophy, papillary dermal fibrosis, vascular ectasia, and abundant melanophages [187].

The histologic differential diagnosis is that of interface dermatoses. Some authors have suggested that erythema dyschromicum perstans represents a variant of lichen planus; however, others have argued that the disease is a distinct entity [184]. It may be virtually impossible to make the distinction between atrophic lichen planus and erythema dyschromicum perstans based purely upon histologic grounds. Clinical correlation is essential. Erythema dyschromicum perstans lacks the marked hyperkeratosis, follicular plugging, mucin deposition and peri-appendageal infiltrate seen in lupus erythematosus. A fixed drug eruption may show similar findings, but also may have dermal neutrophils, which is not a feature of erythema dyschromicum perstans. Erythema multiforme would have a markedly different clinical presentation, and because of its acute nature, rarely demonstrates a significant number of melanophages in the papillary dermis. The absence of parakeratosis and dermal hemorrhage, in addition to the clinical presentation, enables distinction from pityriasis lichenoides.

4.11.3 Pathogenesis

Erythema dyschromicum perstans may be elicited by a number of potential inciting factors such as infections (whipworm and human immunodeficiency virus), toxins, pesticides, medications (ethambutol, penicillins, and benzodiazepines), and endocrinopathies (thyroid disorders) [182–184]. However, in the majority of cases in both children and adults, no inciting factor can be identified. Some reports have suggested that the disorder is due to an abnormal immune response to antigens, which results in damage to melanocytes and basal keratinocytes [188]. In Mexican Mestizo patients with erythema dyschromicum perstans, the disease may be associated with HLADR4 allele [189]. Immunohistochemical analysis of skin lesions shows that there is involvement of cell adhesion and activation molecules, with expression of intercellular adhesion molecule-1 (ICAM-1) and the major histocompatibility complex class II molecules (MHC II) in basal keratinocytes in the epidermis as well as in dermal lymphocytes [188]. Electron microscopy of a pediatric case shows small, immature, irregularly shaped melanosomes in keratinocytes [190].

4.12 Lichen Sclerosus

4.12.1 Clinical Features

Lichen sclerosus has a bimodal incidence distribution with most cases affecting prepubertal females and postmenopausal women. The prevalence is 1 in 900 girls, and 1 in 300 to 1 in 1000 women [191]. Ten to fifteen percent of cases are reported in children [1]. Females are affected disproportionately with female to male ratio of 10 to 1.

Childhood lichen sclerosus frequently affects the anogenital region with less than 10 % of cases occurring at other sites [191]. The most common presenting complaint is anogenital pruritus, dysuria and constipation. Lesions are characterized by coalescence of porcelain white polygonal papules into plaques with wrinkled atrophy, telangiectasia, petechiae, purpura, and fissures (Fig. 4.40) [1]. In cases with more severe inflammation, vesiculation may occur with hemorrhagic bullae and secondary erosions. In boys, perianal involvement is rare. More commonly, male patients

Fig. 4.40 Lichen sclerosus presents as porcelain white sclerotic plaques surrounding an erythematous patch with scattered petechiae

present with circumferential sclerosis at the tip of the prepuce, predisposing patients to phimosis and an inability to retract the foreskin. Pediatric lichen sclerosus typically has a chronic, relapsing course often with remission following puberty. However, continued monitoring is warranted as persistent genital lichen sclerosis has association with squamous cell carcinoma.

4.12.2 Histology

Histologic features vary with the age of the lesion biopsied. Early lesions of lichen sclerosus demonstrate a hyperkeratosis overlying an epidermis of normal thickness. Slight spongiosis is accompanied by a brisk, band-like lymphocytic infiltrate with extensive exocytosis into the epidermis. Scattered dying keratinocytes are present along with extensive vacuolization that in some cases may give rise to a subepidermal blister. The infiltrate may extend around the superficial vessels, but ordinarily it is not deep [1, 192–195]. Eosinophils are not part of the infiltrate, but if the biopsy is from or near a mucosal site, plasma cells may be identified as a site-specific component of the inflammatory response. As the lesions evolve, the lymphocytic infiltrate becomes less intense, with scattered lymphocytes within the epidermis, mild epidermal atrophy, hyperkeratosis, and papillary dermal fibrosis (Figs. 4.41, 4.42 and 4.43). Basal vacuolization persists and dying keratinocytes may be apparent. Late lesions can show extensive atrophy with marked hyperkeratosis. The inflammatory infiltrate is relatively minimal, yet slight basal vacuolization may be present over a greatly expanded and homogenized papillary dermis. The deep component to the inflammatory infiltrate is almost entirely absent.

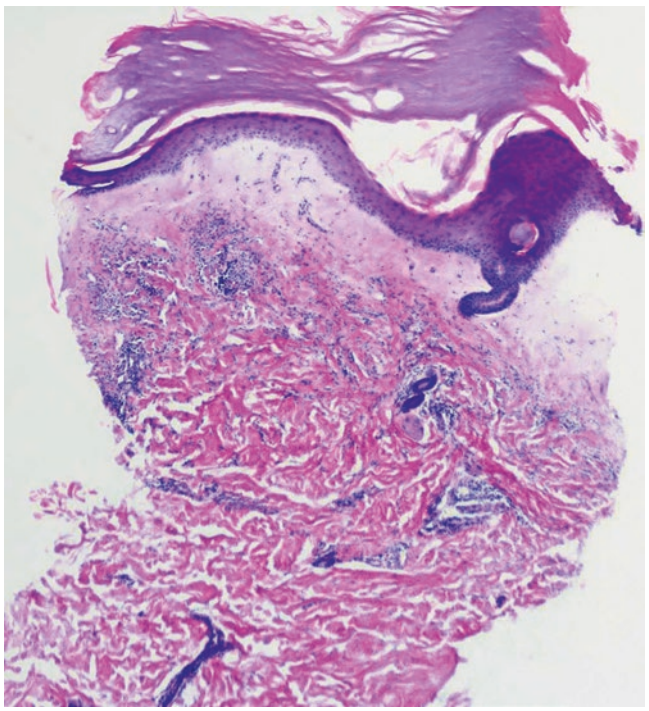

Fig. 4.41 Histologic findings in well-developed lesions of lichen sclerosis include marked hyperkeratosis, atrophic epidermis and homogenization of the papillary dermis

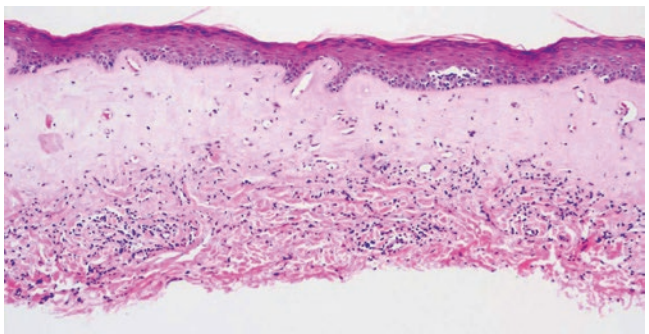

Fig. 4.42 Lichen sclerosus demonstrates homogenization of the papillary dermis as its most characteristic histologic feature

In some cases, changes indistinguishable from lichen sclerosus can be identified overlying reticular dermal changes that are diagnostic of morphea. Lichen sclerosus does not involve the reticular dermis, so when dermal fibrosis, compression of cutaneous appendages and deep inflammation occur, a diagnosis of morphea should be considered. Retention of elastic tissue fibers is also expected in morphea, while they are often markedly diminished or absent in lichen sclerosus [196]. It is not fully known whether there is true co-existence

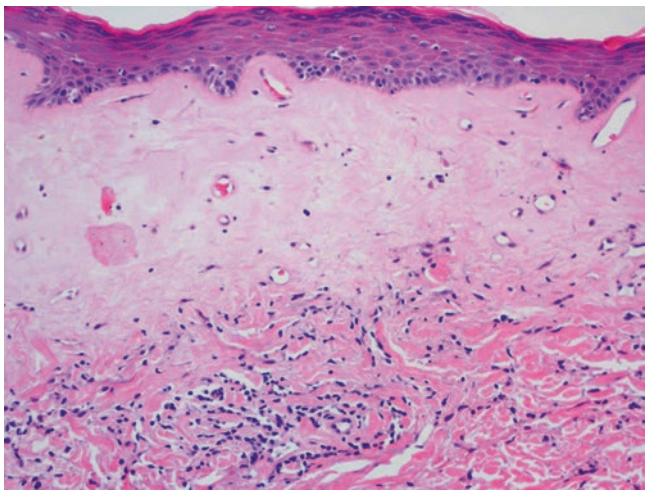

Fig. 4.43 A mild lymphohistiocytic infiltrate persists deep to the homogenized papillary dermis in lichen sclerosus

of the two diseases, or if morphea simply may demonstrate histologic changes in the superficial dermis that are indistinguishable from those seen in lichen sclerosus [194].

The differential diagnosis of lichen sclerosus includes other entities with lichenoid inflammatory reactions, such as lichen planus,lichenoid drug eruption and lupus erythematosus. In the earliest phase of the disease, it may be impossible to make the distinction from lichen planus, although the hypergranulosis seen in lichen planus is not an expected finding in lichen sclerosus. A lichenoid drug eruption characteristically contains eosinophils within the dermis in contrast to lichen sclerosus. Lupus erythematosus may have a deeper inflammatory infiltrate, dermal mucin, and a peri-appendageal inflammatory infiltrate that is not seen in lichen sclerosus. While radiation dermatitis may demonstrate similar papillary dermal sclerosis, epidermal atrophy and basal vacuolization as seen in fully developed lesions of lichen sclerosus, the clinical history can usually easily separate these two entities. As discussed above, the distinction from morphea may be difficult, but can be aided with use of elastic tissue stains. Mycosis fungoides may show some histologic similarity to lichen sclerosus, but this differential diagnosis rarely arises in children due to its rarity in this population [197].

4.12.3 Pathogenesis

Lichen sclerosus is an autoimmune disorder, which can manifest in genetically susceptible individuals following an external trigger [198]. About one-third of patients have an autoimmune disease, and up to 74 % have autoantibodies [199]. The most common autoimmune disorders associated with lichen sclerosus are pernicious anemia, vitiligo, morphea, alopecia areata, and autoimmune thyroiditis. A genetic link with HLA type 2 antigens has been shown, particularly with DQ7, DQ8, and DQ9 [200, 201]. Familial cases have been described, but the inheritance pattern has not been clearly established [198, 202]. The association of lichen sclerosus with DQ7 is high with childhood onset of the disease. In a cohort of pediatric patients, 65 % were homozygous for HLA-DQ7 as compared with 5 % in control population [203]. This finding supports the concept of immunological change in this disorder, and may provide insights into possible antigenic triggers of the disease.

Although the antigenic target of the autoantibodies in lichen sclerosus is not known, it has been postulated to be in the basement membrane region. Studies of patients with lichen sclerosus have identified circulating antibodies to the basement membrane zone [204]. These antibodies, however, may be secondary to tissue damage. Another study has identified circulating autoantibodies to extracellular matrix protein-1 (ECM1) in patients with lichen sclerosus [205]. Monoclonal populations of T lymphocytes have been reported as well [206, 207]. Immune dysregulation may create a permissive milieu for disease development.

Lichen sclerosus occurs predominantly in females, with two incidence peaks involving the vulvar during times of low estrogen (before puberty and post-menopause). It has been postulated that hormones may play a role in the disease pathogenesis [1, 208]. In a study of genital and non-genital lichen sclerosus, there are decreased androgen receptors in lesional skin as compared with normal skin, and decreased receptors in well-developed lesions as compared to early lesions, thus suggesting a potential role for androgen receptors in lichen sclerosus [209].

There is a possible link of lichen sclerosus with infection, but this remains controversial. There is some evidence supporting a role for *Borrelia burgdorferi* as a triggering factor in susceptible individuals in Europe and Japan [210]. However, these findings may be geographically specific, since *Borrelia* has not been identified in patients with lichen sclerosus in North America [211]. Human papillomavirus (HPV) has been implicated in disease pathogenesis. Viral koilocytic changes have been documented in lesional genital tissue, and HPV DNA (types 6, 16, and 18) has been detected in lichen sclerosus lesions in children [212, 213]. HPV is a ubiquitous virus and perinatal transmission has been documented in genital samples of newborns from HPV-positive mothers [214].

4.13 Graft vs. Host Disease

4.13.1 Clinical Features

The skin is the most commonly affected organ in graft-versus-host disease (GVHD), with cutaneous involvement in more than 80 % of patients with acute GVHD, and 75 % of patients

with chronic GVHD [215, 216]. The incidence of acute GVHD is dependent upon a number of factors including histocompatibility differences between donor and recipient, the conditioning regimen, recipient age, and primary disease staging. Contributing factors for chronic GVHD include, but are not limited to, reason for transplantation, HLA mismatch, second allogenic transplant, history of splenectomy, older recipient age, history of acute GVHD, and cytomegalovirus seropositivity in the donor or recipient [216].

Previously, distinctions between acute and chronic GVHD were made based on the timing of symptom onset, with acute being symptoms presenting fewer than 100 days post-transplant and chronic thereafter. However, a 2005 Consensus Group reclassified the definition of the disease entities based on clinical presentation and histologic features [216].

The clinical hallmarks of acute GVHD are skin eruption, diarrhea (gastrointestinal tract involvement) and bilirubin elevation (liver disease with cholestatic jaundice) with grading of severity from I to IV based on the extent of each symptom. The skin changes may begin as erythematous macules or edematous papules, and progress to a generalized folliculocentric or morbiliform morphology with eventual evolution to erythroderma or an exfoliative dermatitis (Figs. 4.44, 4.45, and 4.46) [216]. Vesicular and ulcerative lesions have been described as well. Subjective symptoms include pruritus and dysesthesias [215, 216]. In distinguishing acute cutaneous GVHD from a drug hypersensitivity reaction, studies suggest facial (including ear) involvement with palmoplantar eruption is more suggestive of GVHD as is the presence of diarrhea in the setting of hyperbilirubinemia.

Fig. 4.44 Graft vs. host disease presents as an erythematous desquamating malar rash with foci of vesicles over the nasal tip and upper cutaneous lip in a teenage boy

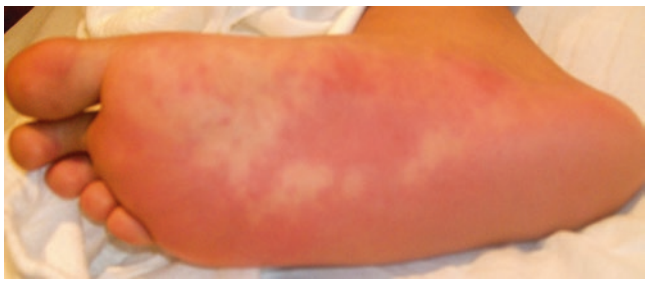

Fig. 4.45 Palmoplantar erythema is more commonly seen in GVHD than in drug eruptions, as noted in the same patient from Fig. 4.44

Fig. 4.46 Palmoplantar erythema is a feature of graft vs. host disease (same patient as in Fig. 4.44)

Chronic GVHD may present with sclerotic (15 % of affected patients) and nonsclerotic skin disease with key features including poikiloderma, lichen planus-like eruptions, lichen sclerosus-like lesions, morphea-like sclerosis, and deep sclerosis/fasciitis [216]. Other targeted organs include the liver, eyes, and, less frequently, the GI tract, lungs, esophagus, genital tract, and musculoskeletal system. Both acute and chronic GVHD may present with oral disease including gingivitis, mucosistis, erythema and pain as well as the more specific findings of lichen-planus like changes (Wickham striae and ulcers), leukoplakia, and restricted range of motion in chronic disease.

Disease management is hampered by the need to minimize the morbidity and mortality of GVHD while maintaining the benefit of graft-versus-tumor effect [216]. Disease resolution is varied with lower remission rates and greater unpredictability of treatment response in patients with more severe clinical presentation [217].

4.13.2 Histology

Acute graft vs. host disease is an interface dermatitis for which a grading system (Lerner system) has been developed that assesses the severity of the disease [218]. Grade I changes are those of a mild spongiotic process with a superficial perivascular lymphohistiocytic infiltrate and mild exocytosis. These changes are not diagnostic and simply correlate with the clinical impression of a mild erythematous clinical eruption. Grade II lesions demonstrate exocytosis of lymphocytes into the overlying epidermis with scattered dying keratinocytes that are usually most prominent along the basal layer (Figs. 4.47 and 4.48). Basal vacuolization is present, and there is an underlying lymphohistiocytic inflammatory process that usually is devoid of eosinophils. A similar interface pattern is seen within the follicular epithelium and eccrine ducts in some cases [219]. Grade III changes are similar to those seen in Grade II but keratinocyte necrosis is much more extensive and confluent, and may result in focal separation of the epidermis from the dermis. The dermal changes are identical to those seen in less severe disease. Grade IV disease is characterized by full thickness epidermal necrosis and a subepidermal blister with an underlying superficial perivascular lymphohistiocytic infiltrate. In some cases, keratinocyte atypia or dysplasia has been described. This is most often attributed to a chemotherapy regimen that predates the transplantation process [220]. A rare case of psoriasiform dermatitis has been described in a child with acute GVHD [221]. In this case, psoriasiform epidermal hyperplasia was co-existent with histologic changes suggestive of acute GVHD.

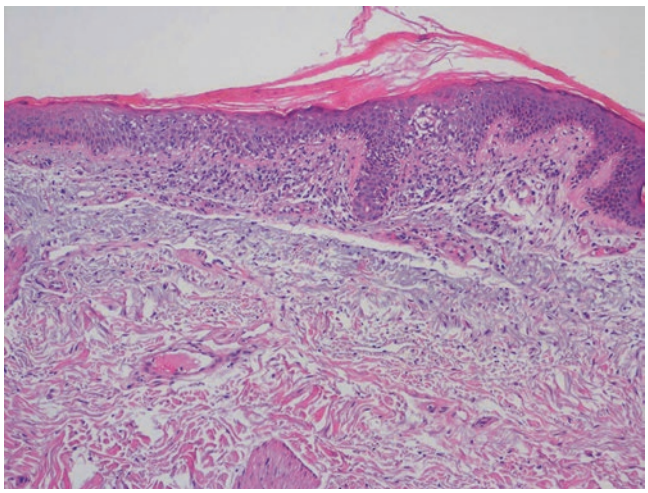

Fig. 4.47 Grade II GVHD is characterized by mild interface dermatitis, focal spongiosis and scattered dying keratinocytes

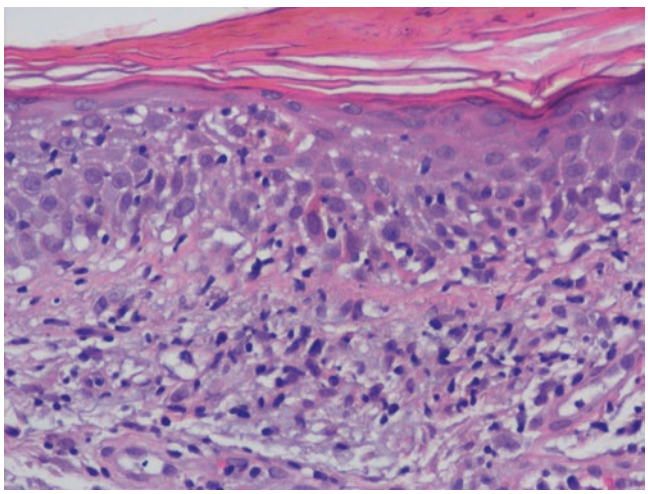

Fig. 4.48 Dying keratinocytes juxtaposed with exocytotic lymphocytes (tagging) are seen in grade II GVHD

The histologic differential diagnosis of GVHD includes drug eruption and viral exanthem [222]. The presence of eosinophils and accentuation of keratinocyte necrosis within acrosyringia would favor a drug-induced interface dermatitis. However, the absence of these findings does not exclude a drug-related process and in some cases, distinction is not possible with biopsy alone. A viral exanthema does not usually have dying keratinocytes, which is a useful feature to distinguish this eruption from acute GVHD, grades II–IV. Grade I acute GVHD cannot be distinguished from any of a wide range of entities that give rise to a mildly spongiotic epidermis.

There are two reaction patterns of chronic GVHD in the skin: a lichenoid reaction pattern and a pattern that resembles scleroderma [223].

Lichenoid chronic graft vs. *host disease* is characterized by histologic changes that may be indistinguishable from lichen planus. The epidermis is acanthotic with hyperkeratosis and focal hypergranulosis. A band-like infiltrate of lymphocytes is present along the dermal-epidermal junction with exocytosis and scattered dying keratinocytes usually along the basal layer. Basal vacuolization is present, occasionally resulting in small subepidermal separations. The inflammatory infiltrate is usually confined to the papillary dermis. Eosinophils and plasma cells are not seen in most cases. Abundant melanophages are present in the papillary dermis in many cases [223].

The s*clerodermoid* reaction pattern has histologic changes that may be difficult to separate from scleroderma in the absence of clinical history. The presence of slight basal vacuolization and papillary dermal melanophages may help to make this distinction, as these changes are not common in scleroderma and morphea. In sclerodermoid pattern, there is thickening of collagen bundles in the reticular dermis with decreased interstitial space. Sclerosis is apparent and results in compression of cutaneous appendages with loss of the wispy adventitial collagen surrounding hair follicles and eccrine ducts. In late stage lesions, this may result in loss of

the adnexa. The overall thickness of the dermis is greatly increased and there is a superficial and deep perivascular inflammatory infiltrate that consists of lymphocytes, histiocytes, and scattered plasma cells. The fibrosis may extend into the septae separating subcutaneous fat lobules [224].

4.13.3 Pathogenesis

Graft vs. host disease is an immunologic reaction that arises as a complication in which competent immune cells from a donor are transplanted into an immunocompromised recipient. This situation most commonly occurs in allogeneic hematopoietic stem cell transplantation, but GVHD also occurs in other conditions, such as autologous and syngeneic transplantation, blood product transfusion, solid-organ transplantation, and maternal–fetal transfusion. In order for GVHD to occur, the graft must contain immunologically competent donor T lymphocytes that recognize and react to recipient proteins (major and minor histocompatibility antigens) [217, 225]. Other immune cells (such as dendritic cells, natural killer cells, macrophages, and mast cells) also play a major role in GVHD [217].

GVHD is more common in adults than children, and it is believed to be the result of decreased thymic function with increased age [226]. Normally, T lymphocytes undergo induction of self-tolerance in the thymus. T lymphocytes are "educated" to recognize self-antigens, and T cell clones that react against self-antigens are deleted. Because the thymus involutes with age, the process of self-tolerance with deletion of self-reactive T cells is not as efficient in adults as it is in children. This may explain why GVHD has an increased incidence and prolonged course in adults.

The pathophysiology of "acute" GVHD consists of three distinct phases. The first phase consists of tissue damage, which releases tissue antigens into the bloodstream. These antigens are recognized and processed by antigen-presenting cells (APCs), leading to the production of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-1. In the second phase, APCs present alloantigens to donor T lymphocytes infused with the graft. These donor T lymphocytes proliferate in response to cytokines. In the third phase, stimulated donor T lymphocytes proliferate and target host cells, leading to tissue destruction. A special type of T lymphocytes, called FoxP3+/CD4+/CD25+ regulatory T cells (Treg), function to suppress auto-reactivity. Treg cells either from the donor graft or in the recipients have been shown to suppress GVHD [227, 228].

The pathophysiology of "chronic" GVHD is poorly understood. Chronic GVHD is driven by type 2 helper T lymphocytes (Th2), and typically results in fibrosis of the affected organs [217]. Chronic GVHD involves T lymphocyte alloreactivity directed against recipient antigens, T lymphocyte auto-reactivity, and B-cell dysregulation [229]. TGF-β and platelet-derived growth factor (PDGF) are involved in the development of skin fibrosis in chronic GVHD. Some patients with chronic disease have been found to have circulating activating antibodies to the PDGF receptor [230]. Targeted inhibition of PDGF receptor may ameliorate tissue fibrosis associated with chronic GVHD [226, 231].

4.14 Eruption of Lymphocyte Recovery

4.14.1 Clinical Features

The exact incidence of eruption of lymphocyte recovery is not known as it is not universally seen in patients undergoing marrow-ablative chemotherapy [232]. Eruption of lymphocyte recovery is described as a generalized exanthem of coalescing and discrete erythematous papules and macules, occurring 17–21 days after chemotherapy initiation [233]. Patients frequently have concomitant fever but no associated visceral disease. The disorder is self-limited with subsequent desquamation and mild hyperpigmentation of previously affected areas [232].

4.14.2 Histology

It has been debated whether this represents a discrete entity or is simply a variant of Grade I graft vs. host disease [234–236]. The histologic findings, as is the case with Grade I graft vs. host disease, are not specific. Less commonly, changes indistinguishable from Grade II graft vs. host disease may be associated with the eruption of lymphocyte recovery. There is a mild superficial perivascular lymphohistiocytic infiltrate with scattered lymphocyte exocytosis and mild spongiosis.

4.15 Acrodermatitis Chronica Atrophicans

4.15.1 Clinical Features

Acrodermatitis chronica atrophicans (ACA) is a late manifestation of Borrelia infection that rarely occurs in children with fewer than ten reports of pediatric cases in published literature [237]. It is more commonly described in elderly women, and is seen almost exclusively in European countries where the bacterial strain of *Borrelia afzelii* is found [237].

ACA presents as bluish-red patches followed by "doughy" induration or swelling at the extensor extremities, including the knees, elbows, and ankles [238]. Later, affected areas become atrophic with hypopigmentation and sclerosis. Unlike erythema chronicum migrans, ACA does not resolve

spontaneously and requires appropriate antibiotic therapy for clearance [237, 238]. Atrophic changes are permanent so diagnosis during earlier stages of disease presentation is key.

4.15.2 Histology

Acrodermatitis chronica atrophicans shows a lymphoplasmacytic infiltrate along the epidermal junction and surrounding the vessels of the superficial vascular plexus (Fig. 4.49). In early lesions, the inflammation can be quite dense and lichenoid. As lesions develop, the epidermis becomes progressively more atrophic and post-inflammatory pigmentary alterations are present as evidenced by papillary dermal melanophages. Papillary dermal fibrosis and slight vascular ectasia are also seen in most cases [239]. A deep perineural infiltrate with scattered plasma cells is highly suggestive of this entity [240] (Fig. 4.50). Special stains such as Warthin-Starry stains and immunohistochemical stains demonstrate *Borrelia burgdorferi* in most cases.

Some authors have reported co-existence of lichen sclerosus with ACA, but there may be overlap in histologic findings and two separate disease processes may not actually be present [241]. Similarly, changes of morphea have been reported in concert with ACA. Others have suggested that preservation of elastic tissue fibers favors morphea, while in ACA these fibers undergo elastolysis and are lost [242, 243]. Again, the relationship between the two entities remains somewhat unclear and controversial [244].

In rare cases of ACA, a prominent nodular lymphocytic infiltrate is present within the dermis [245]. Cutaneous lymphoid hyperplasia is another histologic reaction to the infectious microorganisms, and its coexistence with changes seen in ACA are further evidence of infection.

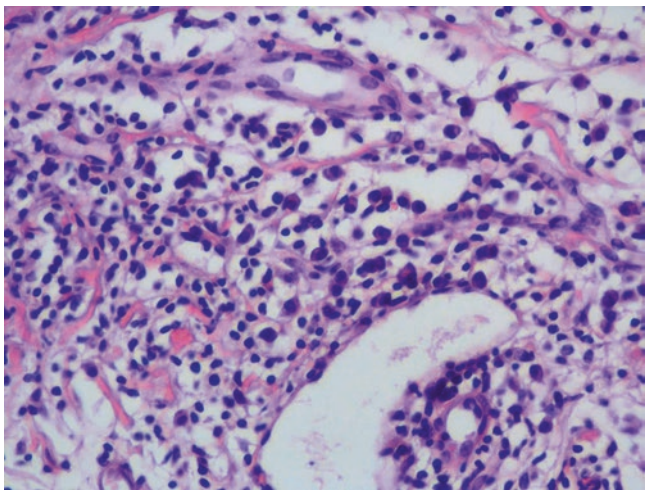

Fig. 4.50 Abundant plasma cells around vessels and dermal nerves are seen in acrodermatitis chronica atrophicans

The histologic differential diagnosis of ACA includes other interface dermatoses such as lichen planus, especially in the late and atrophic phase of that disease. Graft vs. host disease may show similar histologic changes, but it can be readily differentiated based upon clinical history. Similarly, erythema multiforme presents with a very different clinical appearance and does not have papillary dermal fibrosis or other signs of chronicity in most cases. ACA does not display dermal mucin or deep peri-appendageal inflammation seen in lupus erythematosus and dermatomyositis.

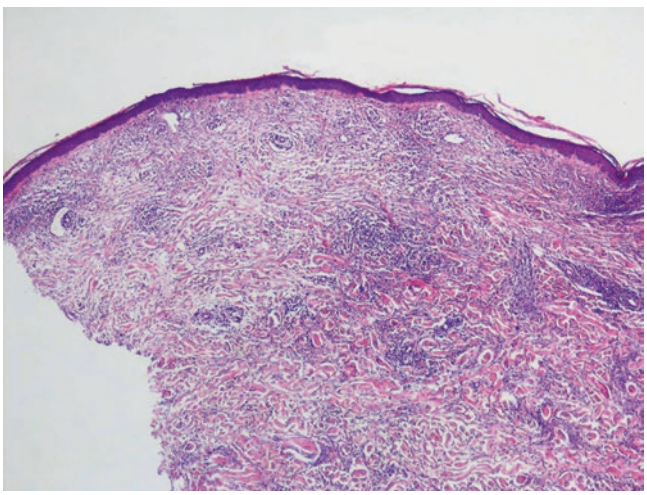

Fig. 4.49 Acrodermatitis chronica atrophicans demonstrates an atrophic epidermis overlying a superficial and deep perivascular infiltrate of lymphocytes, histiocytes and plasma cells

4.15.3 Pathogenesis

ACA is a form of Lyme borreliosis, which is chronic and can be present for months to years after the initial tick bite and subsequent Borrelia infection [237, 246]. It is caused by infection with three specific species of *Borrelia burgdorferi: Borrelia burgdorferi sensu stricto* (considered the most arthritogenic), *Borrelia afzelii* (most often isolated from skin, and common in Europe), and *Borrelia garinii* (most often associated with neuroborreleiosis) [246].

Although the role of *Borrelia* in ACA is clear, its complete pathophysiology is not fully understood. It is known that the outer surface proteins of the microorganism can bind to the extracellular matrix and induce changes in collagen and elastin fibers in the dermis [237]. *Borrelia* has protective mechanisms, which can aid it in escaping the immune system or leading to an inappropriate immune response. The expression of major histocompatibility complex class II (MHC II) on Langerhans cells in the skin is downregulated

in patients with Lyme disease. High levels of the chemokines CXCL9 and CXCL10 have been observed in patients with ACA, which may contribute to the chronicity of the disease [247]. Cross-reactive antibody responses may result in autoimmune damages [237, 248].

4.16 Erythema Ab Igne

4.16.1 Clinical Features

The incidence of erythema ab igne is unknown, and there is no gender predilection [249]. The skin exam of erythema ab igne is characterized by a hyperpigmented reticulate patch, occasionally with concomitant erythema (Fig. 4.51). Over time, the patches become fixed and may develop associated atrophy and telangiectasia. Dyschromia typically fades with withdrawal of the offending heat source. Patients may be at long-term risk of developing cutaneous malignancies, such as squamous cell and Merkel cell carcinomas, at previously affected areas [249].

4.16.2 Histology

Histologic features of erythema ab igne show skin with an epidermis that is commonly atrophic with overlying hyperkeratosis. The normal rete ridge pattern is often effaced. Scattered dying keratinocytes are seen along the basal layer in proximity to exocytotic lymphocytes. Focal keratinocyte atypia is present and in some cases resemble the appearance of an actinic keratosis. Within the dermis, melanophages are present in the papillary dermis, and there is a mild lymphohistiocytic inflammatory infiltrate largely centered on the superficial vessels. Increased elastotic material is present within the superficial dermis [249–251]. In most cases, vascular ectasia and endothelial cell swelling is prominent. In rare cases, reactive angioendotheliomatosis has been described with a lobular proliferation of small, well-formed blood vessels with enlarged and somewhat atypical appearing endothelial cells [252, 253]. Hemosiderin and extravasated erythrocytes may be present [251].

The histologic differential diagnosis includes actinic keratosis and vascular proliferations. Actinic keratoses are uncommon in children. In most cases, they have more intense papillary dermal elastosis than is seen in erythema ab igne. Furthermore, the vascular ectasia and proliferation seen in erythema ab igne are not features of actinic keratoses. The vascular proliferation that occurs in some patients with erythema ab igne is not as florid as one might expect with a tufted angioma, nor is the vascular ectasia as extensive as in a port wine stain (nevus flammeus). Lobular capillary hemangiomas has much greater numbers of vessels than are seen in erythema ab igne. The clinical presentation would serve to easily distinguish each of these entities from erythema ab igne.

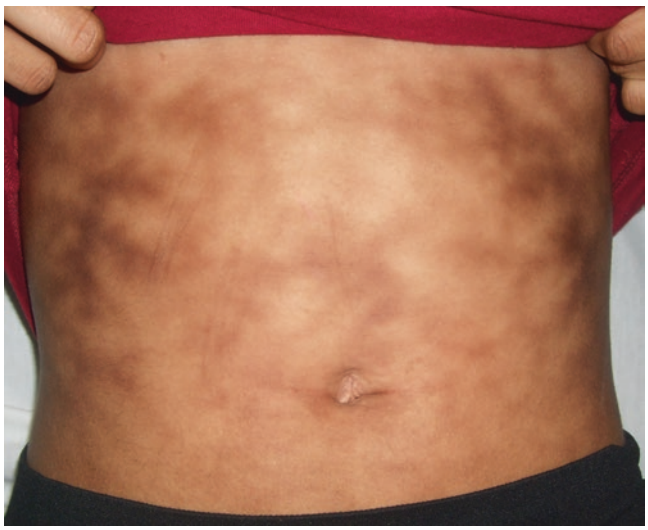

Fig. 4.51 Erythema ab igne is characterized by reticulate hyperpigmented patches as occurred on the abdomen following prolonged use of a heating pad

4.16.3 Pathogenesis

Erythema ab igne results from prolonged, repeated exposure to low levels of infrared radiation to the skin, and it is commonly associated with the use of computer laptops and heating devices, such as heating pads [254–256]. It has been suggested that heat-induced damage to superficial blood vessels in the skin leads to vascular dilation and deposition of hemosiderin in a reticulate distribution [257]. Electron microscopy studies of the lesions show regressive changes in basal keratinocytes, activation of melanocytes with an increase in dendritic processes, and elastic fiber modifications similar to those seen in actinic elastosis [258].

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Dermatoses with Minimal Epidermal Changes

5

5.1 Erythema Annulare Centrifugum

5.1.1 Clinical Features

Erythema annulare centrifugum (EAC) is a reactive dermatitis with a number of reported etiologies, including infectious antigens, drugs, neoplasm, and autoimmune diseases, although the majority of cases are idiopathic [1]. It has a peak incidence in the third and fifth decades of life with no gender predilection.

EAC presents with recurrent crops of erythematous papules that have centrifugal spread and coalesce into arcuate, annular, and polycyclic configurations (Fig. 5.1) [1]. In superficial variants of EAC, the most distinguishing feature is trailing scale along the periphery of the erythematous borders. Although the clinical course is characterized by recurrent crops of individual lesions that last for several days, the condition typically resolves spontaneously, especially after clearance of the inciting factor.

5.1.2 Histology

Erythema annulare centrifugum is characterized by a dermal inflammatory infiltrate described as "tight perivascular cuffing" (Fig. 5.2). The epidermal changes are variable depending upon the biopsy site and the type of lesion biopsied. If the leading edge of the annular lesion is biopsied, the epidermis will demonstrate small foci of spongiosis, exocytosis of lymphocytes, and overlying parakeratosis. If the central portion of the lesion is biopsied, the epidermis will be entirely normal, lacking all of these changes. Papillary dermal edema may be present in some cases. The dermis has a predominantly lymphohistiocytic infiltrate that is centered around superficial blood vessels (Fig. 5.3). There is little interstitial inflammatory infiltrate, giving rise to the "tight cuffing" descriptor that is often associated with this disease. In a minority of cases, small numbers of eosinophils may be present within the dermis [2]. A "deep" variant of the disease has been described in which the inflammatory infiltrate extends to involve deeper vessels within the reticular dermis in addition to the superficial vessels. In these cases, epidermal changes are not present [3].

The histologic differential diagnosis of EAC is extensive because the histologic changes in this entity are not entirely specific. An arthropod bite reaction has much overlap, but the infiltrate usually contains more eosinophils between collagen bundles in the interstitium, often has a superficial punctum and extravasation of erythrocytes at the point of arthropod bite. Lupus erythematosus, especially the tumid variant, may show similar changes, but the presence of a peri-appendageal infiltrate and dermal mucin will help to distinguish lupus from EAC. Polymorphous light eruption has a very different clinical presentation and often demonstrates papillary dermal edema, a feature not associated with EAC. Some authors believe that the deep variant of EAC does not represent a distinct entity, but rather is a manifestation of one of the aforementioned processes or even a borrelial infection [4]. If the leading edge of the lesion is biopsied, the differential diagnosis is that of a mild spongiotic dermatitis and might include nummular eczema, an id reaction and atopic dermatitis.

5.1.3 Pathogenesis

The etiology of EAC is poorly understood. An immunologic basis for the disease has been proposed with the findings of IgG and C3 deposition at the basement membrane zone in lesional skin [5, 6]. EAC may represent a skin manifestation

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Fig. 5.1 Erythema annulare centrifugum as erythematous papules adjacent to the more classically described annular plaque with trailing scale along the leading edge of erythema (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

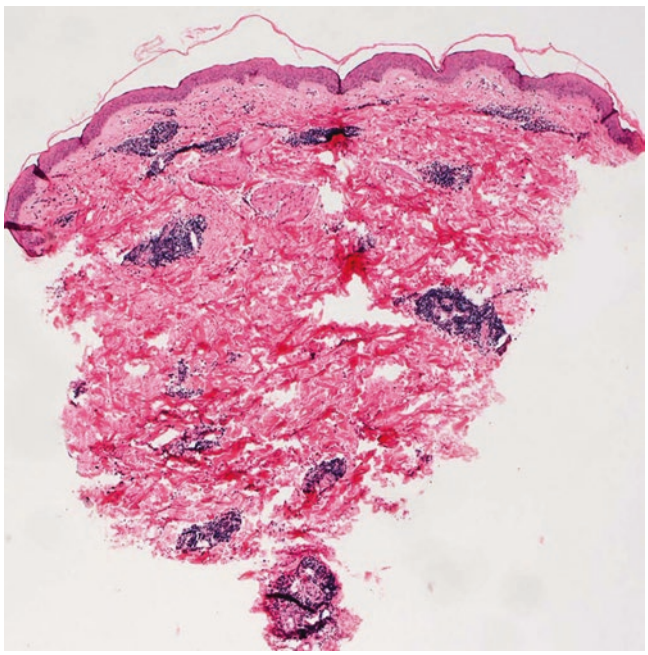

Fig. 5.2 Histologic changes in erythema annulare centrifugum include a superficial perivascular lymphocytic infiltrate that is "tightly cuffed" around vessels with little interstitial inflammation. The epidermis is unremarkable except at the edge of the lesion

of a hypersensitivity reaction to a variety of underlying conditions, including infection, malignancy, and immunologic disorders. However, there is no increased incidence of these associations with EAC as compared with the general population [7, 8].

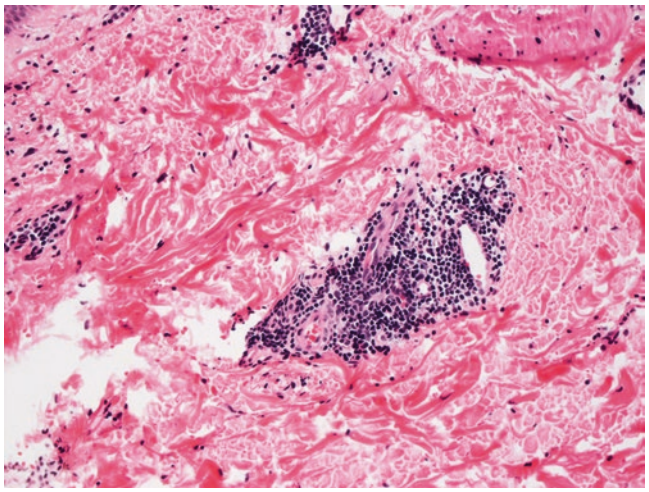

Fig. 5.3 A predominantly lymphocytic infiltrate wraps tightly around dermal blood vessels in erythema annulare centrifugum

5.2 Pigmented Purpuric Dermatoses

5.2.1 Clinical Features

Pigmented purpuric dermatoses (PPD) are more commonly seen in adults, although reports exist of cases in children between 8 and 15 years old [9]. PPD is characterized by petechial and purpuric macules and patches, most commonly localized to the lower extremities (Fig. 5.4). The most common variants seen are described separately below.

Progressive pigmented purpuric dermatosis/Schamberg's disease: asymptomatic, red to slightly orange hued punctate and non-blanching macules (likened to cayenne pepper) that may coalesce into irregular shaped patches. Pruritus is an occasional complaint.

Purpura annularis telangiectoides/Majocchi's disease: bluish-red, annular patches with associated discrete dark-red telangiectatic puncta and centrifugal spread. Occasionally, subtle atrophy is noted centrally. The site of initial involvement is usually the legs with eventual expansion to the arms.

Pigmented purpuric lichenoid dermatosis/Gougerot–Blum Syndrome: red to blue lichenoid papules that coalesce to form larger plaques on the distal legs, thighs, and trunk.

Lichen aureus: described elsewhere in this volume.

Itching and eczematoid purpura of Doucas and Kapetanakis/disseminated pruriginous angiodermatitis: pruritic generalized eruption of brown and deep red purpuric macules.

Overall, the prognosis of PPD varies. It follows a chronic and relapsing course, although spontaneous resolution is expected within months to years [10].

Fig. 5.4 Pigmented purpuric eruption shows coalescence of non-blanching reddish brown macules with interspersed petechiae

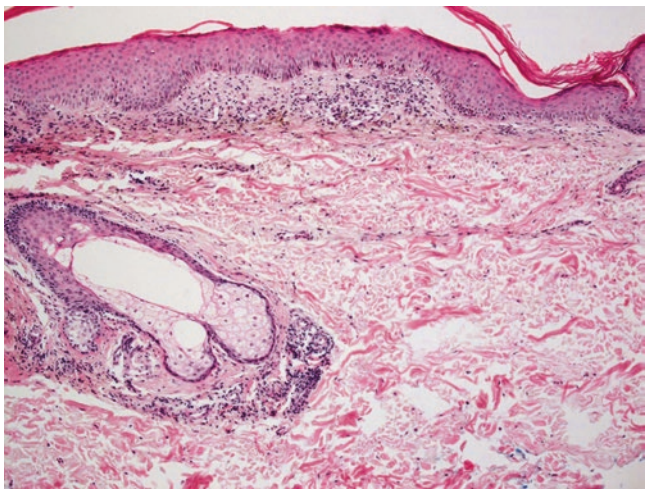

Fig. 5.5 Histologic findings in pigmented purpura are those of a superficial perivascular lymphocytic infiltrate with minimal epidermal involvement. Hemosiderin-laden macrophages are readily apparent even at low magnification

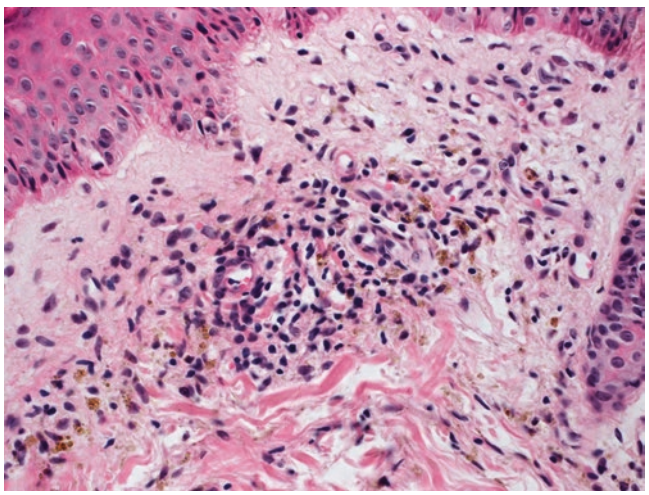

Fig. 5.6 Perivascular macrophages filled with golden brown refractile pigment granules are seen in pigmented purpuric eruptions

5.2.2 Histology

The histologic features of pigmented purpuric dermatoses vary with regards to the subtype of disease. The common features include a perivascular lymphohistiocytic infiltrate, mainly confined to the superficial vascular plexus (Fig. 5.5). Extravasation of erythrocytes and hemosiderin deposition are present within the papillary dermis, occasionally extending into the epidermis [11, 12] (Fig. 5.6). Classic features of leukocytoclastic vasculitis such as vascular wall destruction, fibrin deposition, and vascular thrombosis are not present. Eosinophils and neutrophils are not seen in this entity. In some variants of pigmented purpuric eruption, epidermal changes including lymphocyte exocytosis and spongiosis are present. In another variant, the dermal infiltrate has a lichenoid inflammatory pattern.

The histologic differential diagnosis is quite broad and depends upon the characteristics of the inflammatory infiltrate. The distinguishing feature in all cases is the presence of dermal hemosiderin, which can be highlighted on Perl's iron stain or Prussian blue stain.

5.2.3 Pathogenesis

The etiology of PPD is not known. However, several possible contributing factors include capillary fragility, hypertension, venous stasis, and chemical exposure [13, 14]. Drugs, such as diuretics and nonsteroidal anti-inflammatory drugs, are frequent provocative factors [15].

Cell-mediated immune responses are thought to be involved in the pathogenesis of PPD. Close interactions of CD3+ and CD4+ T lymphocytes with CD1a+ dendritic cells have been identified in Schamberg disease [16]. The infiltrating immune cells in the affected areas have strong expression of leukocyte function associated (LFA)-1 antigen and ICAM-1 (Intercellular Adhesion Molecule 1). Endothelial cells in these lesions also express ICAM-1 and ELAM-1 (E-selectin). These findings suggest that adhesion molecules may be involved in lymphocyte trafficking into the affected area and regulate lymphocyte–dendritic cell interactions.

Deposits of complement factors C3 and C1q on the wall of lesional blood vessels from patients with PPD suggest that immune complexes may also play a role in the pathogenesis of these diseases [17]. The influx of inflammatory cells may predispose capillaries in the papillary dermis to dilatation and fragility with resultant rupture and hemorrhage from end capillaries [18].

5.3 Urticarial Eruptions

5.3.1 Clinical Features

Urticaria is seen in about 15–25 % of people, who will experience urticaria at some point during their lifetime [19]. Most children present with acute urticaria, and up to one-third of children will have chronic disease [19]. A causative source of urticaria can be identified in about one of five cases.

Urticaria is characterized by transient erythematous, annular, arcuate, and polycyclic papules, plaques and wheals that resolve within 24 hours of onset without residual dyschromia (Figs. 5.7 and 5.8). Lesions frequently recur in crops. Acute urticaria is defined as episodes lasting less than 6 weeks, while chronic urticaria lasts longer than 6–12 weeks [19]. Concomitant angioedema with localized swelling at the face and extremities may be seen in up to 50 % of cases of urticaria and may herald more severe episodes with risk of persistent symptoms. While most cases of acute urticaria resolve within 6 weeks, some may last longer, usually with resolution of all recurrences by 12 weeks [20]. In cases of chronic urticaria, children tend to fare better than adults, and typically are symptom-free within 3 years after disease onset.

Fig. 5.7 Urticaria presents as annular, erythematous and edematous papules and plaques on the trunk of a child with preceding symptoms of an upper respiratory infection

Fig. 5.8 Papular urticaria presents as erythematous, edematous papules at exposed skin of the neck and extremities with areas of vesiculation

Giant urticaria of infancy/urticaria multiforme typically is seen in children between 4 months and 4 years of age [21]. It is most commonly reported after infectious insult, although reports exist following various antimicrobial exposures and immunizations. Urticaria multiforme is characterized by annular and arcuate, edematous and erythematous plaques with central patches of dusky-colored or ecchymotic erythema. Vesiculation and necrosis are not seen. Acral edema is a frequent feature. Patients typically have systemic symptoms suggestive of viral prodrome, including fever, malaise, cough, congestion, and diarrhea [21]. The cutaneous eruption seen in urticaria multiforme is self-limiting, usually resolving within 8–10 days without any long-term sequelae.

Papular urticaria is seen most commonly in young children and occasionally in adolescents and adults [22]. The clinical exam is characterized by pruritic, edematous and erythematous papules and wheals of varying sizes (3–10 mm) that are typically distributed at exposed skin on the extremities and face with sparing at the axillae and groin (Fig. 5.8). Lesions may persist for days to weeks, leaving residual dyschromia at previously affected sites. Symptomatic therapy is often required for active dermatitis. Recurrence following reexposure to the causative agent is the norm, although hyposensitization may develop after repeated exposures to the antigen [22].

5.3.2 Histology

In classic cases, the histologic features of urticaria are quite mild. There is a mixed inflammatory infiltrate consisting of neutrophils, eosinophils, and lymphocytes surrounding vessels of the superficial vascular plexus [23, 24] (Figs. 5.9 and 5.10). Papillary dermal edema and vascular ectasia may be present, but in many cases, are so subtle as to be undetectable

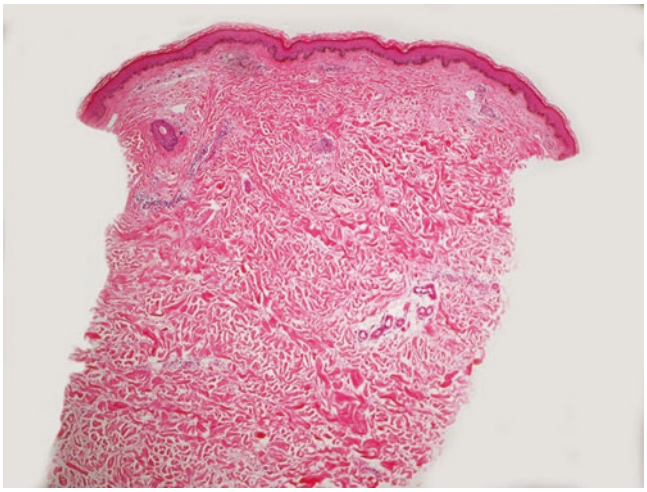

Fig. 5.9 The low magnification appearance of urticaria resembles normal skin in many cases

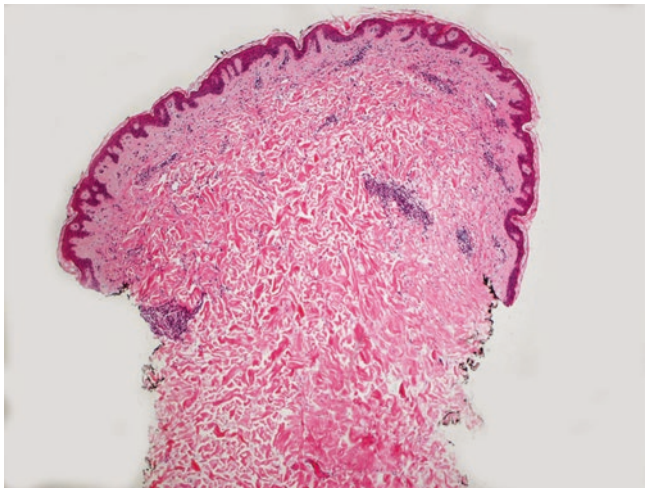

Fig. 5.11 Histologic changes in papular urticaria demonstrate a superficial perivascular mixed inflammatory infiltrate with mild dermal edema

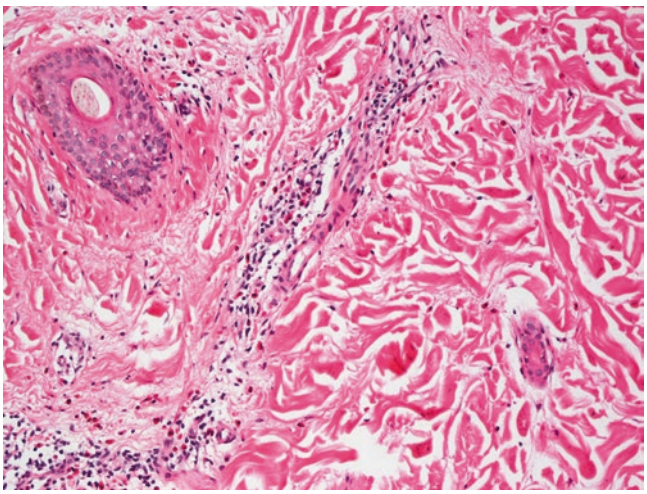

Fig. 5.10 Higher magnification of urticaria lesions demonstrates a mild perivascular inflammatory infiltrate consisting of eosinophils and neutrophils in addition to mast cells and lymphocytes with minimal interstitial edema. The epidermis is usually not involved

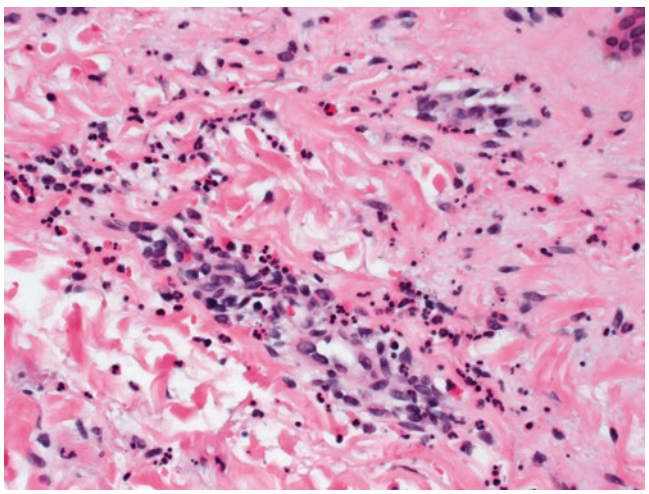

Fig. 5.12 Neutrophils and eosinophils are present around blood vessels in papular urticaria

following routine tissue processing [25]. It is unusual to see degranulated mast cells, and there is no significant increase in numbers of mast cells as seen on routine H&E stains [26].

The differential diagnosis of urticaria includes a wide range of entities that demonstrate a superficial perivascular inflammatory infiltrate; however, these are usually easy to differentiate from urticaria based upon clinical history and the presence of mixed neutrophils and eosinophils in biopsies of urticaria. Urticarial vasculitis and leukocytoclastic vasculitis can be differentiated from urticaria based upon the histologic findings of overt vascular damage in leukocytoclastic vasculitis, and the clinical history and intensity of the inflammatory infiltrate in urticarial vasculitis [27]. There is some histologic overlap between urticaria and urticarial vasculitis and this distinction can be made based upon clinical definition.

Papular urticaria is an ill-defined histologic entity with features that are indistinguishable from the dermal hypersensitivity reactions in arthropod bite reactions. The overlying epidermis may show spongiosis and exocytosis in some cases, but the majority of the changes are confined to the papillary and reticular dermis (Fig. 5.11). There is a mixed inflammatory infiltrate consisting of lymphocytes, histiocytes, eosinophils, and neutrophils in varying amounts [28] (Fig. 5.12). Cases with many eosinophils may also demonstrate "flame figures" (degranulated proteins from eosinophils) [29]. The infiltrate is both perivascular and diffuse, extending between collagen bundles and deeply into the

dermis and subcutis. Edema is present in varying amounts in both the papillary and reticular dermis.

Urticarial vasculitis is described under leukocytoclastic vasculitis.

5.3.3 Pathogenesis

A significant proportion of cases of acute urticaria is idiopathic. When predisposing factors in children can be identified, infection is most commonly seen (identified in 49 % of affected individuals), although it may be precipitated by medication exposure (5 %) and food hypersensitivity (3 %) as well [19]. In chronic variants of urticaria, a physical etiology is more frequently cited. Granulocytes, including eosinophils, mast cells and basophils, are important in the inflammatory process of both subtypes of urticaria. The recruitment of these inflammatory cells to urticarial lesions requires the release of cytokines and chemotactic factors active on the cell types involved. The presence of intercellular adhesion molecule-1 (ICAM-1) and E-selectin in urticarial lesions suggests involvement of endothelial cell activation in active lesions [30]. Although the particular chemokines released in chronic urticaria have not been identified, there is increased plasma IL-4 in patients with chronic urticaria [31]. Lymphocytes in urticaria are both type 1 (Th1) and type 2 (Th2) T-helper cells that produce IFN-γ (by Th1 cells), and IL-4 and IL-5 (by Th2 cells) [32].

The degree of eosinophil accumulation varies among patients. However, even when eosinophils are not evident, major basic protein can be identified within lesions in the majority of cases, suggesting the prior presence of eosinophils [33]. Mast cell degranulation initiates the inflammatory process in chronic urticaria. The inflammatory infiltrate in urticaria often surrounds small venules with abundant CD4+ T lymphocytes and macrophages. Neutrophils and basophils are also present [34, 35]. Basophils have been implicated in chronic urticaria, although they are not believed to be a key activating cellular component. Instead, they may serve as bystanders that degranulate during the course of the disease [36–39].

The coagulation cascade and fibrinolysis may be involved in the pathogenesis of chronic urticaria as certain plasma factors appear to contribute to the development of skin lesions [40]. In animal models, thrombin triggers mast cell degranulation and may activate protease-activated receptor-1 on mast cells [40, 41]. Moreover, there are significantly elevated plasma levels of factor VIIa and prothrombin fragment 1 + 2 (F1 + 2) (a protein fragment that is released during the activation of prothrombin to thrombin by factor Xa) in patients with chronic urticaria as compared with normal individuals [37, 40, 41].

Studies have implicated the hormone dehydroepiandrosterone (DHEA) and its sulfated compound dehydroepiandrosterone sulfate (DHEA-S) in chronic urticaria. DHEA and DHEA-S are major androgens secreted by the adrenal glands, and they may play a role in mediating the inflammatory response in urticaria [42, 43].

Papular urticaria is thought to result from type I hypersensitivity reaction to disseminated antigen(s) deposited by an arthropod bite in a sensitized patient. This is supported by the presence of mast cells and eosinophils in the skin lesion of papular urticaria [28]. The severity of the symptoms is related to the host response to the insect salivary or contactant proteins [44]. It has been suggested that investigation of circulating immune complexes, serum complement levels, and exposure of patients to insect protein extracts may provide more insights into the immunopathogenesis of papular urticaria [28].

5.4 Annular Erythema of Infancy

5.4.1 Clinical Features

Annular erythema of infancy is a rare benign cutaneous hypersensitivity seen in healthy infants [45, 46]. Patients present with recurrent crops of asymptomatic erythematous papules that slowly enlarge and develop into arcuate and annular plaques of varying sizes on the face, trunk, and extremities. The skin eruption has a relapsing course that spontaneously resolves within months with individual lesions lasting for 2–4 weeks [46, 47]. A case of persistence into adolescence has been reported [47].

5.4.2 Histology

The literature regarding *annular erythema of infancy* suggests that there may be more than one process grouped into this disease category, as this is manifest by the different histologic appearances that are described [45–48]. The majority of such reports describe a dense perivascular inflammatory infiltrate consisting primarily of lymphocytes with scattered eosinophils and plasma cells [45]. In other reports of annular erythema of infancy, an interstitial infiltrate with more pronounced eosinophils has been described [46]. Additionally, in one report, a dense neutrophilic infiltrate with leukocytoclasis was noted in an individual described as having annular erythema [47]. Based upon these various histologic descriptions, it seems likely that the etiology of these clinically similar eruptions may be different.

5.5 Erythema Chronicum Migrans

5.5.1 Clinical Features

Lyme disease is the most common tick-borne disease in the USA. Erythema chronicum migrans is considered the hallmark of acute, early stage Lyme borreliosis and develops in ~80 % of affected patients [49].

Erythema chronica migrans typically is seen at the site of the tick bite within 9 days of tick attachment with a range of onset of 1–36 days [49]. It is described as an erythematous patch with centrifugal spread that may have varying degrees of erythema within the larger patch. Occasionally, there is a surrounding rim of normal pigmentation separating the initial patch from the advancing erythematous border (Fig. 5.13). Some lesions are raised but epidermal change is usually minimal. Lesions may be seen anywhere on the body, excluding the palms and soles [50]. Size of the patch is dependent on disease duration. Two-thirds of affected individuals will have concomitant systemic complaints, including fever, fatigue, malaise, arthralgia, myalgia, headache, and lymphadenopathy.

Secondary erythema migrans presents with smaller and less edematous lesions distant from the original bite with the palms, soles, and mucosal surfaces typically spared [49]. Erythema usually resolves by day 8 with complete resolution of erythema chronicum migrans by 3–5 weeks [51].

5.5.2 Histology

Histologic changes of erythema chronicum migrans are those of a superficial and deep perivascular lymphohistiocytic infiltrate with no overlying epidermal changes [52–54] (Fig. 5.14). Characteristic findings include the presence of plasma cells, especially in biopsies taken from the periphery of the lesions. Some authors have described increased eosinophils in biopsies taken closer to the center of the lesions [53, 55]. A perineural infiltrate of lymphocytes and plasma cells has also been described in biopsies of erythema chronicum migrans (Fig. 5.15) [56]. An interstitial inflammatory infiltrate is also seen in some cases. In these situations, abundant histiocytes have been identified [57, 58]. Special stains for microorganisms and polymerase chain reaction testing can be used to identify borrelial microorganisms in the majority of cases.

Other changes that may be seen in conjunction with erythema chronicum migrans due to cutaneous borrelial infection, but are not specific for this eruption include

Fig. 5.13 Erythema chronicum migrans presents as an erythematous patch with centrifugal spread

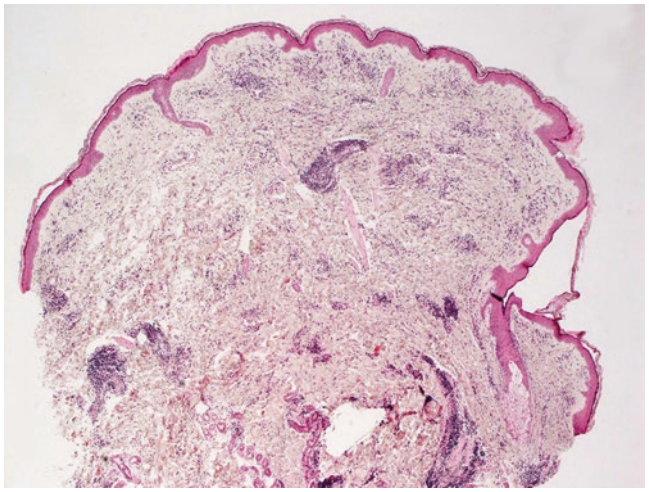

Fig. 5.14 There is a superficial and deep perivascular lymphohistiocytic infiltrate in erythema chronicum migrans. The epidermis is unremarkable

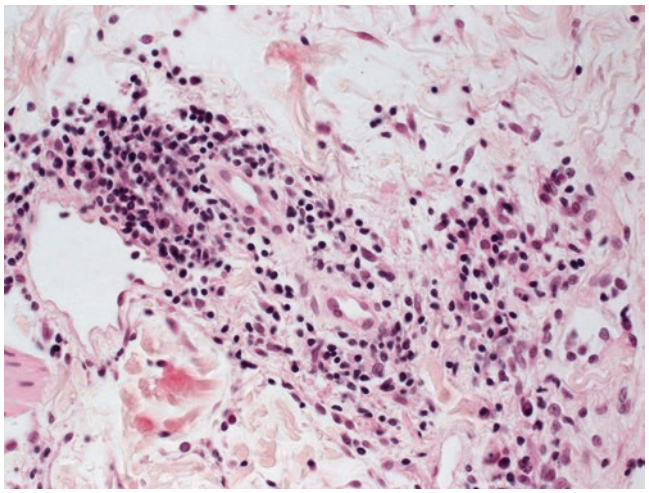

Fig. 5.15 Scattered plasma cells are present within the inflammatory infiltrate in most cases of erythema chronicum migrans

acrodermatitis chronic atrophicans and cutaneous lymphoid hyperplasia [57, 59].

The histologic differential diagnosis includes erythema annulare centrifugum, which does not ordinarily have plasma cells in the infiltrate. Tumid lupus erythematosus may have some similar findings, such as plasma cells, but lupus would be expected to have dermal mucin not seen in erythema chronicum migrans. Polymorphous light eruption has a similar histologic appearance, but many cases also show papillary dermal edema. The clinical presentation of each of these entities is quite different, making the distinction fairly straightforward.

5.5.3 Pathogenesis

Erythema chronicum migrans is a characteristic skin manifestation of Lyme disease caused by *Borrelia burgdorferi* [60]. *B. burgdorferi* is a pathogen that is deposited in the skin by the bite of a tick. The spirochetes can be seen on Warthin–Starry stain of biopsy of lesions, particularly in the peripheral area of the lesion [61, 62]. The disease pathology of *B. burgdorferi* is thought to result mainly from the host inflammatory response [63, 64].

Bacterial adhesion and immune evasion are key aspects of *B. burgdorferi* pathogenesis. Adhesion of the microorganisms to mammalian host cells is mediated by adhesins. A key adhesin in *B. burgdorferi* infection is decorin. Decorin is a small proteoglycan that is a structural component of the extracellular matrix in mammalian cells and is thought to be the extracellular matrix component to which *B. burgdorferi* binds [65].

Immune evasion is important in Lyme disease pathogenesis. Well-studied immune evasion strategies used by *B. burgdorferi* are antigenic variation and complement resistance. In antigenic variation, *B. burgdorferi* harbors a gene that encodes a lipoprotein called V1sE and a series of 15 silent cassettes with sequence similarly to V1sE [66–68]. Random segmented gene conversion of V1sE, in which the silent cassettes replace portions of sequences in the expressed V1sE, results in a V1sE protein with substantial antigenic variation [67, 68]. In complement resistance, *B. burgdorferi* has several complement regulatory factor H-binding proteins that interfere with the complement pathway by promoting inactivation of complement protein C3b [69, 70]. In addition to these immune-mediated mechanisms, the innate immune system is also important in host response to *B. burgdorferi* infection, specifically pathogen-associated molecular patterns (PAMPs) that are recognized by pattern recognition receptors (PRRs) expressed by mammalian immune cells [66].

5.6 Scleroderma/Morphea

5.6.1 Clinical Features

Scleroderma is a chronic connective tissue disorder. It is divided into two main categories: systemic sclerosis and localized scleroderma or morphea. Scleroderma is a rare condition with annual incidence in the pediatric population of 1 per million for systemic sclerosis, and 2 to 3 per 100,000 for localized scleroderma [71]. Fewer than 5 % of patients with systemic sclerosis have onset during childhood, while the majority of patients with localized scleroderma develop disease during childhood. In children, the mean age of onset is between 7 and 8 years old [71]. Ninety percent of children are diagnosed between 2 and 14 years old [72]. Scleroderma is more common in females, with a female to male ratio of 4:1 for systemic sclerosis and 2:1 for localized scleroderma.

Systemic sclerosis is characterized by cutaneous sclerosis with visceral involvement. There are three defined subtypes: diffuse cutaneous, limited cutaneous, and the overlap type.

In localized scleroderma, only the skin and underlying tissues are affected. Localized scleroderma is divided into five subtypes: plaque morphea, generalized morphea, bullous morphea, linear morphea, and deep morphea. Localized areas of indurated skin, often with dyspigmentation, characterize plaque morphea. Active lesions typically have a purplish halo. In the generalized form, patients have indurated plaques involving more than two body sites. Bullous morphea is characterized by the presence of bullae and erosions overlying indurated plaques. Deep morphea commonly presents as a single atrophic lesion on the upper back.

Linear morphea is the most common form of localized scleroderma seen in childhood [72]. Approximately 67 % of patients with linear morphea are diagnosed before 18 years old. Typically, a single unilateral lesion develops on the extremities, face or scalp (Figs. 5.16, 5.17 and 5.18). The underlying muscles and bones can be affected, causing growth disturbance and the potential for significant deformities.

Linear lesions affecting the scalp and forehead are called “en coup de sabre” due to the development of a depressed furrow resembling a blow from a saber. *En coup de sabre* typically is localized to the paramedian forehead with associated ocular and central nervous system (CNS) symptoms, such as headache, seizures, peripheral neuropathy, vascular malformation, and CNS vasculitis [73].

Another variant of linear scleroderma affecting the face is Parry–Romberg syndrome, also known as progressive hemifacial atrophy. In this condition, there is slow unilateral atrophy of the facial tissues, including skin, muscles, cartilage, and bones. There may be associated neurologic and ophthalmologic manifestations. In linear limb morphea, the

Fig. 5.16 Linear morphea presents as a dimpled, slightly hypopigmented linear plaque involving the left nasolabial fold and extending to the nasal ala and upper lip with subsequent asymmetry of the aperture of the ipsilateral nostril

Fig. 5.17 Sclerotic tightening of the digits and ulcerations at the fingertips are seen in a patient with scleroderma (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietna)

involvement usually is unilateral with sequelae including muscle atrophy, joint contractures as well as limb length and limb circumference discrepancy [73].

The majority of patients will have softening and stabilization of disease over a 3–5-year period, although dyschromia and scarring may be permanent [74]. One-third of patients will have persistence of disease into adulthood, warranting continued clinical monitoring. Patients with linear morphea are more likely to have concomitant systemic disease than those with localized scleroderma. About 25 % of affected children have extracutaneous symptoms, often involving the musculoskeletal system [73, 74].

Prognosis depends on the extent and severity of disease. Localized lesions are often treated with topical therapy (e.g., topical steroids, calcineurin inhibitors, and vitamin D derivatives). More widespread debilitating disease is usually treated with one or more immunosuppressants. Phototherapy has also been used with some success. In general, localized forms of scleroderma will have a self-limited course. However, disease activity may persist for months to years and can be recurrent. Systemic sclerosis typically has a chronic course. Children tend to have a better long-term prognosis than adults with less likelihood of severe organ involvement [71].

Fig. 5.18 Linear morphea presents as a hyperpigmented sclerotic band extending from the lateral forehead to the crown of the scalp with concomitant alopecia and hemorrhagic ulceration (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

5.6.2 Histology

Scleroderma and morphea cannot be distinguished based upon histologic changes alone. Regardless of the clinical presentation, the histologic changes vary with the age of the lesion biopsied. Histologic changes are largely confined to the reticular dermis. In late stage lesions, similar changes may extend to the papillary dermis and into the fibrous septae in the subcutaneous fat. Early lesions demonstrate dermal edema leading to expansion of the spaces between reticular dermal collagen bundles. There is a perivascular, periappendageal, and interstitial inflammatory infiltrate that consists of lymphocytes, scattered plasma cells, and eosinophils (Fig. 5.19). As lesions evolve, the edema diminishes and the space between collagen bundles becomes decreased with progressive thickening of these bundles (Fig. 5.20). The overall intensity of the inflammatory infiltrate becomes less

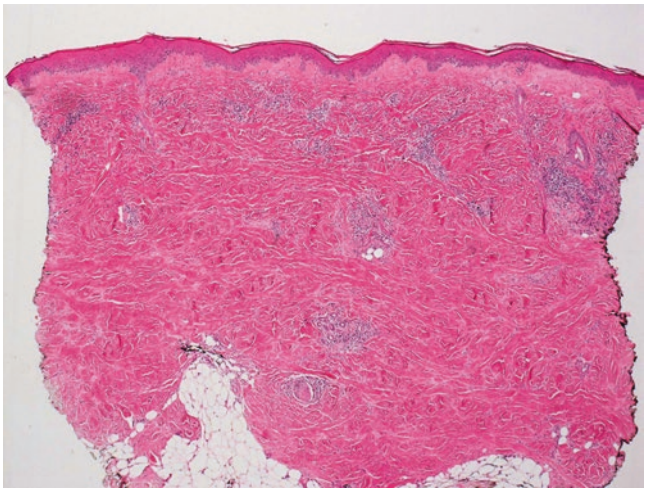

Fig. 5.19 Morphea shows a perivascular and interstitial infiltrate of lymphocytes, scattered plasma cells, and eosinophils. A "square biopsy" sign is characteristic of morphea since the dermis is distended with increased and thickened collagen bundles

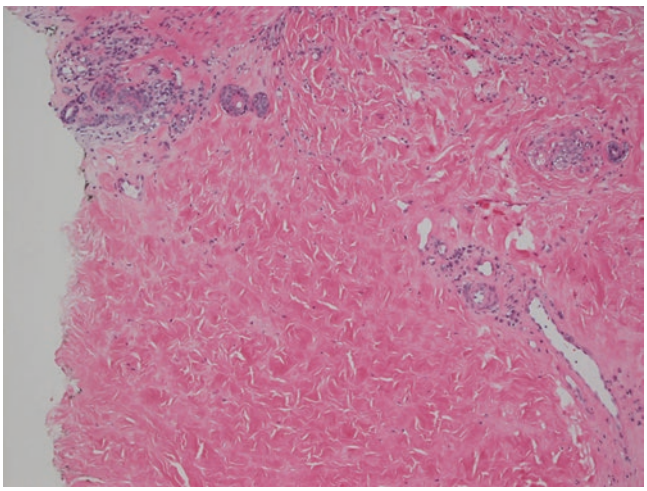

Fig. 5.20 There are thickened collagen bundles, decreased interstitial spaces and minimal interstitial inflammation in morphea

and the inflammation is centered more on blood vessels, hair follicles, and eccrine structures. The presence of plasma cells in these foci is expected and is diagnostically useful (Fig. 5.21). Occasional germinal follicles with scattered plasma cells may be present, especially at the interface between the deep reticular dermis and the subcutaneous fat. In late stage lesions, the inflammation may be entirely absent with only dense sclerotic collagen with minimal interstitial spaces. In this phase, it is common to see fibrous tracts that replace obliterated hair follicles and eccrine ducts. Elastic tissue fibers are preserved throughout the dermis in morphea and scleroderma [75–77]. Similar changes have been described in late stages of *Borrelia burgdorferi* infection and the relationship between this infectious process and scleroderma remains somewhat controversial.

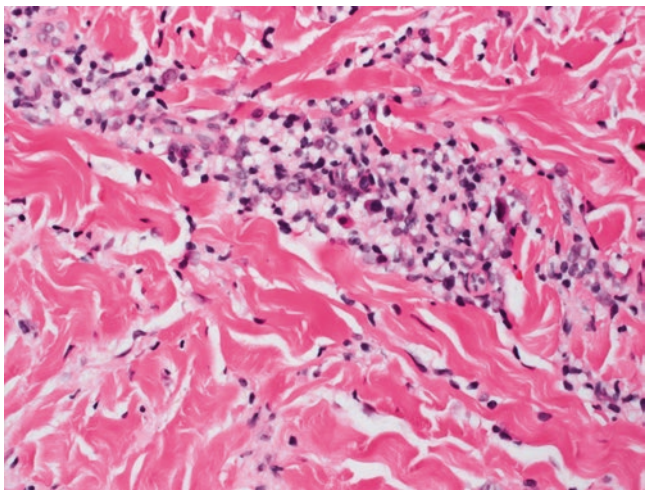

Fig. 5.21 Dense sclerosis and a lympho-plasmacytic cell infiltrate are present in the deep reticular dermis in morphea

The relationship between lichen sclerosus and morphea remains unclear [78]. Certainly, in many patients with morphea, histologic changes of lichen sclerosus are present within the papillary dermis and epidermis, while the reticular dermis has the characteristic features of morphea. A rare variant of morphea has been described in which only the most superficial portion of the dermis is affected by the increased fibrosis [79].

The histologic differential diagnosis of morphea includes a dermal scar, which can be differentiated based upon the linearity of the collagen bundles and the vertical orientation and linearity of dermal blood vessels seen in a scar. Also to be considered is scleredema. In this entity, while collagen bundles may be thickened in late stage lesions, there is increased interstitial space separating the collagen bundles. The spaces are filled with mucin as highlighted with alcian blue or colloidal iron stains. Nephrogenic systemic fibrosis may have some histologic similarity, but demonstrates increased numbers of fibroblasts, which is a feature not seen in morphea and scleroderma. Tumid lupus erythematosus may have a superficial and deep perivascular and periappendageal inflammatory infiltrate with scattered plasma cells. However, the dermal sclerosis seen in morphea and scleroderma are not present.

5.6.3 Pathogenesis

Scleroderma and morphea are characterized by the overproduction of collagen and increased extracellular matrix deposition. It has been suggested that scleroderma is due to microvascular injuries with inflammatory cell infiltrates in the dermis and surrounding blood vessels present in early morphea, resulting in increased production of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion mol-

ecule-1 (ICAM-1) and E-selectin, as well as chemokines (CCL2, CCL5, and CXCL8) [80–82]. These pro-inflammatory molecules stimulate T-helper cell activation and the production of key profibrotic cytokines, such as transforming growth factor-β (TGF-β), tumor necrosis factor (TNF)-α, interferon (IFN)-α, IFN-γ, and interleukins 4, 6, and 8 [83–85]. These cytokines in turn induce inflammation, recruitment and activation of fibroblasts and myofibroblasts, leading to excess collagen production and reduced matrix metalloproteinase (MMP) activity [86].

Autoimmunity is believed to play a role in scleroderma and morphea, since patients with scleroderma have higher rates of autoimmune diseases in their families than expected in the general population [83]. Approximately 2–5 % of children with morphea have an associated autoimmune disease, such as insulin-dependent diabetes mellitus, Hashimoto thyroiditis, Sjogren's syndrome, and celiac disease [87–89]. Several genome-wide association studies (GWAS) have been performed in patients with systemic sclerosis revealing association of this disease with HLA class II gene region and other genes, such as RF5, CD247, BANK1, STAT4, TNFSF4, and BLK [90]. Patients with morphea also have high prevalence of anti-nuclear antibody, single-stranded DNA antibody, anti-histone antibodies, anti-topoisomerase II alpha antibody, and rheumatoid factor [91, 92]. Of note, anti-histone antibodies are more prevalent in juvenile-onset than in adult-onset morphea. Interestingly, anti-topoisomerase II alpha antibody is much more prevalent in morphea patients (76 % of all morphea patients) than in patients with other types of autoimmune disorders (8–14 % of patients) [93].

Triggers of scleroderma include drugs, radiation, infections, and trauma. Among the drugs that have been associated with scleroderma are bleomycin, D-penicillamine, vitamin K1, L-5-hydroxytryptophane, balicatib, and carbidopa [84]. Radiation-induced scleroderma mainly occurs after radiation treatment for breast cancer [94, 95]. Some viruses, such as cytomegalovirus and parvovirus B19, have been implicated in scleroderma [83]. Mechanical trauma has been reported in about 13 % of children with morphea [96, 97]. Morphea has also been reported after vaccination for measles, mumps and rubella; diphtheria, tetanus, and pertussis; hepatitis B and tetanus [98].

Scleroderma in children and adults show similar inflammatory cell infiltrates. In a study of patients with juvenile scleroderma, there is significant perineural inflammation in half of the patients studied. This unique histologic feature has been proposed as a possible histologic marker for juvenile scleroderma in addition to dermal fibrosis [89, 99].

Gene expression analysis revealed distinct gene expression patterns in patients with morphea, limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis [100]. These gene signatures suggest that there are distinct molecular subtypes of scleroderma and morphea.

5.7 Perniosis

5.7.1 Clinical Features

Perniosis (chilblains) is most commonly seen in young girls and women between 15 and 30 years old, although reports exist of occurrence in the elderly and young children [101]. Prevalence may be greater in Europe than in North America, and in climates that are cold and humid with episodes typically noted at the beginning of the fall or winter and disappearance by the spring [102, 103]. The exact incidence in pediatric patients is unknown.

The clinical exam is characterized by the acute onset of erythematous to purpuric, edematous papules and nodules with acral distribution along the dorsum of the proximal digits (most common), pinnae, cheeks and thighs [101]. Secondary sequelae of brown or yellow dyschromia, desquamation, and ulceration may be seen in more extensive disease. Lesions typically occur within 24 hours of cold exposure. Patients may complain of associated burning or pruritus. Disease prognosis is good with spontaneous resolution within months. Conservative measures of keeping exposed areas warm and dry have proven effective in many pediatric case reports [101, 103].

5.7.2 Histology

A histologic diagnosis of perniosis is based upon the findings of a superficial and deep perivascular and peri-appendageal infiltrate of lymphocytes, almost always occurring on an acral site (Figs. 5.22, 5.23 and 5.24). The presence of marked papillary dermal edema is an expected finding. Dermal blood vessels may show histologic changes that resemble those of a lymphocytic vasculitis with fibrinoid necrosis an thrombosis in papillary dermal capillaries [104]. Dermal mucin has been described by some authors, but this is not a typical finding. The epidermis is most commonly uninvolved, although some authors have described a lichenoid inflammatory infiltrate affecting the dermal-epidermal junction in some cases. In other cases, bullous lesions with secondary epidermal necrosis may occur due to the papillary dermal edema [104, 105]. A case of juvenile spring eruption has been described with an interface dermatitis, dermal mucin and other features that suggested perniosis prompting some authors to question whether some cases of this entity are best considered as part of the spectrum of perniosis [106].

The differential diagnosis includes lupus erythematosus. In most cases, the distinction can be made based upon clinical and serologic findings, as well as the presence of an interface dermatitis and dermal mucin. Leukocytoclastic vasculitis might also be considered in the differential diagnosis, but the lymphocytic predominance in perniosis differs

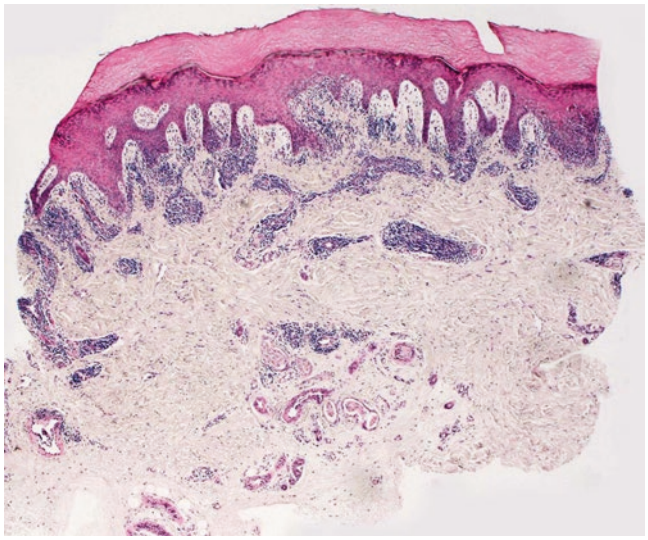

Fig. 5.22 The superficial and deep lymphocytic infiltrate in perniosis is usually intense and surrounds blood vessels and eccrine ducts

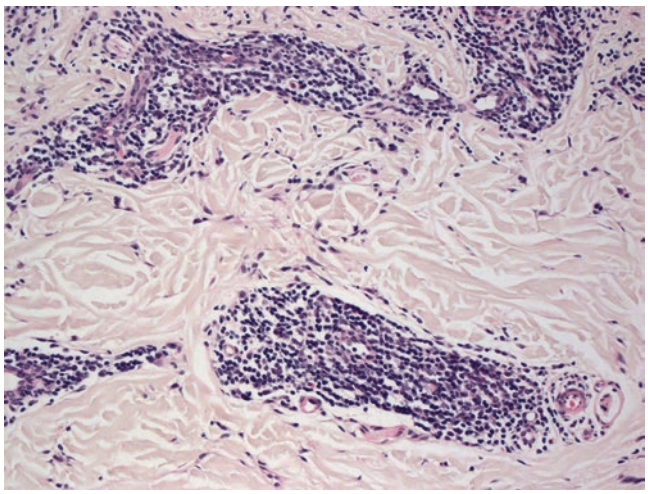

Fig. 5.23 The infiltrate in perniosis extends quite deep involving the dermal blood vessels

from the neutrophilic infiltrate that characterizes leukocytoclastic vasculitis. Polymorphous light eruption displays very similar histologic changes to those seen in perniosis, but it has a markedly different clinical presentation. A non-acral, cold-induced panniculitis with identical histologic features has been described [107].

5.7.3 Pathogenesis

Perniosis may be primary or secondary to an underlying connective tissue disease, monoclonal gammopathy, or cryoglobulinemia [108]. It is a vasculopathy in which there is an abnormal neurovascular response to temperature changes [109]. Vasodilatory reflex induced by cold is a protective physiologic mechanism to allow tissue perfusion and prevent ischemia. Patients with perniosis may have prolonged cold-induced vasoconstriction leading to tissue hypoxia and subsequent inflammatory reaction resulting in tissue damage.

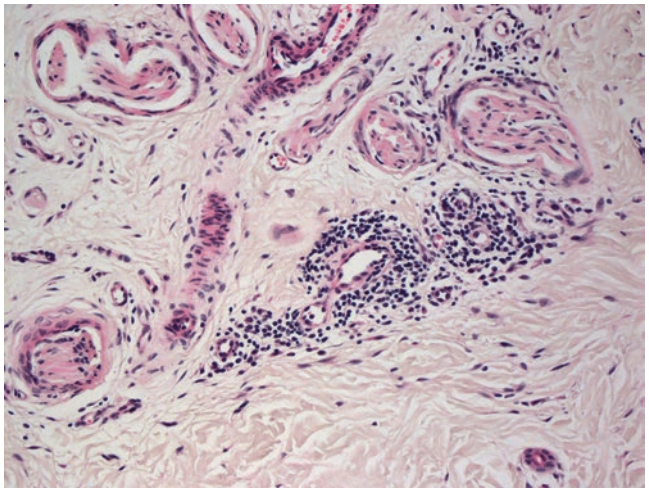

Fig. 5.24 The infiltrate in perniosis can be seen around nerve fibers in some cases

5.8 Eosinophilic Cellulitis (Wells Syndrome)

5.8.1 Clinical Features

Eosinophilic cellulitis is not commonly seen in children [110]. There is no known gender or racial predilection. The clinical exam is defined by the acute onset of pruritic or burning urticarial papules and indurated plaques on the face and distal extremities, with or without associated vesiculation of varying degrees and size (Fig. 5.25) [110]. The inflammatory component of redness transitions to various shades of blue with eventual development of atrophic, grey-colored patches at affected areas [110, 111]. Patients may have concomitant systemic symptoms of fever and arthralgia. Dyschromia and atrophy typically resolve within 2–6 weeks. Episodes may recur even with long periods of latency until complete remission is achieved.

5.8.2 Histology

Eosinophilic cellulitis is characterized by a dense dermal infiltrate of lymphocytes and eosinophils diffusely throughout the dermis (Fig. 5.26). Abundant eosinophils appear degranulated and the eosinophilic material from the

Fig. 5.25 Eosinophilic cellulitis (Wells syndrome) is characterized by urticarial papules and indurated plaques

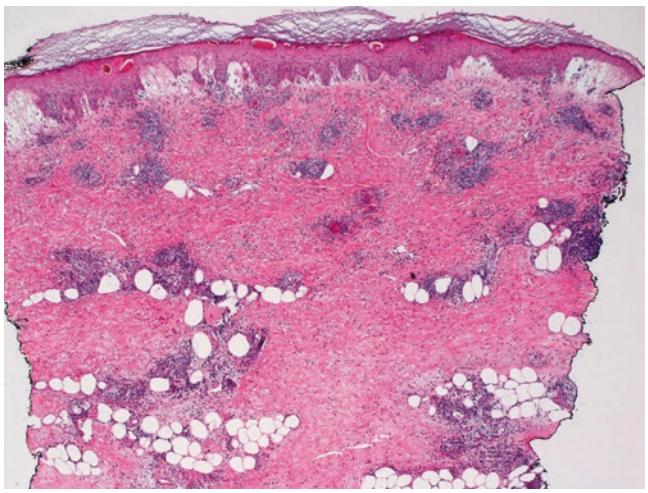

Fig. 5.26 Histologic findings in eosinophilic cellulitis (Wells syndrome) include a superficial and deep perivascular and interstitial infiltrate of lymphocytes and abundant eosinophils

cytoplasm is present surrounding collagen bundles (Fig. 5.27). These brightly eosinophilic structures are involved by histiocytes with their bluish hue, giving rise to the so-called "flame figures" [29, 112] (Fig. 5.28). The presence of flame figures is not specific for eosinophilic cellulitis, but can be seen in any cutaneous eruption that contains abundant eosinophils. Most authors believe eosinophilic cellulitis to be a pronounced hypersensitivity reaction to a wide range of stimuli and not to a specific entity [29, 112, 113]. Congenital eosinophilic cellulitis with identical histologic features has been described [114].

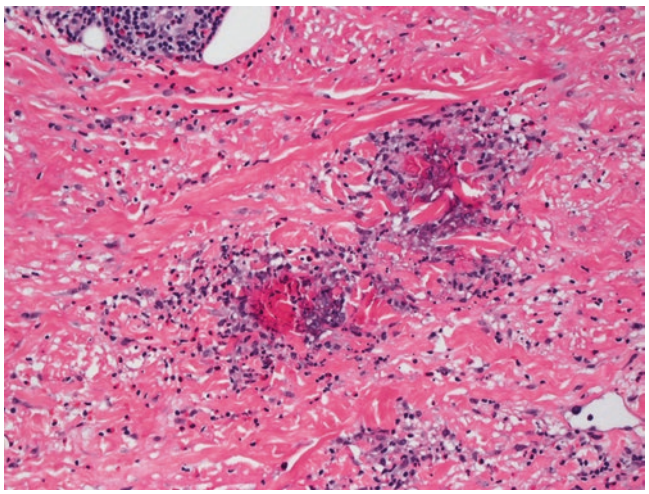

Fig. 5.27 Abundant degranulated eosinophils are often seen in Wells syndrome and in any entities with pronounced tissue eosinophilia

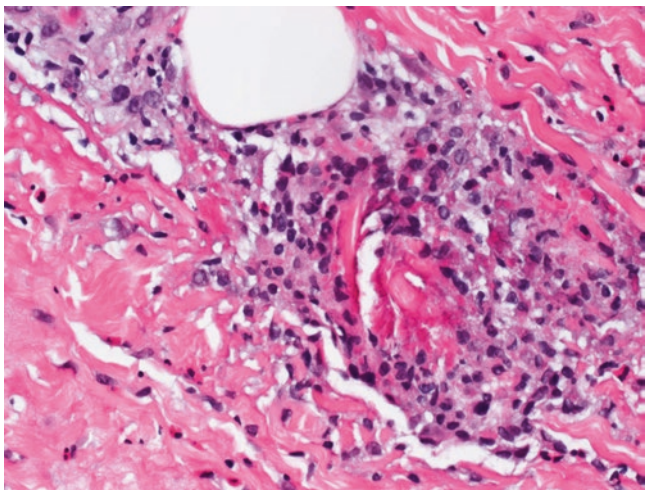

Fig. 5.28 Degranulated eosinophils within the dermis are surrounded by histiocytes, giving rise to "flame figures" in Wells syndrome

The histologic differential diagnosis includes arthropod bite reactions, urticaria, and contact dermatitis. The latter differs by the presence of marked spongiosis. Urticaria manifests with a much less intense dermal inflammatory infiltrate.

5.8.3 Pathogenesis

An abnormal eosinophilic response appears to be implicated in Wells syndrome [115]. Excessive dermal infiltration of eosinophils and degranulation lead to the formation of flame figures in response to a variety of triggering factors. The flame figures in Wells syndrome are composed of eosinophilic proteins deposited on collagen bundles in the dermis [116]. Drugs that are commonly associated with Wells

syndrome are penicillin, tetracycline, anticholinergic agents, anesthetics, and acetyl salicylic acid. Wells syndrome has been linked to excessive production of interleukin-5, which is the main cytokine that induces the accumulation of eosinophils in a local type 2 T-helper immune response [117].

5.9 Polymorphous Light Eruption

5.9.1 Clinical Features

Polymorphous light eruption (PMLE) is the most commonly seen photodermatosis [118]. It typically begins in the second or third decade of life, and more frequently affects females. Family history of disease is reported in ~20 % of surveyed patients [118]. Prevalence appears to be inversely related to latitude with higher rates in locales such as Scandinavia (estimated prevalence of 21 %) and lower rates in places such as Australia (5 %) and Singapore (1 %) [118].

Papules, papulovesicles, vesicles, bullae, and edematous swelling have been all described in PMLE, although similar appearing monomorphic lesions are seen in some cases [110]. Lesions tend to be symmetric and pruritic, appearing within hours or days of initial UV exposure (such as sunny vacation or recreational tanning). Most commonly, patients present with erythematous to skin-colored papules that may coalesce into plaques (Fig. 5.29). Affected areas tend to be those in sun-exposed areas that are covered during winter months, such as the lower neck, central chest, and extensor arms and forearms. In African-Americans, a specific variant exists with pinpoint papules developing in areas of photo exposure [118].

Individual episodes of PMLE resolve without dyschromia or scarring within days to weeks if further photo exposure is avoided. Skin changes tend to be worse in the spring and early summer with gradual tolerance and moderation of skin findings noted over the course of a sunny season. Many patients will experience gradual improvement over time with improvement in sun sensitivity [118].

Juvenile spring eruption is a variant of PMLE, and is characterized by the acute onset of vesicles and papulovesicles along the helices of both ears. It most commonly occurs in young boys. Systemic symptoms of chills, headache, fever, malaise, and nausea are sometimes reported [118].

5.9.2 Histology

As is suggested by the name of the entity, there are many morphologic patterns that can be seen with polymorphous light eruption. The common histologic feature is that of a superficial and deep perivascular lymphocytic infiltrate, largely devoid of eosinophils and plasma cells [119] (Fig. 5.30). In many cases, additional histologic changes include marked papillary dermal edema, mild spongiosis of the lower portion of the epidermis, and slight basal vacuolization [120] (Fig. 5.31). In other cases, the infiltrate may be limited to only the superficial portion of the reticular dermis [121]. In children, histologic findings of juvenile spring eruption are considered by some to be in the spectrum of PMLE. Some of these cases demonstrate a mild interface dermatitis [106].

The differential diagnosis of PMLE includes lupus erythematosus, cutaneous lymphoid hyperplasia and Jessner's

Fig. 5.29 Polymorphous light eruption shows multiple erythematous papules on the extensor surfaces of the forearms and dorsum of the hands

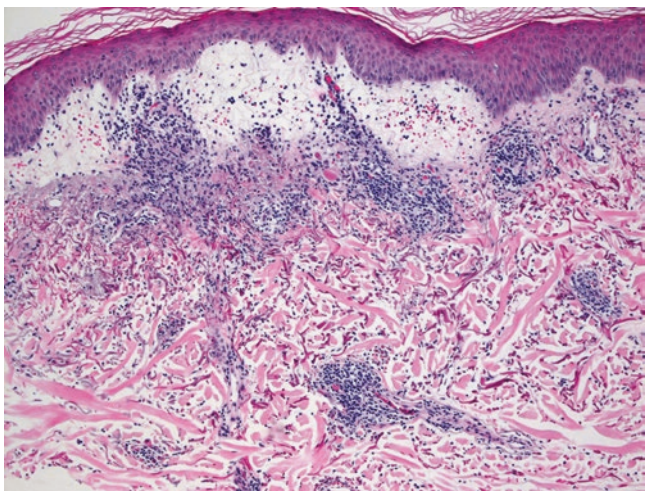

Fig. 5.30 A polymorphous light eruption is characterized by a superficial and deep perivascular lymphocytic infiltrate with varying degrees of papillary dermal edema and an unremarkable epidermis

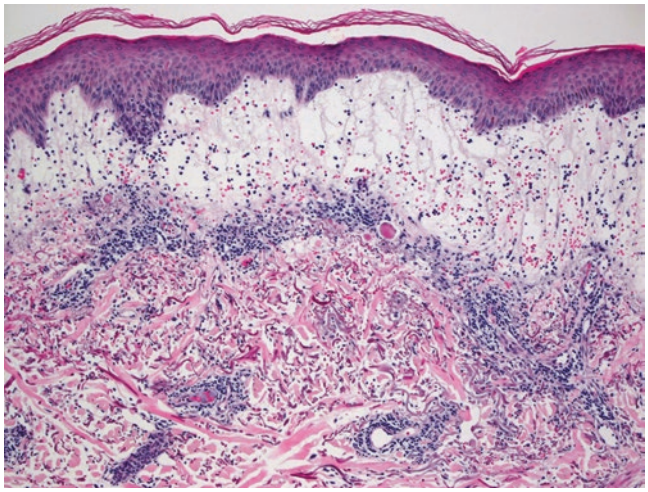

Fig. 5.31 Papillary dermal edema is a salient feature in polymorphous light eruption

lymphocytic infiltrate. Lupus erythematosus can be differentiated based upon the presence of epidermal atrophy, a periappendageal inflammatory infiltrate, dermal mucin, and in most cases, a more extensive interface dermatitis, none of which would be expected findings in PMLE. Cutaneous lymphoid hyperplasia most commonly is characterized by the presence of eosinophils within the lymphoid aggregates and may demonstrate germinal centers that would not be seen in PMLE. Papillary dermal edema is prominent in PMLE and is a less common finding in cutaneous lymphoid hyperplasia. Jessner's lymphocytic infiltrate is a poorly defined entity that should be used as a diagnosis of exclusion. It has been reported only rarely in children [122]. In this entity, there is a superficial and deep perivascular lymphocytic infiltrate, usually lacking in eosinophils and plasma cells similar to the changes seen in PMLE. Many authors consider Jessner's lymphocytic infiltrate as part of the histologic spectrum of lupus erythematosus [123, 124]. Others believe that some cases that are labeled as Jessner's lymphocytic infiltrate are, in fact, polymorphous light eruptions [125].

5.9.3 Pathogenesis

Polymorphous light eruption appears to have a genetic basis. Results of twin studies suggest that PMLE inheritance is polygenic. Family history of PMLE in first-degree relatives is present in 12 % of affected twins, as compared with 4 % in unaffected twins, thus providing evidence of familial clustering [126, 127]. Ultraviolet radiation (UV) is a critical factor in PMLE. In genetically predisposed subjects, UV induces modification of particular molecules in the skin that renders them immunogenic. Ultraviolet B radiation in particular can modify proteins and DNA, creating altered skin components that the immune system may recognize as foreign. Epidermal cells derived from the skin of patients, when exposed to UV radiation, can stimulate peripheral blood mononuclear cells, suggesting that an immune-sensitizing agent is induced by UV light in PMLE skin [128]. The exact identity of the photoantigen is not known, although it seems ubiquitous since 10–20 % of adults in Western countries have symptoms of PMLE [129]. Some potential candidate photo-antigens include heat shock protein 65 and herpes simplex virus [130, 131].

PMLE has been classified as a delayed-type hypersensitivity (DTH) response to an endogenous UV-induced antigen in the skin. Timed biopsies following UV exposure showed a pattern of inflammatory cell infiltrates suggestive of DTH as seen in allergic contact dermatitis [132]. There is a perivascular infiltrate of CD4+ T lymphocytes within a few hours and CD8+ T lymphocytes within a few days after UV as well as increased number of Langerhans cells and macrophages.

Another potential mechanism of PMLE pathogenesis is that UV has immunosuppressive effects. UV has been shown to suppress antitumor immune responses and cell-mediated immune reactions in allergic contact dermatitis [133, 134]. In normal skin, UV induces immunosuppression, and this process may protect the skin from UV-induced photoallergens. Thus, susceptibility of individuals to PMLE could be due to failure of normal UV-induced immunosuppression [118]. At the molecular level, there is reduced expression of TNF-α, IL-4 and IL-10 in UV-exposed skin of PMLE patients, which appears to be due to lack of neutrophils and type 2 helper T lymphocytes and reduced Langerhans cell migration [135].

5.10 Restrictive Dermopathy

5.10.1 Clinical Features

Restrictive dermopathy is a rare autosomal recessive disorder that is universally fatal. The prenatal course is complicated by polyhydramnios, premature membrane rupture, and preterm delivery [136]. The skin exam of affected individuals is defined by varying degrees of a progressively rigid encasement with erosions along points of maximal tension [136]. Other clinical features described are large fontanelles and widely spaced cranial sutures with dysmorphic facies characterized by hypertelorism, ectropion, pinched nose, microstomia, micrognathia, and eclabium. Musculoskeletal abnormalities include hypoplastic bones, pronounced flexion contractures, and rocker bottom feet. Most infants die soon after birth from respiratory failure due to underlying pulmonary hypoplasia, although there are reports of survival to 3 months of life [136, 137].

5.10.2 Histology

Biopsy findings in restrictive dermopathy include thickened collagen bundles that are haphazardly oriented, marked diminution or absence of elastic tissue fibers, and abnormal cutaneous appendages [138]. These appendages appear poorly formed [136]. The epidermis appears either normal or slightly thickened. The histologic findings are not specific and clinical correlation is essential to make the diagnosis.

5.10.3 Pathogenesis

Restrictive dermopathy is a congenital laminopathy disease. It is caused by mutations that alter the processing and maturation of lamin-A (LMNA) gene and by loss-of-function mutations in zinc metallopeptidase STE24 (ZMPSTE24) gene [139–143]. Lamin-A is an intermediate filament component of the nuclear lamina, and it is important in the maintenance of nuclear lamina integrity, regulation of protein transportation, DNA repair and nuclear chromatin stability [144–146]. ZMPSTE24 is responsible for the processing of prelamin-A to lamin-A [140–142, 147]. The majority of cases of restrictive dermopathy have ZMPSTE24 mutations. Mutations in LMNA and ZMPSTE24 lead to the accumulation of truncated prelamin-A form, which cannot be fully processed. Defects in prelamin-A processing to mature lamin-A result in nuclear accumulation of prelamin-A with subsequent cellular toxic injury and impaired DNA repair [148, 149]. Cells in restrictive dermopathy accumulate DNA damage with double-stranded DNA breaks [145, 148, 150]. Restrictive dermopathy shares LMNA mutations with Hutchinson–Gilford progeria syndrome [146, 151]. Understanding of the molecular basis of restrictive dermopathy will aid in the prenatal diagnosis of the disease [152].

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Granulomatous Eruptions

6

6.1 Foreign Body Granulomas

6.1.1 Clinical Features

A foreign body granuloma forms as a response of the skin to foreign material in the tissue. Many types of exogenous materials (e.g., glass, metals, and organic materials) and endogenous materials (e.g., hair, keratin, and urates) may trigger the formation of granulomas [1]. Any age or gender may be affected. There is usually a history of a penetrating trauma (frequently to the foot or hand) followed by the appearance of one or more tender papules or nodules in the affected area. If the lesion is on the foot, there may be pain with weight-bearing activity. Symptoms typically develop weeks to years after the inciting event. Treatment is surgical excision.

6.1.2 Histology

The allergic type of foreign body granulomas contains lymphocytes and epithelioid histiocytes. Multinucleated giant cells are relatively less common. Epithelioid histiocytes aggregate into clusters, forming granulomas. Neutrophilic debris and necrosis are present in some cases.

Nonallergic foreign body granulomas demonstrate an admixture of lymphocytes, histiocytes, multinucleated giant cells and, in early lesions, clusters of neutrophils [2, 3] (Fig. 6.1). The most common foreign material that elicits this type of reaction within the skin is keratin, often secondary to a ruptured folliculitis. The keratin is often readily identified within multinucleated giant cells. Other materials may be similarly located and can be visualized with routine microscopy or in some cases highlighted with light polarization (Fig. 6.2). Foci of necrosis are often seen centrally and surrounded by the granulomatous reaction. Changes within the overlying epidermis are related to route of entry of the foreign material into the dermis, and may display ulceration or epidermal acanthosis if the material has been present for a period of time and caused secondary local trauma from rubbing.

6.1.3 Pathogenesis

Tumor necrosis factor-α (TNF-α) plays a crucial role in inflammatory granuloma formation. TNF-α has been shown to up-regulate adhesion molecules that participate in cellular recruitment and lymphocyte activation. Blocking TNF-α with soluble TNF receptor effectively diminished schistosome-associated granuloma formation and lymphocyte activation in vivo [4, 5]. TNF blockage also reduced intercellular adhesion molecule-1 (ICAM-1) expression. In preclinical animal models, passive immunization of mice with anti-ICAM-1 antibody during primary granuloma formation resulted in an attenuation of lesion development [6].

6.2 Granuloma Gluteale Infantum

6.2.1 Clinical Features

Granuloma gluteale infantum is a rare diaper dermatitis characterized by large, firm, reddish purple nodules or plaques appearing on the inner thighs, perineum, scrotum, and inguinal folds (Fig. 6.3). Granuloma gluteale infantum most commonly affects infants 2–9 months old [7]. Typically, infants have a history of irritant contact diaper dermatitis, with or without secondary yeast infection. There is often a history of previous use of potent topical steroids on the area, suggesting that steroids may be a predisposing factor. Most infants recover completely over time.

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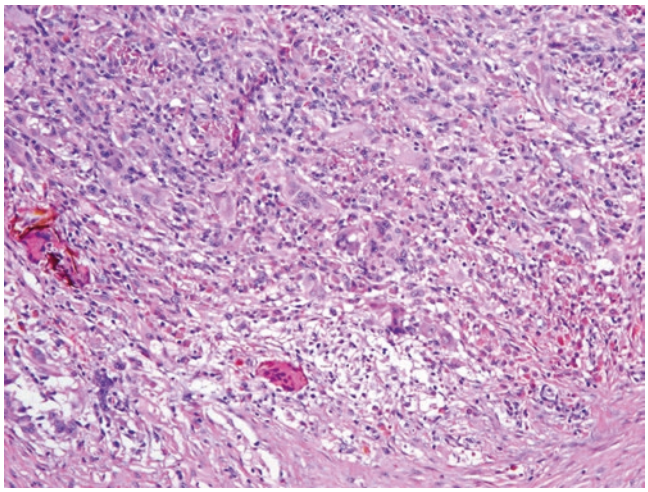

Fig. 6.1 A dense granulomatous infiltrate characterized by multinucleated giant cells and a mixed inflammatory infiltrate is seen in foreign body type granulomas. Foreign material can be apparent on routine H&E sections

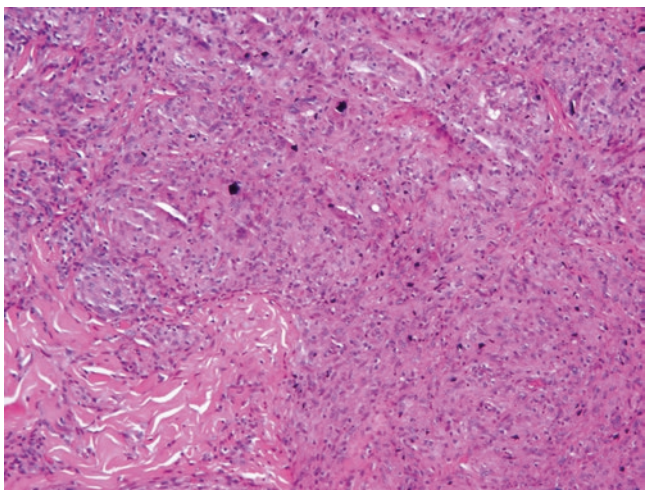

Fig. 6.2 In this case of a granulomatous response to a tattoo, abundant dark tattoo pigment is seen both within giant cells and extracellularly

6.2.2 Histology

Granuloma gluteale infantum is characterized by hyperplastic epidermis with overlying parakeratosis, indicative of mild chronic external trauma. Within the epidermis, there is a mixed inflammatory infiltrate with neutrophils and eosinophils in addition to lymphocytes and histiocytes (Fig. 6.4). Abscesses containing neutrophils and/or eosinophils may be present within the dermis. Plasma cell may also be seen [8]. In well-developed cases, small granulomas resembling those seen in sarcoidosis are present, but these are not observed in the vast majority of cases [7] (Fig. 6.5). Starch granules have been observed within the granulomatous foci in some cases.

Fig. 6.3 Perianal pseudoverrucous papules and nodules, presenting as eroded papules along the anus and medial buttocks, are thought to be a different presentation of granuloma gluteale infantum

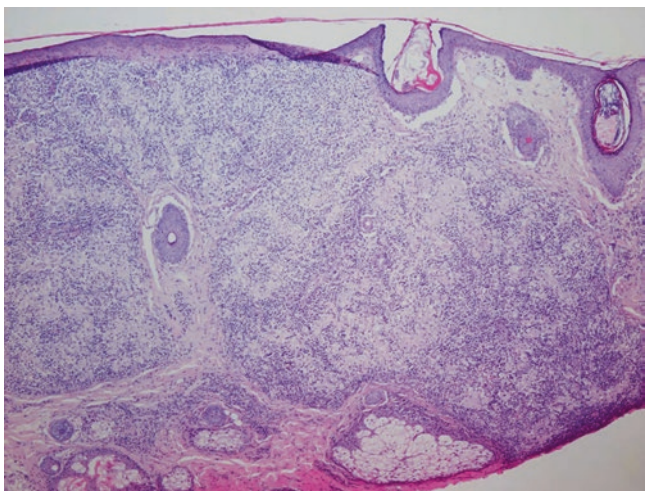

Fig. 6.4 Granuloma gluteale infantum is characterized by a diffuse dermal infiltrate of histiocytes surrounded by a mixed inflammatory infiltrate

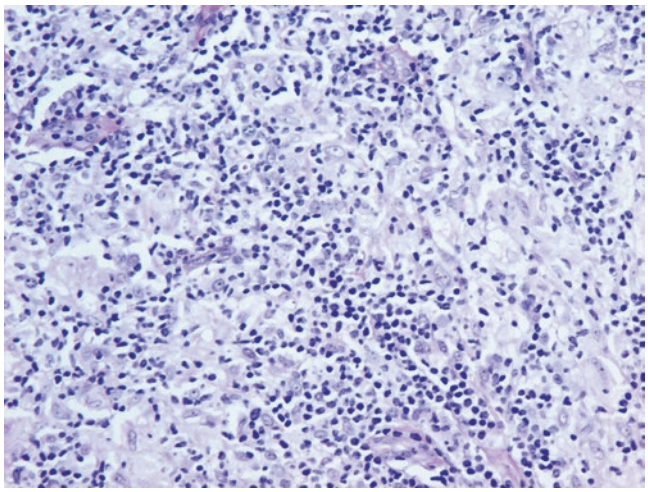

Fig. 6.5 Sarcoidal-type granulomas admixed with lymphocytes and scattered neutrophils are observed in well-formed lesions of granuloma gluteale infantum

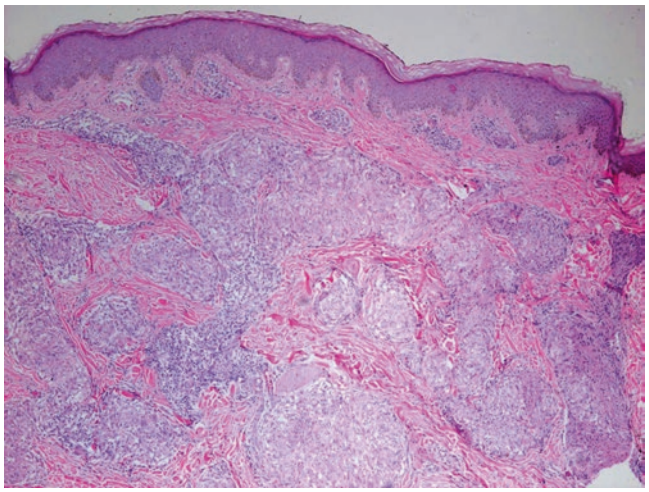

Fig. 6.6 Sarcoidosis demonstrates multiple small well-formed granulomas with a small number of surrounding lymphocytes within the papillary and reticular dermis

6.2.3 Pathogenesis

Granuloma gluteale infantum is a rare dermatosis of infancy of unknown etiology. A number of possible causes include irritant contact dermatitis, *Candida albicans* and rickettsial infections, occlusion from diapers, bromides, and topical fluorinated corticosteroids [9, 10].

6.3 Sarcoidosis

6.3.1 Clinical Features

Sarcoidosis is a systemic condition of unknown etiology and is characterized by the formation of non-caseating granulomas in multiple body tissues. Granulomas commonly affect the lungs, eyes, skin, and reticuloendothelial system. Sarcoidosis is most common in young adults. In the pediatric population, it tends to affect adolescents aged 9–15 years old and occasionally preschool-aged children ("juvenile papular sarcoid") [11]. Initial clinical symptoms are often nonspecific complaints, such as weight loss, fever, fatigue, and anorexia. A variety of pulmonary and eye complaints may occur. Generalized lymphadenopathy is common. About 25 % of patients develop cutaneous involvement at some point during their clinical course [12]. Lesions often appear as red to violaceous or yellow-brown flat-topped papules, nodules, or plaques. There may be an annular configuration. Erythematous, scaly patches and tender subcutaneous nodules are also seen [13]. Ichthyosis, erythroderma, and hypopigmentation have also been reported [14, 15]. Although lesions can occur anywhere, there is a predilection for the face, especially the nares, lips, and eyelids. Lesions may also appear in old scars or other areas of trauma [16].

6.3.2 Histology

Skin biopsies from patients with sarcoidosis may demonstrate various histologic patterns. The primary or specific pattern is a granulomatous dermatitis. The histologic features are those of non-caseating granulomas within the dermis (Fig. 6.6). Well-circumscribed clusters of histiocytes are present at throughout the dermis and in the subcutaneous fat, usually without any changes within the epidermis (Fig. 6.7). The presence of granulomas within the papillary dermis, in close proximity to the epidermis is a relatively specific finding. In most cases, only a scant lymphocytic infiltrate is present around the aggregated histiocytes (giving rise to the "naked granulomas" that are described in this entity). Eosinophils and neutrophils are not abundant in sarcoidosis. Foci of caseation are uncommon in sarcoidosis; however, in some cases, granulomas may be interstitial as opposed to tightly aggregated and may demonstrate focal necrosis [17, 18]. Perivascular and peri-adnexal granulomas can be encountered. Peri-adnexal distribution has been described in hereditary early onset sarcoidosis (Blau syndrome). Foreign bodies can be identified within granulomas in as many as one-third of cases [19].

Various nonspecific cutaneous eruptions are also commonly encountered in patients with sarcoidosis. The most common histologic pattern seen is erythema nodosum, which is a septal panniculitis that is seen in up to 70 % of these patients [20]. This association is strongest in cases of "acute"

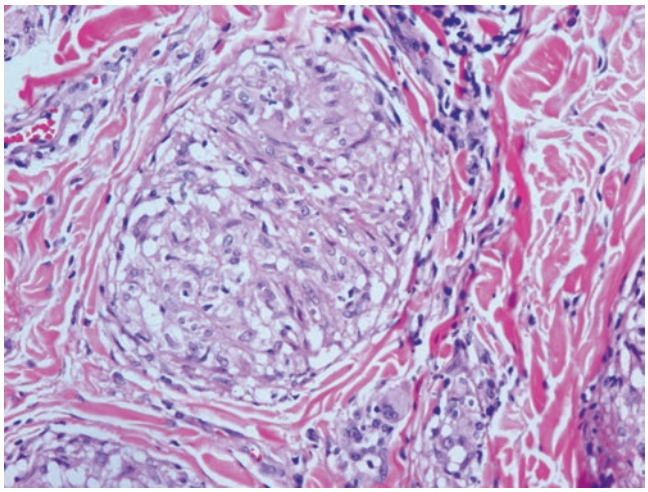

Fig. 6.7 Sarcoidosis is characterized by sharply circumscribed granulomas with relatively little surrounding inflammation

sarcoidosis (Lofgren syndrome) and is more commonly seen in females with the disease. While granulomas may be present within fibrous septa, they are not always seen. Acquired ichthyosis that histologically resembles ichthyosis vulgaris with hyperkeratotic orthokeratosis and loss of the granular layer is also seen in a minority of patients with sarcoidosis [21].

Sarcoidosis should remain a histologic diagnosis of exclusion. While there are characteristic findings, each of these findings can be found in a wide range of other entities, most commonly infectious processes. It is important to perform special stains for microorganisms to exclude infection by fungi and mycobacteria. A search for polarizable foreign material is also recommended before making a diagnosis of sarcoidosis. While not common in children, granulomatous mycosis fungoides should also be considered in cases with a more brisk lymphoid infiltrate.

6.3.3 Pathogenesis

Sarcoidosis has wide variability of disease course and manifestation, thus suggesting that the disease represents a heterogeneous spectrum of disorders. Both genetic susceptibility and environmental factors appear to play a role in disease development. A current concept of the pathogenesis of sarcoidosis is that it is a result of a chronic and aberrant immunological reaction to an antigenic stimulus in genetically susceptible individuals [22–24].

Sarcoidosis has a genetic susceptibility basis that is complex and involves the interplay of multiple genes. The existence of genetic susceptibility is supported by evidence of familial clustering, ethnic variations in disease susceptibility and presentation, as well as the association of this disease with various human leukocyte antigen (HLA) and non-HLA genes [23, 25]. First degree relatives of affected individuals have an increased risk of sarcoidosis as compared to the general population [26]. Several HLA alleles have been found to confer disease susceptibility, including HLA-DR11, 12, 14, 15, 17, HLA-DRB*1101, and HLA-DQB1 [23, 27, 28]. Other HLA alleles found to confer disease protection are HLA-DR1, DR4 and HLA DQ*0202. HLA association suggests that antigen presentation influences sarcoidosis initiation and progression.

Genome-wide association study (GWAS) of single-nucleotide polymorphisms in individuals with sarcoidosis detected a strong association of sarcoidosis with annexin A11 (ANXA11) [29, 30]. ANXA11 association has been found in Europeans, Africans, and European Americans [31, 32]. ANXA11 has regulatory functions in intracellular calcium signaling, cell division, vesicle trafficking, and apoptosis. It has been associated with other autoimmune disorders, including rheumatoid arthritis, lupus erythematosus, and Sjögren syndrome [33]. Another novel risk variant of sarcoidosis has been identified, which is a premature splice site at exon 5 of butyrophilin-like 2 (BTNL2) gene [34].

Infectious pathogens have also been implicated in the etiology of sarcoidosis. *Mycobacterium* and *Priopionibacteria* have been suggested to promote granulomatous inflammation in sarcoidosis [35, 36]. However, the role of infectious agents in sarcoidosis is still unclear. Certain environmental and occupational exposures, such as organic dusts, solvents, mold/mildew, pesticides, and wood stoves, have been reported to increase the risk of sarcoidosis [37, 38]. Of note, during the first year following the World Trade Center disaster in 2001, New York City firefighters developed sarcoidosis or "sarcoid-like" granulomatous pulmonary disease (SLGPD) at significantly higher rates than usual [39].

The molecular pathogenesis of granuloma formation in sarcoidosis is characterized by immune responses mediated by type 1 T-helper cells (Th1) and possibly type 17 T-helper cells (Th17), and dysregulated regulatory T-cell function [40]. Cytokines that promote a Th1 response, such as IL-2 and IFN-γ, are upregulated in sarcoidosis and are associated with new-onset sarcoidosis and exacerbation of preexisting disease [41–43].

6.4 Granuloma Annulare

6.4.1 Clinical Features

Granuloma annulare is a fairly common disorder of childhood characterized by grouped papules and nodules in an annular configuration, often over the dorsal wrists, hands, ankles, and feet. At least four clinical variants have been reported: localized, generalized, perforating, and subcutaneous [44]. Granuloma annulare can appear at any age, but it is

Fig. 6.8 An annular plaque is seen on the eyelid of a child with granuloma annulare

most common in school-aged children. It is more common in females than males by a 2:1 ratio. Typically, asymptomatic grouped annular papules appear over extensor surfaces. Frequently, lesions are initially misdiagnosed as "tinea corporis," but fail to improve with antifungal therapy. In the localized type, skin-colored to pink annular, non-scaly plaques composed of papules and nodules may appear anywhere, but they tend to favor the extensor surfaces of the distal extremities, hands, and feet (Figs. 6.8 and 6.9). Lesions are single or multiple, and typically range in size from a few millimeters to several centimeters. In the generalized form, which is more common in adults, hundreds of small skin-colored to pink papules appear over the entire trunk and extremities. Some may coalesce into small annular plaques. The perforating type is characterized by grouped papules with central umbilication and crusts.

A subcutaneous type of granuloma annulare is relatively common in children, and presents as painless to slightly tender subcutaneous nodules. Although most common on the pretibial surfaces, it has also been reported on other extensor surfaces, as well as on the scalp, eyelids, and buttocks [45–47].

6.4.2 Histology

Pediatric granuloma annulare in many cases differs from that seen in the adult population. While the classic changes of small granulomas occurring within the superficial reticular dermis can be seen in children, the characteristic pattern is that of a single larger palisading granuloma localized in the subcutaneous fat (Figs. 6.10 and 6.11). Less commonly, multiple smaller foci may be present in the deep dermis or subcutaneous fat (Figs. 6.12 and 6.13). This so-called *subcutaneous or deep granuloma annulare* occurs almost extensively in children. A palisade of histiocytes with abundant eosinophilic cytoplasm surrounds a central area of necrobiosis. In some cases, mucin may be identified within the central foci on either H&E sections or with alcian blue or colloidal iron stains (Fig. 6.14). A surrounding perivascular

Fig. 6.9 Granuloma annulare presents as papules and nodules forming a non-scaly annular plaque on the dorsal hand

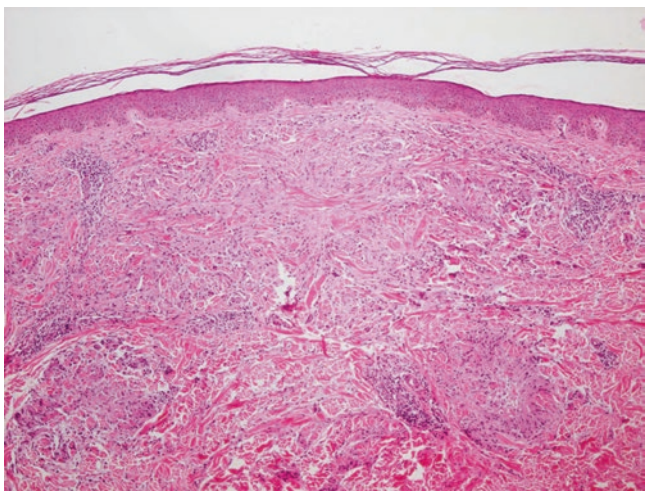

Fig. 6.10 Within the superficial portion of the dermis, several small poorly-formed granulomatous areas are apparent in granuloma annulare

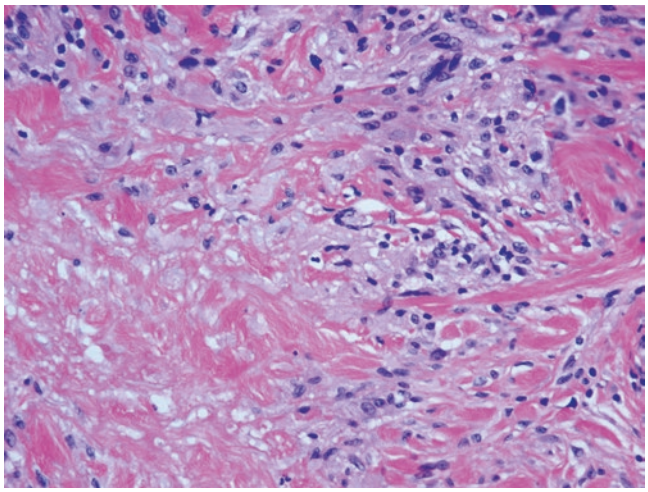

Fig. 6.11 A palisade of epithelioid histiocytes surrounds a paucicellular area of degenerating collagen (necrobiosis) in granuloma annulare. A hint of dermal mucin is present on H&E sections

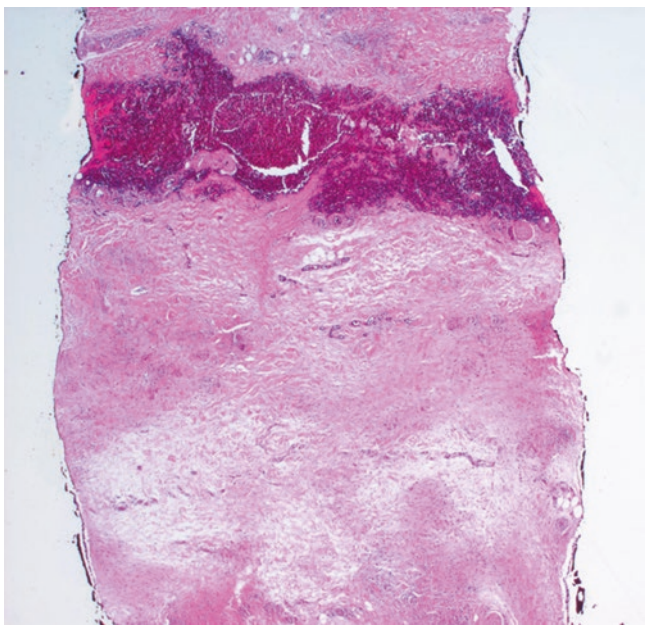

Fig. 6.12 Similar granulomatous foci are present in the reticular dermis and extending into the subcutis in the deep variant of granuloma annulare

infiltrate of lymphocytes is present in most cases. Some authors have suggested that the presence of dilated vessels lateral to the granulomatous foci may serve as a diagnostic clue [48]. *Classic granuloma annulare* demonstrates small granulomatous foci located in the superficial reticular dermis. Palisading histiocytes surround areas of collagen with necrobiosis and mucinous degeneration. *Interstitial granuloma annulare* also occurs in children. In this variant, the histiocytes percolate individually between collagen bundles and do not form true granulomas. Interstitial mucin deposition is present but subtle (Figs. 6.15 and 6.16).

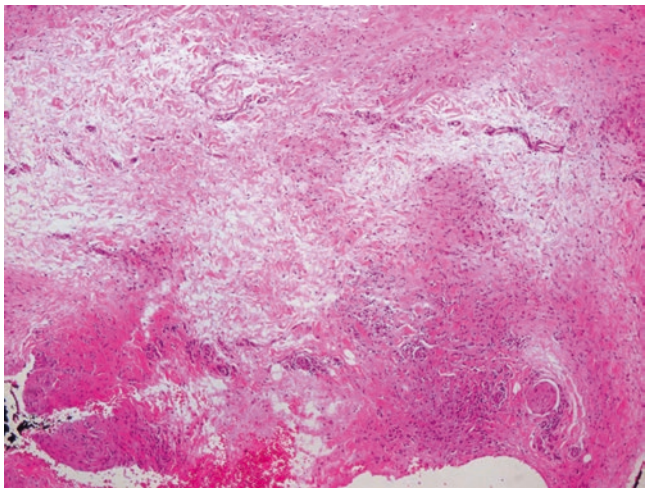

Fig. 6.13 Dermal pallor surrounded by a palisade of histiocytes characterizes the deep variant of granuloma annulare

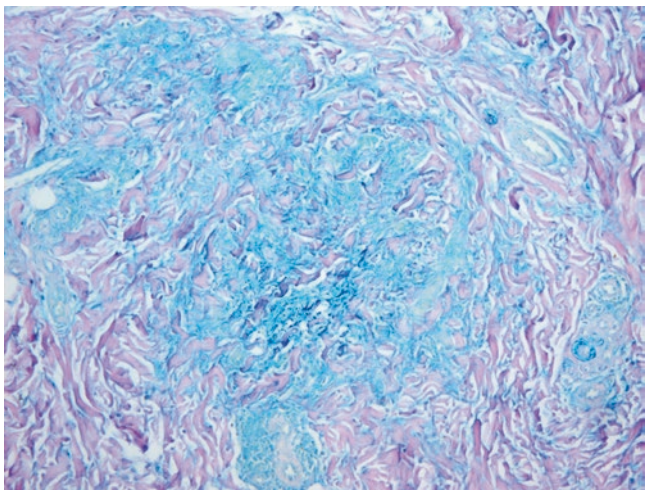

Fig. 6.14 A colloidal iron stain highlights the blue mucin present within the foci of granulomatous inflammation in granuloma annulare

The major differential diagnoses of granuloma annulare are epithelioid sarcoma and rheumatoid nodule [49]. Epithelioid sarcoma can be differentiated based upon true cellular necrosis and the presence of nuclear atypia in the cells palisading around the periphery of the granuloma-like lesion. In cases that are not easily distinguished on routine sections, immunostains highlighting cytokeratin and CD68 stains will help to make the distinction. A rheumatoid nodule may demonstrate identical histologic features and clinical correlation is the best way to make the distinction.

6.4.3 Pathogenesis

The pathogenesis of granuloma annulare is poorly understood with a vast majority of lesions occurring in patients who are otherwise healthy. Infections, such as tuberculosis,

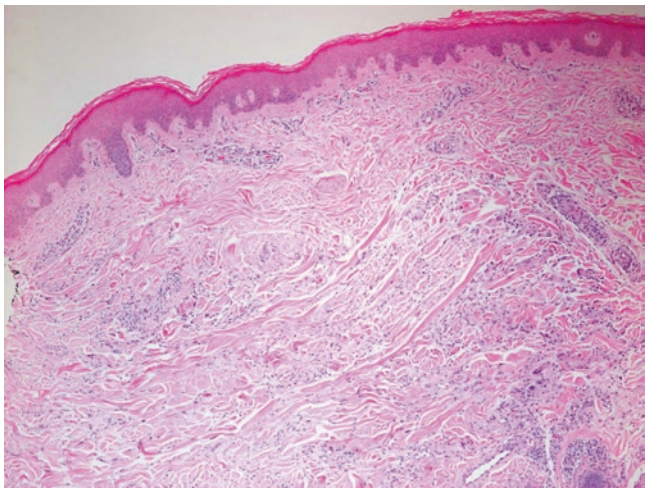

Fig. 6.15 In the interstitial variant of granuloma annulare, histiocytes percolate individually between collagen bundles in the superficial dermis and do not aggregate into granulomas

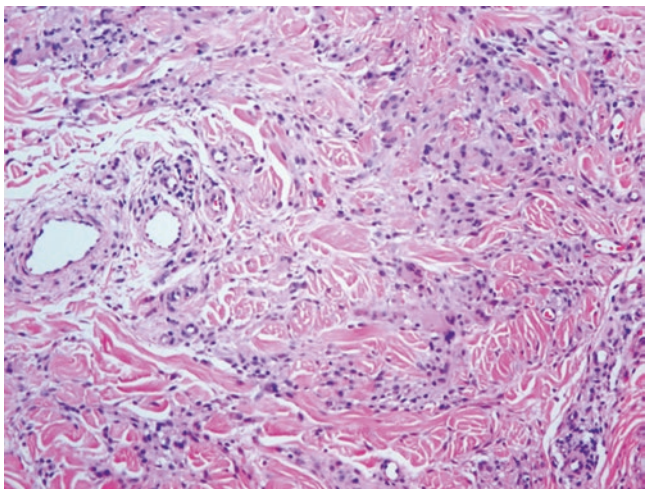

Fig. 6.16 Interstitial granuloma annulare shows individual histiocytes percolating between collagen bundles

hepatitis and viral infections, have been suggested as a possible cause of granuloma annulare. However, other studies have found no molecular or culture-based evidence for bacterial, mycobacterial, or fungal elements in patients with granuloma annulare [50]. The disease may have a genetic component, since it is associated with certain HLA phenotypes. HLA-B8 levels have been reported to be increased in localized forms of granuloma annulare, and HLA-A31 and HLA-B35 levels are increased in the generalized form [51]. The perivascular lymphocytic infiltrate is mainly composed of T lymphocytes, with a predominance of CD4+ T cells over CD8+ T cells, thus granuloma annulare could be a cell-mediated immune response [52, 53]. Granuloma annulare may represent a delayed-type hypersensitivity reaction, and the matrix degradation (necrobiosis) observed in the disease may be elicited by inflammatory mechanisms.

Fig. 6.17 Necrobiosis lipoidica presents as hyperpigmented patches and plaques with areas of atrophy over the dorsal feet and ankles

6.5 Necrobiosis Lipoidica

6.5.1 Clinical Features

Necrobiosis lipoidica is a rare chronic dermatosis that typically affects the lower extremities and is highly associated with type I diabetes. Necrobiosis lipoidica affects 0.3–1.2 % of all diabetic patients (two thirds are with type I diabetes) [54]. In one study, 62 % of patients with necrobiosis lipoidica had diabetes, and nearly half of the patients without clear diabetes had abnormal glucose tolerance tests [57]. The average age of onset is 30 years and it is more common in females [55]. Necrobiosis lipoidica is relatively rare in children with only 2.3 % of reported cases occurring in the pediatric population [56]. Lesions usually begin as erythematous papules that coalesce to form yellowish-brown, telangiectatic plaques with central atrophy and violaceous borders (Fig. 6.17). The classic location is the shins, although lesions have been reported on other body sites, including the arms, trunk, and face/scalp [55]. Ulceration occurs in 35 % of cases [57].

6.5.2 Histology

Necrobiosis lipoidica is uncommon in children as it is usually a late complication of long-standing diabetes mellitus [58]. However, rare cases have been described in children with long-standing diabetes. In these cases, the histology is indistinguishable from that seen in adult cases of necrobiosis

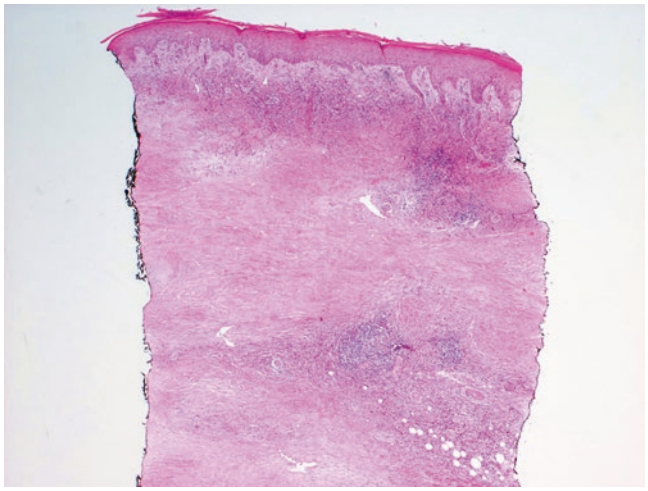

Fig. 6.18 Low magnification demonstrates large foci of necrobiotic collagen surrounded by a rim of histiocytes giving a layered appearance in necrobiosis lipoidica

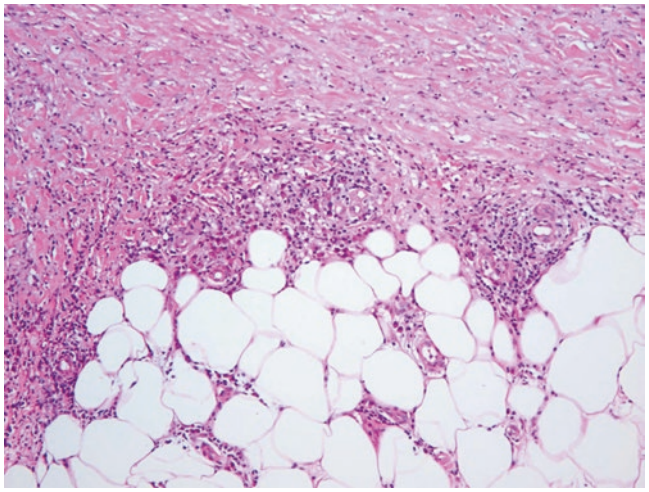

Fig. 6.20 Lymphoid follicles and plasma cells are often seen at the interface between in the deep reticular dermis and the subcutis in necrobiosis lipoidica

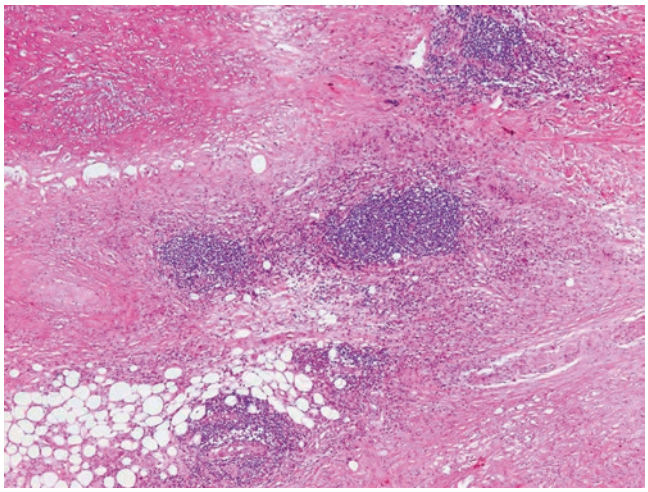

Fig. 6.19 Necrobiosis lipoidica frequently has lymphoid follicles in addition to the palisade of histiocytes

lipodica. Within the reticular dermis, a palisade of histiocytes surrounds a large central area of pale staining necrobiotic collagen (Figs. 6.18, 6.19 and 6.21). The histiocytes may have abundant cytoplasm and in well-developed lesions, lipid may be present within the cytoplasm. Multinucleated giant cells may be present. A superficial and deep perivascular infiltrate of lymphocytes, histiocytes and plasma cells is present. Similar clusters of hematopoietic cells aggregate into well-formed germinal centers may be present at the interface between the deep dermis and subcutaneous fat (Fig. 6.20). Dermal blood vessels demonstrate thickened walls and in some cases occluded vascular lumen.

The differential diagnosis includes granuloma annulare, rheumatoid nodule, and necrobiotic xanthogranuloma. The granulomatous foci in granuloma annulare are smaller than those seen in necrobiosis lipoidica and are located either more superficially (classic type) or more deeply (subcutaneous type seen in children). Mucin is not present in necrobiosis lipoidica, unlike the situation in granuloma annulare. Rheumatoid nodules are also situated deeper within the dermis and in the subcutaneous fat than in most cases of necrobiosis lipoidica. In addition, fibrin coats the dermal collagen giving it a "brick red" color in rheumatoid nodule. The distinction is usually best made by the clinical presentation and not based on histologic differentiation. Necrobiotic xanthogranuloma shares many histologic features with necrobiosis lipoidica, but the changes are much more florid. In necrobiotic xanthogranuloma, the dermis is much more extensively necrobiotic with many more histiocytes present that contain cytoplasmic lipids. Multinucleated giant cells are more abundant and much larger in size in necrobiotic xanthogranuloma than in necrobiosis lipoidica.

6.5.3 Pathogenesis

A theory regarding the pathogenesis of necrobiosis lipoidica involves microangiopathy and thickening of the involved blood vessels as a result of glycoprotein deposition in the vasculature [59–61]. Reduced blood perfusion and hypoxia in necrobiosis lipoidica lesions are thought to play a role with increased expression of glucose transporter-1 receptor detected in fibroblasts in the lesions. However, other studies have refuted the microangiopathy theory and suggested that this is a disease that involves an ongoing inflammatory process [62]. Another possible etiology of necrobiosis lipoidica is antibody-

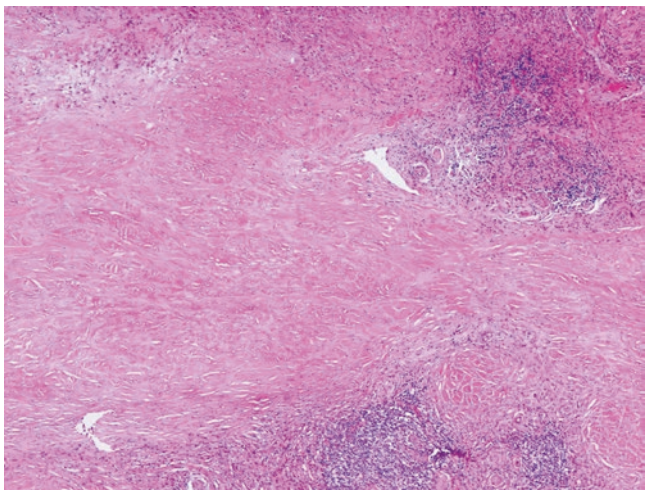

Fig. 6.21 The necrobiotic collagen is lightly eosinophilic and paucicellular in necrobiosis lipoidica

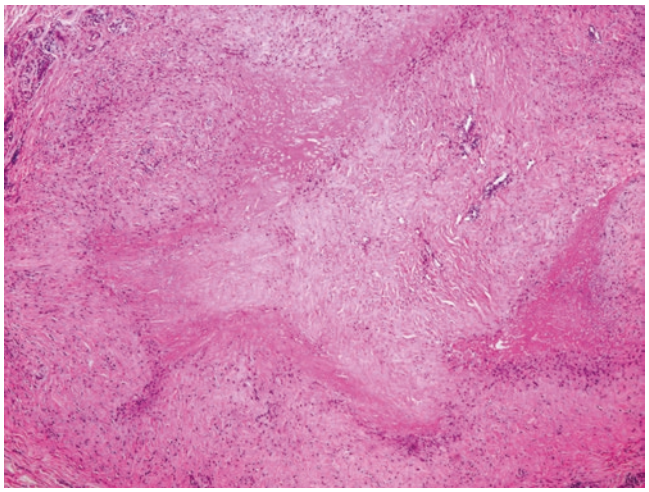

Fig. 6.22 Rheumatoid nodule demonstrates a large focus of eosinophilic collagen with a surrounding palisade of histiocytes in the deep dermis and subcutis

mediated vasculitis with involvement of cytokines, complement, and fibrinogen in the disease process [61].

6.6 Rheumatoid Nodule

6.6.1 Clinical Features

Subcutaneous lesions histologically resembling rheumatoid nodules can be seen in children who do not have rheumatoid arthritis. In one group of 15 affected children, the mean age at onset was reported to be 4 years of age [63]. In a second group of 7 affected children, the mean age at onset was 5.5 years of age [64]. Children are usually healthy at the time of lesion onset. Solitary or multiple non-tender, firm, fixed nodules are present on extensor surfaces, such as the pretibial areas, dorsal feet, and fingers. Lesions have also been reported on the scalp. They range in size from a few millimeters up to 5 cm. There is often a history of sudden onset and rapid increase in lesion size. Nodules tend to remit spontaneously over several years [63].

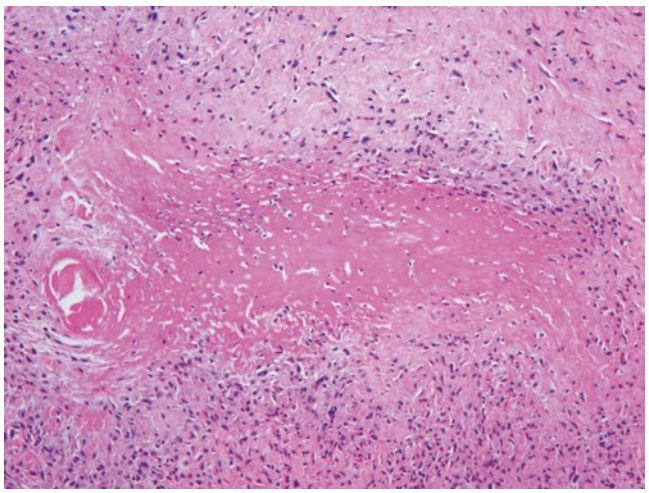

Fig. 6.23 The dense eosinophilia is due to fibrin deposition on the collagen bundles in rheumatoid nodules

6.6.2 Histology

True rheumatoid nodules are rare in children and histologically indistinguishable from subcutaneous granuloma annulare. One large or several smaller palisades of histiocytes are present around a central area of altered collagen (Figs. 6.22 and 6.23). In some cases, the collagen demonstrates an accentuated red color due to fibrin deposition. In other cases, there is a bluish tinge on account of mucin deposition. Clinical correlation is the only reliable way to make the proper diagnosis. In some patients with juvenile rheumatoid arthritis, the increased number of rheumatoid nodules has been associated with methotrexate treatment [65].

6.6.3 Pathogenesis

Rheumatoid nodule is a common skin manifestation of rheumatoid arthritis. The nodule is usually found on pressure points (such as the olecranon process), but it can occur at any body site. Rheumatoid factor is often present in patients with rheumatoid nodules [66]. Smoking may increase the risk of developing these lesions [67]. Complement activation, immune complex deposition in blood vessel walls, and proinflammatory cytokines have been implicated in the pathogenesis of rheumatoid nodule [68].

6.7 Palisaded Neutrophilic and Granulomatous Dermatitis

6.7.1 Clinical Features

Palisaded neutrophilic and granulomatous dermatitis is a rare inflammatory dermatosis most commonly seen in adults with systemic lupus erythematosus, rheumatoid arthritis, and systemic vasculitis (particularly Churg–Strauss syndrome and Wegener's disease). It is rare in the pediatric population with only several known case reports in children have been published. Cases in children have occurred in the setting of diabetes, celiac disease, systemic lupus erythematosus, and pauci-immune focal segmental glomerulonephritis [69]. Children with palisaded and neutrophilic dermatitis usually have small erythematous papules and nodules scattered over the extensor surfaces, such as the ankles, feet, elbows, knees, and hands. Papules may coalesce into a linear or annular distribution. Linear subcutaneous bands may also occur [70]. Adults are more likely to present with linear subcutaneous bands on the trunk.

6.7.2 Histology

Palisaded neutrophilic and granulomatous dermatitis is often associated with collagen vascular diseases [71]. The histologic features include leukocytoclastic vasculitis associated with foci of collagenous degeneration in early lesions (Figs. 6.24 and 6.25). As lesions become more fully developed, areas of leukocytoclasis with fibrin deposition and degenerated collagen are found in the centers of palisading histiocytes (Fig. 6.26). Later lesions have fibrosis, minimal neutrophilic debris, and less cellularity.

The histologic differential diagnosis varies depending upon the age of the lesion biopsied. Early lesions may be difficult to distinguish from leukocytoclastic vasculitis with clinical correlation as the best clue to the final diagnosis. In more advanced lesions, Wegener's granulomatosis and granuloma annulare can bear some histologic resemblance to palisaded neutrophilic and granulomatous dermatitis. Wegener's granulomatosis may involve larger vessels and extend deeper into the reticular dermis and subcutis than is usually seen in palisaded neutrophilic and granulomatous dermatosis; however, these findings are not seen in all cases of Wegener's granulomatosis and the histologic changes may

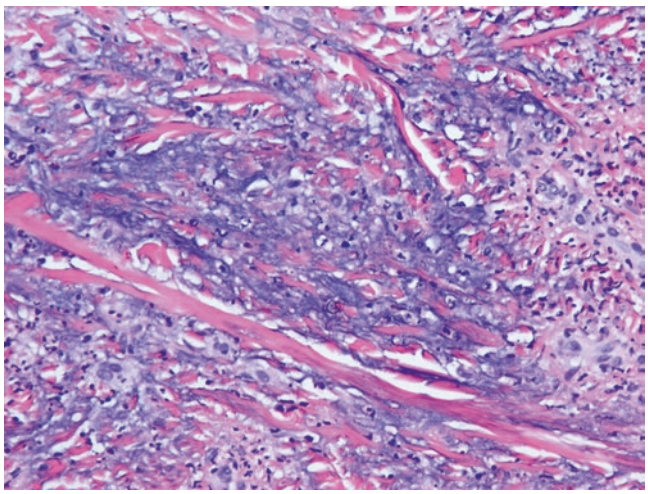

Fig. 6.25 There is abundant interstitial mucin admixed with neutrophils and karyorrhectic debris in palisaded neutrophilic and granulomatous dermatitis

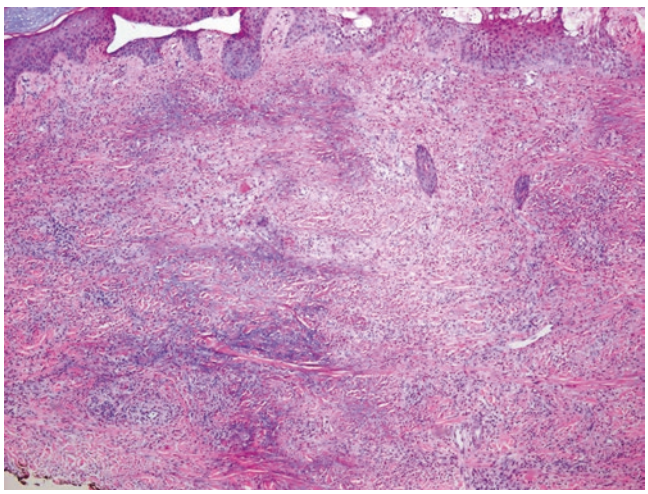

Fig. 6.24 A diffuse infiltrate of histiocytes and neutrophils is seen throughout the dermis in palisaded neutrophilic and granulomatous dermatitis

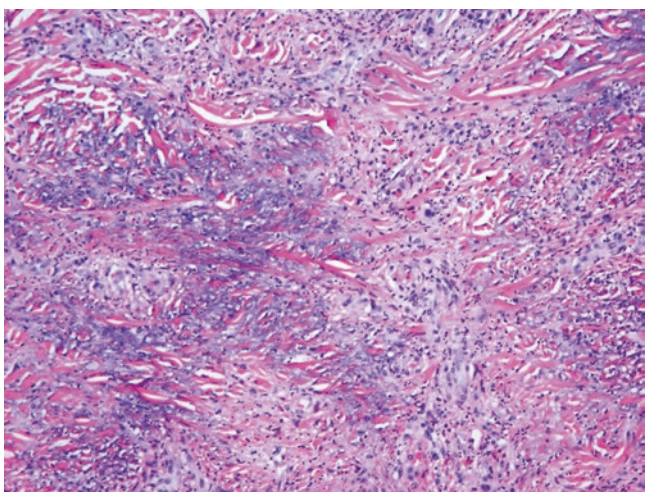

Fig. 6.26 Leukocytoclasis, degenerated collagen and mucin are present in palisaded neutrophilic and granulomatous dermatitis

be virtually identical to palisaded neutrophilic and granulomatous dermatitis [72]. Granuloma annulare does not ordinarily have leukocytoclastic vasculitis. In some early lesions, there may be a slight perivascular or transluminal neutrophilic infiltrate, but in most cases this is relatively scant, whereas neutrophils are abundant in the vascular walls and in foci of collagenous degeneration in palisaded neutrophilic and granulomatous dermatitis.

6.7.3 Pathogenesis

Palisaded neutrophilic and granulomatous dermatitis represents a cutaneous reaction pattern due to underlying systemic inflammatory processes [73]. The disorder is commonly associated with autoimmune diseases, particularly systemic lupus erythematosus and inflammatory arthritis, and sometimes with hematologic disorders, infections or medications, such as tumor necrosis factor-α inhibitors [73, 74].

The pathogenesis of palisaded neutrophilic and granulomatous dermatitis appears to be multifactorial, including abnormal neutrophil activation, circulating immune complex deposition, a delayed-type hypersensitivity reaction, and small vessel vasculitis [73, 75]. It has been suggested that it is a type of leukocytoclastic vasculitis that subsequently progresses to an excessive inflammatory response with collagen degeneration and fibrosis [71, 76]. The exaggerated immune response may be a result of dysregulation of T lymphocytes, affecting the regulation of B lymphocytes with subsequent manifestation of an abnormal antibody response to certain antigens.

6.8 Melkersson–Rosenthal Syndrome

6.8.1 Clinical Features

Melkersson–Rosenthal syndrome is a rare neuromucocutaneous granulomatous disease of unknown etiology. It is characterized by a classic triad of orofacial edema, recurrent facial nerve paralysis and a furrowed tongue (i.e., lingua plicata or "scrotal" tongue). However, presence of the full triad is unusual and monosymptomatic and oligosymptomatic forms are more common [77]. One or two clinical features, along with biopsy proven granulomatous cheilitis, are sufficient to make the diagnosis.

Melkersson–Rosenthal syndrome most commonly affects young adults between the second and third decades of life. It is very rare in children with approximately 30 case reports in the pediatric population [78]. Initial disease presentation with unilateral facial nerve palsy is more common in children than in adults. However, the most common symptom seen in children is painless orofacial swelling which commonly affects one or both lips, but may also affect the chin, cheeks, and periorbital area. Furrowed tongue is less commonly seen in children than in adults. Most children appear otherwise healthy, although one pediatric case was reported in the setting of Hashimoto's thyroiditis. A possible association between Melkersson–Rosenthal syndrome, sarcoidosis and Crohn's disease has been suggested, although the relationship has not been confirmed, and there have been no reports of children with Melkersson–Rosenthal syndrome and either of these conditions.

6.8.2 Histology

Granulomatous cheilitis is a key diagnostic feature of Melkersson–Rosenthal syndrome. It demonstrates well-formed sarcoidal-type granulomas surrounded by a brisk collarette of lymphocytes [78–80] (Figs. 6.27 and 6.28). Edema, dilated lymphatic vessels within the dermis, and a perivascular lymphocytic inflammatory infiltrate are also part of the constellation of findings [81].

The histologic differential diagnosis includes sarcoidosis, infectious processes caused by mycobacteria or fungi, and granulomatous rosacea. Sarcoidosis can be difficult to distinguish from Melkersson–Rosenthal syndrome, but sarcoidosis typically has a lesser lymphoid collarette surrounding the granulomas. Infectious processes may demonstrate more caseation in the center of the granulomas. Special stains for microorganisms may be required to eliminate infectious etiologies. Granulomatous rosacea has perifollicular distribu-

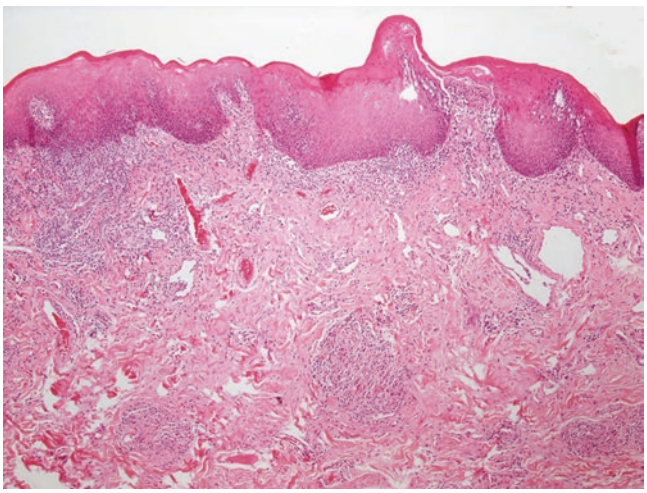

Fig. 6.27 The mucosal surface is slightly hyperplastic and overlies granulomas surrounded by lymphocytes in Melkersson–Rosenthal syndrome

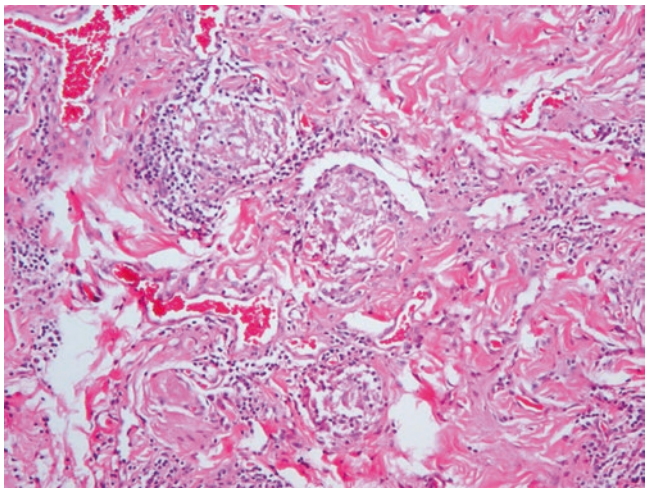

Fig. 6.28 Melkersson–Rosenthal syndrome is characterized by small granulomas surrounded by lymphocytes in most cases. Dilated dermal blood vessels are also a characteristic feature

tion to the granulomas and is most easily differentiated based upon the clinical histories. "Metastatic" Crohn's disease may be virtually impossible to differentiate from granulomatous cheilitis. Some authors have postulated that granulomatous cheilitis in children may in fact be part of the spectrum of Crohn's disease [82, 83].

6.8.3 Pathogenesis

Melkersson–Rosenthal syndrome belongs in a group of orofacial granulomatosis that is a granulomatous disorder with a spectrum of diseases ranging from localized granulomatous cheilitis to Melkersson–Rosenthal syndrome [84]. A genetic predisposition may exist linking Melkersson–Rosenthal syndrome and granulomatous cheilitis to HLA-A3, B7 and DR2 expression [85, 86]. The disorder may also result from reactions to certain foods or medications, particularly cinnamon aldehyde and benzoates, menthol, and monosodium glutamate [84, 87, 88]. Contact antigens such as cobalt, gold, and mercury are sometimes implicated. However, it is not clear whether these substances are the prime causative agents or they simply enhance the preexisting disease. Sixty percent of individuals with granulomatous cheilitis are atopic, and the association of the disease with Crohn's disease in children and adults has been well documented [89, 90]. Studies to explore the role of infectious agents have focused on *Mycobacterium tuberculosis*, *Mycobacterium paratuberculosis*, *Saccharomyces cerevisiae*, and *Borrelia burgdorferi*, but there is insufficient evidence to support an infectious etiology [91].

6.9 Cutaneous Crohn's Disease

6.9.1 Clinical Features

Crohn's disease is a granulomatous disorder of the gastrointestinal tract. Skin and mucosal findings develop in approximately 22–44 % of patients. The most common manifestations are oral and perianal lesions, metastatic (distant) skin lesions, reactive conditions (e.g., pyoderma gangrenosum and erythema nodosum), as well as changes secondary to nutritional deficiency (e.g., acrodermatitis enteropathica seen with zinc deficiency) [92]. Although disease onset is typically between 15 and 30 years of age, Crohn's disease does occur in younger children. Approximately 15–25 % of cases begin before age 18 [93]. Twenty five percent of patients develop perianal skin tags prior to the onset of gastrointestinal symptoms [92] (Fig. 6.29). Aphthous ulcers develop in >50 % of patients [94]. Up to 20 % develop "cobblestoning" of the buccal mucosa. Painless swelling of the lips or genitalia may precede onset of gastrointestinal symptoms by several years [95–97].

Granulomatous infiltration of the buccal mucosa causes a rough "cobblestone" appearance. In the lips, it appears as painless swelling. Likewise, it may cause painless swelling of the vulva, penis, and scrotum. Perianal skin tags are common. Other granulomatous lesions may affect the perineum, buttocks, and abdomen. Fissures and sinus tracts can develop. Metastatic granulomatous lesions can appear at distant sites as dusky red plaques often with ulceration.

Fig. 6.29 Cutaneous Crohn's disease presents as verrucous pink papules and plaques surrounding the anus in a patient newly diagnosed with Crohn's

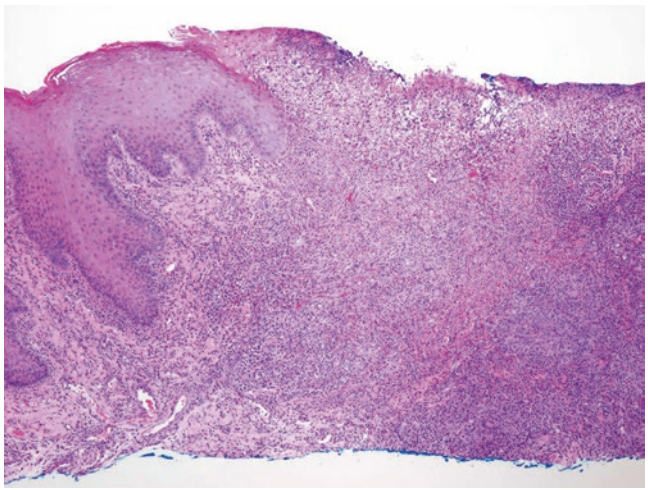

Fig. 6.30 Cutaneous Crohn's disease is characterized by a dense granulomatous inflammatory infiltrate that frequently causes ulceration

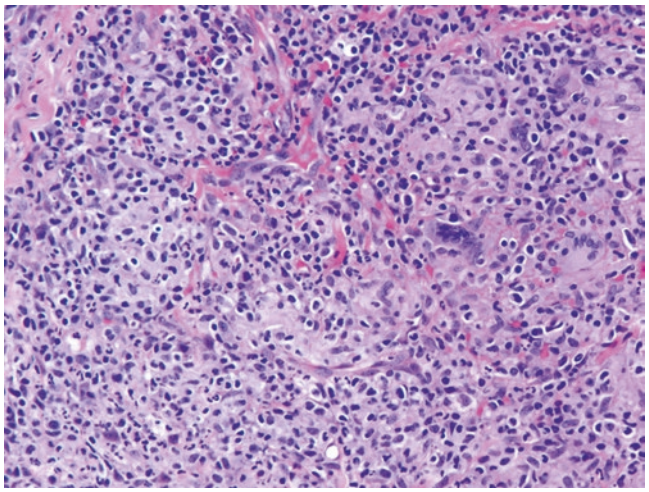

Fig. 6.31 Granulomas contain multinucleated giant cells that are admixed with lymphocytes and histiocytes in cutaneous Crohn's disease

6.9.2 Histology

The histologic manifestations of cutaneous Crohn's disease vary widely from patient to patient. Pyoderma gangrenosum, erythema nodosum, leukocytoclastic vasculitis, and neutrophilic dermatoses are all well described histologic patterns associated with Crohn's disease [98]. However, cutaneous or "metastatic" Crohn's disease is a granulomatous dermatitis [99].

The granulomas are comprised of multinucleated giant cells, epithelioid histiocytes and lymphocytes (Figs. 6.30 and 6.31). Plasma cells are occasionally seen in the infiltrate. In some cases, the foci of granulomatous inflammation may be perivascular, raising the histologic differential diagnosis of Wegener's granulomatosis [100]. In rare cases, necrobiotic collagen has been described [101].

6.9.3 Pathogenesis

The etiology of Crohn's disease is complex with immune-mediated dysfunction as the primary mechanism of disease in genetically susceptible individuals. Disease onset in these individuals is triggered by environmental factors that alter the gut mucosal barrier and microbiota, thereby stimulating abnormal gut immune responses [102].

Three important components in the pathogenesis of Crohn's disease are NOD2, autophagy, and type 17 T helper cell (Th17) immune responses. NOD2 (nucleotide-binding oligomerization domain containing 2, also known as CARD15) is a cytosolic pattern recognition receptor that regulates cellular immune response against intracellular bacteria [103, 104]. Three polymorphisms in NOD2 (amino-acid substitutions Arg702Trp and Gly908Arg, and frameshift FS1007insC) are present in about 40 % of Western patients with Crohn's disease. Interestingly, these polymorphisms are all found in the protein region responsible for the recognition of muramyl dipeptide (MDP) peptidoglycan component of the bacterial cell wall [105]. It has been proposed that NOD2 provides critical antibacterial defense and pro-inflammatory response, and NOD2 acts to regulate innate immune responses [106]. NOD2 can indirectly modulate the gut microbiota [102, 107].

The organic cation/zwitterion transporters OCTN1 and OCTN2 (also known as SLC22A4 and SLC22A5, respectively) have been associated with Crohn's disease [108, 109]. However, it is not known whether these genes are causative. Other genes associated with NOD2 in Crohn's disease are DLG5 (discs, large homolog 5), which encodes a membrane-associated guanylate kinase [110, 111]; the multidrug resistance gene MDR1, which encodes a transporter that regulates efflux of drugs from cells [112]; and PPAR-γ (peroxisome proliferative-activated receptor-γ), which is a nuclear receptor that inhibits NF-kB activity [113].

Autophagy is an important and emerging area of research in the pathogenesis of Crohn's disease. Polymorphisms in autophagy genes (namely, ATG16L1, IRGM, and LRRK2) have been found in Crohn's disease [102, 114]. Autophagy is a lysosomal degradation pathway that is essential for cellular survival and homeostasis [115]. Defective autophagic response to bacteria may contribute to the pathogenesis of Crohn's disease [102]. The autophagy gene ATG16L1 is essential in the induction of autophagy, and it is implicated in the pathogenesis of Crohn's disease [114].

Crohn's disease is an immune process mediated predominantly by type 1 T helper cells (Th1) and Th17 cells [110, 116]. Th1 cytokine profile, which includes interferon-γ and IL-12, is dominant in patients with Crohn's disease [117–119]. In addition, a new subset of innate lymphoid cells that rely on the induction of Th17 cells by IL-23 appears to be important in the disease [120, 121]. Tumor necrosis factor

(TNF) has been implicated in the pathogenesis of Crohn's disease [122]. In addition, microbial composition, host–microbial symbiosis, and barrier functions are likely contributing pathogenic factors in the disease. Reduced complexity and diversity of the gut microbiota have been consistently found in Crohn's disease as well [123].

6.10 Childhood Granulomatous Periorificial Dermatitis/ Granulomatous Rosacea

6.10.1 Clinical Features

Childhood granulomatous periorificial dermatitis is an uncommon granulomatous form of perioral dermatitis. It is clinically similar to rosacea and lupus miliaris disseminatum faciei, which are more common in adults. Typically, childhood granulomatous periorificial dermatitis affects prepubertal children (ages 3–12 years). It is somewhat more common in boys and children with dark skin [124, 125]. Clinically, multiple 1–3 mm, monomorphous skin-colored to pink or yellow-brown papules are seen over the perioral, perinasal, and periocular skin.

6.10.2 Histology

Histologic changes in childhood granulomatous periorificial dermatitis display much overlap with those seen in granulomatous rosacea and many authors consider the two entities to be variants of a single disease process [126]. Peri-follicular lymphocytes often extend into the follicular epithelium and are associated with spongiosis (Fig. 6.32). In florid cases, the epithelial structures rupture with follicular keratin extruded into the dermis, resulting in well-formed epithelioid granulomas. The granulomas are surrounded by a collarette of lymphocytes and occasionally with neutrophils (Fig. 6.33).

Lupus miliaris disseminatus faciei is considered to be the most floridly granulomatous variant of rosacea. This variant is not commonly encountered in children, but when it occurs, the histologic findings are those of a caseating granulomatous process and identical to those described in adults [127] (Fig. 6.34). Granulomas are most commonly peri-follicular, but this anatomic relationship is not readily apparent in all biopsies. As with other variants of rosacea, vascular telangiectasia is usually present within the dermis.

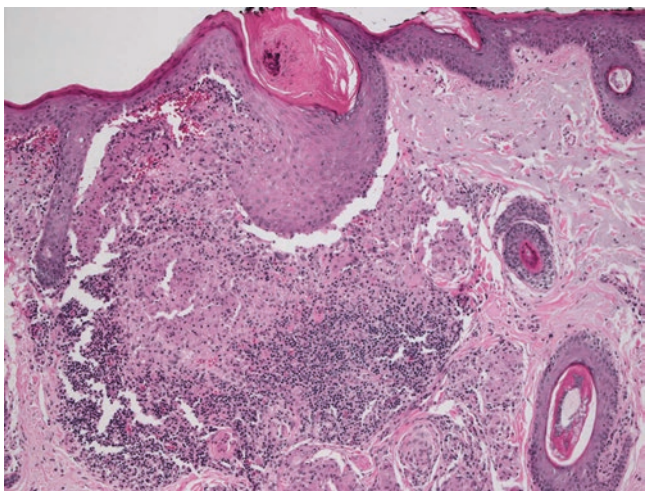

Fig. 6.32 Childhood granulomatous periorificial dermatitis/granulomatous rosacea demonstrates a peri-follicular granulomatous inflammatory infiltrate

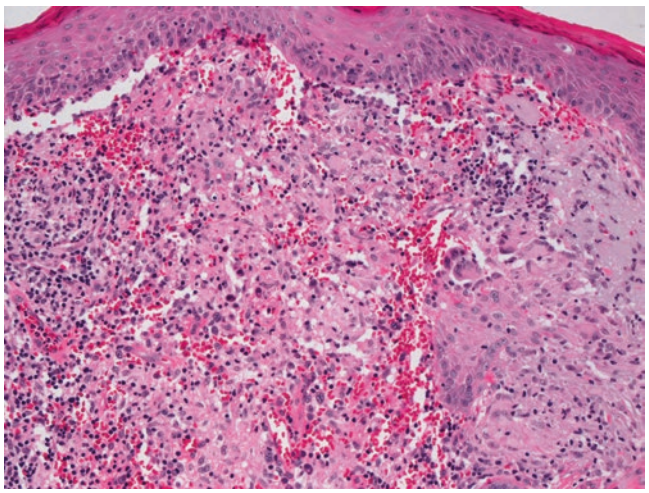

Fig. 6.33 Childhood granulomatous periorificial dermatitis/granulomatous rosacea shows large granulomas surrounding ruptured and distorted pilosebaceous units

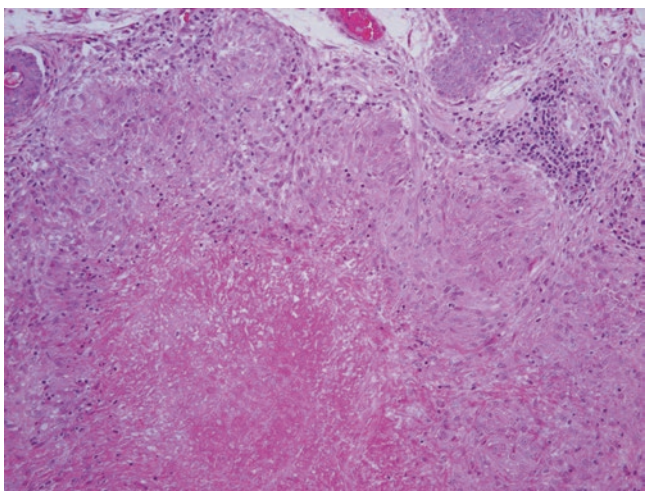

Fig. 6.34 Lupus miliaris disseminatus faciei is characterized by caseating granulomas adjacent to hair follicles in the superficial dermis. The caseation is similar to that seen in tuberculosis and differentiates this type of granulomatous rosacea from other rosacea variants

The histologic differential diagnosis includes sarcoidosis, which does not demonstrate a peri-follicular localization of granulomas and often has a minimal lymphocytic collarette around the granulomas. Infectious processes, such as deep fungal and mycobacterial infections, must be excluded with the use of special stains for microorganisms in some cases. Many authors consider lupus miliaris disseminatus faciei and the other variants of acne rosacea to be synonymous with periorificial dermatitis in children.

6.10.3 Pathogenesis

The cause of childhood granulomatous periorificial dermatitis is not known. Studies of lupus miliaris disseminatus faciei showed that no tuberculosis bacilli have been found in this disorder [129, 130]. It has been hypothesized that damages to the hair follicles cause release of antigens that trigger an autoimmune reaction against hair follicles [131].

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Diseases of Collagen and Elastic Tissue

7

7.1 Ehlers–Danlos Syndrome

7.1.1 Clinical Features

Ehlers–Danlos syndrome (EDS) encompasses a group of heritable connective tissue disorders characterized by joint hypermobility, dermal dysplasia, and increased fragility of vascular tissues and internal organs. Currently there are six major recognized forms of EDS (classic, hypermobility, vascular, kyphoscoliotic, arthrochalasis, and dermatosparaxis) and several rarer subtypes. Clinically, patients often present with abnormal skin texture and defective skin healing, leading to prominent scarring (Fig. 7.1). Disease prognosis depends on the type and severity [1].

7.1.2 Histology

Light microscopic examination contributes little to the diagnosis of Ehlers–Danlos syndrome, and it is not useful in determining the subtype of disease. Collagen bundles appear thinned, resulting in an overall thinning of the dermis (Fig. 7.2). There is increased intercellular ground substance between collagen bundles [2]. Fibroblasts with atypical morphology are present in some EDS cases [3, 4].

Ultrastructural examination reveals pronounced alterations in elastic tissue bundles [5, 6]. In some studies, collagen bundles appear normal [7]. Others have demonstrated curled and twisted fibrils [8].

7.1.3 Pathogenesis

Ehlers–Danlos syndrome is a diverse group of congenital disorders characterized by musculoskeletal, skin, and blood vessel abnormalities. The classic type of EDS (type I and type II EDS) is autosomal dominant and involves defects in type V collagen, specifically genes COL5A1 and COL5A2, as well as COL1A1 [9–11]. Type V collagen is present in many tissues, and it consists of three different α-chains encoded by the COL5A1, COL5A2, and COL5A3 genes [12]. Cysteine residues in the C-propeptide domain of α-chains are essential for disulphide bonding within the chain prior to the assembly and trimerization of collagen chains. Mutations in cysteine residues prevent proper disulphide bond formation and cause reduced levels of functional type V collagen [13, 14]. The hypermobile type of EDS (type III EDS) is autosomal dominant, and involves defects in type I and type VI collagen, and specifically with the gene TNXB [9–11]. The vascular type of EDS (type IV EDS) is autosomal dominant. It is the most severe form because of the risk of spontaneous vascular or visceral rupture. It involves defects in type III collagen, specifically gene COL3A1 [9–11]. There are other minor types of EDS (types VI, VIIA, VIIB, and VIIC), which are autosomal recessive and involve defects in type I collagen, particularly the genes PLOD1 and ZNF469 that are important in collagen I synthesis [9].

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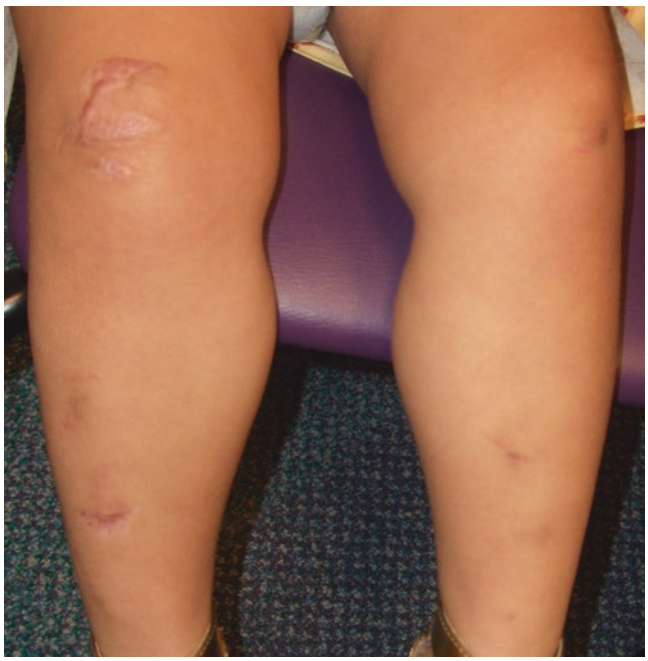

Fig. 7.1 Ehlers–Danlos Syndrome may present with atrophic "fish mouth" scars on the legs

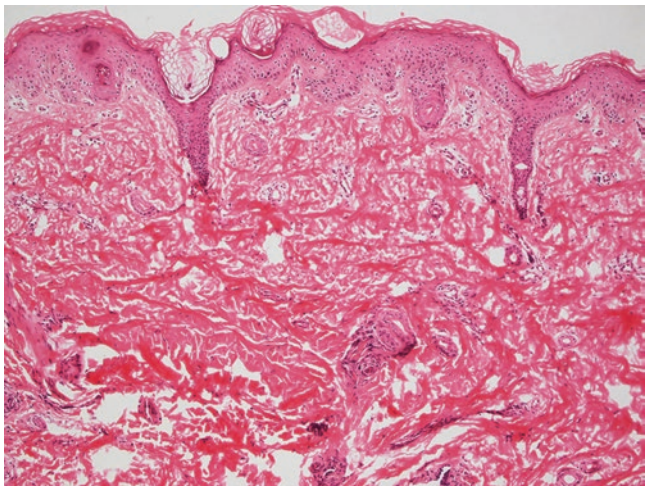

Fig. 7.2 Histologic changes are typically not seen in Ehlers–Danlos syndrome. However, collagen bundles may appear thin with overall thinning of the dermis

7.2 Marfan Syndrome

7.2.1 Clinical Features

Marfan syndrome is an autosomal dominant hereditary connective tissue disorder characterized by abnormalities primarily of the skeletal, ocular, and cardiovascular systems [15]. The main cutaneous feature of Marfan syndrome is spontaneous striae distensae of unclear etiology.

7.2.2 Histology

Skin biopsy is essentially non-diagnostic in Marfan syndrome. The epidermis is normal and the underlying dermis is remarkable only for thinned elastic tissue fibers that are not readily noticed. Ultrastructural analysis and immunofluorescence studies demonstrate decreased numbers of microfibrillar fibers [6, 16, 17]. Striae distensae are commonly seen in patients with Marfan syndrome. These lesions have the same histologic features as similar lesions occurring in patients without the underlying disease [18}.

In a single case, dystrophic nails demonstrating pronounced hyperkeratosis and a sparse inflammatory infiltrate were described in a child with Marfan syndrome. The relationship between the underlying elastic tissue defect and the nail changes is not certain, and the changes may represent coexisting lichen planus [19].

7.2.3 Pathogenesis

Marfan syndrome is a connective tissue disorder with an autosomal dominant inheritance pattern. It is caused by mutations in the fibrillin-1 (FBN1) gene [20]. About 80 % of cases are hereditary, while the rest are due to de novo mutations in FBN1 [21]. Almost all of the mutations identified are unique to a particular individual or family, and there is little correlation between a specific FBN1 mutation and the clinical phenotype [22, 23]. Fibrillin-1 associates with other extracellular matrix proteins to form thread-like microfibrils, which provide elasticity and structural support to connective tissues [21, 23]. Mutations in FBN1 lead to increased degeneration of microfibrils and loss of extracellular matrix integrity.

Another key discovery in the pathogenesis of Marfan syndrome is the key role of transforming growth factor-β (TGF-β) signaling [24]. In experimental animal models of Marfan syndrome, TGF-β signaling is dysregulated in mice with loss of FBN1 gene. These mice have increased levels of TGF-β that correlated with aortic aneurysm and myxomatous changes of the atrioventricular valves, which can be prevented or reversed with neutralizing antibodies against TGF-β [25, 26]. Consistent with these experimental findings, patients with Marfan syndrome have high levels of circulating TGF-β, which can be ameliorated by treatment with drugs that have TGF-β antagonist activity. These findings indicate that TGF-β may be a therapeutic target or a biomarker for Marfan syndrome [27]. Other potential players in the pathogenesis of Marfan syndrome are ADAMTS, disintegrin and metalloproteinase with thrombospondin motif proteins. These proteins interact with fibrillin-1 and accelerate the formation of microfibrils [28, 29]. Mutations in ADAMTS proteins result in phenotypes similar those found

in Marfan syndrome [28]. Thus targeting ADAMTS proteins might be a new therapeutic approach for this disease.

7.3 Cutis Laxa

7.3.1 Clinical Features

Cutis laxa, also known as elastolysis, is a rare connective tissue disorder that may be acquired or inherited. The acquired form is less common and tends to be less severe, affecting the skin only. Cutis laxa has been reported following arthropod stings and use of D-penicillamine and isoniazid [30].

The inherited forms may show autosomal dominant, recessive, or X-linked patterns. Manifestations are typically present at birth and extracutaneous involvement is common (e.g., pulmonary emphysema, umbilical/inguinal hernia, gastrointestinal and vesicourinary tract diverticula). Clinically, patients present with pendulous skin that hangs in loose folds (Fig. 7.3). There is no known effective therapy for cutis laxa.

7.3.2 Histology

It is not possible to distinguish the multiple acquired and inherited subtypes of cutis laxa on microscopic examination. Biochemical and molecular genetic testing are required to achieve this level of specificity [31, 32]. All cases of cutis laxa demonstrate absence of elastic tissue fibers in the papillary dermis and a marked diminution of fibers in the deeper portions of the dermis. Fragmented elastic tissue fibers can also be observed on routine H&E sections and on elastic tissue stains [33–36]. In some acquired cases, an antecedent inflammatory process results in enzymatic dissolution of elastic tissue fibers and remnants of the inflammation are present on biopsy [37–39]. Some authors have demonstrated subtle changes in collagen fibers in cases of cutaneous cutis laxa and suggest that the disease may represent a disorder of both elastin and collagen fibers [40].

Fig. 7.3 Cutis laxa presents as loose folds of intertriginous skin (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

Electron microscopic examination reveals a marked diminution of elastic tissue fibers. In cases acquired secondary to an inflammatory process, degenerating elastic tissue fibers are seen in close proximity to neutrophils [33, 38]. Vacuolated macrophages containing elastic tissue fibers are also present [34]. Marked degenerative structural changes occur within the elastic tissue fibers [41, 42].

Localized and generalized forms of cutis laxa show similar histologic findings and are only differentiated based upon clinical presentation [33, 43]. In Europe, some cases have been attributed to *Borrelia burgdorferi* infection [44]. Penicillamine use has been associated with alteration in cutaneous elastic tissue fibers and development of a cutis laxa-like appearance [45].

7.3.3 Pathogenesis

Cutis laxa is characterized by the loss of intact elastic fibers, resulting in loose and hypoelastic skin, most noticeably on the neck, hands, face, and groin. Cutis laxa can be inherited or acquired. Inherited forms of cutis laxa include autosomal dominant cutis laxa, autosomal recessive cutis laxa types I, IIA, and IIB, Urban–Rifkin–Davis syndrome, macrocephaly–alopecia–cutis laxa–scoliosis syndrome, arterial tortuosity syndrome, and Menkes disease/X-linked cutis laxa (XLCL) [31].

Autosomal dominant cutis laxa (ADCL) is caused by frameshift mutations in the elastin gene (ELN) as well as in the fibulin-5 gene (FBLN5) [31, 46, 47]. ELN mutations result in a missense peptide sequence in the C-terminus of tropoelastin. Mutant tropoelastin is deficient in binding to fibrillin but has enhanced self-association properties [46]. Mutant elastin leads to reduced stiffness of tissues and increased transforming growth factor (TGF)-β signaling [48].

Autosomal recessive cutis laxa-I (ARCL-I) is associated with severe systemic problems, including emphysema, arterial tortuosity and aneurysms, as well as joint laxity and muscular hypotonia [31]. Many patients with ARCL-I die from pulmonary or cardiac complications in early childhood. ARCL-I results from mutations in the genes FBLN4 and FBLN5, which encode for fibrillin-4 and -5 [49–52]. Fibrillin-4 and -5 are required for mature elastic fiber formation and facilitate the deposition of tropoelastin onto microfibrils as well as regulating cell signaling through TGF-β [52–54].

Autosomal recessive cutis laxa-IIA, IIB, and IIIA (ARCL-IIA, IIB, and IIIA) are conditions associated with growth and developmental delay, and skeletal abnormalities [55, 56].

ARCL-IIA and B are caused by two different genes. ARCL-IIA is caused by mutations in the ATP6V0A2 gene (ATPase H+ Transporting V0 Subunit A2), which encodes a proton pump in intracellular vesicles [57, 58]. Mutations in ATP6V0A2 result in the accumulation of tropoelastin in the Golgi apparatus. ARCL-IIB is caused by mutations in PYCR1 gene (pyrroline-5-carboxylate reductase 1), which encodes a mitochondrial enzyme involved in proline metabolism [59]. ARCL-IIIA is due to mutations in the ALDH18A1 gene, which encodes for the mitochondrial enzyme Aldehyde Dehydrogenase 18 Family Member A1 that is important in the synthesis of proline, ornithine and arginine [60].

Urban-Rifkin-Davis syndrome (URDS) is a form of cutis laxa associated with severe pulmonary, gastrointestinal and urinary abnormalities. It is autosomal recessive and is caused by mutations in the latent TGF-beta binding protein 4 (LTBP4) gene [61]. The function of LTBP4 is to localize TGF-β complex to fibrillin microfibrils in the extracellular matrix [62]. Macrocephaly–alopecia–cutis laxa–scoliosis syndrome (MACS syndrome) is caused by mutations in RIN2 (Ras And Rab Interactor 2) gene, which is involved in membrane and protein trafficking in the cell [63]. Some conditions of inborn errors of metabolism, such as Menkes syndrome, are associated with cutis laxa. X-linked cutis laxa (XLCL) and Menkes syndrome are believed to be entities existing along a disease spectrum, in which patients with XLCL mainly have connective tissue problems, whereas patients with Menkes syndrome also have associated severe neurologic defects [31].

Acquired cutis laxa (ACL) is a rare disorder that often occurs in adults, and may be associated with various malignancies, infections, inflammatory dermatoses and drugs [31]. Young children can develop ACL often after a neutrophilic dermatosis, such as Sweet's syndrome (a condition called Marshall syndrome) [64, 65]. Patients with ACL may have low lysyl oxidase activity and α-1-antitrypsin levels, and high cathepsin G levels that could contribute to decreased skin elastin and the clinical manifestation of cutis laxa [66].

In summary, the genetic findings suggest that disruption in elastic fiber formation at various molecular levels can lead to cutis laxa conditions. Moreover, activation of TGF-β signaling is a common downstream pathway seen in these disorders [31].

7.4 Pseudoxanthoma Elasticum

7.4.1 Clinical Features

Pseudoxanthoma elasticum (PXE) is a rare inherited disorder of connective tissue that is characterized by aberrant mineralization and degeneration of elastic fibers in the soft tissues, particularly of the skin, eyes, and cardiovascular system. PXE has a prevalence of 1:50,000 in the general population, and is more common in females than males (2:1 ratio) [67]. PXE presents as small yellow papules that gradually coalesce to form larger plaques. Common locations include the neck and flexural creases. Lesions typically begin to appear during childhood or adolescence and progress into adulthood. There is no known cure for PXE, although some cutaneous lesions may be amenable to surgical excision.

7.4.2 Histology

Pseudoxanthoma elasticum is characterized by clumped and fragmented elastic tissue fibers in the dermis [68]. These abnormal elastic tissue fibers are coated with calcium deposits (Fig. 7.4). This gives a densely basophilic appearance to the elastic fibers, rendering them very apparent with routine histologic staining (Fig. 7.5). Greatly increased numbers of elastic fibers are seen, as is the thickness of the fibers themselves [69] (Fig. 7.6). Von Kossa stains highlight the calcium phosphate deposits [70]. Ultrastructural analysis reveals abnormal elastin with a granular morphology [71]. Thready material comprised of fibrinogen, collagen and glycoprotein is also detected by immunoelectron microscopy [72]. Clinically normal skin from affected individuals demonstrates calcification of normal-appearing elastic tissue fibers in the dermis [70].

The differential diagnosis of PXE includes other conditions with disordered elastic tissue fibers including elastosis perforans serpiginosum, annular elastolytic granuloma, and wrinkling due to mid-dermal elastolysis. However, calcification is not as prominent in the other conditions. While transepidermal elimination can occur in PXE, it is not common,

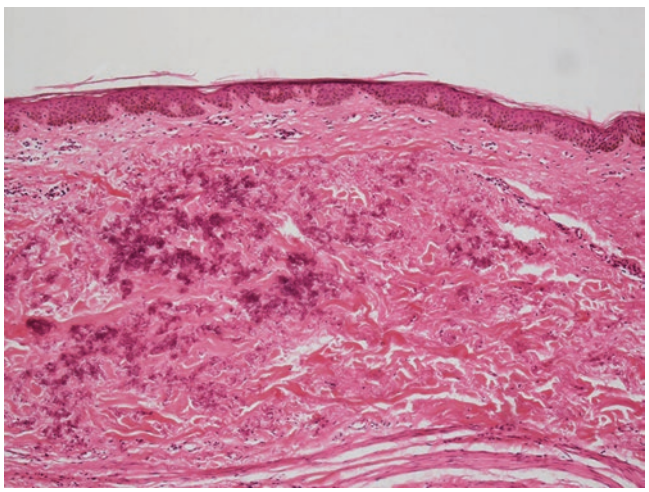

Fig. 7.4 Clumps of elastic tissue with calcification are apparent in the superficial reticular dermis in pseudoxanthoma elasticum

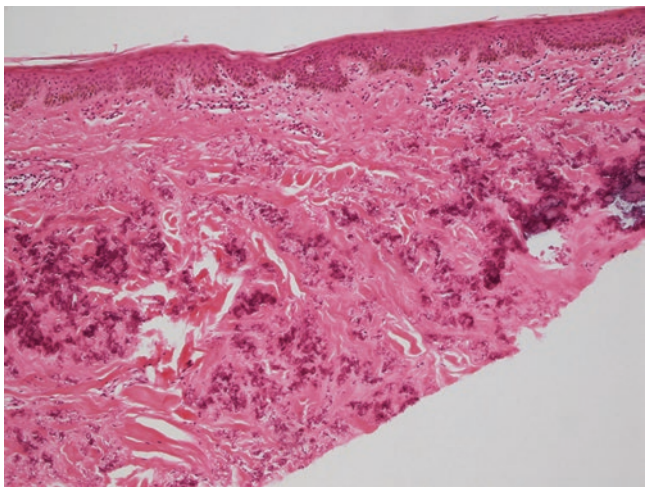

Fig. 7.5 The elastic tissue fibers are largely calcified and appear basophilic in pseudoxanthoma elasticum

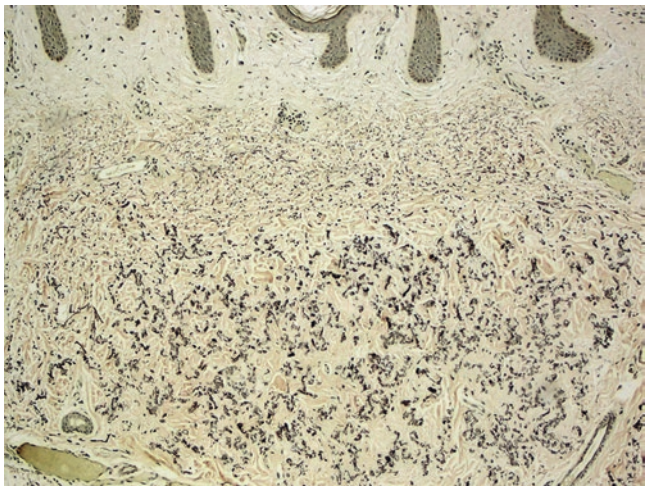

Fig. 7.6 A greatly increased number of highly fragmented elastic tissue fibers is observed on Verhoeff–Van Gieson (VVG) stain in pseudoxanthoma elasticum

while it is a typical finding in elastosis perforans serpiginosum [73, 74]. Annular elastolytic granuloma has more circumscribed lesions with a palisading granulomatous response that is not seen in PXE. Wrinkling due to mid-dermal elastolysis demonstrates elastic tissue alterations confined to perifollicular regions, and the histologic changes are subtler than those seen in PXE. Long-standing treatment with penicillamine can induce changes in elastic tissue fibers that resemble those seen in PXE [75].

7.4.3 Pathogenesis

Pseudoxanthoma elasticum is a multisystem disorder with an autosomal recessive pattern of inheritance. PXE is characterized by abnormal mineralization of soft connective tissue resulting in fragmentation of elastic fibers in the skin, eyes, and cardiovascular system [76, 77]. PXE is caused by mutations in the ABCC6 gene that encodes a transmembrane ATP-binding cassette transporter protein (ABCC6/MRP6), which is normally expressed in the liver and the kidney [78–80]. The most frequent ABCC6 gene mutations are p.R1141X and g.del23-29, which account for up to 45 % of all PXE mutations [81, 82]. In experimental animal models of PXE, deletion of ABCC6 gene in mice recapitulates the genetic and morphological features of PXE with progressive mineralization of connective tissue in the affected animals [83, 84].

The mechanism of elastic fiber mineralization due to defective ABCC6 transporter is still not known. Two theories have been proposed as potential mechanisms of how ABCC6 mutations lead to pathologic mineralization in connective tissues in PXE. The “metabolic hypothesis” states that dysfunction of ABCC6 in the liver results in deficiency of liver factor(s) required to prevent precipitation of calcium phosphate complexes and aberrant mineralization in homeostatic conditions [85, 86]. The “cell hypothesis” states that loss of normal ABCC6 protein in the affected cells, such as skin fibroblasts, alters their biosynthetic expression profile and proliferation as well as cell–cell and cell–matrix interactions [87, 88]. Other studies have suggested that the ectopic mineralization in PXE could partially be due to vitamin K deficiency, leading to reduced levels of fully carboxylated matrix-Gla proteins (MGP) [89, 90]. Fully carboxylated MGP is a potent anti-mineralization factor expressed in connective tissues. It has been found that loss of function of the GGCX gene, which encodes a vitamin K-dependent enzyme responsible for γ-glutamyl carboxylation of Gla-proteins, results in skin lesions similar to PXE [91].

7.5 Wrinkling Due to Mid-dermal Elastolysis

7.5.1 Clinical Features

Wrinkling due to mid-dermal elastolysis (MDE) is a rare connective tissue disorder characterized by loss of elastic fibers in the mid-dermis. The cutaneous features of mid-dermal elastolysis are variable, ranging from patches of fine wrinkles to perifollicular papules and nonspecific reticular erythema [92]. There is no definitive therapy for MDE.

7.5.2 Histology

This uncommon disorder demonstrates subtle histologic changes. Elastic tissue fibers are lost in the mid-portion of the reticular dermis, sometimes with preferential loss in a

perifollicular distribution [92–94]. Early cases demonstrate a mild infiltrate of lymphocytes and histiocytes. Rare multinucleated giant cells may be present and may engulf elastic tissue fibers [95]. Electron microscopic studies demonstrate degeneration of elastic tissue fibers, some of which are in macrophages [96]. While elastin is absent from regions of the dermis, the fibrillin-1 component of the fibers appears intact [97].

7.5.3 Pathogenesis

Elastin degradation in mid-dermal elastolysis is a result of increased elastase activity in the skin and subsequent phagocytosis of damaged elastic fibers by macrophages and mast cells [95, 98]. Elastase is released by inflammatory cells and skin fibroblasts. There is evidence of increased levels of matrix metalloproteinases (MMPs) and elastases, such as cathepsin G, in fibroblasts from lesional skin of patients with MDE [97, 99].

MDE may be due to an imbalance between MMPs and tissue inhibitors of MMPs (TIMPs). The balance between activated MMPs and TIMPs determines the overall MMP proteolytic activity, and the extent of extracellular matrix degradation. Excess MMP activity can lead to pathological degradation of connective tissue, including increased elastolysis [95, 97, 100]. MDE is strongly associated with ultraviolet (UV) light exposure, and disease onset may be triggered by a phototoxic reaction [97, 101, 102]. UV light may induce the production of MMP-1, which can lead to elastic fiber degradation in the skin [103]. Thus, a combination of increased elastase and MMP activities as well as contributing environmental factors, such as UV radiation, may underlie the pathogenesis of this disease.

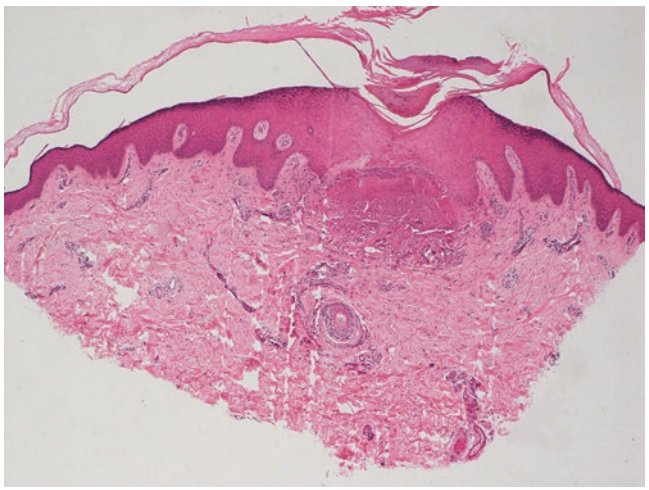

Fig. 7.7 Elastosis perforans serupignosum demonstrates an acanthotic epidermis with a central focus of disruption and underlying amorphous material in the superficial dermis

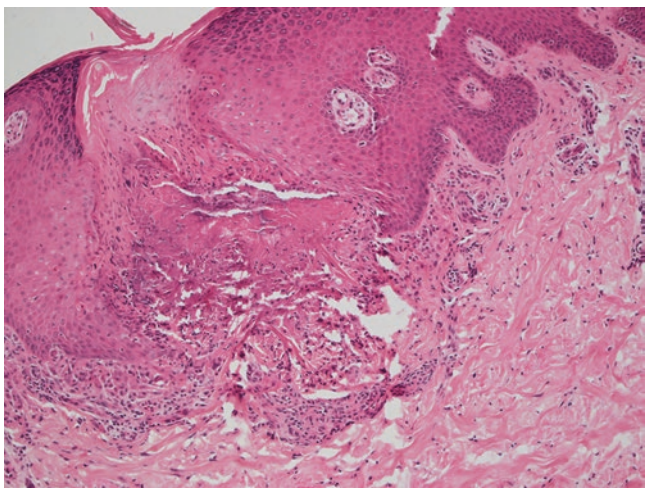

Fig. 7.8 Amorphous material is present within the papillary dermis and extends into the epidermis to the surface through a narrow channel in elastosis perforans serpiginosa

7.6 Elastosis Perforans Serpiginosum

7.6.1 Clinical Features

Elastosis perforans serpiginosum (EPS) is a rare perforating dermatosis characterized by transepidermal extrusion of connective tissue elastic fibers. EPS presents as erythematous keratotic papules that coalesce into serpiginous plaques [104]. Although there is no definitive treatment for EPS, some patients have shown improvement with cryotherapy.

7.6.2 Histology

Biopsies of elastosis perforans serpiginosa demonstrate an acanthotic epidermis with a cup-shaped invagination (Fig. 7.7). Refractile eosinophilic material that is wavy and linear can be seen within the epidermis, creating a channel and extruding out of the skin (Fig. 7.8). Within the underlying dermis, clumped elastic tissue fibers appear basophilic and may be focally calcified. An elastic tissue stain is helpful in correctly identifying the fibrillar material being extruded [105] (Fig. 7.9). An inflammatory infiltrate consists of lymphocytes and occasional histiocytes [106]. A granulomatous response is present in some cases. The relationship between this condition and perforating pseudoxanthoma elasticum remains unclear [73, 107].

A histologic appearance similar to EPS can be caused by long-standing treatment with penicillamine. Ultrastructural analysis D-penicillamine-induced lesions demonstrates a “lumpy-bumpy” pattern to the elastic tissue fibers, which is

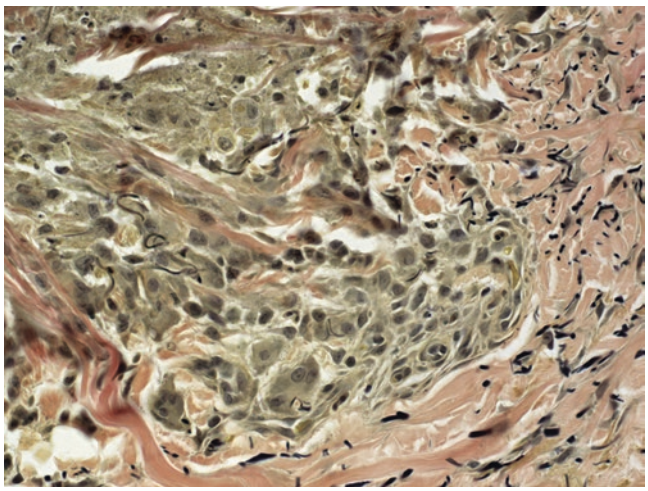

Fig. 7.9 Elastic tissue fibers in this Verhoeff-Van Gieson elastin stain are present within amorphous material that is transepidermally eliminated in elastosis perforans serpiginosa

not seen in EPS and can be used as a distinguishing feature [108, 109]. Other perforating diseases such as Kyrle's disease, perforating folliculitis, and reactive perforating collagenosis also enter the differential diagnosis. These entities can be differentiated in that they lack degenerating elastic fibers within the epidermis.

7.6.3 Pathogenesis

Elastosis perforans serpiginosa is a rare condition of inherited connective tissue disorders, affecting elastic tissue in the skin. EPS can be associated with systemic diseases, such as Down's syndrome, Ehlers–Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, and Marfan syndrome [110, 111]. An acquired form of EPS has been reported in cases of long-term treatment with D-penicillamine [112]. The cause of EPS is not known, but it may be due to abnormalities induced by a variety of underlying connective tissue disorders, leading to altered elastic fibers and elimination of these fibers through the epidermis [110].

7.7 Anetoderma

7.7.1 Clinical Features

Anetoderma is a rare dermatosis characterized by focal loss of elastic tissue in the skin, resulting in circumscribed areas of loose skin. Clinically, these lesions typically present as macular depressions or pouch-like herniations of the skin (Fig. 7.10).

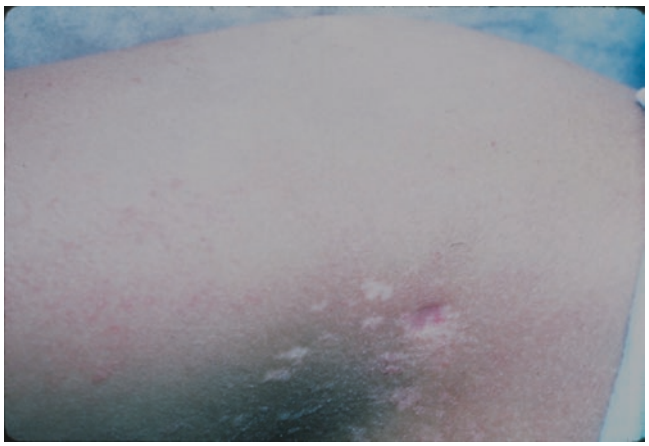

Fig. 7.10 Anetoderma presents as depigmented atrophic plaques on the extremity

Anetoderma has been classified as either primary, when there is no underlying skin disease, or secondary, when it occurs in the aftermath of another process affecting the skin (e.g., acne or varicella). Anetoderma most often affects women aged 20–40 years old [113]. However, both congenital and acquired iatrogenic forms of anetoderma have been reported in newborns. The origin of iatrogenic anetoderma in newborns has been linked to placement of medical monitoring leads on the fragile skin of premature infants [114]. Lesions are usually permanent. Some patients continue to develop new lesions for many years. Although penicillin, aminocaproic acid, and colchicine have been reported as possible therapeutic options for anetoderma, no treatment has been found to be uniformly effective for this disorder [113].

7.7.2 Histology

The epidermis in anetoderma is unremarkable, and the changes in the dermis are quite subtle and might evade detection on superficial examination. The collagen bundles may be slightly thinned, but are often relatively normal. The dermis may have decreased thickness [115]. There is an increase in the interstitial space secondary to focal elastolysis (Fig. 7.11). In early lesions, a lymphocytic or occasionally a neutrophilic infiltrate may be present within the dermis. Histiocytes are also present. It is rare to see elastolysis on routine histologic sections [116], although ultrastructural examination may show this finding [117]. In late, established lesions, elastic fibers are sparse, disrupted or even completely absent in the mid dermis (Fig. 7.12). In the majority of cases, there is an antecedent inflammatory process that is thought to cause dermal elastolysis, but these changes may or may not be present in the biopsy of clinically apparent atrophic lesions.

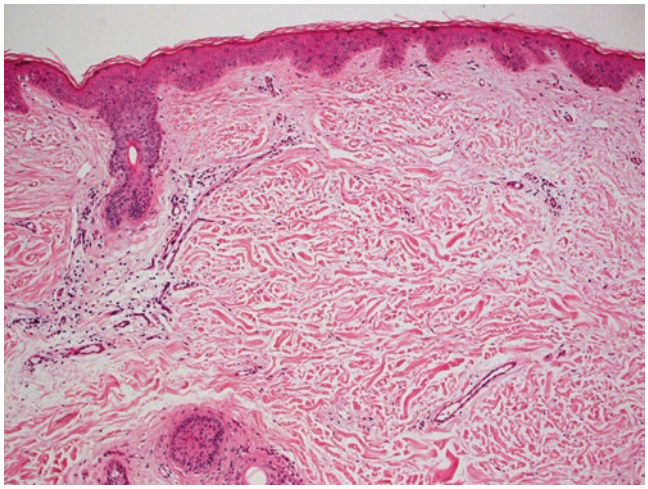

Fig. 7.11 Subtle histologic changes include slightly increased space between collagen bundles in the superficial reticular dermis in anetoderma

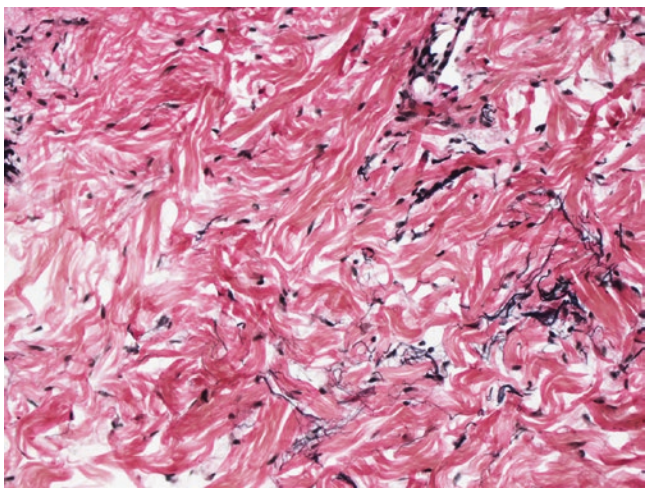

Fig. 7.12 Anetoderma is characterized by elastolysis and decreased elastic tissue fibers in the superficial reticular dermis as highlighted by Verhoeff-Van Gieson stain

7.7.3 Pathogenesis

Anetoderma may be caused by an imbalance between elastic fiber production and its degradation due to dysregulated production and activation of elastolytic enzymes as well as loss of elastase inhibitors. In support of this hypothesis, there is evidence of increased expression of gelatinases in skin explants from patients with anetoderma [118]. Analysis of the expression of matrix metalloproteinases (MMPs) in anetoderma skin showed increased levels of MMPs that degrade elastin as well as decreased levels of tissue inhibitor of MMPs (TIMPs) [119]. Electron microscopic studies have shown phagocytosed fragmented elastic fibers within macrophages, further suggesting an immunological mechanism in elastic fiber destruction in this disorder [117]. Immune complex deposits have been reported in the dermis and blood vessels, and granular deposits of immunoglobulin M and C3 have been found at the epidermal junction in lesional skin of anetoderma patients [120, 121].

There is a substantial body of evidence that associates anetoderma with anti-phospholipid antibodies and other serological markers of autoimmunity [122–125]. Patients with systemic lupus erythematosus and anti-phospholipid antibodies have a high risk of developing anetoderma [126, 127]. Anetoderma may be due to autoimmune-mediated destruction of elastic fibers associated with anti-phospholipid antibodies and possible shared epitopes between elastic fibers and phospholipids. Anetoderma has also been linked with other immunological diseases, such as Graves' disease, systemic sclerosis, and autoimmune hemolytic anemia, thus supporting the clinical association of anetoderma with autoimmunity [128, 129].

7.8 Aplasia Cutis Congenita

7.8.1 Clinical Features

Aplasia cutis congenita is a rare disorder of connective tissue characterized by partial or complete absence of the skin. It may be localized or widespread. The most common site is the scalp, although it may occur anywhere on the body. Lesions appear as well-defined open wounds or translucent membranous areas. Aplasia cutis congenita typically heals with scarring (Fig. 7.13). However, large and deep defects may require skin grafting to achieve complete closure [130].

Fig. 7.13 Aplasia cutis congenita presents as a well-demarcated, round ulcer on the scalp of a neonate

7.8.2 Histology

These lesions in aplasia cutis congenita are rarely biopsied at the time of birth, at which point histologic changes would be those of ulceration and inflammation. At the usual time of biopsy, histologic sections demonstrate an atrophic epidermis with flattening of rete ridges (Fig. 7.14). The dermis has scar formation with collagen arranged linearly beneath the epidermis. The dermis is thin and lacks cutaneous appendages (Fig. 7.15). The scarring often extends into and through the subcutis to the underlying bone [131]. Dermal melanocytosis has been reported as a rare additional histologic finding in patients with aplasia cutis congenita [132].

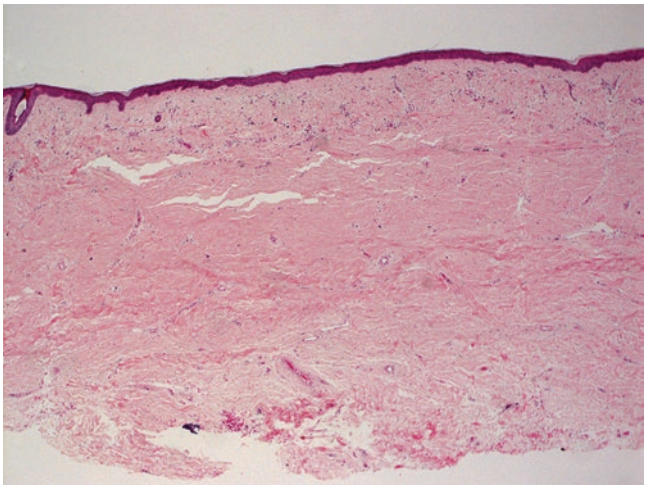

Fig. 7.14 An atrophic epidermis, lack of skin appendages and the appearance of a dermal scar characterize aplasia cutis congenita

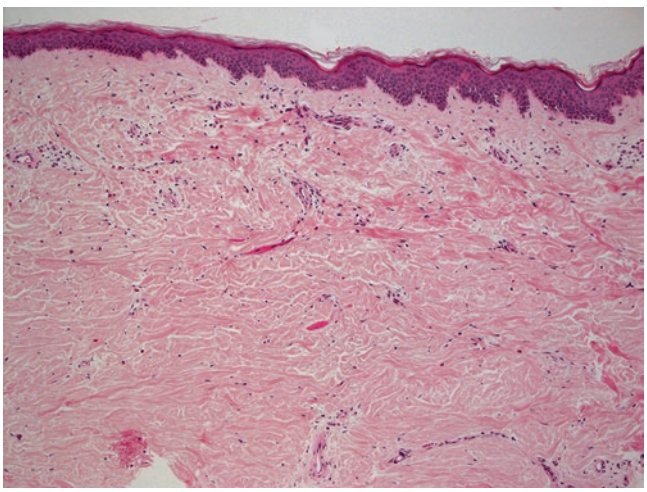

Fig. 7.15 Loss of skin appendages, dermal fibrosis and dermal atrophy are seen in cases of aplasia cutis congenita

A rare variant of aplasia cutis congenita has been described wherein the dermis contains edematous or fibrovascular stroma. A membrane-like appearance develops into bullae. Some authors believe this subtype to be a variant of a cranial neural tube closure defect [133, 134].

The differential diagnosis of aplasia cutis congenita includes a scar secondary to other processes such as epidermolysis bullosa. Clinical history is the best way to make this distinction.

7.8.3 Pathogenesis

Genome-wide linkage analysis and exome sequencing of affected members in a family with autosomal-dominant aplasia cutis congenita identified BMS1, a ribosomal GTPase protein, as a causative gene of this disease [135]. BMS1 is a key component in the formation of the 40S ribosomal subunit, and it is necessary for pre-ribosomal RNA processing of 18S ribosomal RNA [136, 137]. It has been shown that fibroblasts derived from aplasia cutis congenita patients with BMS1 mutation have impaired maturation of the 40S ribosomal subunit, resulting in nucleolar stress response and reduced cell proliferation rate [135]. These genetic findings link BMS1 gene and ribosome biogenesis to skin morphogenesis. In sporadic non-autosomal form of aplasia cutis congenita, many potential etiological factors have been reported, including chromosomal abnormalities, traumatic mechanism, thrombotic events, vascular alterations, and teratogens [138, 139].

7.9 Focal Dermal Hypoplasia

7.9.1 Clinical Features

Focal dermal hypoplasia (Goltz syndrome) is a rare X-linked dominant genetic disorder with a variety of cutaneous and skeletal findings as well as other organ involvement. The hallmark of focal dermal hypoplasia is connective tissue dysplasia of the skin and skeletal system (Figs. 7.16 and 7.17). Typical cutaneous features include blaschkoid linear streaks of skin atrophy and telangiectasias, fat herniations, raspberry papillomas, and dyspigmentation. Rarely, aplasia cutis congenita is also associated with the disease [140].

7.9.2 Histology

In focal dermal hypoplasia, there is a thinned or unremarkable epidermis. The dermis is markedly diminished in thickness [141, 142] (Fig. 7.18). There are greatly reduced numbers of

Fig. 7.16 Focal dermal hypoplasia (Goltz syndrome) shows characteristic ectrodactyly or "lobster claw" deformity of the foot

Fig. 7.17 Focal dermal hypoplasia (Goltz syndrome) presents with ectrodactyly on the hand in the same patient with Goltz Syndrome from Fig. 7.16

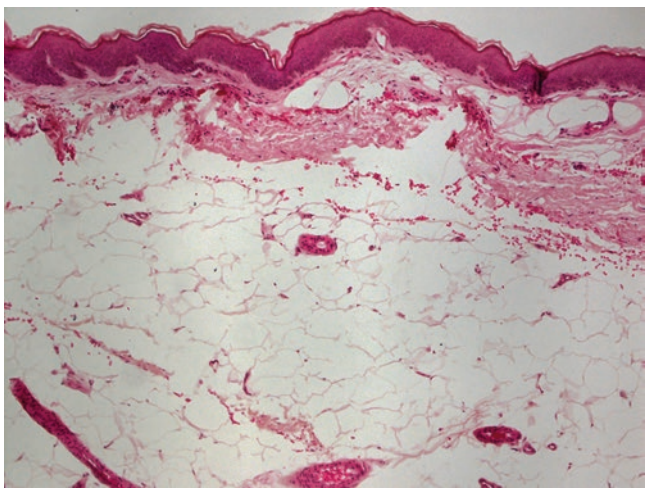

Fig. 7.18 Focal dermal hypoplasia is characterized by a normal epidermis, the absence of dermal collagen and the presence of subcutaneous fat almost adjacent to the epidermis

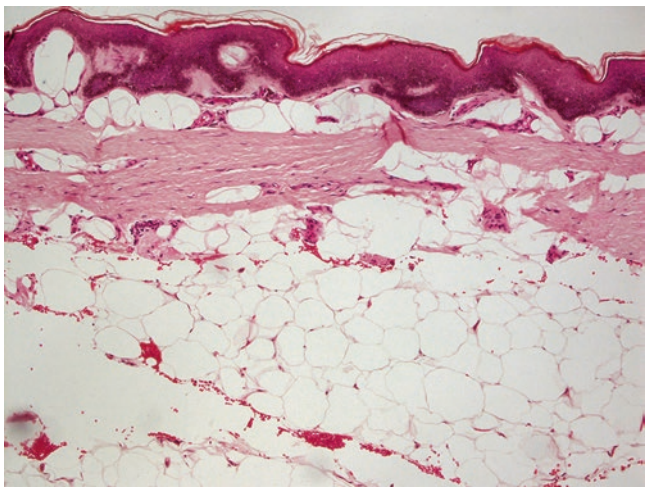

Fig. 7.19 Mature adipose tissue is present in the papillary dermis and there is a lack of dermal appendages in focal dermal hypoplasia

elastic tissue fibers [141]. Mature adipocytes are present around blood vessels and between the few residual thin collagen bundles [143, 144] (Fig. 7.19). There is an increase in number of papillary dermal blood vessels [145]. Ultrastructural analysis reveals abnormally small fibroblasts in sharply reduced numbers [141]. Adipocytes are multiloculated and appear immature [146]. The basement membrane also shows focal disruption and alteration of type IV collagen in this disorder [147]. At the periphery of long-standing atrophic lesions, there are lentigo simplex-like lesions with increased basilar melanin and slightly increased number of melanocytes [148]. Lipomas and verrucous papillomas are common findings in patients with focal dermal hypoplasia [144, 148, 149].

7.9.3 Pathogenesis

Focal dermal hypoplasia affects both mesodermal and ectodermal structures, including the eyes, bones, teeth, and skin. Focal dermal hypoplasia occurs mostly in females (90 %) and is inherited in an X-linked dominant manner [150]. The gene associated with the disease is PORCN [151, 152]. PORCN is located on chromosome Xp11.23 and is a member of the evolutionarily conserved Porcupine gene family, which regulates the posttranslational activity of Wnt signaling proteins [153]. PORCN encodes an O-acyltransferase involved in palmitoylation and secretion of Wnt proteins [154]. Mutations in PORCN identified in patients with focal dermal hypoplasia include intragenic mutations and microdeletions [152, 155, 156]. About 10 % of affected individuals are males, who are mosaic for mutations in the PORCN gene. A broad range of severity and unilateral lesions have been described [157, 158]. This is postulated

to be due to the temporal and spatial occurrence of post zygotic mutations in PORCN.

7.10 Progeria (Hutchinson–Gilford Syndrome)

7.10.1 Clinical Features

Progeria is a rare disorder of premature aging with involvement of the skin, bones, and cardiovascular system. Cutaneous features include sclerodermoid and atrophic changes, early loss of hair, prominent superficial veins (particularly over the scalp), and marked loss of subcutaneous fat [159] (Fig. 7.20). Patients often succumb to myocardial infarction early in life.

7.10.2 Histology

While the earliest clinical manifestations of progeria occur in the skin, the histologic findings may be relatively nonspecific [160]. In many patients, biopsies demonstrate thickened collagen bundles with decreased interstitial space, giving an appearance that resembles scleroderma. This results in a thickened dermis. The thickened collagen bundles extend into the subcutis, which is also markedly thickened [161, 162]. Abundant keloid-like scarring and calcinosis cutis have been described in some patients with progeria [163, 164].

Fig. 7.20 A patient with Hutchinson–Gilford progeria syndrome presents with birdlike appearance, beaked nose, micrognathia, and diffuse alopecia that are characteristic of the disease (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

7.10.3 Pathogenesis

Hutchinson–Gilford progeria syndrome is a fatal genetic disorder caused by mutations in the LMNA gene [165, 166]. LMNA encodes lamin A, which is a filamentous protein component of the nuclear lamina with multiple key roles in gene regulation [167, 168]. Lamin A is localized in the inner nuclear membrane, where it gives shape and support to the nuclear envelope. Lamin A is involved in the organization of nuclear pore complexes and chromatin structure, and it regulates gene expression by binding to DNA and sequestering heterochromatin in the nuclear periphery [168, 169]. Cells from progeria patients have a number of pathologies, reflecting the molecular defects in nuclear lamin A. The cells have abnormal nuclear size and shape, thickened nuclear lamina, loss of peripheral heterochromatin, clustering of nuclear pores, and herniations of the nuclear envelope [166, 170, 171]. These nuclear abnormalities correlate with intranuclear accumulation of defective lamin A [170]. LMNA gene also encodes nuclear lamin C, which is identical to lamin A in the first 566 amino acids [172].

To date, over 460 mutations in LMNA have been identified (UMD-LMNA mutations database, 2012). However, most cases of progeria carry de novo c.1824C > T; p. Gly608Gly mutation in the affected gene [165, 166]. This mutation activates a cryptic mRNA splice site that results in the deletion of 50 amino acids in the C-terminus of pre-lamin A, which also contains the farnesylation cleavage site necessary for correct protein processing. The mis-splicing yields a pre-lamin A protein that is not properly processed and is erroneously farnesylated by the protein zinc metallopeptidase STE24 (ZMPSTE24) [173, 174]. This malformed protein localizes to the nuclear membrane, resulting in disruption of the nuclear laminar integrity and defects in nuclear structure and function [166, 169, 170].

A hallmark of progeria is genome instability with defects in DNA repair and accumulation of double-stranded DNA breaks [175]. The mechanisms of genome instability in progeria are not yet fully understood. However, it is known that progeria cells have telomere shortening and defects in homologous DNA repair as well as in nonhomologous end joining mechanisms of repair.

7.11 Winchester Syndrome

7.11.1 Clinical Features

Winchester syndrome is a rare autosomal recessive disorder characterized by musculoskeletal abnormalities, corneal opacities and varying degrees of cutaneous involvement. Cutaneous features include indurated hyperpigmentation and hypertrichosis, which can be generalized. The physical exam is further characterized by coarse facies, gum hypertro-

phy, short stature and articular contractures. Skeletal deficits include multiple foci of osteoporosis and osteolysis of the affected bones with subsequent functional impairment.

7.11.2 Histology

In early stages of Winchester syndrome, there is a proliferation of fibroblasts largely centered in the deep portion of the dermis. Later stages demonstrate homogenization and thickening of the superficial portions of the dermis [176]. Epidermal hyperplasia is also present [177].

7.11.3 Pathogenesis

Winchester syndrome is an autosomal recessive inherited disorder. It is caused by mutations in the matrix metalloproteinase-2 gene (MMP2) [178, 179]. MMP2 degrades extracellular matrix proteins, particular type IV collagen [180].

Novel loss-of-function mutations in membrane type-1 metalloproteinase (MT1-MMP) that affect MMP2 activity have been identified [181]. MT1-MMP is an upstream activator of MMP2, and mutations that affect MT1-MMP localization in the cell membrane lead to loss of MMP2 activation.

Loss of the catalytic activity of MMP2 results in osteolysis, which is a key pathologic finding in Winchester syndrome. MMP2 modulates the activity of transforming growth factor (TGF-β), which in turns affects the maturation and activity of osteoblasts. Thus, MMP2 is important in bone formation and homeostasis, and MMP2 deficiency results in defective bone deposition and osteolytic phenotype.

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Vasculitides, Vasculopathies, and Neutrophilic Infiltrates

8

8.1 Purpura Fulminans

8.1.1 Clinical Features

Purpura fulminans is a life threatening disorder characterized by cutaneous hemorrhage and necrosis in the setting of disseminated intravascular coagulation (DIC). Purpura fulminans may be idiopathic or it can be caused by infections or inherited abnormalities of the coagulation system [1, 2].

Acute infectious purpura fulminans is the most common form and occurs in the setting of severe bacterial infection. Purpura fulminans in neonates and children may be a presenting feature of severe acute sepsis and it is a cardinal feature of meningococcal septicemia in 1–20 % of cases [3, 4]. Purpura fulminans due to inherited abnormalities of coagulation typically presents in the first 72 hours of life [2]. Ecchymotic, petechial and purpuric lesions progress to areas of necrosis and loss of tissue. Disease management involves supportive therapy and treatment of any existing infection.

8.1.2 Histology

The histologic changes seen in what is recognized clinically as purpura fulminans are identical, regardless of the underlying etiology. They are those of an obstructive vasculopathy (Fig. 8.1). Vessels within the dermis are occluded with fibrin thrombi without much evidence of an inflammatory infiltrate or vascular wall damage [5] (Fig. 8.2). In older lesions, secondary changes such as tissue necrosis, ulceration and reactive inflammation may be seen, but these are not part of the primary pathology.

8.1.3 Pathogenesis

Purpura fulminans can be caused by infectious microorganisms, such as Neisseria meningitidis. N. meningitidis are encapsulated bacteria expressing type IV pili (Tfp), which are essential for meningococcal pathogenesis as they mediate bacterial adhesion onto endothelial cells [6]. Tfp-induced signaling may be responsible for invasive meningococcal infection by enabling crossing of the blood–brain barrier, and the subsequent peripheral thrombosis and leakage syndrome seen in purpura fulminans.

Although rare, purpura fulminans in neonates can be a manifestation of severe heritable defects of the protein C or protein S anticoagulant pathway [7, 8]. Homozygous protein C or protein S deficiency together with homozygous or heterozygous PROC (Protein C, Inactivator Of Coagulation Factors Va and VIIIa) gene mutants often results in fatal cases of neonatal purpura fulminans [9–11]. In some patients, a combination of sepsis and partial defect in the PROC anticoagulant pathway is sufficient to incite purpura fulminans, suggesting synergy between these initiators [3, 12, 13]. The disorder can also occur as an autoimmune phenomenon after an otherwise benign infection, such as Varicella [3].

8.2 Anti-phospholipid Syndrome

8.2.1 Clinical Features

Anti-phospholipid syndrome is a multisystem autoimmune disorder characterized by venous and arterial thrombosis in the presence of persistent antiphospholipid antibodies. Anti-phospholipid syndrome is rare in children with disease onset before 15 years of age occurring in about 3 % of reported cases [14]. A diagnosis of anti-phospholipid syndrome in the setting of systemic lupus erythematosus is more likely and accounts for 9–14 % of pediatric cases [15]. Cutaneous manifestations of anti-phospholipid syndrome are variable, but can include livedo reticularis, Raynaud's phenomenon, skin ulcers, and chronic urticaria (Fig. 8.3) [16]. Treatment of the syndrome includes long-term anticoagulation therapy.

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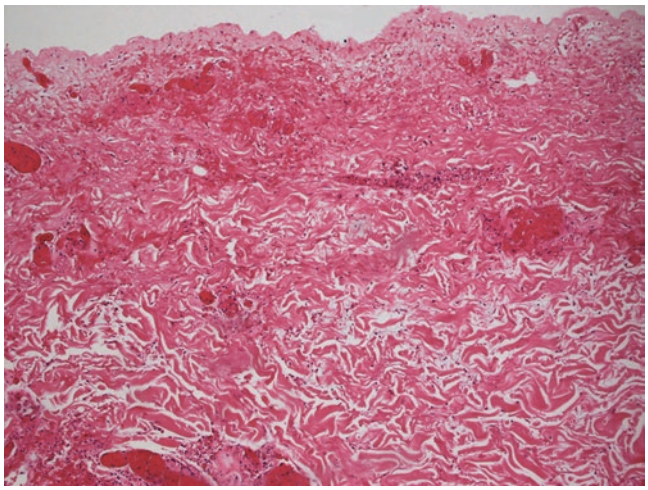

Fig. 8.1 Purpura fulminans is characterized by diffuse vascular occlusion, marked erythrocyte extravasation and minimal inflammation

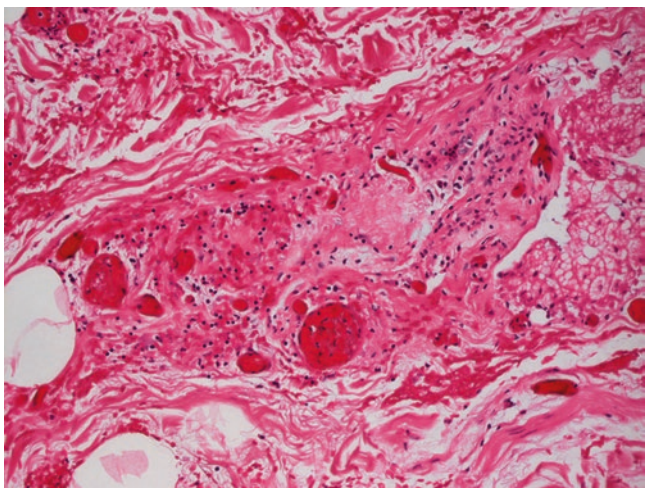

Fig. 8.2 Diffuse vascular thrombosis, minimal inflammation and erythrocyte extravasation are seen in purpura fulminans

8.2.2 Histology

Similar to purpura fulminans, the histologic findings of antiphospholipid syndrome are those of an obstructive vasculopathy. Occlusion of small vessels with fibrin thrombi leads to infarction and secondary tissue necrosis, ulceration and inflammation (Fig. 8.4). Extravasation of erythrocytes is present in some cases. There is minimal inflammation associated with the primary pathology [17–19].

8.2.3 Pathogenesis

Antiphospholipid-induced thrombosis is thought to result from a hypercoagulable state caused by direct activation of monocytes, platelets, endothelial cells and neutrophils by anti-phospholipid

Fig. 8.3 Purpuric patches with small foci of healing erosions on the leg of a patient with purpura fulminans in the setting of anti-phospholipid syndrome (photo courtesy of Raegan Hunt, MD, PhD, Baylor College of Medicine, Houston TX)

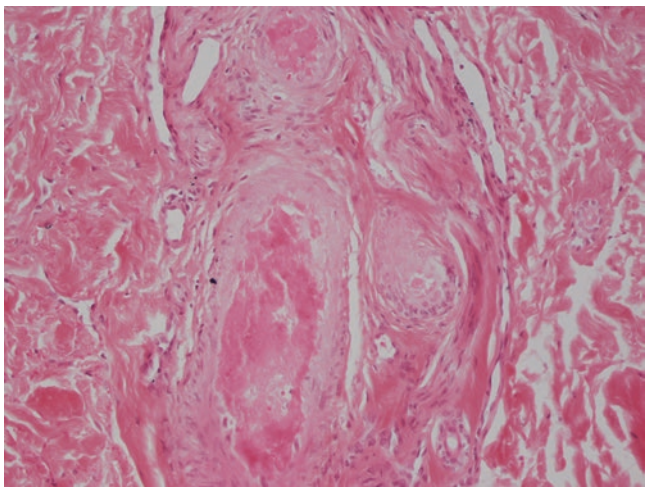

Fig. 8.4 Vessels occluded with eosinophilic material and a lack of surrounding inflammation characterize anti-phospholipid syndrome

syndrome antibodies [20]. Increased levels of tissue factor, a key molecule in the coagulation cascade, and activated complement factors, which have also been associated with antiphospholipid antibodies, may lead to the activation of the coagulation cascade [21]. In the case of pregnant women, placental dysfunction is a hallmark of anti-phospholipid syndrome with complications including preeclampsia and intrauterine growth restriction. Direct interaction between antiphospholipid syndrome antibodies and trophoblast cells may trigger cellular injury by leading to unchecked coagulation reactions [22, 23].

8.3 Leukocytoclastic Vasculitis

8.3.1 Clinical Features

Henoch–Schonlein purpura is a variant of leukocytoclastic vasculitis. It is an IgA-mediated systemic small vessel vasculitis. It is the most common vasculitis seen in children and

Fig. 8.5 Purpuric macules and patches over the hands, legs and feet of a child with Henoch–Schonlein purpura (photo courtesy of John Browning, MD, Baylor College of Medicine and San Antonio Children's Hospital, San Antonio, TX)

affects 8–20 per 100,000 children annually. It typically affects children ages 3–8 years. Henoch–Schonlein purpura is slightly more common in males with a male to female ratio of 1.5:1 [24]. It is often preceded by an acute infectious illness, and more common in the non-summer months.

Clinically, patients present with petechial/palpable purpuric lesions concentrated over the buttocks and legs along with one or more of the following: colicky abdominal pain, arthritis or arthralgia, and renal involvement (proteinuria and hematuria) (Fig. 8.5). Arthritis commonly affects the ankles and knees. Approximately 30 % of children have renal involvement [25].

Treatment is generally supportive, although systemic steroids may be helpful in cases where arthritis is severe or renal involvement is significant. Most patients recover within 6–8 weeks, although a small percentage may develop chronic renal disease and up to one third of patients may experience a recurrence [24].

Acute hemorrhagic edema of infancy is a benign, self-limited leukocytoclastic vasculitis of childhood. It is most common in children between the ages of 4 months and 2 years [26, 27]. Clinically, it is characterized by low-grade fever, edema, and purpura. Purpuric lesions tend to favor the face, ears, and extremities, with relative sparing of the trunk (Fig. 8.6). Treatment is generally supportive and most patients recover spontaneously within 1–3 weeks [26].

Fig. 8.6 Acute hemorrhagic edema of infancy presents as edematous, cockade, purpuric papules and plaques over the hands, legs and feet of an infant

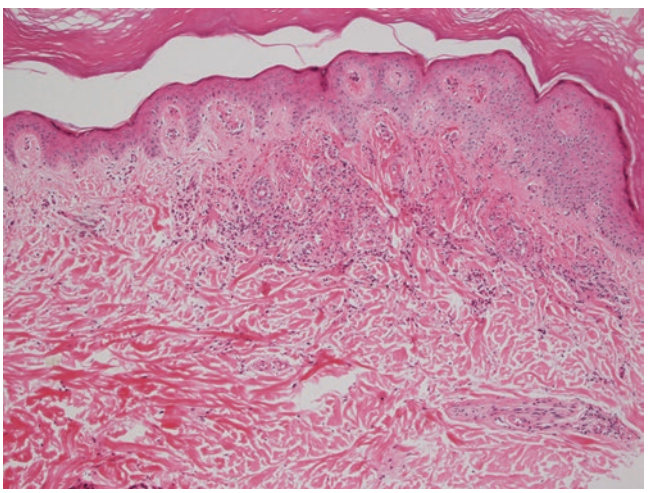

Fig. 8.7 A perivascular infiltrate of neutrophils is seen around vessels in the superficial vascular plexus in leukocytoclastic vasculitis

8.3.2 Histology

Histologic findings of leukocytoclastic vasculitis include an inflammatory infiltrate consisting primarily of neutrophils surrounding and invading dermal blood vessels (Fig. 8.7). In the majority of cases, post-capillary venules are the most affected. In other cases, larger vessels may be involved and extension into the deep dermis and subcutis can be seen. In addition to transmural extension of neutrophils, endothelial swelling and destruction, fibrin thrombi, and extravasated erythrocytes are present [28] (Figs. 8.8 and 8.9). Karyorrhectic debris is commonly seen. In some cases, especially those caused by drugs, eosinophils may be seen in the infiltrate [29]. Infarction with secondary necrosis, ulceration, and diffuse inflammation are seen in florid cases and in late stage lesions. Direct immunofluorescence studies demonstrate IgG, C3, and occasional IgM deposition around and within vessel walls.

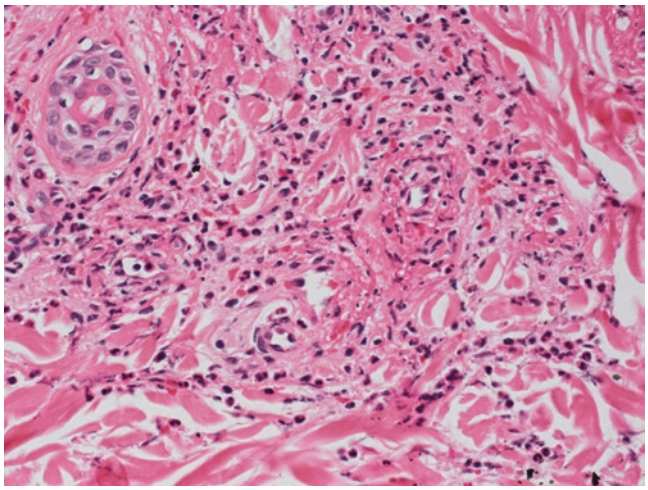

Fig. 8.8 Endothelial cell destruction, perivascular neutrophils and fibrin within the lumen and vessel walls are present in leukocytoclastic vasculitis

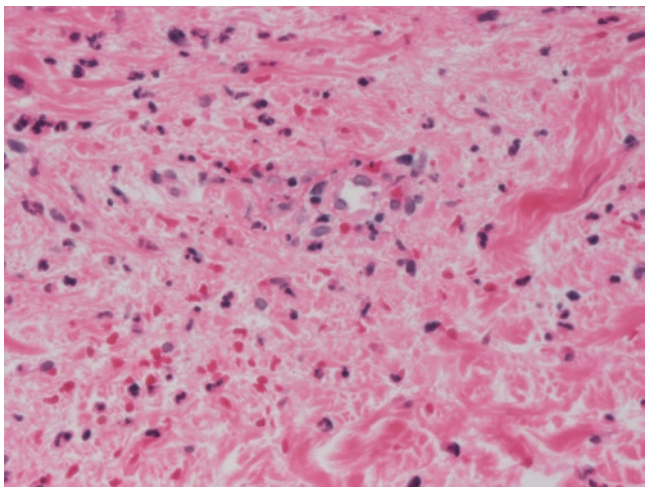

Fig. 8.9 Fibrinoid necrosis and extravasated erythrocytes are features of leukocytoclastic vasculitis

Henoch–Schonlein purpura is histologically indistinguishable from other variants of leukocytoclastic vasculitis. In these cases, the vasculitis is usually confined to small vessels in the superficial portion of the dermis. The diagnosis is made based upon a constellation of clinical findings and the presence of IgA deposits as detected by direct immunofluorescence examination.

Septic vasculitis also gives rise to histologic changes of leukocytoclastic vasculitis. In these cases, there is generally more vascular thrombosis and less intense inflammatory infiltrate than is seen in leukocytoclastic vasculitis caused by other etiologies [30].

Acute hemorrhage edema of infancy is another clinical entity that demonstrates histologic changes of leukocytoclastic vasculitis [31–34]. Direct immunofluorescence studies demonstrate IgG, IgM, IgA, IgE, and C3 deposition within and around dermal blood vessels [33].

Urticarial vasculitis is an entity that is best diagnosed based upon the clinical presentation with histologic changes to support the clinical impression. The histologic findings are those of a mild leukocytoclastic vasculitis. In most cases, there is dermal edema, extravasation of erythrocytes, and an infiltrate of mixed neutrophils and eosinophils surrounding vessels of the superficial vascular plexus. However, it is quite difficult to identify fibrinoid necrosis of vessel walls and unequivocal vasculitis in most cases [35].

The histologic differential diagnosis of leukocytoclastic vasculitis includes other neutrophilic dermatoses, most commonly Sweet's syndrome. While there are cases with overlapping features, Sweet's syndrome characteristically does not demonstrate vascular thrombosis and transmural neutrophils within dermal vessels. Pigmented purpuric eruptions may share the finding of extravasated erythrocytes within the dermis, but these eruptions are lymphocyte mediated, and neutrophils are not part of the inflammatory infiltrate.

8.3.3 Pathogenesis

Small vessel vasculitis of the skin is mediated by immune complex deposition in the affected vessels. Antibodies bind to circulating antigens from drugs (e.g., β-lactam antibiotics), infections (e.g., β-hemolytic Streptococcus group A and hepatitis C virus), autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis, and dermatomyositis), or cancer, forming immune complexes that lodge within small vessels in the skin, kidneys, joints, and gut [36]. These complexes can activate the complement cascade and induce an inflammatory response leading to vessel destruction and extravasation of red blood cells (purpura).

8.4 Cryoglobulinemia

8.4.1 Clinical Features

Cryoglobulins are circulating immunoglobulins that can complex with other immunoglobulins and precipitate with exposure to cold. They can be associated with a number of infectious, autoimmune, and malignant processes. When these immune complexes are deposited in blood vessel walls, vasculitis can occur. In adults, hepatitis C infection causes 80 % of cryoglobulinemia cases [37].

Cryoglobulinema is extremely rare in children. Patients with cryoglobulinemia often present with purpura, arthralgia, and fatigue. However, those with cryoglobulinemic vasculitis can present with a wide variety of skin findings, including purpura, papules, nodules, skin necrosis, bullae,

ulcerations, urticaria, and livedo reticularis [38]. Treatment is supportive therapy and also aimed at treating the underlying disease process. In adults, cryoglobulinemic vasculitis tends to have a relapsing and remitting pattern.

8.4.2 Histology

Histologic features of cryoglobulinema differ depending upon the nature of the circulating cryoglobulins. Monoclonal cryoglobulinemias result in occluded small blood vessels with minimal to no inflammatory response (Figs. 8.10 and 8.11). These are best classified as a vasculopathy and not a vasculitis.

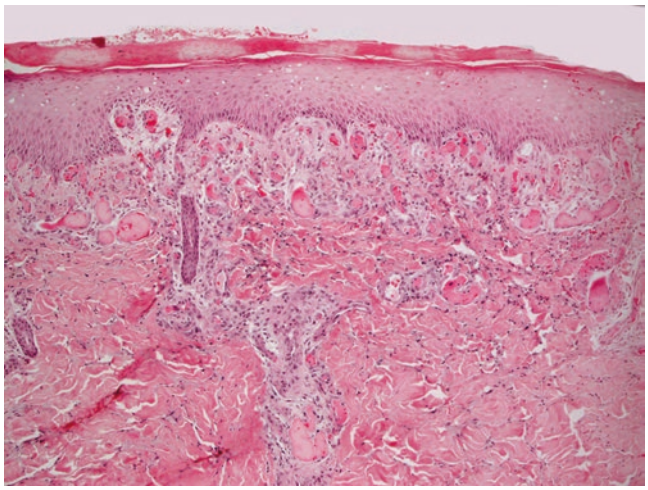

Fig. 8.10 Vessels throughout the dermis are occluded with eosinophilic material in monoclonal cryoglobulinemia. There is minimal or no accompanying inflammation in this disorder

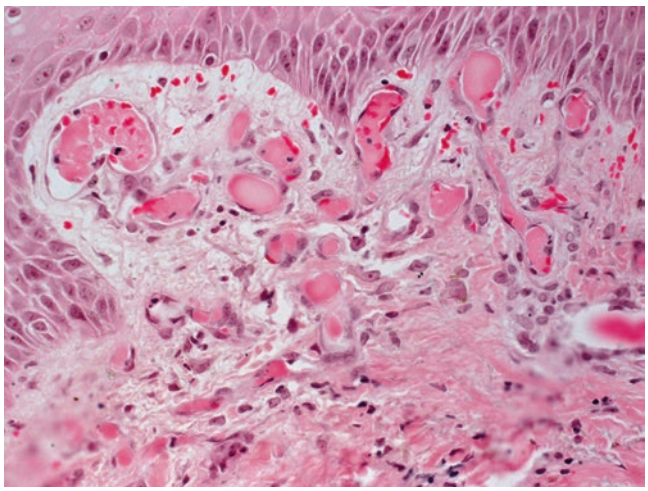

Fig. 8.11 Amorphous, eosinophilic material distends and occludes dermal vessels in monoclonal cryoglobulinemia

Skin biopsies of patients with mixed cryoglobulinemia, however, show changes of leukocytoclastic vasculitis in many cases [39] (Fig. 8.12). Small vessels located within the superficial vascular plexus of the dermis (and occasionally deeper small vessels) demonstrate transmural invasion by neutrophils (Fig. 8.13). Extravasated erythrocytes and karyorrhectic debris are present [40]. Vessels are occluded with eosinophilic material that in some cases may be crystalloid [39, 41]. Secondary ulceration may result from vascular occlusion.

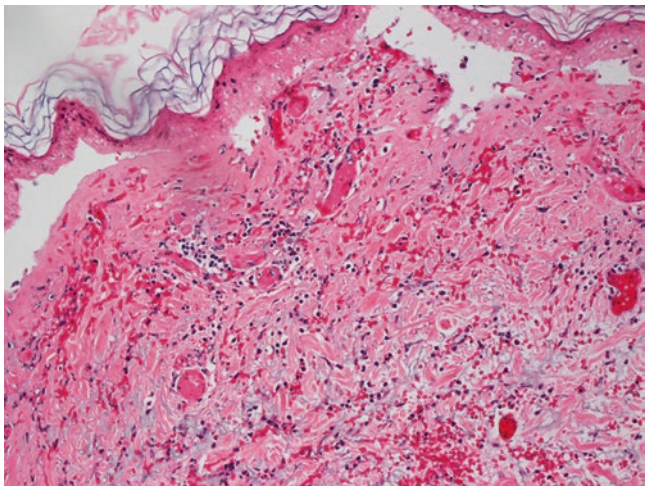

Fig. 8.12 Diffuse vascular occlusion with surrounding mixed inflammation is seen in mixed cryoglobulinemia

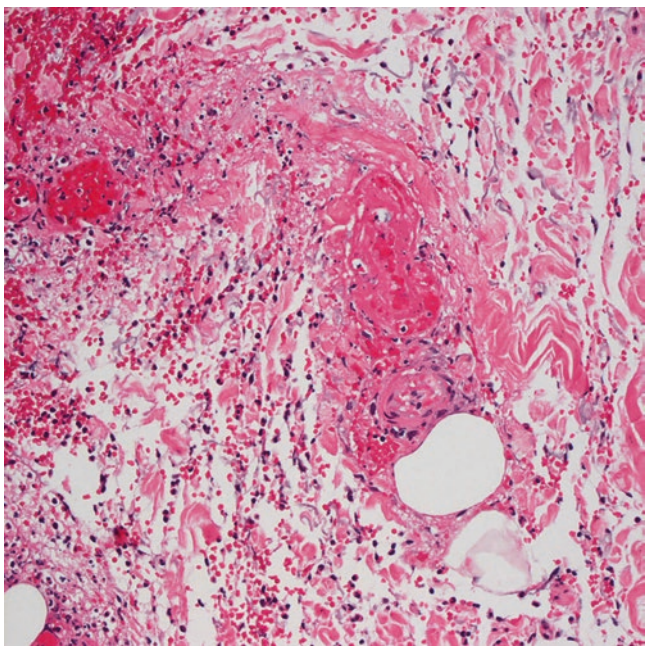

Fig. 8.13 Vessels throughout the dermis are occluded by eosinophilic material and there is a surrounding neutrophilic infiltrate in mixed cryoglobulinemia

8.4.3 Pathogenesis

The clinical manifestations of cryoglobulinemia are secondary to cryoglobulin precipitation and blood vessel occlusion [42]. Cryoglobulinemia is related to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Chronic hepatitis C virus infection is the main pathogenic factor responsible for mixed cryoglobulinemia with >90 % of patients with essential mixed cryoglobulinemia having the infection [43–45]. A landmark study showed the association of HCV infection with cryoglobulinemia may be linked to the binding of the virus to B-lymphocytes via CD81 [46]. B-lymphocytes generate antibodies against HCV, which crosslink with immunoglobulin M (IgM) with rheumatoid factor activity and form cryoglobulin immune complexes. Cryoglobulinemic vasculitis involves immune complex-mediated tissue injury with deposition of immune complexes, recruitment of neutrophils, and activation of the complement cascade [42]. Monoclonal rheumatoid factor (mRF) antibody is present in patients with mixed cryoglobulinemia and HCV infection [47]. There is specific accumulation of hepatitis C virus in cryoglobulins in association with mRF [43]. In recent years, studies have shown that HCV-infected patients with mixed cryoglobulinemia have fewer peripheral-blood immunoregulatory T cells (Treg) than HCV-infected individuals without cryoglobulinemia [48].

8.5 Polyarteritis Nodosa

8.5.1 Clinical Features

Polyarteritis nodosa is a disease characterized by vasculitis of small and medium-sized blood vessels. There is a cutaneous form and a systemic form that can affect multiple organs. The onset of polyarteritis nodosa is typically between 25 and 50 years of age [49]. It is very rare in children with approximately several hundred cases reported in the literature thus far [50]. Cutaneous polyarteritis nodosa has no diagnostic criteria, but it is defined as a disease affecting the skin but without major organ system involvement. Skin lesions in cutaneous polyarteritis nodosa are variable, but may include livedo reticularis, tender nodules, purpura, and signs of superficial (e.g., splinter hemorrhages) or deep skin infarctions (e.g., necrosis and gangrene). Most patients with the disease are managed with systemic steroids and other immunosuppressive drugs. Most children with cutaneous polyarteritis nodosa have a chronic and relapsing benign course [50].

8.5.2 Histology

Polyarteritis nodosa is a neutrophil-mediated vasculitis that involves small to medium-sized vessels [28, 51, 52]. Skin biopsy reveals transmural invasion of vessels with neutrophils, endothelial cell destruction, karyorrhectic debris, extravasation of erythrocytes, and fibrin thrombi within vessels [49] (Figs. 8.14 and 8.15). Small vessels in the superficial dermis are affected in many cases, but the classic diagnostic finding is the involvement of muscular arteries in the deep reticular dermis and the subcutaneous fat. Variants such as benign cutaneous polyarteritis nodosa and microscopic polyarteritis have been described. The benign cutaneous variant demonstrates the classic histologic features but often has clinical manifestations with more cutaneous than systemic symptoms [53]. Smaller vessels are the main focus of vasculitis when the skin is involved with the microscopic variant [54].

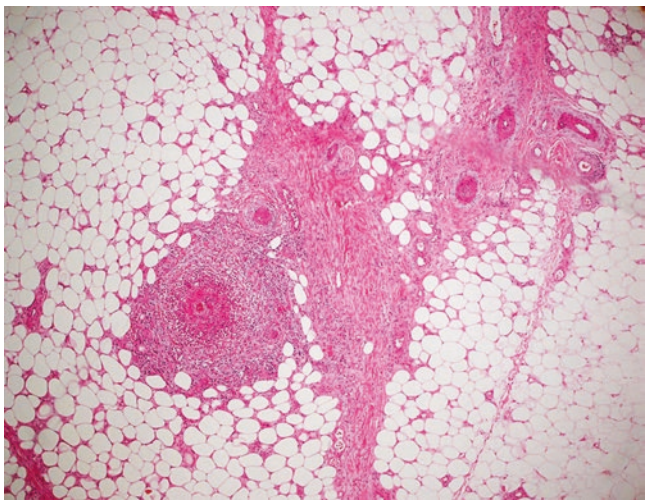

Fig. 8.14 Blood vessels are destroyed and difficult to identify as they are often completely occluded in polyarteritis nodosa

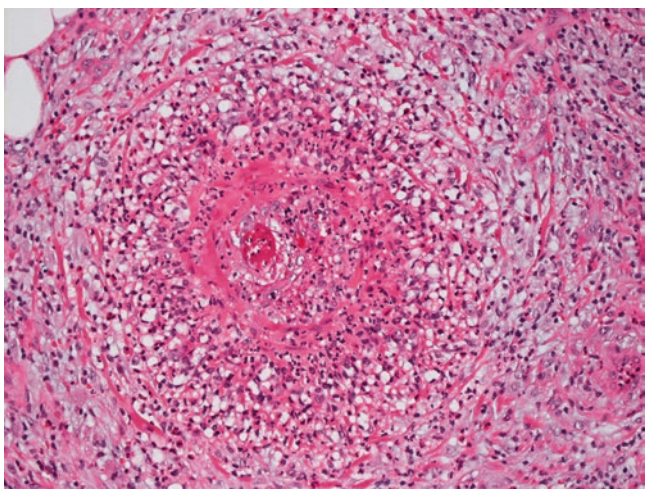

Fig. 8.15 A medium-sized muscular artery demonstrates transmural neutrophilic inflammation, fibrinoid necrosis and extravasation of erythrocytes in polyarteritis nodosa

The main differential diagnosis of polyarteritis nodosa includes superficial thrombophlebitis, although this is quite rare in children. In some cases, an elastic tissue stain can be used to demonstrate the presence of an internal elastic lamina, which is helpful in distinguishing arteries affected in polyarteritis nodosa from veins in thrombophlebitis. In some cases, vasculitis is identified only in smaller dermal vessels. Differentiation from leukocytoclastic vasculitis is not possible in these situations.

8.5.3 Pathogenesis

Genetics studies of Georgian Jewish patients with polyarteritis nodosa identified recessive mutations of Gly47Arg substitution in CECR1 gene that encodes adenosine deaminase 2 (ADA2) as a genetic cause of systemic and cutaneous disease [55].

Aside from possible genetic factors, immune complex-mediated reaction with deposition of IgM and C3 may also play a role in the etiology of polyarteritis nodosa [56–58]. Direct immunofluorescence stains often show IgM and C3 deposits within the affected arterial walls. IgM anti-phosphatidylserine–prothrombin complex has been found in patients with the disease, thus raising the hypothesis that prothrombin bound to injured endothelial cells induces an immune response, leading to the development of anti-phosphatidylserine–prothrombin complex antibodies [57]. Underlying infection or medications may also cause cutaneous polyarteritis nodosa. The most common infectious agent identified is Group A β-hemolytic Streptococcus in upper respiratory infections [59–61]. Streptococcal upper respiratory infections preceding the onset of disease was noted in all four children with polyarteritis nodosa in one reported study [62]. There has also been an association of polyarteritis nodosa with hepatitis B (HBV) infection [53]. Viral antigens may trigger the complement cascade, resulting in a neutrophil- and lymphocyte-rich inflammatory infiltrates within the vessel wall [63]. The mechanism by which immune complexes lead to medium-sized arterial inflammation while sparing smaller vessels (such as capillaries) is not known.

8.6 Kawasaki Disease

8.6.1 Clinical Features

Kawasaki disease is an acute febrile vasculitis that typically affects children under the age of 5 years [64]. The most serious potential complication of Kawasaki disease is coronary artery aneurysms. Kawasaki disease accounts for approximately 25 % of vasculitis cases in the United States, and it is the second most common systemic vasculitis in children behind Henoch–Schonlein purpura. It is more common in males with a male to female ratio of 2:1, and occurs more frequently in people of Asian descent [65].

Cutaneous features that can be seen in Kawasaki disease include widespread polymorphous rash, bilateral conjunctival injection, red, cracked lips, strawberry tongue, erythema, angioedema and peeling of the distal extremities as well as unilateral cervical lymphadenopathy. Acute Kawasaki disease is treated with intravenous immunoglobulin therapy (IVIG) and supportive therapy. Chronic Kawasaki disease is treated with long-term antiplatelet doses of aspirin. For patients who receive IVIG within 10 days of onset of fever, transient coronary artery dilation is typically seen in 3–5 % of the cases, and giant aneurysms develop in about 1 % of the cases [65].

8.6.2 Histology

Histologic changes of Kawasaki disease are those of a leukocytoclastic vasculitis [66]. In most cases, small vessels alone are involved in the skin; however, in rare cases, involvement of medium-sized muscular artery can give rise to an appearance indistinguishable from polyarteritis nodosa [67]. In a subset of patients, spongiform pustules have been described [68]. Recently, a psoriasiform eruption with histologic changes that resemble classic psoriasis has been reported in some children with Kawasaki disease [69].

8.6.3 Pathogenesis

Small and medium-sized arteries are the primary vessels affected in Kawasaki disease. Although a variety of vessels are involved, the coronary arteries are the most severely affected and may suffer chronic damage [70]. The vasculitis is characterized by invasion of the vascular wall by neutrophils, eosinophils and lymphocytes (mainly CD8+ T cells) [71, 72]. The later phase of inflammation also involves plasma cells (particularly IgA-producing cells) and macrophages [73]. These findings suggest an inflammatory process involving the innate immune response, followed by an acquired immune response, leading to rapid destruction of vascular endothelial cells and the vascular smooth muscle wall with subsequent loss of structural integrity and aneurysm formation [70].

A unifying model of the pathogenesis of Kawasaki disease has been proposed [74]. Kawasaki disease may be a result of infection by a single viral infectious agent or a group of very closely related agents. The infection is not

symptomatic in most individuals, but in a small subset of individuals with genetic predisposition, it can lead to Kawasaki disease [74]. Several candidate susceptibility genes for Kawasaki disease have been identified through genome-wide association studies (GWAS). These are BLK (which encodes B lymphoid tyrosine kinase involved in B-cell receptor signal transduction and other immune activities); CD40 (which encodes TNF receptor superfamily member 5); FCGR2A (which encodes low-affinity immunoglobulin-γ Fc region receptor IIa); and ITPKC (which encodes inositol 1,4,5-trisphosphate 3-kinase C, a negative regulator of T-cell activation) [75–77]. These genes have been associated with increased susceptibility to Kawasaki disease, especially in European populations and in Japanese and American children.

In addition to susceptibility genes, there is an oligoclonal, antigen-driven IgA immune response characteristic of Kawasaki disease. Synthetic versions of oligoclonal IgA antibodies from Kawasaki disease patients bind to cytoplasmic inclusion bodies in ciliated bronchial epithelium and in macrophages [74]. IgA antibodies in Kawasaki disease appear to target a microbial antigen rather than an autoantigen.

Investigation into biomarkers for Kawasaki disease has revealed increased erythrocyte sedimentation rate (ESR) and increased levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in the acute phase of Kawasaki disease as compared with febrile controls [78–80]. ESR and NT-proBNP may be promising biomarkers that can be incorporated into a standard test for Kawasaki disease [80].

8.7 Behcet's Disease

8.7.1 Clinical Features

Behcet's disease is a systemic vasculitis characterized by a triad of recurrent buccal and genital ulcers along with uveitis. Some patients experience involvement of additional organs, particularly in the gastrointestinal and neurologic systems. Behcet's disease is very unusual in children with an estimated prevalence in children less than 15 years old at 1 in 600,000 [81]. In addition to the classic mucosal oral and genital lesions, approximately 88 % of patients develop other cutaneous manifestations of Behcet's disease, including erythema nodosum, necrotic folliculitis, erythema, pustules, ulcers, and purpura [82].

Treatment for milder disease is generally supportive. Severe disease is often treated with systemic steroids and other immunosuppressive medications. Some patients experience an indolent course, but the course is typically chronic with unpredictable exacerbations and remissions. There is evidence that onset of disease before the age of 25 years carries a poorer prognosis [83].

8.7.2 Histology

The basic pathologic finding in Behcet's disease is leukocytoclastic vasculitis. A marked neutrophilic infiltrate invades and destroys small vessels in the superficial dermis, resulting in hemorrhage and secondary ulceration. Vascular thrombosis may also be present (Figs. 8.16 and 8.17). Bullous lesions have been described [84]. Suppurative folliculitis has also been described in some patients with Behcet's disease [85, 86]. A lymphocytic vasculitis has been reported in a minority

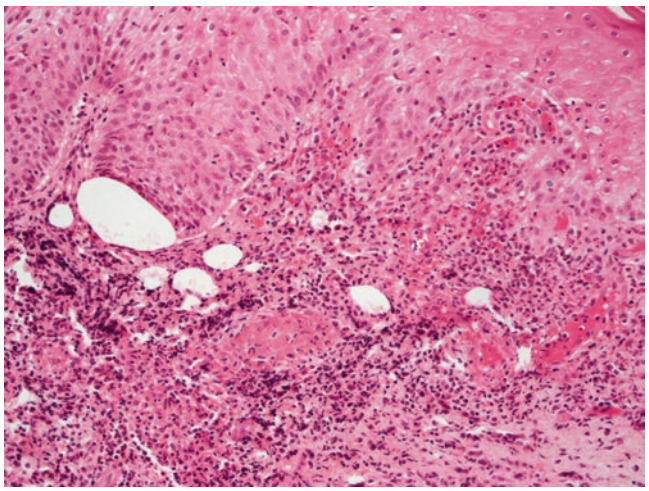

Fig. 8.16 The changes in Behcet's disease are not specific and may include vessels demonstrating vasculitis with fibrinoid necrosis and a marked polymorphous inflammatory infiltrate

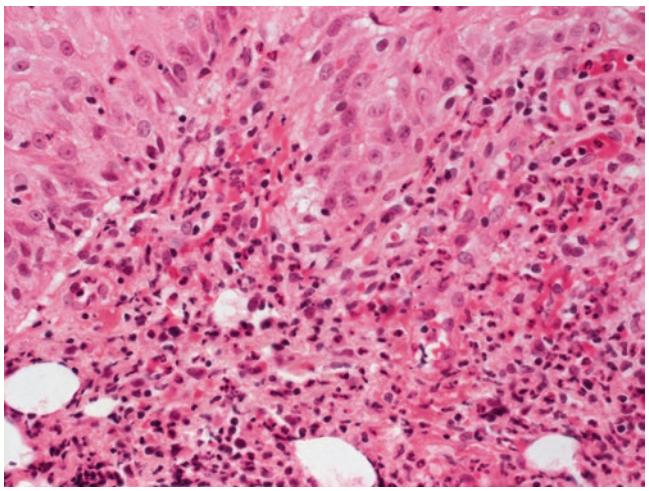

Fig. 8.17 Most cases of Behcet's disease demonstrate a dense infiltrate of neutrophils and vessels with fibrin thrombi and vascular wall damage

of patients with the disease [87]. The histologic findings in Behcet's disease are not specific and identical changes can be seen in leukocytoclastic vasculitis from other etiologies. Correlation with the clinical presentation is essential to make this diagnosis.

8.7.3 Pathogenesis

Behcet's disease is a systemic inflammatory disorder with a complex genetic background coupled with immune system activation. HLA-B51 plays an important role in this disease. A recent meta-analysis has shown increased pooled odds ratio of HLA-B51/B5 carriers developing Behçet disease as compared to non-carriers (odds ratio of 5.78, 95 % CI 5.00–6.67) [88]. The role of HLA-B51 in the disease pathogenesis is not known, but may involve presentation of a specific peptide to CD8+ T cells and interactions between natural killer cells, CD8+ T cells and gamma delta T cells [89]. Genome wide association studies (GWAS) have shown an association of Behcet's disease with IL23/IL17 pathway [90]. Patients with Behcet have reduced production of IL-10, which is an inhibitory cytokine that regulates both innate and adaptive immune responses, and with polymorphisms in IL-23R. Type 17 T helper cells (Th17) have been shown to play key immunomodulatory roles in Behcet disease. There is a predominance of Th17 and type 1 T helper cells (Th1) in the peripheral blood and tissue specimens of Behcet's patients with a Th17/Th1 ratio in Behcet's patients being higher than that in healthy controls [91–93]. Other studies have demonstrated a critical role for IL-21 in driving inflammatory lesions in Behcet's disease by promoting Th17 effectors and suppressing regulatory T cells (Treg) [94].

8.8 Granuloma Faciale

8.8.1 Clinical Features

Granuloma faciale is a rare benign chronic dermatosis that typically occurs on the face. Granuloma faciale is considered a disease of middle-aged white males [95]. It is extremely rare in children with only two known reports in the literature [96]. Granuloma faciale appears as solitary or multiple soft, red brown papules, nodules and plaques (Fig. 8.18). The classic case involves a solitary lesion on the nose, but lesions may also occur on other areas of the face and on extrafacial locations as well.

Granuloma faciale is highly resistant to treatment. Rarely, lesions may resolve spontaneously. A variety of topical and intralesional therapies have been attempted with inconsistent results.

Fig. 8.18 Granuloma faciale presents as red brown papules on the face (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

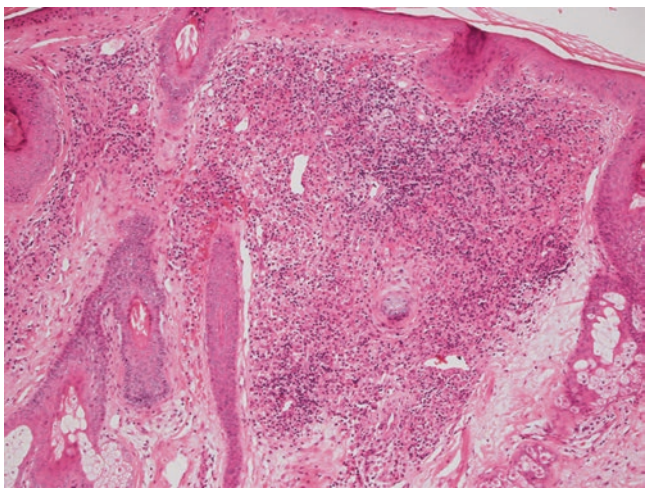

Fig. 8.19 A grenz zone beneath the epidermis and around the cutaneous appendages characterizes granuloma faciale. There is a dense perivascular inflammatory infiltrate in the dermis

8.8.2 Histology

Skin biopsy of granuloma faciale shows a dense polymorphous dermal inflammatory infiltrate. A prominent grenz zone is seen underneath the epidermis and around dermal appendages (Fig. 8.19). Neutrophilic vasculitis involving vessels of the superficial vascular plexus is present along with a dense infiltrate of lymphocytes and eosinophils (Fig. 8.20). Scattered plasma cells are present in some cases. In later lesions, increased dermal fibrosis is seen and the intensity of the inflammatory infiltrate is diminished [96].

The differential diagnosis includes leukocytoclastic vasculitis. Erythema elevatum diutinum is a close histologic mimic, but can be differentiated based upon the clinical pre-

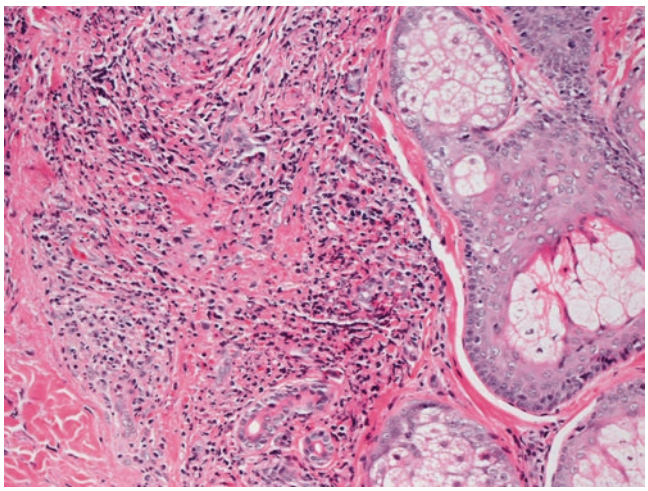

Fig. 8.20 There are abundant neutrophils and eosinophils within the vessel walls and around the dermal vessels in granuloma faciale

sentation [97]. Granuloma faciale usually has a more intense inflammatory infiltrate and lacks the occasional granulomas that can be seen in erythema elevatum diutinum. Given the facial location, pustular folliculitis and granulomatous rosacea could enter into the differential diagnosis, but both of these entities usually do not demonstrate changes of vasculitis.

8.8.3 Pathogenesis

The etiology of granuloma faciale is unknown. Sun exposure might be a possible predisposing factor given the predilection sites of granuloma faciale for the facial area, and the fact that skin lesions are exacerbated by sunlight exposure [98–100]. Studies have suggested that granuloma faciale is mediated by interferon (IFN)-γ produced by CD4+ T helper cells. In support of this hypothesis, tacrolimus, which is a calcineurin inhibitor that decreases interleukin-2 expression and T-cell activation, has clinical utility in disease treatment [101]. In addition, clonal expansion of CD4+ T cells in the skin and local overproduction of IL-5 with eosinophil activation in the lesion may play a role in the pathogenic mechanism [102, 103]. Modulation of T-cell function by dendritic cells and resultant cytokine production may also contribute to the formation of granuloma faciale lesions [104].

8.9 Erythema Elevatum Diutinum

8.9.1 Clinical Features

Erythema elevatum diutinum (EED) is a chronic, recurrent form of leukocytoclastic vasculitis, which is thought to be immune complex-mediated. EED is quite rare in children and typically affects adults between the third and sixth decades of life [105]. Patients present with tender red brown papules, nodules, and plaques located symmetrically over the extensor surfaces of the extremities [106]. The course of EED tends to be chronic, although some lesions may resolve spontaneously. Response to treatment, such as topical or intralesional steroids, colchicine and dapsone, has been variable [106].

8.9.2 Histology

Erythema elevatum diutinum is a low-grade, chronic leukocytoclastic vasculitis. Histologic changes demonstrate vascular destruction by transmural neutrophils with concomitant endothelial cell damage, fibrinoid necrosis, extravasation of erythrocytes, and thrombosis (Figs. 8.21 and 8.22). As lesions become chronic, perivascular fibrosis develops. Concentric rings of fibrosis are described in some cases. Extravascular deposition of lipid secondary to cellular breakdown products can be present and may be surrounded by granulomatous inflammation [97, 107, 108].

The differential diagnosis includes other types of leukocytoclastic vasculitis, although the fibrosis is not commonly seen in these other types, and clinical correlation serves to make the distinction. Granuloma faciale is probably the closest histologic mimic, but it has a different clinical presentation [97]. Sweet's syndrome has been described as a differential diagnostic problem in one patient [109]. One child with EED suffered from hyperimmunoglobulin D syndrome and this association was speculated to be causative [110].

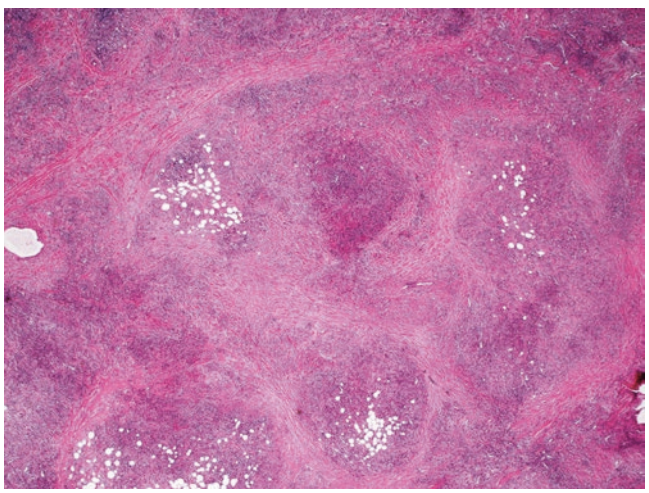

Fig. 8.21 Nodules of marked inflammation centered on dermal blood vessels and surrounded by fibrosis are present in erythema elevatum diutinum

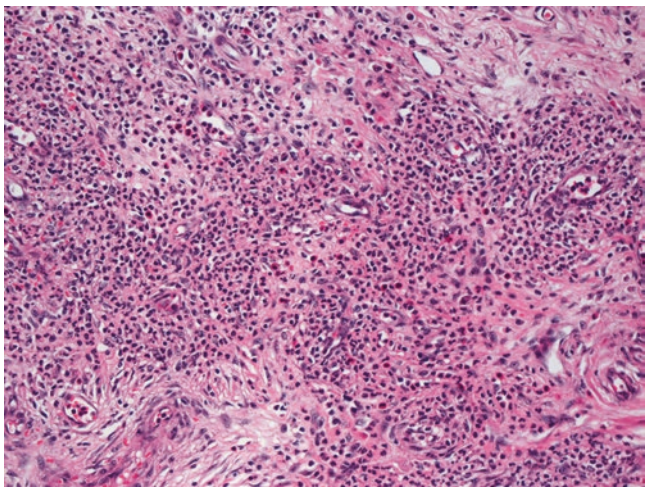

Fig. 8.22 A dense aggregate of neutrophils and eosinophils are seen around and within vessel walls in erythema elevatum diutinum

8.9.3 Pathogenesis

The cause of erythema elevatum diutinum is unknown. EED is believed to be a small vessel vasculitis mediated by immune complexes, and has been associated with underlying diseases, including autoimmune (rheumatoid arthritis, diabetes mellitus, Crohn's disease, and celiac disease), infections (HIV, and streptococcus), malignancies (B-cell lymphoma, multiple myeloma, and breast cancer), and drugs (anti-tuberculosis drugs, cisplatin, and erythropoietin) [111]. Immune complexes may sustain the local inflammatory infiltrate and leukocytoclastic vasculitis that are observed in EED [111–114]. Immune complexes are deposited in post-capillary venules that activate the complement cascade and subsequently initiate an leukocytoclastic vasculitis-type reaction [111]. Langerhans' cells are thought to be involved in the pathogenesis of EED, suggesting that cell-mediated reactions may play a role [115, 116]. It has been postulated that antineutrophil cytoplasmic antibody (ANCA) (especially IgA) may have a role in the development of EED and may act as a marker of disease activity since ANCAs (IgA/G) have been detected in the serum of patients with neutrophilic dermatoses [117].

8.10 Sweet's Syndrome

8.10.1 Clinical Features

Sweet's syndrome (also known as acute febrile neutrophilic dermatosis) is an inflammatory dermatosis characterized by painful skin lesions with fever. In adults, it is often a parainflammatory or paraneoplastic process. The majority of patients with Sweet's syndrome are white females between 30 and 60 years old [118]. Pediatric cases are rare, accounting for approximately 5–8 % of all reported cases [119]. Cases are more common in the spring and fall, and often occur following an upper respiratory tract infection. Patients typically present with scattered tender, edematous and erythematous papules and plaques. These may appear "pseudovesicular" or even targetoid. Sweet's syndrome typically responds rapidly to treatment with systemic corticosteroids. Post-infectious cases have a favorable prognosis, but cases associated with underlying malignancy, immunodeficiency, or another disease process may have a poorer prognosis.

8.10.2 Histology

Histologic changes in Sweet's syndrome include a subepidermal blister caused by marked papillary dermal edema. Within the edematous dermis is a dense and diffuse collection of neutrophils (Figs. 8.23 and 8.24). Abundant karyorrhectic debris is present, but in most cases, true vascular destruction or transumural infiltration by neutrophils is not seen [120, 121]. In early lesions, a lymphocytic predominance is present with only scattered neutrophils. Eosinophils are seen in most cases but vary from rare to relatively abundant in number [118]. Rare cases designated as histiocytoid Sweet's syndrome are described in which there is a large number of histiocytes present in the interstitial collagen [122]. There is an emerging literature suggesting that this variant of Sweet syndrome may have some overlap with cutaneous lupus erythematosus in children [123–125].

The most common presentation is that the infiltrate is centered in the superficial to mid-reticular dermis; however, other cases present with a deeper inflammatory infiltrate that extends throughout the reticular dermis and into the subcuta-

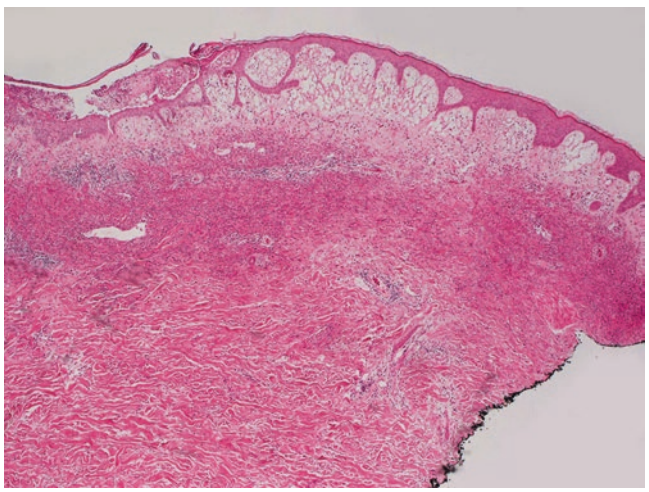

Fig. 8.23 Sweet's syndrome is characterized by papillary dermal edema and a dense band-like neutrophilic infiltrate

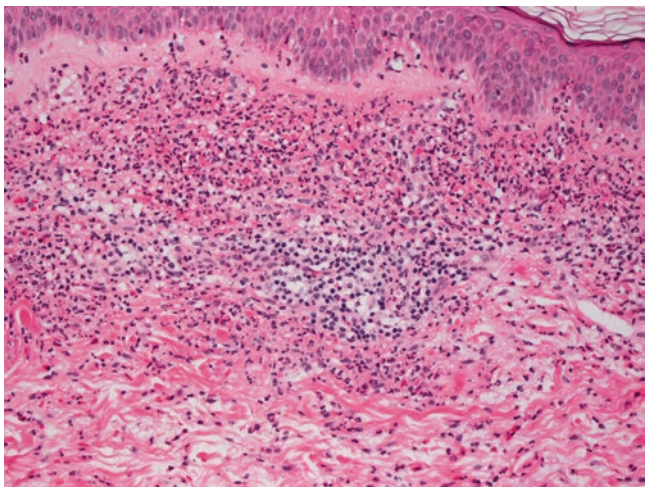

Fig. 8.24 A dense neutrophilic infiltrate that is diffuse and not perivascular is the predominant feature in Sweet's syndrome

neous fat [118]. In this situation, there is great overlap clinically and histologically with pyoderma gangrenosum and gives rise to the concept of a spectrum of neutrophilic hypersensitivity reactions [126, 127]. Elastolysis resulting in clinically slack skin has been described in resolving lesions, presumably secondary to the enzymatic digestion of dermal elastin by neutrophils [128, 129].

Leukocytoclastic vasculitis is the major differential diagnosis. In most cases, the presence of true vascular destruction makes for easy distinction from Sweet's syndrome. However, in some cases, slight vasculitis is present in Sweet's syndrome, and it is not possible to completely exclude either diagnosis [130]. In rare cases, the clinical presentation may give rise to a differential diagnosis that includes erythema elevatum diutinum [109]. The differential diagnosis also includes cutaneous leukemia, and it is important to distinguish an infiltrate of mature neutrophils from one that contains immature forms and may represent acute myelogenous leukemia [131, 132]. Acute hemorrhagic edema of infancy is also in the histologic differential diagnosis and must be distinguished based upon clinical features [32].

8.10.3 Pathogenesis

Sweet's syndrome has many possible etiologies. Classical Sweet's syndrome is frequently associated with infectious and inflammatory disorders (e.g., immunodeficiency, aseptic meningitis, and inflammatory bowel disease), while malignancy-associated Sweet's syndrome is frequently associated with hematologic disorders, including acute myeloid leukemia and myelodysplastic syndrome [133, 134]. In the case of infectious etiology in which there is an upper respiratory tract infection that precedes skin lesions by 1–3 weeks, bacterial infection may have a causative role [133]. Cytokines have been shown to contribute to the development of Sweet's syndrome. Granulocyte-colony stimulating factor (GCSF), granulocyte macrophage colony stimulating factor, interferon-γ, interleukin-1, interleukin-3, interleukin-6, and interleukin- 8 are potential cytokine candidates [133, 135–137]. The production of GCSF in the setting of malignancy may be involved in the development of Sweet's syndrome in cancer patients. In a case report of an infant with classical Sweet's, increased levels of GCSF in the intra-articular synovial fluid were observed [138]. Furthermore, patients with active Sweet's syndrome have significantly higher levels of serum GCSF than individuals with inactive Sweet's [135]. Analysis of a rare variant of Sweet's syndrome known as histiocytoid Sweet's syndrome showed that the inflammatory infiltrate was mainly composed of CD68+ CD163+ myeloperoxidase+ myeloid cells with a phenotype suggestive of M2-like macrophages [122].

8.11 Erythema Marginatum

8.11.1 Clinical Features

Erythema marginatum is a form of annular erythema that occurs in approximately 2–4 % of patients with rheumatic fever [139, 140]. It is seen more often in children than adults. The lesions typically appear on the trunk (especially the abdomen) and proximal extremities as evanescent pink macules and papules that often form annular and polycyclic configurations.

8.11.2 Histology

Histologic features of erythema marginatum include a neutrophilic infiltrate within papillary dermal tips and around vessels of the superficial vascular plexus (Fig. 8.25). True vasculitis with fibrinoid degeneration of vessel walls is not identified (Fig. 8.26). Karyorrhectic debris is present. Occasional dying keratinocytes may be seen in the overlying epidermis [141].

A clinical presentation of urticaria with commensurate histologic changes has been described in a child with rheumatic fever. This pattern could show histologic overlap with the classical appearance of erythema marginatum [142]. Neutrophilic figurate erythema of infancy may have identical histologic features but it is not associated with rheumatic fever [143]. Leukocytoclastic vasculitis is also in the histologic differential diagnosis but it can be distinguished based upon the presence of true vascular wall destruction and the clinical history.

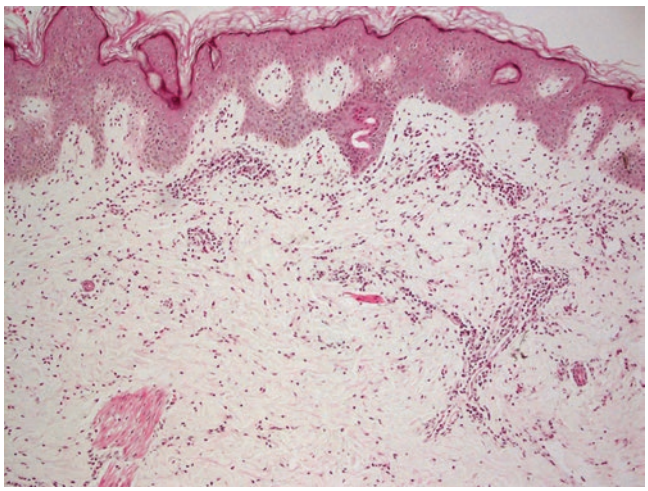

Fig. 8.25 Erythema marginatum demonstrates a perivascular neutrophilic infiltrate

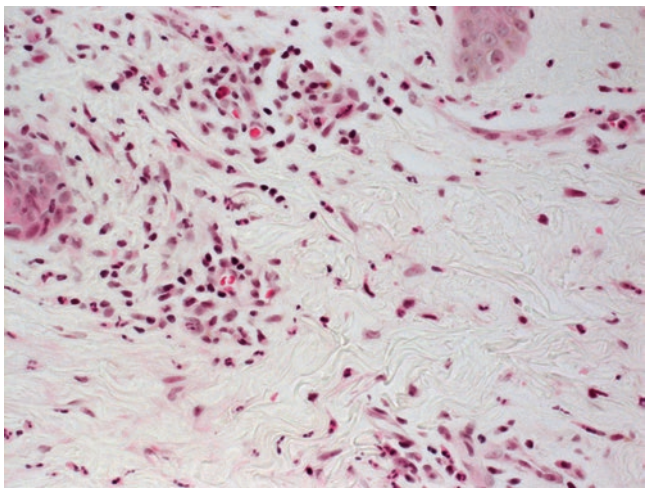

Fig. 8.26 No true vasculitis is seen in erythema marginatum despite the neutrophilic infiltrate and karyorrhectic debris

8.11.3 Pathogenesis

The exact pathogenesis of erythema marginatum is not known. A study has demonstrated accumulation of bradykinin in the stromal tissue and endothelial cells in a skin biopsy [144, 145]. Bradykinin may be important in the causality of erythema marginatum associated with hereditary angioedema.

8.12 Hyperimmunoglobulinemia D Syndrome (Mevalonate Kinase Deficiency)

8.12.1 Clinical Features

Hyperimmunoglobulinemia D Syndrome (HIDS) is one of several autoinflammatory diseases characterized as a periodic fever syndrome. It is an autosomal recessive condition caused by mutations in the mevalonate kinase (MVK) gene. HIDS patients typically present with febrile episodes lasting 3–7 days and recurring every 4–6 weeks. 94 % of patients have their first attack by 4 years of age [146]. Flares can be triggered by immunizations, trauma, or other stress. In addition to fever and chills, patients often have tender cervical lymphadenopathy, abdominal pain, diarrhea, vomiting, headache, and polyarthralgia. Over 80 % of patients will have a skin rash that can be papular, urticarial, nodular, or purpuric. Rarely, oral and genital ulcers have been reported. In most cases, the frequency of flares decreases during adulthood [146].

8.12.2 Histology

The histologic findings in hyperimmunoglobulinemia D syndrome are varied, but most commonly are those of a mild leukocytoclastic vasculitis. Less commonly, a neutrophilic dermatosis lacking overt vascular destruction is seen. In these cases, the differential diagnosis includes Sweet's syndrome and cellulitis [147]. In rare cases, HIDS has been reported in association with the clinical and histologic appearance of Henoch–Schonlein purpura, including IgA deposition in vascular walls [148].

8.12.3 Pathogenesis

Hyperimmunoglobulinemia D syndrome, also known as mevalonate kinase deficiency, is an autosomal recessive metabolic autoinflammatory disease. Increased serum IgD and IgA levels as well as elevated urinary mevalonic acid are found in some patients. Although high serum IgD concentrations are a characteristic feature of the disorder, normal levels of IgD have been reported in a number of patients with confirmed HIDS [148–150]. Increased IgD may be due to changes in the glycosylation of IgD induced by cytokines [151].

Mutations in the mevalonate kinase (MVK) gene, resulting in insufficient enzymatic activity cause HIDS [152–154]. Mevalonate kinase activity in HIDS is usually reduced to 5–10 % of normal levels, resulting in excessive accumulation of mevalonic acid [155, 156]. A variety of mutations in MVK gene have been reported, but the V377I mutation in exon 10 is present in more than 80 % of the patients studied to date [148, 157, 158]. MVK is involved in the biosynthesis pathway of isoprenoids, and deficiency of isoprenoids may contribute to the production of inflammatory cytokines, including interleukin-1β, and the symptoms of HIDS [150, 159]. There is also increasing evidence that overproduction of interleukin-1 through the activation of the inflammasome might be involved in the pathogenesis of the disease [159].

8.13 TNF Receptor-Associated Periodic Syndrome

8.13.1 Clinical Features

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a common autoinflammatory disease in children. It is an autosomal dominant condition and the mean age at onset of symptoms is 10 years of age. In addition to lengthy febrile episodes (often lasting for weeks), patients experience severe abdominal pain, myalgias, and a tender erythematous skin rash. The rash has been described as macular, urticarial, reticular, and serpiginous. TNF-α inhibitors and other anti-inflammatory agents have been used with variable degrees of success [146].

8.13.2 Histology

The histologic findings in TRAPS are those of a mild leukocytoclastic vasculitis. The findings are not specific and resemble those seen in hyperimmunoglobulinemia D syndrome, other causes of leukocytoclastic vasculitis, Sweet's syndrome and cellulitis [146, 160].

8.13.3 Pathogenesis

TRAPS is an autosomal dominant inflammatory disorder in which patients present with symptoms due to dysregulation of the innate immune system and systemic inflammatory attacks [156]. TRAPS is caused by mutations in the TNFRSF1A gene, which encodes the tumor necrosis factor receptor-1 (TNF-R1) [161–163]. Mutational analysis of TNFRSF1A is necessary for the specific diagnosis of TRAPS. TNFRSF1A mutations result in protein misfolding and accumulation of the misfolded receptor in the endoplasmic reticulum, causing TNF-independent signaling by the mutant receptor, and stimulating an unfolded protein response and the production of reactive oxygen species [164, 165]. There are over than 100 high-penetrance and low-penetrance mutations in TNFRSF1A identified in the Infevers database [166]. One of the common mutations is the R92Q substitution, in which the amino acid L-arginine in position 92 is replaced by L-glutamine [165, 167, 168]. Mutations in the extracellular cysteine-rich domain regions of TNFRSF1A protein that are involved in disulfide bond formation and protein folding are highly penetrant and associated with severe clinical phenotypes.

A novel S59P mutation in TNFRSF1A has been identified. This substitution results in constitutive activation of the NF-κB pathway [169]. The lack of TNF signaling may decrease NF-κB activity, block cell apoptosis, increase the survival of inflammatory cells, and induce the release of inflammatory cytokines, such as IL-1, IL-8 and IL-12 [165, 170, 171]. In fact, defect in cell apoptosis is a common result of TNFRSF1A mutations with many mutants causing inhibition of the pro-apoptotic genes BCL-2 and BAD [169].

Since TRAPS is caused by molecular defects in TNFRSF1A, molecules that modulate TNF pathway may provide a rational therapeutic approach for this disorder. Etanercept, which is a recombinant fusion protein consisting of soluble TNF receptor linked to the Fc-fragment of IgG1, has been shown to reduce the severity and duration of the inflammatory episodes in TRAPS [156, 172].

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Panniculitis

9

9.1 Erythema Nodosum

9.1.1 Clinical Features

Erythema nodosum is thought to be a reactive cutaneous process triggered by a variety of infectious and noninfectious causes. Although erythema nodosum typically affects adults ages 20–30 years old, it is the most common form of panniculitis seen in children [1, 3]. The mean age of erythema nodosum in childhood is 8–10 years old. Before puberty, erythema nodosum appears to affect both sexes equally.

Tender erythematous 1–3 cm nodules characterize erythema nodosum. These are most common on the anterior lower legs, but may occur anywhere else on the body. In children, a common infectious trigger is streptococcal infection. Following treatment of identifiable infectious triggers, such as streptococcus, cutaneous lesions usually resolve within weeks, although residual dyschromia may occur. Symptoms of erythema nodosum may be alleviated with nonsteroidal anti-inflammatory agents.

9.1.2 Histology

Erythema nodosum is a septal panniculitis [1]. Early lesions demonstrate septal edema and a mixed inflammatory infiltrate of neutrophils, lymphocytes, eosinophils, and occasional giant cells (Fig. 9.1). As the lesions develop, neutrophils diminish in number with increased number of histiocytes, including multinucleated giant cells (Figs. 9.2 and 9.3). Small granulomatous foci are present in some cases. The septa become thickened and fibrotic, and septal edema is less apparent. The inflammatory infiltrate may extend into the periphery of the fatty lobules, although fat necrosis is not seen. The blood vessels are not inflamed. The overlying epidermis and dermis are usually relatively unremarkable.

The differential diagnosis depends upon the stage of the lesion. Early lesions containing many neutrophils may be mistaken for vasculitis, but the vessels are intact and the dermis is not involved [1]. An infectious etiology might be considered, but there is no necrosis and the anatomic boundaries are respected in a way not usually seen with infectious processes. Later lesions in which septal fibrosis is prominent may give rise to the possibility of scleroderma and necrobiosis lipoidica. In both of these entities, one would expect dermal changes that are not seen in erythema nodosum. Cases of erythema nodosum with granulomas can be mistaken for other granulomatous processes. Special stains and microbiological cultures may be required to rule out infectious processes in these cases, and clinical history helps to distinguish erythema nodosum from sarcoidosis, although the two entities can occur simultaneously [2]. Sarcoidosis also usually involves the dermis and the subcutis. Lobular panniculitides demonstrate more changes in the lobules, and they do not ordinarily involve the septa to any significant degree.

9.1.3 Pathogenesis

A common cause of erythema nodosum in children is upper respiratory infections caused by Group A *Streptococcus pyogenes* [1, 3, 4]. Erythema nodosum can be associated with other underlying infections, including *Mycoplasma pneumonia* and disseminated coccidioidomycosis, as well as sarcoidosis and inflammatory bowel disease [3–7]. Some inflammatory bowel disease susceptibility loci have been shown to be associated with erythema nodosum [7]. Similarly, erythema nodosum can have a genetic predisposition with polymorphisms associated with a specific tumor necrosis factor-α allele, TNF-αII [8]. Additionally, concurrence of Sweet's syndrome and erythema nodosum in the same patient has been observed, and may point to a pathological association between these two disorders involving neutrophils [9]. The exact molecular basis of erythema nodosum is not known, but it may be related to the deposition of immune complexes in blood vessels in the septae of subcutaneous fat, leading to panniculitis [10].

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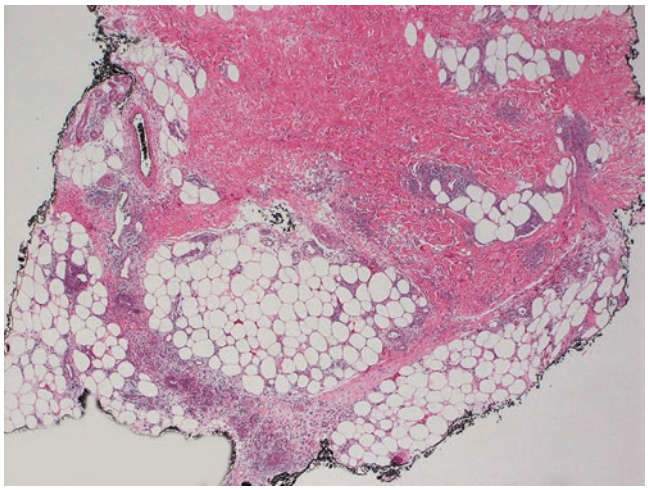

Fig. 9.1 Erythema nodosum demonstrates a septal panniculitis characterized by widening of the fibrous septa and an inflammatory response

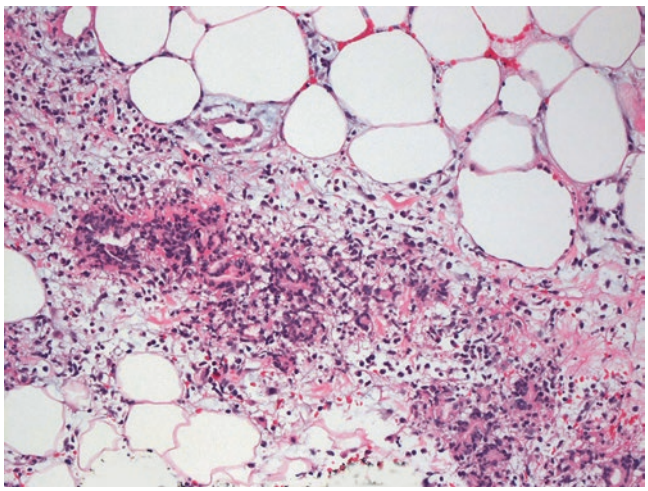

Fig. 9.2 Abundant lymphocytes, scattered eosinophils and histiocytes, including multinucleated giant cells, are seen within the fibrous septa in erythema nodosum

9.2 Sclerema Neonatorum

9.2.1 Clinical Features

Sclerema neonatorum is a rare condition characterized by diffuse hardening of subcutaneous tissues. Sclerema typically affects very ill premature or young infants with a history of sepsis, hypoxemia, and hypothermia. Mortality ranges from 30 to 100 % . Areas of induration, swelling and erythema appear in the skin and tend to spread rapidly. Treatment is aimed at management of the underlying medical issues.

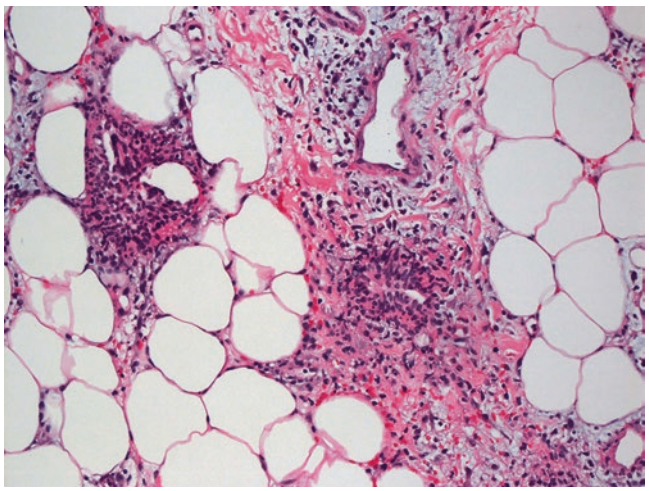

Fig. 9.3 Small foci that resemble granulomas, known as Miescher's radial granulomas, are seen in the fibrous septa in some cases of erythema nodosum

9.2.2 Histology

Histologic changes are those of a lobular panniculitis with a histiocytic response [11]. The adipocytes undergo degeneration with formation of needle-like crystals. These may be present within histiocytes [12]. There is little necrosis or secondary inflammation in most cases. There is thickening of the fibrous septa reported in some cases [13]. Subcutaneous fat necrosis of the newborn is differentiated from sclerema neonatorum based upon the pronounced inflammatory infiltrate seen in the former entity.

9.2.3 Pathogenesis

The pathogenesis of sclerema neonatorum appears to be related to high saturated-to-unsaturated fatty acid ratio in infants, and thus a higher melting point and a low solidification point for fat that enables it to harden with decreased body temperature [13, 14]. Ultrastructural studies show that infants with sclerema neonatorum have increased saturated fats and triglyceride crystals within adipocytes [15–18]. Prematurity, hypothermia, and metabolic abnormalities may further increase the levels of saturated fatty acids. Other possible etiologies of sclerema neonatorum include underlying systemic diseases, edema affecting the subcutaneous tissue, and defective mobilization of fatty acids from adipose tissues [13].

Fig. 9.4 Subcutaneous fat necrosis of the newborn presents as rippled and slightly dusky-colored, indurated plaques along the bilateral flanks, buttocks and proximal thighs

9.3 Subcutaneous Fat Necrosis of the Newborn

9.3.1 Clinical Features

Subcutaneous fat necrosis is a rare panniculitis affecting newborn infants. There is frequently a history of traumatic delivery often complicated by dystocia, hypothermia, hypoxia, and meconium aspiration.

Clinically, firm subcutaneous nodules or plaques are present, typically on the back, buttocks, and thighs (Fig. 9.4). There is potential for associated complications, particularly hypercalcemia. The skin lesions are usually self-limited, but there may be residual skin atrophy or scarring.

9.3.2 Histology

Biopsy of subcutaneous fat necrosis of the newborn demonstrates a lobular panniculitis [19] (Fig. 9.5). There is a diffuse, brisk mixed inflammatory infiltrate within fat lobules. Necrosis of adipocytes results in crystal formation and small granulomas surrounding the degenerating cells [20] (Figs. 9.6 and 9.7). Crystals are needle-shaped, and can be present within degenerating adipocytes and histiocytes [21, 22]. Eosinophilic granules, a manifestation of degenerating eosinophils within the surrounding infiltrate, have been observed in some cases [23–25]. Dystrophic calcification is seen in late cases [20, 26, 27]. Radially oriented needle-like crystals are helpful in establishing the diagnosis on fine needle aspiration cytology [28, 29].

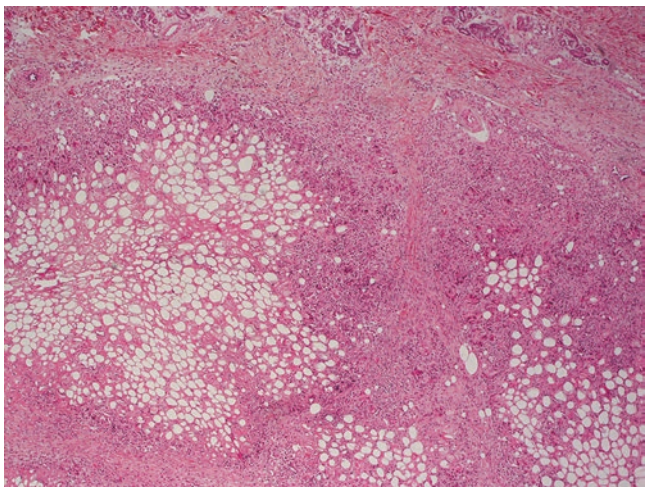

Fig. 9.5 Subcutaneous fat necrosis of the newborn is a lobular panniculitis that is characterized by a predominantly histiocytic response

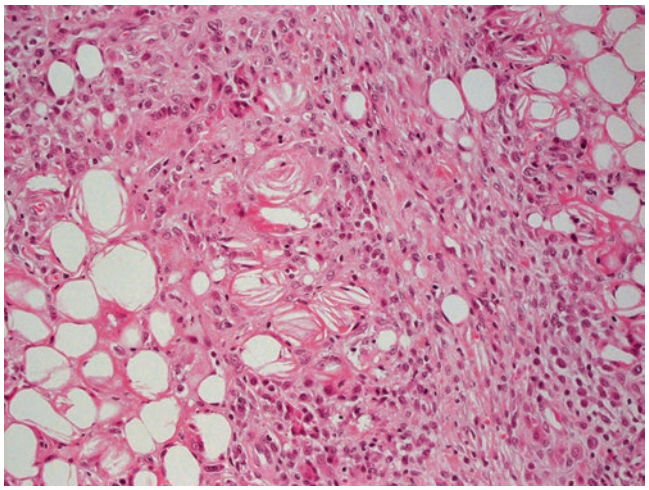

Fig. 9.6 Sheets of histiocytes, some of which contain crystalloid material, are admixed with lymphocytes in subcutaneous fat necrosis of the newborn

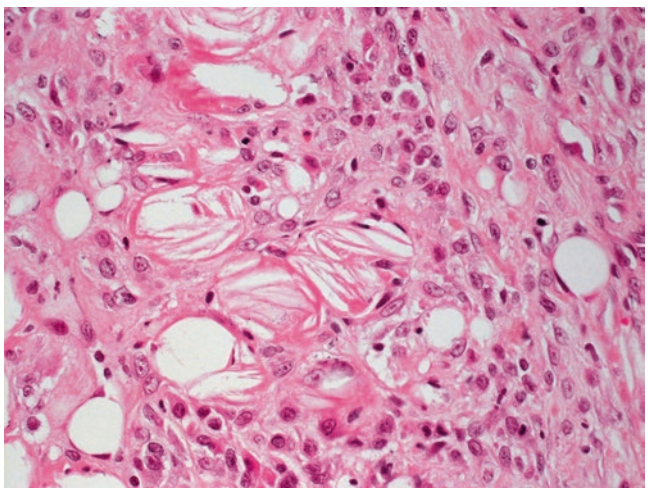

Fig. 9.7 Degenerating fat forms crystals within histiocyte cytoplasm in subcutaneous fat necrosis of the newborn

The differential diagnosis includes sclerema neonatorum, although this process does not usually engender an inflammatory response. An infectious process might enter the differential diagnosis, but the needle-like crystals are not a feature of an infectious process.

9.3.3 Pathogenesis

Subcutaneous fat necrosis of the newborn is a type of panniculitis that affects term infants following birth trauma, such as perinatal asphyxia, meconium aspiration, and hypothermia [30–32]. These inciting factors can impair tissue perfusion, resulting in hypoxia, adipocyte necrosis, and the release of free fatty acids in subcutaneous tissue.

9.4 Post-Steroid Panniculitis

9.4.1 Clinical Features

Post-steroid panniculitis is a rare complication of steroid therapy with a few dozen cases reported, mostly in children. It is usually seen in patients receiving high doses of systemic corticosteroids that are abruptly discontinued.

Clinically, erythematous nodules and plaques appear on the skin. Lesions tend to occur in areas where steroids induce the greatest accumulation of fat, such as the facial cheeks, posterior neck, and upper trunk. Lesions tend to resolve spontaneously.

9.4.2 Histology

Biopsies of this quite rare lobular panniculitis demonstrate degenerating adipocytes containing crystalloid structures (Figs. 9.8 and 9.9). These needle-shaped crystals also can be seen within surrounding histiocytes [33]. Multinucleated giant cells are common, and are most prevalent surrounding areas of fat necrosis [34]. A lymphocytic infiltrate with granulocytes is present within the lobules [35]. Identical histologic changes have been described in a patient receiving etanercept injections [36].

The differential diagnosis includes other lobular panniculitides. Subcutaneous fat necrosis of the newborn has a much different clinical history and occurs primarily in newborns. It tends to have a more mixed inflammatory infiltrate than the panniculitis that occurs following steroid treatment. Sclerema neonatorum is also a lobular panniculitis, but it has virtually no inflammatory response to the degenerating adipocytes and a markedly different clinical history and course. Pancreatitis-induced panniculitis and alpha-1 antitrypsin deficiency-associated panniculitis are more neutrophil-mediated lobular panniculitides, and can be readily distinguished based upon clinical features.

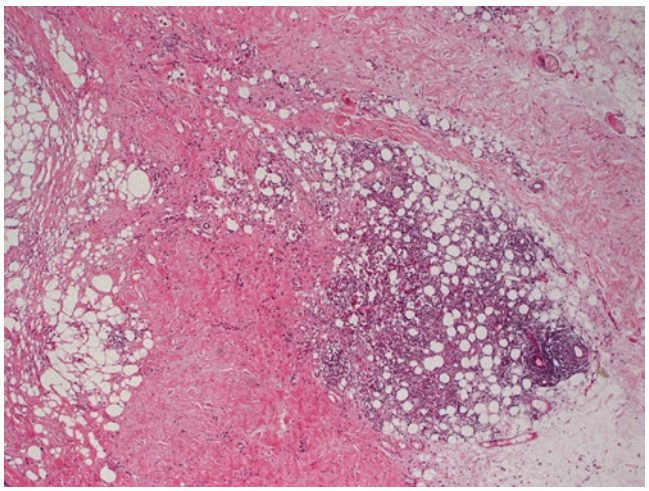

Fig. 9.8 Post-steroidal panniculitis shows necrosis of adipocytes and a dense lymphocytic infiltrate centered within the lobules

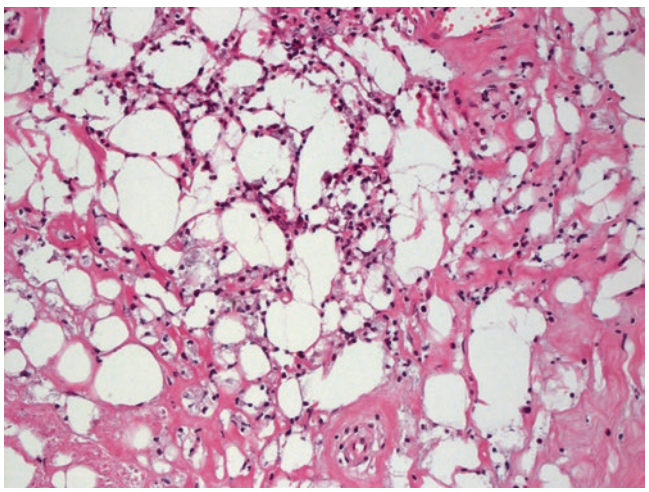

Fig. 9.9 Lobular necrosis with admixed lymphocytes and scattered neutrophils are seen in post-steroid panniculitis

9.4.3 Pathogenesis

The precise mechanism of post-steroid panniculitis is not known [37]. It has been observed that post-steroid panniculitis occurs after a rapid withdrawal of systemic corticosteroids, or if the dose of steroids is reduced but not stopped [38].

9.5 Factitial Panniculitis

9.5.1 Clinical Features

Factitial panniculitis occurs when subcutaneous tissues are injured by the injection of drugs or chemical substances into the skin. In most cases, the injury is self-inflicted as a manifestation of underlying psychiatric disturbance. Factitial panniculitis is most common in young and middle-aged females with a history of psychiatric disorder and/or drug addiction.

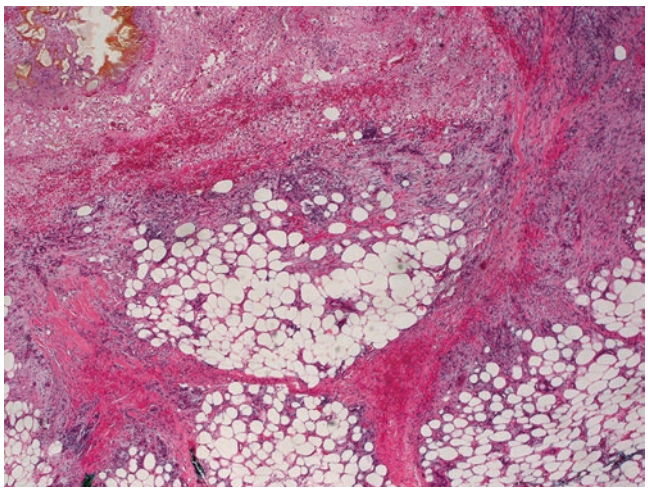

Fig. 9.10 Pancreatic fat necrosis in pancreatic panniculitis results in a lobular panniculitis with abundant neutrophils

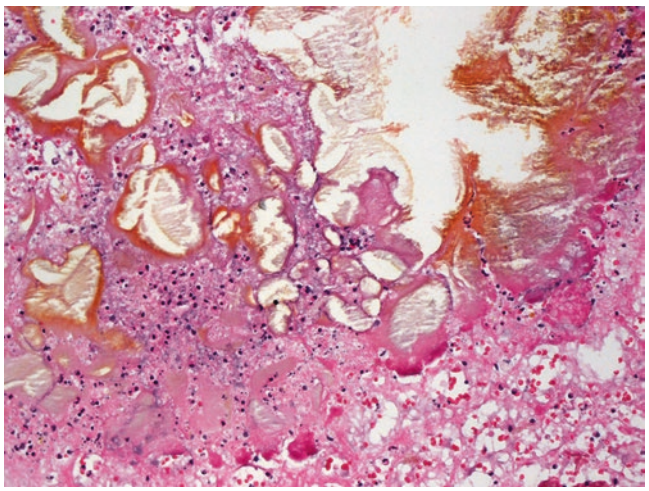

Fig. 9.11 Extensive necrosis in pancreatic fat necrosis results in cystically dilated spaces, hemosiderin deposition, and widespread calcification in late stage lesions

The clinical features vary depending on the agent that is injected. However, lesions are more common in easily accessible areas, such as the hands, buttocks, and thighs. Frequently, there are inflammatory nodules or plaques, often with erosions and ulcerations. Acute wounds should be treated as clinically indicated with antibiotics for infection, and dressings to promote healing. Effective long-term treatment requires social support and appropriate psychiatric care.

9.5.2 Histology

Many cases of factitial panniculitis were previously categorized under the name Weber Christian disease [39, 40]. Factitial panniculitis depicts a predominantly lobular panniculitis characterized by a mixed inflammatory infiltrate and focal fat necrosis. Neutrophils are abundant [41]. Despite the florid inflammatory infiltrate, the septal blood vessels are not involved [19, 42]. Depending upon the nature of the etiology of the disorder, the epidermis and dermis can show changes ranging from no abnormalities to extensive hemorrhage, necrosis, and inflammation.

The differential diagnosis includes pancreatic panniculitis that demonstrates more extensive necrosis and calcification (Figs. 9.10 and 9.11). Alpha-1 antitrypsin deficiency-associated panniculitis is more focal than the diffuse process seen in factitial panniculitis.

9.5.3 Pathogenesis

Factitial panniculitis can be caused by the injection of a foreign substance, such as mineral oil or liquid silicone, into the subcutaneous fat with subsequent induction of an inflammatory reaction characterized by subcutaneous fibrosis and foreign body reaction [41, 43]. Local pressure and repeated blunt trauma to an area on the body can also induce subcutaneous inflammation. Sites of vaccination of tetanus antitoxoid and antihepatitis vaccines, as well as sites of injection of interleukin-2 and granulocyte colony stimulating factor have been documented to develop panniculitis [41, 44, 45]. The skin changes at the site of injury may be due to vasoconstriction and resultant tissue ischemia.

9.6 Traumatic Fat Necrosis

9.6.1 Clinical Features

Traumatic fat necrosis is a potential cause of palpable soft tissue lumps in children. Frequently, there is no definite history of a traumatic injury. The child simply presents with one or more soft tissue nodules, often on an extremity. These nodules require no treatment and resolve spontaneously over time.

9.6.2 Histology

Even though the pathogenesis differs, the histologic findings in traumatic fat necrosis are identical to those described in factitial panniculitis [42, 46]. A lobular panniculitis with abundant fat necrosis and a dense mixed inflammatory infiltrate characterizes traumatic panniculitis (Figs. 9.12, 9.13 and 9.14). Rare cases develop a pseudomembrane that lends a lobulated appearance to the neutrophil-rich inflammatory infiltrate [47]. This pseudomembrane is likely a result of necrotic adipocytes.

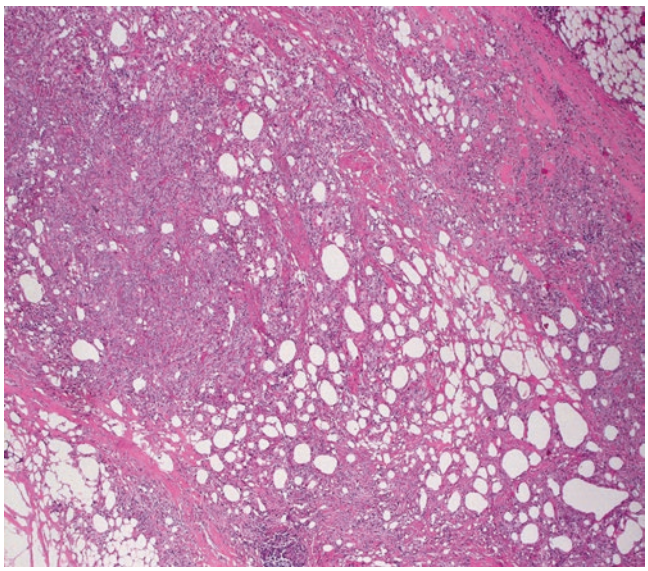

Fig. 9.12 Traumatic fat necrosis causes a lobular and septal panniculitis with no anatomic boundaries

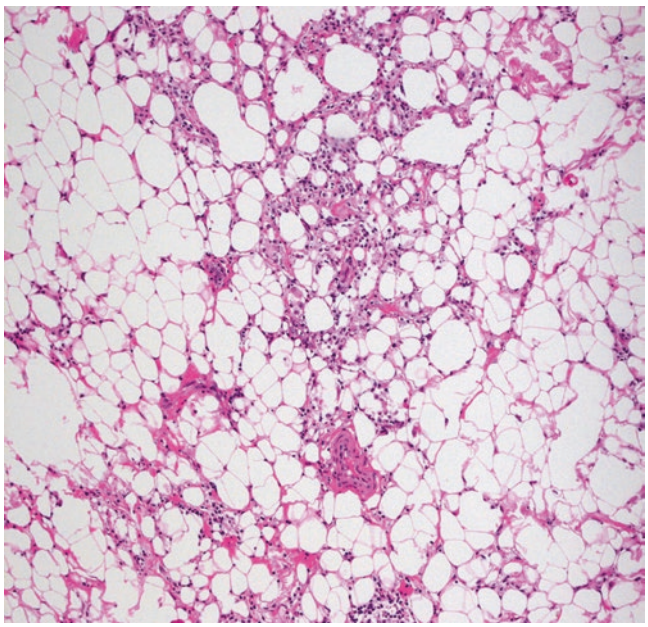

Fig. 9.13 Fat necrosis and a mixed inflammatory response are seen in cases of traumatic fat necrosis

9.6.3 Pathogenesis

Traumatic fat necrosis is caused by injuries to the skin and subcutaneous fat. Sudden trauma-induced pressure in adipose tissue can cause adipocytes and the surrounding capillaries to rupture, resulting in tissue damage [48]. The damaged fat cells release lipids, which are hydrolyzed into glycerols and fatty acids, causing an inflammatory response.

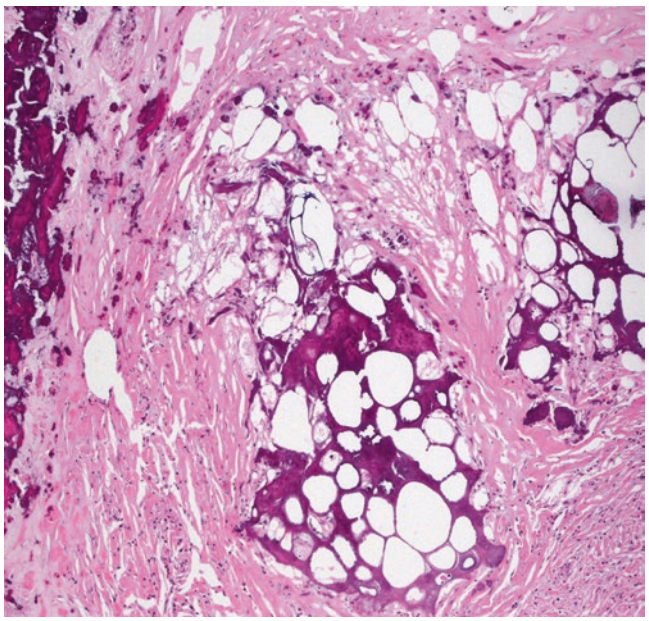

Fig. 9.14 Dystrophic calcification secondary to necrosis of adipocytes is a common finding in late stage lesions of traumatic fat necrosis

9.7 Alpha-1 Antitrypsin Deficiency-Induced Panniculitis

9.7.1 Clinical Features

Alpha-1 antitrypsin deficiency is a rare autosomal recessive hereditary disorder with an array of clinical manifestations, which are rarely observed before the age of 25 years. Skin lesions most commonly occur on the trunk and extremities, and they are characterized by crops of painful, ulcerative, subcutaneous nodules that drain an oily, serosanguinous material.

9.7.2 Histology

Alpha-1 antitrypsin deficiency causes a lobular neutrophilic panniculitis [11, 19]. Foci of liquefactive degeneration of fat lobules are immediately juxtaposed with areas that are seemingly completely uninvolved. The fibrous septa are usually involved, although to a lesser degree [49]. Collagenolysis is seen in these areas with neutrophils percolating between collagen bundles in the fibrous septa and up into the dermis. Enzymatic digestion of the adipocytes results in the formation of overlying ulceration of the epidermis and necrobiosis in the dermis [50, 51]. The dermis may exhibit changes that suggest cellulitis [51]. Destruction of elastic tissue fibers is especially prominent in some cases [52]. There is an occasionally associated vasculitis in this type of panniculitis [53]. Dystrophic calcification occurs in late stage lesions [54]. It is

likely that some previous cases of Weber Christian disease were in fact due to alpha-1 antitrypsin deficiency [40, 49].

Pancreatitis also causes a neutrophil-predominant lobular panniculitis similar to alpha-1 antitrypsin deficiency. It can be distinguished based upon clinical history, the presence of uninvolved areas seen in alpha-1 antitrypsin deficiency but not in pancreatitis, and the more extensive saponification with calcification in cases of pancreatitis-induced panniculitis. Factitial panniculitis is usually more focal and not as diffusely affected as in alpha-1 antitrypsin deficiency.

9.7.3 Pathogenesis

Alpha-1 antitrypsin is an abundant serum glycoprotein produced in the liver. It is a member of the serine protease inhibitor family known as serpins, whose major role is to inhibit neutrophil elastase, cathepsin G, and proteinase 3 [55]. Alpha-1 antitrypsin deficiency results from mutation of glutamate to lysine substitution at residue 342 (Glu342Lys) in the protein. Consequently, the mutant protein is misfolded with protein retention in the endoplasmic reticulum and defects in protein secretion. These result in significantly low plasma and tissue levels of alpha-1 antitrypsin that are 10–15 % that of normal levels [55, 56]. The reduction in serum alpha-1 antitrypsin leads to loss of anti-neutrophil elastase activity. The uninhibited neutrophil elastase, in turn, can destroy tissues, particularly the lung parenchyma and liver of affected individuals [57–59]. Moreover, neutrophils, which are the main source of serine proteinases, are present in large numbers of tissues in patients with alpha-1 antitrypsin deficiency [60, 61].

Autophagy also plays an important role in the pathogenesis of this disease. More autophagosomes are present in human fibroblast cells that express mutated alpha-1 antitrypsin protein [62]. Autophagy can be activated by intracellular accumulation of mutated alpha-1 antitrypsin.

9.8 Erythema Induratum/Nodular Vasculitis

9.8.1 Clinical Features

Erythema induratum is a lobular panniculitis related to infection with *Mycobacterium tuberculosis*. It is rare in children. Most authors consider nodular vasculitis and erythema induratum to share identical histologic features. The generally agreed upon difference in terminology is dependent upon an association with Mycobacterium tuberculosis as seen in cases of erythema induratum, which is not present in patients designated as having nodular vasculitis [63–67]. Atypical mycobacterial infections do not appear to be associated with erythema induratum [68]. Clinically, erythema induratum presents with single or multiple tender erythematous nodules on the legs, and may ulcerate (especially in adults). The lesions tend to resolve when the patient receives a multidrug regimen against M. tuberculosis.

9.8.2 Histology

The histologic findings for both nodular vasculitis and erythema induratum include a predominantly lobular panniculitis with additional involvement of the fibrous septa, especially including blood vessels that demonstrate leukocytoclastic vasculitis [19, 42, 65, 69] (Figs. 9.15 and 9.16). Some cases demonstrate a neutrophilic infiltration of a muscular artery in the fibrous septum, while most cases involve smaller vessels [70] (Fig. 9.17). Neutrophils are prominent in the mixed inflammatory infiltrate that also contains eosinophils, lymphocytes, and histiocytes [71]. Granuloma formation is seen in many cases (Fig. 9.16). The granulomas can be poorly formed or sharply circumscribed. Fat lobules show both coagulative and caseating necrosis [70] (Fig. 9.18). The florid inflammatory infiltrate often extends upwards into the reticular dermis.

Some authors do not endorse the clear-cut pathogenetic separation as elucidated above and report relationships between erythema induratum and other entities including hepatitis C [72]. Magro et al. have suggested that the term "acute infectious id panniculitis" might apply for such situations [73]. A similar reaction pattern has been associated with Bacillus Calmette–Guérin (BCG) vaccine inoculation and Crohn's disease [74, 75]. Some cases that were previously classified as Weber-Christian disease are likely either erythema induratum or nodular vasculitis [39].

The differential diagnosis includes other neutrophil-rich lobular panniculitides, such as pancreatitis-induced panniculitis and alpha-1 antitrypsin deficiency. These latter entities do not have vasculitis and can thus be differentiated from

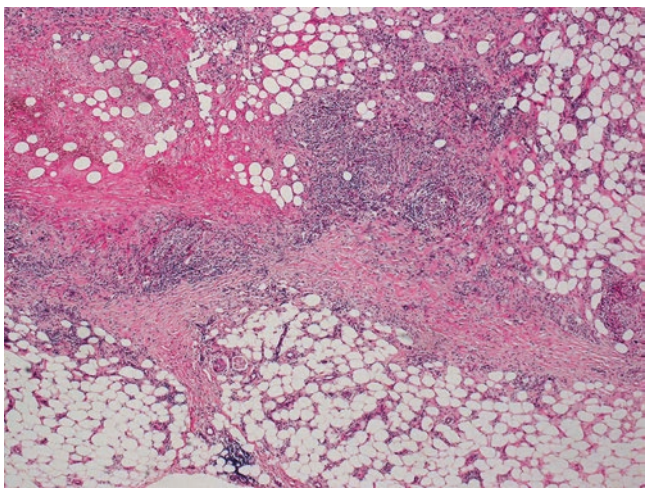

Fig. 9.15 Erythema induratum demonstrates a septal and lobular panniculitis

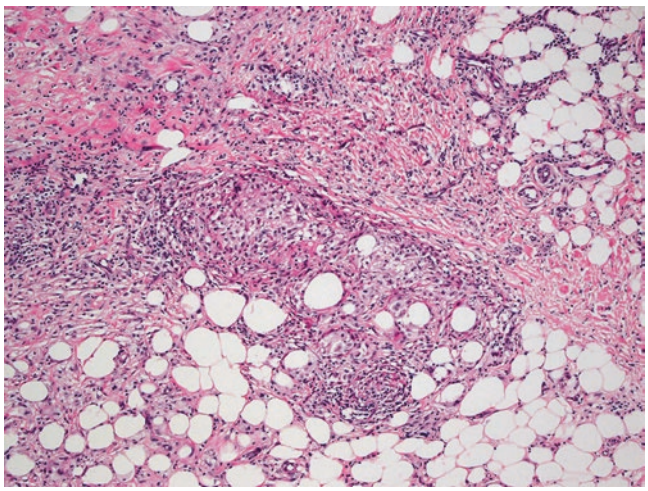

Fig. 9.16 In some cases of erythema induratum, poorly formed granulomas may be observed

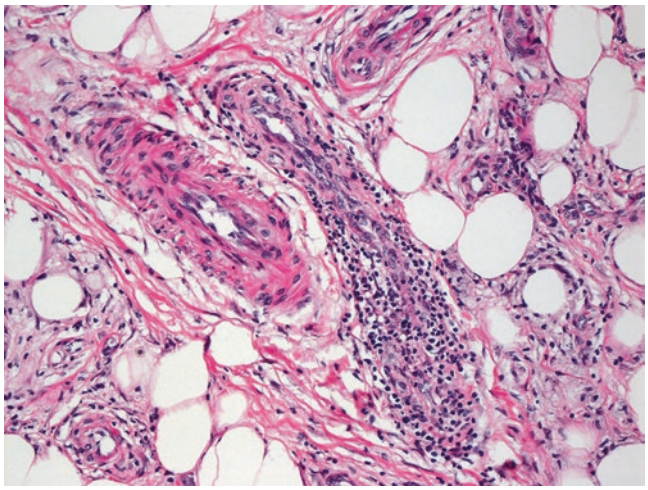

Fig. 9.17 Vasculitis is seen in most cases of erythema induratum

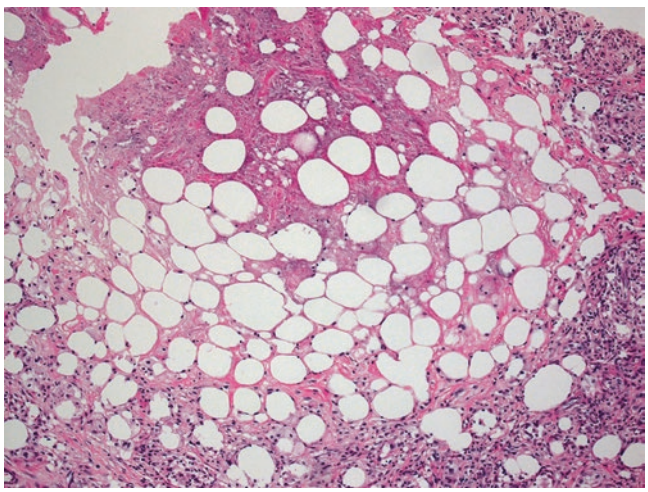

Fig. 9.18 As with most lobular panniculitides, necrosis of the fat lobules can be seen in erythema induratum

erythema induratum. Similarly, vasculitis is not seen in factitial panniculitis. Erythema nodosum, which has granulomas and a mixed inflammatory infiltrate, has a predominantly septal inflammatory pattern whereas the pattern in erythema induratum and nodular vasculitis is predominantly lobular. Leukocytoclastic vasculitis and polyarteritis nodosa may share the vascular changes seen in erythema induratum/nodular vasculitis but they would not be expected to affect the fat lobules to the same extent.

9.8.3 Pathogenesis

Erythema induratum is considered to be a type of tuberculid hypersensitivity reaction to mycobacterial antigens rather than a local mycobacterial infection [67]. More recently, molecular detection by polymerase chain reaction of *Mycobacterium tuberculosis* DNA in tissues of patients with erythema induratum has better established the relationship between erythema induratum and tuberculosis [4, 76, 77]. Patients with tuberculosis-associated erythema induratum have extensive release of cytokines and chemokines, such as interferon-γ, by activated T lymphocytes [4]. Erythema induratum can be associated with other infectious agents, including Nocardia, Pseudomonas, Fusarium, and hepatitis virus [4, 78]. Additionally, changes consistent with erythema induratum can be caused by noninfectious etiologies as well, including superficial thrombophlebitis, hypothyroidism, leukemia, Crohn's disease, and medications such as propylthiouracil [4, 79].

9.9 Lupus Panniculitis

9.9.1 Clinical Features

Lupus panniculitis (also known as lupus profundus) is one of many cutaneous features that may appear in patients with systemic lupus erythematosus. The prevalence of panniculitis in lupus patients is estimated at 3–5 %. It is more common in females and is quite rare in children .

Clinically, lesions present as tender, deep subcutaneous nodules and plaques occurring most often on the shoulders, upper arms, trunk, buttocks, and legs (Fig. 9.19). Facial lesions are more common in children. Main treatment modalities include antimalarials and systemic corticosteroids, as well as other immunosuppressant agents for more severe or refractory cases.

9.9.2 Histology

Some cases of lupus panniculitis may demonstrate changes of cutaneous lupus erythematosus, but in many cases, the changes are restricted mainly to the subcutaneous fat [80–82].

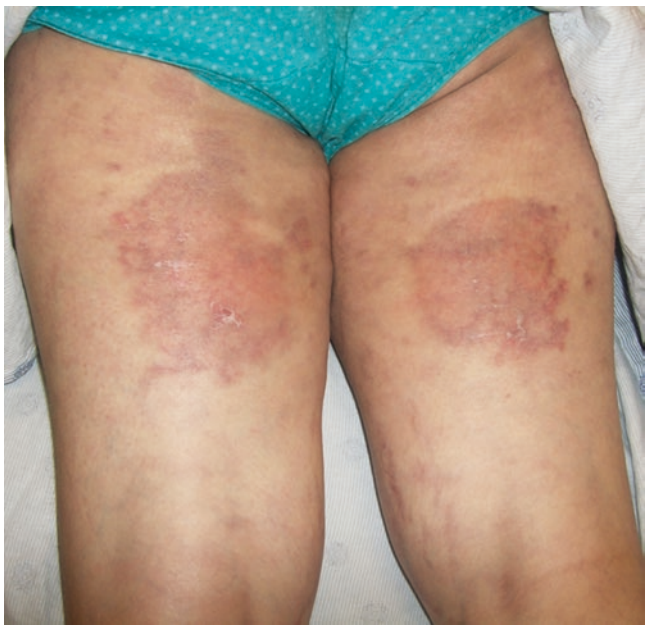

Fig. 9.19 A teenage girl with a known history of systemic lupus erythematosus presents with indurated, slightly ecchymotic subcutaneous plaques on the posterior thighs, characteristic of lupus panniculitis

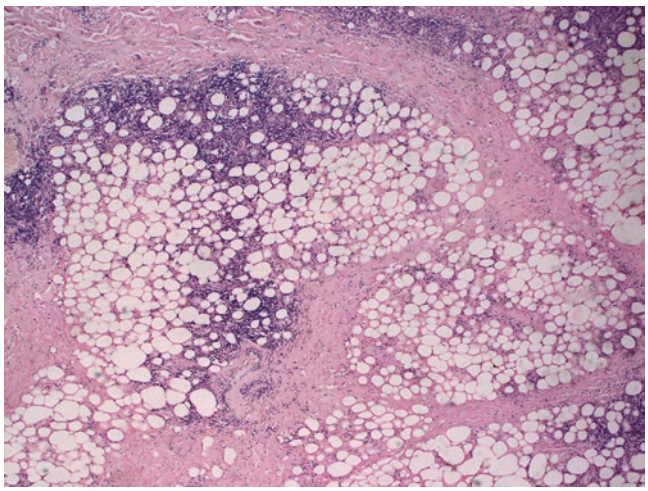

Fig. 9.20 Lupus panniculitis demonstrates a lobular panniculitis with a predominance of lymphocytes in the inflammatory infiltrate

Histologic changes are those of a predominantly lobular panniculitis (Figs. 9.20, 9.21 and 9.22). Inflammation is concentrated around the outer portions of the fat lobules, adjacent to the intervening septa. The inflammatory infiltrate consists of primarily lymphocytes and plasma cells, which is a relatively specific finding. Germinal centers are seen in some cases [83, 84] . A characteristic hyalinization is present within the fat lobules, an observation that is rarely seen except in lupus profundus (Fig. 9.21). Occasional "rimming" of individual adipocytes by lymphocytes is encountered,

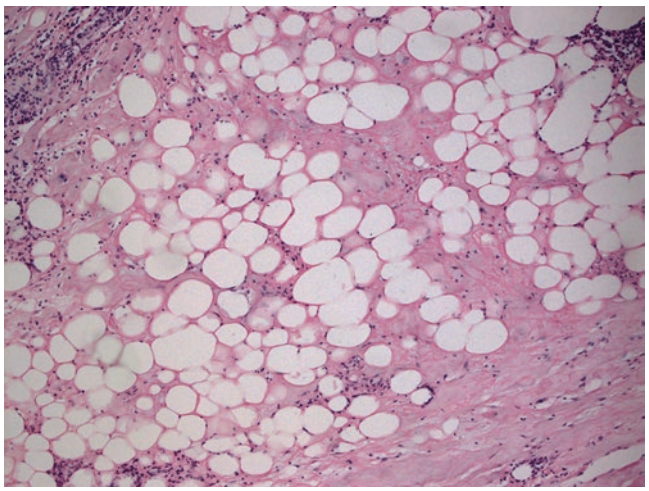

Fig. 9.21 Hyalinization of the fat lobules is a characteristic feature of lupus panniculitis

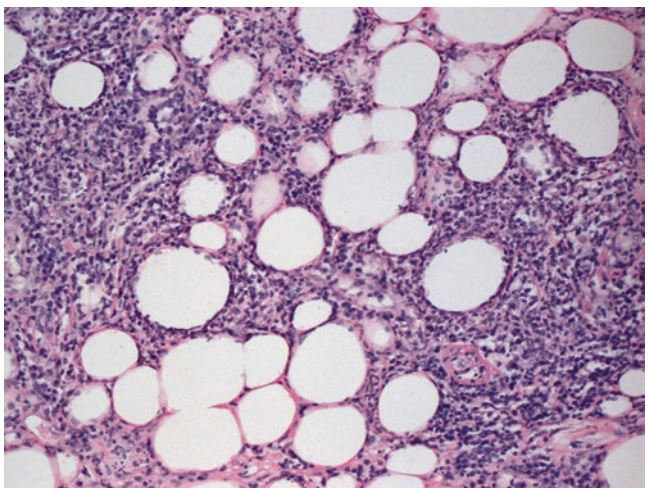

Fig. 9.22 Lupus panniculitis demonstrates a dense infiltrate of lymphocytes with scattered plasma cells

raising the differential diagnosis of subcutaneous panniculitis-like T cell lymphoma. The latter entity can be differentiated on the basis of necrosis, lymphocyte atypia, and T cell-receptor gene rearrangement studies. Some authors have suggested that these two entities may be closely related, or that patients with lupus panniculitis are predisposed towards developing this type of lymphoma [85–87].

9.9.3 Pathogenesis

The pathogenesis of lupus panniculitis is not known, but it likely involves T helper cell-mediated immune response and immune complex deposition, which have been demonstrated in some lesions [88, 89].

9.10 Eosinophilic Fasciitis

9.10.1 Clinical Features

Eosinophilic fasciitis is characterized by fasciitis, peripheral eosinophilia, and progressive induration of the skin and soft tissues. Eosinophilic fasciitis tends to occur mainly in young males, and it is rare in females and children. Clinically, eosinophilic fasciitis presents with redness and progressive thickening or hardening of the skin. The upper extremities are often involved. Children with eosinophilic fasciitis usually respond quite well to high-dose systemic steroids, although other immunosuppressants and immunomodulators have also been used successfully.

9.10.2 Histology

Eosinophilic fasciitis is characterized by thickening of collagen bundles in the fascia deep to the subcutaneous fat [90–92]. In early cases, edema is present and is followed by increasingly progressive fibrosis. The inflammatory infiltrate is diffuse and contains lymphocytes, plasma cells, and, despite the name, relatively few eosinophils [93]. Increased fibrosis extends upwards into the fibrous septa between the fat lobules and downwards into the underlying muscle [91]. In most cases, the overlying epidermis and dermis are uninvolved. In rare cases, dermal features of morphea or scleroderma coexist [94]. A similar histologic appearance developed in some patients taking L-tryptophan preparations, but once the offending impurity and disease association were detected, these cases are no longer seen [95].

9.10.3 Pathogenesis

Eosinophilic fasciitis may be triggered by infections, hematological and autoimmune diseases, as well as drugs, such as simvastatin and phenytoin [92, 96]. Muscle trauma is also implicated as 30–46 % of patients with eosinophilic fasciitis have a history of extreme physical exertion or trauma prior to disease onset [96, 97].

Dysregulated immune response with hypergammaglobulinemia and deposition of IgG and C3 in the affected fascia in some patients is believed to be a cause of eosinophilic fasciitis [96, 98]. Infiltrating eosinophils in the fascia contribute to tissue injury by releasing granules that trigger an aberrant immune reaction. Eosinophil activation and degranulation of products, such as eosinophil-derived neurotoxin, may contribute to the development of pathologic fascia fibrosis [99]. In addition, fibroblasts produce excess collagen and are a chemoattractant for eosinophils. CD8+ cytotoxic T lymphocytes containing granzyme B are present in the fascia and muscles of patients with eosinophilic fasciitis, suggesting a role of cytotoxic cellular immune response in the disease process [100]. Increased serum levels of soluble CD40 ligand (sCD40L) are present in eosinophilic fasciitis, and may be a potential marker of disease activity [101]. Additionally, the levels of matrix metalloproteinase-13 (MMP-13), which is a collagenase involved in extracellular matrix remodeling, is reduced, whereas the levels of tissue inhibitor of metalloproteinase-1 (TIMP-1) is increased in eosinophilic fasciitis patients [102]. These findings point to an imbalance between protease activity and protease inhibition that results in the tissue injury and fibrosis seen in this disorder.

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Inflammatory Disorders of the Cutaneous Appendages

10

10.1 Miliaria

10.1.1 Clinical Features

Miliaria (prickly heat) is the cutaneous manifestation of occlusion of eccrine sweat glands and may occur in up to 15 % of newborns [1]. Predisposing factors include warm, humid environments, fever and excessive bundling.

Lesions tend to occur in areas of the body that are occluded, such as the torso, but may occur on the forehead and cheeks as well. The palms or soles are rarely affected [1]. Patients present with monomorphic, erythematous papules, pustules or vesicles, some of which may have associated induration with morphology dependent upon the level of obstruction within the eccrine unit (Fig. 10.1). Miliaria typically resolves within hours to days following removal of the exacerbating condition. No residual dyschromia or other cutaneous sequelae are expected.

10.1.2 Histology

Miliaria represents a spectrum of eruptions that are characterized by disruption of the eccrine ducts at various points throughout the outflow tract with extravasation of secretions. Histologically, the site of disruption results in slightly different histologic patterns.

Miliaria crystallina is a form of the condition in which the disruption in the sweat duct is closest to the surface of the skin. In this condition, secretion is present at the level of the acrosyringia within the stratum corneum, resulting in intracorneal fluid collections and focal epidermal spongiosis. Inflammation is usually minimal, and it is believed to be a secondary part of the process (Fig. 10.2). Neutrophils are the predominant type of inflammatory cells present (Fig. 10.3) [2, 3].

Miliaria rubra is a variant in which the leakage of secretion occurs in the intraepidermal portion of the eccrine ducts. Secretion is present within the epidermis resulting in marked spongiosis. Inflammation is usually not striking (Fig. 10.4) [4].

Miliaria profunda is the most deep-seated variant of the entity with leakage of secretion occurring within the dermis. A lymphocytic inflammatory infiltrate may be present in some cases. In rare cases, large areas with miliaria profunda may present as dermal plaques and histologic findings demonstrate a granulomatous reaction to the extravasated eccrine secretions [5, 6].

10.1.3 Pathogenesis

Miliaria is caused by occlusion of the sweat duct with extravasation of sweat into the surrounding tissue as well as increased bacterial colonization and subsequent inflammatory reaction [4, 7–9]. Clinical variants include miliaria crystallina, miliaria rubra, and miliaria profunda, and the variant depends on the anatomic location of obstruction in the eccrine duct.

10.2 Erythema Toxicum Neonatorum

10.2.1 Clinical Features

Erythema toxicum neonatorum is common, reportedly occurring in 50–70 % of full-term infants [1]. It appears to have a much lower incidence in preterm and low birth weight newborns. Only 5 % of cases are congenital with most lesions occurring within the first 24–48 hours of life.

Physical exam is characterized by erythematous wheals, papules, pustules, and macules with predilection for the face, torso, proximal extremities, and buttocks. Lesions rarely occur on the palms or soles. The eruption may wax and wane with individual lesions lasting anywhere from a few hours to days. The disease is a self-limited process and typically resolves within 1 week of life with no residual changes in the skin [1].

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Fig. 10.1 Miliaria crystallina is characterized by non-follicular-based skin-colored papules and vesicles on the upper torso of a child

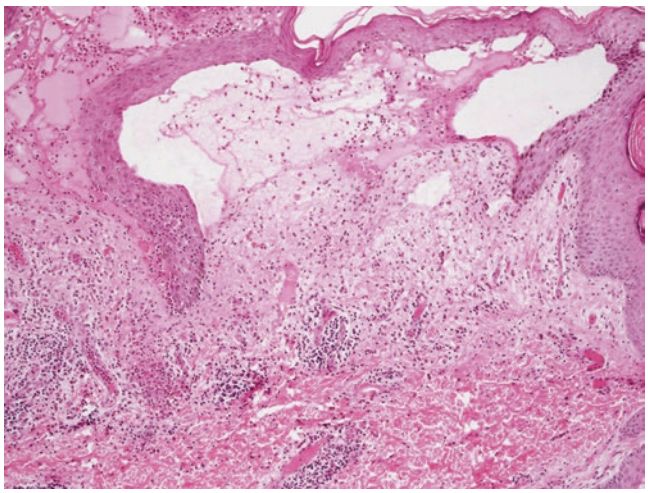

Fig. 10.2 Areas of papillary dermal edema and a mixed inflammatory infiltrate are seen in miliaria crystallina

10.2.2 Histology

Erythema toxicum neonatorum is characterized by subcorneal or intraepidermal pustules of eosinophils and marked inflammation within the pilosebaceous unit, usually at a level just deep to the dermal-epidermal junction [10, 11]. The inflammatory response may also be present in the surrounding dermis. A scant perivascular inflammatory infiltrate with scattered eosinophils is present in the dermis in some cases.

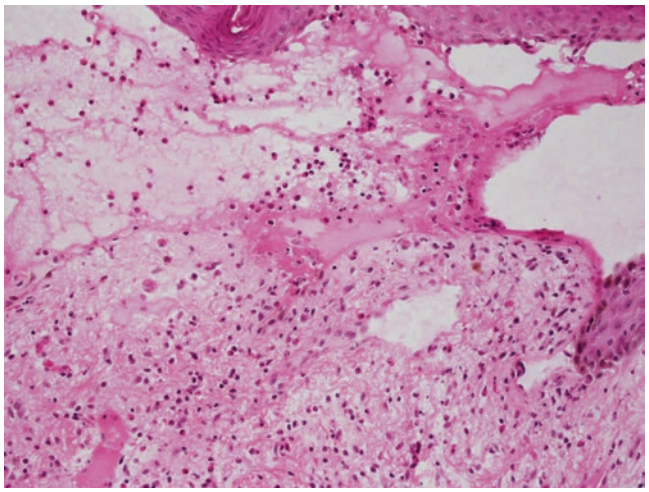

Fig. 10.3 Neutrophils and eosinophils accompany lymphocytes in the inflammatory infiltrate seen in miliaria crystallina

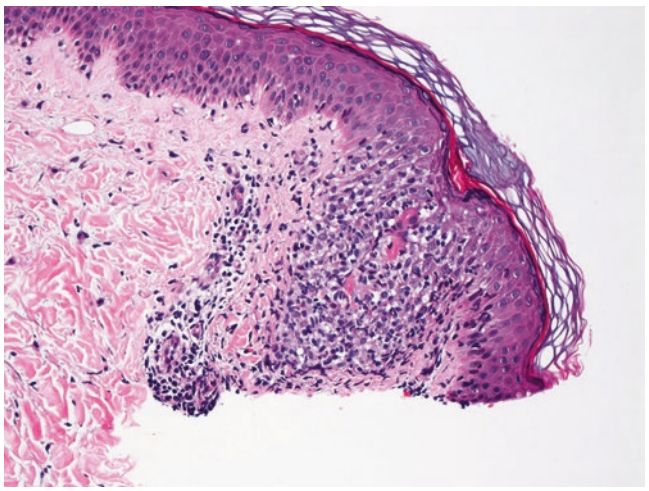

Fig. 10.4 Miliaria rubra demonstrates spongiosis within the epidermis surrounding an acrosyringium

Some authors have suggested that erythema toxicum neonatorum may be closely related to transient neonatal pustular melanosis [12, 13].

10.2.3 Pathogenesis

Erythema toxicum neonatorum may represent a type of cutaneous immunological response to microbial colonization of the hair follicles in the first few days of life of the newborn. A number of proinflammatory molecules have been identified, including interleukin-1 (IL-1), IL-8, eotaxin, aquaporin, psoriasin, and nitric oxide synthase [14]. Other etiologies have been proposed, including the presence of enterotoxins in the newborn, allergic response to transplacental allergens, and response to external stimuli [14, 15].

10.3 Milium

10.3.1 Clinical Features

Milia can be subcategorized into primary and secondary variants with the latter occurring in response to trauma, while the former is idiopathic [16]. Milia are frequently seen in infancy, occurring in 40–50 % of term neonates with delayed onset or lower incidence in premature infants [16]. Primary milia also are seen in children and adults, although lesion distribution on clinical exam varies from that of infantile onset. No racial or gender predilection exists in any studied age group.

Classically, milia are described as 1–2 mm, smooth surfaced white papules. In infants, milia present on the central face, scalp, upper trunk, and upper extremities [16]. In children and adults, milia are more commonly found on the eyelids, cheeks, forehead, and genitalia. Atypical variants exist, including milia en plaque, multiple eruptive milia, and nodular grouped milia. Milia are self-resolving and usually abate within several weeks to months. Treatment is typically not required, but cyst evacuation can be performed easily.

10.3.2 Histology

It is generally believed that primary milia arise from the pilosebaceous units and secondary milia arise from the eccrine ducts [16, 17]. The histologic features can be used to delineate the nature of the milia. Primary milia resemble very small infundibular follicular cysts. Small cystic dilatations are lined by epidermis containing a granular layer and are filled with keratin. These tend to occur in the region of the insertion of the sebaceous ducts into the pilosebaceous units [16]. Secondary milia are also cystically dilated spaces, but the cystic cavities are lined by ductal epithelium. Serial sectioning demonstrates connections to eccrine ducts in most cases [18].

10.4 Acne Neonatorum

10.4.1 Clinical Features

Acne neonatorum is thought to occur in ~20 % of healthy infants. Lesions may be present at birth, but they usually occur within the first 2 weeks to 2 months of life [1]. Male infants appear to be more commonly affected than female infants [19]. Neonatal cephalic pustulosis is thought to be a subset of acne neonatorum seen in the first few months of life. It is likely to be an inflammatory response to skin colonization by pityrosporum yeast (Malassezia species) [1].

In acne neonatorum and neonatal cephalic pustulosis, the primary lesion is an erythematous papule or pustule with multiple lesions scattered on the face, scalp, and neck (Fig. 10.5). In acne neonatorum, while papules and pustules may be seen, comedones (open and closed) and cystic nodules are present as well. Lesions are typically localized to the face. Acne neonatorum and neonatal cephalic pustulosis usually resolve spontaneously within months, and they do not require medical therapy. However, acne neonatorum can be more persistent and inflammatory, predisposing patients to scarring. Hence, a subset of these patients may benefit from treatment.

Fig. 10.5 Erythematous papules and skin-colored comedones on the central face of a child with acne neonatorum (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

10.4.2 Histology

Histologic findings in acne neonatorum are indistinguishable from acne vulgaris, and the entity is defined solely upon the clinical presentation. Changes include dilatation of follicular ostia, keratin plugs, and variable amounts of perifollicular lymphohistiocytic inflammation. Sebaceous hyperplasia has been described. In more florid cases with rupture of the pilosebaceous units, the perifollicular infiltrate may be granulomatous [20].

10.4.3 Pathogenesis

Acne neonatorum often occurs during the first few weeks of life. Sebaceous hyperplasia is present in the lesions, and this is thought to be secondary to the effects of maternal hormones and infant androgens on the neonate's sebaceous glands [21]. There is a strong male predominance in acne neonatorum. Neonatal adrenal glands are hyperactive, pro-

ducing β-hydroxysteroids and particularly in male infants, there is also production of luteinizing hormone and testosterone [20, 22–24]. Sebaceous glands in acne neonatorum are hypertrophic with increased hydroxysteroid dehydrogenase activity and sebum production, similar to sebaceous changes in puberty [20]. *Pityrosporum ovale* has been identified in neonatal cephalic pustulosis, suggesting a possible infectious factor in the pathogenesis of acne neonatorum [25].

10.5 Acne Vulgaris

10.5.1 Clinical Features

Acne affects 85 % of young adults between 12 and 24 years old [26]. People of all ethnicities and racial backgrounds are affected. Symptoms correlate best with pubertal age. The disease is seen infrequently in children from 1 to 7 years old and less commonly in older adults.

The comedo is the primary lesion of acne vulgaris, but affected individuals can have a mixed eruption of comedones with erythematous papules, pustules, and cystic nodules, primarily occurring on the face, chest, and back. Dyschromia and scarring are sequelae seen in response to more inflammatory disease. Severity of acne vulgaris is graded and determined by the type and number of lesions present as well as the distribution of lesions (Fig. 10.6).

Acne conglobata represents a severe suppurative variant of acne vulgaris. It is seen more often in males between 18 and 30 years of age and in those of African descent [26]. Patients with acne conglobata universally present with painful cystic nodules on the face, chest, and back that heal with hypertrophic scarring. In acne fulminans, patients have acne as well as systemic complaints of fever, malaise, and arthralgia. Acne conglobata and acne fulminans are often refractory to treatment and have greater associated morbidity. These variants can be a feature of other systemic inflammatory conditions, such as SAPHO syndrome (Synovitis, Arthritis, Acne, Pustulosis, Hyperostosis, Osteitis).

Approximately 15–20 % of affected individuals have moderate to severe disease with 12 % of females and 3 % of males having persistence of disease into adulthood [26, 27].

10.5.2 Histology

The changes of acne vulgaris include sebaceous hyperplasia and varying degrees of inflammation within and around the pilosebaceous units. Mild cases may demonstrate only a scant lymphohistiocytic infiltrate at the level of the follicular infundibulum with focal follicular spongiosis. More florid cases will show comedones with cystic dilatation of the follicular ostia with keratin plugging (Figs. 10.7 and 10.8). Neutrophilic abscesses can be found within follicular outflow tracts or in the adjacent dermis. Follicular plugging can result in the development of follicular cysts, and in some cases accompanied by marked inflammation. In more extensive cases, there may be disruption of the follicular epithelia, extrusion of keratin into the dermis, and marked inflammation. A granulomatous response with multinucleated giant cells and abundant histiocytes is not unusual in these cases.

The histologic findings in *acne conglobata* are shared with those seen in other conditions including hidradenitis suppurativa. There is marked follicular plugging resulting in multiple follicular cysts that can be quite large (Fig. 10.9).

Fig. 10.6 Multiple erythematous papules, pustules, and cystic nodules admixed with atrophic scars are seen in a teenage boy with acne conglobata

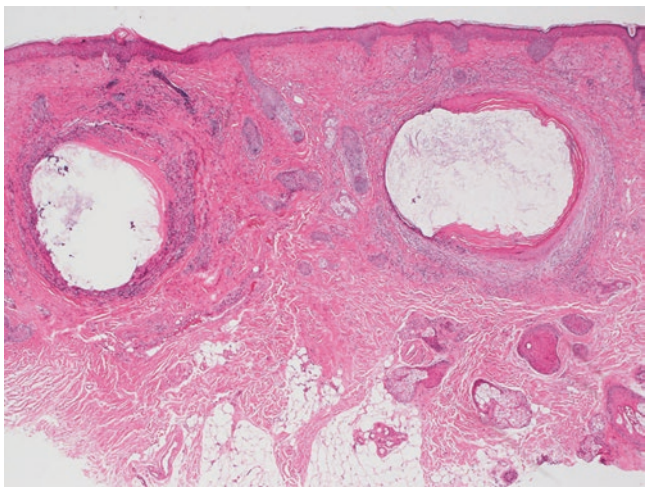

Fig. 10.7 Dilated keratin-filled follicles are surrounded by an inflammatory infiltrate in acne vulgaris

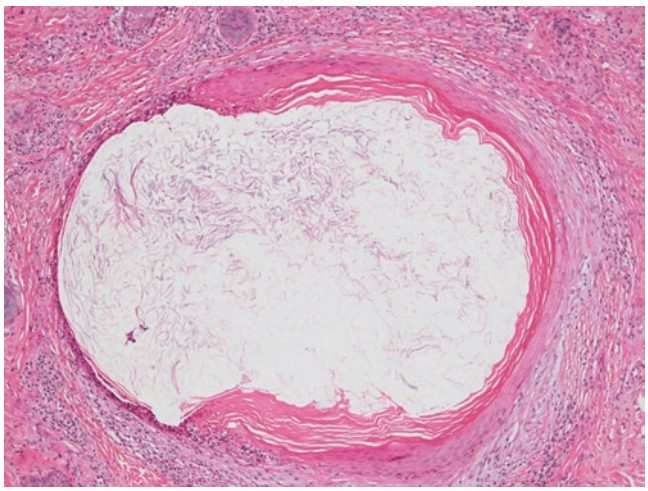

Fig. 10.8 Keratin fills a cystically dilated hair follicle in a comedone in acne vulgaris

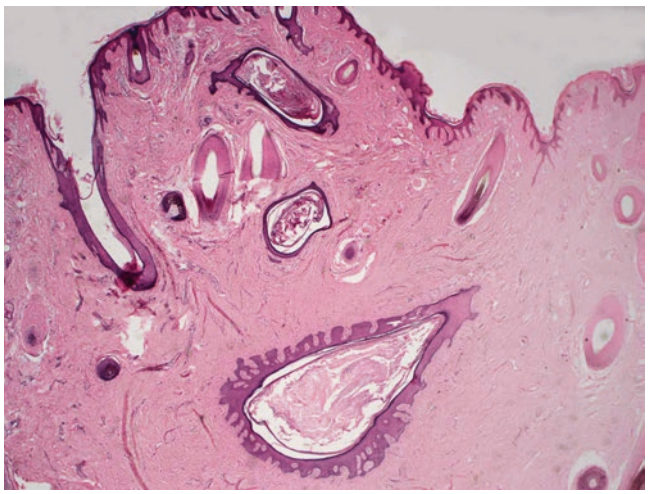

Fig. 10.10 Abundant pilosebaceous units are disrupted and surrounded by dense scarring throughout the dermis in acne conglobata

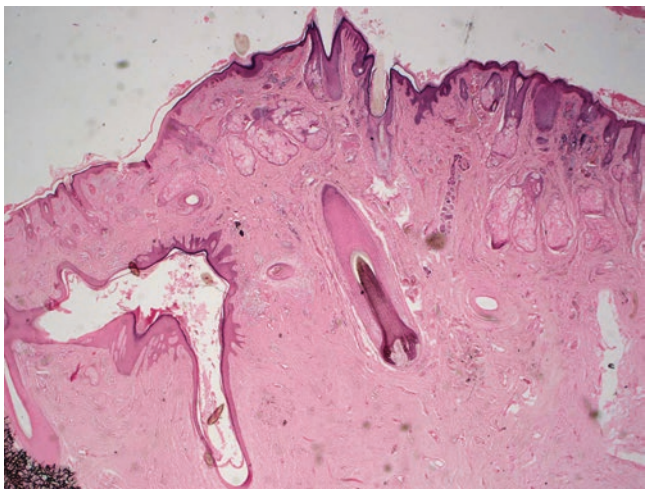

Fig. 10.9 Acne conglobata shows marked distortion of pilosebaceous units with dense scar formation

These cysts are surrounded by dense inflammation including lymphocytes, neutrophils, and often granulomas with abundant multinucleated giant cells. As a result of repeated rupture of follicular cysts, there is extensive dermal scarring and even sinus tract formation (Fig. 10.10).

10.5.3 Pathogenesis

Comedone formation can be induced by *Propionibacterium acnes* overgrowth, hormones (androgens), and lipid composition in sebocytes as well as local cytokines [28, 29]. *P. acnes* are gram-positive anaerobic bacteria that reside in the hair follicles in the skin with resultant sebum accumulation and follicular rupture due to bacterial proliferation and associated local inflammatory reaction [28, 30]. The inflammatory response is a major mechanism behind acne vulgaris. Interleukin-1α (IL-1α) is an important cytokine for comedone formation by increasing sebum production and decreasing linoleic acid (which is important in skin barrier function) [31, 32]. *P. acnes* can induce IL-1α production [28, 33]. Blockade of IL-1α receptor results in the inhibition of follicular hyperkeratinization. Hyperkeratinization and plugging of the follicular infundibulum form comedones, which are the initial lesions of acne vulgaris.

The composition of sebum lipids produced by sebaceous glands can influence inflammation in acne vulgaris. Sebum typically consists of lipids and cholesterols (triglycerides, free fatty acids, wax esters, squalenes, cholesterol, and cholesterol esters) [34]. Changes in the composition of sebum have been associated with follicular hypercornification and acne formation [35, 36]. Lipid peroxidation products can promote inflammatory cytokines (such as IL-1α) and recruitment of inflammatory cells [37]. Sebum lipids also promote the growth of *P. acnes*, and lipases produced by *P. acnes* hydrolyze triglycerides into pro-inflammatory free fatty acids [38]. Recent studies have indicated that peroxisome proliferator-activated receptor-γ (PPAR-γ) may serve a protective role in acne vulgaris by preventing excessive accumulation of lipids in sebaceous glands [39].

Acne conglobata is a highly inflammatory form of acne. It is a chronic inflammatory disease with occlusion of the hair follicles [40]. *Propionibacterium acnes* stimulates keratinocytes to produce IL-1α and tumor necrosis factor (TNF)-α [41, 42]. These pro-inflammatory cytokines are important in the pathogenesis of acne conglobata. TNF-α antagonists have been used in the treatment of acne conglobata [42]. Other studies have revealed additional important factors, such as the modulation of toll-like receptor-4 (TLR4) as a new therapeutic option for severe forms of acne conglobata [43].

10.6 Drug-Induced Acne

10.6.1 Clinical Features

Drug-induced acne (acne medicamentosa) is thought to occur following exposure to systemic glucocorticoids, but it has been associated with a number of other medications, including halogenated compounds, antiepileptic drugs (phenytoin, carbamazepine, and gabapentin), antidepressants (lithium), antitubercular drugs (isoniazid), growth hormone, cyclosporine, contraceptives (medroxyprogesterone), and anabolic steroids (danazol, and testosterone) [44]. A number of chemotherapies have been associated with acneiform eruptions as well, most notably epidermal growth factor-receptor (EGFR) inhibitors and other inhibitors of oncogenic pathways (RAS/RAF/MEK/ERK) [44]. The acneiform eruptions in these cases appear to be dose-dependent and occur almost universally in patients receiving the medication.

Acneiform eruptions secondary to drug exposure frequently are monomorphic with follicular-based papules and papulopustules at the trunk and proximal arms, and comedones are infrequently seen, thus distinguishing this variant of drug eruption from acne vulgaris (Fig. 10.11). In chemotherapy-associated acne, lesions tend to occur within the first 2 to 4 weeks of therapy [44]. Pruritus is a frequent complaint, and more lesions are seen on the head and neck in addition to the upper trunk. These lesions frequently resolve once the inciting agent is removed.

10.6.2 Histology

The histologic changes in drug-induced acne cannot be readily distinguished from those occurring in acne vulgaris. Some authors describe a predominance of a neutrophilic infiltrate in steroid-induced acne [45], but neutrophils are also prominent in many cases of acne vulgaris. Clinical presentation is the best way to make this distinction.

10.6.3 Pathogenesis

A number of drugs can induce acne formation. However, the mechanism of drug-induced acne is not known. Steroids, such as glucocorticoids, can induce toll-like receptor-2 (TLR-2) expression in human keratinocytes. *Propionibacterium acnes* and hormones, such as androgenic or anabolic steroids and estrogen, can induce acne [46–48]. Immunosuppressants, anticonvulsant medications and psychotropic drugs can also cause acne [47].

10.7 Acne Rosacea

10.7.1 Clinical Features

Rosacea sometimes occurs in children, but it more commonly affects men and women over 30 years old [44]. Rosacea is distinguished from acne vulgaris based upon the absence of comedones. Patients typically present with erythematous papules, pustules, and cystic nodules on the central face (Fig. 10.12). Additional presentations in childhood rosacea include facial flushing and persistent telangiectasias, as well as ophthalmologic symptoms, such as blepharitis, meibomianitis, recurrent chalazion (most commonly seen), episcleritis, iritis, and corneal ulceration, neovascularization and scarring [44, 49]. While it appears that cutaneous disease responds well to medical therapy, associated ophthalmo-

Fig. 10.11 Steroid-induced acne is characterized by monomorphic, erythematous, follicular-based papules primarily localized to the trunk

Fig. 10.12 Acne rosacea in a young adolescent girl with erythematous papules and pustules on the central face

logic symptoms may predispose affected children to irreversible vision impairment if the condition is not recognized and managed appropriately [49].

10.7.2 Histology

Acne rosacea demonstrates a perifollicular lymphohistiocytic infiltrate with spongiosis at the level of the infundibulum (Fig. 10.13). Sebaceous hyperplasia is present in many cases. Florid cases may have a granulomatous inflammatory response to ruptured follicular epithelium (Figs. 10.14 and 10.15).

The major histologic differential diagnosis is lupus erythematosus. The presence of an interface dermatitis, epidermal atrophy, diffuse hyperkeratosis, basement membrane thickening, and dermal mucin may all be seen in lupus erythematosus, and these are not characteristic findings in acne rosacea. A peri-eccrine infiltrate would also favor a diagnosis of lupus erythematosus. However, as these findings are not all present in every case, histologic distinction may be difficult.

Acne vulgaris might also enter the differential diagnosis, and there is great overlap in histologic changes. The presence of marked follicular plugging is more common in acne vulgaris. However, in most cases, clinical presentation is the best way to make this distinction.

10.7.3 Pathogenesis

Rosacea is a chronic inflammatory condition of the facial skin. The pathogenesis of rosacea involves kallikrein 5, a trypsin-like serine protease, which is thought to initiate an augmented inflammatory response in rosacea [50]. Increase in kallikrein 5 results in increased production of the cathelicidin peptide LL-37, which is an antimicrobial peptide that provides innate defense immunity against several microbial organisms. LL-37 stimulates inflammation, vasodilation, and angiogenesis, which are characteristic features of the disorder [50]. Patients with rosacea have high levels of LL-37 in the facial skin, with corresponding increase in kallikrein 5 that cleaves an inactive precursor protein into LL-37, which is a pro-inflammatory and pro-angiogenic peptide [51–54]. Injection of LL-37 peptide fragments into animal skin elicits an inflammatory response similar to rosacea [53]. Agents that inhibit kallikrein 5 and the production of LL-37 peptides, such as azelaic acid and doxycycline, are effective in reducing cutaneous lesions in rosacea [55, 56].

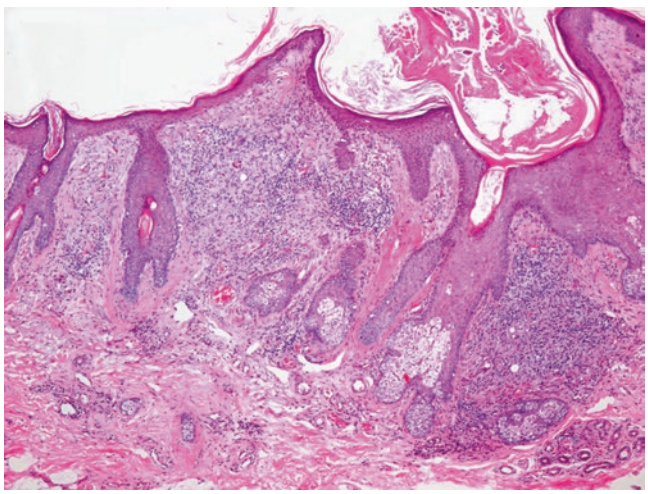

Fig. 10.13 Granulomas with multinucleated giant cells located in the region of pilosebaceous units are characteristic of acne rosacea

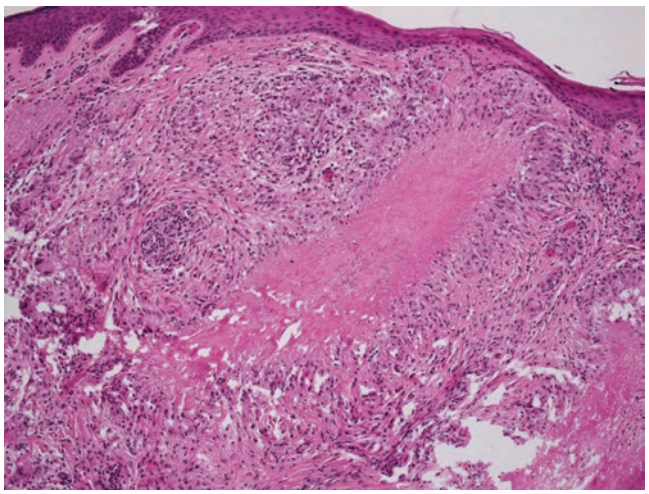

Fig. 10.14 A caseating granuloma is present in acne rosacea

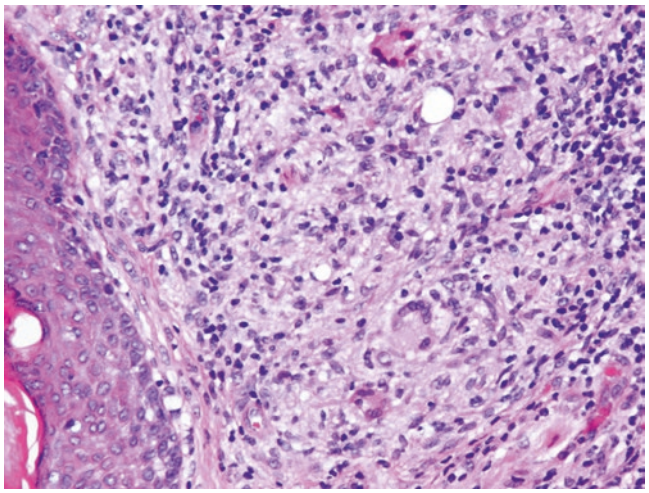

Fig. 10.15 Granulomas adjacent to follicular units are a diagnostic feature of acne rosacea

Toll-like receptors (TLRs) are tightly bound to innate immunity. The expression of TLR2 is increased in rosacea [57]. Through TLR2, the production of serine proteases, such as kallikrein 5, is increased with subsequent increase in LL-37 levels [58, 59]. Ultraviolet (UV) light radiation is a well-known trigger of rosacea. UV light induces the formation of reactive oxygen species (ROS) in skin [60]. The interaction of ROS with TLR2 leads to increased levels of pro-inflammatory chemokines and cytokines that contribute to the pathogenesis of rosacea.

The inflammatory cytokine and chemokine network in rosacea has been under investigation. External and internal trigger factors that induce pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), leads to the recruitment of type 1 T-help cells (Th1) and IL-17-producing T-helper cells (Th17) to facial skin [61]. T lymphocyte-derived cytokines IL-17 and IL-22 can facilitate neutrophil recruitment to the skin. IL-17 promotes angiogenesis by inducing vascular endothelial growth factor (VEGF) and other pro-angiogenic factors. LL-37 can induce the chemokine CXCL8, which is a potent chemo-attractant of neutrophils, leading to the formation of sterile pustules in a mouse model of rosacea [62].

In rosacea, there is dysregulation of the neurovascular/neuroimmune system and the immune response. The neurovascular/neuroimmune system contributes to the pathogenesis of rosacea by enhancing vasodilation of the skin vasculature as well as the associated neurosensory symptoms [63–66]. VEGF may mediate the vascular changes and vascular proliferation that occur in rosacea [59, 67]. Vasoactive intestinal peptide (VIP) receptor (which is increased in skin blood vessels in phymatous rosacea) and substance P (which is a neuropeptide involved in local blood flow regulation) have also been linked to rosacea [68, 69]. Rosacea skin also has lower heat pain threshold than normal skin [59]. Various subtypes of transient receptor potential ion channels of the vanilloid type (TRPV), which are cellular sensors of cold, heat, and pain sensation, may be involved in rosacea. Interestingly, the expression of TRPVs is significantly increased in rosacea [70].

10.8 Fox-Fordyce Disease

10.8.1 Clinical Features

Fox-Fordyce disease (also known as apocrine miliaria) is a chronic pruritic papular eruption of the apocrine gland-bearing areas of the body [71]. It more commonly occurs in post-pubescent females with an age range of 13–35 years of age [71, 72].

On physical exam, patients have pruritic, dome-shaped, skin-colored to erythematous papules primarily at the axillae, mammary areolae, pubis, and gluteal fold [71]. Papules are follicular-based, although non-follicular-based papules secondary to occlusion of apo-eccrine ducts have been reported [71]. The disease may be difficult to manage and may require surgical intervention in patients with more severe presentation and who are refractory to standard topical medications [73].

10.8.2 Histology

Histologic features seen in Fox-Fordyce disease include intraepidermal fluid-filled vesicles within the outflow tracts of apocrine ducts, as well as hyperkeratosis and spongiosis at the infundibular level of the hair follicle, and foamy macrophages [74, 75]. The foamy macrophages are seen in the region immediately surrounding the pilosebaceous unit and may be associated with prior rupture and extravasation of ductal secretions. Hyperkeratosis, follicular dilatation with keratin plugging, focal dyskeratosis, and basal vacuolization along the follicular epithelium have also been described in some cases [74, 76]. In longer standing lesions, perifollicular fibrosis and a surrounding lymphohistiocytic infiltrate are prominent [77].

10.8.3 Pathogenesis

Fox-Fordyce disease in a chronic inflammatory disorder of the skin involving apocrine glands and keratin plugging of the follicular infundibulum at the distal portion of the apocrine sweat duct [71]. Hormonal factors appear to play a role since the disease occurs more commonly in females with 90 % of the cases occurring in individuals between 13 and 35 years of age [78]. Fox-Fordyce disease occurs with the onset of puberty, flares up during menstrual periods, and improves during pregnancy, after menopause, and with use of oral contraceptives [79]. There are reports of Fox-Fordyce disease in prepubertal girls, suggesting that the cause is probably multifactorial and not solely hormone-based [72]. Obstruction of apocrine ducts with keratin plugs can result in sweat retention and subsequent rupture of the obstructed duct, leading to inflammation [80]. Botulinum toxin type A, which inhibits sweat secretion by causing chemical denervation of cholinergic nerve terminals to eccrine and apocrine glands, has been used successfully to treat refractory disease [81].

10.9 Hidradenitis Suppurativa

10.9.1 Clinical Features

Hidradenitis suppurativa is a chronic condition of the intertriginous skin, now thought to be an obstructive inflammatory process of the hair follicle with subsequent involvement

of the adjacent apocrine glands [82]. Hidradenitis suppurativa is seen almost universally in postpubertal individuals with average age of onset between 20 and 30 years of age [83]. Prevalence rates vary with range up to 4 %, depending upon the population studied [83]. The disease appears to occur more commonly in females. No substantiated racial predilection has been demonstrated consistently. Both smoking and obesity have strong associations with disease occurrence and exacerbation.

Physical exam is notable for double comedones, subcutaneous nodules, and fluctuant cysts at the axillae anogenital regions (inguinal, pubis, perianal, and perineal) and the chest (intra- and infra-mammary breasts) with potential for evolution to sinus tract formation and fibrosis. The axillae are the most commonly affected site, while perianal disease has the greatest associated morbidity [83]. Skin lesions have been reported at the occiput and posterior neck as well [84]. Disease may be graded using the Hurley Staging System (I–III), which is based on number of lesions seen, the presence of tract formation and scarring, and the distribution of affected area.

Hidradenitis suppurativa can be difficult to manage with therapy plans dependent on the chronicity and severity of disease. Notable reported sequelae and disease complications include impaired quality of life (with associated economic, psychosocial, and physical disability), contractures, mucosal strictures, and lymphedema at sites of prolonged inflammation and scarring [83]. Additionally, increased incidence of squamous cell carcinoma and other skin malignancies have been reported in more severely affected individuals.

10.9.2 Histology

Hidradenitis suppurativa in its earliest phase demonstrates an infundibulofolliculitis [85, 86]. Spongiosis and a lymphocytic infiltrate occur secondary to keratin plugs occluding the outflow tracts of hair follicles. It is generally believed that the occlusion of apocrine ducts, and cystic dilation and rupture are secondary events, and occur later in the development of the disease process. The marked inflammation that ensues is secondary, and it is often granulomatous in nature and inevitably leads to scar formation as well as the development of sinus tracts in well-established lesions (Fig. 10.16). Diminished numbers of sebaceous glands have been described in biopsies from patients with hidradenitis suppurativa, but this finding may be secondary to the chronic inflammation and scar formation characteristically extend deep into the subcutaneous fat [87, 88].

Another hypothesis is that there may be two subtypes of hidradenitis suppurativa, one in which the pathogenesis is that described above and another subtype that truly is a primary apocrine hidradenitis [89]. This view of the disease is not currently widely accepted.

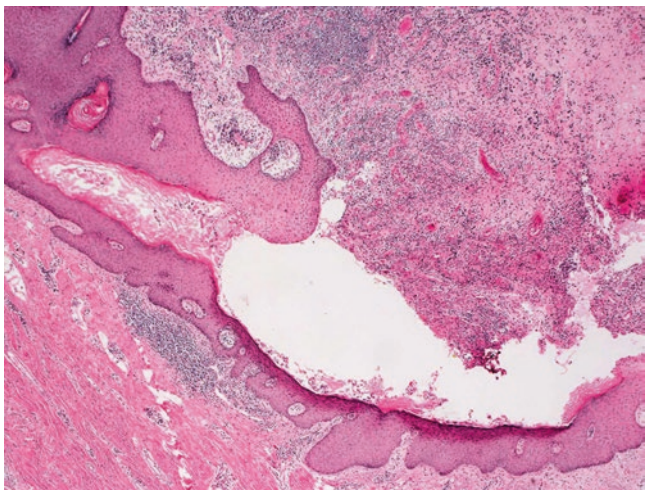

Fig. 10.16 Ruptured pilosebaceous units with abscesses and scar formation are seen in hidradenitis suppurativa

10.9.3 Pathogenesis

Hidradenitis suppurativa is associated with follicular occlusion disorders, including acne conglobata, dissecting cellulitis of the scalp, and pilonidal sinus [90]. Histologic studies suggest that hyperkeratosis of the follicular epithelium may be the initial event in the disease process. The molecular basis of hidradenitis suppurativa involves loss of function mutations in gamma-secretase and defective Notch signaling. Notch signaling is important in the formation of epidermal cysts and in pro-inflammatory processes [91]. Gamma-secretase is a protein complex composed of four subunits encoded by separate genes, namely PSEN1/PSEN2, PSENEN, NCSTN, and APH1A/APH1B [92]. Gamma-secretase regulates Notch signaling by cleaving and activating intracellular Notch [93]. Mutations in the subunits of gamma-secretase have been identified in some patients with hidradenitis suppurativa [94, 95].

Immunological factors also contribute to the etiology of this disease. Increased levels of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-17, have been identified in lesional skin [96, 97]. Bacterial colonization from follicular occlusion, and subsequent infection and inflammatory reaction are also contributing factors [98]. Smoking is another important factor in hidradenitis suppurativa. Patients with hidradenitis suppurativa have higher-than-average smoking rates [99, 100]. Smoking may promote follicular plugging and contribute to inflammation. Androgens and obesity may also play a role in this disease [101].

10.10 Alopecia Areata

10.10.1 Clinical Features

Alopecia areata may affect up to 0.2 % of the general population in the United States with a lifetime risk of 1.7 % [102]. Approximately 60 % of patients will have their first episode of hair loss before their 20th birthday with pediatric cases accounting for 20 % of the affected population [102]. Alopecia areata affects all races and ethnicities, and appears to have no gender predilection. Twenty percent of patients have a positive family history of disease [103].

The most commonly encountered phenotype is "patchy alopecia areata," which is characterized by onset of asymptomatic, well-circumscribed, round to oval patches of non-scarring alopecia without scaling and occasional overlying subtly colored erythema (Figs. 10.17 and 10.18). Alopecia areata totalis is a subtype with complete loss of hair at the scalp, while alopecia areata universalis describes complete hair loss at the scalp and body. Ophiasis is a variant that portends a worse prognosis with hair loss in a band distribution along the periphery of the scalp. Diffuse and total alopecia areata is a newly-described entity with rapid onset of complete hair loss at the scalp over a 3-month period and eventual recovery of hair over 6 months [102].

Alopecia areata frequently waxes and wanes with most patients experiencing more than one episode of hair loss. However, approximately 50 % of patients with alopecia areata will have regrowth of hair and remission of disease within a year of onset [102]. Conversely, 5 % of affected individuals will have more severe disease with eventual progression to alopecia totalis or universalis. Patients with more generalized hair loss (alopecia totalis or universalis) have less than a 10 % chance of full recovery and hair growth [102]. Poor prognostic factors include the extent of hair loss at presentation, longer duration of hair loss, atopy, positive family history of disease, presence of other autoimmune diseases, nail involvement, and younger age at disease onset.

Fig. 10.17 Alopecia areata is characterized by well-demarcated patches of non-scarring alopecia

Fig. 10.18 Exclamation point hairs in alopecia areata

10.10.2 Histology

Most dermatopathologists view horizontal or transverse sectioning (Headington method) to be the optimal way to analyze alopecia biopsies, but others prefer the traditional vertical sectioning technique [104, 105]. Using either method, the histologic findings are the same, but are seen from different angles. A peri-bulbar and intrabulbar lymphohistiocytic infiltrate that is relatively mild is the commonest observation in early lesions (Fig. 10.19) [104]. Scattered eosinophils may be present in nearly half of all cases [106]. As lesions progress, there is a diminution in the size of hair follicles and a shift towards more telogen and catagen (best

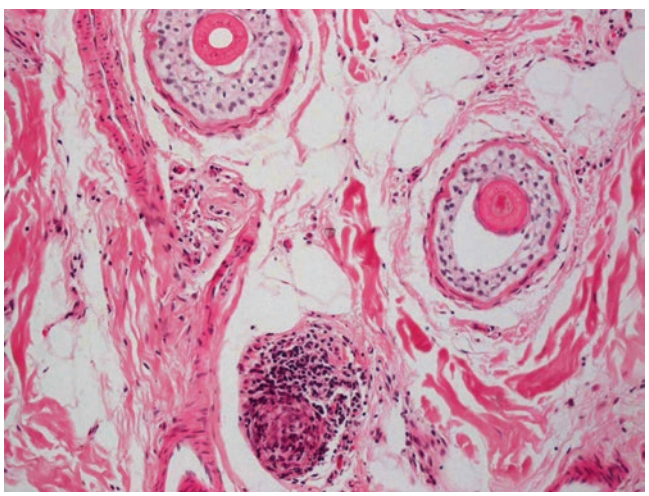

Fig. 10.19 The presence of a peri-bulbar lymphocytic infiltrate is a strong diagnostic criterion in alopecia areata

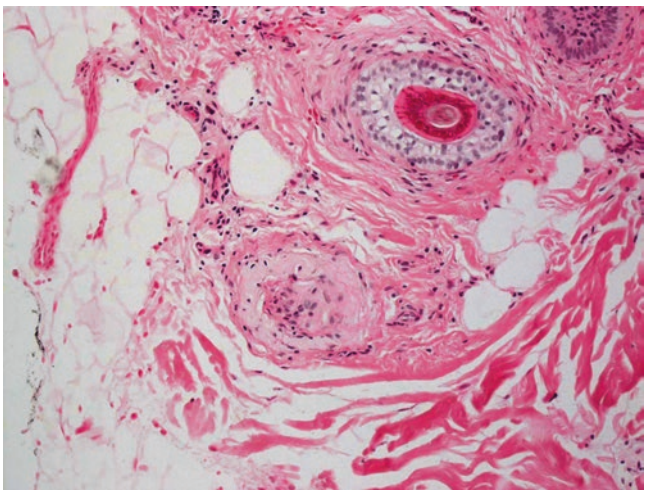

Fig. 10.20 Fibrous tracts representing residuum from follicles in catagen and telogen phase are seen with increased frequency in alopecia areata

regarded as non-anagen) phase hairs [106, 107]. Fibrous tracts or "streamers" are often present in the deep dermis, representing hairs that have shifted towards an involution phase (Fig. 10.20). In these cases, pigment incontinence with melanin in melanophages is seen in and around the follicular bulbs. Pigment casts are also commonly encountered [106]. Increased numbers of vellus-like hairs are present in the subacute and chronic stages of alopecia areata [104]. There is no change in the density of pilosebaceous units, and no scarring or architectural alteration within the dermis.

Alopecia areata incognito is a variant of alopecia areata with a more diffuse pattern of hair loss. In these cases, there is no scarring, as is manifest in the normal density of pilosebaceous units. As in the more traditional variant of this condition, there is an increase in percentage of telogen phase hairs and increased vellus hairs. Follicular dilation is also described in this variant, while this is less commonly observed in the usual cases of alopecia areata [108].

10.10.3 Pathogenesis

The pathogenesis of alopecia areata has genetic and autoimmune contributions that are further modified by unknown environmental influences. There is a positive family history in 10–25 % of the cases of alopecia areata [109–111]. Monozygotic twins have a higher concordance rate (42 %) than heterozygotic twins (10 %) [111]. In a large study of 1054 patients and 3278 controls, 139 single-nucleotide polymorphisms (SNPs) related to the development of alopecia areata were identified [112]. From these findings, eight genes were found to be highly correlated with disease risk. Some of the disease "susceptibility loci" appear to be important in autoimmune diseases, such as type 1 diabetes and rheumatoid arthritis.

Alopecia areata is a T lymphocyte-mediated autoimmune disease. CD8-positive T cells play a key role in disease pathogenesis [113, 114]. In alopecia areata, the hair follicles are primarily affected. There are autoreactive CD8-positive T cells present in the peribulbar region as well as in the follicular epithelium of the hair follicles, where T cells are thought to recognize auto-antigens presented by major histocompatibility complex class I [115]. The nature of the auto-antigens is not known. Attempts have been made to identify alopecia areata-specific intralesional CD8-positive T lymphocytes that might be the basis for specific immunotherapy [116].

10.11 Telogen Effluvium

10.11.1 Clinical Features

Telogen effluvium is a relatively common cause of hair loss, often occurring 3 to 6 months following an inciting event (typically life stressor, such as pregnancy, hospitalization, pronounced illness, or family death). The exact incidence is unknown [117]. Telogen effluvium is characterized by the relatively rapid onset of diffuse non-scarring, thinning of the scalp hair, including along the bi-temporal scalp (Fig. 10.21). Most patients do well with regrowth of hair within 6 to 12 months.

10.11.2 Histology

Histologic changes in telogen effluvium are subtle and most easily observed using horizontal sections to evaluate a larger

Fig. 10.21 Telogen effluvium is characterized by generalized hair shedding with clinically apparent decreased hair density

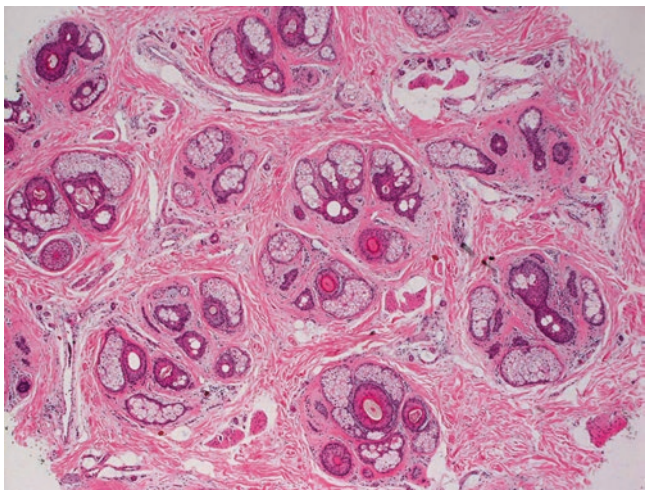

Fig. 10.22 Telogen effluvium is characterized by minimal inflammation and preservation of the pilosebaceous architecture with no scarring

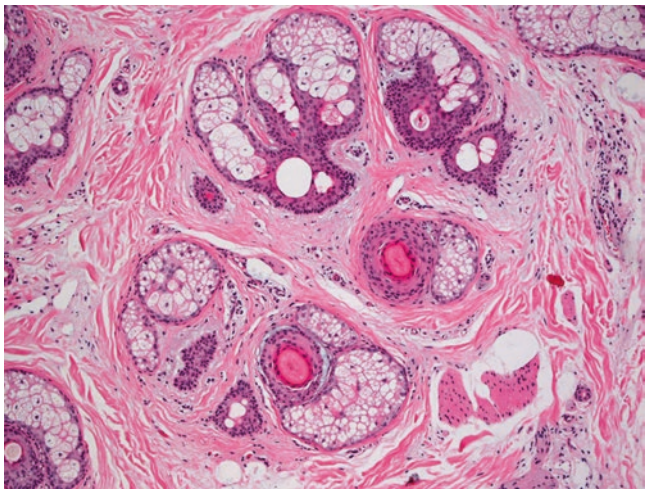

Fig. 10.23 An increased percentage of hair follicles are present in the telogen phase in telogen effluvium

number of hair follicles. The major finding is a phase shift with a disproportionate number of follicles in catagen or telogen phase, and a smaller number in anagen phase (Figs. 10.22 and 10.23). This shift is relatively slight and perhaps as many as 20 % (or double the normal number) of follicles will be non-anagen hairs. Due to this phase shift, biopsies demonstrate an increased number of fibrous tracts in the deepest portion of the dermis. Inflammation is rarely a feature of telogen effluvium and scar formation is not seen in this entity [118].

10.11.3 Pathogenesis

Telogen effluvium is a non-scarring alopecia, in which there is diffuse shedding of telogen hair [119, 120]. To establish the cause of telogen effluvium, relevant history and appropriate diagnostic studies to assess the endocrine and nutritional status, as well as potential autoimmune disorders of the patient are necessary. Hair follicles can shift from anagen (active proliferating phase) to telogen (resting phase) when exposed to stressors, such as infections, systemic illness, surgery, medication, and nutritional deficiency (such as proteins, iron, zinc, and essential fatty acids deficiencies) [117]. Iron deficiency appears to be important in telogen effluvium, because loss of iron reduces the proliferation of matrix cells. Iron deficiency without anemia is seen in 20 % of cases, and the only test indication is serum ferritin below 20 mg/l [121]. Changes in thyroid function, such as decreased thyroid hormone levels, can also result in telogen effluvium.

Telogen effluvium might be due to problems in hair cycle synchronization with shortening of the anagen phase. It has been proposed that hair follicles cycle to anagen phase within a few days, instead of staying in telogen phase for months as would be for normal hair [122]. Other studies also lend support to this "immediate telogen release" mechanism [123].

10.12 Anagen Effluvium

10.12.1 Clinical Features

Anagen effluvium is rapid loss of all terminal hairs in the anagen phase of hair growth. This condition most commonly occurs in patients receiving radiation or chemotherapy with incidence of about 65 % in chemotherapy patients [124]. There are reports of anagen effluvium following exposure to colchicine, boric acid, lead, thallium, arsenic, bismuth, and Coumadin [125]. The degree of hair thinning and subsequent hair loss is dependent upon exposure to the causative agent. Segmental thinning and narrowing may occur with low dose-exposure with hair pull tests yielding tapered "pencil point" hairs. Hair usually regrows once the causative agent is removed [124, 125].

10.12.2 Histology

The diagnosis of anagen effluvium is almost always made based upon clinical impressions and biopsies are rarely necessary in patients suffering from this condition. Cross-sectional analysis of skin biopsies reveals a non-scarring and noninflammatory process with normal number of anagen phase follicles, often lacking in hairs. There are no histomorphologic changes in the pilosebaceous units.

10.12.3 Pathogenesis

Anagen effluvium occurs when there is an abrupt loss of hairs in anagen (active growth) phase due to insults that impair the proliferative activity of the hair follicles.

Examples of such insults include chemotherapy, radiation, toxic chemicals, and inflammatory diseases [126]. The anagen phase of hair growth has the highest proliferative activity. Acute damage of rapidly proliferating bulb matrix cells in this phase can result in failure of hair formation [127, 128]. About 90 % of hair in the scalp is in anagen phase. Therefore, loss of anagen hair can be copious with resulting alopecia. Proliferating bulb matrix cells are primarily affected in anagen effluvium, while quiescent stem cells of the follicular bulge are spared. Thus, anagen effluvium is reversible due to intact stem cell reservoir. The hair follicles typically resume the normal cell cycling pattern shortly after the cessation of events that disrupt hair growth [127–129].

Chemotherapy is a common cause of anagen effluvium. The occurrence and severity of this condition depends on the type of chemotherapeutic agent, the use of combination chemotherapy, and the dose of drug [130]. Depending on the type of chemotherapy, different frequencies of hair loss are induced. For example, 80 % hair loss for antimicrotubule agents (e.g., paclitaxel), 60–100 % for topoisomerase inhibitors (e.g., doxorubicin), 60 % for alkylating agents (e.g., cyclophosphamide), and 10–50 % for antimetabolites (e.g., 5-fluorouracil) [126, 130]. Tyrosine kinase inhibitors (e.g., sorafenib and sunitinib) and inhibitors of sonic hedgehog pathway (e.g., vismodegib) can induce diffuse, reversible alopecia [131–134]. Drugs targeting the epidermal growth factor receptor (EGFR) can induce a set of cutaneous symptoms known as PRIDE (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching and Dryness due to EGFR inhibitors) [135, 136].

10.13 Androgenetic Alopecia

10.13.1 Clinical Features

Androgenetic alopecia is the most common cause of hair loss in adults, with many patients initially experiencing hair loss in adolescence, following onset of puberty, and with complete evolution of hair loss by the mid-forties [137]. Adolescents with androgenetic alopecia more commonly have similarly affected first-degree relatives [138].

Androgenetic alopecia is characterized by progressive patterned hair loss at the scalp. Hair loss is frequently described as thinning and not frank shedding of hair . Boys tend to have recession along the frontoparietal margins, although it may appear along the vertex of the scalp [138]. Girls, on the other hand, have maintenance of hair at the scalp periphery with hair loss at the posterior aspect of the frontal scalp extending to the vertex [137] (Fig. 10.24). Without treatment, hair loss can be persistent and progressive.

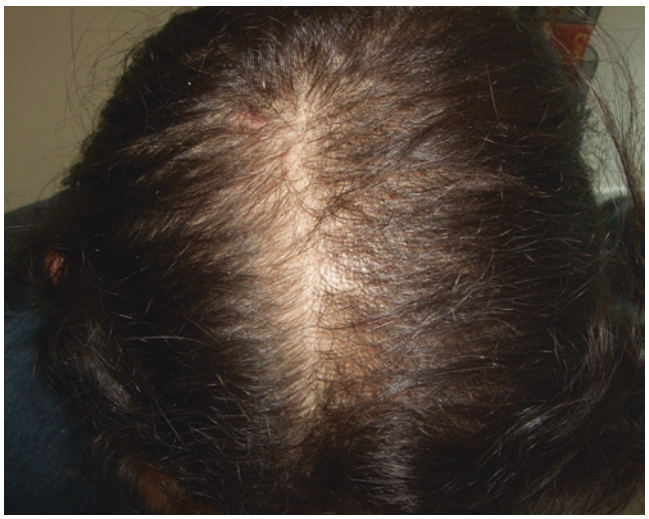

Fig. 10.24 Androgenetic alopecia is seen in a teenage girl with non-scarring hair loss at the vertex of the scalp

10.13.2 Histology

Histologic changes are those of a non-scarring, minimally inflammatory alopecia [139]. Cross-sectional analysis of skin biopsy reveals miniaturization of hair follicles with increased numbers of non-anagen phase hairs [117]. Increased numbers of vellus hairs have been described in these biopsies [105]. Fibrous tracts are seen with increased frequency in the deep dermis, consistent with the shift towards non-anagen phase hairs [140]. The normal pilo-sebaceous architecture is preserved, and there may be some enlargement of sebaceous glands. A mild lymphohistiocytic inflammatory infiltrate is present at the level of the follicular infundibulum in more than half of cases in children [141]. A slight degree of perifundibular fibrosis is also seen in some cases.

10.13.3 Pathogenesis

Androgens are essential for the development of androgenetic alopecia. The enzyme 5-alpha-reductase converts testosterone to dihydrotestosterone (DHT), which is a potent metabolite of testosterone. DHT binds with high affinity to androgen receptors and turns on the expression of genes responsible for the gradual transformation of large terminal follicles to small, miniaturized follicles [142]. 5-Alpha-reductase is important in androgenetic alopecia. Individuals with 5-alpha-reductase deficiency do not develop male patterns of body hair growth, and they do not exhibit male pattern baldness. Inhibition of 5-alpha-reductase with chemical inhibitors, such as finasteride, results in the regrowth of hair in balding males [143]. Androgens regulate hair growth by entering the hair follicles via the dermal papilla's blood supply. Binding of androgens to androgen receptors in the dermal papilla

cells leads to the expression of androgen-regulated genes that affect hair development and growth [144].

Molecular studies have provided some insights into the genetic basis of androgenetic alopecia. It is associated with a variant in the ectodysplasin A2 receptor gene (EDA2R) [145]. However, no definitive genetic defects have been identified. A recent study has proposed a new mechanism of androgenetic alopecia that involves the role of the arrector pili muscle, in which muscle plays a significant role in maintaining hair follicle integrity. With miniaturization of hair follicles, the arrector pili muscle loses attachment to the miniaturized hairs and hair loss becomes irreversible [146].

10.14 Folliculitis Decalvans

10.14.1 Clinical Features

Folliculitis decalvans accounts for about 11 % of cases of primary cicatricial alopecia. It is seen primarily in young and middle-aged adults with male predilection [147]. Patients initially develop hyperkeratotic, erythematous, follicular-based pustules and papules that evolve into a progressive sclerotic alopecia [147] (Fig. 10.25). Multiple tufts of hair from one follicular ostium (tufted folliculitis) may be seen, although this is not a specific feature of the disease. Patients may experience pruritus or tenderness at the affected area. Folliculitis decalvans can be refractory to treatment and disease relapse is common.

10.14.2 Histology

Folliculitis decalvans is an inflammatory scarring alopecia. In the early stages, neutrophilic abscesses are present within the superficial portion of the hair follicles, extending down into the follicular infundibula [147, 148] (Fig. 10.26). With time, the follicles rupture with development of a pronounced inflammatory infiltrate consisting of predominantly lymphocytes and plasma cells [148] (Figs. 10.27 and 10.28). During the latter stages of the disease, there is marked destruction of pilosebaceous units and abundant scar formation. *Staphylococcus aureus* is often cultured from pustular lesions in this entity. The histologic findings are not specific and are shared with other conditions of inflammatory scarring alopecias [149]. Some authors claim that tufted hair folliculitis is a variant of folliculitis decalvans, and occurs as a result of extensive fusion of distorted and destroyed follicular units [148].

Fig. 10.25 Erythematous papules and pustules overlie a patch of scarring alopecia in a teenager with folliculitis decalvans (photo courtesy of MG Mercurio, MD, Rochester, NY)

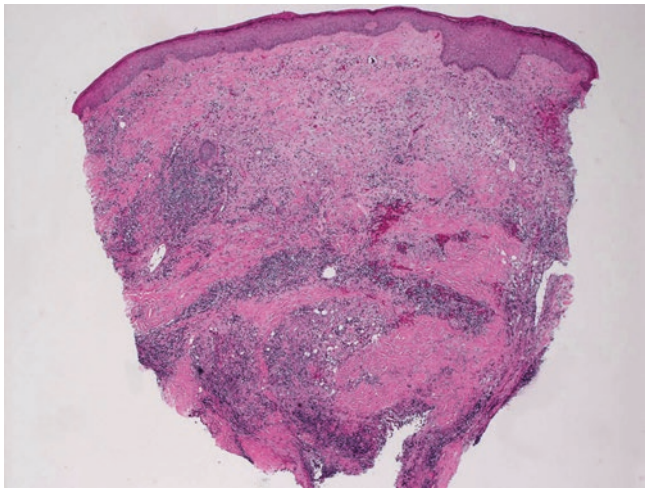

Fig. 10.26 A dense perifollicular and diffuse inflammatory infiltrate with marked dermal scarring is seen in folliculitis decalvans

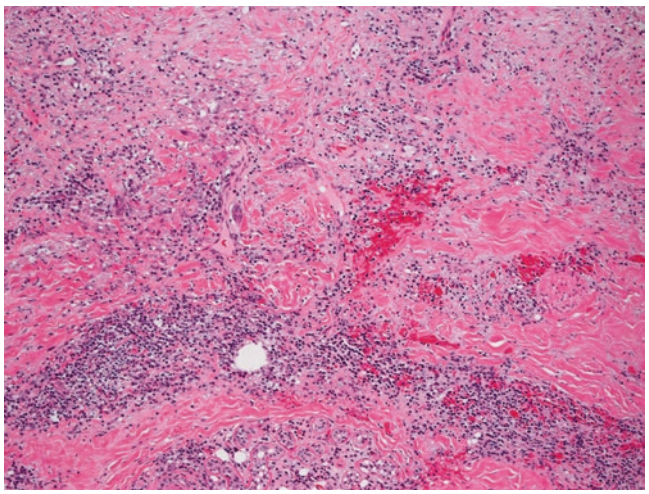

Fig. 10.27 A mixed inflammatory infiltrate and scar formation is seen in well-developed lesions of folliculitis decalvans

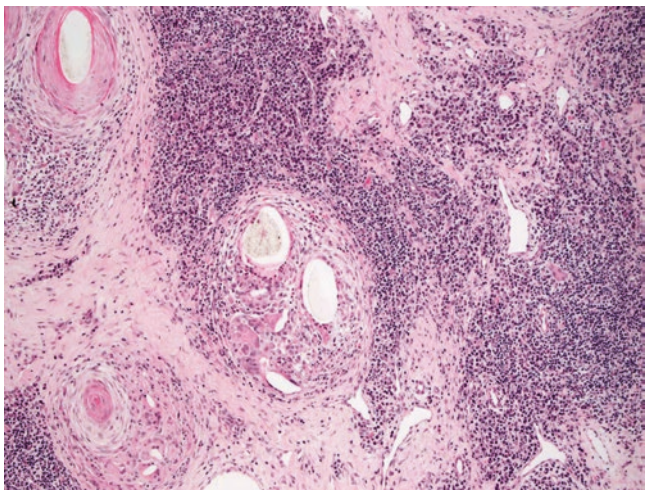

Fig. 10.28 Distortion of follicular architecture secondary to scar formation and a dense inflammatory infiltrate are characteristic findings in folliculitis decalvans

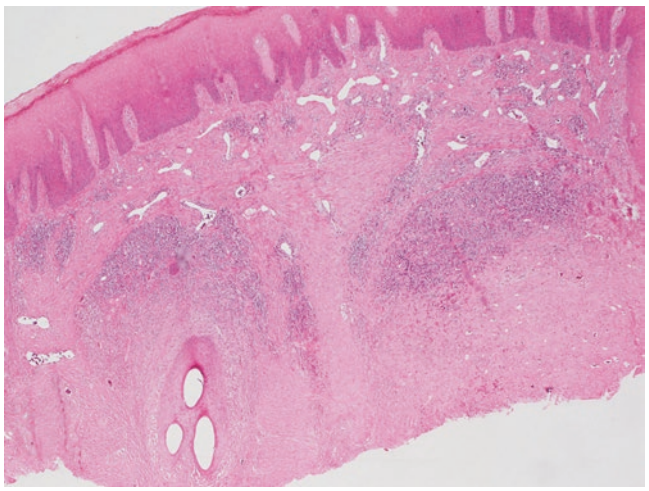

Fig. 10.29 A brisk perifollicular inflammatory infiltrate, destruction of pilosebaceous units, and dense scarring is seen in acne keloidalis nuchae

10.14.3 Pathogenesis

Folliculitis decalvans is a type of neutrophilic cicatricial alopecia whose etiology has been attributed to *Staphylococcus aureus* infection [147, 150]. The prevalence of *S. aureus* is approximately 20–30 % in an average community, but less than 0.05 % of carriers suffer from an infection. An exaggerated immune response and "superantigens" that can bind to major histocompatibility complex (MHC) class II and stimulate T lymphocytes have been postulated to contribute to the pathogenesis of folliculitis decalvans [147]. Genetic factors also appear to play a role in this disorder. Cases of folliculitis decalvans in identical twins and in families have been reported [151]. Folliculitis decalvans has also been reported after scalp injury [152].

10.15 Acne Keloidalis

10.15.1 Clinical Features

Acne keloidalis nuchae primarily affects males of African-American descent between 14 and 25 years of age [153]. Patients initially present with erythematous, follicular-based papules and pustules localized to the occiput and posterior neck. Lesions may extend to the vertex and parietal scalp. Over time, papules become more sclerotic and coalesce, forming keloidal plaques. Patients may experience pruritus and tenderness. Various treatment options exist, but response to therapy is variable.

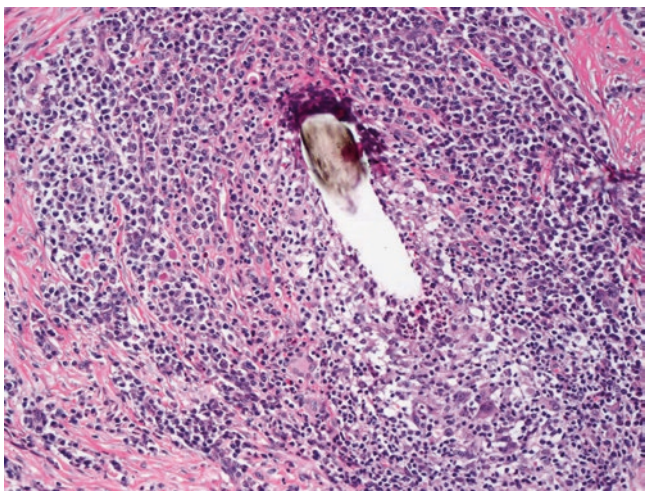

Fig. 10.30 A pilosebaceous unit is completely destroyed by a dense granulomatous inflammatory infiltrate in acne keloidalis

10.15.2 Histology

Earliest changes in acne keloidalis consist of a perifollicular lymphoplasmacellular inflammatory infiltrate at the level of the isthmus, and extending to the lower portion of the follicular infundibulum [127, 128, 154]. Acute lesions may demonstrate a marked neutrophilic infiltrate and focal intrafollicular abscesses [155] (Fig. 10.29). As lesions progress, there is progressive loss of sebaceous glands and thinning of the follicular epithelium. Eventually, the follicles rupture and elicit a marked granulomatous inflammatory response (Fig. 10.30). Marked scarring ensues with keloid formation [127, 128].

10.15.3 Pathogenesis

The pathogenesis of acne keloidalis is not known. However, a number of etiologies have been proposed, including trauma, chronic irritation, seborrhea, infection, and elevated testosterone levels [156, 157]. Excess androgens with stimulation of the sebaceous glands by androgens may be important in the initiation of acne keloidalis. Other studies have proposed that antigens in the follicular epithelium elicit an inflammatory response that damages hair components, resulting in scar formation [158]. Trauma from shaving has been implicated in the etiology of acne keloidalis. Studies have also found association of haircuts by a barber and onset of acne keloidalis [159].

10.16 Infundibulofolliculitis

10.16.1 Clinical Features

Disseminate and recurrent infundibulofolliculitis is seen most frequently in young African-American males, although reports of cases in females and Caucasians do exist [160]. Patients occasionally have a personal or family history of atopy. Patients present with skin-colored, follicular-based papules on the trunk and proximal extremities with minimal scaling or hyperkeratosis [160]. Also known as Hitch and Lund disease, this condition may be difficult to manage medically, but it is a benign condition with a high likelihood of eventual spontaneous resolution.

10.16.2 Histology

Histologic changes include spongiosis and lymphocytic infiltration of the infundibular portion of the hair follicle. Follicular plugging with keratin, and subsequent dilatation of the hair follicle is seen focally. Overlying parakeratosis may be seen. Neutrophilic abscesses are sometimes present [161].

10.17 Eosinophilic Folliculitis

10.17.1 Clinical Features

Eosinophilic folliculitis is subcategorized into three groups: the classic variant described in Japanese individuals, the immunosuppressive variant (most often described in those with HIV), and the infancy-associated variant known as eosinophilic pustular folliculitis of infancy [162].

Eosinophilic pustular folliculitis of infancy is a benign disorder that occurs most frequently in males [163]. It can also be a presenting feature of autosomal dominant hyper-IgE syndrome. The majority of patients demonstrate typical skin changes by 6 months of age. Patients present with crops of pruritic erythematous papules and pustules along the scalp and on the extremities (Fig. 10.31). Two-thirds of patients may have more extensive and generalized disease [163]. Concomitant episodes of peripheral leukocytosis with eosinophilia may occur. Eosinophilic folliculitis is a chronic, relapsing disorder that frequently resolves spontaneously. In more refractory cases, topical steroids may be required.

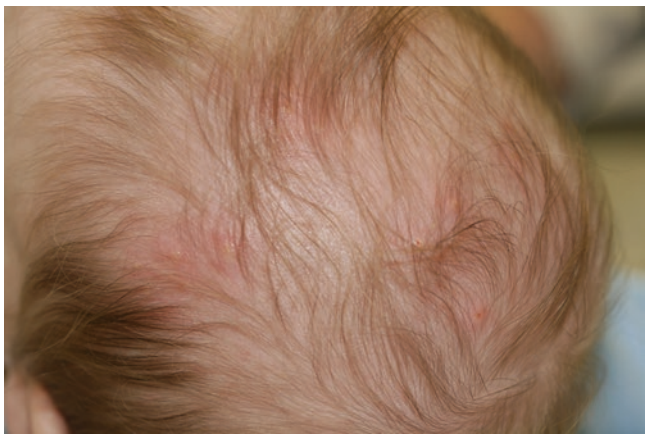

Fig. 10.31 Eosinophilic pustular folliculitis is characterized by erythematous, follicular-based pustules scattered on the scalp in an infant

10.17.2 Histology

There are several variants of this entity, including one that presents most commonly in infants [162, 164]. As the histologic features are identical in these variants, the changes will be described together. Biopsies demonstrate follicular spongiosis and exocytosis of eosinophils into the follicular infundibulum [165, 166] (Fig. 10.32). The infiltrate is moderately intense. While lymphocytes and histiocytes are present in the infiltrate, an eosinophilic predominance is what defines eosinophilic folliculitis (Fig. 10.33) [167]. Fibrosis and scar formation are not characteristic features of this entity, which tends to present in an acute state and resolve without sequelae.

10.17.3 Pathogenesis

The pathogenesis of eosinophilic folliculitis has been postulated to be a reaction to infections, medications, and autoimmune disorders. Some cases may be related to immune-mediated reaction to the fungus *Malassezia* [168]. The mites *Demodex folliculorum* and *Demodex brevis* are also thought to be possible antigen sources, as well as bacteria, such as *Leptotrichia buccalis*, and medications, such as carbamazepine, minocycline, and allopurinol [162].

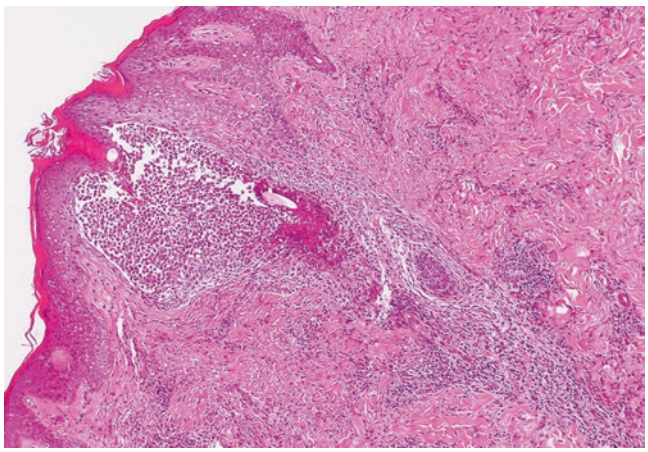

Fig. 10.32 A dense mixed infiltrate containing abundant eosinophils involving hair follicles is present in eosinophilic folliculitis

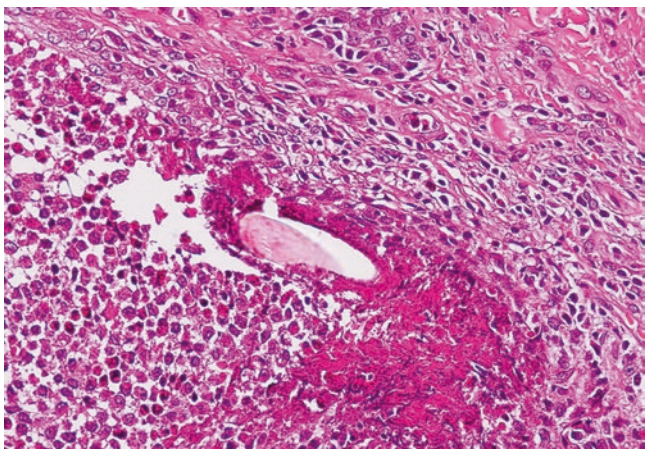

Fig. 10.33 Exocytosis of eosinophils into follicular epithelium is required to establish a diagnosis of eosinophilic folliculitis

Sebaceous glands and sebum products may be a source of self-antigens and eosinophilic chemotactic factors, which can contribute to the pathogenesis of eosinophilic folliculitis [169].

The disease is associated with states of immunosuppression, including HIV and hematologic malignancies [162, 170]. In HIV infection and the accompanied immunodeficiency state, the immune response elicited by type 2 T helper cells (Th2) becomes dysregulated. This is coupled with the production of eotaxin-1, which is an eosinophil-specific chemokine, as well as Th2 cytokines (IL4, IL5 and IL13). These pro-inflammatory molecules are important in the recruitment of eosinophils and the inflammatory response seen in eosinophilic folliculitis [171]. It is not known whether eosinophils play a primary role in the disease process, or whether they are present secondary to an allergic response to some unknown stimulus. Other types of immune dysfunction are also associated with eosinophilic folliculitis. High circulating levels of IgG and IgM are seen [172]. Eosinophils express high levels of neuronal nitric oxide synthase (nNOS) and increased nitric oxide production, which activates mast cells and eosinophils, leading to epidermal damage [173]. The etiology of eosinophilic pustular folliculitis of infancy is not known, but it may be similar to the classic type of eosinophilic folliculitis in terms of immune dysregulation [174].

10.18 Follicular Mucinosis

10.18.1 Clinical Features

Follicular mucinosis/alopecia mucinosa is a rare occurrence in children, more commonly appearing in young adults with no racial or gender predilection [175, 176]. Three variants exist: an idiopathic (primary) form, which is more commonly seen in children and young adults, a secondary form, which occurs in the setting of other inflammatory disorders such as lupus erythematosus or malignancy, and a third form that occurs in conjunction with cutaneous T-cell lymphoma [176].

The clinical features of follicular mucinosis may vary, but most commonly appear as erythematous to skin-colored, slightly scaled, indurated plaques with follicular prominence on the head and neck [177]. Alopecia may be noted on terminal hair-bearing skin. In more severe cases, generalized follicular hyperkeratosis and cysts at the neck, trunk, and extremities can be seen.

In adults with follicular mucinosis, mycosis fungoides is the most commonly seen malignancy with an estimated prevalence of 15–30 % [177]. However, the literature suggests that malignancy is infrequently seen in children. Instead, follicular mucinosis follows a benign course with eventual remission, especially in children with localized disease on the head and neck [175, 177]. However, most experts agree that long-term clinical monitoring is warranted in all pediatric patients with follicular mucinosis [175–177].

10.18.2 Histology

The histologic changes seen in follicular mucinosis are similar regardless of its association with mycosis fungoides or other T-cell proliferations [177–179]. At the level of the follicular infundibulum, there is an accumulation of intraepithelial mucin (Figs. 10.34, 10.35 and 10.36). In some cases, this is readily apparent on routine histologic sections. In other cases, it may be subtler and resemble spongiosis. In florid cases, cystic cavities filled with mucin may develop. In all cases, there is a concomitant lymphocytic infiltrate within the follicular epithelium and in the surrounding dermis. Scattered eosinophils are also present [180]. This is rela-

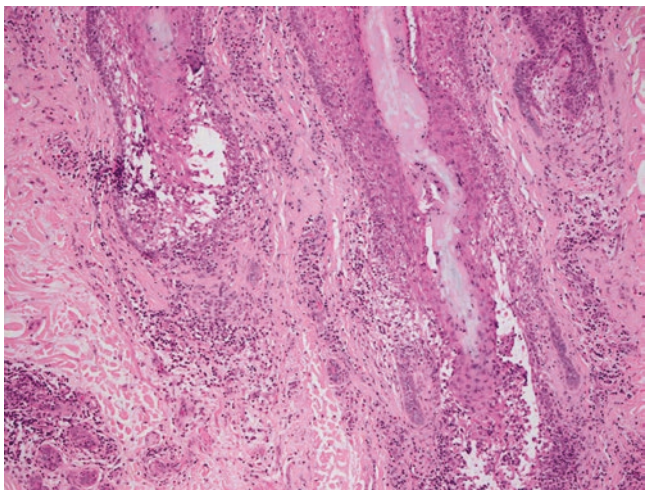

Fig. 10.34 Increased pale staining intercellular spaces resulting in separation of the epithelium is characteristic of follicular mucinosis

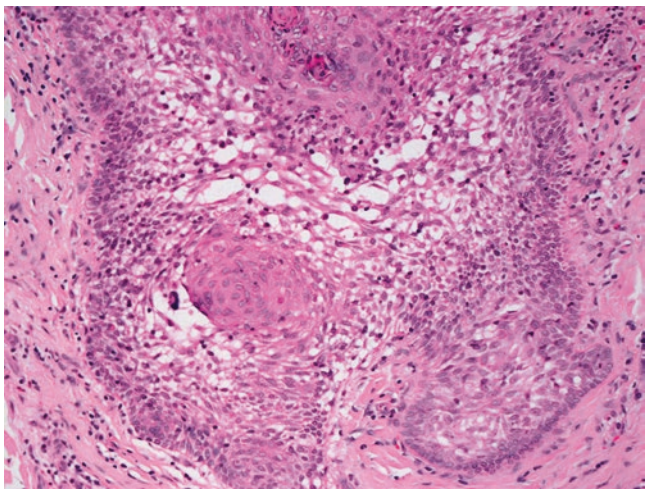

Fig. 10.35 Increased intraepithelial mucin and an accompanying lymphocytic infiltrate are features of follicular mucinosis

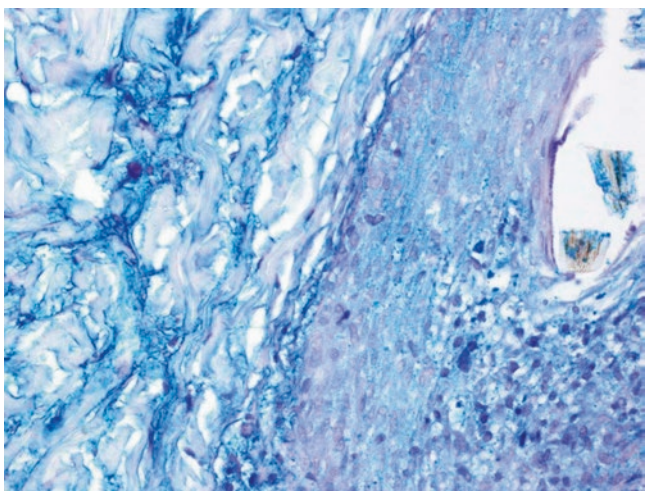

Fig. 10.36 Intraepithelial mucin in follicular mucinosis is accentuated on colloidal iron stain

tively mild in intensity with only slight extension into the interstitial collagen. Exocytosis of lymphocytes into the overlying epidermis may be encountered [180]. Some investigators suggest that the involvement of the overlying epidermis may be indicative of associated mycosis fungoides [181, 182]. The association of follicular mucinosis and mycosis fungoides in children is still a controversial topic, although T-cell receptor gene rearrangements are identified in some cases [175].

10.18.3 Pathogenesis

Follicular mucinosis can occur as a primary idiopathic form in children and young adults, with spontaneous remission as the expected clinical course. Follicular mucinosis can also occur as a secondary form associated with inflammatory conditions, such as eczematous dermatitis, lupus erythematosus, insect bites, and skin reaction to certain drugs [183]. However, more than half of cases of follicular mucinosis occur in association with cutaneous T-cell lymphoma (mainly mycosis fungoides) [180]. Adult T-cell lymphoma/leukemia (ATLL) with follicular mucinosis has also been reported [184, 185]. Mucin deposition in and around hair follicles in follicular mucinosis is thought to be a response of follicular keratinocytes to T-cell infiltrates [186].

10.19 Trichotillomania

10.19.1 Clinical Features

The fourth edition of the Diagnostics and Statistic Manual of Mental Disorders defines trichotillomania, in its simplest terms, as hair loss from repetitive self-pulling of hair [187]. Trichotillomania is seen most commonly in older children and adolescents with mean age of onset between 9 and 13 years of age [187]. Girls are more frequently affected than boys. Hair pulling in children less than 5 years old is habitual, while in adults it is more frequently associated with an underlying psychiatric disturbance.

In trichotillomania, the physical exam is characterized by geometric, bizarrely-shaped patches of hair loss often in areas that are easily accessible by the patient (Figs. 10.37 and 10.38). The overall hair density is normal. Broken hairs of various lengths are seen. Often times, there are no underlying signs of inflammation. The scalp is the most commonly affected area, although hair loss can be seen at the eyebrows, eyelashes, face, arms, legs, and pubis [187].

Younger children with trichotillomania typically outgrow the behavior of hair pulling [187]. However, in older children and adolescents, the clinical course is more chronic and relapsing. Patients that have hair loss associated with an underlying psychiatric disorder may require

Fig. 10.37 Trichotillomania in a child shows odd shaped, geometric patterning of hair loss with hairs of various lengths at the frontal and vertex scalp (photo courtesy of MG Mercurio, MD, University of Rochester, Rochester, NY)

Fig. 10.38 Traction alopecia from hair pulling shows hair loss at the temporal scalp with follicular dropout and hairs of various lengths on closer inspection. Occasionally, accompanying folliculitis is present as shown in this example

management of their psychiatric disease before the hair pulling behavior is resolved [187].

10.19.2 Histology

Trichotillomania is non-scarring and noninflammatory alopecia. There is an admixture of normal hairs and follicular structures lacking hairs. There is a shift away from anagen

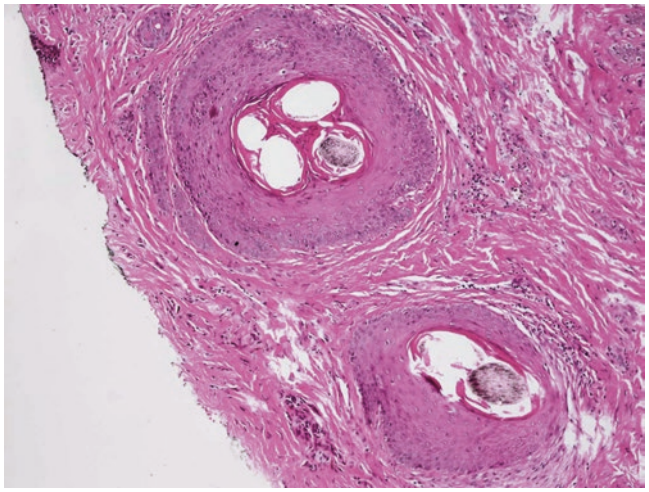

Fig. 10.39 Multiple hairs contained within one follicular epithelial structure is commonly seen in patients with trichotillomania

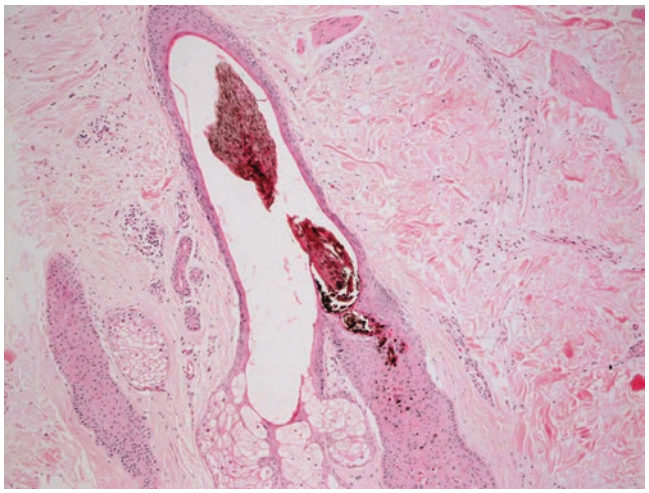

Fig. 10.40 Fractured hairs and pigmented casts are frequent findings in trichotillomania

phase hairs. There may be follicular dilatation with prominent keratin plugging. The follicular epithelium may have clefts separating it from the surrounding connective tissue, which is evidence of forceful tugging on the hair shafts. In addition, pigment casts within the hair canals are seen in almost all cases [106, 188] (Figs. 10.39 and 10.40). Trichomalacia, defined as distortion of the follicular bulb, is commonly seen [189]. Perifollicular hemorrhage may be apparent in severe cases. A vertically-oriented split in the hairs, the so-called "hamburger sign," has been described in some patients with trichotillomania [190].

The histologic differential diagnosis includes primarily alopecia areata and androgenetic alopecia. Alopecia areata will demonstrate a peri-bulbar lymphocytic infiltrate in most cases and trichomalacia and pigment casts are not present [106]. Androgenetic alopecia has more prominent follicular

miniaturization, lack of pigment casts, and a mild peri-infundibular lymphocytic infiltrate, which is not usually seen in trichotillomania.

10.19.3 Pathogenesis

Trichotillomania lies within the obsessive-compulsive disorder spectrum. The trigger of such behavior is not known. It is possible that multiple genes confer vulnerability to trichotillomania. Several potential genes linked to trichotillomania have been identified, including SLITRK1 gene [SLIT and NTRK (neurotrophic tyrosinase kinase receptor, type1)], serotonin 2A receptor gene, and homeobox-B8 (HOXB8) gene [191]. Interestingly, genetically engineered mice with a mutation in HOXB8 show abnormal hair pulling behavior [192].

10.20 Pressure-Induced Sweat Gland Necrosis and Alopecia

10.20.1 Clinical Features

Postoperative (pressure-induced) alopecia is a rare phenomenon, most commonly following cardiac surgery [193]. It is speculated to be the result of localized pressure-induced ischemia secondary to head immobilization during episodes requiring extended intubation [194]. Ischemia may be exacerbated by severe hypotension, pronounced blood loss, and vasoconstrictors. Alopecia typically occurs at the occiput and may be preceded by occipito-parietal discomfort, followed by swelling, ulceration, and crusting [194] (Fig. 10.41). Hair loss is seen 3 to 28 days postoperatively. The alopecia is transient and regrows within 12 weeks, but incidences of permanent hair loss exist. The risk of permanent alopecia appears to correlate directly with the length of surgery [193].

10.20.2 Histology

Histologic sections may show pressure-induced tissue necrosis that is localized primarily to the region around the eccrine and pilosebaceous structures. There is necrosis of the eccrine glands and hair follicles, initially without surrounding inflammation [195]. As the lesions progress, a mixed inflammatory infiltrate appears around the necrotic eccrine glands, and a subepidermal blister may appear overlying the affected cutaneous appendages [196]. The follicles may show histologic changes of trichotillomania, including pigment casts [188, 197].

Fig. 10.41 Pressure-induced alopecia presents as a geometric patch of non-scarring alopecia at the right parietal scalp with hyperpigmentation at previous area of erosion following cardiac transplantation surgery in a teenage boy

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Bacterial and Protozoal Diseases

11

11.1 Toxic Shock Syndrome

11.1.1 Clinical Features

The sudden development of shock and organ failure in an otherwise healthy person with an intact immune system is frequently caused by a wide variety of primary infections with *Streptococcus pyogenes* or *Staphylococcus aureus*.

Cases of streptococcal toxic shock tend to be sporadic with a prevalence of 10–20 per 100,000 individuals. Mortality is estimated at 30–70 % [1]. Up to 90 % of staphylococcal toxic shock cases occur in females, and more than 90 % affect Caucasian females between 15–19 years of age [1]. In the case of a primary soft tissue infection with either pathogen, there is often swelling, redness, and pain at the site. Deeper infectious processes may result in frank bullae on the skin. In addition to systemic symptoms of fever, hypotension, tachypnea, and tachycardia, patients typically develop a diffuse or patchy erythematous rash resembling a sunburn. Mucous membranes may appear erythematous, and there may be a "strawberry" tongue. Patchy superficial desquamation is common about 7–14 days after onset of the illness. Some patients experience transient patchy alopecia or temporary loss of nails.

11.1.2 Histology

Histologic changes unique to children have not been described. The changes include focal spongiosis with small neutrophilic abscesses within the epidermis, along with clusters of dyskeratotic keratinocytes [2] (Figs. 11.1 and 11.2). Within the dermis, there is a mixed inflammatory infiltrate with lymphocytes, neutrophils, and eosinophils, both interstitially and around vessels. In some cases, the pattern resembles a leukocytoclastic vasculitis, but fibrin thrombi are absent [2]. Papillary dermal edema and focal hemorrhage are variably present.

11.1.3 Pathogenesis

Toxic shock syndrome is primarily caused by *Staphylococcus aureus* with fewer reports seen in patients with group A streptococcal infection [1]. While most cases are associated with tampon use during menstruation, other exposures to bacterial colonization may be present in up to 13 % of cases [3]. Following bacterial colonization, toxic shock syndrome toxin type 1 is produced. In rare instances, staphylococcal enterotoxins A-H have been implicated in the disease. Most adults have developed antibodies to these exotoxins, and are relatively resistant to the disease. However, those without sufficient immunity, as well as those with altered levels of serum glucose or magnesium, may be at increased risk. Exotoxins cause tissue destruction through stimulating interleukin 1 (IL-1) and tumor necrosis factor. T lymphocytes are also stimulated and contribute to symptoms of shock and tissue destruction.

11.2 Blastomycosis-Like Pyoderma

11.2.1 Clinical Features

Blastomycosis-like pyoderma is a condition that primarily affects middle-aged individuals with a male-to-female ratio of 3:1 [4]. Although the etiology is unknown, it is thought to represent an exaggerated, chronic inflammatory reaction in the skin, possibly with an infectious component.

The classic skin lesions start as erythematous papulopustules that coalesce into vegetative verrucous plaques with raised borders. They are most common on the face, scalp, axillae, and genitalia, but may also affect the abdomen, trunk, or distal extremities. Oral lesions have been reported and present as white pustules or plaques. Although lesions occasionally heal spontaneously, they tend to be chronic and recurrent. There are no standard treatment recommendations; some cases improve with wound care, systemic antibiotics, and treatment of any underlying systemic disease process (e.g., inflammatory bowel disease).

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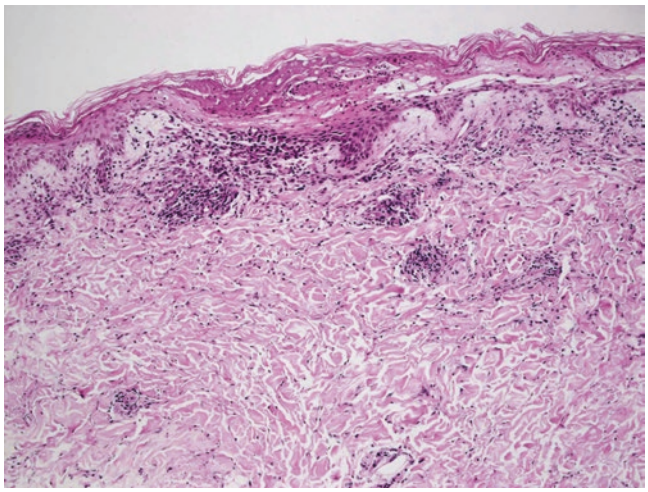

Fig. 11.1 A lymphocytic infiltrate is seen underneath a necrotic epidermis in toxic shock syndrome

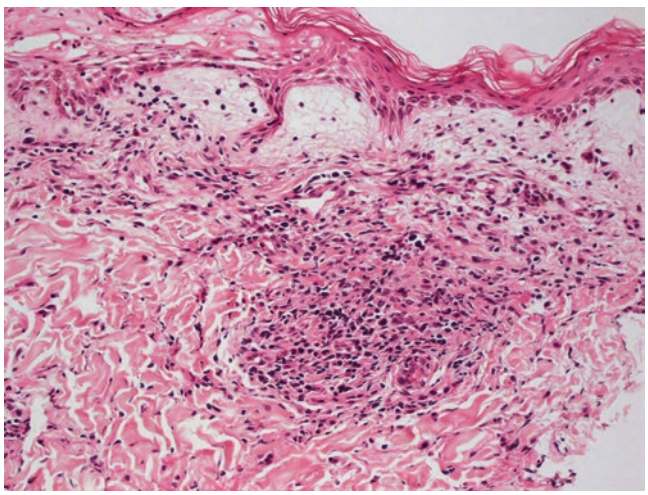

Fig. 11.2 Necrotic epidermis is seen overlying papillary dermal edema and a mild perivascular lymphocytic infiltrate in toxic shock syndrome

11.2.2 Histology

Histologic features of blastomycosis-like pyoderma include florid epidermal hyperplasia that is pseudoepitheliomatous in some cases. A neutrophilic infiltrate is present as abscesses within the stratum corneum, epidermis, and dermis [5]. In florid cases, disruption of follicular units may result in marked diffuse dermal inflammation that can be predominantly neutrophilic or granulomatous. Tissue gram stains may or may not demonstrate microorganisms, but tissue cultures are invariably positive for bacterial growth.

The histologic differential diagnosis includes infectious etiologies, such as deep fungal and mycobacterial infections, as well as halogenodermas and squamous cell carcinoma. Stains for microorganisms may help with this distinction, and tissue cultures can definitively resolve the differential diagnosis with the other infectious etiologies. Halogenodermas tend to have abundant eosinophils that are not characteristic of blastomycosis-like pyoderma. Keratinocyte atypia is more pronounced in most cases of squamous cell carcinoma than the reactive squamous atypia seen in some cases of blastomycosis-like pyoderma. An infiltrative growth pattern seen in squamous cell carcinoma is also not seen in blastomycosis-like pyoderma.

11.2.3 Pathogenesis

The disease is almost always induced by bacterial infection, most commonly Pseudomonas and Staphylococcus [6]. There is a single report of a case caused by *Trichophyton mentagrophytes* [7]. Blastomycosis-like pyoderma is believed to be a hypersensitivity reaction occurring in patients with altered immunity [6, 8]. Impairment of both systemic and local immunologic responses has been associated with this reaction pattern [5].

11.3 Chronic Granulomatous Disease

11.3.1 Clinical Features

Chronic granulomatous disease is a rare primary immunodeficiency. Patients often present in early childhood with symptoms of inflammatory bowel disease and recurrent unusual opportunistic infections. Development of widespread infectious and noninfectious granulomas is common. Skin manifestations include soft tissue infections with formation of abscesses and ulcers. These are often caused by uncommon microorganisms, such as *Serratia marcescens* [9].

11.3.2 Histology

Histologic findings vary depending upon the presence of superinfection. Most cases demonstrate the presence of granulomatous inflammation within the dermis. A characteristic golden-yellow pigmented lipid has been described within giant cells in the granulomatous reaction, especially at the periphery of lesions [10]. This is believed to be a degenerative bi-product of the defective abilities to destroy microorganisms. If there is an active secondary infection, the presence of neutrophils is an expected finding. In some cases, neutrophils may occur as intraepidermal vesicles or dermal abscesses [10]. In patients without current infection, a nonspecific lymphohistiocytic infiltrate may be present [11]. Tissue cultures are usually negative.

11.3.3 Pathogenesis

Chronic granulomatous disease is caused by a one of five genetic defects that result in impairment in phagocyte NADPH oxidase [12]. Functioning phagocyte NADPH oxidase generates reactive oxygen species that are involved in extracellular host defense, and are essential for fully resolving inflammatory processes. Defective oxidase function results in an ineffective respiratory burst in phagocytes that cannot effectively destroy certain bacteria and fungi [13].

11.4 Impetigo

11.4.1 Clinical Features

Impetigo is a common cutaneous infection with high prevalence in children. Non-bullous or "crusted" impetigo accounts for more than 70 % of the cases [14]. It affects children and adults, but is rarely seen in children under 2 years of age. It can be caused by group A ß-hemolytic streptococci and Staphylococcus aureus. The primary lesion is a superficial vesicle, which ruptures easily, leaving an erythematous erosion and purulent exudate that quickly dries and form the classic "honey colored" crust (Fig. 11.3).

The bullous form of impetigo is most common in children between 2 and 5 years of age. It is nearly always caused by *S. aureus* infection. It presents as superficial flaccid vesicles and bullae that rupture easily, leaving erythematous erosions with "collarettes of scale" behind. Although bullous impetigo can occur on any cutaneous surface, it is somewhat more common in moist intertriginous areas. Most localized forms of impetigo can be treated with topical antibiotics. More extensive cases or cases with systemic symptoms, such as fever, are treated with systemic antibiotics.

Fig. 11.3 Impetigo presents as widespread flaccid bullae and superficial erosions with collarettes of scale and foci of honey-colored crust (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

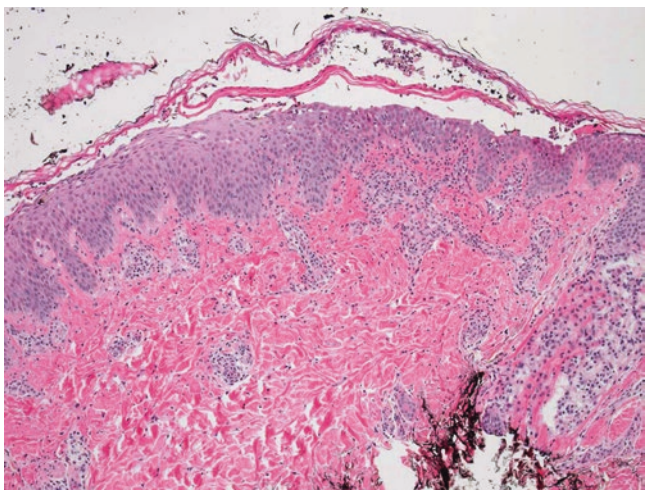

Fig. 11.4 Bullous impetigo displays a subcorneal neutrophilic abscess

11.4.2 Histology

Histologic sections demonstrate a subcorneal neutrophilic pustule (Fig. 11.4). There is spongiosis within the epidermis, and a variably intense inflammatory infiltrate within the dermis. Focal acantholysis may be seen in some cases. Neutrophils may be present throughout the epidermis and focally in the dermis (Fig. 11.5). In older lesions, a thick crust with serum and parakeratosis is seen. Tissue Gram stains will demonstrate gram-positive cocci, most commonly *Staphylococcus* and less commonly *Streptococcus*.

The differential diagnosis includes other subcorneal blistering disorders, such as candidiasis, transient neonatal pustular melanosis, erythema toxicum neonatorum, acute generalized exanthematous pustulosis (AGEP), and acropustulosis of infancy. All of these entities do not demonstrate bacterial infection. In candidiasis, a PAS stain will show fungi. Erythema toxicum neonatorum is characterized by a predominantly eosinophilic pustular infiltrate as opposed to the neutrophil predominant infiltrate seen in impetigo. The other entities are best distinguished based upon the clinical presentation and history as there is no clinical overlap with impetigo.

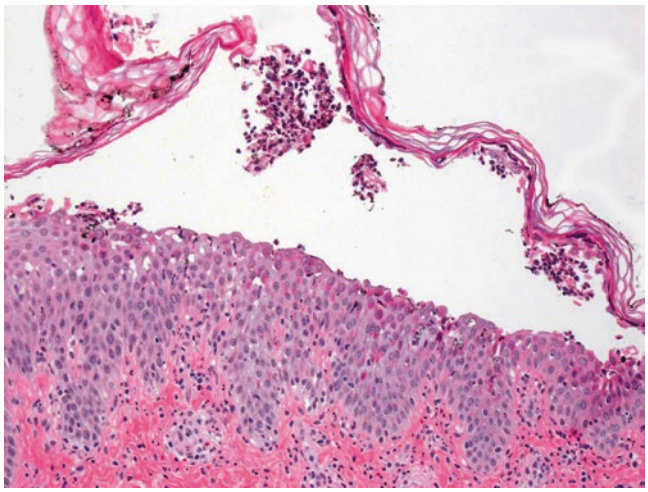

Fig. 11.5 Neutrophilic abscesses and scattered neutrophils within the epidermis and superficial dermis are seen in bullous impetigo

11.4.3 Pathogenesis

Exfoliatin toxin is strongly implicated in the pathogenesis of bullous impetigo associated with *staphylococcus aureus* infection [15]. Likewise, exfoliative toxin A-coding bacteriophages are identified in most cases of impetigo [16]. Group A β-hemolytic streptococcal strains are also the cause of impetigo, although they are less commonly reported [14].

11.5 Scarlet Fever

11.5.1 Clinical Features

Scarlet fever is caused by infection with toxin-producing strains of group A β-hemolytic streptococcus. Most cases affect children between 1 and 10 years of age, although it is occasionally seen in older children and adults [17]. Fever, pharyngitis, and a diffuse erythematous rash characterize scarlet fever. Pinpoint erythematous macules and papules coalesce into a diffuse sunburn-like erythema with a rough, "sandpaper" texture. There is accentuation of erythema with transverse red streaks in the skin creases ("Pastia's lines"). The tongue appears red and swollen with prominent papillae ("strawberry tongue").

11.5.2 Histology

Scarlet fever is almost always diagnosed based upon clinical findings and serologic studies. The histologic findings are nonspecific, but include dilated and congested dermal blood vessels. Edema and hemorrhage have been described, often accompanied by a slight infiltrate of neutrophils. Late stage lesions demonstrate parakeratosis that can be diffuse and confluent.

11.5.3 Pathogenesis

Scarlet fever is a result of infection with group A *streptococcus pyogenes* infection. Exotoxins A, B and C, also known as streptococcal superantigens, are responsible for causing the cutaneous eruption, strawberry tongue, and skin desquamation [18, 19]. These superantigens stimulate T lymphocytes with ensuing release of massive amounts of cytokines, including interleukin-1 and tumor necrosis factor-α [1, 19].

11.6 Cellulitis

11.6.1 Clinical Features

Cellulitis is defined as "a diffuse and spreading infection with inflammation of the deeper dermis and subcutaneous fat" [20]. Clinically, it is characterized by rapid development of swelling, redness, warmth, and tenderness of soft tissues. Vesicles, bullae, ecchymoses, and petechiae can sometimes be seen. Although certain risk factors, such as obesity and chronic edema, may predispose some patients to recurrences, the overall prognosis is favorable with appropriate systemic antibiotic therapy.

11.6.2 Histology

The histologic findings in cellulitis may be somewhat subtle and nonspecific, and they can vary with the duration of the lesion biopsied. Acute lesions show a diffuse dermal infiltrate of neutrophils and interstitial edema separating dermal collagen bundles. Dermal edema may result in the formation of bullae. In most cases, the inflammatory infiltrate is only moderately intense without frank abscess formation. Blood vessels are dilated, and in some cases they may appear preferentially inflamed. However, there is no actual vasculitis. In resolving lesions, granulation tissue and even fibrosis may be present. Tissue culture may be helpful in identifying the causative bacterial pathogen and antibiotic sensitivity.

The histologic differential diagnosis includes neutrophilic dermatoses such as Sweet's syndrome that can be easily differentiated based upon clinical presentation. Leukocytoclastic vasculitis may also enter the differential diagnosis, but there is no destruction of blood vessel walls in cellulitis. Erysipelas

has identical histologic findings, and is separated purely based upon clinical findings. Erythema marginatum may also demonstrate a diffuse neutrophilic dermal infiltrate without significant vascular damage, but it has a markedly different clinical presentation and is associated with rheumatic fever, which is not a feature of cellulitis.

11.6.3 Pathogenesis

Staphylococcus aureus and group A Streptococci are the most frequent infectious agents associated with cellulitis [21]. A wide range of other bacteria have been implicated, often following direct cutaneous inoculation [22].

11.7 Furuncle and Carbuncle

11.7.1 Clinical Features

A furuncle is a deep infection of the hair follicle that forms an abscess [23]. Multiple adjacent infected follicles can sometimes coalesce to form a carbuncle. Furuncles appear as painful red nodules on hair-bearing areas. They may or may not be fluctuant, or have an overlying central pustule. Although some patients develop recurrent episodes, most have a favorable prognosis with appropriate therapy for acute episodes and measures to decrease *Staphylococcus aureus* colonization of the skin and mucous membranes.

11.7.2 Histology

Histologically, carbuncles and furuncles differ in the location of the inflammatory process within the skin. Furuncles represent dermal abscesses, almost always follicularly centered, that result in destruction of the epithelium and formation of sinus tracts deep within the dermis and subcutaneous fat. Large aggregates of neutrophils are present within the follicular epithelium and diffusely throughout the dermis. A granulomatous reaction is sometimes seen in the regions of follicular destruction. Older lesions demonstrate marked fibrosis and scarring. It is not uncommon to see overlying neutrophilic abscesses, and serum and neutrophil crust.

Carbuncles are larger and more deeply situated abscesses, again with collections of abundant neutrophils. These frequently develop as a result of adjacent furuncles fusing together to form a larger area of inflammation, necrosis, and tissue destruction. These are most commonly seen in the deep reticular dermis and centered within the subcutaneous fat.

11.7.3 Pathogenesis

Staphylococcus aureus is the microorganism most commonly associated with the formation of carbuncles and furuncles [23, 24]. In the majority of cases, these lesions arise from folliculitis that worsens. Patients with underlying systemic illness, such as diabetes, kidney and liver disease, are at increased risk for developing furuncles and carbuncles. Rarely, other bacteria have given rise to these types of lesions [25]. Furuncles may rarely be seen in parasitic conditions, including myiasis [26].

11.8 Ecthyma Gangrenosum

11.8.1 Clinical Features

Ecthyma gangrenosum is frequently a skin manifestation of severe systemic infection, typically with *Pseudomonas aeruginosa*. Although it is usually seen in neutropenic and immunocompromised patients, it has also been reported in previously healthy individuals [27].

Clinically, lesions often start as erythematous macules, papules, or nodules that develop into hemorrhagic vesicles and bullae, and later progress to necrotic ulcerations with black eschars and surrounding erythema (Fig. 11.6). Lesions usually affect the perineal and gluteal areas (57 %) and the extremities (30 %) [28]. Mortality rate may be as high as 96 % for septicemic cases, but it is reported at 15 % for non-septicemic cases [27].

11.8.2 Histology

Histologic sections demonstrate skin with marked vascular destruction and thrombosis, often associated with relatively scant inflammatory infiltrate and readily apparent bacterial overgrowth (Fig. 11.7). Blood vessels are necrotic, and there is marked edema and hemorrhage (Fig. 11.8). Gram stains demonstrate abundant gram-negative rods, which can be seen on routine H&E sections as well. In most cases, *Pseudomonas aeruginosa* is the offending microorganism, but many other microorganisms have been implicated in cases with similar histologic changes.

The differential diagnosis includes leukocytoclastic vasculitis, which usually has more neutrophilic infiltrate and less thrombosis. Microorganisms are not seen in leukocytoclastic vasculitis in the absence of septicemia. An invasive fungal process could also demonstrate similar histologic changes, but it can be readily distinguished on PAS stain that demonstrates fungal microorganisms within vascular walls.

Fig. 11.6 Ecthyma gangrenosum presents as an ulcerated plaque with rim of erythema at the dorsum of the foot with similar satellite lesions on the toes in an immunosuppressed toddler

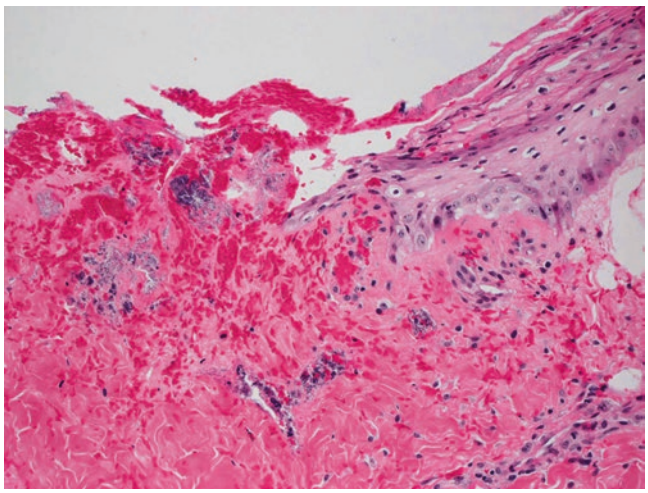

Fig. 11.7 Ulceration and hemorrhage are common findings in ecthyma gangrenosum. Numerous microorganisms are observed on H&E stained sections

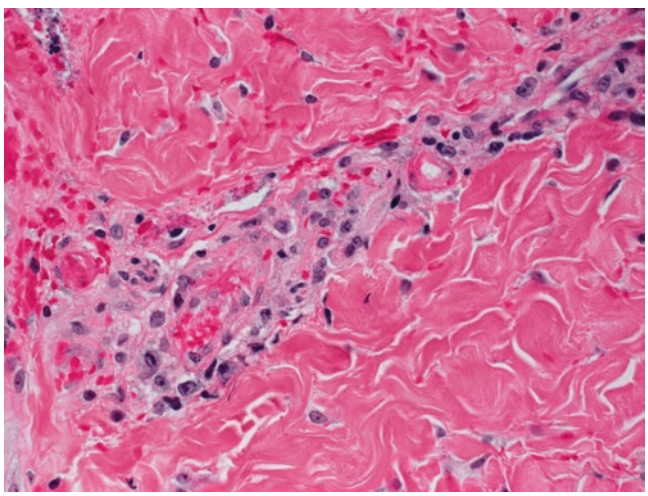

Fig. 11.8 Ecthyma gangrenosum demonstrates blood vessels occluded by fibrin thrombi with surrounding hemorrhage

11.8.3 Pathogenesis

While most commonly associated with *Pseudomonas aeruginosa*, bacteria including *Escherichia coli, Citrobacter freundii, Klebsiella pneumonia, Staphylococcus aureus*, and other Pseudomonas species are also found in ecthyma gangrenosum [29–31]. Rare cases have been associated with *Candida albicans* and Fusarium infections [31]. Most affected individuals are immunocompromised [29, 30]. Underlying neutropenia and other types of impaired immunity are frequently a contributing cause to the disease, although ecthyma gangrenosum has been seen in patients with normal neutrophil counts [30]. Septicemia is present in some patients with ecthyma gangrenosum [32].

11.9 Erysipelas

11.9.1 Clinical Features

Erysipelas is an acute superficial cutaneous cellulitis, affecting the epidermis and upper dermis. Incidence has been estimated at 10–100 cases per 100,000 individuals per year [33]. It more commonly affects the elderly and small children, as well as those who are immunocompromised. Erysipelas tends to favor the face and legs, although it can occur at other cutaneous sites. It is usually caused by group A β-hemolytic streptococcus.

An erythematous patch that rapidly enlarges, becoming tender, edematous, and indurated characterizes this infectious process. Lesions have well-defined raised borders. With more severe infections, bullae may form, and necrosis can develop. Although some patients with impaired circulation may be at risk for recurrences, those who receive appropriate therapy in a timely manner have an excellent prognosis.

11.9.2 Histology

The histologic findings and differential diagnosis of erysipelas are identical to those seen in cellulitis (Sect. 11.6).

11.9.3 Pathogenesis

Streptococcus pyogenes is the usual cause of erysipelas. However, groups B, C and G streptococci can cause a similar eruption, as can *Staphylococcus aureus* [34].

11.10 Necrotizing Fasciitis

11.10.1 Clinical Features

Necrotizing fasciitis is a rare severe soft tissue infection. The annual incidence of necrotizing fasciitis in the United States is approximately 500–1000 cases. Although it can affect any

age group, it is somewhat more common in patients over the age of 50. The male to female ratio is 3:1 [35]. Typical sites include the extremities, perineum, genitalia, and abdomen. In the early stages of disease, the clinical findings are similar to those seen in cellulitis. There is tenderness, erythema, and swelling of the affected tissues. Pain often becomes severe, and classically appears out of proportion to the physical findings. As the infection progresses, bullae, ecchymoses, and necrosis can develop. Early diagnosis and treatment is critical for a favorable outcome. Even with optimal treatment, disease morbidity is significant, and mortality rates are between 25 and 35 % [36].

11.10.2 Histology

The histologic changes are those of a suppurative process involving primarily the deep subcutaneous fat and underlying fascia (Figs. 11.9 and 11.10). In some cases, the process extends into the deeper portions of the reticular dermis. There is marked vascular necrosis and thrombosis as well as extensive tissue necrosis. Sheets of bacteria are seen on routine H&E stains, and generally not requiring Gram stains in order to be observed. While group A streptococcal infections are implicated in most cases, a wide range of bacteria may cause this process.

11.10.3 Pathogenesis

Necrotizing fasciitis occurs as a result of bacterial infection. While many microorganisms have been implicated, group A *Streptococcus pyogenes* is the most commonly associated agent. In many patients, there are associated comorbidities, such as diabetes mellitus, which appear to increase the risk for this potentially lethal infectious process [37]. Streptolysin S produced by group A streptococci may play a role in the virulence of this process by attacking keratinocytes and initiating programmed cell death. Furthermore, this toxin incites inflammatory cascades that result in the downregulation of Akt pathway-mediated cytoprotection. Streptolysin S may play a role in facilitating the deep invasion and extensive cellular destruction seen in necrotizing fasciitis [38].

Serotype M3 group A streptococcus is one of the three most frequently associated strains. It has been shown that M3 serotype has a significant ability to evade neutrophil- and TNF-α-mediated responses to infection, resulting in increased microbial ability to invade soft tissue [39]. Group A streptococci also produce SpeB, which is a potent cysteine protease that appears to play a significant role in the virulence of this process [40].

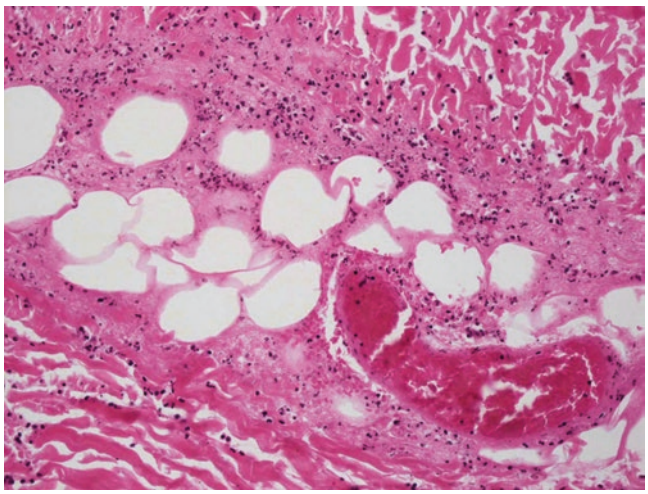

Fig. 11.9 Vascular occlusion by fibrin thrombi, inflammation, and surrounding necrosis of the deep dermis, subcutis, and underlying fascia are seen in necrotizing fasciitis

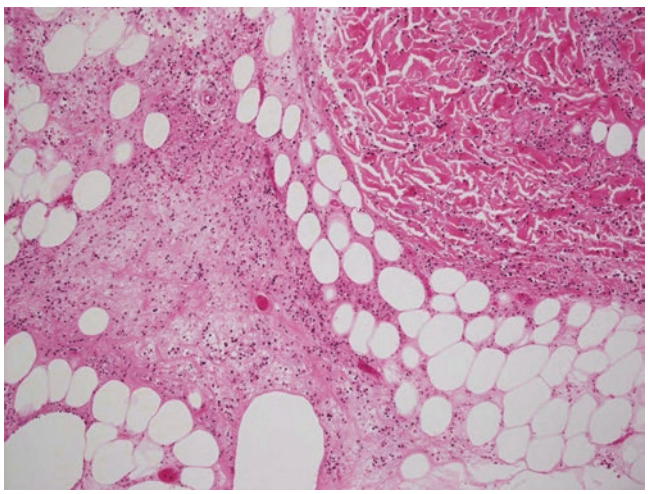

Fig. 11.10 Total necrosis of the subcutis and a dense neutrophilic inflammatory infiltrate characterize necrotizing fasciitis

11.11 Meningococcemia

11.11.1 Clinical Features

Invasive meningococcal disease includes meningitis and meningococcemia. Although meningitis is more common (30–60 % of meningococcal cases), meningococcemia accounts for the initial presentation in 20–30 % of cases [41].

A widespread morbilliform blanching rash is often present early in the disease course, and persists in up to 13 % of cases. A petechial and purpuric eruption develops in up to 80 % of patients. In severe cases with disseminated intravascular

coagulation, purpura fulminans may develop, often leading to extensive necrosis and loss of tissues. The mortality rate of meningococcemia in developed countries is estimated at 10–20 %.

11.11.2 Histology

Histologic findings are those of a marked vascular occlusive process. Within the dermis, there is widespread thrombosis within blood vessel walls with a mild to moderately intense neutrophilic infiltrate surrounding the vessels (Figs. 11.11 and 11.12). Edema and hemorrhage are seen in most cases [42]. Microorganisms are not ordinarily apparent on H&E sections, although they can be seen on tissue Gram stains, and will be evident with tissue microbiological culture.

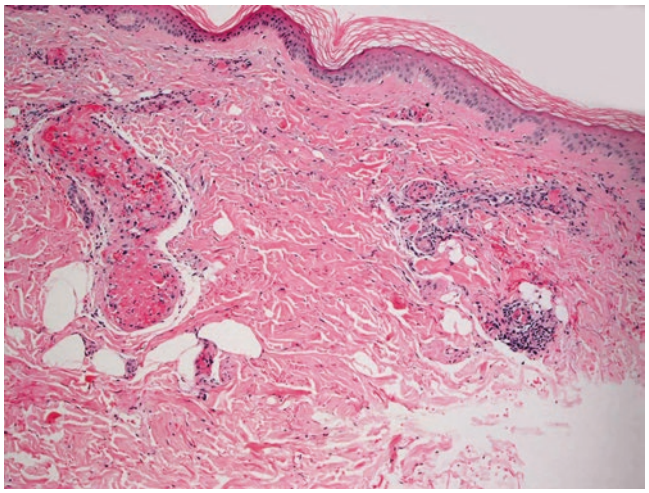

Fig. 11.11 Acute meningococcemia is characterized by distended and thrombosed dermal blood vessels, often lacking significant surrounding inflammatory infiltrate

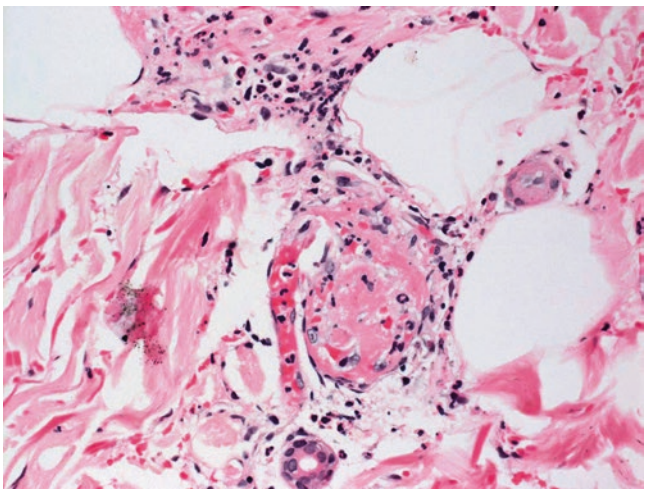

Fig. 11.12 Fibrin thrombi occlude dermal blood vessels in meningococcemia

The differential diagnosis includes other causes of vascular occlusive disease, including gonococcemia, lupus anticoagulant, protein C deficiency, and other primary coagulopathies and cryoglobulinemias. Leukocytoclastic vasculitis generally has more inflammation and less thrombosis than is seen with meningococcemia, although other types of septicemia-induced vasculitis may show identical changes. In these cases, tissue microbiological cultures are required to isolate the offending organisms. Henoch–Schonlein purpura can be differentiated based upon the presence of peri-vascular IgA, which is not seen in meningococcemia, as well as by the different clinical presentation [43].

11.11.3 Pathogenesis

Neisseria meningitidis is the causative microorganism of meningococcemia. It is able to invade vascular endothelial cells by remodeling endothelial barriers [44]. Using type IV pili, the microorganism interacts with endothelial cells, resulting in vascular leakage and thrombosis [45, 46]. Furthermore, *Neisseria meningitidis* produces an endotoxin that results in cytokine-mediated dysregulation of the anticoagulant and procoagulant balance [42]. Interleukin-12, interferon-γ, tumor necrosis factor-α, and interleukin-1 activities can cause a consumptive coagulopathy of proteins C and S, leading to the clinical presentation [42].

11.12 Gonococcemia

11.12.1 Clinical Features

Gonococcemia results from systemic dissemination of untreated primary infection with *Neisseria gonorrhoeae*. Disseminated infection occurs in approximately 1–3 % of individuals with gonorrhea [47]. Approximately 60 % of patients with gonococcemia develop cutaneous involvement [48]. Typically, skin lesions are few in number and localized to the extremities. They usually begin as small papules that evolve into hemorrhagic pustules. Occasionally, bullae, petechiae, or necrotic areas develop.

11.12.2 Histology

The histologic changes in gonococcemia are identical to those seen in meningococcemia as described in Sect. 11.11 above.

11.13 Erythrasma

11.13.1 Clinical Features

Erythrasma is a skin disorder caused by infection with *Corynebacterium minutissimum*. It is more common in patients who are overweight, elderly, and diabetic, especially in warm climates [49]. It tends to occur in intertriginous areas, such as the inguinal, interdigital, intergluteal, and inframammary creases.

Clinically, lesions appear as well-defined red brown patches and thin plaques. Mild pruritus may be present, although most cases are asymptomatic. Examination with a Wood's lamp shows bright purple red fluorescence of affected areas. With appropriate therapy, the prognosis is excellent, although some patients may be prone to recurrences. Immunocompromised patients may sometimes progress to serious systemic infections.

11.13.2 Histology

Biopsies are rarely performed when a diagnosis of erythrasma is clinically suspected. Clinical diagnosis is usually confirmed with Wood's light examination. Histologic changes in skin biopsies are quite subtle. Within the stratum corneum, small foci of parakeratosis are present within which microorganisms may be identified (Fig. 11.13). The term "Chinese characters" has been given to the angulated Corynebacteria that are usually evident with routine H&E staining, but they can be highlighted with tissue Gram stains. Minimal epidermal spongiosis may be present, and there is usually a scant lymphocytic inflammatory response.

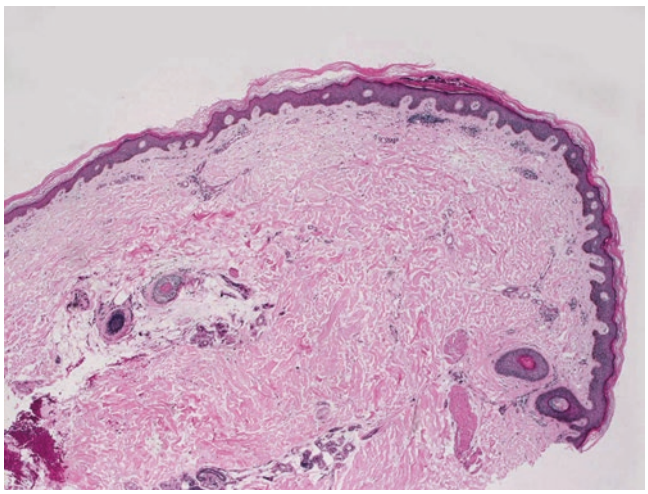

Fig. 11.13 Subtle histologic findings in erythrasma are limited to small foci of bacteria within the stratum corneum with virtually minimal inflammation

The main histologic differential diagnosis is that of normal skin. Close examination of the stratum corneum and clinical correlation will lead to an accurate diagnosis in most cases. While dermatophytosis may have similar histologic changes, PAS stains clearly make the distinction. Candidiasis is usually more inflammatory with abundant neutrophils within the epidermis and occasionally within the superficial dermis.

11.13.3 Pathogenesis

Erythrasma is the direct result of colonization by *Corynebacterium minutissimum*. There is some ultrastructural evidence that suggests the microorganisms are able to invade the stratum corneum by inducing keratolysis [50].

11.14 Malakoplakia

11.14.1 Clinical Features

Cutaneous manifestations are quite unusual in malakoplakia. When present, they most often occur in the genitourinary skin, although lesions have been described in other sites. Lesions are soft, yellow friable plaques and nodules. Malakoplakia is more common in immunocompromised individuals [51, 52]. Treatment with antibiotics may be helpful in resolving cutaneous lesions [53].

11.14.2 Histology

Malakoplakia rarely involves the skin. However, the histologic changes in the skin resemble those seen in other sites. In malakoplakia, aggregates of foamy macrophages fill the dermis. Granulomatous inflammation is often present surrounding foamy macrophages. These cells are filled with calcified basophilic spherules known as Michaelis–Gutman bodies. The spherules are highlighted on PAS, Perl's iron, and von Kossa stains [53]. Bacteria are not readily apparent on routine H&E stains, but they can be identified with antibodies directed against *mycobacterium bovis* [54].

11.14.3 Pathogenesis

Although not fully understood, malakoplakia is widely believed to be the result of an acquired bactericidal defect within macrophages that is frequently encountered in immunosuppressed individuals and those with autoimmune disorders [51, 52]. In malakoplakia, macrophages engulf bacteria appropriately, but their ability to digest the microorganisms intracellularly is impaired [55].

11.15 Tuberculosis

11.15.1 Clinical Features

Cutaneous tuberculosis presents with a wide variety of skin lesions, including papules, verrucous plaques, and chronic ulcers. There are four major categories of cutaneous tuberculosis [56].

- Cutaneous tuberculosis caused by inoculation from an exogenous source include primary inoculation tuberculosis or chancre, and tuberculosis verrucosa cutis. In primary inoculation tuberculosis, a firm reddish brown papulonodule develops 2–4 weeks after inoculation and slowly enlarges, sometimes resulting in a friable ulcer or verrucous plaque. Tuberculosis verrucosa cutis begins as erythematous papules surrounded by a purple halo, and evolve into asymptomatic verrucous plaques that may ulcerate or develop central atrophy.
- Cutaneous tuberculosis resulting from endogenous spread, either contiguously or via autoinoculation, include scrofuloderma and orificial tuberculosis. In scrofuloderma, painless, cold abscesses develop and often evolve into plaques with draining fistulae. The most common site is the cervical lymph node chain. In orificial tuberculosis, lesions are friable, erythematous and painful papules and nodules that develop into painful ulcers.
- Cutaneous tuberculosis resulting from hematogenous spread include lupus vulgaris, acute miliary tuberculosis, and tuberculous gumma, ulcer or abscess. In lupus vulgaris, lesions appear as papules, nodules, or reddish brown plaques. In acute miliary tuberculosis, erythematous papules and vesicles appear, sometimes with overlying crust. In tuberculous gumma, ulcer or abscess, there are a few subcutaneous nodules scattered over the trunk and extremities.
- Cutaneous tuberculosis associated with an underlying focus of infection (tuberculids) include papulonecrotic tuberculid, lichen scrofulosorum, and erythema induratum (also known as Bazin disease). Papulonecrotic tuberculid presents as an eruption of papules and pustules that affect the face, ears, trunk, buttocks, and extensor extremities. Lichen scrofulosorum is characterized by plaques that are composed of indurated grouped small red papules, most commonly located on the trunk. Erythema induratum is characterized by reddish purple subcutaneous nodules over the posterior thighs and legs of young and middle aged females.

11.15.2 Histology

There are several histologic patterns that may be encountered in children with cutaneous involvement by *Mycobacteria tuberculosis* infection. These correlate with the various clinical forms of the disease, but they are all characterized by the presence of necrotizing granulomas in the dermis with a variably intense inflammatory response as well as the presence of microorganisms on acid fast bacilli (AFB) stains. In most cases, a collarette of lymphocytes surrounds the tuberculoid granulomas. Lupus vulgaris, tuberculosis verrucosa cutis and scrofuloderma have all been described in children [57]. Scrofuloderma generally presents with an atrophic or ulcerated epidermis under which is a markedly necrotic dermis with granulomas (Figs. 11.14 and 11.15). In these cases, microorganisms are more plentiful in tissue sections than in the other types of cutaneous tuberculosis infection. In lupus vulgaris, the epidermis may be hyperplastic or even verrucous and papillomatous. In some cases of lupus vulgaris, there may be epidermal atrophy and ulceration [58]. Caseating necrosis is seen in most granulomas, but microor-

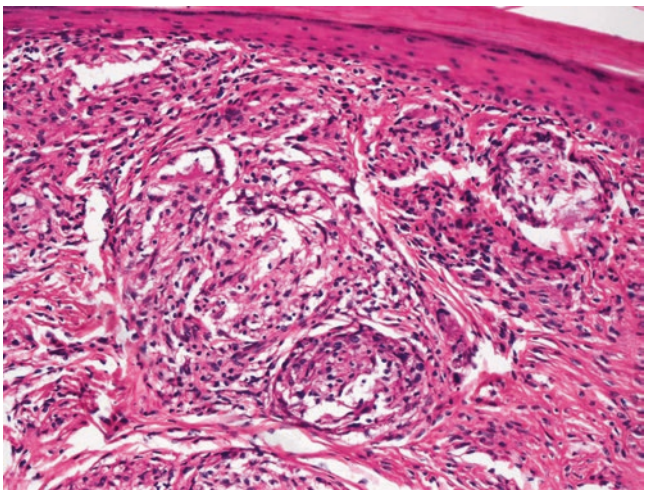

Fig. 11.14 Scrofuloderma demonstrates a thinned epidermis with abundant tuberculoid granulomas surrounded by lymphocytes in the dermis

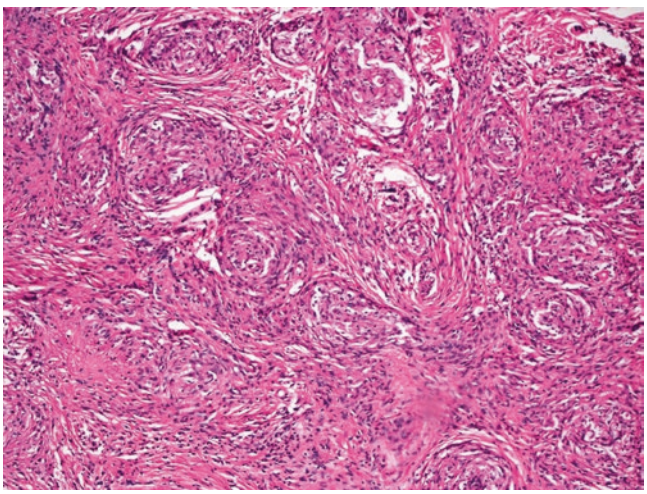

Fig. 11.15 Well-formed tuberculoid granulomas surrounded by lymphocytes and fibrosis are seen in a long-standing case of scrofuloderma

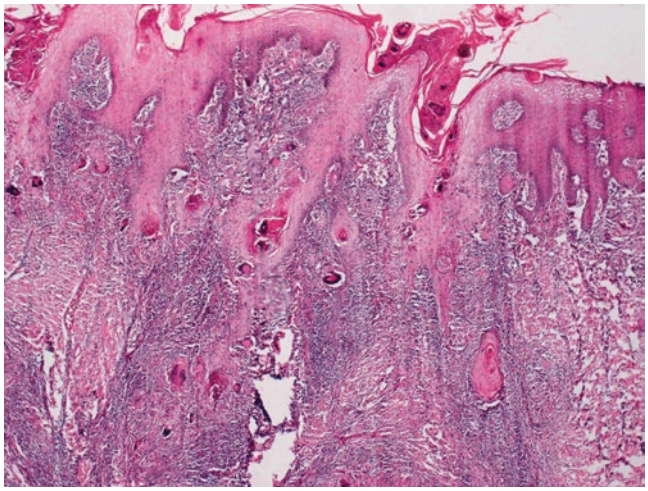

Fig. 11.16 An acanthotic epidermis with hyperkeratosis and elongated rete ridges is seen atop a dermis with a granulomatous and markedly inflammatory infiltrate in tuberculosis verrucosa cutis

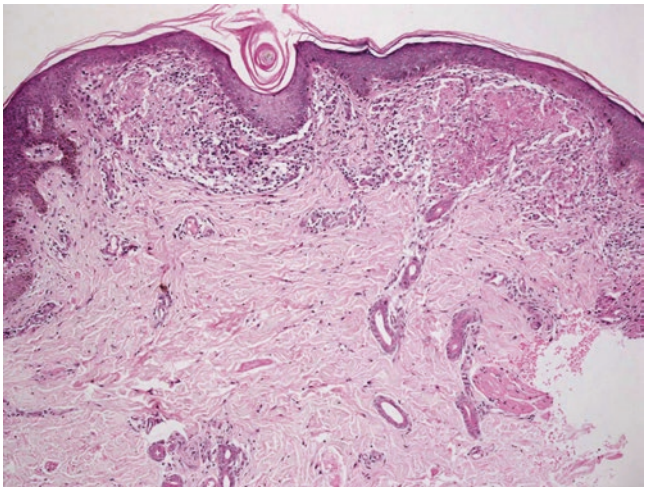

Fig. 11.18 Scattered tuberculoid granulomas are present in the dermis in lichen scrofulosorum

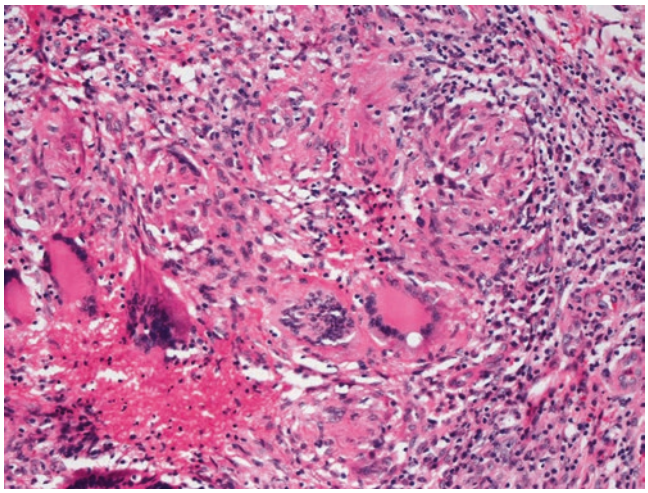

Fig. 11.17 Epithelioid granulomas with multinucleated giant cells are present in tuberculosis verrucosa cutis

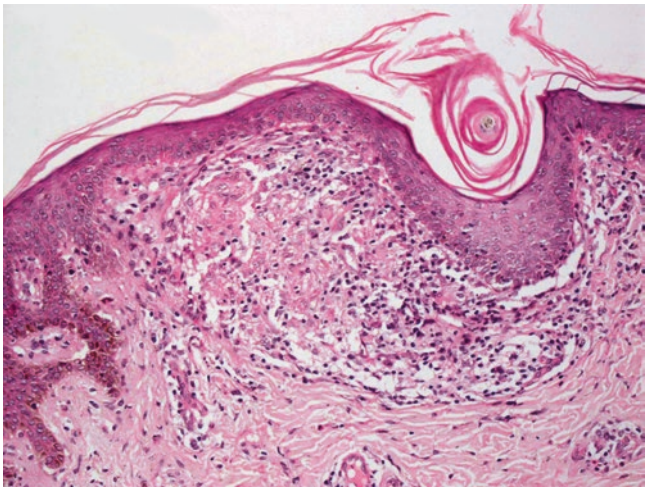

Fig. 11.19 Well-formed granulomas with a collarette of lymphocytes are seen in lichen scrofulosorum

ganisms are relatively difficult to find. Verrucous epidermal hyperplasia and papillomatosis are common features of tuberculous verrucosa cutis, which is caused by direct inoculation of the offending microorganisms into the skin at the affected site (Figs. 11.16 and 11.17). In these cases, bacilli, while not plentiful, are generally found on special stains.

Papulonecrotic tuberculid and lichen scrofulosorum are two types of tuberculid reactions that occur in children. Papulonecrotic tuberculid is characterized by marked tissue necrosis throughout the superficial and deep portions of the dermis with granulomatous inflammation at the periphery of the necrotic regions [59]. Leukocytoclastic vasculitis is seen in most cases [60]. As this is a type of hypersensitivity reaction to a systemic antigen, no microorganisms are identified within biopsies of the lesions. Lichen scrofulosorum demonstrates well-formed granulomas that may or may not have central caseating necrosis (Figs. 11.18 and 11.19). A lichenoid inflammatory infiltrate with a dense lymphocytic infiltrate along the dermal-epidermal junction is seen in some cases. The granulomas have been described as peri-follicular [61–63]. Acid-fast bacilli are not seen in most cases.

The differential diagnosis of cutaneous tuberculosis varies with the type of reaction pattern. In cases of lupus vulgaris, granulomatous rosacea and sarcoidosis must be considered. A peri-follicular distribution of the granulomatous reaction pattern is present in rosacea, and would not

be expected in lupus vulgaris. Caseating granulomas would be most unusual, except in lupus miliaris disseminatum faciei that could be distinguished based upon the clinical presentation. Sarcoidosis generally lacks a significant collarette of lymphocytes surrounding the granulomas. In addition, some cases of sarcoidosis present with small granulomas high in the papillary dermis, which is a useful distinguishing feature if present.

Tuberculosis verrucosa cutis might be confused with squamous cell carcinoma on account of marked epidermal hyperplasia, but it would not be expected to have cytologic atypia seen in a neoplastic process. In addition, granulomatous inflammation would be unusual in the squamous cell carcinoma. Deep fungal infections, particularly blastomycosis, chromomycosis and sporotrichosis, might demonstrate similar histologic patterns, but these entities can be distinguished based upon special stains for microorganisms, including AFB and PAS stains. In rare cases, halogenodermas might have similar epidermal changes and a marked underlying inflammatory response, but granulomas would be unusual. Similarly, pemphigus vegetans and blastomycosis-like pyoderma demonstrate epidermal hyperplasia and marked underlying inflammation, but caseating granulomas would not be expected in these entities. Scrofuloderma could be confused with many types of infectious processes, all of which can be distinguished with the use of tissue Gram, PAS and AFB stains. AFB stains are generally positive in this type of cutaneous tuberculosis.

11.15.3 Pathogenesis

Cutaneous tuberculosis is caused by infection by *mycobacterium tuberculosis*. The bacilli can be isolated from the skin in each of the various types of cutaneous lesions, albeit in varying numbers. Virulent strains of mycobacteria have highly acidic lipids that interact with lysosomal hydrolases, and immobilize and inactivate degradative enzymes. Similarly, these lipids may alter bactericidal basic proteins [64]. Lipoarbinomannan, which is a glycolipid found in the cell wall of *mycobacterium tuberculosis* and *mycobacterium leprae*, is highly immunogenic and a potent inhibitor of macrophages [65]. It has long been believed that tuberculids are type III and IV hypersensitivity reactions to mycobacterium tuberculosis that manifest at some distant site away from the actual cutaneous eruption [59, 60, 66]. However, through polymerase chain reaction (PCR) testing, it is now estimated that mycobacterial DNA can be found in lesional tissue in more than 50 % of cases [59, 66, 67]. Thus, it remains somewhat unclear as to whether these lesions are hypersensitivity reactions or sites of direct bacterial infection, or a combination of both.

11.16 Atypical Mycobacterial Infections

11.16.1 Clinical Features

Lesions often initially appear as an erythematous papule or nodule at the inoculation site that slowly enlarges and may develop ulceration (Fig. 11.20). Some infections progress to multiple lesions.

11.16.2 Histology

Histologic changes are largely identical, independent of the offending mycobacterial species. Early lesions tend to have mixed inflammatory infiltrates, often dominated by neutrophils diffusely within the dermis (Figs. 11.21 and 11.22). A vascular proliferation is commonly seen in early lesions. As the lesions evolve, a granulomatous process becomes more prominent, and the inflammatory infiltrate contains more lymphocytes. Multinucleated giant cells are often seen. Overlying epidermal hyperplasia is a common but not constant finding [68]. Eosinophils are not a prominent part of the inflammatory response in most cases. The inflammatory process and granuloma formation may extend down fibrous septa and into the subcutaneous fat [69].

The histologic differential diagnosis is dependent upon the stage of the lesion biopsied. Early lesions that are pre-

Fig. 11.20 Atypical mycobacterial infection presents as an erythematous indurated plaque with central erosion and crusting on the face of a boy with hypohidrotic ectodermal dysplasia with immunodeficiency

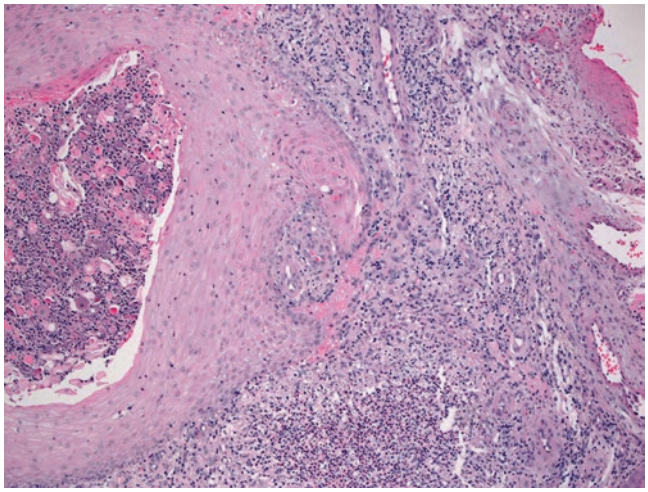

Fig. 11.21 Pseudoepitheliomatous hyperplasia and neutrophilic abscesses are present along with granulomatous inflammation in *Mycobacterium fortuitum* infection of the skin

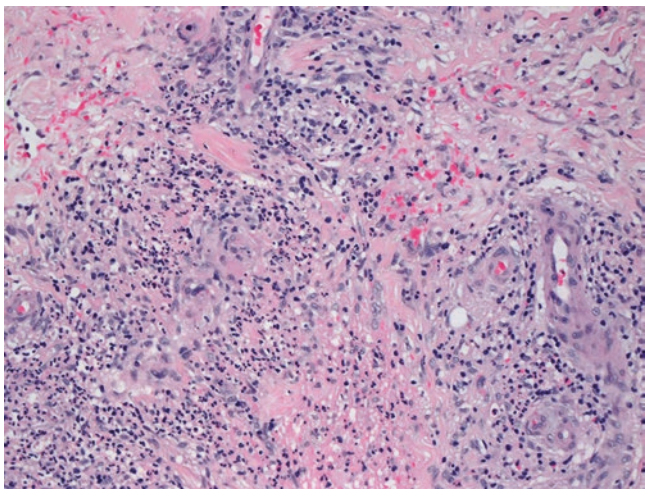

Fig. 11.22 A granulomatous and neutrophilic inflammatory infiltrate is characteristic of *mycobacterium fortuitum* infection

dominantly neutrophilic may raise a differential diagnosis of Sweet's syndrome and leukocytoclastic vasculitis, but they fail to demonstrate true vascular destruction. AFB stains may be helpful in making the distinction, as well as tissue microbiological cultures. Older lesions result in a differential diagnosis of granulomatous processes, including deep fungal infections, sarcoidosis, *Mycobacterium tuberculosis* infection, and, rarely, granuloma annulare or necrobiosis lipoidica. In the latter entities, caseating necrosis would not be expected, while mucin deposition and paucicellular areas with collagen degeneration (necrobiosis) can help to resolve the dilemma.

11.17 Leprosy

11.17.1 Clinical Features

There are several different clinical forms of leprosy, which is caused by *Mycobacterium leprae*. These are often classified based upon the host's immune response to infection. In one classification, a tuberculoid form (TT) is described at one end of the spectrum and a lepromatous form (LL) is at the other end, with borderline forms in between the spectrum [70].

In the TT form, there is a strong host immune response, and the disease is limited. Skin lesions are often single and small. They are typically erythematous plaques with raised borders, hypopigmented centers, and decreased sensation. In the LL form, a lack of host cellular immune response allows hematogenous spread of the infection. Multiple reddish brown, hypopigmented macules and patches appear and develop into nodules and plaques. The patient may also have profoundly dry skin. Lesions of the borderline forms can be a combination of the other two, but vary in size, number and symmetry, based upon the extent of the host's cellular immune response.

11.17.2 Histology

The histologic features and classification of leprosy do not differ between adults and children. Histologic findings cover a spectrum of changes from those cases with well-formed, almost sarcoidal-like granulomas as seen in tuberculoid form to poorly-formed aggregates or sheets of histiocytes as seen in lepromatous form.

Tuberculoid leprosy demonstrates well-formed aggregates of histiocytes surrounded by a collarette of lymphocytes and rare plasma cells (Fig. 11.23). These granulomas are often oblong as they track along cutaneous nerves, and enlarged nerves are not an uncommon finding (Figs. 11.24 and 11.25). Fite stains generally reveal only scant *Mycobacterium leprae* following extensive searching.

The changes in borderline tuberculoid leprosy are similar to those seen in the tuberculoid leprosy, although, in general, granulomas are less cohesive, and the surrounding lymphoid infiltrate is less brisk. The likelihood of finding microorganisms on Fite stains is greatly improved.

Dense sheets of poorly aggregated histiocytes characterize lepromatous leprosy. The cytoplasm of the histiocytes often demonstrates granular clumps of eosinophilic material that represent clusters of intracellular microorganisms, which are easily detected on Fite stains (Fig. 11.26). There is essentially no surrounding lymphocytic infiltrate since there is minimal host immune response.

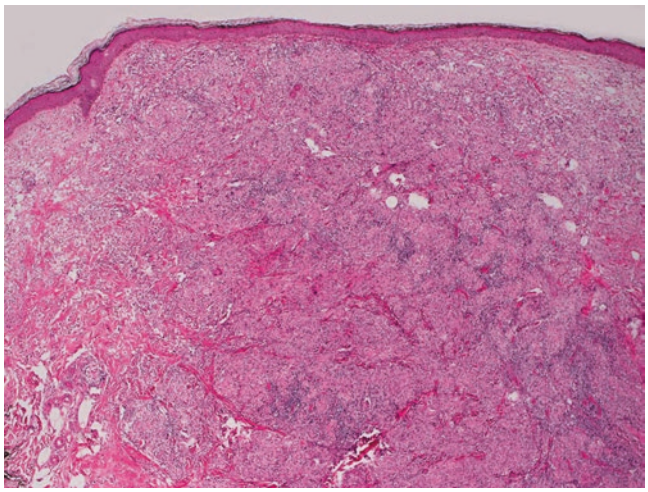

Fig. 11.23 Leprosy demonstrates sheets of granulomas throughout the dermis with variable numbers of intervening lymphocytes

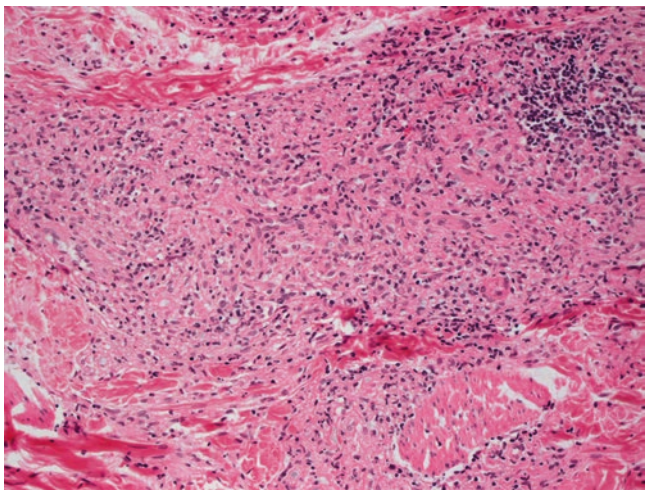

Fig. 11.25 An elongated granuloma surrounded by lymphocytes and plasma cells is a characteristic finding in leprosy

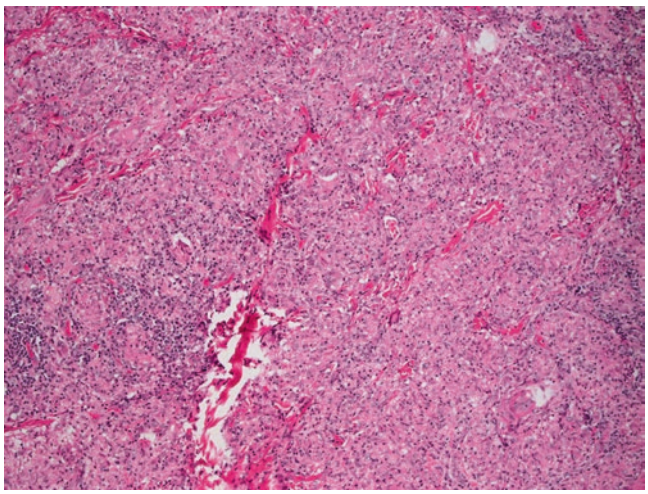

Fig. 11.24 Many granulomas, some of them oblong in shape, with surrounding lymphocytes and plasma cells are seen in leprosy

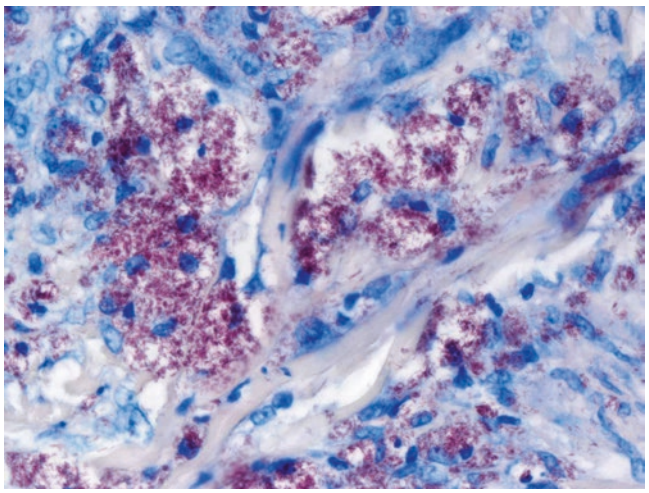

Fig. 11.26 A Fite stain demonstrates numerous acid-fast bacilli within histiocytes in lepromatous leprosy

The changes in borderline lepromatous leprosy are similar to those in lepromatous leprosy, but there is a slightly more intense lymphocytic response. Microorganisms, however, are not quite as readily apparent. It is unusual to see clusters of intracellular microorganisms in the borderline form of the disease. Use of in situ hybridization and immunohistochemistry may be helpful in improving the sensitivity of microorganism detection in these cases [71].

The most difficult variant of the disease to diagnose is the indeterminate form. In these cases, there is a dense lymphocytic infiltrate, often surrounding nerves and hair follicles. There are only small clusters of histiocytes that may be inconspicuous. Microorganisms are difficult to find even on Fite stains [72].

11.17.3 Pathogenesis

Leprosy is caused by infection with *Mycobacterium leprae*. Its thick capsule contains many lipids, including phenolic glucolipid-1, which serve as a target for immunoglobulin-mediated humoral response [73]. Lipoarabinomannan, also present on the bacterial cell wall, serves as a major virulence factor in the bacteria and an antigen for macrophages in which the microorganisms frequently reside.

M. leprae binds to Schwann cells through the G domain of the laminin-α2 chain, which is expressed specifically in the Schwannian basal lamina [74]. This interaction results in the nerve damage that is seen in patients with long-standing leprosy.

The nature of the disease expression is largely a function of the host immune response. Class II HLA major histocompatibility complex genes on chromosome 6 appear to play a role in the type of leprosy that a patient develops. HLA-DR2 and HLA-DR3 are associated with tuberculoid leprosy, while HLA-DQ1 is commonly associated with lepromatous leprosy [73].

11.18 Actinomycosis

11.18.1 Clinical Features

Actinomycosis is a chronic suppurative granulomatous infection caused by anaerobic gram-positive bacteria of the Actinomyces species. The most common form, orocervicofacial actinomycosis, results from odontogenic infection, and accounts for approximately 60 % of reported cases [75]. Although primary skin actinomycosis can occur, it is poorly described. Most cases occur as progressive skin inflammation, resulting in abscess or nodular lesions that develop fistulas.

11.18.2 Histology

Actinomycosis infection in the skin shows a dermis filled with a dense and diffuse neutrophilic infiltrate that surrounds basophilic "sulfur granules," which can be quite large in some cases. These "granules" represent dense aggregates of hyphae, and they are surrounded by eosinophilic material, the peripheral clubs of the microorganisms (Splendore-Hoeppli phenomenon). Later stage lesions demonstrate a granulomatous response [76]. Gomori methenamine silver stains actinomycosis. The microorganisms are negative on acid-fast stains, unlike nocardiosis, which is histologically similar but acid fast positive.

11.18.3 Pathogenesis

Actinomycosis is caused by *Actinomyces israelii*. In most cases, other bacteria coexist with the actinomyces. These bacteria aid in the infectious process by serving as co-pathogens. Actinomyces have very low inherent pathogenicity, and rely upon co-pathogens to produce toxins and inhibit host defenses.

11.19 Nocardiosis

11.19.1 Clinical Features

Primary cutaneous nocardiosis is rare, and its incidence is not known. However, nocardiosis is most prevalent in rural populations, where people are more likely to go barefoot outdoors. Three clinical variants have been described: mycetoma, superficial skin infections, and lymphocutaneous (sporotrichoid) [77]. Mycetoma typically begins as a subcutaneous swelling on the foot, which then develops into a painless, firm, nodular mass with draining sinus tracts. Superficial skin infections present as cellulitis, abscesses, ulcers, and granulomas. Lymphocutaneous type of infection is the least common type, and presents with painful suppurative nodules that spread in a linear fashion along lymphatic channels.

11.19.2 Histology

The histologic changes in nocardiosis are quite similar, if not identical, to those seen in actinomycosis. The dermis is filled with a diffuse and dense infiltrate of neutrophils with frank abscess formation, tissue necrosis, and hemorrhage (Fig. 11.27). Later lesions demonstrate fibrosis, and a more lymphohistiocytic inflammatory infiltrate. The microorganisms are not readily apparent on routine H&E stains, but they can be visualized on Gram stain and Gomori methenamine silver stain. They are also weakly acid fast positive in contrast to actinomycosis microorganisms, which are acid fast negative.

11.19.3 Pathogenesis

Nocardiae are aerobic bacteria that belong to the actinomycetes group of microorganisms. Nocardia species are resistant to phagocytosis, and they are also capable of inhibiting the phagosome–lysosome fusion and resisting hydrolytic destruction. Some species produce superoxide dismutase and catalase that increase their resistance to human neutrophils [78]. Neutrophils and macrophages are the first line of

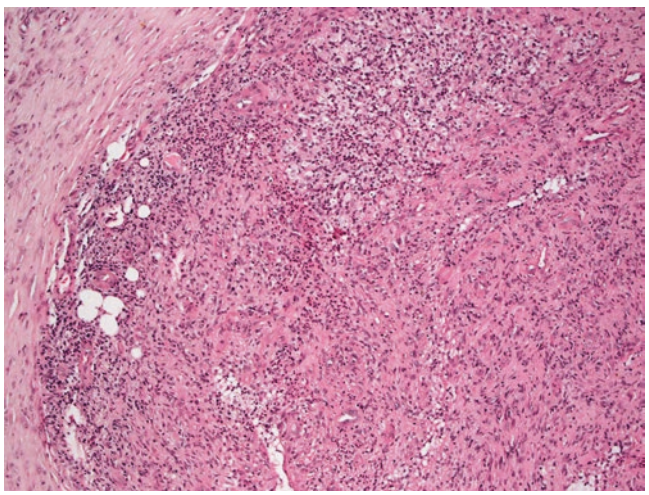

Fig. 11.27 Nocardiosis demonstrates a granulomatous infiltrate with a brisk neutrophil-rich inflammatory infiltrate

defense, slowing the spread of the infection; however, T lymphocytes provide the direct cytotoxicity that destroys the microorganisms [79].

11.20 Syphilis

11.20.1 Clinical Features

Syphilis is caused by the spirochete *Treponema pallidum*, and it spreads primarily via sexual contact. In 2007, there were 3.8 reported cases of primary/secondary syphilis per 100,000 individuals in the United States. In 2008, there were 10.1 cases of congenital syphilis per 100,000 live births [80].

Primary syphilis typically presents as a solitary painless genital chancre. Occasionally, chancres are multiple or located in nongenital sites. If untreated, primary syphilis progresses to secondary syphilis within 6–8 weeks after the chancre. A generalized exanthem of pink macules and papules appears. Other cutaneous features include patchy alopecia and intertriginous flat papules known as condylomata lata. Untreated infection progresses to a latent stage, which is typically asymptomatic. One-third of latent cases will develop into tertiary syphilis. Cutaneous features of tertiary syphilis include granulomas, gummas, and psoriasiform plaques.

Congenital syphilis results from transplacental spread or direct contact with infectious genital lesions during birth. Up to two-thirds of affected infants are asymptomatic at birth. Symptoms may manifest early (during the first 48 months of life) or late (4 to 20 years of age). Early signs of congenital syphilis include a diffuse morbilliform rash.

11.20.2 Histology

Some cases of congenital syphilis have presented with both clinical and histologic features of erythema multiforme. In these cases, there are multiple dyskeratotic cells resulting in subepidermal blister formation and underlying interface dermatitis. Spirochetes have been identified by PCR because they were not readily apparent on skin biopsy even on Warthin–Starry stains [81].

The histologic changes of primary and secondary syphilis are rarely encountered in children. When present, they are indistinguishable from those seen in similarly infected adults. The epidermis may be psoriasiform or slightly spongiotic, resembling either pityriasis rosea or psoriasis. A patchy or dense, band-like infiltrate of lymphocytes with scattered plasma cells is present within the dermis, and it can be only superficial or involve the reticular dermis (Figs. 11.28 and 11.29). Endothelial cell swelling is often seen, but not a specific finding. Spirochetes can be detected in most cases with use of Warthin–Starry stains, although detection using anti-spirochete antibodies is easier to interpret and more sensitive (Fig. 11.30).

11.20.3 Pathogenesis

Syphilis is caused by infection with *Treponema pallidum*. Treponema adheres to epithelial cells in order to initiate the process. Treponemal protein TP0751 binds to laminin and fibrinogen [82]. The spirochete invades through the tight junctions between adjacent endothelial cells, and induces the production of MMP-1 that degrades collagen and facilitates spirochete transport into the bloodstream, leading to subsequent systemic spread [83]. Lipoproteins present on the invading microorganisms induce expression of adhesion molecules ICAM-1, VCAM-1, and E-selectin. They are also responsible for inducing the production of IL-12 and other inflammatory cytokines [84]. Type 1 T-helper cell immune response is seen in primary syphilis that evolves into type 2 T-helper cell response in secondary syphilis [85]. The microorganisms undergo increasing diversity in the Tprk V region of its genome that likely serves as a mechanism to escape immune surveillance.

11.21 Pinta

11.21.1 Clinical Features

Pinta is the mildest form of the endemic human treponematosis. It is caused by *Treponema carateum*. Lesions are limited to the skin, and there is no risk of systemic involvement or vertical transmission. Although the exact mechanism of transmission is not known, it is thought to be via direct contact with infected skin lesions. After a variable incubation period, the early stage begins with a primary erythematous papule or plaque on exposed skin, with or without satellite lesions. Over time, the papules enlarge to form plaques with a pale center. After months to years, multiple small scaly papules may appear diffusely, and enlarge to form psoriasiform plaques. In the late stages, pigmentary changes, atrophy, and hyperkeratosis predominate [86].

11.21.2 Histology

Histologic changes are quite similar to those seen in secondary syphilis with psoriasiform epidermal hyperplasia, basilar vacuolization, and a band-like infiltrate in the papillary der-

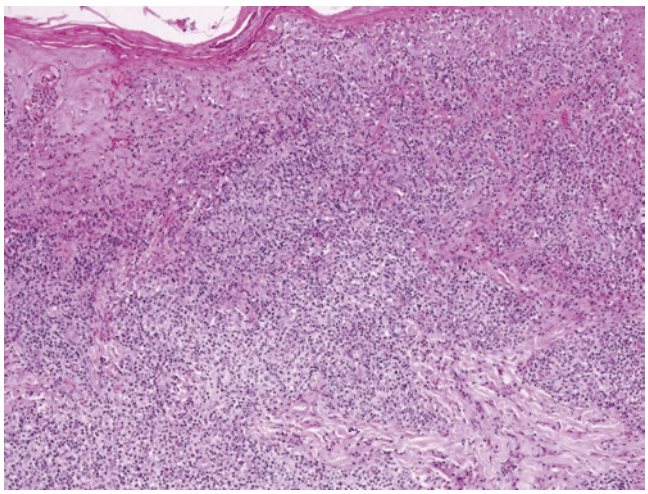

Fig. 11.28 An acanthotic epidermis with a dense band-like inflammatory infiltrate is seen in syphilis

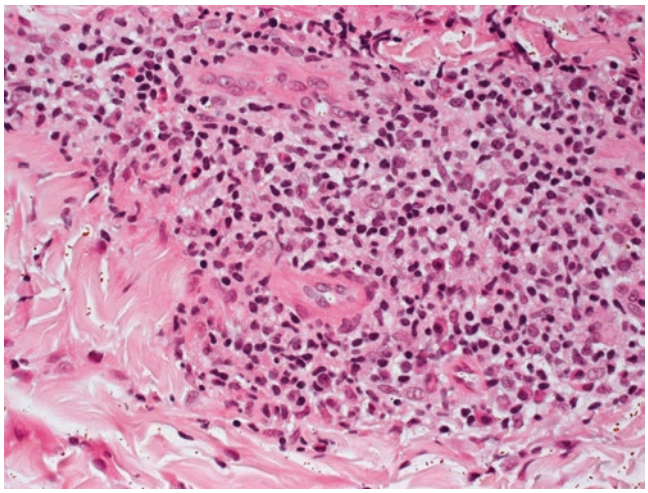

Fig. 11.29 Endothelial cell swelling and a dermal infiltrate with lymphocytes and numerous plasma cells characterize syphilis

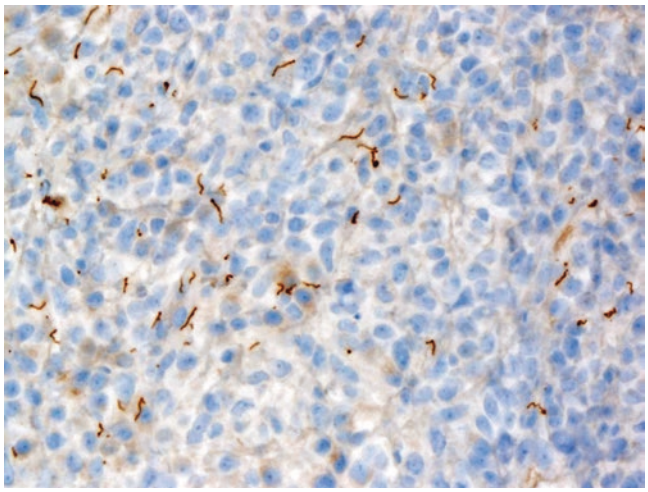

Fig. 11.30 Antibodies directed against *Treponema pallidum* demonstrate abundant spirochetes in secondary syphilis

mis that is predominantly lymphohistiocytic with scattered plasma cells. There is also a superficial perivascular infiltrate with some endothelial cell swelling. As lesions progress, epidermal melanin is found in melanophages within the papillary dermis. The inflammatory infiltrate is less intense in older lesions. Spirochetes can be demonstrated with a Warthin–Starry stain in early and intermediate stage lesions, but they are difficult to find in late stage lesions.

11.21.3 Pathogenesis

Pinta is caused by the *Treponema pallidum* subspecies *carateum*. The clinical manifestations result from the immunologic response to the microorganisms, namely an infiltrate of lymphocytes and plasma cells.

11.22 Lyme Disease

11.22.1 Clinical Features

Lyme borreliosis is an infection caused by the spirochete *Borrelia burgdorferi,* and is transmitted to humans by ticks of the genus *Ixodes*. In the United States, the Center for Disease Control reported an incidence of approximately 30,000 cases in 2009 [87, 88]. Peak incidence for Lyme disease occurs in children 5–9 years of age, and in adults 55–59 years of age.

The clinical manifestations of Lyme disease are divided into three stages: early localized disease, early disseminated disease, and late disseminated disease. In early localized disease, most patients present with erythema chronicum migrans, which is a characteristic skin lesion appearing 7–14 days after a tick bite. This begins as an erythematous macule or papule at the site of the bite that rapidly expands centrifugally, often developing central clearing. Although the lesion may become quite large in size, it is usually asymptomatic. In early disseminated disease, a more diffuse rash consisting of multiple erythematous annular lesions appears. In late disseminated disease, arthritis appears, affecting large joints especially the knees.

11.22.2 Histology

The histologic findings in erythema chronicum migrans are relatively nonspecific, and make this a difficult diagnosis to render without clinical pathologic correlation. There are typically no epidermal changes. However, rare cases may demonstrate focal epidermal spongiosis and neutrophils within the inflammatory infiltrate [89]. Surrounding the superficial (and sometimes deep) vascular plexus, there is an infiltrate of lymphocytes with scattered plasma cells (Figs. 11.31 and 11.32).

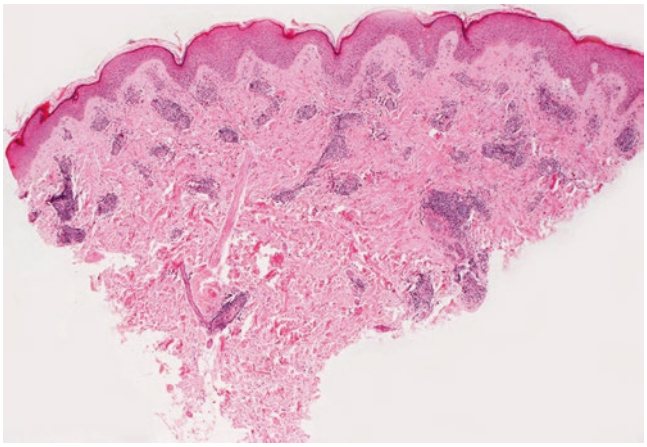

Fig. 11.31 A superficial and deep perivascular lymphocytic infiltrate is seen in erythema chronicum migrans

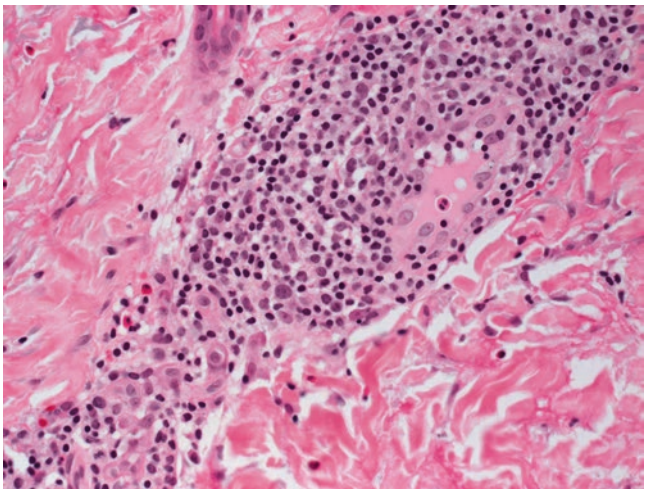

Fig. 11.32 Tightly cuffed perivascular lymphocytes with scattered plasma cells and occasional eosinophils are seen in erythema chronicum migrans

Eosinophils are sometimes present in the central portions of the inflammatory infiltrate [89]. Endothelial cell swelling may be present but not prominent. Peri-neural inflammation is rarely encountered. *Borrelia burgdorferi* are rarely detectable on Warthin–Starry stains.

The differential diagnosis includes erythema annulare centrifugum, in which plasma cells are uncommon but eosinophils may be seen. An arthropod bite demonstrates a punctum and more eosinophils than erythema chronicum migrans. Clinical correlation also helps to make the distinction.

11.22.3 Pathogenesis

Lyme disease is a result of infection with *Borrelia burgdorferi*. Subsequent systemic disease is a consequence of long-term persistence of microorganisms in tissue [90]. The ability of the bacteria to mimic human antigens may result in autoimmune-like symptoms as well as immunologic tolerance that prevents complete elimination of the infectious agent [90]. Borrelia also overcomes host immunity by affecting the host complement system through its production of complement regulator-acquiring surface proteins (CRASPs) [91]. Persistence of disease and degree of systemic symptoms appear to be related to the host's ability to recruit neutrophils and eradicate the microorganisms at the initial site of infection [92].

11.23 Leishmaniasis

11.23.1 Clinical Features

Leishmaniasis refers to cutaneous and visceral infections caused by vector-borne protozoa of the genus *Leishmania*. Worldwide, the annual incidence of Leishmaniasis is estimated at two million cases [93]. Cutaneous disease is caused by several different species of *Leishmania*. The most common form of leishmaniasis seen in the United States is the mucocutaneous form caused by *Leishmania braziliensis*, although the other forms of the disease caused specifically by *Leishmania tropica* and *Leishmania mexicana* are seen with increased frequency due to more extensive global travel. Simple disease presents as a solitary nodule or ulcer near the site of a sandfly bite. More severe diffuse disease may present with multiple diffuse eruptive nodules. Mucocutaneous disease may occur via direct extension or spread of local skin lesions to mucocutaneous tissues. These infections tend to affect the nose, mouth, eyelids, and oro- and nasopharynx. They can be extremely disfiguring.

11.23.2 Histology

Biopsy results demonstrate a diffuse and dense inflammatory infiltrate consisting of abundant histiocytes, eosinophils, plasma cells, and lymphocytes [94] (Figs. 11.33 and 11.34). Histiocytes do not tend to aggregate into granulomas in early stage lesions. A peri-neural inflammatory infiltrate resembling leprosy has been described [95]. Some cases also display a neutrophilic infiltrate. The cytoplasm of the histiocytes is distended with abundant amastigotes, and kinetoplasts can be visualized on H&E sections (Fig. 11.35). Giemsa stains highlight the microorganisms. Epidermal hyperplasia is seen in many cases, although some may develop ulceration [96]. Michaelis–Gutman bodies are described in several cases [97]. As the lesions become older, small granulomas appear, and the inflammatory infiltrate diminishes in intensity. It is more difficult to find microorganisms in late stage lesions. Transepidermal elimination of *Leishmania* is present in some cases [98].

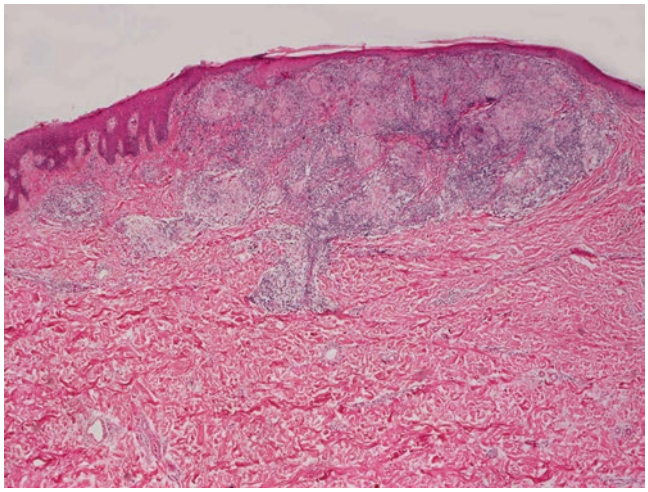

Fig. 11.33 The papillary dermis demonstrates a granulomatous inflammatory infiltrate with many lymphocytes and multinucleated giant cells in leishmaniasis

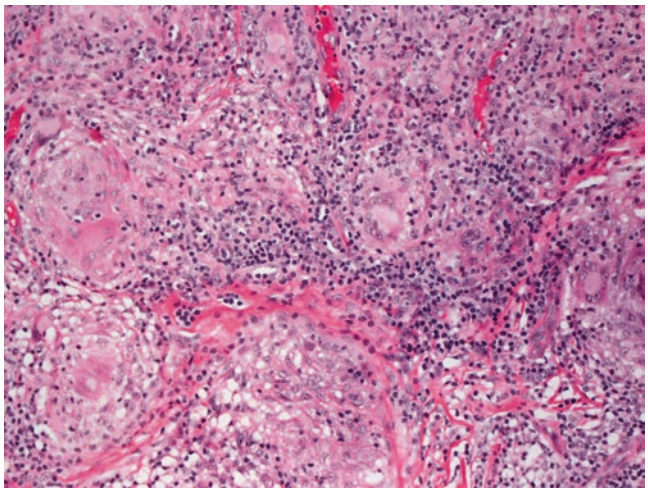

Fig. 11.34 Multinucleated giant cells are admixed with an inflammatory infiltrate in leishmaniasis

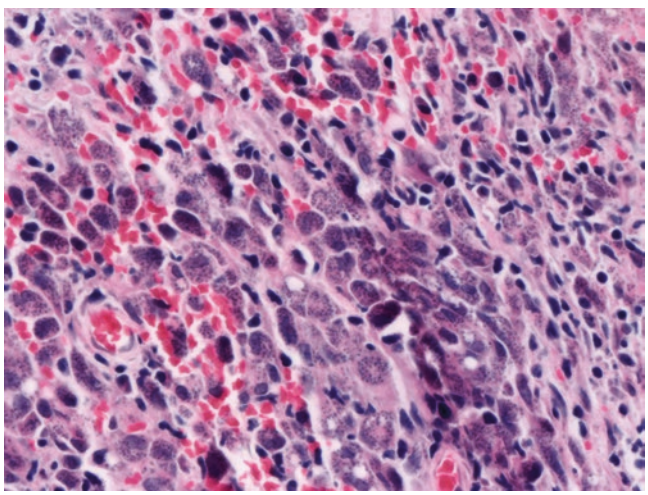

Fig. 11.35 Intracytoplasmic microorganisms are present within histiocytes in leishmaniasis

The main differential diagnosis is histoplasmosis based upon the presence of similarly-sized intracytoplasmic microorganisms. Histoplasma has a capsule that is positive on PAS stains and is not present in the amastigotes of leishmaniasis. On the other hand, kinetoplasts are not present in *Histoplasma capsulatum.*

11.23.3 Pathogenesis

Cutaneous leishmaniasis occurs as the result of infestation with the Leishmaniasis parasite. The trypanosomes enter the skin following a sandfly bite. Once in the skin, they elicit a macrophage response, and the microorganisms are engulfed and reside within the phagolysosomes of macrophages [99]. *Leishmania* has a dense surface glycocalyx composed of lipophosphoglycans that protects it from host hydrolases and serum complement [100]. *Leishmania* also induce several heat-shock proteins, including HSP70, HSP90 and STIP1 (stress-inducible protein 1), that enable the microorganisms to survive at human body temperature [101]. They also have the ability to resist oxidative stress induced by host macrophages [102].

The host response to leishmania infection includes recruitment of CD4+ and CD8+ T cells in addition to macrophages. CD4+ T cells produce cytokines that activate macrophages in order to kill the parasites, and contribute to the observed inflammatory response. CD8+ T cells contribute to type 1 T-helper cell (Th1) response seen in the early stages of the infection [103]. Increased expression of caspase-9 induced by cytotoxic T cells plays a significant role in the observed tissue destruction present in the lesions.

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Viral and Rickettsial Diseases

12

12.1 Herpes Simplex Virus

12.1.1 Clinical Features

In the United States, approximately 1,500 cases of neonatal herpes simplex virus infection are diagnosed annually [1]. The clinical manifestations of neonatal herpes are classified in three categories: SEM disease (limited to the skin, eyes and mouth), central nervous system disease, and disseminated disease. Skin lesions may or may not be present in central nervous system and disseminated infections. Approximately 60–70 % of infants with central nervous system disease have associated skin vesicles and erythematous erosions. Similarly, most of those with disseminated disease have cutaneous manifestations, with only 20 % of infants not having skin vesicles at any time during their illness.

The majority of oro-labial herpetic disease is caused by herpes simplex virus-1 (HSV-1). Approximately 70–80 % of adults are HSV-1 seropositive by age 40 [2]. Genital herpes infections can be caused by HSV-1 or HSV-2. Historically, the majority of genital infections are caused by HSV-2. However, there has been an increase in the incidence of genital infections by HSV-1.

Classic lesions of cutaneous herpes infection consist of small grouped monomorphous vesicles on an erythematous background (Fig. 12.1). These evolve into shallow erosions and crusted papules, which typically heal without leaving permanent scarring.

12.1.2 Histology

Skin biopsy of mucocutaneous HSV infection primarily demonstrates intraepidermal changes. Keratinocytes exhibit balloon cell changes and reticular degeneration, resulting in acantholysis and suprabasilar blister formation (Fig. 12.2). Blisters appear at multiple levels of the epidermis, and can be variable in size. Intranuclear inclusions are present within keratinocytes. These appear as clear nuclei with chromatin margination (Fig. 12.3). Molding of keratinocyte nuclei and multinucleation are also present. Follicular herpetic infection demonstrating the same changes within follicular keratinocytes has been described more commonly in immunosuppressed patients [3, 4]. Verrucous lesions with marked epidermal hyperplasia have also been associated with underlying immunosuppression [5].

The underlying dermis frequently demonstrates a marked inflammatory infiltrate, especially in primary infections. The infiltrate is polymorphous and contains many neutrophils, resembling leukocytoclastic vasculitis in some cases. Inflammation of eccrine ducts is also encountered in cutaneous herpes infection [6]. A variety of atypical reactions have been described within the dermis, including marked lymphoid atypia, plasmacellular atypia, presence of CD30-positive cells, florid pseudolymphomatous infiltrate, and granulomatous reaction pattern [7–11]. As a rule, reinfections are less inflammatory than primary infections with herpes simplex virus, although it is difficult to make this distinction with any degree of accuracy.

12.1.3 Pathogenesis

Herpes simplex virus is a DNA virus in the alpha herpes virus family. HSV exists as two distinct types: herpes simplex virus-1 (HSV-1) and herpes simplex virus-2 (HSV-2) [12]. HSV-1 mainly causes oral lesions, and HSV-2 commonly causes genital herpetic ulcers and neonatal herpes [13–15]. The DNA genomes of HSV-1 and HSV-2 share approximately 50 % homology with significant antigenic cross-reactivity [16]. HSV-1 and HSV-2 can be distinguished based on glycoprotein G (gG-1 for HSV-1, and gG-2 for HSV-2) with an antigen-specific antibody response, as well as by molecular tests, including DNA sequencing and real-

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Fig. 12.1 Herpes simplex virus lesions present as multiple monomorphic, erythematous vesicles, some of which coalesce to form large erosions with scalloped borders and overlying hemorrhagic crust

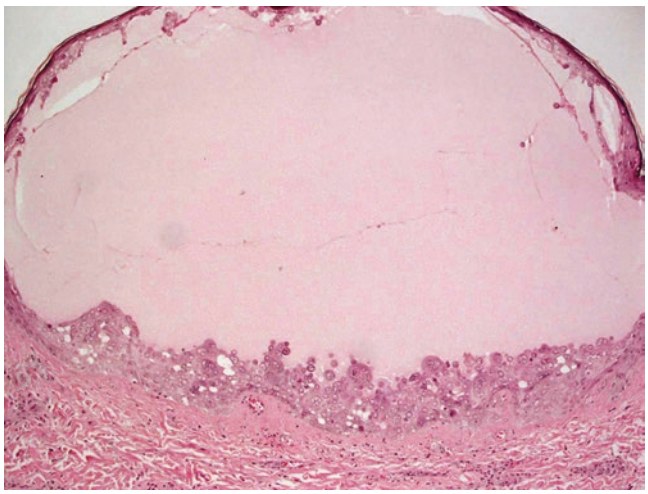

Fig. 12.2 Herpes simplex virus infection demonstrates an intraepidermal blister with abundant nuclear viral inclusions

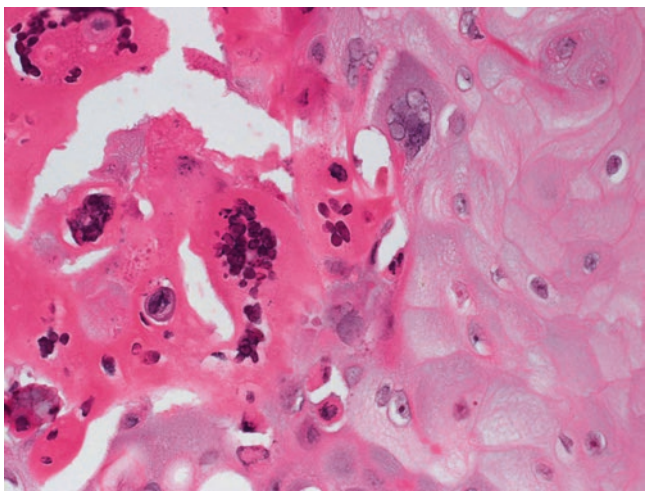

Fig. 12.3 Multinucleated cells with nuclear clearing, molding, and acantholysis characterize viral cytopathic changes in herpes simplex virus infection

time polymerase chain reaction (PCR) [17, 18]. HSV-2 is transmitted sexually with persistent chronic infection. HSV-2 infects epithelial cells and nerve endings with retrograde axonal transport to establish chronic infection in the sacral ganglia. The virus can lie dormant and remain "latent" in the ganglia until reactivation by a triggering event, in which the virus travels along the nerve axon to the skin and mucosal surfaces [15].

The innate immune response is the first line of host defense that limits HSV spread, and it is important in the activation of the adaptive immune response [19]. Toll-like receptors (TLRs) are important in the recognition of HSV antigens by host immune cells. Viral glycoproteins on HSV virions are first detected by TLR2 present on the cell surface [20, 21]. Viral replication and synthesis of viral intermediate double-stranded DNA are sensed by endosomal TLR3 [19, 22]. Viral double-stranded DNA is recognized by TLR9, and consequently stimulates interferon-α production, and the induction of interferon-response genes that encode antiviral effectors to limit viral replication and spread [23–25].

Cellular apoptosis and necroptosis are other important host defense mechanisms in the elimination of pathogen-infected cells. Necroptosis is a regulated form of necrosis that can occur in the absence of caspase activity [26]. Since the death of HSV-infected cells can limit viral replication and spread, HSV has evolved ways to evade cellular apoptosis. It has been found that HSV encodes anti-apoptotic viral proteins to block apoptosis. The immediate-early viral genes, such as ribonucleotide reductase large subunit (R1), are capable of inhibiting apoptosis and necroptosis during HSV infection [27]. Receptor-interacting kinase-3 (RIP3) has emerged as a central signaling molecule in necroptosis [28]. R1 is a suppressor of caspase-8-induced apoptosis and RIP3-induced necroptosis in human cells [29–31]. Thus, HSV appears to block cell death via the suppression of RIP3 signaling during HSV infection to allow viral replication in live host cells.

12.2 Human Herpesviruses 6, 7 and 8

12.2.1 Clinical Features

Human herpesviruses (HHV) are common in the general population with evidence of previous HHV-6 and HHV-7 infections present in nearly everyone over 6 years of age. It is estimated that 80–90 % of the entire population intermittently sheds these viruses in saliva. HHV-8 is somewhat less common than HHV-6 and HHV-7, with seroprevalence in the United States estimated at less than 10 % [32].

Infections with HHV-6, -7, and -8 are associated with a variety of cutaneous diseases. HHV-6 and HHV-7 are associated with the childhood eruption roseola infantum. The typical child with roseola is a toddler, who develops widespread morbilliform eruption after experiencing relatively high

fever for about 3 days. HHV-6 and HHV-7 have also been implicated in pityriasis rosea, although a clear association has not been proven conclusively. Other conditions that may be associated with HHV-6 and HHV-7 infections include Stevens-Johnson syndrome, thrombocytopenic purpura, purpura fulminans, papular purpuric gloves and socks, Gianotti-Crosti syndrome, drug-induced hypersensitivity syndrome, and post-transplant graft vs. host disease. HHV-7 may also have a causative role in the development of lichen planus. HHV-8, also known as Kaposi sarcoma-associated herpes virus, has been found in endemic, classic, and post-transplant forms of the disease.

12.2.2 Histology

HHV-6 infection affects the skin, but lesions are rarely biopsied. The changes are often nonspecific, and include a superficial perivascular lymphocytic infiltrate. Scattered large and atypical cells with intranuclear and intracytoplasmic viral inclusions and cytopathic changes are seen in some cases [33]. Infected cells are described as medium- to large-sized lymphocytes with large centrally-located basophilic inclusions surrounded by halos [34].

The exact relationship between HHV-7 and skin infection is unknown. To date, there are no specific changes that are directly linked to HHV-7; however, there is emerging literature linking HHV-7 and pityriasis rosea [35–37]. The virus has also been linked to atypical lymphoid proliferations, although the data is less convincing [32]. No specific viral cytopathic changes in the skin that have been directly attributed to HHV-7.

Roseola infantum is caused by human herpesvirus, and demonstrates changes of spongiotic dermatitis, occasionally with vesicle formation. There is an underlying superficial perivascular lymphocytic infiltrate with papillary dermal edema and focal exocytosis [38].

While HHV-8 plays an important role in several cutaneous diseases, there are no specific viral cytopathic changes that are currently recognized [32]. HHV-8 has been intimately associated with Kaposi's sarcoma, and it is readily identified in most cases on anti-HHV-8 immunostains [39]. Recently, HHV-8 has also been identified in eruptive cherry angiomas, but not in sporadic, commonly-occurring angiomas [40]. Rare cases of cutaneous lymphoma also demonstrate the presence of the virus [41, 42].

12.2.3 Pathogenesis

HHV-6 and HHV-7 are members of the *Roseolovirus* genus within the *beta herpesvirinae* subfamily [43]. They are genetically related to cytomegalovirus [44, 45]. HHV have a tropism for lymphocytes and macrophages, and have a long latency period [43]. The viruses can shut down DNA synthesis of infected host cells, induce protein synthesis and upregulate various cytokines and chemokines, causing viral cytopathic effects and ballooning appearance in affected cells [43].

HHV-8 is an oncogenic gamma herpesvirus [46]. It infects endothelial and epithelial cells, B lymphocytes, monocytes, and CD34+ hematopoietic progenitor stem cells [47]. It also targets antigen-presenting cells, including monocyte-derived dendritic cells [46]. HHV-8 has both latent and lytic cycles [48]. The virus is known to produce proteins that enable it to promote cell survival, evade the immune system, stimulate angiogenesis, and induce inflammation. Furthermore, it induces the production of vascular endothelial growth factor (VEGF), which is a potent pro-angiogenic growth factor that induces vascular proliferation [47]. Through its latent gene expression, the virus is able to block endothelial cell apoptosis and promote cell survival, which may contribute to the pathogenesis of Kaposi's sarcoma. HHV-8 also induces cytokine production that contributes to angiogenesis and inflammation characteristic of these vascular neoplasms [48].

12.3 Congenital Varicella Zoster Virus

12.3.1 Clinical Features

Intrauterine infection occurs in up to 25 % of women who contract primary varicella zoster virus during the first two trimesters of pregnancy. Approximately 12 % of infected babies will have congenital anomalies [49]. In pregnant women who are infected between the 8th and 26th weeks of pregnancy, about 2 % of fetuses will develop congenital varicella syndrome. This is characterized by cutaneous scarring, severe central nervous system damage, eye abnormalities, and limb deformities [5].

12.3.2 Histology

The histologic changes seen in congenital varicella zoster infection are largely the same as those seen in primary herpes simplex virus infections as described elsewhere in this chapter. At least one case has been reported in which the changes resemble the verrucous type of infection most commonly described in immunosuppressed patients [5, 51].

12.3.3 Pathogenesis

Congenital varicella is caused by infection with varicella zoster virus, which is a DNA virus of the herpesvirus family.

Approximately 12–30 % of fetuses contract varicella transplacentally from mothers who contract the disease before the 24th week of pregnancy [51–53]. Congenital varicella syndrome with all of its manifestations occurs in less than 1 % of infants under the same conditions [54]. It is generally believed that as immunocompetence develops later in pregnancy, the fetus is able to mount an immune response to the invading virus, leading to a more benign disease course. The syndrome results from damage to the nervous system that occurs early in gestational development as the neurotropic virus invades these primitive cells [55]. As a result of incompletely developed immune system in fetuses, there is a very short latency period following viral infection of neural tissue. Upon reactivation, the viruses lead to maldevelopment of the musculoskeletal system as well as somatic and autonomic nervous system [56].

12.4 Varicella Zoster

12.4.1 Clinical Features

The incidence of chickenpox is not well established since it is not a reportable disease. However, incidence was estimated at between 1.6 and 4.6 per 1,000 individuals between 15 and 44 years of age in the United States during the 1990s [49]. In varicella, there is a generalized rash with lesions that begin as small erythematous macules and papules, and then evolve into vesicles, pustules, and crusted papules (Fig. 12.4). Lesions tend to be more densely distributed on the trunk than the extremities, and can range in number from very few to many lesions.

Herpes zoster or shingles is a secondary varicella zoster virus disease caused by reactivation of latent viral infection. Lesions are typically erythematous macules and papules that become vesicular or pustular, and then scab over. The classic eruption is largely unilateral, and tends to occur in a dermatomal distribution.

12.4.2 Histology

The histologic changes seen with varicella zoster are identical to those seen with herpes simplex and herpes zoster infections (See Sects. 12.1 and 12.3) (Figs. 12.5 and 12.6). These entities cannot be differentiated with routine histologic sections.

Fig. 12.4 Varicella zoster lesions present as erythematous vesicles and erosions in various stages of development on the trunk

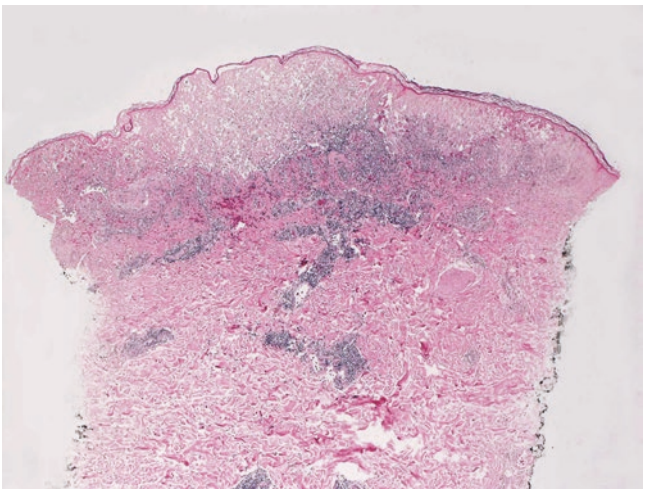

Fig. 12.5 Varicella zoster demonstrates an epidermis that is focally disintegrating secondary to balloon degeneration of keratinocytes

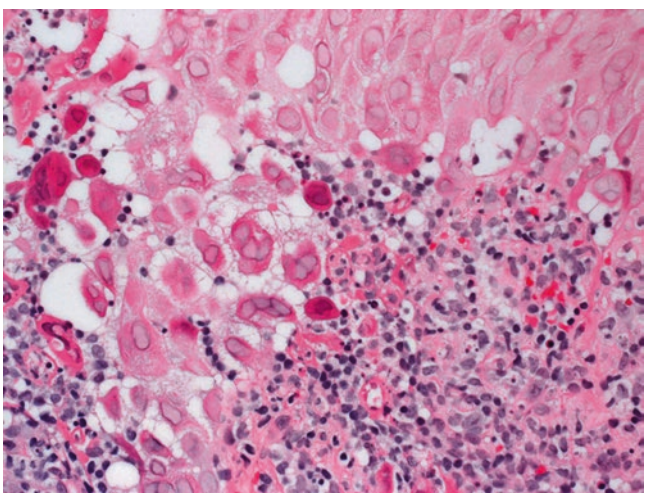

Fig. 12.6 Herpetic viral inclusions are present in varicella zoster. Multinucleated cells, nuclear molding and clearing can be seen in most cases

12.4.3 Pathogenesis

Varicella zoster virus, the causative agent of chickenpox and shingles, is a member of the alpha herpesvirus family of double-stranded DNA viruses. The virus is transmitted by direct contact or airborne infection [57, 58]. T lymphocytes are infected by spread of the virus from the inoculation site at mucosal epithelium. T lymphocytes that are infected with varicella zoster virus undergo a surface remodeling resulting in activation of T-cell receptor and the PI3-kinase pathway [59]. Infected T cells transport viral particles to the skin and other target sites [59]. Nerve ganglia serve as repositories for the virus. In certain circumstances that are not fully understood, varicella zoster virus begins to replicate and migrate down sensory nerves into the skin with concomitant cutaneous vesicular eruption and pain [60]. In children, varicella zoster is most frequently encountered in the setting of immunosuppression [61].

12.5 Congenital Rubella

12.5.1 Clinical Features

Rubella virus infections (German measles) in a healthy child or adult generally cause a mild illness characterized by a diffuse morbilliform eruption. However, rubella infection during the first trimester of pregnancy can cause fetal loss or fetal defects in up to 90 % of cases. There are approximately 100,000 cases of congenital rubella syndrome worldwide each year [62]. Fetal abnormalities are rarely seen with infections that occur after the 16th week of pregnancy, although hearing loss has been reported with infections up to 20 weeks. The organs most commonly affected are the eyes, ears, heart, and brain. Affected children are also at increased risk for developmental delay and disability.

12.5.2 Histology

It is rare to see biopsies from patients with cutaneous manifestations of congenital rubella, and published reports of histologic findings are uncommon. The histologic changes are nonspecific, and consist of a superficial and deep perivascular lymphohistiocytic infiltrate [63]. The infiltrate can be quite dense, extend into the subcutis, and consist of B lymphocytes deep in the infiltrate [64]. Epidermal changes are not present, and no viral inclusions are identified. On electron microscopic examination, abundant tubuloreticular structures are seen within capillary endothelial cells, fibroblasts, and dermal lymphocytes [64].

12.5.3 Pathogenesis

Rubella virus belongs to the *Rubivirus* genus of the *Togaviridae* family of single-stranded RNA viruses [62, 65]. Rubella virus occurs by respiratory transmission from person-to-person, or transplacentally [65]. Proteins located on the external surface of the virus facilitate endocytosis [62]. Once host cells are infected, the virus induces cell-cycle arrest by generating tetraploid nuclei [65]. This leads to cell apoptosis, which may be one of the initiating events that result in the fetal birth detects seen with congenital rubella.

12.6 Cytomegalovirus

12.6.1 Clinical Features

In the United States, approximately 33,000 infants per year are born with congenital cytomegalovirus (CMV). However, only about 10 % of these cases are symptomatic at birth [66]. Cutaneous features of congenital CMV infection are variable, and may include petechiae or purpura, a morbilliform rash, or a "blueberry muffin" appearance.

12.6.2 Histology

It is rare to biopsy a skin eruption resulted from direct cutaneous infection by CMV. When this situation occurs, which is most common in the setting of immunosuppression, large cytoplasmic eosinophilic inclusions of CMV are commonly seen in endothelial cells [67, 68]. This leads to vascular thrombosis, vasculopathy, and occasionally vasculitis with hemorrhage and variable amounts of peri-vascular inflammation [69]. Viral inclusions have been described in dermal fibroblasts, histiocytes, eccrine apparatus [67, 73] and dermal nerves [74]. CMV has also been associated with scleroderma-like changes in some patients [68]. In children, CMV has been implicated in the pathogenesis of acute hemorrhagic edema, in which abundant dermal edema accompanies changes of leukocytoclastic vasculitis [70–72].

12.6.3 Pathogenesis

CMV is a member of the beta-herpesviridae subfamily [75]. Cutaneous manifestations of CMV are most frequently encountered in neonates as a result of in utero transmission [76]. The virus infects epithelial cells, hematopoietic cells, endothelial cells and connective tissue, and may have a prolonged latency period [75]. Viral glycoproteins play a key role in specific cellular entry and infection [77]. The virus persists

by virtue of its "immune evasion genes," which allow it to escape from immune cells and neutralizing antibodies [78]. The high level of genomic diversity in CMV enables reinfection by heterotypic strains. Invasion of endothelial cells with subsequent cellular damage, loss of vascular integrity, and thrombosis can be directly attributed to CMV infection in patients with cutaneous manifestations [69].

12.7 Orf

12.7.1 Clinical Features

Orf is a skin infection caused by parapoxvirus that typically infects goats and sheep [79]. Human infections usually occur in teens and adults with occupational exposure, although cases have been reported in children who visit petting zoos or livestock fairs. Lesions usually occur on the hands or fingers, and start as small erythematous papules that enlarge to form tender nodules which can ulcerate and crust over. The natural history of orf is spontaneous resolution over a few weeks.

12.7.2 Histology

Early lesions demonstrate a moderate degree of epidermal acanthosis with significant pallor within keratinocytes at superficial levels of the epidermis (Figs. 12.7, 12.8 and 12.9). Within these cells, viral cytoplasmic inclusions are seen. Intraepidermal vesicles are often present secondary to marked edema within the dermis. The dermis demonstrates a proliferation of thin-walled vessels with a surrounding infiltrate of lymphocytes, histiocytes, and rare eosinophils and plasma cells [80, 81]. As the lesions evolve, epidermal necrosis is almost invariably present, often prominent in the central portions of the lesions. Neutrophils are present adjacent to the necrotic foci. Viral particles are readily apparent on electron microscopy [81].

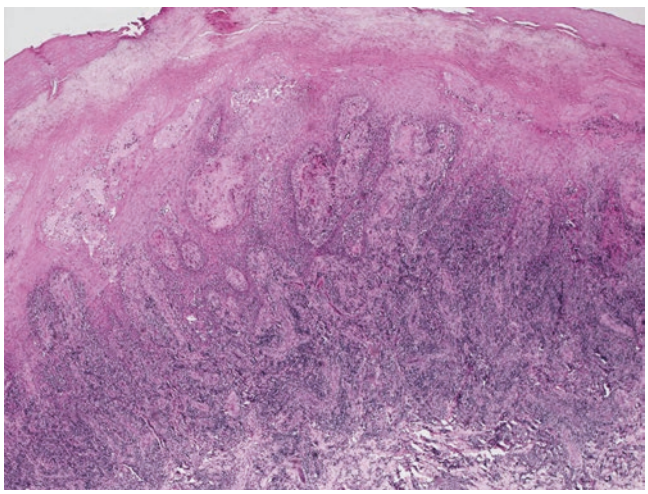

Fig. 12.7 An acanthotic and spongiotic epidermis overlies a dense lymphohistiocytic inflammatory infiltrate in orf

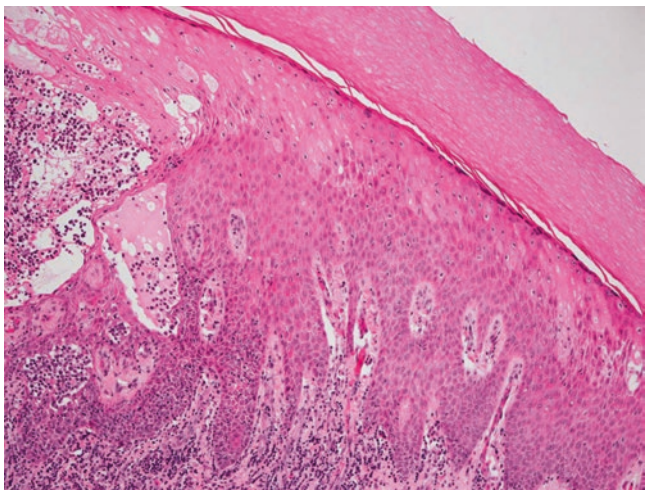

Fig. 12.8 Prominent epidermal spongiosis and dense inflammation are seen in orf

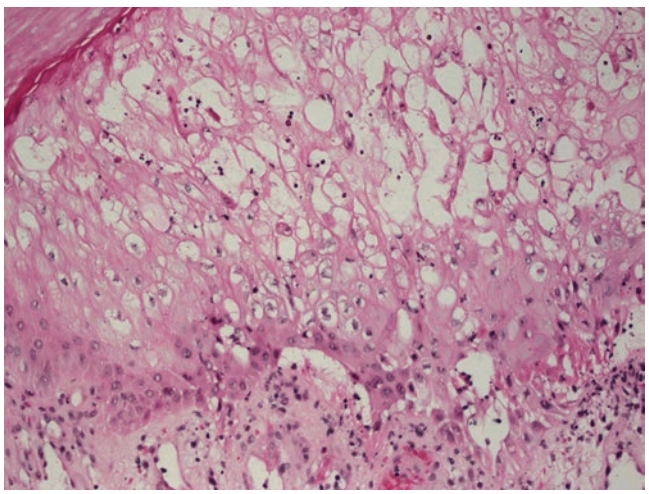

Fig. 12.9 Dissolution of the epidermis and eosinophilic cytoplasmic inclusions resembling erythrocytes are present in orf

The differential diagnosis includes a milker's nodule that is histologically identical to orf, but can be differentiated by electron microscopy. Early lesions may resemble spongiotic dermatitis, but the epidermal pallor helps to make this distinction. The presence of viral particles establishes the diagnosis. The epidermal pallor may also be seen in nutritional disorders, although the clinical presentation is markedly different, and these entities do not have cytoplasmic inclusions within keratinocytes. Epidermal acanthosis along with proliferation of small well-formed capillaries may raise the diagnostic possibility of a pyogenic granuloma. Again, the presence of epidermal pallor and cytoplasmic viral inclusions are helpful in making the distinction.

12.7.3 Pathogenesis

Orf is a DNA parapoxvirus that is transmitted to humans through direct contact with infected goats and sheep [82]. The virus expresses an anti-apoptotic factor (similar to Bcl-2) and develops interferon resistance that enable it to survive in the host. It also expresses a soluble factor similar to interleukin-10 that suppresses pro-inflammatory cytokines, and a chemokine-binding protein that inhibits immune cell tracking [81, 83].

12.8 Milker's Nodule

12.8.1 Clinical Features

Milker's nodules usually affect the hands of individuals who work with cattles. One or aseveral small red papules appear and develop into large and tender nodules. The nodules spontaneously resolve without scarring over a few weeks.

12.8.2 Histology

Histologic features vary with the stage of the lesion biopsied, and they are histologically indistinguishable from the changes seen in orf. The viruses can be visualized by electron microscopic examination.

12.8.3 Pathogenesis

Milker's nodule is a skin infection caused by a virus that typically infects the teats of cows and mouths of calves [84]. The causative agent is the DNA pseudocowpox virus [85].

12.9 Molluscum Contagiosum

12.9.1 Clinical Features

The classic cutaneous lesion of molluscum is a small waxy, skin-colored, dome-shaped papule that may have a central dell or umbilication (Fig. 12.10) [86]. At times, lesions become inflamed with swelling, erythema, purulent discharge, and crusting. Molluscum infection can trigger development of an eczematous dermatitis with erythema and scale surrounding the affected areas.

12.9.2 Histology

Histologic changes include a lobular proliferation of keratinocytes that contain eosinophilic cytoplasmic inclusions with a very characteristic appearance (Figs. 12.11 and 12.12). The inclusions begin in suprabasilar keratinocytes, and become progressively larger and more basophilic with upward progression in the epidermis. The epidermis is acanthotic with variable amounts of spongiosis. Transepidermal elimination is seen in many cases. An intense inflammatory response is present, and this is accentuated following rupture of the lesions. In some cases, atypical CD8+ lymphocytes and CD30+ cells are present within the infiltrate, leading to concern for lymphoma [10, 87]. Similarly, an intense inflammatory response has been identified in patients with altered immune systems [88]. Follicular involvement is commonly seen in immunosuppressed patients [4, 89].

Fig. 12.10 Multiple domed, erythematous and skin-colored, umbilicated papules are seen on the trunk in molluscum contagiosum

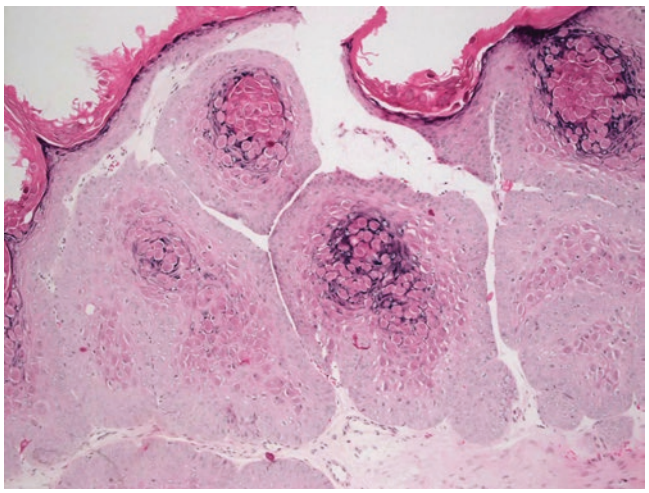

Fig. 12.11 The epidermis is acanthotic and has a lobular appearance with abundant viral inclusions within keratinocytes in molluscum contagiosum

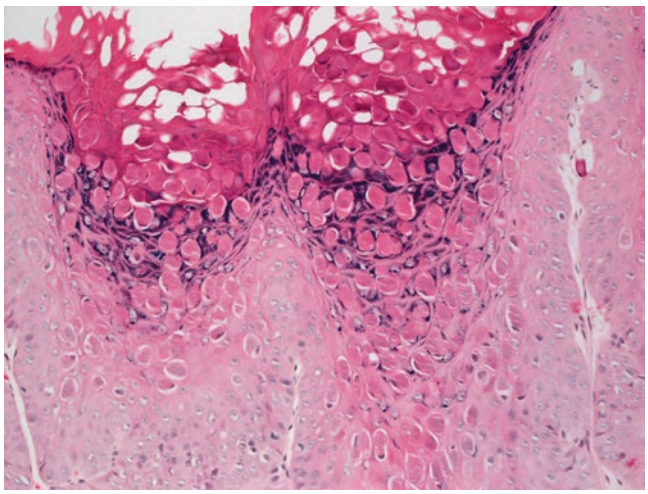

Fig. 12.12 Eosinophilic viral inclusions are present in keratinocytes and extruded at the epidermal surface in molluscum contagiosum

12.9.3 Pathogenesis

Molluscum contagiosum is caused by molluscipoxvirus, which is a double-stranded DNA virus in the family *Poxviridae* [86]. The virus induces cell mitosis and disrupts epidermal cell differentiation. It is limited to the epidermis, and replicates within the cytoplasm of keratinocytes. Molluscipoxvirus upregulates epidermal growth factor and interferes with cell signaling pathways that activate nuclear factor-κB, thus inhibiting host immune response [90, 91].

12.10 Eczema Herpeticum/Kaposi's Varicelliform Eruption

12.10.1 Clinical Features

Eczema herpeticum (Kaposi's varicelliform eruption) is a widespread cutaneous infection with herpes simplex virus occurring in the setting of preexisting chronic skin disease, usually atopic dermatitis [92]. Patients present with many small monomorphous vesicles on an erythematous background. The lesions typically spread rapidly over the skin and evolve into vesiculopustules, crusted papules, and superficial "punched out" erosions (Fig. 12.13). Patients may also have fever, malaise, and lymphadenopathy, and they often require hospitalization for intravenous fluids, medications, and proper skin care.

12.10.2 Histology

Histologic changes in eczema herpeticum are those of a herpetic dermatitis superimposed upon mild spongiotic dermatitis. Multinucleation, nuclear molding, margination of

Fig. 12.13 Monomorphic, punched out erosions overlie a generalized eczematous eruption on the lower trunk in eczema herpeticum

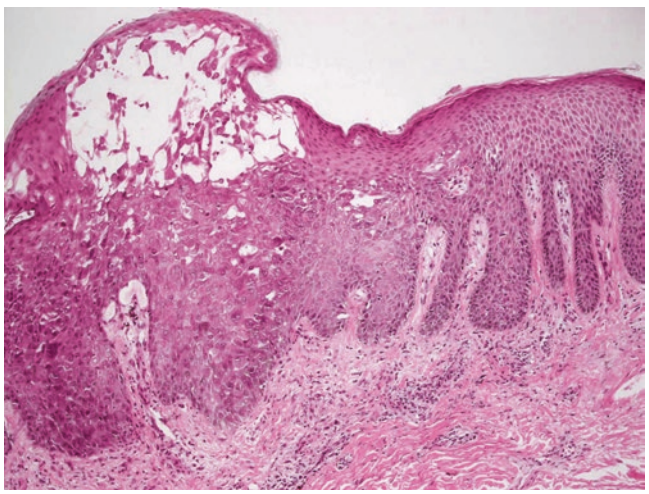

Fig. 12.14 A spongiotic epidermis has blistering with acantholysis and viropathic changes in eczema herpeticum/Kaposi's varicelliform eruption

chromatin, and acantholysis are characteristics of herpes virus infection seen in the epidermis (Figs. 12.14 and 12.15). These changes reflect the nature of the condition that is essentially a generalized infection with herpes virus in the setting of atopic dermatitis. Cowpox and vaccinia infections may demonstrate a similar clinical appearance, but the changes on biopsy vary based upon distinct histologic features specific to the offending viral agent. Similar clinical eruptions have been described in patients with Darier's disease, Hailey-Hailey disease, rosacea, and mycosis fungoi-

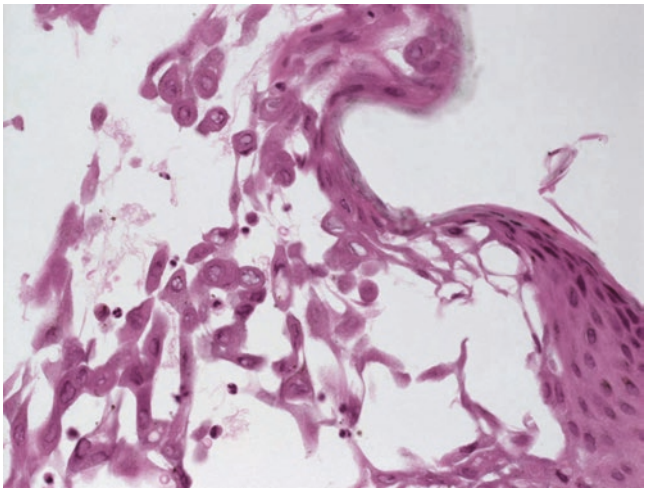

Fig. 12.15 Viropathic changes of herpes virus infection, including acantholysis as well as nuclear molding and clearing, are seen in eczema herpeticum/Kaposi's varicelliform eruption

des, the changes are not specific [93–95]. In these cases, histologic evidence of the underlying conditions is apparent when the appropriate clinical sites are biopsied.

12.10.3 Pathogenesis

Eczema herpeticum is caused by dissemination of herpes virus or vaccinia virus in the setting of an underlying cutaneous eruption [96]. Cases may also result from infection with coxsackie A16 virus [97]. The viral spread is believed to be due to humoral and cellular immunity dysfunction. Decrease in inflammatory cytokines, such as interferon and CXCL10 as well as altered type 1 T-helper cell immune response, have been observed in affected individuals [98]. Patients also have increased levels of interleukin-4, which inhibits γ-interferon activity [99].

12.11 Verruca Vulgaris

12.11.1 Clinical Features

Common warts (verruca vulgaris) tend to be caused by human papilloma virus (HPV) types 1, 2 and 7. Disease prevalence is estimated at 3.5 % in adults and up to 33 % in school-aged children [100]. Common sites of infection are the fingers and hands, although they may appear in other anatomic sites. Individual lesions appear as hyperkeratotic skin-colored papules and plaques. When present on the face, they are often slender filiform papules.

Plane warts or flat warts are common in children and women, but rare in men. They are most often caused by HPV types 3 and 10. Lesions typically appear on the face, dorsal hands, and shins. Individual lesions are small thin, flat-topped, tan to skin-colored papules that tend to Koebnerize in areas of trauma.

12.11.2 Histology

In verruca vulgaris, focal parakeratosis is present at the tips of exophytic papillomatous proliferations of the epidermis. The epidermis is acanthotic, and demonstrates hypergranulosis with focal clumping of keratohyalin granules (Figs. 12.16 and 12.17). In some cases, there is a slight pallor to the keratinocytes in the mid-portions of the epidermis. At low magnification, slight cup-shaped inward turning of the rete ridges at the periphery of the lesion may be apparent, and these

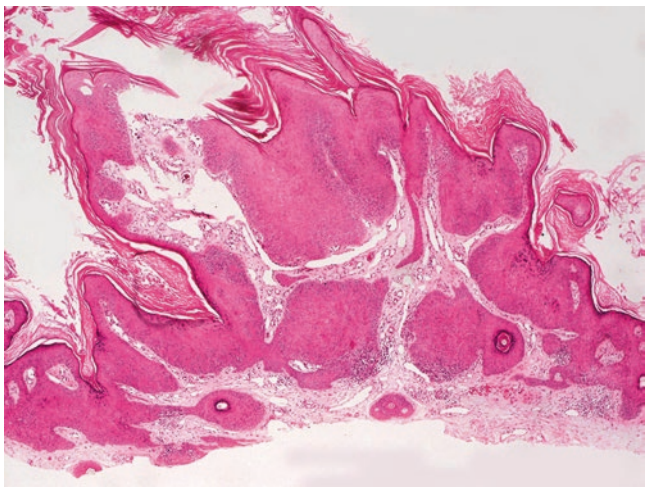

Fig. 12.16 Verruca vulgaris demonstrates an acanthotic and papillomatous epidermis

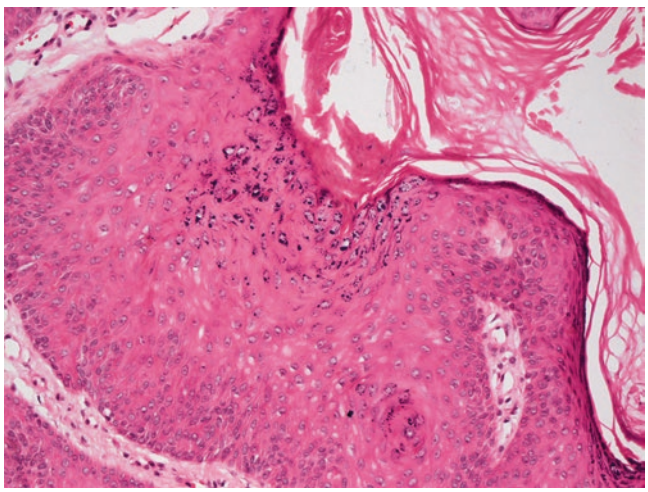

Fig. 12.17 Clumping of keratohyaline granules within the granular layer is characteristic of verruca vulgaris

features can be a useful diagnostic clue. There are dilated capillaries within the dermal papillae, and may result in foci of hemorrhage and thrombosis within the stratum corneum.

The differential diagnosis includes epidermal nevus, seborrheic keratosis, acanthosis nigricans, and trichilemmoma. Epidermal nevi ordinarily do not have parakeratosis at the tips of the papillae, or intervening orthokeratosis as seen in verruca vulgaris. They also do not have inward turning rete ridges, epidermal pallor, and clumping of keratohyaline granules. Seborrheic keratosis and acanthosis nigricans have some similar histologic changes to verruca vulgaris, but they can be easily distinguished based upon clinical history. Trichilemmoma shares many histologic features with verruca vulgaris, but it can be differentiated based upon a characteristic thickened and eosinophilic basement membrane that underlies pale keratinocytes. However, in some cases, it is not possible to make the distinction between these two entities with absolute certainty.

12.11.3 Pathogenesis

Verruca vulgaris is caused by infection with human papillomaviruses (HPV), which are small DNA viruses of the papovavirus family. Infection by HPV requires inoculation of the virus into basal epithelial cells. Active viral DNA replication has been observed to occur in the spinous layer of the epidermis, and the assembly of live virions occurs in the granular layer.

Over 120 HPV subtypes have been identified based on their distinct DNA properties [101]. For practical purposes, HPV are classified as cutaneous and mucosal subtypes according to their tissue tropism. Cutaneous HPV subtypes are those common in the general population (such as HPV-1, 2, and 4) and those found in epidermodysplasia verruciformis (such as HPV-5 and HPV-8 that are high risk for inducing malignant transformation) [100]. They are characterized as low risk, with additional subtypes including types 27 and 57 [102–104]. Mucosal HPV subtypes are classified as low-risk and high-risk types. Low-risk HPV (such as HPV-6, 11, and 53) are usually not found in squamous cell carcinoma. In contrast, high-risk HPV (such as HPV-16, 18, 31, 33, 35, 52, 58, and 67) are often associated with both cutaneous squamous cell carcinoma and cervical cancer [100, 104].

The HPV viral genome encodes for seven to nine open reading frames, depending on the viral subtype. The coding region encodes early and late proteins. Early proteins, including E1–E7, are important in gene transcription, DNA replication, and cellular transformation [100, 105]. E1 and E2 proteins, in combination with various cellular factors, mediate viral replication. Some of the early proteins, such as E4, can disrupt the cytokeratin network in keratinocytes, leading to the morphological viral-induced changes of "koilocytosis" in the affected cells. Some late viral proteins, such as L1 and L2, form viral structures including the viral capsid.

The host immune response is important in the elimination of viral particles. The immune mechanism is partially dependent on cell-mediated immunity with lymphocytes infiltrating viral lesions. The host innate immune response via toll-like receptors (TLR), interferon-β, and tumor necrosis factor-α are also important in the initial recognition of viral particles by host immune cells and the subsequent immune reaction [106–109].

Malignant transformation induced by high-risk HPV subtypes requires, at least in part, persistent overexpression of the viral oncoproteins E6 and E7. These proteins affect the host cell cycle and apoptosis, leading to unchecked cell proliferation and transformation. Mechanistically, E6 and E7 interfere with the function of the tumor suppressors p53 and Rb to promote dysregulated cell growth [110–112].

12.12 Verruca Plantaris

12.12.1 Clinical Features

Plantar warts are associated with HPV types 1 and 4. They are common in children and typically affect the sole of the foot. Clinically, there is a hyperkeratotic nodule surrounded by a raised rim (Fig. 12.18). "Black dots" (thrombosed capillaries) can be seen over the surface. They are frequently tender with weight bearing or pressure.

Fig. 12.18 Verruca plantaris presents as skin-colored hyperkeratotic papules and plaques with hemorrhagic dotting on the sole

12.12.2 Histology

Verruca plantaris displays histologic features that can be distinguished easily from verruca vulgaris. The lesions are generally flat. While parakeratosis may be present, it is not a constant finding. The most superficial keratinocytes show vacuolization, and eosinophilic cytoplasmic vacuoles are present in the epidermis, usually sparing the most basilar cells (Figs. 12.19 and 12.20). The cytoplasmic vacuoles are large, and marked keratohyaline granule clumping are readily apparent at low magnification. While there is some epidermal acanthosis, the rete ridges are generally not markedly elongated as seen in verruca vulgaris. In most cases, there is an underlying inflammatory infiltrate, and foci of regression are frequently present in the dermis.

While plantar warts are most commonly caused by HPV-1, 2 and 4, other HPV subtypes are occasionally responsible. HPV-60 has been associated with the development of plantar warts, and demonstrate similar findings [103, 113, 114]. There are hyperkeratosis and single large eosinophilic cytoplasmic inclusions. Due to the surface changes, these have been designated "ridge" warts, and show many similarities to the cystic warts that have also been described on plantar surfaces [115].

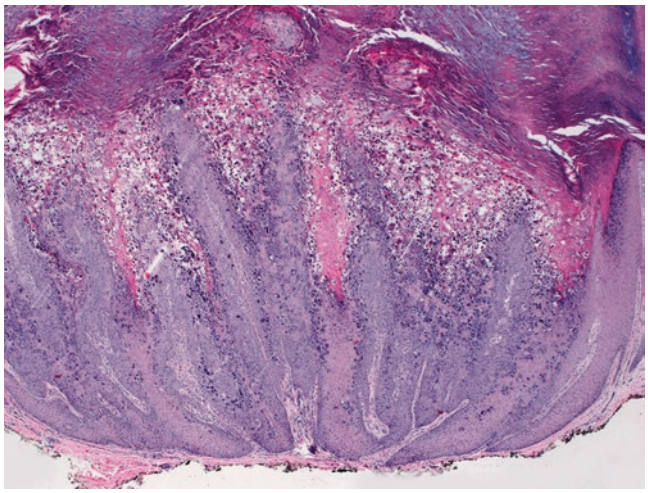

Fig. 12.19 Epidermal hyperplasia, papillomatous growth pattern, and marked keratohyaline granule clumping are seen in verruca plantaris

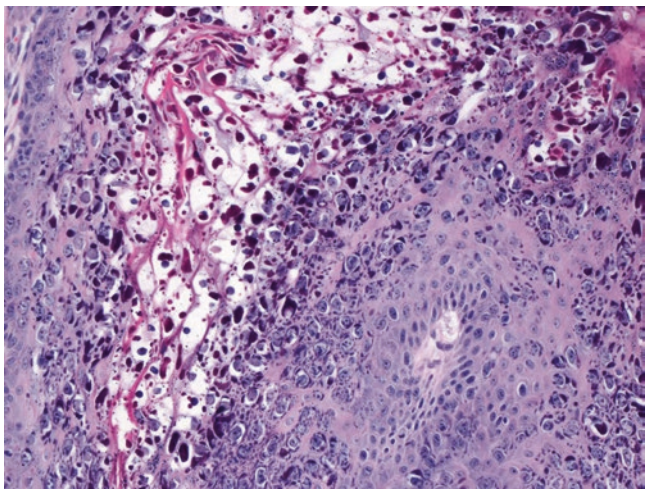

Fig. 12.20 Eosinophilic viral inclusions and keratohyaline granule clumping in the granular layer of the epidermis are characteristic changes of verruca plantaris

12.13 Condyloma Acuminatum

12.13.1 Clinical Features

Many different HPV types can cause condyloma acuminatum, although the most common viruses are HPV-6 and HPV-11. Multiple exophytic papillomatous growths occur in the anogenital region.

12.13.2 Histology

Histologic findings include an exophytic papule that may have a gently lobulated configuration. The epidermis is acanthotic with elongated rete ridges in some cases, and the pathognomonic and required finding is koilocytes within the upper layers of the epidermis (Figs. 12.21 and 12.22). Keratinocytes

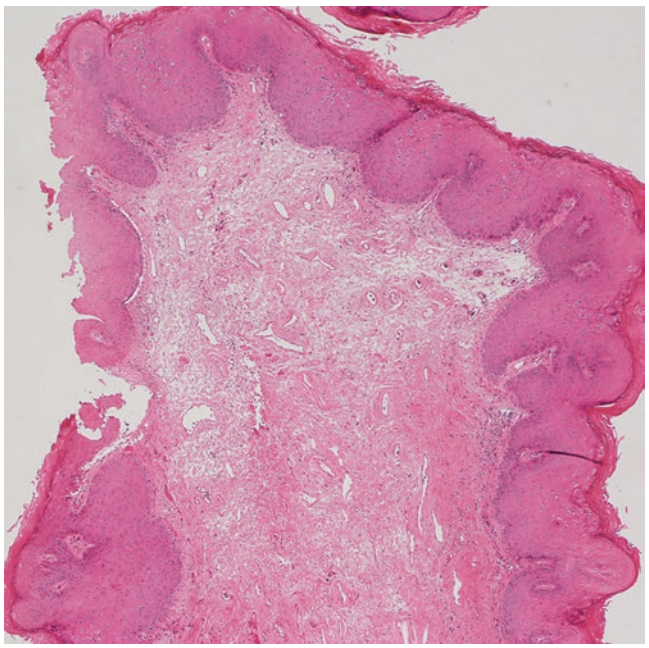

Fig. 12.21 An acanthotic epidermis with characteristic koilocytic changes in condyloma acuminatum

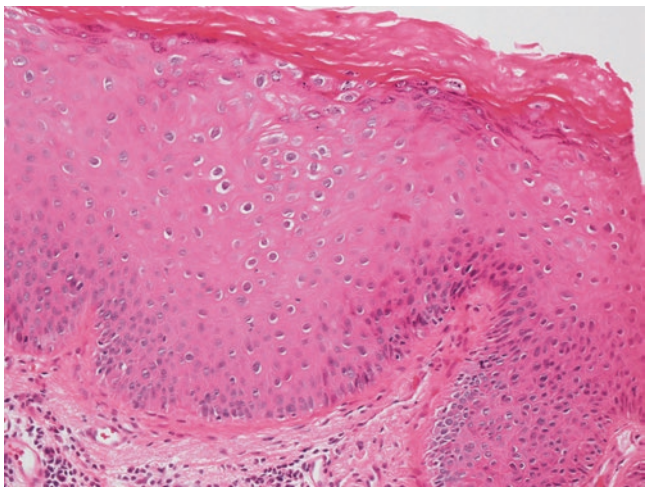

Fig. 12.22 The uppermost layers of the epidermis demonstrate perinuclear clearing and convoluted nuclei in condyloma acuminatum

have cytoplasmic vacuolization and hyperchromatic nuclei. There may be slight keratinocyte atypia in the epidermis.

It is important to differentiate a condyloma acuminatum from an acrochordon, mostly for psychosocial implications. Koilocytes are required in order to establish the diagnosis of condyloma, and are the characteristic viral cytopathic changes associated with this entity. Acrochordons do not demonstrate these changes.

12.13.3 Pathogenesis

HPV is transmitted by skin-to-skin or mucosa-to-mucosa contact [116]. Most condyloma acuminata are caused by HPV-6 and HPV-11. Both of these are "low-risk" HPV subtypes that have minimal ability to induce malignant transformation [116]. They replicate independent of the host, as opposed to the "high risk" HPV subtypes that result in the inactivation of tumor suppressor genes, and lead to uncontrolled cellular proliferation and neoplastic transformation [116]. Occasionally, "high-risk" subtypes can be isolated from these lesions [117].

12.14 Epidermodysplasia Verruciformis

12.14.1 Clinical Features

Epidermodysplasia verruciformis is a rare autosomal recessive genodermatosis characterized by early onset of widespread flat warts, and skin lesions resembling tinea versicolor and seborrheic keratoses. Patients appear to have a 30–50 % chance of developing squamous cell carcinomas, particularly on sun-exposed areas of skin [100].

12.14.2 Histology

The histologic findings of lesions in epidermodysplasia verruciformis are those of verruca plana. Orthokeratotic hyperkeratosis is present overlying a flat epidermis. The stratum granulosum is characterized by prominent intracellular vacuoles, and the lower portions of the epidermis are unremarkable (Figs. 12.23 and 12.24). Keratohyalin clumping can sometimes be seen. Keratinocytes in the upper portion of the epidermis have a peculiar bluish hue that is helpful in establishing the diagnosis [118]. An underlying inflammatory response is variable and may be entirely absent.

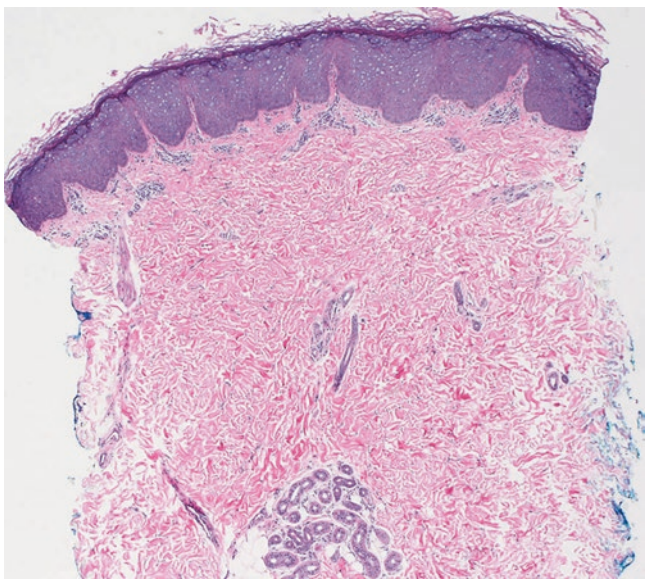

Fig. 12.23 An acanthotic epidermis demonstrates vacuolization, and a bluish hue within the superficial layer

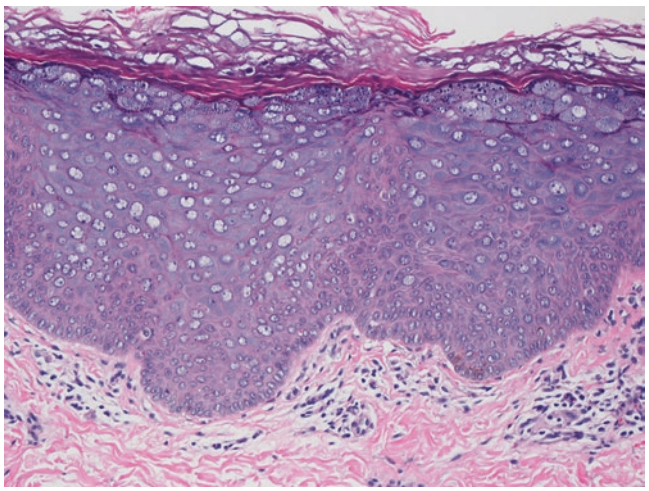

Fig. 12.24 Keratohyaline clumping, cytoplasmic vacuolization and blue staining are seen in the upper layers of the epidermis in epidermodysplasia verruciformis

12.14.3 Pathogenesis

Multiple types of human papilloma virus (HPV) appear to be associated with epidermodysplasia verruciformis. The disease occurs in individuals infected with one or more of a wide range of HPV, including HPV-4, 5, 8, 9, 12, 14, 15, 19–25, 27, 36–38 and 47 [119]. However, HPV types 5 and 8 appear to be the most common [120]. An autosomal recessive inheritance pattern is seen in most patients, although autosomal dominant and sporadic mutations may also occur [119]. Acquired cases have been reported in immunocompromised individuals [120, 121]. In affected patients, mutations in EVER1 and EVER2 genes result in the downregulation of cell-mediated immunity. These defects are found in approximately 75 % of affected individuals [122]. EVER1 and EVER2 regulate the distribution of zinc in the nucleus, and zinc is a required cofactor for many viral proteins. In addition, defective Fas functions and perforin gene variation have been reported, and may play a role in the cutaneous manifestations [119].

12.15 Measles

12.15.1 Clinical Features

Measles was declared eliminated from the United States in 2000 [123]. However, cases have recently increased due to spread among unvaccinated individuals. Measles are characterized by fever, cough, conjunctivitis, nasal congestion, and skin rash. The skin eruption is a diffuse morbilliform rash composed of pink macules and thin papules that coalesce into patches and thin plaques. Classically, Koplik's spots, which is the viral enanthem of measles, is characterized by white spots along the buccal mucosa.

12.15.2 Histology

The exanthema caused by measles is no longer encountered with any great frequency, and it is even less commonly biopsied. In most cases, skin eruption is characterized by nonspecific changes, including upper dermal edema and a mild superficial perivascular lymphocytic infiltrate. The epidermis is largely uninvolved, although slight exocytosis of lymphocytes into the basal layer and focal basilar vacuolization may be seen. In rare cases, multinucleation of keratinocytes may be present [124]. Dying keratinocytes are not common. Eosinophils should be absent or present in very small numbers. However, rare cases with a prominent eosinophilic infiltrate have been described [125].

The major differential diagnosis includes a drug eruption. This is usually distinguished by the presence of abundant eosinophils in a drug rash, but in some cases, it may not be possible to separate these entities with absolute certainty.

12.15.3 Pathogenesis

Measles virus is a large single-stranded RNA virus that is part of the *Paramyxoviridiae* family [126]. Humoral and cell-mediated immune responses are involved in anti-viral host defense. The observed cutaneous eruption is the physical manifestation of an Arthus type of immune reaction elicited by viral particles in endothelial cells of dermal capillaries [124].

Measles is transmitted via respiratory secretions [126]. The virus initially infects monocytes and lymphocytes, which carry viral particles to other organs, including the skin [127]. Hemagglutinin, which is an outer membrane glycoprotein, enables the virus to attach to target cells. An additional fusion glycoprotein permits the virus to fuse with cell surfaces, and facilitates cell-to-cell transmission. Infected cells fuse to form multinucleated giant cells (called Warthin–Finkeldey cells) [126]. A protein found on the inner surface of the viral envelope is responsible for the production of intact viral particles [126].

12.16 Erythema Infectiosum

12.16.1 Clinical Features

Erythema infectiosum is caused by infection with Parvovirus B19, which is prevalent worldwide. Most people are infected during childhood, and primary infection rates peak in late winter and early spring [128]. Most affected individuals are asymptomatic, or have a very mild nonspecific illness. However, children aged 4–10 years old often develop erythema infectiosum (Fifth disease). Initially, the cheeks become erythematous ("slapped cheek" appearance) with pallor around the mouth (Fig. 12.25). After 1–4 days, a diffuse morbilliform eruption appears over the trunk and extremities, then fades to a lacy reticular pattern. The lacy rash is usually asymptomatic and can last up to 6 weeks, often becoming more prominent with exposure to heat, such as bathing and increased physical activity.

12.16.2 Histology

There is a superficial perivascular infiltrate consisting primarily of lymphocytes with rare eosinophils. Lymphocyte exocytosis with dying keratinocytes and focal hemorrhage is seen in some cases. In some patients, a lymphocytic

Fig. 12.25 Erythema infectiosum presents as ill-defined erythema at both cheeks in a young boy who presented with symptoms of an upper respiratory infection

vasculitis is reported, whereas some authors have described a leukocytoclastic vasculitis. Abnormal blood vessels containing parvovirus particles within endothelial cells have been described [129]. The lymphocytic infiltrate may extend around dermal nerves, causing a peri-neuritis [130]. An interstitial histiocytic infiltrate with dermal mucin, giving rise to a granuloma annulare-like or lupus-like appearance, has been reported in a small series of patients [131].

12.16.3 Pathogenesis

Erythema infectiosum is caused by a small DNA parvovirus B19V. The virus is highly contagious, and spreads through respiratory droplets [128]. Its ability to infect erythrocyte precursors results in a transient aplastic anemia in some affected children with a large viral load [132]. The virus also infects endothelial cells in cutaneous vessels, and viral particles can be visualized on electron microscopic examination [129]. Antibodies directed against parvovirus are part of host immune response, and contribute to the cutaneous manifestations [131, 133].

12.17 Coxsackievirus

12.17.1 Clinical Features

One of the most common childhood infections caused by coxsackievirus is hand, foot and mouth disease (HFMD). Primary infections most frequently occur in summer and early fall [134]. Classic HFMD presents with pink macules, papules, and vesicles located primarily in the oral cavity and on the palms and soles. Recently, a variety of atypical forms have been described, in which lesions are more widespread and often more vesiculobullous in appearance (Fig. 12.26). Onychomadesis and nail shedding may occur weeks to months following the infection. Most affected children experience complete recovery without long-term sequelae of dyschromia or scarring.

12.17.2 Histology

Histologic changes in HFMD are those of a vesicular spongiotic dermatitis (Figs. 12.27 and 12.28). There is a microvesicular reaction pattern with spongiosis and exocytosis of lymphocytes into the epidermis or mucosal surface. The spongiosis may result in reticular and ballooning degeneration. Papillary dermal or submucosal edema is present. There is associated underlying perivascular lymphohistiocytic infil-

Fig. 12.26 Polymorphic erythematous papules and vesiculopapules on the extensor arms, legs and buttocks in a child with atypical hand, foot and mouth disease

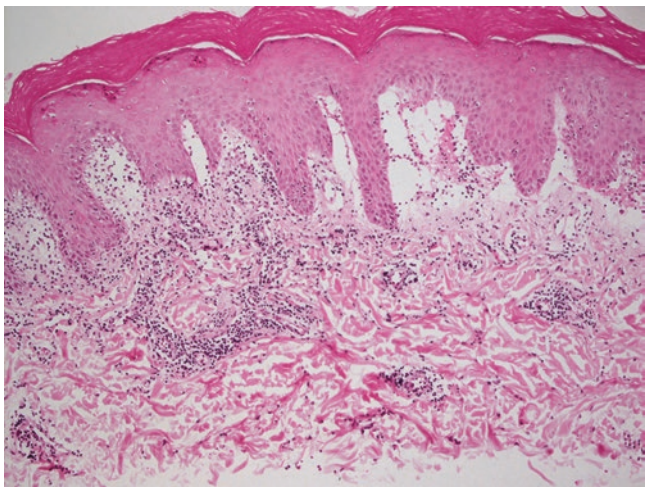

Fig. 12.27 Acral skin demonstrates papillary dermal edema and a lymphocytic infiltrate in the dermis in hand, foot, and mouth disease

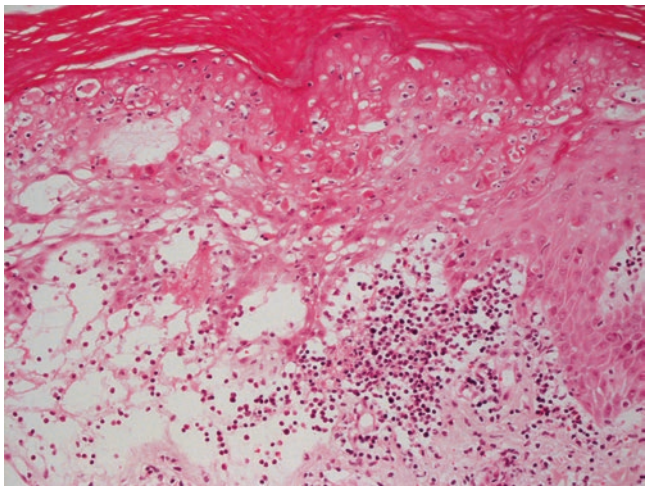

Fig. 12.28 Well-developed lesions of hand, foot, and mouth disease show abundant dermal edema and focal epidermal necrosis

trate without eosinophils. Viral inclusions are usually not seen on routine H&E sections.

The reticular and ballooning degeneration raises the differential diagnosis of herpetic dermatitis. However, multinucleation, nuclear molding and clearing that are characteristic of herpes infection are not seen with coxsackievirus infections. Other spongiotic processes may present with overlapping histologic changes, but they can be easily distinguished based upon the clinical presentation and disease course.

12.17.3 Pathogenesis

Coxsackievirus A16 is a member of the *Enterovirus* genus and *Picornavirales* family. It is the infectious agent responsible for most cases of hand, foot and mouth disease. Rare cases are also caused by Coxsackieviruses A5, A7, A9, A210, B2, B5, as well as enterovirus 71. These are single-stranded RNA viruses, typically 28–30 nm in size [135]. Enteroviruses spread between cells through a process called autophagosome-mediated exit without lysis (AWOL), which is regulated by lipids and metabolizing enzymes [136].

12.18 Kikuchi's Disease

12.18.1 Clinical Features

Kikuchi's disease presents with cutaneous findings in approximately 40 % of cases [137]. In many of these cases, the cutaneous eruption is malar in distribution, and resembles cutaneous lupus erythematosus [138]. Some patients present with targetoid lesions with an appearance of erythema multiforme in conjunction with malar erythema, giving rise to consideration of Rowell syndrome [139].

Kikuchi's disease is self-limiting in most patients, although evolution into lupus erythematosus has been described in up to one-third of affected children [140]. In other patients, the disease is believed to coexist with systemic lupus erythematosus [141]. A causative relationship with Epstein–Barr virus infection has been described in children with Kikuchi's disease [137]. In some patients, treatment with acetaminophen has resulted in complete resolution without relapse [142].

12.18.2 Histology

The most common histologic presentation of Kikuchi's disease is an interface dermatitis. There is basal vacuolization and exocytosis of lymphocytes into the epidermis. Scattered dying keratinocytes are present. There is a superficial perivascular lymphohistiocytic infiltrate and slight papillary dermal edema [142, 143]. Occasionally, the infiltrate may extend more deeply into the dermis, and even into the subcutaneous fat with mucin deposition [137]. A less common presentation is reminiscent of the changes seen in affected lymph nodes. Aggregates of histiocytes are present along with karyorrhectic debris, patchy necrosis, and atypical lymphocytes [137].

The differential diagnosis of Kikuchi's disease includes lupus erythematosus with both entities demonstrating interface dermatitis, superficial and deep perivascular lymphocytic infiltrates, and dermal mucin deposition. Clinical correlation is the most useful way to distinguish between the two entities. Erythema multiforme might also be considered, but it can be excluded based upon the clinical presentation, the presence of a deep inflammatory infiltrate and dermal mucin in Kikuchi's disease. Infectious and granulomatous processes may enter the differential diagnosis when aggregates of

histiocytes and tissue necrosis are present, but microbiological cultures and special stains for microorganisms can resolve this diagnostic dilemma.

12.18.3 Pathogenesis

The causative agent of Kikuchi's disease remains unknown. A large meta-analysis suggests that there is an association with HHV-8 in some cases [144], while others implicate parvovirus B19 [145]. No microorganisms have been isolated in most cases, leaving the question of causation completely unknown at this time.

12.19 Rocky Mountain Spotted Fever

12.19.1 Clinical Features

There are 600–1,200 reported cases of Rocky Mountain spotted fever in the United States each year. Ninety percent of infections occur between April and September. The incidence is higher in children (especially between 5 and 9 years old), Caucasians, and males [146]. The illness typically begins with a fever. After 2–3 days, a skin rash of small pink macules appears at the ankles and wrists, and then spreads to the palms, soles, and trunk. The macules typically become petechial, and may even coalesce to form larger ecchymotic/purpuric or even necrotic areas of skin. The overall mortality rate of Rocky Mountain spotted fever is 5–10 % [147].

12.19.2 Histology

Rocky Mountain spotted fever is characterized by a dense lymphocytic infiltrate centered on superficial and deep dermal vessels with transmural migration of lymphocytes through the vessel walls (Fig. 12.29). Fibrinoid necrosis of blood vessel walls leads to vascular thrombosis and hemorrhage, giving rise to the suggestion that this entity may represent a true lymphocytic vasculitis [148] (Fig. 12.30). There is subsequent necrosis of the overlying epidermis. In addition, an interface dermatitis with lymphocyte exocytosis, basal cell vacuolization, and dyskeratosis of keratinocytes may be present [149]. In some cases, a leukocytoclastic vasculitis with a neutrophilic infiltrate is seen in later lesions. Microorganisms cannot be identified on routine histologic sections [150].

12.19.3 Pathogenesis

Rocky Mountain spotted fever is caused by infection with *Rickettsia rickettsii t*hrough a bite from one of several species of infected ticks [151, 152]. Rickettsiae are small gram-negative intracellular bacteria. Once contracted, they disseminate through hematogenous route and invade endothelial cells of capillaries and arterioles. Outer membrane protein B (OmpgB) functions to provide adhesion to endothelial cells. The bacteria induce cytoskeletal changes within infected endothelial cells, heralding the ensuing endocytosis. When intracellular, they multiply and induce an immune host response [153]. There is oxidative injury to endothelial cell membranes due to the activities of phospholipases, proteases, and free radicals. Endothelial cells are subsequently disrupted, leading to loss of vascular integrity and increased permeability [152].

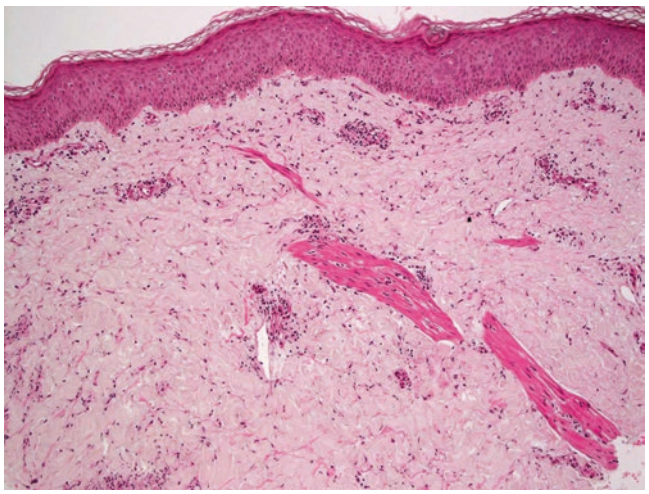

Fig. 12.29 Rocky Mountain spotted fever demonstrates a perivascular inflammatory infiltrate. The epidermis is unremarkable in early lesions

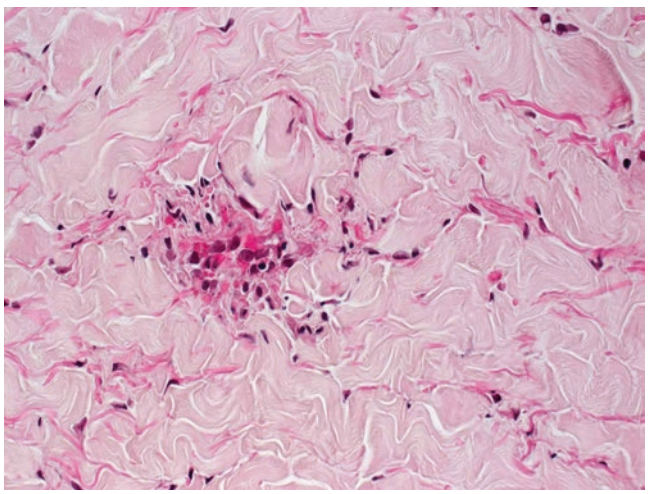

Fig. 12.30 Vascular damage with extravasation of erythrocytes into the dermis is seen in Rocky Mountain spotted fever

12.20 Cat Scratch Disease

12.20.1 Clinical Features

There are approximately 22,000 cases of cat scratch disease annually in the United States. Infection is most common in August through October [154]. Children are affected more often than adults. Typical signs and symptoms are fever and tender regional lymphadenopathy. Cutaneous features consist of an initial erythematous papule at the site of inoculation, which progresses to a vesicle, then a crusted papule that typically lasts for 1–3 weeks (Figs. 12.31 and 12.32). Approximately 5 % of patients develop additional cutaneous findings. These include morbilliform or urticarial rash, granuloma annulare, erythema nodosum, erythema marginatum, and leukocytoclastic vasculitis [155].

12.20.2 Histology

The cutaneous histologic changes resemble those seen in affected lymph nodes. The epidermis is often focally ulcerated and acanthotic laterally. Within the dermis, there is a large stellate abscess with central necrosis, and abundant neutrophilic infiltrate and karyorrhectic debris. Eosinophils are also present in most cases (Figs. 12.33 and 12.34). Granulomatous inflammation surrounds the centrally necrotic foci, and microorganisms are present within histiocytes and areas of necrosis [156]. The appearance of leukocytoclastic vasculitis has been reported in some patients [157]. Warthin–Starry stains can be used to identify microorganisms, as can more specific tests, such as polymerase chain reaction. In immunosuppressed patients, a pattern of epithelioid angiomatous proliferation has been described. It is likely that these cases should now be classified as bacillary angiomatosis [158, 159].

Fig. 12.31 An erythematous, crusted papulonodule is seen on the forehead at the site of a scratch from a new kitten in cat scratch disease

Fig. 12.32 A child with cat scratch disease has cervical lymphadenopathy with a crusted papulonodule on the ipsilateral scalp (top of photo)

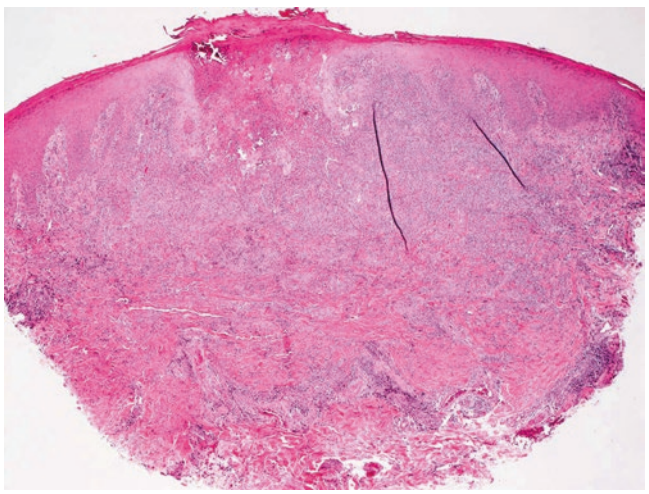

Fig. 12.33 Cat scratch disease results in a dense and diffuse inflammatory infiltrate within the dermis

12.20.3 Pathogenesis

Cat-scratch disease is caused by *Bartonella henselae*. It is a facultative intracellular gram-negative rod that infects erythrocytes and endothelial cells [160]. The bacteria are transmitted to humans by the cat flea, via infected feces or bites [161].

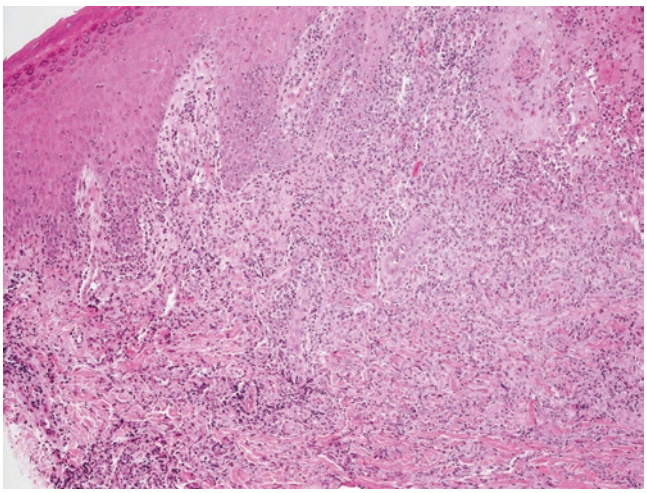

Fig. 12.34 Granulomatous inflammation and neutrophilic infiltrate are present in cat scratch disease

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Fungal Diseases

13

13.1 Toxoplasmosis

13.1.1 Clinical

Toxoplasmosis is a parasitic infection caused by the protozoa *Toxoplasma gondii*. Congenital infection usually results from transplacental transmission of protozoa after primary infection of a woman during pregnancy. Prevalence of congenitally acquired disease in the United States is 10 to 33 per 100,000 live births or 40 to 4000 cases per year [1].

Cutaneous lesions of congenital toxoplasmosis are variable, and include generalized morbilliform eruption, scarlatiniform eruption, subcutaneous nodules, and a "blueberry muffin" rash characterized by scattered violaceous papules and nodules [2].

13.1.2 Histology

Toxoplasmosis only rarely involves the skin, and biopsies are seldom performed. The microorganisms can be present at any level of the epidermis, dermis, and subcutis [3, 4]. They may be present as pseudocysts or trophozoites within macrophages or in extracellular space in the dermis. The most common finding is that of a superficial and deep inflammatory infiltrate consisting of lymphocytes and histiocytes that is nonspecific and remarkable only for the presence of microorganisms [5]. A panniculitis reaction pattern, also specific only for the presence of toxoplasmosis, is also possible [6]. Less commonly, cases that have clinical and histologic features of a lichenoid dermatitis, graft vs. host disease, dermatomyositis, or erythema multiforme have been described [7, 8]. The presence of microorganisms within keratinocytes has also been described in an immunocompromised host [4]. In rare cases, pseudoepitheliomatous hyperplasia may occur.

13.1.3 Pathogenesis

Toxoplasmosis is caused by *Toxoplasma gondii,* a prevalent obligate intracellular parasite [9]. Infection occurs by ingestion of parasite cysts present in contaminated food or water [10]. The definitive host of *T. gondii* is cats, which can shed millions of sporozoites in their feces [11]. *T. gondii* tachyzoites can invade host cells, replicate, enter the circulation, and disseminate to multiple body sites [10]. *T. gondii* is found predominantly in macrophages shortly after infection [12]. The microorganism can cross the blood brain barrier by traveling inside parasitized leukocytes [13]. Toxoplasma induces chronic infection with tissue cysts persisting for the lifetime of the host.

13.2 Dermatophytosis

13.2.1 Clinical

Dermatophytosis refers to superficial fungal infections of the skin, hair, and nails. These infections are caused by dermatophyte fungi in three genera: Trichophyton, Microsporum, and Epidermophyton [14]. Dermatophytosis affects approximately 20–25 % of the world's population and about 10–15 % of people are infected at some point in their lives [15]. Dermatophyte infections are generally named and classified by the affected anatomic locations, for example, tinea capitis for the hair and scalp (Fig. 13.1), tinea faciei on the face (Fig. 13.2), tinea manuum for the hands, tinea corporis for the body (Fig. 13.3), tinea cruris for the groin, tinea pedis for the feet, and tinea unguium for the nails. Majocchi's granuloma is the name given to a similar fungal infection involving hair follicles (Fig. 13.4).

Erythematous scaly plaques that are annular or nummular in shape typically characterize dermatophyte skin infections.

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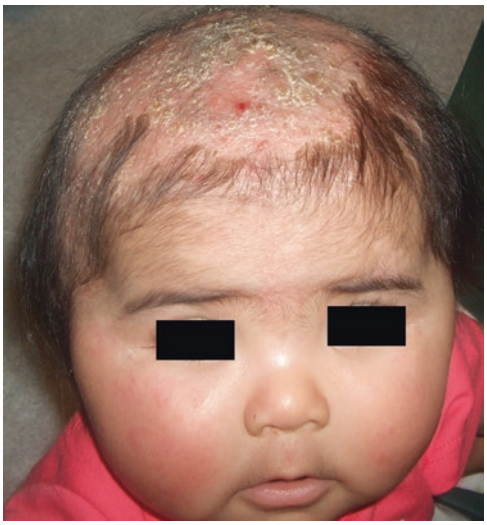

Fig. 13.1 Tinea capitis presents as scarring alopecia, pronounced scale and scattered erosions affecting the majority of the scalp in an infant treated with high potency topical steroids

Fig. 13.2 Tinea faciei is seen in a girl with multiple erythematous, scaly, annular plaques along the left side of the face

Fig. 13.3 Tinea corporis presents as adjacent erythematous, concentric annular plaques with scales

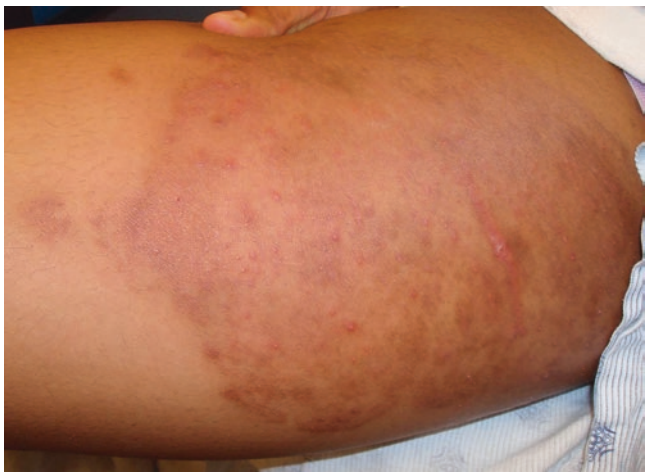

Fig. 13.4 Majocchi's granuloma presents as a well-circumscribed, indurated, erythematous annular plaque studded with pustules

On the scalp, there is commonly associated hair loss and breakage. Sometimes there is significant inflammation with swelling and pustules. Affected nails are often thickened, discolored, and brittle. Treatment consists of topical or oral antifungal medications, depending on the location and severity of infection. Prognosis is generally good with appropriate therapy.

13.2.2 Histology

Histologic findings of dermatophytosis include parakeratosis and mild spongiosis with an underlying superficial perivascular lymphohistiocytic infiltrate (Fig. 13.5). Eosinophils are scant, and the infiltrate is mild in most cases. Small numbers of neutrophils and serum may be seen in the stratum corneum, usually adjacent to areas with parakeratosis. Onychomycosis demonstrates similar findings within the keratin of the nail plate [16]. In some cases, yeast and hyphal forms are readily apparent on routine H&E sections, while in other cases, Periodic acid–Schiff stains with diastase are very helpful in highlighting the microorganisms. While some authors have advocated pretreating histologic sections with NaOH as a means of enhancing detection, this technique is not currently widely practiced by pathologists [17]. Histologic changes are essentially independent of the inciting species of dermatophyte or the site affected [18]. In some cases, the fungi are pigmented, giving rise to tinea nigra (Figs. 13.6 and 13.7). This fungal pigmentation is easily observed on routine histologic sections.

Dermatophytes involving hair follicles in the scalp result in suppurative folliculitis, in which case the inflammatory infiltrate is much more pronounced and may include abun-

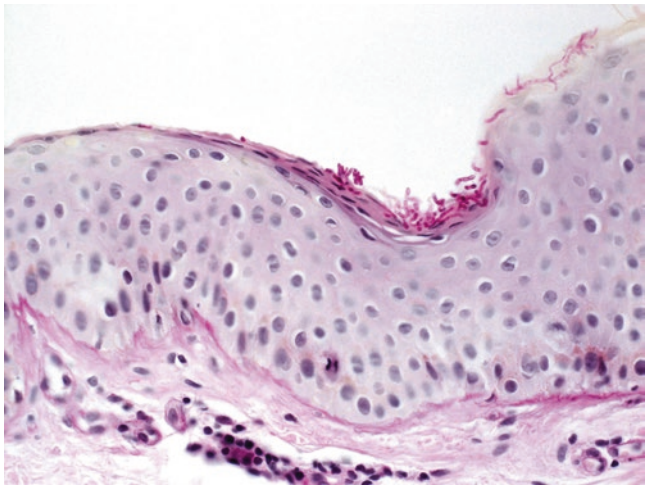

Fig. 13.5 Dermatophytes are present within the stratum corneum, often adjacent to foci of parakeratosis. Inflammation is variably present. Spores and hyphae are visualized with Periodic acid–Schiff stains

Fig. 13.6 Tinea nigra presents as a well-circumscribed, round, brown patch with dry scale along the medial aspect of the foot in a young boy

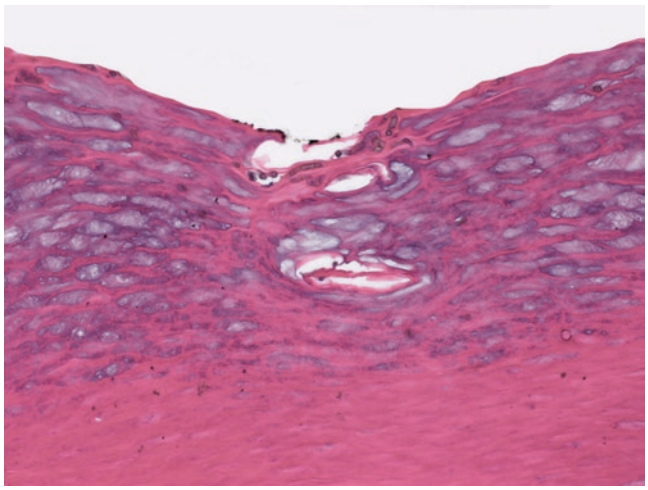

Fig. 13.7 Tinea nigra demonstrates pigmented yeast and hyphal forms in hyperkeratotic stratum corneum on acral skin

dant dermal neutrophilic abscesses [19]. In florid and long-standing cases, dense dermal scarring with pronounced alopecia may occur [20]. In children, tinea capitis is the most common presentation of folliculo-centric dermatophytosis. Majocchi's granulomas also occur in children [21]. In cases of kerion or Majocchi's granuloma, fungal organisms are present within the keratinaceous portions of the pilosebaceous structures. Microorganisms are not ordinarily found in the dermis despite the brisk inflammatory response secondary to follicular rupture.

The histologic findings of *tinea capitis* include inflammation within and around follicular epithelium, with or without involvement of the overlying epidermis. Depending upon the severity of the process and the acuity of the condition, the inflammation may be predominantly neutrophilic with abscess formation within hair follicles, or may consist of a less intense lymphocytic infiltrate. In florid cases, rupture of the follicular epithelium may result in a granulomatous response with neutrophils and abundant multinucleated giant cells. Fungi may be identified with routine H&E staining, but they are highlighted and easily visible on a Periodic acid–Schiff stain using diastase or a methenamine silver stain [22]. Tinea capitis is primarily caused by *Microsporum canis* or *Trichophyton tonsurans* which can be confirmed with fungal cultures [20, 23]. Majocchi's granuloma can occur in children. It is a suppurative fungal-induced folliculitis. Histologic findings demonstrate neutrophilic abscesses primarily within follicular structures. Abscesses may extend into the surrounding dermis, and result in a suppurative process throughout the dermis [19]. As hair follicles rupture, a granulomatous response is seen with abundant multinucleated giant cells admixed with a dense neutrophilic infiltrate [21]. Extension into the subcutaneous fat is not uncommon. Frequently, there are epidermal hyperplasia, parakeratosis and neutrophilic abscesses within the stratum corneum. With chronic infection, dermal fibrosis and distortion of the follicular architecture may develop [19].

13.2.3 Pathogenesis

Dermatophytes can survive solely on the outer stratum corneum layer of the skin [24]. Studies have shown that dermatophytes require about 6–12 hours to adhere to the host tissue, 16 hours to germinate, and 72 hours to invade into the stratum corneum [25, 26]. Once they adhere to keratinized tissue, dermatophytes release enzymes, such as keratinases, metalloproteases and serine proteases, as well as lipases and ceramides. These enzymes cleave proteins and lipids in keratinized tissue and induce an inflammatory response,

resulting in tissue injury [27, 28]. Infections by dermatophytes generally induce a type 1 T-helper cell response with the production of interleukin-2 and interferon-γ [28]. The production of antibodies is also important in the overall immune response to dermatophytes. In acute fungal infections, cellular-type immune response predominates, whereas in chronic fungal infections, antibody-mediated response, involving mainly IgE and IgG, is the primary reaction [26].

In tinea capitis, fungal hyphae grow in the stratum corneum and the hair follicles, extending upward as the hair grows [29]. Endothrix infection occurs when arthroconidia (spores) are present in the hair shaft. In tinea capitis, there is severe inflammation leading to subcutaneous pustule formation and hair loss. Th17, a type of CD4-positive helper T cells, may have a role in the pathogenesis. Increased number of circulating Th17 cells have been reported in a patient with tinea capitis [30].

Majocchi's granuloma results from chronic dermatophyte infection of the skin or nails that eventually disseminates into the dermis and subcutaneous tissue. Predisposing factors that affect cell-mediated immunity and the inflammatory response include long-term use of steroids, chemotherapy, and immunosuppressive drugs [21, 31]. Dermatophyte infection induces toll-like receptor (TLR)-mediated activation of keratinocytes and monocytes that can inhibit a number of antimicrobial peptides, such as cathelicidins, which are important in skin defense mechanisms against pathogens [32]. Neutrophils and macrophages are crucial for the control of invasive fungal infections by ingesting and killing fungal spores and hyphae [33]. Type 1 T-helper cell (Th1)-mediated immunity is important in dermatophytic infections [21, 34]. Immunosuppressive therapy that impairs cellular immunity can result in generalized Majocchi's granuloma.

The physical barrier integrity of the skin is important in the pathogenesis of Majocchi's granuloma. Factors that impair the barrier integrity, such as physical trauma, can lead to hair follicle disruption and entry of microorganisms from the epidermis into the dermis. Keratinous materials that are introduced into the dermis after follicular disruption can potentially provide proteinaceous substrates for the survival of dermatophytes [35, 36]. Changes in the dermal milieu due to fungal infection may create a favorable environment for fungal pathogens to survive and grow.

13.3 Candidiasis

13.3.1 Clinical

Congenital cutaneous candidiasis is defined as widespread cutaneous candida infection that typically presents within the first 6 days of life. Up to 25 % of pregnant women harbor Candida albicans in their vaginal flora, and mucocutaneous candida infection is fairly common in infants. However, congenital cutaneous candidiasis is relatively uncommon with few confirmed reports in the literature [37].

Fig. 13.8 Erythematous thin plaques are present at the mons pubis, labia majora, and medial thighs with satellite papules and pustules in irritant contact diaper dermatitis with superimposed candida

Affected infants may have cutaneous involvement alone or serious systemic infection with respiratory distress and even sepsis [37]. The most common clinical presentation is a generalized eruption consisting of small erythematous macules, papules, and pustules which resolves without serious sequelae (Fig. 13.8) [38]. Approximately half of affected infants respond well to topical antifungal therapy. The majority of infants have a benign course with complete recovery.

13.3.2 Histology

Histologic findings in cutaneous candida infection are those of a pustular dermatosis. Within the epidermis, there is focal spongiosis with neutrophils extending from the superficial dermis into the epidermis, and frequently forming subcorneal pustules (Fig. 13.9). The dermis is relatively uninvolved with only scattered superficial neutrophils admixed with lymphocytes and occasional eosinophils. Diagnosis is confirmed on Periodic acid–Schiff stains with diastase that demonstrate abundant yeast forms. Candidiasis can also be seen in biopsies taken from nails, in which cases the microorganisms are found within the nail keratin with neutrophils and serum deposition [39]. Invasive candidiasis is encountered in severely immunocompromised hosts. Microorganisms can be present in great abundance in the dermis or in blood vessels with candidal septicemia [40].

The differential diagnosis includes other subcorneal pustular dermatoses, including psoriasis, acute generalized

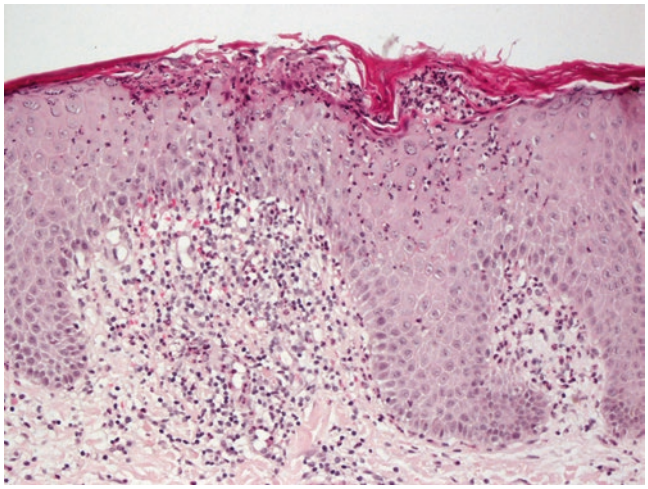

Fig. 13.9 Candida infection of the skin shows subcorneal neutrophilic abscesses with inflammation of the underlying dermis

exanthematous pustulosis, pustular dermatophytic infections, some cases of IgA pemphigus, infantile acropustulosis, and transient neonatal pustular melanosis. The clinical history and special stains for microorganisms make the distinction relatively straightforward [41].

13.3.3 Pathogenesis

Candida albicans is a dimorphic fungus that can colonize a variety of tissues, including the skin and oral and vaginal mucosa. Competing commensural bacteria and the local host immune response prevent an overabundance of Candida [42]. When the normal flora is altered by antibiotic treatment or in immunocompromised states, the result can be an overgrowth of Candida, such as candidiasis on mucosal surfaces (thrush).

Recognition of Candida by the host immune system requires toll-like receptor (TLR) 2 and Dectin-1 on immune cells [43–45]. The NLRP3 (NACHT, LRR, and PYD domain-containing protein) inflammasome is important in the host immune response to fungal infection. NLRP3 inflammasome is associated with interleukin-1 response to a variety of pathogens, including *Candida albicans* [46]. Dendritic cells are important in the host immune defense against Candida. Dendritic cells phagocytoze the yeast form of *Candida albicans* and induce the differentiation of CD4+ T lymphocytes into type 1 T helper cells (Th1 cells) and the activation of B lymphocytes and the maturation of phagocytic cells [47, 48]. Among the cytokines involved in Candida infection, IL-33, which induces a type 2 T helper cell (Th2) inflammatory response and activates both innate and adaptive immunity, has a pivotal role in the host immune defense against fungal pathogens [48].

13.4 Chronic Mucocutaneous Candidiasis

13.4.1 Clinical

Chronic mucocutaneous candidiasis is seen in a variety of disorders in which patients experience persistent or recurrent *Candida albicans* infections of the mucous membranes, skin, and nails. Some of these conditions are inherited or associated with primary or secondary immunodeficiency [49]. Infants often present with persistent oral thrush and candida diaper dermatitis. Over time, they develop more widespread erythematous, scaly plaques, especially on the scalp and extremities. Occasionally, these plaques develop into thick granulomas. Nails may become thick, dystrophic, and discolored [50]. Most patients require systemic antifungal medications for disease control.

13.4.2 Histology

Histologic changes in chronic mucocutaneous candidiasis resemble those seen in acute candida infections. Subcorneal pustules, mild epidermal spongiosis, and the presence of yeast forms and pseudohyphae are seen. The microorganisms may be apparent on routine H&E sections, but they are better visualized on Periodic acid–Schiff stains [51]. In long-standing lesions, psoriasiform epidermal hyperplasia is present. In some patients, a granulomatous dermal infiltrate is seen, and microorganisms may be present within the granulomas [52]. Microorganisms are identified within affected nail plates [53].

13.4.3 Pathogenesis

Chronic mucocutaneous candidiasis affects patients with immunodeficiency, most commonly individuals with defects in the T-cell compartment, and those with diverse genetic defects that result in impaired IL-17 and IL-22 immunity [54]. Chronic candida infections during infancy serve as an indicator of primary immunodeficiency [55].

Signaling pathways associated with IL-17+ T helper cells (Th17) are important in immunodeficiency syndromes associated with chronic mucocutaneous candidiasis [56]. Mutations in CARD9, STAT3, IL17RA, IL17F, STAT1, and IL12RB and polymorphisms in Dectin 1 and interleukin-22 (IL-22) that cause impairment of function of Th17 cells are associated with the disease [57]. Studies have suggested that IL-17A- and IL-17F-producing cells are important Th17 cells in the host immune response against Candida.

Neutrophils are important in acute mucosal defense against *C. albicans* by preventing fungal dissemination [58]. Neutrophil mobilization and trafficking are induced in an IL-17RA-dependent manner [59]. IL-17 can induce the expression of antimicrobial peptides (AMPs), including S100A8 and S100A9 (which form the heterodimeric complex calprotectin), β-defensin 3 and lipocalin 2. These molecules have direct antifungal activities through membrane depolarization and depriving the fungus of essential metal ions [60]. In patients with chronic mucocutaneous candidiasis, gain-of-function mutations in STAT1 shift the cellular response toward Th17 cell-inhibiting cytokines. Th17 cells secrete IL-17 and IL-22, which are cytokines with potent antifungal properties that induce the production of antimicrobial peptides and activation and recruitment of neutrophilsto mediate microbial killing. Mutations in IL17F and IL17R in patients with chronic mucocutaneous candidiasis, as well as neutralizing autoantibodies against IL-17 and IL-22 in patients with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy can directly impair IL-17 and IL-22 immunity.

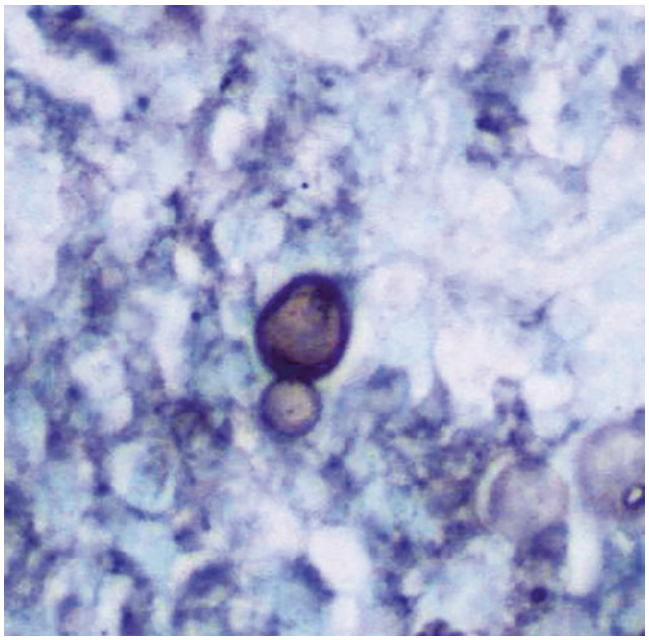

Fig. 13.10 Gomori-methenamine silver stain demonstrates the broad-based budding yeasts seen in blastomycosis

13.5 Blastomycosis

13.5.1 Clinical

Blastomycosis is caused by the dimorphic fungus *Blastomyces dermatitidis*. In the United States, annual incidence of blastomycosis is estimated at 0.3–1.8 cases per 100,000 people [61]. The typical patient with blastomycosis is a middle-aged man who spends significant time outdoors [62]. Blastomycosis is rare in children and adolescents. The majority of patients with blastomycosis have primary pulmonary involvement. Sometimes there is hematogenous spread of infection to extrapulmonary sites. Rarely, primary infection is acquired via cutaneous inoculation [63]. Skin involvement has been reported in 40–80 % of blastomycosis cases [62, 63]. Typical skin lesions appear as verrucous nodules and plaques or ulcerative lesions with raised borders. Therapy consists of systemic antifungal medication. Most patients with localized cutaneous disease have a favorable prognosis.

13.5.2 Histology

The histologic findings of blastomycosis in children are the same as those described in adults. The epidermis typically demonstrates pseudoepitheliomatous hyperplasia. Neutrophilic abscesses are present within the stratum corneum, epidermis, and dermis [64]. Foci of granulomatous inflammation can also be seen. Microorganisms are present mainly within the dermis, and they can be identified on routine H&E sections and highlighted with Gomori methenamine silver and Periodic acid–Schiff stains (Fig. 13.10). Blastomyces are broad budding yeasts with capsules that are approximately 6 μm in diameter. Microorganisms can also be detected on Tzanck smears, but this is not the normal method for establishing the diagnosis [65].

The differential diagnosis includes other deep fungal infections that cause pseudoepitheliomatous hyperplasia, such as chromomycosis and sporotrichosis. Tuberculosis, especially lupus vulgaris, may have similar histologic features, but it can be distinguished on acid-fast bacilli stain. Blastomycosis-like pyoderma, which is caused by bacterial infection, can induce pseudoepitheliomatous hyperplasia, but it is differentiated on special stains for microorganisms [66, 67]. Halogenodermas may be considered, but these typically contain abundant eosinophils within the dermis. Keratoacanthoma-type of squamous cell carcinoma may also demonstrate similar histologic features, but it is quite rare in the pediatric population.

13.5.3 Pathogenesis

Blastomycosis is caused by *Blastomyces dermatitidis*, which is a dimorphic fungus that causes systemic granulomatous disease [68]. The infection is prevalent in North America,

most notably in the Ohio and Mississippi river valleys, and in some countries in Africa (such as Zimbabwe and South Africa) [69]. Infection by *Blastomyces* often originates in the lungs by inhalation of conidia of the fungus with secondary systemic spread via the lymphatics to other anatomic sites [70]. The most frequent site of dissemination of pulmonary blastomycosis is the skin (40–80 % of the cases), followed by bone (10–50 %), genitourinary tract (10–30 %), and central nervous system (1–5 %) [71]. *Blastomyces* can infect both immunocompetent and immunocompromised hosts. Studies have shown that 25 % of patients with blastomycosis have an immunocompromised status, such as diabetes mellitus, HIV, and malignancies [72].

13.6 Sporotrichosis

13.6.1 Clinical

Sporotrichosis is an infection caused by the dimorphic fungus *Sporothrix schenckii.* Although there is a pulmonary form of sporotrichosis, most infections are limited to the skin and subcutaneous tissues, and occur via direct inoculation following a puncture wound or skin abrasion [73]. The majority of individuals affected are males between the ages of 20 and 50 years old [74]. Although sporotrichosis can occur in children, it is relatively uncommon.

Clinically, there are three cutaneous patterns of sporotrichosis: fixed cutaneous, lymphocutaneous, and multifocal or disseminated cutaneous. In fixed cutaneous disease, a single papule forms at the site of inoculation, and develops into a crusted or verrucous plaque. In lymphocutaneous disease, an ulcerated nodule develops at the inoculation site, followed by the development of a string of similar nodules overlying the proximal lymphatic vessels. Multifocal disease is the least common disease presentation, and it refers to the development of three or more lesions appearing at two or more different anatomical locations. Although lymphocutaneous disease is the most common variety, accounting for 70–80 % of all reported cases, children are more likely to present with solitary lesions often located on the face [74, 75].

Fig. 13.11 Sporotrichosis demonstrates pseudoepitheliomatous hyperplasia and a dense inflammatory dermal infiltrate with granulomas

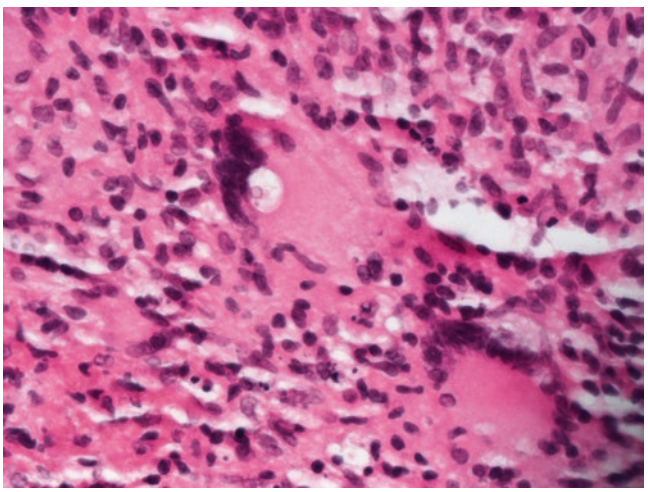

Fig. 13.12 Abundant granulomas, multinucleated giant cells, and intracellular organisms are present in sporotrichosis

13.6.2 Histology

Sporotrichosis demonstrates pseudoepitheliomatous hyperplasia overlying a suppurative and granulomatous dermatitis (Figs. 13.11 and 13.12). Abundant neutrophilic abscesses are present along with caseating granulomas, multinucleated giant cells, histiocytes, and other inflammatory cells. The inflammatory process is diffuse throughout the dermis, and can involve the subcutis. The microorganisms are found in variable numbers of cases, and they are more readily identified in areas adjacent to caseating granulomas [76, 77]. Cases in which there are more epithelioid granulomas and a lymphocytic predominance tend to have fewer numbers of microorganisms [78]. Asteroid bodies are present in the great majority of cases, and microorganisms are frequently associated with these structures with spores ranging from 2 to 6 μm in diameter. They are most easily identified on Periodic acid–Schiff stains [79].

The differential diagnosis includes cutaneous tuberculosis, particularly the lupus vulgaris variant with concomitant pseudoepitheliomatous hyperplasia. Acid-fast bacilli stains help to distinguish tuberculosis from sporotrichosis. Other deep fungal infections, such as chromomycosis and blastomycosis, can be distinguished based upon the morphology of the fungi. Halogenodermas do not tend to have caseating granulomas, and they are characterized by abundant eosinophils, which are not typically seen in sporotrichosis.

13.6.3 Pathogenesis

Sporotrichosis is an endemic disease caused by *Sporothrix schenckii*, a dimorphic fungus [80]. The fungal conidia usually enter the host by skin trauma and implantation of fungal microorganisms in the skin. The infection may extend deeply, involving the subcutaneous tissue, muscles, and fascia.

13.7 Chromoblastomycosis (Chromomycosis)

13.7.1 Clinical

Chromoblastomycosis is a chronic fungal infection of the skin and soft tissues. It is a result of traumatic injury to the skin followed by direct inoculation with fungal microorganisms [81]. Most patients with chromoblastomycosis are males between 50 to 60 years of age. Infection is uncommon in children [82]. Lesions commonly occur on the legs.

Clinically, five different presentations have been described: (a) nodular, where single or multiple pink to purple nodules are present; (b) tumoral, where larger nodular masses occur; (c) verrucous, where lesions have hyperkeratosis; (d) plaque, where there is one or more red to purple scaly plaques; and (e) cicatricial type, where there are large annular lesions with atrophic scarring [81]. Treatment is often difficult with low cure rates and high incidence of relapse [81]. However, systemic antifungal therapy, cryotherapy and thermotherapy, as well as surgical excision for limited lesions, have been tried with some success.

13.7.2 Histology

Chromoblastomycosis represents infection by one of a group of dematiaceous pigmented fungi [83]. Pseudoepitheliomatous hyperplasia is present and may be pronounced (Fig. 13.13). Fibrosis appears as the lesions become chronic [88]. In long-standing cases, transformation to squamous cell carcinoma has been reported [84–86]. As this transformation can take 10–20 years, it is not seen within the pediatric population. Within the dermis, there is a florid and diffuse granulomatous and neutrophilic inflammatory infiltrate. Neutrophilic abscesses can extend into the epidermis, and may be keratolytic. Brown yeast forms, ranging in size from 5 to 12 μm, are identified and appear as "copper pennies" [87] (Fig. 13.14). They may be present in both the epidermis and dermis [88]. These fungal elements are also known as "sclerotic bodies". Ultrastructural examination demonstrates that microorganisms are directly engulfed by neutrophils [89]. While microorganisms can be identified on Periodic acid–Schiff stains, in most cases, they

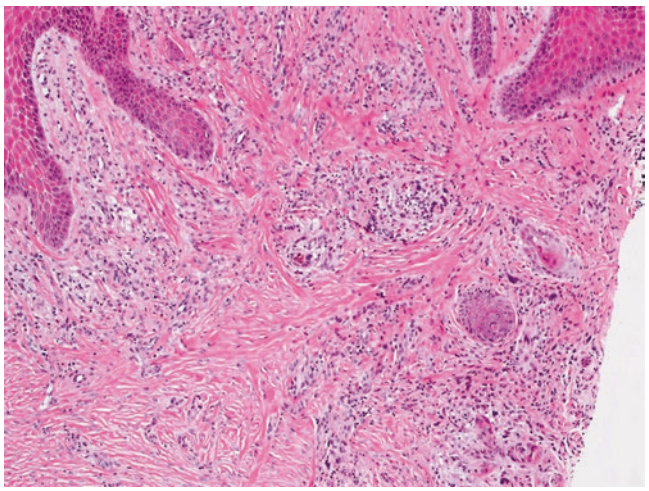

Fig. 13.13 Chromoblastomycosis demonstrates epidermal hyperplasia and mixed, focally granulomatous dermal infiltrate

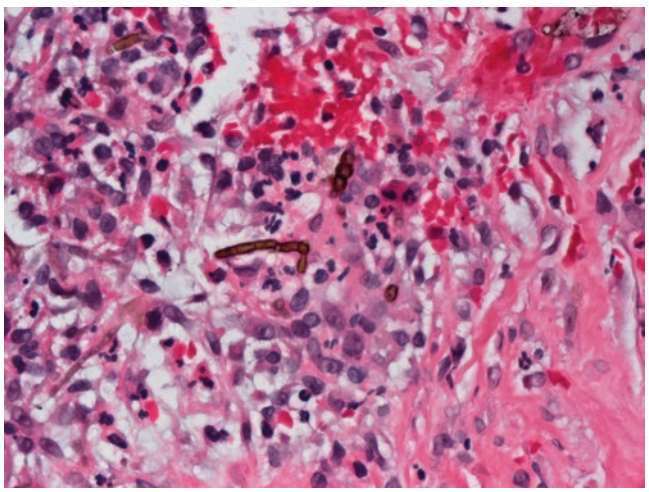

Fig. 13.14 Pigmented spores and hyphae are present within histiocytes and in the dermis in chromoblastomycosis

are readily apparent on routine H&E sections due to their characteristic brown color [90]. A rare cystic variant has been reported, in which microorganisms are confined to a cystic cavity within the dermis [91].

The histologic differential diagnosis includes other disease entities that induce pseudoepitheliomatous hyperplasia, including sporotrichosis and blastomycosis. The presence of pigmented fungi makes the distinction straightforward. Halogenodermas do not contain fungi, often have many eosinophils, and can be distinguished based upon clinical history. Blastomycosis-like pyoderma demonstrates bacteria and does not contain dermal fungi.

13.7.3 Pathogenesis

Chromoblastomycosis is defined as a chronic fungal infection of the skin that typically develops after traumatic injury and inoculation of fungi into the skin. The causative agents are three fungal species: *Fonsecaea pedrosoi, Phialophora verrucosa,* and *Cladophialophora carrionii* [92]. *F. Pedrosoi* and *C. carionii* are the most common responsible agents in the USA [93]. These saprophytic fungi live on plants or vegetable debris in the soil. The characteristic dark, thick-walled cells (Medlar bodies) are present in chromoblastomycosis.

Neutrophils and macrophages are important cells in the immune response in chromoblastomycosis. Dermal macrophages and dendritic cells are antigen-presenting cells that present fungal antigens to lymphocytes. In response to fungal spores, dendritic cells produce TNF-α, IL-10, and IL-12 [81]. CD4+ T lymphocytes play an important role in chromoblastomycosis by producing IFN-γ in response to the microorganisms [94, 95]. Additionally, stimulation of the Toll-like receptor (TLR) pathway is important for activation of the adaptive immune response to chromoblastomycosis.

13.8 Coccidioidomycosis

13.8.1 Clinical

Coccidioidomycosis is an infectious disease caused by *Coccidioides immitis*, which is considered to be endemic in the Southwestern United States, with an annual incidence of approximately 150,000 cases [96].

Rarely, *C. immitis* may cause a primary inoculation infection at a site of skin trauma. This will typically result in a localized ulcerated plaque that heals over several months. More commonly, *C. immitis* causes pulmonary infection after the spores are inhaled. At least 60 % of individuals with acute pulmonary infection have no symptoms or only a mild respiratory illness [96, 97]. During this acute illness, patients may experience a generalized morbilliform skin eruption [98]. Approximately 5 % will develop erythema nodosum or erythema multiforme [99]. Symptomatic disseminated extrapulmonary disease develops in approximately 1 in 200 infected individuals [97]. Skin manifestations in disseminated extrapulmonary disease include multiple verrucous papules and plaques.

Most patients with primary infection recover spontaneously. However, patients with disseminated disease are treated with systemic antifungal therapy. Patients who are pregnant or immunocompromised are particularly vulnerable to severe, aggressive infection.

13.8.2 Histology

Histologic sections demonstrate variable degrees of epidermal hyperkeratosis and pseudoepitheliomatous hyperplasia (Fig. 13.15). Within the dermis, there is a marked granulomatous and suppurative inflammatory infiltrate with large microorganisms that contain endospores [100] (Fig. 13.16). Some cases display a predominance of neutrophils with extensive necrosis within the inflammatory infiltrate, while other cases develop more prominent granulomas and appear less suppurative. A third reaction pattern characterized by a proliferation of small dermal blood vessels and a vasculitic pattern has also been described [101]. Microorganisms can be found in most cases on H&E sections, but can be highlighted with periodic acid Schiff stains. *Coccidioidomycosis immitis* form spherules that measure from 10 to 80 μm in diameter, and contain abundant 2–5 μm endospores.

Secondary reaction patterns are often seen in patients with disseminated disease. These include erythema nodosum, Sweet's syndrome, generalized exanthems, and erythema multiforme [102–104].

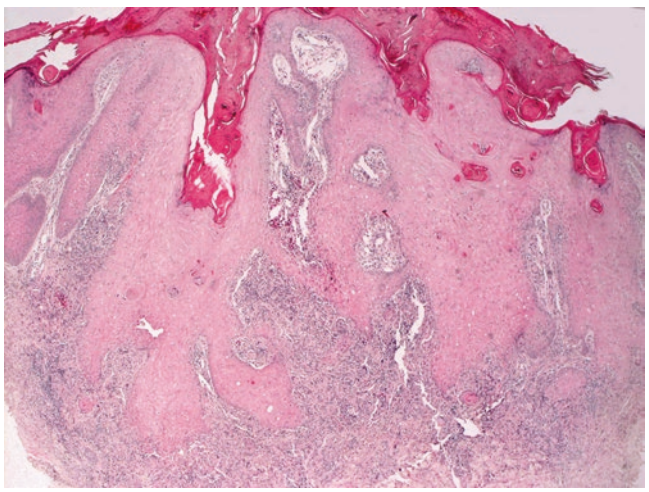

Fig. 13.15 Pseudoepitheliomatous hyperplasia is seen in some cases of coccidioidomycosis. There is a dense and mixed inflammatory infiltrate present in the dermis

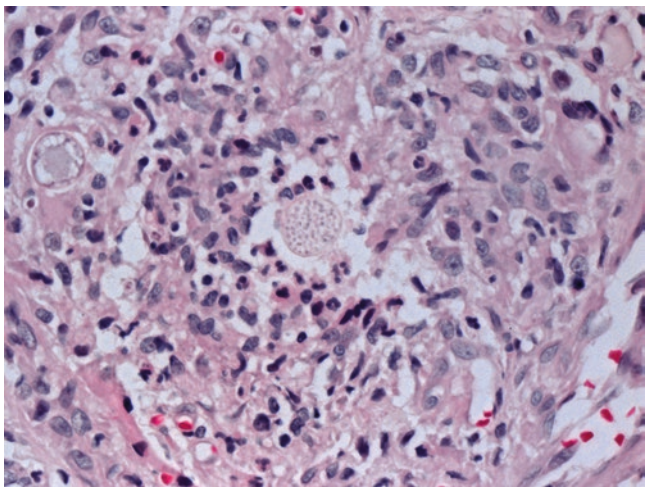

Fig. 13.16 Large morules containing endospores are present surrounded by granulomatous inflammation in coccidioidomycosis

13.8.3 Pathogenesis

Coccidioidomycosis (also known as valley fever) is caused by two species of fungi, *Coccidioides immitis* and *C. posadasii* [105]. *C. immitis* is a fungus found in the soil in southwestern USA, while *C. posadasii* is found predominantly in South America. Immunosuppressive states and underlying autoimmune diseases are predisposing conditions for the activation of underlying Coccidioides infection.

Infection by arthroconidia elicits an innate immune response involving neutrophils [106]. Toll-like receptor-2 and Dectin-1 are necessary to trigger an innate immune response to fungal microorganisms [107]. Soluble factors derived from the fungus generate complement components that attract neutrophils, which phagocytose fungi [108]. Coccidioides bind to human peripheral monocytes and dendritic cells through the mannose receptor [109, 110]. Fungal arthroconidia can stimulate macrophages to produce tumor necrosis factor-α, interleukin-1β and interleukin-6 [111]. Type 1 T-helper cell response is important in host defense against Coccidioidomycosis with current research for treatment on identifying T cell antigens capable of inducing such type 1 immune response [112].

13.9 Histoplasmosis

13.9.1 Clinical

Histoplasmosis is an infectious disease caused by the dimorphic fungus, *Histoplasma capsulatum*. Most cases of histoplasmosis are limited to only pulmonary involvement. Skin involvement is uncommon, but it is estimated to occur in approximately 4–11 % of patients who develop disseminated disease [113]. Rarely, primary inoculation disease can occur after trauma to the skin.

Clinically, skin lesions occur as erythematous papules, pustules, or ulcerations. Some patients may also develop erythema multiforme [114]. Many patients have mild disease with a self-limited course. Those with disseminated disease are treated with systemic antifungal therapy. Patients who are immunocompromised are more vulnerable to severe infection.

13.9.2 Histology

Histoplasma capsulatum induces a brisk dermal inflammatory infiltrate. Overlying ulceration is seen in some cases. Within the dermis, histiocytes are present as single cells coursing diffusely and occasionally forming granuloma [115] (Fig. 13.17). Within the cytoplasm of these cells, 2–4 μm microorganisms are present in large numbers (Fig. 13.18). There is a brisk neutrophilic infiltrate in most cases. Karyorrhectic debris is present, and dermal necrosis is rarely seen. In immunosuppressed patients, microorganisms are so numerous that diagnosis is possible on fine needle aspiration cytopreparations [115, 116]. Vasculitis has been reported in severely immunocompromised hosts [117].

The differential diagnosis includes leishmaniasis due to the size of the microorganisms. However, PAS stains will highlight Histoplasma, whereas Giemsa stains are effective in highlighting leishmania (Fig. 13.19). The identification of kinetoplasts in leishmania further helps with this distinction.

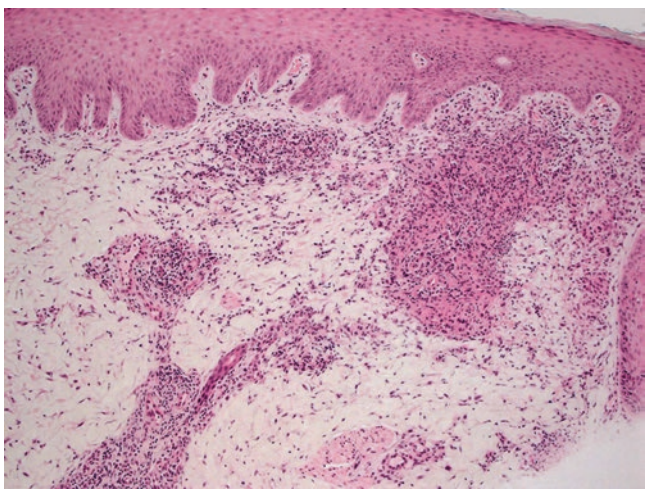

Fig. 13.17 Histoplasmosis induces a diffuse and granulomatous inflammatory response

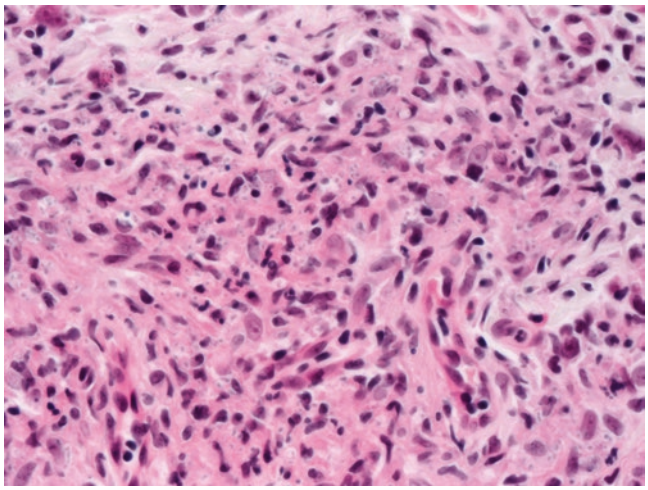

Fig. 13.18 Intracellular histoplasmosis microorganisms are present in the cytoplasm of enlarged histiocytes

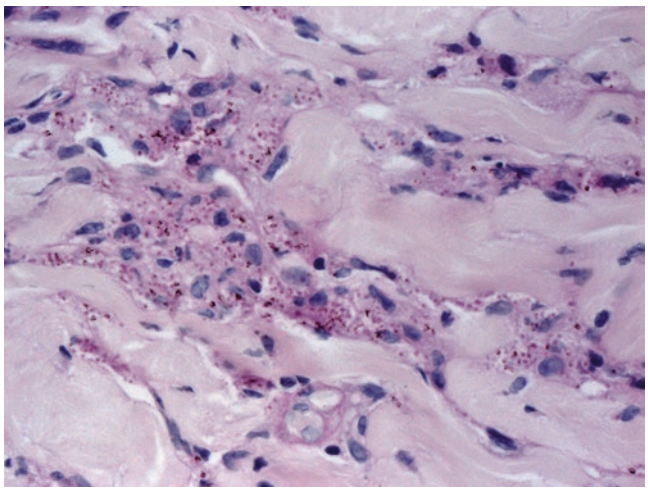

Fig. 13.19 Fungal PAS stains highlight small intracellular microorganisms in histoplasmosis

13.9.3 Pathogenesis

There are three varieties of *H. capsulatum*: var *capsulatum*, var *farciminosum*, and var *duboisii* [118]. The most common variant is *H. capsulatum* var *capsulatum*. Infection is acquired by inhalation of microconidia from contaminated bat or bird droppings. Microconidia are transported through the pulmonary bronchioles to the alveoli, where they generate a primary infection. Distant spread to the lymph nodes and spleen may occur. The severity of histoplasmosis depends on the immune status of the infected host and the strain virulence [118]. Most infections are asymptomatic, but severe disease can develop with hematogenous spread of fungi in immunocompromised patients with low CD4+ T lymphocyte counts [119, 120].

13.10 Rhinosporidiosis

13.10.1 Clinical

Rhinosporidiosis is a rare infection caused by the fungus *Rhinosporidium seeberi*. Infection occurs when the endospores are inhaled and penetrate the nasal mucosa. Rhinosporidiosis is common in men between the ages of 20 and 35 years old, with a male-to-female ratio of 4:1. The disease is uncommon in children [121, 122]. Most cases are limited to lesions affecting the mucosa of the nasal and oral cavity, although disseminated disease and widespread cutaneous lesions also occasionally occur. Clinically, it is characterized by verrucous and polypoid vascular papules and nodules on mucosal surfaces. Large tumors can sometimes occur. Treatment consists of surgical excision and systemic therapy, typically dapsone and antifungal medications.

13.10.2 Histology

Histologic changes include a granulomatous inflammatory infiltrate surrounding enormous fungi within the dermis [123]. Giant histiocytes engorged with sporangia of rhinosporidia are present [123]. Globular cysts of sporangia are the characteristic diagnostic feature [124]. The sporangia are thick-walled, and can be seen in an extracellular location coursing in highly vascular stroma [125]. They range from 100 to 400 μm in diameter. Papillomatous epidermal hyperplasia is seen in some cases, and gives rise to a verrucous clinical appearance [126–128]. Microorganisms are easily detected on fine needle aspiration cytology specimens [126, 129, 130].

13.10.3 Pathogenesis

Rhinosporidiosis is a chronic and localized infection of the mucus membranes caused by *Rhinosporidium seeberi* [131]. *R. seeberi* belongs to a group called Mesomycetozoa, which is located phylogenetically between the fungal and animal divergence [132]. Rhinosporidiosis is transmitted from animal sources through contaminated air and water [126]. The spores can enter humans through traumatized nasal mucosa and multiply to form sporangia. The sporangia burst and release more spores, causing reactive tissue hyperplasia and the formation of polypoid masses [133].

13.11 Aspergillus

13.11.1 Clinical

Aspergillosis is an uncommon fungal infection caused by a variety of Aspergillus species. Aspergillus infections often involve the lungs, particularly in immunocompromised individuals. However, cutaneous Aspergillus infections do occur, and are typically classified as primary or secondary. Primary cutaneous Aspergillus is rare, usually occurring in immunosuppressed individuals as the result of direct inoculation of the fungus into open skin. For example, infection may be seen in association with catheters and dressings, and in patients with burn wounds [134]. Secondary cutaneous Aspergillus is due to hematogenous dissemination of pulmonary disease, or from contiguous extension of disease from underlying tissues. Cutaneous lesions occur in 5–10 % of patients with invasive Aspergillosis [135, 136].

Primary cutaneous disease presents as erythematous macules, papules, pustules and plaques, as well as hemorrhagic bullae and necrotic ulcers with overlying black eschars [136]. Secondary cutaneous disease may present as multiple subcutaneous nodules. Therapy is systemic antifungal medications. Disease prognosis depends on the extent of disease and the overall immune status of the patient.

13.11.2 Histology

Aspergillus is an angioinvasive fungus that is seen almost exclusively in patients who are severely immunocompromised [137, 138]. However, occasional cases have been reported in immunocompetent individuals [139]. The most common histologic pattern is that of distended vessels throughout the dermis that appear thrombosed at low magnification; however, higher magnification reveals the vessels are distended with branching hyphal forms that are lightly stained on routine histologic sections [140] (Figs. 13.20 and 13.21). The hyphae are septate and branch at 45° angles [141]. Gomori methenamine silver and Periodic acid–Schiff stains greatly highlight the fungi and make the diagnosis relatively straightforward. Diagnosis has also been made on Tzanck smears [65]. In the majority of patients with Aspergillus involving the skin, there is minimal immune response to the microorganism, in part due to the immunosuppressed nature of the affected hosts. In some cases, these same microorganisms are present outside of the blood vessels. In affected patients with intact immunosurveillance mechanisms, the histologic findings may include pseudoepitheliomatous hyperplasia with neutrophilic microabscesses in the epidermis and dermis. Granulomas may be present, and microorganisms may be seen within multinucleated giant cells. Scattered eosinophils and extravasated erythrocytes are also present [138, 141].

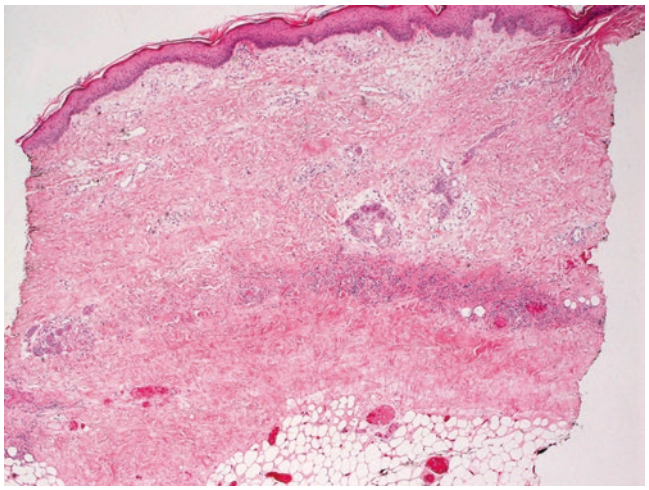

Fig. 13.20 Aspergillus in the skin is characterized by a dense inflammatory infiltrate with dilated and thrombosed blood vessels

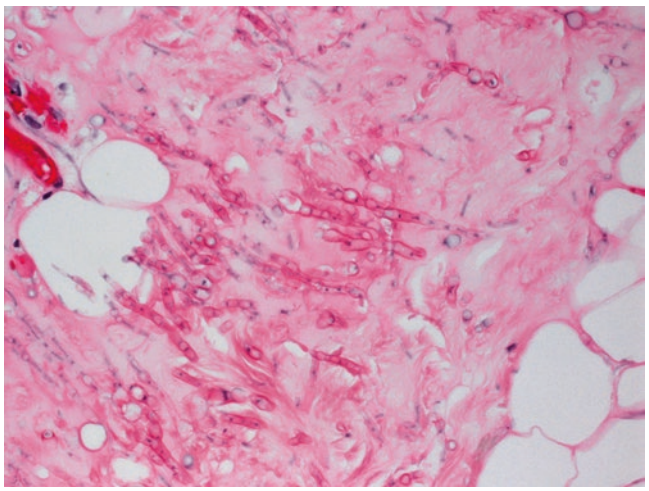

Fig. 13.21 Septate hyphae are present in the dermis and often within blood vessels in cutaneous aspergillus

The histologic differential diagnosis includes mucormycosis. These fungi are slightly larger and do not have septae. In rare situations, the morphology of Aspergillus may resemble that of a dermatophyte and result in misdiagnosis. Tissue culture remains the gold standard [142].

13.11.3 Pathogenesis

Aspergillus fumigatus, a ubiquitous saprophytic fungus, is a major cause of life-threatening invasive aspergillosis in immunocompromised individuals) [143]. Fungal spores are airborne, and they can globose into larger sizes (2–3 mm in

diameter) that can bypass mucociliary clearance and reach the lower airways in the lungs [144]. *Aspergillus fumigatus* conidia can adhere to the epithelium of airways and alveoli more effectively than other fungal species with similarly sized airborne spores. The fungus lacks virulence factor, and is cleared quickly by the immune system in immunocompetent individuals [145]. However, immunocompromised individuals are highly susceptible to infection by the fungus because of failure of the immune system to clear the microorganisms.

Neutrophils play a crucial role in controlling the early stages of fungal infection. Neutropenia increases susceptibility to aspergillosis, as neutrophils produce reactive oxygen species and antimicrobial enzymes that aid in the elimination of the fungus [146]. Common genetic variants that can affect antifungal function of neutrophils have been identified as major risk factors for aspergillosis in immunocompromised conditions.

13.12 Mucormycosis

13.12.1 Clinical

Mucormycosis is a rare fungal infection caused by microorganisms of the class *Zygomycetes*. Mucormycosis is extremely rare in immunocompetent individuals, and it mainly affects immunocompromised and debilitated patients [147]. It mostly affects adults, and is quite rare in children [148]. Cutaneous infections are very rare, and typically occur in the setting of diabetes or skin trauma, such as wounds from burns. Skin lesions are characterized by hemorrhagic papules and plaques, which can ulcerate and become necrotic (Fig. 13.22). Patients require treatment with systemic antifungal therapy, and may need extensive surgical debridement.

Fig. 13.22 Mucormycosis presents as an ulcerated plaque with erythematous border and central eschar on the back of a premature neonate with very low birthweight

13.12.2 Histology

Mucormycoses are angioinvasive fungi and demonstrate similar histologic findings to those seen in aspergillosis. Fungi are present within dermal blood vessels, and can also be found within dermal collagen [149] (Figs. 13.23, 13.24 and 13.25). Secondary necrosis and ulceration occur as a result of vascular injury [150]. Extravasated red blood cells are present in the dermis, and a granulomatous immune

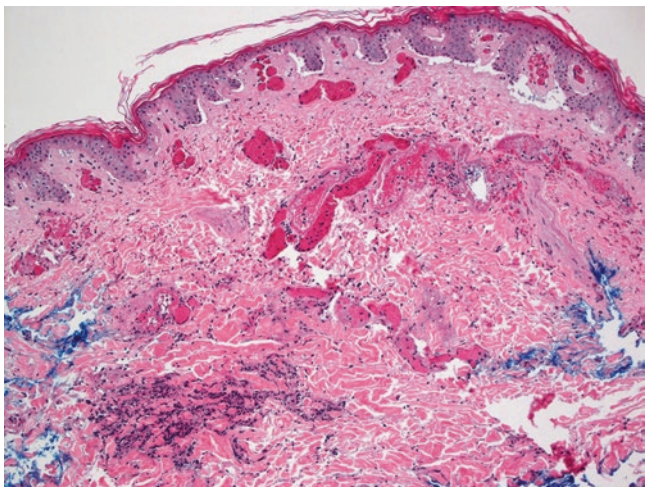

Fig. 13.23 Mucormycosis is characterized by dilated and thrombosed dermal blood vessels with a surrounding inflammatory response

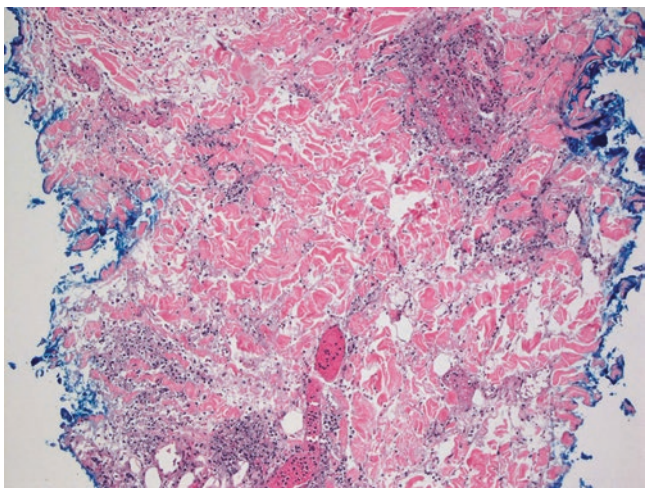

Fig. 13.24 Superficial and deep dermal vessels are thrombosed in mucormycosis, and a diffuse and perivascular infiltrate with abundant neutrophils is present

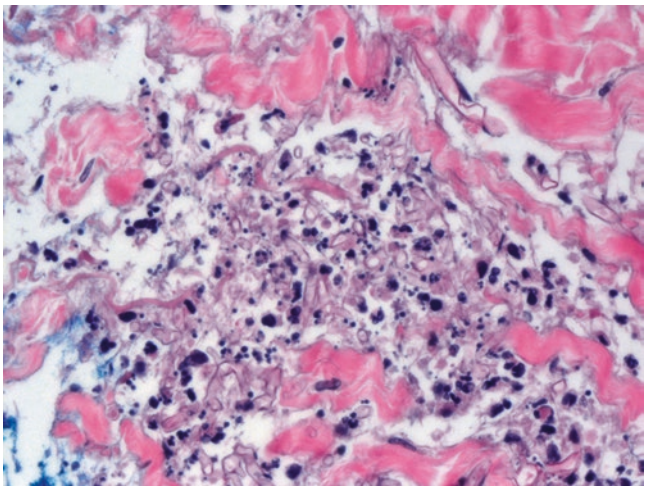

Fig. 13.25 Pale staining, ribbon-like hyphae are present within the dermis and within blood vessels in mucormycosis

response is noted in some cases. A variably intense inflammatory response is present, and leukocytoclastic vasculitis can sometimes be seen. However, in most cases, the patient is markedly immunosuppressed, and the immune response is minimal. There are rare cases reported in immunocompetent individuals [151].

The microorganisms are "ribbon-like" in appearance without septae, and stain poorly with Periodic acid–Schiff stains. Diagnosis of mucormycosis has been established on Tzanck smears, although this is not generally standard practice [65]. The major differential diagnosis is aspergillosis, which can be differentiated based upon fungal morphology, but tissue culture remains the gold standard for speciating fungi.

13.12.3 Pathogenesis

Mucormycosis is an opportunistic infection caused by the fungi Lichtheimia (formerly Absidia), Mucor, and Rhizopus. Immunocompromised individuals are susceptible to mucormycosis. In children, neutropenia, prematurity, malignancy, and diabetes are common predisposing conditions for mucormycosis [152].

One of the key characteristics in mucormycosis is the extensive angioinvasion that results in vessel thrombosis and tissue necrosis [153]. This leads to hematogenous spread of the infectious microorganisms, and ischemic necrosis of the infected tissue. It has been postulated that fungal cell-wall constituents and ligands are important in the recognition patterns by toll-like receptors and dectin receptors with downstream expression of chemokines and cytokines. Rhizopus induces significant amounts of TNF-α and IL-6 release by mononuclear cells [154].

13.13 Tinea Versicolor

13.13.1 Clinical

Tinea versicolor is a common superficial mycosis caused by the lipophilic yeast of the genus *Malassezia*. Prevalence ranges from about 1 % in dry climates to 50 % in tropical regions [155]. It is most commonly seen between the ages of 10 and 19 years old [156].

Clinically, tinea versicolor is characterized by slightly scaly macules and patches that range in color from white or pink to tan (Fig. 13.26). It tends to favor areas of the body with a higher concentration of sebaceous glands, such as the neck, upper trunk, and shoulders. However, it can also affect the flexural creases. Treatment for localized disease is topical antifungals. More widespread disease may be treated with systemic therapy. Most patients improve with appropriate therapy, although infection relapse and recurrence rates tend to be high.

Fig. 13.26 Tinea versicolor is characterized by multiple hyperpigmented macules with powdery scales that coalesce into patches at the lateral neck, central chest, and back

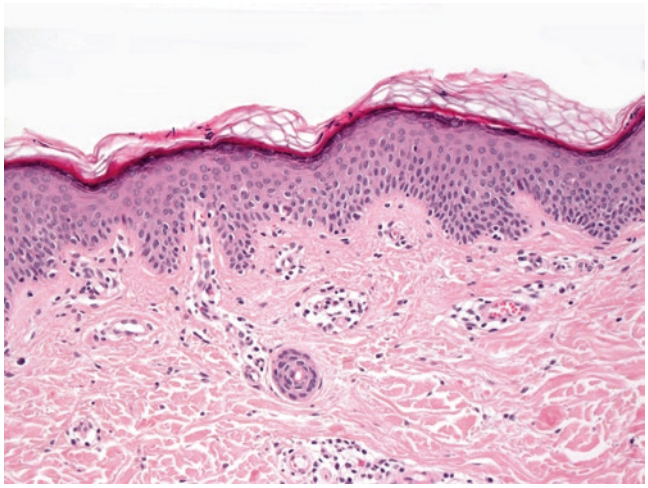

Fig. 13.27 Scattered spores and hyphae are present in the stratum corneum in tinea versicolor. There is minimal inflammation in most cases

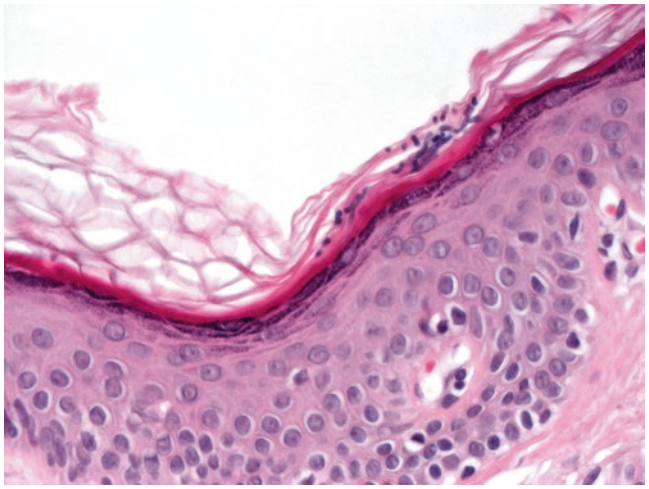

Fig. 13.28 Tinea versicolor organisms are present in the stratum corneum, often without any other histologic changes

13.13.2 Histology

Histologic sections are quite subtle and resemble those seen in normal skin. There is mild epidermal hyperkeratosis and acanthosis. Focal parakeratosis is seen in some cases. A superficial perivascular lymphohistiocytic infiltrate is present, and some cases demonstrate rare plasma cells [157]. Routine H&E stained sections may reveal yeast and hyphal forms within the stratum corneum and the keratinaceous portion of the hair follicles, but these can be highlighted with Periodic acid–Schiff stains (Figs. 13.27 and 13.28).

13.13.3 Pathogenesis

Tinea versicolor is caused by fungi of the Malassezia genus, with the most common species being *Malassezia globosa* and *Malassezia furfur* [158]. Malassezia are lipophilic and favor the skin due to the presence of fatty acids. The release of skin lipids by sebaceous glands provides a fertile environment for Malassezia to develop in large numbers. Predisposing factors for the development of tinea versicolor include the application of oil, which provides lipid substrates for the growth of yeasts; exposure to sunlight, which modifies the metabolism of the fungus and increases the production of azelaic acid; corticosteroids that stimulate yeast growth; underlying genetic predisposition to Malassezia infection; malnutrition; and hyperhidrosis [28].

Hypomelanotic macules in tinea versicolor are thought to be due to the release of azelaic acid by Malassezia. Azelaic acid inhibits the activity of dopa-tyrosinase, which converts tyrosine to melanin, leading to the development of hypopigmented macules with smaller melanosomes present in these areas [159, 160]. Malassezia can also stimulate melanin production in the hyperpigmented variety of tinea versicolor. The hyperpigmented spots have melanosomes of large size and high number.

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Insect Bites and Infestations

14

14.1 Scabies

14.1.1 Clinical Features

Scabies is a common parasitic infestation of the skin caused by the mite *Sarcoptes scabiei.* Scabies affects individuals of all ages. Over 300 million cases are reported annually worldwide [1]. Clinically, patients experience intense pruritus and develop a cutaneous hypersensitivity reaction that manifests as a widespread eruption of erythematous papules and nodules [2] (Figs. 14.1 and 14.2). Vesicles and bullae may be seen. Upon close inspection of the skin, linear burrows can be detected as well. The hands, wrists, abdomen, and genitalia tend to be heavily involved. A crusted form may occur, manifesting as thick hyperkeratotic plaques and crusts particularly over the dorsal hands, feet, and extensor elbows and knees [3]. Therapy consists of topical and oral insecticides, and the prognosis is generally good, although post-scabies dermatitis may exist for weeks after the mite has been eliminated [2].

14.1.2 Histology

Biopsies from children with *Sarcoptes scabiei* infestations demonstrate changes of a dermal hypersensitivity reaction. Within the stratum corneum, small foci of parakeratosis and serum may be the first clue to the diagnosis. A spiky appearance to the epidermis has been described as a clue to the diagnosis [4]. Occasionally, mites or body parts from the mites may be identified within the stratum corneum, although frequently this requires study of multiple histologic levels [5] (Figs. 14.3 and 14.4). Some authors have advocated that a shave biopsy of the epidermis is the most sensitive method for detecting mites or their eggs, but this is not standard practice [6]. It is unusual to find organisms in the skin beneath the stratum corneum. The dermis contains a dense superficial and deep infiltrate of lymphocytes, histiocytes, and abundant eosinophils that may extend into the subcutaneous fat. Presence of germinal centers is not uncommon.

Norwegian scabies, which are a rare variant that usually occurs in immunocompromised patients, are abundant and can be easily detected on routine sections (Figs. 14.5, 14.6 and 14.7). There is marked hyperkeratosis and epidermal acanthosis. Scabietic body parts are present diffusely throughout the stratum corneum [7, 8].

Persistent or nodular scabetic reactions that may remain after the organisms are treated can result in pronounced dermal inflammatory infiltrate. Abundant eosinophils are admixed with lymphocytes, and germinal centers may be present. The infiltrate is superficial and deep and may be peri-appendageal. In some cases, lymphoma may be in the differential diagnosis [9]. A lymphocytic vasculitis has been reported in rare cases, although this is not a common finding [10]. Enlarged lymphocytes with cytologic atypia are described in persistent scabietic nodules. These cells may express CD30, resulting in further diagnostic overlap with T cell dyscrasias, such as lymphomatoid papulosis [11].

The histologic differential diagnosis of scabies infection includes Langerhans cell histiocytosis. This is due to the abundance of intraepidermal Langerhans cells present as a reaction to scabietic mite, as well as to the eosinophilia within the dermis. However, presence of organisms and a marked inflammatory infiltrate enable distinction in most cases [12, 13]. Acropustulosis of infancy may also present a diagnostic challenge, but this entity is usually neutrophil predominant, and it does not display intense eosinophilia [14]. Some authors believe there is a relationship between infantile acropustulosis and scabietic infestation [15]. Eosinophilic pustular folliculitis is also a differential consideration, but this is not a specific histologic finding, but rather a reaction pattern that can be seen in patients with scabies infestation [16].

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Fig. 14.1 Scabies presents as crusted erythematous, edematous papules scattered on the lower abdomen

Fig. 14.2 Similar crusted, erythematous papules are noted along the upper back in the same infant from Fig. 14.1

14.1.3 Pathogenesis

Sarcoptes scabiei is transmitted by person-to-person contact. Female mites lay up to three eggs per day in skin burrows in the epidermis. The larvae hatch into nymphs, from which adult males or females emerge in 10–14 days. Inactivated serine proteases and glutathione S-transferases from scabies mites are important immunogenic antigens [17, 18]. Inactivated serine proteases act as inhibitors of inflammation, thus protecting scabies mites from the host inflammatory response [19]. Scabies infestation results in delayed type-IV hypersensitivity reaction against mites and mite-product antigens with a latency period of up to 4 weeks, during which time the patient is asymptomatic [19].

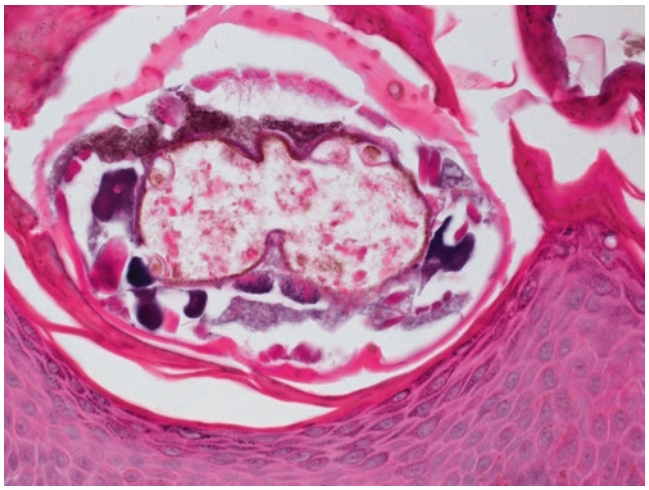

Fig. 14.3 Entire mites are readily observed at the base of the stratum corneum in some cases of scabietic infestation

Fig. 14.4 Scabies mite

14.2 Spider Bites

14.2.1 Clinical Features

There are more than 30,000 species of spiders, but most cannot or do not inflict serious bites to humans [20]. There are two medically important spiders in the United States: the black widow (*Latrodectus mactans*) and the brown recluse (*Loxosceles reclusa*).

The black widow spider is identifiable by a red hourglass marking on its ventral abdomen. The venom of a black widow spider mainly causes severe crampy muscle spasms and no significant or diffuse cutaneous changes [21].

The brown recluse spider bite, however, has the potential to cause significant skin necrosis. Typically, a tender

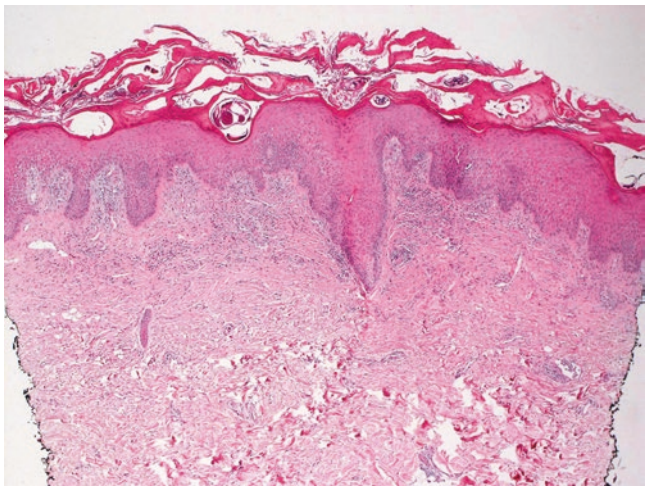

Fig. 14.5 Scabies are present within the stratum corneum in a case of Norwegian scabies. They are abundant and readily apparent on H&E stains

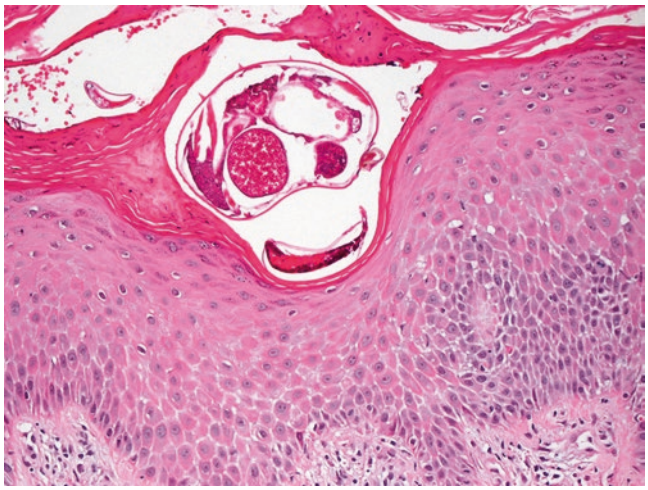

Fig. 14.6 Female mites are present within the stratum corneum in Norwegian scabies

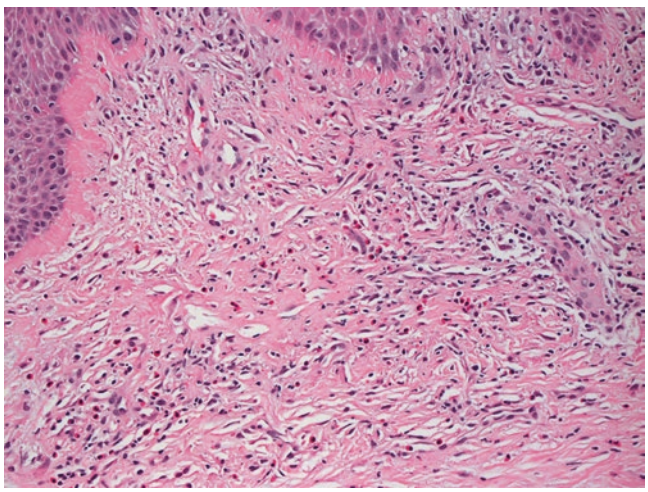

Fig. 14.7 The dermis demonstrates a diffuse and dense inflammatory infiltrate with abundant eosinophils in Norwegian scabies

Fig. 14.8 Spider bite shows well-circumscribed ulceration with surrounding irregularly shaped, edematous erythema

erythematous patch or edematous plaque develops at the site of the bite, occasionally with concomitant pain at the time of injury (Fig. 14.8). The majority of bites heal within 3 weeks without significant complications [22]. In 40 % of cases, an expanding area of necrosis develops, and 10–15 % of patients will experience significant scarring [20, 21].

Black widow bites are treated with antivenom, as well as pain control and benzodiazepines for muscle spasms. Brown recluse bites are treated with local wound care. Dapsone treatment is controversial, but may be helpful in some cases [21].

14.2.2 Histology

Spider bites induce a characteristic, but not specific histologic reaction pattern. Vascular destruction in the mid to deep reticular dermis results in a large area of dermal necrosis, and overlying epidermal ulceration (Figs. 14.9 and 14.10). This coagulative necrosis has been described as "mummified necrosis" [23]. Transmural inflammation of vessel walls gives rise to local vasculitis involving medium-sized dermal vessels. This pattern can resemble that seen in polyarteritis nodosa, but this is a localized phenomenon [23]. The necrosis can be extensive and destructive [24]. There is a diffuse and dense mixed inflammatory infiltrate in the dermis. Abundant neutrophils may be present in the regions with necrosis, resulting in an eosinophilic cellulitis appearance in some cases [25].

Lymphohistiocytic hematophagocytosis and severe hemolytic anemia have been described as a consequence of spider bites [26, 27]. Erythema multiforme and acute generalized exanthematous pustulosis (AGEP) reaction patterns have been described in patients with spider bites [28, 29]. Lyme disease

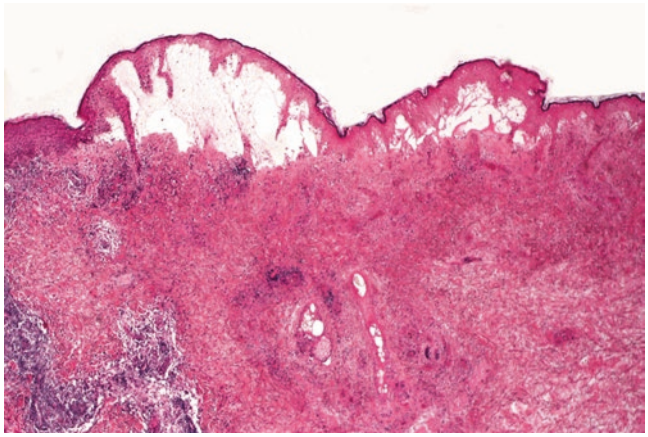

Fig. 14.9 Spider bites demonstrate epidermal necrosis, vascular thrombosis, and a dense and diffuse inflammatory infiltrate

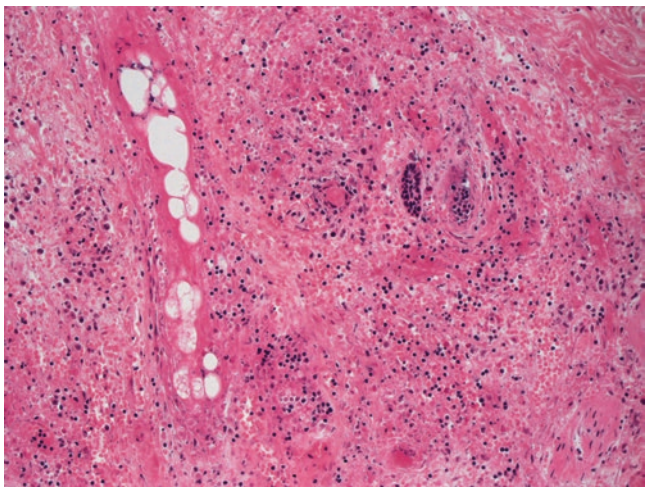

Fig. 14.10 Thrombosed vessels give rise to necrotic dermis and karyorrhectic debris in spider bites

can enter the differential diagnosis [30]. However, the inflammatory infiltrate in Lyme disease is far less intense in most cases, and overt vascular destruction is extremely uncommon.

14.2.3 Pathogenesis

Spiders that can cause serious injuries to people include the funnel web spider of Australia (genus Atrax), armadeira spider (genus Phoneutria), black widow spider (genus Latrodectus), and brown recluse spider (genus Loxosceles). The first three spiders release neurotoxin that can cause serious injuries and even death, with little or no skin changes [31]. Black widow spider (Latrodectus mactans) causes intense pain at the bite site. The spider venom contains α-latrotoxin, which causes the release of catecholamine from nerve synaptic terminals [32, 33]. Clinical symptoms resulting from this spider bite include severe muscle spasms, tachycardia, high blood pressure, agitation, and pain [34]. Brown recluse spider (Loxosceles reclusa) bites, by contrast, cause marked skin changes from local tissue injury. The venom of the brown recluse spider contains enzymes that cause tissue damage. Key enzymes in the venom are sphingomyelinase D and hyaluronidase [34–36]. These enzymes cause damage to blood vessel walls and red blood cells, leading to extensive tissue damage and necrosis. In about 5 % of cases, hemolysis from red blood cell damage leads to acute kidney failure [36, 37]. Hyaluronidases also degrade extracellular matrix components, and increase the diffusion of other toxins from the inoculation site [38].

Proteomic analysis of brown spider venom revealed a number of toxins generally found in animal venoms, and are believed to cause tissue damage in loxoscelism [39]. Among these, phospholipase D (PLD) is a key enzyme in spider venom. PLD enzymatic activity leads to dermal necrosis in vivo, making it a dermal necrotic toxin [38]. Mechanistically, PLD hydrolyzes cell membrane sphingomyelin to ceramide 1-phosphate, leading to an exuberant inflammatory response [40]. There are at least 11 isoforms of PLD in the venom of Loxosceles [39]. There are two PLD isoforms from Loxosceles (class I and class II phospholipase D), which cause complement-dependent hemolysis, dermal necrosis and hydrolysis of sphingomyelin [41, 42].

Besides PLD, other key enzymes in Loxosceles spider toxins are metalloproteases, hyaluronidases, TCTP (Translationally Controlled Tumor Protein) member family toxin, and Inhibitor Cystine Knot peptide from brown spider venom [38].

14.3 Tick Bites

14.3.1 Clinical Features

Ticks are arachnids that serve as hosts and vectors of human infectious diseases. Tick parts embedded in human skin may cause local acute erythematous lesions or chronic granulomatous response. Rarely, tick bites can lead to panniculitis, vesicles and hemorrhage. Complete removal of all tick parts is important to minimize adverse cutaneous sequela. Erythema chronicum migrans is a cutaneous manifestation of Lyme disease from the bite of hard ticks of the genus Ixodes, and it is described elsewhere in this volume. Likewise, Rocky Mountain spotted fever is also a tick-borne disease with cutaneous manifestations that is addressed elsewhere.

14.3.2 Histology

The local cutaneous reaction to a tick bite is essentially a dermal hypersensitivity reaction, not unlike arthropod bite

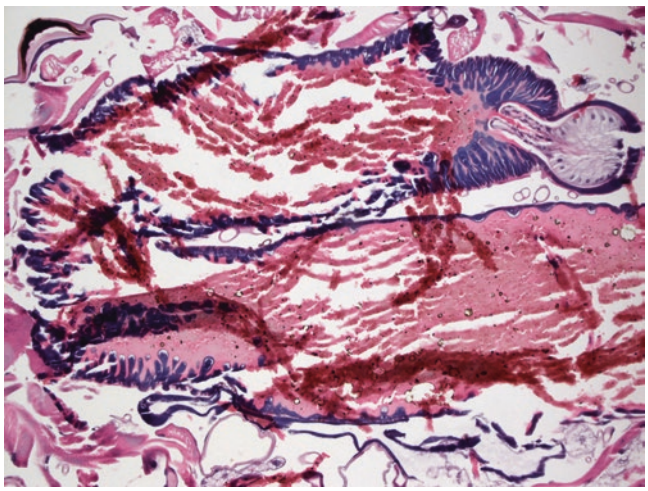

Fig. 14.11 Histologic sections demonstrate the anatomic structures characteristic of a tick

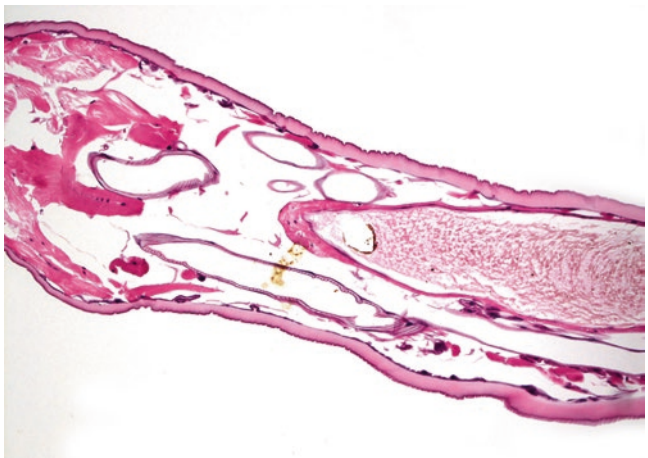

Fig. 14.12 A thick eosinophilic cuticle is observed surrounding internal structures in a tick

reactions. In some cases, tick body parts can be identified within the epidermis, especially the stratum corneum (Fig. 14.11 and 14.12). Within the dermis, there is a brisk inflammatory response of neutrophils, lymphocytes, and often abundant eosinophils. When present, the reaction pattern is that of Wells syndrome or eosinophilic cellulitis [25]. The infiltrate is superficial, deep and diffuse, and may extend into the subcutaneous fat. Endothelial cell swelling has been described within dermal vasculature and extravasation of erythrocytes is common [43]. A granulomatous response to actual tick parts has been described, but it is not commonly encountered [43]. Eosinophilic deposits that resemble cryoglobulins have been described in tick bite reactions [44]. In some cases, florid cutaneous lymphoid hyperplasia arises at the site of a tick bite [45]. In rare situations, the dermal lymphocytes may have cytologic atypia and express CD30, giving rise to concern for lymphoma [46–48].

14.4 Lice

14.4.1 Clinical Features

Pediculosis capitis or head lice is caused by the insect *Pediculus humanus capitis*. Head lice infestation affects 6–12 million children in the United States annually [49, 50]. Most affected individuals are between 3 and 11 years of age, since this population has higher rates of head-to-head contact with their peers and more often share hair utensils and garments [50]. Head lice are least likely to affect African-Americans. Clinical findings in the scalp hair include numerous live lice and egg cases ("nits"), which are firmly adherent to the hair shafts within a few millimeters of the scalp (Fig. 14.13). Another kind of body lice that are commonly found worldwide are crab lice or pubic lice. These are parasitic insects found mainly in hair-bearing genital/pubic area (Fig. 14.14).

There are three basic treatment approaches for head lice: physical removal of lice and nits ("bug busting"), application of topical pesticides, and oral treatment [51]. Typically, use of topical preparations along with manual nit picking is favored [50].

14.4.2 Histology

Infestation with lice rarely requires biopsy diagnosis as organisms and their eggs are grossly apparent [52]. When a biopsy is performed, chitinous arthropod may be seen within the stratum corneum and epidermis. If the entire organism is present, erythrocytes may be found in the insect gut, and insect striated muscle is apparent. The dermis demonstrates a dermal hypersensitivity reaction with a diffuse and dense polymorphous inflammatory infiltrate, often with abundant eosinophils [53]. Overlying excoriation is common due to intense pruritus [54]. In rare cases, lymphocytes within the dermal infiltrate may be cytologically atypical and express CD30, thus giving rise to concerns for cutaneous lymphoma [55].

14.4.3 Pathogenesis

Head lice are ectoparasites that live in the scalp and feed on human blood. Racial predilection purportedly exists due to the inability of the louse to attach to particular hair types [50]. Adult lice are 2–3 mm long with elongated, flattened torsos, and they do not have wings. Lice eggs are glued to the

Fig. 14.13 Head louse nits are often found on hairs in children (photograph courtesy of Eric Rosenbaum, MD, University of Arkansas for Medical Sciences)

Fig. 14.14 The characteristic shape of a crab louse is easily identified when the organism is submitted intact for processing

hair shaft close to the scalp. The warmth and moisture of the scalp help incubate the eggs, which hatch into nymphs in 6 to 10 days [56]. The nymphs molt several times over 9 to 12 days and become adult lice. Body lice are known to transmit bacteria that cause epidemic typhus (Rickettsia prowazekii), louse-borne relapsing fever (Bartonella recurrentis), and trench fever (Borrelia quintana) [57].

14.5 Cutaneous Larva Migrans

14.5.1 Clinical Features

Cutaneous larva migrans is a pruritic zoodermatosis caused by penetration of the skin by larvae of animal hookworms. Eggs are deposited in the soil via the feces of infested dogs and cats. Humans become infected by contact with contaminated soil, often while going barefoot or sitting on the ground wearing shorts or swimsuits. *Ancylostoma braziliense* is the hookworm species that most commonly affects humans [58]. Lesions are characterized by intensely pruritic, erythematous, linear or serpiginous plaques, often located on the feet, ankles, posterior thighs, and buttocks [59] (Fig. 14.15).

Cutaneous larva migrans typically heals spontaneously within weeks to months. However, given the intense pruritus and potential for secondary infection due to scratching, treatment is warranted. Although a variety of methods have been reported, the most effective treatments are topical or oral anti-helminthic agents, such as thiabendazole and ivermectin.

14.5.2 Histology

Cutaneous larva migrans caused by toxocariasis seldom needs to be biopsied [60]. Routine sections reveal a superficial and deep perivascular inflammatory infiltrate with lymphocytes and scattered eosinophils. Neutrophils are also present in most cases, and plasma cells may be seen in some cases. Dermal edema giving rise to the appearance of urticaria is common. In some cases, the burrowing tunnels can be seen in the epidermis, but this is usually quite difficult to appreciate. When present, they appear as round to oval spaces within the epidermis [4]. In most cases, the histologic findings are not diagnostic. On rare occasions, the larvae can be seen within the epidermis and occasionally within cutaneous appendages [61]. Lesions may resolve with post-inflammatory hyperpigmentation that can be diagnosed on biopsy, but without any possibility of attribution for the antecedent condition [62].

14.5.3 Pathogenesis

The hookworms live in the gastrointestinal tract of cats and dogs, which are the definitive hosts [63]. Worm eggs are passed in animal feces. The eggs are incubated in the soil and mature into infective larvae, and can remain infective in the environment for years. Humans become infected through ingestion or transmission through the skin when exposed to

Fig. 14.15 Cutaneous larva migrans presents as serpiginous plaque at the ankle

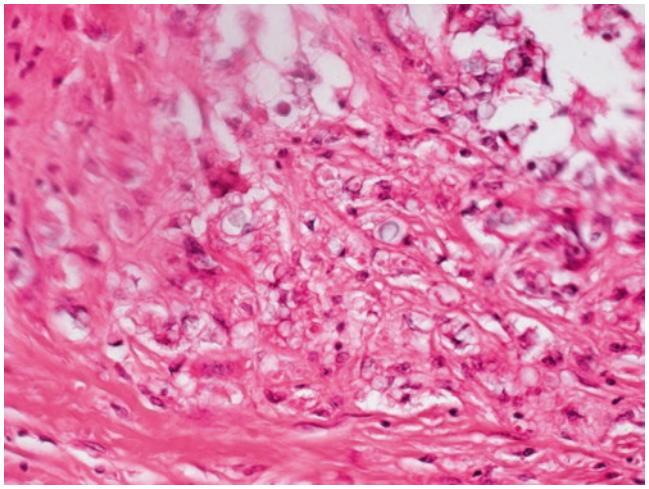

Fig. 14.16 Morulae are present in the dermis in protothecosis. The microorganisms are usually not within cells

infective larvae in the soil. In the host, larvae can become encapsulated within granulomas. The host immune response to migrating larvae is directed against the larval excretory-secretory antigens (TES-Ag) [64]. The infection induces both humoral and cellular immune responses, mainly type 1 and type 2 T helper cells. Parasite destruction is mediated mainly by type 1 response. Type 2 response mediates cellular immune response with interleukin production, induction of IgE, and activation of eosinophils and mast cells characteristic of parasite infections [65, 66]. After a long period of time (months to years), the immune system may eventually clear the parasites [67].

14.6 Protothecosis

14.6.1 Clinical Features

Cutaneous protothecosis is a very rare infection caused by algae of the *Prototheca* species. As of 2013, there were a total of 77 cases of cutaneous protothecosis reported in the literature [68]. There are very few case reports in children. Most cases occur in immunocompromised individuals and are related to trauma occurring on exposed areas of skin.

Cases are classified in three categories: cutaneous, olecranon bursa, and systemic [69]. Reported cutaneous manifestations are variable and include papules, plaques, pustules, erosions, scales, and crusts. Solitary localized lesions are sometimes treated with excision, and a variety of systemic antifungals have been used, but the results have been inconsistent.

14.6.2 Histology

Prototheca wickerhamii is normally encountered post-traumatically in immunocompromised individuals [68, 70]. Ulceration is seen in most cases. Within the dermis, morulae containing 6–10 μm endospores are found amidst a dense granulomatous inflammatory infiltrate (Fig. 14.16). Multinucleated giant cells are abundant. In some cases, a neutrophilic infiltrate predominates, resulting in dermal abscess formation [71]. The microorganisms can be visualized on H&E stained sections, but are highlighted with Periodic acid-Schiff and Gomori methenamine silver stains [72] (Fig. 14.17). There are also specific antibodies directed against the organisms that can be utilized to confirm the diagnosis [73].

14.6.3 Pathogenesis

Prototheca microorganisms infect humans through contact with potential sources of the algae [74]. Infections often occur in individuals with underlying immunodeficiency, such as chronic steroid use, cancer, AIDS, organ transplantation, and diabetes mellitus [75]. It has been postulated that defects in neutrophil function play an important role in host defense mechanism against prototheca microorganisms [76, 77]. In addition, optimal killing response requires the presence of IgG and serum opsonins. Natural killer cells may also be involved in the pathogenesis of protothecosis. In general, prototheca microorganisms are considered to be rare opportunistic pathogens with low virulence [74].

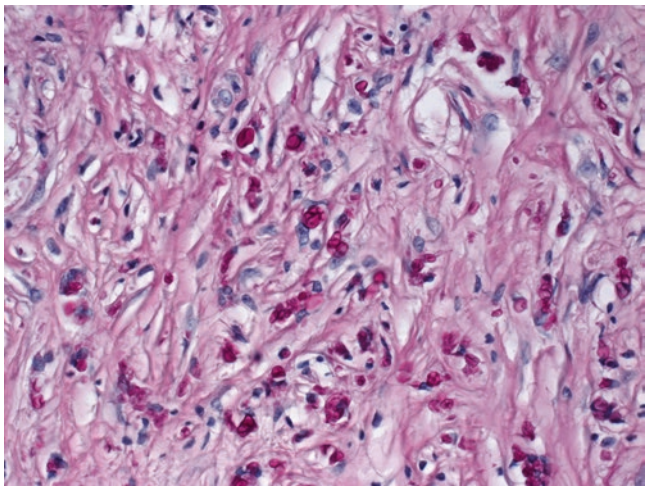

Fig. 14.17 Periodic acid-Schiff stains are helpful in accentuating and further delineating the architecture of the microorganisms in protothecosis

14.7 Cysticercosis

14.7.1 Clinical Features

Cysticercosis is one of the most commonly seen human cestode infections, typically caused by the tape worm *Taenia solium*. It primarily occurs in rural areas, and it is endemic in Mexico, Central and South America, sub-Saharan Africa, India, and East Asia [78]. It typically causes gastrointestinal disease, but may involve the skin as well. In a Brazilian review of 30 individuals with cysticercosis, 90 % of the patients had involvement of the subcutaneous tissue, mucosa, or skeletal muscle. The clinical examination is characterized by multiple, non-tender, subcutaneous nodules or cysts of varying sizes that may appear from 1 month to 27 years after exposure to the parasite [78]. Active disease requires systemic anti-helminthic therapy, while older, inactive lesions may be excised. Preventive measures include better sanitation practices.

14.7.2 Histology

Subcutaneous nodules can be biopsied or easily accessed by fine needle aspiration that provides rapid cytologic diagnosis of cysticercosis [79, 80]. The histologic findings demonstrate a large cystic organism that can measure up to 2 cm in diameter. An epithelial lining is present, and there is surrounding dense fibrosis [81]. Abundant histiocytes, eosinophils, and multinucleated giant cells are present as host immune response. A granulomatous response is common, but caseation is not ordinarily present [82]. When there is extensive skin involvement, a systemic work-up is warranted [83].

14.7.3 Pathogenesis

Cysticercosis is caused by infection with the larvae of the pork tapeworm *Taenia solium* [84]. It commonly occurs where pigs range freely, and sanitation conditions are poor. Ingestion of undercooked pork meat containing larval cysts (cysticerci) results in the development of adult tapeworms in the small intestine of affected individuals. The ingested eggs hatch into embryos, which can actively cross the intestinal wall, enter the blood stream, and disseminate widely in the host body. Infection leads to a mixed Th1 and Th2 immune response [84].

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Nutritional Disorders

15

15.1 Acrodermatitis Enteropathica

15.1.1 Clinical Features

Zinc deficiency may be acquired or inherited. The inherited form is termed "acrodermatitis enteropathica" and affects 1 in 500,000 infants [1]. Acrodermatitis enteropathica most commonly presents within weeks of transitioning from breast milk to formula milk secondary to the decreased bioavailability of zinc in manufactured, dairy-derived milk product [1]. Acquired forms of disease may be secondary to inadequate intake (as seen in diets with limited animal-derived food), excessive losses (as seen in some malabsorption diseases, such as celiac disease, ulcerative colitis, and cystic fibrosis), and increased demand (as seen in pregnancy, lactation, and prematurity) [2].

The classic mucocutaneous feature of zinc deficiency is an eruption of erosive and desquamating, scaly eczematous plaques at the distal extremities, anogenital and peri-orificial skin (Figs. 15.1 and 15.2). Alopecia, angular cheilitis, and paronychia can be seen as well. Diarrhea is also a frequent feature. In the majority of cases, symptoms resolve with treatment of the predisposing condition and zinc supplementation [2]. Seventy percent of patients have improvement in zinc levels within 6 months of initiation of zinc supplementation. Unfortunately, patients with acrodermatitis enteropathica require life-long zinc supplementation.

15.1.2 Histology

Histologic changes in acrodermatitis enteropathica include confluent parakeratosis, psoriasiform epidermal hyperplasia, marked diminution or total loss of the granular layer, marked spongiosis, and pronounced epidermal pallor limited to the upper one-half to one-third of the epidermis [3–5] (Figs. 15.3 and 15.4). Ballooning degeneration of the keratinocytes contributes to the pale staining within the epidermis. There are neutrophilic abscesses within the stratum corneum and upper portions of the epidermis. Within the dermis, the most common findings are a superficial perivascular, predominantly lymphoid infiltrate, occasionally with scattered eosinophils or neutrophils. Focal acantholysis has been described in lesions of acrodermatitis enteropathica [6]. Bullous variants and the presence of interface dermatitis have also been reported [7].

The histologic changes of acrodermatitis enteropathica are identical to those seen in necrolytic migratory erythema and necrolytic acral erythema. The former is associated with glucagonoma, and the latter is associated with hepatitis. Both diseases are rarely encountered in children, and are easily differentiated based upon clinical presentation. Another entity that must be considered in the differential diagnosis is psoriasis. The epidermal pallor that is characteristic of acrodermatitis enteropathica is not seen in psoriasis; however, early lesions of acrodermatitis enteropathica do not demonstrate this finding. The earliest changes may be virtually indistinguishable from psoriasis, and close clinical examination and follow-up may be the only way to make the distinction. In some situations, spongiosis may be the most significant histologic alteration in early lesions, and the differential diagnosis includes other causes for spongiotic dermatitis, such as atopic dermatitis, contact dermatitis, an id reaction, and nummular eczema. Again, clinical correlation is the most reliable way to make the distinction. As the lesions develop, the distinction becomes clearer based upon the specific and often dramatic epidermal pallor.

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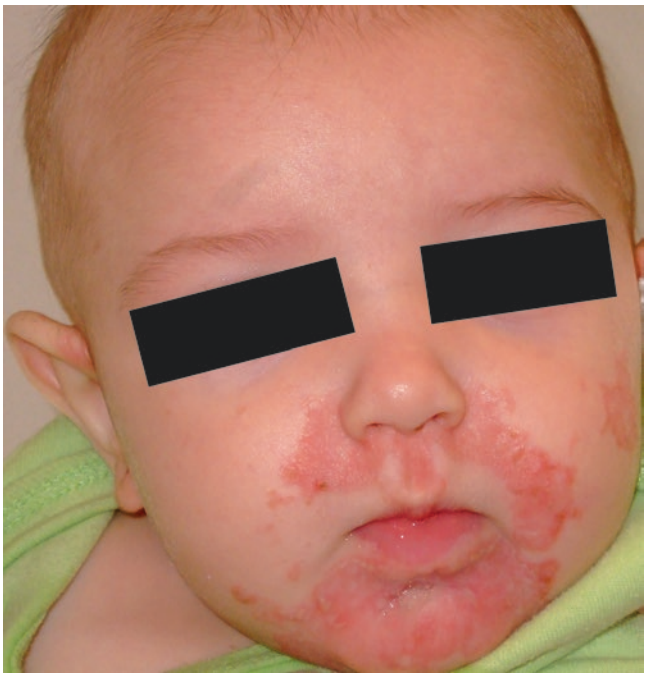

Fig. 15.1 Peri-oral erythematous scaly plaques are seen in an infant with acrodermatitis enteropathica

Fig. 15.2 Peri-anal and genital erythematous, scaly papules and plaques with superficial erosions in the same infant with acrodermatitis enteropathica

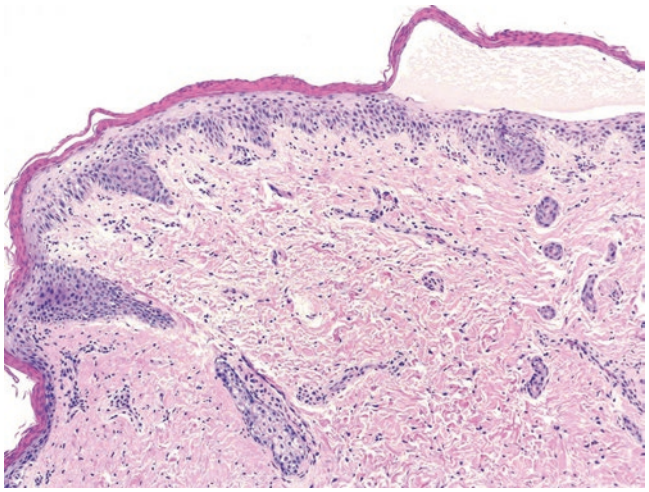

Fig. 15.3 Histologic findings in acrodermatitis enteropathica include pallor of keratinocytes in the upper portion of the epidermis, sometimes resulting in superficial blister formation. Minimal dermal inflammation is seen in most cases

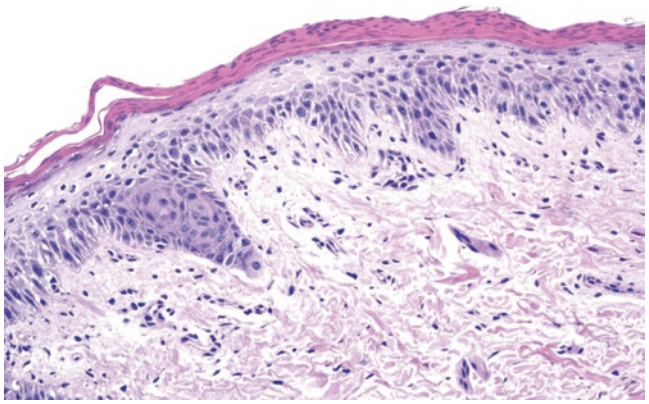

Fig. 15.4 Thick parakeratosis overlies pale staining epidermis with focal hypogranulosis in acrodermatitis enteropathica

15.1.3 Pathogenesis

Acrodermatitis enteropathica is caused by an autosomal recessive defect in the zinc transporter SLC39A4 (Zip4 transporter) [8, 9]. SLC39A4 is expressed at the apical surface of mature enterocytes of the intestinal villi [10, 11]. The function of SLC39A4 is to transport zinc to enterocytes in the small intestine [12]. Thus far, 41 mutations in SLC39A4 have been identified in patients with acrodermatitis enteropathica. A number of mutations occur in the N-terminal domain of the gene. These mutations appear to block the proteolytic cleavage of the protein product, leading to impaired protein function. Interestingly, acrodermatitis enteropathica with hereditary zinc deficiency due to mutations in SLC39A4 also exists in animals, including Holstein-Friesian cows, northern-breed dogs, and goats [13–15]. Thus, SLC39A4-associated zinc deficiency is not restricted to humans.

A condition called transient neonatal zinc deficiency is due to zinc deficiency that arises from inadequate supplementation in total parenteral nutrition or low breast milk

levels. The defect is due to mutations in the SLC30A2 gene that causes decreased secretion of zinc into the mother's breast milk [10, 16, 17]. As a consequence, the breast-fed child develops a zinc deficiency. This condition can be rapidly corrected with zinc supplementation.

15.2 Pellagra

15.2.1 Clinical Features

Pellagra is niacin/vitamin B3 deficiency. Vitamin B3 is a water-soluble vitamin found in whole grains, meat, dairy, nuts, and beans. Pellagra is characterized by a triad of dermatitis, diarrhea, and dementia. It was previously most commonly seen in populations with diets primarily consisting of corn [1]. Following initiation of food fortification efforts, more recent cases of disease are associated with dietary restrictions, medical conditions, such as malabsorption disorders, alcoholism, carcinoid syndrome and HIV disease, as well as certain medications, including isoniazid, pyrazinamide, 6-mercaptopurine, 5-fluorouracil, hydantoins, ethionamide, phenobarbital, azathioprine, and chloramphenicol [1].

Patients present with eczematous patches around the neck (Casal's necklace) with progression to a well-demarcated, photodistributed erythematous eruption, which may be exudative, vesicular, or desquamative [1]. Lesions evolve to become more hyperkeratotic and brown in color over time. Initial neurologic symptoms may be minimal, including headache and irritability, with progression to encephalitis, neuritis, and myelitis in more severe disease. Patients may improve with correction of the underlying disorder or supraphysiologic dosing of niacin.

15.2.2 Histology

Histologic features of pellagra are essentially indistinguishable from those seen in acrodermatitis enteropathica [18–20]. Confluent parakeratosis overlies psoriasiform epidermal hyperplasia with marked epidermal pallor in the superficial portion of the epidermis in well-developed lesions (Figs. 15.5 and 15.6). Ballooning degeneration of keratinocytes is present. Spongiosis is present in early lesions, but less common in later stages of development. Vascular ectasia and a mild perivascular lymphocytic infiltrate is present in the papillary dermis.

The differential diagnosis includes other nutritional disorders that display cutaneous manifestations, including necrolytic acral erythema, necrolytic migratory erythema, and acrodermatitis enteropathica, each of which is distinguished based upon clinical factors. Psoriasis and spongiotic dermatoses also enter the differential diagnosis, depending upon the stage of lesion biopsied, but can usually be distinguished based upon clinical presentation.

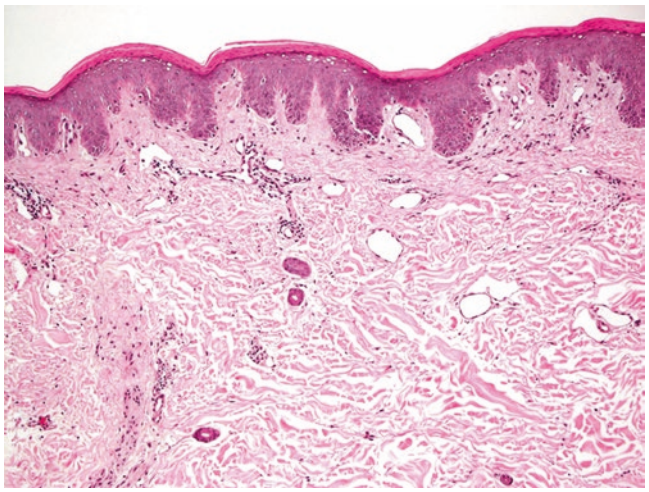

Fig. 15.5 Pellagra is characterized by confluent parakeratosis overlying an epidermis that contains vacuolization and pallor in its upper layers. Psoriasiform epidermal hyperplasia is seen in some cases

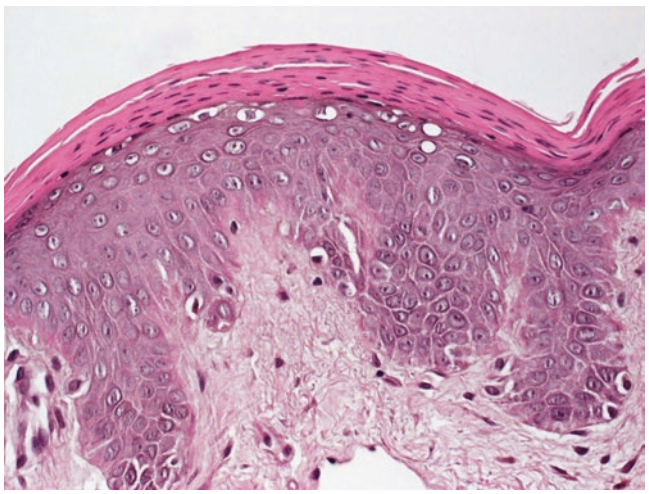

Fig. 15.6 Thick adherent parakeratosis and vacuolar degeneration of the superficial layers of the epidermis are common findings in biopsies from patients with pellagra

15.2.3 Pathogenesis

Niacin is an essential component in the synthesis of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) [1, 21, 22]. NAD and NADP are important coenzymes in catabolic and anabolic reactions. Numerous enzymes require NAD and NADP to act as hydrogen ion donors and acceptors in the catabolism of carbohydrates, fat, and proteins, as well as in anabolic reactions in the synthesis of fatty acids and cholesterol [23]. One of the cutaneous manifestations of pellagra is photosensitivity. Although the mechanism of photosensitivity is not known, there are several proposed theories, including cutaneous deficiency in urocanic acid, accumulation of kynurenic acid, NAD/NADP deficiency, and abnormal metabolism of porphyrin [22, 24, 25].

15.3 Kwashiorkor

15.3.1 Clinical Features

Kwashiorkor is protein deficiency in the setting of appropriate calorie ingestion. Children at greatest risk for disease are those in developing countries recently weaned from breast milk [1]. In developed countries, kwashiorkor is the most common form of malnutrition in hospitalized children, and it is most often seen in the setting of prematurity, chronic malabsorption conditions, and restrictive diets.

Patients present with generalized edema, "flaky paint dermatitis," hair loss with lightened pigmentation, and "flag sign" (alternating bands of normal pigmentation and hypopigmentation in the hairs) on microscopy. Body weight is typically >60 % of age matched controls [1]. Neurologic sequelae of irritability and lethargy can be seen in more advanced disease. Severely affected children are at increased risk for sepsis and circulatory collapse secondary to low protein production.

15.3.2 Histology

The histologic findings in kwashiorkor are not specific, and essentially the same as those found in acrodermatitis enteropathica and other nutritional deficiencies [26–28]. Similar changes can be seen on mucosal surfaces, especially the tongue [28]. Extreme malnutrition in kwashiorkor can also lead to decreased melanin production in hair follicles, resulting in spotty, focal hypopigmentation of hair [26, 29, 30]. The histologic differential diagnosis includes other nutritional deficiencies as described elsewhere in this chapter.

15.3.3 Pathogenesis

A number of nutrients have been suggested to play a role in kwashiorkor, including proteins, sulfur amino acids, zinc, and essential fatty acids [31–33]. Children with kwashiorkor have been shown to have different amino acid and collagen status in their skin as compared with normal healthy children [34, 35]. In this condition, there are higher concentrations of markers of oxidative stress and lower levels of antioxidants in the blood, indicating excessive oxidative stress [31, 36]. Kwashiorkor may be a result of an imbalance between the production and removal of free radicals [36–38]. Excess free radicals, as well as reduced levels of glutathione, have been demonstrated in kwashiorkor [39, 40].

15.4 Scurvy

15.4.1 Clinical Features

Routine screening for vitamin C deficiency in the general population has demonstrated a prevalence of 13–30 % for vitamin C depletion, and 5–17 % for frank vitamin C deficiency [1]. Affected persons range in age from neonates to the elderly. Decreased levels may be secondary to avoidance diets, gastrointestinal illness with malabsorption, and psychiatric illnesses, such as substance abuse. Frank deficiency typically is not seen until patients have had almost no intake for 2–3 months. Möller-Barlow disease is a disease of vitamin C deficiency in infants with pain and pseudoimmobilization of the hips and knees, frequently secondary to subperiosteal hemorrhage [1].

Physical exam is characterized by follicular hyperkeratosis with progression to perifollicular hemorrhage, corkscrew hairs, and generalized ecchymoses. Patients may also complain of poor wound healing. Anemia and gingivitis with subsequent tooth loss can be seen. Deficiency is corrected with vitamin C supplementation, but death can occur in untreated patients secondary to bleeding complications.

15.4.2 Histology

Histologic changes of scurvy include hyperkeratosis overlying the acrotrichia, resulting in plugged hair follicles [41, 42]. Follicular epithelium within the dermis may appear hyperconvoluted, and demonstrate dilated medullary cavities. In the dermis surrounding hair follicles, there is a mild to moderate infiltrate of lymphocytes. Perifollicular hemorrhage is also an expected finding with hemosiderin present in more chronic lesions.

The histologic differential diagnosis includes pigmented purpuric eruption and leukocytoclastic vasculitis [42, 43]. There is no transmural infiltrate of neutrophils, or fibrinoid necrosis of vessel walls in scurvy, unlike in leukocytoclastic vasculitis. Pigmented purpuric eruptions are not expected to have follicular dilatation or overlying hyperkeratosis.

15.4.3 Pathogenesis

Scurvy is due to a deficiency in vitamin C (ascorbic acid). Vitamin C has many important cellular functions, including its role as an antioxidant, and its function in hydroxylation of collagen in connective tissues, biosynthesis of carnitine and norepinephrine biosynthesis, and tyrosine metabolism

[44–46]. Scurvy is more commonly encountered in adults, but it can also be seen in children [47, 48]. Groups at risk for scurvy include infants who are fed evaporated or boiled milk, in which vitamin C is destroyed by heat, and children with dietary restrictions stemming from psychiatric or developmental disorders [47, 49]. Scurvy can also mimic child abuse or parental neglect. Scurvy is easily diagnosed by testing for serum levels of vitamin C (a level of less than 11 micromol/L suggests scurvy) [48]. The disorder can be corrected rapidly with vitamin C supplementation.

15.5 Vitamin A Deficiency

15.5.1 Clinical Features

Vitamin A deficiency is seen most commonly in patients with malabsorption secondary to medical or surgical interventions and with liver disease [1]. Patients with vitamin A deficiency usually present with vision changes, including poor adaptation to light, corneal xerosis, ulceration, and keratomalacia, with potential for progression to blindness [1]. Mucocutaneous features of disease include xerosis with severe scaling and fissuring, as well as perifollicular hyperkeratosis (phrynoderma), which is highly characteristic but not specific of disease. In phrynoderma, patients present with filiform papules that evolve into larger papules and plaques with hyperkeratotic horny centers. These lesions present along the extensor surface of the extremities, shoulders, and buttocks. In more severe disease, lesions may generalize and involve the entire body [50]. Patients often improve with better overall nutrition.

15.5.2 Histology

Histologic findings in perifollicular hyperkeratosis/phrynoderma are subtle and can be easily overlooked. Biopsies demonstrate hyperkeratosis, perhaps more prominent overlying the outflow tracts of hair follicles. There is subtle follicular dilatation and minimal lymphocytic infiltrate [50, 51]. A perforating folliculitis is also present in some cases [52].

15.5.3 Pathogenesis

Natural and synthetic vitamin A derivatives (collectively called retinoids) are important for cell growth and differentiation as well as for vision. Vitamin A (retinol) is synthesized in the small intestine by the hydrolysis of retinyl esters, or the oxidation of carotenoids from food constituents [53–55]. Children with severe acute malnutrition are among the most susceptible to vitamin A deficiency [56]. Vitamin A deficiency can also result from reduced synthesis of retinol binding protein and transthyretin in the liver, which are necessary for vitamin A transport in the body [57–59]. Thus, vitamin A stored in the liver may fail to mobilize from the liver, resulting in reduced circulating vitamin A levels. Severe diarrhea and resulting severe acute malnutrition are also associated with a loss of vitamin A [56]. Another route of vitamin A loss is urinary losses of retinol in children with dysentery [60]. Laboratory diagnostic testing for vitamin A deficiency in children includes testing for retinol concentration in the blood [61].

15.6 Hartnup Disease

15.6.1 Clinical Features

Hartnup disease is an autosomal recessive condition resulting in impaired transport of tryptophan in the small intestine and kidneys [62]. Based on newborn screening programs in Australia and North America, the incidence of Hartnup disease is 1:30,000. The disease has been identified in other countries and ethnicities as well [63]. Hartnup disease is the second most common aminoaciduria.

Patients present with cerebellar ataxia and intermittent, variable, photodistributed erythematous and scaly plaques on the face, neck, and arms, as well as the inframammary chest and lower legs [62]. Blistering with subsequent crusting can occur following sun exposure. Psychiatric issues may include emotional lability and confusion. Symptoms can be well controlled with photoprotection and supraphysiologic dosing of nicotinic acid or nicotinamide.

15.6.2 Histology

The histologic changes in skin biopsies taken from patients with Hartnup disease are not specific. They have been described as demonstrating the clinical and histologic features of acrodermatitis enteropathica, pellagra, and kwashiorkor [27, 64, 65]. Confluent parakeratosis is present overlying psoriasiform epidermal hyperplasia. Epidermal pallor confined to the upper portions of the stratum malpighii is seen in well-developed lesions. The inflammatory infiltrate is relatively mild and may contain neutrophils, some of which may be present in the epidermis. Capillary dilatation is seen within the papillary dermis.

15.6.3 Pathogenesis

Hartnup disease is caused by mutations in the neutral amino acid transporter SLC6A19 (B0AT1) [66, 67]. High levels of neutral amino acids in the urine are the first indicator of the disorder. To date, 21 mutations have been identified in Hartnup disease [64, 68]. SLC6A19 interacts with its associated proteins collectrin and angiotensin-converting enzyme 2 (ACE2). SLC6A19 requires collectrin for its surface expression in the kidney, and ACE2 for its expression in the intestine [69, 70]. Therefore, SLC6A19 possibly connects Hartnup disease to complex functions, such as blood-pressure control and kidney glomerular function [68, 71].

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Deposition Disorders

16

16.1 Calcinosis Cutis

16.1.1 Clinical Features

Calcinosis cutis is a rare phenomenon characterized by calcium salt deposition in the skin [1]. Skin lesions present as indurated subcutaneous plaques and nodules with or without associated erythema and tenderness. They may ulcerate and extrude creamy or chalky material, and can cause pressure erosions of underlying bones (Fig. 16.1). Calcinosis cutis is subdivided into four groups based on the etiology of deposition: dystrophic, metastatic, iatrogenic, and idiopathic.

Dystrophic calcinosis cutis is the most common variant, occuring in areas of preexisting skin disease in the setting of normal phosphocalcium metabolism [1]. For example, dystrophic calcinosis cutis has been described in autoimmune connective tissue diseases, such as dermatomyositis and systemic sclerosis [2]. An alternative type of dystrophic calcinosis cutis is heel stick calcinosis or calcified nodules on the heels. This entity is seen in low birthweight infants after frequent heel pricks during the neonatal period. The skin changes tend to appear at 4–12 months of life with spontaneous resolution within 18 to 30 months of occurrence.

Metastatic calcification occurs in previously normal tissue following systemic disturbance with hyperphosphatemia and/or hypercalcemia [1]. Metastatic calcinosis is seen in individuals with hypervitaminosis D, sarcoidosis, osteolytic bone disease, and chronic renal failure.

Iatrogenic calcinosis has been reported following parenteral administration of solutions containing calcium or phosphate, as well as after electrophysiologic studies with calcium-impregnated electrode pastes [1].

Idiopathic calcinosis occurs without preceding evidence of tissue or metabolic disease. The most common variants of this subtype in children are milia-like calcinosis cutis of Down syndrome, idiopathic calcinosis of the scrotum, and subepidermal calcified nodules [1, 3]. Subepidermal calcified nodules can present during childhood or at birth, most commonly on the face or ears. Lesions may be persistent, requiring surgical excision.

16.1.2 Histology

In calcinosis cutis, deposits of blue material that may appear spherular or fractured are surrounded by granulomatous inflammation (Fig. 16.2). In cases with dystrophic calcification, areas of follicular or eccrine disruption with keratinaceous debris may be seen adjacent to foci of calcium deposition. This is a frequent finding in pilomatricomas that occur in children and can also be seen in syringomas [7, 8]. Milia formation can also give rise to small calcium deposits in the dermis [9]. In many cases, the overlying epidermis becomes acanthotic and hyperkeratotic, suggesting lichen simplex chronicus-like changes. Ulceration with transepidermal elimination may be present [10]. Particularly in children, widespread dermal calcium deposits may be seen as a complication of dermatomyositis [5, 11–14]. In some cases, the etiology for the calcium deposition is not readily apparent [15]. Occasionally, calcium deposits are seen within infectious granulomatous processes [16].

16.1.3 Pathogenesis

Calcinosis cutis is caused by the deposition of insoluble calcium salts in the skin and subcutaneous tissue due to abnormalities in serum calcium and phosphorus levels [17]. Dystrophic calcification is caused by tissue damage that induces the release of phosphate-binding proteins by necrotic cells, resulting in calcified deposits that contain hydroxyapatite and amorphous calcium phosphate [18]. Proinflammatory cytokines such as interleukin-6 (IL-6), IL-1, and tumor necrosis factor play an important role in this process [17, 19, 20]. Metastatic calcification is characterized by abnormally high

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levels of serum calcium and/or phosphorus, resulting in the precipitation of calcium salts in normal tissue with no structural damage. The levels of serum phosphorus affect the number and size of calcium deposits in tissues. The most frequent cause of metastatic calcification is chronic kidney failure with hyperphosphatemia. Other causes include hyperparathyroidism, sarcoidosis, and malignancies [21, 22].

Fig. 16.1 Calcinosis cutis (heel stick calcinosis) is a firm, skin-colored nodule extruding chalky white material on the heel of a premature infant (photo courtesy of Audrey Chan, MD, Baylor College of Medicine, Houston, TX)

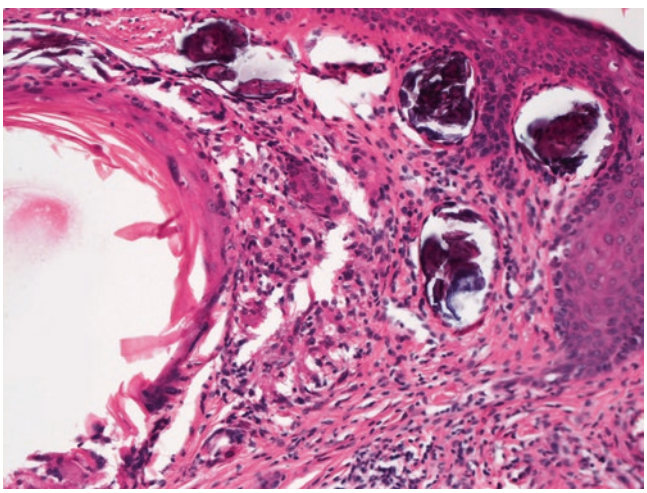

Fig. 16.2 Calcinosis cutis with calcium deposition within the dermis

16.2 Calciphylaxis

16.2.1 Clinical Features

Calciphylaxis affects 1–4 % of patients with end-stage renal disease [23]. Clinical associations include hyperparathyroidism, elevated calcium-phosphate product, hemodialysis, hypercoagulability, and renal transplantation. It is rare in children, with fewer than 10 reported cases, all of which occurred in boys [23, 24]. This differs from the demographics seen in adults, in which there is a striking female predilection.

Initial presenting clinical features include violaceous subcutaneous nodules or plaques, as well as reticulate erythema, which progress to cutaneous ulceration (Fig. 16.3). Most patients have severe recalcitrant pain and hyperesthesia associated with the skin changes. In children, lesions are seen with equal occurrence in the arms and legs with increased incidence of distal involvement. In contrast, in adults, skin lesions are most often localized to the proximal trunk and lower extremities [23].

The clinical course of calciphylaxis is often marked by poor treatment response and non-healing ulcerations, predisposing individuals to gangrene. Mortality rates range from 60–80 % with most patients succumbing to sepsis within months of diagnosis [23]. Acral calcification portends a worse prognosis in children.

Fig. 16.3 Calciphylaxis presents as stellate ulceration with an eschar overlying an ill-defined, purpuric and indurated plaque on the thigh of a girl with end-stage renal disease

16.2.2 Histology

Histologic changes can be quite focal and subtle, or can be extensive [25]. In early lesions, calcium deposits may be identified solely within the walls of blood vessels. Vessels located in the deep dermis or subcutaneous fat are commonly affected (Fig. 16.4). There is little or no associated inflammatory infiltrate associated with the calcium deposits. In more extensive cases, calcium deposits also appear within the fat, unrelated to vascular deposits (Fig. 16.5) [26]. Pericrine calcium deposition is a highly specific finding [27]. In severe cases, ulceration is present secondary to vascular occlusion and tissue ischemia. In these cases, a brisk and diffuse inflammatory process is observed. Interestingly, in one series, there was little evidence of internal organ calcium deposition at postmortem examination [28]. The histologic differential diagnosis includes atherosclerotic changes with secondary calcification, but this is not a frequent consideration in children.

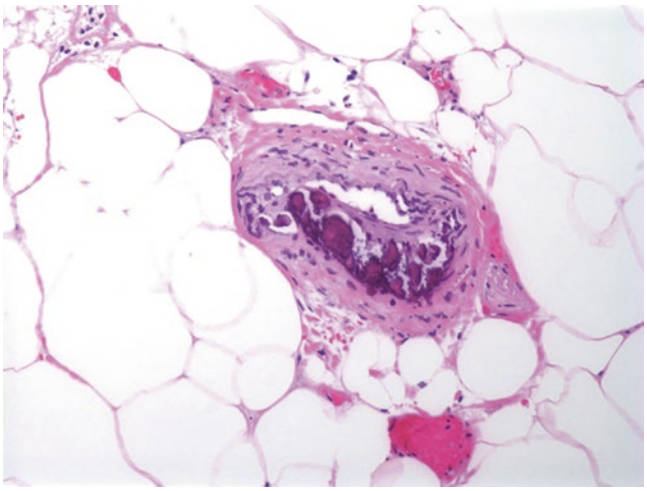

Fig. 16.4 Calciphylaxis is characterized by calcium deposits within the wall of blood vessels located in the deep dermis and subcutis

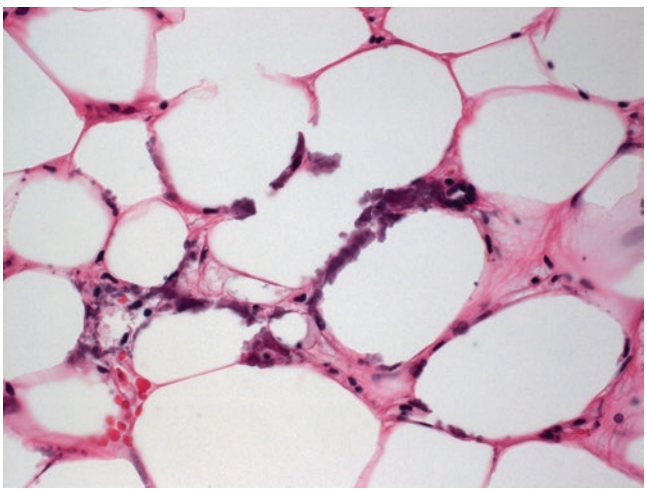

Fig. 16.5 Calcium deposits are seen in subcutaneous adipose tissue away from blood vessels in some cases of calciphylaxis

16.2.3 Pathogenesis

Calciphylaxis is a manifestation of severely dysregulated calcium–phosphorus metabolism, usually occurring in patients on dialysis for kidney failure [29]. There is a high prevalence of mineral bone abnormalities in dialysis patients. Kidney failure is known to affect calcium and phosphate status that can lead to calciphylaxis. Parathyroid hormone abnormalities may also be a cofactor in the pathogenesis of the disease since chronic hyperparathyroidism causes high bone turnover, hypophosphatemia, hypercalcemia, and vascular calcium deposition [29, 30].

Thrombotic vascular occlusion leads to tissue ischemia and necrosis in calciphylaxis [29]. There are reduced blood flow, vascular endothelial injury, and hypercoagulation state in this disorder. Calcium deposition and subintimal fibrosis involving small arteries lead to luminal narrowing and blood stasis. Inflammatory mediators, such as tumor necrosis factor-α and interleukin (IL)-1 and IL-6, are increased in chronic dialysis. These factors mediate endothelial cell dysfunction and promote a pro-coagulant state by vascular release of tissue factor, reduced protein C and protein S levels, and decreased thrombomodulin and heparin-like molecules [31, 32]. In addition to a localized pro-coagulant state, some patients with calciphylaxis also have systemic hypercoagulation [33, 34]. This may increase thrombus formation in calcified blood vessels.

A major molecular factor in calciphylaxis is nuclear factor-κB (NF-κB) and the receptor activator of NF-kB (RANK) and its ligand (RANKL) [35]. Agents, such as hormones, medications, and cytokines that affect NF-κB function can result in vascular calcification. Inhibitors of the RANK-NF-κB cascade, such as bisphosphonates and anti-RANKL antibodies, have the potential to prevent vascular calcification in calciphylaxis [35, 36].

16.3 Osteoma Cutis

16.3.1 Clinical Features

Osteoma cutis is a rare condition characterized by bone formation within the skin [37]. The condition can be subdivided into primary and secondary forms depending on the absence or presence of a preceding neoplastic process or cutaneous inflammation [37]. Primary disease is further subcategorized

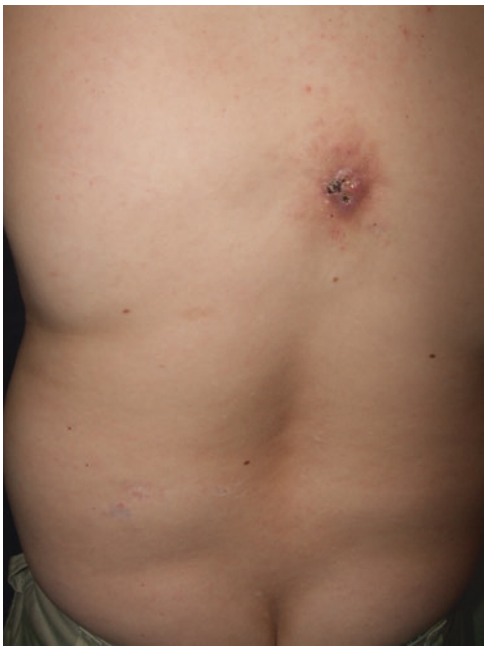

Fig. 16.6 Osteoma cutis presents as subcutaneous rock hard plaques and nodules on the back of a teenage boy with Albright hereditary osteodystrophy

into progressive and limited forms. Osteoma cutis is characterized by subcutaneous rock-hard plaques or nodules with distribution dependent on the subtype of disease (Fig. 16.6). Lesions tend to be persistent, although a number of medical and surgical management options exist [37, 38].

16.3.2 Histology

Osteoma cutis represents small bone deposits located in the dermis. In many cases, well-formed bone, even containing marrow, is present in the dermis without eliciting an inflammatory response (Figs. 16.7 and 16.8). In other cases, a granulomatous response can be seen. Osteoma cutis is an end stage of the dystrophic calcification process [39–41]. This is especially well described in some patients as a consequence of acne vulgaris. In such cases, the usual histologic changes of acne vulgaris may still be present in the biopsy [42].

Primary dermal osteoid formation occurs as part of several syndromes [39, 43–46]. One of these involves a plate-like deposition of bone within the dermis, and epidermolytic hyperkeratosis may be seen in the overlying epidermis [41, 47, 48]. Another syndrome involves café-au-lait spots and woolly hair anomalies in association with osteoid deposits in the dermis [49]. In rare cases, patients with metabolic disorder or endocrinopathies may develop osteoid deposits in the dermis [50].

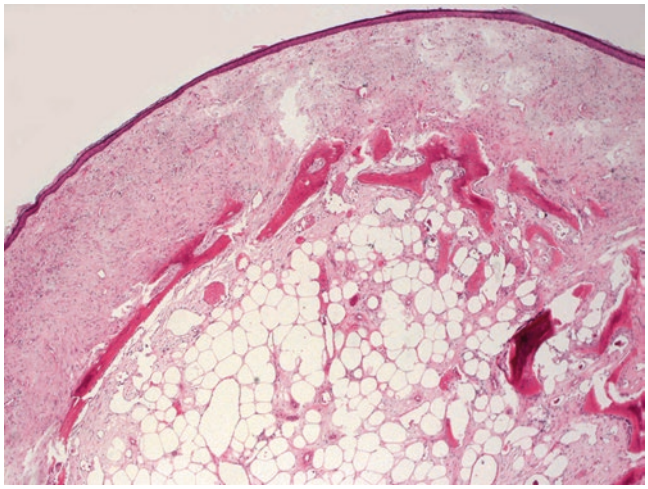

Fig. 16.7 Irregular osteoid formation is present in the dermis in osteoma cutis

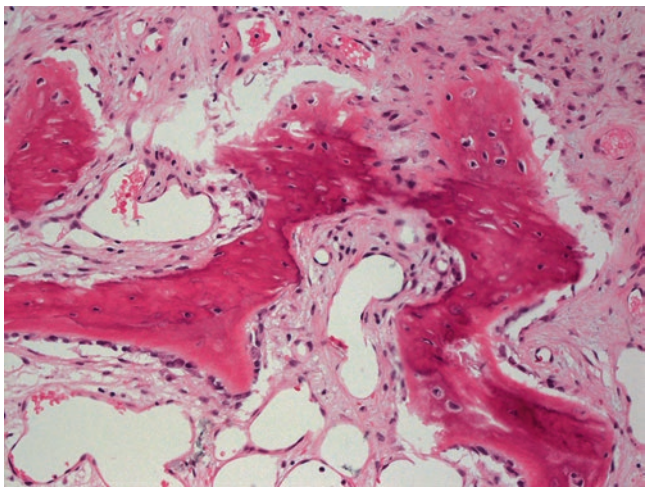

Fig. 16.8 Osteoma cutis demonstrates osteoid formation within the dermis. In well-developed cases, apparent marrow can be seen within the osteoid deposition

16.3.3 Pathogenesis

Osteoma cutis is caused by abnormal deposition of bone in the dermis. The pathogenesis of osteoma cutis is unknown, but it has been postulated to be associated with the metaplasia of fibroblasts into osteoblasts and subsequent bone production [51]. In situ hybridization studies have shown that dermal fibroblasts can differentiate into osteoblasts, and produce type 1 collagen and osteonectin characteristic of bone-forming cells [52]. Disorders of ossification in the skin may be linked to Albright hereditary osteodystrophy, progressive osseous heteroplasia, and congenital plate-like osteoma as well as disorders with non-syndromic mutations in GNAS gene [45, 53, 54]. GNAS is the α subunit of the G

protein of adenylyl cyclase (Gsα), which promotes the differentiation of mesenchymal stem cells into osteoblasts. Other common causes of osteoma cutis include infection, surgical procedures, granulomatous diseases, tumors, and trauma [45, 53–55].

16.4 Erythropoietic Protoporphyria

16.4.1 Clinical Features

Erythropoietic protoporphyria is the most common type of porphyria seen in children [56]. This inherited porphyria is a result of partial deficiency in ferrochelatase with subsequent accumulation of the photoreactive metabolite protoporphyrin IX in erythrocytes, plasma, liver, and skin.

Symptoms typically present in infancy or early childhood with photodistributed skin pain, burning or itching immediately upon sun exposure [56]. Mild edema and erythematous to purpuric patches can be seen on the hands. In chronic disease, waxy indurated plaques and scarring can develop on the dorsum of the hands and the central face, specifically along the nasal bridge. Twenty-five percent of patients have involvement of the hepatobiliary system secondary to accumulation of protoporphyrin IX in the liver [56]. Ten to twenty percent of patients have liver dysfunction. Patients are also at risk for cholelithiasis with 2 % of affected individuals developing acute fulminant cholestatic liver failure.

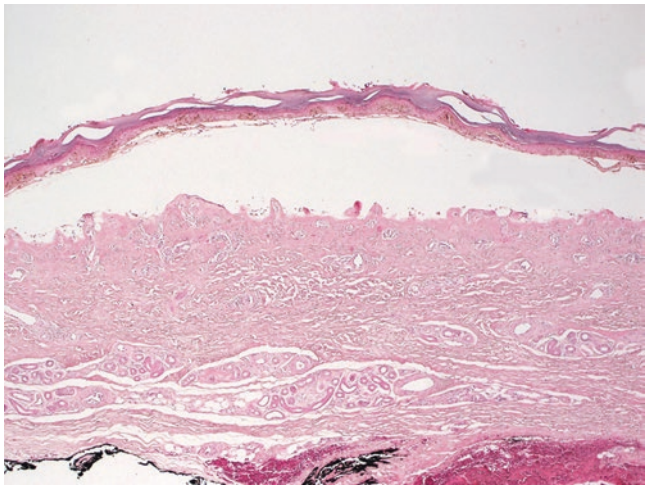

Fig. 16.9 Erythropoietic protoporphyria demonstrates a noninflammatory subepidermal blister

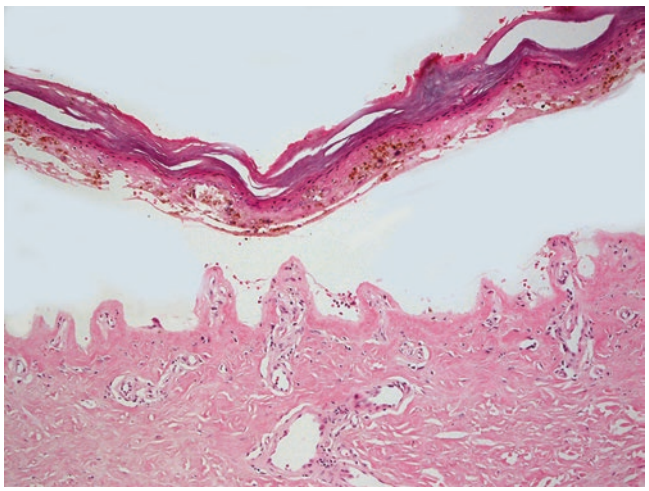

Fig. 16.10 Prominent festooning of the papillary dermal tips into the blister cavity is a frequent finding in erythropoietic protoporphyria

16.4.2 Histology

There is a cell-poor subepidermal blister with prominent festooning of the papillary dermal tips in erythropoietic protoporphyria (Figs. 16.9 and 16.10). Within the stratum corneum, eosinophilic bodies that have been called "caterpillar bodies" may be observed when intact epidermis is available for examination. These elongated and segmented figures comprise laminin and type IV collagen [57]. Acute lesions demonstrate basal vacuolization in the epidermis with intercellular edema. Cytolysis of endothelial cells is also present. As the lesions become more chronic, PAS-positive hyaline material is deposited around dermal blood vessels (Fig. 16.11). The capillary basement membranes are also thickened [58, 59]. Late stage lesions show extensive reduplication of vascular basement membranes on electron microscopic examination [58]. Direct immunofluorescence examination shows linear IgG, IgA, IgM, and C3 concentrically around the dermal blood vessels [59].

Lipoid proteinosis can be distinguished from erythropoietic protoporphyria by a more diffuse deposition of hyaline material than that seen in porphyria [61]. Deposition of hyaline material is a frequent finding in lipoid proteinosis, but it is not seen in erythropoietic protoporphyria. Clinical presentation also makes the distinction relatively simple. Porphyria cutanea tarda demonstrates similar hyaline deposits around dermal blood vessels, but it does not have the marked thickening in capillary walls due to basement membrane reduplication as seen in erythropoietic porphyrias.

16.4.3 Pathogenesis

Erythropoietic porphyrias are characterized by elevations of porphyrins in the bone marrow and red blood cells with skin photosensitivity that develops in infancy or early childhood

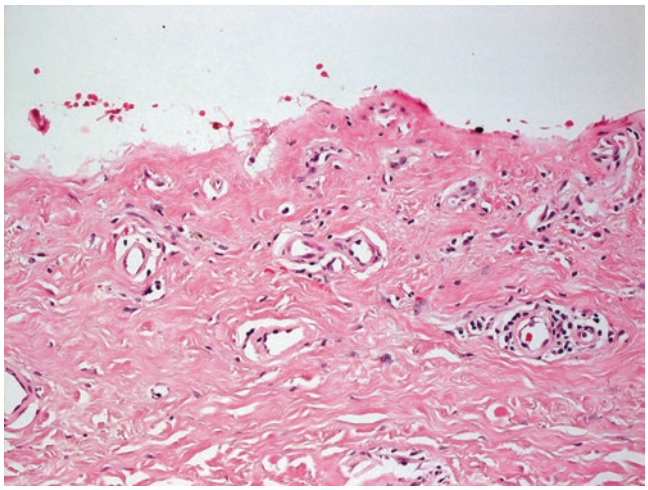

Fig. 16.11 Erythropoietic protoporphyria demonstrates dilation of papillary dermal blood vessels that are often lined by a rim of eosinophilic material

[62, 63]. The mechanism of cutaneous photosensitivity in erythropoietic porphyrias is due to the accumulation of excess protoporphyrin in the skin and cutaneous blood vessels, and photoactivation of protoporphyrin by sunlight.

Congenital erythropoietic porphyria (CEP) is an autosomal recessive disorder associated with hemolytic anemia and severe skin photosensitivity. CEP results from deficiency in the activity of uroporphyrinogen III synthase due to mutations in the GATA1 and CP2 transcriptional binding elements in the promoter region of uroporphyrinogen III synthase gene. Deficient uroporphyrinogen III synthase leads to the accumulation of uroporphyrin I and coproporphyrin I isomers [62, 64, 65]. Patients with CEP that have uroporphyrinogen III synthase mutations plus gain-of-function mutations in the 5-aminolevulinate synthase 2 (ALAS2) gene, which encodes for a rate-limiting enzyme of erythroid heme synthesis, have a more severe disease phenotype than patients without concomitant ALAS2 mutations [66]. An X-linked variant of CEP has been identified that is caused by mutation in GATA1 gene, which encodes a transcription factor that regulates the expression of globin and heme biosynthetic genes [67].

Erythropoietic protoporphyria is one of the most common erythropoietic porphyrias in children [62]. It is an autosomal recessive disorder caused by loss of function mutations in the ferrochelatase (FECH) gene. FECH is an enzyme in the heme biosynthetic pathway. Defects in FECH lead to increased levels of protoporphyrins in red blood cells. The protoporphyrins are not complexed with zinc, and are free to bind to hemoglobin. There is an X-linked form of erythropoietic protoporphyria that is due to activating mutations in the ALAS2 gene with increased ALAS2 activity and accumulation of protoporphyrins. Mutational analyses for FECH and ALAS2 genes establish the genetic diagnosis for the disease [62].

16.5 Tattoo

16.5.1 Clinical Features

Approximately 7–20 million people in the United States are estimated to have at least one tattoo with a prevalence rate of 10–26 % in men and 10–22 % in women [68]. Prevalence is relatively similar across different ethnic groups [69]. The appearance of tattoos is varied and characterized by the permanent inking of colors in various patterns on the skin. They can be removed or lightened with lasers. However, risk of removal includes secondary dyschromia, especially in more darkly pigmented skin types. Graphite tattoos generally occur through traumatic implantation. In these situations, small areas of dermal pigmentation may be present (Fig. 16.12).

16.5.2 Histology

Histologic findings in a tattoo include the observation of various pigments in the dermis (Figs. 16.13 and 16.14). The pigments tend to aggregate around blood vessels, and can be present within macrophages and in the interstitial space. The pigment can be relatively superficial or extend much deeper into the dermis. In some patients, there is little immunologic reaction to the pigment. However, tattoos are often associated with immune reactions.

One of the most common reactions to a tattoo is the presence of overlying pseudoepitheliomatous hyperplasia [70–74]. This reaction pattern can be so florid as to raise the

Fig. 16.12 Graphite tattoo shows a bluish gray macule on the chest following puncture wound with a lead pencil

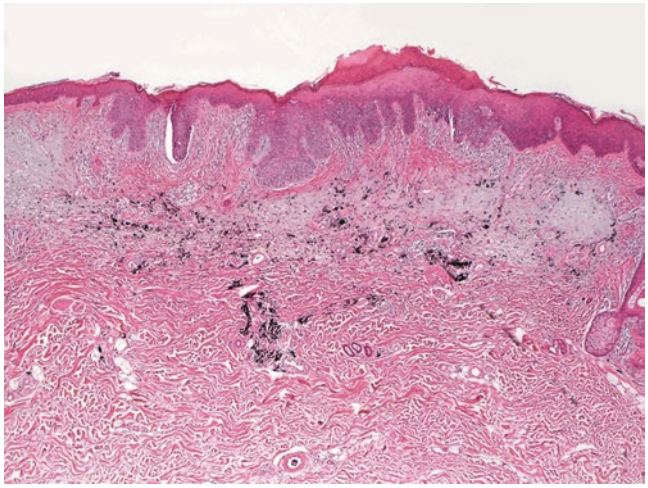

Fig. 16.13 Dermal pigment is present in a tattoo, often centered on dermal blood vessels. The pigment may be seen in the superficial and deep dermis

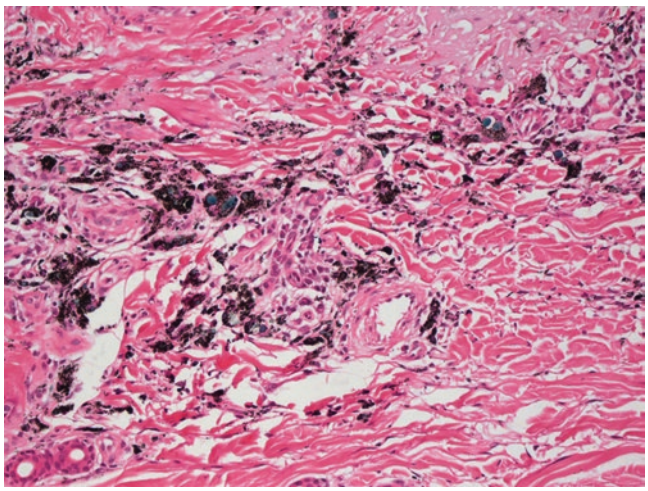

Fig. 16.14 It is often possible to identify various colors in a tattoo

possibility of a squamous cell carcinoma [72]. A rare reaction pattern is a chronic fibrosing vasculitis-type of pattern that is localized entirely within the tattoo, and specifically to areas with red pigment [73]. An intense lichenoid inflammatory reaction has been described in response to red pigment within a tattoo [75]. Acute contact dermatitis, lupus-like inflammatory reactions, and foreign body granulomas are also described as immune responses to tattoos [76]. Necrobiotic granuloma-like reactions to tattoos are also seen, but they are far less common that foreign body type granulomas [77]. A florid cutaneous lymphoid hyperplasia resembling a lymphoma occurs as a reaction to tattoos with the majority of lymphocytes in these hyperplastic responses are T cells [78, 79]. Interestingly, this reaction is also more commonly associated with red pigment. A rare tattoo reaction resembling cutaneous morphea has also been reported [80].

16.6 Papular Mucinosis

16.6.1 Clinical Features

The exact incidence of papular mucinosis is unknown with some authors suggesting that occurrence is underreported [81]. Papular mucinosis is characterized by small indurated, waxy papules, usually localized to the trunk and proximal extremities [82]. Lesions may coalesce to form nodules and plaques.

Papular mucinosis can be subcategorized based on the clinical appearance. The variants most commonly seen in children are self-healing juvenile papular mucinosis and papular mucinosis of infancy. Self-healing juvenile papular mucinosis is characterized by the rapid onset of linearly arranged papules that coalesce into plaques on the face, neck, scalp, abdomen, and thighs. The reported age of onset ranges between 13 months and 15 years of age [82, 83]. Systemic complaints of fever, arthralgias, and weakness may occur with onset of skin lesions, although there is no association with an underlying systemic disease. In contrast, papular mucinosis of infancy is described as firm, shiny papules at the upper arms and trunk, particularly along the elbows. The condition tends to be persistent, and is not associated with underlying paraproteinemia or other systemic abnormalities [82, 84]. As most cases of papular mucinosis are not associated with underlying systemic disease, treatment is not required. The self-healing variant often resolves within weeks to months with similar reports of eventual spontaneous resolution noted in the infantile form as well [82].

16.6.2 Histology

The precise nature of papular mucinosis of infancy is still very much in question with some investigators favoring a discrete entity, and others considering this to be an early presentation of lichen myxedematosus [81, 84–86]. The histologic findings include an accumulation of mucin within the superficial portion of the dermis accompanied by an increased number of dermal fibroblasts. However, in some cases, fibroblasts are not significantly increased. The epidermis is either unremarkable or slightly flattened due to the accumulation of

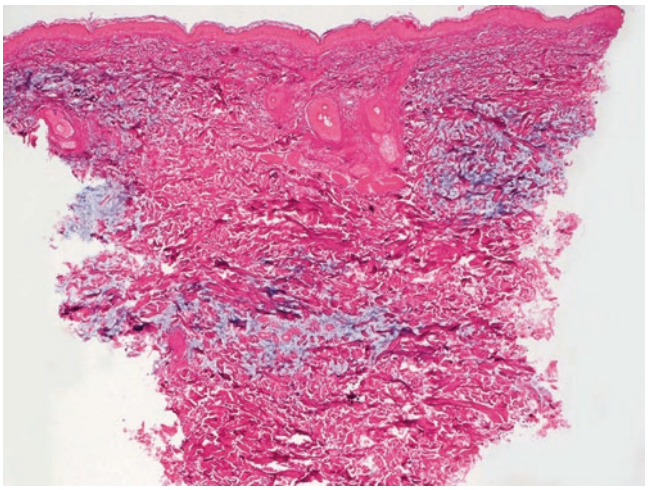

Fig. 16.15 Routine histologic sections demonstrate increased mucin diffusely throughout the dermis in self-healing juvenile cutaneous mucinosis

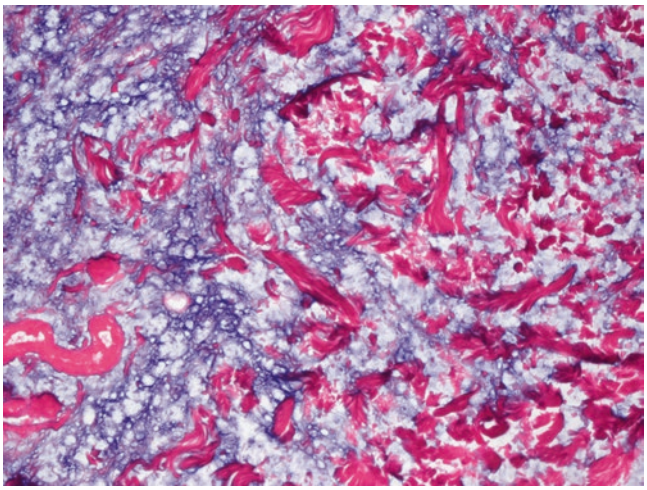

Fig. 16.16 Dermal mucin is readily apparent with routine staining in most cases of self-healing juvenile cutaneous mucinosis

dermal mucin. There is a mild lymphohistiocytic inflammatory infiltrate in some cases. Older lesions demonstrate thickening of collagen bundles.

Self-healing juvenile cutaneous mucinosis is a rare disorder that is characterized by dermal mucin deposition, usually in the absence of increase in dermal fibroblasts (Fig. 16.15). Some cases show a slight increase in fibroblasts and mast cells [87]. Mucin deposition predominates in the superficial portion of the reticular dermis [88, 89] (Fig. 16.16). The accumulation of mucin is relatively well circumscribed, and can be better visualized on colloidal iron stains [90].

A rare variant has been described in which mucin deposition is deeper and more extensive, extending into the subcutis. The histologic appearance is quite similar to nodular fasciitis or proliferative fasciitis with relatively inconspicuous mucin deposits [83, 91]. Myxoid stroma and gangliocyte-like giant cells may be present in this rare variant [83]. A single case with apparent disease progression of the self-healing condition, as opposed to spontaneous remission, exists in the literature [92].

The differential diagnosis includes other cutaneous mucinoses, such as scleromyxedema and lichen myxedematosus. While these entities generally display a more excessive increase in dermal fibroblasts than that seen in self-healing juvenile cutaneous mucinosis, resolution of the dilemma usually resides in a thorough clinical work-up to exclude any systemic involvement, and close clinical follow-up to monitor the course of the disease.

16.7 Digital Mucous Cyst

16.7.1 Clinical Features

Digital mucous cysts are benign ganglion cysts that are rare in children, and most commonly occur in adults between 40 and 70 years of age [93]. Females are affected twice as often as males [94]. Lesions typically appear as an isolated skin-colored to slightly erythematous nodule on the dorsum of the digit along the distal interphalangeal joint or proximal nail fold. The hands are affected more often than the feet [93]. Clustered or multiple lesions have been described. As most cysts are asymptomatic, no treatment is required but surgical management can be offered.

16.7.2 Histology

A digital mucous cyst consists of a collection of alcian blue or colloidal iron-positive ground substance present in the superficial dermis (Figs. 16.17 and 16.18). Despite the name, there is no cyst lining present. Surrounding the pseudocyst is a fibrous and myxoid stroma with increased numbers of fibroblasts [94, 95]. Alcian blue or colloidal iron stain demonstrates pools of mucin within the dermis (Fig. 16.19). The epidermis is usually unremarkable. The histologic findings in a digital mucous cyst are quite similar to those seen in a ganglion cyst. The anatomic site determines the diagnosis.

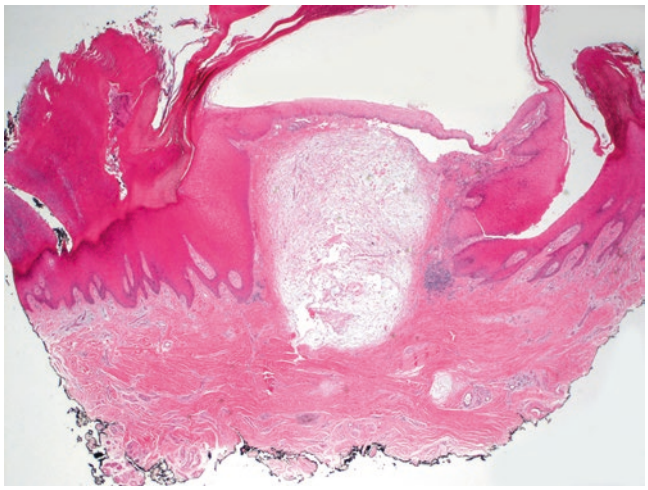

Fig. 16.17 Digital mucous cyst is a pseudocyst that demonstrates a collection of mucin within the papillary and reticular dermis of acral skin

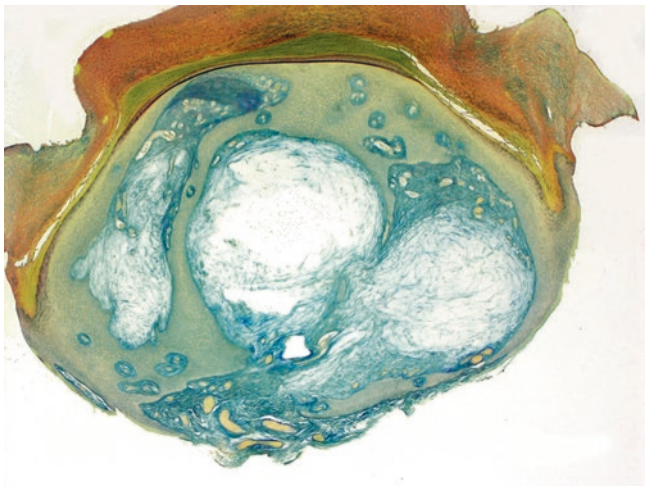

Fig. 16.19 Alcian blue stains highlight the loculated collections of dermal mucin in digital mucous cyst

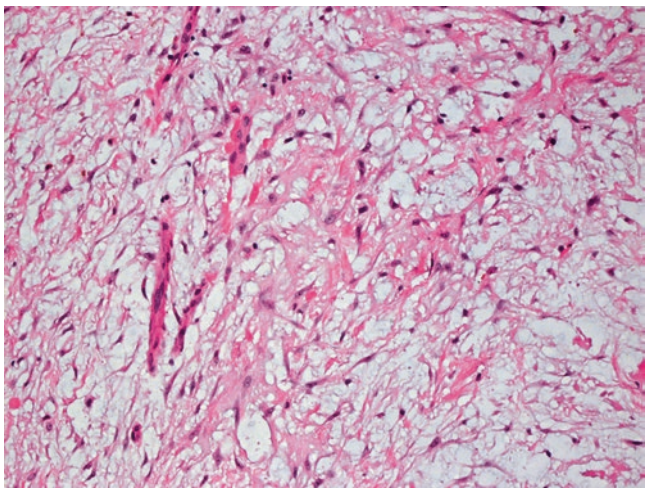

Fig. 16.18 Increased dermal mucin is readily apparent with routine H&E staining of digital mucous cyst

16.7.3 Pathogenesis

Digital mucous cyst does not have a true epithelial lining, so it is more accurately classified as a pseudocyst. The superficial (mucinous) type is thought to arise from metaplasia of dermal fibroblasts with excess production of hyaluronic acid and mucin [96, 97]. The deep (ganglion) type is thought to result from degenerative changes in the fibrous capsule or synovial tissue of the joint with excess production and accumulation of hyaluronic acid through a communication channel or peduncle to form a digital mucous cyst [98, 99]. Radiographic and surgical evidence has shown communication between the pseudocyst and adjacent joint space [100, 101]. There is evidence of the association of digital mucous cyst with osteoarthritis. It has been suggested that the development of osteophytes, and an increase in synovial fluid in osteoarthritis contribute to the cyst formation [97, 102, 103].

16.8 Scleromyxedema/Lichen Myxedematosus

16.8.1 Clinical Features

Scleromyxedema is a rare disorder usually of middle-aged adults with no gender predilection [81]. It is typically associated with an underlying systemic disorder, most commonly paraproteinemia, which is seen in approximately 83 % of cases [81]. Scleromyxedema typically presents as widespread coalescent shiny papules, often in linear arrangement distributed symmetrically on the hands, forearms, face, neck, upper trunk, and thighs. Indurated longitudinal furrowing may be seen along the glabella. With progression of disease, erythematous indurated plaques may develop with concomitant skin-stiffening and decreased mobility. The mucous membranes and scalp are spared with absence of telangiectases and calcinosis.

Treatment of the condition is difficult, but cutaneous lesions may resolve with successful management of the underlying disorder. Approximately 10 % of patients with an associated monoclonal gammopathy eventually develop multiple myeloma [81]. Additional systemic sequelae include other hematologic malignancies, proximal muscle weakness, central nervous system disturbances, joint disease, Raynaud's phenomenon, pulmonary disease, dysphagia, laryngeal involvement, scleroderma-like renal disease, and ocular changes.

16.8.2 Histology

Scleromyxedema and lichen myxedematosus have identical histologic findings, and are differentiated based upon the clinical presentation and associated systemic symptoms [81, 86]. The superficial dermis is distended with mucin (acid mucopolysaccharides) that is apparent on routine histologic sections, and can be better visualized on colloidal iron or alcian blue stains [104] (Figs. 16.20 and 16.21). There is an increase in dermal fibroblasts. In more established lesions, thickening of dermal collagen further increases the thickness of the dermis. A proliferation of eccrine ducts can be seen in some cases [105]. Degradation of collagen has been demonstrated by ultrastructural examination [106]. A rare variant of scleromyxedema with foci histologically resembling the interstitial type of granuloma annulare has been described [107, 108].

Involvement of the fibrous septa is quite unusual in scleromyxedema, and in most cases, deep extension can be used to favor a diagnosis of nephrogenic systemic fibrosis over lichen myxedematosus/scleromyxedema. It has been proposed that the presence of iron within dermal fibroblasts as seen in nephrogenic systemic fibrosis might aid in making this histologic distinction [109]. Careful attention to clinical history is the easiest way to distinguish between these entities that have great histologic overlap [110]. Scleroderma is differentiated based upon the lack of dermal mucin, and scleredema lacks a proliferation of fibroblasts within the dermis. Furthermore, mucin deposition in scleredema is more subtle and deeper within the reticular dermis. Pretibial myxedema can be differentiated from scleromyxedema based upon the clinical presentation, and the lack of significant fibroblast proliferation to accompany the dermal mucin deposition.

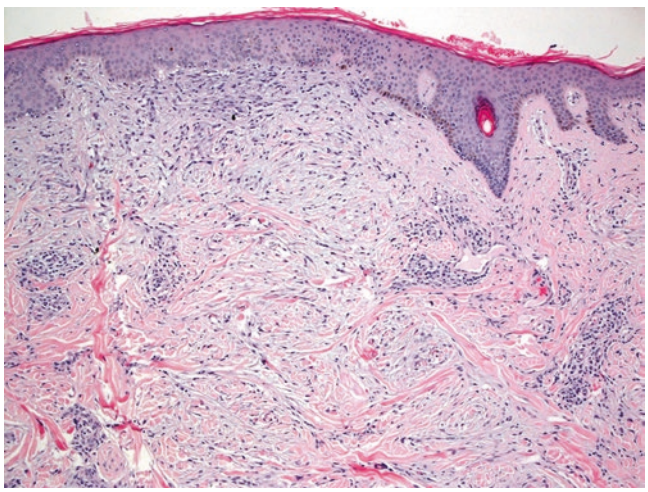

Fig. 16.20 Increased numbers of fibroblasts are present in the papillary and superficial reticular dermis in scleromyxedema

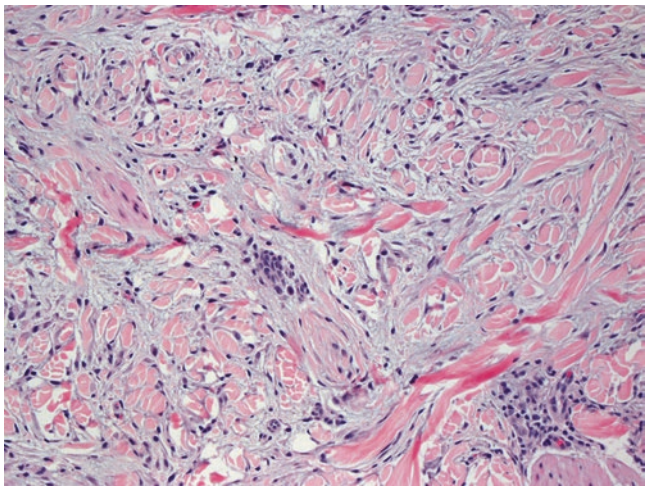

Fig. 16.21 Dermal mucin is seen interspersed between collagen bundles within the superficial dermis in scleromyxedema

16.8.3 Pathogenesis

Scleromyxedema is a generalized form of dermal mucin deposition, and it is often associated with monoclonal gammopathy, particularly of immunoglobulin G [111, 112]. Serum from patients with scleromyxedema has been shown to enhance the proliferation of skin fibroblasts in vitro, but immunoglobulins purified from the serum do not affect fibroblast growth [113, 114]. Therefore, other serum factor(s), and not immunoglobulins, may be responsible for the enhanced fibroblast proliferation, and the subsequent induction of mucin deposition in the skin. Intrinsic dysregulation of skin fibroblasts in scleromyxedema may be another possible mechanism of increased fibroblast proliferation.

16.9 Pretibial Myxedema

16.9.1 Clinical Features

Up to 4 % of patients with thyrotoxicosis of Graves' disease, and 13 % of those with more advanced ophthalmopathy develop thyroid dermopathy and pretibial myxedema [115]. Pretibial myxedema is characterized by symmetric circumscribed, light-colored to brownish yellow, non-pitting, indurated plaques at the pretibial legs and feet [115]. Follicular ostia may become more prominent with a peau d'orange appearance of affected skin. Nineteen to twenty-five percent of patients with severe thyroid dermopathy will develop thyroid acropachy, presenting as clubbing of the digits. Eighteen percent of patients will develop a nodular variant with only 5

% developing the most severe subtype with coalescent nodular, fungating plaques (elephantiasis). Hyperhidrosis is a common feature, while pruritus and tenderness are infrequently seen.

The likelihood of disease remission is inversely correlated with the severity of disease at initial presentation [115]. Specific treatment of the skin changes may not be required as mild dermopathy may demonstrate partial or complete resolution over time.

16.9.2 Histology

Histologic findings in pretibial myxedema include the presence of increased dermal mucin located primarily in the superficial reticular dermis (Fig. 16.22). A grenz zone within the papillary dermis is reported to be associated with Graves' disease, although it is usually absent in patients with pretibial myxedema in the absence of this disease [116]. Mucin extends deeper into the reticular dermis in patients with Graves' disease. Only a minimal increase in dermal fibroblasts is seen in most cases (Fig. 16.23). A mild lymphohistiocytic inflammatory response may be present [117]. The overlying epidermis may range from normal to displaying verrucous epidermal hyperplasia with overlying hyperkeratosis. A rare variant of pretibial myxedema demonstrates a nodular aggregation of mucin within the dermis [118].

The histologic differential diagnosis includes other mucinoses. The mucin deposition in scleromyxedema and lichen myxedematosus is accompanied by a brisk fibroblastic infiltrate not seen in pretibial myxedema. Scleredema shows mucin in the deep reticular dermis, and the deposition is less apparent on routine H&E sections. Stasis dermatitis may also present with mucin in the superficial dermis, but this is an uncommon finding in children [116].

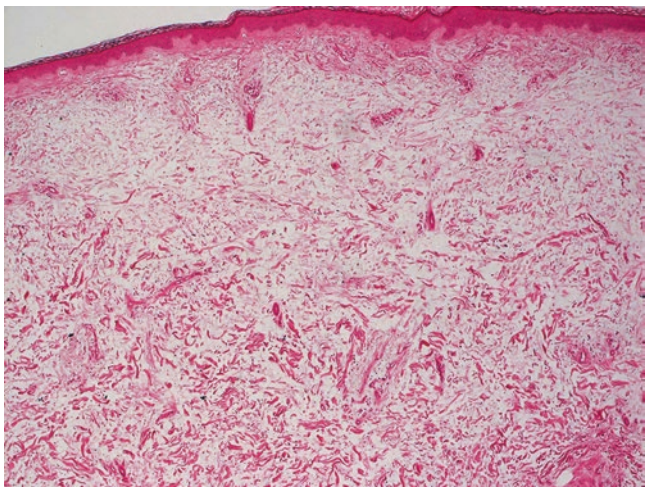

Fig. 16.22 Pretibial myxedema shows increased amount of mucin in the superficial portion of the dermis. Mucin may also be present in the deeper dermis in extensive cases

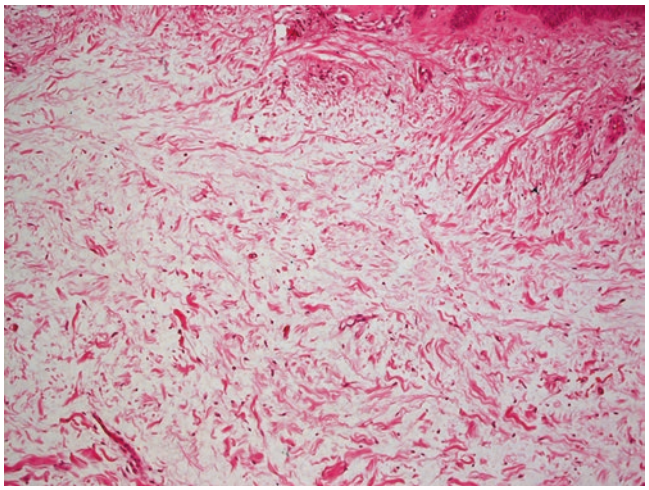

Fig. 16.23 Increased mucin is seen in the dermis in pretibial myxedema. There is no appreciable increase in dermal fibroblasts in this disorder

16.9.3 Pathogenesis

Pretibial myxedema is a skin manifestation of autoimmune Graves' disease [119, 120]. Activation of fibroblasts with excessive production of glycosaminoglycans is the main pathologic process in pretibial myxedema. Local accumulation of glycosaminoglycans leads to compression of dermal lymphatics and results in nonpitting edema [115, 121]. The mechanism of fibroblast activation in pretibial myxedema involves thyroid stimulating hormone (TSH) receptor-stimulating antibodies, and TSH receptors present in the skin that initiate the immune process. There is evidence that thyroid-specific T lymphocytes accumulate in pretibial tissues in patients with Graves' disease and pretibial myxedema [122]. Cytokines produced by T lymphocytes can stimulate dermal fibroblasts to produce glycosaminoglycans and hyaluronic acids [119, 123]. Another potential mechanism of fibroblast activation involves the insulin-like growth factor-1 receptor (IGF-1R). IGF-1R acts as an antigen to Graves' disease immunoglobulins, resulting in the upregulation of T-cell cytokines and fibroblast activation [124, 125].

16.10 Nephrogenic Systemic Fibrosis

16.10.1 Clinical Features

Nephrogenic systemic fibrosis is a rare disorder seen in patients with renal dysfunction following exposure to gadolinium-based contrast media [126]. There is no gender or racial predilection. It primarily occurs in middle-aged adults, with only a few published cases in children [127].

Nephrogenic systemic fibrosis is characterized by a coalescence of brawny, indurated papules and plaques, most often along the trunk and extremities with sparing of the face [126]. Patients may complain of concomitant pruritus or pain, especially if contractures develop over involved joint spaces. The clinical course is usually progressive, although spontaneous resolution may occur following recovery of normal renal function [127]. The associated skin fibrosis and joint contractures cause significant debilitation, but ultimately, prognosis is determined by the degree of systemic involvement [126, 127]. Fibrosis of the heart, lungs, diaphragm, skeletal muscles, and kidneys contribute most significantly to the mortality and morbidity of disease.

16.10.2 Histology

Biopsy findings include a fibroblastic deposition in the mid-reticular dermis extending down the fibrous septae into the subcutis (Fig. 16.24). There is accompanying mucin deposition throughout the dermis and subcutis. Early lesions appear edematous with a hypercellular appearance due to increased fibroblasts, while later lesions appear less cellular and have more sclerotic and eosinophilic collagen with less obvious mucin (Figs. 16.25, 16.26 and 16.27). Collagen bundles are thickened in late-stage lesions with decreased interstitial spaces. Small multinucleated giant cells have been described in some cases [128].

The differential diagnosis of early lesions is scleromyxedema or lichen myxedematosus [110]. The clinical course and presentation are the easiest way to make the distinction, although nephrogenic systemic fibrosis involves the deep reticular dermis and subcutis, which are unusual findings in the other disorders. It has been suggested that the presence of hemosiderin in fibroblasts is more indicative of nephrogenic systemic fibrosis than scleromyxedema, and can be used as a discriminating feature [109]. Later lesions may bear some resemblance to scleroderma, but the increased number of

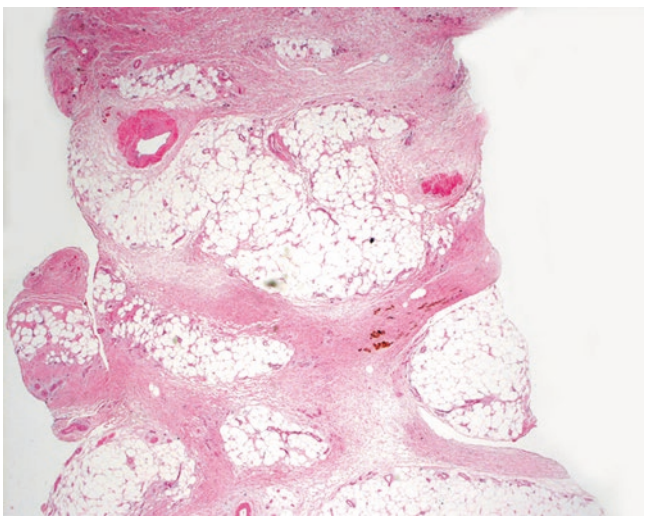

Fig. 16.24 Marked thickening of the dermal and subcutaneous collagen are seen in nephrogenic systemic fibrosis, giving rise to the appearance of a septal panniculitis in some cases

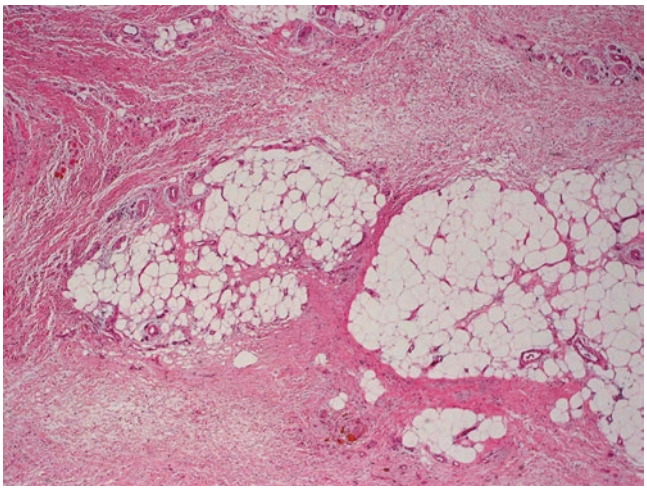

Fig. 16.25 Increased fibroblasts are seen within the thickened collagen in all levels of the dermis and subcutis in nephrogenic systemic fibrosis

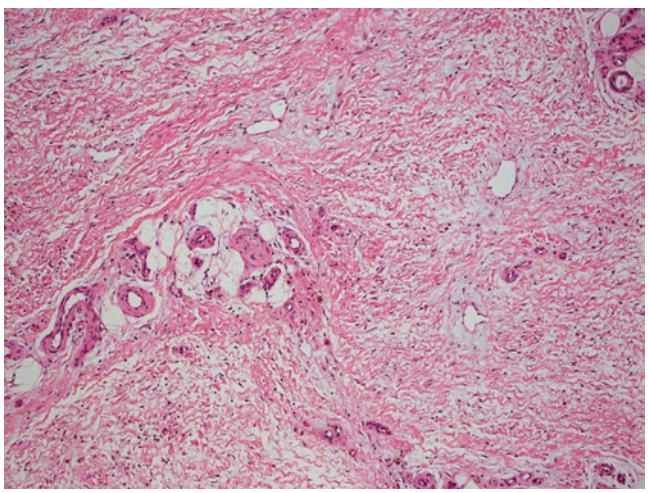

Fig. 16.26 Increased ground substance consisting primarily of mucin is seen in nephrogenic systemic fibrosis

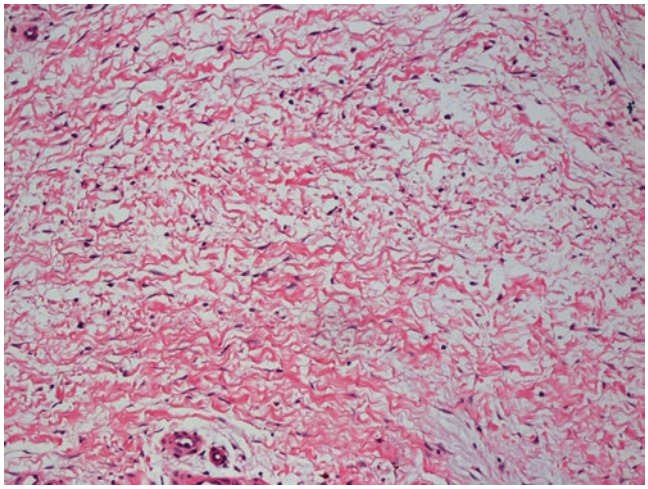

Fig. 16.27 The combination of increased cellularity and dermal mucin resulting in separation of collagen bundles in the deep dermis is characteristic of nephrogenic systemic fibrosis

fibroblasts is unusual in scleroderma. Scleredema involves the deep reticular dermis, but it is not associated with a hypercellular dermis.

16.10.3 Pathogenesis

Nephrogenic systemic fibrosis is an iatrogenic fibrosing disorder in patients with chronic kidney disease who have been exposed to gadolinium-based contrast agents during imaging procedures [129]. Instead of being cleared rapidly by the kidney, gadolinium–chelate complexes remain in the body longer in patients with impaired renal function. During this time, gadolinium can dissociate from its chelate and bind to tissue. Gadolinium deposition has been found in the skin and other tissues from patients with nephrogenic systemic fibrosis [130, 131]. In vitro studies have shown that gadolinium induces the production of pro-inflammatory and profibrotic cytokines by human macrophages and monocytes through Toll-like receptors (TLRs) 4 and 7 [132, 133]. Some key cytokines involved are interleukin (IL)-4, IL-6, IL-13, and interferon (IFN)-γ as well as nuclear factor-κB-dependent cytokines [132, 134]. These cytokines activate dermal fibroblasts to synthesize extracellular matrix proteins and induce fibrosis. Fibroblasts exposed to gadolinium become fully differentiated myofibroblasts that exhibit an activated phenotype and produce increased amounts of types I and III collagen, fibronectin, and hyaluronic acid [135]. A study has provided evidence that iron is important in the pathogenesis of nephrogenic systemic fibrosis in an animal model of the disease [136]. Iron chelation with deferiprone significantly improves gadolinium-induced nephrogenic systemic fibrosis-like skin changes in mice.

16.11 Tangier Disease

16.11.1 Clinical Features

Tangier disease is a rare autosomal recessive disorder with defects in lipid transport and accumulation of cholesterol esters in tissues, such as the tonsils. The skin usually appears normal, but can present with small firm papules.

16.11.2 Histology

Tangier disease is characterized by deposition of cholesterol esters within histiocytes surrounding blood vessels in the superficial dermis, leading to their having a foamy appearance [137, 138]. Vacuolization of Schwann cells within cutaneous nerves is apparent on H&E sections, and it is greatly accentuated in ultrathin sections or electron microscopic examination [139]. Similar vacuoles can be seen in melanocytic nevus cells and perineurial cells [140].

16.11.3 Pathogenesis

Tangier disease is a genetic disorder of deficiency of high-density lipoprotein (HDL) with less than 5 % of normal plasma HDL levels and increased incidence of early cardiovascular disease [141, 142]. The underlying molecular defect in Tangier disease is mutations in the ATP-binding cassette transporter-1 (ABCA1) [143–145]. Over 50 distinct mutations in ABCA1 have been identified in this disease. Most of the mutations lie in the extracellular domains and the nucleotide-binding domains of ABCA1 [146].

ABCA1 plays a key role in the formation of nascent HDL. ABCA1 is a transmembrane protein that functions as a cholesterol transporter, and is involved in the transport of lipids across the plasma membrane [147, 148]. ABCA1 is also a binding partner of apolipoprotein A-I (apoA-I), which is the major protein constituent of HDL. Impaired cholesterol transfer to apoA-I is a major feature in cells from patients with Tangier disease [149, 150]. The interaction of ABCA1 with apoA-I promotes the efflux of phospholipids and cholesterols from the cell, and activates intracellular signal transduction, including the small G proteins Cdc42 and Rac1, and protein kinases PKA, JAK2, and p54JNK. These signaling pathways result in cholesterol transport and lipidation of apoA-I to form HDL [149, 151]. Since the interaction of ABCA1 with apoA-I as well as lipid efflux occurs in the plasma membrane, the inability of mutant ABCA1 to be correctly localized in the plasma membrane is a mechanism leading to defects in the formation of HDL.

16.12 Mucopolysaccharidoses

16.12.1 Clinical Features

The mucopolysaccharidoses (MPS) are an inherited group of metabolic disorders caused by defects in lysosomal hydrolases that are responsible for the degradation of glycosominoglycans [152]. Seven subtypes exist, with a worldwide incidence of approximately 1 in 25,000 individuals. The most common variant is Sanfilippo syndrome (MPS III) [153]. While most babies appear normal at birth, the condition is progressive with affected individuals demonstrating features of the disease in infancy. The most common clinical signs include coarse facies and brawny thickening of the skin with broad nose, macroglossia, short neck, and macrocephaly [153] (Fig. 16.28). Other common manifestations include hypertrichosis, organomegaly, skeletal abnormalities, impaired hearing, and varying levels of mental retardation. Cutaneous features of the disease may include widespread progressive congenital dermal melanocytosis as well as white to skin-colored papules and papulonodules along the back, particularly in types I and II MPS [154]. Disease prognosis varies depending upon the underlying subtype, but many affected individuals experience premature death secondary to complications from systemic involvement [152].

Fig. 16.28 A boy with Sanfilippo syndrome (mucopolysaccharidosis) demonstrates a number of the most common clinical features of mucopolysaccharidosis including macrocephaly, coarse facial features, broad nose, macroglossia, and a short neck

16.12.2 Histology

Ultrastructural studies are required to make a histologic diagnosis of MPS. The likelihood of diagnostic findings on ultrastructural analysis is quite high, and skin biopsy is an effective means for confirming such a diagnosis, while most routine studies fail to demonstrate significant abnormalities [155]. Occasionally, increased mucopolysaccharides can be seen as metachromatic "mucin deposits" within the dermis [156]. Dermal fibroblasts and macrophages demonstrate vacuolar inclusions that are either clear or have a fuzzy appearance [157–160]. These inclusions appear to be membrane bound. Similar observations have been made in keratinocytes, Schwann cells, and smooth muscle cells, as well as worm-like inclusions within mast cells [157]. Other cutaneous findings, such as angiokeratomas and Mongolians spots, are sometimes associated with mucopolysaccharidoses [161–163].

16.12.3 Pathogenesis

The mucopolysaccharidoses are genetic disorders of lysosomal storage diseases with impairment in glycosaminoglycans and mucopolysaccharides catabolism due to deficiency in activity of lysosomal enzymes responsible for the normal degradation of these molecules [152, 164, 165]. As a result, there is accumulation of glycosaminoglycans in the lysosomes in most cells as well as secretion of these polysaccharides in the blood, cerebral spinal fluid, and urine, leading to cellular and tissue damage and multi-organ failure [166–168].

There are seven types of MPS (I, II, III, IV, VI, VII, and IX) based upon the affected enzyme [152, 165]. Mucopolysaccharidosis type I (MPS I) is caused by a lack of a-L-iduronidase (IDUA) that is required for the breakdown of glycosaminoglycans, particularly heparan sulfate and dermatan sulfate. MPS II (also called Hunter syndrome) is an X-linked genetic disorder caused by deficiency in iduronate-2-sulfatase (I2S), resulting in the accumulation of heparan sulfate and dermatan sulfate within the lysosome [164]. MPS III (also called Sanfilippo syndrome) is caused by a lack of enzymes necessary for the degradation of heparan sulfate [169]. MPS IV (Morquio syndrome) is caused by deficiency in N-acetylgalactose-amine-6-sulfate sulfatase (GALNS) and beta-galactosidase (GLB1), which are involved in the catabolism of keratan sulfate and chondroitin sulfate. MPS VI (Maroteaux–Lamy syndrome) is caused by the lack of N-acetylgalactosamine 4-sulfatase (ASB) with accumulation of dermatan sulfate and chondroitin sulfate. MPS VII (Sly syndrome) is caused by β-glucuronidase (GUSB) deficiency, and results in the deposition of chondroitin sulfate, heparan sulfate, and dermatan sulfate in the

cell [170]. MPS IX (Natowicz syndrome) is caused by defects in hyaluronidase [165, 171].

16.13 Mucolipidoses

16.13.1 Clinical Features

The mucolipidoses are a group of metabolic disorders of variable phenotype caused by malfunction of a number of different enzymes responsible for appropriate lysosomal functioning [152]. Presentation and prognosis is dependent upon the affected enzyme. The most severe variant is mucolipidosis type II. Individuals with mucolipidosis type II present as neonates with severely malformed bones, microcephaly and dysmorphic facies, similar to that seen in Hurler syndrome [152]. Additional clinical features include severe neurologic impairment, respiratory difficulty, feeding problems, hernias, hepatosplenomegaly and cardiomyopathy, which portends a worse clinical course. Most patients die from cardiorespiratory complications by 10 years old.

16.13.2 Histology

Skin biopsies are generally helpful in establishing a diagnosis of mucolipidosis and other lysosomal storage disorders [155, 172–176]. Ultrastructural examination is most revealing, demonstrating lamellar and pseudomyelinitic structures in a variety of cell types [177]. Epithelial cells and endothelial cells can show membrane lamellar inclusions [178]. Vacuolated fibroblasts and macrophages may be seen in some cases [179]. Other cutaneous lesions, such as Mongolian spots, are sometimes seen in patients with mucolipidosis [180].

16.13.3 Pathogenesis

There are multiple subtypes of mucolipidoses, in which distinct genes are affected. Mucolipidosis type I is caused by deficiency in lysosomal hydrolase neuraminidase (NEU1) [152, 181, 182]. Mucolipidoses types II and III are caused by loss-of-function mutations in GNPTAB gene which encodes for the α and β subunits of the multimeric enzyme N-acetylglucosaminyl-1-phosphotransferase [183, 184]. GNPTAB enzyme catalyzes the addition of mannose-6-phosphate to lysosomal precursor proteins, and it is important for their proper trafficking from the endoplasmic reticulum to the lysosomes [185]. Interactions of mannose-6-phosphate residues on proteins with receptors on the lysosomal membrane trigger endocytosis of proteins into the lysosome. Thus, loss of GNPTAB results in defects in the trafficking of lysosomal proteins. Mutations in GNPTG gene that encodes for the γ subunit of N-acetylglucosaminyl-1-phosphotransferase are associated with mucolipidosis type III [186]. Mucolipidosis type IV is caused by mutations in TRPML1 (transient receptor potential mucolipin 1, also known as mucolipin 1 (MCOLN1)) [187–189]. TRPML1 is a lysosomal calcium efflux channel that can affect autophagy, and its activity is regulated by the mammalian target of rapamycin (mTOR), which is a nutrient-sensitive protein kinase that negatively regulates autophagy [190].

16.14 Amyloidosis

16.14.1 Clinical Features

Localized cutaneous amyloidosis typically begins in adolescence with most pediatric cases categorized as macular, lichen, or biphasic with features of both macular and lichenoid lesions [191]. Disease usually affects individuals of Asian, Middle Eastern, and Latin American ancestry. Reported systemic associations include atopy, progressive systemic sclerosis, primary biliary cirrhosis, systemic lupus erythematosus, pachyonychia, and multiple endocrine neoplasia type 2.

Lichen amyloidosis is characterized by the coalescence of 1–10 mm skin-colored to gray or yellow, brown papules on the extensor aspects of the extremities. Some children with localized cutaneous amyloid deposits may have multiple endocrine neoplasia (MEN) type 2 syndrome, including medullary thyroid carcinoma. Lichen amyloidosis is common in these cases [199–201]. Macular amyloidosis presents as brown to gray hyperpigmented, lichenified macules with a rippled surface [191] (Fig. 16.29). Pruritus is frequently the presenting symptom in both variants. Lesions typically are persistent and progress over time. Continued trauma or rubbing may exacerbate the condition and should be discouraged.

Fig. 16.29 Cutaneous macular amyloidosis presents as lichenified brown macules with subtle rippling of the skin on the scrotum of a boy (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

16.14.2 Histology

Cutaneous amyloidosis has several manifestations in children. *Macular amyloidosis* appears as small, amorphous eosinophilic deposits in the papillary dermis, often with overlying epidermal hyperpigmentation. Scattered melanophages may be seen in the papillary dermis, and a mild lymphocytic infiltrate is present in some cases [192]. This type of amyloidosis can be seen as part of X-linked pigmentary dermatosis or familial cutaneous amyloidosis [193, 194]. Some published series describe patients with this syndrome and lichen amyloidosis. The histologic findings seen in macular amyloidosis has also been described in one form of the pachyonychia congenita syndrome [195].

Lichen amyloidosis has a similar histologic appearance to macular amyloidosis, but the epidermis demonstrates lichen simplex chronicus-like changes (Fig. 16.30). Hyperkeratosis sits atop an acanthotic epidermis with hypergranulosis and elongation of the rete ridges. Eosinophilic deposits are present within the elongated papillary dermal tips (Fig. 16.31). Rare dying keratinocytes may be seen. Melanophages are present in the papillary dermis along with a scant lymphocytic infiltrate. A familial lichen amyloidosis syndrome is also described [196, 197].

Regardless of the epidermal manifestations, the dermal deposits are accentuated with crystal violet stains and polarize with Congo red staining. Anti-keratin antibodies also strongly label these eosinophilic deposits. Of note, patients with these forms of amyloidosis do not have systemic gammopathies.

Nodular amyloidosis is rare in children as it is associated with plasma cell dyscrasias, which are not encountered in children with any significant frequency [198]. Nodular amyloidosis shows large acellular sheets of eosinophilic material in aggregates within the dermis (Fig. 16.32).

The differential diagnosis of amyloidosis includes juvenile colloid milium. The dermal material in juvenile colloid milium is believed to derive from degenerating keratinocytes [202]. It is possible that this entity is identical in its pathogenesis to lichen and macular amyloidosis, in which the amorphous eosinophilic amyloid-like material in the dermis comprises keratin breakdown products [192, 203, 204]. Lichen simplex chronicus shows identical epidermal changes to those seen in lichen amyloidosis. Close examination of the papillary dermis is essential in order to distinguish lichen simplex chronicus from lichen amyloidosis.

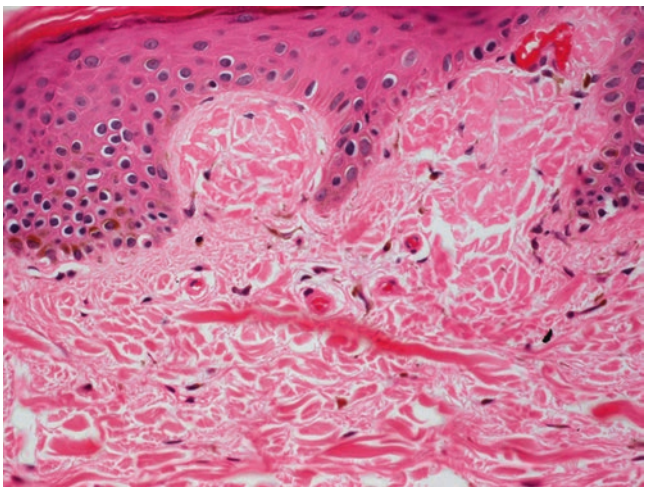

Fig. 16.31 Papillary dermal tips are expanded and filled with eosinophilic bodies (degenerating keratinocytes) in lichen amyloidosis

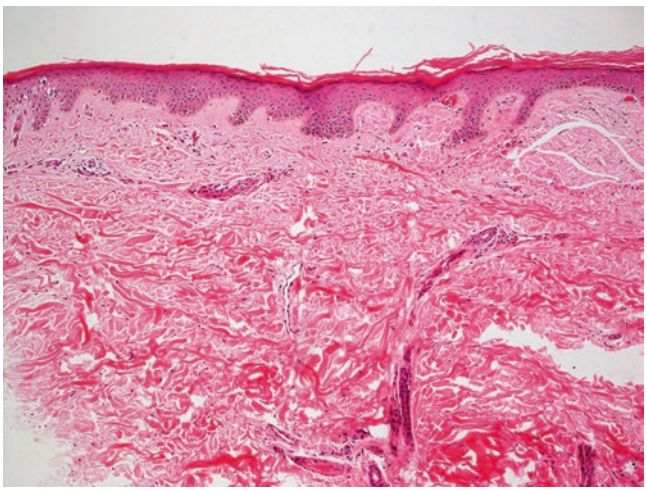

Fig. 16.30 The stratum corneum demonstrates compact orthokeratotic hyperkeratosis and the epidermis is mildly acanthotic in lichen amyloidosis

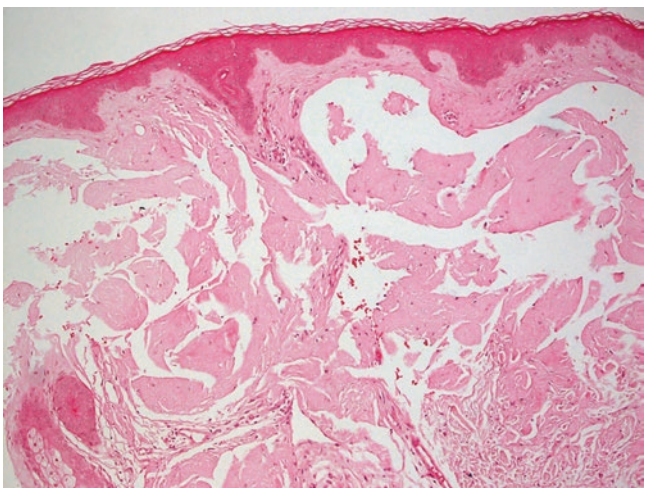

Fig. 16.32 Nodular amyloidosis demonstrates large acellular sheets of eosinophilic material in aggregates within the dermis. A characteristic "cracking" pattern is seen within the amyloid deposition

16.14.3 Pathogenesis

Amyloidosis is a disease of protein misfolding. It is caused by aggregation of insoluble deposits of misfolded proteins in β-pleated sheets, and the deposition of these abnormal fibrils lead to toxic effects and progressive organ dysfunction [205, 206]. Amyloid protein deposits are made up of abnormally folded serum amyloid, glycosaminoglycans and fibrillar proteins, and when bound to Congo red dye, give rise to the characteristic red-green birefringence when viewed by polarized light under the microscope [207].

There are over two dozen subtypes of amyloid deposits depending on the type of fibrillar component. The most common types of fibrillar proteins are amyloid light chain (AL) and serum amyloid A (AA) [208]. AL fibrillar protein is associated with primary amyloidosis. AL is produced by the abnormal breakdown of immunoglobulin light chains produced in plasma cell dyscrasia [209]. AA fibrillar protein is associated with secondary amyloidosis. AA is produced from an acute phase reactant made by the liver, and secreted in large amounts into the circulation in conditions of chronic inflammation [208, 210, 211]. Systemic infections and inflammatory disorders, such as rheumatoid arthritis and chronic bronchitis, cause elevation of AA. A subset of patients with inflammatory conditions and abnormally folded AA deposits develop systemic amyloidosis. Amyloidosis can also be hereditary, as in transthyretin amyloidosis. In this autosomal dominant inherited disease, the fibrillar component is derived from transthyretin, which is a plasma transport protein for thyroxine and vitamin A [212].

Prolonged sun exposure is important in the pathogenesis of colloid milium. Juvenile colloid milium is a rare familial form of the disease with onset before puberty [202, 213]. Hereditary predisposition to damage of basal keratinocytes by prolonged sun exposure is a contributing factor to the development of colloid milium. Ultrastructurally, the colloid material in colloid milium is a product of degenerating keratinocytes [202, 213].

16.15 Lipoid Proteinosis

16.15.1 Clinical Features

Lipoid proteinosis is a rare autosomal recessive genodermatosis with variable phenotypic expression, affecting males and females with equal frequency [214]. The prevalence appears to be highest in Europe and South Africa, most notably in individuals of Dutch or German heritage, although case reports exist in various ethnicities around the world [214].

Patients most frequently present with voice hoarseness, even as newborns as demonstrated by a weak cry [214]. Cutaneous manifestations typically appear within the first 2 years of life and consist of pustules that evolve into "ice-pick" acneiform scars or shiny, yellow papules, nodules and plaques. Discrete skin lesions may coalesce rendering diffuse, coarse thickening of the skin. Lesions most often occur on the face and extremities. Beaded papules along the eyelid margins (moniliform blepharosis) are pathognomonic, and occur in about two thirds of reported cases [214]. Patients may have xerostomia, dental anomalies, corneal opacities, glaucoma, and central nervous system disease with epilepsy, memory loss, and schizophrenic behaviors. Other associated symptoms include respiratory impairment, dysphagia, and woody induration of the tongue with restricted movement and subsequent speech impairment. The life expectancy of individuals with lipoid proteinosis is normal, even though generalized deposition of the PAS-positive hyaline material is noted in almost all viscera.

16.15.2 Histology

Histologic changes include the presence of hyaline-like deposits along the dermal-epidermal junction and surrounding blood vessels within the dermis (Fig. 16.33). The material is homogeneous and acellular (Fig. 16.34). It is PAS positive and diastase resistant [215]. Similar hyaline deposits are also seen around eccrine ducts [216] (Fig. 16.35).

An early stage with formation of vesicles and ulceration has been described in lipoid proteinosis [217]. It is difficult to establish the diagnosis, however, in the absence of the characteristic hyaline deposits [218]. On ultrastructural analysis,

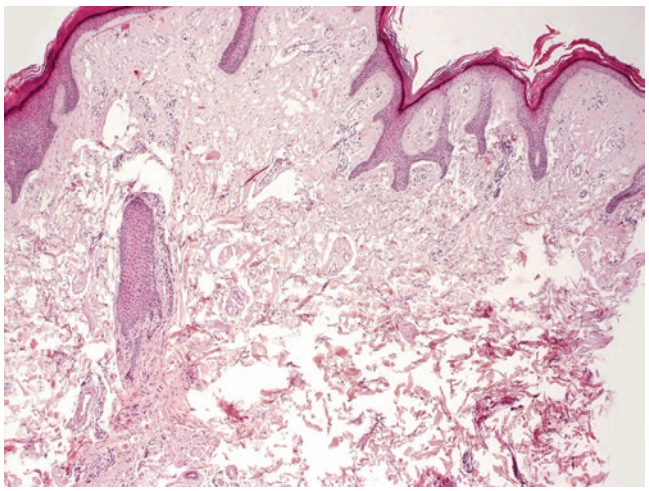

Fig. 16.33 There is marked expansion of the dermis with amorphous eosinophilic material in lipoid proteinosis. Similar material is seen surrounding eccrine structures and dermal blood vessels

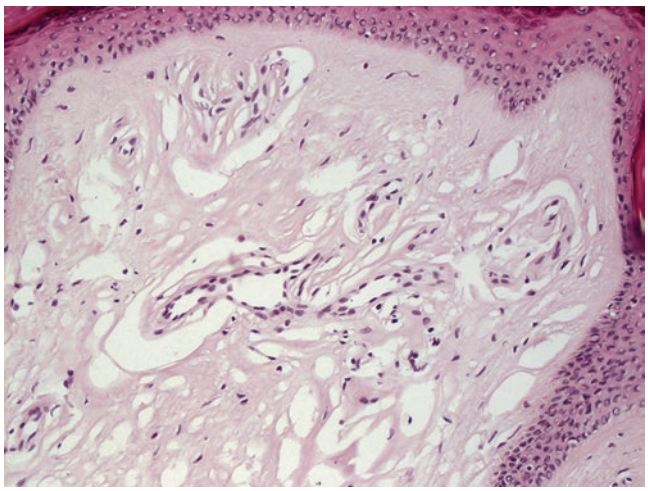

Fig. 16.34 Amorphous and acellular material in the papillary dermis results in vascular ectasia in lipoid proteinosis

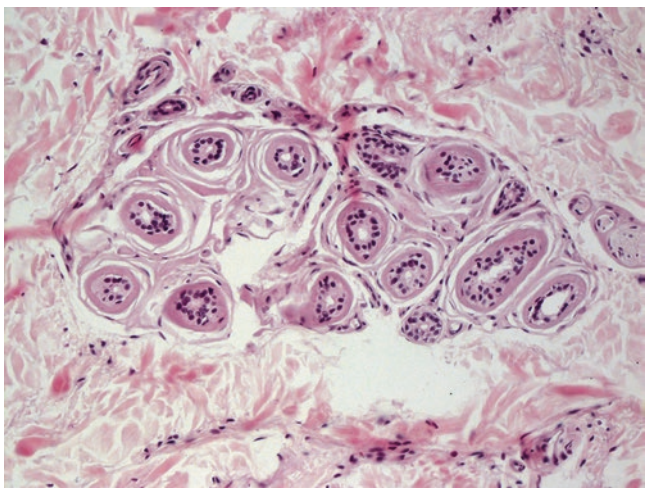

Fig. 16.35 Thickened rims of eosinophilic material surrounding eccrine structures are present in lipoid proteinosis

there is marked thickening of the basal lamina surrounding blood vessels [215, 219]. The basement membrane zone underneath the epidermis is also markedly thickened [220].

The differential diagnosis includes amyloidosis and porphyrias. Amyloid deposits are more globular and less linear along the dermal-epidermal junction, and the types of cutaneous amyloidosis that occur in children do not form concentric deposits around blood vessels. Porphyrias demonstrate the perivascular eosinophilic deposits, but do not show the thickening and deposition at the dermal-epidermal junction as seen in lipoid proteinosis.

16.15.3 Pathogenesis

Lipoid proteinosis is a rare autosomal recessive disorder characterized by the deposition of hyaline materials in various organs in the body [221, 222]. Studies have pointed to loss-of-function mutations in the extracellular matrix protein 1 (ECM1) gene as the causative gene in lipoid proteinosis [223]. ECM1 is a glycoprotein of unknown function that is expressed in the skin and other organs. Mutations in ECM1 result in the deposition of hyaline material in the dermis with thickening of the skin and the basement membrane around dermal blood vessels and adnexal structures [223]. There are also changes in the synthesis and metabolism of collagen with decrease in dermal collagen types I and II, and increase in basement membrane collagen types IV and V that tend to deposit in the skin and other organs in this disorder [224].

16.16 Infantile Systemic Hyalinosis

16.16.1 Clinical Features

Infantile systemic hyalinosis is an uncommon autosomal recessive condition, most frequently seen in individuals of Middle Eastern ancestry [225]. Signs and symptoms of the disorder present by 6 months of life with some clinical features noted at birth. Mucocutaneous manifestations of disease include small, shiny facial papules, gingival hyperplasia, skin induration, erythematous or dark discoloration over bony prominences, and perianal nodules [225]. Additional clinical features include joint contractures, osteopenia, persistent diarrhea, malnutrition, failure to thrive, recurrent infections, and death within the first 2 years of life secondary to these systemic insults.

16.16.2 Histology

Increased amorphous hyaline material contributes to a thickened dermis and subcutis in infantile systemic hyalinosis. PAS stains highlight increased granular material surrounding collagen bundles. Increased fibroblasts are present in the dermis [226]. Ultrastructural changes include the presence of fibrillogranular material within the dermis. There are also structural changes in collagen that are most pronounced around dermal blood vessels [227, 228].

16.16.3 Pathogenesis

Infantile systemic hyalinosis is a rare autosomal recessive disorder caused by cutaneous accumulation of hyalinized materials, comprised of types I and VI collagen and glycosaminoglycans [229]. Abnormalities in the extracellular matrix (ECM) with altered expression of ECM molecules, such as matrix metalloproteinases and proteoglycans, are present in lesional skin [228].

Infantile systemic hyalinosis is caused by mutations in the capillary morphogenesis protein-2 gene (CMG2, also called anthrax toxin receptor-2 (ANTXR2)) [230–232]. CMG2 is a

transmembrane protein, and plays an important role in the formation of capillaries. It binds to type IV collagen and laminins, and contributes to the formation of the basement membrane. About 25 different mutations in CMG2 gene have been reported, consisting of missense, nonsense, and splice-site mutations [233, 234].

16.17 Eruptive Xanthoma

16.17.1 Clinical Features

Eruptive xanthomas are seen in the setting of hypertriglyceridemia, typically with triglyceride levels greater than 2000 mg/dL [235, 236]. They occur rarely in children, although they may present in a variety of systemic diseases, including genetic or secondary hyperlipidemias, or as a result of medication use [236].

Eruptive xanthomas are characterized by 1–4 mm yellow papules with an erythematous border that develop rapidly in crops over pressure points and extensor surfaces of the arms, legs, and buttocks (Fig. 16.36) [235]. With resolution or control of underlying hypertriglyceridemia, eruptive xanthomas usually resolve within several weeks.

16.17.2 Histology

Biopsy findings demonstrate an unremarkable or flattened epidermis. The superficial reticular dermis contains variable numbers of lipid-laden macrophages with foamy cytoplasm (Figs. 16.37 and 16.38). Touton-type giant cells and extracellular lipid deposits can also be seen. These deposits contain polarizable, needle-like crystals [237]. An admixture of inflammatory cells including eosinophils and neutrophils are present [238]. A perivascular inflammatory infiltrate is also seen [239]. When the infiltrate is less dense, the lesion may resemble interstitial granuloma annulare [237, 239].

Papular xanthoma may demonstrate similar histologic features, but patients with papular xanthomas have normal lipid levels [240]. Rare cases of eruptive xanthomas demonstrating identical histologic features have been seen in normolipemic patients [241]. Other xanthomatous processes can be differentiated based upon the clinical presentation and the relative paucity of the inflammatory infiltrate when compared with eruptive xanthomas. Granuloma annulare is best differentiated by the presence of mucin within the center of the granulomatous foci.

Fig. 16.36 Eruptive xanthoma presents as yellowish brown papules and plaques scattered diffusely on the extremities and torso of an infant boy with hypercholesterolemia and triglyceridemia following liver transplantation for hepatoblastoma

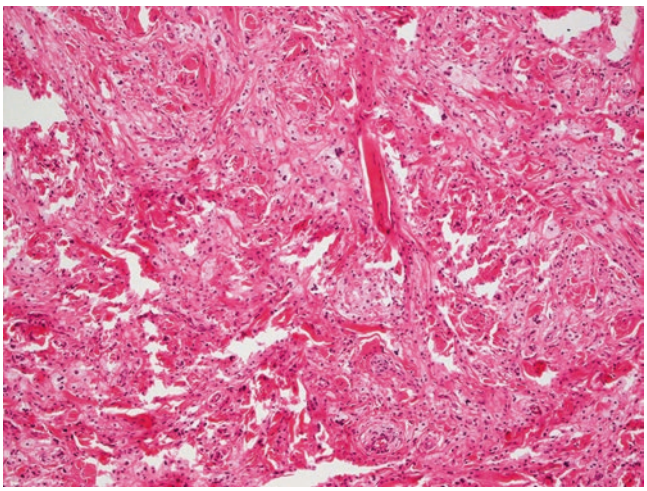

Fig. 16.37 Abundant lipid-laden histiocytes are present diffusely throughout the dermis in eruptive xanthoma

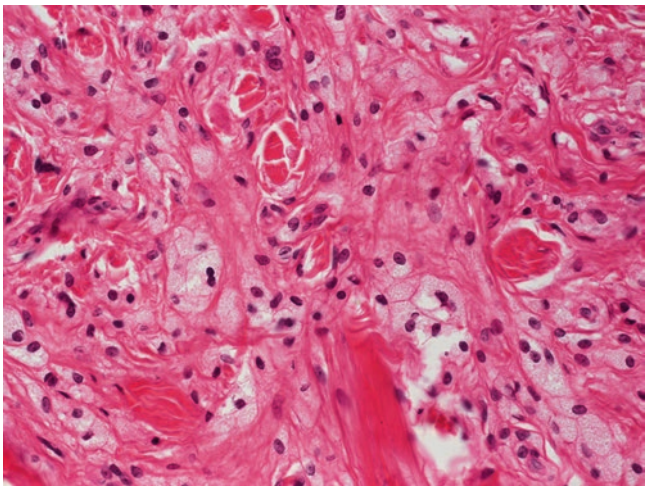

Fig. 16.38 Microvesiculation is seen within the lipid-laden histiocytes in eruptive xanthoma

16.17.3 Pathogenesis

Eruptive xanthoma is caused by primary hypertriglyceridemia (with triglyceride levels greater than 2000 mg/dL) and uncontrolled diabetes mellitus [242, 243]. Conditions that cause secondary hypertriglyceridemia, such as hypothyroidism

and end-stage renal disease, can also lead to the development of eruptive xanthoma.

16.18 Tuberous Xanthoma

16.18.1 Clinical Features

Tuberous xanthomas occur as a result of the abnormal metabolism of cholesterol or triglycerides, and can be seen in patients with atherosclerotic vascular disease [235]. They initially present as soft yellow papules that evolve into reddish yellow nodules at the extensor surfaces of the arms, legs and buttocks [235]. Over time, they may coalesce into firm fibrotic plaques (Fig. 16.39) [235]. Tuberous xanthomas tend to be refractory to treatment, and may not resolve completely even after resolution of the underlying metabolic dysfunction [235].

16.18.2 Histology

Histologic findings are those of a dense dermal infiltrate of foamy histiocytes filling the dermis and causing a flattening of the overlying epidermis (Fig. 16.40). Abundant mononuclear histiocytes filled with foamy cytoplasm are seen along with Touton-type giant cells with cytoplasmic lipid [244] (Fig. 16.41). Early lesions have dendritic-shaped fibrohistiocytic cells and histiocytes without significant amounts of cytoplasmic lipid [245]. A scant lymphohistiocytic infiltrate is present in some cases. A perivascular distribution to the lipid-laden cells is seen in some cases, although in larger lesions, the infiltrate becomes nodular as it fills the dermis.

Fig. 16.39 Tuberous xanthoma presents as a large, bulky, yellowish nodule on the extensor surface of the elbow

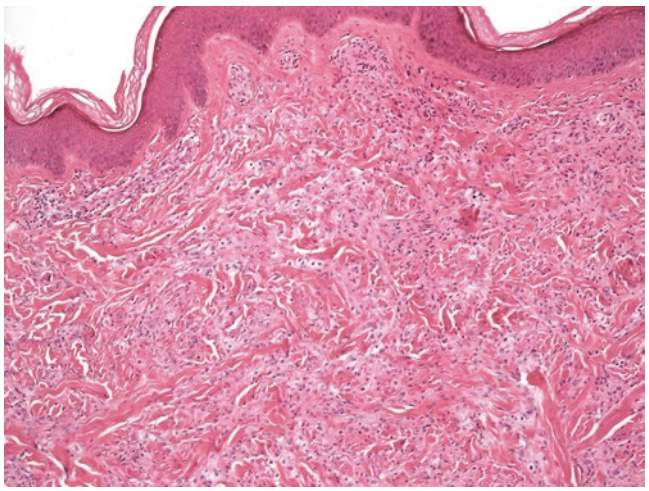

Fig. 16.40 Sheets of histiocytes containing lipid within their cytoplasm fill the dermis in tuberous xanthoma

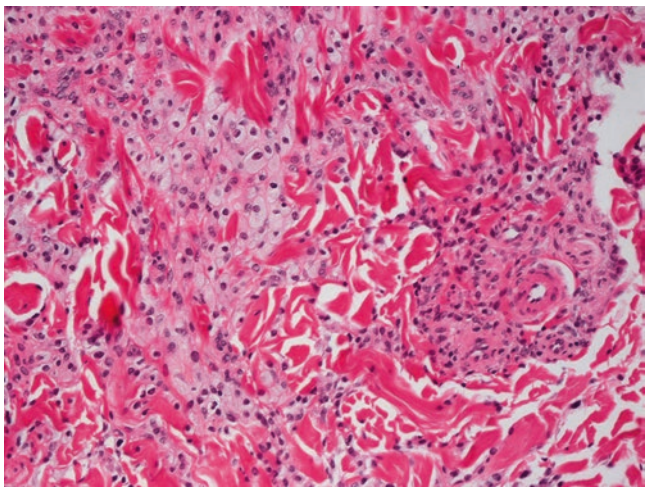

Fig. 16.41 Microvesiculation characteristic of lipids fills histiocyte cytoplasm in tuberous xanthoma

Xanthelasma is differentiated from tuberous xanthoma based upon the anatomic site. Eruptive xanthomas tend to have a denser inflammatory infiltrate, and are easily distinguished based upon the clinical presentation. Lipidized fibrous histiocytomas can be difficult to distinguish based solely upon histologic features. A more heterogeneous cell population is seen in fibrous histiocytomas, but in early tuberous xanthomas, this distinction might not be possible. A perivascular distribution seen in some tuberous xanthomas might help to distinguish these lesions from the nodular growth pattern of a xanthogranuloma, along with the clinical history.

16.18.3 Pathogenesis

Tuberous xanthoma is linked with lipid disorders, since it occurs in the setting of familial heterozygous hypercholesterolemia (type II a) due to mutations in the low-density lipoprotein (LDL) receptor [246].

16.19 Planar Xanthoma

16.19.1 Clinical Features

Planar xanthomas are categorized clinically based on lesion distribution with the most common variant being xanthelasma or xanthelasma palpebrarum. Approximately half of xanthelasma cases have no underlying hypercholesterolemia, although there is a greater likelihood for lipid level abnormality in affected individuals under 40 years old [235].

Xanthelasma presents as yellow macules or soft, slightly elevated papules and thin plaques on the eyelids [235]. Xanthoma striatum palmare or xanthochromia striatum palmaris are yellow-orange linear plaques and patches along the creases of the palms and fingers in the setting of elevated cholesterol and triglycerides. The rarest form of planar xanthoma is planar xanthomatosis with generalized yellow-orange papules and plaques on the face, neck, upper trunk, and arms in conditions of paraproteinemia, with or without concomitant hyperlipidemia [235]. The skin changes of planar xanthomas tend to be refractory to treatment, but they may improve with correction of the associated dyslipidemia or management of the underlying systemic disease.

16.19.2 Histology

Histologic features of planar xanthomas are similar to those described for other types of xanthomas. The epidermis is normal or somewhat flattened by a dermal infiltrate of lipid-laden histiocytes. Touton giant cells are present in well-developed lesions. However, in early lesions, histiocytes without significant cytoplasmic lipids are seen along with scattered elongated fibrohistiocytic cells [247]. Crystalloid structures may be present in the lipid-rich cytoplasm [248]. In some cases, there is a perivascular distribution of the histiocytes. Scattered lymphocytes are seen in the dermis [249]. Necrobiotic collagen and cholesterol clefts are present in rare cases, leading to a resemblance with necrobiotic xanthogranuloma and suggesting the possibility of a biological relationship between these two entities when associated with paraproteinemias [250].

16.19.3 Pathogenesis

Planar xanthoma is associated with familial ApoA-I deficiency syndrome [251]. It can also be a manifestation of an underlying monoclonal gammopathy, such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, and chronic myelomonocytic leukemia [249, 252]. It has been postulated that monoclonal immunoglobulins bind to low density lipoproteins, and form lipid complexes in the skin [253].

16.20 Verruciform Xanthoma

16.20.1 Clinical Features

Verruciform xanthoma is a benign mucocutaneous lesion not associated with an underlying hyperlipidemia [254, 255]. It has been described in the setting of various conditions, including lymphedema, recessive dystrophic epidermolysis bullosa, graft versus host disease, epidermal nevi, and CHILD syndrome (congenital hemidysplasia, ichthyosiform nevus, and limb defects) [254]. Verruciform xanthoma is most commonly described as a yellowish to skin colored hyperkeratotic plaque on the oral mucosa, and anogenital and periorificial skin [256].

16.20.2 Histology

Histologic findings include an acanthotic epidermis with psoriasiform elongated rete ridges, and a stratum corneum that is markedly orthokeratotic or parakeratotic when occurring on a mucosal surface [257, 258] (Fig. 16.42). The epidermis can be papillomatous or flat [259, 260]. The elongated papillary dermal tips are distended and filled by histiocytes with abundant foamy, lipid-rich cytoplasm (Fig. 16.43). These cells contain scalloped nuclei. In some cases, an intense neutrophilic infiltrate is present, and extends into the overlying epidermis [261]. A plasmacellular infiltrate has been described in some cases. A lichenoid inflammatory infiltrate may be present lateral to the lesion [258], and the papillary dermis is highly vascular [257, 262].

As these lesions frequently arise in conjunction with epidermal nevi, changes of this hamartomatous process are often part of the histologic pattern [263, 264]. Verruciform xanthomas can also arise in association with many other inflammatory conditions or even as isolated lesions [265, 266].

The differential diagnosis includes entities that cause pseudoepitheliomatous hyperplasia, including granular cell tumors and tumors with acanthotic epidermis lacking in significant cytologic atypia, such as verrucous carcinoma [267]. Granular cell tumors comprise cells with granular

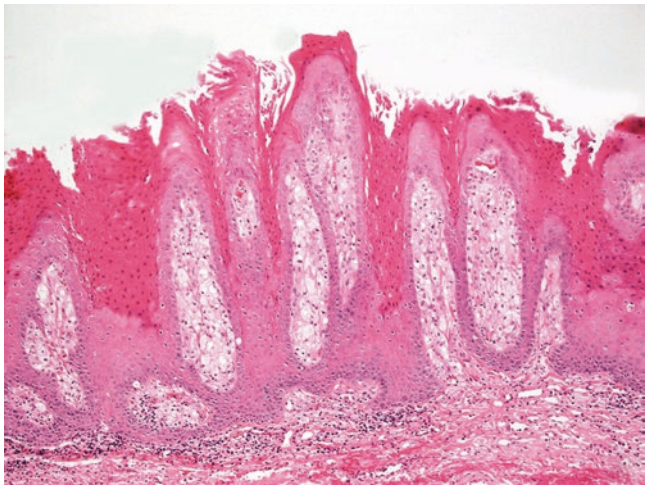

Fig. 16.42 A papillomatous epidermis overlies dermal papillae that are distended by large cells with abundant clear cytoplasm in verruciform xanthoma

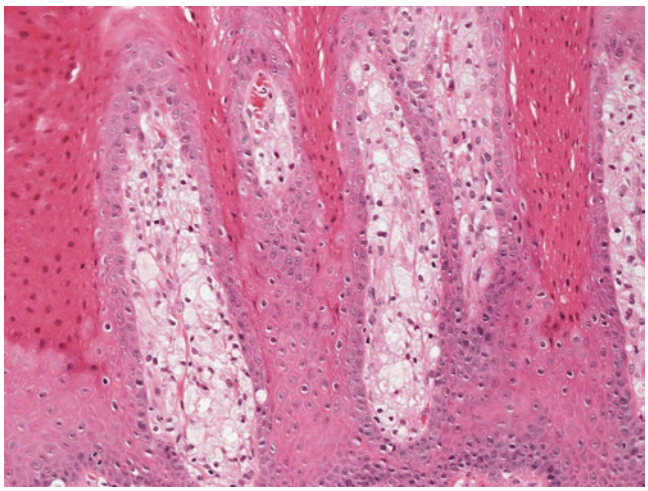

Fig. 16.43 Verruciform xanthoma is characterized by dermal papillae filled with lipid-laden histiocytes

eosinophilic cytoplasm as opposed to cells with foamy cytoplasm as seen in verruciform xanthoma. Similarly, verrucous carcinoma does not have an underlying dermal infiltrate of lipid-laden cells as seen in verruciform xanthoma [268].

16.20.3 Pathogenesis

It has been proposed that verruciform xanthoma is linked to chronic inflammation that results in keratinocyte proliferation and degeneration, and the release of cellular lipids that are taken up by dermal macrophages [265, 269]. Impaired lymphatic function and chronic lymphedema are also associated with the development of verruciform xanthoma [270, 271]. Foamy macrophages in verruciform xanthoma express macrophage scavenger receptor-1, monocyte chemoattractant protein-1, CD68, and oxidized low density lipoprotein (LDL) [264, 272, 273]. There has been no evidence of human papilloma virus in verruciform xanthoma [274, 275].

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Disorders of Pigmentation

17

17.1 Vitiligo

17.1.1 Clinical Features

The worldwide prevalence of vitiligo is between 0.5 and 2 % with a high prevalence rate reported in Gujarat, India at approximately 9% [1]. Disease prevalence in the United States and Europe is estimated at 1 % with approximately half of cases beginning in childhood [1]. The incidence appears to be equal between males and females and affects all skin types. Twenty percent of individuals with vitiligo have a positive family history of the disease [2].

Vitiligo is characterized by white, depigmented macules and patches often occurring along sites of pressure or trauma. Mottled pigmentation and hypopigmentation can be seen at the periphery of affected areas along with islands of follicular centric and normal coloring, suggesting repigmentation (Fig. 17.1). Depigmentation is highlighted by a Wood's lamp fluorescence. Vitiliginous patches are usually asymptomatic, but pruritus has been reported in some cases [2]. Erythema is not frequently seen.

Vitiligo can be subcategorized as localized, segmental, generalized, and universal. Segmental vitiligo, which is a variant of localized disease, often begins in childhood, most commonly along a trigeminal dermatome with associated poliosis [2]. Skin changes are typically symmetric and progressive. Universal vitiligo is a variant that affects > 80 % of body surface area, and portends the worst prognosis [2]. Segmental vitiligo, on the other hand, is stable over time and usually responds well to therapeutic interventions.

17.1.2 Histology

Vitiligo in children demonstrates similar histologic changes to those described in adults [3]. The histologic changes are quite subtle. The epidermis appears essentially unremarkable, although on closer examination, a loss of basilar melanocytes may be apparent (Figs. 17.2 and 17.3). The dermis is characterized by a superficial perivascular infiltrate of lymphocytes with scattered cells extending into the lower portions of the epidermis. Pigment incontinence into the dermis is either absent or minimal. Older lesions lack the dermal inflammatory infiltrate. In some cases, pigment loss may be peri-follicular in distribution, which is a pattern that is reflected with regional loss of melanocytes on histologic examination [4].

The histologic differential diagnosis of vitiligo includes normal skin. In many cases, it is difficult if not impossible to detect the loss of basilar melanocytes on routine H&E stains. In these situations, S100 or Melan-A stain for melanocytes may be helpful in detecting the loss of melanocytes, especially if adjacent uninvolved skin is present within the biopsy for comparison (Fig. 17.4). Other interface dermatoses can also enter the differential diagnosis, but they are readily distinguished based upon the clinical history and other characteristic histologic changes that are not seen in vitiligo.

Another differential diagnosis is post-inflammatory hypopigmentation or depigmentation. Fontana-Masson stain for melanin pigment is helpful in making this distinction (Fig. 17.5). In vitiligo, there is significant reduction in melanin pigment, whereas in post-inflammatory pigmentary alterations, melanin is present in macrophages or free in the papillary dermis. Nevus depigmentosus is also a differential consideration, but it has residual melanocytes, albeit diminished in number, while in established vitiligo, melanocytes are not present in lesional skin.

17.1.3 Pathogenesis

Vitiligo is an acquired pigmentary disorder. Most authorities now support a "convergence theory," highlighting a multifactorial etiology with chronic autoimmunity serving as a source of melanocyte destruction and subsequent functional impairment [2]. Research on vitiligo has been focused on understanding the initial triggering mechanism, immune propagation, and cytotoxicity against dermal

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Fig. 17.1 Widespread depigmented macules and patches with islands of folliculocentric normopigmentation are seen in a patient with vitiligo

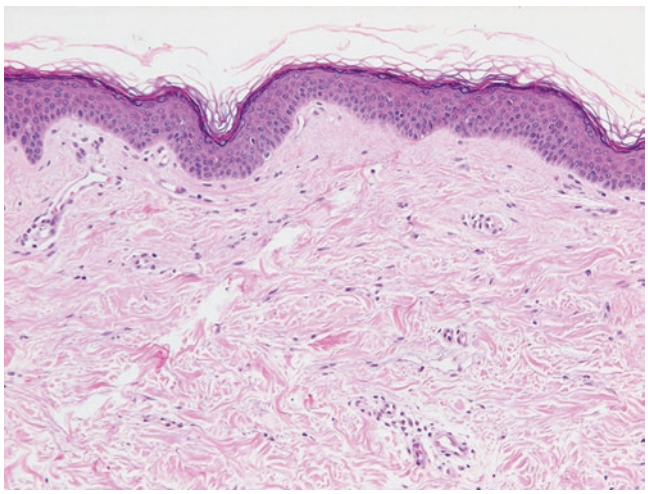

Fig. 17.2 The epidermis is largely devoid of melanocytes and melanin pigment in the basal layer in vitiligo

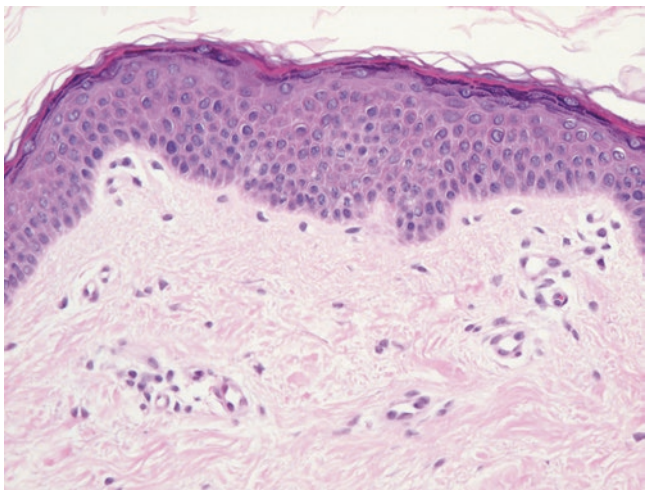

Fig. 17.3 There is lack of melanocytes along long stretches of involved epidermis in vitiligo. There is no pigment incontinence within the dermis

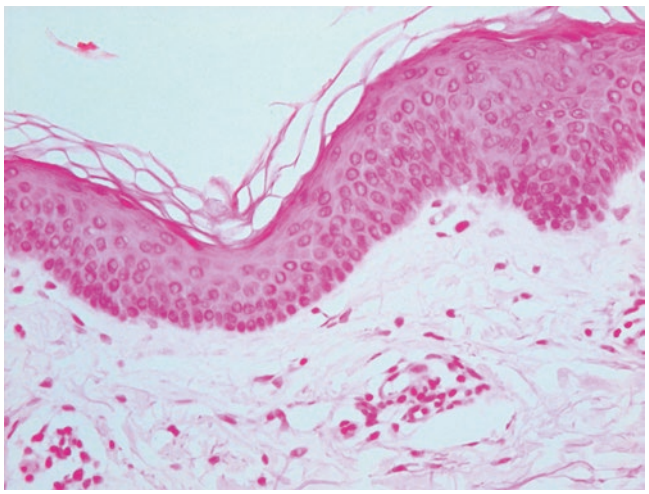

Fig. 17.4 Melan-A stain highlights the total loss of melanocytes in lesional vitiligo skin

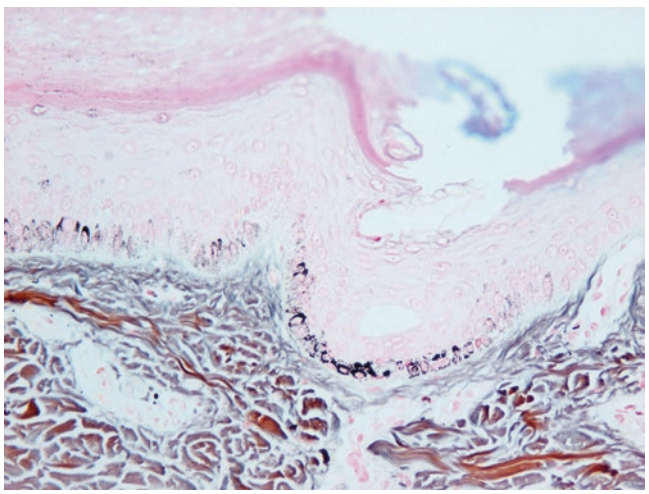

Fig. 17.5 Fontana-Masson stain demonstrates areas of reduction in epidermal melanin pigment in vitiligo

melanocytes. Multiple genetic loci have been linked with vitiligo susceptibility. Many of the genes present near or in these loci encode immunoregulatory or melanocyte proteins that likely serve as autoantigens for melanocyte-specific immune response [5]. Genome-wide association studies (GWAS) identified multiple genetic risk factors for vitiligo, including genes in innate and adaptive immunity. Immune response genes implicated in vitiligo include IFIH1 and NLRP1 (genes that activate innate immune responses) and TICAM1 (an adaptor protein in toll-like receptor signaling) [6, 7]. Adaptive immune response genes implicated in vitiligo include class I and class II HLA molecules (T cell antigen recognition), PTPN22 (T cell signaling), CD80 (T cell activation), IL2Ra (T cell activation/regulation), GZMB (T cell cytotoxicity), FoxP3, and BACH2 (Treg development and function) [8]. Together,

these genes constitute an immunoregulatory network that may mediate vitiligo susceptibility.

Numerous studies have implicated the role of antigen-specific CD8+ T lymphocytes in the immune-mediated destruction of melanocytes in vitiligo. Lesional skin from patients with vitiligo contains an infiltration of CD8+ T lymphocytes present adjacent to dying melanocytes in the epidermis [9]. Interestingly, the frequency of CD8+ T lymphocytes that are capable of destroying melanocytes, and the number of these cells in the blood of vitiligo patients correlate with disease severity [10, 11]. CD8+ T lymphocytes from vitiligo patients are capable of inducing melanocyte apoptosis, indicating the important role of CD8+ T cells in the pathogenesis of vitiligo [12]. Several candidate antigenic proteins in vitiligo include gp100, Mart-1, tyrosinase, and tyrosinase-related proteins 1 and 2 [13–15].

Cellular stress in melanocytes is important in disease pathogenesis. Melanocytes from vitiligo patients are intrinsically abnormal since they are more sensitive to exogenous stressors [16, 17]. They are susceptible to oxidative stress as evident by dilated endoplasmic reticulum and elevated levels of oxidative byproducts [18]. Exogenous stressors, such as monobenzone and other phenols commonly found in commercial products (e.g., rubber, leather, and cosmetic dyes), are known to both induce and exacerbate vitiligo [19, 20]. Reactive oxygen species (ROS) and heat-shock proteins generated by melanocytes in response to stress can produce damage-associated molecular patterns (DAMPs) that activate innate immune response to induce inflammation. Transcriptome analysis of skin from vitiligo patients reveals an innate immune signature particularly that of natural killer (NK) cells, and lesional skin in these patients has more NK cells than skin from healthy individuals [21].

In light of the key role of the immune system in melanocyte destruction in this disorder, combined therapeutic approaches that target both immunosuppressive and immunoregulatory responses in order to inhibit melanocyte destruction, while including regenerative approaches to promote melanocyte repopulation of depigmented regions would be an important therapeutic avenue to explore [5, 7].

17.2 Piebaldism

17.2.1 Clinical Features

Poliosis at the frontal scalp ("white forelock") is a hallmark of piebaldism and is seen in 80–90 % of reported cases. Additionally, hyperpigmented macules at the periphery of affected areas as well as central islands of hyperpigmentation may be seen, thus distinguishing it from other achromic skin conditions [22, 23]. The disorder has a benign course, although treatment of leukoderma may be difficult.

17.2.2 Histology

Piebaldism is a clinical diagnosis, and does not ordinarily require biopsy for diagnosis. The histologic findings are subtle, and include changes in melanocytes that are not readily detected on routine histologic sections. Electron microscopy demonstrates areas of nonfunctional melanocytes, and areas of melanocytes that synthesize abnormal melanosomes [24]. In depigmented areas, epidermal melanocytes are either absent or only minimally present. There are increased numbers of both Langerhans cells and mast cells within the epidermis [25].

17.2.3 Pathogenesis

Piebaldism is an autosomal dominant disorder, and has been linked to inactivating mutations or deletions of c-Kit gene or SLUG gene [26–28]. Loss-of-function mutations of c-Kit or SLUG result in impaired melanoblast development and decreased melanogenesis. The severity of piebaldism phenotype reflects the type of c-Kit mutation. Missense mutations in the tyrosine kinase catalytic domains of c-Kit result in impaired signal transduction activity, and cause a more severe phenotype [27]. On the other hand, missense mutations in the c-Kit ligand-binding domain result in a milder form of piebaldism. SLUG is a zinc-finger transcriptional factor [29]. It is important for melanoblast migration and survival. Some patients with piebaldism were found to have heterozygous deletions of SLUG coding region [26].

17.3 Idiopathic Guttate Hypomelanosis

17.3.1 Clinical Features

Idiopathic guttate hypomelanosis is not commonly seen in children, although cases in individuals as young as 3 years old have been reported [30]. The condition frequently occurs symmetrically on sun-exposed areas of the distal arms and legs. It is characterized by 2–5 mm "porcelain-white" hypopigmented macules [30]. Younger patients have a higher frequency of facial lesions. Skin changes tend to persist once present.

17.3.2 Histology

Biopsies from hypopigmented lesions demonstrate hyperkeratosis overlying an atrophic epidermis in a few cases. Flattened rete ridges are also seen in some cases. More commonly, basal keratinocytes from affected areas of skin demonstrate decreased melanin when compared with non-lesional

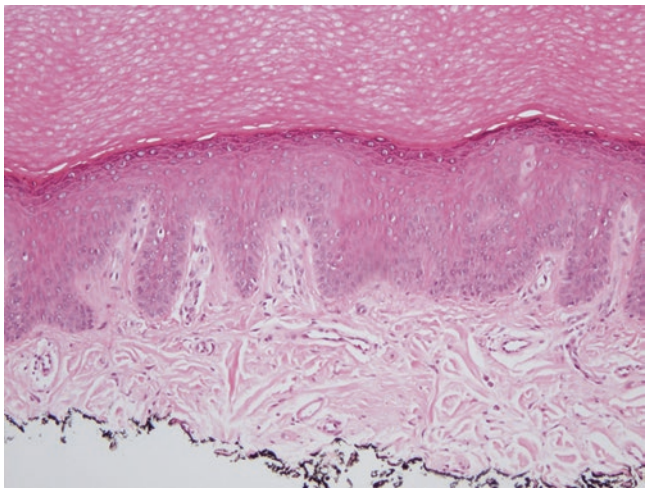

Fig. 17.6 Hyperkeratosis overlies an epidermis with marked reduction in melanocytes and little to no basilar melanin in idiopathic guttate hypomelanosis

basal keratinocytes in the same individual (Fig. 17.6). On electron microscopic examination, degenerating melanocytes and fewer melanocytes are observed [30].

17.3.3 Pathogenesis

The cause of idiopathic guttate hypomelanosis is not known. However, actinic influences over years of sunlight exposure may play a role in its development [31, 32]. Significantly fewer dopa oxidase-positive melanocytes are seen in idiopathic guttate hypomelanosis lesions. Reduction in the number of melanocytes and melanosomes as well as increased melanocyte degeneration has been observed. The condition may have a genetic basis. Arrunategui et al. have reported statistically significant association of HLA-DQ3 with idiopathic guttate hypomelanosis in a group of renal transplant patients [33].

17.4 Albinism

17.4.1 Clinical Features

Oculocutaneous Albinism (OCA) is an autosomal recessive disorder of impaired melanin biosynthesis. Albinism affects 1 in 17,000 people worldwide [34]. OCA Type 1 has a prevalence of 1 in 40,000, and it is seen more commonly in individuals of European ancestry [34]. Conversely, OCA Type 2 is the variant seen most commonly in those of African heritage with a prevalence of 1 in 10,000 amongst African-Americans versus 1 in 36,000 in the general population. Similarly, OCA Type 3 is seen infrequently in Caucasians and Asians, but has a prevalence of 1 in 8,500 in Africans. Oculocutaneous albinism-4 (OCA-4) is a common variant seen in Japan [26]. In all variants of OCA, patients share some degree of pigmentary dilution, congenital nystagmus, iris hypopigmentation, foveal hypoplasia, impaired visual acuity with color vision deficits, photophobia, and strabismus [34].

In OCA Type 1A, hairs at the scalp, eyebrows, and eyelashes are snow-white, and the skin does not tan. Irises are light blue and fully translucent with prominent red reflex. Ocular symptoms are more severe with poor vision and pronounced photophobia [34]. Patients may develop amelanotic nevi. In OCA Type 1B, hair and skin may develop pigmentation after infancy, and eye coloring may darken from blue to green/brown [34]. OCA Type 2 and Type 4 share the same clinical phenotype. Affected individuals have milky white to yellow-colored skin, light brown or blonde hair with varied colored irises. Patients may develop nevi and ephelides. OCA Type 3 patients have red hair and reddish brown skin. Ocular symptoms frequently are not detectable. Temperature-sensitive OCA (OCA1TS) is a form of OCA in which patients have white hair and skin at birth. At puberty, they gradually develop darker hair at cooler areas of the body, such as the extremities, but retain white hair in warmer areas, such as the scalp and axilla [26, 35]. The incidence of skin cancer is increased in individuals with albinism, thus necessitating adherence to consistent photoprotection [34].

17.4.2 Histology

Skin biopsies from patients with all forms of oculocutaneous albinism demonstrate marked decrease in melanin pigment both within the epidermis and the follicular epithelium. Melanocytes appear normal in size and shape [36]. A Fontana-Masson stain for melanin pigment highlights the absence of melanin within the biopsy specimen, but this is rarely required for diagnosis.

17.4.3 Pathogenesis

Oculocutaneous albinism is known to be associated with four genes: TYR, OCA2, TYRP1, and MATP (also called SLC45A2) [37]. OCA Type 1 is due to mutations in tyrosinase (TYR), which is a type I transmembrane monophenol monooxygenase [38, 39]. Tyrosinase catalyzes multiple steps in melanin synthesis, including the critical hydroxylation of tyrosine to L-DOPA, and oxidation of L-DOPA to DOPA-quinone [40]. Mutations in TYR can cause complete or partial OCA depending on the extent of loss of TYR enzymatic activity. Patients with TYR mutations have no melanin formation throughout their life because the first step of melanin synthesis is blocked.

Oculocutaneous albinism-2 (OCA2) is due to mutations in the OCA2 gene, which is an integral membrane trans-

porter protein that regulates the processing and transport of tyrosinase to melanosomes [37, 41].

Oculocutaneous albinism-3 (OCA3) is caused by mutations in the TYR-related protein-1 (TYRP-1) gene [26]. TYRP1 is structurally similar to TYR, and it is necessary for the synthesis of black/brown eumelanin [42]. TYRP1 complexes with and stabilizes tyrosinase [43]. In the absence of TYRP1, tyrosinase is rapidly degraded.

Oculocutaneous albinism-4 (OCA4) is due to mutations of TYRP-1 and membrane-associated transporter protein (MATP) (also called SLC45A2) [26]. MATP is involved in the intracellular processing and trafficking of melanosomal proteins. Mutations in MATP cause mistrafficking of tyrosinase [37, 44, 45]. Lastly, patients with temperature-sensitive OCA have a missense mutation in the tyrosinase gene that produces a mutated enzyme, which is temperature-sensitive and exhibits some activity at 35 °C and no activity at temperature above 35 °C [46].

17.5 Chediak–Higashi Syndrome

17.5.1 Clinical Features

Chediak–Higashi syndrome is an autosomal recessive genetic disease characterized by partial albinism, recurrent pyogenic infections, and blood cell dyscrasia with subsequent severe immunodeficiency and lymphoproliferative syndrome [47]. Patients typically present with generalized pigmentary dilution and much lighter skin color than their parents or siblings [47]. They have hair with a silvery-gray sheen, and ocular symptoms of photophobia, nystagmus, and retinal pigmentary dilution [48].

The childhood form of Chediak–Higashi syndrome is the most severe, and is seen in 85–90 % of affected individuals [47]. These individuals experience an often fatal accelerated phase with diffuse lymphohistiocytic organ infiltration and death by the second decade of life. The mildest form is seen in 10–15 % of patients. In this variant, patients are not predisposed to infections, but they develop progressive and fatal neurologic sequelae. The rarest form is "adolescent" disease in which individuals present with developmental delay, hypopigmentation, and recurrent infection but no accelerated phase [47]. For those with hematologic disease, a cure can be achieved with bone marrow transplantation prior to the accelerated phase.

17.5.2 Histology

Biopsy is rarely indicated or performed in patients with Chediak–Higashi syndrome as the findings on histology are rarely contributory in establishing a diagnosis. Diminished basilar melanin has been identified in biopsies taken from depigmented areas of the skin (Figs. 17.7 and 17.8). The pattern of enlarged membrane-bound granules within neutrophils that characterizes the syndrome has also been reported in melanocytes and Langerhans cells [49, 50].

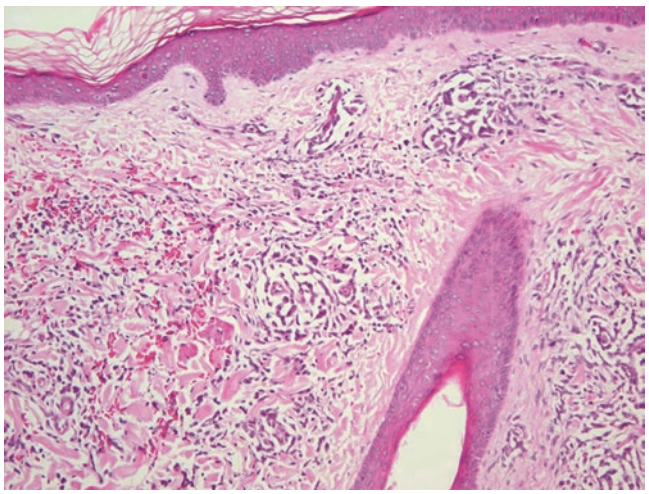

Fig. 17.7 Decreased basilar melanin is observed in the epidermis in Chediak–Higashi syndrome

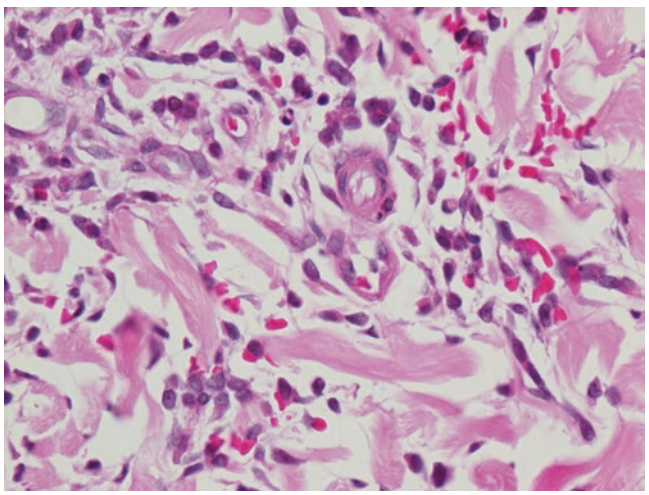

Fig. 17.8 The dermis in Chediak–Higashi syndrome contains a mixed inflammatory infiltrate with abundant red blood cell extravasation

17.5.3 Pathogenesis

Chediak–Higashi syndrome is characterized by giant lysosomal and non-lysosomal inclusions in cells containing granules, such as melanocytes and hematopoietic granulocytes [26, 40]. Giant inclusions within various vesicular organelles, such as lysosomes, melanosomes, cytosolic granules, and platelet dense bodies, are observed in various cell types. The presence of giant melanosomes in melanocytes,

and the abnormal distribution of these melanosomes to keratinocytes may account for the hypopigmentation phenotype in patients with Chediak–Higashi syndrome.

The causative gene is CHS1/LYST, which is important in intracellular vesicular transport and vesicular size [51, 52]. The mouse homolog of CHS1 is the beige gene, and studies of transgenic mice with CHS1/LYST overexpression provide molecular insights into the role of this molecule. Mice with overexpression of the affected gene beige have smaller lysosomes as compared with wild-type mice. A screen for CHS1-binding partners using a yeast two-hybrid system identified several interacting proteins in vesicle trafficking, including hepatocyte growth factor-regulated tyrosine kinase substrate (HRS), 14-3-3, casein kinase II, and LIP5 [53, 54]. These proteins are involved in protein sorting and trafficking to the lysosome. Loss of CHS1/LYST may result in abnormal incorporation of lysosomal proteins into lysosomal membranes, or ineffective removal or recycling of these proteins in membrane trafficking.

17.6 Incontinentia Pigmenti

17.6.1 Clinical Features

Incontinentia pigmenti is a multisystem disorder of ectodermal origin with extracutaneous manifestations affecting the dental, ocular, and central nervous systems. As of 2013, there were 800 registered cases of incontinentia pigmenti with global incidence of 1:40,000 [55]. Incontinentia pigmenti overwhelming affects females, and is usually fatal to males in utero.

Cutaneous manifestations classically present in four successive stages, although they may overlap or not even occur [56] (Figs. 17.9 and 17.10). The stages are (stage 1) erythema followed by blaschkoid vesicles and pustules within the first 2 weeks of life, typically clearing by 4 months of age; (stage 2) hyperkeratotic to verrucous papules and linear plaques; (stage 3) linear hyperpigmentation; and (stage 4) hypopigmentation and possible scarring [55].

Additional clinical features include dental anomalies, such as partial anodontia and conical teeth, which can be seen in as many as 70 % of affected individuals [55, 56]. Patients may also present with nail dystrophy and alopecia along the vertex of the scalp. Ocular disease can be seen in 20–40 % of patients with complications including retinal disease, strabismus, cataract, and pigmentation of the conjunctiva [55]. The greatest morbidity and mortality are associated with neurologic disease, which occurs in approximately one-third of patients with infantile seizures as the most common finding. Eight percent of patients will have some degree of mental retardation.

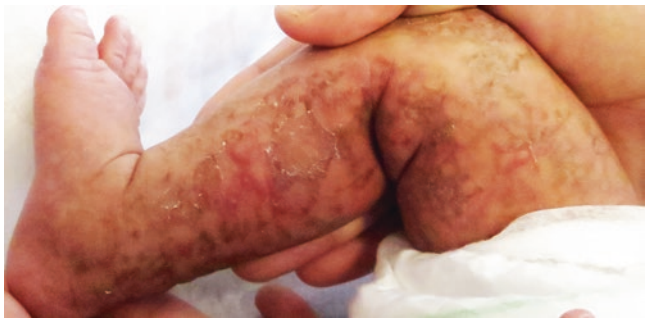

Fig. 17.9 Hyperkeratotic papules and reticulate hyperpigmentation in a Blaschkoid distribution are present on the leg of an infant with incontinentia pigmenti

Fig. 17.10 Incontinentia pigmenti in this infant presents as Blaschkoid plaques comprised of erythematous papules, vesiculopapules, and yellow-colored vesicles, mostly concentrated on the extremities and lateral torso typifying stage 1 of the disease

17.6.2 Histology

The histologic changes seen in incontinentia pigmenti are dependent upon the stage of the lesion biopsied. In the earliest stage 1 lesions (vesicular stage), the characteristic findings are those of an "eosinophilic spongiosis" (Fig. 17.11). The epidermis is markedly spongiotic, often with coalescing spongiotic microvesicles [57]. Focal necrosis within the epidermis is present, and widely scattered apoptotic keratinocytes are easily apparent both within the epidermis and follicular epithelium (Fig. 17.12). The dermis demonstrates lymphocytes and eosinophils around the vessels of the superficial vascular plexus and extending into the epidermis.

Stage 2 (verrucous stage) lesions demonstrate an acanthotic epidermis, with marked overlying hyperkeratosis.

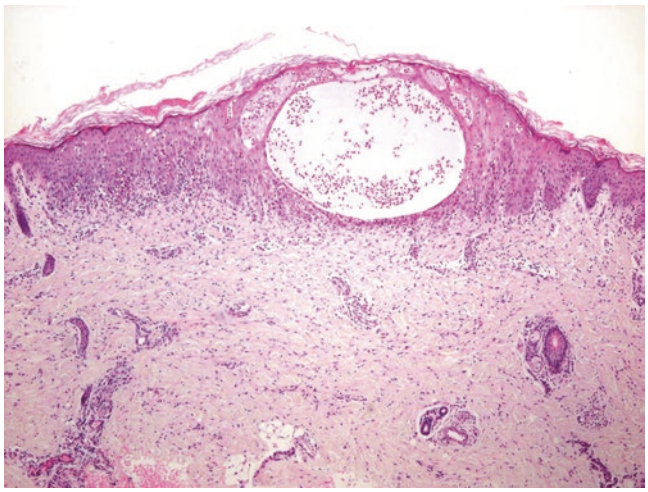

Fig. 17.11 Early stage lesions of incontinentia pigmenti show intraepidermal vesicles, abundant exocytosis, and scattered dying keratinocytes

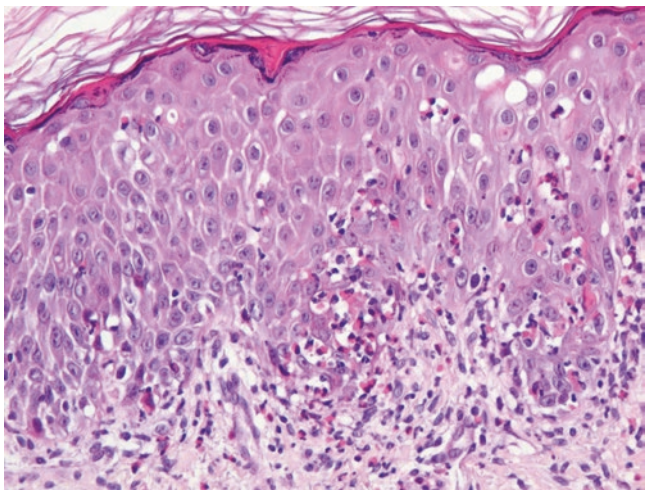

Fig. 17.12 Higher magnification shows abundant eosinophils within the dermis and epidermis and multiple dying keratinocytes that characterize incontinentia pigmenti

Dyskeratotic cells are prominent within the epidermis, and a whorled configuration to these cells has been described. Epidermal eosinophilia is no longer a prominent feature in lesions that have progressed to the verrucous stage, but can still be identified focally.

Stage 3 lesions are essentially those of post-inflammatory pigmentary alteration. The prominent histologic changes include loss of epidermal pigment with abundant accumulation of melanin within melanophages in the papillary dermis. Focal basal vacuolization and dyskeratosis of basal keratinocytes are present. In this stage, the lesions are no longer diagnostic but require clinical correlation in order to arrive at the correct diagnosis. In the late Stage 4 lesions, there is epidermal atrophy and a variable reduction in the number of melanocytes.

Twenty-nail dystrophy has been described in patients with incontinentia pigmenti with hyperkeratosis and hypergranulosis. Pseudoepitheliomatous hyperplasia is present with abundant dyskeratotic cells, similar to the findings in the verrucous stage of cutaneous lesions [58].

17.6.3 Pathogenesis

Incontinentia pigmenti is a rare genodermatosis that segregates as an X-linked dominant disorder. Females with incontinentia pigmenti exhibit skewed X-inactivation because cells expressing the mutated X chromosome are eliminated selectively in utero. Although the majority of patients are females, male patients have been identified. The survival of males is linked to hypomorphic NEMO mutations that have residual NEMO and NF-κB activities and therefore are not lethal [59, 60]. Males with incontinentia pigmenti tend to have additional medical features not usually associated with the disease, including immune dysfunction, osteopetrosis, and lymphedema.

A landmark study showed that the cause of incontinentia pigmenti is due to genomic rearrangement in NEMO (nuclear factor-κB essential modulator, also known as inhibitor κB kinase, γ-subunit) [61]. Mutation in NEMO, resulting in the deletion of exons 4 through 10, has been found to account for more than 80 % of all incontinentia pigmenti cases. NEMO is the regulatory subunit of the inhibitor κB kinase (IKK) complex, and it is essential for the activation of the transcription factor NF-κB [62, 63]. Loss of NEMO disrupts NF-κB activity in the cell. As a consequence, incontinentia pigmenti cells are highly sensitive to pro-apoptotic signals. Genetically engineered mice with loss of NEMO develop a phenotype closely resembling that of incontinentia pigmenti in humans, including generalized erythematous vesicular eruptions, followed by hyperkeratotic scaly lesions and lines of altered pigmentation. Histologic examination of NEMO-knockout mice showed eosinophil- and neutrophil-rich intraepidermal microvesicles with spongiosis and dyskeratotic keratinocytes [64, 65]. Conditional deletion of NEMO only in skin keratinocytes shows that loss of NEMO in these cells is sufficient to induce inflammatory skin lesions, indicating that expression of NEMO in keratinocytes is a potent initiator of skin inflammation in incontinentia pigmenti [66].

Another key player in the pathogenesis is eotaxin, which is an eosinophil-selective chemokine that has been isolated from the blister fluid and crusted scales of patients with incontinentia pigmenti [67, 68]. Eotaxin has a NF-κB binding site. Lesional skin from patients shows strong expression of eotaxin in the epidermis by immunohistochemical staining, and eotaxin expression corresponds to areas of eosinophil accumulation in the epidermis [69]. The peripheral eosinophilia observed in incontinentia pigmenti is due

to increased production of eosinophils in the bone marrow, and increased migration of eosinophils into the circulation. Granulocyte-monocyte colony-stimulating factor (GM-CSF) induces eosinophil differentiation and maturation in the bone marrow, and is also released by activated eosinophils, thus providing a feedback regulatory loop for eosinophil activation [69].

17.7 Xeroderma Pigmentosum

17.7.1 Clinical Features

Xeroderma pigmentosum is an autosomal recessive disorder with 8 complementation groups and a variant subtype [70]. There is an estimated disease prevalence of 1 per 1,000,000 individuals in the United States and Europe [71]. Prevalence is greater in North Africa and the Middle East in populations with higher incidence of consanguinity. Additionally, the number of cases is higher in Japan with reported prevalence of 1 in 22,000 individuals [71].

Xeroderma pigmentosum is characterized by severe photosensitivity, ocular disease, and increased risk of skin malignancy. Approximately 50 % of individuals have an acute sunburn reaction with erythema and blistering following minimal UV light exposure [72]. They may have pronounced photodistributed freckling before 2 years of age (Fig. 17.13).

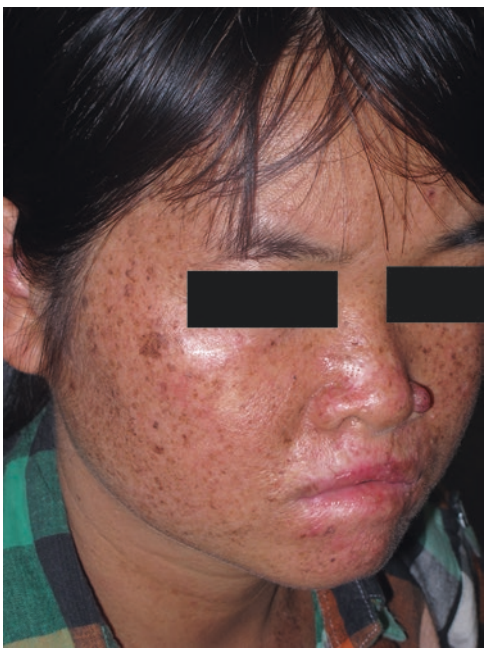

Fig. 17.13 Xeroderma pigmentosum presents with pronounced photodistributed freckling and poikiloderma. Scleral injection and actinic cheilitis also can occur as seen in this patient (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

With continued sun exposure, patients develop poikiloderma, actinic keratosis, and dry parchment-like hyperpigmentation of the skin [73]. Patients are predisposed to premature accelerated photoaging with 1000-fold increased risk of skin malignancies with many patients developing their first skin cancer by 10 years of age.

17.7.2 Histology

The diagnosis of xeroderma pigmentosum cannot be established based upon skin biopsy alone. The earliest observable skin changes include epidermal atrophy and telangiectasia. These findings are not specific, but they are unusual findings in children and suggest abnormal skin. Clumping of melanin pigment in the basal layer is another early but nonspecific finding [74]. Papillary dermal fibrosis representing early scarring is also a preliminary finding.

Patients with xeroderma pigmentosum are at a greatly enhanced risk for developing a myriad of cutaneous neoplasms. The most frequent include squamous cell carcinoma and basal cell carcinoma [75–77]. Basosquamous carcinomas have also been described [78]. The risk for melanoma is also greatly increased [79]. Atypical fibroxanthoma, which is a tumor ordinarily associated with elderly individuals, arises in patients with xeroderma pigmentosum [77, 80]. Cutaneous appendageal tumors also appear with increased frequency in this population [81, 82]. The histologic findings in each of the aforementioned malignancies are identical to those seen in individuals without underlying xeroderma pigmentosum. The difference is that in this population, these tumors occur at a very early age, while in the general population, they are tumors associated with sun-damaged skin occurring in an elderly population.

17.7.3 Pathogenesis

The pathogenesis of xeroderma pigmentosum is due to defective mechanism to repair UV radiation-induced damage to DNA [83, 84]. In normal cells, UV-induced DNA damage is repaired by the nucleotide excision repair (NER) pathway and double-strand breaks are repaired by homologous recombination or nonhomologous end-joining [85, 86]. Due to defects in DNA repair, key genes that regulate genomic stability (such as the p53 tumor suppressor gene) are mutated earlier and more frequently in these patients.

There are at least eight complementation groups (genetic subtypes) of xeroderma pigmentosum (XP-A to XP-G, plus XP variant) with each subtype associated with at least a unique gene defect [87, 88]. These groups are associated with defects in one of the many proteins involved in NER process, which is the primary mechanism by which

UV-induced adducts in cellular DNA are removed. The genes involved in some of these groups have been identified. The helicases ERCC3 (encoded by XPB gene), ERCC2 (encoded by XPD gene), and ERCC5 (encoded by XPA and XPG genes) are involved in the unwinding of DNA in the region of damaged DNA [87]. DDB2, which is the XPE gene product, recognizes UV-induced DNA damage and marks it for repair. The endonucleases ERCC4 (encoded by XPF) and ERCC5 (encoded by XPG) incise DNA strand and excise small fragments of the damaged genome for repair [89, 90]. Mutations in any of the proteins involved in the "transcription coupled DNA repair (TCR)" pathway, the global genomic repair (GGR) pathway, or the common nuclear excision repair pathway lead to genomic instability and cancer predisposition as observed in xeroderma pigmentosum. There are some cases called XP variant (XP-V) group, which are characterized by a defect in "trans-lesion DNA synthesis." With these mutations, the DNA polymerase-eta that synthesizes DNA past these adducts is defective, allowing synthesis by DNA polymerases that are more "error prone," thus introducing errors during DNA replication [91, 92].

17.8 Poikiloderma Congenitale (Rothmund Thomson Syndrome)

17.8.1 Clinical Features

Poikiloderma congenitale (Rothmund-Thomson syndrome) is a rare autosomal recessive disorder [93]. Rothmund–Thompson syndrome is characterized by poikiloderma, sparse hair at the scalp, eyebrows, and eyelashes, small stature, skeletal abnormalities, cataracts, and an increased risk for cancer, specifically osteosarcoma [93]. There are two subtypes of disease, types I and II. Individuals with type I disease develop juvenile cataracts with no incidence of osteosarcoma or bone disease, while those with type II disease have skeletal abnormalities and increased risk of osteosarcoma without developing cataracts. At 3 to 6 months of age, patients often present with erythema, swelling, and blistering of the face with sparing of the trunk and intertriginous folds [93]. Skin changes evolve into poikiloderma with punctate atrophy involving the extensor extremities, trunk, abdomen, and buttocks. Hyperkeratotic plaques and edema may develop on the elbows, knees, hands, and feet in association with plantar keratoderma [73, 93, 94]. Ten to fifty percent of patients develop juvenile cataracts, usually between 4 and 7 years of age [93, 94]. Osteosarcoma is the most frequently seen malignancy with a prevalence of approximately 30 %. Cutaneous tumors are also increased in these patients with a prevalence of ~5 %.

17.8.2 Histology

Histologic changes of affected skin in Rothmund-Thomson syndrome include epidermal atrophy with marked variability in basilar melanin deposition. The rete ridges are flattened, and occasional basal vacuolization is present. Early lesions demonstrate a band-like lymphocytic infiltrate that may infiltrate the lower portions of the epidermis. In some areas, the basal layer appears to have normal amount of melanin, while melanin is markedly decreased in other areas in the epidermis. Melanophages are present within the papillary dermis and around the vessels of the superficial vascular plexus. Papillary dermal edema is seen in most cases. Vascular ectasia is present throughout the superficial portions of the dermis [95].

17.8.3 Pathogenesis

Karyotypic analysis of cells isolated from Rothmund-Thomson syndrome patients shows a high frequency of chromosomal abnormalities. RECQL4 has been identified as a causative gene [96], and it is present in 66 % of clinically diagnosed patients [97]. Rothmund–Thompson syndrome type I does not have mutations in RECQL4 gene [98], while type II patients demonstrate documented mutations in RECQL4. The identified mutations result in early termination codon in the helicase domain of RECQ4, resulting in truncation and loss of function of RECQL4 protein [96]. RECQL4 analysis showed that patients with Rothmund–Thompson syndrome who developed osteosarcoma carried at least one deleterious RECQL4 mutation, thus implicating a role for RECQL4 in osteosarcoma formation in these patients.

RECQL4 functions in several aspects of genomic stability maintenance, and plays an important role in DNA replication initiation and double-strand break repair [99, 100]. RECQL4 is a RecQ DNA helicase important in DNA replication whose function is to unwind and separate the two complementary DNA strands. The RecQ family of DNA helicases unwinds DNA in the 3′ to 5′ direction in relation to the DNA strand to which the enzyme is bound. RECQL4 also forms a stable complex with components of ubiquitin ligases, which are essential for chromosome stability [96]. Animal models in which the RECQL4 gene is deleted have a high perinatal mortality, while the survivors have severe growth retardation and developmental defects similar to the abnormalities seen in Rothmund–Thompson syndrome patients, thus strongly implicating a role for RECQL4 in disease pathogenesis [101]. Mutations in RECQL4 give rise not only to Rothmund–Thompson syndrome but also to two other known autosomal recessive diseases, RAPADILINO and Baller–Gerold syndrome. Both Rothmund–Thompson syndrome and RAPADILINO patients have increased risk for osteosarcoma and lymphoma [98].

17.9 Bloom Syndrome

17.9.1 Clinical Features

Bloom syndrome is a rare autosomal recessive disorder. Affected children are often males, and there is greater incidence in individuals of Ashkenazi Jewish ancestry [102]. Bloom syndrome is characterized by growth retardation, type II diabetes, and recurrent infections [73]. Photodistributed erythematous patches and telangiectasia along the malar region of the face, dorsum of the hands, and extensor forearms often appear within the first few years of life. Patients may also lose the lower eyelashes, and have blistering and fissuring along the lower lip. Many patients also have café-au-lait spots with hypopigmentation along the peripheral edges [73, 102]. A wide array of ocular abnormalities, narrow facies with prominent nose as well as malar and mandibular hypoplasia can also be seen [102]. Photoprotection is encouraged in these patients, although skin manifestations often improve with time. Patients are predisposed to a multitude of malignancies, including skin and hematologic cancers frequently by the second decade of life [73, 102–104] (Fig. 17.14). Males are infertile, while females are fertile but may experience early menopause [103].

Fig. 17.14 Pigmented basal cell carcinoma in a patient with Bloom syndrome

17.9.2 Histology

Histologic features in Bloom syndrome resemble those seen in lupus erythematosus. There is interface dermatitis, and the epidermis demonstrates extensive basal vacuolization with exocytosis of lymphocytes (Figs. 17.15 and 17.16). Melanophages are present in the dermis with a moderately intense superficial perivascular lymphocytic infiltrate. Dilated capillaries are present, resulting in clinically apparent telangiectasias [105].

The histologic differential diagnosis includes lupus erythematosus and other interface processes. Unlike lupus erythematosus, basement membrane thickening and mucin deposition are not seen in Bloom syndrome skin biopsies. Direct immunofluorescence stains do not reveal immunoglobulin deposits at the dermal-epidermal junction [105]. A phototoxic drug eruption could also be considered. Clinical correlation is the best way to make this distinction because the histologic findings in these entities are identical.

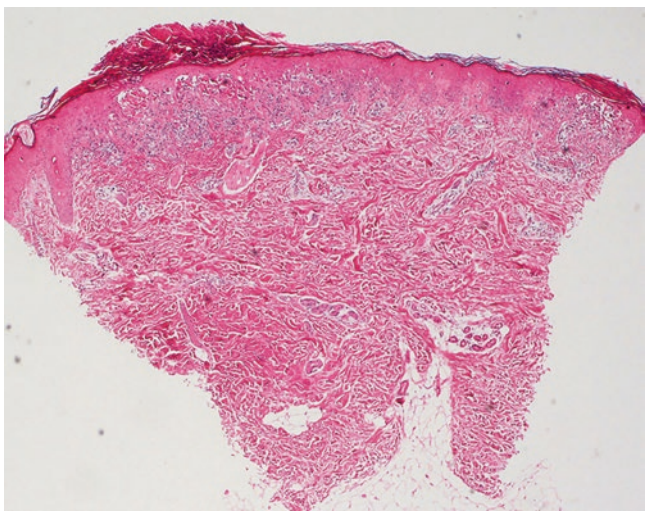

Fig. 17.15 Bloom syndrome is characterized by an interface dermatitis with abundant dying keratinocytes within the basal layer of the epidermis

17.9.3 Pathogenesis

Bloom syndrome is an autosomal recessive disease caused by mutations in the BLM gene (Bloom syndrome, RecQ Helicase-Like) [107]. BLM encodes for RecQL3 helicase, which has important function in the fidelity of DNA replication. RecQL3 is an enzyme that repairs breaks in double-stranded DNA [108, 109]. BLM also functions to suppress crossover formation between sister chromatids during DNA replication. More than 60 mutations in BLM gene have been associated with Bloom syndrome. The most common mutation is the deletion of six nucleotides at position 2281, and the insertion with seven other nucleotides at this position [110, 111]. Mutation in BLM causes a tenfold increase in the

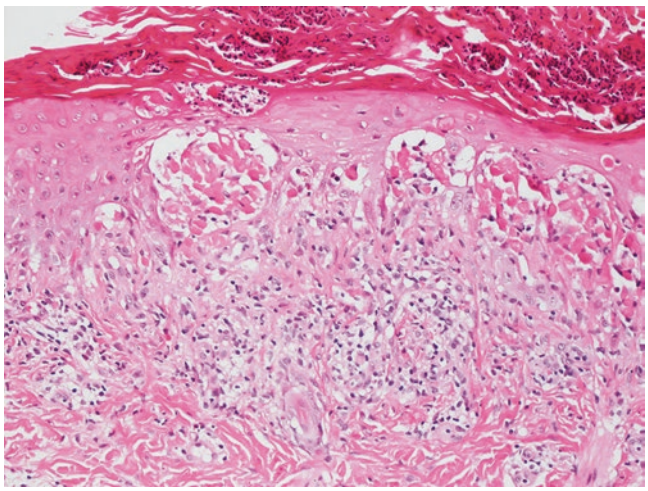

Fig. 17.16 A lymphocytic infiltrate is present in the papillary dermis and extends into the epidermis with dead keratinocytes in Bloom syndrome

frequency of DNA exchange between sister chromatids, and prevents the removal of Holliday junctions during DNA replication, resulting in segmented and entangled sister chromatids [112]. Bloom syndrome cells have increased chromosome breaks, spontaneous mutation rates and frequency of spontaneous sister chromatid exchanges, thus contributing to genomic instability and cancer predisposition [113–115]. Patients with Bloom syndrome are 150–300 times more likely to develop malignancy than the general population [110].

17.10 Nevus Depigmentosus

17.10.1 Clinical Features

Nevus depigmentosus is present at birth or appears soon after, most commonly within the first year of life [116]. Nevus depigmentosus is characterized by an irregularly shaped, hypopigmented patch or macule that does not fluoresce with Wood's Lamp examination. The distribution and location of a nevus depigmentosus are stable with growth proportional to that of the child. The lesion persists over a lifetime [116].

17.10.2 Histology

Histologic sections of nevus depigmentosus resemble that of normal skin on first examination. The changes are quite subtle and may only be evident with use of Fontana-Masson stain that demonstrates marked reduction in basilar keratinocytic melanin [117]. A decrease in melanocytes has been reported by some authors [117], but other authors find normal numbers of melanocytes as identified with immunomarkers [116, 118].

The differential diagnosis includes post-inflammatory hypopigmentation, but dermal melanophages are not present in nevus depigmentosus. Vitiligo can be difficult to distinguish from nevus depigmentosus, but the presence of lymphocytes with exocytosis into the epidermis favors the diagnosis of vitiligo. Low magnification suggests normal skin, and close attention to the clinical history should raise concerns for a diagnosis of nevus depigmentosus. The diagnosis is easily confirmed with Fontana-Masson stain for melanin.

17.10.3 Pathogenesis

Nevus depigmentosus is considered to be a nevoid anomaly due to functional defects in melanocytes. Ultrastructural studies show a significant reduction in the number of melanosomes in melanocytes in nevus depigmentosus as compared with normal skin, and the melanosomes in keratinocytes are often aggregated in lesional skin [116–118]. The number of melanocytes is also reduced when examined by staining for Mart-1 (a melanocyte marker).

17.11 Drug-Induced Pigment Disorders

17.11.1 Clinical Features

Drug-induced pigmentary disorders of the skin and mucosa account for up to 20 % of acquired skin dyspigmentation [119]. The most common causative medications are antimalarials, chemotherapy drugs, heavy metals, amiodarone, zidovudine, psychotropic medications, and tetracyclines [119] (Fig. 17.17). One of the drug-induced dyschromias most likely to be encountered in children is that of minocycline-induced hyperpigmentation. This is characterized by discoloration of the skin, mucosa, nails, bone, and teeth (Fig. 17.18). It can appear regardless of duration or dose of medication, but it is seen most frequently in patients taking more than 100 gm of minocycline daily for 3 years or more. There are three subtypes of minocycline-induced hyperpigmentation. Type 1 is characterized by blue-black discoloration occurs in scars and sites of inflammation. Type 2 is characterized by blue-gray macules and patches on the extremities, and Type 3 demonstrates photodistributed muddy brown pigmentation. Dyschromia tends to abate spontaneously once the medication has been stopped. However, more persistent cases may require laser intervention.

Fig. 17.17 Argyria is characterized by slate gray pigmentation on sun-exposed skin, nails, sclera, and mucous membranes as demonstrated in this boy with recessive dystrophic epidermolysis bullosa who applied silver sulfadiazine multiple times throughout the day for years as part of his wound care regimen

Fig. 17.18 Minocycline-induced hyperpigmentation type 1 in a teenage girl with bluish gray macules overlying atrophic scars at the cheeks after receiving minocycline for management of her acne

17.11.2 Histology

Papillary dermal pigmentation induced by medications may be caused by deposition of melanin or drug metabolites within the dermis. These metabolites may be detected by positive staining reactions with Fontana-Masson stain for melanin, and with iron or lipofuscin stains, depending upon the particular drug [120, 121]. Administration of drugs that result in cutaneous hyperpigmentation are infrequently given to children, so the findings described are rarely encountered in the pediatric population.

Independent of the causative agent, the histologic changes demonstrate an epidermis that is essentially unremarkable except for the presence of a mild lymphocytic exocytosis and scattered vacuolization of basal keratinocytes. Within the dermis, there is a superficial lymphohistiocytic infiltrate surrounding vessels of the superficial vascular plexus. Pigment is present within macrophages that are similarly clustered around the superficial dermal vasculature (Figs. 17.19 and 17.20). The color and shape of the pigment-laden macrophages varies depending upon the material deposited. Amiodarone results in macrophages that contain yellow-brown material that demonstrates the histologic properties of both melanin and lipofuscin [122]. Clofazimine demonstrates a similar ceroid lipofuscin type pigment within dermal macrophages [123]. Minocycline-induced hyperpigmentation also results in pigmented-laden macrophages that are positive when stained with Fontana-Masson stains for melanin (in addition to the positive staining with Prussian blue for iron) [124, 125]. With minocycline-induced hyper-

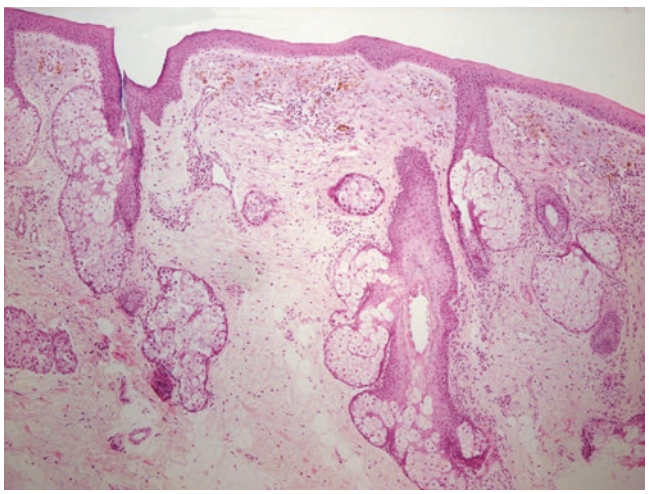

Fig. 17.19 The papillary dermis contains abundant pigment-laden macrophages. The epidermis is not hyperpigmented in this case of chlorpromazine-induced hyperpigmentation

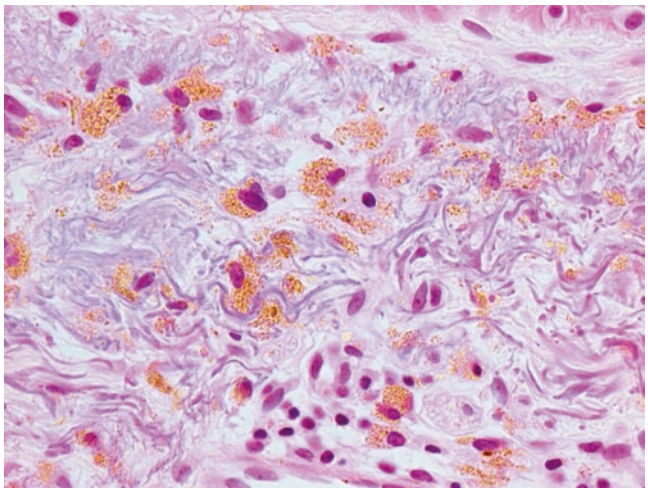

Fig. 17.20 Melanin fills and distends the cytoplasm of dermal macrophages induced by chlorpromazine

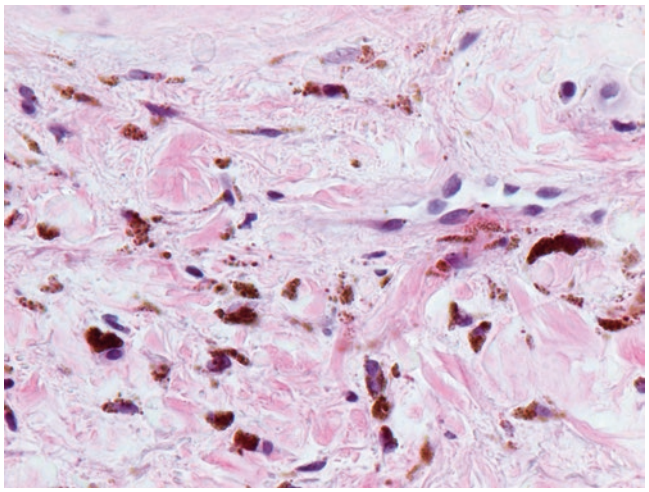

Fig. 17.22 Minocycline-induced hyperpigmentation demonstrates densely granular deposits within macrophages and in dermal collagen and elastic tissue fibers

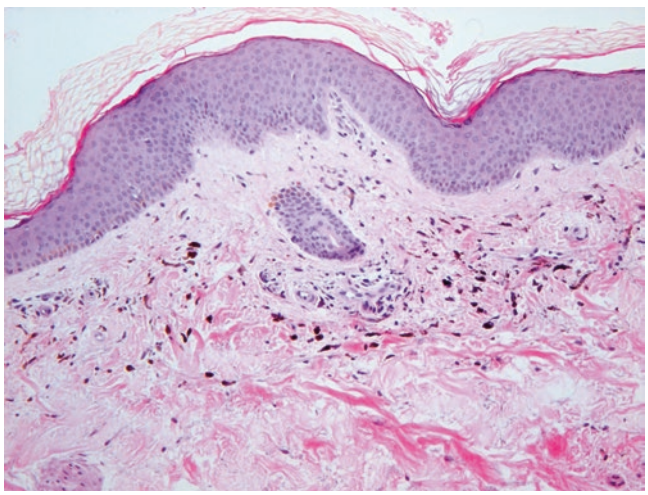

Fig. 17.21 Minocycline-induced hyperpigmentation is characterized by pigmented dermal macrophages that contain both iron and melanin deposits

pigmentation, pigmented granules are also deposited along elastic fibers within the papillary dermis and surrounding eccrine units (Figs. 17.21 and 17.22).

Long-standing chlorpromazine therapy may result in dermal melanin deposition (Figs. 17.19 and 17.20) [126]. However, in these cases, it is believed that the chlorpromazine causes increased melanin production by melanocytes, and drug metabolites are not responsible for the increased melanin deposition [126]. Chronic quinine therapy results in "ochronosis-like" yellow-brown ribbons that also stain on Fontana-Masson stain [127].

Long-standing treatment with imipramine may result in dermal pigment deposition. The pigment appears gold-brown and forms round globules that label on Fontana-Masson, but not Prussian blue stains [128]. Similar findings have been described with prolonged desipramine therapy [129]. Diltiazem-induced hyperpigmentation also results in deposition of melanin in the dermis. In these cases, it is believed that the effect of photosensitization with UVA and UVB light plays a central role in the pathogenesis of this process [130].

The histologic differential diagnosis includes post-inflammatory hyperpigmentation due to interface dermatitis. In these cases, dermal melanin is present within macrophages in a superficial perivascular lymphocytic infiltrate. If clinical history does not provide adequate information to make the distinction, histochemical stains may be helpful. The presence of Prussian blue positivity excludes post-inflammatory processes, in which the pigment is entirely melanin. A pigmented purpuric dermatosis might also enter the histologic differential diagnosis. This group of diseases (uncommon in children) demonstrates dermal hemosiderin as highlighted on Prussian blue stain and does not label on Fontana-Masson stain as there is no deposition of melanin.

17.11.3 Pathogenesis

Pigmentary disorders of the skin and mucous membranes due to drugs are thought to be associated, at least in part, with increased melanin pigment [131]. For example, prostaglandins can stimulate the activity of tyrosinase and increase the dendritic structures of melanocytes and melanin synthesis [132]. Skin pigmentation caused by the antibiotic minocycline may be due to pigment granules of iron chelates of minocycline, metabolites of minocycline in the skin, and increased amounts of melanin pigment in the epidermis and dermal macrophages [133, 134]. Anticancer drugs, such as

doxorubicin, imatinib, dasatinib, and interferon-α, can induce dyschromia in the form of vitiligo [135]. Depigmentation tends to persist even after discontinuing the offending drug.

17.12 Post-Inflammatory Pigmentary Alteration

17.12.1 Clinical Features

Post-inflammatory pigmentary alteration occurs in all skin types with no gender predilection [136]. It may be more noticeable in darker skin types. Post-inflammatory dyschromia may be hyperpigmented or hypopigmented, and tends to respect the confines of the initial inflammatory or traumatic insult. This feature is important in distinguishing post-inflammatory changes from other pigmentary disorders. The prognosis of this disorder is good with potential for complete resolution within weeks to months if the underlying cause is appropriately managed and eliminated. More significant dyschromia with depigmentation may be permanent [136].

17.12.2 Histology

Post-inflammatory pigmentary alteration is not a primary disorder, but rather a constellation of secondary changes that occur as a result of basal keratinocyte disruption. In early lesions, basal vacuolization with scattered dying keratinocytes are present, and exocytotic lymphocytes appear within the lower portions of the epidermis (Figs. 17.23 and 17.24). There is no increase in basilar melanocytes. A superficial (with or without a deeper component) lymphohistiocytic infiltrate is present surrounding the superficial blood vessels. Scattered melanophages are clustered around these vessels. As the lesions become more chronic, the intensity of the inflammatory infiltrate diminishes. Dying keratinocytes are much less prevalent and may be absent. The papillary dermis appears fibrotic and contains perivascular melanophages [137].

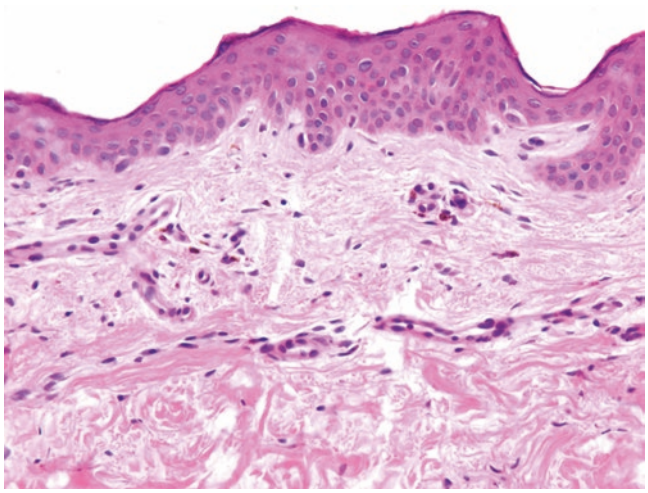

Fig. 17.23 In post-inflammatory pigmentary alteration, the epidermis appears unremarkable and contains normal numbers of melanocytes along the basal layer. Pigment is present within macrophages in the papillary dermis

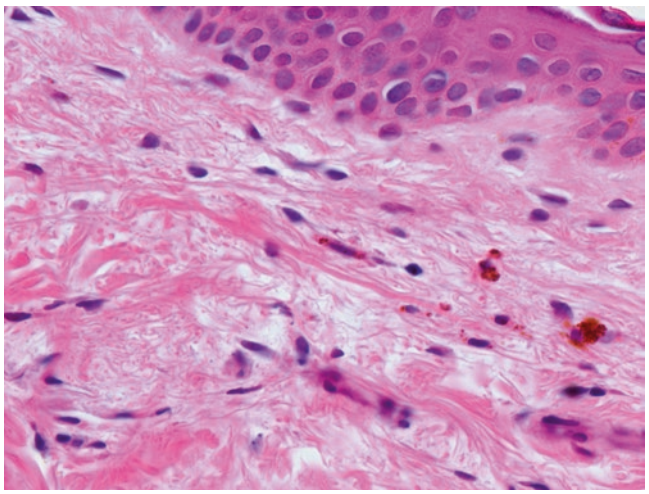

Fig. 17.24 Clusters of melanophages are present surrounding small vessels in the superficial vascular plexus in post-inflammatory pigmentary alteration

Post-inflammatory pigmentary alteration is not a histologic diagnosis, but rather a description. As it is difficult and often impossible to distinguish between hypopigmented and hyperpigmented lesions based upon loss of epidermal melanin and accumulation of dermal melanophages, the aforementioned phrase seems most appropriate for describing the histologic changes. The antecedent causes for post-inflammatory pigmentary alteration are numerous. The findings can be seen in subacute to chronic interface dermatoses, such as lupus erythematosus, lichen planus, and fixed drug eruption. The changes seen in erythema dyschromicum perstans (ashy dermatosis) are distinguished from these nonspecific ones based upon the clinical presentation.

The differential diagnosis includes a blue nevus or other densely pigmented melanocytic proliferations, such as nevus of Ito and nevus of Ota. Melanocytes in nevi do not demonstrate the perivascular clustering that is seen in melanophages that characterize post-inflammatory pigmentary alteration. Furthermore, melanocytes tend to form nests and show cellular maturation with progressive descent into the dermis. In some cases, it is possible to distinguish between the melanin present in cytoplasmic melanosomes in melanocytes, and the processed melanin granules present in melanophages. Some drug eruptions may result in dermal pigmentation. Drug-related pigment deposition can be distinguished with the use of Prussian blue stain (see drug-induced pigmentary disorders).

17.13 Reticulate Hyperpigmentary Disorders

17.13.1 Clinical Features

Dowling Degos disease is a rare autosomal dominant disorder with incomplete penetrance, although sporadic cases have been described [138]. The disorder typically presents in adolescence or adulthood [139]. Dowling-Degos disease is characterized by reticulated hyperpigmented patches of the proximal extremities and intertriginous skin of the neck, axillae and groin. Additional clinical features include pitted scars around the mouth and dark-colored, hyperkeratotic follicular papules overlying hyperpigmented patches at the neck and axillae [140]. An alternative phenotype exists with generalized hypopigmented papules [138]. Although benign, Dowling-Degos disease may be cosmetically disfiguring and difficult to manage as poor success has been demonstrated with topical retinoids, topical steroids, hydroquinone, and systemic retinoids [140].

Galli-Galli disease is a rare acantholytic variant of Dowling-Degos disease [141]. It is characterized by reticulate hyperpigmented patches at the flexural folds with pruritic scaly papules and papulovesicles in a similar distribution. Papular lesions can also be seen at the trunk and extremities.

Kitamura acropigmentation is a rare genodermatosis characterized by autosomal dominant transmission with variable penetrance that is primarily seen in individuals of Asian ancestry [139]. Skin changes typically present during the first or second decade of life, and may be exacerbated by sun exposure. The condition is characterized by hyperpigmented, angulated, atrophic macules in reticulate patterning on the dorsum of the hands and feet. Over time, lesions may progress to involve the distal extremities with rare reports of involvement of the face and eyelids. Affected areas tend to darken with time and may be exacerbated by sun exposure [139]. Pits and dermatoglyphic breaks can be found on the palms, soles, and along the dorsal phalangeal surfaces. The skin changes in Kitamura acropigmentation are refractory to treatment. They are persistent and often respond poorly to medical therapies and laser interventions.

Haber's syndrome is a rare genodermatosis inherited in an autosomal dominant manner [142]. Patients present with telangiectasia and erythematous papules in childhood, mimicking rosacea. On the torso, there are multiple hyperpigmented, keratotic papules and plaques with accentuation at the flexural folds. There are reports of skin malignancies (Bowen's disease, squamous cell carcinoma and basal cell carcinoma) in Haber's syndrome [142]. However, the clinical significance of these occurrences and relevance to the overall morbidity associated with the condition is not known.

17.13.2 Histology

Based upon the extensive histologic overlap and the clinical similarities, most authors now consider Kitamura acropigmentation, Dowling-Degos disease, Galli-Galli disease, and possibly Haber syndrome to represent a spectrum of a single disorder [142–149]. Histologic changes in all conditions include elongation of the rete ridges with suprapapillary thinning. There is marked hyperpigmentation at the base of the elongated rete ridges with no significant increase in the number of melanocytes (Figs. 17.25, 17.26 and 17.27). Some cases also have dilated follicles [150]. A mild lymphohistiocytic inflammatory infiltrate is present in the dermis, often with by melanophages [140]. Galli-Galli disease has the additional histologic feature of non-dyskeratotic acantholysis, resulting in small suprabasilar lacunae or blisters [144, 151]. A hypopigmented variant of this spectrum of disease has also been described in which histologic findings are identical except for the basilar hyperpigmentation [152, 153].

Acanthosis nigricans may enter into the differential diagnosis, but it can be differentiated based upon its papil-

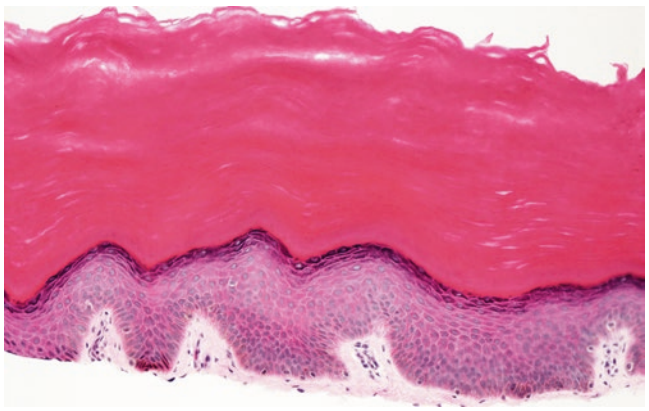

Fig. 17.25 Acral skin demonstrates increased basilar melanin in acropigmentation of Kitamura

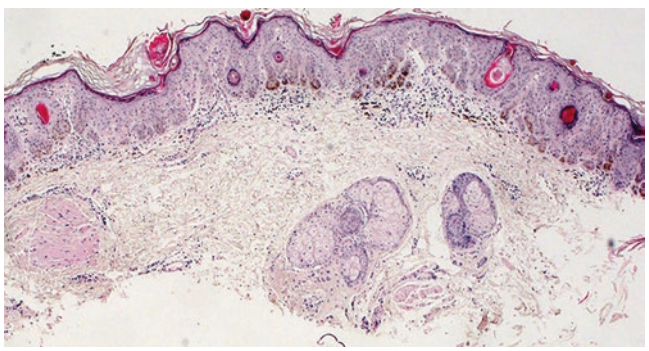

Fig. 17.26 Elongated rete ridges with basilar hyperpigmentation characterize Dowling-Degos disease

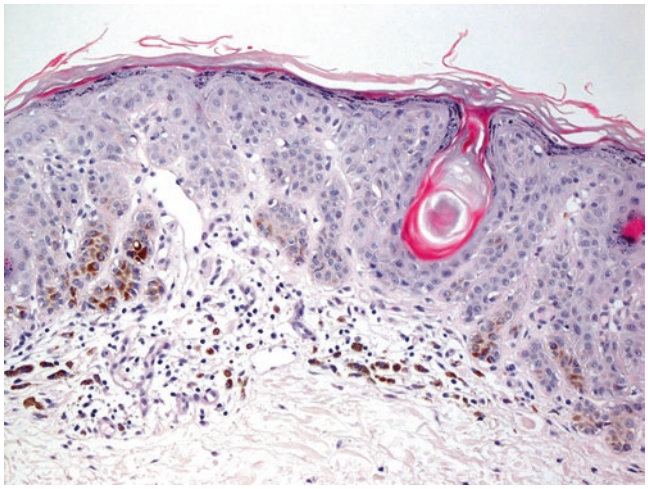

Fig. 17.27 Increased basilar melanin but no increase in number of melanocytes characterizes Dowling-Degos disease

lomatous architecture and marked overlying orthokeratotic hyperkeratosis without significant basilar hyperpigmentation [154].

17.13.3 Pathogenesis

Dowling-Degos disease is an autosomal dominant genodermatosis caused by mutations in the keratin 5 (KRT5) gene [155, 156]. KRT5 is made by keratinocytes and is a component of keratin intermediate filaments that form the structural framework of the cell and attach keratinocytes together. KRT5 plays an important role in the organization of cell adhesion, nuclear anchorage, organelle transport, and melanosome uptake into keratinocytes [157]. In Dowling-Degos disease, haplo-insufficiency of KRT5 due to mutations in one of the two gene alleles leads to decreased amount of functional KRT5 protein produced. This results in impaired transport of melanosomes and melanin, leading to the disease-associated dyspigmentation.

Mutations in other genes, namely O-glucosyltransferase 1 (POGLUT1) and O-fucosyltransferase 1 (POFUT1), have also been found to cause Dowling-Degos disease [158, 159]. POGLUT1 functions by adding O-linked glucose and O-linked fucose to the epidermal growth factor-like repeats of Notch receptors [160, 161]. A mutation 652C > T (p.Arg218*) in POGLUT1 leads to the synthesis of a truncated protein of about 30 kD and reduced expression of POGLUT1 [158]. Both POGLUT1 and POFUT1 are essential regulators of Notch activity by affecting post-translational modification of Notch proteins. These findings indicate the important role of Notch pathway in skin pigmentation and differentiation of the epidermis.

17.14 Dyschromatosis Universalis Hereditaria

17.14.1 Clinical Features

Dyschromatosis universalis hereditaria primarily occurs in individuals of East Asian descent and has a female predominance [162]. Eighty percent of patients have cutaneous stigmata by 6 years of age. The physical exam is characterized by a coalescence of variably colored, pigmented and hypopigmented small macules in generalized distribution, often with marked involvement at the abdomen. Dyschromatosis symmetrica hereditaria or reticulate acropigmentation of Dohi is a variant of the disorder in which lesions are limited to the extremities [162]. The skin changes persist over a lifetime without seasonal variation, and there is no associated systemic disease.

17.14.2 Histology

The histologic appearance of dyschromatosis universalis hereditaria is essentially unremarkable. Normal numbers of intact melanocytes are present in both hyper- and hypopigmented lesions [163]. Pigment accumulation within dermal melanophages is present in some hyperpigmented macules [164]. Fontana-Masson stain for melanin demonstrates increased pigment within basal keratinocytes in hyperpigmented macules, and absence of pigment within hypopigmented lesions.

Ultrastructural analysis reveals significant changes. Keratinocytes from hyperpigmented macules have fully melanized melanosomes that are aggregated into large melanosome complexes. This is in contrast to hypopigmented or depigmented macules in which no melanosomes are detected despite the presence of intact melanocytes [164, 165].

17.14.3 Pathogenesis

Dyschromatosis universalis hereditaria and dyschromatosis symmetrica hereditaria are two forms of pigmentary dermatoses with an autosomal dominant pattern of inheritance, although autosomal recessive cases have been reported [166–169]. Dyschromatosis universalis hereditaria phenotype is caused by deficiency of melanin synthesis and melanosome sorting [163, 165]. This disorder is caused by mutations in the ABCB6 gene (ATP-binding cassette, sub-family B) [170–172]. ABCB6 protein is a member of the superfamily of ATP-binding cassette (ABC) transporters that transport molecules through extra- and intracellular membranes. Dyschromatosis symmetrica hereditaria is caused by mutations in the ADAR

(Adenosine Deaminase, RNA-Specific) gene, which encodes for an enzyme responsible for RNA editing by site-specific deamination of adenosines [173].

17.15 Hereditary Sclerosing Poikiloderma

17.15.1 Clinical Features

Hereditary sclerosing poikiloderma is a rare autosomal dominant genodermatosis reported in many different races and ethnicities [174]. The clinical exam is characterized by widely distributed poikiloderma, most pronounced at the intertriginous folds and bony prominences, as well as linear reticulated, sclerotic bands on the axillae, antecubital and popliteal fossae [174]. Poikilodermatous changes become apparent between 2 and 4 years of age, followed by the onset of flexural sclerosis. Additional reported features include palmoplantar sclerosis, clubbing of the digits, soft tissue calcinosis, micrognathia, maxillary bossing, mandibuloacral dysplasia, Raynaud's phenomenon, and growth retardation. Cardiovascular or lung disease may be a feature of the condition and carries some degree of morbidity and mortality risk.

17.15.2 Histology

Hereditary sclerosing poikiloderma is characterized by the presence of dense sclerotic bands of collagen within the dermis. Telangiectatic vessels are present. Fragmented elastic tissue fibers contribute to the disorganized-appearing dermis [174, 175].

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Diseases of the Hair and Nails

18

18.1 Trichorrhexis Nodosa

18.1.1 Clinical Features

The hair shaft defects of trichorrhexis nodosa can be seen in a number of genetic conditions and can also be acquired as a result of persistent trauma [1].

Trichorrhexis nodosa is characterized by brittleness and increased fragility [1]. Patients with acquired disease frequently have curly hair styled with various chemicals and straightening devices, predisposing them to the characteristic disruption of the distal hair shaft. Hair changes may improve with hairstyle modification. In congenital varieties, the hair may be normal at birth but becomes dry, dull, and more brittle during infancy and early childhood.

18.1.2 Histology

Hair mounts demonstrate the changes of trichorrhexis nodosa. There are beaded swellings along the hair shaft that are associated with focal loss of the hair cuticle (Fig. 18.1). Frayed hairs extrude out from the regions without intact cuticle giving rise to the nodular beading appearance.

18.1.3 Pathogenesis

The pathogenesis of trichorrhexis nodosa is not known. It can develop in association with genetic disorders, including argininosuccinic aciduria, Menkes syndrome, Netherton's syndrome, trichohepatoenteric syndrome, and trichothiodystrophy [2]. Trichorrhexis nodosa can also be acquired due to repeated trauma to the hair shaft [3].

18.2 Trichoclasis

18.2.1 Clinical Features

Trichoclasis is a hair shaft disorder resulting from physical or chemical trauma that is not associated with an underlying defect of the cuticle, cortex, or chemical composition [4]. It is characterized by incomplete, ragged transverse fracturing of the hair shaft, demonstrated phenotypically by hair fragility [4].

18.2.2 Histology

Trichoclasis is simple transverse fracturing of the hair shaft. The hair cuticle remains intact, resulting in the hair being partially fractured but not entirely separated. The shaft itself, along with the cuticle, is structurally normal. Trichoclasis is seen in a wide range of hair disorders, and it is not a specific finding.

18.3 Loose Anagen Hair Syndrome

18.3.1 Clinical Features

Loose anagen hair syndrome has an estimated incidence of 2 cases per 1,000,000 per year [5]. The typical patients are Caucasian females with light-colored or blonde hair, who present with hair thinning or poor hair growth after 2 years of age. The mean age of diagnosis is 6 years of age, although there are reports of adult-onset hair loss [6]. Detection bias may contribute to the 6:1 female to male predominance of disease, since boys typically wear shorter hairstyles. Similarly, the microscopic features may be more difficult to appreciate in darker-haired children.

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Fig. 18.1 A nodular appearance resulting in hair breakage is seen in trichorrhexis nodosa (photo courtesy of Thomas Nicotri, MD)

Diffuse non-scarring hair loss in loose anagen hair syndrome most often occurs at the scalp, although the eyebrows and eyelashes can be affected as well [5]. Parents frequently complain that their child's hair does not grow long, and appears dull, fine, or unruly. Parents may note increased hair shedding with hundreds of hairs lost in a day [6]. Three phenotypes of the disorder have been described: type A with sparse hair that does not grow long; type B with diffuse unruly hair; and type C with increased hair shedding [6]. Most cases resolve spontaneously over a few years with hair growing longer, thicker and darker.

18.3.2 Histology

Hair mounts demonstrate short and twisted hair shafts lacking a surrounding cuticle and displaying distorted anagen bulbs (Fig. 18.2). Portions of the hair shafts show the expected ruffled cuticle and absent hair sheaths. There is premature keratinization of Henle's layer that has been described as tortuous and irregularly thickened [7].

18.3.3 Pathogenesis

Loose anagen hair syndrome is due to premature keratinization of the inner root sheath of the hair follicles, leading to impaired adhesion between the cuticle of the inner root sheath and the cuticle of the hair shaft [8, 9]. Mutations in the keratin gene K6HF, which is required for the development of the inner root sheath, have been identified in some individuals with loose anagen hair syndrome [10]. Besides K6HF, another gene K6IRS, which is specific for inner root sheath keratin formation, is also involved in disease pathogenesis

Fig. 18.2 The hair demonstrates a distorted anagen bulb and a short, twisted hair shaft lacking a cuticle in loosen anagen hair syndrome (photo courtesy of Trevor Beer, MD, Clinipath Pathology, Osborne Park, Australia)

[11]. This abnormal keratinization leads to impaired adhesion between the inner root sheath and the outer root sheath, resulting in short duration of the anagen hair phase and reduced hair growth [9]. These findings may explain why hair strands are loosely anchored and easily pluckable in loose anagen hair syndrome.

18.4 Trichorrhexis Invaginata

18.4.1 Clinical Features

Trichorrhexis invaginata is the pathognomonic hair shaft abnormality found in Netherton syndrome. The affected hair is sparse, short, and brittle with breakage along nodes highlighted on microscopy. The changes typically become apparent in infancy at hairs on the scalp as well as the eyebrows [1]. Hair fragility may improve with age as the hair shaft thickens [1].

18.4.2 Histology

On routine hair mounts, invagination of the hair cuticle into hair cortices can be observed [12] (Fig. 18.3). The proximal hair shaft is expanded and surrounds the distal club-shaped hair fragment. This results in an appearance of multiple small nodules or nodes [13].

Fig. 18.3 Associated with Netherton's syndrome, linear interruptions in the hairs shafts are evidence of the invaginations seen in trichorrhexis invaginata (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

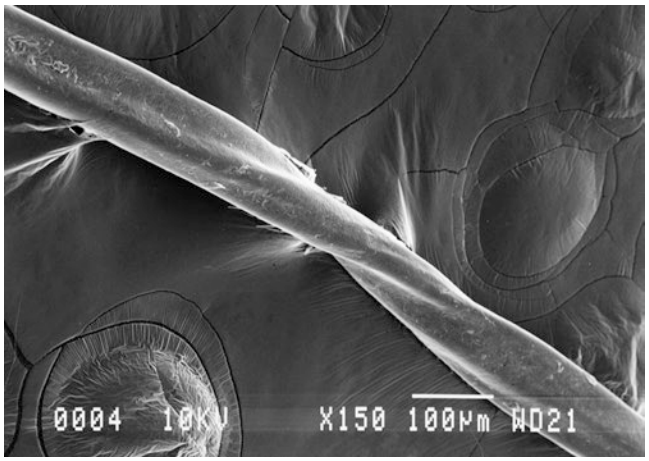

Fig. 18.4 Electron microscopy of hair shafts demonstrates a twisted appearance in pili torti (photo courtesy of Lauren Stuart, MD, Emory University, Atlanta, GA)

18.4.3 Pathogenesis

Trichorrhexis invaginata (also called bamboo hair) occurs in the setting of Netherton's syndrome [14], and mutations in the SPINK5 (serine peptidase inhibitor, Kazal type 5) gene have been linked to this disease [15, 16]. SPINK5 encodes LEKTI (SPINK5 encoding lympho-epithelial Kazal-type inhibitor) protein, which is a secreted serine protease inhibitor expressed in stratified epithelium [17]. LEKTI is present in the stratum corneum and stratum granulosum in the skin, and it is crucial for the maintenance of epidermal barrier function [18].

18.5 Pili Torti

18.5.1 Clinical Features

Pili torti usually presents in children before 2 years of age. It may be inherited in an autosomal dominant or autosomal recessive manner, and it can also occur sporadically [1]. Hair in pili torti is short, brittle, and sparse. Late-onset disease has been reported in older white children and adolescents with dark-colored, coarse hair at the scalp and hair fragility at the eyebrows and eyelashes. Pili torti can be seen as a feature of many genetic diseases including Bjornstad syndrome, Crandall syndrome, ectodermal dysplasia, monilethrix, and Menkes kinky hair syndrome [1].

18.5.2 Histology

On a hair mount preparation, there are hair shafts that twist upon their axes to varying degrees (Fig. 18.4). These can be 90°, 180° or 360°, and the twisting occurs with either regular or irregular frequency along the shafts. The hair shafts are somewhat flattened in appearance, and longitudinal fractures can be seen. Electron microscopy reveals irregularities in the thickness of the outer root sheath and focal vacuolization [19].

18.5.3 Pathogenesis

Pili torti is an autosomal dominant and acquired hair disorder in which the hair shaft is flattened at irregular intervals and twisted along its axis. The twisting of the hair strand is likely due to abnormalities in the inner root sheath, which may induce an uneven molding of the hair shaft [19]. Pili torti occurs in association with Björnstad syndrome (with sensorineural deafness) and Menkes syndrome (with early onset growth retardation and focal brain degeneration). Björnstad syndrome is caused by mutations in the BCS1L (BC1 (Ubiquinol-Cytochrome C Reductase) Synthesis-Like) gene that affect mitochondrial metabolism [20]. Menkes syndrome is an X-linked recessive disorder caused by mutations in the ATP7A (ATPase, Cu++ Transporting, Alpha Polypeptide) gene, which encodes a copper-transporting ATPase [21, 22]. Copper is an essential element in the formation of disulfide bonds in hair keratin. Therefore, defects in copper transport or metabolism may lead to abnormal keratin production, causing twisting of the hair.

18.6 Pili annulati

18.6.1 Clinical Features

Pili annulati is an uncommon disorder of hair shaft keratinization that exhibits autosomal dominant or sporadic inheritance [1]. Growth of hair is normal with normal texture and

Fig. 18.5 Pili annulati hair appears normal with no demonstrated abnormality (photo courtesy of MG Mercurio, MD, University of Rochester School of Medicine, Rochester, NY)

strength (Fig. 18.5). Hair at the scalp, axillae, beard, and pubis may be affected. Since hair does not demonstrate any phenotypic abnormality or fragility, treatment is not required.

18.6.2 Histology

The diagnosis is established by the detection of alternating light and dark banding along the hair shafts. They can be seen with routine light microscopy, and the pattern of banding is reversed with reflected light. The cause of the banding is abnormalities in the hair cortex as evidenced by vacuoles within the cells [23].

18.6.3 Pathogenesis

Pili annulati is a rare autosomal dominant hair disorder. The characteristic pattern of alternating bright and dark bands of the hair strands is due to the presence of air-filled cavities along the hair cortex, which scatter and reflect the light while precluding its transmission [24]. Although the genetic cause of pili annulati is not known, the susceptibility gene locus for this hair disorder is located in the telomeric region of chromosome 12q, and may include the Frizzled gene, which encodes the transmembrane receptor for Wnt proteins [25–27].

18.7 Griscelli Syndrome

18.7.1 Clinical Features

Griscelli syndrome is a rare autosomal recessive disorder with approximately 60 confirmed cases since it was first described in 1978 [28]. There are three clinical subtypes. Type 1 is characterized by pronounced neurologic disease; type 2 by immunodeficiency with mild psychomotor disease; and type 3 has no consistent systemic abnormalities identified. There is a greater prevalence of Griscelli syndrome type 3 in individuals of Turkish and Arab ancestry, but no racial predilection has been recognized in other subtypes [29]. Griscelli syndrome is characterized by generalized pigmentary dilution with silvery, gray-colored hair at the eyebrows and scalp. Additional physical exam findings in Griscelli syndrome type 2 are pyogenic infections and cutaneous granulomas [30].

Patients with Griscelli syndrome type 1 present with severe neurologic disease at an early age, mimicking the clinical features of Elejalde syndrome (neuroectodermal melanolysosomal syndrome), in which patients present with bronze-colored skin, silver hair, and severe neurologic impairment [28]. Griscelli syndrome type 2 has the poorest prognosis with hemophagocytic syndrome and universal fatality if bone marrow transplantation is not performed early on in the disease course [28]. Griscelli syndrome type 3 is the mildest variant of disease with no requirement for medical or surgical intervention [29].

18.7.2 Histology

In most cases, the microscopic diagnosis of Griscelli syndrome is established based upon the observation of dense clumps of pigment in an irregular distribution within the hair shaft [28, 31] (Fig. 18.6). Although not required to make the diagnosis, other histologic anomalies that have been described include giant granules in granulocytes, and enlarged and hyperpigmented melanocytes along the basal layer of the skin [28].

18.7.3 Pathogenesis

Griscelli syndrome is an autosomal recessive disorder with three clinical subtypes that are caused by distinct genetic defects. The causative mutations in type 1 Griscelli syndrome are in myosin 5A gene (Myo5A) [32]. Myo5A gene encodes an organelle motor protein that is important in neuron function [33]. A genetic mouse model that recapitulates features of type 1 is the “dilute” mouse model with loss of Myo5a [34].

Type 2 Griscelli syndrome is characterized by the same hypopigmentation of the skin and a severe immune defect of uncontrolled T lymphocyte and macrophage activation syndrome (known as hemophagocytic syndrome), which results in severe tissue damage and organ failure [35]. Type 2 is due to mutations in Rab27a gene, which encodes a small GTPase protein involved in intracellular secretory pathways [36, 37]. There is loss of expression of Rab27a in melanocytes and

Fig. 18.6 Mottled pigmentation is seen throughout the hair shaft in a patient with Griscelli syndrome (photo courtesy of Anne Pham-Huy, MD, University of Ottawa, Ontario, Canada)

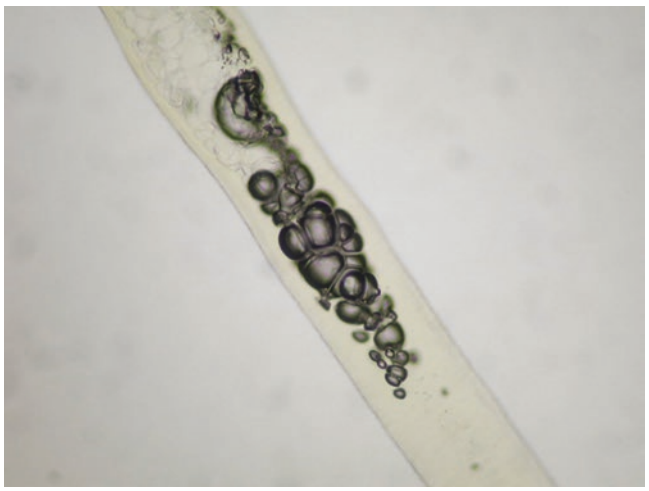

Fig. 18.7 The hair shaft contains internal cystic cavities secondary to thermal injury (photo courtesy of Catherine Antley, MD, Burlington,VT)

cytotoxic T lymphocytes in type 2, resulting in dysfunction of lysosome-related organelles (melanosomes in melanocytes and lytic granules in cytotoxic T lymphocytes) [38, 39]. Melanocytes in Griscelli syndrome have impaired transport of melanosomes, resulting in the abnormal accumulation of mature melanosomes in the perinuclear region, in contrast to the even distribution of melanosomes throughout the cytoplasm in normal melanocytes [40]. The immune dysregulation in type 2 patients is accounted for by the requirement of Rab27a in the release of cytotoxic granules in T lymphocytes [37, 41]. A genetic mouse model with defects in melanosomes that recapitulates features of type 2 is the "ashen" mouse model with loss of Rab27a, resulting in abnormal mouse coat [42].

Type 3 Griscelli syndrome is due to mutations in the melanophilin (MLPH) gene, leading to impaired interaction of Rab27a with MLPH [43]. The same phenotype also occurs with deletion of MYO5A F-exon, an exon with a tissue-restricted expression pattern [43]. Thus, the genetic defects in the three types of Griscelli syndrome highlight the importance of Rab27a, MLPH, and Myo5A in vesicular trafficking of intracellular organelles such as the melanosome and lysosome [44].

18.8 Bubble Hair

18.8.1 Clinical Features

Bubble hair is an acquired defect in the clinical appearance and texture of the hair. It can appear at any age but is most common in adolescents and young adults. It is the result of direct heat application to wet hair during styling [45, 46]. The clinical presentation is that of tufts of wiry hair admixed with normal-appearing hair. The affected hair is dry, brittle and breaks easily. A gentle hair care technique may resolve the defect in some cases [47].

18.8.2 Histology

The hair shaft demonstrates clear bubbles in the medullary cavity that are readily visualized on direct whole mount of hair [46, 47] (Fig. 18.7). Electron microscopic examination shows loss of cortical cells and medulla at the sites of the bubbles [47].

18.8.3 Pathogenesis

Bubble hair occurs due to heat injury to the hair by blow dryers or electric curlers used to style hair. The affected hair appears wiry with patchy loss of hair due to excessive fragility [46].

18.9 Monilethrix

18.9.1 Clinical Features

Monilethrix typically presents in early childhood [1]. The condition is characterized by autosomal dominant transmission with high penetrance but incomplete expression. The hair is "stubbled" and brittle with breaks along the characteristic elliptical nodes that are seen on microscopy. Medical therapy with topical minoxidil or oral etretinate may improve hair growth.

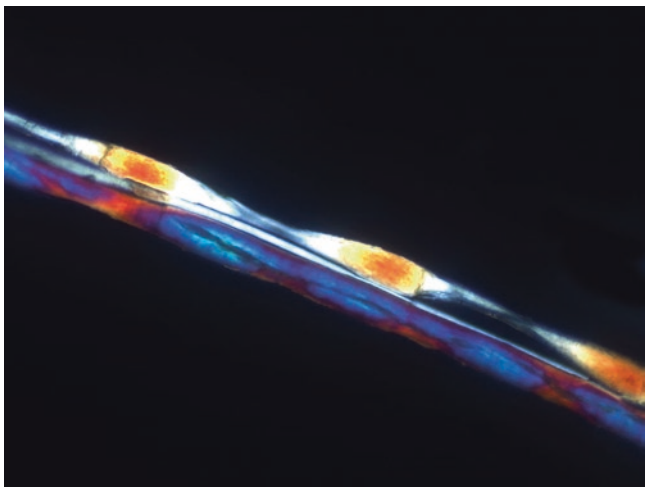

Fig. 18.8 Polarized microscopy accentuates the beaded pattern that characterizes monilethrix (Photo courtesy of Rob Law, MD, Propath Dermatopathology, Dallas, TX)

18.9.2 Histology

Routine light microscopy reveals a regular beading pattern within the hairs. In between the dark beads, pale constrictions are visible with fracturing in these regions (Fig. 18.8). There is a characteristic longitudinal grooving overlying the internodal pale regions, and the cuticle is absent in areas of nodes or beads [48–50].

18.9.3 Pathogenesis

Monilethrix is an autosomal dominant hair disorder caused by heterozygous mutations in the hard type II (basic) keratin genes KRT81, KRT83, and KRT86 [51–53]. The most common mutations are in KRT81 and KRT86 [54]. An autosomal recessive form of monilethrix has been reported with mutations in the desmoglein 4 (DSG4) gene [55–57]. Mutated DSG4 protein predominantly accumulates in the endoplasmic reticulum (ER). Mutated DSG4 undergoes ER-associated degradation, and induces the unfolded protein response and ER stress. These biochemical changes, particularly ER stress, are important in the pathogenesis of monilethrix [56].

18.10 Trichothiodystrophy

18.10.1 Clinical Features

Trichothiodystrophy is a group of rare autosomal recessive disorders characterized by brittle hair with low sulfur content [1]. Clinical findings are vast and varied, affecting almost every organ system with eight defined primary subgroups [1, 59]. On clinical exam, patients have dry, brittle hairs that break easily. More pronounced hair shedding may occur cyclically or following infections. Hair changes typically are not amenable to therapy. Nail changes also are a prominent feature of the condition with over 60 % of affected individuals demonstrating some type of nail abnormalities, including onychodystrophy, onychoschizia, koilonychia, ridging, onychogryphosis, and yellowish discoloration [58, 59]. Forty to fifty percent of patients exhibit significant photosensitivity; however there is no increased risk for skin cancer in these patients. There is a higher incidence of premature death in affected individuals with greatest risk of mortality in children under 10 years of age, most often secondary to sepsis [58, 59].

18.10.2 Histology

The diagnosis is best established on whole hair mount and polarized microscopy. Under light polarization, alternating dark and light bands in the hair strands are evident [60] (Fig. 18.9). The hair demonstrates a regular undulating pattern, and may have some areas that appear similar to the fractures seen in trichorrhexis nodosa. The hair folds over itself creating a ribbon-like appearance [61, 62].

18.10.3 Pathogenesis

Trichothiodystrophy has an autosomal recessive pattern of inheritance. About half of the cases exhibit skin photosensitivity and altered cellular responses to ultraviolet light. The cause of trichothiodystrophy is defects in nucleotide excision repair (NER), which is corrects DNA damage, including that induced by ultraviolet light [63]. The causative molecular defects in the photosensitive form of trichothiodystrophy are the genes xeroderma pigmentosum complementary group B (XPB) and group D (XPD), and general transcription factor IIH subunit 5 (TTDA) [63]. XPB, XPD, and TTDA code for distinct subunits of the transcription factor IIH (TFIIH) [64]. TFIIH is a protein complex involved in both NER and transcriptional regulation [63]. XPB and XPD are ATP-dependent helicases involved in the unwinding of DNA during gene transcription and DNA repair [65, 66].

Because TFIIH functions in both gene transcription regulation and DNA damage repair, defects in the different subunits of TFIIH that affect either gene transcription or DNA repair activity provide the molecular basis for the wide variety of clinical phenotypes associated with mutations in XPB and XPD genes [67–71]. For example, mutations in the XPD subunit of TFIIH that cause defects in DNA repair mechanisms result in xeroderma pigmentosum, a distinct clinical entity of cancer-prone disorder [69].

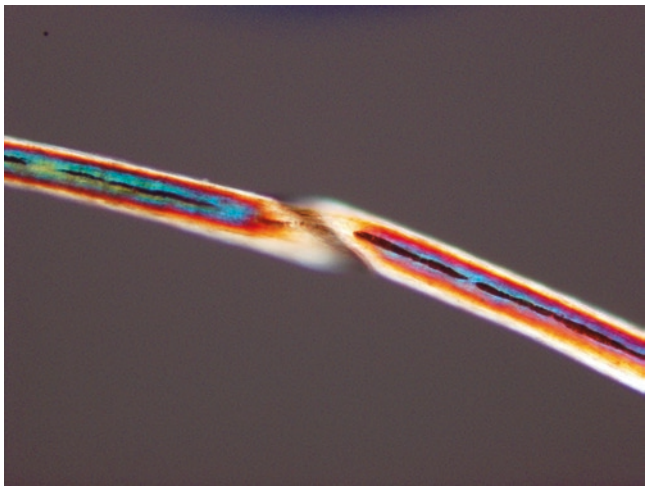

Fig. 18.9 Polarized light demonstrates features of banding and irregular twisting in trichothiodystrophy (photo courtesy of Trevor Beer, MD, Clinipath Pathology, Osborne Park, Australia)

Trichothiodystrophy also presents as a non-photosensitive form with mutations in the TTDN1 gene (TTD non-photosensitive-1) [63, 67, 72]. This form has normal response to ultraviolet light and normal levels of TFIIH. However, dermal fibroblasts from the skin of these patients overexpress matrix metalloproteinase 1 (MMP-1) that degrade collagen in the extracellular matrix [73]. The increase in MMP-1 expression is dependent on TFIIH, and leads to changes in the extracellular matrix and wound-healing properties in the skin in trichothiodystrophy.

18.11 Trichoptilosis

18.11.1 Clinical Features

Trichoptilosis or "split ends" refers to fraying and longitudinal separation of the distal aspects of the hair shaft. It is not specific to any particular type of alopecia, but it is the end result of persistent chemical and physical trauma to the hair [74, 75]. The condition can be associated with other hair shaft abnormalities, such as trichorrhexis nodosa and trichoclasis, and it can be seen in those with congenital brittle hair [74]. In acquired cases, affected individuals may have normal appearing hair with a primary complaint of hair breakage and shedding at the scalp. Acquired trichoptilosis resolves with modification of haircare practices and products.

18.11.2 Histology

Whole mounts of hair shafts reveal fragmented and frayed ends. These changes are secondary to repeated trauma.

18.12 Melanonychia

18.12.1 Clinical Features

Melanonychia is the descriptive term for pigmentation of the nail. Longitudinal melanonychia is the most common variant of melanonychia [77]. Most cases of longitudinal melanonychia are secondary to benign melanocytic hyperplasia, primarily nevi [77]. Nail matrix nevi most commonly occur on the fingers, especially the thumb. Longitudinal melanonychia is a linear band of tan, brown, or black pigmentation extending from the nail matrix (beneath the proximal nail fold) to the distal nail plate. Even brown-black pigmentation is seen in about two-thirds of cases, with periungual pigmentation present in one-third of cases [77] (Fig. 18.10).

Management is dependent upon the presentation and behavior of the pigmentary band. Nail matrix melanoma in children is rare [77]. However, the focus of melanocytic hyperplasia should be removed completely if excision is pursued.

18.12.2 Histology

The clinical term melanonychia refers to pigmentation of the nail. This raises a differential diagnosis that is often easily resolved by biopsy. The histologic findings differ greatly based upon the etiology of the subungual pigment. In some cases, the pigmentation is hemosiderin secondary to subungual trauma and hemorrhage. In other cases, the pigment is melanin that resides within melanophages, and is secondary to inflammation. In these cases, it is important to completely exclude a melanocytic proliferation [78]. Fungal infection can also give rise to melanonychia. The diagnosis is established by the identification of fungal elements within the biopsy, either on routine H&E sections or on fungal stains [79]. Other cases of melanonychia are seen as part of Laugier-Hunziker syndrome, wherein increased basilar melanin pigment is present without melanocytic proliferation [80]. Lentigo simplex occurring within the subungual plate also has similar findings with many pigmented basal keratinocytes and an essentially normal number of melanocytes. In these cases, pigment incontinence may result in melanin within melanophages in the papillary dermis.

Melanoma must be excluded in all cases of clinical melanonychia [81]. The findings are those of acral melanoma with cytologically atypical melanocytes present as nests and single cells within the epidermis, often with prominent Pagetoid upward migration. Within the dermis, similar melanocytes may be present and do not mature with progressive descent. Mitoses may be present [82].

Fig. 18.10 A longitudinal pigmented streak extends across the nail in melanonychia (photo courtesy of Visual DX, Rochester, NY)

18.12.3 Pathogenesis

Melanonychia can be due to a variety of etiologies. It can result from activation of nail matrix melanocytes, melanocytic hyperplasia, and invasion of the nail matrix by melanin-producing pathogens [82–84]. Melanocytic activation is a major cause of melanonychia. There is increased production of melanin pigment by activated melanocytes in the nail matrix. Melanonychia often originates in the distal portion of the nail matrix, because most active melanocytes reside in the germinative layers of the distal nail bed [85, 86]. In melanocytic hyperplasia, there is increased number of melanocytes, such as in a melanocytic nevus or melanoma, thus leading to more melanin production [87]. Skin conditions that are associated with melanocytic hyperplasia include psoriasis, lichen planus, and amyloidosis [87].

Fungal infection of the nail can also result in melanonychia. The fungal species that produce melanin pigment include the dematiaceous fungus *Scytalidium dimidiatum* and the non-dematiaceous dermatophyte *Trichophyton rubrum*, as well as less common fungi of the genera *Alternaria* and *Exophiala* [79].

Melanonychia that manifests as multiple bands, and involves both fingernails and toenails is often due to systemic causes, such as Addison's disease, nutritional disorders, and AIDS [87, 88]. Other causes of melanonychia include onychotillomania, nail biting, frictional trauma, carpal tunnel syndrome, medications (especially chemotherapeutic agents), and electron beam therapy [89–91].

18.13 Erythronychia

18.13.1 Clinical Features

Erythronychia is defined most simply as "red nails" with categorization based upon the location of the redness in the nail plate, specifically the lunula or the nail bed [92]. Redness of the nail plate is often a consequence of exposure to exogenous agents. Red lunulae can be a manifestation of almost any underlying systemic disease [92].

Fig. 18.11 Erythronychia presents as linear red bands extending across the nail plate of multiple fingernails in this patient with Darier Disease. V-shaped nicking at the distal edge of the nail is also present (photo courtesy of Danielle Applebaum, MD, Baylor College of Medicine, Houston, TX)

Longitudinal erythronychia is characterized by a linear red band or streak across the nail plate, and represents involvement of the lunula and nail bed (Fig. 18.11). Longitudinal erythronychia affecting only one digit is usually secondary to a localized cutaneous neoplasm. Polydactylous longitudinal erythronychia is often the result of an underlying local or systemic inflammatory dermatosis, such as Darier Disease, lichen planus, and graft-versus-host disease [92].

18.13.2 Histology

The red lunula that gives rise to erythronychia is often caused by dilated capillaries in the papillary dermis [93]. This is a nonspecific secondary phenomenon that can occur as a result of many different conditions. In other cases, the clinical erythema is secondary to inflammation that occurs in many dermatologic conditions [94]. Rarely, erythronychia may be secondary to a tumor in the nail plate [84].

18.13.3 Pathogenesis

Erythronychia can be caused by a neoplastic process, particularly if limited to one digit. The most common cause is onychopapilloma with other causes including glomus tumor, Bowen's disease, melanoma, basal cell carcinoma, and subungual arteriovenous malformation [95, 96]. When erythronychia is present on multiple digits, there is often an underlying local or systemic etiology, the most common being lichen planus, Darier's disease, systemic amyloidosis, and graft-versus-host disease.

18.14 Yellow Nail Syndrome

18.14.1 Clinical Features

Yellow nails may be secondary to advanced age, medications, or systemic disease. Yellow nail syndrome is characterized by the triad of yellow chromonychia, respiratory disturbance, and lymphedema with the associated nail changes being the most specific characteristic of the disorder [92]. The nails in yellow nail syndrome grow slowly and are discolored, thickened, and hard with cuticular loss and longitudinal over-curvature of the nail plate [93] (Fig. 18.12). Secondary onycholysis and onychomadesis with subsequent loss of the nail plate can be seen. Ten to thirty percent of cases resolve spontaneously. Treatment success has also been reported with high-dose vitamin E [92].

18.14.2 Histology

Nails in this condition are rarely biopsied, and the histologic findings are not well described. In a single case, the normal site-specific, vascular-rich stroma is replaced by dense sclerosis leading to lymphatic obstruction [97].

18.14.3 Pathogenesis

The pathogenesis of yellow nail syndrome is not known. However, genetics, immune status (immunodeficiency and autoimmunity), and paraneoplastic diseases have been suggested as contributing factors in the disease etiology [98]. Yellow nail syndrome has been associated with a number of systemic diseases, including rheumatoid arthritis, Guillain–Barre syndrome, and malignancies [99]. Studies of the role of genetics in yellow nail syndrome showed that some patients have a positive family history [100, 101]. However, other studies have suggested that this is an acquired disorder [102]. Given the triad of slow-growing yellow nails, lymphedema, and chronic respiratory symptoms (e.g., pleural effusions) in yellow nail syndrome, the nail changes may be associated with structural or functional abnormalities in the lymphatic system [103–105]. Dilated vascular channels, possibly lymphatic vessels, have been observed in the nail beds of affected individuals [97]. An increase in microvascular permeability may also be a contributing factor [106]. Accumulation of lipofuscin in the nail plate due to lipid oxidation could give rise to the characteristic yellow discoloration of the nails [105, 107].

Fig. 18.12 All the nails on both hands and feet demonstrate thickening and discoloration in yellow nail syndrome. Several nails also show irregular curvature (photo courtesy of Visual DX, Rochester, NY)

18.15 Ectodermal Dysplasia, Anhidrotic and Hidrotic

18.15.1 Clinical Features

X-linked anhidrotic (hypohidrotic) ectodermal dysplasia accounts for the majority of cases of ectodermal dysplasia [108]. Autosomal dominant and autosomal recessive variants exist, but they are far less common. Prevalence reports vary, but in a national cross-sectional study in Denmark, the prevalence was estimated between 1.6 to 22 per 100,000 individuals [108]. Incidence in the United States is estimated at 1 per 100,000 live births [109].

The cardinal features of the most severe variants of anhidrotic ectodermal dysplasia are hypohidrosis, hypotrichosis, and hypodontia [110] (Figs. 18.13 and 18.14). Additional dental abnormalities include conical-shaped incisors and abnormally-shaped molars. Hair at the scalp, eyebrows, and eyelashes is sparse, thin, and brittle. Atopy and atopic dermatitis are seen commonly, with most cases presenting prior to the first year of life [110]. Other clinical features include frontal bossing, periorbital hyperpigmentation, retruded mid-face, saddle nose deformity, and thick, everted lips. The greatest morbidity is seen within the first 3 years of life with mortality rates between 2 and 20 %, primarily attributed to complications of hyperthermia [109, 111]. Patients are also at increased risk for poor nutrition, impaired growth, foul smelling nasal discharge, and recurrent respiratory infections.

18.15.2 Histology

There is a rapidly growing number of syndromes that are characterized by various components of ectodermal dysplasia involving many ectodermal arenas. The histologic findings

Fig. 18.13 A child presents with frontal bossing, sparse scalp hair and eyebrows, and thick everted lips that are characteristic of anhidrotic ectodermal dysplasia

Fig. 18.14 Conical teeth are a frequent feature of anhidrotic ectodermal dysplasia

are more dependent upon the hidrotic or anhidrotic status than upon the particular syndrome, and they will be presented with that separation.

Anhidrotic ectodermal dysplasia demonstrates loss or hypoplasia of eccrine and apocrine structures [112] (Figs. 18.15 and 18.16). Acrosyringia may be present but are not fully developed. The overlying epidermis is generally thinned with blunting of the rete ridge pattern. Pilosebaceous

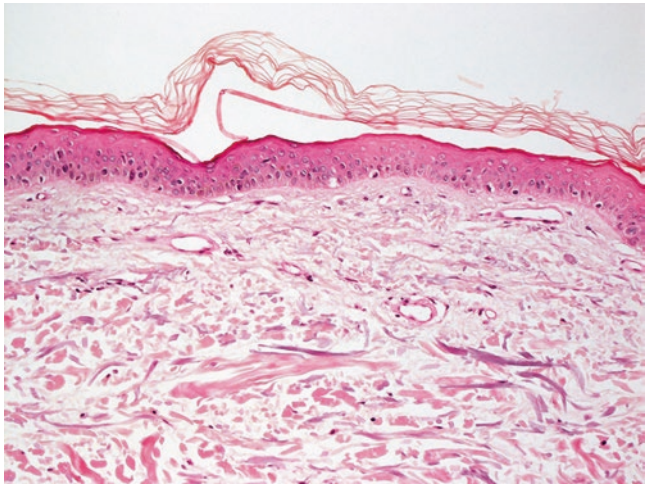

Fig. 18.15 A thin epidermis overlies a dermis that lacks eccrine structures in anhidrotic ectodermal dysplasia

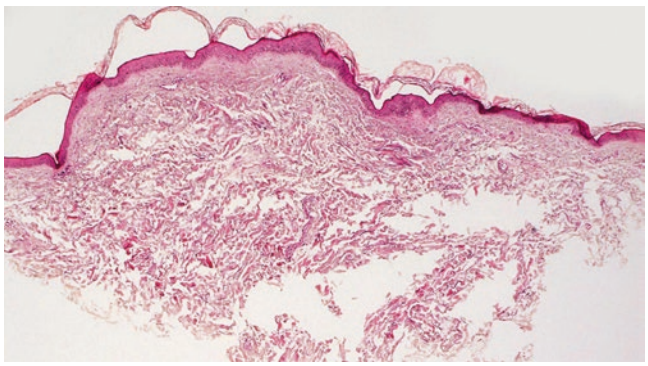

Fig. 18.16 Acrosyringia and dermal eccrine structures are absent in anhidrotic ectodermal dysplasia

units are usually reduced in patients with anhidrotic ectodermal hyperplasia, although a rare case of sebaceous hyperplasia has been described in a patient with anhidrotic ectodermal dysplasia [113].

Hidrotic ectodermal dysplasia demonstrates marked overlying hyperkeratosis. An atrophic epidermis is present overlying a dermis that has normal numbers of eccrine structures. The changes are most pronounced on acral skin. In other sites, diminished numbers of sebaceous glands may be apparent [114]. A definitive histologic diagnosis is not possible, but one sees features that would correlate with a clinical syndrome.

18.15.3 Pathogenesis

Ectodermal dysplasia is a hereditary disorder characterized by morphological and functional hypoplasia of ectodermally-derived tissues, such as abnormal teeth, sparse hair, and sweat

gland dysplasia [115, 116]. Two common types of ectodermal dysplasia are X-linked recessive anhidrotic/hypohidrotic type and autosomal dominant hidrotic type. X-linked anhidrotic ectodermal dysplasia is caused by mutations in ectodysplasin-A (EDA), which is a tumor necrosis factor (TNF) ligand, and ectodysplasin-A receptor (EDAR) [117–119]. Ectodysplasin has important functions in embryonic development and the formation of ectodermal structures. Anhidrotic ectodermal dysplasia with immunodeficiency has been found to be caused by TRAF6 (TNF receptor-associated factor 6, E3 ubiquitin protein ligase) gene mutations and impairment of ubiquitin binding [120, 121]. Other studies have revealed small deletions or non-sense mutations in the zinc-finger domain of NEMO (IKK-γ) that leads to altered or reduced function of the NF-κB pathway [122]. Other studies have found mutation in the gene KREMEN1 (kringle-containing transmembrane protein 1), which is a modulator of Wnt signaling that is responsible for ectodermal dysplasia including oligodontia in some families [123]. Hidrotic ectodermal dysplasia is caused by mutations in the GJB6 (gap junction protein, beta 6) gene, which encodes connexin 30 [124]. Connexins are transmembrane proteins that are important in the formation of intercellular gap junctions [125].

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Iatrogenic Dermatologic Conditions

19

19.1 Halogenodermas

19.1.1 Clinical Features

Halogenoderma is a rare dermatosis that results from the accumulation of halogenides following therapeutic exposure to bromide, fluoride, iodide, or iodine-containing products [1]. Occurrence appears to be greater in individuals unable to clear these compounds, such as those with acute or chronic renal failure [2]. Cutaneous lesions vary and may include acneiform eruptions, vegetative plaques, bullae, and ulcers [1–4]. With elimination of iodides and bromides, lesions slowly resolve over weeks, although resolution may be hastened by supplemental use of diuretics and corticosteroids [2, 5].

19.1.2 Histology

This group of disorders includes iododerma and bromoderma. The histologic features are quite similar, and they will be described together. The epidermis is hyperkeratotic and demonstrates pseudoepitheliomatous hyperplasia in some cases, or it can be entirely normal in others [6]. Within the dermis and occasionally within the epidermis, there is a brisk lymphohistiocytic infiltrate with abundant eosinophils and neutrophils (Figs. 19.1 and 19.2). Intraepidermal abscesses are frequently encountered [2, 4].

Halogen-induced panniculitis has been attributed to treatment with potassium bromide. A lymphocyte-mediated panniculitis with overlying ulceration was described. Unlike the majority of eruptions in halogenodermas, abundance of neutrophils and eosinophils was not noted in bromoderma. There have been no subsequent reports of a similar process, so if this occurs, it appears to be extremely uncommon [7].

The histologic differential diagnosis of halogenoderma is primarily based upon the epidermal hyperplasia. It includes deep fungal infection, mainly chromoblastomycosis, blastomycosis, and sporotrichosis. Special stains for microorganisms are helpful in excluding these infectious entities, along with the lack of significant granulomatous reaction in halogenodermas. Pemphigus vegetans is also in the differential diagnosis, but the acantholysis seen in that entity is not present in halogenodermas. Blastomycosis-like pyoderma also enters into the differential diagnosis. Observation of microorganisms or positive tissue cultures is helpful in resolving this dilemma. Squamous cell carcinoma and keratoacanthoma may demonstrate similar histologic changes, but cytologic atypia is more pronounced in these cases. Moreover, these tumors are uncommon in the pediatric population.

19.1.3 Pathogenesis

The pathogenesis of halogenoderma is unknown. Halogenoderma usually occurs in association with iodide and bromide ingestion as well as fluoride and chloride ingestion. Halogens such as lithium act at the level of the thyroid gland to block the release of thyroxine. There are reports of association between lithium use, and the development of goiter and hypothyroidism [8]. Lithium also inhibits iodide uptake in the thyroid gland [9].

19.2 Anticonvulsant-Induced Lymphoid Hyperplasia/Pseudolymphoma Syndrome

19.2.1 Clinical Features

Pseudolymphoma syndrome is a rarely reported cutaneous hypersensitivity to anticonvulsant therapy. Two to three weeks following initiation of the causative medication, patients develop skin lesions characterized by erythematous,

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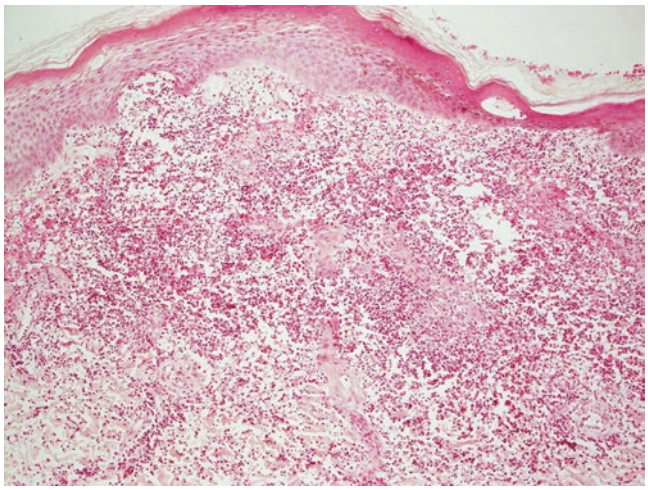

Fig. 19.1 A dense dermal infiltrate of neutrophils and eosinophils is present in iododerma

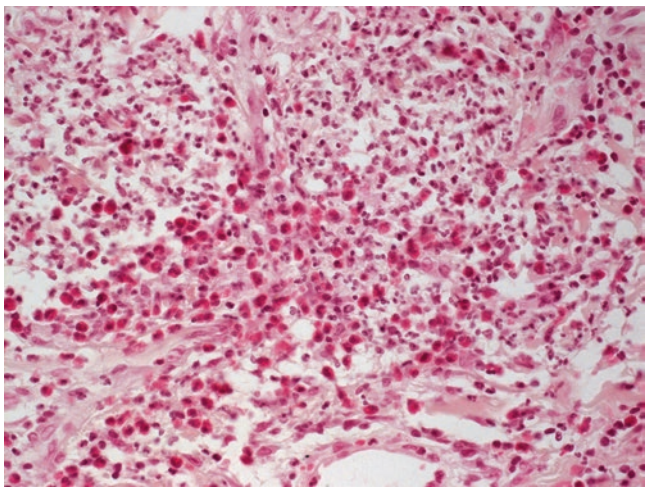

Fig. 19.2 Iododerma demonstrates abundant and diffuse dermal neutrophils and eosinophils

firm subcutaneous nodules or papulonodules with the potential for progression to erythroderma [10]. Some reports highlight the minimal degree of concomitant systemic symptoms, while others describe associated fever, lymphadenopathy, arthralgia, transaminitis with hepatosplenomegaly, and blood cell dyscrasia, such as eosinophilia and, less commonly, leukopenia and agranulocytosis [10, 11]. Additionally described clinical features include a generalized morbilliform eruption, although this may be more appropriately qualified as DRESS syndrome (drug rash with eosinophilia and systemic symptoms), especially when striking systemic insult is noted [11]. Significant improvement is seen within weeks of cessation of the responsible anticonvulsant drug [10, 11].

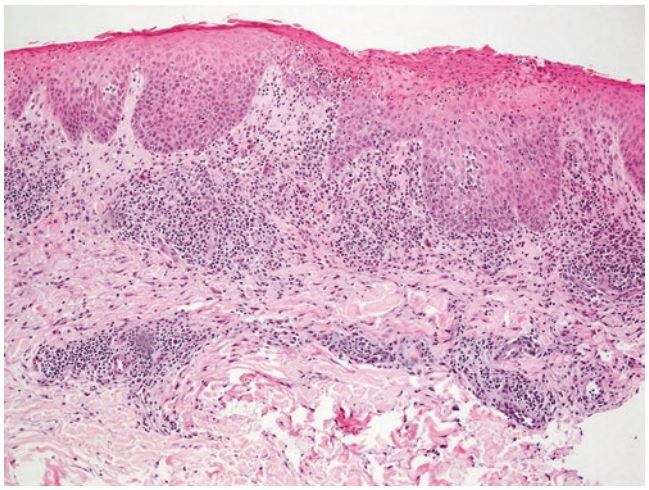

Fig. 19.3 Dilantin hypersensitivity reaction demonstrates a brisk lymphoid infiltrate, often with abundant exocytosis into the overlying epidermis in anticonvulsant-induced lymphoid hyperplasia

19.2.2 Histology

Anticonvulsant therapy may result in a florid cutaneous lymphocytic hyperplasia [12]. While originally described secondary to phenytoin, a similar process also may occur secondary to treatment with other anticonvulsants [13, 14]. In some cases, the changes are strikingly similar to those seen in mycosis fungoides [13, 15]. There is slight epidermal hyperplasia with marked exocytosis of lymphocytes into the epidermis (Fig. 19.3). Spongiosis is present to varying degrees or may be virtually absent. Pautrier's microabscesses may be present as well [11]. The lymphocytes are present within the superficial dermis, and may or may not extend deeper into the reticular dermis (Fig. 19.4). Scattered eosinophils are present in some but not all cases. In other cases, they may be abundant. Lymphocytes may appear atypical and enlarged.

Immunophenotyping and genotyping are helpful in making the distinction from mycosis fungoides. In drug-induced eruption, there is a mixture of CD4+ and CD8+ T lymphocytes, while in mycosis fungoides, a marked predominance of one population (usually CD4+ cells) is seen [16]. Increased numbers of CD30+ cells are present in some cases of this drug-mediated process [14]. Clonal rearrangement studies are detected in most cases of mycosis fungoides, and would be unusual in drug eruption.

19.2.3 Pathogenesis

The mechanism of anticonvulsant-induced lymphoid hyperplasia is not known. It has been suggested that anticonvulsants, such as phenytoin, suppresses both cellular and

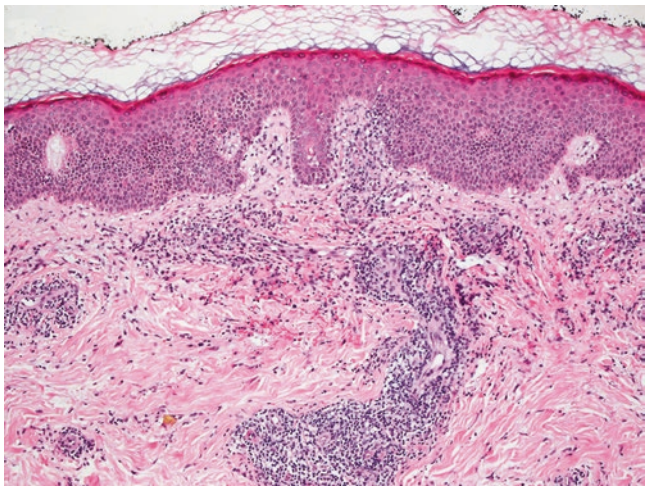

Fig. 19.4 A dense lymphoid infiltrate within the dermis and focally extending into the epidermis is seen in Dilantin hypersensitivity reaction in anticonvulsant-induced lymphoid hyperplasia

humoral immune responses, and the loss of suppressor T-cell function may result in increased proliferation of clones of aberrant T lymphocytes [17–19].

Fig. 19.5 DRESS presents as morbilliform eruption of erythematous papules and macules that coalesce along the trunk in a teenage patient who presented with lymphadenopathy, transaminitis, and eosinophilia weeks after starting a new antiepileptic medication

19.3 Drug-Induced Hypersensitivity Syndrome and Protease Inhibitor-Induced Eruptions

19.3.1 Clinical Features

Drug-induced hypersensitivity syndrome (DIHS), also known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), is a multi-organ reaction to a number of different medications. DRESS is classically defined by the onset of fever, rash, lymphadenopathy, and hepatitis. Symptoms typically begin 2–6 weeks following initiation of the inciting drug [20].

According to the European Registry of Severe Cutaneous Adverse Reaction study group, the bulk of cases (35 %) are secondary to aromatic antiepileptic medications, specifically carbamazepine, phenobarbital, and phenytoin, although there are reports of DRESS with valproic acid and zonisamide [21]. Antimicrobial sulfonamides and dapsone account for 12 % of cases, while other antibiotics account for 11 % of cases [21]. Individuals with certain HLA-haplotypes may be at increased risk for the disorder secondary to predisposition to impaired drug metabolism [20]. However, no consistent racial or gender predilection has been demonstrated [22].

Dermatitis is present in >90 % of affected individuals, beginning as an erythematous, morbilliform eruption of coalescing macules and papules at the face, upper trunk, and proximal extremities with distal spread and potential for erythroderma (Figs. 19.5 and 19.6) [22]. Pustules may be noted in darker-skin individuals. Pronounced facial edema and symmetric lymphadenopathy are key features (Fig. 19.7). Mucosal surfaces can be involved as well with conjunctivitis, "strawberry tongue," pharyngitis, and oral ulcerations. However, the frank necrosis of erythema multiforme and Stevens Johnson syndrome/Toxic Epidermal Necrolysis are not frequently seen [22]. Hematologic abnormalities include eosinophilia, anemia as well as lymphocyte and platelet dysregulation [22].

Fig. 19.6 DRESS may present in darker-skin with pustules interspersed within the morbilliform eruption. Erythema may be more difficult to appreciate

Fig. 19.7 Facial edema and cervical lymphadenopathy are key features of DRESS

Rapid recognition of the clinical features of DRESS and immediate discontinuation of the offending agent are key to clinical management in order to minimize symptoms and prevent more damaging sequelae. Further treatment is dependent upon the clinical progression, and the degree of systemic involvement. Skin changes may persist for weeks to months after stopping the offending drug with subsequent desquamation and possible post-inflammatory dyschromia.

Morbidity and mortality in DRESS are primarily due to hepatic disease, which was noted in 60–80 % of pediatric cases in one report [22]. Severity ranges from mild transaminitis and hepatomegaly to fulminant hepatic failure [22]. Renal manifestations (nephritis, hematuria, and proteinuria) were noted in 15 % of patients [22]. Acute and chronic thyroid dysregulation may be seen as well, warranting screening and monitoring even after resolution of symptoms. Pancreatitis, pneumonitis, pulmonary edema, myositis, and myocarditis have been reported in DRESS with only rare incidence of associated central nervous system dysregulation [22]. The mortality rate has been reported to be as high as 10 %, although death is less likely in children [21, 23].

19.3.2 Histology

Cutaneous eruption in DRESS syndrome demonstrates a superficial and deep perivascular inflammatory infiltrate with abundant eosinophils [27–29]. Epidermal spongiosis is a common finding, and scattered dying epidermal keratinocytes are present in a minority of cases [30] (Figs. 19.8 and 19.9). In some cases, eosinophils are not abundant in the skin lesions despite systemic eosinophilia [31]. This diagnosis requires clinical correlation, since it has no specific diagnostic histologic features.

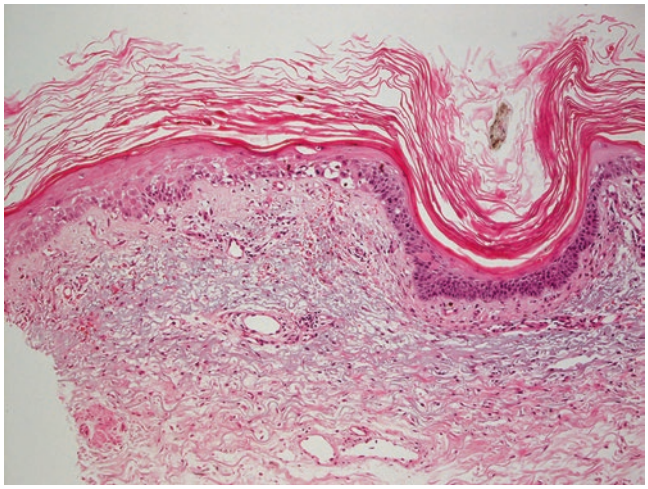

Fig. 19.8 An interface dermatitis with focal exocytosis of lymphocytes into the epidermis in a reaction to protease inhibitors in DRESS

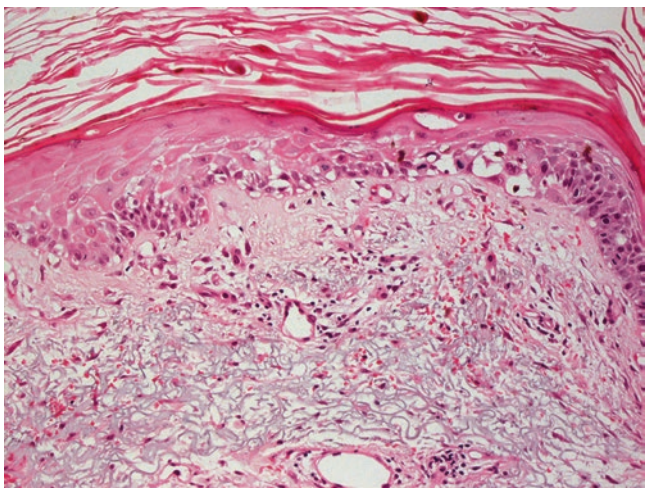

Fig. 19.9 Extensive basal vacuolization is seen with a drug-induced reaction in DRESS

Protease inhibitors are responsible for inducing cutaneous eruptions with myriad histologic patterns. Nonspecific superficial and deep perivascular lymphohistiocytic infiltrate is a common finding [24, 25]. An interstitial dermal infiltrate is described in some patients, as well as an interface dermatitis with scattered dying keratinocytes and a superficial perivascular lymphocytic infiltrate [25]. Other presentations include neutrophil- and lymphocyte-mediated vasculitis [24, 26].

19.3.3 Pathogenesis

The pathogenesis of DRESS remains to be determined. However, DRESS is believed to be associated with the reactivation of the human herpesvirus family, particularly Epstein–Barr virus (EBV) and human herpesvirus-6 (HHV-6) [35–38].

Immunological reactions to certain drugs and HHV-6 reactivation appear to play a key role in the severity of DRESS. It has been suggested that detection of HHV-6 reactivation is a useful marker in the diagnosis and prognosis of this syndrome [38]. In the case of HHV-6 reactivation, there are increased HHV-6 antibody titers and virus DNA levels [37, 38]. Moreover, the levels of tumor necrosis factor-α (TNF-α) are elevated in early disease stage. It has been proposed that TNF-α levels may be a useful marker of the disease process because it is an early marker of HHV-6 reactivation [39]. Another marker that could be useful in distinguishing DRESS with HHV-6 reactivation from other drug reactions is serum TARC (thymus and activation-regulated chemokine)/CCL17 levels, which is elevated in patients with HHV-6 reactivation and not in those without [40].

Induction of CD8+ T lymphocytes in response to EBV infection, and the production of TNF-α and interferon-γ (IFN-γ) by activated T lymphocytes may contribute to the immunological response in DRESS [41]. CD8+ T lymphocytes are induced in the early stage of disease, followed by CD4+ T lymphocytes and FoxP3+ regulatory T (Treg) cells in the later stage [42]. The levels of FoxP3+ Treg cells are significantly increased in the skin lesions of DRESS as compared with other skin eruptions, such as graft-versus-host disease [43]. Moreover, the ratio of FoxP3+ Treg cells to CD3+ T lymphocytes is significantly higher in DRESS lesions. The increased number of FoxP3+ T cells that infiltrate skin lesions in DRESS may play a protective role in limiting the extent of epidermal damage in this disorder. Skin eruptions associated with protease inhibitors may be related to the interferon pathway. For example, the protease inhibitors telaprevir and boceprevir for the treatment of hepatitis C are targeted to NS3/NS4 proteases [32]. NS3/NS4 complex suppresses the activation of interferon regulatory factor-3 (IRF-3), which is a major transcription factor [33, 34]. IRF-3 promotes the production of interferon, and regulates many of the interferon-stimulated genes in response to viral infection. Protease inhibitors may increase interferon efficacy, but they also increase skin rash associated with interferon [32].

19.4 Radiation Dermatitis

19.4.1 Clinical Features

Skin reactions are a common and expected effects of radiotherapy. Acutely, dermatitis to radiotherapy is characterized by in-field erythema that evolves to desquamation that can last for weeks [44]. Localized erosions and hemorrhagic crusting can occur as well. Patients may complain of mild discomfort (tenderness or pruritus) at the affected area. Skin changes are graded from a level of 1 to 4 dependent upon the degree of erythema, edema, desquamation, and presence of necrosis, with grade 4 disease characterized by hemorrhagic ulcerations [45]. In patients with long-term unprotected sun exposure at treated areas, chronic changes may be seen months to years following therapy, most often characterized by some degree of poikiloderma [44]. The likelihood of secondary skin cancer is greater in those who have received ionizing radiation, with Caucasians and those with exposure at younger ages at greatest risk for cutaneous malignancy [45].

19.4.2 Histology

Early radiation dermatitis is characterized by the presence of dying keratinocytes, spongiosis, vascular thrombosis, and extravasation of erythrocytes [46]. In severe acute radiation dermatitis, a dense neutrophilic infiltrate and necrosis may be present. Neutrophils extend into the epidermis with concomitant apoptosis. Well-developed lesions demonstrate more characteristic changes. Hyperkeratosis overlies an epidermis that may be slightly atrophic. Spongiosis and basal vacuolization are present in some cases, but may not be apparent. Within the dermis, there is dense dermal fibrosis with elastotic degeneration of collagen surrounding dilated blood vessels (Figs. 19.10 and 19.11). Endothelial cells are often edematous. A perivascular lymphocytic infiltrate and fibrin thrombi within blood vessels results in a pseudovasculitis appearance [47]. A useful diagnostic clue is the presence of radiation fibroblasts, which are enlarged and hyperchromatic fibroblasts seen coursing between collagen bundles throughout the dermis. A pattern of subacute changes that resembles those present in cutaneous graft-versus-host disease has been described. In these cases, an interface dermatitis with abundant dying keratinocytes and lymphocytes is present [46].

19.4.3 Pathogenesis

Ionizing radiation induces dermal and vascular injuries [45]. Transforming growth factor (TGF)-β plays an important role in the development of chronic radiation dermatitis. Ionizing radiation activates TGF-β, which in turn promotes the differentiation of skin fibroblasts into myofibroblasts. TGF-β induces the production of extracellular matrix proteins (such as collagen, fibronectin and proteoglycan) and inhibits the degradation of these proteins, leading to tissue fibrosis [48–51]. Studies of individuals exposed to radiation showed increased collagen production in cells from skin after a single dose of radiation in comparison with nonirradiated skin [52]. In animal models

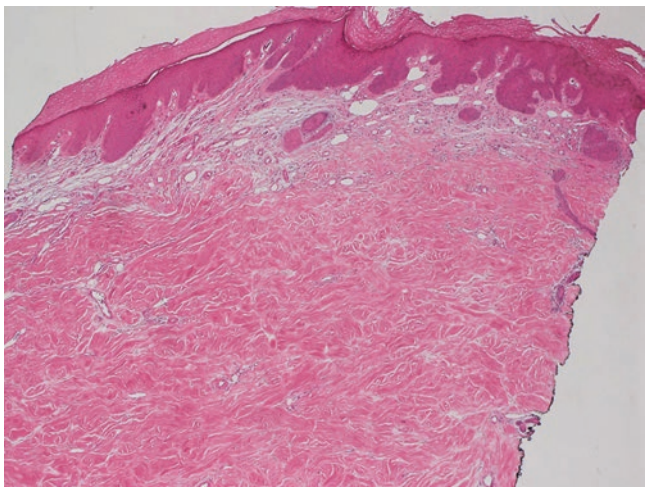

Fig. 19.10 Dense dermal sclerosis characterizes the changes seen in radiation dermatitis

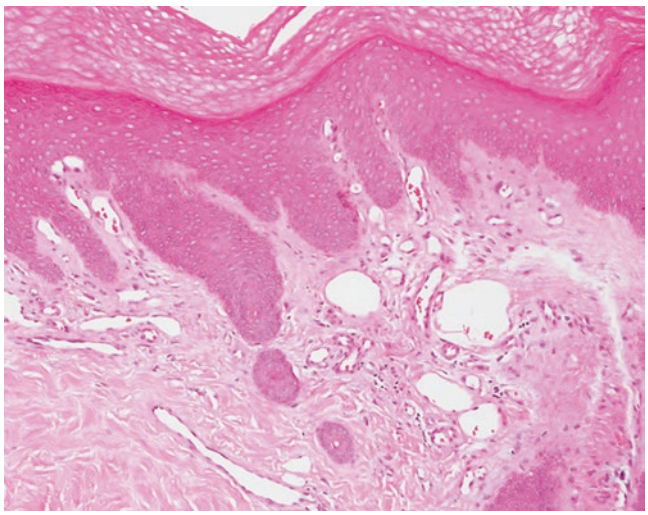

Fig. 19.11 Vascular ectasia and some endothelial cell prominence are seen in radiation dermatitis

with defective TGF-β pathway, the animals have less tissue fibrosis after irradiation, and have increased tissue-healing processes [53]. Conversely, upregulation of TGF-β has been observed in fibrotic tissue of irradiated patients but not in non-irradiated controls [49]. These findings confirm the role of TGF-β in cellular and tissue responses to radiation. In addition, endothelial cell and vascular damages due to radiation can activate the coagulation system, which in turn promotes cytokine production and leads to a robust inflammatory response and matrix deposition [45, 54]. Importantly, radiation-induced tissue injury can result in cutaneous malignancies later on, such as basal cell carcinoma, squamous cell carcinoma, fibrosarcoma, and angiosarcoma, but these complications are rarely seen during childhood [45, 55].

19.5 Striae Distensae

19.5.1 Clinical Features

Striae distensae are a common finding in the general population, most notably in adolescents. They occur in approximately 35 % of girls and 15 % of boys between 9 and 16 years old [56]. Predisposing factors include rapid growth, obesity, puberty, pregnancy, positive family history, Cushing syndrome, and prolonged use of corticosteroids (both systemic and potent topicals) [57].

Striae are characterized by atrophic, linear, pink to purple depressions at areas predisposed to stretching, such as the lower back, buttocks, thighs, breasts, abdomen, and shoulders (Figs. 19.12 and 19.13). Treatment is difficult with cosmetically disappointing results. However, striae frequently lighten over time, especially those occurring during adolescence [57].

19.5.2 Histology

Biopsies from striae distensae demonstrate minimal epidermal changes. Atrophy is seen in some cases. The major changes are within the dermis and are quite subtle. The easiest way to detect these changes is by comparison with adjacent normal skin. Collagen fibers in striae distensae are thinned and run parallel to the overlying epidermis. Elastic fibers travel in parallel, and are also thinned with diminished waviness as compared with the adjacent normal dermis. Decreased elastic tissue fibers are seen on elastic tissue stains, but scanning electron microscopy suggests that abundant immature fibers persist [58]. It has been suggested that the earliest changes in striae distensae include mast cell degranulation and subsequent elastolysis. Macrophages phagocytize these fragmented elastic tissue fibers [59]. Another study suggests that fine, non-wavy elastic tissue fibers are associated with relatively early lesions, but late-stage lesions develop thick and highly tortuous fibers [60]. Histologic features are not completely delineated for this entity, although all studies suggest that there are changes in dermal elastic tissue fibers that can be distinguished from adjacent normal skin.

Long-term use of penicillamine is associated with similar histologic findings, although a “lumpy-bumpy” pattern of elastic tissue fibers has been described. These changes are apparent on elastic tissue stains and ultrastructural examination [61].

The differential diagnosis of striae distensae includes normal skin and a dermal scar. Normal skin will demonstrate a typical pattern on elastic tissue stains that is not seen in striae distensae. Recent scar tissue is devoid of elastic tissue fibers,

Fig. 19.12 Striae distensae presents as symmetric erythematous, atrophic, linear plaques (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

Fig. 19.13 Striae distensae also may be hypopigmented as seen in this example of the lower back

differentiating this from the appearance of striae distensae [62]. Some authors have even postulated that striae distensae are a form of dermal scarring, although this hypothesis has not been universally accepted [58].

19.5.3 Pathogenesis

Striae distensae have been described in monozygotic twins and Marfan syndrome, indicating a genetic component in their development [63, 64]. Striae distensae commonly develop in adolescents with rapid weight gain, obesity, and growth spurt as the primary influencing developmental factors [57]. Several possible etiologies of striae distensae have been suggested, including mechanical stretching of the skin, hormonal influences, and abnormalities in the skin connective tissue [57]. Hormones, such as adrenocorticotropic hormone and cortisol, are believed to affect fibroblast activity, leading to abnormal changes in collagen and elastin fibers [65]. There is decreased expression of connective tissue proteins, such as collagen, elastin, and fibronectin in striae distensae [66, 67]. Genome-Wide Association Analysis (GWAS) has suggested that elastic microfibrils and variations in elastic fiber component of the skin contribute to the development of non-syndromic striae distensae [68]. Some potential genes that may have a role in striae distensae are ELN (elastin), SRPX (sushi-repeat containing protein, X-linked), HMCN1 (hemicentin-1), and TMEM18 (transmembrane protein 18) [68].

19.6 GM-CSF-Related Drug Eruption

19.6.1 Clinical Features

Cutaneous effects of granulocyte-macrophage colony stimulating factor (GM-CSF) are described in both adult and pediatric populations [69]. A distinct eruption of erythematous papules and plaques in arcuate and annular arrangements has been seen in patients with a myriad of underlying conditions requiring GM-CSF [70]. A number of other neutrophilic dermatoses have been reported with the use of GM-CSF as well, including localized injection reactions, pyoderma gangrenosum with or without bullae, Sweet's syndrome, hypersensitivity vasculitis, and generalized folliculitis [70]. Skin lesions regress following cessation or lowering the dose of GM-CSF therapy [69, 70].

19.6.2 Histology

Histologic changes seen after administration of GM-CSF include a diffuse dermal inflammatory infiltrate consisting of mainly neutrophils with scattered lymphocytes, eosinophils, and macrophages [71–74]. Macrophages are characteristically enlarged, and percolate individually between collagen bundles. This finding may present a clue to the diagnosis. Ingested elastin can be observed within these cells [74, 75]. The infiltrate is centered mainly in the superficial papillary dermis, especially in the papillary dermal tips, and there is no predilection for vascular involvement. Rare dying keratinocytes may be present [72].

The histologic differential diagnosis includes Sweet syndrome, which can be differentiated by clinical history and the lack of enlarged macrophages. A purely neutrophilic dermal

infiltrate is more characteristic following treatment with GM-CSF [76]. Dermatitis herpetiformis could also enter the histologic differential diagnosis, but it would lack the characteristic macrophages and has a very different clinical history. Direct immunofluorescence findings in dermatitis herpetiformis are not seen in GM-CSF-related drug eruptions. Leukocytoclastic vasculitis is also a consideration, and it is easily differentiated from GM-CSF eruptions by the lack of vascular destruction.

19.6.3 Pathogenesis

GM-CSF is a pro-inflammatory cytokine. It contributes to the establishment of a favorable milieu for the recruitment, functional differentiation, and survival of various leukocyte populations [77]. GM-CSF expression is transcriptionally-controlled downstream of epidermal growth factor receptor (EGFR) and ERK1/2 pathway. EGFR together with GM-CSF may act as a skin immunomodulator [78]. It has been shown that the EGFR ligand TGF-α potentiates keratinocyte response to the pro-inflammatory cytokines TNF-α and IFN-γ with an enhanced expression of GM-CSF [78]. Of note, this synergy may be active in lesional skin of chronic inflammatory diseases, since there is strong GM-CSF expression in skin lesions from patients with atopic dermatitis, allergic contact dermatitis, and psoriasis [79].

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Melanocytic Proliferations and Other Pigmented Lesions

20

20.1 Lentigines/Lentigo Simplex

20.1.1 Clinical Features

Lentigines (lentigo simplex) are small (typically <5 mm), tan to brown-black macules that can develop on any cutaneous surface, including mucous membranes and palmoplantar skin. They may be present at birth or may appear during childhood, and often increase in number well into adulthood. They can be single or multiple as well as disseminated, clustered, or segmental. Lentigines do not have a predilection for sun-exposed areas, and they do not darken with sun exposure. Occasionally, they are associated with multisystem genetic disorders. The frequency of lentigines in children is unknown. They affect all races and both sexes equally [1].

20.1.2 Histology

Lentigo simplex is characterized by orthokeratotic keratin overlying an epidermis with elongated rete ridges. There is increased melanin within basilar keratinocytes (Fig. 20.1). Melanocytes are minimally increased in number, and they are not atypical [2]. There is no nesting of melanocytes as seen in a junctional nevus. The dermis is unremarkable. Specifically, it is distinctly unusual for a lentigo simplex to induce a significant inflammatory response or upper dermal fibrosis. The presence of such changes warrants careful examination to exclude histologic mimics.

The differential diagnosis of lentigo simplex includes melanocytic nevus with or without features of atypia. In many cases, examination of multiple levels reveals small intraepidermal nests of melanocytes. Most dermatopathologists make the arbitrary distinction that nests of melanocytes establish a diagnosis of a melanocytic nevus, and exclude the diagnosis of a lentigo simplex. The presence of a lymphoid infiltrate within the papillary dermis with or without accompanying fibrosis should provoke additional search for changes of a dysplastic nevus because these features are not part of the constellation of findings associated with lentigo simplex. The differential diagnosis also includes café au lait macules. In this case, histologic distinction may be impossible. While macromelanosomes are often associated with café au lait macules, similar observations have been described in lentigo simplex, and their presence does not exclude either diagnosis [3].

20.1.3 Pathogenesis

Mutations in the growth regulatory factors BRAF, FGFR3, and PIK3CA are frequently found in melanocytic nevi. Studies examining the presence of these gene mutations in 58 lentigo simplex and 46 melanocytic nevi showed that lentigo simplex did not harbor BRAF, FGFR3, or PIK3CA mutations [2]. In contrast, melanocytic nevi had frequent BRAF V600E mutation. It has been suggested that the absence of BRAF, FGFR3, and PIK3CA mutations differentiates lentigo simplex from solar lentigo and melanocytic nevi. These findings indicate that lentigo simplex has a distinct yet unknown genetic basis from that of solar lentigo and nevi. Other genes have been identified in association with lentigo simplex. The development of lentigines in German and Japanese women has been shown to correlate with variants in the SLC45A2 gene [4]. In addition, a somatic mutation in KRT10 gene is associated with extensive lentigo simplex, linear epidermolytic nevus, and epidermolytic nevus comedonicus [5].

20.2 Labial Melanotic Macule

20.2.1 Clinical Features

Labial melanotic macules are brown, gray, or blue spots on the oral mucosa. They are usually solitary. Most lesions are less than 1 cm in diameter, although they are occasionally larger

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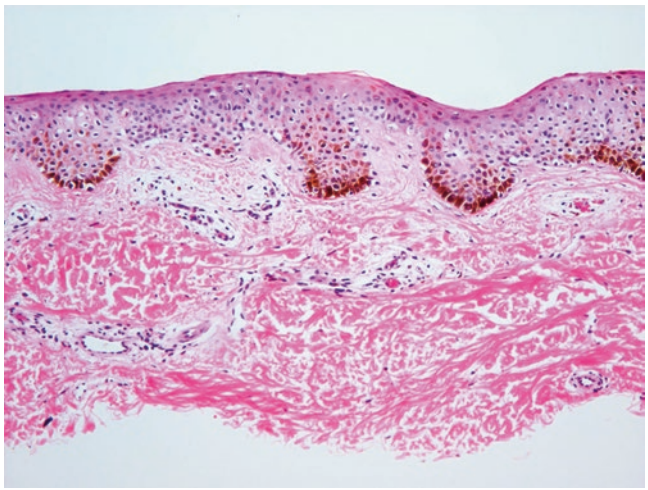

Fig. 20.1 Lentigo simplex has elongated rete ridges and increased basilar melanin. There are essentially normal numbers of melanocytes present in the epidermis. Sun damage is not present in the underlying dermis

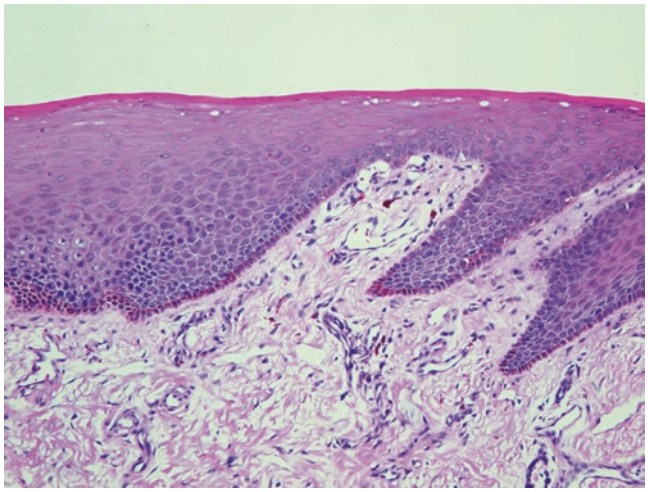

Fig. 20.2 A labial melanotic macule demonstrates a mucosal surface with increased basilar melanin in the absence of increased numbers of basilar melanocytes

[6]. They are most common in adults over 40 years of age, but have been reported in children >4 years of age. They appear to be somewhat more common in females than in males [7].

20.2.2 Histology

Labial melanotic macule demonstrates a mucosa that has increased basal layer melanin without increased numbers of melanocytes (Fig. 20.2). Many of the intralesional melanocytes may have a dendritic configuration. Dermal melanin secondary to pigment incontinence is often present. The changes are essentially those of a lentigo simplex occurring on a mucosal surface [8, 9]. Melanocytes have densely pigmented melanosomes [10].

20.2.3 Pathogenesis

The cause of labial melanotic macule is not known. It is thought to be a reactive process and related to sun exposure [7]. It has been proposed that hyperpigmentation in the epidermal basal layer as well as the presence of dermal melanophages may be due to faulty transfer of melanosomes from melanocytes to keratinocytes, resulting in a lack of melanosomes in keratinocytes in the upper epidermis and pigment incontinence in the dermis.

20.3 Ephelis

20.3.1 Clinical Features

Ephelides (freckles) are small (<3 mm) light-brown macules that occur mainly on sun-exposed areas in individuals with fair skin and red hair. Ephelides typically appear during childhood (especially between 2 and 4 years of age), and tend to fade by adulthood. They darken with sun exposure, and fade in the winter. Ephelides do not undergo malignant transformation, but they are considered to be a sign of UV-induced skin damage, and their presence correlates with an increased lifetime risk of malignant melanoma [11].

20.3.2 Histology

Ephelis is histologically quite similar to lentigo simplex, differing only in a slightly fewer number of basilar melanocytes (Fig. 20.3). Ephelis is characterized by increased amounts of basilar melanin within keratinocytes, and normal to slightly increased numbers of melanocytes [12]. Pigment incontinence may be present within the papillary dermis.

The histologic differential diagnosis of an ephelis includes a lentigo simplex. Another entity that should be considered is café au lait macule that is distinguished based upon the clinical appearance.

20.3.3 Pathogenesis

Ephelides are commonly associated with light skin and blond or red hair color, and are generally considered to be genetically determined. The melanocortin-1-receptor (MC1R) gene is strongly associated with the formation of ephelides [11, 13, 14]. Other genes, including IRF4, ASIP, OCA2, and tyrosinase, are also associated with ephelides

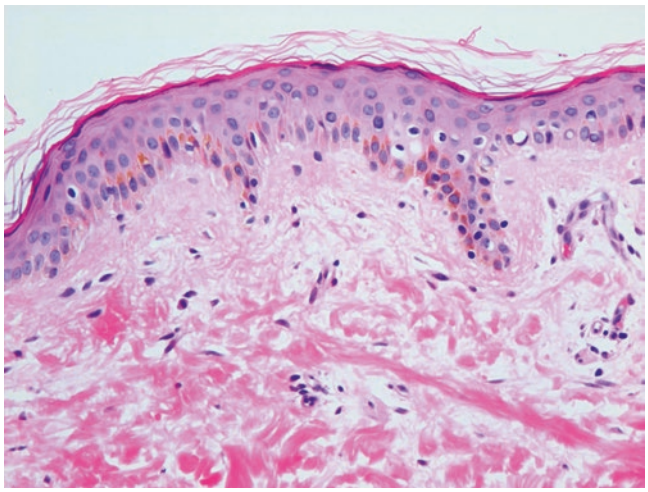

Fig. 20.3 An ephelis demonstrates increased basilar melanin within keratinocytes and only a minimal increase in melanocytes

[15–17]. Exposure to sunlight accentuates the pattern of ephelides. It has been shown that ultraviolet light interacts with MC1R and OCA2 variants to enhance facial ephelides in children [18].

20.4 Becker's Nevus

20.4.1 Clinical Features

Becker's nevus appears as a localized area of hypermelanosis and often hypertrichosis, most common on the chest, shoulder, and upper back of an adolescent male. It has been reported on other areas of the body, including the face, trunk, arms, and legs. Becker's nevus is sometimes congenital, but it usually appears in adolescence. Rarely, it affects younger children. It is more common in males than females. Although Becker's nevus is usually an isolated finding, associated abnormalities are occasionally seen (e.g., ipsilateral breast hypoplasia and limb asymmetry) [19]. Typically, a unilateral blotchy, grayish-brown patch appears over the chest, shoulder, and upper back (Fig. 20.4). Terminal hairs often develop within the lesion.

Fig. 20.4 Becker's nevus presents as a well-demarcated hyperpigmented patch with overlying hypertrichosis at the lower torso in a teenage boy (photo courtesy of Audrey Chan, MD, Baylor College of Medicine, Houston, TX)

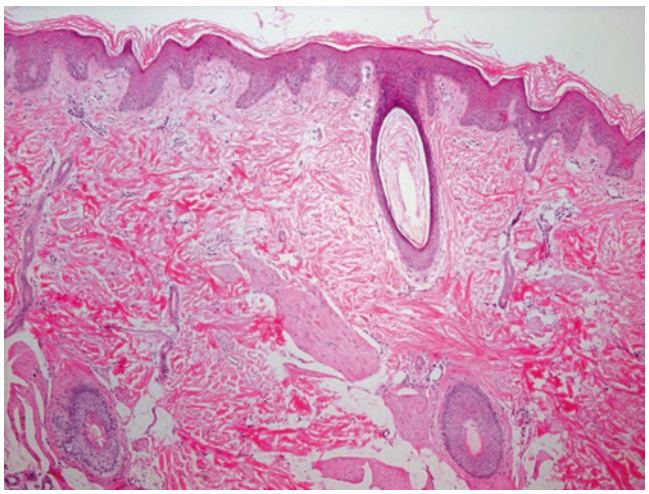

Fig. 20.5 A Becker's nevus is characterized by a slightly acanthotic epidermis that may be papillomatous. The basal layer has increased melanin with only minimally increased number of melanocytes. Abundant large smooth muscle bundles are present in the dermis

20.4.2 Histology

This hamartomatous process involves changes within the epidermis and dermis. The epidermis is occasionally papillomatous with slight epidermal acanthosis and elongation of the rete ridges (Fig. 20.5). The basal layer demonstrates increased melanin pigment within keratinocytes, but only a slight increase in the number of melanocytes [20]. Occasional giant melanosomes may be seen, but these are not a specific finding [21]. The changes within the epidermis may resemble those seen in a lentigo simplex. Multiple large hair follicles are present in many cases. The underlying dermis often contains a smooth muscle hamartoma, but this is not a universal finding [22].

The histologic differential diagnosis includes lentigo simplex, which is differentiated based upon clinical presentation. A nevus spilus has intraepidermal changes that resemble

Becker's nevus, but it also has foci with nests of melanocytes that help to make the distinction. The smooth muscle proliferation within the dermis raises the differential diagnosis of leiomyoma. The nodular configuration of smooth muscle fascicles helps make the diagnosis of leiomyoma.

20.4.3 Pathogenesis

Becker's nevus is a benign hamartomatous proliferation. It has been hypothesized that during embryogenesis, somatic gene mutations can occur in healthy heterozygote individuals resulting in loss of heterozygosity (LOH) where the hamartomatous area presumably originates [23]. There is some evidence that Becker's nevus is a hormone-dependent disorder caused by dysregulation of androgen receptor activity [24]. Congenital and familial cases have been reported, and suggest a hereditary component in the etiology of this lesion [25].

20.5 Café Au Lait Macule

20.5.1 Clinical Features

Café au lait macules are well defined oval to round, light-brown macules or patches. They are present at birth or in early childhood, and can appear anywhere on the body. They may range in size from approximately 1 cm up to 20 cm in diameter (Fig. 20.6). Café au lait macules are often an isolated finding, but they may also be a sign of neurofibromatosis or other systemic disorders. Café au lait spots are present in up to 33 % of children [26].

20.5.2 Histology

Histologic changes seen in café au lait macules are subtle and nonspecific. The epidermis generally has normal thickness with no changes in the stratum corneum. There is increased basilar melanin pigment without increased number of melanocytes. Macromelanosomes have been reported in these lesions, and they are said to occur with increased frequency in lesions from patients with neurofibromatosis type 1 [27, 28]. Pigment incontinence may result in the presence of melanophages within the papillary dermis.

20.5.3 Pathogenesis

Café au lait macules in children are common dermatologic findings that can arise in a variety of disease conditions, such as neurofibromatosis type 1 and certain types of hereditary syndromes, such as McCune-Albright, Cowden, LEOPARD, and Bannayan-Riley-Ruvalcaba syndromes [29]. The pathogenesis of these lesions can be found under the specific disease syndrome.

Fig. 20.6 Café au lait macules appear as well-defined tan macules and patches

20.6 McCune-Albright Syndrome

20.6.1 Clinical Features

McCune-Albright syndrome is a condition characterized by the classic triad of café au lait spots, polyostotic fibrous dysplasia, and endocrine dysfunction (e.g., precocious puberty). In comparison to the lesions seen in neurofibromatosis, café au lait spots of McCune-Albright syndrome tend to be fewer in number, larger, and darker. They are typically unilateral, often with sharp demarcation at the midline (Fig. 20.7). They also have more jagged margins that are classically described as a "coast of Maine" appearance [30].

20.6.2 Histology

The most common cutaneous manifestation in patients with McCune-Albright syndrome is that of pigmented lesions that are clinically and histologically indistinguishable from café au lait macules. There is increased basilar melanin within basal keratinocytes and melanocytes. Some cases may contain macromelanosomes [31].

Fig. 20.7 A child with McCune-Albright syndrome presents with a large, sharply defined tan patch with jagged border

Fig. 20.8 Multiple brown macules are seen on the lips of a patient with Peutz-Jeghers syndrome

Melanocytic nevi with intranuclear pseudoinclusions [32] and diffuse scarring alopecia with fibrous convolutions [33] have been described with histologic changes that may be relatively unique to McCune-Albright syndrome. There are other cutaneous lesions that have been biopsied in patients with the syndrome. These include oral pigmented lesions, osteoma, calcifying aponeurotic fibroma-like lesions, and calcinosis cutis [32, 34, 35].

20.6.3 Pathogenesis

McCune-Albright syndrome is caused by mutations in GNAS1, which encodes the G-protein subunit Gsα [36, 37]. Conversion of Arg201 to histidine or cysteine is a frequent mutation in GNAS1. Mechanistically, mutations in GNAS1 lead to constitutive activation of GNAS1 and the coupled protein adenylyl cyclase, resulting in an increase in intracellular cyclic adenosine monophosphate (cAMP) levels [38, 39]. Activation of G-protein-coupled receptors, such as luteinizing hormone and follicle-stimulating hormone receptors, may be the molecular underpinning of the signs and symptoms of the syndrome. The formation of brown/black pigments is normally stimulated by melanocyte-stimulating hormone (MSH) binding to MSH receptor, which is a G-protein receptor coupled to Gsα. Constitutive activation of the Gsα subunit in melanocytes results in increased brown pigmentation characteristic of autonomous endocrine hyperfunction and café au lait spots seen in McCune-Albright syndrome [40, 41]. There are sporadic somatic mutations in one of the two alleles of GNAS1 gene with mosaicism, in which the severity and specific features of the disorder depend on the number and location of cells that have mutated GNAS1. There is no autosomal dominant transmission of this syndrome because activating GNAS1 mutations are lethal when they occur early in embryogenesis [42].

20.7 Peutz-Jeghers Syndrome

20.7.1 Clinical Features

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by multiple mucocutaneous lentigines and hamartomatous intestinal polyps. Lentigines of Peutz-Jeghers syndrome are small (<5 mm) bluish brown to black spots that are present at birth or develop in early childhood (Fig. 20.8). They tend to affect the lips and buccal mucosa, nasal and periorbital skin, elbows, dorsal fingers and toes, palms and soles, and periumbilical, perianal and labial skin. Lesions on the lips and skin may fade after puberty.

20.7.2 Histology

The predominant cutaneous lesions are simple lentigines that are histologically indistinguishable from lentigo simplex. These pigmented lesions occur on the skin, and in and around the oral cavity. Those occurring on mucosal surfaces demonstrate the histologic changes of labial melanotic macules [43, 44]. Prominent palmoplantar pigmentation with lentigo simplex-like histology on acral skin is also described in these patients [45, 46]. An interesting phenomenon is the late onset of lentigines occurring at the sites of psoriatic plaques in Peutz-Jeghers syndrome [45]. In any of the aforementioned situations, the histologic changes are nonspecific, and result in the histologic diagnosis of lentigo simplex. Clinicopathologic correlation is required to establish a diagnosis of Peutz-Jeghers syndrome.

Sebaceous lesions including sebaceous adenomas and sebaceomas, which are more commonly encountered as cutaneous tumors associated with Muir-Torre syndrome, have been described in patients with Peutz-Jeghers syndrome [44].

20.7.3 Pathogenesis

Peutz-Jeghers syndrome is a cancer-susceptibility syndrome that is due to inactivating germline mutations in STK11/LKB1 gene on chromosome 19p [47, 48]. Some studies demonstrate a detection rate of germline mutations in STK11/LKB1 to be between 80 and 94 % of the cases [49]. However, other studies have shown that LKB1 mutations account for only 40–60 % of familial cases of Peutz-Jeghers syndrome [50]. STK11/LKB1 is expressed ubiquitously in fetal and adult tissues. It is a tumor suppressor with serine-threonine protein kinase activity [51]. A major function of STK11/LKB1 is to control the metabolism and energy homeostasis in the cell by regulating AMP-activated protein kinase (AMPK) cascade [52, 53]. STK11/LKB1 has multiple other important functions, including the regulation of cell proliferation via G1 cell-cycle arrest. STK11/LKB1 mutations affect the phosphorylation of β-catenin and regulation of WNT signaling [54]. LKB1 also associates with p53 and regulates p53-dependent apoptotic pathways [55].

20.8 Congenital Dermal Melanocytosis (Mongolian Spot)

20.8.1 Clinical Features

Congenital dermal melanocytosis (Mongolian spot) is present in about 96 % of black infants, 46 % of Hispanic infants, and 10 % of white infants [56]. Skin lesions are deep brown to slate gray or blue-black patches that are present at birth (Fig. 20.9).

Fig. 20.9 Congenital dermal melanocytosis appears as a faint blue patch over the lumbosacral area (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

They are most common at the lumbosacral area and buttocks, but can occur in other locations. Mongolian spots may be single or multiple, and range in size from a few mm to several cm or more. Many tend to fade during the first few years of life, although a small percentage can be more persistent. Affected infants are usually healthy. Congenital dermal melanocytosis can occur sporadically or, in cases of extensive and large lesions, can be associated with inborn errors of metabolism, such as mucopolysaccharidosis, gangliosidosis, Niemann-Pick disease, Hunter syndrome, and mannosidosis [59–63]. Lesions can also be associated with other pigmentary abnormalities, such as phacomatosis pigmentovascularis [64].

20.8.2 Histology

Skin lesion is characterized by a normal dermis. Within the mid- to deep reticular dermis, there is a fairly sparse collection of densely pigmented dendritic melanocytes that often display a horizontal orientation (Figs. 20.10 and 20.11). These pigmented cells may extend into the subcutis [57, 58].

The histologic differential diagnosis includes other entities characterized by densely pigmented dendritic melanocytes in the dermis. Nevus of Ota and nevus of Ito have similar histologic features to congenital dermal melanocytosis, but these two entities (with identical histologic features) are more densely cellular, and the melanocytes are located higher within the dermis. A blue nevus also has similar histo-

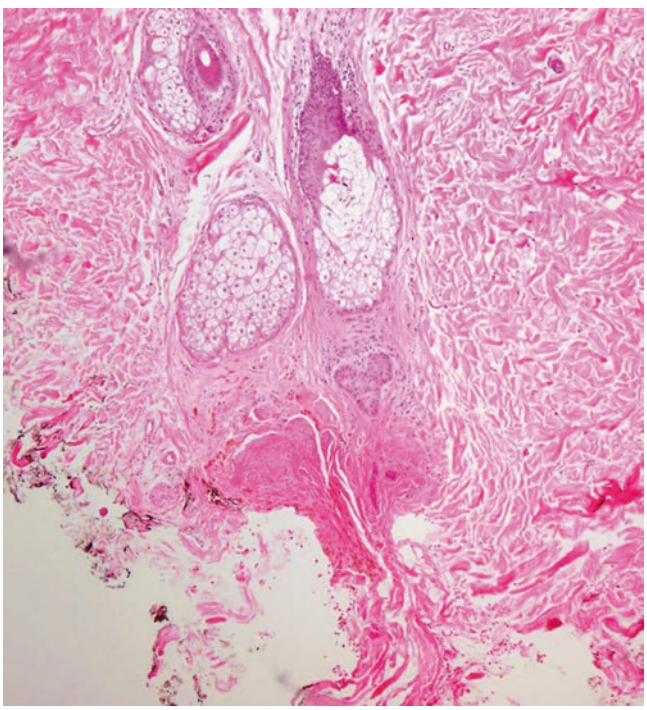

Fig. 20.10 Histologic changes in congenital dermal melanocytosis consist of scattered hyperpigmented spindle-shaped cells deep in the reticular dermis

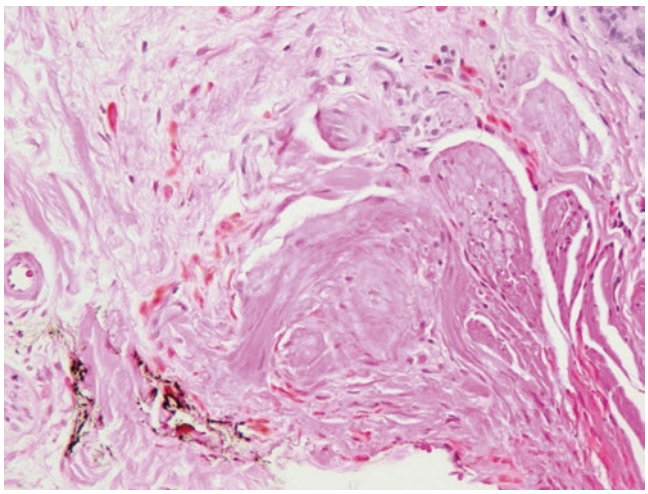

Fig. 20.11 Spindle-shaped and dendritic melanocytes are seen in the deep dermis in congenital dermal melanocytosis. There is no cytologic atypia

logic features; however, there is far more pigment and dense cellularity in blue nevi.

20.8.3 Pathogenesis

Congenital dermal melanocytosis is thought to be due to the failure of migration of melanocytes from the neural crest to the epidermis during fetal life, resulting in the presence of melanocytes in the dermis.

20.9 Nevus Spilus (Speckled Lentiginous Nevus)

20.9.1 Clinical Features

Speckled lentiginous nevus or nevus spilus is a pigmented lesion composed of a tan patch with multiple small, darkly pigmented macules and papules superimposed within it (Fig. 20.12). It affects 1–2 % of the population [65]. It is most common on the trunk and extremities. The background tan patch is rarely present at birth, but usually appears within the first year of life. The darker superimposed lesions typically appear and increase in number during childhood. Rarely, they may develop atypical nevi or malignant melanoma.

20.9.2 Histology

Most authors consider nevus spilus to be synonymous with speckled lentiginous nevus, and thus the histologic changes will be described as if they refer to the same entity [66, 67]. However, several recent publications have sought to make a distinction based upon subtle histologic differences, and these will be addressed [68, 69].

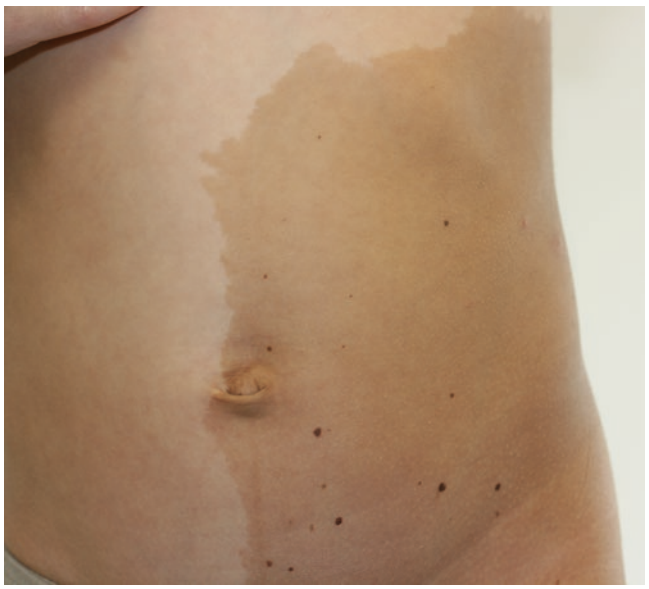

Fig. 20.12 A nevus spilus is characterized by a large tan patch with superimposed small dark macules

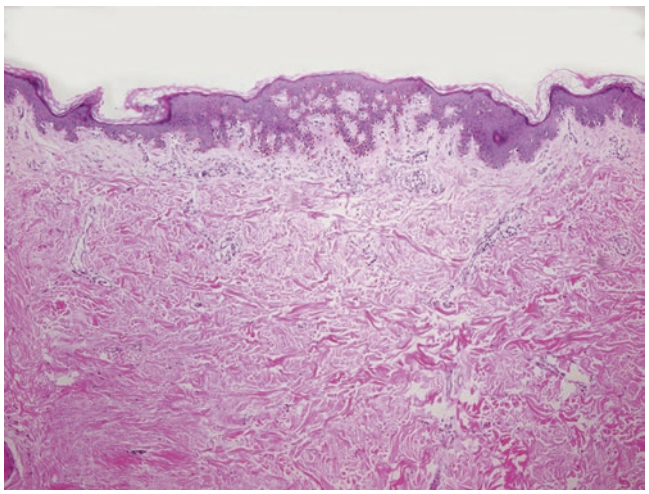

Fig. 20.13 Nevus spilus is characterized by epidermal changes that resemble those seen in a lentigo simplex in some areas, and a junctional nevus in others. In some foci, a dermal melanocytic proliferation is present

The major part of the surface of a nevus spilus is that of a flat, tan-colored macule that demonstrates the histologic features of a café au lait macule. The epidermis is remarkable for increased basilar melanin deposition with a slight increase in numbers of melanocytes, which are not enlarged and do not have cytologic atypia (Figs. 20.13, 20.14 and 20.15). The darker, also flat macules seen within these lesions demonstrate small nests of junctional melanocytes resembling a very small junctional melanocytic nevus. More papular lesions may show changes of a compound or

intradermal melanocytic nevus. Rarely, these nevi are neurotized [70]. It has been proposed that nevus spilus that contains larger and more papular compound and intradermal melanocytic lesions is best categorized separately on the basis of different systemic associations [68].

20.9.3 Pathogenesis

Little is known about the pathogenesis of nevus spilus. The lesion may represent localized defect in the migration of neural crest melanoblasts that populate a particular area of the skin [67, 71]. Environmental and genetic factors may also play a role.

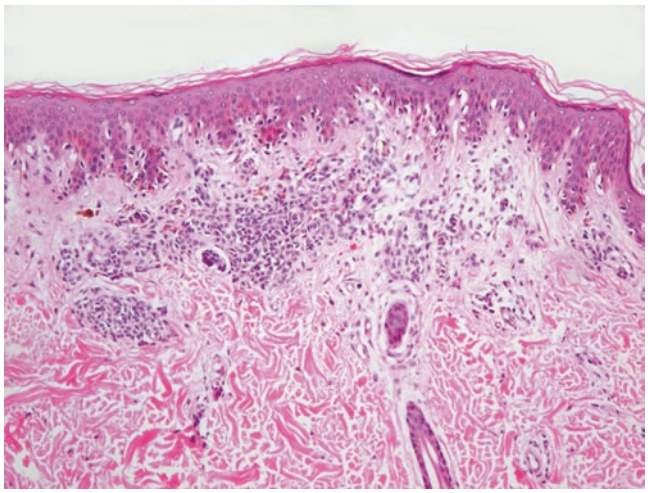

Fig. 20.14 Foci indistinguishable from a compound nevus are present within nevus spilus

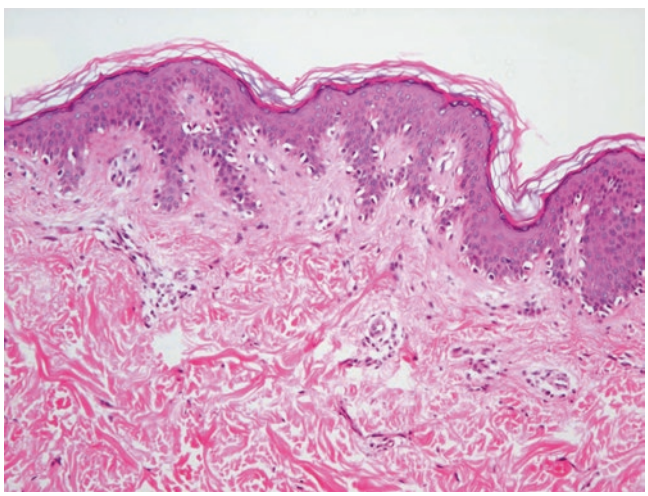

Fig. 20.15 Other areas of nevus spilus resemble lentigo simplex with slightly increased numbers of single melanocytes on elongated rete ridges within the epidermis

20.10 Nevus of Ito

20.10.1 Clinical Features

Nevus of Ito has a similar appearance and natural history to nevus of Ota (see Sect. 20.11), but it is located over the shoulder and supraclavicular area (Fig. 20.16). Nevus of Ito is common in Asian and black skin types, and more common in females than males [72].

20.10.2 Histology

Histologic findings consist of a loose aggregation of densely pigmented, dendritic-shaped melanocytes within the superficial portion of the reticular dermis (Figs. 20.17 and 20.18). There is no intraepidermal melanocytic proliferation. Cytologic atypia and mitotic activity are not present, and the melanocytes tend to course as single cells and do not form nests. The histologic changes are indistinguishable from those of nevus of Ota, and the distinction is made based on the affected body site [73].

The histologic differential diagnosis includes a blue nevus. However, the dermal melanocytosis in a blue nevus is much more cellular and tightly aggregated than the diffuse and paucicellular collection in a nevus of Ito. Mongolian spots also share some histologic characteristics; however, these lesions are even less cellular with less apparent melanin pigment, and localized more deeply

Fig. 20.16 Nevus of Ito appears as a large blue patch over the arm and shoulder of a child

within the reticular dermis. In some cases, a tattoo might enter into the differential diagnosis. Stains for melanin or S100 to identify the melanocytic nature of the pigment-laden dendritic cells help make this distinction.

20.10.3 Pathogenesis

Similar to nevus of Ota, nevus of Ito is a dermal melanocytosis that may be caused by the failure of melanocytes to migrate to the epidermis during fetal development, and become arrested in the dermis [58, 74].

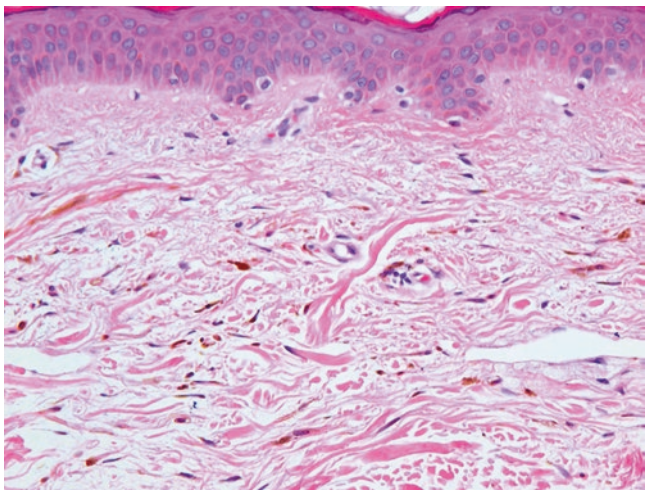

Fig. 20.17 Sparse numbers of densely pigmented spindled melanocytes are present in the superficial dermis in nevus of Ito. The epidermis is unremarkable

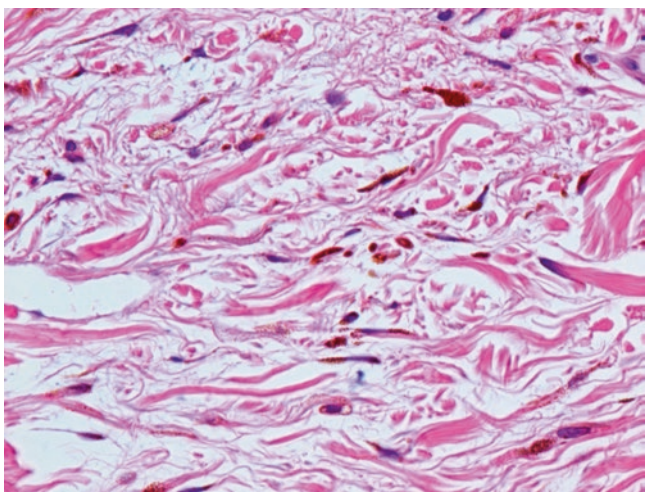

Fig. 20.18 Spindled melanocytes and melanophages course individually between reticular dermal collagen bundles in nevus of Ito

20.11 Nevus of Ota

20.11.1 Clinical Features

Nevus of Ota is most common in Asian and black skin types, and more common in females than males [72]. It is characterized by a unilateral patch of blue-gray to brown pigmentation on the face in the distribution of the ophthalmic and maxillary branches of the trigeminal nerve (Fig. 20.19). This corresponds to the temple, forehead, periorbital area, malar cheek, and nose. The ipsilateral eye is affected in 45–65 % of cases [75]. At least 50 % of the cases are congenital, and most lesions appear by puberty. They tend to be persistent and may darken after puberty. Although the lesions are usually benign, transformation to malignant melanoma has been reported.

20.11.2 Histology

Histologic findings consist of a loose aggregation of densely pigmented, dendritic-shaped melanocytes within the superficial portion of the reticular dermis (Figs. 20.20 and 20.21). The melanocytes tend to course singly and do not form nests. There is no intraepidermal melanocytic proliferation. Cytologic atypia and mitotic activity are not present. The changes are indistinguishable from those of nevus of Ito, and the distinction is made on the basis of the affected

Fig. 20.19 Nevus of Ota is a bluish-gray hyperpigmented patch on the side of the face in the distribution of trigeminal nerve innervation (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam)

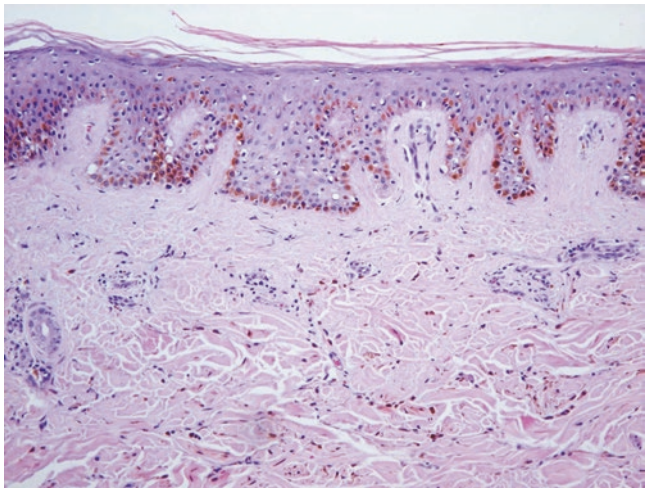

Fig. 20.20 Sparse numbers of densely pigmented and spindled melanocytes are present in the superficial dermis in nevus of Ota. The epidermis may be uninvolved or may demonstrate increased basilar melanin

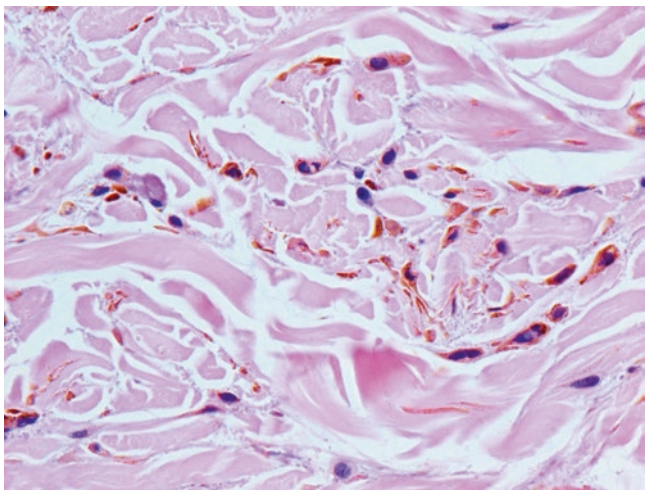

Fig. 20.21 Spindled melanocytes and melanophages course individually between reticular dermal collagen bundles in nevus of Ota

anatomic body site. An attempt to classify nevus of Ota into subtypes based upon the depth of the lesion has not been widely incorporated into diagnostic practice [76].

The histologic differential diagnosis for nevus of Ota is similar to that described for nevus of Ito in Section 20.10.

20.11.3 Pathogenesis

Nevus of Ota can involve the periorbital skin, conjunctiva, neurovascular bundles, ganglia, and the uvea. The lesion may be due to aberrant migration of melanocytes from the neural crest to the dermal-epidermal junction, and subsequent arrest within the dermis [77]. Nevus of Ota generally does not change with age. However, the lesion may darken or enlarge in children during puberty and in postmenopausal women, indicating possible influence of sex hormones on dermal melanocytes.

Malignant transformation can occur in nevus of Ota, resulting in uveal, cutaneous, or dural melanoma [78, 79]. Genomic studies have identified mutations in the guanine nucleotide-binding protein G(q) subunit α (GNAQ) in nevus of Ota and uveal melanoma [80]. GNAQ is a subunit of the heterotrimeric G protein that mediates diverse receptor signal transduction pathways. The finding of GNAQ mutations in both nevus of Ota and uveal melanoma suggests a genetic link between these two lesions, and may provide the molecular basis for nevus of Ota being a risk factor for melanoma.

20.12 Congenital Melanocytic Nevus

20.12.1 Clinical Features

Congenital melanocytic nevi are melanocytic lesions that appear as pink/tan/brown to black macules and patches or papules and plaques (Figs. 20.22 and 20.23). Although typically present at birth, a subset of smaller nevi may appear later in the first year of life. Over time, they tend to thicken and often develop coarse terminal hairs. They are classified by size as small (<1.5 cm), medium (1.5–19.9 cm), and large (≥20 cm). Some classify "giant" lesions as ≥40 cm. Large and "giant" lesions, in particular, carry a significant risk of malignant melanoma, and may also be associated with neurocutaneous melanosis (pigmented lesions in the brain and spinal cord).

Small congenital melanocytic nevus occurs in approximately 1 % of all newborns [81]. Large lesions are less common, occurring in approximately 1:20,000 newborns [82]. Larger lesions tend to occur on the trunk, especially over the back and buttocks, and they are often accompanied by multiple scattered smaller pigmented lesions (satellite nevi).

20.12.2 Histology

There are no histologic features that reliably serve to distinguish a congenital melanocytic nevus from an acquired melanocytic nevus. Both congenital and acquired nevi can be identified with involvement of solely the epidermis (junctional) and solely the dermis (intradermal), or involvement of both the epidermis and dermis (compound) [83].

Junctional melanocytic nevi demonstrate nests of melanocytes along the dermal-epidermal junction, with the majority of nests located at the base of the rete ridges. In children, the nests tend to be larger than those seen in adults. Similarly, the intraepidermal melanocytes themselves tend to be somewhat larger and contain more cytoplasm. Single melanocytes are

Fig. 20.22 Small congenital melanocytic nevus appears as a well-defined brown patch present at birth

Fig. 20.23 Giant congenital melanocytic nevus is a large thin brown plaque with multiple darker-brown macules and papules within it as well as coarse terminal hairs over the surface

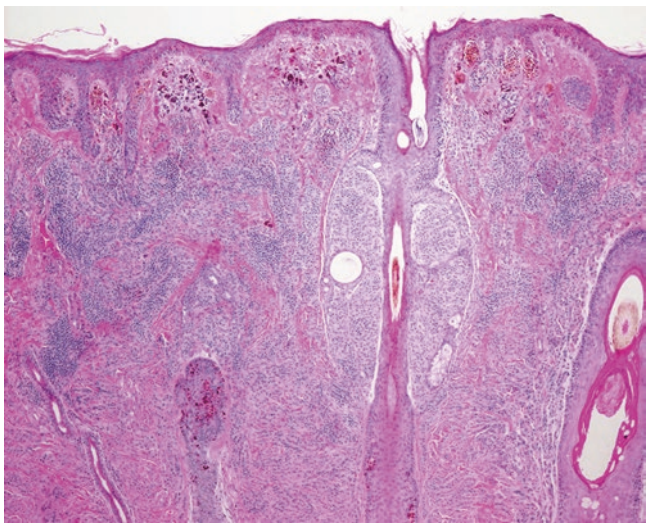

Fig. 20.24 A congenital nevus demonstrates pigmented melanocytic nesting in the superficial portion of the dermis, while deeper down the cells form a sheet-like growth pattern and lose much of their pigment

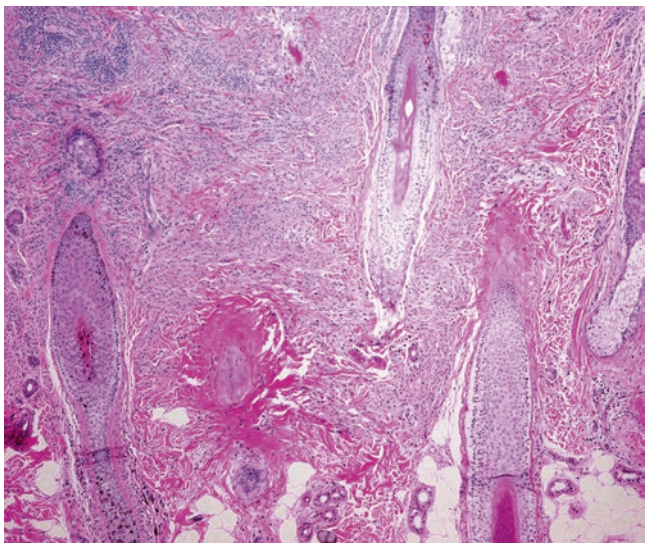

Fig. 20.25 Congenital nevi extend deep into the reticular dermis and may grow around cutaneous appendages and infiltrate arrector pili muscles. The cells develop a neuroid appearance in the deep portion

frequently encountered along the basal layer, and scattered pagetoid cells are not infrequent, especially in the central portion of the lesion. These features, while concerning in acquired nevi within adults, are an expected finding in congenital nevi, and they are more prominent in lesions biopsied in infants. Care should be taken to not interpret these findings as those seen within a superficial spreading melanoma, and to not make the diagnosis of melanoma in this population.

Compound congenital melanocytic nevi demonstrate similar intraepidermal melanocytic components but, in addition, there are collections of melanocytes within the dermis. There are several features that are more commonly seen in congenital nevi than in acquired ones, although none of these is pathognomonic. Congenital-pattern nevi tend to extend deep into the lower two thirds of the reticular dermis, a feature not usually associated with acquired nevi (Figs. 20.24, 20.25 and 20.26). There is characteristic growth around and extension down cutaneous appendages in congenital nevi. Sheets of benign-appearing melanocytes may replace the typical melanocytic nesting pattern. There is maturation of the melanocytes with progressive descent into the dermis, which is analogous to that seen in acquired nevi. Unlike most acquired melanocytic nevi, rare mitoses may be seen within the dermal component of congenital nevi, but mitoses should not occur near the base of the lesion [84].

In rare cases, one may encounter nodules of melanocytes in which there is an apparent lack of maturation, and the cells appear remarkably clonal (Figs. 20.27 and 20.28). These are *proliferative nodules*, and require more careful histologic examination. In general, these are areas that at low magnification demonstrate increased cellular density and lack of maturation as well as increased mitotic activity, but

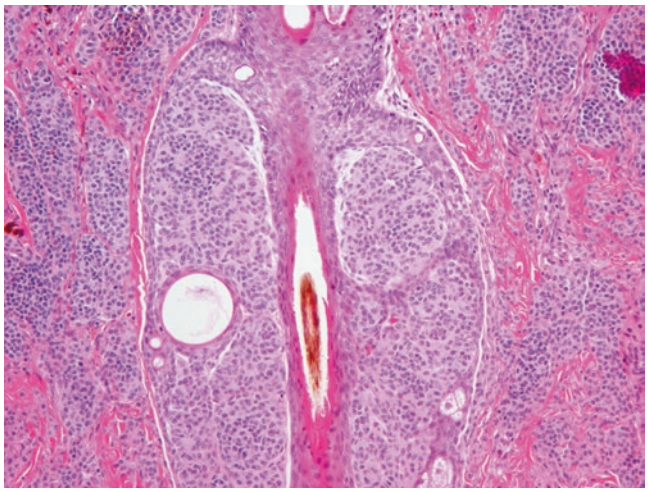

Fig. 20.26 Melanocytes are seen intimately associated with cutaneous appendages in congenital nevi

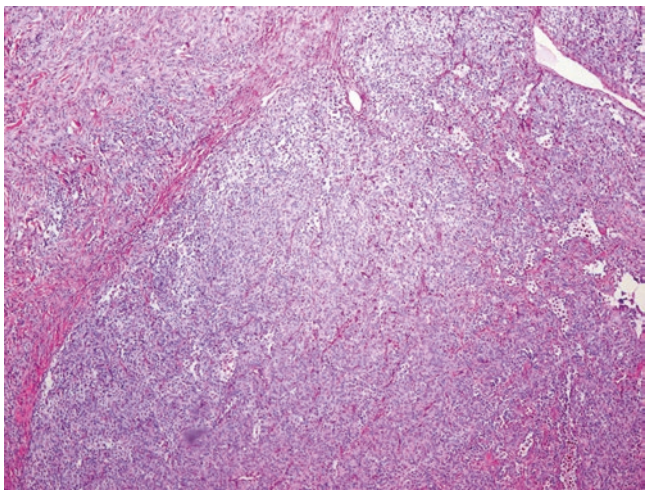

Fig. 20.28 Proliferative nodules are clearly demarcated from the surrounding dermal melanocytes

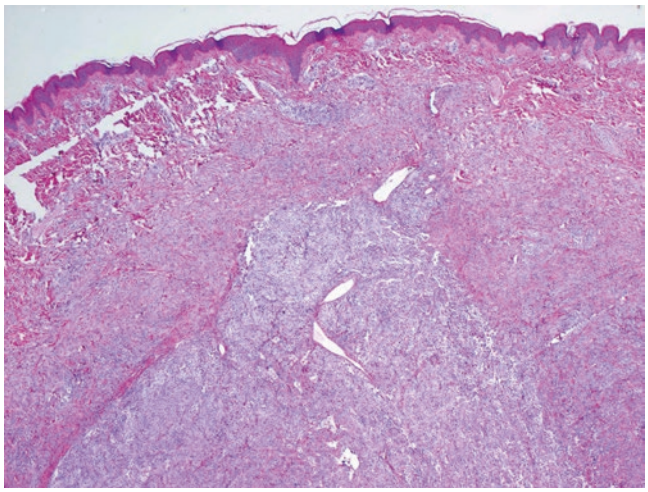

Fig. 20.27 A proliferative nodule is easily observed at low magnification as a clearly demarcated nodule of melanocytes with increased cellularity and lack of maturation

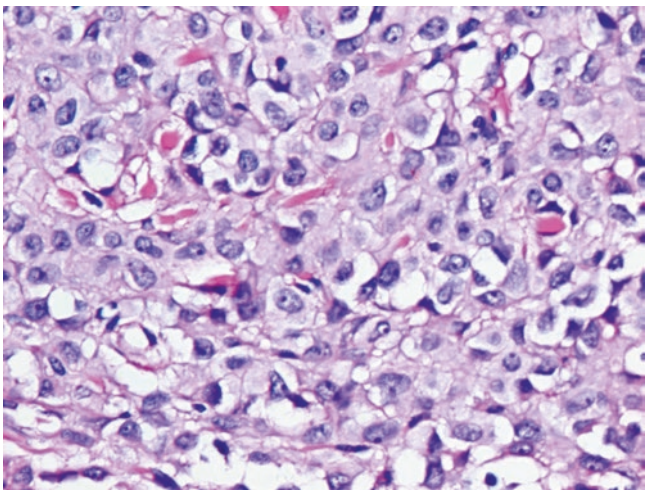

Fig. 20.29 The melanocytes within a proliferative nodule have vesicular nuclei, scattered nucleoli, and increased mitotic activity

no atypical mitoses [85] (Fig. 20.29). Necrosis is also not a feature of benign proliferative nodules, and in many cases, there is a smooth transition from the surrounding dermal nevus components to the proliferative nodule [86] (Fig. 20.28). Some authors have suggested that the absence of destructive expansile growth is another feature that distinguishes a benign proliferative nodule from melanoma [87].

Intradermal congenital melanocytic nevi demonstrate similar histologic features within the dermis to those seen in compound nevi. Nests of epidermal melanocytes are absent in purely intradermal nevi. Additional features, such as neurotization of the melanocytes, may also be seen, especially in older lesions [85].

The histologic differential diagnosis includes melanoma and dysplastic nevus. Melanomas, while rare in children, certainly do occur, and with increased frequency in association with large congenital melanocytic nevi. Melanomas may arise within the epidermis, and in such cases resemble melanomas that occur in adults. These are characterized by increased numbers of single melanocytes present at all levels of the epidermis, and display marked cytologic atypia. Melanomas can also occur in association with proliferative nodules. In these situations, the presence of marked cytologic atypia, nuclear pleomorphism, increased cellular density, increased mitoses including atypical forms, clear demarcation from surrounding populations of benign-appearing melanocytes, and necrosis all point toward the diagnosis of melanoma.

There are situations in which the changes along the dermal-epidermal junction seen in a congenital nevus are quite similar to those that have been described in dysplastic

nevi. The presence of nests of melanocytes between the rete ridges, basilar lentiginous melanocytic hyperplasia, fibrosis, and a lymphocytic inflammatory response are commonly encountered in congenital nevi. The melanocytes themselves may be enlarged depending on the age of the patient, further enhancing the histologic similarity. However, dysplastic nevi do not ordinarily extend into the reticular dermis, which is a feature seen in virtually all congenital nevi, and this may help in making the histologic distinction.

20.12.3 Pathogenesis

Congenital melanocytic nevi present at birth frequently harbor NRAS mutations. In a study of 32 congenital nevi, 81 % of the lesions had NRAS mutations with 70 % of proliferative nodules that developed within the congenital nevi also having mutations in NRAS [88]. No mutations in BRAF were found in this study. Interestingly, melanocytic nevi with a "congenital pattern," but no clear history of the nevus being present since birth (i.e., truly congenital), harbor BRAF V600E mutation [89–91]. It has been suggested that the discrepancies in these reports may be due to differences in the classification of nevus as congenital based upon histologic criteria and not on the actual presence of the nevus at birth [88]. Congenital nevi that develop in utero appear to be genetically distinct from acquired nevi that develop later in life.

The development of melanocytes in utero is regulated by c-Met (MET proto-oncogene, receptor tyrosine kinase) and c-Kit (V-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homologue) [92, 93]. c-Met encodes a receptor tyrosine kinase that binds hepatocyte growth factor (HGF). Overexpression of HGF and c-Met receptor activation are associated with disorders of differentiation, proliferation, and migration of melanocytes, and could be related to the occurrence of congenital nevi [94, 95]. c-Kit gene encodes a receptor tyrosine kinase that binds to stem cell factor (SCF), which is important in the development of melanocytes [96]. Increased c-Kit expression is seen in proliferative nodules in congenital nevi [97]. Given their known roles in melanocyte development, c-Met and c-Kit may play important roles in the development of congenital nevi.

20.13 Spitz Nevus

20.13.1 Clinical Features

Spitz nevus (spindle and epithelioid cell nevus) is a subtype of melanocytic nevi seen primarily in children. In the past, it was known as "benign juvenile melanoma" due to histologic features similar to those seen in malignant melanoma. It usually appears as a red to brown dome-shaped papule or nodule, often located on the face of a child or adolescent (Fig. 20.30). Most range in size from a few millimeters up to one centimeter in diameter. On occasion, the pigment is quite dark brown to black. Although most Spitz nevi are benign, they can have a range of histologically atypical features and can show aggressive behavior at times.

Fig. 20.30 Spitz nevus may appear as a small reddish-brown papule as seen on the cheek of this child

The true incidence and prevalence of Spitz nevi are unknown. It has been estimated that they account for approximately 1 % of all surgically-excised melanocytic lesions [98]. Spitz nevi are most common in the pediatric age group. In one series, 70 % were seen in individuals under 20 years of age, and 50 % were seen in children under 10 years of age [98].

20.13.2 Histology

Spitz nevus demonstrates histologic changes that are usually quite distinctive [99]. As with other melanocytic nevi, Spitz nevi can be seen in the junctional, compound, or purely intradermal stages of evolution.

The most commonly encountered stage of development, and the most classic histologic changes are seen in compound Spitz nevus. In this lesion, a well-circumscribed proliferation of melanocytes is present within the epidermis (Fig. 20.31). The nests tend to be quite large and, in most cases, the melanocytes demonstrate a vertical orientation (Fig. 20.32). A characteristic finding is the presence of clefts separating the overlying keratinocytes from the large intraepidermal melanocytic nests. Scattered single melanocytes, including pagetoid cells, are present throughout the epidermis, but the pagetoid extension is usually confined to the central portion of the lesion. Epidermal hyperplasia is a common feature in Spitz nevi. Epidermal changes, in which the epidermis is focally atrophic and large nests of junctional melanocytes occupy the majority of the epidermis, have also been described [100]. Eosinophilic globules, known as

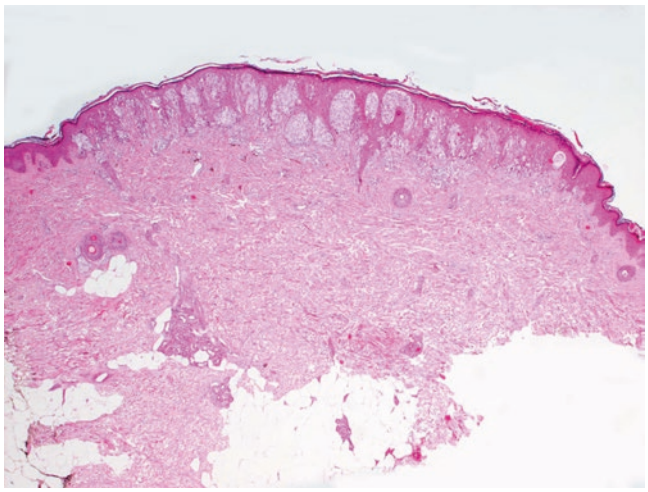

Fig. 20.31 A Spitz nevus is characterized by a sharply-circumscribed proliferation of large nests of intraepidermal and dermal melanocytes with abundant cytoplasm

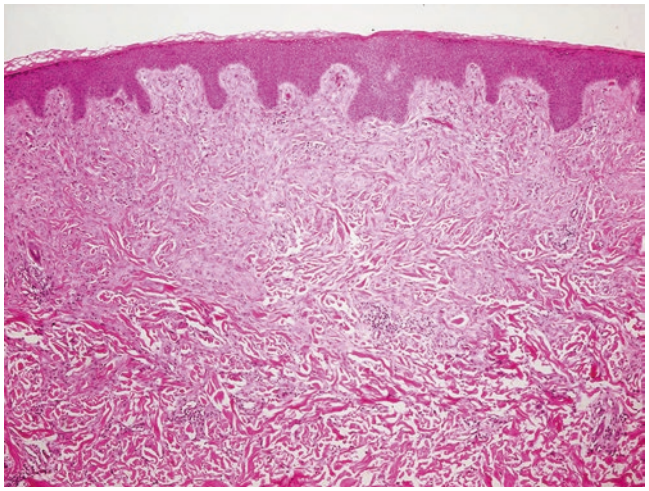

Fig. 20.33 A dermal Spitz nevus lacks an epidermal component of melanocytic proliferation. The dermis is filled with large cells that have abundant cytoplasm

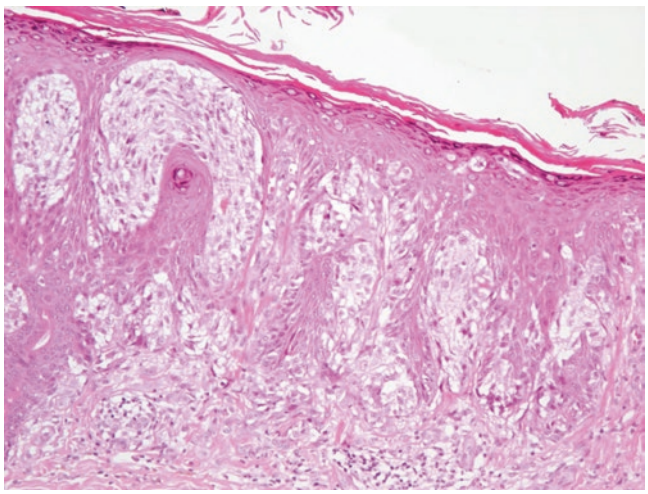

Fig. 20.32 Spitz nevus cells have characteristic morphology with abundant cytoplasm, vesicular nuclei, and conspicuous nucleoli. Pagetoid cells are sometimes present

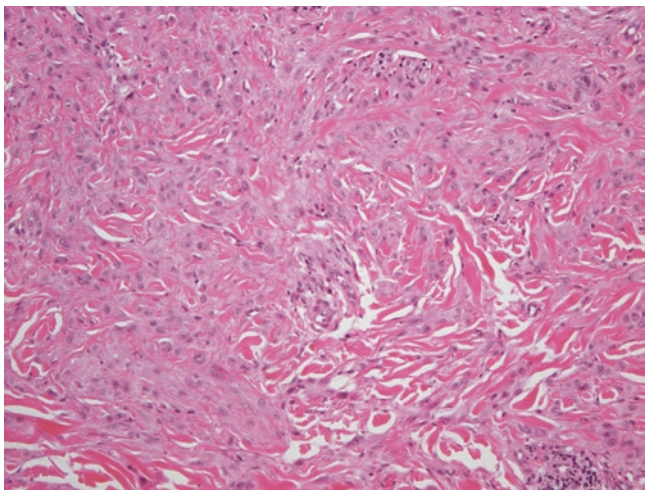

Fig. 20.34 Spindled and epithelioid cells with abundant cytoplasm, characteristic of Spitz nevi, fill the dermis which is often separated by sclerotic collagen

Kamino bodies, are present at the base of the epidermis or in the papillary dermis in many cases, but these globules are not entirely specific for Spitz nevi.

In compound Spitz nevus, nests of melanocytes displaying similar morphologic features are present in the dermis as well as in the epidermis. The cells are characteristically quite large with abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. They may be purely epithelioid, purely spindled, or an admixture of shapes. As is the case with other benign melanocytic proliferations, there is cellular maturation with progressive descent into the dermis. Melanocytes become smaller, and the nests of cells diminish in size and are separated by increasing amounts of dermal collagen. In marked distinction from ordinary acquired nevi and congenital nevi, rare dermal mitoses are an expected finding in Spitz nevi. However, the mitoses should not be atypical, and they should be present in the upper portions of the dermis [101]. In some cases, a lymphocytic immune response is present [102]. Lymphatic invasion has been identified in up to 15 % of ordinary Spitz nevi, and should not prompt a diagnosis of melanoma [103].

A purely dermal Spitz nevus demonstrates identical changes within the dermis to that described in compound Spitz nevus with the exception that the intraepidermal component is not present (Figs. 20.33, 20.34 and 20.35). Some dermal Spitz nevi have abundant dermal sclerosis separating the dermal melanocytes.

A purely junctional Spitz nevus has been described. It is the least commonly biopsied variant of Spitz nevi. In a junctional Spitz nevus, the melanocytic proliferation is con-

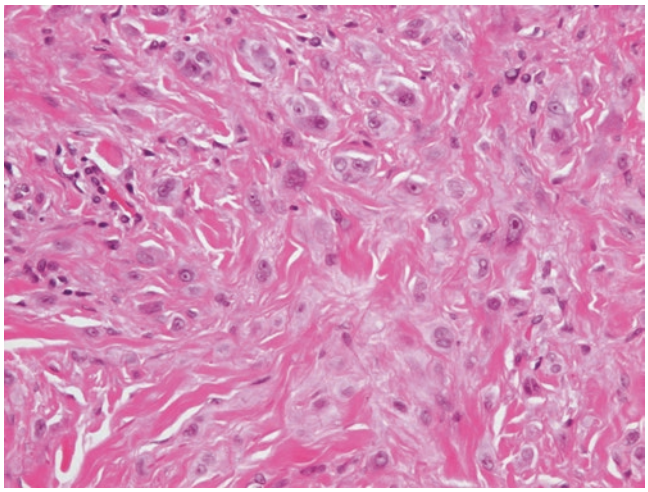

Fig. 20.35 The melanocytes within a dermal Spitz nevus have abundant cytoplasm, vesicular nuclei, and prominent nucleoli, and are indistinguishable from the cells that comprise a compound Spitz nevus

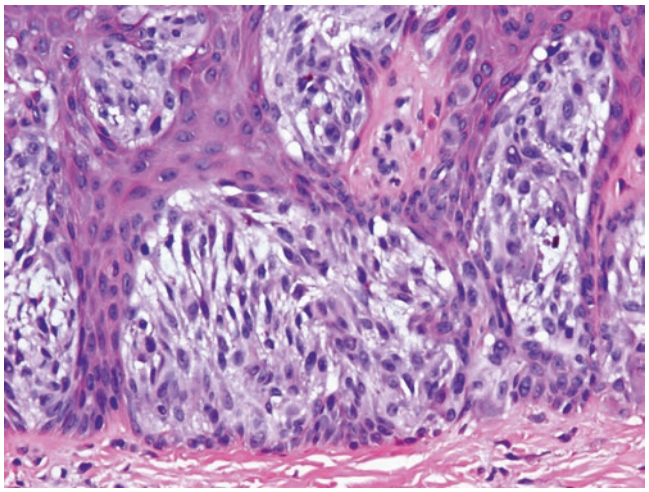

Fig. 20.37 Spitz nevus cells are spindled and epithelioid with abundant eosinophilic cytoplasm, vesicular nuclei, and occasionally visible nucleoli

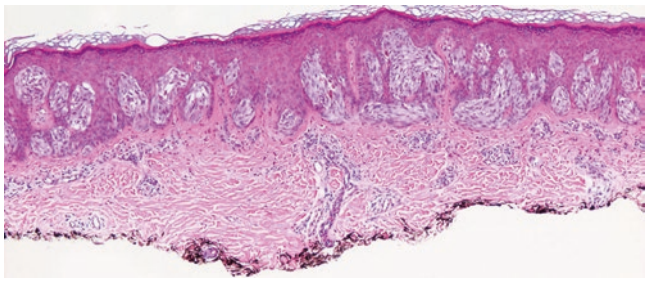

Fig. 20.36 A junctional Spitz nevus displays all of the histologic features of a compound Spitz nevus without a dermal component. There are large nests of melanocytes with characteristic cytomorphology

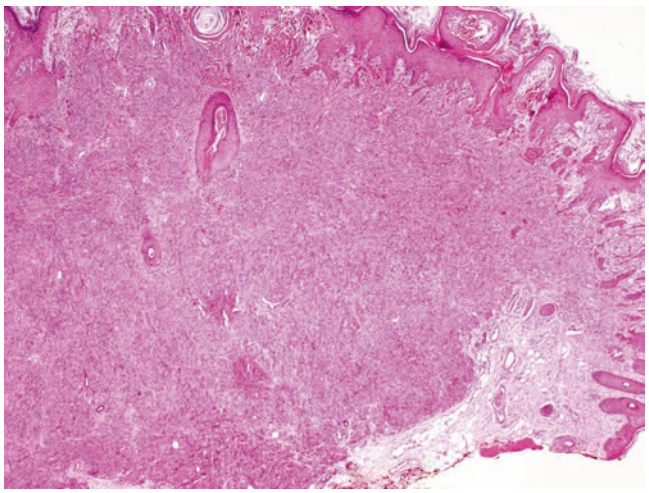

Fig. 20.38 Atypical Spitz nevus is a sharply-circumscribed lesion composed of spindled and epithelioid melanocytes that are nested but have a slightly increased nuclear to cytoplasmic ratio

fined to within the epidermis, and is identical to the epidermal component described for a compound Spitz nevus (Fig. 20.36). The lesion may demonstrate many pagetoid cells, but it should be small, relatively circumscribed, and symmetrical with an even distribution of melanocytic nests and no significant cytologic atypia (Fig. 20.37) [104].

In most cases, it is relatively straightforward to distinguish a Spitz nevus from a Spitzoid melanoma. Key distinguishing features of melanoma include a higher degree of pagetoid spread, greater cellular density, nuclear pleomorphism and hyperchromasia, and increased mitotic activity [105, 106]. Mitoses near the base of the lesion and atypical mitoses are further indicators of malignancy [107]. However, there are some instances where this distinction is not simple. For these cases, the term "atypical Spitzoid tumor" has been proposed (Figs. 20.38, 20.39, 20.40, 20.41, and 20.42). Features that should prompt this diagnosis include Spitzoid cellular morphology with age greater than 10 years, diameter greater than 10 mm, ulceration, involvement of the subcutaneous fat, and greater than six mitoses per mm^2 [108]. Lack of complete cellular maturation with progressive dermal descent should also raise the possibility of an atypical lesion. Fluorescence in situ hybridization (FISH) testing has been useful in distinguishing between Spitz nevus and Spitzoid melanoma, although this technique may be more reliable in adults than in children [109]. Atypical Spitzoid lesions appear to have minimal malignant potential in children [110]. In some cases, sentinel lymph node biopsies have demonstrated the presence of atypical Spitz nevus (or Spitzoid melanoma) cells in the lymph nodes. The prognosis in these cases appears to be excellent, but the series of cases is small [111, 112].

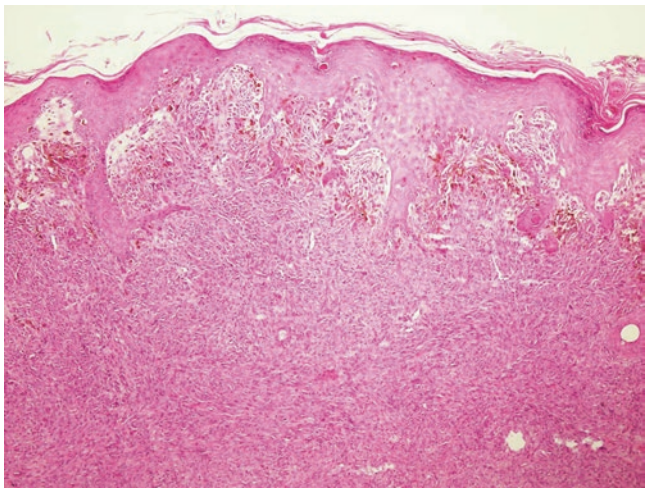

Fig. 20.39 Epidermal hyperplasia and large nests of cells are present within the epidermis of an atypical Spitz nevus

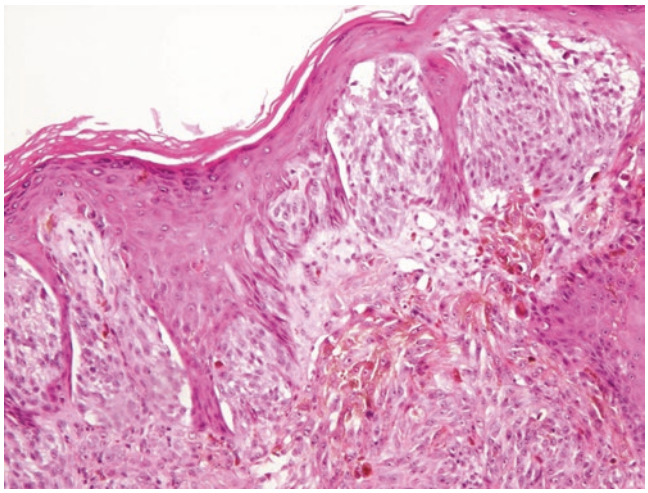

Fig. 20.40 Characteristic Spitzoid morphology with clefting over the nests is seen in the epidermis of an atypical Spitz nevus

20.13.3 Pathogenesis

Spitz nevus is known to carry mutations and copy number increase in the HRAS gene [113]. Since HRAS mutations are found in Spitz nevus, but not in Spitzoid melanoma, HRAS may be used as a diagnostic test to help differentiate between these two lesions [114, 115]. Analysis for BRAF mutations has not shown mutations in Spitz nevus in most reported studies [116–118]. However, a few studies have reported mutations in BRAF in a subset of Spitz nevi, some of which have atypical histologic features [119, 120]. RAS is an upstream activator of the MAP-kinase pathway, and consistent with this, Spitz nevus has high levels of phosphorylated ERK, which is a component in this pathway [121]. Spitz nevus also has high levels of p16 INK4a (CDKN2A), which is a cell-cycle inhibitory protein and a tumor suppressor [122, 123].

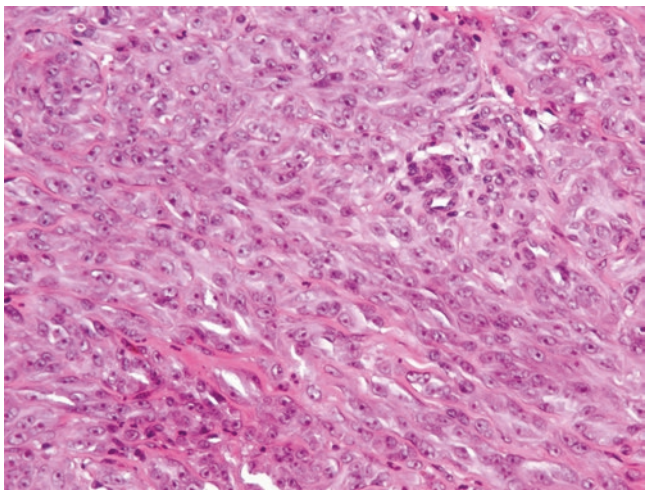

Fig. 20.41 The dermal component of an atypical Spitz nevus demonstrates cells with characteristic Spitzoid morphology of abundant eosinophilic cytoplasm, vesicular nuclei, and visible nucleoli. Cellularity is higher than in a common Spitz nevus

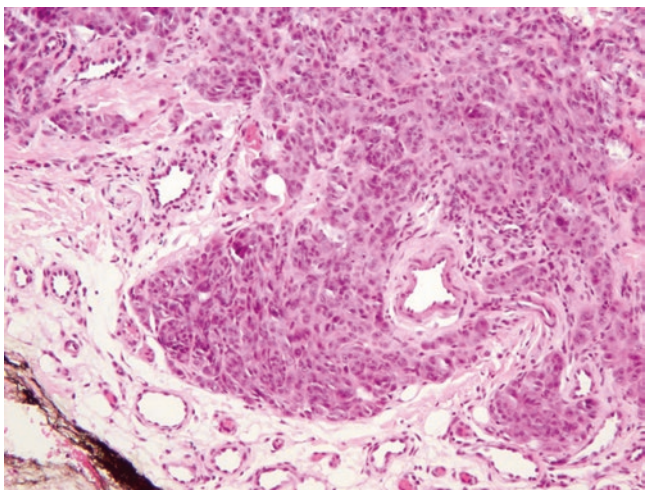

Fig. 20.42 The deepest component of an atypical Spitz nevus shows melanocytes with incomplete maturation and increased cellularity

20.14 Pigmented Spindle Cell Nevus (Reed Nevus)

20.14.1 Clinical Features

Pigmented spindle cell nevus is considered to be a more heavily pigmented variant of Spitz nevus, although this has been somewhat controversial [124]. It is most common in young adults, although it does occasionally occur in children (Fig. 20.43). The nevus tends to appear as a dark brown to black macule or papule measuring 3–5 mm, often on the lower extremity (particularly the thigh) of a young woman.

Fig. 20.43 Pigmented spindle cell nevus appears as a dark brown to black papule with irregular borders

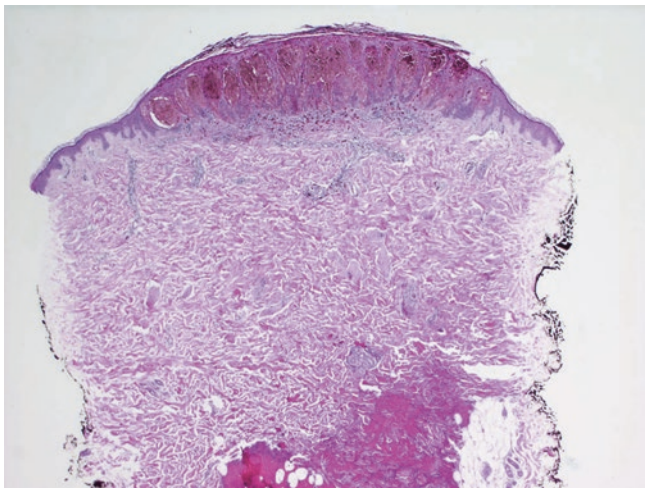

Fig. 20.44 A pigmented spindle cell nevus is a well-circumscribed proliferation of nested and densely pigmented melanocytes within the epidermis and usually the dermis

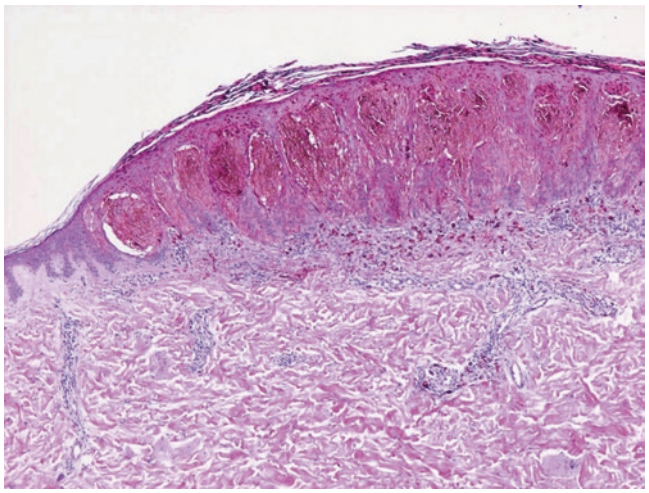

Fig. 20.45 Large nests of spindle-shaped melanocytes that are vertically oriented are present within the epidermis of pigmented spindle cell nevi

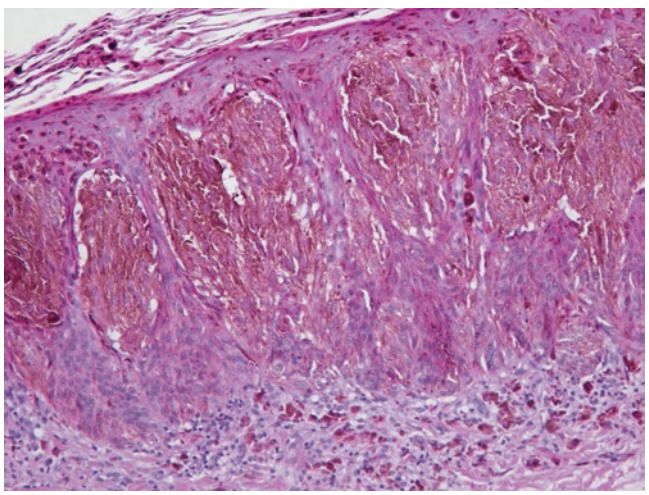

Fig. 20.46 Densely pigmented spindle-shaped melanocytes are present in nests with occasional single pagetoid cells in pigmented spindle cell nevi

20.14.2 Histology

Pigmented spindle cell nevus is characterized by a symmetrical, sharply circumscribed proliferation of nested and densely pigmented spindle-shaped melanocytes located along the dermal-epidermal junction (Figs. 20.44, 20.45 and 20.46). The nests of melanocytes tend to be large, and have a vertical orientation similar to those seen in a Spitz nevus [127, 128]. The nests may be confined solely in the epidermis, or extend into the dermis with similar morphologic features. Scattered pagetoid cells are present in the central portion of the lesion, but they should not occur at the periphery. The melanocytes display striking uniformity in appearance, and cytologic atypia is not a feature of these lesions. Eosinophilic globules (Kamino bodies) are seen in up to 50 % of cases, and clefting between keratinocytes and epidermal nests of melanocytes is frequently present. Rare mitoses may be seen, but they should not be atypical or present at the base of the lesion. As with other benign nevi, maturation of nevus cells should be present with progressive descent into the dermis. While the melanocytes are predominantly spindle-shaped, epithelioid melanocytes may be admixed, resulting in histologic overlap with ordinary Spitz nevi. Up to 7 % of cases can have some histologic features of a dysplastic nevus [129]. An underlying lymphocytic immune response is seen in many pigmented spindle cell nevi.

The main differential diagnosis is melanoma. Architectural features that favor the diagnosis of pigmented spindle cell nevus include sharp circumscription, pagetoid spread limited to the central portion of the lesion, and a predominantly nesting pattern consisting of uniformly distributed nests of melanocytes. The melanocytes have minimal cytologic atypia. Dermal nests demonstrate full maturation, and mitotic activity is sparse and limited to the papillary dermis.

20.14.3 Pathogenesis

A study of pigmented spindle cell nevus and spindle cell melanoma showed that in 15 cases of pigmented spindle cell nevus tested, 14 cases were negative for fluorescence in situ hybridization (FISH) analysis using probes targeting 6p25 (RREB1), 11q13 (CCND1), 6q23 (MYB), and centromere 6, whereas 4 out of 15 cases of spindle cell melanoma were positive for FISH, indicating lack of molecular aberrations in the genetic loci tested in pigmented spindle cell nevus [130].

20.15 Dysplastic Nevus

20.15.1 Clinical Features

Although there is lack of a consensus regarding the best definition of an "atypical nevus," this designation is generally based on a combination of clinical and histologic features. Atypical melanocytic nevi are seen in children [133], although the incidence is quite low in the general population [134]. Estimates of the prevalence of atypical nevi vary widely given the lack of agreement on a definition, but one study in Turkish children found it to be 3.45 % [132]. Atypical nevi are present with high frequency in patients from melanoma-prone families, with an incidence as high as 37 % [135].

Atypical nevi are generally acquired and often appear around puberty, but they may develop well into adulthood. They tend to be larger (often ≥6 mm) than common acquired nevi, display asymmetry of shape, have irregular borders, and contain multiple colors (Fig. 20.47). Dysplastic nevi may occur on any cutaneous or mucosal surface. Although somewhat controversial, they are felt to be markers for possible development of malignant melanoma [131].

Fig. 20.47 Dysplastic nevus presents as an irregularly-shaped reddish-brown papule

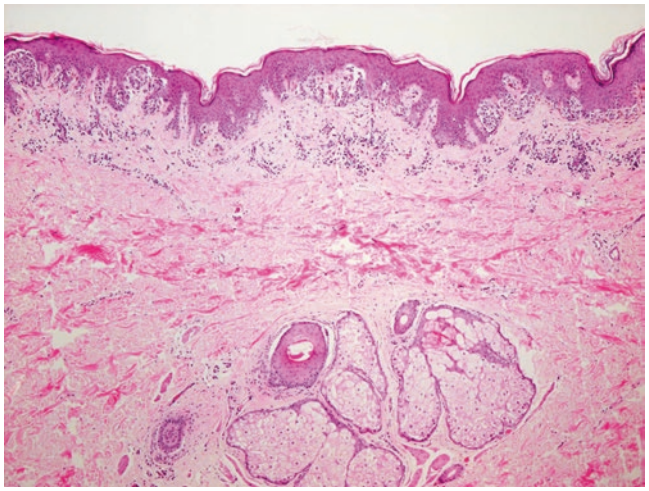

Fig. 20.48 A dysplastic nevus is characterized by a proliferation of nests of melanocytes and occasional single melanocytes within the epidermis. Some nests are aberrantly located between rete ridges or bridge from one elongated rete ridge to the adjacent one. The dermis has a benign-appearing melanocytic proliferation with scattered lymphocytes and dermal fibrosis

20.15.2 Histology

In children, histologic changes associated with dysplastic nevi are more common in nevi from the scalp [136]. The histologic features of dysplastic nevi in children are identical to those described in adults. They can be either junctional, involving solely the epidermis, or compound, involving both the epidermis and the dermis. The epidermal changes in both types of nevi consist of nests of melanocytes located at the base and between the rete ridges (Figs. 20.48 and 20.49). The nests of nevus cells are haphazardly distributed and variable in size. They may be horizontally oriented, and connection of nests across adjacent rete ridges is a common feature. Proliferation of single melanocytes along the basal layer, which is a feature known as lentiginous basilar melanocytic hyperplasia, is a common finding. Pagetoid upward migration of melanocytes may be present to a small degree over the central portion of the lesion, but it is concerning if there is extensive pagetoid spread. Dysplastic nevi tend to be relatively more sharply circumscribed as compared to melanomas, but the lesional border is not as clearly defined as in clearly benign nevi.

In compound nevi, nests of melanocytes are present within the papillary dermis, but only rarely extend into the reticular dermis. Appropriate cellular maturation is present, and mitoses should not be seen. Within the papillary dermis, bands of fibrosis are present in a lamellar pattern known as lamellar fibroplasia. In addition, concentric eosinophilic fibrosis may be seen surrounding elongated rete ridges. A lymphocytic infiltrate is always present, albeit to varying degrees.

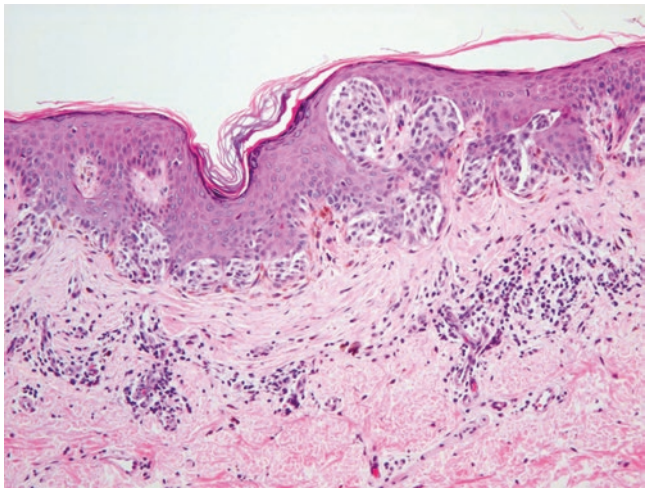

Fig. 20.49 Dysplastic nevi have enlarged melanocytes with varying degrees of cytologic atypia. Bridging and aberrant placement of melanocytic nests are present within the epidermis. The papillary dermis contains fibrosis, a lymphocytic infiltrate, and scattered melanophages

Melanocytic atypia is considered to be a *sine qua non* for making the diagnosis of dysplastic nevus. Melanocytes are enlarged with pleomorphic nuclei and focal hyperchromasia. Changes associated with dysplastic nevi have been seen in Spitz nevi [137] and congenital nevi [138]. In some cases, it is not possible to make a clear distinction, and the histologic diagnosis should include reference to each type of growth pattern.

The major differential diagnosis includes melanoma of the superficial spreading type. In most cases of this type of melanoma, there are many more single melanocytes than nests of cells within the epidermis. Pagetoid extension is more diffuse and prominent, and cytologic atypia is more pronounced and involves the vast majority of tumor cells. Within the dermis, cellular maturation may be absent, and dermal mitoses would be expected. Another entity that might be considered in the differential diagnosis is a pigmented spindle cell nevus (of Reed). These nevi are more sharply circumscribed than dysplastic nevi. They have fewer single melanocytes within the epidermis, demonstrate vertically-oriented nests of uniform spindle-shaped melanocytes, and are densely pigmented.

20.15.3 Pathogenesis

There is evidence that similar to common nevi, dysplastic melanocytic nevi are clonal. A study has reported clonality in 81 % of common nevi, 25 % of which are dysplastic nevi [139]. Some dysplastic nevi have chromosomal alterations, microsatellite instability, mutations in tumor suppressor genes p16 (CDKN2A) and p53, and activation of RAS and Myc genes [140]. p16 (CDKN2A) appears to be important in a subset of dysplastic nevi in patients with familial dysplastic nevus syndrome. Patients with germline p16 mutations often develop large atypical nevi [141]. p16 is a tumor suppressor and a major melanoma predisposition gene that is commonly mutated in families with inherited melanoma [142]. Dysplastic nevi that occur sporadically, however, do not appear to carry p16 mutations as reported in some studies [143, 144]. Similar to common benign nevi, dysplastic nevi have mutations in BRAF (most commonly V600E) and sometimes mutations in NRAS [90, 142]. Several studies have indicated that the presence of BRAF mutations does not appear to be a distinguishing factor between dysplastic and common nevi [145, 146].

20.16 Deep Penetrating Nevus

20.16.1 Clinical Features

Deep penetrating nevus is a rare melanocytic lesion that may resemble malignant melanoma, both clinically and histologically. It usually presents in the second to third decade of life as a deeply pigmented solitary papule, measuring less than 1 cm in diameter. It is most common on the head and neck but can also occur on the trunk and extremities. Congenital occurrence is rare. Reports of age at which deep penetrating nevus appears range from 3 years to 64 years of age. It is slightly more common in females than in males [147].

20.16.2 Histology

Deep penetrating nevus has been described relatively recently. It has features of a congenital melanocytic nevus and a cellular blue nevus [148, 149]. As a rule, there is no epidermal component to this melanocytic proliferation. Melanocytes are present in the papillary dermis, but are concentrated primarily as nests in the reticular dermis (Fig. 20.50). Extension into the subcutaneous fat is frequent. The characteristic pattern that gives rise to the name of the entity is the tendency for the proliferation to track deeply down and around hair follicles in a "dumbbell-like" configuration (Fig. 20.51). The proliferation tracks down the dermis and within the adventitial collagen surrounding the cutaneous appendages, thus giving the melanocytes the appearance of incomplete maturation [150, 151].

Melanocytes in deep penetrating nevus have a biphasic appearance (Fig. 20.52). Ovoid nests of plump cells that are relatively devoid of pigment are admixed with densely pigmented dendritic cells. The cells may have more nuclear pleomorphism than cells in common acquired melanocytic nevi, and scattered mitotic activity has been reported. However, mitoses should be relatively few and not atypical.

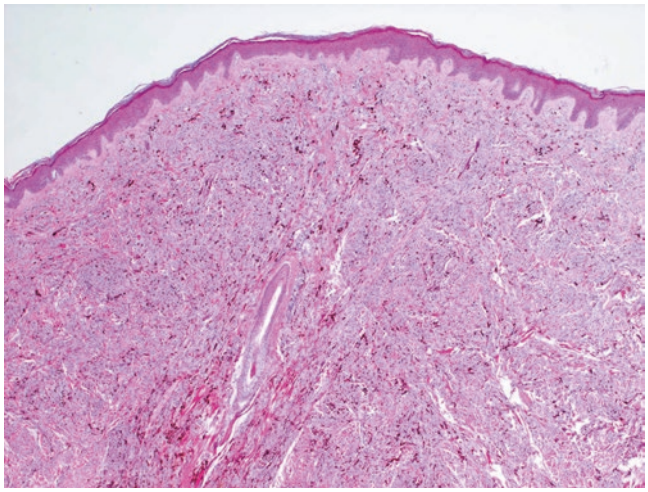

Fig. 20.50 A deep penetrating nevus has an unremarkable epidermis and dense aggregation of melanocytes within the dermis. Sheets of melanocytes fill the dermis and extend down and around hair follicles

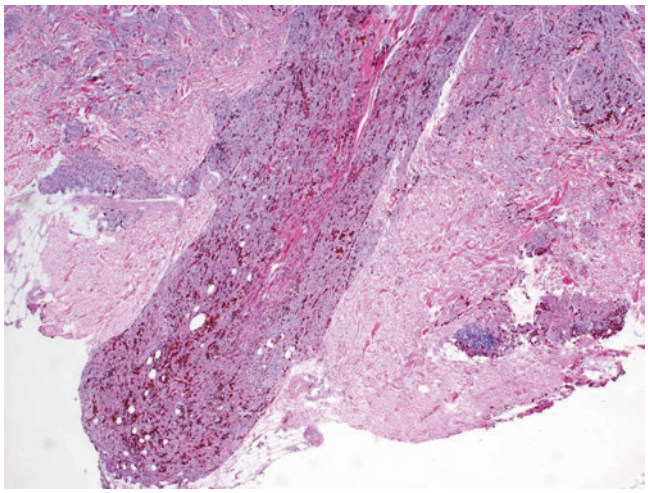

Fig. 20.51 A "dumbbell-shape" growth pattern characterizes deep penetrating nevus as the melanocytes extend down hair follicles

Deep penetrating nevus has been described as being a frequent component of a combined nevus, in which more than one pattern of melanocytic nevi is present [151, 152].

The differential diagnosis includes cellular blue nevus and melanoma. The distinction from cellular blue nevus is of academic interest only with no clinical importance. While the biphasic appearance of melanocytes is identical in these two types of benign nevi, cellular blue nevus does not track down hair follicles in the manner seen in deep penetrating nevus. Melanoma can be differentiated based upon more nuclear pleomorphism and higher mitotic rate. Furthermore, the lack of melanocytic maturation is diffuse in melanoma rather than being limited to the perifollicular dermis. In some cases, this distinction can be quite difficult [153].

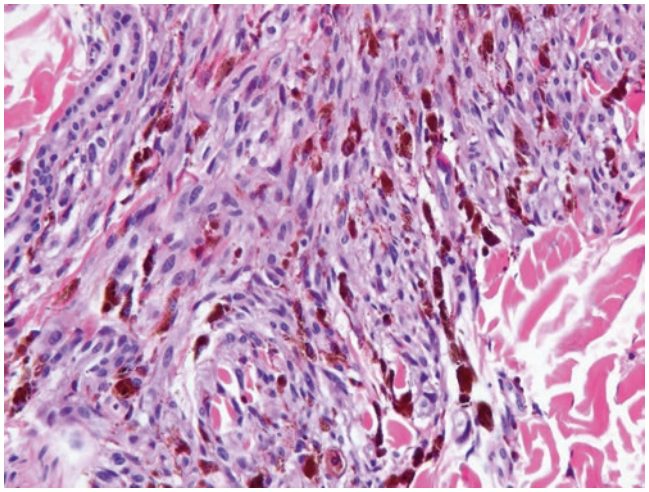

Fig. 20.52 Two populations of melanocytes are present in deep penetrating nevi. Ovoid cells that lack pigment are nested within clusters of densely pigmented dendritic and spindled cells. The cytomorphology is quite similar to the cells seen in cellular blue nevi

20.16.3 Pathogenesis

A recent study has identified HRAS mutations in deep penetrating nevi [154]. In this study, 38 deep penetrating nevi were analyzed, and 6 % of these lesions had HRAS mutations. GNAQ or GNA11 mutations, which are frequently found in benign and malignant blue nevi as well as uveal melanoma, were not observed [154]. Interestingly, HRAS is mutated in approximately 15 % of Spitz nevi. It has been suggested that the presence of HRAS mutations and absence of GNAQ or GNA11 mutations in deep penetrating nevi indicate that these lesions share more similarity with Spitz nevi than with blue nevi at the molecular level. Other studies have shown that the ataxia-telangiectasia-mutated (ATM) gene is significantly upregulated in nodular melanoma as compared with deep penetrating nevi, and that ATM may serve as a diagnostic marker to distinguish between these two entities [155].

20.17 Nevus of Special Sites

20.17.1 Clinical Features

Nevus of special sites refers to melanocytic nevi with atypical clinical and histologic features that occur in certain anatomic regions, including the embryonic milk line/flexural skin, genitalia, palms/soles, ears, and scalp (Fig. 20.53). Clinically, the appearance of a nevus of special sites varies, depending on its location. Most nevi of special sites are thought to have a benign course [156].

Fig. 20.53 Nevus of special site on the breast appears as a thin papule with irregular borders and two shades of brown color (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

20.17.2 Histology

Acquired and congenital melanocytic nevi that occur on acral, genital and flexural skin have histologic features that may raise the differential diagnosis of melanoma [157]. These lesions are especially frequent in children. Most of these lesions have a junctional melanocytic proliferation (Figs. 20.54 and 20.55). In some cases, this proliferation may take the form of lentiginous single-cell growth along elongated rete ridges, while in others the proliferation may be predominantly nested. Some nests occur between rete ridges rather than at their bases. Nests of melanocytes may extend down along cutaneous appendages. Retraction artifact around the nevus nests and cellular dyscohesion may be seen. Single pagetoid cells are present in the majority of cases. The intraepidermal melanocytes may be enlarged and atypical [158]. While focal atypia may be present in the superficial dermis, maturation of nevus cells is present with progressive descent through the dermis. Dermal mitoses are quite unusual in these lesions. Dermal fibrosis has been described in some cases [159, 160]. Similar histologic changes have been described in nevi occurring along the milk line [156, 161].

More recently, the concept of "nevus of special sites" has been expanded, with similarly atypical nevi observed on the scalps of adolescents. These lesions are characterized by large, bizarrely-shaped nests of melanocytes along the basal layer and extending down the hair follicles. Pagetoid cells are commonly seen, and there is dyscohesion of melanocytes within the junctional nests. Cytologic atypia is relatively mild [162].

The major differential diagnosis is melanoma, and care should be taken to avoid the tendency to overdiagnose melanoma in nevi occurring on these "special sites." The attention to sharp circumscription, dermal melanocyte maturation, and absence of dermal mitoses may help in making a diagnosis of nevus of special sites.

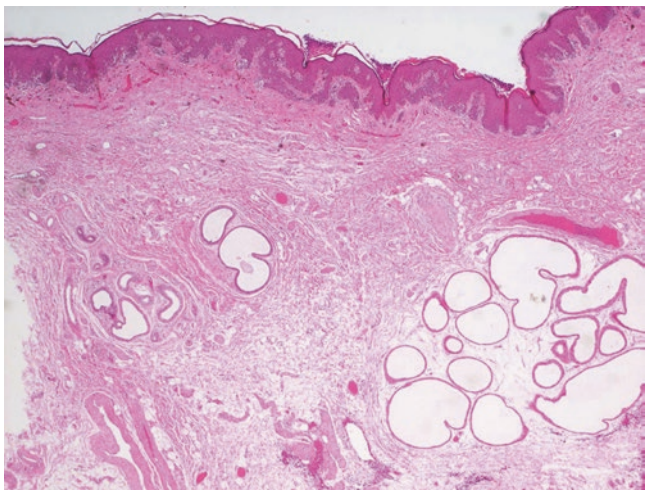

Fig. 20.54 Nevi occurring on genital areas or acral sites demonstrate large nests of melanocytes within the epidermis along with increased numbers of single melanocytes along the epidermal junction in a somewhat disordered growth pattern

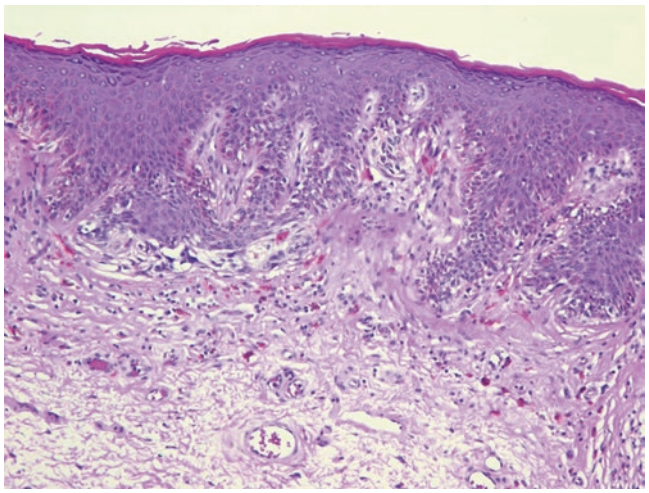

Fig. 20.55 Nevus of special sites demonstrates some architectural disorder of the melanocytic proliferation within the epidermis that bears some resemblance to dysplastic nevus. Some epidermal melanocytes are enlarged and have cytologic atypia

20.18 Halo Nevus

20.18.1 Clinical Features

A halo nevus consists of a central melanocytic nevus with a surrounding ring of hypo- or depigmentation (Fig. 20.56). Halo nevi are most common on the trunk, especially the back. Children with multiple halo nevi appear to be at increased risk for development of vitiligo. The pigmented lesion often will disappear, and the halo will re-pigment over a period of several years [163].

Fig. 20.56 Halo nevus is an irregularly-shaped brown papule surrounded by a depigmented rim

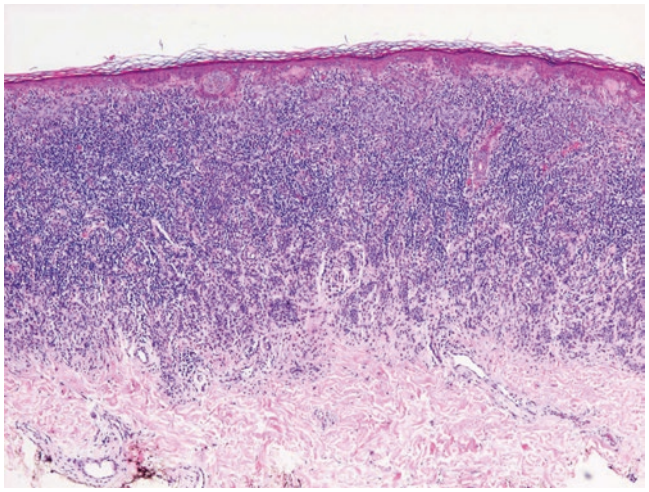

Fig. 20.57 A halo nevus is characterized by a brisk lymphocytic infiltrate within the dermis that may largely obscure any residual melanocytic proliferation

20.18.2 Histology

Evidence for a "halo phenomenon" can be seen in conjunction with any type of benign or malignant melanocytic proliferation. Independent of the antecedent lesion, the histologic changes of this reaction are identical [164]. In association with a melanocytic proliferation, there is a dense band-like infiltrate of lymphocytes that are admixed with remaining dermal and intraepidermal melanocytes (Fig. 20.57). Depending upon the stage of development, residual melanocytes may be difficult to detect [165] When present, the cells may demonstrate focal reactive atypia, and appear to lack the usual features of maturation (Figs. 20.58 and 20.59). In addition, scattered mitoses are an expected finding in the regions with marked lymphocytic infiltrates. Other than these changes, which are related to the dense inflammatory response, the histologic features of the initial lesion will retain the characteristics of the type of nevus that is undergoing the halo response, such as the characteristic morphologies of Spitz nevus, congenital nevus, and acquired nevus. It is difficult to see actual destruction of the melanocytes within the dense inflammatory infiltrate; however, at the lateral margins of the lesion, close examination will reveal an absence of melanocytes along the basal layer of the epidermis. It is the absence of melanocytes that contributes to the clinical appearance of the peripheral halo. With late-stage, well-developed lesions, the presence of an antecedent melanocytic proliferation may be difficult to identify. The histologic changes may demonstrate solely a lymphocytic infiltrate and linear fibrosis within the papillary dermis. In some cases, pigment-laden macrophages can also be present. Halo nevi may develop overlying hyperkeratosis and become almost verrucous [166]. Coexistence of halo nevi and vitiligo has also been reported with speculation of a similar pathogenesis [167].

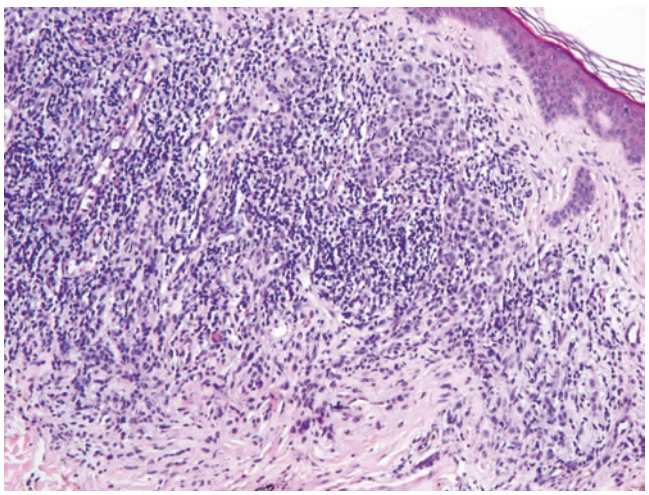

Fig. 20.58 In most cases, small foci of residual melanocytes with slight degree of reactive atypia can be seen surrounded by a dense lymphocytic infiltrate

The histologic differential diagnosis includes regressed melanoma and lichenoid inflammatory reactions to either keratinocytic neoplasms or as primary cutaneous eruptions. Regressed melanomas generally have a much more intense deposition of pigment-laden macrophages within the dermis, although this is not a reproducible difference. A thorough examination of tissue sections in search of residual foci of significant melanocytic atypia is warranted to exclude a melanoma. In children, halo nevi are quite common, while completely regressed melanomas are relatively rare. Regression, with similar if not identical histologic changes, is commonly seen underlying keratinocytic neoplasms. However, these types of neoplasms are quite uncommon in children and rarely enter into the differential diagnosis. While the changes

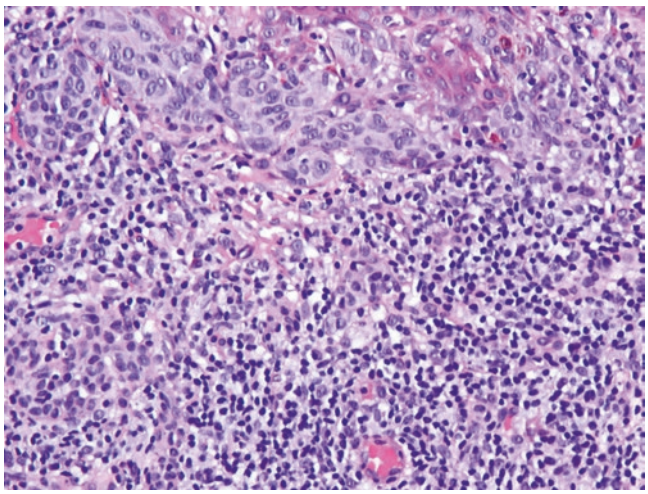

Fig. 20.59 Remaining melanocytes in halo nevi frequently demonstrate vesicular nuclei and occasional nucleoli. An occasional mitosis is seen in some cases

in lichen planus, lichen striatus, and other lichenoid processes may bear some similarity to the immune response that characterizes a halo nevus, simple clinical correlation resolves any diagnostic dilemma.

20.18.3 Pathogenesis

The presence of marked inflammatory reaction in halo nevi suggests an immune-mediated process. T cell-mediated immunity is thought to play a role in the development of halo nevi. Immunohistochemical studies of these nevi show that the majority of lymphocytes within the inflammatory infiltrate are T lymphocytes, mainly CD8+ T cells with a small number of CD4+ T helper cells [168]. Dendritic cells, mainly Langerhans cells within the epidermis, are present in increased numbers during the regression of halo nevi. A case report of a patient who developed multiple halo nevi a few weeks after the start of β-interferon therapy suggests that the immune response induced by interferon therapy results in an inflammatory reaction to the nevus [169].

20.19 Blue Nevus

20.19.1 Clinical Features

Blue nevi are melanocytic lesions that can be congenital or acquired. It is estimated that they occur in approximately 3 % of the population [170]. Clinically, they appear as a blue-black papule or nodule (Fig. 20.60). Blue nevi are typically single lesions occurring on the skin surface, but they may be multiple, and may appear on mucosal surfaces and other tissues, such as lymph nodes.

Fig. 20.60 Blue nevus typically presents as a bluish-colored macule or papule

Common blue nevi usually appear early in life, measure less than 1 cm in diameter, and occur mainly on the face or limbs. Cellular blue nevi are more likely to be present at birth. They are often larger than 1 cm in diameter, tend to affect the buttocks and sacral area, and appear to have a higher risk of malignant transformation [170].

20.19.2 Histology

Blue nevi in children are histologically indistinguishable from blue nevi in adults. They are almost always purely intradermal collections of melanocytes, and lack any intraepidermal melanocytic nests (Fig. 20.61). In some cases, a slight increase in single basilar melanocytes can be seen, and rare cases that demonstrate a junctional proliferation of melanocytes have been described in children [171]. Within the papillary and superficial reticular dermis, there are densely pigmented dendritic melanocytes, and interspersed melanophages are seen in most cases (Fig. 20.62). There is minimal nuclear pleomorphism or atypia, and mitotic activity is absent in most cases. In older lesions, abundant sclerotic collagen separates the melanocytes, giving rise to the term sclerotic blue nevus (Figs. 20.63 and 20.64). Blue nevi may represent one component of a combined nevus, in which more than one histologic pattern is present [172].

The closest histologic mimics to blue nevus are nevus of Ota, nevus of Ito, and Mongolian spot. In each of these entities, there is much less melanocytic cellularity within the dermis. They are not as sharply circumscribed as blue nevi. In Mongolian spots, the concentration of melanocytes is much

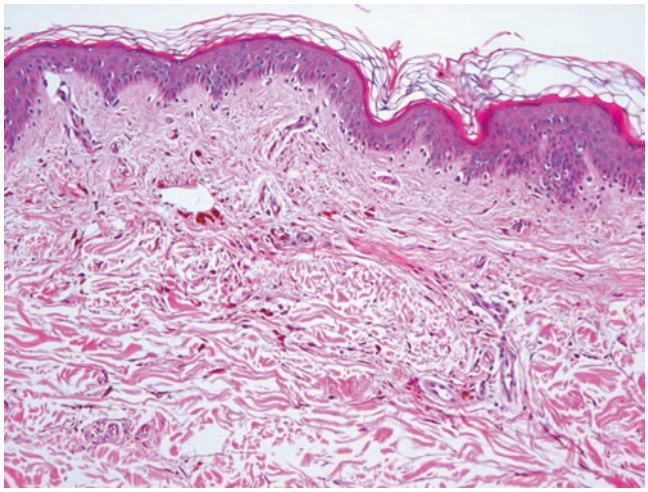

Fig. 20.61 A blue nevus has an unremarkable epidermis overlying a population of densely pigmented dendritic and spindle-shaped melanocytes in the superficial reticular dermis

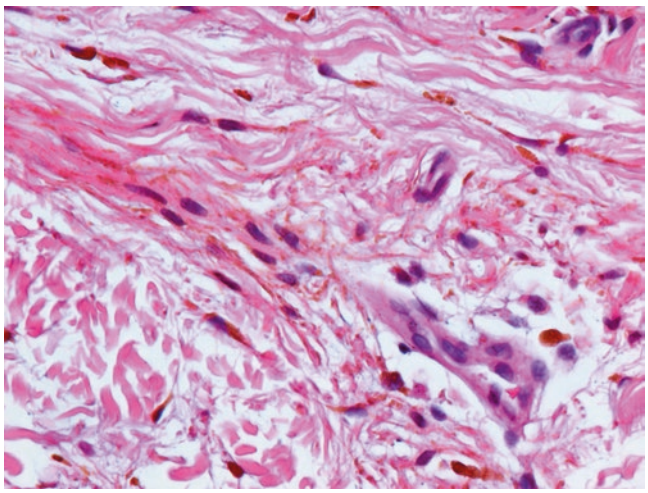

Fig. 20.62 Melanocytes are spindle-shaped in blue nevi, and scattered melanophages are present in the dermis

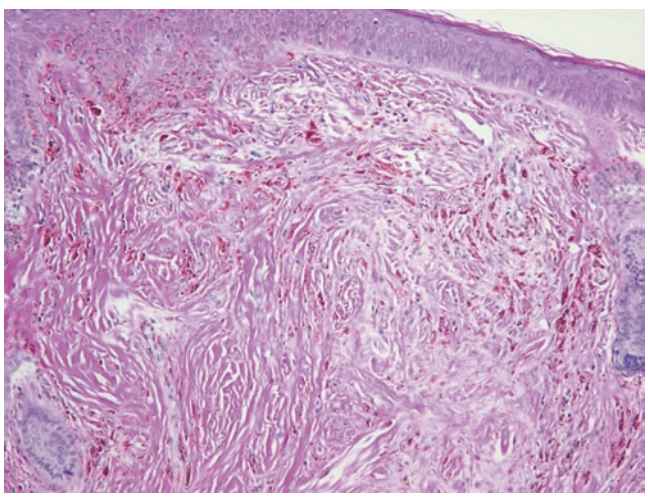

Fig. 20.63 Densely pigmented spindled melanocytes are present interspersed between sclerotic collagen bundles in a sclerotic blue nevus

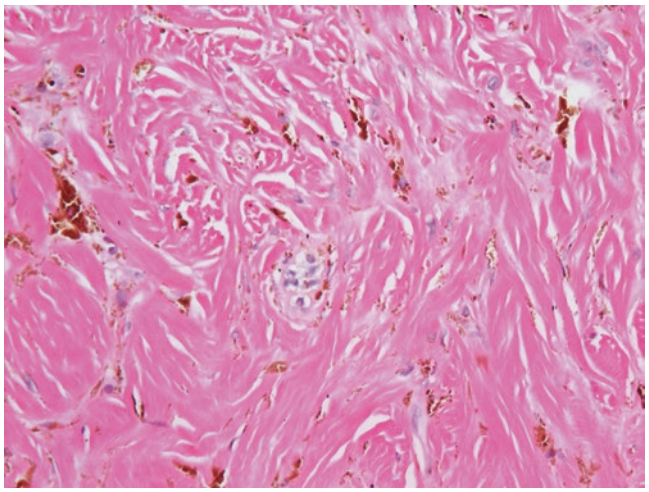

Fig. 20.64 Some sclerotic blue nevi demonstrate marked dermal fibrosis and only minimal numbers of residual pigmented melanocytes

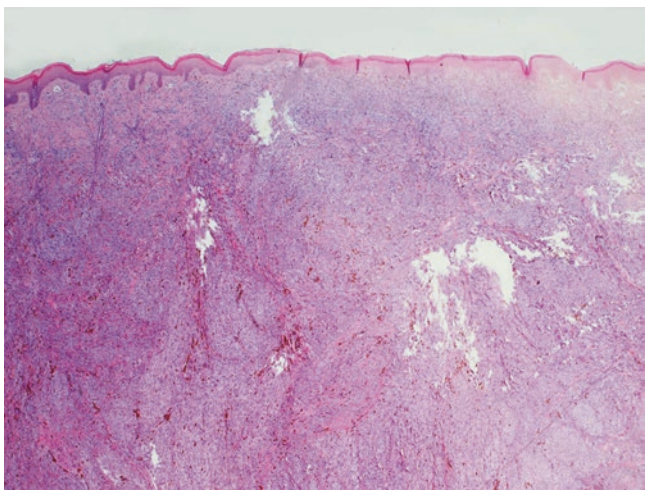

Fig. 20.65 An unremarkable dermis overlies a densely cellular infiltrate of ovoid and spindle-shaped cells in cellular blue nevi

deeper in the reticular dermis. Late sclerotic blue nevi may resemble dermatofibromas in that the pigment can be relatively inconspicuous, and the sclerotic component may be the dominant histologic feature. In some cases, it is difficult to distinguish an ordinary blue nevus from a cellular blue nevus, although cellular blue nevus tends to extend much more deeply into the reticular dermis (Figs. 20.65, 20.66, and 20.67).

The differential diagnosis of blue nevus also includes desmoplastic melanoma, but this entity is quite rare in children. Desmoplastic melanomas have an intraepidermal melanocytic proliferation in most cases, and demonstrate dermal nuclear atypia, pleomorphism and scattered mitoses. In these melanomas, there is frequently a perivascular lymphoid infiltrate that is not usually seen in blue nevi. A malignant blue nevus is also in the differential consideration, and it is characterized by nuclear atypia, mitotic activity, zonal necrosis, and extension into the deep reticular dermis. Some cases of metastatic melanoma can be virtually indistinguishable from

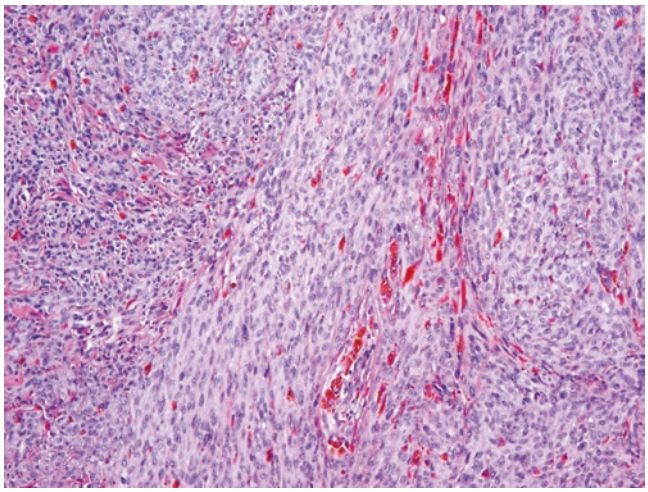

Fig. 20.66 Cellular blue nevi are comprised of two cell populations. A population of ovoid cells lacking pigment is nested and compresses a second population of dendritic and spindle-shaped pigmented cells

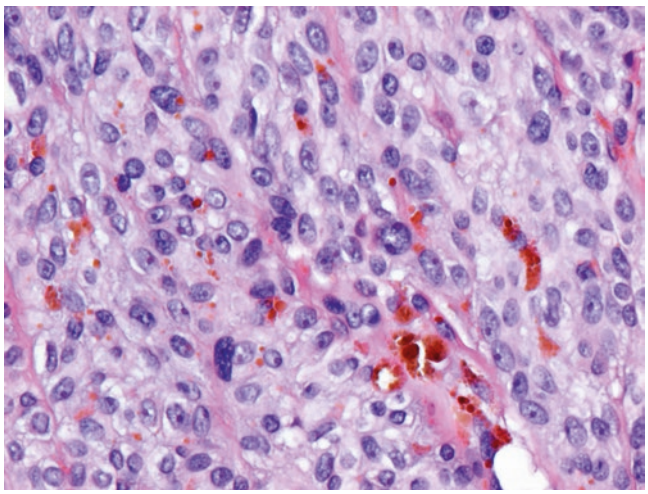

Fig. 20.67 Melanocytes in cellular blue nevi have vesicular nuclei with scattered nucleoli. Rare mitoses can be seen

blue nevus. In these cases, careful search for cytologic atypia, epithelioid morphology, mitotic activity, and an associated inflammatory infiltrate may help, but these features are not always identified [173].

20.19.3 Pathogenesis

Blue nevus is believed to arise from dendritic melanocytes remaining in the dermis during the embryonic migration of melanocytes from the neural crest to the epidermis. Recent studies have provided insights into the molecular basis of dermal melanocytic migration and the genetics of blue nevus. Somatic mutations in GNAQ, a gene encoding the G-protein α-subunit q that is involved in signaling by G-protein-coupled receptors, have been found in up to 80 % of blue nevi [80]. Mutation in GNAQ occurs mainly at codon 209 in the Ras-like domain of GNAQ (GNAQ Q209L). This domain is essential for GTPase activity (GTP hydrolysis), and mutations is this domain result in constitutive activation of G-protein-coupled receptors with oncogenic potential [80]. GNAQ Q209L mutation causes anchorage-independent growth of cells in soft agar (a cellular feature of transformation), and induces MAP-kinase activation, which appears to be an early event in tumors with GNAQ mutations. GNAQ mutations are also found in amelanotic/hypomelanotic blue nevi, indicating that the mechanisms underlying pigment homeostasis in these nevi are similar to the mechanisms in melanotic lesions [174]. Somatic mutations in GNA11, another member of the heterotrimeric G-protein α-subunits, are also found in some blue nevi, and commonly occur in uveal melanoma [175]. Activating mutations in GNAQ and GNA11 result in an increase in the number of dermal melanoblasts [176].

Blue nevi are generally stable lesions that rarely become malignant. They generally do not harbor mutations of genes implicated in the pathogenesis of melanoma, such as BRAF, NRAS, and c-Kit [177]. It is possible that GNAQ mutation alone is not sufficient for full progression to melanoma but requires additional oncogenic mutations that are necessary for malignant transformation.

20.20 Recurrent Melanocytic Nevus

20.20.1 Clinical Features

A nevus may recur following biopsy or incomplete excision of the lesion (Fig. 20.68). Recurrent nevus phenomenon may also be encountered as a result of prior trauma or chronic irritation of a nevus. Assessment of melanin pigmentation pattern by dermoscopy may assist in the clinical evaluation of recurrent nevi to rule out atypical melanocytic proliferations and melanoma.

Fig. 20.68 Recurrent nevus has brown pigment appearing in an atrophic scar at site of previous nevus excision on the back (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

20.20.2 Histology

The histologic changes in a recurrent nevus share many of the features seen in melanoma [178]. The easiest way to make this distinction is at low magnification. An overview of the lesion demonstrates a sharply circumscribed melanocytic proliferation in which the atypical epidermal component is seen to be located directly over a dermal scar, and has no extension beyond the lateral limits of the scar (Fig. 20.69). The epidermis often has flattened rete ridges. Melanocytes are present as single cells along the dermal-epidermal junction with only scattered nest formation (Fig. 20.70). Scattered pagetoid cells may be present [179] (Fig. 20.71). The melanocytes have variable degrees of cytologic atypia and dyscohesion [180]. Prominent nucleoli and enlarged melanocytes are expected findings [181]. Within the dermis, there may be nests of melanocytes lateral to and deep to the scar. The scar can appear relatively insignificant if the initial insult to the lesion is local trauma and not a previous surgical procedure. In these cases, the diagnosis is more difficult to establish.

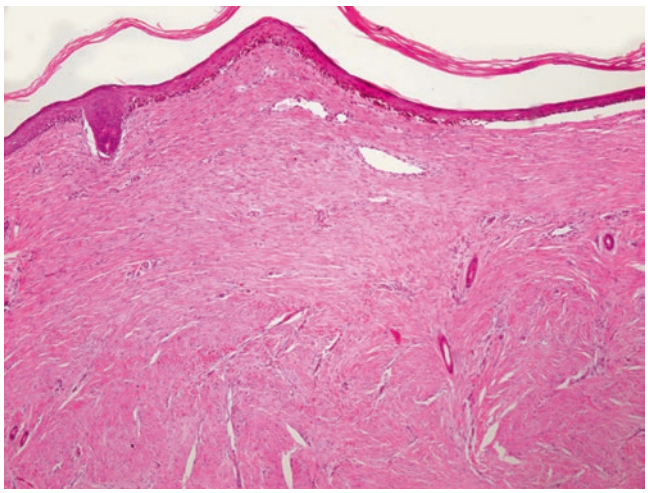

Fig. 20.69 In a recurrent nevus, there is a dermal scar that is readily apparent beneath an atrophic epidermis with a lentiginous proliferation of single melanocytes along the basal layer

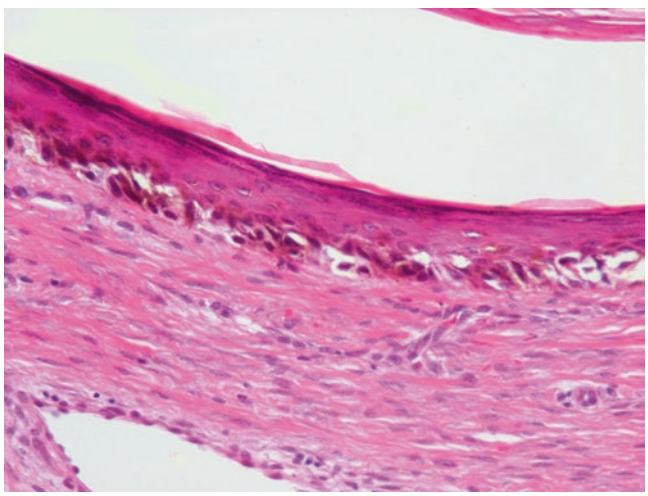

Fig. 20.70 Single melanocytes, some with cytologic atypia, are present along the basal layer in a recurrent nevus

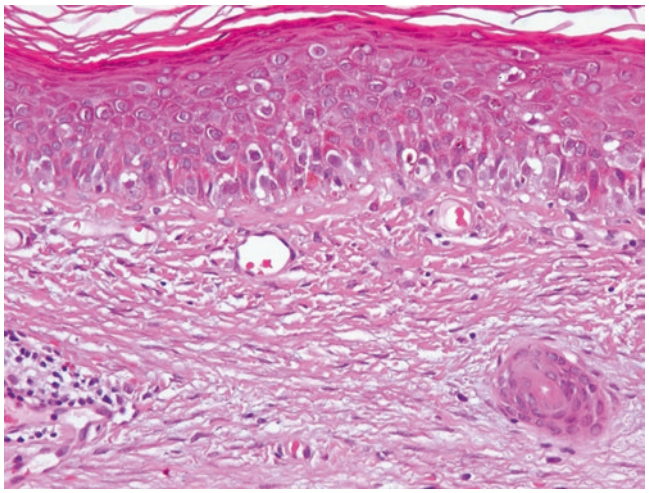

Fig. 20.71 Scattered pagetoid cells characterize a recurrent nevus. Careful attention to the scar as seen in the dermal fibrosis allows distinction from a melanoma in situ

The major differential diagnosis includes a regressed melanoma. This lesion may demonstrate focal residual features of melanoma with abundant upward pagetoid spread, and marked cytologic atypia of melanocytes [182]. A clinical history of prior procedure is the best way to make the distinction between a recurrent nevus and a regressed melanoma.

20.20.3 Pathogenesis

The mechanism of recurrence of a melanocytic nevus subsequent to prior excision of the original nevus is not fully known. The repopulation of melanocytes in the epidermal junction may be due to the presence of melanocytic stem cells that reside in the bulge of the hair follicles. Stem cells may migrate to sites in the epidermis that lack melanocytes, and differentiate and proliferate at that location [180, 182, 183]. The repopulation of melanocytes in the dermis may also be due to the regrowth of residual dermal nevus cells [184].

20.21 Cutaneous Neurocristic Hamartoma

20.21.1 Clinical Features

Neurocristic hamartoma is a rare cutaneous tumor that can be congenital or acquired. Although neurocristic hamartoma is more common in adults, it can sometimes present in childhood. The most common location is the scalp. It presents as an enlarging cutaneous pigmented lesion. The potential for malignant transformation of neurocristic hamartoma is not well understood [185].

20.21.2 Histology

This is a rare dermal hamartoma that consists of neurosustentacular, neuromesenchymal, and melanocytic components (Figs. 20.72, 20.73 and 20.74). The melanocytic components can resemble cellular blue nevi or congenital nevi [186, 187, 188]. There is variable pigmentation of the dermal melanocytes with deep pigmentation in some populations and virtually no pigmentation in others. A plexiform growth pattern is also described in many cases. There is a proliferation of Schwann cells admixed with polymorphous melanocytes [189]. In these cases, the intervening stroma is loose and myxoid with delicate vascular channels and small nerve fascicles. Adipose tissue may also comprise a portion of the hamartoma [190]. In some cases, a collection of densely pigmented dendritic melanocytes courses through collagen bundles that resembles a blue nevus [191].

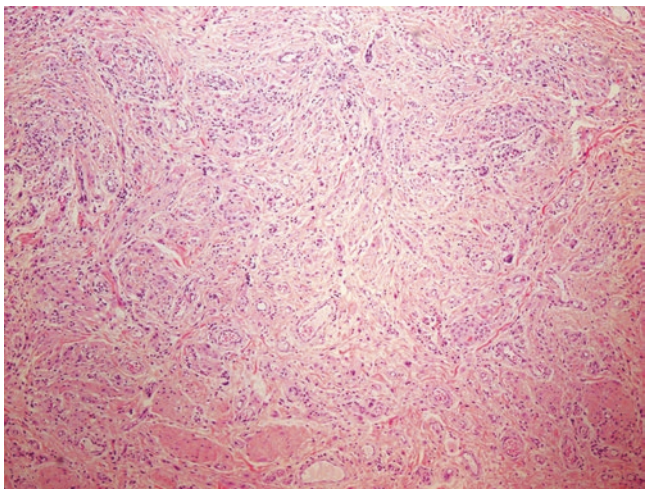

Fig. 20.72 Foci of neural differentiation with myxoid loose stroma are apparent in a neurocristic hamartoma

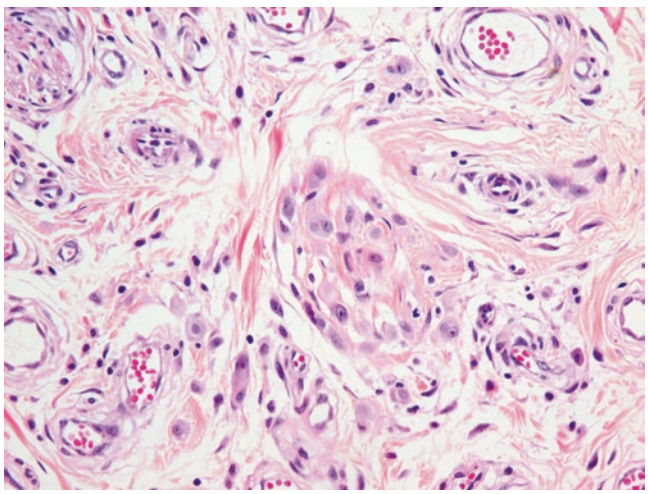

Fig. 20.73 Dilated blood vessels, melanocytes and neural structures coursing in a loose myxoid stroma in a neurocristic hamartoma

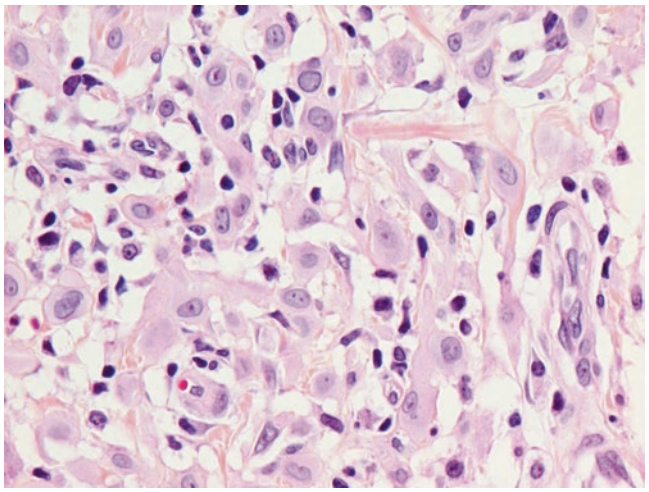

Fig. 20.74 Individual melanocytes can demonstrate some nuclear atypia and pleomorphism in a neurocristic hamartoma

Malignant transformation can occur in neurocristic hamartomas. In these cases, there is increased cellularity, although the melanocytes are bland, small, and spindled or oval. The malignant component consists of multifocal dermal nodules with no overlying epidermal melanocytic proliferation. They have a nested and trabecular growth pattern [189].

The differential diagnosis depends upon the predominant type of cells within the hamartomatous proliferation. Blue nevus and cellular blue nevus present the most diagnostic difficulty. Searching for divergent neuromesenchymal differentiation is the best way to make the histologic distinction.

20.21.3 Pathogenesis

The pathogenesis of cutaneous neurocristic hamartomas is not known. It is believed to result from aberrant development of cells derived from the neural crest that give rise to nerve cells (such as Schwann cells and ganglion cells), melanocytes, neuroendocrine cells, as well as the local mesenchyme within cephalic areas [192]. Malignant melanocytic component has been found in some cases [189].

20.22 Spitzoid Melanoma

20.22.1 Clinical Features

Although cases of malignant melanoma in children are rare, and account for only 0.7 % of all cases reported in the United States, the incidence of pediatric melanoma has been rising by 2.6 % annually. Malignant melanoma lesion can be flat or raised, and pigmented or amelanotic. Generally, prognosis and recommended therapy depend on the depth and other

histologic features of the tumor. Spitzoid melanomas are a special type of melanoma that share features with Spitz nevus. Spitzoid melanomas are more common in adults, but can occasionally occur in children. Lesions tend to appear more commonly on the head and extremities [193]. A typical Spitzoid melanoma is a changing nodular tumor, often greater than 1 cm in diameter. It may be erythematous or pigmented, and can sometimes be ulcerated or crusted.

20.22.2 Histology

Spitzoid melanoma has been discussed previously in the differential diagnosis of Spitz nevus and atypical Spitz tumor. Essentially, the designation of Spitzoid melanoma is given to melanomas in which the cytomorphologic features are those described in Spitz nevi [194].

Spitzoid melanomas occurring in children may demonstrate an overtly malignant clone of melanocytes within the dermis that is morphologically quite different from the background Spitz nevus [195]. In other cases, the morphological features resemble classical Spitz nevi, but the lesion also has surface ulceration, lack of dermal melanocytic maturation, vascular and perineural invasion, regression, and deep dermal mitoses, some of which are atypical (Figs. 20.75, 20.76, 20.77 and 20.78). Other diagnostic features include large lesion size, asymmetry of the lesion, poor lateral demarcation, an expansile deep margin, diffuse sheets of melanocytes rather than the usual nesting pattern, and extensive nuclear pleomorphism [194].

The distinction of Spitzoid melanoma from a benign spindle and epithelioid Spitz nevus is usually quite difficult [193, 196]. The most reliable histologic features that serve to make the distinction include increased dermal cellularity, mitoses at the

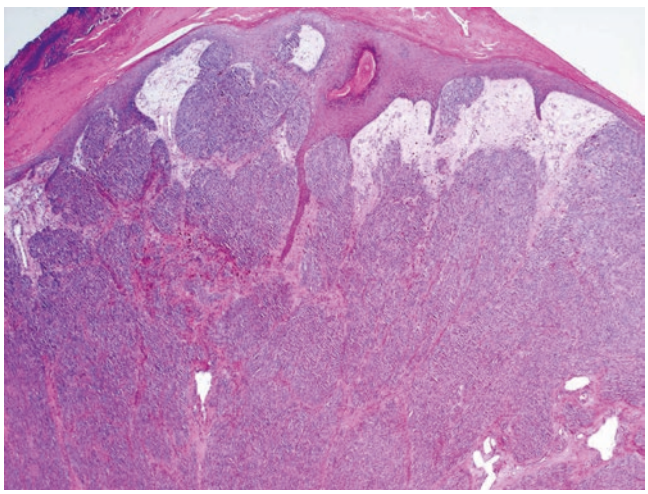

Fig. 20.75 A Spitzoid melanoma has the appearance of a Spitz nevus comprised of cells with increased nuclear to cytoplasmic ratio

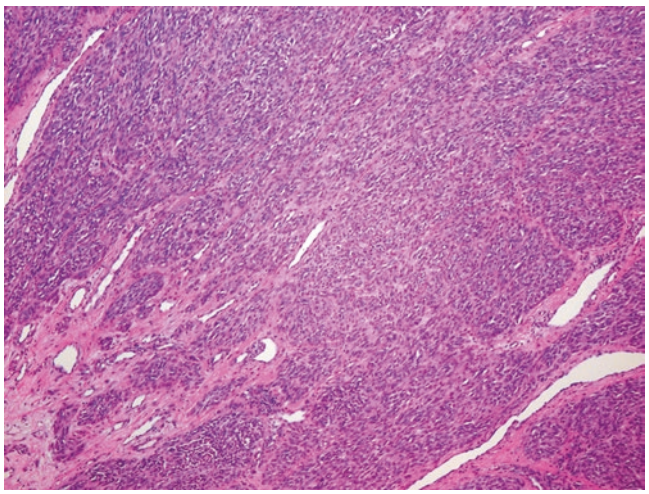

Fig. 20.76 The dermal tumor cells fail to demonstrate maturation in Spitzoid melanoma, and the cellularity is markedly increased over that in a Spitz nevus

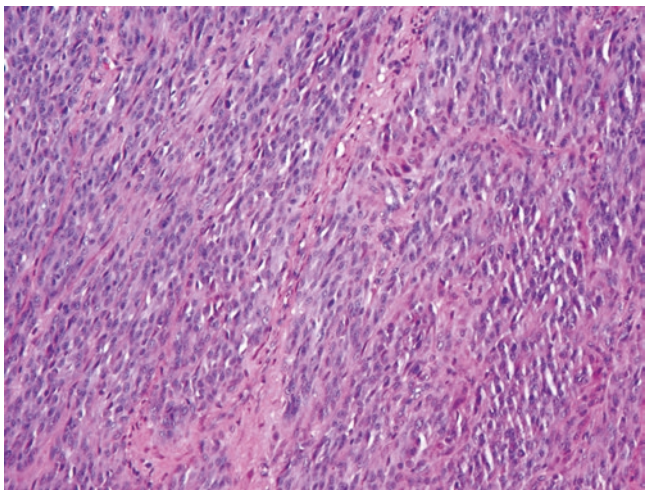

Fig. 20.77 Lack of maturation, nuclear atypia, and increased cellularity, especially in the deep dermis, characterize Spitzoid melanoma

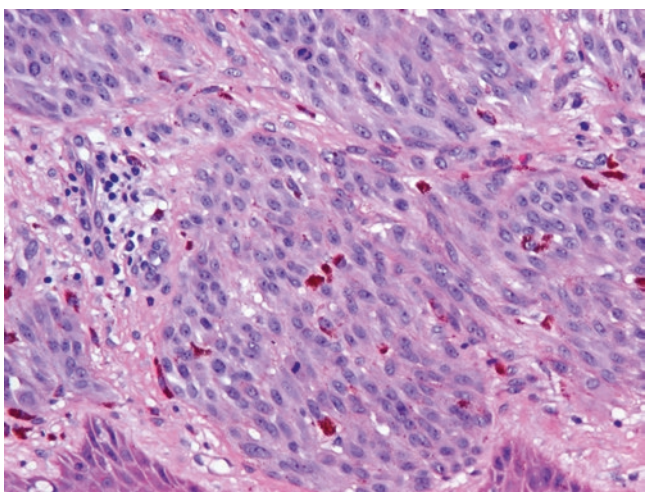

Fig. 20.78 Many mitoses in the deep dermis are seen in Spitzoid melanoma

base of the lesion, atypical mitotic forms, and an asymmetrical inflammatory infiltrate often present in a melanoma [197].

20.22.3 Pathogenesis

Spitzoid neoplasms, including Spitzoid melanoma, harbor kinase fusions that are important mechanisms of oncogene activation in these lesions. In one study, over 51 % of Spitzoid neoplasms had fusions involving the receptor tyrosine kinases ROS1, NTRK1, ALK, RET, and BRAF [198]. Other studies have reported the absence of activating mutations of BRAF, NRAS, and HRAS genes in Spitzoid melanoma in children under 10 years of age [199]. It has been suggested that Spitzoid melanoma (along with classic Spitz nevus) is a distinct subtype of melanocytic tumor in which mutations in BRAF and NRAS are uncommon [200, 201].

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Vascular Anomalies

21

21.1 Capillary Malformations

21.1.1 Cutaneous and Mucosal Capillary Malformations (Port-Wine Stains)

21.1.1.1 Clinical Features

Capillary malformations (also known as port-wine stains) are superficial vascular malformations. They occur in 0.3–0.5 % of the population [1]. Capillary malformations appear as pink to erythematous or violaceous macules and patches (Fig. 21.1). They can occur anywhere on the body, but are most common on the neck and head, particularly the face. They may darken and thicken over time. Port-wine stains can occur in isolation or as part of a syndrome. Syndromic presentations include Sturge–Weber syndrome with central nervous system lesions, Klippel–Trenaunay–Weber syndrome with limb hypertrophy, and phakomatosis pigmentovascularis with a variety of melanocytic lesions [2–6]. The melanocytic lesions can include nevus of Ota, nevus spilus, congenital dermal melanocytosis, and melanosis oculi. Capillary malformations can be treated with a variety of vascular-specific lasers, particularly pulsed-dye laser.

21.1.1.2 Histology

Capillary malformations have variable histologic patterns, depending upon the age of the lesion. Early lesions demonstrate only subtle histologic changes, and could be misinterpreted as normal skin. There is minimal vascular dilatation of small vessels in the papillary and superficial reticular dermis. Vascular congestion is prominent. With increasing age, the vessels progressively dilate, initially remaining thin-walled and demonstrating a single layer of flattened endothelial cells (Fig. 21.2). Eventually, the vascular walls have increased thickening from compensatory hyperplasia due to increased blood flow. The vessel walls can attain marked thickening resulting in a nodular appearance [7, 8].

The incidence of misdiagnosis of pediatric vascular neoplasms is high, and attention to the differential diagnostic features is crucial [9]. The histologic differential diagnosis includes infantile hemangioma. Capillary malformations fail to demonstrate the focality or lobularity seen in an infantile hemangioma, and they are diffuse across the entire biopsy specimen. Later lesions may be confused with arteriovenous malformations due to the thickened vessels walls. Arteriovenous malformations tend to have increased vascular density, more vascular luminal red blood cells, more branching of dermal vessels, and thicker vessels than are seen in capillary malformations [10]. Some acquired port-wine stains can appear post-traumatically, providing evidence to the hypothesis that these vascular malformations are the result of focal defects in autonomic innervation [11–15]. An eczematous inflammatory reaction pattern has been described in association with capillary malformations [16]. Angiolymphoid hyperplasia with eosinophilia has developed within the vascular ectasia of a port-wine stain [17].

21.1.1.3 Pathogenesis

Port-wine stain is a superficial cutaneous vascular malformation of capillaries. Abnormal alterations in the sympathetic vascular innervation of the capillaries in capillary malformations have been postulated to play a role in the development of these vascular lesions [15].

Significant insights into the pathogenesis of capillary malformations/port-wine stains came with the finding of an underlying somatic mutation in non-syndromic port-wine stains and in those associated with Sturge–Weber syndrome. The mutation is a single-nucleotide variant (c.548G > A, p.Arg183Gln) in the GNAQ gene, in which 88 % of patients with Sturge–Weber syndrome and 92 % of patients with non-syndromic port-wine stains harbor the mutation [18]. Guanine nucleotide-binding protein (G protein) Q polypeptide [GNAQ] gene encodes an α-subunit in the Gq class [19]. GNAQ is involved in cell signaling to activate mitogen-activated protein kinase (MAPK) and phospholipase C pathways to regulate cell proliferation and functions. GNAQ p.Arg183Gln substitution can acti-

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Fig. 21.1 Capillary malformation may appear as a thin, well-defined red patch or plaque on the face

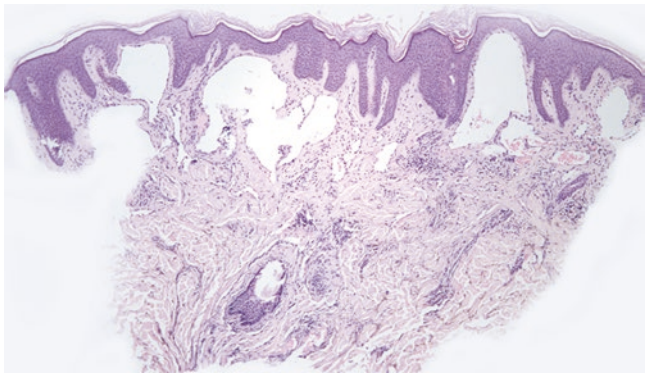

Fig. 21.2 Dilated capillaries are present in the superficial dermis in capillary malformations. They may be congested in older lesions

vate ERK/MAPK signaling pathway, a mechanism that can lead to the capillary malformations seen in port-wine stains and Sturge–Weber syndrome [18]. In addition to the known mutation in GNAQ, somatic mutations in a number of other genes, namely, SMARCA4, EPHA3, MYB, PDGFR-β, and PIK3CA, have been found in a single case of isolated port-wine stains [20].

Inactivating mutations in Ras p21 protein activator 1 (RASA1) gene have been identified in some families with multiple capillary malformations, including those with capillary malformation–arteriovenous malformation syndrome (CM–AVM) [21–23]. RASA1 encodes for p120 Ras-GAP, which is a GTPase-activating protein that negatively regulates Ras activity. Loss-of-function mutations of RASA1 lead to increased Ras activation and unregulated cell proliferation, including vascular growth.

Pulsed dye laser (PDL) is a gold standard of treatment for capillary malformations. PDL induces an increase in hypoxia-inducible factor (HIF)-1α, vascular endothelial growth factor, and activated ribosomal protein S6 (pS6), indicating that angiogenesis pathways are involved in skin blood vessel regeneration and revascularization [24]. These angiogenic effects can be blocked by rapamycin (sirolimus), which is an inhibitor of the mammalian target of rapamycin (mTOR), implicating a role of the mTOR pathway in port-wine stains [25]. Studies of combined therapy of PDL and rapamycin to inhibit neovascularization in port-wine stains following laser ablation have shown that the combination approach provides a novel way to block lesion recurrence [26–28]. A phase II clinical trial of combination therapy of topical rapamycin and PDL has shown this to be an effective treatment for port-wine stains [29].

21.1.2 Sturge–Weber Syndrome

21.1.2.1 Clinical Features

Sturge–Weber syndrome (SWS) (also known as encephalofacial angiomatosis) is a sporadic congenital condition characterized by facial capillary malformations (port-wine stains) in the V1 distribution of the trigeminal nerve, ipsilateral glaucoma, and venous-capillary abnormalities of the leptomeninges (Fig. 21.3) [30]. A child born with port-wine stains located in the distribution of the V1 branch of the trigeminal nerve has a 26 % risk of having Sturge–Weber syndrome [31]. Patients often have seizures and other neurologic problems.

21.1.2.2 Histology

The histologic changes of port-wine stains that occur sporadically and as part of Sturge–Weber syndrome are identical. Some patients with Sturge–Weber syndrome also demonstrate pigmented lesions and can be classified as having phakomatosis pigmentovascularis, type IIb [2].

21.1.2.3 Pathogenesis

An underlying somatic mutation has been identified in Sturge–Weber syndrome. The mutation is a single-nucleotide variant (c.548G > A, p.Arg183Gln) in GNAQ gene with 88 % of patients with Sturge–Weber syndrome harboring the mutation [18]. GNAQ [guanine nucleotide-binding protein (G protein), Q polypeptide] gene codes an α-subunit in the Gq class [19]. GNAQ is involved in cell signaling to activate mitogen-activated protein kinase (MAPK) and phospholipase C pathways to regulate cell proliferation and vascular growth. GNAQ p.Arg183Gln substitution causes increased activation of the ERK/MAPK signaling pathway, a mechanism that can lead to the capillary malformations and tissue overgrowth seen in Sturge–Weber syndrome [18].

Fig. 21.3 Sturge–Weber syndrome patient with a large pink patch (port-wine stain) primarily involving the V1 distribution of the face. The child also has seizures and glaucoma (photo courtesy of Marcelo Hochman, MD, Hemangioma & Malformation Treatment Center, Charleston, SC)

21.2 Venous Malformations

21.2.1 Common Venous Malformations

21.2.1.1 Clinical Features

Venous malformation is a congenital vascular anomaly that is present at birth and continues to grow with the child. Venous malformation consists of collections of abnormal veins. It can be localized or diffuse, and often presents as a soft, compressible bluish mass [32]. Due to low blood flow, venous malformation is prone to the development of intravascular thrombi, which may calcify to form phleboliths. Localized intravascular coagulopathy with elevated D-dimers is a characteristic of the lesion [33, 34]. Venous malformation grows and enlarges over time, and can cause substantial morbidity because of disfigurement, bleeding, and pain. Sclerotherapy is a first-line treatment of venous malformation, although it is not entirely effective [32, 35]. Therapy is typically aimed at alleviation of symptoms as many lesions are too extensive for complete surgical resection.

21.2.1.2 Histology

Venous malformation is composed of enlarged blood vessels lined by flat endothelial cells with irregular lumen size and shape. The lesion often involves the dermis and subcutaneous adipose tissue. The vascular wall has a variable thickness of smooth muscles, and some areas lack smooth muscle altogether [36, 37]. Intravascular thrombi and phleboliths are common. Areas of fibrosis, red blood cell extravasation, and hemosiderin deposition are frequent findings.

21.2.1.3 Pathogenesis

Sporadic venous malformation is caused by somatic mutation in TEK2 gene, which encodes endothelial cell receptor tyrosine kinase TIE2 [38–40]. TIE2 mutations are found in about half of the cases of venous malformations. The most common TIE2 hot-spot mutation in *sporadic* venous malformations is the somatic mutation L914F, which accounts for over 70 % of patients with TIE2 mutations [38, 39, 41]. *Hereditary* venous malformation (as in familial mucocutaneous venous malformation) is also caused by TIE2 mutations, and the most common inherited mutation is R849W [38, 40, 42]. These mutations cause constitutive activation of TIE2, leading to chronic activation of Akt signaling pathway, and abnormal cell proliferation and differentiation. TIE2 signaling is also critical for communications between endothelial cells and smooth muscle cells in venous morphogenesis [40].

The importance of TIE2 in the development of venous malformation has been shown in experimental animal models. Normal human endothelial cells expressing the TIE2 mutation L914F develop lesions similar to human venous malformation in a mouse model [43]. Rapamycin (sirolimus), which is a selective inhibitor of mammalian target of rapamycin (mTOR), prevents venous malformation growth in this model. Extending these findings into a prospective clinical pilot study, rapamycin has been shown to reduce pain, bleeding, and functional impairment in six patients with venous anomalies [43]. Inhibition of the Akt/mTOR signaling pathway with rapamycin provides some clinical improvement in patients with venous malformation.

Not all venous malformations carry TIE2 mutations. Somatic mutations in the PIK3CA gene have been found in over 50 % of venous malformations with no detectable TIE2 mutations [44–46]. The hot-spot mutations are c.1624G > A, c.1633G > A, and c.3140A > G (p.Glu542Lys, p.Glu545Lys, and p.His1047Arg), and they account for more than 90 % of individuals with venous malformations who carry PIK3CA mutations. PIK3CA encodes for the p110-α catalytic subunit of PI3-Kinase [47]. PIK3CA mutations cause constitutive activation of the Akt signaling pathway, leading to dysregulation of important angiogenic factors and abnormal endothelial cell proliferation [46, 47]. A genetically-engineered animal model with mosaic expression of constitutively active PIK3CA (H1047R) mutation recapitulates features of human venous malformation [45]. Rapamycin treatment can induce venous malformation regression in animal models. PIK3CA and TIE2 mutations appear to operate via the same pathogenic pathways leading to Akt activation. However, there are gene-specific

effects between PIK3CA and TIE2 mutations, since there is significant genotype–phenotype correlation in lesion localization and histology between these two genes [46].

21.2.2 Blue Rubber Bleb Nevus Syndrome

21.2.2.1 Clinical Features

Blue rubber bleb nevus syndrome (BRBNS) is a rare condition characterized by multifocal cutaneous and visceral venous malformations [48]. Lesions are often present at birth, but may also appear in childhood or adulthood. Some lesions may enlarge over time. Venous malformations in the small intestine can cause serious acute and chronic blood loss. Cutaneous lesions appear as blue papules and compressible nodules (Fig. 21.4). Prognosis depends on the extent of disease and the organs involved.

21.2.2.2 Histology

Histologic changes in BRBNS are those of venous malformations. While earlier literature suggested these lesions to be cavernous hemangiomas [49], current classifications define the dilated vessels as veins [48]. Large dilated, thin-walled veins are present within the reticular dermis and extending into the subcutis [50]. The blood vessels may be surrounded by fibrosis, and some vessels may have slight thickening in the vascular walls. Occasional vessels may be congested, or if they are traumatized, thrombi and intravascular papillary endothelial hyperplasia (Masson's lesions) may be present [51]. A rare case of a blue rubber bleb nevus with an infiltrative lymphangiomatosis-like growth pattern and focal podoplanin (lymphatic marker) expression has been reported [52]. Similar venous malformations may be seen in the viscera, including the gastrointestinal tract where bleeding can be clinically significant [50, 53, 54]. Some syndrome cases have been associated with leukemia and visceral tumors [55].

21.2.2.3 Pathogenesis

According to the International Society for the Study of Vascular Anomalies (ISSVA) classification, BRBNS is a disease of multifocal venous malformations primarily involving the skin and gastrointestinal tract [56]. Most cases are sporadic. However, several familial cases have been identified, and have an autosomal pattern of inheritance [57, 58].

Activating mutations in TIE2, a receptor tyrosine kinase highly expressed in endothelial cells, have been identified in some cases of BRBNS [40, 59]. BRBNS also has been found to harbor mutations in c-Kit (stem cell growth factor receptor), which is a tyrosine kinase that activates mTOR (mammalian target of rapamycin) [60]. mTOR is a key mediator of growth factor receptor signaling, including the proangiogenic vascular endothelial growth factor [61]. BRBNS is highly responsive to treatment with rapamycin (sirolimus), which is a potent and selective inhibitor of mTOR [62, 63]. Even though BRBNS is primarily a venous malformation, it also has a lymphatic component and shows cell proliferative activity based on staining for MIB-1. Together with the findings of increased receptor tyrosine kinase signaling and activation of mTOR signaling, this may be a possible explanation for the therapeutic response seen with rapamycin in BRBNS, since rapamycin has been consistently demonstrated as being effective in the management of complicated vascular malformations with lymphatic component [62].

Fig. 21.4 A large venous malformation is seen in the palm of an infant with blue rubber bleb nevus syndrome

21.3 Lymphatic Malformations

21.3.1 Microcystic Lymphatic Malformations (Lymphangioma Circumscriptum)

21.3.1.1 Clinical Features

Microcystic lymphatic malformations (lymphangioma circumscriptum) are a superficial variant of cutaneous lymphatic malformation. Most lesions typically are noticed at or soon after birth [64]. Common locations include axillary folds, shoulders, proximal extremities, and genitalia. Cutaneous lesions appear as clusters of vesicles containing clear, yellow, pink, or hemorrhagic fluid (Fig. 21.5). They are often asymptomatic, but can exude clear or bloody fluid, especially after trauma. Areas may become infected. Treatment modalities include surgical excision and other destructive therapies, such as laser ablation, cryotherapy, and sclerotherapy. Recurrence is common.

21.3.1.2 Histology

Histologic features of microcystic lymphatic malformation include an epidermis that is focally atrophic with elongated rete ridges that extend down and surround superficially located and dilated vascular channels [65–67]. The epidermis directly overlying the vascular channels is often atrophic, but rare cases of verrucous epidermal hyperplasia with papillomatosis and acanthosis have been described [66, 68]. The ectatic vessels are thin-walled and lined by flattened endothelial cells (Figs. 21.6 and 21.7). The spaces are often filled with eosinophilic proteinaceous material. When traumatized, hemorrhage into the vascular spaces may be present. Lymphocytes surround the dilated vessels in some cases. Dilated lymphatic spaces may extend into the deeper dermis and subcutaneous fat, but this feature is not seen on all biopsies [65, 67, 69, 70]. Ultrastructural analysis has suggested that the primary pathology of these lesions resides in the deep and enlarged malformed vessels, and the superficial vessels represent secondary changes of long-standing lymphostasis [71].

A single case study of Dabska tumor arising within a lymphangioma circumscriptum has been reported [72]. The relationship between lymphangioma circumscriptum and lymphangioendothelioma, which is a more cellular and invasive lesion, is still uncertain, since they both appear to be lymphatic malformations and not neoplastic processes [73].

The main histologic differential diagnosis is angiokeratoma, especially when trauma results in hemorrhage into the vascular spaces. Clinical correlation often helps in resolving the diagnostic dilemma. D2-40 immunostain that labels lymphatic endothelial cells can also be used in most cases to establish a definitive diagnosis. A newly identified lymphatic malformation has been described that is characterized by dilated and thin-walled vascular channels in the upper dermis. Prominent endothelial cells protrude into the lumen. In this lesion, there is no epidermal change identified, and the clinical presentation is distinct from lymphangioma circumscriptum. Based upon the clinical appearance, the authors have suggested the name *lymphatic netlike malformation* [74].

21.3.1.3 Pathogenesis

It has been proposed that microcystic lymphatic malformation may be caused by abnormal lymphatic cisterns that grow separately from normal lymph vessels during develop-

Fig. 21.5 Lymphangioma circumscriptum presents as a cluster of small clear and hemorrhagic fluid-filled vesicles

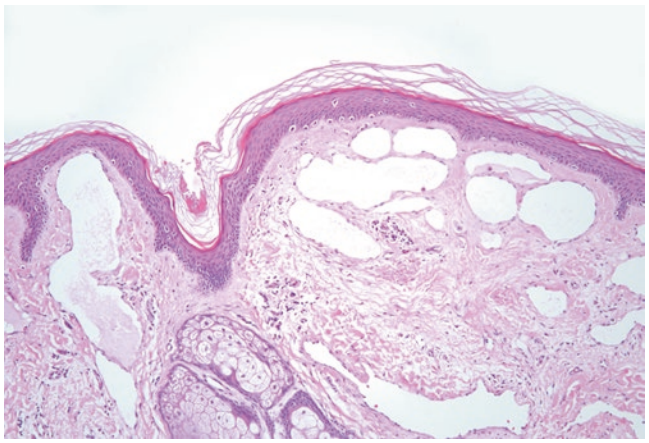

Fig. 21.6 Within the superficial dermis, large thin-walled, and dilated vascular channels are surrounded by acanthotic epidermis in lymphangioma circumscriptum

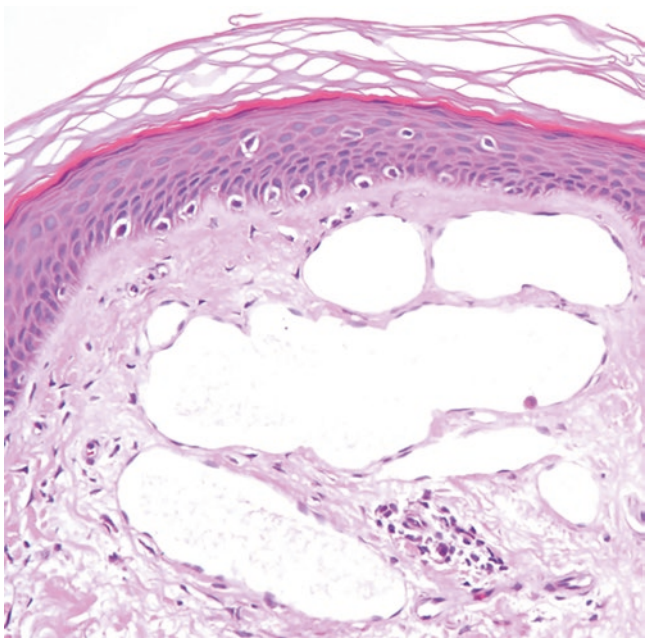

Fig. 21.7 Vessels are lined by flattened endothelial cells and often do not contain erythrocytes in lymphangioma circumscriptum

ment [66, 67]. Contractions of the smooth muscles lining the cisterns can cause the formation of abnormal and dilated lymphatic vessels.

Molecular studies of a patient with a lymphatic malformation show that endothelial cells within the lymphatic malformation harbor mutations in PI3-Kinase with associated hyperactivation of downstream Akt signaling pathway [75, 76]. Moreover, treatment with rapamycin (sirolimus), which is an inhibitor of the mammalian target of rapamycin (mTOR), blocks the proliferation and sprouting angiogenesis of lymphatic malformation cells, implicating a role for PI3-Kinase/Akt/mTOR signaling in lymphatic malformations.

21.3.2 Macrocystic Lymphatic Malformations (Cavernous Lymphangioma)

21.3.2.1 Clinical Features

Macrocystic lymphatic malformation (alternative names include cavernous lymphangioma, cystic lymphangioma, and cystic hygroma) is typically seen on the head, neck, or axilla of newborn infants [77]. An unusual variant may affect the abdominal viscera and cavity [78]. Most lesions present as a large soft mass in the neck or axilla. Problematic lesions are managed with sclerotherapy and surgical excision.

21.3.2.2 Histology

In macrocystic lymphatic malformation, deep-seated dilated vessels are present in the deep dermis and often extend into the subcutaneous fat [65]. The vessels are lined by flattened endothelial cells [79]. However, in some cases, underlying lymphoid nodules result in endothelial cell protrusions into the vascular lumen. Increased fibrosis may result in vascular wall thickening in some lesions. Vascular valves are observed in some cases, and due to trauma, hemorrhage may be encountered within vessels and in the surrounding dermis. When extensive hemorrhage is present, differentiation from other types of vascular malformations can be difficult. D2-40 immunostain, which is a lymphatic marker, is sometimes helpful in resolving this diagnostic dilemma based upon the strong staining of lymphatic endothelial cells.

The relationship between macrocystic lymphatic malformation and microcystic lymphatic malformation is not fully understood. Microcystic lesion demonstrates widely ectatic lymphatic vessels in the superficial dermis. However, in some cases, there is extension of the malformation into the deep dermis, subcutis, and even musculature. In these cases, the deeper components are indistinguishable from those seen in macrocystic lesion, thus blurring the histologic distinction between microcystic and macrocystic malformations [66, 70].

21.3.2.3 Pathogenesis

Microcystic and macrocystic lymphatic malformations share similar pathogenesis (see previous section of the pathogenesis for microcystic lymphatic malformation).

21.3.3 Primary Congenital Lymphedema (Milroy Disease)

21.3.3.1 Clinical Features

Primary congenital lymphedema (Milroy disease) is a disorder with an autosomal dominant inheritance, and disease incidence is approximately 1:6000 births [80]. Infants present prenatally or perinatally with tense edema of one or both feet and legs. Swelling is typically painless and non-pitting. Complications are rare, but bacterial infections and discomfort are possible. Long-term complications of massive congenital lymphedema include development of angiosarcoma [81]. There is no definitive treatment. However, compression garments and lymphatic massage may be helpful.

21.3.3.2 Histology

Histologic changes are primarily in the dermis and subcutis. Overlying epidermal changes are secondary, and may include verrucous epidermal hyperplasia, epidermal acanthosis and papillomatosis, and overlying hyperkeratosis. Widened intercellular spaces are present as evidenced by increased spaces between collagen bundles. There is no increase in cellularity, and in most cases, the lymphatic channels are atrophic so that endothelial cells are not readily apparent [82] (Figs. 21.8 and 21.9).

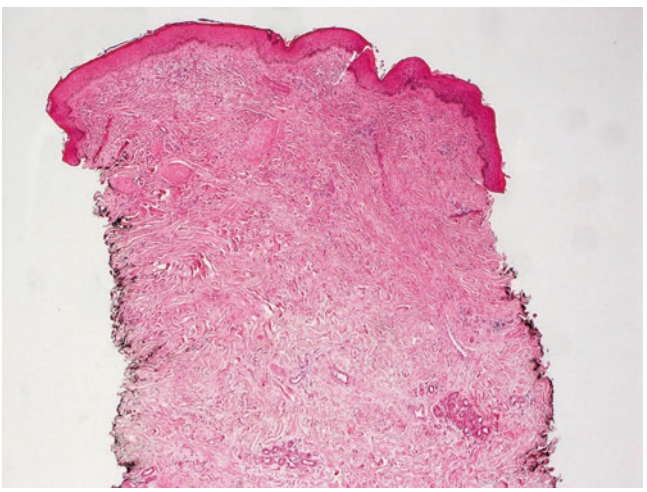

Fig. 21.8 Milroy lymphedema gives rise to a markedly thickened dermis with densely fibrotic stroma and relatively inconspicuous thin-walled vascular channels

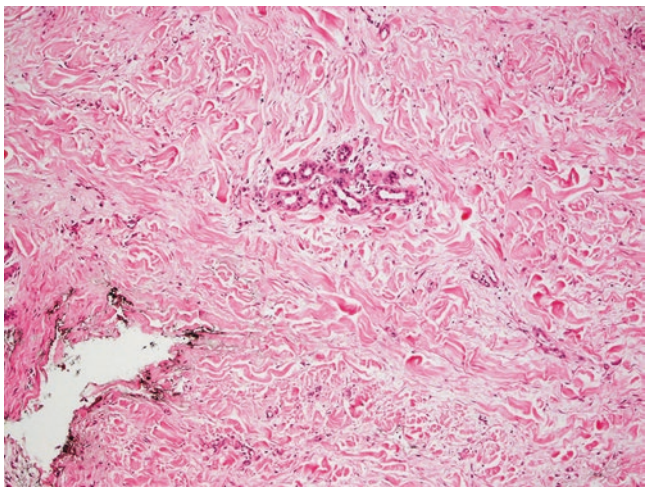

Fig. 21.9 Dermal collagen is fibrotic and often demonstrates areas with increased interstitial edema in Milroy lymphedema. It is often difficult to identify the affected vessels

Pigmented purpuric eruption has been described in a patient with Milroy disease. It is unclear whether there is any true association other than coincidental coexistence of these two entities [83]. Verruciform xanthoma has been described with overlying massive lymphedema in some patients. These changes are not unexpected as being secondary to verrucous epidermal hyperplasia seen in some cases of chronic lymphedema [84, 85].

21.3.3.3 Pathogenesis

Primary congenital lymphedema is an autosomal dominant genodermatosis caused by dysfunction of the lymphatic system. A known causative gene is vascular endothelial growth factor receptor-3 (VEGFR-3) [86–89]. Although not all individuals with the disease have identifiable mutations in VEGFR-3, in one case series, 90 % of 71 individuals found to carry a VEGFR-3 mutation had signs of Milroy disease with edema confined to the lower legs [86, 90]. Another study indicated that VEGFR-3 mutations have been found in 75 % of patients with familial Milroy disease, and in 68 % of patients with sporadic disease [91]. Over 50 different mutational variants in VEGFR-3 have been observed [92]. Most of the mutations are missense mutations with a few deletions and splicing variants.

VEGFR-3 is an important gene in the development and growth of lymphatic vessels. It is a receptor tyrosine kinase, and is activated when bound to vascular endothelial growth factor-C (VEGF-C) and VEGF-D [93, 94]. Mutations in the tyrosine kinase domains of VEGFR-3 are sufficient to reduce tyrosine kinase activity and affect lymphatic development [89]. The importance of VEGFR-3 in lymphedema has been demonstrated in an animal model, in which transgenic mice with inhibition of VEGFR-3 develop hind limb lymphedema similar to that seen in Milroy disease [95].

21.4 Arteriovenous Malformations

21.4.1 Sporadic Arteriovenous Malformations

21.4.1.1 Clinical Features

Arteriovenous malformations (AVM) are congenital vascular malformations that contain variable degrees of arteriovenous shunting. They have a tendency to worsen and become more problematic over time. Focal lesions may expand rapidly and ulcerate. They can also result in cardiac failure, hemorrhage, and stroke. The clinical appearance of AVM varies depending on the size and extent of the lesion [96, 97]. Some present as a pink patch that resembles a capillary malformation, while others may appear more blue and nodular. AVM typically feels warm to the touch, and has a palpable thrill with audible bruit when examined (Fig. 21.10).

21.4.1.2 Histology

Histologic findings vary with the types of vessels involved in arteriovenous malformation. Combinations of lymphatic, venous, capillary, arterial, and glomus cells have all been described in malformations in the skin [98–101]. Thin-walled vessels can be seen admixed with thicker-walled vessels surrounded by smooth muscle (Figs. 21.11 and 21.12). In other cases, thin-walled vessels are lined by endothelial cells that label focally as venous, and in other regions as lymphatic vascular channels [102]. In general, these lesions tend to have widely dilated vascular channels at least in some foci, and tend to extend through the dermis into the subcutis.

The histologic differential diagnosis includes vascular proliferative processes, and it is dependent upon the various components present within the malformation. A rare variant of capillary arteriovenous malformation with ancient or symplastic change demonstrates cytologic atypia, and it could be mistaken for a malignant vascular neoplasm [103].

21.4.1.3 Pathogenesis

Arteriovenous malformation can occur sporadically or in association with inherited disorders, such as hereditary hemorrhagic telangiectasia (HHT) and capillary malformation–arteriovenous malformation syndrome (CM–AVM) [97]. HHT is an inherited vascular disorder with AVM involving the skin and mucosa, and has significant morbidity [104, 105]. The genetic cause of HHT is mutations in endoglin (ENG), activin A receptor type II-like 1 (ACVRL1), and SMAD4 [106–108]. Importantly, these genes are all involved in various aspects of transforming growth factor-β (TGF-β) signaling pathway.

CM–AVM is a vascular malformation syndrome with capillary malformations of the skin, and they are often associated with underlying AVM [109]. CM–AVM is caused by

Fig. 21.10 A violaceous nodular plaque is seen on the ear of an infant with an arteriovenous malformation

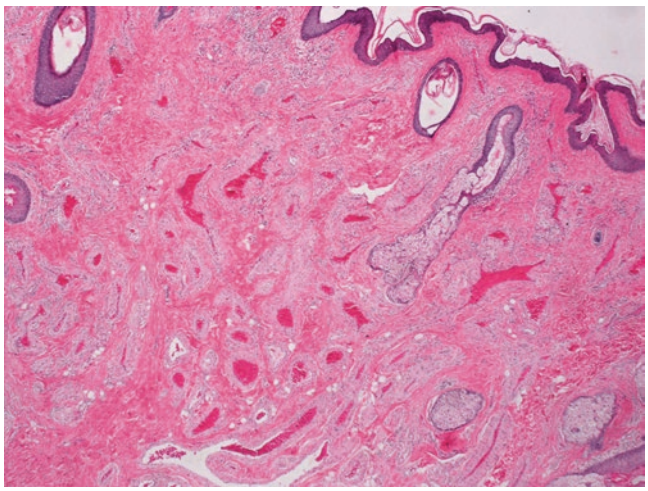

Fig. 21.11 AVM demonstrates increased numbers of dermal blood vessels, some of which have thin walls and others have thickened walls, resembling arterioles

mutations in RASA1 (Ras p21 protein activator 1) gene [21, 22]. RASA1 encodes for p120 Ras-GAP, which is a GTPase-activating protein that negatively regulates Ras activity [110]. Loss-of-function mutations of RASA1 lead to increased Ras activation and unregulated cell proliferation, including vascular growth.

21.4.2 Cobb Syndrome

21.4.2.1 Clinical Features

Cobb syndrome is characterized by the presence of a spinal arteriovenous malformation and an overlying cutaneous vascular anomaly in the same dermatome [111]. Cobb syndrome is quite rare, but usually presents in late childhood with neurological symptoms [112]. Disease management varies but may include surgery and endovascular embolization.

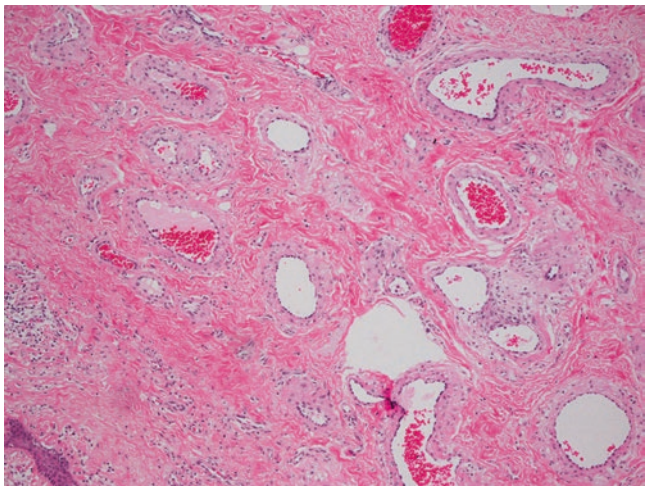

Fig. 21.12 A collection of dermal blood vessels with vascular walls of varying thickness in an AVM

21.4.2.2 Histology

The literature is replete with case reports of Cobb syndrome, although there is very poor concordance with regard to the types of vascular lesions described. Associated cutaneous vascular lesions include angiokeratoma circumscriptum, port-wine stain, and angioma [113–116].

21.4.2.3 Pathogenesis

It has been postulated that Cobb syndrome may be associated with errors in neural plate migration due to somatic mutations in the region of the neural crest or the cephalic mesoderm [117, 118].

21.5 Vascular Malformations Associated with Other Anomalies

21.5.1 Klippel–Trenaunay Syndrome

21.5.1.1 Clinical Features

Klippel–Trenaunay syndrome (KTS) is a congenital vascular disorder with capillary malformations, venous malformations, and hypertrophy of the affected tissues [119, 120]. Capillary malformations (port-wine stains) are the most common cutaneous vascular anomaly seen in KTS. Port-wine stains are red to purplish in color, and can be present on any part of the body. Varicose veins and lymphatic malformations with subsequent nodular hypertrophy of the affected area also occur in patients with KTS. Vascular mal-

Fig. 21.13 Klippel–Trenaunay syndrome presents with characteristic soft tissue overgrowth, capillary malformation, and venous varicosity in the limb

formations in visceral organs can cause severe bleeding. Limb hypertrophy, mostly in the leg, occurs in the majority of patients [121] (Fig. 21.13).

21.5.1.2 Histology

The cutaneous histologic changes of KTS are indistinguishable from those seen in port-wine stains not associated with limb hypertrophy. Ectatic thin-walled capillary vessels are present initially in the superficial dermis. With time, the vascular lesions become progressively dilated, and the vessel walls have greater thickness. Vessels deeper in the dermis are also affected. Thrombi may be present in congested vessels. These lesions can become nodular and are likely to recur [122]. In rare cases, angiokeratomas have been described in patients with KTS [123].

Secondary changes, such as spongiotic dermatitis with inflammation (Meyerson's phenomenon) and acro-angiodermatitis (marked stasis changes or pseudo-Kaposi's sarcoma) are found in some patients with KTS. The spongiotic changes include intraepidermal edema and lymphohistiocytic infiltrate [16]. Acro-angiodermatitis is characterized by proliferation of slit-like vascular spaces and lobular proliferations of markedly thick-walled vessels. There is abundant extravasation of erythrocytes and hemosiderin deposition. The histologic changes are those of prominent stasis dermatitis [124]. A subset of patients with KTS vascular lesions have associated pigmented lesions, and thus have the designation of phakomatosis pigmentovascularis type IIb [2, 125].

21.5.1.3 Pathogenesis

Klippel–Trenaunay syndrome occurs sporadically without a definite mode of familial inheritance. A novel angiogenic gene VG5Q (vascular or vasculogenesis gene on 5q, also called AGGF1) was identified as a susceptibility gene of KTS through the presence of activating mutation E133K in some of the KTS patients investigated [126]. However, this finding has since been disputed because the same E133K mutation has been found in healthy individuals as well, suggesting that this is a polymorphism and not a causative mutation [127]. A study of patients with lymphatic malformations and KTS revealed somatic mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) [76]. The study also demonstrated that there is low-level somatic mosaicism in these lesions because of a low abundance of mutant cells in lesional tissue.

21.5.2 Maffucci Syndrome

21.5.2.1 Clinical Features

Maffucci syndrome is a rare condition characterized by multiple venous malformations of the skin and gastrointestinal tract as well as enchondromas, which are benign cartilaginous tumors [128]. Features of the condition typically appear in children by 4 to 5 years of age [128–131]. Skin vascular lesions (usually spindle cell hemangioma) often protrude as soft blue subcutaneous nodules on the distal extremities. These vascular tumors often develop intravascular thrombi and form phleboliths [128, 130, 131]. Other types of vascular lesions, such as venous-lymphatic malformation and hemangioendothelioma, can occur but they are less common. Enchondromas in Maffuci syndrome appear in the phalanges and long bones, and can cause secondary fractures. There is a 30 % risk of an enchondroma undergoing malignant transformation into chondrosarcoma in these patients. Therefore, attention should be paid to lesions that rapidly increase in size with localized swelling and persistent pain, especially at night [129].

21.5.2.2 Histology

Vascular lesions seen in Maffucci syndrome are varied. In addition to venous malformations, lymphatic malformations are also commonly seen [132]. Spindle cell hemangioendothelioma (now reclassified as spindle cell hemangioma) was reported in a patient with Maffucci syndrome [133]. Enchondromas, which are benign cartilaginous tumors comprising of lobules of hyaline cartilage encased by bone and covered by fibrous tissue, are the other classic finding in this syndrome. Several neoplastic processes, including malignant transformation of enchondromas, are seen in patients with Maffucci syndrome. Cutaneous angiosarcoma is reported in a single patient with the syndrome [134].

21.5.2.3 Pathogenesis

Maffucci syndrome is a non-hereditary mesodermal dysplasia. The syndrome carries somatic mutations in IDH1 (isocitrate dehydrogenase 1) and IDH2 (isocitrate dehydrogenase 2) genes [135–137]. The mutation hotspots are R132C and R132H in IDH1 and R172S in IDH2. It has been reported that 77 % patients with Maffucci syndrome carry IDH1 (98 %) or IDH2 (2 %) mutations in their tumors with evidence for

intraneoplastic and somatic mosaicism [137]. IDH1 mutations in cartilage tumors are associated with DNA hypermethylation and downregulation of expression of several genes. IDH1 is a metabolic enzyme that generates α-ketoglutarate and NADPH [138]. Gain-of-function mutations in IDH1 may lead to increased production of D-2-hydroxyglutarate. Hydroxyglutarate can exert aberrant epigenetic effects on gene expression by inhibiting histone and DNA demethylation, thus causing hypermethylation and inhibition of gene expression [139, 140]. IDH1 may also activate hypoxia-inducible factor-1α pathway to increase cell proliferation [141].

21.6 Vascular Tumors

21.6.1 Infantile Hemangioma

21.6.1.1 Clinical Features

Infantile hemangiomas are the most common benign tumor of childhood, affecting 4–5 % of Caucasian infants. These lesions are more common in infants who are Caucasian, female, premature and have a history of low birth weight [142]. Infantile hemangiomas can occur anywhere on the skin, but appear to have a predilection for the head and neck region. Occasionally, they may occur in internal organs, particularly the liver.

Clinically, superficial infantile hemangiomas appear as erythematous papules, nodules, masses, and plaques [143] (Fig. 21.14). Deep infantile hemangiomas appear as subcutaneous bluish masses, often with fine erythematous telangiectasias at the surface. Combined infantile hemangiomas are characterized by a deep bluish swelling with overlying erythematous papules and plaques. Infantile hemangiomas are also described as focal or localized lesions arising from a single focus or as segmental with lesions that appear to cover an entire territory of skin. Infantile hemangiomas exhibit a characteristic pattern of behavior, which includes early rapid growth during a proliferative phase, followed by gradual stabilization and slow involution over a period of months to years.

Fig. 21.14 An infantile hemangioma presents as an erythematous nodule on the forehead of an infant

The vast majority of infantile hemangiomas do not require medical intervention. For complex lesions that cause functional impairment or significant cosmetic deformity, oral propranolol is currently the gold standard of medical therapy [144, 145]. Other medications that can sometimes be utilized include systemic corticosteroids, vincristine, and α-interferon. Laser therapy is generally reserved for treatment of ulceration and post-involution residual erythema and telangiectasias. Surgical excision is rarely indicated.

21.6.1.2 Histology

Infantile hemangiomas are densely cellular endothelial cell tumors that occupy the entire dermis, and may extend into the underlying subcutis [146]. Small blood vessels are present with a dense cellularity that includes endothelial cells, pericytes, and stromal fibroblasts [147] (Figs. 21.15, 21.16 and 21.17). Abundant mitoses are present, but there is minimal cytologic atypia. Frequent apoptotic endothelial cells are seen [148]. Many lesions demonstrate extensive areas of dense cellularity with relatively insignificant vascularity; however, on close inspection, areas of vascular proliferation can be detected focally (Fig. 21.18). An infiltrative growth pattern with extension of the hypercellular areas into surrounding collagen and subcutaneous fat causes these lesions to resemble malignant neoplasms [147]. As the lesions progress, the cellularity diminishes, blood vessels become more dilated and lobular in their configuration.

The differential diagnosis includes spindle cell neoplasms, such as fibrous tumors, neural tumors, and smooth muscle tumors. The identification of vascular differentiation helps to distinguish infantile hemangiomas from other benign and malignant spindle cell tumors. Other cellular vascular neoplasms, such as congenital hemangiomas, may present some diagnostic difficulties. Glucose transporter-1 (Glut-1) immunostaining has been useful in making the distinction, since virtually all infantile hemangiomas strongly and diffusely express Glut-1, whereas congenital hemangiomas are Glut-1 negative (Figs. 21.19 and 21.20) [148]. Pyogenic granuloma may also present a diagnostic challenge, but it can be differentiated based upon the clinical presentation, the architectural changes of a lobular proliferation overlying a single large "feeder vessel," and the lack of an infiltrative growth pattern. Angiosarcoma and Kaposi's sarcoma may also be considered, but they demonstrate far more cytologic atypia than that seen in infantile hemangioma. The clinical presentation would exclude these malignant vascular tumors in most cases, but in rare cases where the differential diagnosis includes Kaposi's sarcoma, HHV-8 immunostains are strongly positive in Kaposi's sarcoma and negative in infantile hemangioma.

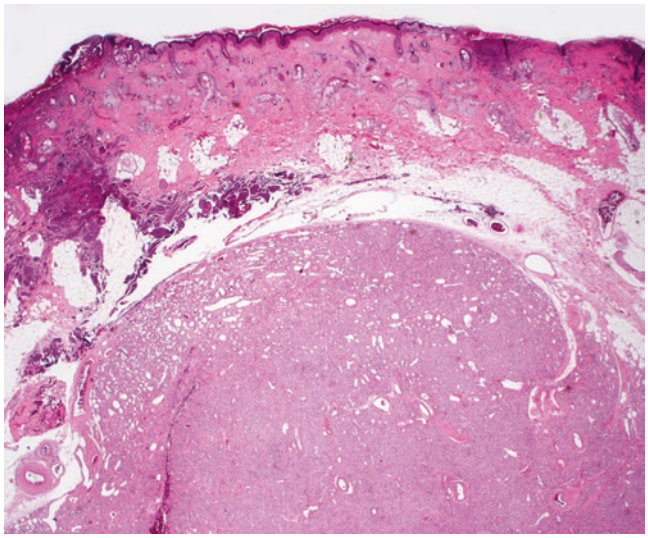

Fig. 21.15 Infantile hemangioma demonstrates densely cellular lobules of small, well-formed blood vessels in the dermis

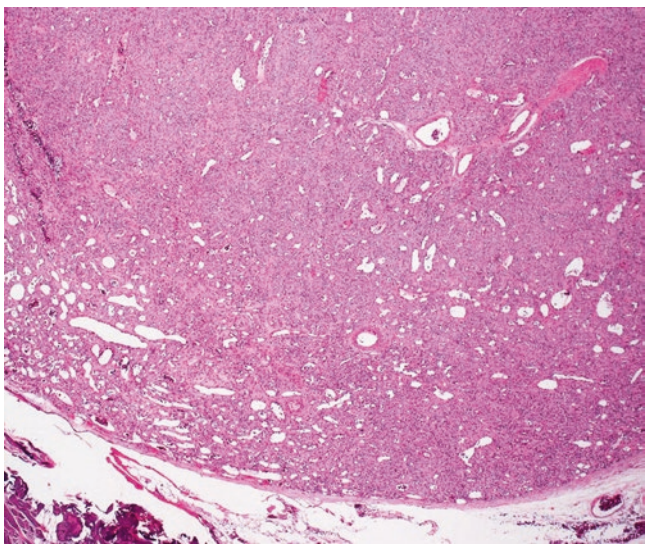

Fig. 21.16 Well-formed blood vessels and a dense proliferation of ovoid cells are present in infantile hemangioma. The relative amounts of vascularity and surrounding cellularity vary with the age of the lesion

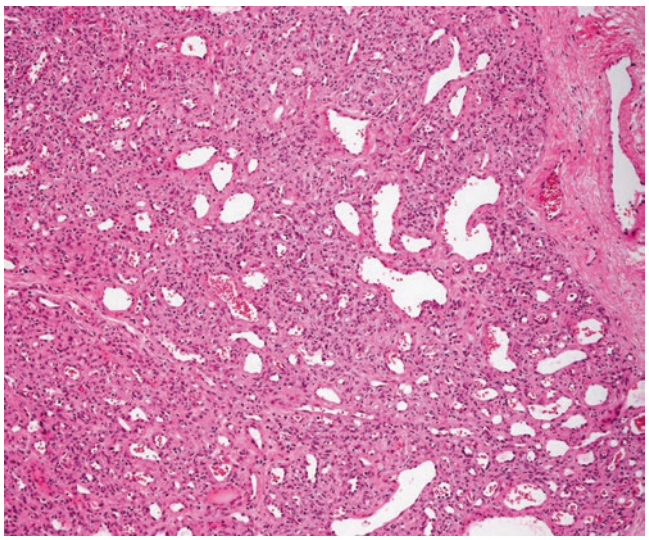

Fig. 21.17 A dense proliferation of blood vessels lined by benign endothelial cells and surrounded by pericytes and stromal cells characterizes the appearance of an infantile hemangioma

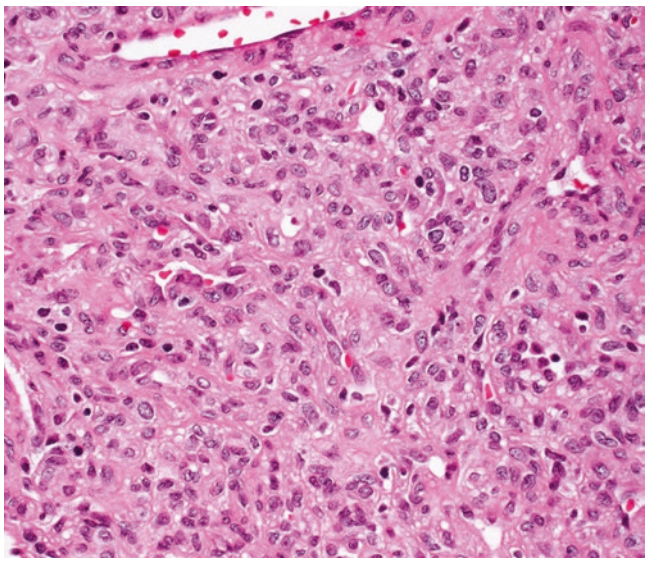

Fig. 21.18 A hypercellular proliferation of epithelioid and spindle-shaped cells is present in infantile hemangioma

21.6.1.3 Pathogenesis

Infantile hemangioma has been well studied in terms of molecular drivers of its development and growth. It has been shown that molecular markers of hemangioma vessels are also expressed in normal placental fetal microvessels, including merosin, laminin, Lewis Y antigen, Fcγ receptor II, and glucose transporter-1 (Glut-1) [149–151]. Glut-1 in particular is strongly expressed in the vessels in infantile hemangioma and placenta, but not in normal skin, vascular malformations, and other types of vascular tumors. Glut-1 serves as a useful diagnostic marker of infantile hemangioma [149]. Global gene expression profiling also shows striking similarities in the mRNA profiles of infantile hemangioma and placenta [152]. The significance of the molecular similarities between infantile hemangioma and placenta is unclear, although it has been postulated that infantile hemangioma may have its origin in the placenta [150–152].

Endothelial cells from proliferating infantile hemangioma appear to be clonal as shown in the patterns of X chromosome inactivation [153, 154]. Multipotent stem cells and endothelial progenitor cells are present in infantile hemangioma. These stem cells can recapitulate features of infantile hemangioma when implanted in an animal model [155, 156].

Somatic mutations in vascular endothelial growth factor (VEGF) receptors have been found in some hemangiomas, and they may lead to abnormal endothelial cell proliferation

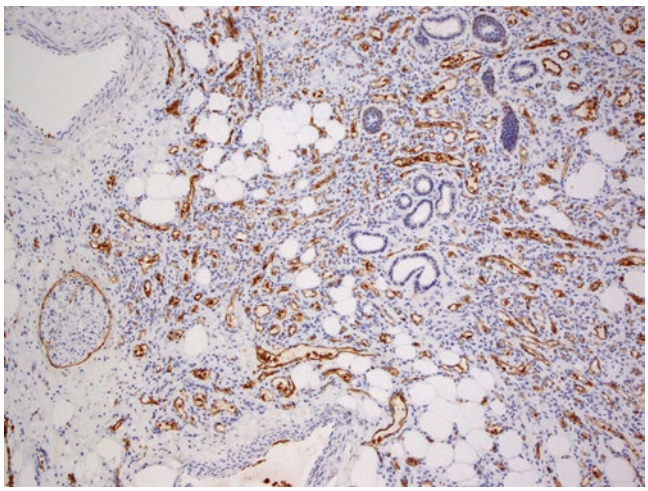

Fig. 21.19 Glut-1 expression is strong and diffuse in infantile hemangioma

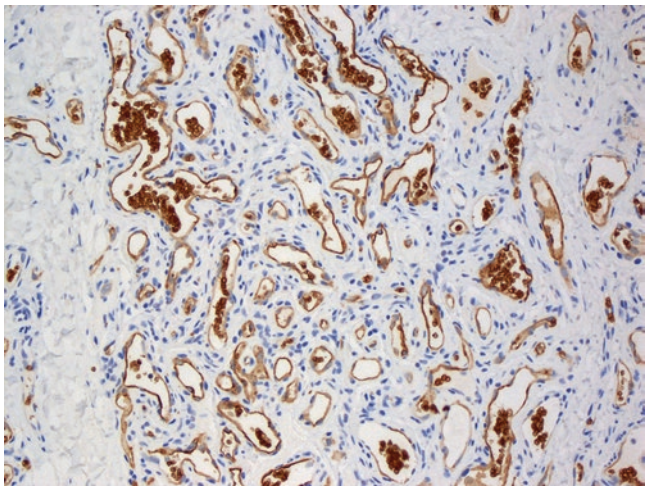

Fig. 21.20 Infantile hemangiomas demonstrate strong endothelial cell staining with Glut-1. Note that red blood cells also strongly express Glut-1 on their membranes and serve as a good internal control for staining

as a result of abnormal VEGF signaling. A landmark study has shown that infantile hemangioma endothelial cells have low VEGF receptor-1 (VEGFR-1) expression and increased levels of constitutively activated VEGF receptor-2 (VEGFR-2). VEGFR-1 acts as a decoy receptor that binds to VEGF ligand. The lack of VEGFR-1 decoy receptor results in constitutively activated VEGFR-2 [157]. The downregulation of VEGFR-1 appears to be due to reduced activity of a pathway involving β-1 integrin, integrin-like receptor tumor endothelial marker-8 (TEM8), VEGFR-2, and nuclear factor of activated T cells (NFAT). Increased VEGFR-2 signaling leads to increased cell proliferation and migration, which can result in the vascular growth in proliferating hemangioma.

VEGF signaling activates a number of proangiogenic signaling pathways, including Akt. Akt has three isoforms (Akt1, Akt2, and Akt3), which have overlapping as well as distinct structures and functions [158]. It has been shown that endothelial Akt1 drives the growth of a variety of vascular tumor cells, including infantile hemangioma endothelial cells [159]. In contrast, Akt3 inhibits vascular tumor growth. Moreover, these opposing effects by different Akt isoforms are mediated by p70 S6-kinase, a protein involved in protein translation. Infantile hemangioma has increased activation of p70 S6-kinase signaling, and loss of the protein reduces hemangioma cell proliferation and migration [160]. p70 S6-kinase is activated by the mammalian target of rapamycin (mTOR). Inhibition of mTOR with rapamycin (sirolimus) reduces the proliferation of hemangioma endothelial cells as well as the self-renewal potential and differentiation of hemangioma stem cells, leading to the regression of hemangioma blood vessels [160, 161].

Local hypoxia may play a central role in the pathogenesis of infantile hemangioma. There is increased hypoxia-inducible factor-1α (HIF-1α) expression in infantile hemangioma that can lead to increased production of VEGF-A, matrix metalloproteinase-9, and stromal cell-derived factor-1 (SDF-1), all of which can promote hemangioma stem cell trafficking and angiogenesis [162, 163].

Propranolol, which is a nonselective β-adrenergic receptor blocker, has been widely used as the first-line therapy for infantile hemangioma [145, 164, 165]. Despite the well-documented efficacy of propranolol, its mechanism of action has not been fully elucidated. However, the striking efficacy of propranolol points to the importance of the β-adrenergic pathway in infantile hemangioma. The immediate effects of propranolol in hemangioma are likely to be caused by vasoconstriction due to increased contractility of hemangioma pericytes induced by propranolol [166, 167]. These effects manifest as a rapid change in the color and softening of the lesion. The vasoconstrictive effects of propranolol also likely reduce oxygen availability with subsequent tissue hypoxia. The longer-term effects of propranolol may be through blocking receptor-mediated activation of mitogen-activated protein kinase (MAPK), reducing VEGF expression, inhibiting endothelial cell proliferation, and increasing apoptosis [168]. Of note, there is a significant reduction in serum VEGF levels in infants with infantile hemangioma after a few months of propranolol treatment [169, 170]. Propranolol also targets hemangioma stem cells to suppress proliferation and promote apoptosis via β2-adrenergic receptor [171].

Infantile hemangioma undergoes natural regression or involution with replacement of vascular tissue with fibroadipose tissue. A possible mechanism of regression of hemangioma is immune mediated, involving T lymphocytes and

indoleamine 2,3-dioxygenase (IDO) [172]. IDO is an enzyme involved in tryptophan metabolism, which is important for the function of T lymphocytes. Low tryptophan levels block T-lymphocyte proliferation and promote apoptosis, thus raising the possibility that inhibition of T lymphocytes through IDO could contribute to the slow regression of hemangioma [173, 174]. Another possible mechanism of hemangioma involution involves mesenchymal stem cells, which are present in infantile hemangioma [175]. These stem cells may differentiate into connective tissue cells and adipocytes to give rise to fibrofatty tissue seen in involuting hemangioma.

21.6.2 Congenital Hemangiomas: Rapidly Involuting Congenital Hemangioma (RICH) and Non-involuting Congenital Hemangioma (NICH)

21.6.2.1 Clinical Features

Congenital hemangiomas are benign vascular tumors that are fully formed at the time of birth. Postnatally, the tumor either involutes quickly (rapidly involuting congenital hemangioma, RICH) or partially regresses and stabilizes (non-involuting congenital hemangioma, NICH) [176, 177]. RICH tends to present as a vascular mass with a surrounding halo of pallor (Fig. 21.21). It typically improves rapidly in the first few months of life. NICH is more likely to present as a telangiectatic patch or plaque, but may also occur as a nodule (Fig. 21.22). NICH does not show a tendency to involute and remains stable over time.

Fig. 21.21 Rapidly involuting congenital hemangioma (RICH) is a large vascular tumor with ulcerations present at birth on the posterior scalp and neck of a newborn

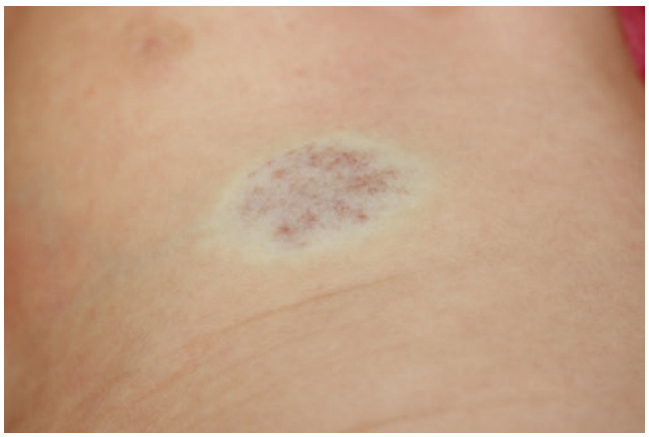

Fig. 21.22 Non-involuting congenital hemangioma (NICH) presents as a thin, telangiectatic plaque with a surrounding blanched "halo"

21.6.2.2 Histology

Both types of congenital hemangiomas can be differentiated histologically from infantile hemangioma.

Rapidly involuting congenital hemangioma is characterized by a lobular proliferation of well-formed blood vessels with surrounding dermal fibrosis. Surrounding pericytes comprise part of the lobular proliferation. Thrombosis is seen within some vessels, and hemosiderin deposition is prominent in some cases. Mitotic activity is relatively scant, and cytologic atypia is not seen in endothelial cells, but they are sometimes characterized as "plump" endothelial cells [176, 178]. Cyst formation, dermal fibrosis, and extramedullary hematopoiesis are seen up to half of cases.

Non-involuting congenital hemangioma is characterized by a lobular capillary proliferation. The lobules are surrounded by dense fibrosis and abundant hemosiderin deposition. The entire lobules may be thrombosed and sclerotic. The neoplastic vessels are sharply circumscribed, and do not appear to be interspersed within the normal dermal vasculature [150, 151]. Arteriovenous fistulas occur within the vascular proliferations, and a large, stellate vessel may appear in the central portion of the lesions [179]. Some authors have described the lobular proliferations as being immediately adjacent to large, malformed vessels [177]. Rarely, these tumors have been associated with multiple epidermal inclusion cysts believed to occur as a consequence of repeated infection [179].

The major differential diagnosis is infantile hemangioma. Infantile hemangiomas are more densely cellular, usually do not have zones of fibrosis, and express Glut-1, which is a marker that is typically not present in congenital hemangiomas [176, 178, 180].

21.6.2.3 Pathogenesis

Genomic DNA and mRNA sequencing of congenital hemangioma tissues revealed somatic activating mutations in the genes GNAQ and GNA11 [181]. Guanine nucleotide-binding proteins (G proteins) are transducers of transmembrane signaling pathways. G proteins are composed of three units: alpha, beta, and gamma. GNAQ encodes for guanine nucleotide-binding protein G(q) alpha subunit, and GNA11 encodes for the guanine nucleotide-binding protein (G protein), alpha-11 subunit [182]. GNAQ shares 90 % protein sequence similarity with GNA11. The mutation found in GNAQ and GNA11 in congenital hemangiomas is a mosaic missense mutation that alters glutamine at amino acid 209 (Gln209) with variant allele frequencies ranging from 3 to 33 %. The same GNAQ or GNA11 mutation is found in both RICH and NICH. The mutation can lead to hyperactivation of downstream pathways, including MAPK, Hippo-Yap, and mTOR pathways [183, 184]. Interestingly, the Gln209 GNAQ and GNA11 missense mutation is also a common mutation in uveal melanoma [185, 186].

Molecular analysis of congenital hemangiomas shows that insulin-like growth factor-2 (IGF-2) is expressed in both RICH and NICH at a level comparable to that detected in infantile hemangioma [187]. In contrast, the expression of vascular endothelial growth factor receptor-1 (VEGFR-1) mRNA is uniformly higher in congenital hemangiomas as compared with infantile hemangioma. These findings indicated molecular similarities as well as distinction between congenital and infantile hemangiomas.

Fig. 21.23 Pyogenic granuloma appears as a pink, pedunculated papule with hemorrhagic crust on the face of a toddler

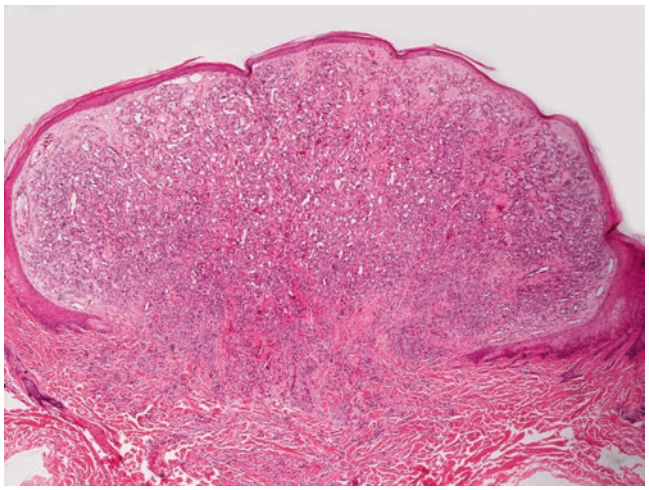

Fig. 21.24 Lobular capillary hemangioma (pyogenic granuloma) demonstrates an exophytic proliferation of small, well-formed blood vessels surrounded by a proliferation of spindle-shaped cells

21.6.3 Pyogenic Granuloma (Lobular Capillary Hemangioma)

21.6.3.1 Clinical Features

Pyogenic granuloma, also known as lobular capillary hemangioma, is a common acquired benign vascular lesion. It is most common in adults between 30–40 years of age. In children under age 10, pyogenic granuloma is 2.6 times more common in males than females. Pyogenic granuloma often appears on the head and neck.

Pyogenic granuloma appears as an erythematous papule or mass that is typically pedunculated, and has a tendency to bleed repeatedly and persistently [188] (Fig. 21.23). Since the majority of lesions do not resolve spontaneously, pyogenic granuloma is usually managed with surgical excision or other physical destruction (e.g., cryotherapy, electrocautery, and laser ablation).

21.6.3.2 Histology

Pyogenic granuloma has a polypoid architecture with an attenuated or even ulcerated epidermis. There may be an epidermal collarette with elongated rete ridges extending around the lesion in the dermis. A dense lobular proliferation of capillaries is present in the superficial portion of the dermis (Fig. 21.24). In some cases, a larger "feeder" vessel can be identified deep to the lobular proliferation. Small capillaries lined by benign endothelial cells form the tumor with pericytes present around the vessels (Fig. 21.25). Early lesions are densely cellular and may have abundant mitotic activity, but atypical mitoses are not seen. In ulcerated lesions, secondary inflammation may be present with admixed lymphocytes [189].

The differential diagnosis includes an infantile hemangioma and bacillary angiomatosis. Infantile hemangiomas are differentiated based upon the clinical presentation, lobular configuration, and polypoid architecture. Bacillary angiomatosis can be differentiated based upon the clinical history of multiple lesions, and the presence of neutrophils and amorphous granular material (sheets of microorganisms) within the lesion. A congenital epithelioid angioma might enter into the differential diagnosis, but the presence of endothelial cell atypia is not expected in pyogenic granuloma [190]. Pyogenic granulomas can develop within

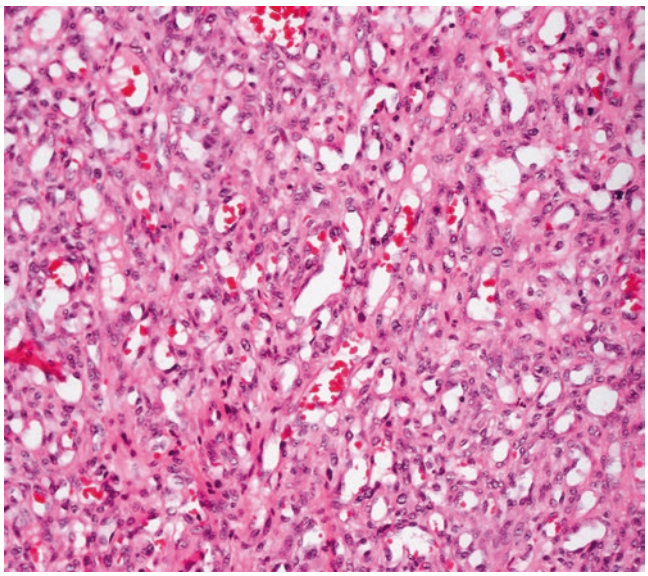

Fig. 21.25 Well-formed blood vessels interspersed with benign-appearing spindle-shaped cells and scattered mitoses are seen in lobular capillary hemangioma

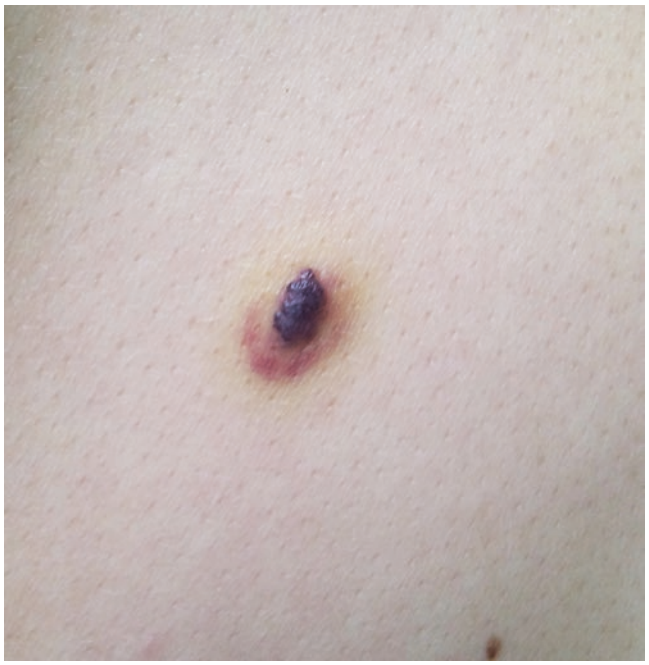

Fig. 21.26 Targetoid hemosiderotic hemangioma is a dark purple papule with surrounding ecchymotic patch (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

underlying vascular lesions, such as port-wine stains, in which case histologic features of both processes can be seen [191, 192].

21.6.3.3 Pathogenesis

Pyogenic granuloma is thought to be related to prior trauma and drug reaction [193, 194]. Molecular analysis by genome-wide transcriptional profiling of blood vessels from pyogenic granuloma reveals a gene signature unique to this entity that includes genes in the nitric oxide pathway, hypoxia-induced angiogenesis, and vascular injury [195]. A gene found to be highly associated with pyogenic granuloma is FLT4 (vascular endothelial growth factor receptor-3 (VEGFR-3)), which is a receptor tyrosine kinase important in lymphangiogenesis. There is increased expression of vascular endothelial growth factor (VEGF), transcription factors pATF2 and pSTAT3, as well as MAPK signal transduction in pyogenic granuloma that can potentially act as proangiogenic regulators to induce angiogenesis [196–198]. Somatic activating mutations in RAS and B-RAF have also been identified in pyogenic granuloma [199, 200].

21.6.4 Targetoid Hemosiderotic Hemangioma (Hobnail Hemangioma)

21.6.4.1 Clinical Features

It was proposed that this entity be named "superficial hemosiderotic lymphovascular malformation" [201]. This is an uncommon cutaneous vascular lesion thought to be primarily lymphatic in nature. It usually occurs in young to middle-aged adults (median age is 30 years old) on the trunk and extremities. There are rare reports in children [201, 202]. Clinically, the lesion presents as a solitary violaceous papulonodule surrounded by a pale halo and an ecchymotic rim (Fig. 21.26). Lesions are sometimes tender, especially with pressure. They are usually small and amenable to surgical excision if symptomatic.

21.6.4.2 Histology

Histologic changes in targetoid hemosiderotic hemangioma include a poorly circumscribed vascular proliferation that is centered in the reticular dermis and extends into the subcutis. Dilated blood vessels demonstrate intraluminal papillary projections (Fig. 21.27). A single layer of endothelial cells protrudes into the vascular lumen in a pattern that resembles hobnails [203] (Fig. 21.28). Deeper angular and narrow vascular spaces are present around eccrine structures. The deep component dissects through collagen bundles in an invasive pattern, giving rise to an angiosarcoma-like growth pattern [204]. Mitotic activity is scant [204]. There are abundant extravasated erythrocytes with dermal hemosiderin deposition. Strong expression of the lymphatic marker podoplanin (D2-40) and lack of CD34 suggest that these lesions may be of lymphatic origin [205, 206].

The differential diagnosis includes angiosarcoma, Kaposi's sarcoma, and retiform hemangioendothelioma [204]. Lack of cytologic atypia and mitotic activity helps to exclude angiosarcoma. Lack of a spindle cell proliferation, promontory sign and plasmacellular response argues against Kaposi's sarcoma. Retiform hemangioendothelioma has a more retiform growth pattern that is not seen in target-

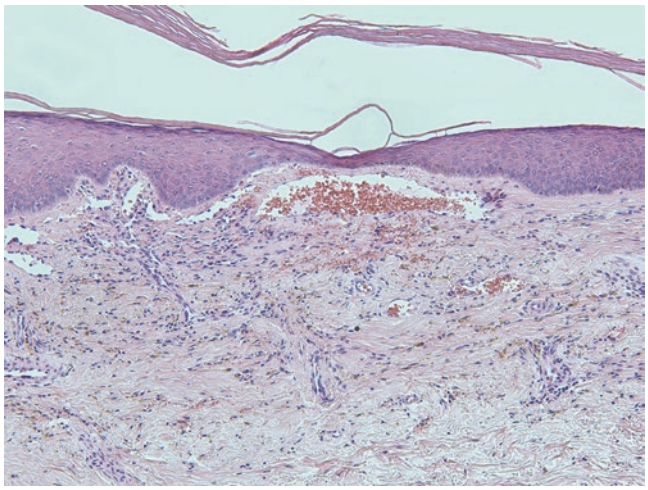

Fig. 21.27 Targetoid hemosiderotic hemangioma demonstrates diffusely arranged blood vessels that are occasionally slit-like and have surrounding hemosiderin

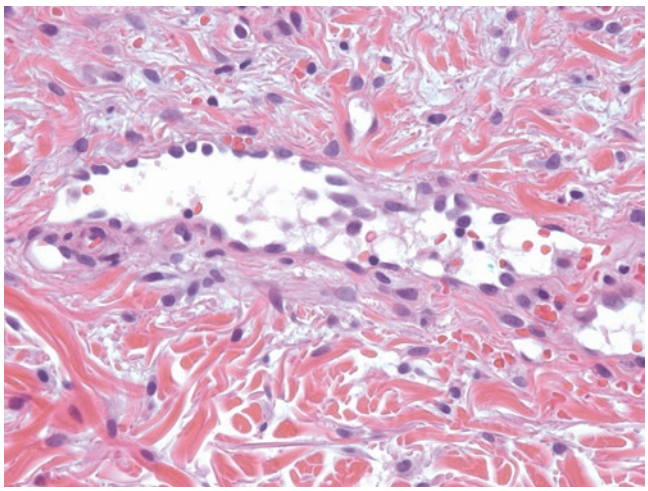

Fig. 21.28 Blood vessels in targetoid hemosiderotic hemangiomas are lined by endothelial cells that protrude into the lumen (hobnail endothelial cells)

oid hemosiderotic hemangioma. Epithelioid hemangioma and progressive lymphangioma may also enter the differential diagnosis. The invasive growth pattern would be unusual in an epithelioid hemangioma. The hobnail morphology characteristic of targetoid hemosiderotic hemangioma is not seen in progressive lymphangiomas.

21.6.4.3 Pathogenesis

It has been postulated that targetoid hemosiderotic hemangioma is a result of trauma [203, 207]. It has been proposed that obstruction of lymphatic vessels from trauma could result in inflammation, hemosiderin deposition, and fibrosis, which are histologic features seen in targetoid hemosiderotic hemangioma. Hormonal influence during the menstrual cycle can also potentiate the progression of this lesion [208].

Endothelial cells in targetoid hemosiderotic hemangioma express the lymphatic markers vascular endothelial growth factor receptor-3 (VEGFR-3) and podoplanin, indicating a lymphatic origin of this lesion [202, 203]. Moreover, this lesion has a low cell proliferative index by MIB-1 immunostain and no WT-1 expression, which is a molecular marker selectively expressed in vascular tumors but not in vascular malformations [102, 209]. These findings further indicate that this entity is a type of vascular malformation of lymphatic origin rather than a true vascular tumor [102, 202, 205].

21.6.5 Tufted Angioma

21.6.5.1 Clinical Features

Tufted angioma is a rare cutaneous vascular tumor. Approximately 25 % of lesions are present at birth, and 50 % become evident in the first year of life. Most lesions occur on the neck, shoulder, upper trunk and extremities [210]. Lesions often begin as erythematous macules or patches resembling a port-wine stain, and progress to larger purple/violaceous plaques or nodules over time [211] (Fig. 21.29). Some lesions are painful and tender. Acquired tufted angioma is also associated with a risk of coagulopathy or development of Kasabach–Merritt syndrome, which is a potentially fatal thrombocytopenic coagulopathy secondary to bleeding and platelet trapping within the lesion [212]. The mortality rate of Kasabach–Merritt syndrome has been estimated at 20 % [211, 213]. Some lesions improve or regress spontaneously over time. Smaller symptomatic lesions may be amenable to surgical excision.

21.6.5.2 Histology

Tufted angioma, previously known as angioblastoma [214], demonstrates multiple lobules of blood vessels and surrounding cells within the reticular dermis and extending into the subcutis [215] (Figs. 21.30 and 21.31). The vessels are lined by endothelial cells and surrounded by pericytes. Mitotic activity is minimal, and there is no significant cytologic atypia in endothelial cells and surrounding pericytes. The tumor has a clear lobular growth pattern with foci of vascular proliferation, marked cellularity and interspersed zones of paucicellular dermis. The vascular spaces can be round or somewhat slit-like. As there is some tendency toward local recurrence and progressive growth, some authors consider these tumors to be of intermediate biologic behavior, although there are no known reports of distant metastasis [216]. A rare case of acquired tufted angioma occurring within an existing port-wine stain has been reported, and several of these lesions have arisen during pregnancy [191, 217].

The differential diagnosis of tufted angioma includes Kaposi's sarcoma due to the infiltrative growth pattern and

Fig. 21.29 Tufted angioma is a firm infiltrative mass with overlying telangiectasias on the shoulder of an infant

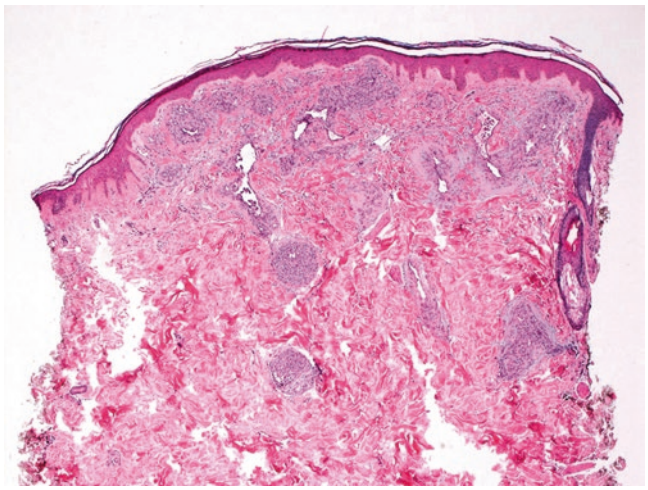

Fig. 21.30 Tufted angioma demonstrates a pattern of multiple lobules of vascular proliferation separated by normal collagen throughout the superficial and deep dermis

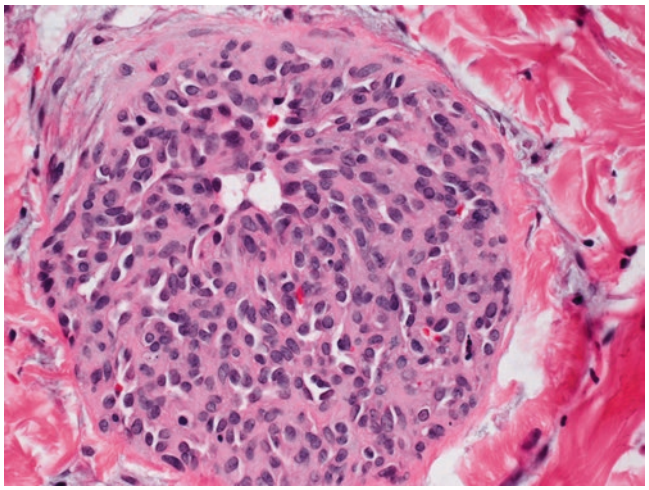

Fig. 21.31 Each of the cellular lobules in tufted angioma contains multiple small vessels surrounded by a proliferation of bland-appearing spindle-shaped cells

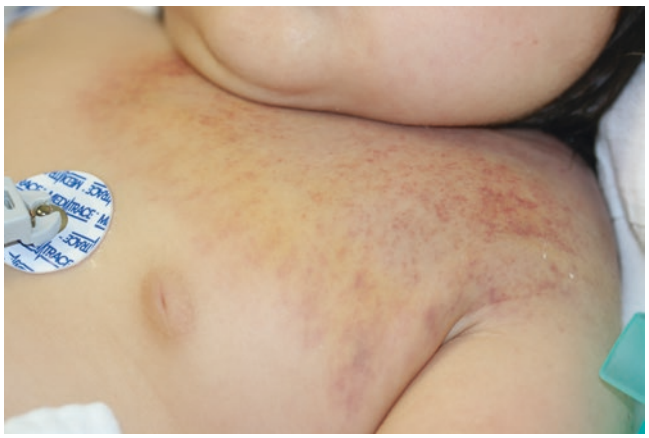

Fig. 21.32 A firm mass with overlying telangiectasias suddenly enlarged and became painful in a child with Kasabach–Merritt syndrome due to a kaposiform hemangioendothelioma of the chest

the abundant cellularity beyond simple endothelial cells. Recognition of the central lobules of well-formed blood vessels as well as the clinical presentation should enable easy distinction in most cases. In addition, HHV-8 immunostain, which is positive in virtually all cases of Kaposi's sarcoma, would be negative in acquired tufted angiomas [218]. Angiosarcomas also have an infiltrative growth pattern, but the proliferation is limited to endothelial cells that display marked cytologic atypia and mitosis [218].

21.6.5.3 Pathogenesis

Tufted angioma is a benign vascular tumor whose pathogenesis is unknown. Endothelial cells in tufted angioma express the lymphatic marker Prox-1, indicating their lymphatic origin or differentiation [219]. As has been noted previously, patients with tufted angioma may develop Kasabach–Merritt syndrome, which is a potentially life-threatening condition of thrombocytopenia, coagulopathy, and purpura. It has been postulated that the abnormal and convoluted vascular architecture in tufted angioma results in turbulent blood flow, thus promoting platelet trapping, platelet activation, and consumptive coagulopathy within the abnormal vasculature [212].

21.6.6 Kaposiform Hemangioendothelioma

21.6.6.1 Clinical Features

Kaposiform hemangioendothelioma (KHE) is a locally aggressive vascular neoplasm according to the current International Society for the Study of Vascular Anomalies (ISSVA) classification of vascular anomalies [56]. It mainly affects infants and children, although it may occasionally present in adulthood [220, 221]. KHE usually presents as firm violaceous nodules or plaques on the extremities or

upper trunk (Fig. 21.32) [220, 222]. Rarely, they may involve visceral organs or bone.

Similar to tufted angioma, KHE can be associated with Kasabach–Merritt syndrome [212]. Patients with Kasabach–Merritt syndrome typically present with a rapidly enlarging tumor mass in the setting of severe thrombocytopenia and coagulopathy. Disease management depends on the location and extent of the lesion. Although surgical excision is the definitive treatment, the location and large size of many lesions precludes complete resection. Medical treatment has historically included systemic steroids, interferon, and chemotherapeutic agents such as vincristine. Recent studies have provided evidence that rapamycin (sirolimus), an inhibitor of the mammalian target of rapamycin, is a new effective therapy for KHE [223, 224].

21.6.6.2 Histology

KHE is comprised of diffuse nodular proliferations of slit-like vessels surrounded by endothelial cells (Figs. 21.33 and 21.34). In some areas, the vessels are well formed, whereas in other areas, the vessels are poorly formed and have an infiltrative growth pattern, strongly mimicking Kaposi's sarcoma [222]. Areas of dense cellularity comprised of endothelial cells and pericytes, and no apparent vascular differentiation may also be encountered. These areas may have a glomeruloid growth pattern [225]. Cytologic atypia is slight, and mitoses are infrequent and without atypical forms [226] (Fig. 21.35). Hemosiderin and hemorrhage are present in some cases [226]. These tumors occupy the entire dermis and can extend into the subcutaneous fat. Lateral and deep to the central tumor, large malformed lymphatic channels are present in more than half of the described cases [222, 225, 226]. Immunostaining shows that the neoplastic cell population consists of lymphatic endothelial cells as evidenced by focal staining with the lymphatic marker D2-40 [225] (Figs. 21.36 and 21.37). KHE is often associated with Kasabach–Merritt syndrome, and extensive intravascular thrombus formation is observed in such cases [222]. The tumor has a propensity for local recurrence and persistence, although distant metastasis appears to be uncommon [216, 225, 227].

The differential diagnosis includes Kaposi's sarcoma, spindle cell hemangioma, and acquired tufted angioma [226, 228]. The tufted architecture helps to distinguish tufted angioma from KHE. Also, the presence of malformed large lymphatic channels would not be expected in a tufted angioma. Kaposi's sarcoma is distinguished based upon clinical history, the presence of areas of capillary formation in KHE, and positive HHV-8 staining in Kaposi's sarcoma but not in

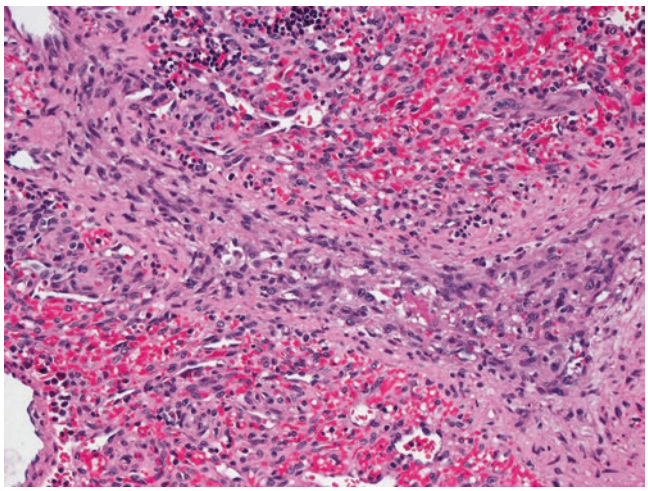

Fig. 21.34 Spindle-shaped endothelial cells, slit-like vascular spaces, and large ectatic vessels are seen in KHE

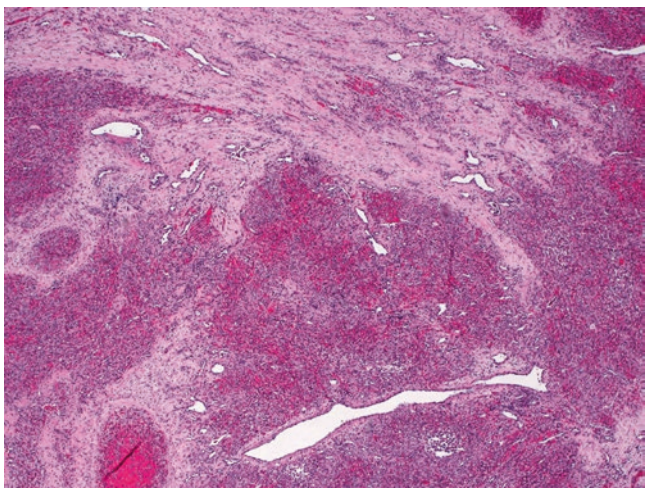

Fig. 21.33 A lobular configuration of dense cellularity and vascular differentiation characterizes KHE

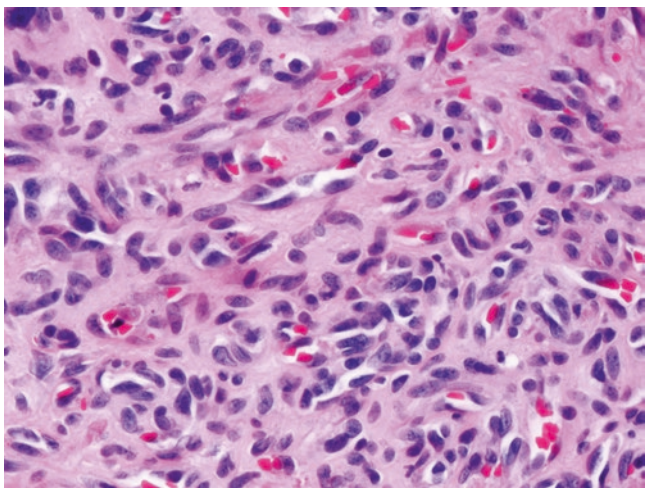

Fig. 21.35 Tumor cells in KHE are spindled and epithelioid with some cytologic atypia

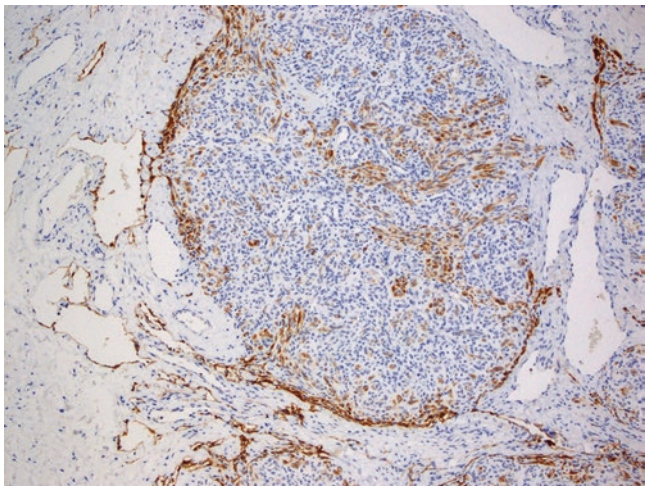

Fig. 21.36 Podoplanin (D2-40) expression can be seen focally in KHE

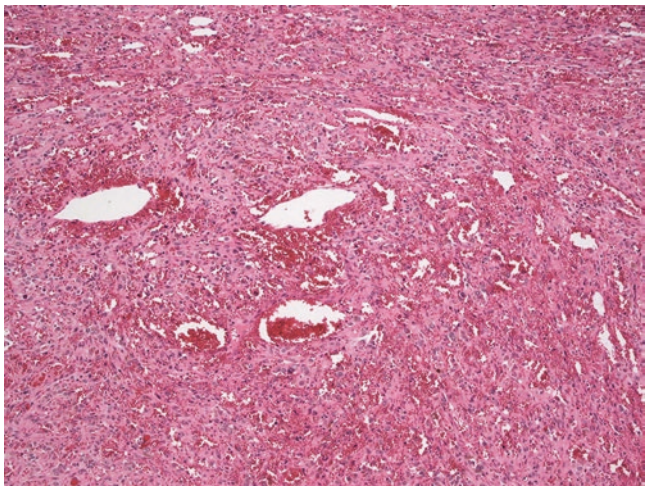

Fig. 21.38 Spindle cell hemangioma shows a hypercellular mass of spindle-shaped cells with abnormal vascular channels that resemble those seen in Kaposi's sarcom

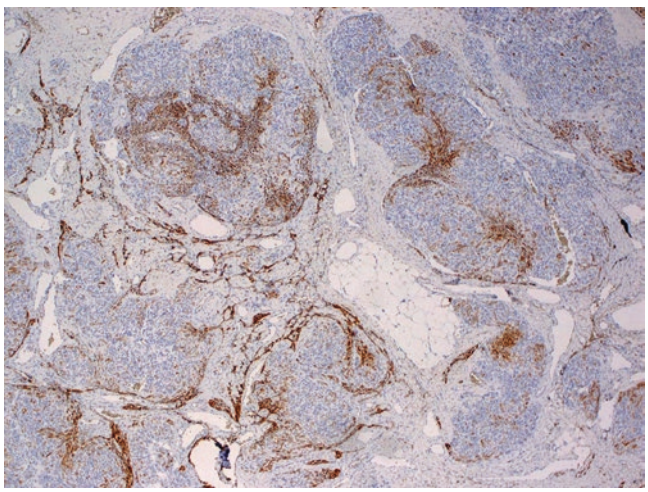

Fig. 21.37 KHE has patchy and strong expression of podoplanin (D2-40), particularly in the periphery of the tumor lobules

KHE. Spindle cell hemangioma does not demonstrate peripheral lymphatic channels as seen in kaposiform hemangioendothelioma.

21.6.6.3 Pathogenesis

To date, there has been no definitive causative gene identified for kaposiform hemangioendothelioma. As mentioned previously, the tumor can trigger Kasabach–Merritt syndrome, a process of intravascular coagulation with platelet trapping, subsequent thrombocytopenia and consumption of fibrinogen and coagulation factors, which manifest clinically by elevated D-dimers and low fibrinogen [229]. The mechanism of the development of Kasabach–Merritt syndrome is not known, but it may occur because of turbulent blood flow in small, convoluted capillaries in KHE [222]. Moreover, the basal lamina of KHE endothelial cells is poorly formed and discontinuous, which may expose collagen to circulating clotting factors [221].

Rapamycin (sirolimus) has been shown to be efficacious and well tolerated in patients with complicated vascular anomalies, including KHE [223, 224]. KHE has a significant lymphatic component that may be a basis for the responsiveness of the tumor to rapamycin. Rapamycin is a selective inhibitor of the mammalian target of rapamycin (mTOR), a key molecule in signal transduction pathways that control vascular proliferation [61, 230].

21.6.7 Spindle Cell Hemangioma

21.6.7.1 Clinical Features

Spindle cell hemangioma is a rare benign vascular tumor that is more common in young adults, although it has occasionally been reported in children. Lesions may be single or multiple, and they tend to occur in the lower extremities. Lesions appear as skin-colored to blue firm nodules, which may be painful or asymptomatic [231]. Approximately 10 % of cases are seen in the setting of other disorders, such as Klippel–Trenaunay syndrome and Maffucci syndrome [232]. Most patients have an excellent prognosis after treatment with wide local excision.

21.6.7.2 Histology

Spindle cell hemangiomas demonstrate alternating areas that have markedly dilated thin-walled vessels, and others with dense proliferations of spindle-shaped cells and slit-like vascular spaces [233] (Figs. 21.38, 21.39 and 21.40). The dilated vessels are filled with fibrin thrombi in some cases and collapsed in others [234]. The endothelial cells may have epi-

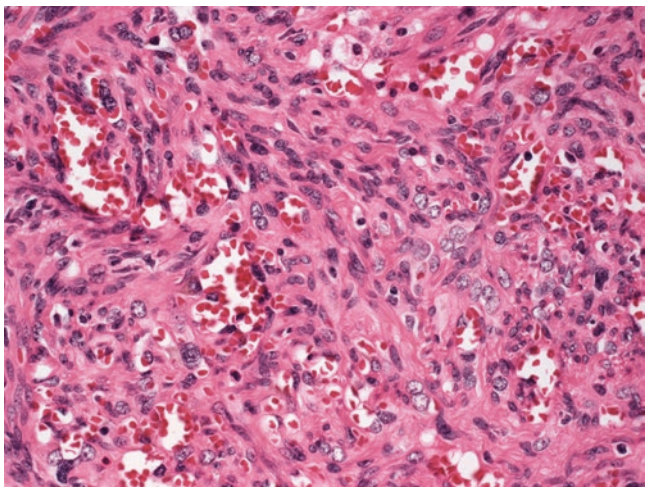

Fig. 21.39 There are areas of dense cellularity admixed with well-formed vessels and some irregular vascular spaces in spindle cell hemangioma

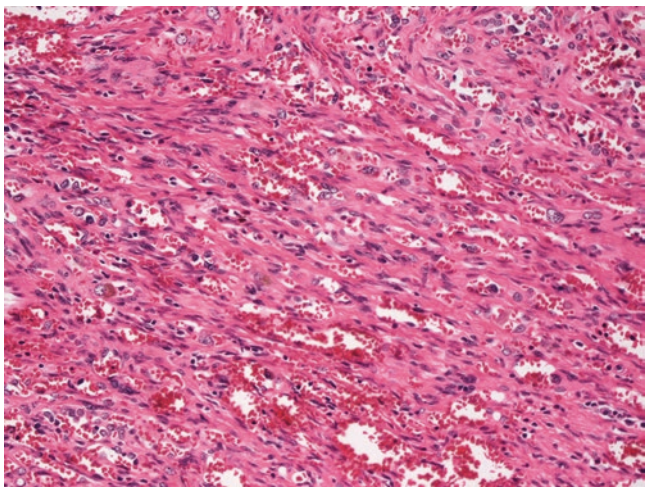

Fig. 21.40 Proliferation of spindle-shaped endothelial cells in a spindle cell hemangioma

thelioid morphology and contain cytoplasmic vacuoles [233, 234]. Mitotic activity is not high. When originally described, these lesions bore the name spindle cell hemangioendothelioma, and were believed to represent a variant of a low-grade malignant vascular tumor [234]. At this point, the name has been changed to spindle cell hemangioma since it appears to have a clinical course of a benign tumor [225].

Composite hemangioendotheliomas are complex vascular proliferations that contain components resembling more than one type of vascular tumor. In many cases, the composite lesions contain areas that are indistinct from spindle cell hemangiomas [235–237].

The differential diagnosis includes kaposiform hemangioendothelioma, which would not normally demonstrate admixed areas of thin-walled dilated vessels [226]. Kaposi's sarcoma can be differentiated based upon the presence of HHV-8 staining.

21.6.7.3 Pathogenesis

Spindle cell hemangioma is considered to be a benign vascular tumor, or even a reactive lesion with vascular proliferation [239–241]. Multifocal spindle cell hemangiomas are associated with a number of syndromes, including Maffucci syndrome, Ollier disease, Milroy disease, and Klippel–Trenaunay syndrome.

Mutations in the isocitrate dehydrogenase 1 (IDH1) gene have been found in spindle cell hemangioma, but not in other types of vascular tumors or vascular malformations [242]. Spindle cell hemangioma that occurs in Maffucci syndrome also harbors mutations in IDH1 (R132C mutations) [137]. It has been suggested that IDH1 R132C hotspot mutation is highly specific for spindle cell hemangioma, and may serve as a diagnostic aid for this lesion. There is also evidence for isocitrate dehydrogenase 2 (IDH2) hotspot mutations in some cases, indicating genetic heterogeneity in spindle cell hemangioma [137, 242]. IDH1 is a metabolic enzyme that generates α-ketoglutarate and NADPH. Gain-of-function mutations in IDH1 can lead to increased production of D-2-hydroxyglutarate. Hydroxyglutarate can exert aberrant epigenetic effects on gene expression by inhibiting histone demethylation and DNA demethylation [139, 140]. IDH1 can also activate hypoxia-inducible factor-1α pathway to increase cell proliferation [141].

21.6.8 Retiform Hemangioendothelioma

21.6.8.1 Clinical Features

Retiform hemangioendothelioma is a rare vascular tumor that is considered to be a locally aggressive vascular tumor [243]. Most cases affect adults during the second to fourth decades of life (mean age is 36), although there are rare reports in children [243–245]. The female-to-male ratio is 2:1. Clinically, retiform hemangioendothelioma presents as a slow-growing, asymptomatic nodule or plaque, usually on the trunk or extremities [243]. Complete surgical excision is the recommended treatment.

21.6.8.2 Histology

Within the dermis, long arborizing, thin vascular channels lined by enlarged endothelial cells course throughout collagen bundles in retiform hemangioendothelioma. The endothelial cells have a hobnail-like appearance [246]. The pattern resembles that seen in the rete testis, hence the name of the entity [225]. The tumor is poorly circumscribed and has an invasive growth pattern. Occasional vessels contain fibrin thrombi, and there is a brisk lymphocytic infiltrate. Mitotic activity is low with relatively minimal cytologic atypia. In

some cases, there is a papillary architecture with collagenous papillary cores, resembling a Dabska tumor [245].

The tumor is believed to be derived from blood vessel endothelial cells due to their failure to express podoplanin, which is a lymphatic marker as detected by the antibody D2-40 [247]. However, at least one case is described to have D2-40 positivity, suggesting a lymphatic vascular origin [248]. Retiform hemangioendothelioma expresses the vascular endothelial markers von Willebrand factor, CD31, and CD34 [225]. The spindle cells in the solid areas also express CD31, indicating their endothelial cell differentiation. The lymphocytic infiltrate in the lesion is a mixed population of both CD20+ B lymphocytes and CD3+ T lymphocytes [246].

A retiform growth pattern is seen in lesions designated as composite hemangioendotheliomas based upon the presence of more than one type of growth pattern. Admixed epithelioid and spindle cell patterns have also been described [236]. The prognosis seems to be the same for composite hemangioendotheliomas and retiform hemangioendotheliomas as a low-grade malignancy [235].

Angiosarcoma is in the differential diagnosis but it can be distinguished based upon the clinical history and histologic appearance of atypical endothelial cells with brisk mitotic activity. Benign vascular neoplasms typically do not have the invasive growth pattern seen in retiform hemangioendothelioma.

21.6.8.3 Pathogenesis

The International Society for the Study of Vascular Anomalies (ISSVA) has classified retiform hemangioendothelioma as a locally aggressive or borderline vascular tumor [56]. Rare cases of retiform hemangioendotheliomas have also been reported to carry human herpesvirus type 8 (HHV-8) DNA [249]. However, the significance of HHV-8 in the pathogenesis of this tumor is not known.

21.7 Unclassified Vascular Anomalies

21.7.1 Angiokeratoma

21.7.1.1 Clinical Features

Angiokeratomas are benign vascular skin lesions. The prevalence of angiokeratomas increases from 0.6 % in the first and second decade of life to 16.6 % in the seventh decade [250]. They are most common in Caucasian and Japanese populations [250]. Diffuse angiokeratomas (angiokeratoma corporis diffusum) in the skin are a hallmark feature of lysosomal storage diseases, including Fabry disease, fucosidosis type II, galactosialidosis, and aspartylglycosaminuria [251, 252]. For example, they are present in over 60 % of male and 30 % of female patients with Fabry disease [253].

Angiokeratomas present as single or multiple red to blue/black hyperkeratotic papules measuring up to 10 mm in diameter [250, 252]. Individual lesions are most common on the legs, penis, vulva, and clitoris. Problematic lesions can be surgically removed or destroyed by cryotherapy, electrocautery, and laser ablation.

21.7.1.2 Histology

Histologic changes are similar for different types of angiokeratomas, independent of the clinical subtype or an association with underlying Fabry disease. The changes include epidermal hyperplasia with elongated rete ridges that form collarettes around markedly dilated papillary dermal vessels. Hyperkeratosis is present in most cases. The affected vessels are thin-walled and enclosed by a single layer of flattened endothelial cells (Fig. 21.41). There is no obvious proliferation of dermal vessels. The dilated vessels are confined to the superficial dermis, and should not extend deep in angiokeratoma. Secondary changes, including thrombosis and intravascular papillary endothelial hyperplasia (Masson's lesion), have been described in angiokeratomas, especially in posttraumatic lesions [254, 255]. Lack of staining with WT-1 antibodies suggests that these lesions are likely vascular malformations and not true neoplasms [102, 256].

Electron microscopic examination of angiokeratomas associated with Fabry syndrome demonstrates vacuolization of the endothelial cells, surrounding smooth muscle cells and Schwann cells. In addition, lamellar bodies are found in these cells [257, 258]. These findings are not seen in sporadically appearing angiokeratomas.

The differential diagnosis includes verrucous hemangioma (also known as verrucous venous malformation), which poses a major diagnostic confusion in that the superficial changes may be identical. However, verrucous hemangioma has a deep vascular component that is not a feature of angiokera-

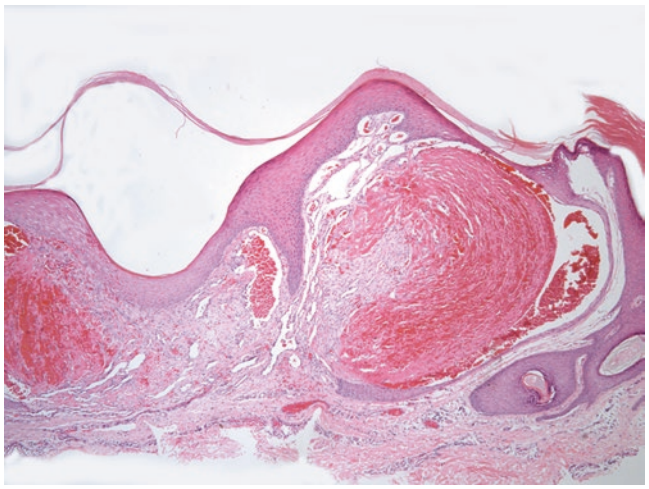

Fig. 21.41 Elongated rete ridges envelop around enlarged blood vessels located within the papillary dermis in angiokeratoma

toma, thus enabling straightforward distinction on biopsies that contain deeper reticular dermis [259–261]. Angiokeratoma-like lesions have been described in association with Cobb syndrome [114] and with pseudolymphomatous lesions with the acronym APACHE, although these likely have an entirely different and unrelated pathogenesis [262, 263]. Angiokeratoma-like lesions have also been described in a single patient with juvenile dermatomyositis [264], but since this association has not been verified by other investigators, it is not certain that these are truly angiokeratomas.

21.7.1.3 Pathogenesis

Angiokeratomas often occur in isolation. When presenting in a generalized distribution, these lesions can be a feature of any number of lysosomal storage diseases, such as Fabry disease. The pathogenesis of these lesions is unknown.

21.7.2 Angioma Serpiginosum

21.7.2.1 Clinical Features

Angioma serpiginosum is a cutaneous vascular anomaly that typically presents in childhood (90 % of cases appear before age 16) [265]. It is more common in females [266]. Clinically, angioma serpiginosum appears as multiple small, deep red macules arranged in clusters and sheets, most often on the legs and buttocks [265]. Lesions are usually asymptomatic and do not require treatment.

21.7.2.2 Histology

Histologic features show a proliferation of dilated vessels in clusters within the papillary dermis [267, 268]. Most blood vessels are thin-walled, although some authors have described thick-walled vessels within these lesionsl [269]. In some cases, there is downward growth of the overlying epidermal rete ridges, resulting in a resemblance to angiokeratoma. Precise diagnosis requires clinicopathologic correlation because the histologic findings are not specific.

21.7.2.3 Pathogenesis

Little is known about the etiology of angioma serpiginosum. Interestingly, mutations in porcupine homolog (PORCN), which is involved in the processing of Wnt (wingless and int homolog) proteins and in Wnt signaling, have been identified in angioma serpiginosum. However, others have disputed the significance of this finding [270, 271].

21.7.3 Verrucous Venous Malformation (Verrucous Hemangioma)

21.7.3.1 Clinical Features

Verrucous venous malformation (also known as verrucous hemangioma) is a rare localized congenital venous vascular malformation. It is usually apparent at birth or during early childhood [272]. Verrucous venous malformation can be single or multiple. Over 90 % of reported lesions occurred on the legs and 9 % on the trunk [273]. Clinically, lesions appear as hyperkeratotic bluish-red papules coalescing into plaques. Smaller problematic lesions can be surgically excised, although larger lesions may require a combination of surgical/ablative therapies and multiple procedures to achieve improvement.

21.7.3.2 Histology

Verrucous venous malformation is characterized by an acanthotic and papillomatous epidermis that is hyperproliferative [274]. A proliferation of blood vessels is present within the reticular dermis and extends into the subcutis. The vessels are small and have thick wall [261]. These lesions spread over time and tend to recur after local excision [275, 276]. Satellite nodules develop in long-standing lesions [259].

Some studies have shown that verrucous venous malformations express WT-1, which is a molecular marker often expressed in vascular tumors but not in vascular malformations [102, 275, 277]. However, other studies have reported opposite findings with the presence of the lymphatic marker Prox-1 and the absence of WT-1 in these lesions [102, 209, 279]. It appears that verrucous venous malformation has been better defined as a venous malformation with an incomplete lymphatic immunophenotype rather than a true vascular tumor. However, according the International Society for the Study of Vascular Anomalies (ISSVA) classification, verrucous venous malformations are considered to be "provisionally unclassified vascular anomalies."

The major differential diagnosis is angiokeratoma. Verrucous venous malformation is differentiated based upon its extension into the deeper dermis and subcutis, which are features not associated with angiokeratoma [278]. However, the superficial portion of the lesion is indistinguishable from angiokeratoma [276].

21.7.3.3 Pathogenesis

Whole exome sequencing has revealed mosaicism for a somatic missense mutation (c.1323C > G; p.Iso441Met) in mitogen-activated protein kinase kinase kinase 3 (MAP3K3) in some cases of verrucous venous malformations [273]. It has been suggested that the mutation in MAP3K3 is a cause of these lesions. MAP3K3 is a member of the MAP kinase kinase kinase family of serine/threonine protein kinases [280]. MAP3K3 is important in vascular development as shown in genetically engineered mouse models in which deletion of MAP3K3 gene leads to defects in embryonic cardiovascular development [281]. MAP3K3 acts in signal transduction pathways downstream of angiopoietin-1 (ANG-1) and TIE2 [282]. Interestingly, TIE2 is a known causative gene of venous malformations [38, 40]. The finding that ver-

rucous venous malformations carry MAP3K3 mutation lends supports that these lesions are a type of venous malformation.

21.7.4 Nevus Anemicus

21.7.4.1 Clinical Features

Nevus anemicus is a congenital localized vascular anomaly that can occur sporadically or can be associated with certain genodermatoses in children, such as neurofibromatosis-1 (NF-1) and phakomatosis pigmentovascularis [283]. Most notably, it is now recognized that the presence of nevus anemicus may assist in the early diagnosis of NF-1 [284]. Clinically, nevus anemicus is usually located on the trunk as an irregularly-shaped patch of pallor [285].

21.7.4.2 Histology

There are no histologic abnormalities seen on biopsies taken from lesions of nevus anemicus by light or electron microscopic examination [6, 285, 286].

21.7.4.3 Pathogenesis

It is postulated that nevus anemicus exists as an aberrant hypersensitivity response to catecholamines due to abnormal sympathetic vasoconstriction [285]. Other studies have suggested that increased stimulation of vasoconstrictive fibers, or inhibition of vasodilator fibers of the arterioles in the lesion may be a causative factor [287]. For these reasons, nevus anemicus has been called a "pharmacologic nevus" due to its unique catecholamine dependency [288].

21.7.5 Generalized Essential Telangiectasia

21.7.5.1 Clinical Features

Generalized essential telangiectasia is a rare skin condition characterized by the development of widespread cutaneous telangiectasia in the absence of systemic disease. Generalized essential telangiectasia is most common in adult white women, typically in the fourth and fifth decades of life [289]. Lesions commonly develop in late childhood or early adult life. Erythematous, blanching telangiectasias usually begin on the lower extremities and spread proximally to involve the trunk and arms, and rarely the face (Fig. 21.42). Some patients may improve with oral tetracyclines or laser therapy.

Fig. 21.42 Telangiectasia may appear as fine erythematous superficial capillaries on the cheek of a child

21.7.5.2 Histology

Histologic findings include an unremarkable epidermis. There are dilated blood vessels within the papillary dermis that make up the superficial vascular plexus [290]. The vessels are thin-walled venules [291]. Occasional thrombi may be seen in blood vessels, especially if they are traumatized.

21.7.5.3 Pathogenesis

The pathogenesis of blood vessel dilatation in generalized essential telangiectasia is unknown. Vitamin C deficiency has been suggested to contribute to its development [292].

21.7.6 Angiolymphoid Hyperplasia with Eosinophilia

21.7.6.1 Clinical Features

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare benign vasoproliferative disease that typically affects young to middle-aged females [293]. It is uncommon in children but has been described [294]. It usually presents with solitary or multiple flesh- to plum-colored papules or nodules on the head and neck [295]. The lesion usually has no associated symptoms. However, tenderness and bleeding due to the vascular nature of the lesion may occur. Surgical excision is the treatment of choice.

21.7.6.2 Histology

ALHE, previously known as epithelioid hemangioma [296] and histiocytoid hemangioma [297], is generally regarded to be a vascular proliferation with a brisk inflammatory response. Within the dermis, there is a nodular proliferation of small vessels with markedly edematous endothelial cells (Figs. 21.43 and 21.44). Endothelial swelling results in partially or fully occluded vascular lumina, resulting in the low-power impression of granulomatous foci comprised of histiocytes. Early reports suggested a relationship to an underlying artery in about half of the cases [298]. There is a dense infiltrate of lymphocytes, often with lymphoid follicles, surrounding the

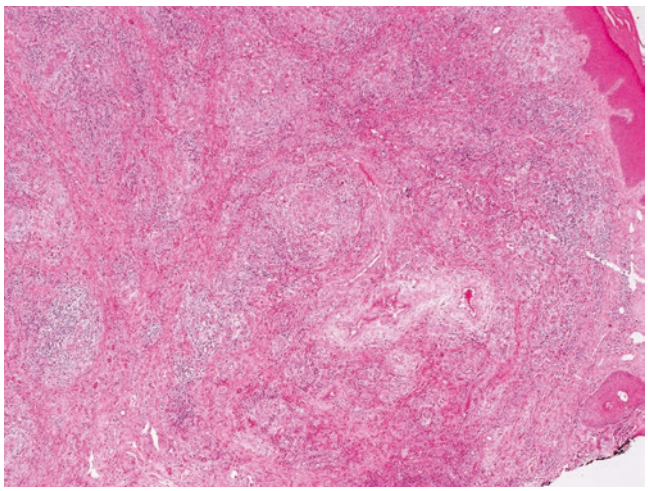

Fig. 21.43 Angiolymphoid hyperplasia with eosinophilia is characterized by a dense dermal infiltrate of inflammatory cells and blood vessels with swollen endothelial cells that often obliterate vascular lumens

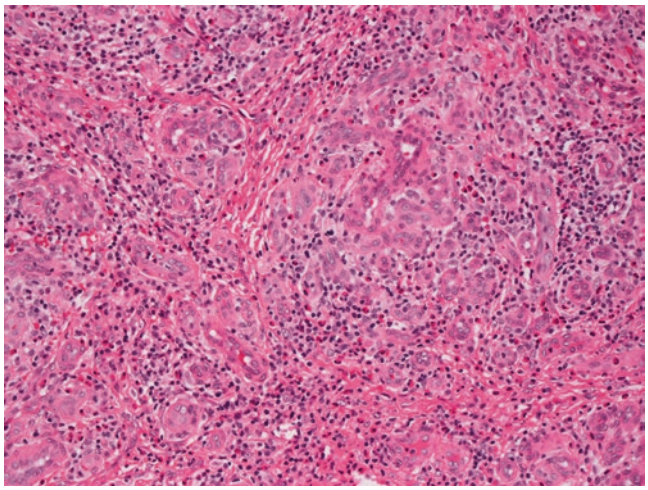

Fig. 21.44 Blood vessels with swollen endothelial linings may resemble granulomas in angiolymphoid hyperplasia with eosinophilia. Abundant eosinophils are present in the surrounding inflammatory response in most case

small vessels. Varying numbers of eosinophils are present within the infiltrate, ranging from only scattered cells to large aggregates of cells. Neutrophils and plasma cells have been described in the lesion [299], but they are not commonly encountered to any great extent. In some cases, the density of the infiltrate largely obscures the vascular proliferation. While in other cases, the vascular component predominates.

In children, a differential diagnosis to consider is Kimura's disease. While this disease is most commonly encountered in Southeast Asia, it can occur in any population. Histologically, changes similar to ALHE are found in Kimura's disease, but they are located deeper in the dermis and involve lymph nodes. Careful attention to the clinical presentation usually makes the distinction straightforward [300]. The differential diagnosis also includes cutaneous epithelioid angiomatous nodule. This entity differs in being a single lesion in comparison with the multiple small nodules often seen in ALHE and in having more prominent endothelial cell atypia that can mimic angiosarcoma [190, 301].

Granulomatous dermatitis also enters the differential diagnosis when there is prominent endothelial cell swelling and vascular lumina are not prominent. Diagnosis is possible with CD31 or other immunostains that identify the nature of the endothelial cells with abundant pink cytoplasm. In other cases, the inflammatory infiltrate is so prominent as to raise the differential diagnosis of cutaneous lymphoid hyperplasia or even lymphoma. The presence of abundant eosinophils favors a reactive process, and immunostains demonstrate a mixed inflammatory infiltrate.

21.7.6.3 Pathogenesis

Various mechanisms of pathogenesis have been proposed for ALHE, including reactive and neoplastic processes, but none are conclusive [295]. It has been suggested that preceding trauma may trigger a reaction that induces vascular growth (angiogenesis) and reactive lymphocytic infiltration in ALHE [296, 302]. The characteristic inflammatory infiltrate in ALHE appears to be a key component of this disease, and it is accompanied by vascular proliferation. Other factors, such as arteriovenous shunting and increased estrogen levels, may contribute to the development and progression of ALHE as well [303, 304]. Additionally, ALHE has been associated with lymphoproliferative disorders. Some cases of ALHE show T-cell receptor gene rearrangement and monoclonality, suggesting that this may be a monoclonal T-cell process [305, 306]. However, the clinical course of ALHE indicates that the majority of the cases are completely benign.

A single case of dermal ALHE has been found to have a mutation in TIE2 gene (TEK), which is an endothelial cell receptor tyrosine kinase [307]. However, the significance of this finding is unknown.

21.7.7 Papillary Intralymphatic Angioendothelioma (Dabska Tumor)

21.7.7.1 Clinical Features

Dabska tumor is a rare locally aggressive vascular tumor occurring primarily in childhood with a few cases reported in adults. It often appears as a slow-growing nodule with overlying discoloration ranging from pink or violaceous to blue or black [308]. The head and extremities are often affected, although there is no predilection for a particular site. Frequently, it may be associated with an underlying vascular tumor. Although prognosis is generally favorable, this tumor is locally invasive and has low metastatic potential. Treatment consists of surgical excision.

21.7.7.2 Histology

Dabska tumor occupies the mid-reticular dermis and extends into the subcutaneous fat. Inter-anastamosing vascular channels dissect between collagen bundles. Proliferations of hobnail-like endothelial cells protrude into the vascular lumen in glomeruloid formations [309, 310]. The papillary projections have hyaline or fibrous cores [225, 246]. D2-40, a marker of lymphatic endothelial cells, is strongly expressed by the cells in Dabska tumor, which supports the idea that this tumor has lymphatic origin [311].

There is a single case report of a malignant intralymphatic angioendothelioma arising from within a lymphangioma circumscriptum, suggestive of the purported lymphatic origin of the endothelial cells [72, 310]. Another case arose within a vascular malformation that was not further characterized, but resulted in the development of Kasabach–Merritt syndrome [312].

The differential diagnosis includes targetoid hemosiderotic hemangioma (hobnail hemangioma) based upon the protrusion of endothelial cells into the vascular lumen. However, hobnail hemangiomas do not display the papillary and glomeruloid growth patterns as seen in Dabska tumor [206]. Retiform hemangioendothelioma also shares some histologic features, but the endothelial cells often fail to express D2-40, which helps to make the distinction from Dabska tumor [245, 247]. The retiform growth pattern is not characteristic of malignant papillary intralymphatic angioendothelioma.

21.7.7.3 Pathogenesis

There are controversies about Dabska tumor, which has been thought to be a type of low-grade malignant vascular tumor in the group of hemangioendotheliomas. Dabska tumor has now been renamed papillary intralymphatic angioendothelioma, since it appears to have lymphatic origin based on lymphatic marker studies [311, 313].

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Hematopoietic Proliferations

22

22.1 Langerhans Cell Histiocytosis

22.1.1 Clinical Features

Langerhans cell histiocytosis (LCH) can affect individuals at any age, but the peak incidence occurs at 1–4 years of age [1]. The most classic presentation of LCH is a seborrheic dermatitis-like eruption of the skin. Pink scaly papules and plaques, often with crusting and petechiae, tend to favor the scalp, postauricular area, axillae, and perineum. Less commonly, nodules and ulcerative lesions occur (Fig. 22.1). Mucosal involvement is seen, especially with more severe disease. Erythema and erosions of the gingiva, as well as natal teeth, can be seen. Bony lesions in LCH tend to present with painful swelling. The skull and long bones of the extremities are the most commonly affected sites [2].

In general, LCH involving a single organ has an excellent prognosis and a high rate of spontaneous remission. Up to 50 % of skin LCH lesions regress within a few months [1]. Patients with multisystem or disseminated disease have a much poorer prognosis.

Congenital self-healing reticulohistiocytosis is a rare form of Langerhans cell histiocytosis that presents at birth or during the neonatal period. Cutaneous lesions consist of single or multiple reddish-brown crusted papules or nodules (Fig. 22.2). Although the skin lesions tend to heal spontaneously within days, some patients may have involvement of internal organs, particularly the bones, liver, and spleen [3]. Prognosis depends on the extent of disease.

With special contribution from Andrea L. Haws, MD, The Children's Hospital of San Antonio.

22.1.2 Histology

There are many variants of Langerhans cell histiocytoses [4]. While there is great variation in the clinical presentation and clinical course of these subtypes, the histologic changes are largely the same and will be described collectively, concentrating solely on mucocutaneous findings. It should also be noted that involvement of the bone, lung, and pituitary glands might occur in some variants of this process.

In LCH, the epidermis demonstrates focal parakeratosis overlying varying degrees of spongiosis that is diffuse throughout the epidermis. In most cases, there is abundant exocytosis of Langerhans cells into the epidermis (Fig. 22.3). Langerhans cells can usually be identified based upon cytologic features that include reniform-shaped, grooved, or folded nuclei and abundant cytoplasm (Figs. 22.4 and 22.5). Anti-CD1a immunohistochemistry is useful in cases when the nature of the infiltrating cells is not readily apparent. Intraepidermal eosinophils are also quite common. Cytologic atypia and significant mitotic activity are rarely encountered. Some cases fail to demonstrate exocytosis of Langerhans cells into the dermis. Treatment with topical corticosteroids prior to biopsy may also suppress exocytosis and mask the diagnostic features.

Within the dermis, there is an infiltrate that consists of Langerhans cells, eosinophils, lymphocytes, and neutrophils. The infiltrate may be diffuse and virtually always involves the papillary dermis. In some cases, extension into the deeper reticular dermis may be present. Less commonly, the infiltrate can appear granulomatous. In these cases, multinucleated giant cells may be present and obscure the true nature of the Langerhans cell process. Touton-type and osteoclast-like giant cells have been described. These same histologic changes have been identified on mucosal surfaces and in the nails when these sites are similarly affected in LCH [5, 6].

Congenital self-healing reticulohistiocytosis demonstrates identical histologic features as described above, and cannot be distinguished from the more progressive LCH by histologic

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Fig. 22.1 Langerhans cell histiocytosis is characterized by an erythematous, indurated plaque with central ulceration and overlying eschar

Fig. 22.2 Congenital self-healing reticulohistiocytosis presents as multiple firm, erythematous and ulcerated papulonodules on the shoulder of an infant

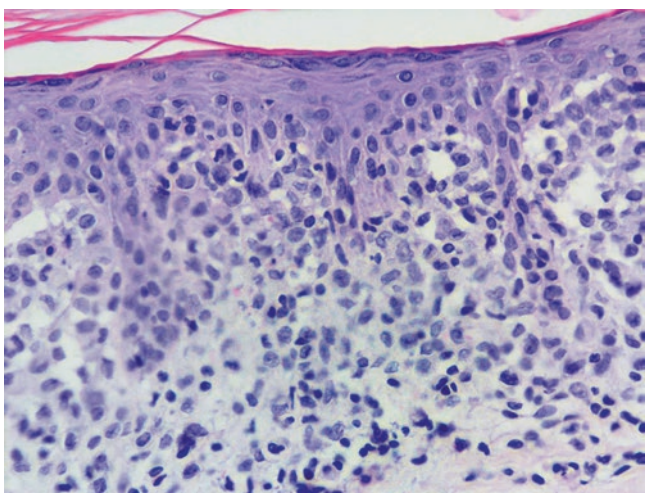

Fig. 22.3 Marked epidermotropism of Langerhans cells into the epidermis is seen in most cases of Langerhans cell histiocytosis

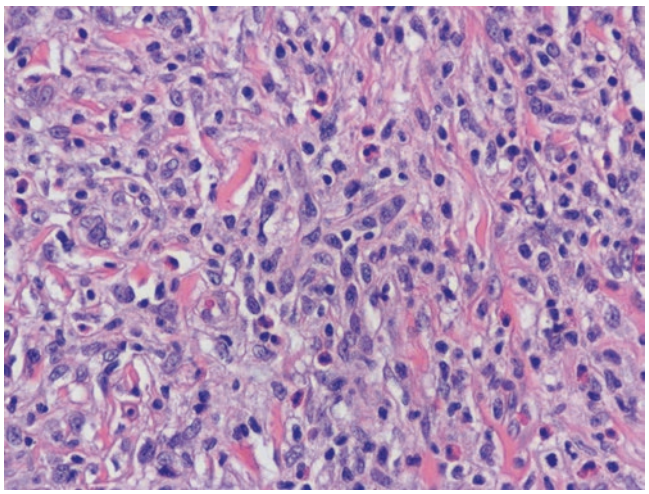

Fig. 22.4 Langerhans cell histiocytosis is comprised of sheets of Langerhans cells with grooved or reniform nuclei and ample eosinophilic cytoplasm. Eosinophils are usually present throughout the infiltrate

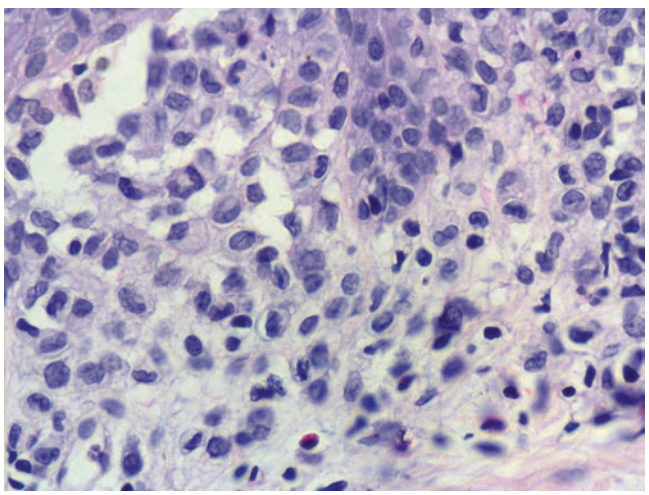

Fig. 22.5 Langerhans cells have a characteristic reniform nuclei, often with a grooved appearance. They are readily identifiable on routine H&E sections in most cases, although immunostains can be used to confirm the histologic impression

or immunologic means. Clinical observation is the best way to separate these entities. A single case of congenital self-healing reticulohistiocytosis appearing as a solitary nodule has been reported [7]. Rare cases of aggressive congenital Langerhans cell histiocytosis have also been reported. In one such case, the expression of CD56 by the infiltrating cells was noted [8]. Further confounding this distinction, late-onset "congenital" self-healing reticulohistiocytosis has been described as initially appearing in a child 8 years of age [9].

Indeterminate cell disorder demonstrates identical histologic changes to those seen in LCH. However, electron microscopy reveals that Langerhans cells do not contain Birbeck granules, although they share the immunostaining

characteristics of traditional Langerhans cells. Rare cases with mucosal involvement have been described [10]. The existence of this variant as a separate and discrete entity has been questioned [11].

Langerhans cell hyperplasia can be seen in many conditions, including some as common as contact dermatitis, and these causes must be excluded before establishing a diagnosis of LCH [12]. Persistent scabetic nodules may also contain abundant Langerhans cells or indeterminate cells [13].

Immunostains can usually distinguish LCH from xanthoma disseminatum, in which the infiltrating cells do not express CD1a [14]. Mast cell disease as it occurs in children may also present some diagnostic dilemma, but there is usually minimal infiltration of the epidermis by mast cells. Giemsa, mast cell tryptase and CD117 stains can also characterize the infiltrating mast cells and differentiate them from Langerhans cells.

Fig. 22.6 Xanthoma disseminatum is characterized by multiple firm, yellow papules along the trunk

22.1.3 Pathogenesis

The pathogenesis of LCH remains enigmatic. A debate persists on whether LCH results from immune dysregulation or malignant transformation of Langerhans cell precursors. LCH has a prominent inflammatory component and can have a benign course, suggesting that LCH may not be a neoplasm. However, supporting evidence that LCH is a neoplasm includes clonality, the presence of the activating BRAF V600E point mutation in addition to KRAS and TP53 mutations, and avoidance of cell death through overexpression of BCL21 and BAX [15, 16].

22.2 Xanthoma Disseminatum

22.2.1 Clinical Features

Xanthoma disseminatum is a rare non-Langerhans cell disorder. It may appear at any age and is more common in males than females by 2:1. Three clinical variants have been described: a persistent form, a progressive form with systemic involvement, and a self-limited form.

Cutaneous lesions consist of multiple small orange papules on the face, flexures, and mucosal membranes (Fig. 22.6). The disease course of xanthoma disseminatum is typically benign. Localized lesions may be amenable to surgical excision. Chemotherapy has been used for systemic disease with variable success [17].

22.2.2 Histology

Histologic changes are those of a dense, confluent infiltrate of histiocytes throughout the papillary and reticular dermis (Fig. 22.7). Mononuclear and multinucleated giant cells

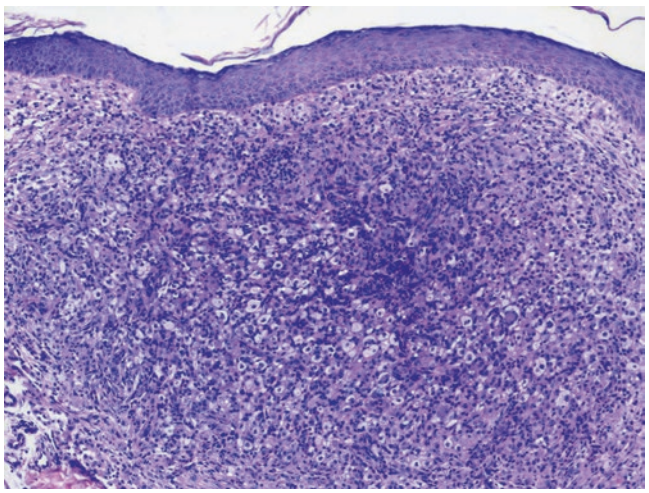

Fig. 22.7 A flattened epidermis overlies a dermis that is distended with sheets of lipid-laden histiocytes admixed with inflammatory cells, including eosinophils in xanthoma disseminatum

with varying amounts of cytoplasmic lipids are admixed with eosinophils and scattered lymphocytes. Touton giant cells are often abundant (Fig. 22.8). Nuclei develop a scalloped appearance due to the presence of cytoplasmic lipid droplets [18, 19]. In very early lesions, lipid may be relatively inconspicuous. In later lesions, fibrosis may be present.

The histologic differential diagnosis of xanthoma disseminatum mainly includes juvenile xanthogranuloma. This entity is histologically indistinguishable, but can easily be separated based upon clinical presentation. A rare entity described as papular xanthoma may also have similar histologic features, but it is easily distinguished based upon clinical presentation [20].

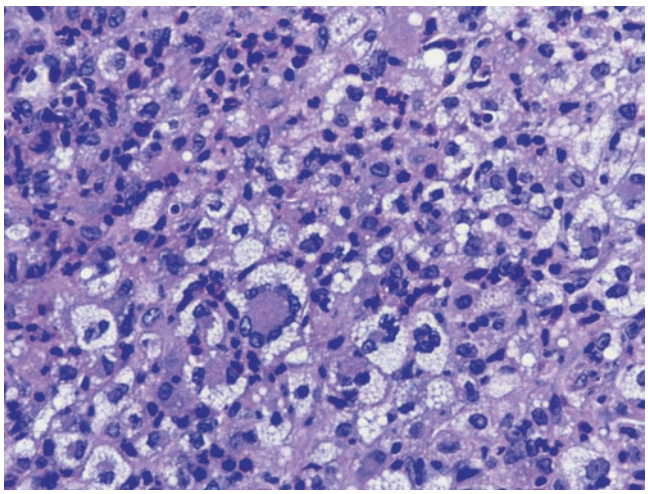

Fig. 22.8 Touton-type giant cells are abundant in xanthoma disseminatum

Fig. 22.9 Juvenile xanthogranuloma may present as multiple yellowish-orange papules and papulonodules scattered on the face of a young girl

22.2.3 Pathogenesis

Xanthoma disseminatum is a rare disease and belongs to the group of non-Langerhans cell histiocytoses, the pathogenesis for which is unknown. The lipid profiles in these patients are normal [21]. Involvement of the pituitary gland with accompanying diabetes insipidus is present in 30–50 % of patients [21, 22].

22.3 Juvenile Xanthogranuloma

22.3.1 Clinical Features

Juvenile xanthogranuloma (JXG) is a form of non-Langerhans histiocytosis that typically affects infants and young children, but it is occasionally seen in adults. Most lesions are present at birth (20 % of cases) or appear within the first few months of life [2].

A typical JXG lesion is a firm, round papule or nodule, often with a distinctly yellow color (Fig. 22.9). Lesions occur most commonly on the head, neck, and trunk but may be seen on the mucous membranes as well. Lesions are usually solitary (90 % of cases) and asymptomatic. Extracutaneous involvement is possible, with the eye being the most common non-cutaneous site. Other organs are rarely affected [2]. Lesions often spontaneously improve and regress over a period of 3–6 years [23].

22.3.2 Histology

Juvenile xanthogranuloma is characterized by a nodular infiltrate of histiocytes within the dermis [24, 25]. The overlying epidermis is either unremarkable or demonstrates slight compression of the rete ridges by the dermal infiltrate in fully developed lesions. Within the dermis, abundant mononuclear and multinucleated histiocytes are present, admixed with an inflammatory infiltrate that contains lymphocytes and variable numbers of eosinophils (Fig. 22.10). The earliest lesions may be difficult to diagnose based upon the lack of visible lipids within histiocytes [26, 27]. In these cases, an infiltrate of mononuclear histiocytes with abundant cytoplasm admixed with scattered eosinophils may be the only findings. As the lesions evolve, abundant lipid is present within histiocytic cytoplasm, resulting in scalloped nuclei and ultimately the formation of Touton giant cells (Fig. 22.11). An inflammatory infiltrate persists in some cases. Late lesions may have dermal fibrosis, and a slightly less pronounced inflammatory infiltrate [28–31].

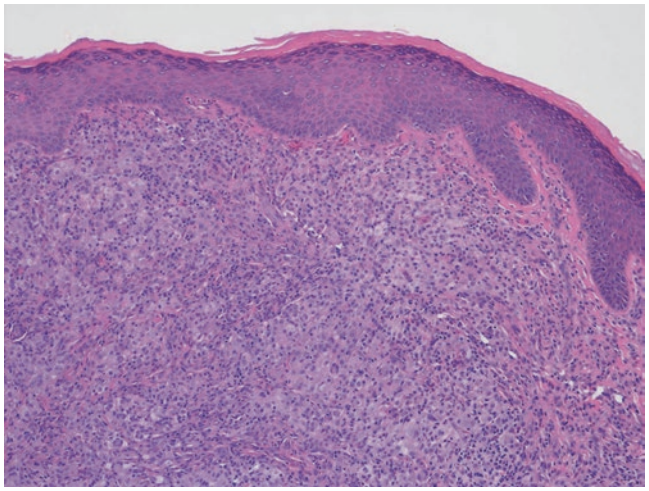

Fig. 22.10 The dermis is filled with histiocytes admixed with inflammatory cells, often including many eosinophils in juvenile xanthogranuloma

Reticulohistiocytoma differs from JXG in lacking significant lipid in histiocytes and the relative paucity of multinu-

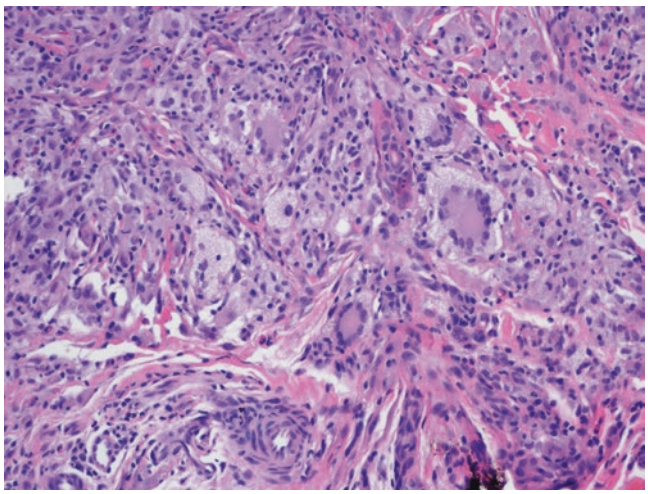

Fig. 22.11 Touton giant cells containing abundant peripherally-located cytoplasmic lipid is characteristic of well-formed juvenile xanthogranulomas

cleated cells. Xanthogranuloma disseminatum may be histologically indistinguishable from JXG, but it is easily separated based upon the clinical presentation [32]. Langerhans cell histiocytoses may demonstrate some overlap, but generally display more infiltration of the epidermis by the cellular process. Furthermore, the reniform morphology of Langerhans cells, and the immunostaining profile can easily make this distinction. Other non-Langerhans cell histiocytic proliferations are best distinguished based upon clinical findings [33].

22.3.3 Pathogenesis

Juvenile xanthogranuloma is thought to be a reactive response to a yet unidentified stimulus. Associations of JXG with cafe au lait spots, epilepsy, neurofibromatosis, and childhood leukemias (most commonly juvenile chronic myelogenous leukemia) have been reported, and implicate Ras pathway hyperactivity in this disorder [16, 24]. A recent review highlights the observed association of xanthogranulomas with hematologic malignancies, and suggests that xanthogranulomas are linked to underlying hematologic malignancies through induction of cytokines [34].

22.4 Reticulohistiocytoma

22.4.1 Clinical Features

Reticulohistiocytomas when present as single lesions are clinically indistinguishable from juvenile xanthogranulomas. Reticulohistiocytomas present as papules or nodules, occasionally with a yellow hue.

Multicentric reticulohistiocytosis is rare in children [35, 36]. There may be multiple such lesions that are commonly found overlying joints [37]. In these cases, joint symptoms and mutilating arthritis can occur. While there is a strong association with internal malignancies in adults with this condition, a similar association has not been found in affected children with reticulohistiocytomas. The associated arthritis may respond to treatment with methotrexate, but the cutaneous lesions do not [36].

22.4.2 Histology

Reticulohistiocytoma demonstrates a nodular proliferation of epithelioid histiocytes within the superficial and mid-dermis [38, 39] (Fig. 22.12). This has given rise to the alternate name of epithelioid histiocytoma. The epidermis is either unremarkable or slightly compressed by the dermal infiltrate. Ulceration is distinctly uncommon. The infiltrate consists predominantly of mononuclear histiocytes with abundant granular and eosinophilic cytoplasm (Fig. 22.13). Other cells may contain varying amounts of cytoplasmic lipid. Multinucleated cells, including Touton giant cells, may be encountered, but they are less abundant than in xanthogranulomas. A smaller population of spindle-shaped histiocytes is often seen within the infiltrate. Mitoses are seen in small numbers, but no atypical forms are expected. Admixed lymphocytes, neutrophils, and scattered eosinophils are present. Older lesions have interspersed fibrosis.

The differential diagnosis includes xanthogranuloma, and the lesions may represent a spectrum of a single entity. Cells in xanthogranulomas generally lack the granular eosinophilic cytoplasm, and display more intracytoplasmic lipid. Similarly, xanthogranulomas demonstrate many more Touton giant cells than are usually encountered in reticulohistiocytoma. The differential diagnosis is unimportant in most cases, and only becomes significant if a diagnosis of multicentric reticulohistiocytosis is being considered in association with internal malignancy. However, this entity is

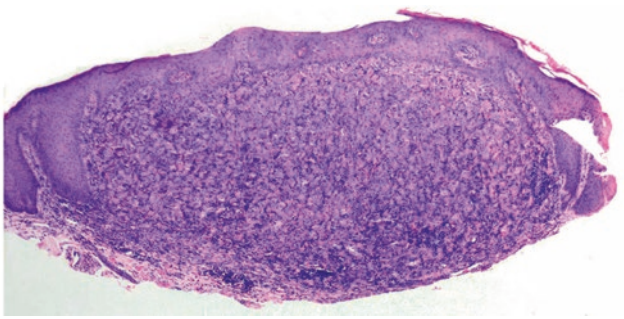

Fig. 22.12 The dermis is filled with an aggregation of large pale-staining histiocytes admixed with inflammatory cells in reticulohistiocytoma

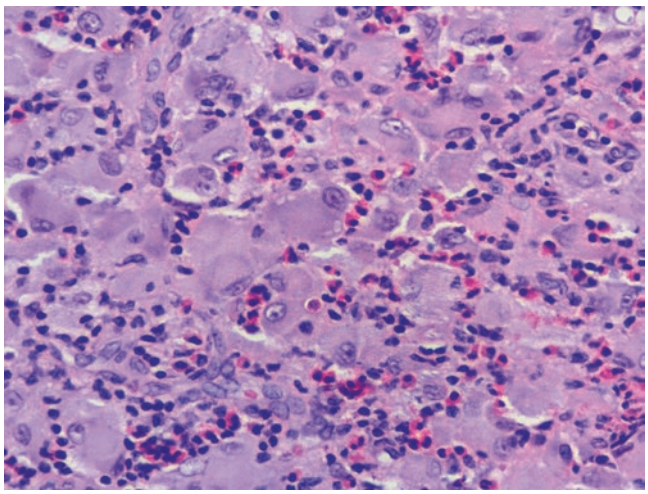

Fig. 22.13 Reticulohistiocytoma is characterized by large mononuclear histiocytes with oncocytic, focally granular cytoplasm and associated inflammatory infiltrate, often with abundant eosinophils. Cytoplasmic lipid is not as prevalent as in xanthogranuloma

very rare in children [35]. A Spitz nevus can also enter into the differential diagnosis, but it can be discriminated from reticulohistiocytoma based upon the nesting pattern, the intraepidermal component, and the progressive maturation of cells with descent into the dermis. S100 or melanocyte marker immunostain can also resolve the differential diagnosis if needed.

22.4.3 Pathogenesis

Reticulohistiocytoma is thought to be a disorder of macrophage cells involving non-Langerhans histiocytes, which are stimulated by some yet unknown precipitating factor [38]. Although a neoplastic process has not been excluded, it likely represents a reactive process, resulting in a localized inflammatory reaction. Various precipitating factors have been proposed, including infections, inflammation, as well as autoimmune and paraneoplastic processes [40]. The presence of a large number of neutrophils in some lesions suggests an infectious etiology, although an infectious agent has not yet been identified in these lesions [38].

22.5 Benign Cephalic Histiocytosis

22.5.1 Clinical Features

Benign cephalic histiocytosis is a form of non-Langerhans cell histiocytosis that is seen primarily in infants and young children. The average age of onset is 15 months and approximately 45 % of cases occur in infants less than 6 months old [2].

Typical lesions are small (up to a few mm) yellow-brown macules and thin papules that occur mainly on the head, face, and neck (Figs. 22.14 and 22.15). A small percentage of children develop lesions on the trunk and extremities [2]. Although this condition has shown some overlap with other histiocytic disorders, it generally has a benign course. Lesions regress over months to a few years, but may leave flat or atrophic hyperpigmented macules behind [41].

Fig. 22.14 Benign cephalic histiocytosis may present as multiple reddish-brown papules scattered on the face in this young boy

Fig. 22.15 Benign cephalic histiocytosis, a closer view of lesions in the same patient in Fig. 22.14

22.5.2 Histology

Biopsies taken from patients with benign cephalic histiocytosis display a well-circumscribed proliferation of histiocytes centered mainly in the upper half of the dermis with no tendency for upward migration [42]. Mononuclear histiocytes are the predominant cell type with little cytoplasmic lipid. Touton giant cells may be observed, but they are relatively scant in most cases.

Ultrastructural analysis has demonstrated comma-shaped bodies in the cytoplasm of infiltrating histiocytes [41, 43, 44]. The existence of benign cephalic histiocytosis as a distinct entity has been called into question, with some authors suggesting that it represents a variant of generalized histiocytosis or juvenile xanthogranuloma [26, 45, 46]. The differential diagnosis includes other non-Langerhans cell histiocytic proliferations, and the distinction is primarily made based on the clinical presentation and disease course.

22.5.3 Pathogenesis

The etiology of benign cephalic histiocytosis is unclear. It is a diagnosis that seems to belong in the spectrum of non-Langerhans histiocytoses [42]. It has also been suggested that benign cephalic histiocytosis represents a localized form of generalized eruptive histiocytoma [41]. A recent report describes a case of accelerated regression of benign cephalic histiocytosis with antibiotic administration. Interestingly, *Staphylococcus aureus* was isolated from the dermal histiocytic collections, and the affected child was found to have low plasma levels of IgA [47].

22.6 Progressive Nodular Histiocytosis

22.6.1 Clinical Features

Progressive nodular histiocytosis is more common in adults than in children [48]. Typically, there is a generalized eruption of hundreds of small yellow-brown papules as well as scattered, larger subcutaneous nodules. Lesions on the face may coalesce to give a "leonine" appearance. Larger nodules may develop ulceration and bleeding, which can be painful. There can be mucous membrane involvement [2]. The disease course is typically chronic and progressive, although it is generally benign with patients usually remaining in relatively good health [48].

22.6.2 Histology

Histologic findings of progressive nodular histiocytosis are those of a predominantly spindle-shaped histiocytic infiltrate that is histologically identical to a spindle cell xanthogranuloma [49, 50]. Rare cytoplasmic lipid may be seen, but it is usually quite focal. Systemic involvement with histiocytic tumors has been reported and helps to differentiate this entity from similar limited cutaneous eruptions [51, 52]. Most authors believe progressive nodular histiocytosis to be part of a spectrum of non-Langerhans cell histiocytoses and is closely related to xanthogranulomas [46, 52, 53]. The histologic differential diagnosis includes a dermatofibroma with focal lipidization [53].

22.6.3 Pathogenesis

The pathogenesis of this rare disease is unknown. Cytogenetic analysis of a patient with progressive nodular histiocytosis revealed a normal karyotype [49]. It has been debated whether this is a reactive or neoplastic process.

22.7 Sinus Histiocytosis with Massive Lymphadenopathy

22.7.1 Clinical Features

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is a disorder that primarily affects young children [54]. It typically presents with massive lymphadenopathy, which affects the cervical region in up to 90 % of affected individuals [54]. Extranodal disease can occur, and the skin may be affected, typically appearing as nonspecific papules and nodules. Sinus histiocytosis with massive lymphadenopathy is typically a self-limited disease and spontaneously regresses [54].

22.7.2 Histology

The cutaneous lesions in Rosai-Dorfman disease are histologically quite similar to changes described in the more common lymph node-based sinus histiocytosis with massive lymphadenopathy. A dense infiltrate of inflammatory cells fills much of the dermis with no tendency for invasion of the epidermis or cutaneous appendages [55, 56] (Figs. 22.16 and 22.17). Admixed with sheets of histiocytes are lymphocytes, neutrophils, plasma cells, and occasional eosinophils [57]. The histiocytes resemble those seen in lymph node sinuses and demonstrate *emperipolesis*, in which histiocytes engulf other inflammatory cells [58, 59]. While this finding is not pathognomic for the disease, it is a very characteristic finding in this entity, and is usually readily apparent on H&E staining. Plasma cells are often found rimming blood vessels within the midst of the lesions. Thick-walled vessels and lymphoid nodules have been described at the periphery of lesions [55].

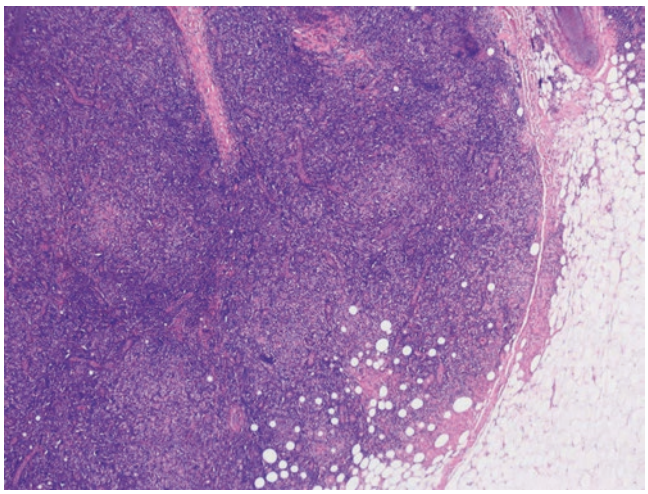

Fig. 22.16 The dermis is filled with large histiocytes admixed with a dense inflammatory infiltrate. The infiltrate may extend into the subcutis in sinus histiocytosis with massive lymphadenopathy

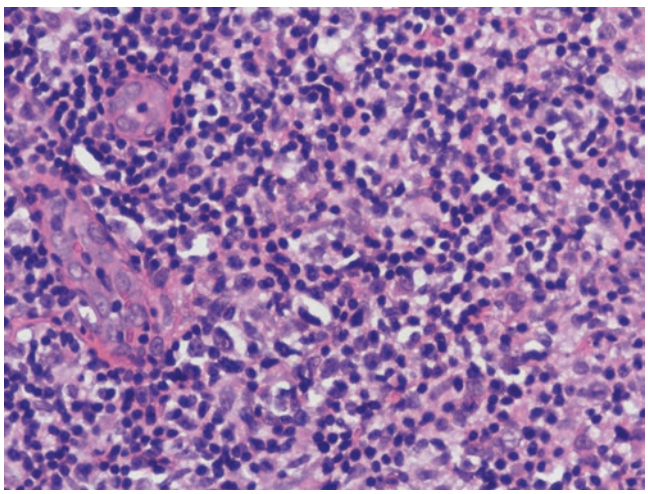

Fig. 22.17 Large histiocytes may demonstrate emperipolesis, and may be surrounded by a dense collection of lymphocytes with occasional plasma cells and eosinophils in sinus histiocytosis with massive lymphadenopathy. Endothelial cells in dermal vessels are edematous and resemble small granulomas

When purely cutaneous, these lesions can be mistaken for metastatic melanoma, a problem further confounded by the diffuse S100 positivity of the histiocytes in this disorder [60]. Careful attention to morphologic detail, clinical history, and other immunostains will allow for distinction. The differential diagnosis also includes infectious granulomatous processes, xanthogranuloma, reticulohistiocytoma, other histiocytic accumulations, and lipidized dermatofibroma [61, 62]. Histiocytes in these other entities do not express S100, and the pattern of plasma cellular cuffing of vessels, and histiocytes with marked emperipolesis would not be the expected findings.

22.7.3 Pathogenesis

The systemic form of sinus histiocytosis with massive lymphadenopathy is thought to involve an abnormal histiocytic response to a viral stimulus (such as Epstein-Barr virus and human herpesvirus 6 or 8) [63]. There has been a report of regression with acyclovir administration [64]. The disorder is associated with abnormalities of the immune system, such as infection, autoimmune disease, leukemia/lymphoma, and HIV [63]. Molecular investigation of a case of generalized pure cutaneous form of Rosai-Dorfman disease indicates that the histiocytes may have undergone a transition to mesenchymal cells, having both macrophage and mesenchymal characteristics, which may best be classified as a histiocyte-mesenchymal transition [65]. The molecular underpinning of sinus histiocytosis with massive lymphadenopathy may be related to the findings of germ line mutations in SLC29A3, which encodes an intracellular equilibrative nucleoside transporter (hENT3) with affinity for adenosine. Mutations in SLC29A3 have been found in familial histiocytosis syndrome and familial sinus histiocytosis with massive lymphadenopathy [66]. It is not known whether SLC29A3 is involved in sporadic disease.

22.8 Mast Cell Disease

22.8.1 Clinical Features

Fifty-five percent of patients with cutaneous mast cell disease present before 2 years of age, and about 10 % of cases appear between 2 and 15 years of age [67]. Three variants of mastocytosis tend to affect children: solitary mastocytoma, urticaria pigmentosa, and diffuse cutaneous mastocytosis. Solitary lesions are present at birth in approximately 40 % of cases, and typically appear by 1 year of age. Lesions appear as reddish-brown macules, patches, papules, or plaques that have a tendency to urticate with pressure or friction (Fig. 22.18). Urticaria pigmentosa is the most common form of cutaneous mastocytosis in children. It presents with diffuse reddish-brown macules and papules (Fig. 22.19). Diffuse cutaneous mastocytosis is the least common type, characterized by skin that may appear normal to diffusely doughy, reddish brown or have a “peau d’orange” texture [67]. Individual lesions may become irritated and pruritic, occasionally even forming a blister. Patients with more extensive skin lesions or systemic involvement can have gastrointestinal and respiratory symptoms as well as more severe allergic reactions. There is a tendency for individual skin lesions to improve over time. Typically, many lesions involute by puberty [67].

Fig. 22.18 Mastocytoma often presents as an erythematous, faint orange plaque with peau d'orange surface changes

Fig. 22.19 Urticaria pigmentosa presents as scattered brown macules and papules on the torso and extremities of an infant. Some lesions demonstrate localized redness and edema after being stroked (Darier's sign)

22.8.2 Histology

Mast cell disease has a wide range of clinical patterns. However, the histologic manifestations are quite similar in each of these forms, differing solely in the density of dermal mast cells. A common finding is basilar hyperpigmentation with minimal increase in melanocytes but marked increase in melanin throughout the basal melanocytes [68]. Within the dermis, increased numbers of mast cells may appear as small perivascular clusters of fusiform or cuboidal cells, making it difficult to discern from lymphocytes (Figs. 22.20 and 22.21). Alternatively, large sheets of cuboidal cells may fill the dermis. In most cases of mast cell disease independent of the number of mast cells, there are scattered eosinophils within the infiltrate and varying amounts of dermal edema. Later lesions may also show fibrosis and some necrosis [69]. In children, it is uncommon for mast cells to demonstrate cytologic atypia, pleomorphism, or markedly increased mitotic activity [70, 71].

There have been many attempts to quantify the number of dermal mast cells required to establish a diagnosis in more subtle cases. These include attempts at absolute cell counts, counts per unit area around dermal blood vessels, and minimum percentages of dermal inflammatory cells [72]. No formulas have yet proven to be completely reproducible. In these cases, it is best to have a biopsy with affected skin adjacent to clinically normal skin, or two adjacent biopsies in

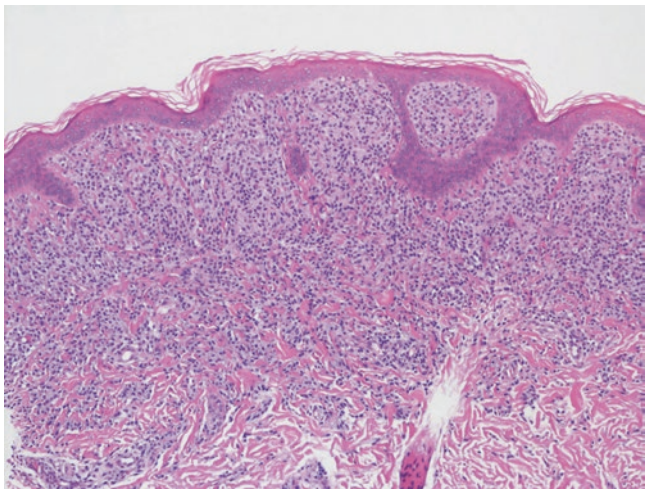

Fig. 22.20 The dermis is filled with monotonous-appearing cuboidal cells with central nuclei and abundant cytoplasm in mastocytosis. In children, a tumoral infiltrate is more common than the variants of the disease seen in adults

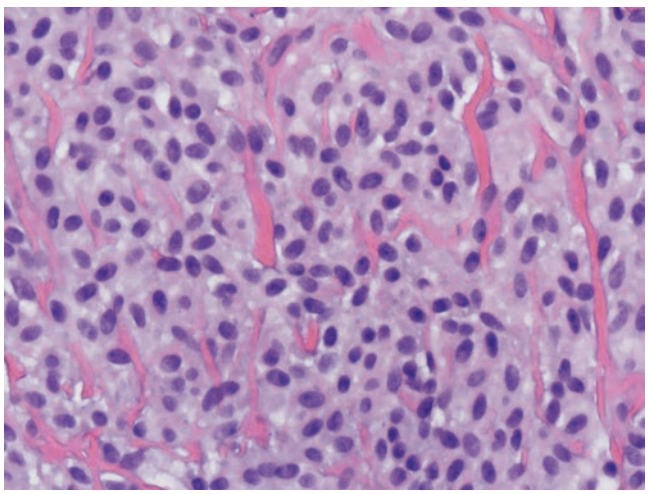

Fig. 22.21 Mast cells in mastocytosis appear as monotonous sheets of cuboidal to slightly spindled cells with amphophilic cytoplasm. There is some resemblance to melanocytic nevus cells, although the nesting pattern in a nevus makes the distinction straightforward

order to provide a "normal" control against which to compare mast cell numbers.

The differential diagnosis of mastocytosis varies with the number of dermal mast cells. In cases with a relatively scant infiltrate, the differential diagnosis includes entities that have a superficial and deep perivascular infiltrate with scattered eosinophils and dermal edema, such as an arthropod bite reaction and a drug eruption. If only minimal dermal infiltrate is present, the basilar hyperpigmentation may raise the differential diagnosis of a lentigo simplex. When it is difficult to identify precisely the nature of the dermal infiltrate, special stains such as Giemsa stain and immunostains for c-Kit (CD117) and mast cell tryptase may be helpful in making these distinctions and resolving the etiology of the cells [73].

In cases with sheets of mast cells infiltrating the dermis, the appearance may resemble an intradermal nevus. The lack of dermal pigmentation, maturation, and a nesting pattern should all help to make the distinction fairly straightforward. Other hematopoietic infiltrates may also enter into the differential diagnosis, but use of special stains and other immunomarker studies should serve to readily distinguish these other entities.

22.8.3 Pathogenesis

Mast cells express c-Kit (CD117), which is a receptor tyrosine kinase that plays a crucial role in mast cell development. It is a transmembrane receptor for stem cell factor (SCF). The interaction between c-Kit and SCF seems to play an essential role in the development of mastocytosis [74, 75]. Most mastocytosis cases are associated with somatic gain of function mutations in the c-Kit gene, resulting in constitutive activation of c-Kit as well as augmented mast cell proliferation and survival [74, 76]. The most common gene mutation is D816V, and it is detected in more than 95 % of adult patients with systemic mastocytosis, and in about one-third of pediatric patients with cutaneous mastocytosis [67, 77]. In addition to c-Kit, activating mutations in N-Ras have been identified in patients with systemic disease. Clonal mast cells in some of these patients harbor both N-Ras and c-Kit mutations [78]. These findings suggest that N-Ras mutations may have the potential to precede c-Kit mutations in clonal development. Since mast cell survival is dependent on c-Kit, it has been proposed that the presence of these two activating mutations may have a greater impact on the expansion of mast cells and disease severity [78].

Other c-Kit-independent pathways may be important in the pathogenesis of mast cell disorder. It has been reported that a subgroup of patients with hypereosinophilic syndrome have FIP1L1/PDGRFA fusion tyrosine kinase, which can be found in mast cells, eosinophils, and other cell lineages [74, 79]. This genetic abnormality is associated with increased mast cells in the bone marrow, and increased tryptase levels and eosinophils in the peripheral blood.

22.9 Cutaneous Leukemias and Lymphomas

22.9.1 Clinical Features

Leukemia cutis is most common in congenital leukemia and acute myelogenous leukemia (AML). The frequency of leukemia cutis is 25–30 % in congenital leukemia and 10–15 % in AML [80, 81]. Skin involvement is very rare in children with lymphoma, although the most common form of cutaneous lymphoma is cutaneous T-cell lymphoma (CTCL). Incidence of CTCL is 0.3 cases per 100,000 per year, and approximately 0.5–5 % of these cases occur in children [82]. Hydroa vacciniforme-like lymphoma that is an Epstein-Barr virus-associated lymphoproliferative disorder that has been primarily described in those of Asian and South American descent [83].

Lesions of leukemia cutis are highly variable. Common presentations include erythematous to violaceous papules, nodules, and plaques occurring anywhere on the head, trunk, and extremities (Fig. 22.22). Most children with CTCL present with erythematous, scaly patches, papules and plaques, often on the trunk and buttocks. The hypopigmented form of CTCL is more common in children than adults [82]. In general, leukemia cutis tends to be associated with a high tumor burden and a relatively poor prognosis.

22.9.2 Histology

The complete work-up of leukemia and lymphoma includes evaluation of bone marrow biopsies and aspirations, and lymph node examination. It is uncommon for the skin to be the only manifestation of these processes. In rare cases, the skin may be the presenting, or even sole evidence of such a disease process [84–88], and exceptionally, the disease may spontaneously regress [84]. Cutaneous manifestations of leukemic or lymphomatous processes are not at all unusual, and pathologists may be asked to evaluate biopsies taken from patients with cutaneous eruptions that manifest such malignant hematopoietic infiltrates.

The histologic features of such infiltrates vary widely and range from scant perivascular to dense cutaneous infiltrates that can be diffuse or nodular [89, 90] (Figs. 22.23 and 22.24). A vasculitic appearance is rarely encountered [91]. The precise classification, when possible, is based upon cytomorphologic characteristics of the infiltrating

Fig. 22.22 Leukemia cutis presents as indurated purpuric plaques on the temple and upper eyelid of a child with known diagnosis of acute myeloid leukemia

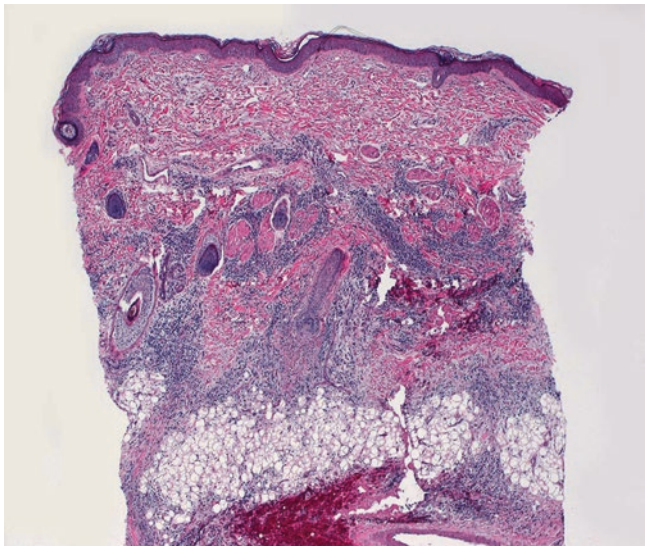

Fig. 22.23 Leukemia cutis demonstrates sheets of markedly atypical hematopoietic cells throughout the dermis

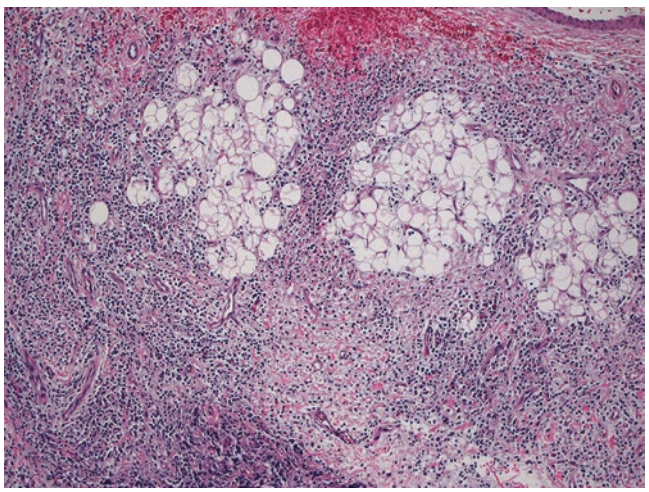

Fig. 22.24 The sheets of atypical hematopoietic cells often extend deep into the subcutis in leukemia cutis

cells interpreted in context with immunologic, cytogenetic, and molecular genetic testing (Fig. 22.25). The subtypes of leukemia and lymphoma that are seen within the skin in children are a direct reflection of the incidence of these diseases within the pediatric population, and these differ markedly from the types of malignant hematopoietic infiltrates that occur in adults [92]. It is beyond the scope of this volume to pursue in great detail the specific histologic features of each type of infiltrate that may be encountered, as comprehensive descriptions are more appropriately addressed in works devoted solely to this category of disease. However, several of the more common subtypes that are seen largely in children will be addressed in some more detail. A leukemic vasculitis is a rarely reported pattern characterized by leukemic cells with transmural vascular wall invasion and destruction [93].

Acute monoblastic leukemia is quite uncommon in adults, but it is one of the more commonly encountered pediatric leukemias, and frequently involves or even presents with cutaneous manifestations [94–96]. A cutaneous eruption is the presenting sign in up to 7 % of the cases [97]. The dermis is filled with an infiltrate of blast cells resembling premature monocytes that demonstrate lineage-appropriate immunostains and characteristic cytogenetic abnormalities. Epidermotropism is not readily apparent, and a grenz zone may be observed. There is often a dense collection of such cells in the dermis surrounding eccrine structures [98].

Acute plasmacytoid dendritic cell leukemia is another neoplasm that is overrepresented in children. Again, the cutaneous infiltrate is one of a diffuse accumulation of large, atypical-appearing lymphoid cells with a characteristic immunophenotypic and cytogenetic profile [99].

The prevalence of lymphomas in children also differs widely from adults. Cutaneous involvement is commensurately different [92]. Acute B-cell lymphoblastic lymphoma demonstrates a proliferation of histologically malignant lymphocytes diffusely throughout the dermis [100–102]. As is the case with all such hematopoietic infiltrates, precise classification requires a constellation of immunostains and cytogenetic studies.

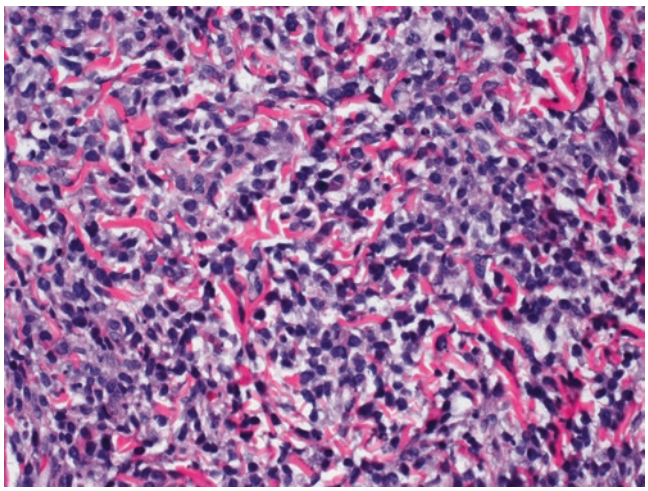

Fig. 22.25 The morphology of immature hematopoietic cells is a function of which type of leukemia is involving the skin. This is a case of a myeloid-based leukemia

Many other types of lymphoma can involve the skin in children, including mycosis fungoides and extranodal marginal zone lymphoma [103]. Mycosis fungoides displays myriad clinical appearances in children including hypopigmented, unilesional, and folliculotropic forms [104–106]. Despite the varied clinical presentations, the histologic features are similar to those seen in the adult population, and include marked epidermotropism, minimal spongiosis, increased size and hyperconvolution of cell nuclei, and papillary dermal fibrosis [105, 107, 108]. The relationship between follicular mucinosis and mycosis fungoides remains controversial, but at least some children with follicular mucinosis develop unequivocal mycosis fungoides based upon clinical course, histologic and immunologic features, and evidence of T-cell clonality [109, 110]. CD30+ lymphoproliferative disorders, including lymphomatoid papulosis, are discussed elsewhere in this chapter. Subcutaneous panniculitis-like T-cell lymphoma only rarely affects children. The histologic appearance is identical to that described in the adult population, and hemophagocytic syndrome can develop in affected children [111].

Epstein-Barr-virus-driven cutaneous lymphomas that resemble hydroa vacciniforme clinically, but have dense dermal lymphoid aggregates have also been described. In some cases, testing for Epstein-Barr virus may be warranted [83, 112]. Epstein-Barr virus has also been associated with cutaneous mature T/NK lymphomas in children, but this association is more prevalent in Central and South America and in Asia [113].

22.9.3 Pathogenesis

It is beyond the scope of this volume to describe in detail the knowledge to date regarding the pathogenesis of the various leukemias and lymphomas. Although data seems to point towards a common mechanism for lymphomagenesis, there is significant etiologic heterogeneity. Statistical analysis suggests carcinogenic roles of infectious agents, such as viruses, including Epstein-Barr virus, human T-cell lymphotropic virus (HTLV-1), Kaposi sarcoma-associated herpesvirus (also known as human herpesvirus 8), and hepatitis C virus (HCV), as well as environmental factors, lifestyle factors, immune modulation, autoimmune conditions, chronic antigen stimulation, and host genetic status [114, 115].

22.10 Waldenstrom's Macroglobulinemia

22.10.1 Clinical Features

Waldenstrom's macroglobulinemia is a B-cell lymphoma of IgM-producing lymphoplasmacytoid cells. It is quite uncommon in children. The cutaneous manifestations are usually secondary to the hyperviscosity associated with the syndrome. Skin findings are often non-specific and include purpura, discoloration of the digits in the hands and feet, and even ulcers. Violaceous macules, nodules and plaques may appear on the face, trunk and extremities, and these contain lymphoplasmacytoid cells.

22.10.2 Histology

Clinically apparent lesions, when biopsied, demonstrate small cutaneous blood vessels filled with thrombi (Fig. 22.26). Less commonly, changes suggestive of leukocytoclastic vasculitis may be seen, and in very rare cases,

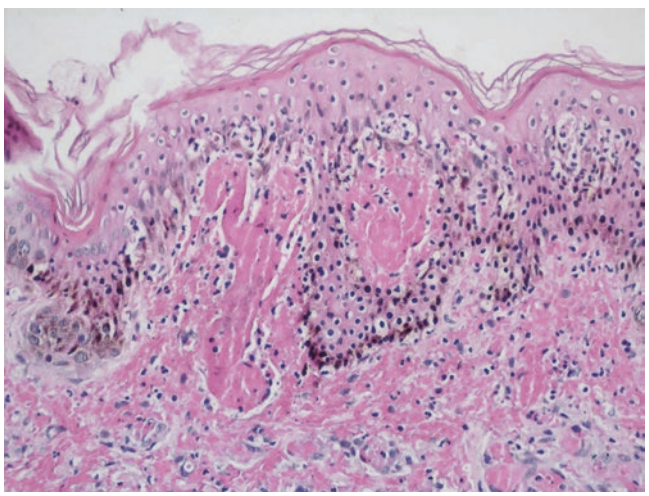

Fig. 22.26 The major histologic finding in the skin in patients with Waldenstrom macroglobulinemia is an obstructive vasculopathy. Small dermal blood vessels are occluded with fibrin thrombi, usually without significant inflammation

circulating abnormal B lymphocytes or plasma cells may be seen around dermal blood vessels [116–118].

22.10.3 Pathogenesis

Waldenstrom's macroglobulinemia is a B-cell neoplasia, in which B cells are arrested between somatic hypermutation and terminal differentiation into plasma cells [119]. Chronic immune stimulation (i.e., chronic infection, autoimmune diseases) and genetic factors are thought to play an important role in the disease development [120]. Whole-genome sequencing showed a somatic mutation in MYD88 gene, leading to a leucine to proline substitution in codon 265 (L265P) in 90 % of patients with the disease [121]. MYD88 is an adaptor molecule in Toll-like receptor (TLR) and interleukin-1 receptor signaling, mediating interleukin-1 receptor-associated kinase 4 (IRAK4) and IRAK1 activation, as well as signaling through nuclear factor κB (NF-κB). Recent studies have shown that the genomic landscape of Waldenstrom's macroglobulinemia is characterized by not only MYD88 mutations but also WHIM-like CXCR4 mutations [122]. Other molecular insights have been found in which inhibition of Akt or PI3K/mTOR pathway displays activity against Waldenstrom macroglobulinemia cells [119]. Waldenstrom's macroglobulinemia also has an overexpression of microRNAs, including hsa-miR-363, hsa-miR-206, hsa-miR-494, hsa-miR-155, hsa-miR-184, and hsa-miR-542-3p [119].

22.11 Lymphomatoid Papulosis

22.11.1 Clinical Features

Most cases of lymphomatoid papulosis occur in adults 40–60 years old, but children are occasionally affected. It appears to be more common in males [123]. Papulonodules and vesiculopustules tend to appear in crops, and favor the trunk and proximal extremities. Some may have hemorrhagic necrotic centers with crusting (Fig. 22.27). They tend to involute spontaneously over a few weeks with residual dyspigmentation, although varioliform scarring is occasionally seen. Most patients will experience spontaneous resolution within months to years, although there have been rare reports of progression to lymphoma.

22.11.2 Histology

Lymphomatoid papulosis is now categorized by the World Health Organization (WHO) as part of the spectrum of CD30+ lymphoproliferative disorders [124, 125]. The histologic manifestations vary somewhat from patient to patient, and there is an increasing number of subtypes described [126]. These distinctions are generally thought to be of minimal prognostic concern. In all cases, the dermis is filled with a superficial and deep infiltrate of lymphocytes, often with small numbers of eosinophils (Figs. 22.28, 22.29, 22.30 and 22.31). This infiltrate is predominantly perivascular, although perifollicular variants have been described and an interstitial infiltrate is commonly encountered as well. The infiltrate has been described as "wedge shaped" by some observers in

Fig. 22.27 Erythematous papules, some of which are eroded with overlying scale, are seen on the extremity in lymphomatoid papulosis (photo courtesy of Irina Margaritescu, MD, Bucharest, Romania)

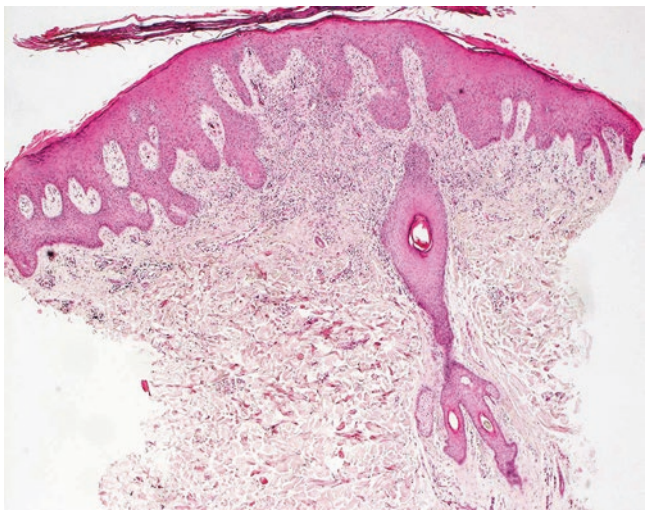

Fig. 22.28 Lymphomatoid papulosis biopsy shows a wedge-shaped infiltrate of lymphocytes with epidermal hyperplasia

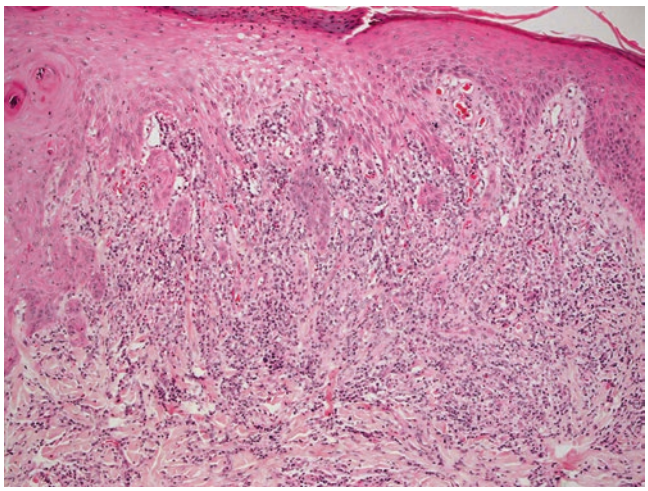

Fig. 22.29 Lymphomatoid papulosis demonstrates a superficial and deep inflammatory infiltrate in the dermis

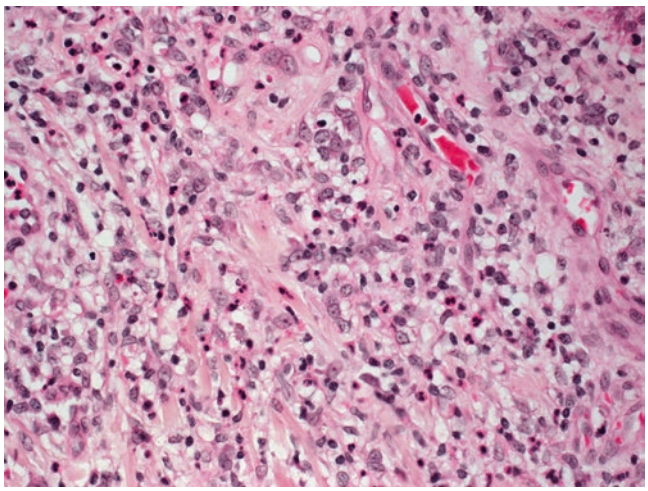

Fig. 22.30 Large atypical lymphocytes are admixed with lymphocytes, eosinophils, and occasional neutrophils in the dermis in lymphomatoid papulosis

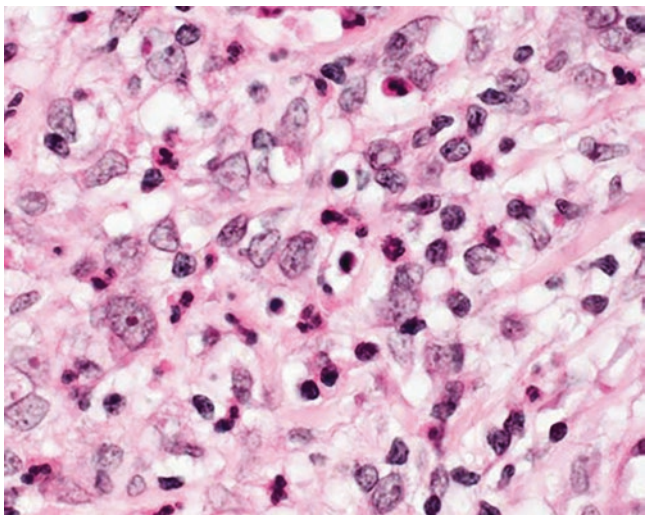

Fig. 22.31 The large atypical lymphocytes are distinctive and readily identified with routine histologic sections in lymphomatoid papulosis

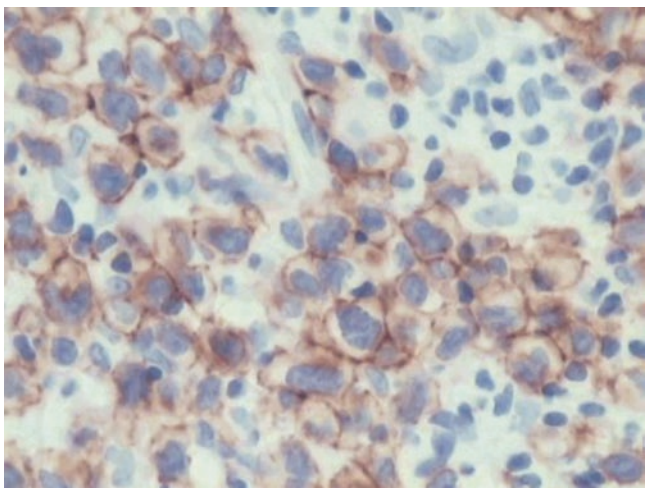

Fig. 22.32 CD30 immunostain labels the atypical cells in most cases of lymphomatoid papulosis

attempting to describe the density of the infiltrate superficially compared to the deep component of the dermis. Extension into the subcutis is not uncommon. Depending upon the particular subtype, varying numbers of enlarged, markedly atypical lymphocytes with abundant cytoplasm, vesicular nuclei, and prominent nucleoli are present (i.e., type A, 20–30 % of cells in the infiltrate; type B, only rare cells; type C, a majority is dermal lymphocytes). In some cases epidermotropism is present either focally or diffusely. It is not uncommon to see perivascular collections of neutrophils, raising the question of focal leukocytoclastic vasculitis; however, in most cases, overt vasculitis is not identified.

The histologic differential diagnosis includes epidermotropic T-cell lymphoma, such as mycosis fungoides, arthropod bite reactions, and pityriasis lichenoides [127, 128]. The presence of markedly atypical cells and a deep component to the dermal infiltrate would be highly unusual in mycosis fungoides and helps to make the distinction. The presence of CD30+ cells is also a useful discriminator in lymphomatoid papulosis (Fig. 22.32). Arthropod bite reactions demonstrate a punctum not seen in lymphomatoid papulosis, but this depends upon sampling, and it may not be present in many biopsies. The presence of eosinophils within the interstitial collagen is fairly characteristic of bite reactions and may help in the distinction. While reactive atypia is seen in some bite reactions, it does not usually attain the level of cytologic atypia demonstrated in the usual case of lymphomatoid papulosis. Furthermore, epidermotropism present in most cases of lymphomatoid papulosis is not a feature of an arthropod bite reaction. The presence of dying keratinocytes is a useful

discriminator of pityriasis lichenoides from lymphomatoid papulosis, although occasional dying cells can also appear in the latter. The cytologic atypia, density, and depth of the dermal infiltrate are all more prominent in lymphomatoid papulosis than in pityriasis lichenoides.

The histologic distinction from primary cutaneous large cell anaplastic lymphoma is often difficult and rendered relatively unimportant by the new WHO classification, which puts lymphomatoid papulosis and this type of cutaneous lymphoma into the same group as a spectrum of a single disease that is differentiated from one another by the number of CD30+ cells and the clinical presentation.

22.11.3 Pathogenesis

The etiology of lymphomatoid papulosis is unknown. It seems to have a loose association with atopy. Many cases of lymphomatoid papulosis have clonal expansion of regulatory T cell population. It has been shown that there is shared monoclonal T-cell receptor gene rearrangement in lymphomatoid papulosis and mycosis fungoides lesions occurring in the same patients, suggesting a clonal origin shared between these two distinct diseases [129, 130].

22.12 Cutaneous Lymphoid Hyperplasia

22.12.1 Clinical Features

Cutaneous lymphoid hyperplasia is rare in children and appears to be common in young adults [114]. Lesions appear as single or multiple papules, nodules, and plaques that can be skin-colored, erythematous, or violaceous. They typically favor the face, ears, and scalp, although other body parts can be affected. Lesions triggered by drug exposure usually improve and resolve within weeks to months after cessation of the offending agent.

22.12.2 Histology

Cutaneous lymphoid hyperplasia is not a diagnosis, but rather, a simple description of a histologic reaction pattern. The cutaneous findings are those of a dense lymphoid infiltrate within the dermis, and in some cases recapitulating lymph node architecture (Figs. 22.33, 22.34, 22.35 and 22.36). A nodular accumulation of lymphocytes is present, admixed with histiocytes and scattered eosinophils and plasma cells in some cases. Formation of germinal centers with surrounding mantle zones is seen in florid cases. The lymphoid aggregates are usually centered in the reticular dermis, but extension into both the papillary dermis and the underlying subcutis is not unusual. Destruction of cutaneous appendages is most unusual, and in most cases, a slight grenz zone is apparent surrounding these structures and beneath the epidermis. The lymphocytes may demonstrate slight degrees of reactive atypia.

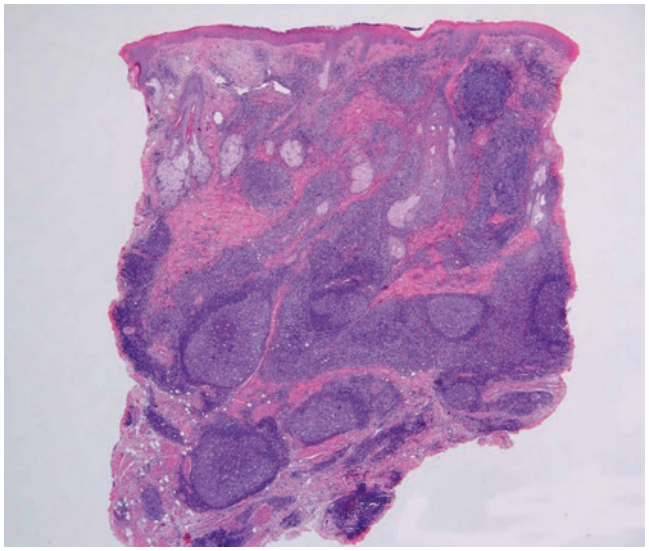

Fig. 22.33 Histologic changes of cutaneous lymphoid hyperplasia include a dense dermal infiltrate of lymphocytes. In florid cases, prominent germinal centers are apparent at low magnification. The epidermis is usually uninvolved by these infiltrates

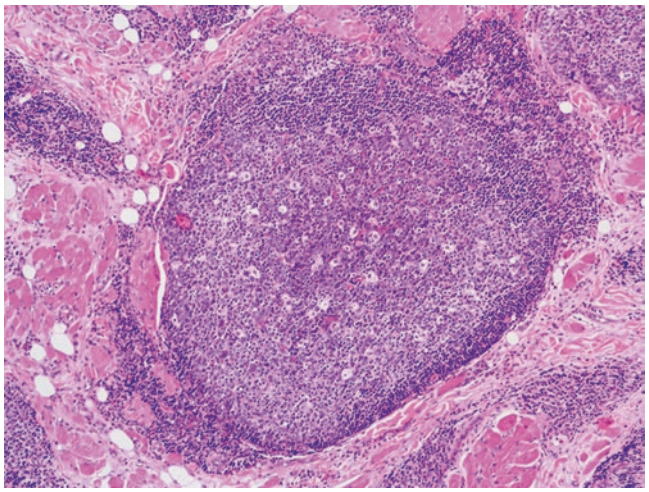

Fig. 22.34 Germinal centers with tangible body macrophages recapitulate lymph node architecture in cutaneous lymphoid hyperplasia

The histologic differential diagnosis includes cutaneous lymphoma, Jessner's lymphocytic infiltrate, and dermal hypersensitivity reactions. The distinction can be made based upon the presence of tingible body macrophages within germinal centers pointing toward a benign process, the presence of eosinophils within the reactive infiltrates, and the heterogeneity in the lymphocyte morphology. Jessner's lymphocytic infiltrate is a poorly defined entity about which there is little to

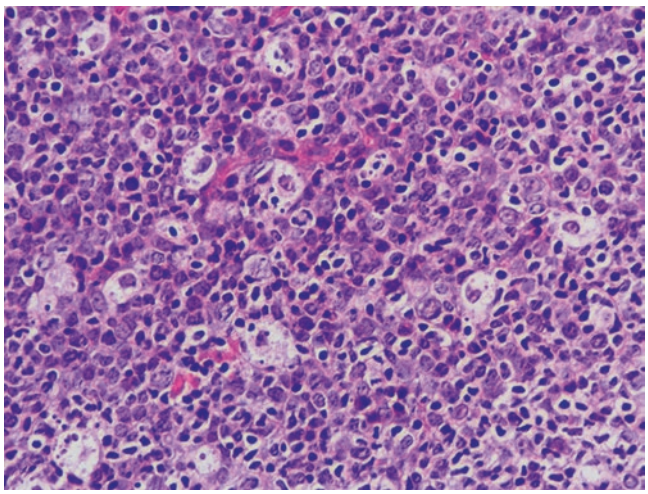

Fig. 22.35 Prominent tingible body macrophages help to differentiate reactive germinal centers from neoplastic lymphoid follicles in cutaneous lymphoid hyperplasia

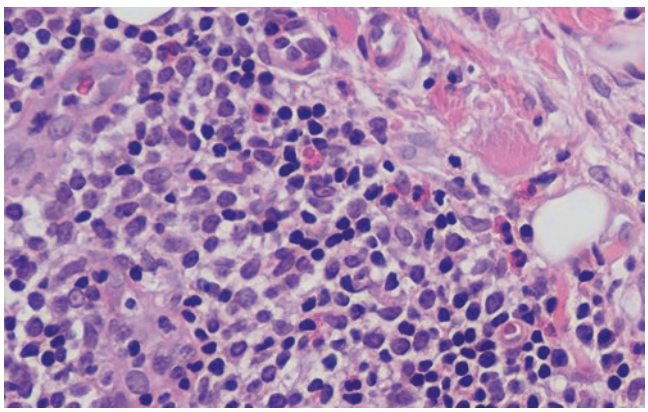

Fig. 22.36 The presence of admixed eosinophils is additional evidence in favor of cutaneous lymphoid hyperplasia over lymphoma

no consensus [131, 132]. The presence of eosinophils and germinal centers would be unusual in this entity. The distinction between a dermal hypersensitivity reaction and cutaneous lymphoid hyperplasia is one of semantics in that they are both reactive processes and differ mainly in the degree of dermal cellularity, with cutaneous lymphoid hyperplasia being the most florid extent of the hypersensitivity reaction pattern.

22.12.3 Pathogenesis

Although the pathogenesis of cutaneous lymphoid hyperplasia is unknown, it is believed to be the result of chronic antigenic stimulation. Some hypothesize that cutaneous lymphoid hyperplasia could be a pathogenic manifestation of acquired B-cell skin-associated lymphoid tissue, resulting from a variety of known or unknown stimuli. Continued antigenic stimulation could potentially result in progression to lymphoma, similar to the development of lymphoma in the stomach from chronic *Helicobacter pylori* infection [133]. Possible inciting stimuli include an arthropod assault, drug reaction, tattoo, vaccination, and infection, such as chronic *Borrelia burgdorferi* skin infection [114]. In most cases, there is no identifiable cause.

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Keratinous Cysts and Hamartomas

23

23.1 Apocrine Cystadenoma

23.1.1 Clinical Features

Apocrine cystadenoma is a rare apocrine tumor that can present in children [1, 2]. It has been described as a bluish to skin-colored cystic nodule most often occurring on the head or neck and sometimes on the trunk. The tumor is amenable to surgical excision [1].

23.1.2 Histology

Histologic sections demonstrate skin with a cystic proliferation within the dermis. Two types of cells are seen in the cyst lining. Eosinophilic cuboidal cells with decapitation secretion are seen emptying into the lumen. Another layer of myoepithelial cells is present in most cases [3]. This lining demonstrates papillary infoldings into the luminal cavity with true fibrous papillary cores within the papillae. Mitotic activity is present, but cytologic atypia is not seen [2, 4]. Mucinous metaplasia of closely apposed eccrine ducts has been reported. The relationship between the eccrine structures and this neoplasm is not apparent [1].

23.2 Eccrine/Apocrine Hidrocystoma

23.2.1 Clinical Features

Multiple hidrocystomas most often occur in middle-aged to elderly females, while solitary lesions are seen with equal frequency in males and females [5]. Although uncommon, hidrocystoma has been reported in children. Hidrocystomas are characterized by shiny, skin-colored to slightly bluish cystic nodules and smaller papulonodules on the face [5, 6].

With special contributions from Haider Mejbel, MD, Baylor College of Medicine.

Apocrine hidrocystomas typically are solitary, occurring along the eyelid, while eccrine hidrocystomas are more commonly multifocal and may enlarge with heat exposure [5, 6]. Hidrocystomas are benign with no known reports of malignant transformation.

23.2.2 Histology

Biopsy of hidrocystoma demonstrates a dermal cystic cavity lined by two thin layers of cuboidal epithelium that resemble eccrine ductular epithelium (Fig. 23.1). Features of apocrine glandular epithelium are not present. Eosinophilic eccrine secretions are found in a minority of cases. In some cases, the cyst is lined by cells with apocrine differentiation (Figs. 23.2 and 23.3).

23.2.3 Pathogenesis

Eccrine hidrocystoma is a cyst of eccrine sweat ducts. A possible factor in hidrocystoma formation is duct obstruction due to increased sweat production [7]. Interestingly, botulinum toxin A, which denervates the sweat glands and reduces sweating, has been used effectively in the treatment of eccrine hidrocystoma [8], thus implicating a role for enervation and sweat production in its formation.

23.3 Branchial Cleft Cyst

23.3.1 Clinical Features

Branchial cleft cysts are an uncommon anomaly of the branchial apparatus, most frequently the second arch [9]. They usually present in the second or third decade of life. Branchial cleft cysts are soft, skin-colored nodules along the lateral aspect of the neck at the anterior border of the sternocleidomastoid muscle. Lesions slowly increase

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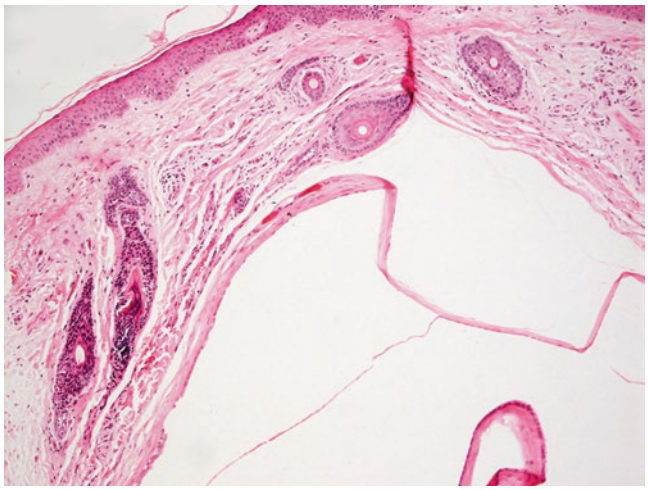

Fig. 23.1 Eccrine hidrocystoma demonstrates a thin-walled cystic structure lined by a flattened epithelium

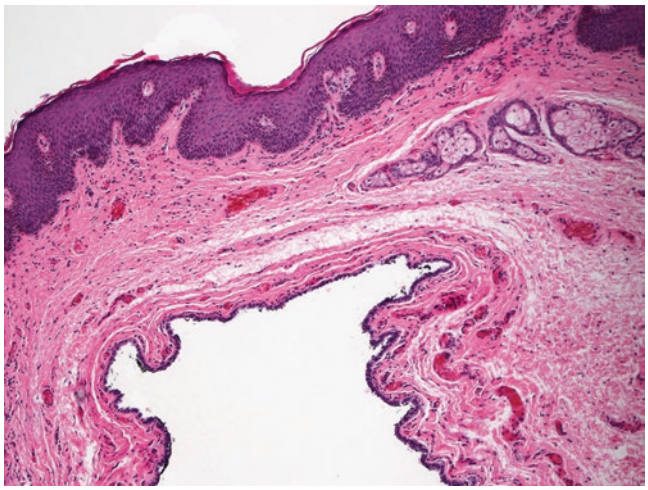

Fig. 23.2 Apocrine hidrocystoma is a cystic structure in the superficial reticular dermis that is lined by apocrine-type epithelium

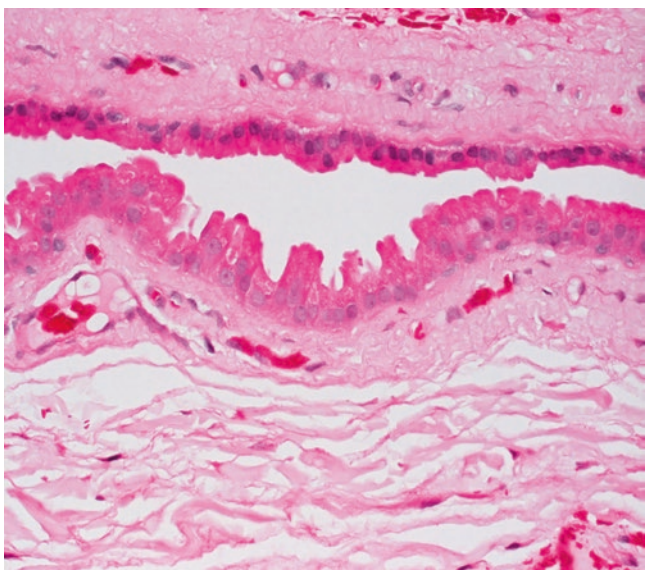

Fig. 23.3 Hobnailing of the luminal epithelium with brightly eosinophilic cytoplasm is seen in apocrine hidrocystoma

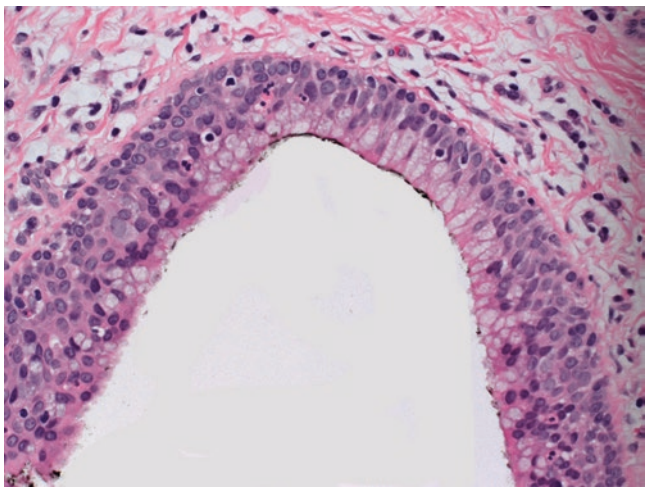

Fig. 23.4 Respiratory-type columnar and ciliated epithelium lines a cystic space and is surrounded by lymphocytes in a branchial cleft cyst

in size over time, and may become red and tender following infection or rupture [9]. As the cysts are at risk for infection, surgical excision is recommended once lesions are found.

23.3.2 Histology

Branchial cleft cysts arise from one of four branchial clefts, and demonstrate variable histologic changes depending upon the site from which they arise [10, 11]. The epithelial cyst lining may be either squamous or columnar with ciliated respiratory epithelium (Fig. 23.4). Some cases demonstrate both types of lining [10]. Cutaneous appendages may be present in some cases [11]. The constant feature is a dense lymphoid infiltrate that extends into the lining epithelium regardless of cell type. Prominent germinal centers can be observed. Mucous glands and cartilage are variably present. Older lesions may have fibrosis and granulation tissue consistent with prior rupture and inflammation.

23.3.3 Pathogenesis

The origin of branchial cyst is not known. Some authors have proposed that the origin of a branchial cleft could depend on the anatomic location. Cysts in the upper neck region could develop from salivary gland inclusions in parotid lymph nodes, or from epithelial remnants of the upper portion of the branchial apparatus [12]. Cysts in the mid-neck region could develop from epithelial remnants of the cervical sinus or the branchial pharyngeal pouches. Cysts in the lower neck area could develop from remnants of the thymic duct or from the lower portions of the branchial apparatus.

23.4 Bronchogenic Cyst

23.4.1 Clinical Features

The exact incidence of bronchogenic cyst is not known. Boys appear to be more commonly affected than girls. There is no reported racial predilection [13, 14]. Bronchogenic cyst presents as a solitary subcutaneous nodule, and it can have associated fistula or verrucous change. Lesions are commonly located at the presternal notch, followed by the neck and scapula. Limited data exists on long-term prognosis as many of the cysts are excised in childhood. Recurrence may occur with incomplete excision.

23.4.2 Histology

Histologic findings of bronchogenic cyst include a cystic structure lined by cuboidal or columnar epithelium that may be pseudostratified and ciliated [15] (Figs. 23.5, 23.6 and 23.7). Surrounding the epithelium are concentric smooth muscle bundles and fibrous tissue. Cartilage may be present in some cases, and mucous glands are sometimes encountered [16]. In rare cases, the presentation may be that of a polypoid lesion or a nodule [17, 18]. Branchial cleft cysts demonstrate a brisk lymphoid infiltrate within the cyst wall, which is a distinguishing feature not seen in bronchogenic cysts.

23.4.3 Pathogenesis

Bronchogenic cyst is a type of bronchopulmonary malformation. It has been proposed that the cyst results from a developmental error in the budding of the foregut [19, 20]. The primitive foregut is the origin of the respiratory tract and esophagus. Abnormal budding of the tracheal primordial may lead to the formation of the cyst. Bronchogenic cyst in children has been found in unusual anatomic locations, such as the scapula, and has been attributed to heterotopia and metaplasia of the growth of respiratory epithelium in the skin [21].

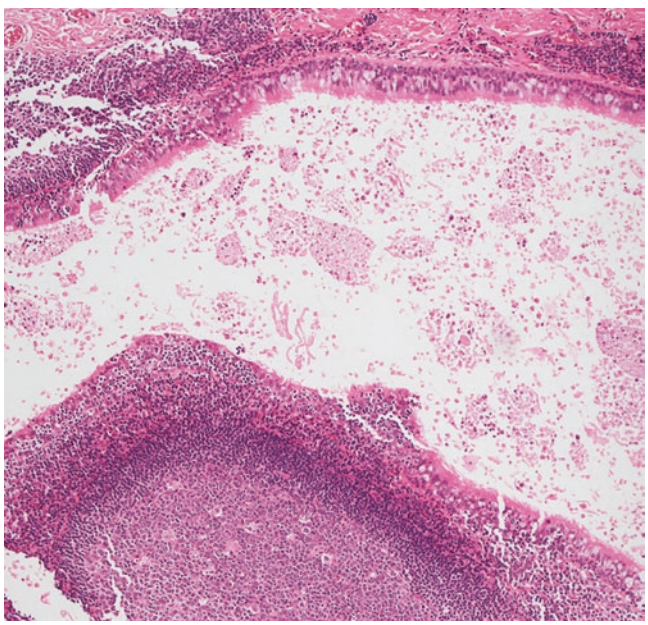

Fig. 23.5 Respiratory-type columnar epithelium lines a cystic cavity in bronchogenic cyst

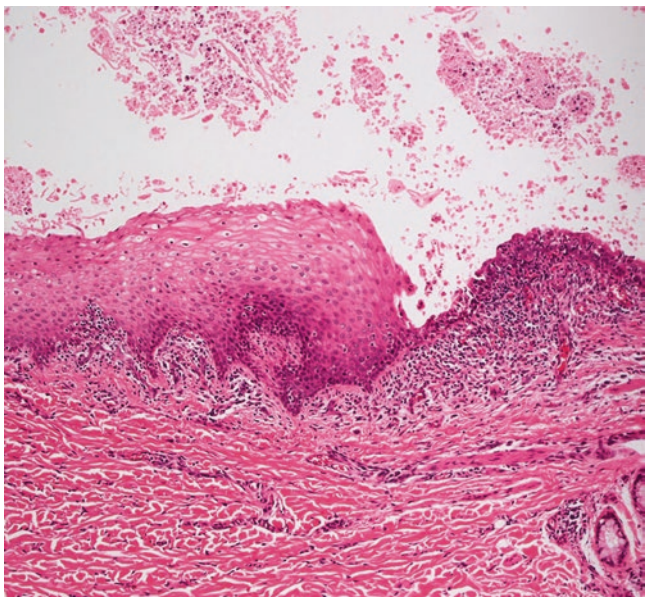

Fig. 23.6 In some bronchogenic cysts, both columnar and squamous epithelium can be seen in the lining epithelium

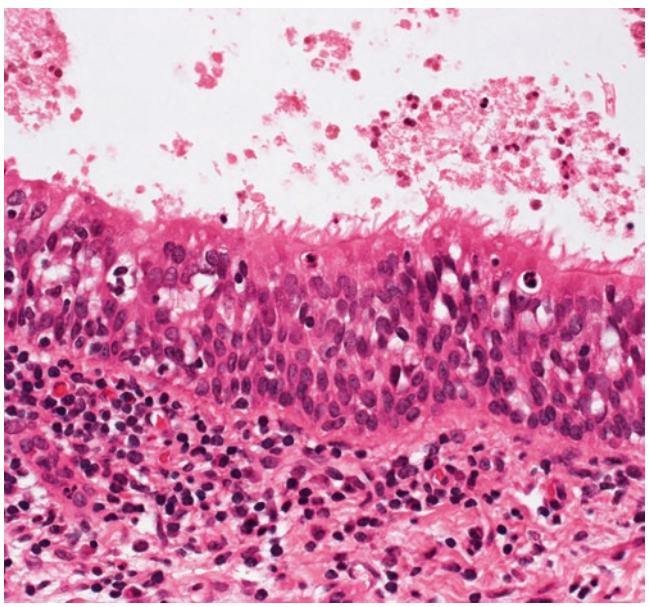

Fig. 23.7 Ciliated epithelium lines some bronchogenic cysts

23.5 Thyroglossal Duct Cyst

23.5.1 Clinical Features

Thyroglossal duct cysts are the most common congenital cyst of the neck [9]. They may be located anywhere along the tract between the posterior tongue and the superficial anterior neck. The cyst presents as a slowly expanding, mobile midline nodule that moves with swallowing secondary to its attachment to the hyoid bone.

Patients with thyroglossal duct cysts may be at risk for development of papillary thyroid carcinoma in adulthood, although this is rare [9]. Cysts are also at risk for infection and rupture with subsequent inflammation. Because of this potential for complications, surgical excision is encouraged.

23.5.2 Histology

Biopsy of thyroglossal duct cyst demonstrates a fibrous tract lined by stratified squamous or pseudostratified ciliated columnar or cuboidal epithelium, depending upon the anatomic relationship with the hyoid bone [22] (Fig. 23.8). Within the cyst wall, ectopic thyroid tissue can be identified (Fig. 23.9). In some cases, this tissue may function and lead to clinical symptoms. Most cases display a dense lymphoid infiltrate, and mucus glands may be present in some cases. Fine needle aspiration biopsy yields an accurate diagnosis in most cases, demonstrating thyroidal colloid, macrophages, and neutrophils [23]. It is unusual to identify the lining epithelium with this technique, and most authors do not recommend fine needle aspiration for establishing a diagnosis [23, 24]. Rare malignant transformation has been reported in thyroid tissue [25, 26].

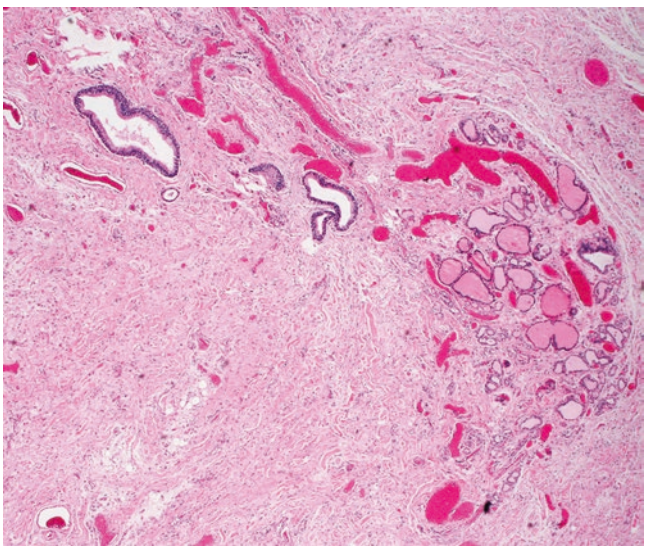

Fig. 23.8 Thyroid ducts and glands are present within the dermis in a thyroglossal duct cyst

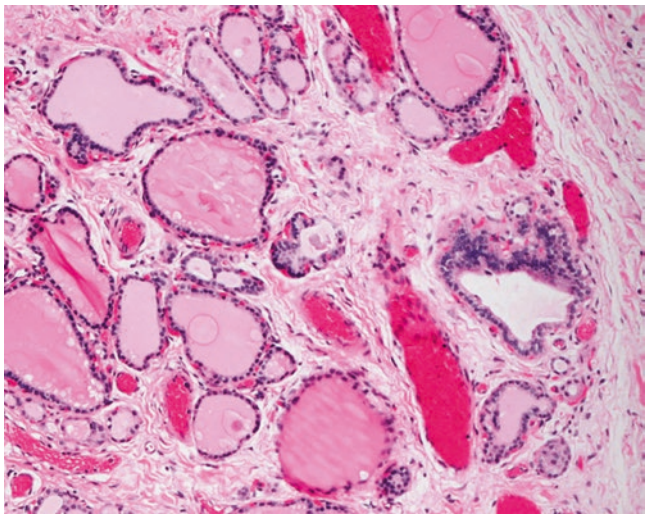

Fig. 23.9 Thyroid glands with colloid material are seen within the well-formed glandular structures in a thyroglossal duct cyst

23.5.3 Pathogenesis

During embryogenesis, the median thyroid anlage elongates proximal to the descending gland, forming the thyroglossal duct. This duct generally obliterates by week 5 of gestation. However, failure of the thyroglossal duct to obliterate before the formation of the mesodermal anlage of the hyoid bone results in its persistence during development [27]. Other studies suggest that proliferation of remnants of the thyroid gland and the thyroglossal tract may be stimulated by inflammatory processes, and inflammatory reaction to infection during childhood may stimulate epithelial remnants of the thyroglossal tract to undergo cystic changes [28].

23.6 Dermoid Cyst

23.6.1 Clinical Features

Dermoid cysts are congenital anomalies occurring over embryonic fusion lines. They may slowly expand over time, leading to delayed appearance and subsequent diagnosis [29]. Dermoid cysts present as non-translucent, mobile subcutaneous, blue or skin-colored nodules. They are frequently seen on the orbital ridge along the lateral eyebrow. Approximately 3 % of lesions are located at the nasal midline, with an increased risk for deep extension and central nervous system (CNS) involvement [9]. Associated dimple, ostia, or hair tuft increases the likelihood of intracranial extension or associated CNS malformation.

Dermoid cysts are at risk for infection and when they have CNS communication, place the patient at risk for meningitis and/or abscess formation, thus necessitating surgical exci-

sion. Lesions along the lateral eyebrow do not communicate with the CNS so imaging studies are not required [9, 29].

23.6.2 Histology

Being true epidermal inclusions cysts, dermoid cysts contain all epidermal components. Within the mid-reticular dermis, a cystic cavity that is often filled with keratin is apparent. The cyst wall is lined by stratified squamous epithelium, complete with a granular layer. Pilosebaceous units emanate from the cyst lining into the surrounding dermis (Figs. 23.10 and 23.11).

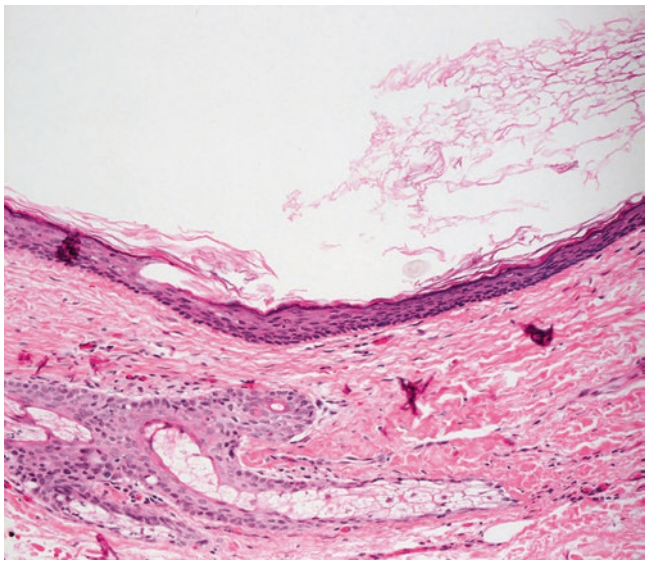

Fig. 23.10 A dermoid cyst demonstrates squamous epithelium, keratinaceous cyst contents, and cutaneous appendages in the wall of the cyst

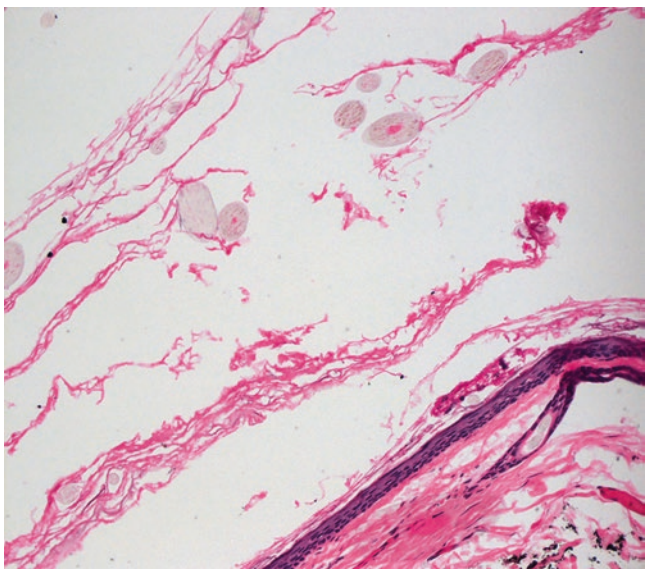

Fig. 23.11 Vellus hairs, squamous epithelial lining, and cutaneous appendages in the cyst wall are seen in dermoid cysts

Apocrine and eccrine ducts are present, and smooth muscle bundles are seen in a minority of cases. In some dermoid cysts occurring close to the eyes, conjunctival type mucosa with goblet cells have been reported in the cyst lining [30]. When the cysts have been traumatized, a granulomatous foreign body giant cell reaction may ensue [31]. Late lesions may flatten and only dense fibrosis is apparent in senescent lesions [32].

The differential diagnosis may include a follicular cyst of the infundibular type, also called epidermal inclusion cyst. Since this name is a misnomer, cutaneous appendages are not present within the cyst lining in these cysts. The cyst lining cells are derived from dilatation of follicular units at the level of the follicular infundibulum.

23.6.3 Pathogenesis

Cutaneous dermoid cyst is a type of congenital cyst that is derived from the ectoderm and mesoderm. It is formed from epithelial rests found along embryonic fusion lines and contains cutaneous structures such as keratinizing squamous epithelium and hair follicles [33].

23.7 Follicular Cyst

23.7.1 Clinical Features

Follicular cysts most commonly occur in young and middle-aged adults, and rarely occur in childhood [34]. Multiple lesions may be seen as a clinical feature of Gardner syndrome, especially with generalized distribution at the face, scalp, trunk, and extremities. Follicular cysts are characterized as 1–2 cm subcutaneous dome-shaped nodules with an overlying punctum. The overlying skin may be red and tender when inflamed.

Vellus hair cysts are more common in children. Eruptive vellus hair cysts appear as multiple small folliculocentric cysts on the trunk (Fig. 23.12). Solitary lesions are amenable to excision. When cysts are inflamed, incision and drainage or treatment with oral antibiotics may be required.

Pilar cysts are far less common than follicular cysts. They occur most frequently in middle-aged women [34]. Pilar cysts typically present as skin-colored, slightly mobile, smooth and firm subcutaneous nodules without an overlying punctum. The great majority of pilar cysts occur at the scalp [34]. Solitary lesions exist but they are frequently multiple. If desired, lesions can be removed surgically often without rupture.

23.7.2 Histology

There are several types of follicular cysts that arise from different portions of the hair follicle. The most common, fre-

Fig. 23.12 Eruptive vellus hair cysts present as multiple brown, hyperpigmented 1–2 mm folliculocentric papules on the central trunk

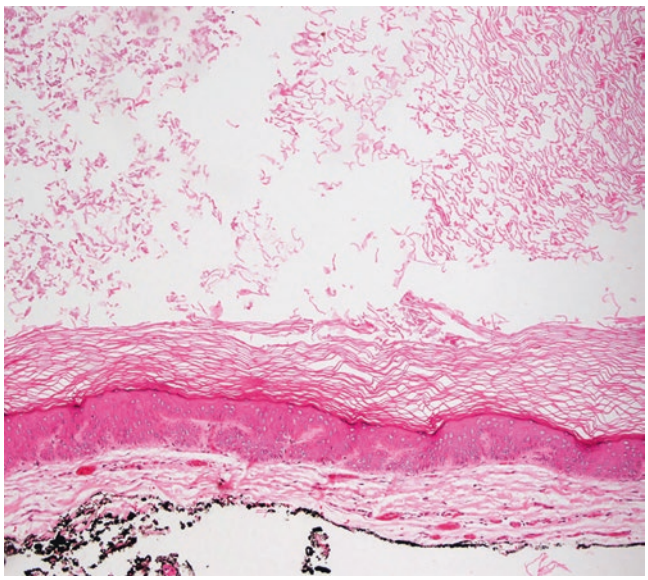

Fig. 23.13 A follicular cyst is filled with wispy orthokeratotic keratin and lined by epidermis that has a granular layer

quently misnamed as an epidermal inclusion cyst or a sebaceous cyst, arises from the infundibular portion of the hair follicle (Fig. 23.13). Keratinizing epithelium that has a granular layer with prominent keratohyalin granules forms the cyst lining. The cyst wall typically lacks rete ridge formation, and dermal appendages do not emanate from it. The lack of appendages distinguishes this from a dermoid cyst, which is truly an invagination or inclusion cyst of the epidermis. The cystic cavity is filled with wispy keratin that resembles normal stratum corneum.

Fig. 23.14 A pilar cyst is lined by squamous epithelium that lacks a granular layer and is filled with dense, compact orthokeratotic keratin

Another type of follicular cyst is a pilar or isthmus-catagen cyst. These cystic dilatations arise from the isthmus portion of the hair follicle and, as such, are lined by stratified squamous epithelium that lacks a granular layer. There is abrupt keratinization, and the cyst cavity is filled with densely packed and hyper-eosinophilic keratin (Fig. 23.14). The cyst epithelium can proliferate, resulting in heaping up of the epidermis. Mitotic activity is readily apparent in these situations, and there can be some cytologic atypia. Proliferating pilar tumors may give rise to the differential diagnosis of squamous cell carcinoma, although they do not grow down from the surface epithelium. In addition, they are well circumscribed and not invasive. Squamous cell carcinoma would be most uncommon in this setting in the pediatric age group.

Vellus hair cysts are simple cysts lined by stratified squamous epithelium with a granular layer. The cystic space is filled with wispy stratum corneum-like keratin, and many small vellus hairs are present (Fig. 23.15).

Hybrid cysts with features of more than one of the aforementioned cyst types have been described. These cysts may also demonstrate features of pilomatricoma or trichilemmoma and may have apocrine features [35–37].

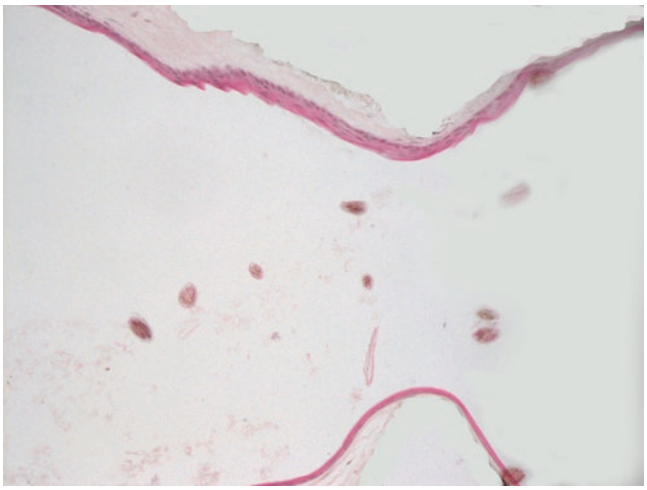

Fig. 23.15 A vellus hair cyst is lined by squamous epithelium and contains wispy keratin and abundant vellus hairs

23.8 Human Papillomavirus-Related Cyst

23.8.1 Clinical Features

The incidence of human papillomavirus (HPV)-related cysts is unknown, and reports in the literature are few, suggesting that this is a rare phenomenon. Lesions are primarily described in adults, although there are cases in older adolescents [38]. Lesions frequently are reported to follow trauma. There is no reported gender or racial predilection. HPV-related cysts, located on acral sites, are skin-colored subcutaneous cystic nodules without overlying verrucous change that mimic the appearance of an epidermoid cyst [39].

23.8.2 Histology

Biopsy changes include cystic structures occurring primarily on acral skin. The cystic lining consists of keratinocytes with foci of hypergranulosis and overlying parakeratosis within the cystic cavities. Papillomatous processes extend into the luminal cavity, and vacuolated keratinocytes are present at the tips of the projections. Keratinocytes in the cells demonstrate marked hyperkeratosis [40]. Amorphous eosinophilic cytoplasmic inclusions appear within keratinocytes in the uppermost layers of the cyst lining cells [41]. The so-called ridged warts demonstrate similar histologic changes, although without the cyst formation and similar cytoplasmic viral inclusions [39].

In situ hybridization demonstrates the presence of HPV inclusions within the cytoplasm of the cyst-lining cells and also within adjacent eccrine structures [39, 41]. Similar viral inclusions have been found in lesions arising on non-acral skin [38, 42].

23.8.3 Pathogenesis

HPV-related cysts have been postulated to develop from eccrine ducts and are commonly associated with HPV-60 and sometimes HPV-57 subtypes [43–45]. It has been proposed that HPV initially infects the upper part of the eccrine duct and then migrates into the dermal portions of the eccrine duct, where virus-associated cysts develop [39]. Other studies have suggested that a combination of ultraviolet light exposure and HPV infection is a risk factor for the formation of cysts [39, 46].

23.9 Median Raphe Cyst

23.9.1 Clinical Features

Patients with median raphe cyst typically present in the second or third decade of life, although pediatric cases exist [47]. Median raphe cyst can occur anywhere between the urinary meatus and the anus. It most commonly presents as an asymptomatic, skin-colored to bluish subcutaneous nodule along the ventral aspect of the penis, near the glans penis [47]. Following persistent friction or trauma, the lesion may become inflamed with secondary infection. Surgical excision is the treatment of choice and is curative.

23.9.2 Histology

Histologic findings of median raphe cyst are those of a cystic structure within the mid-reticular dermis lined by pseudostratified columnar epithelium (Figs. 23.16 and 23.17) [47–49]. Some of the lining cells may be ciliated, columnar, or squamatized [50–52]. Mucinous cells are present in a minority of cases [48]. Rare cases are described in which abundant melanocytes are present within the cyst lining, giving the cyst a pigmented appearance [53, 54].

23.9.3 Pathogenesis

Median raphe cyst is thought to be an embryologic developmental defect of the male genitalia. It has been proposed that the cyst represents embryologic split-off outgrowths of the epithelium after primary closure of the urethral or genital folds.

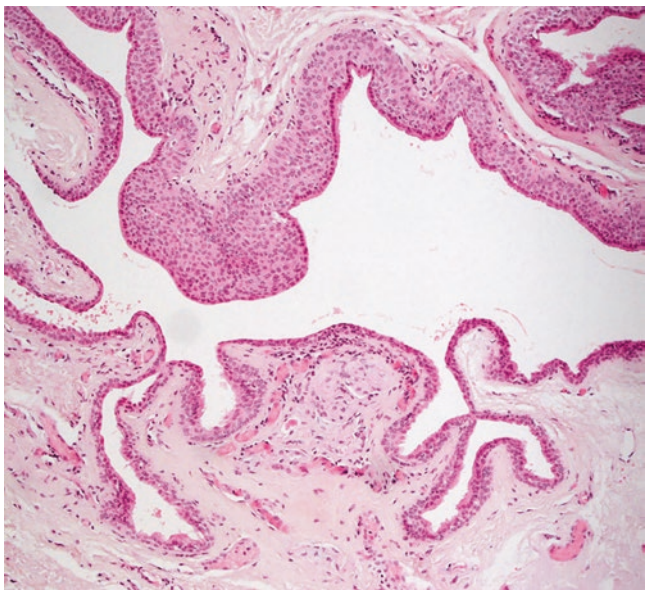

Fig. 23.16 There are two or more layers of cells lining a cystic cavity in a median raphe cyst

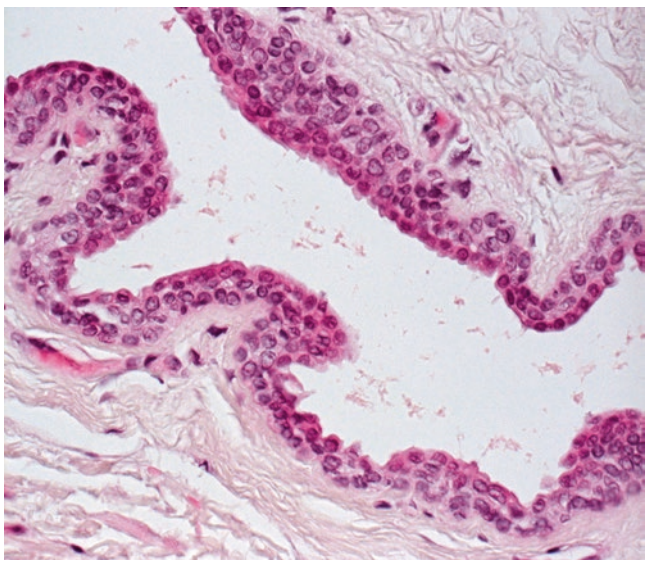

Fig. 23.17 The luminal cells demonstrate a hobnail pattern of growth into the lumen in a median raphe cyst

Others suggest that median raphe cyst arises from epithelial rests incidental to incomplete closure of the folds [55, 56].

23.10 Cutaneous Ciliated Cyst

23.10.1 Clinical Features

Cutaneous ciliated cyst is an uncommon growth that frequently appears in postpubertal girls. It is an asymptomatic, soft, skin colored, cystic mass, most often occurring on the lower extremity [57]. The lesion is benign and amenable to simple surgical excision [57].

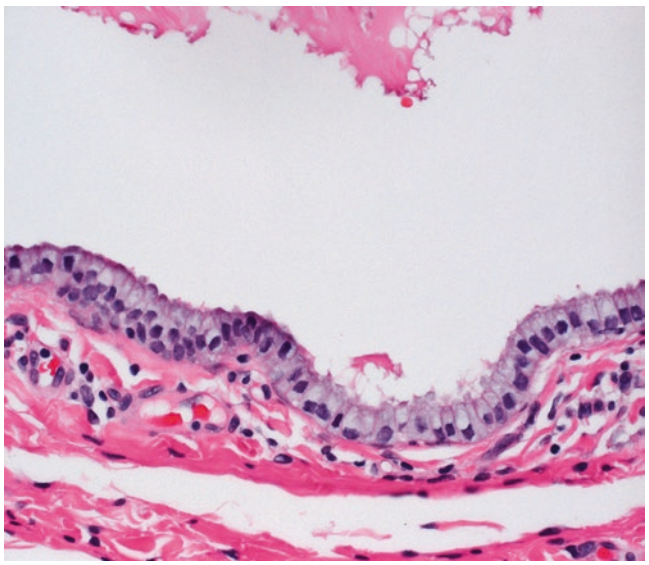

Fig. 23.18 A cutaneous ciliated cyst is lined by columnar epithelium with delicate cilia extending into the cystic cavity

23.10.2 Histology

While cutaneous ciliated cysts are much more predominant in young girls, they have also been described in boys and men, and are thought to be of Mullerian origin [58, 59]. Histologic findings demonstrate a dermal-based cyst lined by ciliated cuboidal or columnar cells (Fig. 23.18). Squamous metaplasia, apocrine change, and cells producing mucin have been described in these lesions, but they are not common findings [60, 61].

Positive immunohistochemical staining with antibodies against PAX-8, progesterone receptors and epithelial membrane antigen as well as lack of staining for carcinoembryonic antigen suggests that despite the anatomic proximity to eccrine structures in some cases, these cyst are not derived from eccrine ducts or glands [57, 62–64].

23.10.3 Pathogenesis

It has been proposed that cutaneous ciliated cyst in females is a result of heterotopia and sequestration of Mullerian tissue [65]. Supporting evidence for this theory includes the predilection of cyst for the lower extremities, and its resemblance to fallopian tube tissue histologically. Cutaneous ciliated cyst also expresses molecular markers similar to the

fallopian tube in terms of estrogen, progesterone, and PAX-8 expression [66–68].

23.11 Steatocystoma

23.11.1 Clinical Features

Steatocystomas commonly occur in adolescence, during and following puberty. Solitary lesions present at birth and in early infancy have been reported as well [69]. Steatocystoma multiplex is a rare autosomal dominant disorder with high penetrance, and is characterized by multiple steatocystomas [69, 70].

Steatocystomas present as 0.5–2 cm, skin-colored to yellowish subcutaneous cystic nodules, primarily localized to the chest, although they may sometimes appear on the face, genitals, arms and thighs (Fig. 23.19) [70]. Widespread involvement may occur with palmoplantar sparing. Lesions express an oily material when punctured. Patients may also have eruptive vellus hair cysts, most notably in the setting of pachyonychia congenita. Lesions are rarely symptomatic, but may be surgically excised or incised and drained.

23.11.2 Histology

Histologic changes of steatocystomas are identical regardless of whether the lesions are single (simplex) or multiple (multiplex). Growing down from the dermis with or without obvious connection is a cystic structure lined by a thick, refractile eosinophilic cuticle (Fig. 23.20). The remainder of the cyst wall consists of stratified squamous cells lacking a granular layer [71, 72]. In many cases, small sebaceous glands can be identified. Smooth muscle may be present in the wall of the cyst [71]. The cystic dilatation is believed to emanate from the junction at the insertion of the sebaceous duct into the follicular epithelium [69]. The diagnosis can be rendered with a high degree of certainty based solely on the lining cuticle and in the absence of readily identifiable sebaceous structures. The so-called hybrid cysts demonstrate features of steatocystoma adjacent to features of vellus hair cysts, and coexistence of both types of cysts has been described in some patients [73–76]. Diagnosis can be made on fine needle aspiration cytology specimens, but this is not the usual manner for establishing the diagnosis [77]. The presence of multiple steatocystomas has been associated with pachyonychia congenita. There are no differentiating characteristics based upon histologic presentation between sporadic lesions and those associated with the pachyonychia congenita [78, 79].

Fig. 23.19 Steatocystoma presents as a subcutaneous nodule without overlying skin changes at the axilla in an adolescent girl

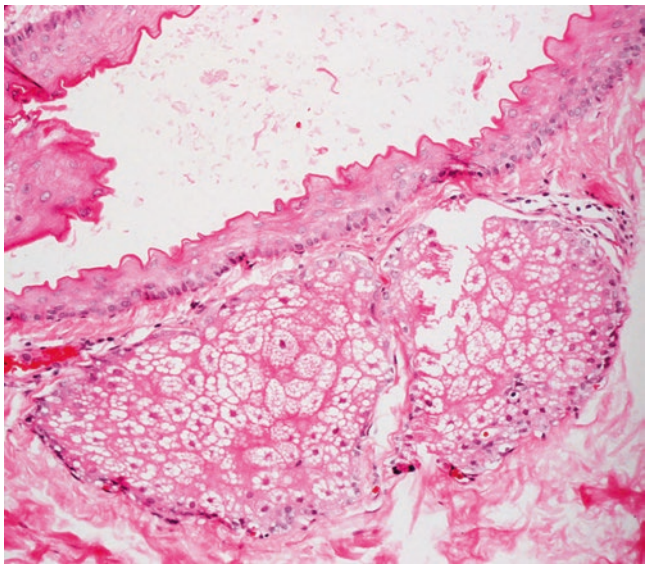

Fig. 23.20 Steatocystoma is characterized by epithelial lining with an eosinophilic cuticle and contains sebaceous glands within the cyst wall in some cases

23.11.3 Pathogenesis

Steatocystoma multiplex is a condition in which multiple steatocystomas are present. It has an autosomal dominant inheritance pattern [70]. However, numerous sporadic cases with no apparent genetic association have been reported. Mutations in the keratin-17 (K17) gene have been found in familial cases [80, 81]. Sporadic forms of the disease do not show associated K17 gene mutations. Keratin-17 is a type I keratin present in cutaneous appendages, such as the nail bed, hair follicles, and sebaceous glands. Steatocystoma multiplex has been found to be associated with pachyonychia congenita type II, and the same mutations in K17 have been

described in both disorders, leading to the hypothesis that steatocystoma multiplex is a limited form of pachyonychia congenita type II [81].

23.12 Pilonidal Sinus

23.12.1 Clinical Features

Pilonidal sinus disease most often occurs in young men between 15 and 24 years of age [82]. It can occur in any ethnicity or race, but it is uncommonly seen in Asians and most frequently reported in hirsute Caucasians [83]. Pilonidal sinus disease is characterized by painful, intermittent swelling, erythema, and purulent draining of the superior gluteal cleft or sacrococcygeal area of the back [84]. The condition frequently is associated with an underlying cyst or sinus tract. Lesions often require surgical management [82].

23.12.2 Histology

The histologic changes seen in a pilonidal sinus are not specific. An epithelial-lined sinus tract is present, and in most cases appears ulcerated and inflamed. Isolated hair shafts may be observed within the sinus tract or in the adjacent dermis. Within the surrounding dermis, there is a dense inflammatory infiltrate that is diffuse and variable. In acutely inflamed cases, there is a brisk neutrophilic infiltrate, and eosinophils may be present. In less acute situations, a lymphohistiocytic infiltrate may be observed. In many cases, a granulomatous response is present with abundant multinucleated giant cells and mononuclear histiocytes. In these situations, keratinaceous debris is present within the giant cells.

23.13 Apocrine Nevus

23.13.1 Clinical Features

Apocrine nevi are uncommon benign tumors that may be congenital or acquired and appear as late as adulthood [85]. They are well-circumscribed, skin-colored nodules or pedunculated masses, ranging in size from 2 to 8 cm [86]. Lesions most commonly present at the axillae but can also occur on the scalp, sternum, and groin [85]. Apocrine nevi are primarily asymptomatic, although some individuals complain of associated tenderness, hyperhidrosis, alopecia, or draining. Malignant transformation has rarely been reported.

23.13.2 Histology

In apocrine nevus, the dermis contains mature apocrine glands that extend from the papillary into the reticular dermis. These glandular structures are often larger than normal apocrine glands, and may arise in sites not normally associated with apocrine glands (Fig. 23.21). Large eosinophilic cells with decapitation secretion into the luminal structures line the glandular structures (Fig. 23.22). There are no cytologic atypia and mitotic activity [86].

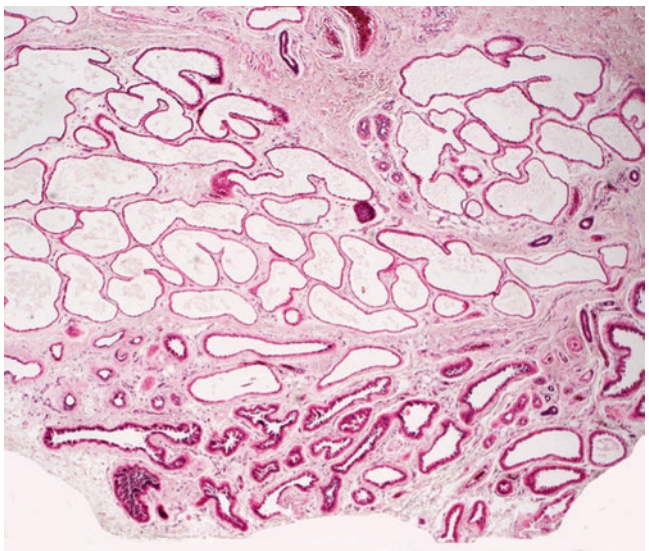

Fig. 23.21 The dermis is filled with abundant fully mature apocrine glands in an apocrine nevus

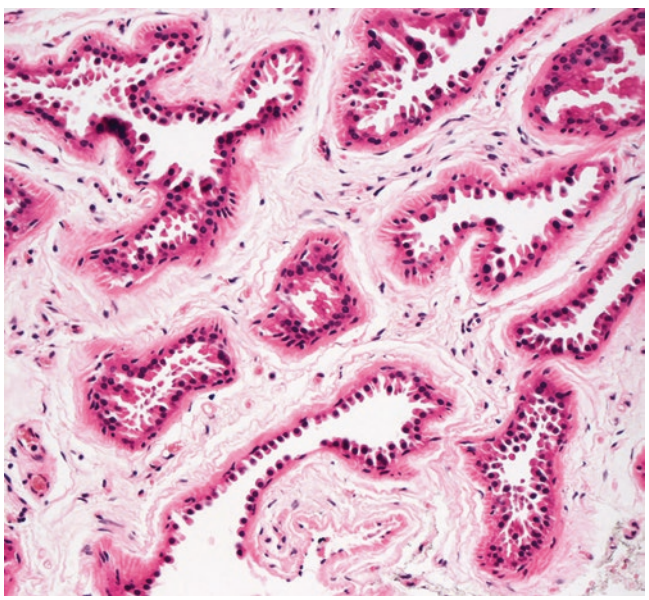

Fig. 23.22 Apocrine epithelium with typical hobnailing and eosinophilic cytoplasm is seen in apocrine nevus

23.14 Eccrine Nevus

23.14.1 Clinical Features

Eccrine nevus is an uncommon hamartoma comprised of an increased number and size of eccrine glands [87]. Eccrine nevus has a variable clinical presentation, but it is primarily characterized by localized hyperhidrosis [87]. Subtle brown hyperpigmentation has been described with overlying depressed area of skin, solitary sweat-discharging pore, and discrete papules. Spontaneous resolution has been described, although treatment of symptomatic cases can be difficult.

23.14.2 Histology

The histologic findings in an eccrine nevus are those of increased number and size of eccrine secretory coils within the mid-dermis (Figs. 23.23 and 23.24). The epidermis is usually unremarkable as is the surrounding dermis [88]. A polypoid configuration is sometimes described [89]. A porokeratotic eccrine nevus demonstrates similar findings, but the overlying epidermis is hyperkeratotic and acanthotic [90–92].

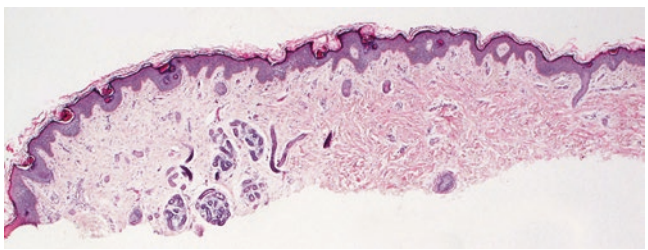

Fig. 23.23 A cluster of well-formed, fully mature eccrine structures characterizes eccrine nevus

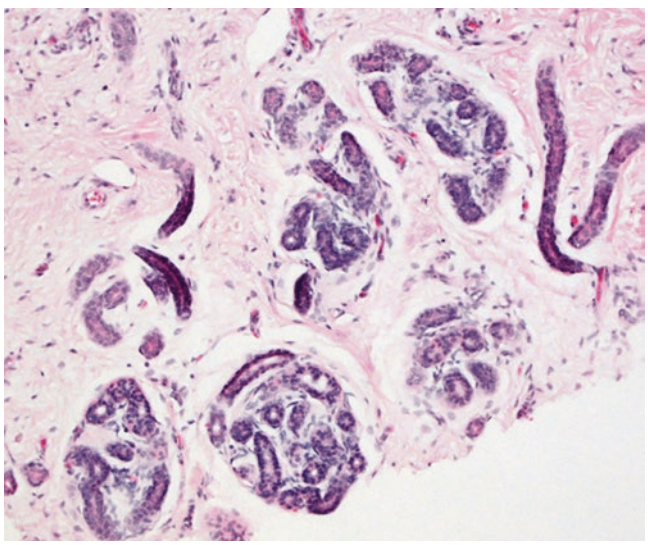

Fig. 23.24 Eccrine nevus demonstrates increased numbers of mature eccrine structures

23.15 Eccrine Angiomatous Hamartoma

23.15.1 Clinical Features

Eccrine angiomatous hamartoma is an uncommon malformation characterized by hyperplasia of both eccrine and vascular structures [93]. Lesions may be congenital or present in early childhood, and rarely develop in adolescence or adulthood [93, 94].

Eccrine angiomatous hamartoma is described as a red to violaceous plaque, typically occurring on the distal extremity and may have associated pain, hyperhidrosis, and hypertrichosis. Lesions tend to expand proportionately to the child's growth. Eccrine angiomatous hamartoma is benign, but may be surgically excised if symptomatic.

23.15.2 Histology

A biopsy specimen of eccrine angiomatous hamartoma demonstrates skin with a benign proliferation of eccrine ductules and glands within the mid-reticular dermis (Figs. 23.25 and 23.26) [95]. The epithelial structures are cytologically normal, and there is no keratinocyte proliferation within the excessive numbers of normal-appearing eccrine ducts and glands. Rare cases with verrucous epidermal hyperplasia have been described [96]. In these cases, the differential diagnosis includes verrucous hemangioma. There is also a proliferation of blood vessels of mixed size with varying amounts of muscle in the vessel walls [97]. The nature of the vessels is controversial with some authors claiming that the vessels are of

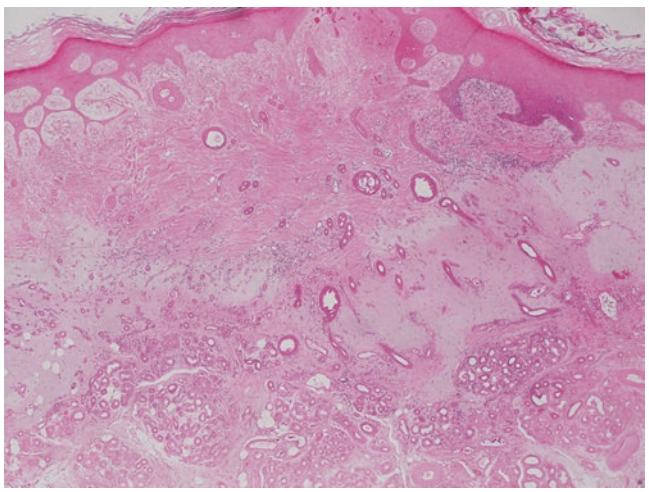

Fig. 23.25 Abundant well-formed eccrine structures and dermal blood vessels are present in the dermis in eccrine angiomatous hamartoma

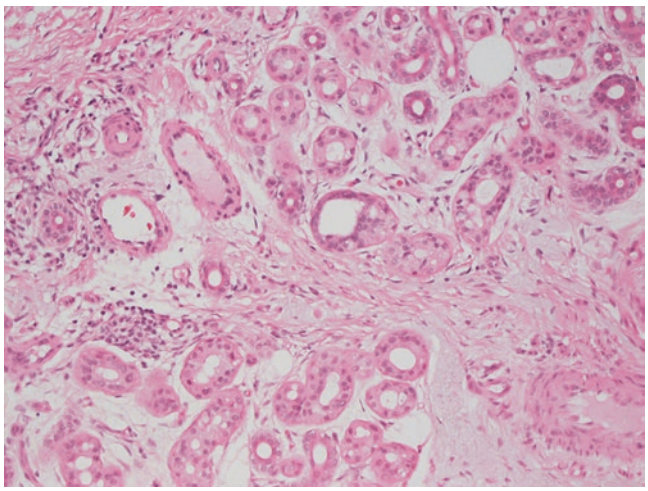

Fig. 23.26 Eccrine angiomatous hamartoma has abundant well-formed eccrine structures admixed with thin- and thick-walled vessels

lymphatic origin and others refuting this finding [98, 99]. The surrounding stroma is usually fibromyxoid with occasional cases demonstrating increased amounts of dermal mucin. Collagen bundles are thickened, haphazard in distribution, and may be perpendicular to the skin's surface. Admixed adipocytes and neural structures are described in some cases [100].

23.15.3 Pathogenesis

Eccrine angiomatous hamartoma is a benign growth of eccrine and vascular structures. Some authors believe that the lesion is primarily a vascular malformation with associated eccrine abnormalities [97, 98, 101]. A proposed model of the pathogenesis of congenital cases of eccrine angiomatous hamartoma describes the dysregulation of epithelial and mesenchymal tissues during embryonic development, leading to the abnormal proliferation of adnexal structures and blood vessels [97, 102].

23.16 Epidermal Nevus

23.16.1 Clinical Features

Epidermal nevi are usually present at birth or appear during early childhood. They occur with equal frequency in males and females [103]. Epidermal nevi present as hyperpigmented, clustered, velvety to verrucous papules or plaques arranged in a linear configuration (Fig. 23.27). They are most commonly seen on the extremities and typically distributed in a Blaschkoid pattern [103]. Lesions are usually solitary, although multiple lesions may occur. Epidermal nevi are benign tumors of epidermal structures. They may continue to expand but have no malignant potential. Treatment may be difficult and is dependent on the location, size, and patient preference.

Fig. 23.27 Epidermal nevus appears as a cluster of soft to slightly rough mamillated brown papules in a linear configuration along the lateral neck

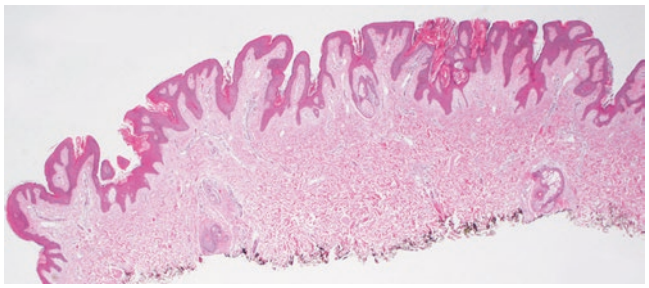

Fig. 23.28 An epidermal nevus has a papillomatous surface and acanthotic epidermis that is histologically indistinguishable from a seborrheic keratosis

23.16.2 Histology

There are several different histologic patterns that can be seen in these hamartomatous lesions. The histologic changes include hyperkeratosis and acanthotic epidermis (Figs. 23.28, 23.29 and 23.30). Hypergranulosis is seen in some cases, but it is not pronounced. The rete ridges are elongated. Cytologic atypia is not present, and mitotic activity is not increased.

One variant of epidermal nevus includes collections of lipid-laden macrophages within the papillary dermis, which is known as a verruciform xanthoma [104]. This pattern is seen in patients with CHILD syndrome [104, 105]. Another histologic pattern of epidermal nevus shows acantholytic dyskeratosis. In this pattern, premature keratinization is present within the epidermis, and foci of acantholysis lead to slight blister formation [105, 106]. Some lesions with this histologic pattern also have eccrine differentiation [107].

The differential diagnosis includes seborrheic keratosis, acanthosis nigricans, nevus sebaceous of Jadassohn, and ver-

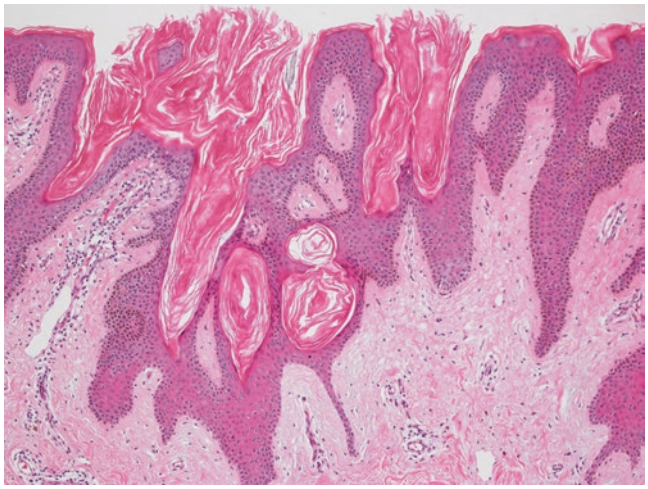

Fig. 23.29 The epidermis is comprised of basaloid cells with focal horn cysts and overlying hyperkeratosis in epidermal nevus

Fig. 23.30 In some cases, changes of epidermolytic hyperkeratosis are seen in an epidermal nevus

ruca vulgaris. The histologic changes in epidermal nevus are identical to those seen in seborrheic keratosis, but seborrheic keratosis is quite unusual in children. Acanthosis nigricans is frequently hyperpigmented, which is a feature not necessarily associated with epidermal nevus; however, a rare variant of an epidermal nevus that closely resembles acanthosis nigricans clinically and histologically has been described [108]. The clinical history makes the distinction straightforward in most cases. Nevus sebaceous demonstrates similar changes within the epidermis. However, it is also associated with changes in sebaceous glands that are not associated with epidermal nevus. Verruca vulgaris has clumped keratohyalin granules, parakeratosis overlying papillomatous tips, and ectasia of postcapillary venules within papillary dermal tips that are not seen in epidermal nevus.

23.16.3 Pathogenesis

Epidermal nevi are hamartomatous epidermal growths occurring as a result of genetic mosaicism from postzygotic somatic mutations during embryogenesis. They are thought to originate from a clonal proliferation of the germinative cells of the basal cell layer along Blaschko's lines [109]. Mutations in fibroblast growth factor receptor-3 (*FGFR3*), phosphatidylinositol-4,5-biphosphate 3 kinase-catalytic subunit-α (*PIK3CA*), and RAS genes have been identified in syndromic and sporadic cases of epidermal nevi [110–113]. A common FGFR3 mutation identified in these lesions is R248C substitution. Activating mutations in PIK3CA are detected in one-third of patients, either alone or in association with FGFR3 mutations [110]. A common PIK3CA mutation is E545G substitution [114]. Mutation in KRAS gene at G12D residue has been identified in the epidermal component of epidermal nevus in an infant with epidermal nevus, polycystic kidneys, and rhabdomyosarcoma [115].

Epidermal nevi can sometimes occur in association with complex developmental abnormalities, such as epidermal nevus syndrome and Proteus syndrome [116, 117]. Interestingly, Proteus syndrome has inactivating PTEN mutations that enhance PIK3CA activity, which, as noted previously, is also a gene identified in non-syndromic epidermal nevi. Additionally, a key activating mutation in Proteus syndrome is the c.49GA, p.Glu17Lys mutation in Akt1, which is an important regulator of growth signaling downstream of PIK3CA [118]. Some epidermal nevi also have an activating mutation in Akt1 in keratinocytes, which is believed to be a primary factor in their pathogenesis [119]. Noonan and cardio-facio-cutaneous syndromes with PTPN11, KRAS, and BRAF mutations are also susceptible to epidermal nevus development [120, 121].

23.17 Nevoid Hyperkeratosis of the Nipple and Areola

23.17.1 Clinical Features

Nevoid hyperkeratosis of the nipple and areola is an uncommon benign condition primarily affecting young females between 15 and 24 years of age [122]. Patients present with dark-colored, verrucous thickening of the nipple, areola, or both. The skin changes are usually bilateral and asymptomatic, although mild pruritus or odor can occur. Nevoid hyperkeratosis of the nipple and areola is persistent once present but may be amenable to medical or surgical interventions, but recurrence is likely especially after discontinuing topical therapy.

23.17.2 Histology

This hamartomatous process is characterized by papillomatous epidermal hyperplasia. The epidermis is acanthotic and there is

prominent overlying orthokeratotic hyperkeratosis [123]. A lymphocytic infiltrate is present and may demonstrate significant exocytosis into the overlying epidermis. In rare cases, the lymphocytes may form Pautrier's-like microabscesses, and the histologic findings may resemble mycosis fungoides [124].

23.18 Folliculosebaceous Cystic Hamartoma

23.18.1 Clinical Features

Folliculosebaceous cystic hamartoma is a rare growth, occurring in both pediatric and adult populations with likely onset in childhood [125]. There is no reported racial or gender predilection. Folliculosebaceous cystic hamartoma presents as a firm to rubbery, small, skin-colored, waxy papulonodule on the head, most notably along the central face [125, 126]. Larger lesions have been described on the torso.

23.18.2 Histology

This recently described entity shares many histologic features with sebaceous trichofolliculoma [127–129]. A central cystic cavity is lined by follicular infundibular epithelium. Mature sebaceous glands extend out from the cyst lining and are present within the dermis. A characteristic stroma surrounds the cyst and its associated sebaceous glands. This stroma is the distinguishing feature that differentiates folliculosebaceous cystic hamartoma from sebaceous trichofolliculoma. Adipocytes are present within the stroma, admixed with collagen [130, 131]. The stromal elements, including both mature and immature adipocytes, can be labeled with antibodies to S100, CD34, and nestin in order to establish the diagnosis [125, 132]. Approximately 5 % of cases are associated with melanocytic nevi, and some authors suggest that the melanocytic element be considered part of the hamartomatous process [133]. Congenital cases have been described [131, 134].

Sebaceous trichofolliculoma presents a major diagnostic dilemma, but it is differentiated by the lack of associated stromal elements that include adipocytes [127, 129]. In addition, trichofolliculomas demonstrate secondary follicular differentiation not seen in folliculosebaceous cystic hamartomas [129]. In rare cases in which there is a predominance of stromal elements, it can be difficult to distinguish these lesions from neurofibromas [135].

23.18.3 Pathogenesis

Folliculosebaceous cystic hamartoma is a hamartomatous growth of follicular, sebaceous, and mesenchymal components [128]. The pathogenesis of this lesion is not known. Several theories have been proposed, including one suggesting that it is a trichofolliculoma at its very late stage [136]. However, others have disputed this theory [134]. Another theory proposes that the coexistence of Miescher-type melanocytic nevi may have a role in the pathogenesis of this lesion [133].

23.19 Basaloid Follicular Hamartoma

23.19.1 Clinical Features

Basaloid follicular hamartoma is a rare benign tumor that may be present at birth or acquired later in life [137]. It may occur in isolation or in association with genetic skin diseases including Bazex-Dupre-Christol syndrome, basaloid follicular hamartoma syndrome, and Brown-Crounse syndrome. Basaloid follicular hamartoma also has been reported in association with systemic diseases including cystic fibrosis, myasthenia gravis, and systemic lupus erythematosus [137].

Basaloid follicular hamartoma has variable clinical features and may present as a macule, nodule, or exophytic to pedunculated papule [137]. Clinical disease and presentation may be subcategorized into different groups depending on associated cutaneous or systemic stigmata. The lesions are benign, but additional diagnostic work-up for associated systemic disease may be warranted if there are other presenting complaints.

23.19.2 Histology

This is a poorly defined entity with several histologic descriptions in the literature. The common features include one or several small clusters of mature follicular units surrounded by nests and islands of basaloid epithelium. Anastamosing cords give rise focally to islands with follicular maturation (Figs. 23.31 and 23.32). All epithelial structures course within a dense eosinophilic stroma. There is no cytologic atypia, and the lesions are well-circumscribed. Comparisons exist to fibroepithelioma of Pinkus, tumor of the follicular infundibulum, and trichoepithelioma.

23.19.3 Pathogenesis

Sonic hedgehog signaling pathway appears to be important in the development of basaloid follicular hamartoma. In experimental animal models, transgenic mice with overexpression of genes in the Sonic hedgehog pathway, namely Smoothened, Frizzled Class Receptor (SMO) and GLI Family Zinc Finger 2 (GLI2), develop skin lesions similar to basaloid follicular hamartoma in humans [138]. Hedgehog gene transcripts are upregulated in human lesions [138]. Lesions in generalized basaloid follicular hamartoma syndrome have an autosomal dominant inheritance pattern [139]. The development of basaloid follicular hamartoma has also been linked with autoimmune diseases, including myasthenia gravis and systemic lupus erythematosus [140–142].

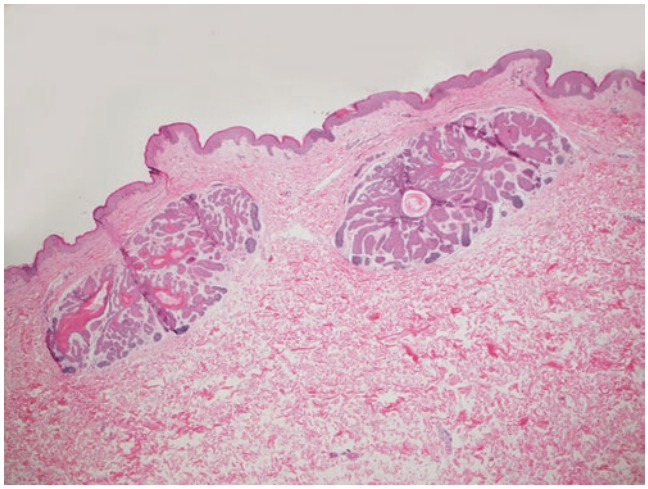

Fig. 23.31 Basaloid follicular hamartoma is characterized by multiple small foci of benign-appearing keratinocytic islands with follicular differentiation

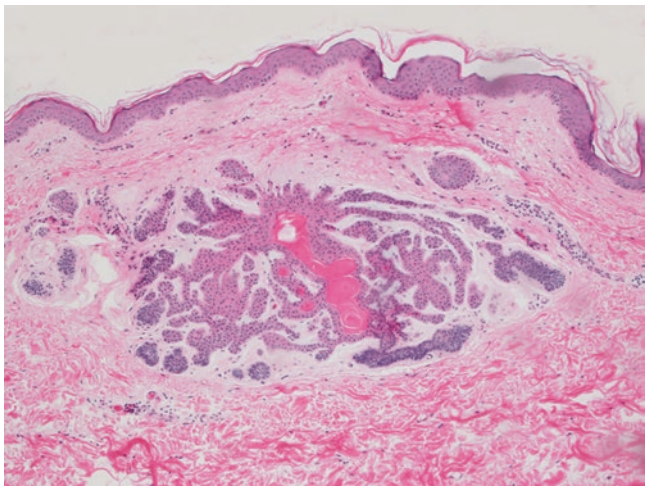

Fig. 23.32 Basaloid buds and follicular differentiation with keratinization are seen in basaloid follicular hamartoma

23.20 Inflammatory Linear Verrucous Epidermal Nevus

23.20.1 Clinical Features

Inflammatory linear verrucous epidermal nevus (ILVEN) is a rare variant of epidermal nevus, representing 5 % of cases [143]. Lesions typically are present at birth or appear sometime during infancy. Girls are more commonly affected than boys with a ratio of 4:1. Familial cases have been reported, although occurrence usually is sporadic.

ILVEN presents as erythematous, scaly, hyperkeratotic, Blaschkoid papules and plaques, most commonly localized to an extremity (Fig. 23.33). Recalcitrant pruritus is a predominant feature of the condition. Treatment of ILVEN is difficult, but good clinical outcomes have been reported with full-thickness excision when feasible [144].

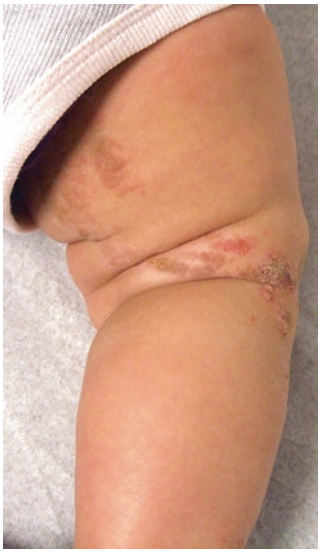

Fig. 23.33 Inflammatory verrucous epidermal nevus presents as a series of hyperpigmented, rough papules overlying an erythematous papular, scaled plaque in Blaschkoid distribution on the posterior leg of an infant

23.20.2 Histology

ILVEN demonstrates histologic changes that are quite similar to, if not indistinguishable from, psoriasis. In the ideal case, there is an alternation between hyperkeratosis and parakeratosis in the stratum corneum (Fig. 23.34). The epidermis is papillomatous and acanthotic with psoriasiform elongation of the rete ridges [145, 146] (Fig. 23.35). The granular layer is markedly diminished or absent in the regions immediately subjacent to areas of parakeratosis, and it is thickened in areas beneath the hyperkeratosis [147]. These areas may have a cup-shaped configuration [148]. Ectasia of postcapillary venules within the papillary dermis, and a moderate lymphohistiocytic infiltrate in the superficial dermis are present. The nature of ILVEN remains unclear. Cases have been described that follow Blaschko's lines, and one case arose within a Becker's nevus [150].

The main differential diagnosis of ILVEN, both clinically and histologically, is that of linear psoriasis. It may be impossible to make the distinction based upon histologic changes alone [151]. Some authors postulate that they may represent the same entity, although some immunologic markers suggest that the entities are truly distinct [152]. The presence of spongiosis within the epidermis in psoriasis may serve as a distinguishing feature in some cases [149].

23.20.3 Pathogenesis

ILVEN is regarded as a genetic dyskeratotic disease reflecting genetic mosaicism [153]. The pathogenesis of ILVEN may involve T lymphocytes with possible contributions of

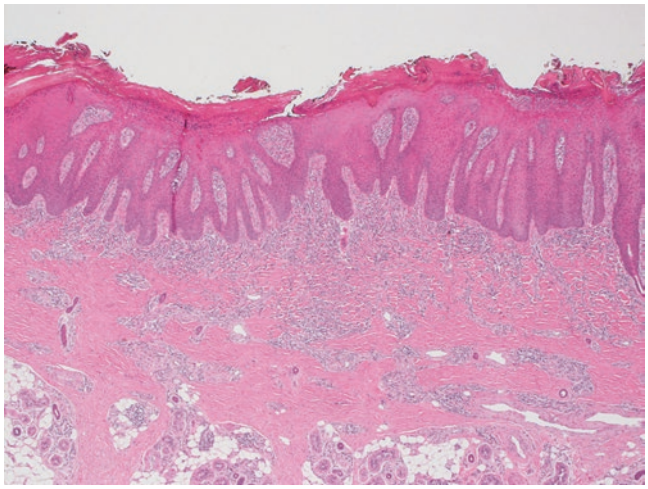

Fig. 23.34 Inflammatory verrucous epidermal nevus demonstrates focal parakeratosis, psoriasiform epidermal hyperplasia, and a superficial dermal lymphocytic infiltrate

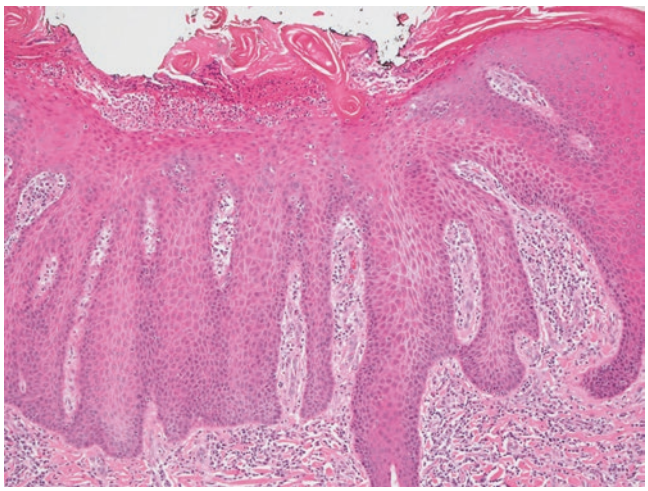

Fig. 23.35 Focal loss of the granular layer, parakeratosis, collections of neutrophils, and psoriasiform epidermal hyperplasia are seen in ILVEN

interleukins 1 and 6 and tumor necrosis factor-α in the growth regulation and inflammation in ILVEN [154].

23.21 Nevus Comedonicus

23.21.1 Clinical Features

Nevus comedonicus is a relatively rare organoid nevus, resulting from a developmental defect of the pilosebaceous apparatus [155]. Nevus comedonicus presents as a Blaschkoid plaque comprised of discrete, clustered and firm comedo-like papules (Fig. 23.36). Lesions are most often found on the face, neck, upper extremities, chest, and abdomen [155]. Nevus comedonicus is a benign hamartoma whose growth is proportional to that of the child.

Fig. 23.36 Nevus comedonicus appears as a cluster of open and closed comedones on the superior aspect of the shoulder

23.21.2 Histology

This is a hamartomatous proliferation of small keratinocyte-lined cysts within the dermis. In some sections, the cysts are seen to arise from within hair follicles and connect up to the surface epidermis [156, 157]. Keratin plugs fill the dilated follicular openings [158]. The cystic structures in the subjacent dermis are filled with wispy stratum corneum-like keratin and are often inflamed and ruptured [159].

23.21.3 Pathogenesis

Nevus comedonicus is thought to be caused by developmental defects of the pilosebaceous unit [160]. It typically occurs sporadically, although familial cases have been described [161]. Hyperactivation of fibroblast growth factor receptor-2 signaling may be involved in the formation of this lesion [162].

23.22 Nevus Sebaceous of Jadassohn

23.22.1 Clinical Features

Nevus sebaceous is a congenital hamartoma of the epidermis, hair follicles, sebaceous glands, and apocrine glands. At birth, lesions are yellow to pink, well-demarcated patches or thin plaques of varying size and are devoid of hair. Nevus sebaceous most often occurs on the scalp but it may also be present on the face, neck, and trunk [163]. Lesion grows proportionately with the child but has the potential to thicken and become more verrucous in appearance during puberty (Fig. 23.37).

Fig. 23.37 Nevus sebaceous of Jadassohn presents as a well-demarcated, orange-colored, verrucous alopecic plaque at the posterior vertex of the scalp

The risk of associated malignancy is unknown but may be less than 2 % of cases [163]. Malignant tumors, including squamous cell carcinoma, apocrine carcinoma, sebaceous carcinoma, eccrine porocarcinoma, adenocarcinoma, and mucoepidermoid carcinoma, have been noted [163]. Reports of malignancy in patients less than 18 years of age are few. The most commonly occurring neoplasms within nevus sebaceous are trichoblastoma and syringocystadenoma papilliferum, both of which are benign and typically appear in adulthood. The prevalence of benign neoplasms ranges between 1.7 and 11.6 % in published retrospective studies with incidence increasing with age [163, 164].

23.22.2 Histology

The histologic features of nevus sebaceous vary with the age of the patient. During the few months after birth, maternal hormones contribute to the sebaceous hyperplasia that characterizes this entity and makes the diagnosis rather straightforward. These structures become much less pronounced as the hormonal effect abates, and remains relatively inconspicuous until the onset of puberty. In the prepubertal child beyond the first few months of age, the most striking histologic change is the abrupt absence of terminal hairs (Figs. 23.38 and 23.39). The ideal biopsy specimen will demonstrate normal size and distribution of terminal hairs extending into the subcutaneous fat and a sharp demarcation to an area with no such hair. Ectopic apocrine glands are seen in many cases.

At the onset of puberty, the changes become more florid, classic, and easily diagnosable. The epidermis appears papillomatous and acanthotic with overlying hyperkeratosis (Fig. 23.40). The sebaceous glands become enlarged, and abnormal insertion of the sebaceous ducts directly into the epidermis

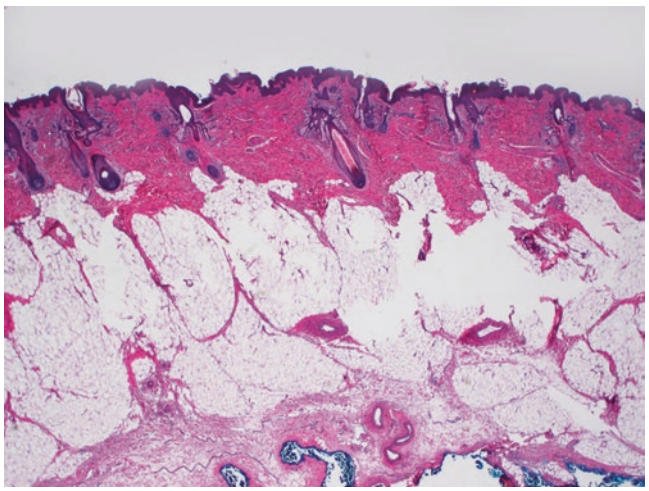

Fig. 23.38 Nevus sebaceous of Jadassohn is recognized by lack of terminal hair formation in prepubertal children. Sebaceous hyperplasia is not a prominent feature

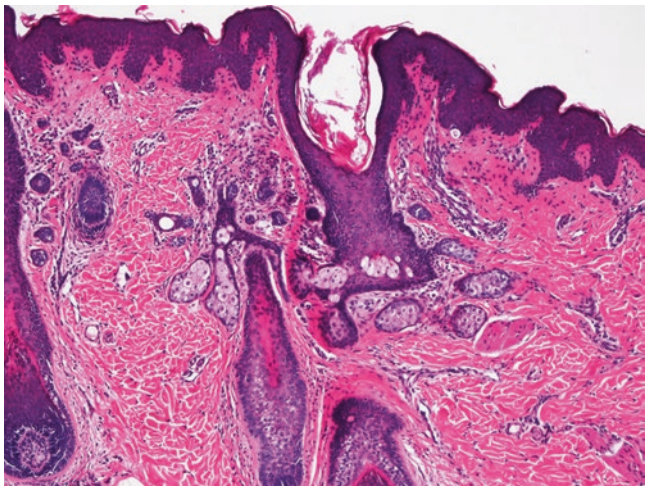

Fig. 23.39 A papillomatous epidermal surface and abundant primitive follicular structures are features of nevus sebaceous in prepubertal children

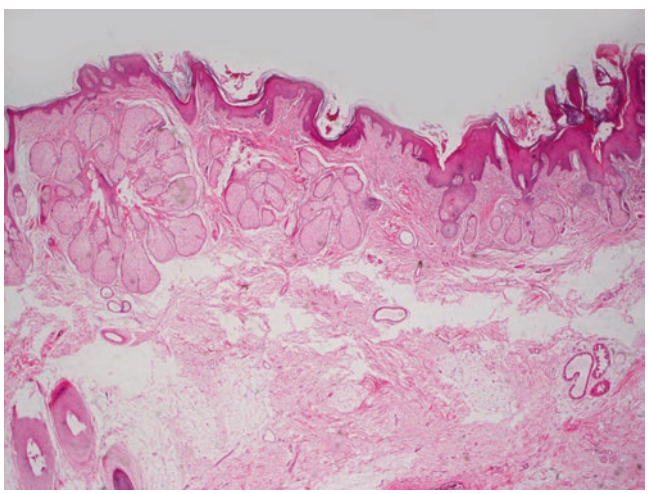

Fig. 23.40 Sebaceous gland hyperplasia and a papillomatous and acanthotic epidermis are seen in nevus sebaceous after the onset of puberty

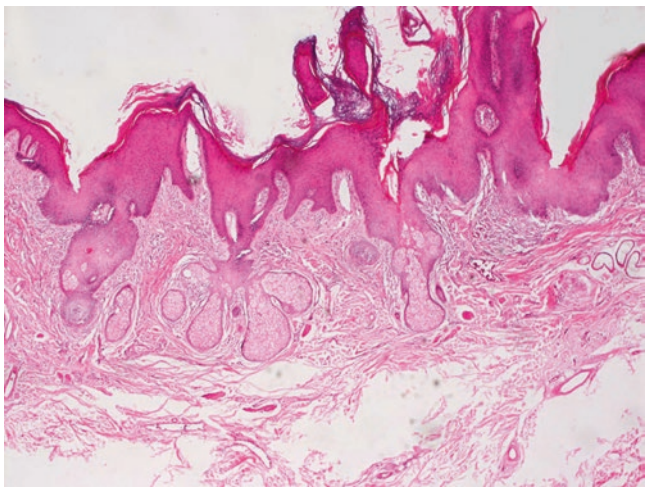

Fig. 23.41 Verrucous epidermal hyperplasia, hyperkeratosis, and abundant sebaceous glands characterize fully formed nevus sebaceous

(as opposed to into the infundibular portion of the hair follicles) is apparent (Fig. 23.41). The abrupt lack of terminal hairs within the lesion still remains. Ectopic apocrine glands are present.

Abundant appendageal neoplasms arise from within nevus sebaceous. The most common tumor is a trichoblastoma. Previously, these tumors were thought to be basal cell carcinoma, but the preponderance of evidence at this point suggests that the basaloid follicular neoplasms are best categorized as trichoblastomas. Another common neoplasm that frequently arises in association with nevus sebaceous is syringocystadenoma papilliferum. An entire range of appendageal tumors can arise from this hamartomatous process. Many of them defy precise classification and share characteristics with one or more common tumors. Mesenchymal neoplasms, such as leiomyosarcomas, also occasionally arise within nevus sebaceous.

23.22.3 Pathogenesis

Whole exome sequencing of nevus sebaceous has revealed somatic mutations in HRAS and KRAS in these lesions. In a study in which 27 nevus sebaceous lesions were analyzed, 25 of these lesions were found to have an identical activating HRAS mutation (p.Gly13Arg), and 2 lesions had a KRAS mutation in the adjacent paralogous residue (p.Gly12Asp or p.Gly12Val) [165]. Other independent studies also revealed similar genetic findings in HRAS and KRAS [166–168].

In addition to the discovery of HRAS and KRAS mutations, another important finding is that tissue microdissection revealed the presence of "somatic mosaicism," in which activating RAS mutations were found in lesional keratinocytes of nevus sebaceous, but not in adjacent normal skin, dermal fibroblasts, or peripheral blood cells from the same patient [166]. Activating mutations of HRAS and KRAS lead to the activation of downstream signaling pathways, including MAPK and PI3K. This activation results in increased cell proliferation, and may explain the coexistence of secondary tumors within nevus sebaceous lesions.

23.23 White Sponge Nevus

23.23.1 Clinical Features

White sponge nevus is a genetic condition with autosomal dominant inheritance but variable penetrance [169]. Lesions typically are present at birth, although they may not be noted until late in childhood or in adolescence.

White sponge nevus is characterized by asymptomatic white, adherent, velvety plaques most commonly along the buccal mucosa, followed by the labial and gingival mucosa, and the floor of the mouth [169]. Reports exist of lesions occurring outside of the oral cavity, including the nasal, esophageal, laryngeal, and anogenital mucosa, but extraoral incidence is rare. White sponge nevus is a benign condition, but it has limited response to therapies.

23.23.2 Histology

Biopsies demonstrate oral mucosa with hyperkeratosis and increased parakeratosis. The mucosa is acanthotic but lacks cytologic atypia and increased mitotic activity [170]. Intracellular edema of keratinocytes is present, which is what accounts for the clinical appearance as well as the histologic pallor seen within lesional mucosa [170, 171] (Fig. 23.42). Ultrastructural analysis reveals abnormal aggregation of tonofilaments and anomalies in distribution of

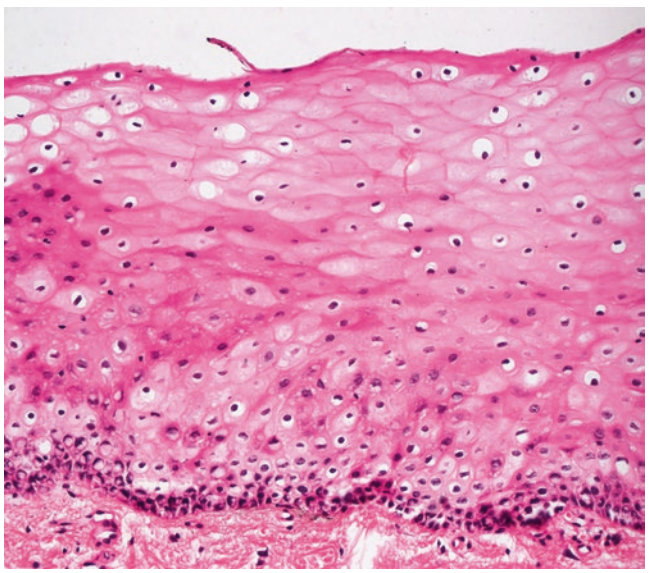

Fig. 23.42 Oral white sponge nevus is characterized by mucosal epithelium comprised of keratinocytes with abundant cytoplasmic glycogen, giving rise to epidermal pallor

increased Odland bodies [172]. Identical lesions have been described on the vulva and in the perianal region [173].

The histologic differential diagnosis of white sponge nevus includes verruca vulgaris, although there is no abnormal keratohyaline granule clumping or papillomatosis as is seen with human papillomavirus infection. Squamous cell carcinoma is differentiated based upon the lack of cytologic atypia in white sponge nevus mucosa.

23.23.3 Pathogenesis

White sponge nevus is a rare autosomal dominant disorder that primarily affects the squamous epithelium in the oral mucosa and, less frequently, the mucosa in the nose, esophagus, rectum, and vulvovaginal areas [174, 175]. The pathogenesis is attributed to mutations in keratin 4 and keratin 13, which compose keratin-intermediate filaments in the spinous layer of non-keratinizing stratified squamous epithelium [176, 177]. Genetically engineered mice with a missense mutation in keratin 4 develop a phenotype similar to white sponge nevus [178]. Mutations in keratin 4 or keratin 13 lead to keratin defects, and the formation of tonofilament aggregates ultrastructurally [175].

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Tumors of the Cutaneous Appendages and the Epidermis

24

24.1 Pilomatricoma

24.1.1 Clinical Features

Pilomatricomas are common benign hair matrix tumors most frequently seen in individuals less than 20 years old [1]. Incidence of pilomatricomas is sporadic, although reports of heritable forms have been described with multiple lesions appearing in association with myotonic dystrophy, Gardner syndrome, Rubinstein–Taybi syndrome, and trisomy 9 [2].

Pilomatricomas usually present as a solitary, mobile, firm, skin-colored to whitish subcutaneous nodules, occasionally with overlying bluish red discoloration (Fig. 24.1). In cystic variants, rapid enlargement with more pronounced erythema can occur secondary to hemorrhage. Overlying bulla can be seen in rare incidences. This bullous subtype is more common on the shoulders and upper extremities of females [3]. Surgical excision is curative, and it is generally recommended as lesions are at risk for inflammation secondary to trauma or infection. Potential for malignant transformation has been suggested, but this remains controversial with low reported incidence [4, 5].

24.1.2 Histology

Biopsy of pilomatricoma demonstrates a well-circumscribed proliferation of basaloid cells giving rise to a central cavity comprised of "shadow" or "ghost cells" (Fig. 24.2). Germinative follicular basaloid cells rim the space and undergo abrupt transition to central squamous cells that lose their nuclei and are pink in color (Fig. 24.3). There is a tendency for the development of calcification in the central portion of the lesion (hence, the old name calcifying pilomatricoma of Malherbe). In cases where there is disruption of the intact cystic architecture, there is a marked granulomatous inflammatory infiltrate with multinucleated giant cells, keratin debris, and additional foci of calcification.

The outermost portions of the cystic proliferation contain cells that are quite immature in appearance, and abundant mitotic figures are present. If only this portion of the lesion is available for examination, the tumor may resemble an undifferentiated malignant process. However, identification of the portion with "ghost" cells makes the diagnosis rather straightforward. The issue of tissue sampling is more a problem with fine needle aspiration specimens, as most punch or shave biopsies will contain both major elements of this neoplasm [6, 7]. Malignant transformation of these tumors can occur, but it is usually in long-standing, large lesions occurring in elderly patients, and these are not ordinarily encountered in children.

24.1.3 Pathogenesis

Pilomatricoma commonly carries somatic mutations in Bcl-2 (a gene that regulates cell apoptosis) and CTNNB1 (a gene that encodes β-catenin, which is important in hair follicle development) [8–10]. Pilomatricoma often occurs sporadically. However, there are reports of cases of multiple familial pilomatricomas as well as cases of pilomatricomas that occur in association with autosomal dominant conditions, such as myotonic dystrophy and familial adenomatous polyposis, and with syndromic conditions, such as Rubinstein–Taybi syndrome, Gardner syndrome, and Turner syndrome [11–13].

24.2 Trichoepithelioma

24.2.1 Clinical Features

Multiple trichoepitheliomas can be inherited in an autosomal dominant manner, appearing in early adulthood or less commonly in childhood [14]. Sporadic nonheritable occurrences of solitary lesions typically develop during

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Fig. 24.1 Pilomatricoma appears as a firm nodule on the cheek of a child with overlying red and blue discoloration

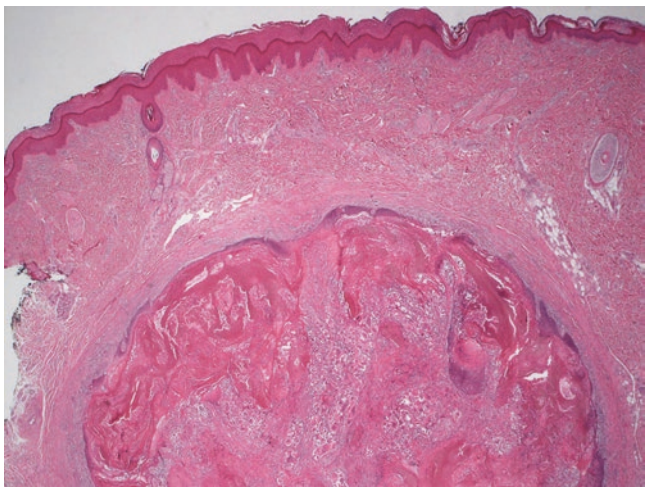

Fig. 24.2 Pilomatricoma demonstrates a sharply circumscribed dermal tumor consisting of basaloid cells at the periphery, ghost cells and a keratinaceous center

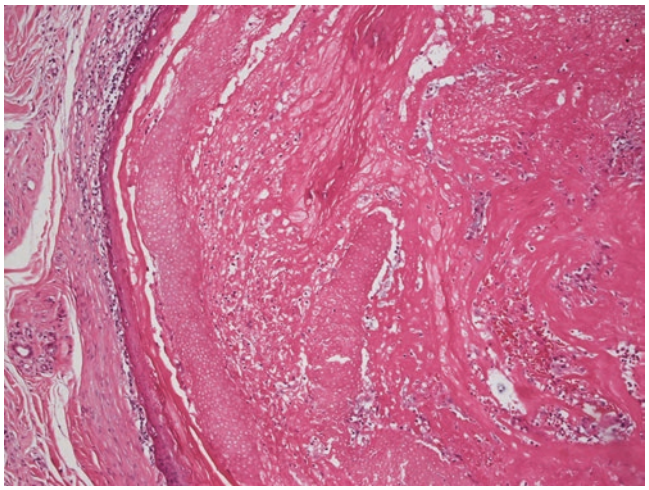

Fig. 24.3 Ghost cells and keratinocytes with no residual nuclei are the characteristic cells seen in pilomatricoma

Fig. 24.4 Trichoepitheliomas present as multiple small, skin-colored papules over the face

the second and third decades of life [14]. Trichoepithelioma can present as solitary or multiple lesions, and it can be associated with multiple familial trichoepitheliomas, Brooke–Spiegler syndrome, Rasmussen syndrome, and Rombo syndrome [15–17].

Trichoepitheliomas present as small (2–5 mm), firm, waxy, skin-colored papules and papulonodules on the central face, specifically along the nose, forehead, upper lip, and eyelids (Fig. 24.4) [14]. Lesions can also be found at the scalp, neck, trunk, and perianal skin. Discrete papules may aggregate to form nodular plaques. Larger lesions may have telangiectasias along the surface. Trichoepitheliomas are benign but they may be removed for cosmetic or confirmatory purposes.

24.2.2 Histology

Histologic findings of trichoepithelioma demonstrate a dermal tumor comprised of basaloid cells with follicular differentiation (Fig. 24.5). Connection to the overlying epidermis is unusual. Nests of basaloid cells are present surrounded by cellular eosinophilic stroma. The epithelial nests demonstrate varying degrees of follicular differentiation, with some foci being entirely basaloid cells, and others demonstrating full maturation with cystic cavities lined by granulated keratinocytes and containing hair follicles. In some nests, papillary mesenchymal bodies, which are in-pouchings of densely

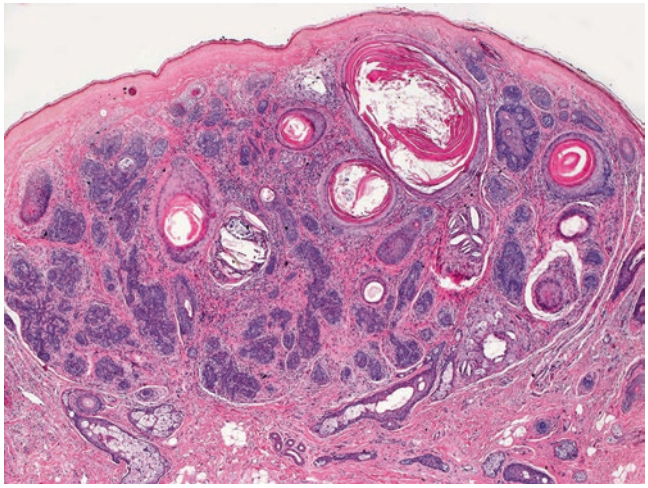

Fig. 24.5 Trichoepithelioma is characterized by nests of basaloid epithelium with follicular differentiation coursing through the dermis

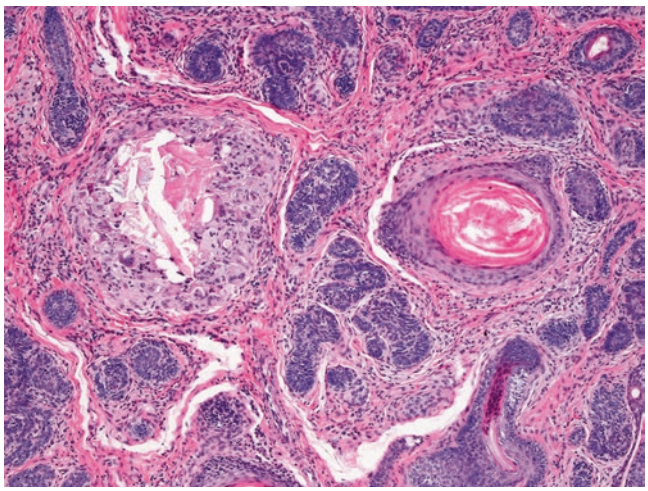

Fig. 24.6 Trichoepithelioma demonstrates follicular structures, basaloid nests, and foci with granulomatous inflammation surrounding ruptured cysts

cellular mesenchymal cells resembling dermal papillae, are observed. It is common to see foci of granulomatous inflammation with abundant giant cells in areas where the keratin-filled cystic spaces have ruptured (Fig. 24.6). A variant of trichoepithelioma with sclerotic stroma and compressed thin strands of follicular basaloid cells is known as desmoplastic trichoepithelioma [18, 19]. Rarely, trichoepithelioma may have intradermal melanocytic nevus as part of the lesion. It remains unclear if this is a single neoplasm or coexistence of two common tumors [20].

The main differential diagnosis is basal cell carcinoma, although these tumors are not common in children. Trichoepitheliomas lack the classic cleft formation between the epithelial and stromal components that are usually found in basal cell carcinoma. In addition, the stroma in basal cell carcinomas is more densely cellular and contains mucinous ground substance not seen in trichoepithelioma [18–20]. Papillary mesenchymal bodies are quite rare in basal cell carcinoma, which has more peripheral palisading of tumor cells at the edges of epithelial lobules [21]. Desmoplastic trichoepithelioma may also be confused with microcystic adnexal carcinoma, although this neoplasm is distinctly uncommon in children. In addition, no ductule differentiation is seen in desmoplastic trichoepitheliomas.

Trichoadenoma and trichoblastoma may share some histologic features with trichoepithelioma, but the distinction is of academic interest only. These are closely related benign follicular neoplasms. Trichoadenomas have less basaloid component and more complete follicular maturation than trichoepitheliomas. Trichoblastomas demonstrate more undifferentiated basaloid component and less follicular maturation than trichoepitheliomas.

24.2.3 Pathogenesis

Trichoepithelioma is a benign skin tumor of follicular germinative cells [22]. The patched gene (PTCH) appears to play an important role in the pathogenesis of trichoepithelioma. Frameshift and in-frame somatic deletions of PTCH as well as overexpression of PTCH mRNA have been identified in trichoepithelioma [23]. Brooke–Spiegler syndrome (BSS) is an autosomal dominant syndrome with adnexal tumors, including cylindromas, spiradenomas, and trichoepitheliomas. Germline mutations in the cylindromatosis (CYLD) gene have been identified in BSS [17, 24, 25]. CYLD is a deubiquitinating enzyme that negatively regulates the NF-κB and c-Jun N-terminal kinase pathways [26].

24.3 Trichofolliculoma

24.3.1 Clinical Features

Trichofolliculoma usually appears in adulthood [27]. It is a benign asymptomatic and solitary papule or nodule on the head or neck with greatest frequency on the face. Less common sites of involvement include the lip, nose, external auditory meatus, genitals, and extremities. There are very few cases of multiple lesions in the literature [27].

24.3.2 Histology

Trichofolliculoma appears as a single invagination at the point of a pilosebaceous unit. On rare occasions, more than one such invagination may occur. The central follicular

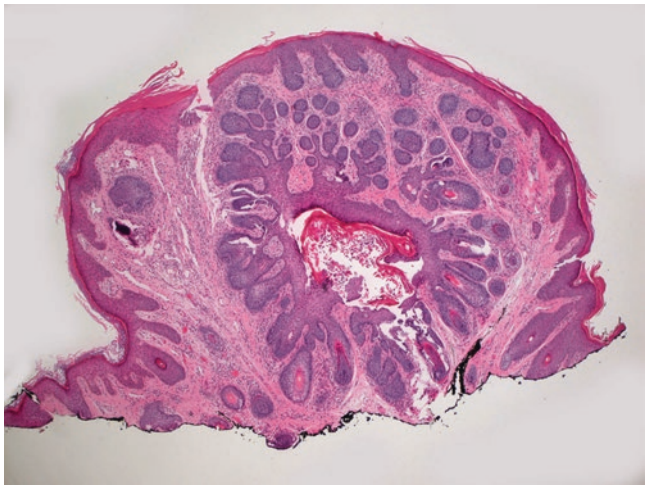

Fig. 24.7 A central hair follicle gives rise to abundant basaloid and primitive follicular structures in trichofolliculoma

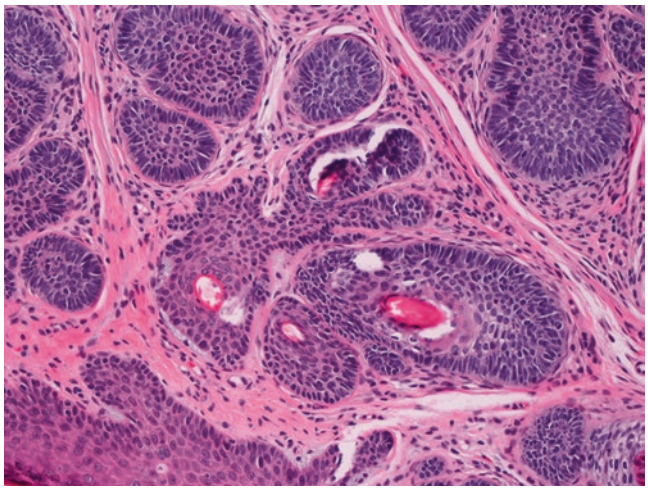

Fig. 24.8 Basaloid buds and primitive follicular structures characterize trichofolliculoma

cavity is slightly dilated. It is a fully mature hair follicle. Emanating from the sides of the dilated follicle are multiple follicular buds comprised of basaloid follicular epithelium with varying degrees of differentiation (Figs. 24.7 and 24.8). Vellus hairs may be present within these small basaloid buds. These may appear to attach to the central cavity or to be separate, although they do attach on other tissue planes of sectioning. These secondary follicular units occasionally give rise to tertiary follicular units. Surrounding the epithelial constellation is a cellular and eosinophilic stroma that separates the neoplasm from the surrounding dermis. Follicles may be in anagen, catagen, or telogen phase [28]. Mitotic activity is not abundant and atypical forms are not seen. The tumor is well circumscribed and has benign cytologic features. A rare variant occurs that contains sebaceous glands as part of the follicular growth. This tumor is known as a sebaceous trichofolliculoma [29, 30].

24.3.3 Pathogenesis

Trichofolliculoma is a benign hair follicle hamartoma. It is thought to form from an abortive differentiation of hair follicle stem cells towards a fully developed hair follicle during the hair cycle. Histological and immunohistochemical studies suggest that in trichofolliculoma, cytokeratin 15-positive hair follicle stem cells proliferate and form abnormal secondary hair follicles from a primary infundibulo-follicular primordium [31]. There are also abnormalities in the hair cycle and the regulation of hair follicle size in trichofolliculoma.

24.4 Chondroid Syringoma

24.4.1 Clinical Features

Chondroid syringoma presents as a nondescript slow-growing, asymptomatic, well-demarcated subcutaneous nodule, most frequently on the head or neck [32]. Occurrence of chondroid syringoma is rare with reported incidence of 0.01–0.02 % [32, 33]. Tumors are typically benign, but malignant transformation has been described.

24.4.2 Histology

Histologic features of chondroid syringoma include a dermal-based neoplasm comprised of tubular and ductular

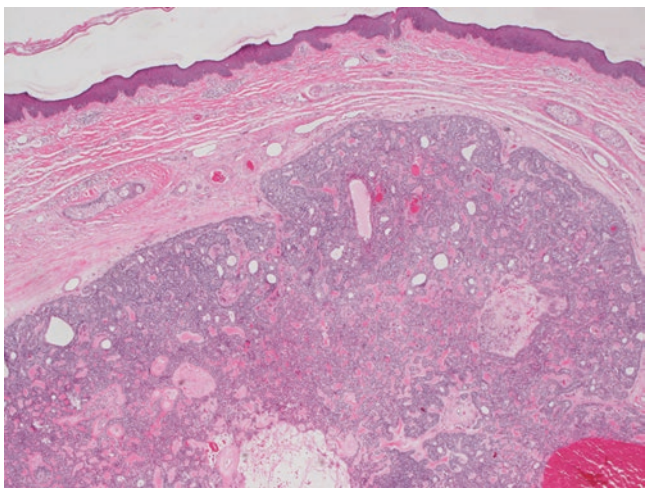

Fig. 24.9 Chondroid syringoma is a well-circumscribed dermal tumor with glandular structures surrounded by small blue cells

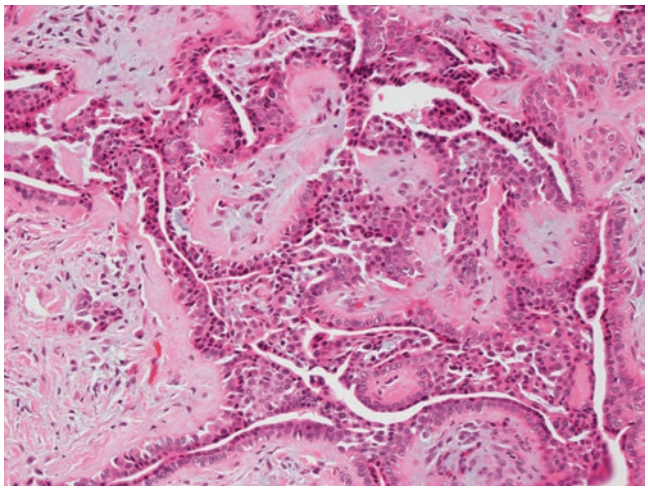

Fig. 24.10 Glandular structures and tubules interanastamose in a mucinous stroma in chondroid syringoma

epithelium coursing in a myxoid stroma (Fig. 24.9). There is great variation in the proportions of stroma and epithelial components. Some tumors have abundant myxoid or mucinous stroma that bears histologic resemblance to cartilage. Others have more fibrous stroma with only scant foci of myxoid change. The epithelial component varies from cases with small glandular structures lined by cuboidal epithelium and underlying myoepithelium to cases with interanastamosing tubular structures (Fig. 24.10). The tubular structures are similarly lined by cuboidal epithelium, and in most cases, myoepithelium is present as well. These have been designated as eccrine and apocrine types of chondroid syringomas, respectively [34]. While this distinction helps to describe the varying histologic patterns and perhaps pathogenesis, there is no difference in biologic behavior, and the separation is of academic interest only. In some cases, the tumors consist solely of myoepithelial cells and are called myoepitheliomas, bearing some resemblance to similarly named salivary gland neoplasms [35]. While a malignant counterpart of chondroid syringoma sometimes occurs, this benign tumor is exceedingly uncommon in children, and malignant lesions have not been described in children [36].

24.4.3 Pathogenesis

Chondroid syringoma is a tumor of epithelial origin with the capacity to form adnexal structures and produce chondroid matrix [37]. It can have apocrine or eccrine differentiation with frequent occurrence of folliculo-sebaceous differentiation in the apocrine type of chondroid syringoma [34]. Merkel cells have been identified in this tumor. However, the clinical significance of the presence of Merkel cells in this lesion is unknown [38].

24.5 Myoepithelioma

24.5.1 Clinical Features

Cutaneous myoepithelioma is an uncommon and relatively recently identified tumor. In one cohort of patients, the median age of onset was 39 years old with a range of age presentation between 2 months and 74 years old. Another retrospective review suggested peak incidence in childhood with a younger median age of 22 years old [39, 40]. Slight male predominance was noted in both studies. Lesions are commonly described as slow-growing painless nodules on some aspect of an extremity, although tenderness, swelling, and erythema have been noted in at least one case [39]. Myoepitheliomas appear to follow a benign course, but local recurrence may occur following incomplete excision [40].

24.5.2 Histology

Closely related to mixed tumors (chondroid tumors), myoepitheliomas are composed entirely of myoepithelial cells [35]. The tumors are sharply circumscribed and the stroma can be densely fibrotic or myxoid (Fig. 24.11) [41]. The cells grow in fascicles, and can be ovoid, spindly, or even histiocytoid (Fig. 24.12). A solid or cystic growth pattern is seen in most cases, but syncytial pattern has also been described [40]. The syncytial pattern shows cells with abundant eosinophilic cytoplasm and indistinct cellular borders. Cytologic atypia is minimal, and necrosis and vascular invasion are not found. In most cases, there is only slight pleomorphism [42]. The proliferation of myoepithelial cells can display a plexiform growth pattern [43]. Rare cases exist

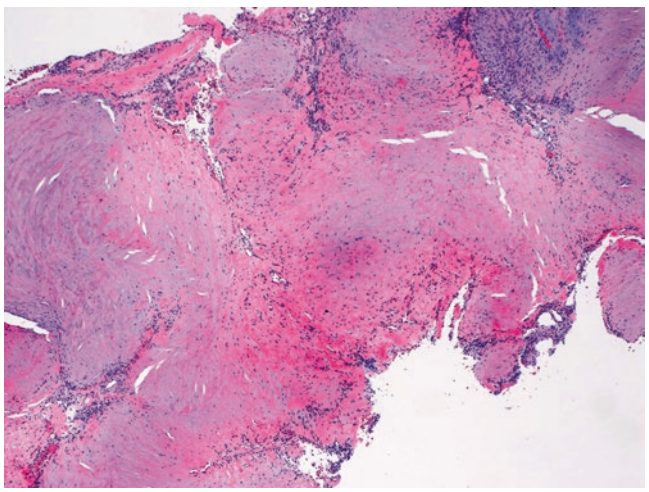

Fig. 24.11 A spindle cell proliferation is present within a background that is focally myxoid and fibrotic in myoepithelioma

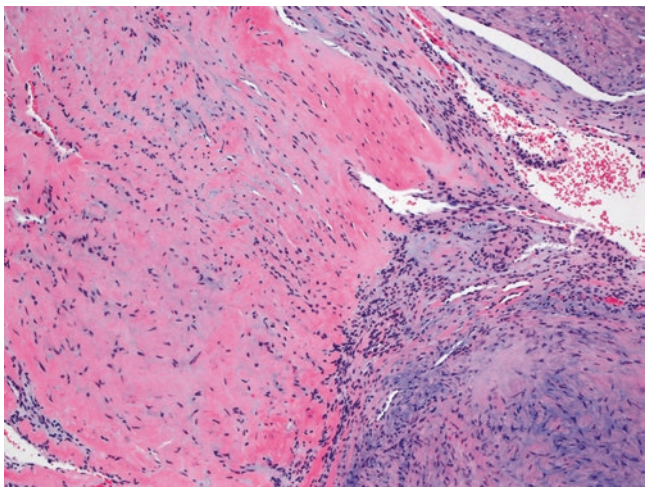

Fig. 24.12 Bland spindle cells course within focally myxoid stroma in myoepithelioma

Fig. 24.13 An eccrine poroma appears as an exophytic, erythematous lobulated plaque with collarette of hyperkeratotic scale on the plantar foot

with dendritic or spindle-shaped melanocytes present within the lesions [44].

24.5.3 Pathogenesis

Cutaneous myoepitheliomas harbor EWSR1 gene rearrangement [45]. The frequency of EWSR1 rearrangement varies in these tumors, ranging from 29 to 44 % of the cases [45, 46]. Myoepithelial tumors with EWSR1 fusion affect children and young adults [40]. Documented fusion partners of EWSR1 include POU5F1, PBX1, and ZNF444 [46–48].

24.6 Eccrine Poroma

24.6.1 Clinical Features

It is estimated that sweat gland tumors represent approximately 1 % of cutaneous growths, and eccrine poroma accounts for 10 % of these cases with no reported gender or racial predilection [49]. Eccrine poromas typically occur in adults over 40 years old, although cases in children exist.

Eccrine poromas most commonly present as an asymptomatic, solitary nodule or papulonodule on the palm or sole, but they may occur on any area of the body that has a large number of eccrine sweat glands, including the fingers, trunk, head, and neck (Fig. 24.13) [49]. There are reports of porocarcinoma in long-standing lesions as well as recurrence of lesion following incomplete excision, thus making complete surgical excision the treatment of choice [49].

24.6.2 Histology

Eccrine poroma has sheets and cords of interanastamosing, bland cuboidal epithelium that grow down from the overlying epidermis (Fig. 24.14). The base of the lesion is flat, and it does not have an infiltrative deep border. Scattered ducts are present within the epidermis (Fig. 24.15). Cystic dilatations may be seen, and eosinophilic secretion is often present within them. Eosinophilic cuticles are apparent surrounding the ducts and cystic spaces. Rare mitoses are seen within the proliferations, but there is no tissue necrosis. Cytologic atypia is minimal. The underlying dermis contains abundant ectatic vessels, often located high within the papillary dermal tips.

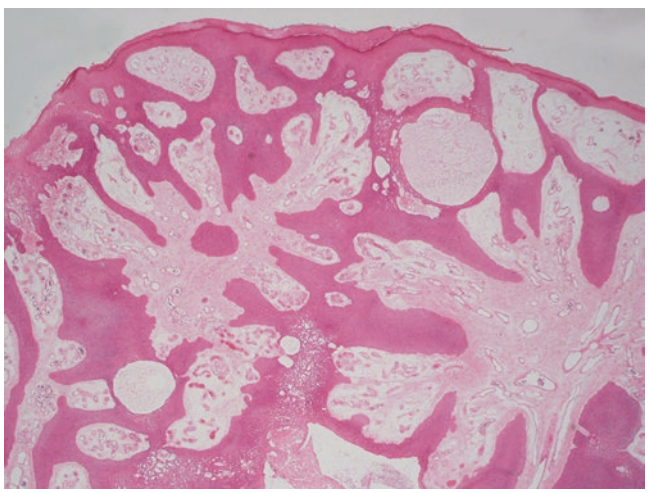

Fig. 24.14 Eccrine poroma is characterized by sheets of monomorphous cuboidal epithelium growing down from the epidermis in interanastamosing sheets

Rare malignant transformation to porocarcinoma has been described in a child [50, 51]. In this case, necrosis, cytologic atypia, an invasive growth pattern and Pagetoid extension within the epidermis were detected.

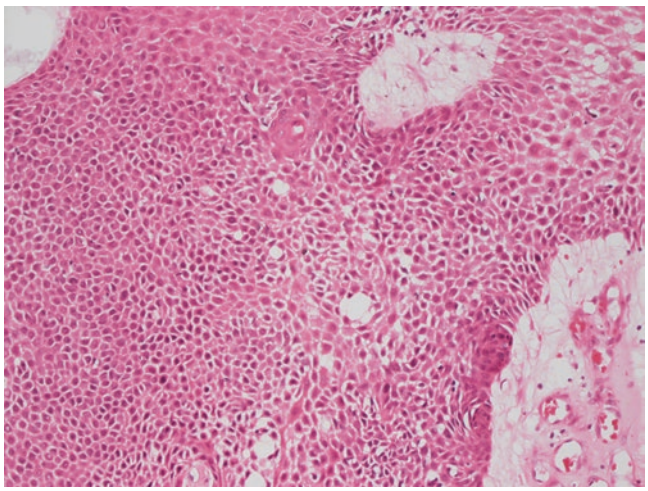

Fig. 24.15 Eccrine poroma demonstrates small glandular ducts within the sheets of monomorphous and benign-appearing epithelium

24.6.3 Pathogenesis

Eccrine poroma arises from the proliferation and expansion of basal cells of eccrine ducts. Comparative immunohistochemical studies of eccrine poroma and normal eccrine glands of the skin have shown that poroma cells have a similar immunophenotype to basal cells of eccrine ducts [52].

24.7 Papillary Eccrine Adenoma

24.7.1 Clinical Features

Papillary eccrine adenoma is an uncommon benign sweat gland tumor, most often occurring in young black women with an age range between 9 and 69 years old [53]. Papillary eccrine adenoma is described as 0.5–2 cm reddish brown or gray nodules or papules, most often presenting on the wrist or foot. There are no reports of metastasis, and there is low likelihood of recurrence with complete excision of the lesion [53].

24.7.2 Histology

Histologic changes of papillary eccrine adenoma are those of a well-circumscribed proliferation of dilated eccrine structures present in the dermis. The glandular structures are lined by one or several layers of cuboidal epithelium resembling eccrine structures [54]. There are abundant infoldings and papillomatous projections into the glandular lumen (Figs. 24.16 and 24.17). Each of the glandular units remains intact, and there is no invasion into the surrounding dermis. Cytologic atypia and mitotic activity are minimal. The surrounding stroma can be somewhat fibrotic [55]. There is great overlap between papillary eccrine adenoma and what has been called tubular apocrine adenoma. Some authors consider them to be synonymous. They may represent a spectrum of benign glandular neoplasms of cutaneous appendages that demonstrate varying degrees of apocrine differentiation [56]. The distinction is of academic interest only as these tumors have the same propensity to recur, but they do not metastasize [57].

The differential diagnosis includes eccrine carcinoma. These tumors are quite rare in children and are differentiated from papillary eccrine adenoma based upon cytologic

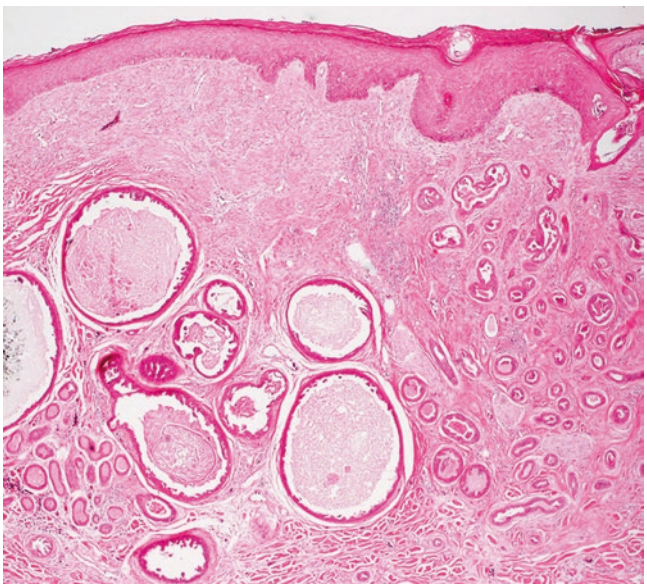

Fig. 24.16 Papillary eccrine adenoma demonstrates well-formed glands within the dermis, some of which contain papillary infoldings

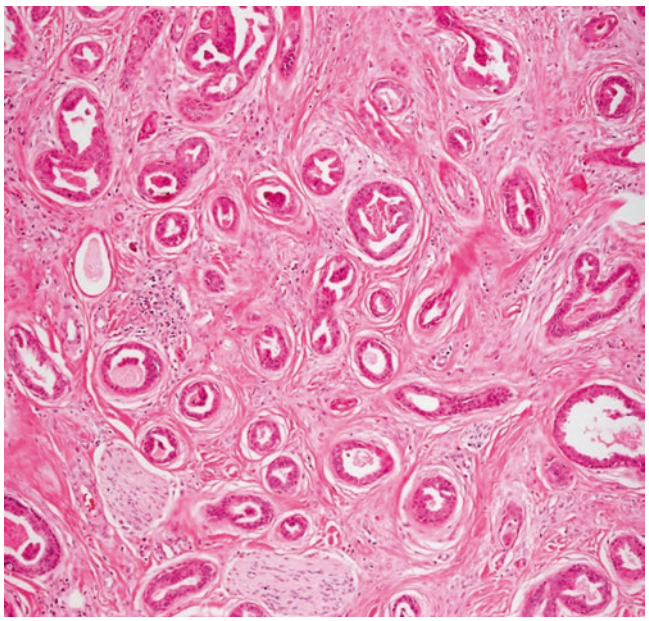

Fig. 24.17 Dermal glandular structures are lined by cells with either eccrine or apocrine appearance in papillary eccrine adenoma

atypia, mitotic activity, foci of necrosis, and an invasive growth pattern.

24.8 Syringoma

24.8.1 Clinical Features

Syringomas occur most frequently in adolescence and early adulthood with greater prevalence among females [58]. Familial cases have been reported as well as increased incidence in certain patient populations, such as those with Down syndrome [58].

Syringomas are small, skin-colored to pink papules occasionally with a translucent appearance, most commonly distributed symmetrically on the face (specifically at the lower eyelids and cheeks), neck, and upper chest [58]. Syringomas are benign but may be treated for cosmetic purposes [58].

24.8.2 Histology

Histologic features of syringomas include a proliferation of well-formed tubular and ductular structures coursing in a dense fibrous stroma in the superficial portion of the dermis (Fig. 24.18). The dense stroma clearly delineates this benign proliferation from the surrounding uninvolved dermis, and it is a useful feature for establishing the diagnosis. Small tadpole-like or comma-like structures and other fully mature eccrine structures are present (Fig. 24.19). Two layers of cuboidal epithelium that resemble eccrine ductular cells line the structures. Cytologic atypia is not present, and mitotic activity is quite rare. A variant that is comprised of ductular lining cells with abundant clear cytoplasm, known as a clear cell syringoma, is found in some patients with diabetes [59, 60].

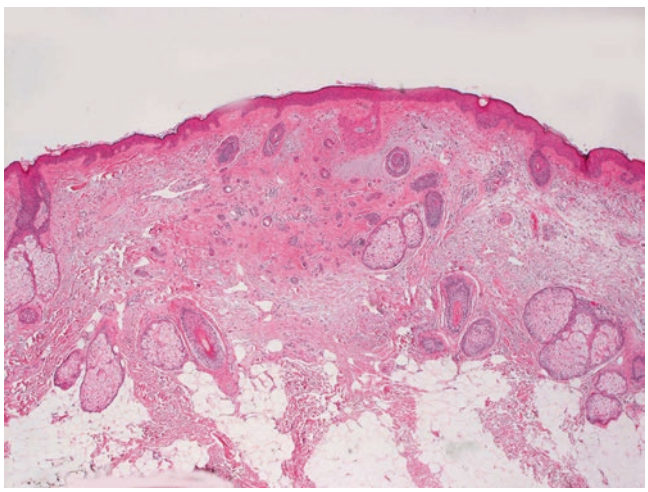

Fig. 24.18 Small glandular structures coursing in fibrous stroma are present in the superficial dermis in syringoma

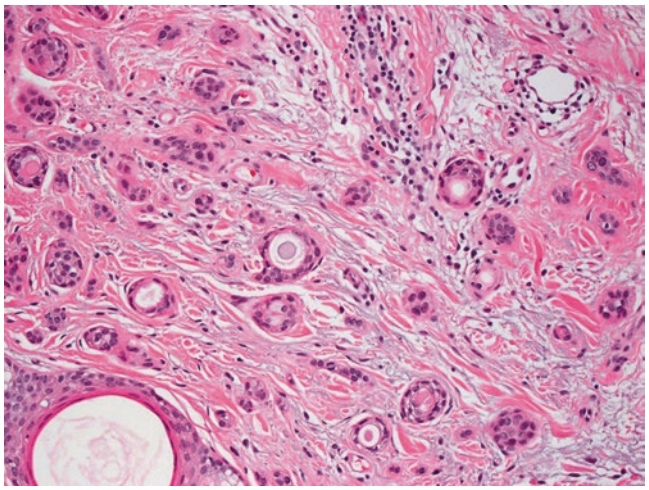

Fig. 24.19 Tadpole-like configurations and well-formed ductules are seen in syringoma

The major differential diagnosis of syringoma is microcystic adnexal carcinoma (MAC), which is a tumor that essentially does not occur in children. MAC differs from syringoma in that it is not sharply circumscribed but has a deeply invasive growth pattern with perineural invasion. There is also biphasic differentiation with a follicular component in MAC. While cytologic atypia and mitotic activity are not seen in MAC, the deep invasion and lack of circumscription make histologic distinction possible. Desmoplastic trichoepithelioma may also enter the differential diagnosis, but it is distinguished based upon cystic structures with granular layers and keratin-filled centers as opposed to the ductular structures seen in syringoma.

24.9 Hidradenoma Papilliferum

24.9.1 Clinical Features

Hidradenoma papilliferum often occurs in adult females [61]. This lesion has nondescript clinical features and is characterized as a solitary subcutaneous nodule, occasionally with a cystic quality that may contain serous material. Hidradenoma papilliferum specifically affects anogenital mammary-like glands in the vulva and perianal skin [61]. The lesion is benign but may be surgically excised if desired.

24.9.2 Histology

Hidradenoma papilliferum occurs most frequently on the vulva, but it has been described in many other sites [62]. The

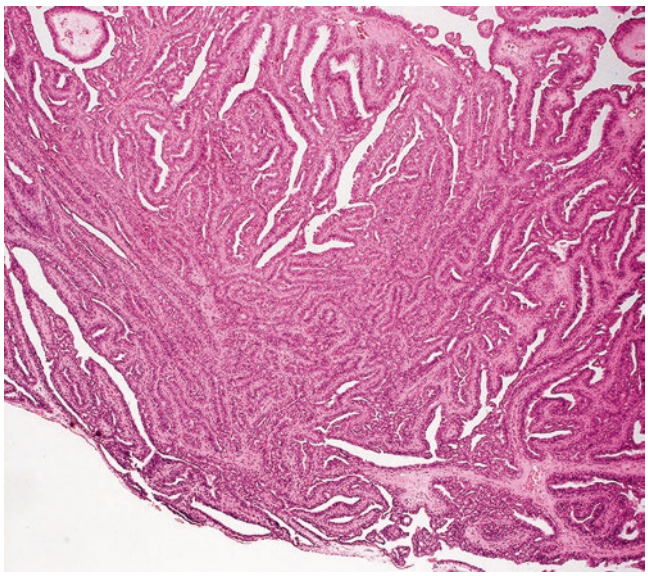

Fig. 24.20 Glandular epithelium with a papillomatous architecture is seen in hidradenoma papilliferum

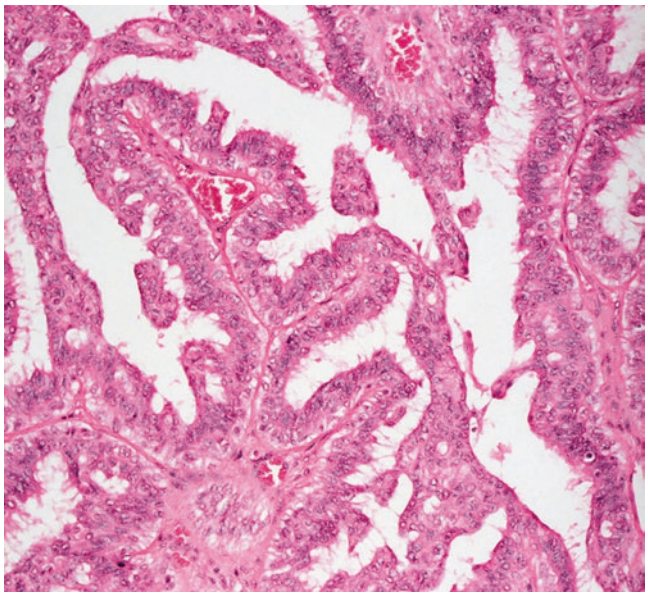

Fig. 24.21 Apocrine-type epithelium with hobnailing into the lumen is seen lining the papillomatous spaces in hidradenoma papilliferum

usual histologic presentation is that of a sharply circumscribed dermal-based tumor with no connection to the overlying epidermis. However, invagination down from the epidermis has been observed in some cases [63, 64]. The tumor consists of epithelial-lined papillomatous growths with focal cystic spaces (Figs. 24.20 and 24.21). The lining is composed of cuboidal or columnar-type epithelium with focal subjacent myoepithelial cells. Mitoses can be found within the epithelial lining, but are not predictive of biologic behavior [65]. Oxyphilic or apocrine metaplasia, characterized by marked eosinophilia within the lining epithelial cells, occurs in some cases [66]. Clear cell metaplasia of the myoepithelial layer has also been described [66]. The intervening stroma is fibrous, but unlike syringocystadenoma papilliferum, which shares some histologic characteristics, plasma cells do not fill the surrounding dermis. Recent literature suggests that these tumors arise from mammary-like anogenital glands [67]. Fine needle aspiration biopsy is not the standard procedure for establishing the diagnosis, but it has been described as effective [68].

Malignant transformation of hidradenoma papilliferum is exceedingly uncommon [61]. No cases have been described in children. Several cases, including one that underwent malignant transformation, have been associated with human papillomavirus 16 , but this association remains unclear [61, 66].

The histologic differential diagnosis includes syringocystadenoma papilliferum which is distinguished primarily based upon its anatomic site with a predilection for the scalp and forehead. Other distinguishing features include the connection to the epidermis and plasma cell infiltrate. These features are present in syringocystadenoma papilliferum but are not ordinarily seen in hidradenoma papilliferum. Metastatic carcinoma might also enter the differential diagnosis, but the sharp circumscription, lack of significant cytologic atypia, relative paucity of mitoses in most cases, and lack of necrosis all favor a diagnosis of hidradenoma papilliferum.

24.10 Syringocystadenoma Papilliferum

24.10.1 Clinical Features

More than half of syringocystadenoma papilliferum are present at birth with an additional 13–15 % of cases presenting during childhood [69]. Up to 40 % of cases occur within a nevus sebaceous, while the remainder present de novo.

Syringocystadenoma papilliferum commonly occurs on the scalp and forehead. The clinical appearance of this tumor is variable. The surface may be smooth or verrucous [69]. Syringocystadenoma papilliferum is most commonly described as a 1–4 cm solitary plaque with overlying alopecia. Occasionally the plaque may be comprised of discrete small papules in a linear configuration with central invagination, reminiscent of molluscum contagiosum. The surface may become more mammillated and exophytic during puberty or pregnancy. Lesions may ulcerate with subsequent crusting. Very rarely, malignant transformation may occur in later life with a few reports of syringocystadenocarcinoma occurring in adults [69].

24.10.2 Histology

Syringocystadenoma papilliferum invaginates down from an otherwise unremarkable epidermis (Fig. 24.22). Two layers

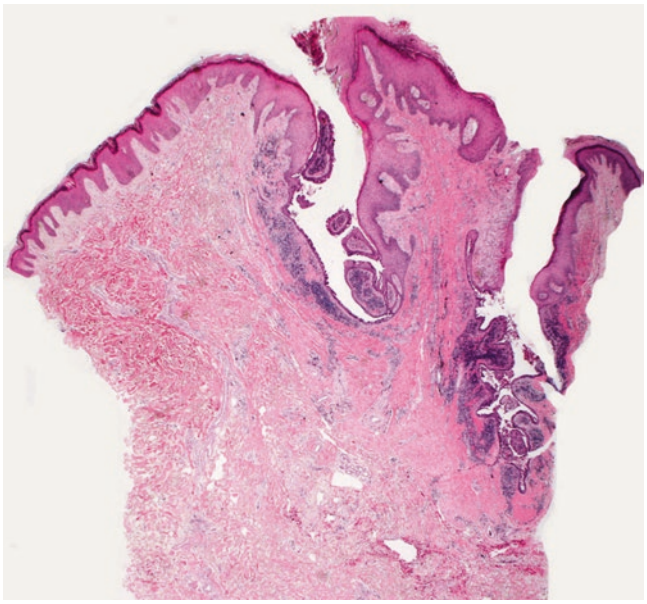

Fig. 24.22 Syringocystadenoma papilliferum demonstrates an invagination down from the surface epidermis and is lined by glandular epithelium

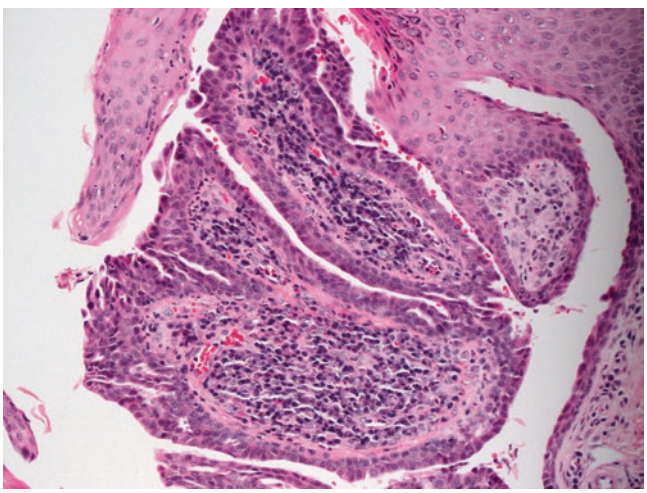

Fig. 24.23 A papillomatous growth pattern lined by glandular epithelium and a dense underlying plasmacellular infiltrate are seen in syringocystadenoma papilliferum

of cells line the cystic invagination. The layer closest to the cystic cavity is a layer of columnar cells that are eosinophilic and occasionally demonstrate apocrine-type decapitation secretion. Deep to this layer of cells is a layer of flattened myoepithelial cells. The superficial portion of the invagination may be lined with epithelial cells that have undergone squamous metaplasia [70]. Emanating from the cystic space are papillary infoldings of the epithelial lining (Fig. 24.23). As they extend deep to the invagination, these papillomatous infoldings may give rise to apocrine cystadenomas [71]. Deep to the lining is a brisk inflammatory infiltrate that is composed primarily of plasma cells.

Syringocystadenoma papilliferum is one of the most common tumors to arise within nevus sebaceous [72]. However, up to two thirds of cases arise *de novo* and are not associated with this hamartoma [73]. A rare agminated clustering of these tumors has been described in a child [70].

24.10.3 Pathogenesis

Syringocystadenoma papilliferum harbors HRAS mutations, which are present in 26 % of cases of sporadic tumors [74]. The HRAS hotspot mutation (c.37GNC) is the predominant mutation in this lesion. In addition to HRAS mutations, BRAF V600E mutation has been found in 50 % of sporadic cases [74, 75]. These findings indicate that activating mutations in HRAS and BRAF contribute to the tumorigenesis of syringocystadenoma papilliferum. Other studies have suggested that p16 may also be a relevant tumor suppressor gene in the development of this tumor [76].

24.11 Tubular Apocrine Adenoma

24.11.1 Clinical Features

Tubular apocrine adenoma is a rare sweat gland neoplasm most often occurring on the scalp, although reports exist of tumors at the lower extremities, back, and genitals, including a case presenting on the vaginal introitus of an 8-year-old girl [77]. The tumors are described as a slow-growing nodule or papule that may be darkly pigmented or erythematous [77, 78]. The lesions are benign with no demonstrated potential for metastasis, but they can be locally invasive.

24.11.2 Histology

Histologic findings of tubular apocrine adenoma are identical to those described in papillary eccrine adenoma (see Sect. 24.7), and most authors believe these entities to be identical (Figs. 24.24 and 24.25) [54, 56]. Others find slight histologic distinction of no biologic significance [55].

24.12 Sebaceous Hyperplasia

24.12.1 Clinical Features

Sebaceous hyperplasia typically occurs in individuals over 40 years old [79]. Premature sebaceous hyperplasia is defined as non-pathologic proliferation of sebaceous glands occurring during or immediately following puberty, although reports in infants also exist [80]. Functional familial sebaceous hyperplasia, which is considered by some authors to be a variant of

Fig. 24.24 Tubular apocrine adenoma demonstrates well-formed glands with papillary infoldings within the dermis

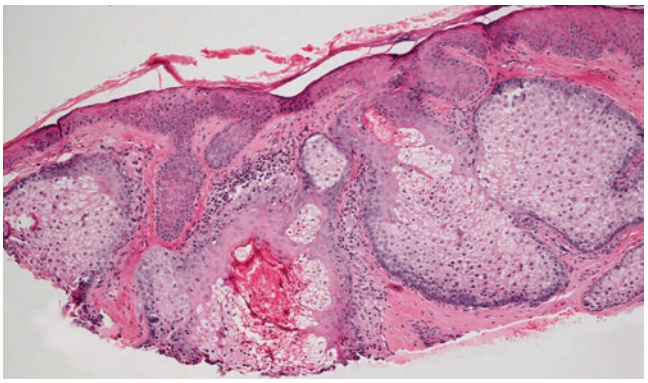

Fig. 24.26 Large and fully mature lobules of sebocytes are present in sebaceous hyperplasia

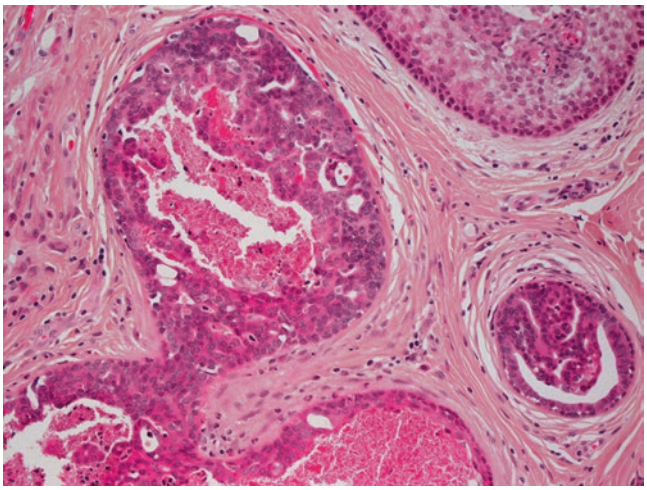

Fig. 24.25 Apocrine-type epithelium lines the papillary infoldings in tubular apocrine adenoma

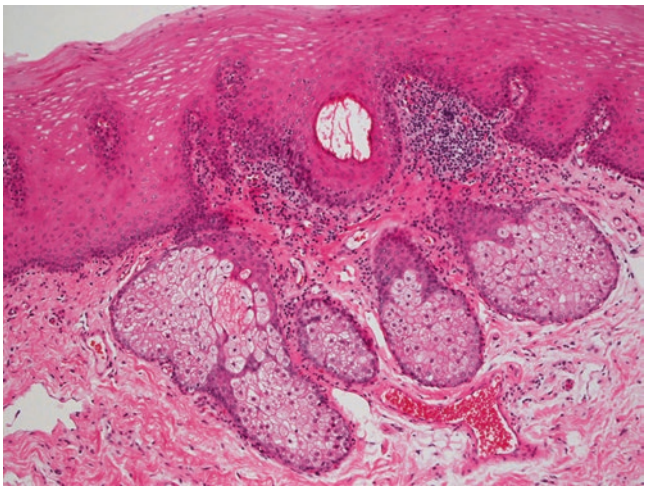

Fig. 24.27 Mature and fully developed sebaceous glands are seen beneath normal mucosa in Fordyce spot

nevus sebaceous of Jadassohn, often presents in pubertal children. No gender predilection has been identified.

Sebaceous hyperplasia is characterized by yellowish small papules, typically located on the forehead, cheeks, neck, and lips. Lesions may coalesce linearly or form Blaschkoid plaques [81]. Lesions also occur less frequently on the oral mucous membranes, vulva, chest, areola, and penile shaft. Sebaceous hyperplasia and visible sebaceous glands on the oral and genital mucosa are termed Fordyce spots. Functional familial sebaceous hyperplasia is characterized by a yellowish plaque with peau d'orange surface on the face, chest, and upper back, with sparing around the orbits, nose, and ears [79]. Treatment may be pursued for cosmetic purposes with lesions amenable to retinoids or various surgical therapies.

24.12.2 Histology

Histologic findings include enlarged clusters of mature sebocytes that have a single layer of basaloid cells with full maturation with progression into the center of each cluster of cells (Fig. 24.26). Mitotic activity is rare, and cytologic atypia is not present [82]. The frequency of sebaceous hyperplasia may be increased in individuals who have undergone organ transplantation [83]. Similar histologic changes, although with secondary inflammation and glandular rupture and distortion, are seen in neonates with acne neonatorum [84].

A *Fordyce spot* demonstrates the presence of ectopic sebaceous glands on either genital or oral mucosa without concomitant follicular units (Fig. 24.27) [85]. The normal appearing sebaceous glands are connected to the overlying

epidermis by a duct. There is neither host immune response nor cytologic atypia in these lesions. In some cases, the glandular units may appear slightly hyperplastic. Recently, increased incidence of Fordyce spots has been recognized in patients with Lynch syndrome [86, 87].

24.12.3 Pathogenesis

Sebaceous gland hyperplasia is a benign hypertrophy of normal sebaceous glands. Sebaceous hyperplasia commonly occurs in adults with aging, but some cases in children have been reported. Sebaceous hyperplasia has been reported to occur in association with cyclosporine treatment, which is an immunosuppressive agent to prevent tissue rejection after solid organ transplantation [88]. It is present in 6–30 % of immunosuppressed organ transplant recipients as compared with 1 % of matched controls [83, 89, 90]. In these cases, the patients were receiving cyclosporine, suggesting that cyclosporine may be a causative factor in the development of sebaceous hyperplasia. Of note, this phenomenon has not been reported in children who received organ transplants. This may be due to the immaturity of the pilosebaceous unit in children [90].

24.13 Sebaceous Adenoma

24.13.1 Clinical Features

Sebaceous adenomas are rare tumors, typically presenting in individuals over 60 years old. They are the most common type of sebaceous neoplasm seen in Muir–Torre syndrome [79, 91].

Sebaceous adenomas appear as subcentimeter skin-colored to slightly yellow papules or nodules on the head, neck, and, less frequently, upper trunk [79]. While they represent a benign process, their association with Muir–Torre syndrome warrants evaluation for other cutaneous stigmata of disease as well as screening for urinary and colonic adenocarcinoma. Additionally, some authors argue for complete excision to rule out a basal cell carcinoma with sebaceous differentiation or a sebaceous carcinoma.

24.13.2 Histology

Sebaceous adenomas present as dermal tumors that may or may not arise from the overlying epidermis. They are lobulated and well circumscribed (Fig. 24.28). Each of the lobules has several layers of basaloid keratinocytes at the periphery with progressive maturation to mature sebocytes towards the center of each lobule (Fig. 24.29). Scattered mitoses may be seen, but they are not atypical. Cytologic atypia is not prominent, and necrosis is not apparent. Cases that have cystic spaces in the center are more frequently associated with Muir–Torre syndrome and mutations in DNA mismatch repair genes [92, 93].

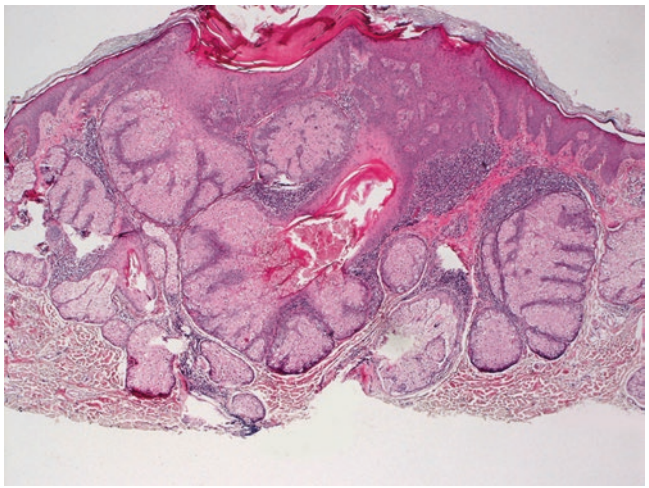

Fig. 24.28 Sharply circumscribed lobules of sebocytes are present in sebaceous adenoma

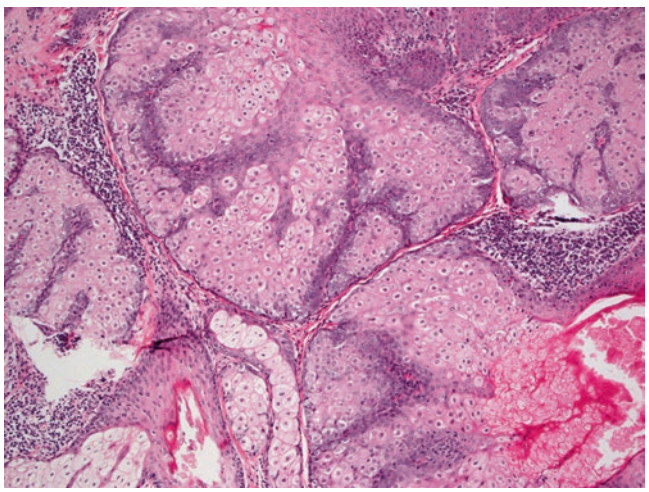

Fig. 24.29 Lobules of sebocytes with incomplete maturation and a slightly increased number of basaloid cells at the periphery characterize sebaceous adenomas

24.13.3 Pathogenesis

Sebaceous adenoma has been found in association with Muir–Torre syndrome [94, 95]. About 40 % of Muir–Torre syndrome patients with sebaceous adenoma have visceral

malignancies [95, 96]. In this syndrome, skin manifestations are found before the diagnosis of visceral malignancy in 22 %, concurrently in 6 %, and afterward in 56 % of the cases examined [94, 97]. Thus, skin lesions may serve as initial clues for earlier screening and detection of visceral malignancy.

Muir–Torre syndrome is thought to be a variant of hereditary nonpolyposis colorectal cancer. Both disorders are autosomal dominant with mutations in the genes hMSH2 and hMLH1 [98, 99]. In Muir–Torre syndrome, the majority of mutations are in hMSH2 gene. hMSH2 and hMLH1 are DNA mismatch repair genes, and alterations of these genes have been linked to microsatellite instability and defects in mismatch repair during DNA replication that are found in hereditary nonpolyposis colorectal cancer [100]. The identification of these gene mutations could aid in the histologic and immunohistochemical studies for hMSH2 and hMLH1 protein expression in the molecular diagnostic work-up of Muir–Torre syndrome [94].

24.14 Basal Cell Carcinoma

24.14.1 Clinical Features

Basal cell carcinoma (BCC) is the most common type of skin cancer, accounting for 75 % of nonmelanoma skin cancers with peak incidence in late adulthood [101]. Occurrence in pediatric populations is exceedingly rare with only approximately a hundred de novo cases of BCC reported in children [102]. Pediatric BCC more commonly presents in the setting of a predisposing genodermatosis, such as basal cell nevus syndrome, xeroderma pigmentosum, Bazex syndrome, and Rombo syndrome [101]. Additional risk factors include light skin phenotype, extensive sun exposure, radiotherapy-treated cancers, and solid organ transplantation [101–103].

BCCs usually occur on the head and neck [101, 102, 104, 105]. Various morphologic varieties exist with tumors most commonly presenting as a pearly, telangiectatic papule that may have associated pigmentation. Alternative presentations include more nondescript, poorly circumscribed erythematous and crusted papules or plaques. Tumors typically have an indolent clinical course and infrequently metastasize, although they can be locally invasive [104]. Morpheaform variants of BCC tend to have a more aggressive clinical course [104].

24.14.2 Histology

The histologic findings of BCC in children, for the most part, are identical to BCC that arise in adults. Basaloid proliferations grow down from the overlying basal layer of the epidermis into the dermis (Fig. 24.30). The tumor islands may remain connected to the epidermis in the superficial variant, or may grow as island nests or small cords in the deeper dermis with varying degrees of infiltration. The tumor islands demonstrate peripheral palisading of basal cells. The cells have a high mitotic rate, high nuclear to cytoplasmic ratio, and high number of necrotic cells. There is characteristic cleft formation between the epithelial islands and the myxoid and cellular tumor stroma. Varying degrees of follicular differentiation with cyst formation and keratinization are present (Fig. 24.31). Some authors suggest that there is more follicular differentiation in tumors associated with the basal cell nevus syndrome, but others refute this contention. Other BCC may demonstrate adenoid cystic growth patterns, and some demonstrate huge cysts with necrotic centers. The dermal component may be nodular or have a more infiltrative growth pattern. Morpheaform tumors are characterized by a predominance of dense sclerotic stroma, and only thin epi-

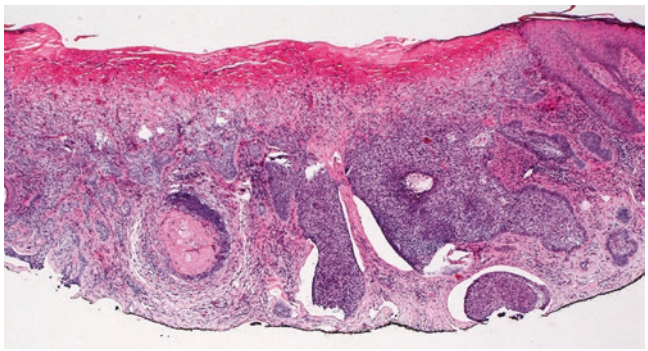

Fig. 24.30 Basal cell carcinoma demonstrates palisaded nests of basaloid epithelium with clefting that separates the epidermis from surrounding mucinous stroma

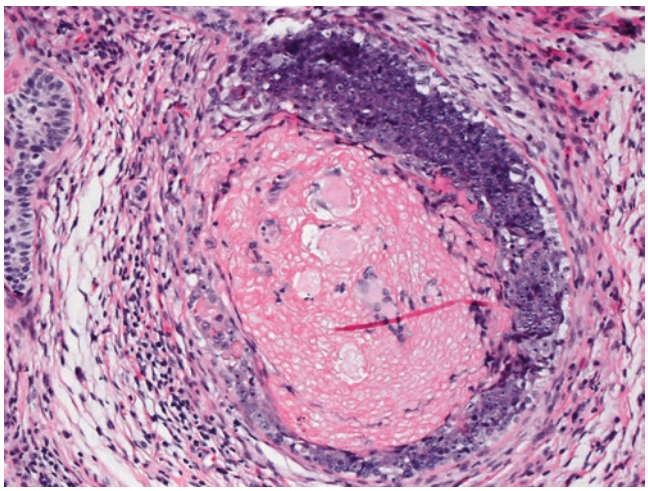

Fig. 24.31 Follicular differentiation with abrupt keratinization is seen in some basal cell carcinomas

thelial islands. These tumors are the most difficult to completely excise and have the high rate of recurrence. Pigmented BCCs are not uncommon, and may occur with increased frequency in patients with the basal cell nevus syndrome [106].

The major differential diagnosis of BCC is trichoepithelioma, which is a much more common tumor in children. Trichoepithelioma has more extensive follicular differentiation, often with readily apparent papillary mesenchymal bodies. The tumor islands do not have good peripheral palisade, and the nuclear to cytoplasmic ratio is not as high as that seen in BCC. The stroma is more eosinophilic and not ordinarily myxoid as in BCC. The cleft formation characteristic of basal cell carcinoma is not present in trichoepithelioma.

24.14.3 Pathogenesis

Genetic, immunological, and environmental factors influence the development of basal cell carcinoma. The sonic hedgehog–patched signaling pathway is important in the pathogenesis of sporadic BCC and in nevoid basal cell carcinoma syndrome (Gorlin syndrome), which is an autosomal dominant disease with multiple BCCs, pits on the palms and soles, jaw cysts, and other developmental abnormalities [107, 108]. The sonic hedgehog–patched pathway consists of three major interacting proteins: sonic hedgehog (SHH) protein, Patched protein, and Smoothened protein. SHH binds to Patched, thus releasing Smoothened to transduce growth signals [107]. Activating mutations in this pathway have been found in BCC and Gorlin syndrome. Mutations in the tumor suppressor gene p53 are also found in BCC [109]. Environmental factors, such as exposure to ultraviolet light and ionizing radiation, also appear to play a role in the pathogenesis of BCC [109, 110]. Immunodeficiency increases the risk of developing BCC as seen in organ transplant recipients and those with HIV infection [111, 112].

24.15 Squamous Cell Carcinoma, Keratoacanthoma and Bowenoid Papulosis

24.15.1 Clinical Features

The incidence of *squamous cell carcinoma* (SCC) in children is exceedingly rare with most affected children having a predisposing condition [113]. Reported risk factors include photosensitive genodermatoses, such as xeroderma pigmentosum, human papillomavirus infection, organ transplantation, history of chemotherapy with immunosuppression, radiation therapy, as well as chronic wounds and scars as seen in recessive dystrophic epidermolysis bullosa or pansclerotic morphea [114, 115]. SCC more commonly occurs in individuals with lighter skin with an increasing incidence noted in both males and females in recent studies [113].

SCC typically presents as indurated, scaled, and erythematous papules or plaques. Lesions may be necrotic with secondary ulceration and crusting. SCC primarily occurs on sun-exposed areas of the skin, most frequently on the head and neck and especially at the lower lip and pinna of the ear [113]. Smaller lesions in sun-exposed areas typically have a more benign and indolent course than lesions arising in areas of previous trauma (such as scars, radiation fields and chronic wounds), which have a greater tendency to metastasize [115, 116].

Solitary *keratoacanthoma* typically appears in older adults with fair skin [117]. Multiple keratoacanthomas, in comparison, tend to appear in adolescence or young adulthood, with some reports in infancy [117]. Sporadic and rare familial cases with autosomal dominant patterning (Ferguson–Smith syndrome) have been reported in cases of multifocal disease with males being more frequently affected.

Keratoacanthomas are 1–3 cm, firm and dome-shaped nodules with a central hyperkeratotic plug overlying a keratin-filled core. They are characterized by rapid growth with eventual spontaneous involution, and atrophic or cribriform scarring at the affected site [117]. In the multifocal subtype of Ferguson–Smith syndrome, lesions tend to appear in photoexposed areas of the body [117]. Keratoacanthomas may cause destruction secondary to local invasion and metastasis, although no reports of fatality exist [118]. For solitary lesions, complete surgical excision is the treatment of choice, but risk of recurrence is 1–8 %. Multiple lesions can be treated with retinoids or intralesional chemotherapy.

Bowenoid papulosis is not frequently seen in children [119]. Reported associations include infection with human immunodeficiency virus, sexual abuse, and severe atopic dermatitis [58, 120, 121]. It has been suggested that Bowenoid papulosis exists along the spectrum of condyloma acuminatum and carcinoma in situ with human papillomavirus serving as a factor in disease etiology.

Lesions of Bowenoid papulosis are reddish brown, flat papules affecting the genital mucosa. Spontaneous resolution of lesions may occur over months to years [58, 121]. However, more invasive disease, particularly in the setting of immunosuppression, may warrant therapy with treatment modality dependent on the extent of disease [120].

24.15.2 Histology

SCC is quite rare in children and displays the same histologic changes as SCC arising in adults [122, 123]. While childhood onset tumors are a result of genetic diseases or

immunosuppression, some tumors develop following radiation or from chronic nonhealing wounds [124–128]. Others are probably induced by human papillomavirus (HPV) infection [129]. Another group arises from within nevus sebaceous of Jadassohn [72].

In SCC, there is a proliferation of atypical squamous cells growing down from the epidermis. The cellular atypia starts within the basal layer, and extends both upward to develop squamous cell carcinoma in-situ and downward as it invades the basement membrane and becomes an invasive SCC (Figs. 24.32 and 24.33). The tumor cells are usually large with abundant eosinophilic cytoplasm and enlarged vesicular nuclei. Nuclear pleomorphism is present to varying degrees depending upon how well differentiated the tumor is. Keratin pearls may be present in well-differentiated lesions, while poorly-differentiated lesions may show little evidence of keratinization and little cytoplasm. Perineural and vascular invasion can confer an increased risk of metastasis and local recurrence. Some SCC show a spindle-shaped proliferation, and others have a more acantholytic appearance.

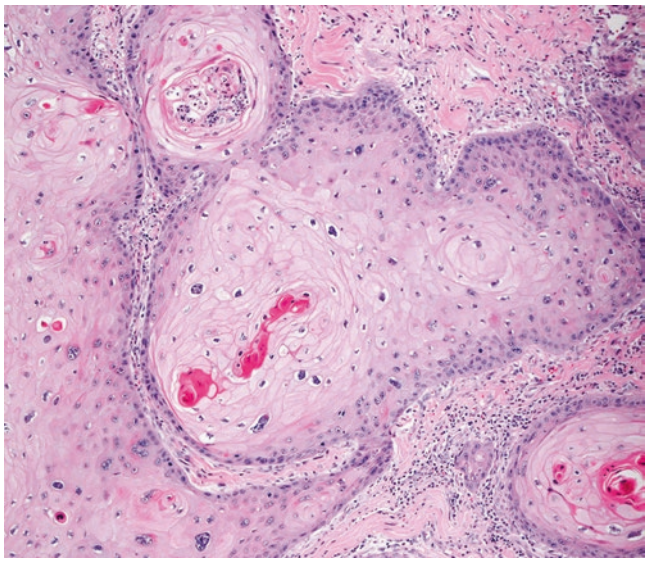

Fig. 24.32 Well-differentiated nests of squamous epithelium invade the epidermis and show viral cytopathic atypia and pleomorphism in HPV-related squamous cell carcinoma

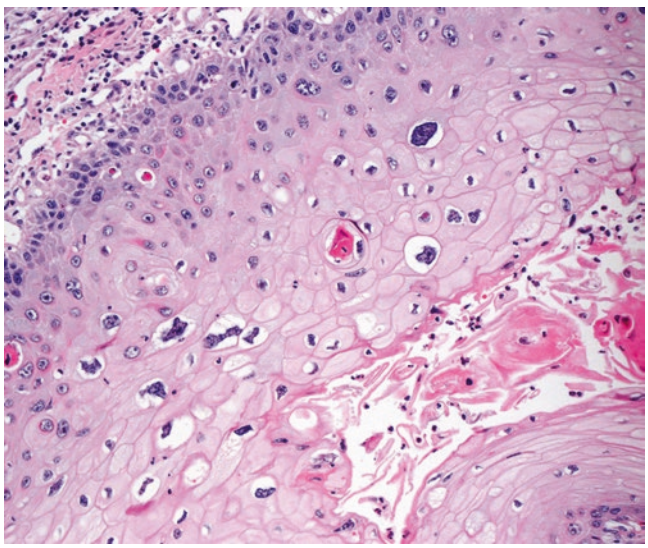

Fig. 24.33 Viral cytopathic changes are pronounced in some cases of squamous cell carcinoma

Keratoacanthoma is probably best regarded as a variant of well-differentiated SCC that engenders a brisk and effective host response, resulting in regression. The tumor has a characteristic cup-shaped architecture, and in the proliferative phase, it is indistinguishable from a well-differentiated SCC (Figs. 24.34, 24.35, and 24.36). A brisk host immune response results in flattening of the epidermal growth and scarring in the underlying dermis. The cup shape seen during the proliferative phase flattens out, and it becomes difficult to make a definitive diagnosis. Children with Ferguson–Smith syndrome may develop multiple small keratoacanthomas.

Histologic findings of Bowenoid papulosis are those of squamous cell carcinoma in-situ. There is full-thickness epidermal atypia with lack of keratinocyte maturation in the epidermis (Fig. 24.37). Scattered cells demonstrate pronounced atypia, and mitoses are increased within the epidermis (Fig. 24.38). Overlying parakeratosis is diffuse and confluent. The basement membrane is intact, and there is no dermal invasion. Viral cytopathic changes are identified in some cases. HPV 16 is the most frequently implicated virus in the pathogenesis of these lesions.

Pseudoepitheliomatous hyperplasia is a major differential diagnosis that may be confused with SCC. Pseudoepitheliomatous hyperplasia occurs in many settings,

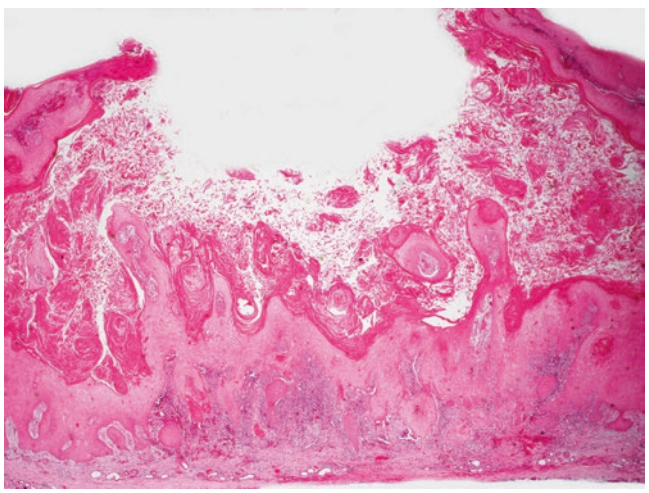

Fig. 24.34 A cup-shaped epidermal proliferation with a central keratin plug is a key feature of a keratoacanthoma type of squamous cell carcinoma

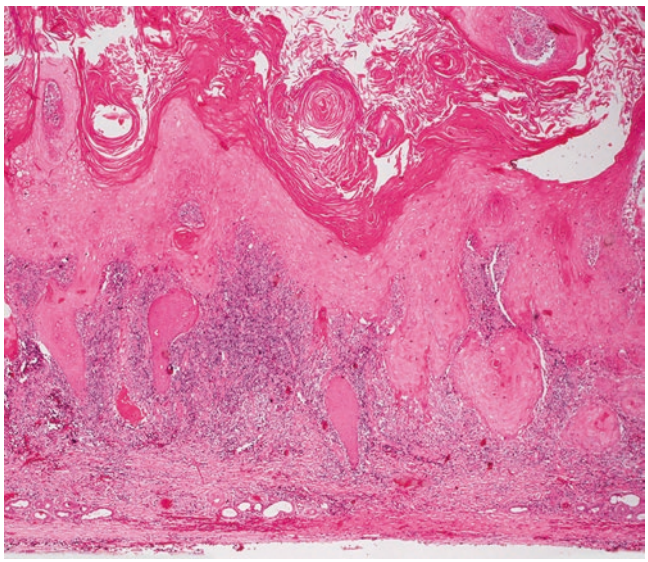

Fig. 24.35 Well-differentiated nests of squamous epithelium grow down into the dermis in a keratoacanthoma type of squamous cell carcinoma

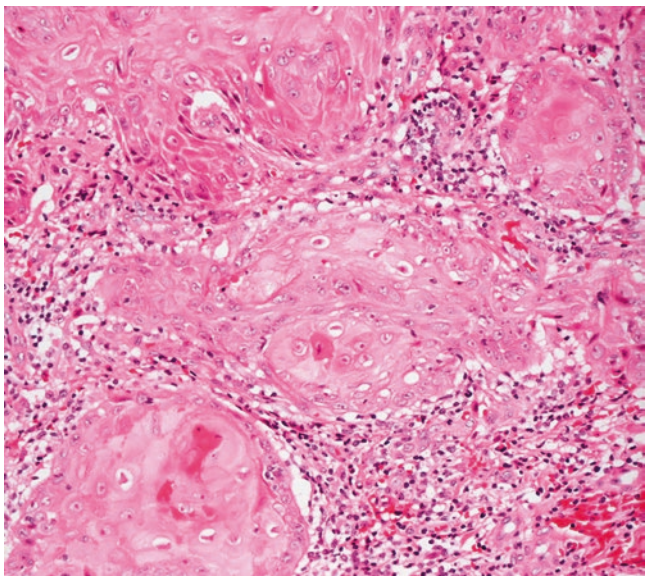

Fig. 24.36 At high magnification, the nests of squamous epithelium in keratoacanthoma are indistinguishable from other well-differentiated squamous cell carcinomas

including deep fungal and mycobacterial infections, non-healing wounds, halogenodermas, as well as in association with other tumors, such as granular cell tumors and Spitz nevi [130, 131]. Close attention to the clinical situation, other subtle histologic findings, and the relatively slight atypia in reactive conditions should make the distinction straightforward in most cases.

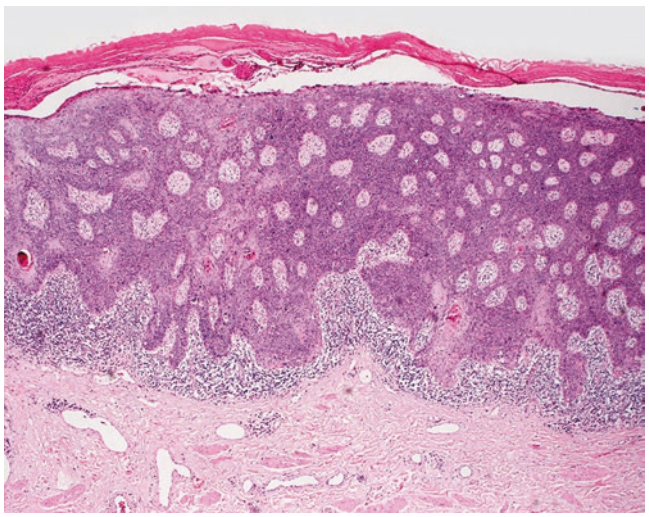

Fig. 24.37 Bowenoid papulosis is characterized by full-thickness epidermal atypia and focal acanthosis

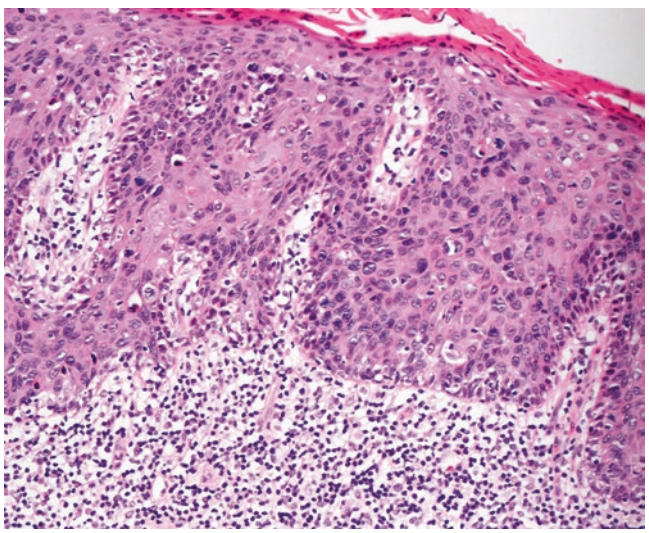

Fig. 24.38 Keratinocytes lack the normal maturation sequence in Bowenoid papulosis and demonstrate nuclear pleomorphism

24.16 Acanthoma Fissuratum

24.16.1 Clinical Features

Acanthoma fissuratum is characterized by a well-demarcated, lichenified, erythematous to hyperpigmented plaque localized to areas of the skin exposed to persistent low-grade pressure or friction [132]. Acanthoma fissuratum typically resolves over weeks to months once the inciting trauma is removed.

24.16.2 Histology

Histologic findings in acanthoma fissuratum are nonspecific and must be correlated with the clinical information to establish a diagnosis. The epidermis is acanthotic with overlying hyperkeratosis and elongation of rete ridges (Figs. 24.39 and 24.40). The granular layer is increased in thickness. In the center of the lesion, attenuation of the epidermis and focal ulceration develop. The underlying dermis contains increased small vessels, fibroblasts, and ultimately scarring. There is a mixed inflammatory infiltrate consisting primarily of lymphocytes and histiocytes with scattered plasma cells.

The differential diagnosis includes lichen simplex chronicus and prurigo nodularis with distinction made based primarily upon clinical features.

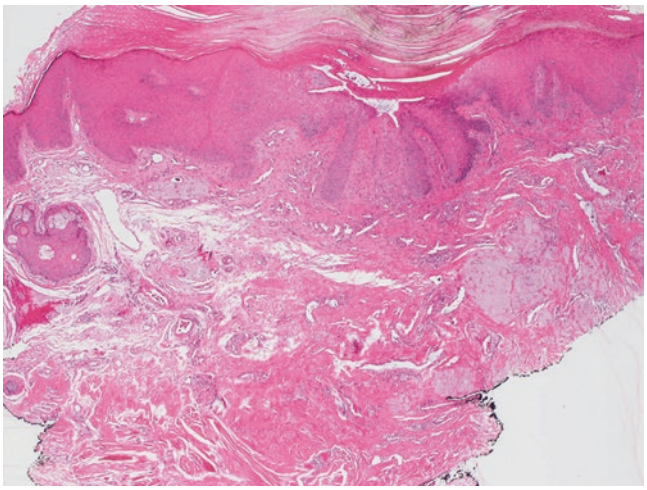

Fig. 24.39 Acanthoma fissuratum demonstrates hyperkeratosis, acanthosis, and often a focal disruption in the epidermal surface

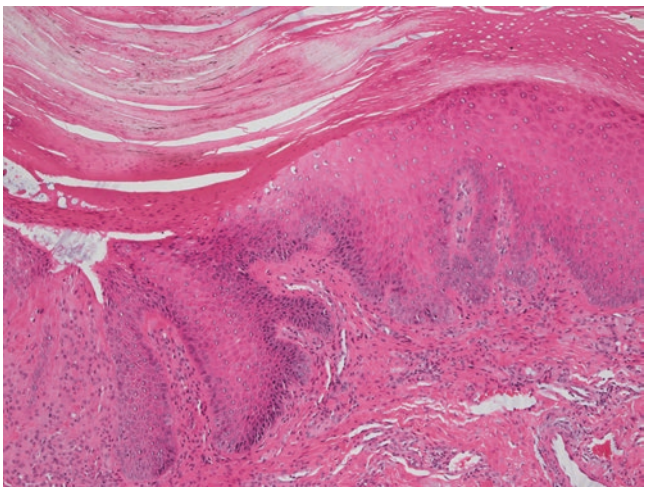

Fig. 24.40 Parakeratosis and orthokeratotic hyperkeratosis overlie an acanthotic epidermis and dermal fibrosis in acanthoma fissuratum

24.16.3 Pathogenesis

Acanthoma fissuratum is a keratotic papule or nodule that develops at sites of constant irritation, such as under eyeglasses or in the oral cavity. Chronic contact irritation is believed to be a precipitating factor in the formation of acanthoma fissuratum [133].

24.17 Dyskeratosis Congenita

24.17.1 Clinical Features

Dyskeratosis congenita is primarily inherited in an X-linked recessive pattern, although reports of autosomal recessive or autosomal dominant inheritance exist [134]. Eighty percent of affected individuals are males. Dyskeratosis congenita is defined by the classic triad of reticulate hyperpigmentation, dystrophic nails, and premalignant leukoplakia of mucosal surfaces (Figs. 24.41 and 24.42) [134, 135]. Nail dystrophy and skin manifestations typically appear within the first 10 years of life and precede the onset of leukoplakia, which more commonly occurs after 20 years of age [134, 136]. Reticulate hyperpigmentation usually involves the face, neck, shoulders and trunk, and can evolve into poikiloderma. The affected nails may develop longitudinal ridging and brittleness with subsequent nail loss over time.

Bone marrow failure can be a presenting feature of dyskeratosis congenita, occurring in more than 80 % of patients with pancytopenia being the most common complaint [134]. Malignancies develop in 10 % of patients with squamous cell carcinomas at various locations being the most commonly seen cancer. Approximately 50 % of patients with

Fig. 24.41 Oral leukoplakia (white patches and thin plaques on the tongue) overlying reticulate hyperpigmentation is a key feature of dyskeratosis congenita

Fig. 24.42 Diffuse reticulate hyperpigmentation over the palms and soles in the same patient with dyskeratosis congenita

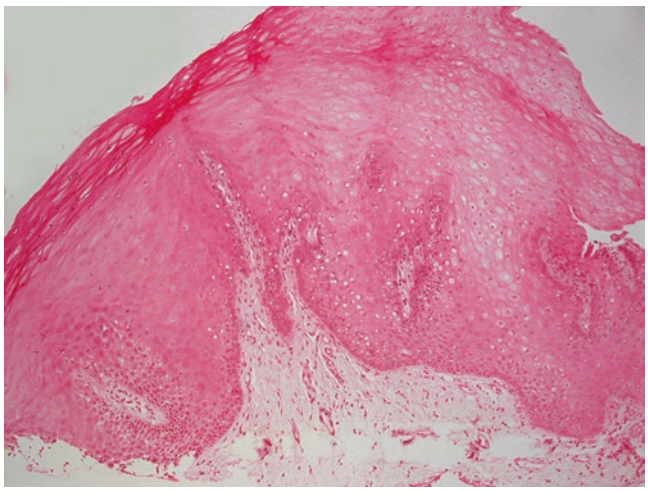

Fig. 24.43 Mucosal surfaces demonstrate acanthosis, marked hyperkeratosis, and increased cytoplasmic glycogen in dyskeratosis congenita

X-linked disease develop aplastic anemia [134]. Because of impaired immunologic functioning, patients are predisposed to infections, which is frequently the cause of death in affected persons.

24.17.2 Histology

Histologic changes are seen in the nails, oral mucosa and the skin. Nail changes include marked hyperkeratosis. Oral mucosal lesions, clinically described as leukoplakia, include a markedly thickened stratum corneum, which may be either orthokeratotic or parakeratotic (Fig. 24.43). Similar changes are seen on anal mucosal surfaces. Rare cases may also have a lichenoid inflammatory infiltrate with abundant lymphocytes and scattered plasma cells [137]. The concern with these lesions is the predisposition for malignant transformation to squamous cell carcinoma [138, 139].

The cutaneous lesions, described as reticular hyperpigmentation, show epidermal atrophy with underlying vascular telangiectasia. A mild lymphocytic infiltrate is present around the vessels in the superficial vascular plexus with some exocytosis into the basal layer. Basal cell vacuolization is present, and the rete ridges are blunted [140]. Dyskeratotic keratinocytes are present, and melanophages are seen in varying numbers in the papillary dermis. The cutaneous changes bear a striking resemblance to chronic graft vs. host disease, and close attention to clinical history is essential in making this distinction [141, 142]. Amorphous eosinophilic deposits may also be present in the papillary dermis. In these cases, macular amyloidosis enters the differential diagnosis, and the clinical history is required in order to establish the correct diagnosis [143].

24.18 Pachyonychia Congenita

24.18.1 Clinical Features

Pachyonychia congenita (PC) is an uncommon autosomal dominant condition, previously divided into two primary subtypes, PC-1 (Jadassohn–Lewandowsky type) and PC-2 (Jackson–Lawler type), but it is now categorized based on the underlying genetic defect [144]. The current classification system is based on the specific keratin gene that carries the mutation, i.e. PC-K6a, PCK6b, PC-K6c, PC-K16 and PC-K17.

Pachyonychia congenita is almost universally characterized by pronounced nail dystrophy at the hands and feet, often noted within the first year of life [145, 146]. The nails may be thickened, shortened, and friable with pronounced subungual thickening and V-shaped curvature of the nail plate. Painful plantar keratoderma, most notably along pressure points of the sole, affects 75 % of patients by 5 years of age and almost 90 % of patients by 10 years of age. Oral leukokeratosis and hoarseness within the first year of life can be seen in 70 % of affected patients, most commonly in those with PC-K6a subtype [145]. Natal teeth are often present in patients with PC-K17. Steatocystomas and eruptive vellus hair cysts appear before 20 years of age, and usually occur in those with PC-K6a, PC-K6b, or PC-K17.

From a systemic standpoint, pachyonychia congenita follows a benign course [145]. However, quality of life may be affected greatly by the abnormal appearance of the skin and nails. Additionally, delay in diagnosis may expose patients to unnecessary treatments.

24.18.2 Histology

Mucosal and skin surfaces are affected in patients with pachyonychia congenita. Mucosal changes include ballooning of the superficial layers of the epithelium with increased cytoplasmic glycogen. The epithelium is acanthotic with overlying increased parakeratosis [147]. Follicular keratoses are described in these patients, and show hyperkeratosis and acanthosis of follicular epithelium as well as keratin plugging of the follicular cavities and eccrine pores [148]. Horns of parakeratosis may be present in the overlying stratum corneum, giving the identical appearance to cornoid lamellae that may be seen in patients with pachyonychia congenita [149].

Callosities demonstrate similar degenerative changes within the upper layers of the keratinocytes with acantholysis resulting in intraepidermal blisters [150]. Hyperkeratosis, hypergranulosis, and acanthosis are seen in most biopsies of these lesions. An underlying inflammatory infiltrate is unusual [151]. Ultrastructural examination reveals abnormal clumping of keratin tonofilaments [150]. Nail hypertrophy is also a feature of pachyonychia congenita.

Some patients with pachyonychia congenita develop alopecia with characteristic histologic changes. These include pronounced miniaturization of hair follicles with retention of the pilosebaceous architecture and lack of scarring. There is overlying hyperkeratosis and parakeratosis as well as dyskeratosis of cells within the outer root sheath of the hair follicles [152, 153]. Steatocystoma multiplex occurs with increased frequency in these patients, and shares the histologic features of sporadic lesions [154, 155]. Some patients with pachyonychia congenita develop amyloid deposits within the papillary dermis that resemble those seen in macular amyloidosis [156].

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Fibrous Proliferations

25

25.1 Connective Tissue Nevus

25.1.1 Clinical Features

Connective tissue nevi frequently are present at birth but may be acquired. They occur sporadically or may be a feature of certain genodermatoses such as Proteus syndrome, Buschke Ollendorff syndrome, multiple endocrine neoplasia type 1, and tuberous sclerosis [1]. For example, the cerebriform connective tissue nevus is a pathognomonic feature of Proteus syndrome, and it is characterized by an expansive furrowed plaque, most often on the soles of the feet. Incidence and prevalence of these lesions are not known.

Connective tissue nevi are skin-colored dermal plaques frequently with overlying epidermal thickening, cobblestoned or cerebriform changes described as "pigskin" or "peau d'orange" (Fig. 25.1). They may be solitary or multiple with symmetric distribution at the back, buttocks, and extremities [1]. Connective tissue nevi are persistent. However, excision is usually not required as lesions are often asymptomatic and not cosmetically noticeable.

25.1.2 Histology

Various hamartomatous proliferations of connective tissue fall under the term connective tissue nevus and these will be described separately. However, in many cases, the patterns are mixed.

Collagenoma is the most common type of connective tissue nevus, and is characterized by a proliferation of thickened, haphazardly-oriented dense and coarse collagen bundles throughout the dermis [2] (Figs. 25.2 and 25.3). In some cases, electron microscopy has demonstrated increased number of myofibroblasts admixed with the dense collagen bundles [3]. A trichrome stain highlights the haphazard orientation of the dermal collagen bundles, and an elastic tissue stain may demonstrate fewer elastic tissue fibers within the lesional skin. In many cases, the diagnosis is subtle, and it is easiest to establish when lesional skin is compared with a biopsy taken from adjacent, clinically normal skin.

Elastoma is a hamartomatous proliferation of elastic tissue fibers. Increased elastic tissue fibers, which may appear thickened and clumped, may be readily apparent on routine histologic sections. However, the changes may not be visualized without the aid of elastic tissue stains, in which case the elastic tissue changes are easily detected [4] (Fig. 25.4). Structural anomalies within elastic tissue fibers have been observed by electron microscopy [5].

A recently described variant of connective tissue nevus has been named a *mucinous nevus*. In one case, overlying epidermal acanthosis and hyperkeratosis indicate that the mucin present in the superficial portion of the dermis occurred in concert with an epidermal nevus [6]. In other cases, typical changes of the collagenoma type of connective tissue nevus have been described, in addition to the epidermal nevus and dermal mucin [7].

A rare type of connective tissue nevus called *fibroblastic connective tissue nevus* demonstrates a poorly circumscribed accumulation of fibroblasts admixed with thickened and haphazardly-oriented collagen bundles. These lesions are located in the deep reticular dermis and may extend into the subcutis. Clusters of bland-appearing fibroblasts are seen in intersecting bundles and may entrap appendages [8]. The fibroblasts are CD34+, similar to those seen in dermatofibrosarcoma protuberans. It is important to be aware of this rare entity in order to prevent over diagnosing a malignant proliferation.

25.1.3 Pathogenesis

Connective tissue nevi are cutaneous hamartomas characterized by an abnormal proliferation of collagen, elastin, or proteoglycans [1, 9, 10]. They can occur sporadically, or in association with genetic syndromes, such as Proteus syndrome, which is characterized by progressive, mosaic, and segmental overgrowth. As mentioned above, the cerebriform connective tissue nevus is a key cutaneous marker of Proteus syndrome [11, 12].

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Fig. 25.1 Connective tissue nevus presents as symmetric skin-colored, subcutaneous plaques in linear bands along the upper back

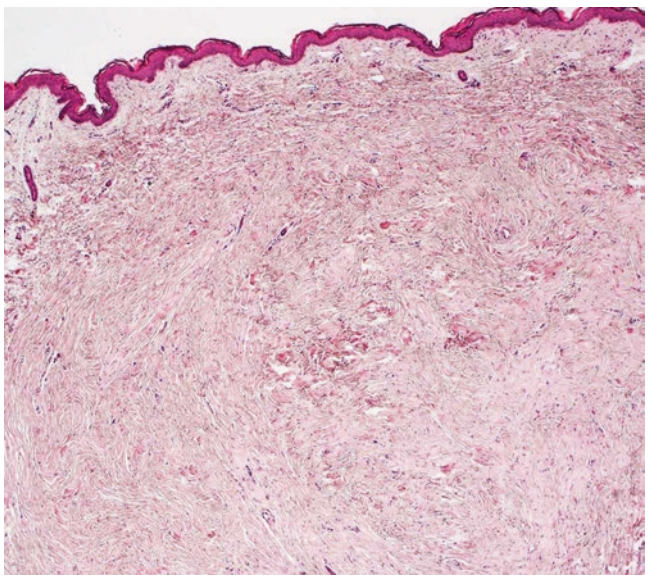

Fig. 25.2 A collagenoma is a type of connective tissue nevus that demonstrates a nodule of thickened collagen bundles haphazardly oriented with some bundles lying perpendicular to the surface of the skin

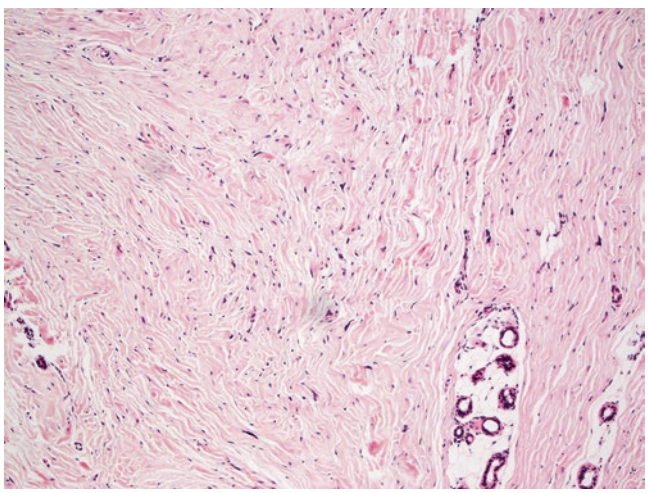

Fig. 25.3 Increased bundles of thickened and poorly oriented collagen are seen in collagenoma. Decreased elastic tissue fibers as seen on an elastic tissue stain are also a feature (not shown here)

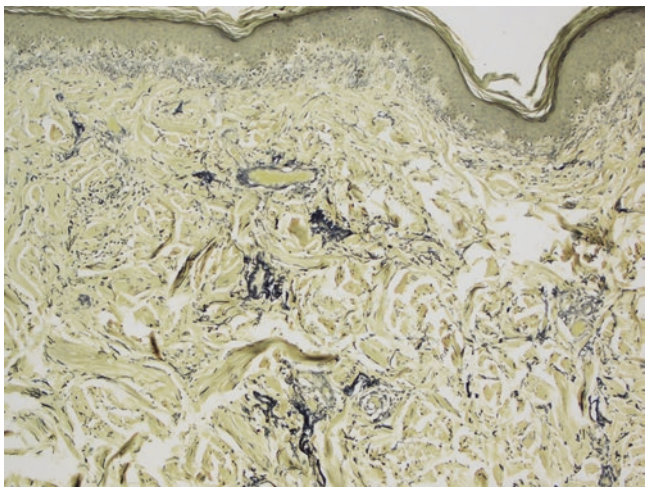

Fig. 25.4 An elastoma is another form of connective tissue nevus characterized by increased number and abnormal clumping of elastic tissue fibers as seen on Verhoeff-van Gieson (VVG) stain

25.2 Keloid and Hypertrophic Scar

25.2.1 Clinical Features

Keloids are most commonly seen in those with darkly pigmented skin. There is a reported incidence of 4.5 % in Hispanic populations and 16 % in those of African descent [13]. Peak occurrence is between puberty and 30 years of age with rare appearance in infancy [13]. Keloids also may appear or expand during pregnancy.

Hypertrophic scar may be more common than keloids [13]. The propensity for both hypertrophic scar and keloid formation appears to be partially familial. These scars most commonly occur in wounds under tension as well as in body locations with a higher density of melanocytes. Early lesions may be erythematous, while older lesions tend to be more hyperpigmented. Keloids are smooth, firm nodules or plaques with a rubbery consistency that do not respect the borders of the original wound margins. This is in contrast to hypertrophic scars which demonstrate boundary limitation (Fig. 25.5). Patients may experience associated pruritus or pain. While various treatment options exist, keloids have greater incidence of recurrence than hypertrophic scars, which often resolve spontaneously [13].

25.2.2 Histology

The histologic changes in keloid include a dense overgrowth of markedly thickened and eosinophilic collagen bundles in the dermis (Figs. 25.6 and 25.7). The collagen bundles are often densely packed with less than the expected amount of interstitial ground substance. In early lesions, increased fibroblasts may be present, but in well-developed lesions, the dermis appears relatively hypocellular. Virtually no elastic tissue fibers

Fig. 25.5 Erythematous, firm nodular plaque at the pinna of the ear extends beyond the original wound margins in a patient with a keloid scar (photo courtesy of Minh Hoang, MD, Ho Chi Minh City, Vietnam).

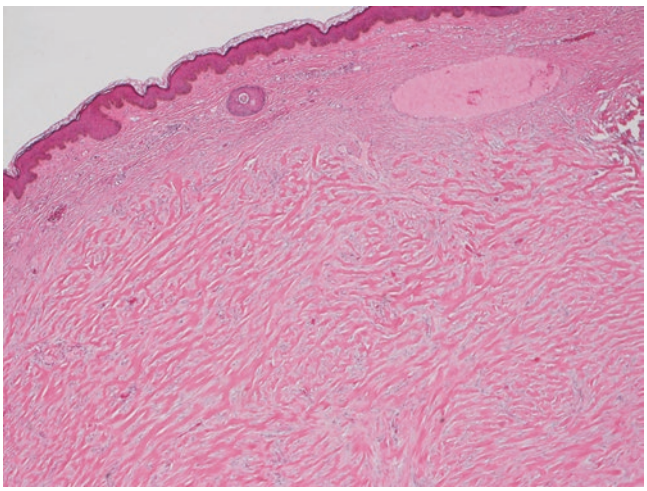

Fig. 25.6 A keloid demonstrates abundant thick eosinophilic bands of collagen that are easily observed at low magnification

are identified within keloids [14]. The thin vertically-oriented vessels usually seen in well-formed scars may be present, but they can be obscured by thickened collagen bundles.

The histologic findings of a hypertrophic scar include a proliferation of fibroblasts in a nodular configuration (Figs. 25.8 and 25.9). Neovascularization is present and blood vessels are often vertically oriented within the dermis. The epidermis may be flattened with loss of rete ridges, as well as loss of appendages in the areas of fibroblastic proliferation. The cellularity of the lesion varies with its age. In early hypertrophic scar, there are abundant small vessels and dermal fibroblasts, while in late stage lesion the number of cells

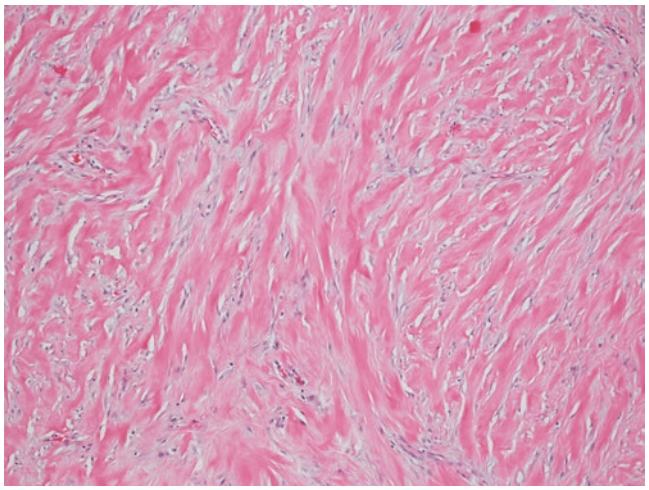

Fig. 25.7 Keloidal collagen bundles are haphazardly oriented and can be perpendicular to the skin surface

in the dermis is much lower. The fibroblasts retain an orientation that is parallel to the surface of the skin in most cases. Elastic tissue fibers are markedly diminished within the area of new collagen formation.

The nodular configuration in a hypertrophic scar may raise the differential diagnosis of a leiomyoma, although a trichrome stain or immunostains to identify smooth muscle actin can easily make this distinction. A keloid demonstrates much thicker and more eosinophilic bundles of collagen, but scattered bundles of keloidal collagen may be seen in small quantity within a hypertrophic scar.

25.2.3 Pathogenesis

Keloid scar is a result of dysfunctional wound healing in the skin with excess deposition of extracellular matrix materials. Altered lipid metabolism may play a role in the pathogenesis of keloid scar. Keloids express high levels of arachidonic acid, which is a precursor of pro-inflammatory eicosanoids, such as leukotrienes, prostaglandins, and thromboxanes [16]. It has been proposed that lipids are important in the chronic inflammatory processes that drive keloid development [17].

Systemic hypertension has been suggested to play a role in keloid scar. Hypertension-associated changes in pathological scars are mediated in part by inflammation, hypoxia, and the angiotensin/renin–angiotensin–aldosterone system [18]. Hypoxia can promote fibrosis by stimulating an epithelial-to-mesenchymal transition that is important in fibrosis [19, 20]. Stem cells may play a role in keloid scar formation [21]. Mesenchymal-like stem cells have been identified in keloid tissues [22–24]. These stem cells exhibit the potential to differentiate into cells of bone, cartilage, fat, and endothelial cell lineages.

Interleukin-6 (IL-6) is an inflammatory cytokine important in tissue fibrosis. IL-6 is highly expressed in keloid scar

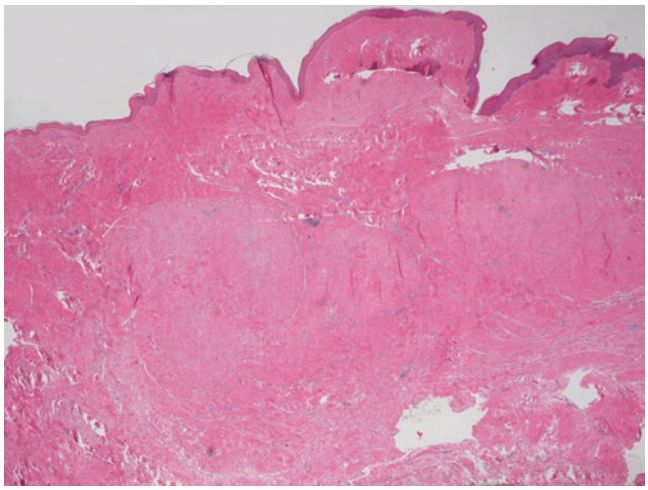

Fig. 25.8 A hypertrophic scar demonstrates a lobular appearance within the dermis. The epidermis is often flattened and there is loss of cutaneous appendages in the region of the scar

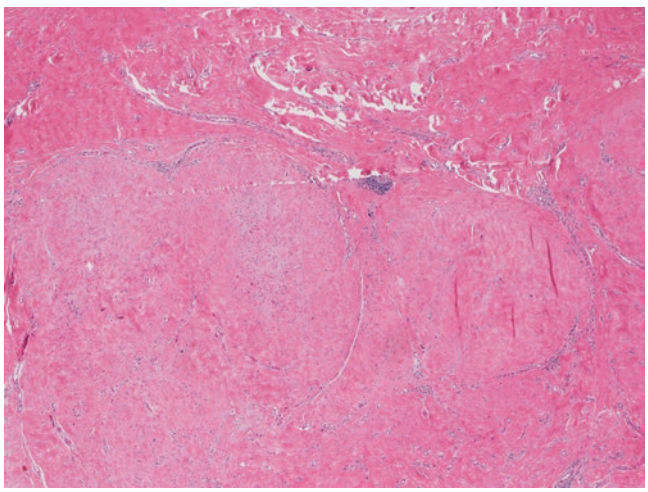

Fig. 25.9 Lobules of new collagen can be distinguished from the background native collagen in a hypertrophic scar, and may resemble the lobularity seen in a leiomyoma

as compared with normal skin [25, 26]. IL-6 induction may contribute to the formation of keloids by promoting the proliferation and differentiation of keloid precursor cells [21].

Hypertrophic scar may be caused by an imbalance between excessive extracellular matrix formation and inadequate matrix remodeling [27]. Hypertrophic scar results from a prolonged inflammatory response to injury, leading to increased vascularization, hypercellularity, excessive collagen deposition, and a decrease in small leucine-rich proteoglycans [28, 29]. Molecular signals, such as stratifin secreted by keratinocytes, exert downstream effects on skin fibroblasts and the production of extracellular matrix proteins [30]. Bone marrow–derived mesenchymal stem cells have been identified in hypertrophic scar and may play a role in scar formation [31].

Hypertension has been linked to pathological fibrosis and scarring, including hypertrophic scar [18]. Hypertension results in increased activation of transforming growth factor (TGF)-β and tumor necrosis factor (TNF)-α signaling [32]. Hypertrophic scar demonstrates an increased number of fibroblasts compared to normal skin and increased activity of TGF-β, which results in overproduction of collagen by dermal fibroblasts [33]. Fibroblasts in scar can differentiate into myofibroblasts, which can also account for increased collagen and extracellular matrix production [34].

Studies have shown that TSG-6 (TNF-α Induced Protein 6), which is an anti-inflammatory cytokine, is important in hypertrophic scar formation. TSG-6 can suppress inflammation and reduce the extent of hypertrophic scar formation in an experimental animal model [35]. TSG-6 reduces the formation of hypertrophic scar by decreasing the synthesis of collagens I and III [35]. TSG-6 inhibits the expression of the inflammatory cytokines IL-6 and IL-1β as well as neutrophil infiltration [35, 36]. Given these anti-inflammatory effects, TSG-6 may be a new therapy for hypertrophic scar treatment.

25.3 Dermatofibroma

25.3.1 Clinical Features

Dermatofibromas are common tumors, accounting for 3 % of the cutaneous specimens assessed by one dermatopathology laboratory in a published report [37]. Dermatofibromas are most frequently seen in young and middle-aged adults and more common in females [37]. Lesions present as a well-defined, hyperpigmented and firm dermal nodule that dimples with lateral compression ("dimple sign"). They may occur anywhere on the body, but are most commonly seen on the lower extremities (Fig. 25.10). Dermatofibromas are typically solitary, although multiple lesions have been reported in 10 % of affected individuals [37]. Dermatofibromas are benign but can persist following onset. They are amenable to surgical excision, and can recur if not completely removed [38].

25.3.2 Histology

The classic dermatofibroma demonstrates a proliferation of fibroblasts underlying an acanthotic and hyperpigmented epidermis (Fig. 25.11). The rete ridges are elongated, and there is increased basilar melanin. In some cases, follicular induction can give rise to a basilar proliferation that resembles basal cell carcinoma. Within the dermis, most cases demonstrate a slight zone of sparing within the papillary dermis. Beginning in the superficial reticular dermis and extending throughout the dermis but not usually into the subcutis, fibroblasts are present in a whorled or storiform pattern around collagen bundles ("collagen trapping") (Fig. 25.12). The lesion sometimes extends into the fibrous septa between the fat lobules, but ordinarily does not involve the subcuta-

Fig. 25.10 Dermatofibroma presents as a firm erythematous papulonodule that dimples with lateral compression on the thigh of a teenage boy

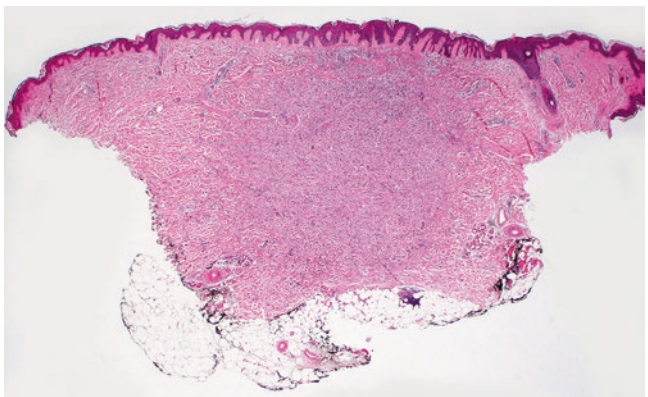

Fig. 25.11 An acanthotic and hyperpigmented epidermis overlies a proliferation of spindle-shaped cells in the dermis in dermatofibroma

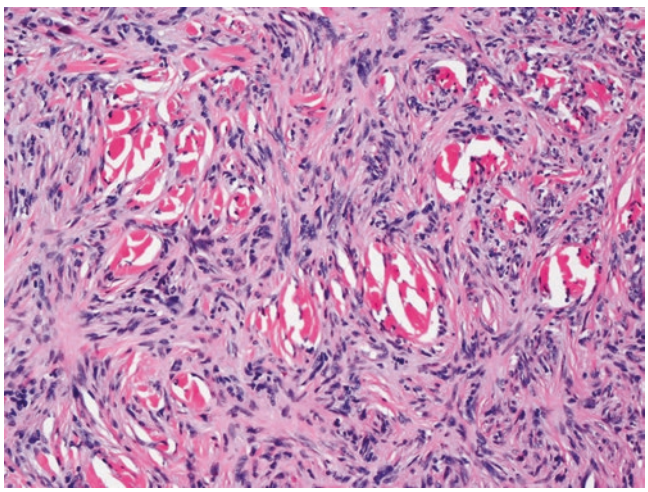

Fig. 25.12 A storiform pattern of spindle-shaped cells surrounds and isolates collagen bundles (collagen trapping) in dermatofibroma

neous lobules. The cells are somewhat pleomorphic with spindle-shaped cells admixed with plumper cells with abundant cytoplasm. Multinucleated cells may be present. The cells may contain variable amounts of cytoplasmic lipid, and in some cases, extensive lipidization may be apparent [39]. Scattered mitoses can be seen. Collagen bundles separate the individual fibroblasts that do not grow in a fascicular pattern. At the periphery of the lesion, keloid-like collagen may be apparent with interspersed fibroblasts. Older lesions may demonstrate zonation with cellular areas at the periphery and a more sclerotic region present in the center.

Several variants of dermatofibroma share the overall architectural pattern with the classic form but have distinctive histologic characteristics that lead to subtyping with minor clinical relevance [40]. The aneurysmal or angiomatoid variant demonstrates abundant large, ectatic blood vessels admixed with narrow vascular channels. A myxoid variant shows areas with abundant myxoid matrix in the setting of a dermatofibroma. Another variant demonstrates keloidal collagen. A variant with abundant eosinophils has also been described [41].

The major differential diagnoses include dermatofibrosarcoma protuberans (DFSP), dermatomyofibroma, and xanthogranuloma. The spindle cell proliferation in DFSP often extends up right to the base of the epidermis unlike the zone of sparing that characterizes most dermatofibromas. DFSPs are generally more cellular, and have a more uniform appearance within the spindle cell population that course within interlacing fascicles. The proliferation often extends into the subcutis, and envelops individual adipocytes within the lobules. While scattered mitoses are present, there is minimal cytologic atypia. Minimal collagen is present between tumor fascicles, unlike the case with dermatofibroma. Dermatomyofibroma is a dermal-based proliferation of spindle shaped cells that generally have more abundant eosinophilic cytoplasm than is seen in dermatofibroma. The proliferation tends to grow in a plate-like pattern than is parallel to the surface of the skin. Immunostains for smooth muscle actin, calponin, and muscle-specific actin label the majority of the spindle-shaped cells in dermatomyofibroma [42]. Xanthogranuloma enters the differential diagnosis of a lipidized dermatofibroma. This distinction is generally not one of clinical importance, and in some cases the overlap is so great as to prevent a distinction [43]. The angiomatoid variant may be confused with Kaposi's sarcoma, but can be distinguished on the basis of areas that resemble a classic dermatofibroma.

25.3.3 Pathogenesis

Dermatofibroma is a benign fibrohistiocytic proliferation. It has some features of a reactive tissue process as well as a proliferative neoplastic process. Some studies have proposed that dermatofibroma is a local response to inflammation or trauma, in which there is an inflammatory response with

granulation tissue formation, followed later by a reparative fibrous response [44]. Other studies have indicated that dermatofibroma is a neoplastic process due to its clonal proliferative growth [45]. Multiple dermatofibromas can occur in association with systemic lupus erythematosus [46].

Molecular factors such as syndecan-1, fibroblast growth factor receptor 2, and transforming growth factor-β might be inducers of fibrosis in dermatofibroma [46–49]. Mast cells, which are present in high numbers, may be a cellular source of these fibrinogenic factors. Fibroblasts derived from dermatofibroma lesions are more responsive to IL-1α and IL-1β than fibroblasts derived from normal skin [50]. IL-1 may play a role in fibroblast proliferation in an autocrine manner. Gene fusions involving protein kinase C gene have been identified in some cases of dermatofibroma [51], while rearrangement of ALK gene has been identified in epithelioid and atypical variants [52, 53].

25.4 Dermatomyofibroma

25.4.1 Clinical Features

Dermatomyofibroma is a rare benign cutaneous tumor of mesenychmal derivation. It is most commonly diagnosed in young women [54]. However, in pediatric cases there is no sex predilection. Dermatomyofibroma is described as reddish-brown plaque or nodule, most often occurring on the neck and upper trunk (Fig. 25.13) [54]. It responds well to surgical excision with no reports of metastasis or recurrence. Interestingly, dermatomyofibroma in male children may involute spontaneously, while continued growth is seen in females.

Fig. 25.13 Dermatomyofibroma presents as a firm, reddish brown nodular plaque extending across the left lower abdomen

25.4.2 Histology

Dermatomyofibroma appears as a plaque-like growth of spindle-shaped cells with uniform, long and tapered nuclei [55]. A pattern of intersecting fascicles is seen in some cases. The lesions are centered in the reticular dermis and may extend down into the superficial portion of the subcutaneous fat. In rare cases, lesions percolate deeper into the subcutis in a perpendicular orientation [56]. These neoplasms are variably cellular but have minimal cytologic atypia, and mitotic activity is quite rare. Thickened elastic tissue fibers and collagen fibers are interspersed between the slender nuclei [57].

Muscle actin is expressed by the tumor cells in some cases, which helps to differentiate this tumor from a cellular dermatofibroma, as does the horizontal orientation of the tumor cell population [57]. Dermatomyofibromas express smooth muscle actin in a minority of cases and do not express desmin. Calponin expression has also been described in these tumors [42]. Piloleiomyoma is another differential consideration. The fascicular growth pattern in piloleiomyomas is not present in dermatomyofibromas. Additionally, smooth muscle actin staining is uniform and intense in piloleiomyomas. A fibroblastic connective tissue nevus is also in the differential diagnosis, but the spindle-shaped cells in this entity express CD34 and not smooth muscle actin [58]. Electron microscopy shows that the tumor population consists of myofibroblasts [55].

25.4.3 Pathogenesis

The pathogenesis of dermatomyofibroma has yet to be determined, although it is known that the cellular component of this benign tumor has both fibroblastic and myofibroblastic differentiation [42].

25.5 Infantile Myofibromatosis

25.5.1 Clinical Features

Infantile myofibromatosis is a common fibrous tumor of infancy [59]. The exact incidence is unknown. Boys are more often affected than girls [60]. The majority of lesions appears within the first 2 years of life with 50–90 % appearing at birth or soon after [59, 60]. Three clinical variants exist. The most common variant is the solitary form, and it is characterized by a single firm, skin-colored or violaceous nodule [60]. Overlying telangiectasia or ulceration may occur. The multicentric variant is defined by involvement of the skin, subcutaneous tissues, muscles, and bones. The third variant is the generalized form with both cutaneous and visceral lesions.

Spontaneous regression is the rule in infantile myofibromatosis with involution over a 12- to 18-month period [60]. Local destruction secondary to mass effect can occur in the multicentric variant, although metastases are not seen. In the generalized variant, mortality rates approximate 75 % with death most often from complications due to cardiopulmonary or gastrointestinal involvement [59]. Surgical excision can be offered for symptomatic tumors without visceral compromise. The estimated risk of recurrence is 7–10 %. Other management options include radiotherapy, chemotherapy, and intralesional corticosteroids.

25.5.2 Histology

In infantile myofibromatosis, short fascicles of spindle-shaped cells form relatively sharply circumscribed nodules in the dermis. In some cases, there is a slightly infiltrative border. Collagen bundles surround these short fascicles. Necrosis and mitotic activity can be present, but are not abundant and atypical mitoses are not identified [61]. Some areas may resemble a hemangiopericytomatous growth pattern, and intravascular proliferation of the spindle-shaped cells has been reported. A bi-phasic growth pattern with a population of smaller, darker cells in the central portions of the lesions, and cells with more cytoplasm resembling smooth muscle located at the margins of the tumor is often described [62]. Monophasic variants also have been reported. In these cases, an abundance of small capillaries is recognized, raising the differential diagnosis of a primary vascular neoplasm [63]. Infantile myofibromatosis expresses smooth muscle actin, but it usually does not express desmin and myoglobin [64]. Ultrastructural examination reveals that the tumor cells have the appearance of myofibroblasts [65].

25.5.3 Pathogenesis

Infantile myofibromatosis is a benign fibrous tumor of childhood caused by abnormal proliferation of fibroblasts and myofibroblasts [66]. Mutations in platelet-derived growth factor receptor-beta (PDGFRB), a receptor tyrosine kinase, is a cause of autosomal dominant infantile myofibromatosis. It has been shown that the mutations c.1681C>T (p.Arg561Cys) and c.1978C>A (p.Pro660Thr) in PDGFRB segregate with the disease in affected individuals [67, 68]. These mutations are activating mutations causing constitutive activation of the PDGF receptor.

Mutations in NOTCH3 have also been identified in infantile myofibromatosis [69]. NOTCH3 is a membrane protein involved in the NOTCH signaling pathway critical for embryonic development. Small molecule inhibitors of receptor tyrosine kinases that block PDGFRB and NOTCH3 may potentially be utilized to treat infantile myofibromatosis.

25.6 Fibroblastic Rheumatism

25.6.1 Clinical Features

Fibroblastic rheumatism is a rare disorder with approximately 30 reported cases to date, 31 % of which involve children [70]. Males are more commonly affected than females. The physical exam is characterized by tender, erythematous to skin-colored, small nodules usually on the hands and around the joints [70]. Additional features include sclerodactyly, joint contractures, thickened palmar fascia, and Raynaud's phenomenon. Fibroblastic rheumatism also can be associated with an erosive arthropathy, which may predispose affected individuals to pronounced and persistent disability. A number of systemic therapies have been tried, including methotrexate with variable response [70].

25.6.2 Histology

Histologic sections of fibroblastic rheumatism reveal a poorly circumscribed dermal proliferation of spindle-shaped and stellate fibroblasts [71]. The proliferative cells have histologic and ultrastructural features of myofibroblasts [72]. The surrounded collagen bundles are markedly thickened, and there are diminished numbers of elastic tissue fibers within the proliferation. Surrounding fibrosis may be prominent [73]. A mild perivascular and interstitial lymphocytic infiltrate is observed in some cases [74, 75]. Immunohistochemical studies support the myofibroblastic differentiation in fibroblastic rheumatism with cells expressing smooth muscle actin [76]. Some authors have questioned whether this entity represents a variant of a non-Langerhans cell histiocytosis [77], while others believe it to be within the category of fibromatoses [74].

25.6.3 Pathogenesis

Fibroblastic rheumatism is a disorder with increased fibroblast proliferation. Histologic features suggest a myofibroblastic response to an unidentified stimulus [78, 79]. Transforming growth factor-β and granulocyte-macrophage colony-stimulating factor may be important in the development of this lesion, since they are known to induce the differentiation of fibroblasts into myofibroblasts [80].

25.7 Angiofibroma

25.7.1 Clinical Features

Multiple facial angiofibromas are commonly described as pathognomonic features of tuberous sclerosis and multiple endocrine neoplasia type 1 (Fig. 25.14) [81, 82]. However,

Fig. 25.14 Angiofibromas appear as innumerable waxy, reddish brown papules primarily distributed along the central face in a patient with tuberous sclerosis

Fig. 25.15 Koenen tumors present as firm, skin-colored, filiform papules at the proximal nail fold of multiple toes in a teenage patient with tuberous sclerosis

there are other cutaneous variants of angiofibromas, including fibrous papule of the nose, pearly penile papules, and acral fibrokeratomas. Treatment may be warranted for cosmetic reasons as lesions are persistent [84].

Angiofibromas are described as skin-colored to erythematous papules with clinical subtype dependent on the anatomic location. They are rarely symptomatic. Examples include the following:

(a) Fibrous papule—solitary, skin-colored papule typically on the nose of an adult.
(b) Pearly penile papule—shiny, skin-colored or white 1 mm papules along the corona of the penis in postpubertal males [83].
(c) Periungual fibroma/Koenen tumor—a pathognomonic feature of tuberous sclerosis. This is skin-colored to pink papule typically found along the nail folds of multiple digits (Fig. 25.15) [82].

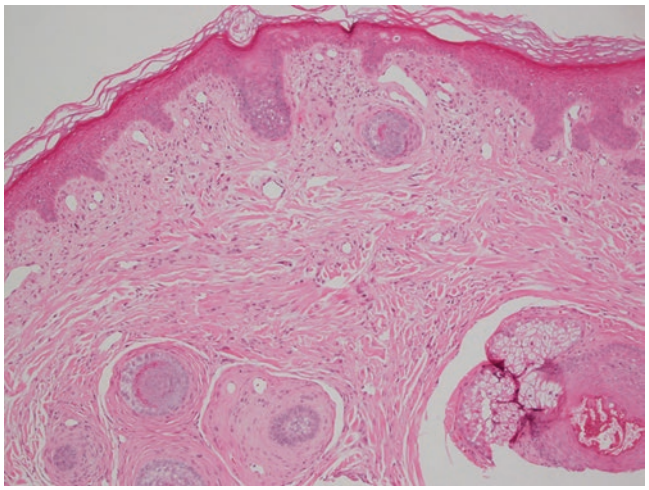

Fig. 25.16 Angiofibroma demonstrates collagenous overgrowth with concentric rings of fibrosis around hair follicles

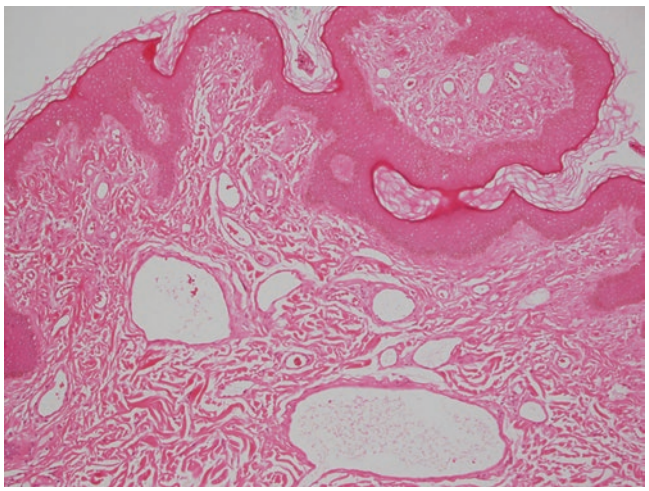

Fig. 25.17 Vascular ectasia is a prominent finding in angiofibroma. Lesions occurring in patients with tuberous sclerosis are indistinguishable from sporadic ones

25.7.2 Histology

The histologic changes in angiofibroma are identical to those seen in fibrous papules of the nose and pearly penile papules. It is likely that these entities are closely related, if not identical. The epidermis is either unremarkable or slightly flattened. The papillary dermis is characterized by dense fibrosis that obscures the boundary between papillary and reticular dermis (Fig. 25.16). Stellate and enlarged fibroblasts are present within the sclerotic collagen. Vessels within the dermis are enlarged (Fig. 25.17). "Onion skin" fibrosis is present as concentric rings around cutaneous appendages. Inflammatory, pleomorphic, and pigmented variants occur rarely [85]. A rare variant characterized by clear stellate fibroblasts has been reported in adults but not in children [86]. Other reported variants have granular stellate cells and epithelioid cells [87, 88].

25.7.3 Pathogenesis

Angiofibroma is a cutaneous hamartoma of the face and nose that occurs sporadically and in genetic conditions such as tuberous sclerosis complex (TSC). In TSC, angiofibroma presents as multiple lesions on the face before puberty [89, 90].

There is considerable overlap in the histologic features and pathogenesis between sporadic angiofibroma and angiofibroma associated with TSC. TSC is caused by germline mutation of either the TSC1 or TSC2 gene that encodes hamartin and tuberin, respectively [91, 92]. TSC1/TSC2 complex functions to inhibit the activation of the mammalian target of rapamycin (mTOR) signaling pathway. Loss of function of TSC complex leads to dysregulated activation of mTOR, and its downstream effectors p70 ribosomal protein S6 kinase (p70S6K) and ribosomal protein S6 (S6) [93, 94].

It has been proposed that keratinocytes in the epidermis and stromal cells in the dermis are the most likely cells that drive the formation of angiofibroma [95]. Stromal cells in angiofibroma express activated mTOR, p70S6K, and S6, which are effector molecules in the mTOR signaling pathway that cause TSC [91–93]. The proliferation of blood vessels, which is a feature in angiofibroma, may be induced by vascular endothelial growth factor (VEGF) produced by mTOR-activated cells [95]. Therapeutic intervention with mTOR inhibitors, such as topical rapamycin, has been successful in the treatment of angiofibroma in children and adults [96, 97].

The formation of angiofibroma in TSC patients may also be related to sun exposure and second-hit mutations. Studies of cells from skin tumors in TSC patients revealed germline and second-hit mutations in TSC1 and TSC2 genes [98]. Fifty percent of the somatic point mutations identified in TSC skin tumors were found exclusively in facial angiofibroma from sun-exposed sites. These results suggest that sun exposure may cause second-hit mutations and the development of TSC facial angiofibroma [98]. Avoidance of sun exposure may reduce the development of facial angiofibroma in children and adults with TSC.

25.8 Tuberous Sclerosis

25.8.1 Clinical Features

Tuberous sclerosis (TSC) is a hamartomatous disorder affecting the skin, brain, eyes kidneys, liver, heart, and lungs. Approximately 2 million people worldwide have tuberous sclerosis with an estimated prevalence of 1 in 6000–9000 individuals [99]. It is defined as an autosomal dominant disorder, although an estimated 50–65 % of affected individuals have a spontaneous mutation [99].

TSC is characterized by the triad of seizures, mental retardation, and facial angiofibromas, but only one third of affected individuals present with all of these features [82]. Asymmetrically distributed hypopigmented macules along the trunk and buttocks (an example being the "ash leaf macule") appear by 2 years of age, and they are the initial cutaneous finding in many of the patients. Between 2 and 5 years of age, most patients develop angiofibromas at the central face, which are expansive especially following puberty [82]. Additional cutaneous features include fibrous forehead plaque, Shagreen's patch at the lumbosacral cutaneous spine, periungal fibromas (Koenen tumors), molluscum fibrosum pendulum (soft pedunculated papules at the neck, axillae, and groin), and "confetti-like" hypopigmented macules at the distal extremities.

Phenotypic presentation and prognosis varies in TSC. However, the majority of patients will have some degree of epilepsy, often presenting in the first year of life [99]. Approximately fifty percent of affected individuals will have behavioral problems or autism spectrum disorders. Pulmonary lymphangiomyomatosis, which is primarily seen in women, and renal cell carcinoma, which has been reported in 2–4 % of cases, can be life threatening [99, 100].

25.8.2 Histology

Hypopigmented macules, Shagreen patches, forehead plaques, angiofibromas, and subungual fibromas are all seen with increased frequency in patients with TSC [101–103]. Café-au-lait macules are also present in patients with TSC [82].

The hypopigmented lesions show skin with unremarkable appearing epidermis and dermis. In contrast to the surrounding skin, the basal layer of the epidermis demonstrates decreased melanin within keratinocytes. The number of basilar melanocytes is normal. However, on ultrastructural examination, the melanocytes have fewer and smaller melanosomes. There appears to be decreased melanogenesis [104].

Shagreen patches are collagenomas or hamartomatous proliferations of collagen. Collagen bundles are increased in number and somewhat haphazard in their organization. The overgrowth of collagen bundles results in diminished number of elastic tissue fibers. The altered pattern of elastic tissue fibers is most easily detected on elastic tissue stains. The changes can be quite subtle, and comparison with adjacent tissue highlights the altered pattern.

Angiofibromas and subungual fibromas share similar histologic features with fibrous papules and pearly penile papules seen in individuals who do not have TSC. Subungual fibromas are uncommon in childhood [103]. The epidermis is flattened, and in some cases demonstrates slight melanocytic hyperplasia. The dermis shows increased and thickened collagen bundles that may be oriented perpendicular to the epidermis. Increased fibroblasts are present and may be somewhat enlarged. Concentric rings of collagen surround arterioles, venules, and capillaries that are somewhat dilated [105]. Forehead plaques demonstrate identical histologic features to those seen in angiofibroma and subungual fibroma [106].

25.8.3 Pathogenesis

Tuberous sclerosis complex is an autosomal dominant genetic disorder with an incidence of about 1 in 6000 [107]. The underlying pathogenesis of TSC is due to dysregulated intracellular signaling pathways that affect many cellular functions, including cell metabolism, survival and proliferation. TSC is caused by inactivating mutations of either the TSC1 or TSC2 tumor suppressor gene that encodes for the proteins hamartin (TSC1) and tuberin (TSC2) [91, 92]. Mutations in both TSC1 and TSC2 can produce the same phenotype with individual variations [108, 109]. Mutations in TSC2 are more common than mutations in TSC1, whether in familial cases (about 65 %) or in sporadic cases (about 75 %), and account for a ratio of TSC2:TSC1 mutations of about 2:1 to 3.5:1 [99]. Mutations in TSC2 produce more severe clinical manifestations with more hypomelanotic macules, more frequent neurologic and ophthalmologic symptoms, renal cysts, and perungual fibromas in male individuals [108].

TSC1/TSC2 complex is a tumor suppressor that negatively regulates the mammalian target of rapamycin (mTOR) signaling pathway, which is a serine/threonine kinase central to many cellular functions, including cell survival and metabolism [110–112]. mTOR is activated by the GTPase Rheb. Rheb in turn is negatively regulated by TSC1/TSC2 complex, which is a GTPase-activating protein that inactivates Rheb by stimulating the conversion of active Rheb-GTP to inactive Rheb-GDP. Loss of function of TSC1 or TSC2 leads to unregulated Rheb-GTP signaling and downstream mTORC1 activation. Constitutive activation of mTOR and its downstream effectors, including 4E-BP1 (eukaryotic translation initiation factor 4E-binding protein 1) and p70 S6-kinase, results in dysregulated cellular metabolic processes, protein synthesis and growth [113]. Given the pivotal role of mTOR signaling in the pathogenesis of TSC, mTOR inhibitors, such as rapamycin and its derivatives "rapalogs," have been successfully used in the treatment of TSC [114, 115].

25.9 Sclerotic Fibroma

25.9.1 Clinical Features

Multiple sclerotic fibromas are commonly considered a feature of autosomal dominant hamartomatous genodermatoses, such as Cowden disease and tuberous sclerosis. However, isolated cases of solitary lesions have been described, most commonly in Caucasian adults [116]. Sclerotic fibromas are skin-colored to white, shiny to translucent papules with diameters between 2 and 9 mm, and may occur on any part of the body [116]. These lesions are benign but can be excised if desired.

25.9.2 Histology

The epidermis in sclerotic fibroma is flattened and overlies densely sclerotic collagen that has a "wood grain" appearance with alternating bands of white and dense eosinophilia (Figs. 25.18 and 25.19). The lesion is well circumscribed and displays minimal cellularity. Scattered fibroblasts are seen within the sclerotic dermis [116].

25.10 Infantile Digital Fibroma

25.10.1 Clinical Features

Infantile digital fibroma is a rare variant of superficial juvenile fibromatosis. The majority of lesions appear within the first 12 months of life, with one-third of cases present at birth [117].

Infantile digital fibromas present as skin-colored to erythematous papules and nodules along the dorsal and lateral aspects of the fingers or toes (Fig. 25.20) [117]. They are

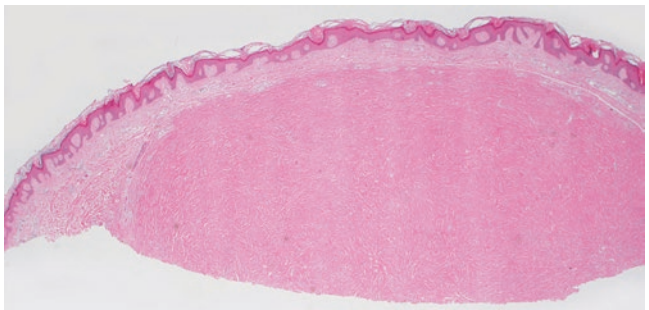

Fig. 25.18 Sclerotic fibroma demonstrates a well-circumscribed and sharply demarcated nodule consisting of thickened collagen bundles

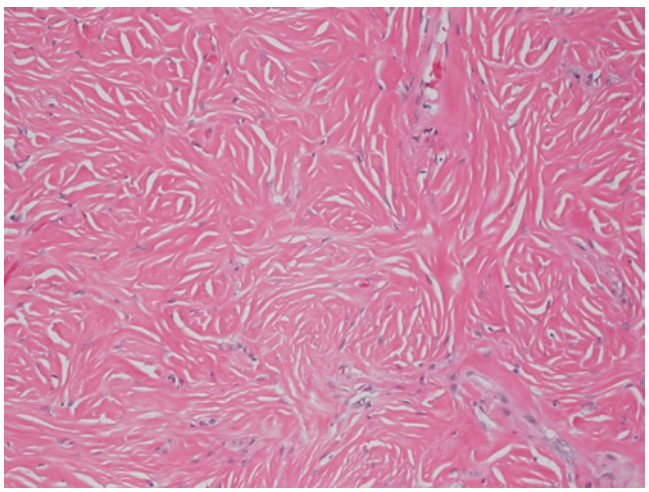

Fig. 25.19 Areas with dense collagen and few nuclei give rise to a "wood grain" appearance in sclerotic fibroma

Fig. 25.20 Infantile digital fibroma appears as a shiny erythematous nodule on the dorsum of the right third toe in a young infant

commonly multiple in number, affecting many digits and ranging in size to as large as 2 cm. Although benign with no known reports of local bony invasion or metastasis, larger lesions may cause joint deformities and contractures. Spontaneous regression appears to be the rule, making watchful waiting appropriate, especially since high recurrence rates are reported following excision.

25.10.2 Histology

In infantile digital fibroma, the epidermis demonstrates flattened rete ridges. Within the reticular dermis, there is a proliferation of plump myofibroblasts that have the characteristic peri-nuclear eosinophilic inclusions (Figs. 25.21 and 25.22) [118]. The inclusions are clumped actin filaments and stain strongly with anti-smooth muscle actin antibodies [119]. The nuclei are spindled with some stellate forms. In some cases, the fascicles of tumor cells and interspersed collagen may display a vertical orientation. Cytologic atypia is not present, and mitoses are rare. While based in the reticular dermis, the tumor is poorly circumscribed and may extend into the subcutis.

25.11 Acquired Digital Fibrokeratoma

25.11.1 Clinical Features

Acquired digital fibrokeratoma is rare and typically appears in middle-aged adults with a mean age of onset of 40 years of age [120]. Rare reports exist in individuals less than 18 years old.

Lesions most commonly occur on the fingers, but may be seen on other acral surfaces. They are skin-colored to pink, hyperkeratotic and exophytic papules, frequently with a surrounding collarette of skin. Acquired digital fibrokeratoma is usually solitary, but reports of multiple lesions have been described [120]. The lesion is a benign growth and may be removed by surgical excision.

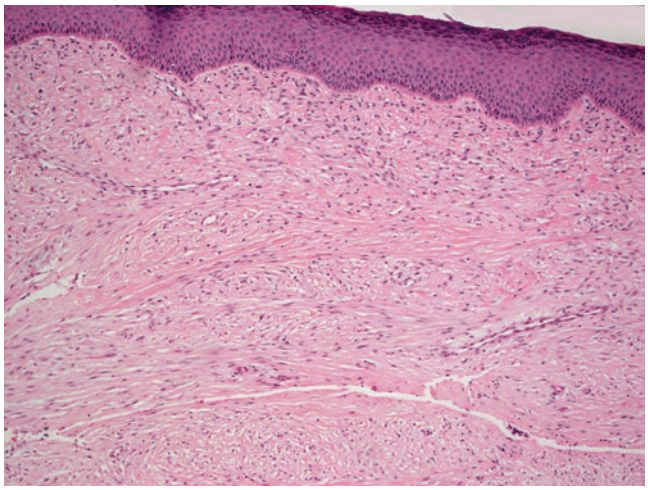

Fig. 25.21 Recurrent infantile digital fibroma is characterized by a dermis filled with fascicles of spindle-shaped cells with abundant eosinophilic cytoplasm

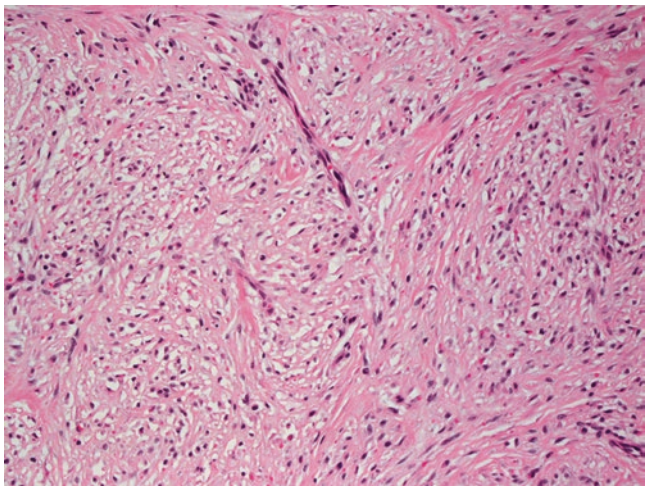

Fig. 25.22 Bland-appearing spindled cells demonstrate focal vacuolization and peri-nuclear inclusions in infantile digital fibroma

25.11.2 Histology

Histologic changes in acquired digital fibrokeratoma include a normal or acanthotic epidermis overlying dense dermal collagen (Figs. 25.23 and 25.24). Hyperkeratosis is present as a secondary phenomenon due to trauma related to the exophytic nature of the lesion on an acral site. Markedly thickened collagen bundles are vertically oriented within the

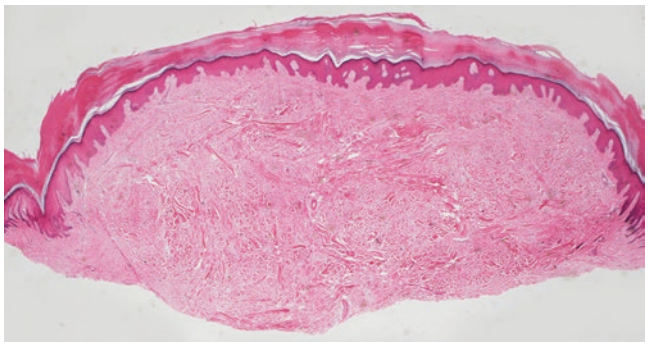

Fig. 25.23 Acquired digital fibrokeratoma demonstrates a polypoid growth on acral skin with collagenous overgrowth and lack of dermal appendages

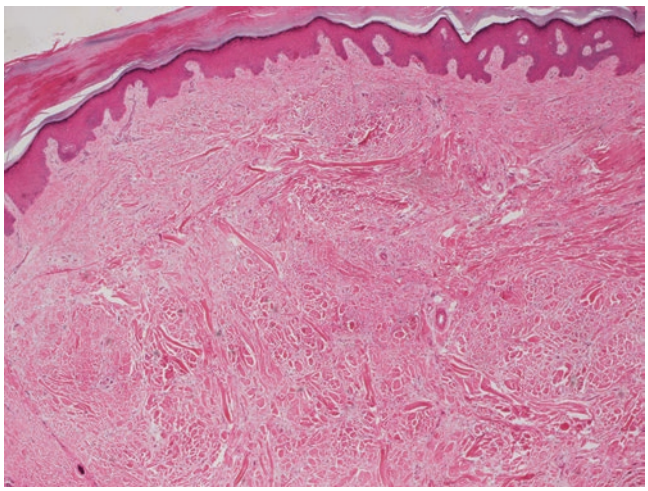

Fig. 25.24 Collagen bundles are haphazardly arrayed and may be perpendicular to the skin surface in acquired digital fibrokeratoma

reticular dermis and extending into the papillary dermis (Fig. 25.24). Overgrowth of the collagen bundles results in loss of cutaneous appendages. Rare variants display increased numbers of fibroblasts and marked edema [121].

The differential diagnosis includes other dermal-based acral tumors, including supernumerary digits, subungual fibromas, neuromas, neurofibromas and sometimes plantar warts [122]. It is not clear whether peri-ungual fibrokeratomas represent the same tumor arising in a peri-ungual location [123, 124]. Supernumerary digits, neuromas, and neurofibromas display neural elements that are not present in acquired digital fibrokeratomas. In most cases, these structures are easily identified on routine sections, but special stains to identify neural elements may be helpful in some cases. Subungual fibromas do not have vertically oriented collagen, but often demonstrate peri-appendageal concentric fibrosis, stellate fibroblasts, and ectatic vessels. In some cases, the distinction from acquired digital fibrokeratoma may be difficult.

25.12 Acrochordon

25.12.1 Clinical Features

Acrochordons or "skin tags" are the most commonly seen fibrous proliferation. Prevalence increases with age, occurring equally in males and females [125]. Acrochordons are frequently seen in association with metabolic syndrome and in obese individuals [125].

Acrochordons present as skin-colored to hyperpigmented, pedunculated papules most commonly occurring at sites predisposed to persistent friction, such as the neck, axillae, and groin. Larger lesions with diameter up to 2 cm may be seen on the trunk. Acrochordons are benign but may be painful if they are irritated. Lesions can be removed easily by excision, cryosurgery, or electrodessication.

25.12.2 Histology

This common lesion has an epidermis that may be entirely normal, papillomatous, or acanthotic (Fig. 25.25). The dermis consists of variably ectatic blood vessels coursing in an unremarkable collagenous stroma. When there is trauma, the vessels may be markedly ectatic and thrombosed. Cutaneous appendages and adipocytes are ordinarily not present. Some authors use terms such as dermatolipoma for similar lesions that contain adipocytes, although there is little reason for this distinction because there is no difference in clinical course, prognosis or known systemic associations. Inflammation is present only secondary to trauma. Occasional stellate or pleomorphic fibroblasts may be present within the dermis in acrochordons. When they are extensive in number and mitoses are recognized, the name pseudosarcomatous polyp has been suggested, although these rare variants have not yet been described in children [126].

The differential diagnosis most commonly includes verruca vulgaris, although the characteristic epidermal changes of clumping of keratohyalin granules, focal parakeratosis, and keratinocyte vacuolization are not seen in acrochordons.

25.12.3 Pathogenesis

Acrochordon is often linked to type 2 diabetes mellitus and obesity. Acrochordon is also associated with hereditary autosomal dominant Birt–Hogg–Dube syndrome, which is characterized by multiple fibrofolliculomas, trichodiscomas, and acrochordons [127]. Increased levels of tumor necrosis factor-α (TNF-α), which is produced by mast cells and macrophages, have been found in acrochordon as compared with normal skin [128]. Some studies have suggested the role of

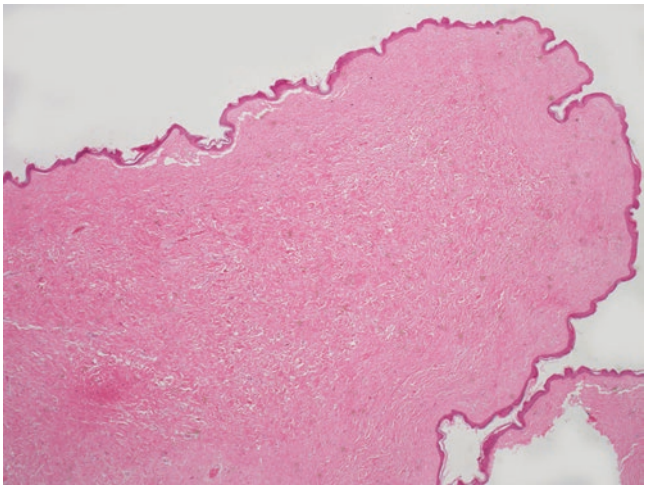

Fig. 25.25 Acrochordons are polypoid structures that generally lack cutaneous appendages and are composed largely of collagen

local trauma in the pathogenesis of acrochordon through possible trauma-induced upregulation of TRAIL and induction of mast cells migration into the site of trauma [128]. TNF-α released by mast cells may result in changes leading to acrochordon formation.

25.13 Angiofibroblastoma

25.13.1 Clinical Features

Angiofibroblastoma is a newly described rare fibrous growth occurring on the extremities. The exact prevalence is unknown with no documented gender predilection [129]. Lesions are characterized as solitary, non-descript subcutaneous nodules typically presenting on the extremities. Angiofibroblastomas have a benign clinical course and respond well to simple excision with no documented evidence of recurrence or metastasis.

25.13.2 Histology

This rare neoplasm is characterized by a dermal proliferation of fibroblasts coursing in a myxoid stroma. The epidermis is uninvolved. The fibroblasts are spindled with abundant stellate-shaped cells. Mitotic activity is rare, and there is no significant cytologic atypia in the fibroblastic proliferation. In some areas, the stroma is comprised of dense collagen instead of the myxoid stroma seen in the majority of the lesions. Many small capillaries are present admixed throughout the myxoid stroma and account for the naming of this entity [129, 130].

25.14 Epithelioid Cell Histiocytoma

25.14.1 Clinical Features

Epithelioid cell histiocytomas typically occur in adults with mean age of onset of 40 years old [131]. There may be a slight male predominance [40]. Lesions are red exophytic or pedunculated papules typically occurring on the extremities, most commonly on the leg [40, 131]. Epithelioid cell histiocytomas have a benign clinical course and respond well to simple excision.

25.14.2 Histology

Epithelioid cell histiocytoma is characterized by a dome-shaped flattening of the epidermis caused by nodular aggregates of histiocytes within the dermis. The proliferation is centered within the papillary dermis, although extension into the reticular dermis and the underlying subcutis is not unusual. A relatively sharply circumscribed, nodular aggregation of large cells with abundant cytoplasm, vesicular nuclei, and focally prominent nucleoli is seen. Abundant vascularity is present within the lesion. Mitoses are rare and cytologic atypia is not present [131, 132]. Multinucleated cells may be seen, and lipid accumulation is present within the cytoplasm in some cases. Simultaneous occurrence of several lesions with this histologic pattern has been reported [133]. A granular cell variant wherein the tumor cells demonstrate granular, eosinophilic cytoplasm has been described [134].

Most investigators believe epithelioid cell histiocytoma to represent a variant of dermatofibroma, and its distinction from other variants does not appear to have major clinical importance [40]. The major differential diagnoses include a Spitz nevus and a vascular neoplasm. Spitz nevus is differentiated based upon maturation of melanocytes with progressive descent into the dermis and a nested growth pattern that is not present in epithelioid cell histiocytoma. Vascular tumors do not have the sheets of epithelioid cells unrelated to the vessels that are seen in epithelioid cell histiocytoma. In some cases the vessels may resemble those seen in what has previously been called hemangiopericytoma [135]. It has been suggested that this entity may be endothelial in origin, but most authors do not support this hypothesis [136–138]. S100 and CD31 immunostains are helpful in resolving the differential diagnosis in cases where there is some uncertainty based upon histologic findings [132]. There is some histologic overlap of epithelioid cell histiocytoma with nodular fasciitis, although the clinical presentation, and the myxoid stroma and mitotic activity seen in nodular fasciitis usually serve to make this distinction [139].

25.15 Fibrous Hamartoma of Infancy

25.15.1 Clinical Features

Fibrous hamartoma of infancy most commonly presents before 2 years of age with 90 % occurring within the first year of life and 20 % present at birth [140]. Male predominance exists with no known racial predilection.

Fibrous hamartoma of infancy is described as poorly circumscribed, mobile subcutaneous mass less than 4 cm in diameter and usually occurring along the trunk or limbs. The mass is characterized by rapid initial growth with local destruction in some cases [141]. Additional symptoms may include warmth or tenderness as well as hyperpigmentation, hypertrichosis, and hyperhidrosis [142]. Excision is curative with a recurrence rate of less than 15 % [141].

25.15.2 Histology

Fibrous hamartoma of infancy is a proliferation that is comprised of three basic cell types in various proportions. The three cell types include adipocytes, spindle-shaped myofibroblasts coursing in a fibrous stroma, and small round primitive mesenchymal cells within a myxoid matrix [144, 145] (Figs. 25.26 and 25.27). Scattered mitoses may be seen in the primitive cell population. However, cytologic atypia and pleomorphism are not present. In some cases, the epidermis may be slightly acanthotic and hyperpigmented [143]. A pseudoangiomatous pattern has also been reported in many cases [146]. Eccrine duct hyperplasia, ductular dilatation, and squamous syringometaplasia have also been described in association with the hamartomatous proliferation, but they are thought to be secondary phenomena and not part of the primary lesion [147]. Diagnosis of fibrous hamartoma of infancy has been rendered on cytologic preparations of fine needle aspiration based upon the recognition of short spindled cells and adipocytes [148].

Ultrastructural analysis reveals cells with features of fibroblasts and myofibroblasts [149]. Immunostains may be helpful in identifying the various cell types with S100 staining the mature adipocytes, CD34 staining the immature mesenchymal proliferation, and smooth muscle actin staining the mature fibrous population (Fig. 25.28) [146].

The differential diagnosis is dependent upon the proportions of cells comprising the hamartoma. Lipoma and spindle cell lipoma could be considered, but the latter would be

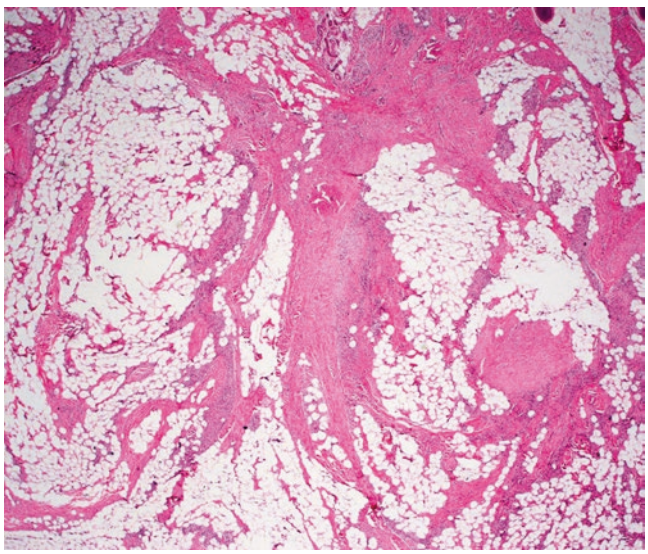

Fig. 25.26 Adipocytes and spindle cells coursing within fibrous stroma are seen in fibrous hamartoma of infancy

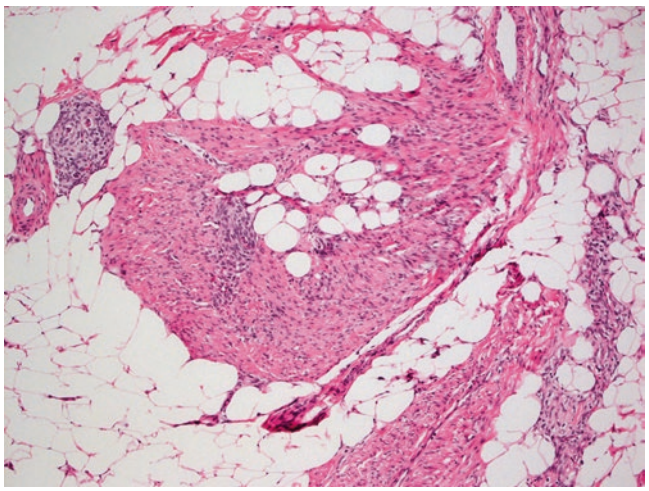

Fig. 25.27 Fibrous hamartoma of infancy is characterized by clusters of spindle-shaped cells within myxoid matrix. Other areas have more sclerotic collagen and foci of adipocytes

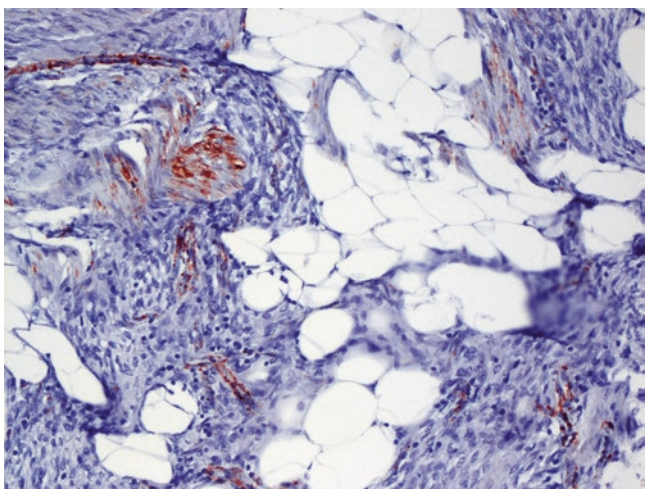

Fig. 25.28 Fibrous hamartoma of infancy shows focal positivity when stained with smooth muscle actin antibodies

extremely uncommon in the pediatric population. A benign neural tumor could be considered, but it would not be expected to have the other types of cells. Similarly, a smooth muscle tumor could be considered, but it would not have the heterologous elements.

25.15.3 Pathogenesis

Cytogenetic findings have been described in fibrous hamartoma of infancy. The findings include balanced translocations of chromosomes 2 and 3 (t(2;3)(q31;q21)) in one case, and chromosomes 6, 12, and 8 (t(6;12;8)(q25;q24.3;q13)) in another [150, 151]. Complex structural rearrangements involving chromosomes 1, 2, 4, and 17 have also been reported in this lesion [152]. There is genetic linkage fibrous hamartoma of infancy to Williams syndrome [153]. It has been proposed that a 28 base-pair microdeletion in the elastin gene may be a predisposing factor in the development of the lesions associated with Williams syndrome.

25.16 Dermatofibrosarcoma Protuberans

25.16.1 Clinical Features

Dermatofibrosarcoma protuberans (DFSP) accounts for 0.1 % of all cancers and 18.4 % of cutaneous soft tissue sarcomas [154]. Pediatric cases are thought to comprise between 6 and 20 % of all confirmed cases, with an incidence of 1 per 1 million children [154, 155]. Congenital lesions have been reported, but DFSP most commonly occurs in individuals between the second and fifth decade of life [154]. There is some thought that lower diagnostic rates in children may be secondary to slow growth and misdiagnosis.

Lesions most commonly occur on the trunk and proximal extremities [154]. Clinical appearance is varied but most frequently is described as a fixed and indurated plaque between 1 and 5 cm in greatest diameter. DFSP may be blue, violaceous, red or skin-colored. Surgery with wide local excision is curative as is Mohs micrographic surgery since it offers the lowest recurrence rates.

25.16.2 Histology

Histologic features of DFSP in children share many characteristics seen in the same tumors in the adult population. Spindle-shaped cells with tapered nuclei are present as fascicles and cartwheels coursing throughout the dermis with little or no intervening collagen (Figs. 25.29, 25.30 and 25.31). The dermis is densely cellular, and the cells are remarkably uniform in appearance with little pleomorphism or cytologic atypia. Mitotic activity is present, but atypical

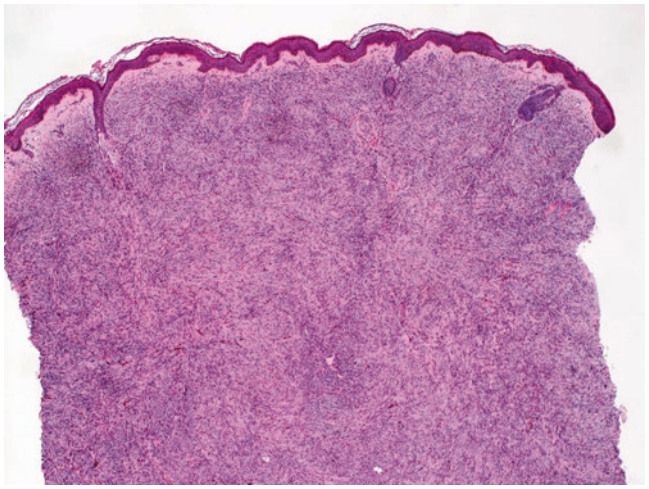

Fig. 25.29 Dermatofibrosarcoma protuberans demonstrates a diffuse proliferation of spindle-shaped cells throughout the dermis and into the subcutis

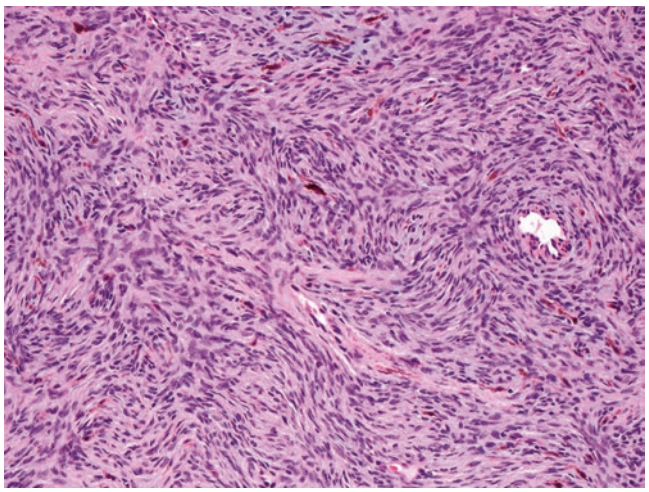

Fig. 25.30 A densely cellular monomorphous proliferation of spindled cells is seen in DFSP. Some cases demonstrate scattered pigmented cells

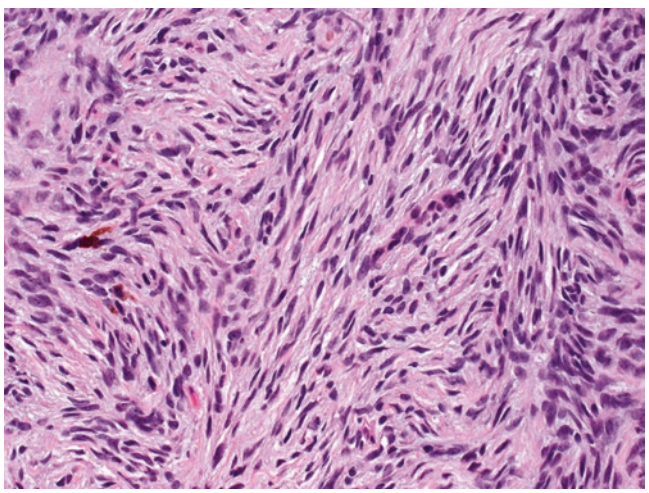

Fig. 25.31 Marked pleomorphism, cytologic atypia, and extensive mitotic activity are not seen in DFSP

mitoses are uncommon. The tumor extends into the papillary dermis, and may abut the epidermis and down into the subcutis where it envelops individual adipocytes. Tumor cells also extend around cutaneous appendages. In children, the presence of multinucleated cells admixed with the spindle cell proliferation gives rise to the name giant cell fibroblastoma, which is now believed to be a variant of DFSP [156, 157]. Myxoid stroma is present in some cases [158]. In rare cases, the epidermis is atrophic, and the tumor grows in a plaque-like pattern [159, 160]. Pigmented cells may be seen in the variant known as a Bednar tumor, and this raises the differential diagnosis of neurocrest neoplasms [161]. In areas with fibrosarcomatous transformation, foci with increased numbers of mitoses, atypical mitotic figures, and nuclear pleomorphism may be apparent [158].

A variant that is unique to the pediatric population is known as a *giant cell fibroblastoma* on account of the population of giant cells present in the dermis. These tumors may be less cellular than DFSP with the spindle-shaped cells coursing in a myxoid matrix (Figs. 25.32 and 25.33).

The differential diagnosis of DFSP mainly includes dermatofibroma, dermatomyofibroma, and neurofibroma. Dermatofibroma demonstrates epidermal hyperplasia, usually presents with a Grenz zone sparing the papillary dermis, has collagen bundles interspersed between a more pleomorphic population of cells, and is less fascicular than is the pattern of DFSP. Dermatofibroma rarely extends into the subcutis and when it does, involves the fibrous septa and not the fat lobules. Neurofibroma is less cellular than DFSP, has a more myxoid matrix than is the usual pattern in DFSP, and does not infiltrate between the individual adipocytes. Dermatomyofibroma generally has a more horizontal plaque-like growth pattern, and the cells have more eosinophilic cytoplasm than is the case with DFSP. The cellularity is also not usually as great. Expression of CD34, while not specific, helps to differentiate DFSP from these other spindle cell neoplasms that occur in the dermis.

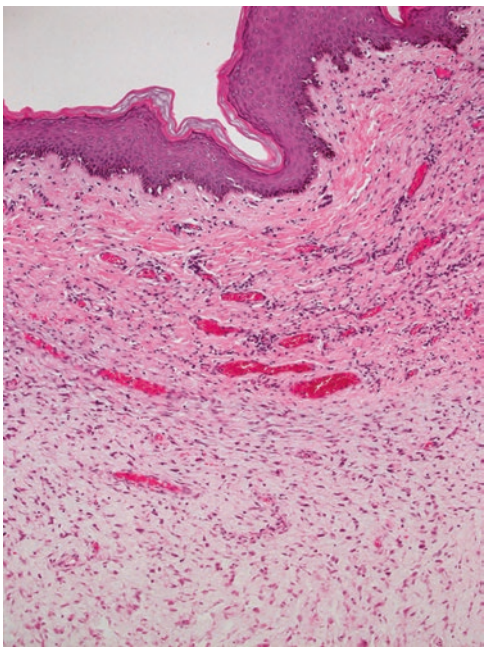

Fig. 25.32 Giant cell fibroblastoma demonstrates a dermal proliferation of pleomorphic cells, often coursing in a focally myxoid stroma

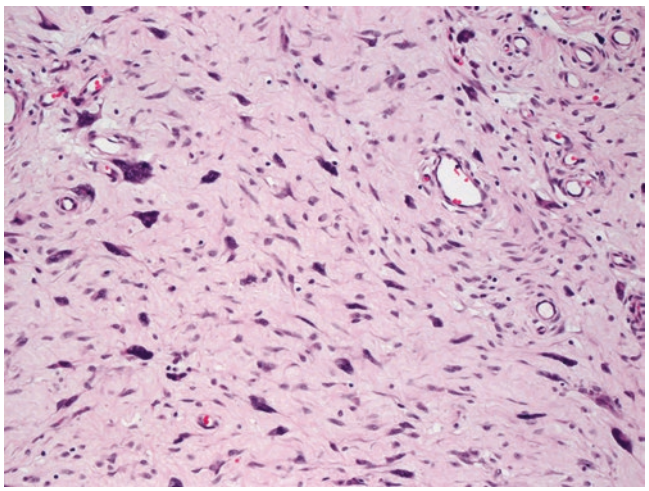

Fig. 25.33 Abundant multinucleated and pleomorphic giant cells are admixed with more typical appearing fibroblast-like cells in giant cell fibroblastoma

25.16.3 Pathogenesis

Dermatofibrosarcoma protuberans has a unique translocation between chromosomes 17 and 22 (t(17;22)(q22;q13) that is critical in the pathogenesis of the tumor. The rearranged chromosomes contain sequences of α1 type I collagen gene (COL1A1;17q21) and platelet-derived growth factor β-chain gene (PDGFB;22q13) [162]. This unique translocation of COL1A1 and PDGFB occurs in over 90 % of the cases [163]. The breakpoint in COL1A1 is highly variable and can span from exon 6 to exon 49. In contrast, the breakpoint in PDGFB consistently occurs in exon 2 [164]. There are 34 different COL1A1/PDGFB fusion variants that have been identified in DFSP [163–165].

The fusion of COL1A1 to PDGFB results in constitutive expression of PDGFB and activation of the PDGF signaling pathway [162]. When PDGF ligand binds to PDGFB receptor, the complex activates major signaling pathways including the Ras-MAPK and PI3K-AKT-mTOR pathways to stimulate cell proliferation, differentiation, and migration [166]. Increased levels of activated STAT3, ERK, and thrombospondin-1 are also found in DFSP [167, 168]. The t(17;22)(q22;q13) translocation event is an important initial step in the pathogenesis of DFSP because introduction of

the gene rearrangement in normal cells results in the neoplastic transformation of these cells [169, 170]. Activation of epidermal growth factor receptor and insulin receptor is also present in many cases of DFSP. Another potential mechanism of pathogenesis in DFSP involves small noncoding microRNA-205 (miR-205). Loss of miR-205 results in ERK activation with a possible increase in subsequent cell proliferation [171].

A targeted therapy for DFSP has been developed in light of the discovery of the t(17;22)(q22;q13) (COL1A1;PDGFB) translocation. Imatinib (Gleevec), which is a receptor tyrosine kinase inhibitor that blocks PDGFB receptor, is currently the standard therapy for the treatment of DFSP to reduce tumor size and to treat metastatic disease [164, 172, 173]. However, tumor resistance to imatinib has been identified in some patients. Whole genome sequencing of drug-resistant tumor shows no changes in PDGFB gene, but mutations were found in other signaling pathways [174]. Therefore, it is possible that resistance to PDGFB receptor inhibitor is secondary to the development of alternative pathways for tumor survival independent of PDGF. Notably, not all DFSP tumors have COL1A1;PDGFB translocation. A new translocation involving CSPG2 and PTK2B genes between chromosomes 5 and 8 has also been identified [175].

25.17 Epithelioid Sarcoma

25.17.1 Clinical Features

Epithelioid sarcoma is seen infrequently, accounting for less than 1 % of all reported soft tissue sarcomas [176]. Reports of affected individuals as young as 10 years old exist, although tumors often occur in males between 20 and 40 years old [176]. Lesions are firm, slow-growing subcutaneous nodules or swellings on the distal extremities that may ulcerate and extend proximally. The tumor is often multifocal and infiltrative with associated pain, paresthesia, and muscle wasting when a large nerve is affected. Local recurrence and metastasis, both regional and distant, frequently occur following excision.

25.17.2 Histology

Histologic changes in epithelioid sarcoma are those of a dermal nodule that is not encapsulated, but relatively well-circumscribed. A palisade of large epithelioid cells surrounds a central area of necrosis (Fig. 25.34). The palisading cells have cytologic atypia, nuclear pleomorphism, and scattered mitotic activity (Fig. 25.35). Rhabdoid cells are seen in some cases. The cytologic features suggest a malignant process in most cases; however, the overall architectural pattern resembles that of a dermal granulomatous process. Calcification is frequently found, especially within the areas of necrosis.

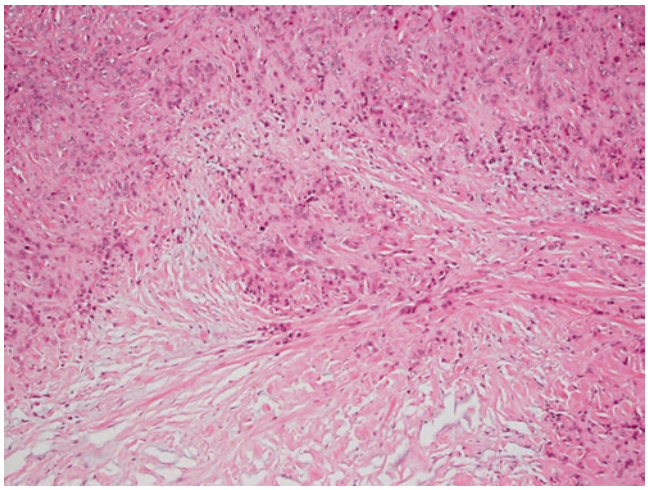

Fig. 25.34 Epithelioid sarcoma demonstrates a central area of necrosis with a palisade of tumor cells with an appearance that resembles a granulomatous process

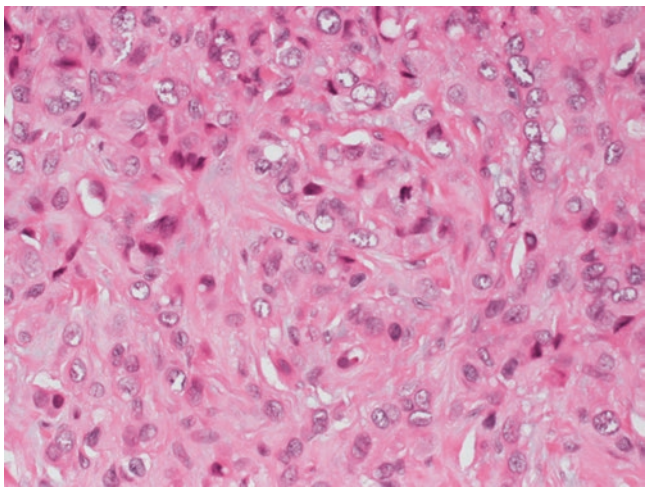

Fig. 25.35 Closer analysis demonstrates pleomorphism, cytologic atypia, and mitotic activity in epithelioid sarcoma

The differential diagnosis of epithelioid sarcoma includes deep granuloma annulare and rheumatoid nodule. Granuloma annulare is characterized by a central area of mucinous degeneration but no cellular necrosis as seen in epithelioid sarcoma. Rheumatoid nodules have central foci of eosinophilic, fibrin-coated collagen, but no cellular necrosis. Neither of these granulomatous processes demonstrates cytologic atypia, nuclear pleomorphism or abundant mitotic activity as seen in epithelioid sarcoma. In cases where there is some diagnostic uncertainty, use of a cytokeratin stain will show strong staining of cells in epithelioid sarcoma, but not in either of the granulomatous processes.

25.17.3 Pathogenesis

Epithelioid sarcoma is a mesenchymal malignancy with predominant epithelial differentiation. Epithelioid sarcoma expresses both epithelial and mesenchymal markers, such as cytokeratin, epithelial membrane antigen, vimentin, and CD34 [177, 178]. The tumor has two histologic subtypes, distal (classic) subtype and proximal subtype. Classic subtype usually affects young adults and arises in the distal extremities. Proximal subtype arises in the truncal region (pelvis, perineal, and genital regions) and is frequently associated with epithelioid or rhabdoid morphology with higher mitotic activity and worse clinical outcome [179].

The molecular aberrations in epithelioid sarcoma consist of mutations or deletions in chromosome 22q11.2 or gains in chromosome 8q [180, 181]. The causative gene on chromosome 22q11.2 is the SMARCB1 gene (also called BAF47, INI1, or hSNF5) [182]. Loss of function of SMARCB1 is the most common genetic mutation in this tumor, found in about 90 % of cases and is believed to be a major driver of the tumor [183]. Loss of function of SMARCB1 has been found in both classic and proximal subtypes, with studies of tumor cell lines suggesting that genetic inactivation of SMARCB1 is responsible for the tumorigenic characteristics because loss of function leads to uncontrolled cell proliferation [184, 185]. SMARCB1 encodes a core protein subunit of the SWI/SNF chromatin remodeling complex involved in regulating the nucleosome architecture and chromatin structure, which in turn affects gene expression by regulating the accessibility of gene promoters to transcription factors [186, 187]. Interestingly, SMARCB1 is also a tumor suppressor gene in infantile malignant rhabdoid tumors. In addition to loss of SMARCB1, concurrent loss of other subunits of the SWI/SNF complex, including PBRM1 and BRM, has also been identified in epithelioid sarcoma [188]. Other epigenetic modifiers are important in the pathogenesis of epithelioid sarcoma. Studies have indicated that epigenetic modifiers such as histone deacetylase (HDAC) inhibitors in combination with inhibitors of the histone methyltransferase EZH2 may have a therapeutic role in tumor treatment [189].

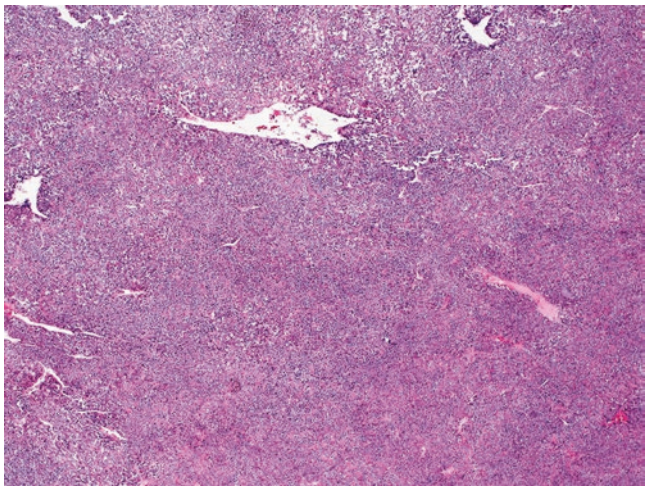

Fig. 25.36 Gland-like spaces are seen within a densely cellular proliferation of single cells in synovial sarcoma

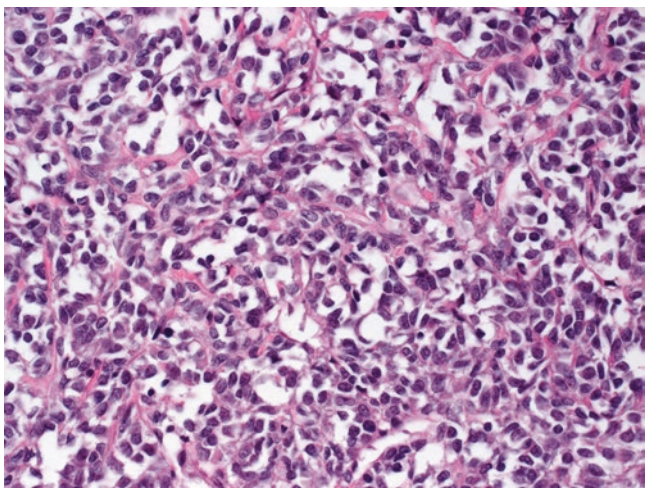

Fig. 25.37 Focal gland-like spaces are present in biphasic synovial sarcoma

25.18 Synovial Sarcoma

25.18.1 Clinical Features

Synovial sarcomas are rare tumors in the general population, but they are a common type of pediatric soft tissue sarcomas [190]. Disease appears to occur more commonly in Caucasians, and affects males and females equally. In one pediatric cohort from St. Jude Children's Research Hospital, most of the primary tumors occurred on the extremities, although tumors on the head, neck, and trunk have been reported as well [190]. The tumor has poor morbidity and mortality due to local recurrence and distant metastasis [191]. Tumor size, degree of invasion, and histologic grade independently adversely affect the clinical outcome.

25.18.2 Histology

Synovial sarcomas are almost always based in the deep soft tissues, but they have been described in the dermis [192]. Two histologic patterns have been described for synovial sarcomas. The *monophasic pattern* is characterized by a fascicular growth pattern of spindle-shaped cells with variable cytologic atypia and mitotic activity (Figs. 25.36 and 25.38). The *biphasic pattern* demonstrates a glandular proliferation

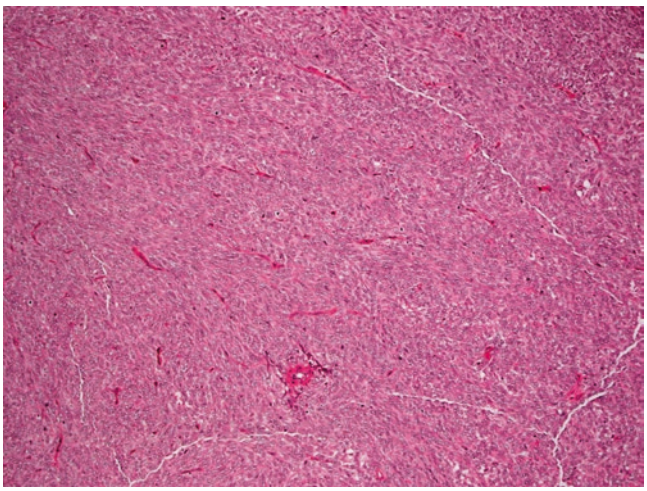

Fig. 25.38 Fascicles of monomorphous spindle-shaped cells are present in monophasic synovial sarcoma

admixed with fascicular spindle cells (Fig. 25.37). Cytokeratin and epithelial membrane antigen (EMA) antibodies label virtually all of the biphasic lesions and the great majority of the monophasic ones.

25.18.3 Pathogenesis

Although synovial sarcoma originates in the periarticular regions, it is not derived from the synovium, nor does it differentiate into synovial tissue. The true cell of origin of synovial sarcoma or its line of differentiation is not entirely known. The majority (75 %) of the cases of synovial sarcoma are "monophasic" spindle cell tumors, and the less common "biphasic" variant exhibits features of true mesenchymal–epithelial transition [193].

Tumorigenesis in synovial sarcoma is driven by the fusion of SS18 (synovial sarcoma translocation, chromosome 18) and SSX (synovial sarcoma, X breakpoint) genes on chromosomes X and 18 (t(X,18; p11,q11)) [194–196]. SS18 is a subunit of the SWI/SNF complex, which functions to affect chromatin structure by repositioning nucleosomes on genomic DNA, and promoting nucleosome disassembly and histone exchange [197]. SS18/SSX fusion is present in up to a third of the cases of synovial sarcoma [198], and a genetically engineered animal model that expresses this fusion gene develops synovial sarcoma with 100 % penetrance [199]. Analysis of the gene-expression profile of the tumor reveals high expression of mediators involved in the patterning systems of early embryogenesis, including WNT, NOTCH, Hedgehog, fibroblast growth factor, and BMP pathways [193]. These findings suggest that synovial sarcoma arises from cells with stem cell-like or early progenitor phenotype.

The WNT/β-catenin pathway is important in synovial sarcoma. There is nuclear accumulation of β-catenin in 30–60 % of tumors [200, 201]. Canonical activating mutations in the β-catenin gene CTNNB1 have been found in synovial sarcoma [202]. Genetic loss of β-catenin inhibits tumor formation in a transgenic animal model, and inhibition of β-catenin signaling impairs the growth of human synovial sarcoma cell lines [203]. In addition to β-catenin, synovial sarcoma also exhibits aberrant activation of the PI-3 Kinase/Akt signaling pathway, which is a key cell survival regulatory pathway [204, 205].

Small non-coding microRNA regulates gene expression at the post-transcriptional level [206]. MicroRNA miR-17 has been identified as an oncogene that causes aggressive growth of synovial sarcoma cells by directly inhibiting the expression of p21CIP1/WAF1, which is a potent cyclin-dependent kinase inhibitor that blocks G1/S phase transition [207].

A Complexity Index in Sarcoma (CINSARC) score that is based on a 67-gene signature related to chromosome integrity, mitotic control, and genome complexity has been used as a tool to predict the risk of metastasis and response to chemotherapy in synovial sarcoma [208, 209]. Tumor metastasis is strongly associated with chromosomal complexity in both children and adults, although chromosome instability is more frequently seen in adult patients [209].

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Neural Proliferations

26

26.1 Traumatic Neuroma

26.1.1 Clinical Features

The exact incidence of traumatic neuromas is not known, but they appear to be the most common subtype of cutaneous neuromas described [1, 2]. They may occur following any variety of injuries and at any age, including neonates and young infants, as a result of in utero amputation of a supernumerary digit [3]. Traumatic neuromas are skin colored to slightly erythematous, intermittently painful nodules, occurring at sites of previous trauma, most commonly on the digits [1, 2]. Neuromas are almost universally painful and persistent. Surgical excision may be curative.

26.1.2 Histology

The histologic findings are identical in traumatic neuroma and amputation neuroma secondary to polydactyly. The findings are confined to the dermis, in which there is a proliferation of nerve bundles that are readily apparent at low magnification (Fig. 26.1). Large bundles of sharply circumscribed neural elements are present throughout the dermis and in the subcutis. The neural elements do not have cytologic atypia and mitotic activity is not present. Perineurial sheaths confine each bundle. Concentric rings of fibrosis resembling onion skins surround each of the nerve fascicles and are responsible for the characteristic histologic appearance (Fig. 26.2).

26.1.3 Pathogenesis

Traumatic neuroma represents a hyperplastic response of the affected nerve to injury, trauma, or chronic inflammation [4, 5]. It is believe to be secondary to dysregulated proliferation of the nerve and connective tissue in the process of reinnervation of the affected area. The development of traumatic neuroma appears to be dependent on local neurotropic molecules, particularly nerve growth factor (NGF) [6–8]. NGF is an important neurotropic factor that is essential for the survival of peripheral neurons [9]. Studies have shown that inhibition of NGF activity by blocking NGF receptor can prevent traumatic neuroma formation in rodents [7].

26.2 Neurofibromatosis Type 1

26.2.1 Clinical Features

Neurofibromatosis type 1 (NF1) is a progressive multisystem disease, secondary to genetic mutation of the NF1 gene on chromosome 17, which encodes the tumor suppressor protein, neurofibromin. The disorder has a prevalence of 1 per 3,500 people worldwide with autosomal dominant inheritance pattern, although approximately 50 % of cases occur as a result of spontaneous mutation [10]. There is significant phenotypic variability among affected individuals, but almost all patients have stigmata of disease by 20 years of age. Cutaneous diagnostic criteria include more than six café au lait macules, neurofibromas, intertriginous freckling, and plexiform neurofibroma. Additional clinical features that are commonly seen include learning disabilities, Lisch nodules, optic gliomas, and osseous lesions, such as scoliosis and sphenoid wing dysplasia. Studies indicate that the life expectancy of individuals with NF1 is lower than that of healthy individuals with increased mortality secondary to early onset vasculopathy and soft tissue malignancies, particularly malignant peripheral nerve sheath tumors [11]. The histology and pathogenesis of neural tumors in the skin that are commonly associated with NF1 are described elsewhere in this chapter (Sects. 26.4 and 26.5).

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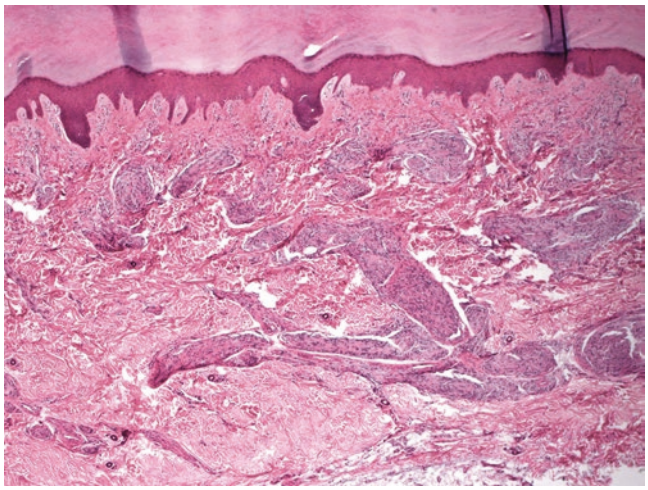

Fig. 26.1 A traumatic neuroma demonstrates multiple foci of neural proliferations throughout the dermis

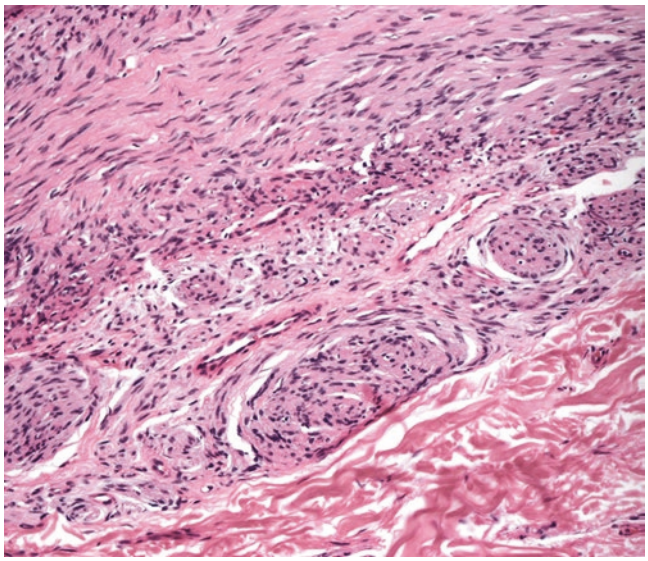

Fig. 26.2 When cut en face, the neural proliferations may resemble onion bulbs in a traumatic neuroma

26.3 Neurofibromatosis Type 2

26.3.1 Clinical Features

Neurofibromatosis type 2 (NF2) has an incidence between 1 per 33,000 and 1 per 87,000 individuals [12]. Fifty percent of cases are attributed to spontaneous mutation of the NF2 gene region of chromosome 22, while the remainder is inherited in an autosomal dominant manner [13, 14]. Only 20 % of cases are diagnosed in children. Small café au lait macules may be present, but they are fewer in number than those seen in NF1. Multiple cutaneous schwannomas are a well-established feature of NF2 [13, 14]. The schwannomas of NF2 frequently are slightly pigmented plaques with overlying hypertrichosis. Adults frequently present with tinnitus, hearing loss, and problems with balance secondary to acoustic schwannomas. Eighty percent of children with NF2 have cataracts at the time of diagnosis as an initial sign of disease, preceding hearing loss in most cases [13]. NF2 in children portends a worse prognosis with greater mortality secondary to increased number of rapidly progressive central nervous system tumors. The histology and pathogenesis of neural tumors in the skin that are commonly associated with NF2 are described elsewhere in this chapter (Sects. 26.4 and 26.5).

26.4 Neurofibroma

26.4.1 Clinical Features

Solitary or isolated neurofibromas are relatively common benign tumors of neuromesenchymal tissue that are seen equally in both males and females. Lesions rarely occur in infancy, and more frequently present in middle to late childhood after puberty [11]. Four classifications exist: (1) discrete cutaneous neurofibromas, (2) discrete subcutaneous neurofibromas, (3) nodular plexiform neurofibromas, and (4) diffuse plexiform neurofibromas.

Neurofibromas typically present as solitary, soft, skin-colored nodules with a variable diameter between 0.2 and 2 cm in size. Lesions grow slowly and can become more exophytic or pedunculated over time [11]. A characteristic feature is invagination into the dermis when direct pressure is applied on top of the lesion, known as the "buttonhole sign." These are benign lesions and can be treated with simple excision. Patients with multiple lesions or other cutaneous stigmata (specifically café au lait macules and intertriginous freckling) warrant evaluation for neurofibromatosis.

Plexiform neurofibromas are subcutaneous masses or plaques, often with overlying hyperpigmentation and a rubbery consistency on palpation likened to a "bag of worms" (Fig. 26.3). These lesions are pathognomonic of neurofibromatosis type 1, and have a reported risk of malignant degeneration in 2–5 % of cases [15].

Malignant peripheral nerve sheath tumor is an uncommon neural malignancy with an estimated incidence of 0.0001 % in the general population [16]. Patients with neurofibromatosis type 1 (NF1) share a greater burden of disease with incidence of 1 case per 100 NF1 patients per year [16]. Tumors typically present in middle-aged adults, although median age of onset in those with NF1 is younger (mid-30s), including reports of diagnosis in adolescents. Lesions commonly occur in the setting of nodular and plexiform neurofibromas, and present as painful, expanding masses.

Fig. 26.3 Plexiform neurofibroma presents as a large brown patch overlying a soft subcutaneous mass on the right buttock

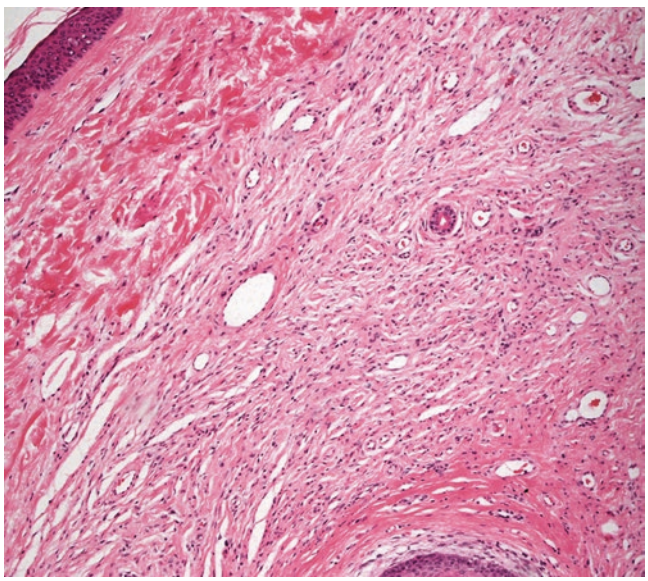

Fig. 26.4 Unencapsulated spindle-shaped cells coursing in pale eosinophilic neuropil characterize neurofibroma

Poor prognostic factors include tumor size at the time of diagnosis and axial location. Surgical excision is the standard of care as tumors have poor response to radiotherapy and chemotherapy. Ultimately, the diagnosis carries a poor prognosis with a 50 % 5-year survival rate in those without NF1 and 15 % in those with the disease [16].

26.4.2 Histology

Histologic findings in neurofibromas are those of a spindle cell proliferation based in the dermis (Fig. 26.4). The epidermis is either unremarkable or somewhat flattened when the underlying neoplasm extends higher in the dermis. Occasional cases demonstrate changes within the epidermis and appendages [17]. The tumor consists of a population of spindle-shaped cells with tapered nuclei. The surrounding stroma is characteristically pale staining, especially when compared with surrounding dermis (Fig. 26.5). In some cases, the stroma may have foci of myxoid change. The tumor is relatively well-circumscribed and not encapsulated. Diffuse neurofibromas that are not at well-circumscribed are more prevalent in children [18]. Occasional cells demonstrate cytologic atypia in some cases with this appearance usually being attributed to "ancient change." When the cytologic atypia is more pronounced, a diagnosis of atypical neurofibroma may be warranted [19]. Mitotic activity is rare, and should raise concern for malignancy when abundant. Similarly, marked increase in cellularity should raise suspicion of malignant peripheral nerve sheath tumor [19]. Most cases do not have a significant inflammatory response, but mast cells are present in neurofibromas. Admixed adipocytes may be present as either diffuse or focally dispersed throughout the lesion.

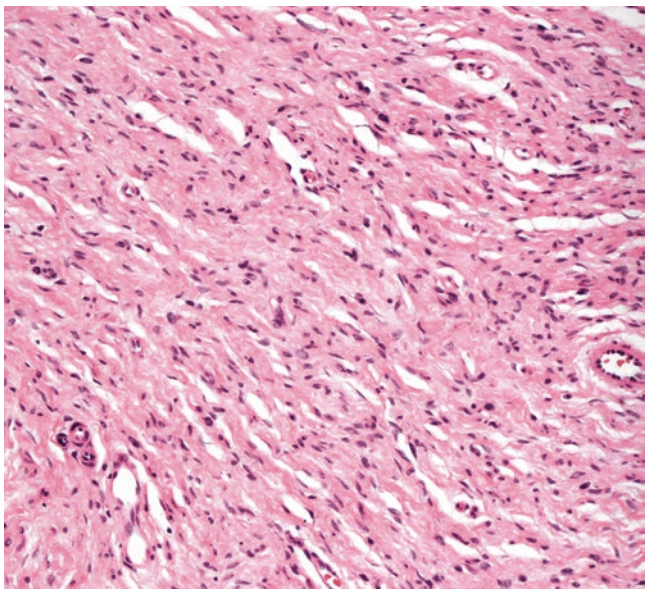

Fig. 26.5 The cells in neurofibroma as wavy and thin with tapered ends

Plexiform growth pattern can be seen in the skin with several separate lobular configurations, but extreme caution is advised regarding making the diagnosis of plexiform neurofibroma on a skin biopsy. This diagnosis confers a diagnosis of neurofibromatosis, and gross examination of lesions and genetic testing are the preferred ways to establish this diagnosis. Rare variants may contain nests of nonpigmented melanocytes, and are designated cutaneous epithelioid melanocytic neurofibromas [21]. It is unclear whether these tumors represent a largely neurotized melanocytic nevi. Another variant known as a pigmented storiform neurofibroma demonstrates a storiform growth pattern and scattered pigment-laden cells [22].

The differential diagnosis includes dermatofibroma. These tumors usually demonstrate overlying epidermal hyperplasia and hyperpigmentation, which are features not associated with neurofibroma. Furthermore, the interspersed collagen tends to be deeply eosinophilic as opposed to the pallor of the stroma in neurofibromas. Neuromas consist of a more lobulated growth pattern with individual nerve fascicles surrounded by perineurium. These findings are not seen in neurofibromas. Schwannomas demonstrate palisading as well as Antoni A and Antoni B areas with marked differences in cellularity, which are features not seen in neurofibroma. Moreover, Schwannomas are encapsulated unlike neurofibromas which are not.

Malignant peripheral nerve sheath tumors are very uncommon in children but can arise in patients with NF1 [23, 24]. In most cases, the tumors appear to arise from within a plexiform neurofibroma. A proliferation of spindle-shaped cells with tapered nuclei and relatively scant cytoplasm is present within the dermis, growing in a fascicular and infiltrative pattern (Fig. 26.6). These tumors are markedly hypercellular with abundant pleomorphism, cytologic atypia, and mitotic activity (Fig. 26.7) [19]. Single cell necrosis and areas of zonal necrosis help to identify this as a malignant neoplasm.

The differential diagnosis includes monophasic synovial sarcoma, leiomyoma, melanoma, and dermatofibrosarcoma protuberans. Immunohistochemistry is helpful in making the diagnosis as well as genetic testing of the tumor (Fig. 26.8) [25]. Melanotic schwannoma also enters the differential diagnosis, but it can be distinguished based upon the abundant pigment within the tumor and its Schwannian growth pattern [26].

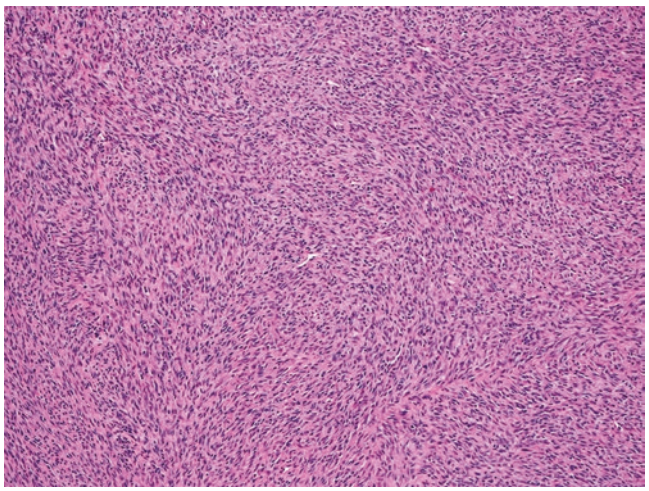

Fig. 26.6 Malignant peripheral nerve sheath tumor demonstrates sheets of wavy cells coursing in fascicles

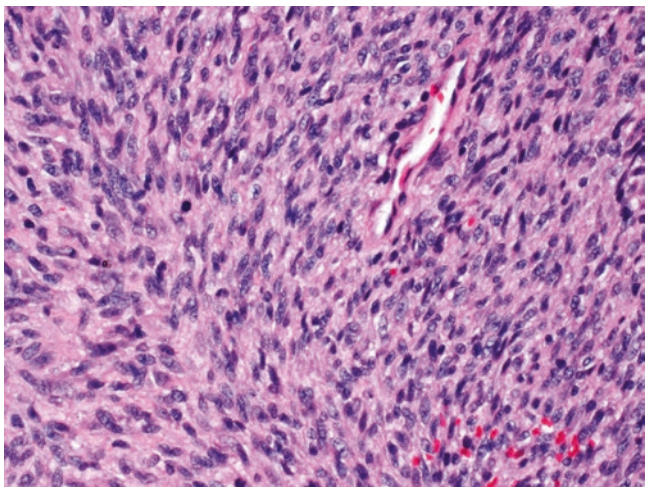

Fig. 26.7 Malignant peripheral nerve sheath tumor demonstrates pleomorphism and cytologic atypia

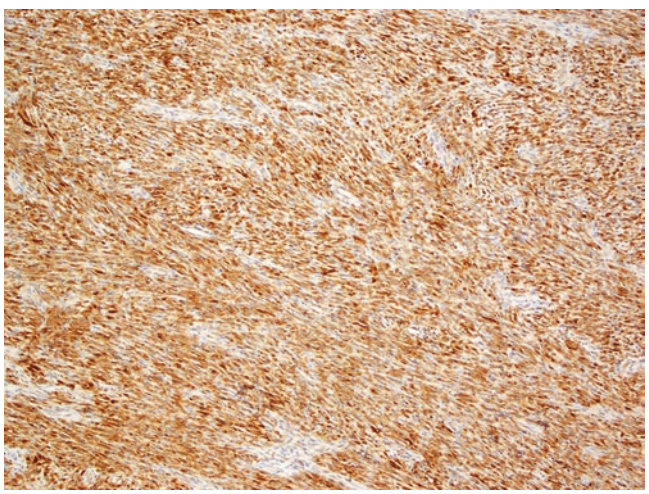

Fig. 26.8 Diffuse S100 staining helps to differentiate malignant peripheral nerve sheath tumor from other spindle cell neoplasms that may occur in the dermis

26.4.3 Pathogenesis

Neurofibroma is a benign peripheral nerve tumor that is composed of Schwann cells, perineurial cells, axons, fibroblasts, and mast cells [27]. Neurofibroma is likely to arise from Schwann cell lineage [28]. Mast cells can promote neurofibroma growth, and fibroblasts and endothelial cells can enhance angiogenesis and collagen synthesis in neurofibroma [29, 30]. Cutaneous neurofibroma is a benign growth, and does not undergo malignant transformation, unlike plexiform neurofibroma, which can be associated with transformation to malignant peripheral nerve sheath tumor [31, 32]. Neurofibroma can occur sporadically or in the setting of neurofibromatosis type 1.

The RAF/MEK/ERK signaling pathway has a key role in the growth of neurofibroma and malignant peripheral nerve sheath tumor [33]. Inhibitors of MEK effectively reduce the growth of neurofibroma in vitro and in experimental animal models [32]. There are currently active clinical trials of MEK inhibitors for patients with neurofibromatosis-associated neurofibromas and plexiform neurofibromas [32, 34].

26.5 Schwannoma

26.5.1 Clinical Features

Cutaneous schwannomas are rare and may occur at any age, but lesions most frequently are described in adults [35]. Cutaneous schwannomas typically are asymptomatic soft, pink to yellow, smooth and deep-seated subcutaneous nodules or plaques of the head and neck with diameter between 0.5 cm and 3 cm in size [35, 36]. They can sometimes be painful. Lesions are usually solitary, but descriptions of multiple schwannomas have been reported in familial cases, and in association with genodermatoses, such as neurofibromatosis type 2 and neurilemmomatosis (when other features of neurofibromatosis type 2 are not seen) [13, 14]. Schwannomas are benign nerve sheath tumors, and can be treated with simple excision [35].

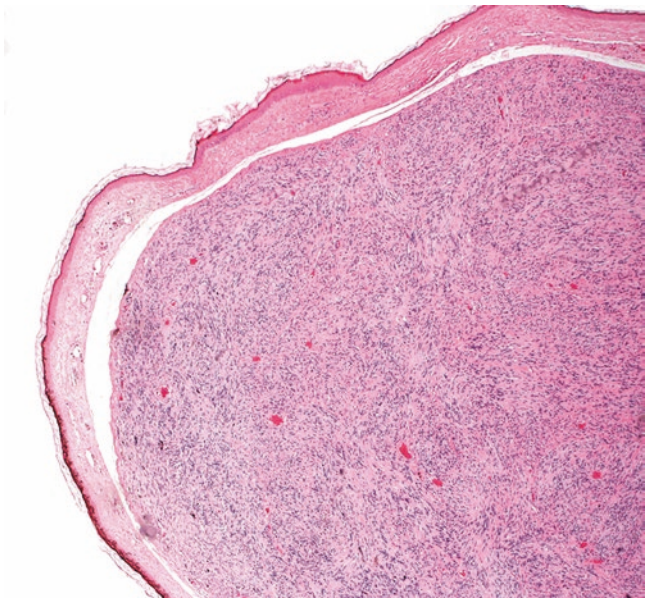

Fig. 26.9 Schwannomas are sharply circumscribed dermal tumors comprised of spindle-shaped cells

26.5.2 Histology

Cutaneous schwannomas share histologic features with those occurring in other organs. They are a well-circumscribed and encapsulated proliferation of neural elements in the dermis. Cellular areas (Antoni A) and paucicellular areas with more myxoid matrix (Antoni B) are interspersed. Verocay bodies, which are a palisade of tumor cells, are readily identifiable in many cases (Figs. 26.9, 26.10, 26.11, and 26.12). Ancient change may account for slight cytologic atypia seen in some cases. Mitoses are not a feature of this neoplasm, and their presence should raise suspicion for malignancy. Rarely, a plexiform growth pattern has been described in the skin, most often associated with neurofibromatosis [14, 37]. This growth pattern has also been described in the rare epithelioid schwannoma variant characterized by tumor cells with an epithelioid morphology and less spindly than the usual schwannoma [38–40].

A variant with multiple pigment-containing cells and psammoma bodies has been reported to be a marker for Carney syndrome, and is known as a melanotic psammomatous schwannoma [41, 42]. A melanotic component in the absence of psammoma bodies does not always confer a diagnosis of Carney syndrome [26]. A pseudoglandular schwannoma demonstrates the usual characteristics of schwannoma but also has pseudoglandular spaces. There is no significance to this particular histologic variant [43]. A very rare neuroblastoma-like schwannoma variant has been described with smaller cells and rosette formations [44, 45].

The differential diagnosis includes other neural neoplasms. Neurofibromas do not demonstrate Verocay bodies and, while usually well-circumscribed, they are not encapsulated. S100 immunohistochemistry diffusely and strongly stains schwannomas, in which most of the tumor elements

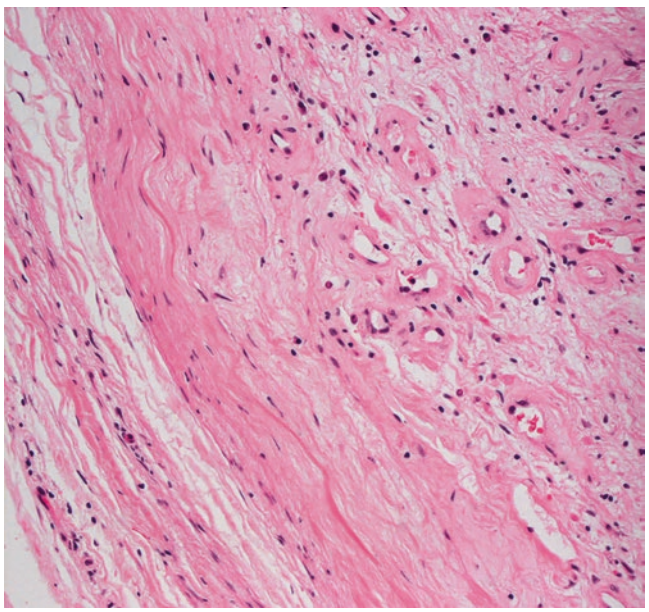

Fig. 26.10 Some areas of schwannoma may have wispy background collagen and a proliferation of small vessels

are axons, but only show partial S100 positivity in neurofibromas, which contain many cell types. Palisaded encapsulated neuromas may share some features with schwannomas, but they are not encapsulated and rarely demonstrate palisading (despite the name). They are also readily differentiated based upon the clinical presentation. Traumatic neuromas are characterized by a more lobulated proliferation of nerve fascicles than schwannoma.

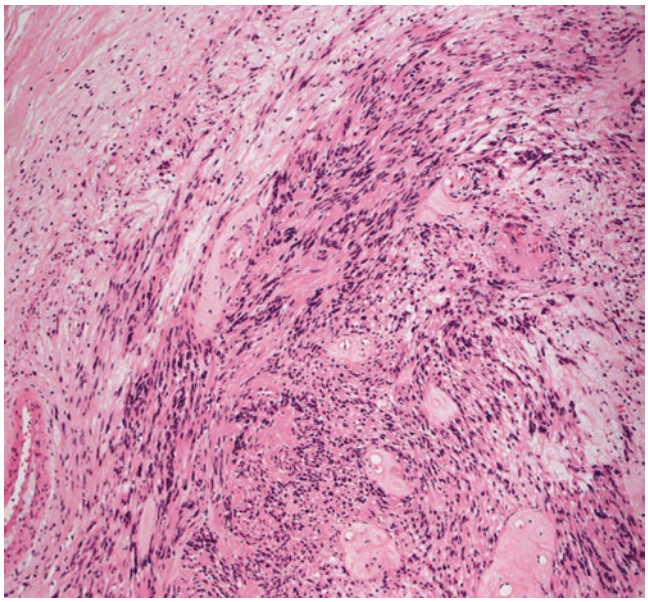

Fig. 26.11 More cellular areas of schwannomas may demonstrate a pseudopalisading pattern, giving rise to Verocay bodies

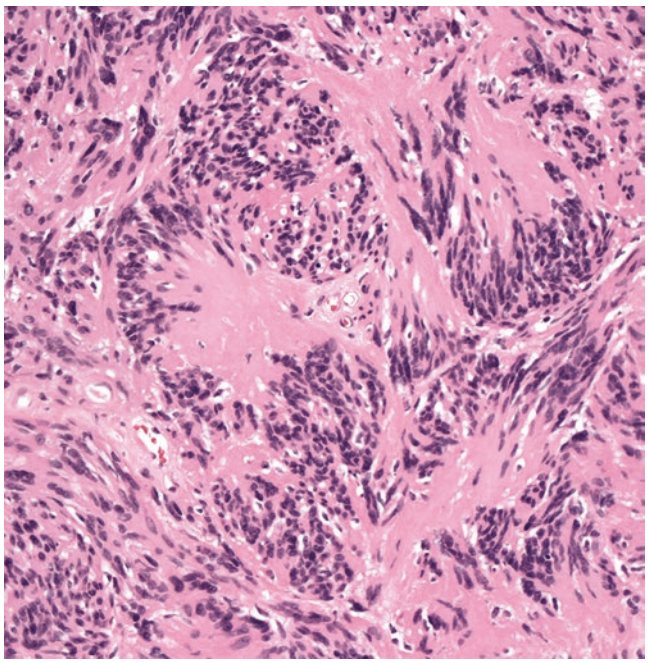

Fig. 26.12 Verocay bodies demonstrate nuclear palisades and a characteristic appearance

26.5.3 Pathogenesis

Schwannoma is a benign tumor, consisting of a clonal population of Schwann cells. Most cases of schwannoma are sporadic. However, some cases are associated with radiation exposure and syndromic disorders, such as neurofibromatosis type 2 (NF2), schwannomatosis, and Carney's complex [46–50]. Schwannoma in children is most commonly located in the skin in individuals with neurofibromatosis [48, 51].

The identification of NF2 (merlin) gene has led to a better understanding of the disease pathogenesis [52, 53]. Mutations in NF2 are found in sporadic and NF2-associated schwannomas, many of which are de novo mutations [48, 54]. The phosphorylation state of merlin is important for the mechanism of the loss of function and inactivation of merlin in schwannoma [55].

Schwannomas can occur as multiple lesions in some individuals (schwannomatosis). Germ-line mutations in SMARCB1 have been reported in a number of patients with schwannomatosis [56, 57]. SMARCB1 has tumor suppressor functions, and forms part of an adenosine triphosphate (ATP)-dependent chromatin-remodeling complex that is important in central nervous system development [58]. It has been found that germ-line loss of function mutations of another tumor suppressor gene called LZTR1 is common in patients with schwannomatosis. LZTR1 is known to interact with proteins that regulate SMARCB1 expression [59].

26.6 Granular Cell Tumor

26.6.1 Clinical Features

Granular cell tumor is a rare neoplasm, primarily affecting adults between 30 and 60 years of age, with rare reports of such tumors in children [60]. They occur twice as frequently in females, and are more commonly seen in African-Americans [61]. Granular cell tumors usually present as an asymptomatic solitary, skin-colored or brownish red, firm subcutaneous nodule with diameter between 0.5 cm and 3 cm in size [60]. They may occur anywhere on the body, but 45–65 % of cases present at the head or neck with most lesions described as intraoral tumors, generally affecting the tongue [62]. Patients sometimes experience associated mild tenderness or pruritus. Malignant transformation with local infiltration or metastasis occurs in approximately 2 % of cases [61]. Complete excision is recommended for symptomatic or rapidly enlarging lesions since the likelihood of recurrence is high when tumors are not completely removed.

26.6.2 Histology

Marked pseudoepitheliomatous hyperplasia is seen overlying many cases of granular cell tumors. One such tumor occurring in a child has been described with marked overlying hypertrichosis [63]. The dermis is filled with a proliferation of large cells with abundant granular and eosinophilic cytoplasm (Figs. 26.13 and 26.14). The larger cytoplasmic

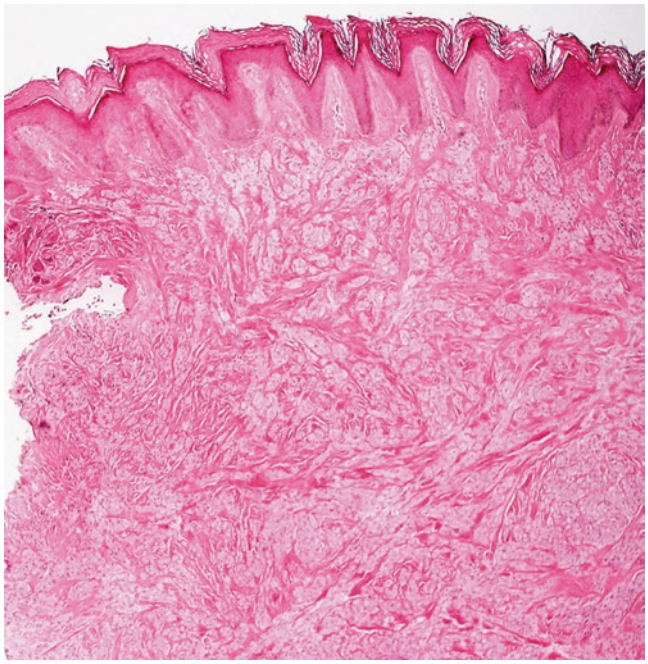

Fig. 26.13 An acanthotic epidermis overlies diffuse dermal proliferation of large cells with abundant eosinophilic cytoplasm in granular cell tumor

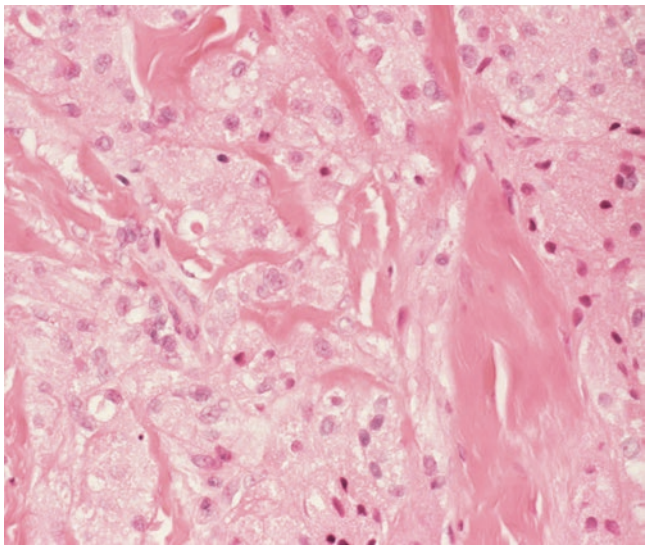

Fig. 26.14 Granular cell tumor is characterized by a proliferation of cells with abundant granular, eosinophilic cytoplasm, and small, banal appearing nuclei

granules may be surrounded by a halo, in which case they are given the name pustulo-ovoid bodies of Milian. There is no significance to this finding other than recognition of this feature in some granular cell tumors [64]. The cell nuclei are small, dark, and uniform in appearance. Nucleoli are inconspicuous. Cytologic atypia is absent or minimal in most cases, and the mitotic rate is low. The tumor may be locally invasive, and is not well circumscribed. Extension into the subcutis is common. Perineural invasion and extension into arrector pili muscles are present in many cases, and vascular invasion is seen in some tumors [65]. A plexiform growth pattern has been described, and this is expected given the Schwannian origin of these neoplasms [66–68].

A rare nonneural granular cell tumor has recently been described. The exact nature of this tumor is still not fully delineated, but it appears to behave in an indolent fashion despite having a higher likelihood of mitotic activity than the usual schwannian granular cell tumor [69, 70].

A type of granular cell tumors called congenital gingival granular cell tumor of the newborn, or congenital granular cell epulis, is a rare lesion seen in the maxillary alveolar ridge in the mouth in newborns [74, 75]. This tumor is histologically similar to granular cell tumor that often occurs in adults, with cells showing abundant eosinophilic granular cytoplasm. Ultrastructurally, the granules are membrane-bound phagolysosomes present in the cytoplasm [76]. There is no accompanying pseudoepitheliomatous hyperplasia, and importantly, this tumor is negative for S100, whereas common granular cell tumor in adults is positive for S100 [73]. Malignant transformation has not been described in this rare tumor [71].

The differential diagnosis of granular cell tumor includes other tumors with granular cell changes, such as rare fibrous papules and epithelioid cell histiocytomas. Some leiomyomas may present a diagnostic challenge, although immunohistochemistry can easily distinguish S100-positive granular cell tumors from leiomyomas that express smooth muscle actin. It is important to recognize the frequency and extent of pseudoepitheliomatous hyperplasia in granular cell tumors, and not to overcall these changes as squamous cell carcinoma. This is especially a problem with superficial shave biopsies or with lesions involving the tongue, in which the epidermal growth may be extensive and entirely reactive.

26.6.3 Pathogenesis

The etiology of granular cell tumor is not known. It has been postulated that the tumor originates from undifferentiated mesenchymal cells. It occurs in almost every tissue of the human body, and can involve nerve fiber bundles, skeletal muscle, smooth muscle, and fibrous connective tissue. These findings appear to favor the hypothesis that granular cell tumor is derived from mesenchymal cells [72]. Some immunohistochemical studies also support the mesenchymal origin of these tumors [73]. Ultrastructural studies show that granular cells contain autophagosomes with collagen precursors, suggesting the tumor cells represent early mesodermal cells that express myofibroblastic features.

26.7 Cutaneous Meningioma

26.7.1 Clinical Features

Cutaneous meningiomas are extremely rare, and may represent ectopic meningo-epithelial cells, metastasis from central nervous system tumors, or may be seen in association with acoustic neuromas in the setting of neurofibromatosis type 2 [77]. They usually occur in adults, although congenital primary cutaneous meningiomas in children have been reported [77].

Cutaneous meningiomas are described as a soft to firm, hairless nodule of variable size (between 0.5 and 4 cm in diameter), most commonly occurring on the scalp, but may be found along the spine as well [77]. The tumors are locally destructive, but they can be managed surgically. However, lesions with central nervous system communication tend to have a worse prognosis and possible metastasis from the neuraxis.

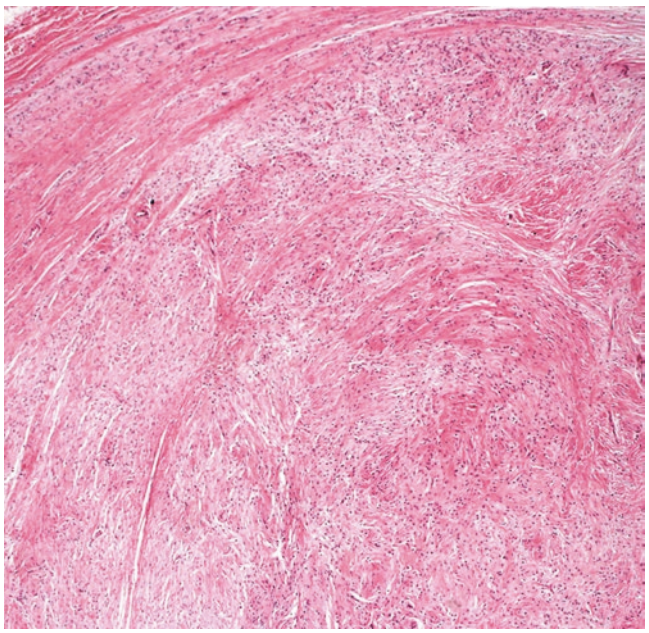

Fig. 26.15 Whorls of spindle-shaped cells admixed with fibrotic collagen in cutaneous meningioma

26.7.2 Histology

There are several different variants of meningothelial proliferation that occur within the skin. Type I lesions are derived from ectopic arachnoid cells, and present at birth [78]. Type II lesions are more likely to arise in adults, and derived from a similar population of cells surrounding nerves. Type III lesions occur from direct extension from the underlying tissue or metastases. The overlying epidermis may be atrophic or unremarkable, and in several cases has been associated with marked hypertrichosis [79, 80]. Meningiomas can be well circumscribed, or display a slightly more infiltrative growth pattern in the dermis [81]. Intimate attachments to nerves have been described [82]. Nests of spindle-shaped cells that have a whorled configuration can be located in the subcutis or the dermis in all types of meningioma (Figs. 26.15, 26.16 and 26.17). The ovoid to spindle-shaped cells are bland and uniform, and mitotic activity is not present [83]. The nuclei have finely stippled chromatin, eosinophilic cytoplasm, and indistinct cellular borders [84]. Scattered psammoma bodies are present, and foci of calcification are apparent in most cases [85]. The psammoma bodies have central areas of hyalinization and calcification surrounded by concentric rings of fibrous collagen [84]. The calcifications are most prevalent in the cellular areas of the tumor. Additional similar structures lacking calcification have been called collagen bodies or pseudopsammoma bodies [81, 84]. The stroma consists of admixed fibrous collagenous stroma, adipocytes, and a proliferation of small dilated blood vessels [86]. Small cords of meningothelial cells course through the densely fibrous collagen, and this gives rise to a pseudovascular pattern [87]. Some authors suggest that type I congenital lesions demonstrate more fibrous connective tissue and less cellularity than types II and III lesions [84]. The diagnosis can be established on fine needle aspiration cytology based upon the finding of characteristic appearing cells in a whorled configuration and psammoma bodies [88].

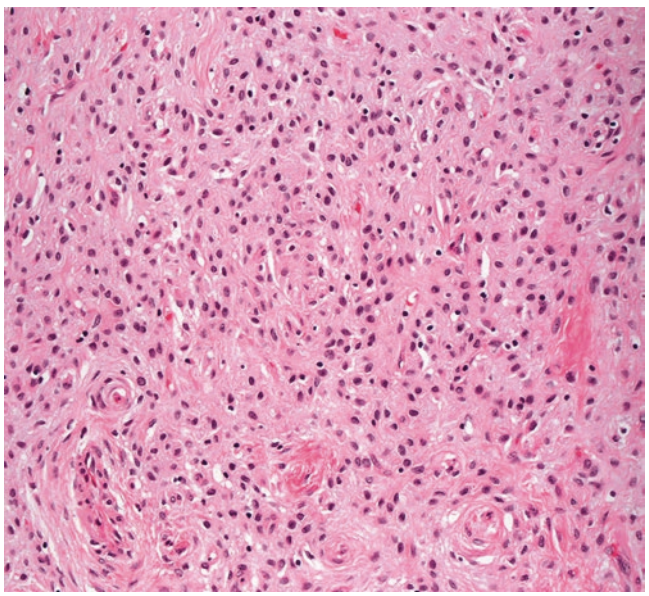

Fig. 26.16 Bland-appearing cells with abundant pale staining cytoplasm and central nuclei are present in the more cellular areas of cutaneous meningioma

The differential diagnosis is wide ranging and complex. The nests of cells might be confused with nevoid cells, and the diagnosis of melanoma or nevus could be

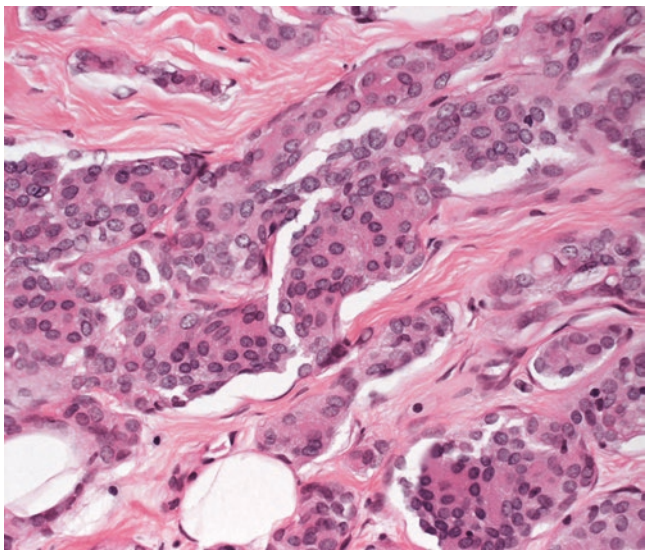

Fig. 26.17 Nests of bland-appearing round cells can give rise to a pseudoglandular pattern in cutaneous meningioma

considered. The lack of overlying epidermal involvement and lack of a true nevoid nesting help to make the distinction. Other epithelial neoplasms might enter the differential diagnosis but can be separated based upon the bland morphology, lack of mitotic activity, and the presence of psammoma bodies.

26.7.3 Pathogenesis

Cutaneous meningioma is a proliferation of ectopic meningothelial cells present in the dermis and subcutis [81]. A classification of cutaneous meningioma based on clinical and histologic criteria has been established [84]. Type I is congenital cutaneous meningioma that occurs on the scalp and paravertebral regions. The lesion is thought to derive from meningothelial cells that become trapped in the dermis and subcutis during development, and may have connection with the central nervous system through a sinus tract [84, 89]. Type II cutaneous meningioma is an acquired lesion often seen in adults that probably arises from ectopic arachnoid cells extending along cranial and spinal nerves to the skin. This lesion often locates around sensory organs (such as eyes, ears, nose, and mouth) and along cranial and spinal nerves. Type III cutaneous meningioma often occurs on the face, temple, and scalp. It is an intracranial meningeal tumor that extends directly from the central nervous system through the bone into the skin. Patients with neurofibromatosis may present with cutaneous meningioma [81]. There are no known specific genetic defects in cutaneous meningioma. However, cases of familial inheritance have been reported. One study highlights a familial presentation of type I cutaneous meningioma with autosomal dominant transmission [90]. These lesions were found in 11 of 24 family members, spanning 4 generations.

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Adipocyte Proliferations

27

27.1 Nevus Lipomatosus Superficialis

27.1.1 Clinical Features

Nevus lipomatosus superficialis is a rare benign cutaneous hamartoma. Two variants have been described. The classical form is present at birth or in the first 2 years of life. It presents as multiple soft, skin-colored to yellow papules and nodules that sometimes coalesce into plaques. Nevus lipomatosus superficialis is most common on the buttocks, lower back, and upper thighs [1]. A solitary type may appear in adulthood and is more likely to affect other areas of the body. These lesions are benign, and treatment is generally not necessary [2].

27.1.2 Histology

Nevus lipomatosus superficialis is characterized by a polypoid growth covered by normal-appearing epidermis. The dermis is remarkable for mature adipocytes extending high up into the dermis, admixed with normal-appearing collagen and cutaneous appendages [1]. There is often a mild perivascular inflammatory infiltrate consisting of lymphocytes and mast cells [3]. There are multiple reports of nevus lipomatosus superficialis occurring in association with other pilosebaceous hamartomatous proliferations [2, 4–6], vascular proliferations [7], and vascular anomalies [8].

The differential diagnosis of nevus lipomatosus superficialis includes acrochordon (skin tag). The presence of dermal-based fat is used as a distinguishing histologic feature in separating the two entities.

27.1.3 Pathogenesis

Some proposed mechanisms of the pathogenesis of nevus lipomatosus superficialis include metaplasia of adipocytes secondary to degenerative changes in the skin connective tissue, developmental displacement of adipose tissue in the dermis, and differentiation of lipoblasts around the blood vessels into adipocytes [9, 10]. It has been suggested that mutations in the PORCN (porcupine homolog) gene, which is involved in the processing of Wnt proteins, may have a role in the etiology of these lesions [11, 12].

27.2 Hibernoma

27.2.1 Clinical Features

Hibernoma is a rare tumor of brown fat, most commonly occurring in young adults [13]. Studies to determine sex predilection have been contradictory [13]. Hibernomas present as slowly expanding soft subcutaneous masses at the thigh or areas with higher density of brown fat deposition, such as the neck, axilla, back, and mediastinum. Lesions are benign and amenable to surgical excision with low rates of recurrence.

27.2.2 Histology

These tumors are usually located in the subcutis, but can appear within the reticular dermis [14]. They are comprised of multivacuolated fat cells with centrally placed scalloped nuclei [15] (Figs. 27.1 and 27.2). Several tumor variants including typical, myxoid, spindle cell, and lipoma-like have been described [13]. The typical type contains eosinophilic and pale cells. The myxoid variant has a loose, slightly basophilic stroma. The spindle cell type shares some histologic features with a spindle cell lipoma, and the lipoma-like variant is composed of primarily mature adipocytes with only scattered hibernoma-like cells. Mitoses are not common, and there is minimal cytologic atypia [16].

The histologic differential diagnosis is dependent upon the histologic subtype, and consists of spindle cell lipoma and typical lipoma. A sebaceous gland neoplasm is another differential consideration and it has a palisade of basaloid cells around tumor lobules that is not seen in hibernoma.

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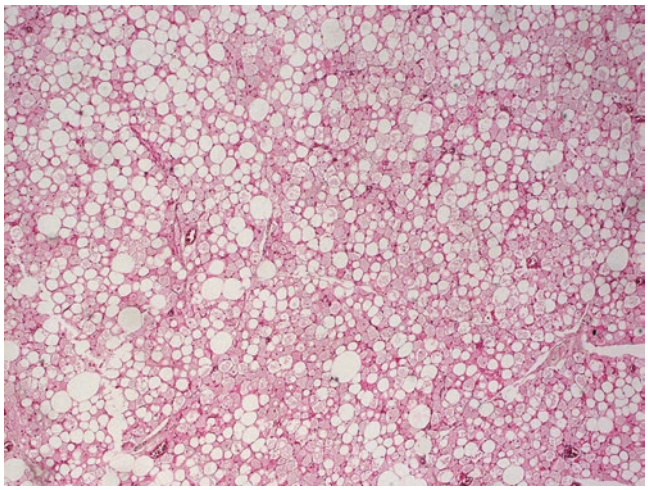

Fig. 27.1 Sheets of adipocytes with microvesiculation in the cytoplasm are seen in hibernoma

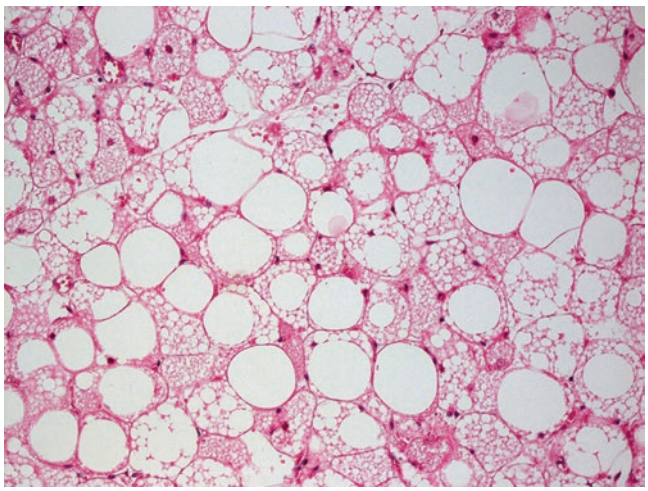

Fig. 27.2 Adipocytes demonstrate cytoplasmic microvesicles in hibernoma. No cytologic atypia is present

27.2.3 Pathogenesis

Hibernoma is a tumor of brown adipose tissue, which is rich in mitochondria and generates heat in response to cold exposure and food intake [13, 17]. In white fat, fatty acids are metabolized to produce energy in the form of adenosine triphosphate (ATP). In contrast, brown fat, owing to abundant mitochondria and thermogenin, metabolizes fatty acids into heat [18]. Brown fat is present in high abundance in neonates, and in decreased amounts in adults. Hibernoma often has chromosomal translocations involving chromosome band 11q13 [19, 20]. These aberrations have been shown to be associated with concomitant deletions of AIP and MEN1, which are two tumor suppressor genes that underlie the hereditary syndromes pituitary adenoma predisposition and multiple endocrine neoplasia type 1 (MEN1) [21]. Hibernoma has low expression levels of AIP and MEN1, and high expression levels of genes that are upregulated in brown fat (such as PPAR-α, PPAR-γ, PPARGC1A, and UCP1). It has been proposed that loss of MEN1 and AIP may be important for hibernoma development [21]. AIP functions as a repressor of peroxisome proliferator-activated receptor (PPAR)-α, and MEN1 regulates adipocyte differentiation through PPAR-γ [22, 23].

27.3 Lipoblastoma

27.3.1 Clinical Features

Lipoblastomas are uncommon soft tissue tumors, accounting for 1.6–3.1 % of soft tissue tumors in children less than 1 year old [24]. Over 80 % of cases occur before 3 years of age with 50 % diagnosed by one year of age, and include reports of congenital lesions [24]. Males are three times more likely to be affected than females, and most cases are reported in whites. Lipoblastomas are described as rapidly growing soft, nontender subcutaneous masses on the extremities [24]. Lesions are benign but clinically may mimic liposarcoma or other malignant soft tissue tumors. Therefore, tissue biopsy is prudent to confirm diagnosis. Definitive treatment is complete surgical excision as recurrence is frequently reported following incomplete excision.

27.3.2 Histology

Lipoblastoma is a neoplasm that occurs in the dermis or subcutis. The tumor is composed of lobules of cells that show varying degrees of adipocyte maturation, and it is characterized by lipoblasts [25, 26] (Figs. 27.3, 27.4 and 27.5). Primitive stem cells are also present within the tumor cell population [25]. The lobules are irregularly sized and shaped, and can be well circumscribed or show an infiltrative growth pattern within the dermis and subcutis [26]. Well-defined septa separate the lobules of adipocytes [27]. There is an increase in vascularity, and a plexiform growth pattern has been described within the vascular proliferation [25]. A myxoid stroma is present [28]. Mitoses are rare or nonexistent [25, 26]. Diagnosis can be made on fine-needle aspiration cytology based upon the presence of lipoblasts and a myxoid matrix [29]. The absence of necrosis or mitotic activity in cytologic specimens is helpful in making this diagnosis.

A related entity is known as lipoblastomatosis, in which multiple lesions with identical histologic features are present [30]. Some authors differentiate lipoblastoma from

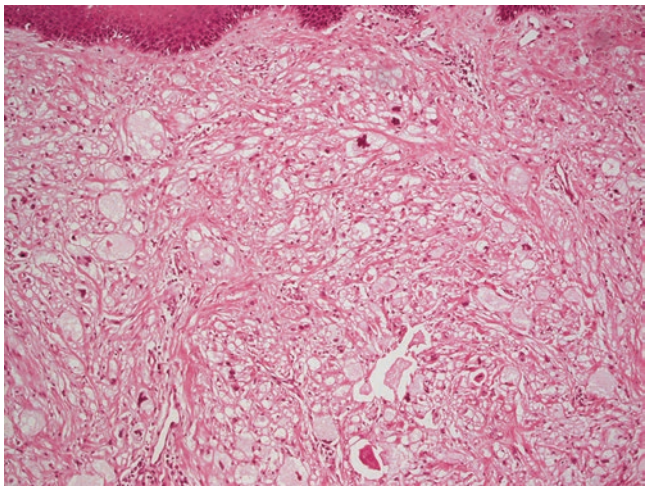

Fig. 27.3 Sheets of adipocytes are present throughout the dermis in lipoblastoma. They often appear to be diffuse and not well circumscribed

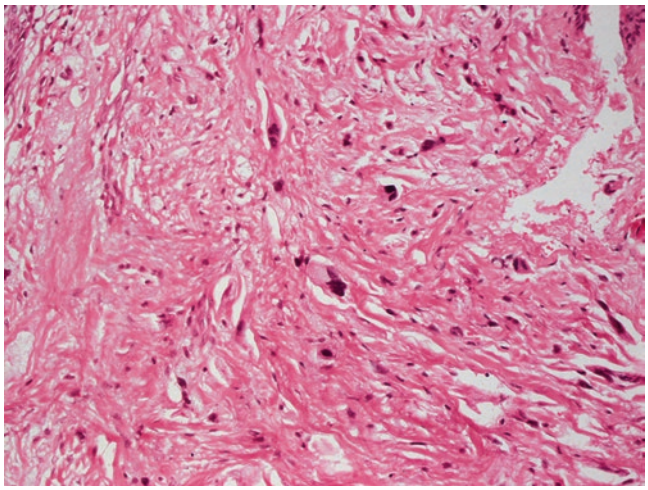

Fig. 27.4 Scattered lipoblasts with markedly hyperchromatic nuclei and cytologic atypia are seen in lipoblastoma

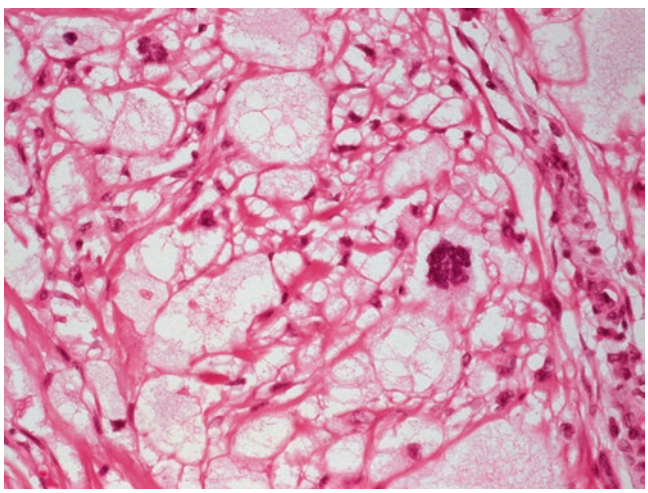

Fig. 27.5 Adipocytes with multinucleation, microvesiculation, and atypical nuclei are present in lipoblastoma

lipoblastomatosis based upon the latter's infiltrative growth pattern [26].

Due to the myxoid stroma and lipoblasts, it may be difficult to separate lipoblastoma from myxoid liposarcoma, although cytogenetic studies now make this distinction a straightforward one [28, 31]. Lipomas also enter the differential diagnosis in some cases, but they are separated from lipoblastomas based upon the presence of lipoblasts [27]. Some authors consider lipofibromas to be a sclerosing variant of lipoblastomas, but others argue that based upon different immunostaining properties, lipofibromas are best thought of as discrete entities [32].

27.3.3 Pathogenesis

Lipoblastoma is an adipose tissue tumor that sometimes occurs in children. Chromosomal rearrangement of the 8q11–q13 region is a sensitive (77 %) and specific (98 %) marker for lipoblastoma [33, 34]. PLAG1, located at 8q12.1, has been identified as a target gene in this tumor [35], and FISH analysis for the detection of specific rearrangements of PLAG1 is a sensitive test for lipoblastoma [34]. Translocations or inversions involving PLAG1 in lipoblastoma generate fusions with a variety of other genes, including COL1A2, HAS2, RAD51L1, COL3A1, and RAB2A [34–37]. The fusion of PLAG1 with its partner results in promoter swapping in which the PLAG1 gene is placed under the control of a transcriptionally active promoter, resulting in the ectopic over-expression of PLAG1. PLAG1 is a zinc finger protein that functions as a transcription factor and regulates the expression of key growth factors, such as insulin growth factor II, resulting in dysregulated cell proliferation and tumorigenesis [38, 39].

27.4 Lipoma

27.4.1 Clinical Features

Lipomas are benign mesenchymal tumors of mature adipocytes. They are not commonly seen in children, but they are a common type of soft tissue tumors described in adults [40]. Prevalence is higher in males than in females. No racial predilection exists.

Superficial lipomas are the subtype most commonly seen, and present as variably sized, well-circumscribed, soft, rubbery, skin-colored subcutaneous nodules at the neck, upper torso, abdomen, shoulders, and proximal extremities [40]. These tumors are benign and may be surgically excised if desired.

27.4.2 Histology

Lipoma can occur in the dermis or the subcutis as a well-circumscribed proliferation of mature adipocytes (Fig. 27.6). A thin fibrous capsule encapsulates the tumor. Fibrous septa comprised of collagen-containing blood vessels surround each of the lobules within the lesion. Some lipomas contain foci of fibrosis, giving rise to the term lipofibromas. There are other cases in which smooth muscle or eccrine ducts comprise part of the tumors.

27.4.3 Pathogenesis

Most lipomas in children are sporadic. However, some pediatric lipomas occur in syndromic conditions, such as Proteus syndrome, multiple endocrine neoplasia type 1 (MEN1), and Bannayan-Riley-Ruvalcaba syndrome [34, 41–43]. The cytogenetics of lipoma in children is similar to that in adult lipoma. Rearrangements of chromosomal regions 12q14–q15 and 6p21 involving HMGA2 and HMGA1 genes frequently occur in this tumor [34, 44]. So far, six genes have been identified to fuse with HMGA2 in lipoma. The most frequent partner is the lipoma preferred partner (LPP) gene [45]. The other genes are CXCR7, EBF1, LHFP, PPAP2B, and NFIB [34]. It is not known whether some partner genes of HMGA2 may have a specific role in the onset of lipoma. A recent study identified the presence of CD34-positive cells in lipoma around small adipocytes, and showed altered biological activity such as proliferation, apoptosis, and stemness. These findings suggest the involvement of precursor cells in the development of this tumor [46].

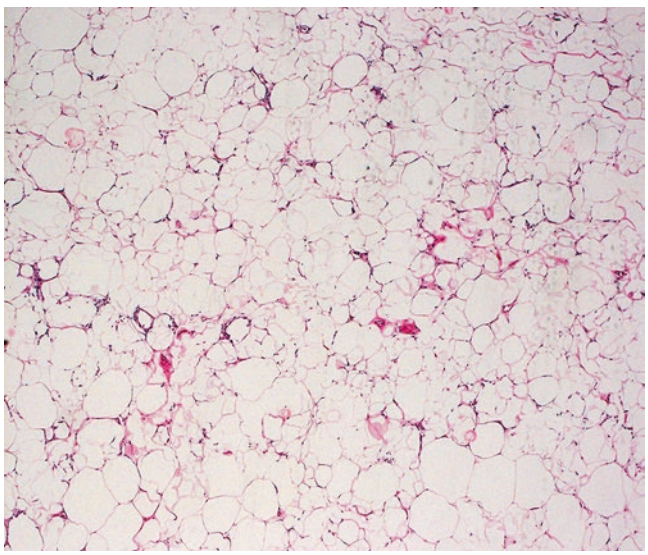

Fig. 27.6 Lipoma is characterized by a well-circumscribed proliferation of mature adipocytes without cytologic atypia or nuclear pleomorphism

27.5 Angiolipoma

27.5.1 Clinical Features

Angiolipomas represent 5–17 % of all lipomas [47]. Lesions are subcategorized into a non-infiltrating variant and a deeper, infiltrating variant with extension into the underlying smooth muscle and soft tissues [47]. Non-infiltrating angiolipomas most often occur in male adolescents and young adults, rarely presenting before puberty.

Angiolipomas are soft rubbery, skin-colored nodules of varying sizes, mimicking the appearance of lipomas but differ in that they are often painful and multiple [47]. Lesions most commonly occur on the trunk and upper extremities. Angiolipomas may be surgically excised with low rates of local recurrence, but new tumors may develop at other sites.

27.5.2 Histology

Angiolipomas are lipomas that display small well-formed blood vessels constituting more than 5 % of the tumor volume (Fig. 27.7). Abundant fibrin thrombi are seen within the vessels in most cases [48, 49] (Fig. 27.8). The differential diagnosis is only problematic when the vascular component represents the major component in which cases angiomatous proliferations might be considered.

27.5.3 Pathogenesis

Cytogenetic analysis of subcutaneous angiolipoma showed a normal karyotype, which is unlike other lipomatous tumors, such as lipoma and lipoblastoma, most of which have clonal chromosomal abnormalities [50].

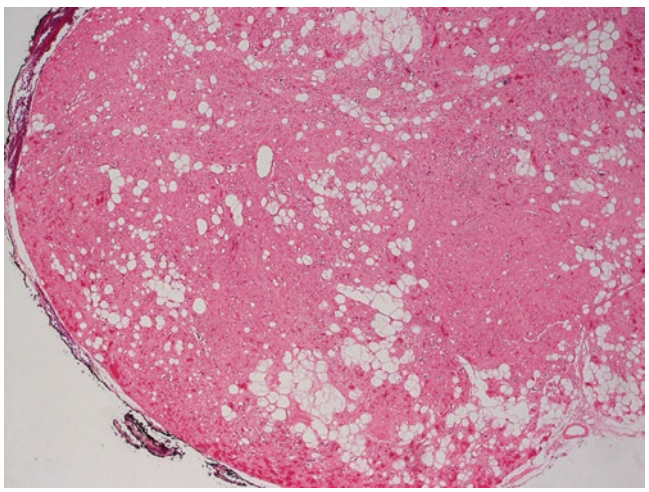

Fig. 27.7 Admixtures of adipocytes, small, well-formed blood vessels and fibrous tissue characterize angiolipomas

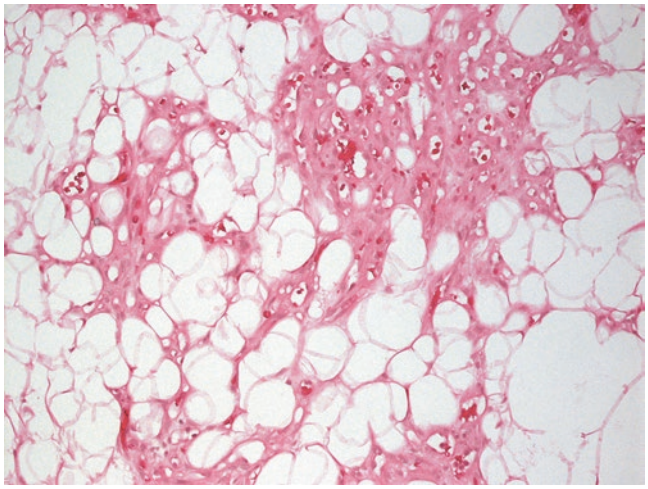

Fig. 27.8 Abundant small blood vessels, often containing fibrin thrombi, are present in angiolipomas

27.6 Lipofibromatosis

27.6.1 Clinical Features

Lipofibromatosis is a rare soft tissue tumor in children. It may be present at birth, and can occur on the hands and feet. The tumor may recur if it is not completely excised.

27.6.2 Histology

In lipofibromatosis, there is an admixture of mature adipose tissue and spindle-shaped fibroblasts in the deep dermis and subcutis. The fibroblasts are dispersed as fascicles and have minimal cytologic atypia with only scant mitotic activity. Univacuolar cells have been described at the interface between the fat and the spindle cell population. The tumor envelops blood vessels, nerves, skin adnexal structures, and skeletal muscles. The tumor cells variably express CD99, CD34, and α-smooth muscle actin [32]. Some authors postulate a myofibroblastic component in the proliferation [51].

27.6.3 Pathogenesis

Lipofibromatosis is a rare benign, slow-growing fibro-fatty tumor of childhood [52]. It has been shown to have cytogenetic abnormalities with t(4;9;6) karyotype [53]. The fibroblastic component of lipofibromatosis has high expression of connective tissue growth factor (CCN2), which may have a role in the pathogenesis of this lesion [54].

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Muscle and Bone Proliferations

28

28.1 Smooth Muscle Hamartoma

28.1.1 Clinical Features

Most smooth muscle hamartomas are congenital, although acquired lesions have been described. Prevalence is greater in males [1]. Smooth muscle hamartomas present as skin-colored to hyperpigmented indurated plaques, which may have concomitant hypertrichosis and perifollicular papules or accentuation. Pseudo-Darier sign may be present and transient piloerection is seen after the lesion is rubbed. Proportional enlargement with patient growth may occur with associated hypertrichosis, pigmentation, and induration [1]. Lesions most commonly occur on the trunk and proximal extremities. Since these lesions are benign, excision is not required.

28.1.2 Histology

A smooth muscle hamartoma is a proliferation of haphazardly oriented smooth muscle bundles arising from the arrector pili muscles in the reticular dermis (Fig. 28.1 and Fig. 28.2) [2]. There is no cytologic atypia or mitotic activity in the lesion [3]. The lesion is poorly circumscribed. In some cases, there may be overlying hypertrichosis [4]. The relationship between a smooth muscle hamartoma and a Becker's nevus is still uncertain, and these two entities may represent a spectrum along the same hamartomatous process [5–7].

The differential diagnosis includes leiomyoma. In leiomyoma, the proliferation of smooth muscle cells is better organized into bundles and appears more sharply circumscribed. Occasional mitoses may be seen.

28.1.3 Pathogenesis

Cutaneous smooth muscle hamartoma is a benign developmental proliferation of smooth muscle fibers in the dermis and subcutis. Most lesions are congenital; however, acquired lesions also have been reported [1, 8].

28.2 Striated Muscle Hamartoma

28.2.1 Clinical Features

Striated muscle hamartoma is an unusual benign cutaneous lesion. Although typically congenital, it may sometimes appear in an older child or adult [9]. Lesions most commonly occur on the midline head and neck, but they have been reported in other locations, including the vagina, perianal area, tongue, and toes. Striated muscle hamartoma appears as a non-tender skin-colored nodule or tag, ranging from a few millimeters up to 2 cm in size [10]. Most lesions are solitary, but multiple lesions have been reported. Treatment consists of surgical excision.

28.2.2 Histology

Haphazard fascicles of striated muscles course throughout the dermis and the subcutis in a striated muscle hamartoma (Fig. 28.3). These muscle fibers are mature, and do not have cytologic atypia or mitotic activity (Fig. 28.4). Striated muscle hamartoma has been associated with hemangiomas [11].

28.2.3 Pathogenesis

Striated muscle hamartoma (also called rhabdomyomatous mesenchymal hamartoma) is comprised of skeletal muscle, adipose tissue, and adnexal structures [12, 13]. The pathogenesis of striated muscle hamartoma is not known, but theories regarding genetic predisposition and abnormalities in the migration of mesodermal tissue during embryogenesis have been proposed [14, 15].

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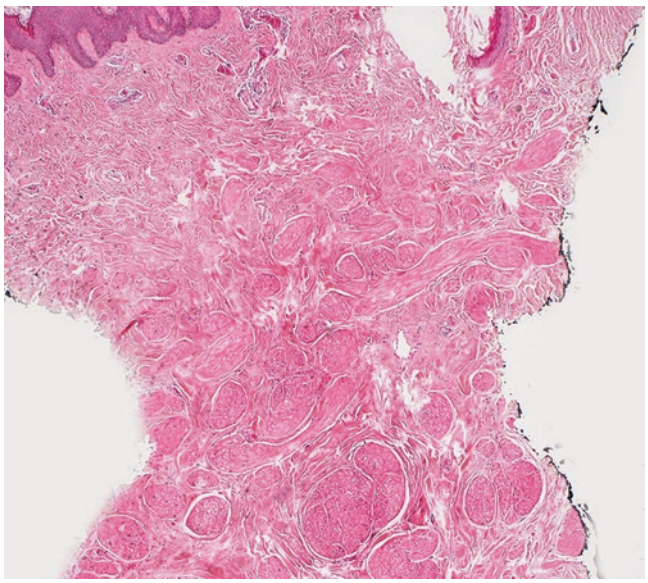

Fig. 28.1 A diffuse proliferation of mature smooth muscle bundles lacking in cytologic atypia is seen in smooth muscle hamartoma

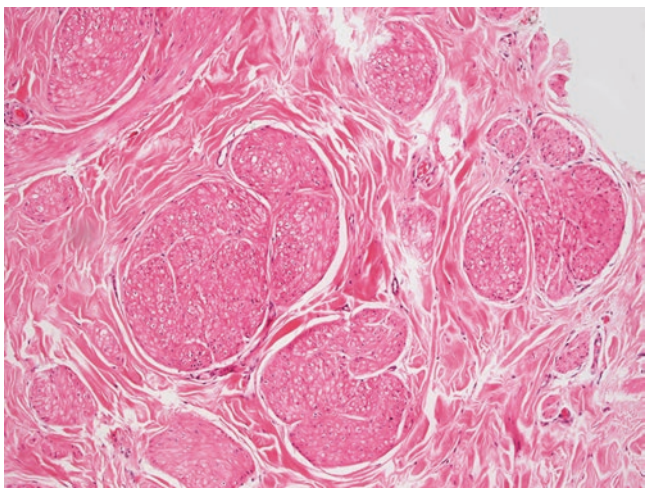

Fig. 28.2 Abundant fascicles of smooth muscles are present throughout the dermis in smooth muscle hamartoma

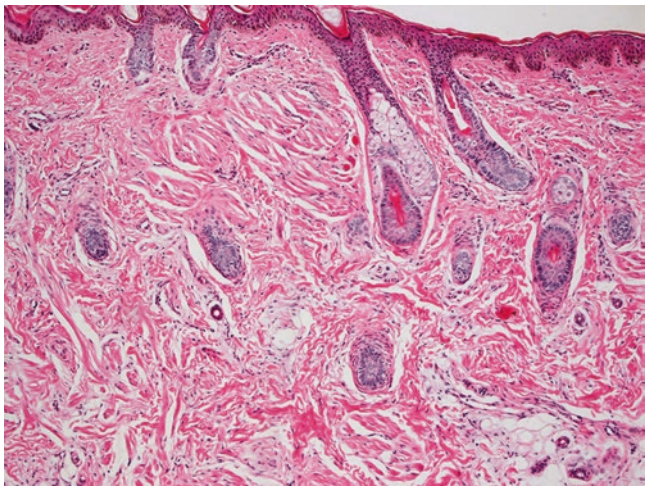

Fig. 28.3 Striated muscle bundles course haphazardly throughout the dermis in striated muscle hamartoma

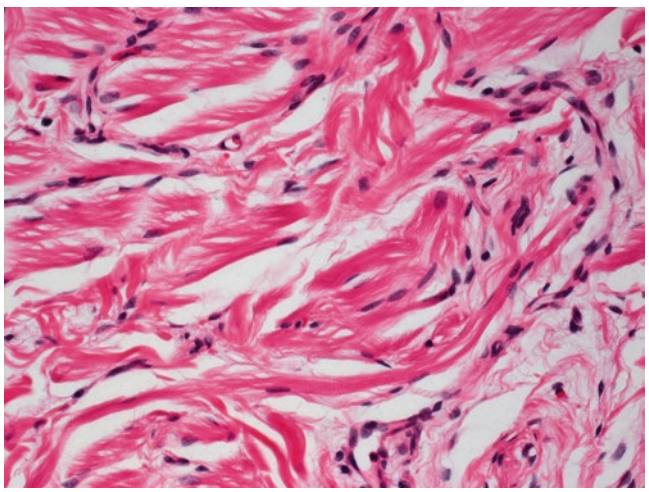

Fig. 28.4 Striations are clearly visible on histologic sections in striated muscle hamartoma

28.3 Leiomyoma

28.3.1 Clinical Features

Multiple piloleiomyomas are the most frequently reported variant of cutaneous leiomyoma. Additional subtypes include solitary piloleiomyoma and solitary genital leiomyoma [1]. Most leiomyomas occur in adults during the second and third decade of life, and there are rare reports of congenital lesions [16]. Multiple piloleiomyomas present as painful, reddish brown, indurated nodules in grouped or even dermatomal pattern [1]. Lesions most commonly occur on the extensor extremities, followed by the trunk, face, and neck. Most patients present with at least two affected body sites.

Leiomyomas have an indolent course with persistence and expansion of old lesions and development of new ones [1]. Spontaneous resolution is not likely, and lesions frequently recur following excision. Female patients with multiple leiomyomas may be at increased risk for uterine leiomyomas. Even more rarely, leiomyosarcoma may occur in affected individuals.

28.3.2 Histology

Leiomyoma is as a proliferation of smooth muscle bundles in the dermis (Fig. 28.5). The overlying epidermis is generally

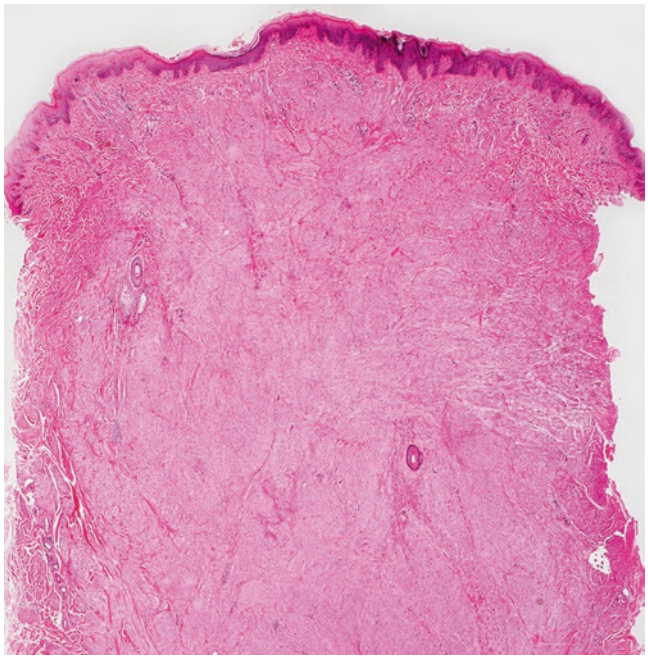

Fig. 28.5 Fascicles of smooth muscles are present in increased numbers in the dermis. They are well circumscribed in most cases, and are slightly different in color than the surrounding dermal collagen

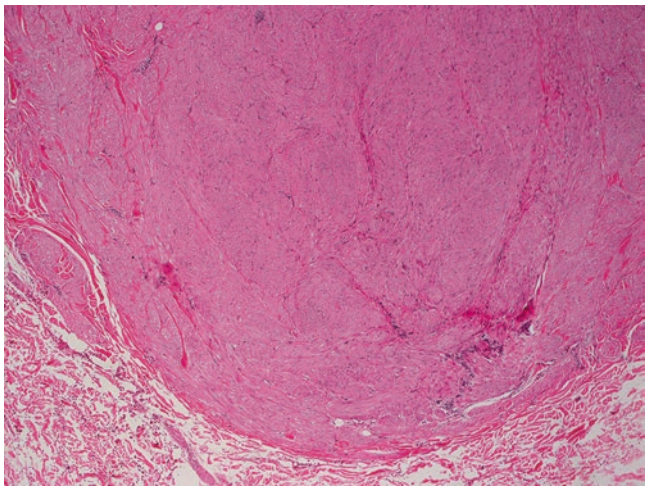

Fig. 28.6 A well-circumscribed nodule comprised of smooth muscle fascicles is seen in leiomyoma

unremarkable or flattened, but epidermal hyperplasia can be seen in some cases [17]. Cutaneous leiomyomas arise from smooth muscle bundles within the arrector pili or from vascular smooth muscle. Tumors arising from arrector pili are more superficially located in the dermis and less well circumscribed. In leiomyomas, bundles of eosinophilic cells with ample cytoplasm and blunted, spindle-shaped nuclei course throughout the dermis (Figs. 28.6 and 28.7). Cytologic atypia is usually minimal, and mitoses are rare.

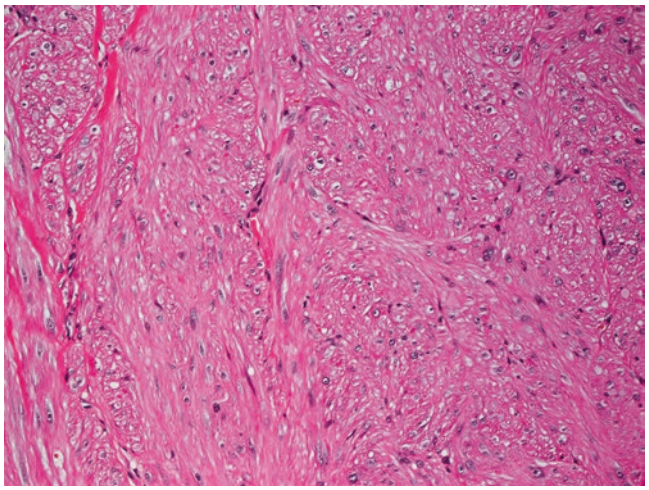

Fig. 28.7 Mature smooth muscle myocytes with eosinophilic cytoplasm and relatively blunted nuclei are seen in leiomyoma

The tumor cells are arranged in fascicles, and may have a whorled appearance. Leiomyomas that arise from vascular wall smooth muscle tend to occur deeper within the reticular dermis and are more sharply circumscribed. In many cases, the tumor grows concentrically around a central blood vessel that can be identified on routine tissue sections. Genital leiomyomas are more infiltrative in appearance, and smooth muscle bundles are separated by bundles of collagen. Some authors suggest that the tumor cells are more slender in appearance in this location [18].

Atypical leiomyoma is a term used for smooth muscle tumors that have increased cellularity and nuclear pleomorphism but minimal mitotic activity [19–21]. Some authors use the term "symplastic" to describe these types of lesions, which are analogous to the symplastic leiomyoma in the uterus [21].

28.3.3 Pathogenesis

Cutaneous leiomyoma often arises from arrector pili muscle that attaches to the hair follicle [1]. Leiomyoma can occur as solitary or multiple lesions [22]. There is no significant histologic difference between solitary and multiple leiomyomas. However, the pathogenesis of multiple leiomyomas is unique. Multiple leiomyomas can be inherited in an autosomal-dominant manner in a cancer syndrome known as Reed syndrome or hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome, in which affected individuals develop multiple cutaneous leiomyomas, uterine leiomyomas, and renal cell cancer [23]. It has been established that HLRCC syndrome is associated with mutations in the fumarate hydratase (*FH*) gene [24]. FH is an enzyme in the Krebs cycle responsible for the conversion of fumarate to malate. Germline FH mutations have been found in a large percent-

age of families with clinical features suggestive of HLRCC syndrome [25]. Mechanistically, loss-of-function mutations in FH can lead to activation of the hypoxia-inducible factor 1 (HIF-1) pathway as well as increased expression of HIF-1-regulated genes important for tumor angiogenesis, such as vascular endothelial growth factor (VEGF) [26].

28.4 Osteosarcoma

28.4.1 Clinical Features

The skin is rarely the site of primary or metastatic osteosarcoma [27]. Osteosarcoma most commonly affects children and adolescents with median age at diagnosis of 17–18 years of age [27, 28]. No gender predilection has been described. Cutaneous osteosarcomas are described as firm nodules near the site of the primary tumor, and may present as solitary lesion or multiple lesions. Cutaneous metastasis may be a hallmark of more widespread metastatic disease.

28.4.2 Histology

Osteosarcoma involving the skin is quite rare [27]. While most cases are metastatic lesions, primary cutaneous osteosarcomas have been reported [29–35]. In either situation, the tumor appears as a dermal proliferation of atypical spindle-shaped cells with marked nuclear pleomorphism, cytologic atypia, mitotic activity, and frequently multinucleated osteoblasts (Fig. 28.8). Eosinophilic osteoid material is produced by the tumor [29, 31, 36] (Fig. 28.9). A chondroblastic variant has also been reported as arising in the skin [37]. A form of carcinosarcoma is described in which there are features of basal cell carcinoma comingled with features of osteosarcoma. This neoplasm has not been seen in children [38].

The major point of differential diagnosis is determining the site of origin of the tumor. Metastatic osteosarcomas are far more common than primary cutaneous osteosarcomas. Therefore, a complete clinical evaluation is essential before determining that such neoplasms are primary to the skin [34].

28.4.3 Pathogenesis

The initiation of osteosarcoma appears to correlate with skeletal development. The peak incidence of osteosarcoma coincides with a period of rapid bone growth in adolescents. Osteosarcoma tends to occur near the major joints of longitudinal bone growth, such as the distal femur, proximal tibia, and proximal humerus [39]. Genetic predisposition syndromes with loss of function of tumor suppressor genes, such as Li-Fraumeni syndrome (p53 mutations) and hereditary bilateral retinoblastoma (Rb mutations), have higher incidence of multiple cancers, including osteosarcoma [40–42]. The p53 gene is mutated in 22 % of osteosarcomas [43]. Both germline and somatic mutations of the Rb gene confer an increased risk of osteosarcoma [44]. Mutations in p53 and Rb genes have been shown to be important in osteosarcoma pathogenesis [39].

The activator protein 1 complex (AP-1) is a transcription factor, and its protein components Fos and Jun are significantly upregulated in high-grade and metastatic osteosarcoma [45, 46]. Genetically engineered mice with overexpression of Fos and Jun develop osteosarcoma, thus demonstrating the important roles of these transcription factors in tumor formation [47]. Myc is another key transcription factor whose amplification has been implicated in

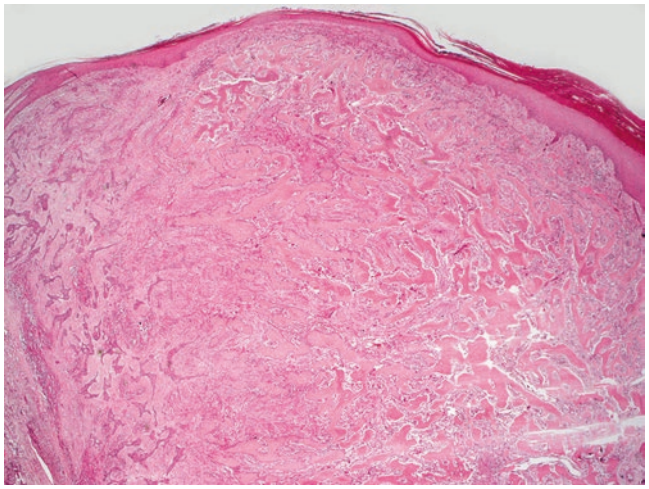

Fig. 28.8 Osteosarcoma demonstrates osteoid formation admixed with a proliferation of atypical cells in the dermis

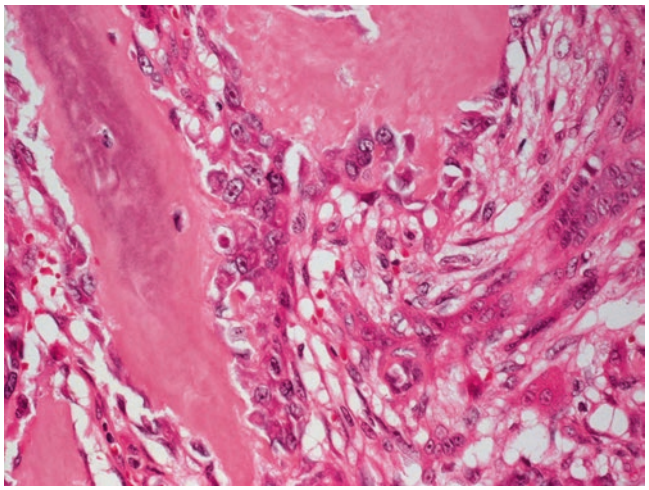

Fig. 28.9 Atypical cells are seen adjacent to poorly formed osteoid in the dermis in osteosarcoma

osteosarcoma pathogenesis and in tumor resistance to chemotherapeutics [39].

Hedgehog signaling has been shown to be important in the pathogenesis of osteoblastic osteosarcoma in an experimental mouse model. Mice genetically engineered to overexpress Yes-Associated Protein 1 (Yap1) and long noncoding RNA H19 (molecules that are involved in hedgehog signaling) develop osteosarcoma [48]. Yap1 is also highly expressed in human osteosarcoma.

Pigmented epithelium-derived factor (PEDF) is a serine protease inhibitor and a potent inhibitor of angiogenesis. PEDF has been shown to target tumor vasculature and induce osteosarcoma cell apoptosis and differentiation [49]. There is some evidence that the IGF-1 and TGF-β pathways play a role in osteosarcoma formation. Transcriptional profiling by serial analysis of gene expression (SAGE) showed that dysregulation of these signaling axis might be an important step in osteosarcoma tumorigenesis [50].

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Benign Hamartomatous Proliferations

29

29.1 Accessory Tragus

29.1.1 Clinical Features

Accessory tragus is a common congenital abnormality of the external ear with prevalence of 1–10 per 10,000 live births and bilateral involvement in 6 % of cases [1, 2]. No gender or racial predilection exists. Accessory tragi are skin-colored, soft, polypoid papules that occur along an arc on the preauricular cheek and extending from the tragus to the angle of the mouth and the anterior margin of the sternomastoid muscle (Fig. 29.1). Lesions typically are solitary but may be multiple or bilateral. When located along the neck, lesions may be qualified as a "wattle," a cartilaginous rest on the neck of cervical accessory tragus. Most cases of accessory tragus occur in isolation, but some have been reported as a feature in some genodermatoses with additional anomalies involving the first and second branchial arches.

29.1.2 Histology

The histologic appearance of an accessory tragus is that of a polypoid lesion with thin epidermis. The dermis is remarkably thin with subcutaneous fat very close to the epidermis (Fig. 29.2). Abundant vellus hairs are present throughout the hamartoma (Fig. 29.3). There is no cytologic atypia, and all elements of the skin appear fully mature. Cartilage is present in only a minority of cases and is not required to establish the diagnosis when the other histologic criteria are present in the appropriate clinical setting.

An acrochordon is in the differential diagnosis, but the presence of subcutaneous fat close to the epidermis and abundant vellus hairs helps in resolving the dilemma. When cartilage is present, the diagnosis is straightforward.

29.1.3 Pathogenesis

Accessory tragus is a common benign congenital malformation of the first and second branchial arches. During early embryonic development, hillocks, which are soft tissue swellings on the surface of the embryo derived from the first and second branchial arches, are formed. The hillocks grow and fuse to form the helix, antihelix, and tragus. Abnormalities that occur during this process can result in the formation of an accessory tragus. Interestingly, accessory tragus may be a sign of other syndromes, such as oculoauriculavertebral syndrome (Goldenhar syndrome) [3].

29.2 Supernumerary Nipple

29.2.1 Clinical Features

Polythelia or supernumerary nipple is the most common anomaly on the breast in children with reported incidence of approximately 5 % [4, 5]. Occurrence usually is sporadic. Supernumerary nipple presents as a hyperpigmented papule, which may be atrophic/concave or exophytic, along the embryologic milk lines at the anterior torso (Fig. 29.4). Less commonly, they can occur on the face, neck, shoulder, back, genitals and thighs [4].

Some authors favor prepubertal excision of supernumerary tissue because of the risk of glandular growth as well as the potential for malignant degeneration of the accessory nipple/areola complex, even though this risk is low [5, 6]. Increased risk of renal malformations in association with accessory nipples has been reported but not substantiated in larger studies [7].

29.2.2 Histology

Supernumerary nipple demonstrates the same histologic findings as normal nipple skin in an aberrant location.

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Fig. 29.1 Two skin-colored papules on the preauricular skin represent accessory tragi

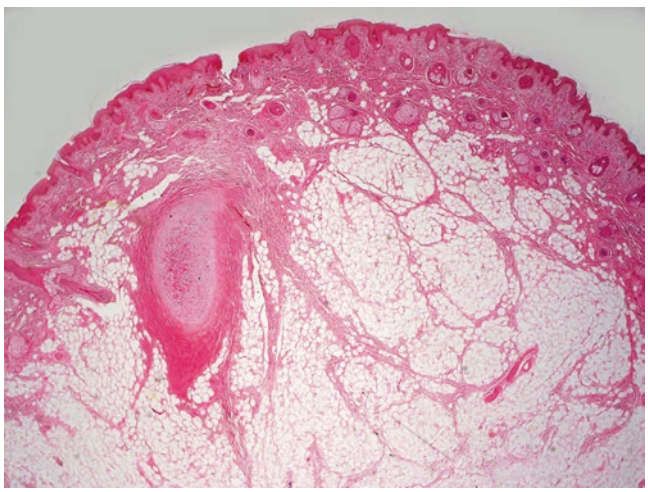

Fig. 29.2 Abundant vellus hairs, ectopic cartilage, and fat located high in the dermis are present in an accessory tragus

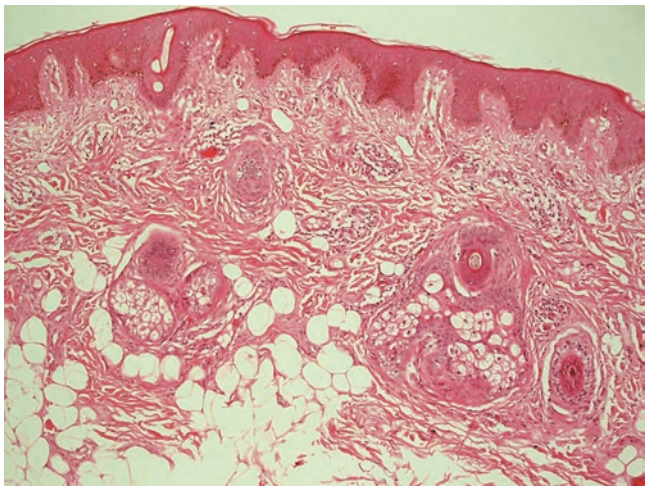

Fig. 29.3 The diagnosis of an accessory tragus can be made based upon clinical presentation, abundant vellus hairs, and superficially located fat within the dermis even in the absence of ectopic cartilage

Fig. 29.4 A tan pink papule beneath the breast along the embryonic mammary lines is characteristic of a supernumerary nipple

Epidermal hyperplasia and hyperpigmentation overlie a dermis with increased smooth muscle bundles (Fig. 29.5). Increased numbers of enlarged pilosebaceous glands are present. In some cases, ductular epithelium resembling normal breast architecture is apparent, but this is not detected in all cases [8] (Fig. 29.6).

The histologic differential diagnosis includes a Becker nevus based upon the acanthotic and hyperpigmented epidermis with increased numbers of pilosebaceous units and underlying smooth muscle bundles. The presence of dermal apocrine glands establishes the diagnosis of supernumerary nipple. A benign eccrine neoplasm may enter the differential diagnosis based upon the glandular proliferation, but this can be excluded based upon the accompanying changes in the epidermis and the smooth muscle bundles.

29.2.3 Pathogenesis

Supernumerary nipple is a common congenital malformation consisting of nipple tissue and related mammary glands and ducts [9]. In mammals, supernumerary nipple is present along the embryonic milk lines that extend bilaterally from the axilla to the chest and abdomen toward the groin. It has been postulated that during embryogenesis, embryonic milk

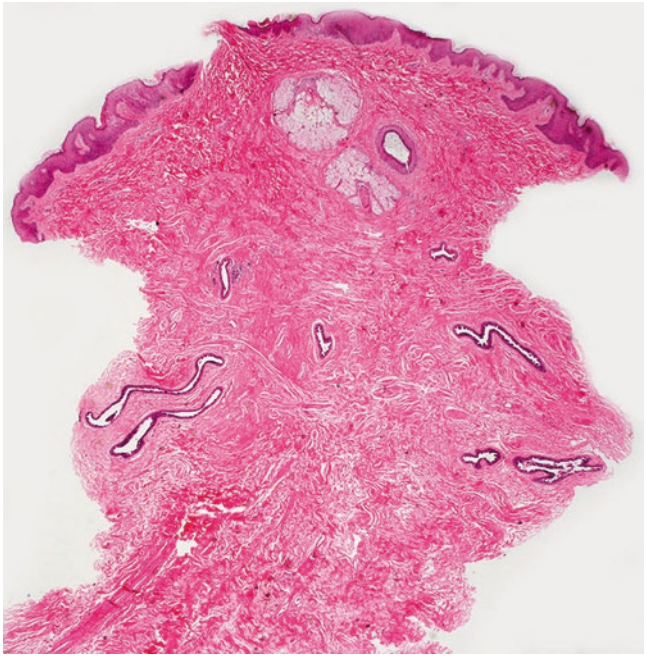

Fig. 29.5 A slightly acanthotic epidermis overlies a dermis with enlarged sebaceous glands, ectopic mammary glandular epithelium, and smooth muscle bundles in a supernumerary nipple

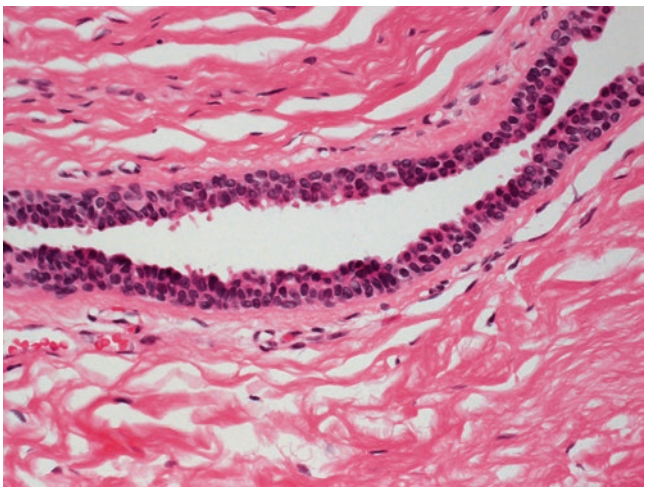

Fig. 29.6 The glands are lined by two layers of cells with the luminal cells showing a hobnail appearance in some cases of supernumerary nipple

lines are formed by an ectodermal thickening symmetrically along the ventral lateral sides of the embryo, extending from the axillary area to the inner thigh to form the milk lines. At a later phase in embryonic development, mammary tissues form near the fourth and fifth ribs, and the remainder of the thickened ectodermal streaks regress. However, some areas may fail to completely regress, resulting in supernumerary nipple. Interestingly, some studies suggest possible association of supernumerary nipple with abnormalities of the urinary tract, such as supernumerary kidney, failure of kidney formation, and kidney tumor [10, 11]. However, other studies have disputed this association [12, 13].

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Cutaneous Metastases

30

30.1 Clinical Features

A wide range of cutaneous manifestations has been reported in systemic malignancies of children. Childhood malignancies that are more likely to involve the skin include leukemias, lymphomas, neuroblastoma, sarcomas, and Langerhans cell histiocytosis [1]. Cutaneous lesions of leukemias are highly variable and may include erythematous to violaceous papules, nodules, and plaques on the face, trunk, and extremities (see also Chap. 22). Skin lesions of lymphomas are most common in the head and neck, followed by the abdomen. Solitary or multiple erythematous papules, nodules, and plaques may occur. Lesions may be painful and prone to ulceration. Typical skin lesions of neuroblastoma are firm, blue to purple papules and nodules with a "blueberry muffin" appearance. In children, sarcomas are most likely to involve the head and neck, followed by the genitourinary tract and extremities. Skin lesions are typically asymptomatic solitary soft tissue masses. Therapy is generally aimed at treatment of the underlying malignancy.

30.2 Histology

The prevalence of cutaneous metastases in children is markedly different than that seen in adults, and it is largely a reflection of the types of neoplasms in children. Neuroblastomas, leukemias, and lymphomas are the neoplastic processes most likely to be encountered in children with histologic features that resemble the primary tumors [2]. As many as one third of patients with neuroblastomas will have cutaneous metastases at some point in the course of their disease progression [3]. Lymph node-based lymphomas can spread to involve the skin. In these cases, it is important to search for systemic involvement before determining that a malignant cutaneous lymphoid infiltrate arose within the skin [4].

Tumors such as medulloblastoma, embryonal and alveolar rhabdomyosarcoma, and choriocarcinoma develop cutaneous metastases much more commonly in children, as these neoplasms are quite rare in adults [5, 6].

Diagnostic work-up of metastatic lesions frequently requires the use of immunostains selected to highlight various specific lines of cellular differentiation of the tumor. A detailed description of all possible visceral malignancies with potential for cutaneous metastasis is beyond the scope of this volume, but knowledge of pediatric tumor pathology is essential in order to fully recognize the full range of diagnostic possibilities. Several examples of cutaneous metastases are seen in the accompanying figures, and demonstrate the characteristic histologic features (Figs. 30.1, 30.2, 30.3, 30.4, 30.5, and 30.6).

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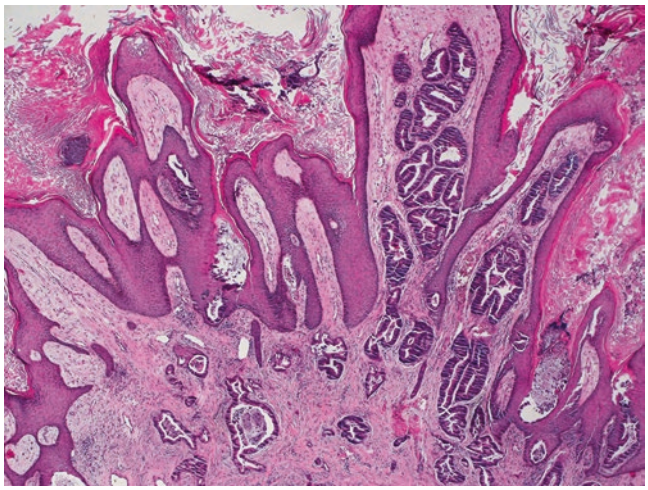

Fig. 30.1 Metastatic adenocarcinoma (Sister Mary Joseph nodule seen here) demonstrates atypical glandular epithelium throughout the dermis

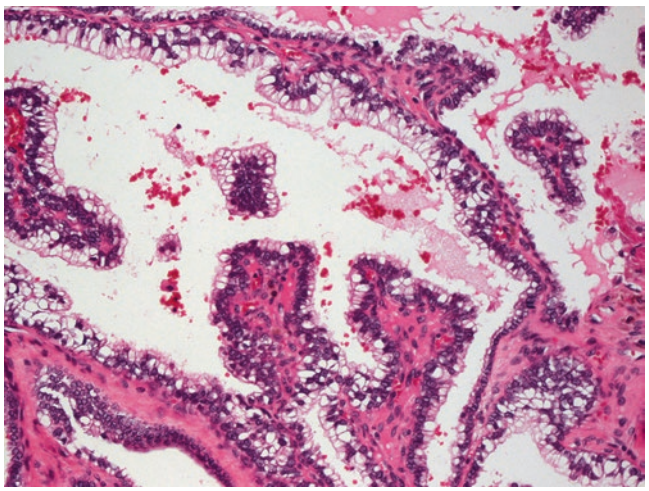

Fig. 30.4 Characteristic cells with clear cytoplasm and a papillary growth pattern are seen in papillary thyroid carcinoma when it metastasizes to the skin

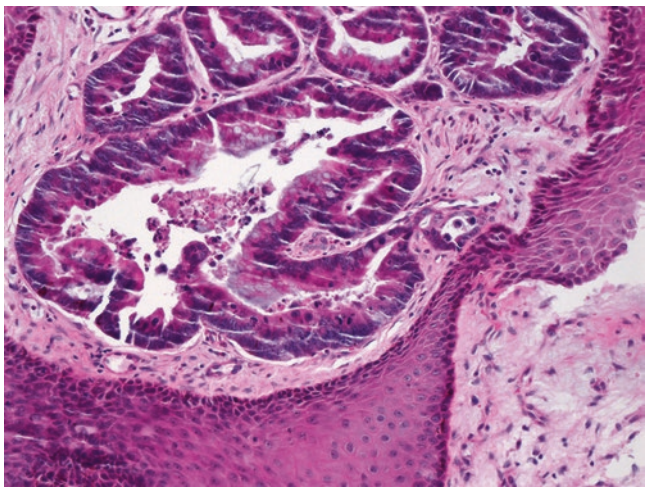

Fig. 30.2 The malignant glands have marked cytologic atypia and focal necrosis in adenocarcinoma metastatic to the skin

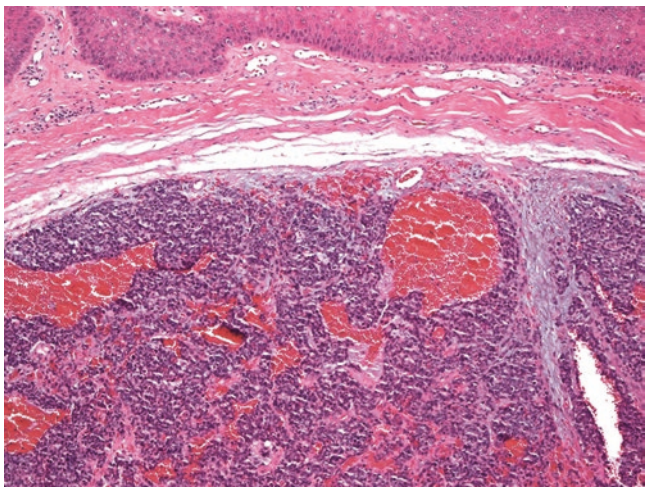

Fig. 30.5 Within the dermis, large nests of small cells with hyperchromatic nuclei and minimal cytoplasm are seen in metastatic small-cell lung carcinoma

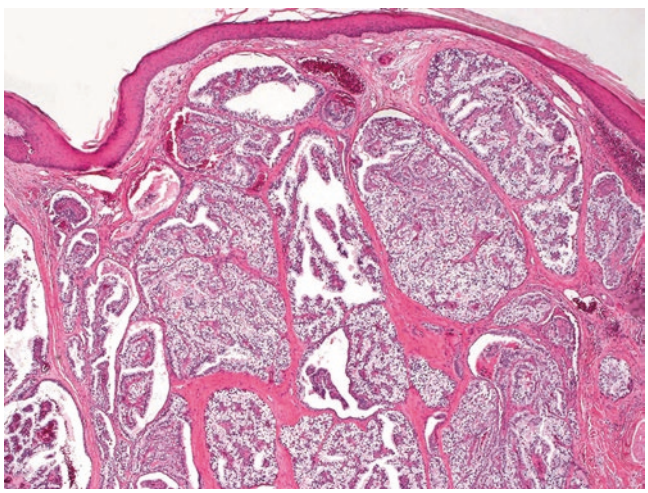

Fig. 30.3 Metastatic papillary thyroid carcinoma demonstrates large nests of clear-staining cells with papillary architecture in the dermis

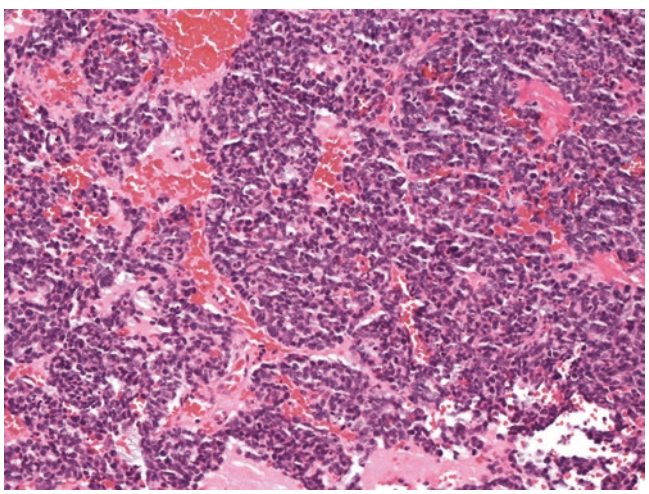

Fig. 30.6 Mitotic activity, nuclear pleomorphism, and inconspicuous cytoplasm characterize metastatic small-cell lung carcinoma

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