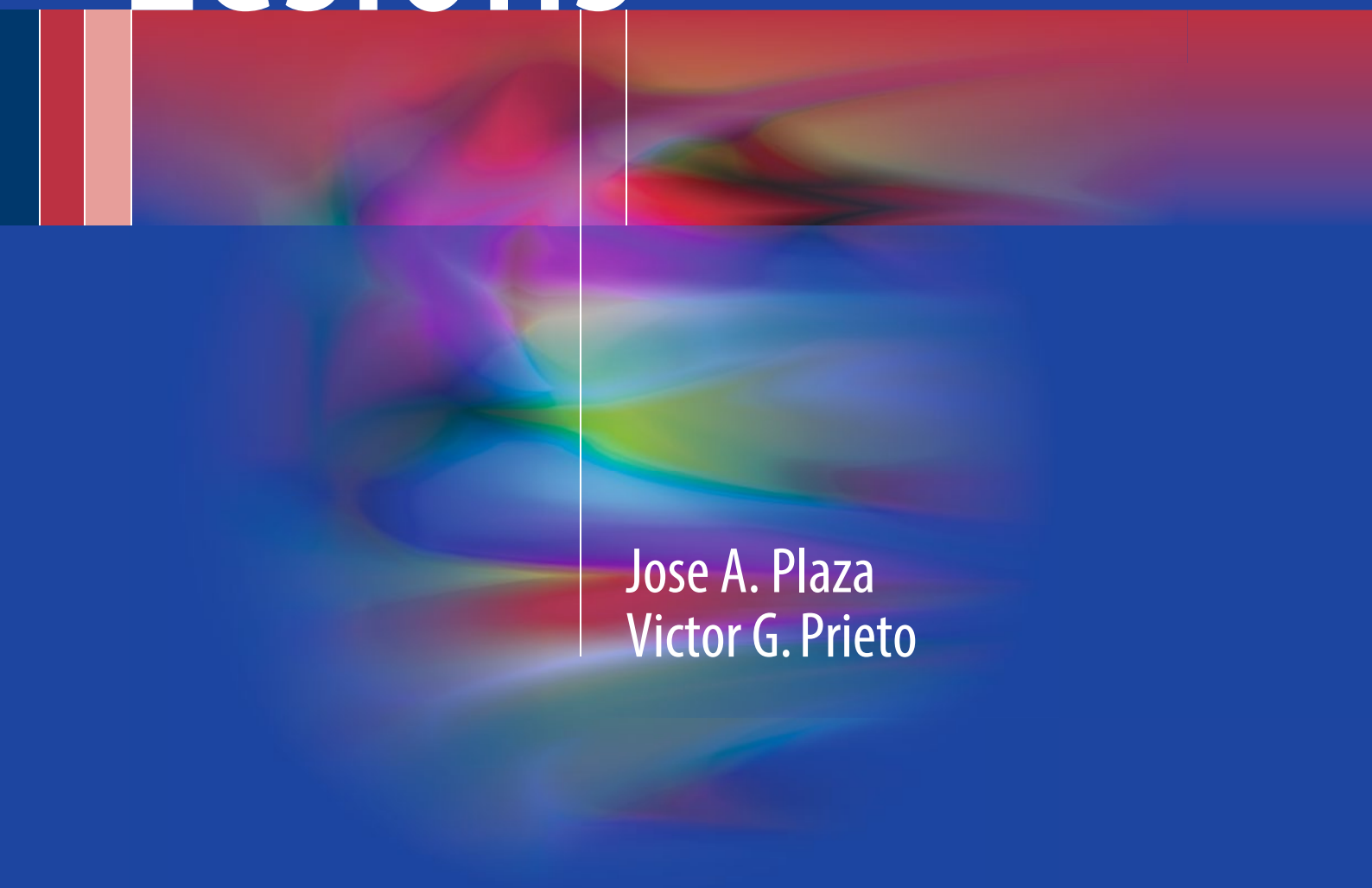
Pathology of Pigmented Skin Lesions



Jose A. Plaza
Victor G. Prieto

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Preface

The histomorphologic study of pigmented lesions of the skin constitutes the majority of our daily dermatopathology practice. In this book, we have compiled our experience in regard to pigmented lesions of the skin and have illustrated not only stereotypical examples of pigmented lesions but also unusual variants and a wide spectrum of variations that can be observed in such lesions. Our goal in this book is to illustrate thoroughly the most difficult topics in melanocytic tumors and to describe our view on how to diagnose these lesions. The opinions stated in this book represent our personal views on the topics. As with other topics in the field of pathology, the reader should consider the information provided and assimilate it to her/his own experience.

The histological diagnosis of melanocytic lesions is one of the most difficult areas in pathology, given the subjectivity and histologic variations that some of such entities may depict. In the last decade, there have been major advances in terms of diagnosis and prognosis of such lesions. It is well known that a number of these lesions cannot be precisely and reproducibly classified as either entirely benign or malignant just by using conventional histologic and immunohistochemical techniques. New understandings of molecular pathogenesis of melanocytic proliferations have revealed genetic differences between nevi and melanoma that can be used as targets for developing molecular diagnostic tests. FISH has emerged as a preferred molecular technique to interrogate chromosomal abnormalities, with proven utility as a diagnostic adjunct in lymphoid lesions and solid tumors and that has been recently validated for the diagnosis of melanocytic lesions. In this book, in addition to special mention to immunohistochemistry, we cover also the utility of adjunct molecular studies applied to the diagnosis of certain melanocytic lesions that are exceedingly difficult to diagnose on pure histomorphologic grounds.

We are in debt with our teachers, colleagues, and students who have guided and challenged us over the years. We also are thankful to many pathologists who have shared their challenging cases with us on consultation, and we have learned from them. The major sources of material used in book are from the dermatopathology divisions of Medical College of Wisconsin, University of Texas MD Anderson Center, and Miraca Life Sciences. And last, but not least, we are much in debt with our families who have supported us during all these years.

Dallas, TX, USA — Jose A. Plaza
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Lentigines

1

Ephelides

Clinical Features

Ephelides (freckles) are common, uniformly pigmented, multiple macules (1–5 mm in size) mainly limited to body regions above the waist. These macules are more numerous on sun-exposed areas (face, shoulders, and upper back) and usually fade and become smaller in the winter season. Ephelides appear early in childhood and partly disappear with age and are closely related to pigmentary host characteristics such as fair skin and/or red hair. Only rarely ephelides are seen in individuals with dark skin. Ephelides may manifest an autosomal dominant pattern of inheritance (appearing in sequential generations). High levels of freckling may indicate a raised susceptibility to the development of melanoma. In contrast to solar lentigines, ephelides are not strongly associated with age [1–4]. There is a strong relation between variants in the gene encoding the melanocortin-1 receptor (MC1R) and ephelides in childhood suggesting the MC1R gene is the major ephelide gene [5].

Histopathology

The epidermis appears normal in structure. The basal cells in the affected areas are more heavily pigmented with melanin than those in the surrounding skin, and there is usually sharp delimitation of the abnormal from the normal areas. There are normal and sometimes decreased numbers of melanocytes within epidermis; however, the melanosomes in those cells are larger than those in the surrounding skin and can sometimes be seen with the microscope as dark, large, intracytoplasmic granules (macromelanosomes). The adnexal structures are not involved. By electron microscopy studies, the melanocytes contain enlarged spherical granular melanosomes as opposed to the striated ellipsoid forms seen in normal skin [3, 6, 7] (Fig. 1.1a–c).

Differential Diagnosis

The clinical differential diagnosis of ephelides includes lentigo simplex and café au lait spot. The diagnosis of café au lait spot will rely on the identification of giant melanosomes and mild increased number of melanocytes. Lentigo simplex (as explained in detail below) will show elongated rete ridges with hyperpigmentation of basal keratinocytes (some authors accept also mild increased in numbers of melanocytes) (Fig. 1.1a–c).

Lentigo Simplex

Clinical Features

Lentigo simplex is a very common, benign, pigmented lesion that can be found anywhere on the body surface and is preferentially observed in young people, although it may occur at any age. They usually appear early in life and are typically not associated with sun exposure. Clinically, lesions present as non-palpable, relatively symmetric, uniform, homogeneous, light-brown to black macules, on the trunk, extremities, genitals, and mucosa surfaces, usually measuring less than 5 mm in size (in certain anatomic sites such as the palms, soles, genitalia, and mucosal membranes, they can be larger). It is rare for a lentigo simplex to be asymmetrical or to have irregular borders. Lentigo simplex may occur as single or multiple lesions. It has been proposed that lentigo simplex may evolve into a lentiginous/junctional melanocytic nevus when melanocytes start proliferating and aggregating to form small nests in the junctional zone. On the other hand, a recent study has shown that absence of BRAF, FGFR3, and PIK3CA mutations can clearly differentiate lentigo simplex from melanocytic nevi and solar lentigo. These results furthermore indicate that lentigo simplex has a distinct yet unknown genetic basis, which does not necessarily exclude the proposed lentigo-nevus sequence [8].

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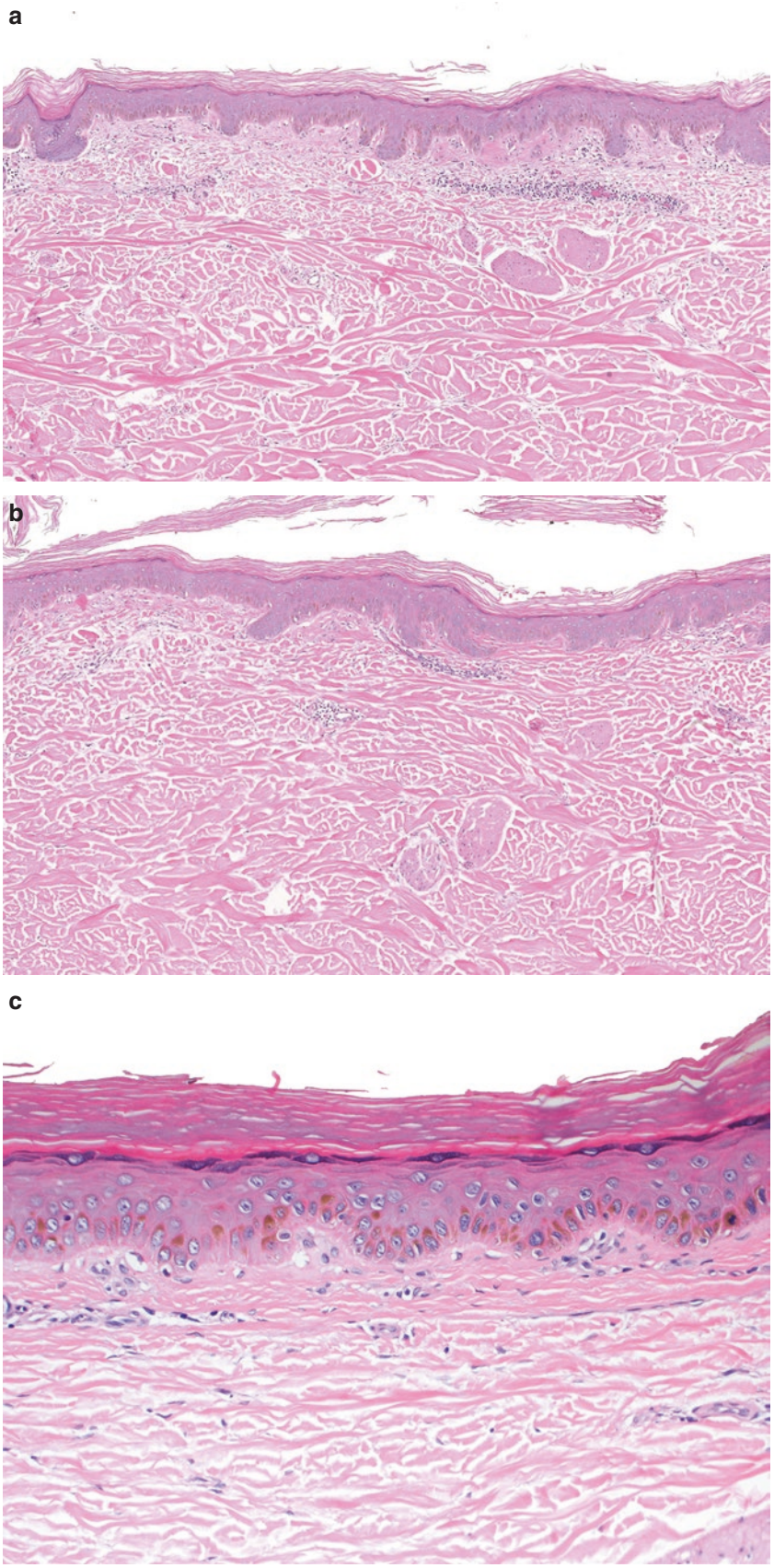

Fig. 1.1 Ephelides. Note the pigmented basal keratinocytes and the decreased number of melanocytes within epidermis (**a**). Higher magnification showing melanocytes with rare melanosomes (**b**). Observe the lack of melanocytes (**c**)

In some instances, multiple lentigines are associated with rare genetic disorders. These include LEOPARD syndrome (lentigines, EKG changes, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, growth retardation, and deafness), Carney complex (lentigines, atrial myxoma, mucocutaneous myxoma, and nevi), Peutz-Jeghers syndrome (oral and perioral lentigines, multiple gastrointestinal polyps, and visceral tumors), xeroderma pigmentosum (lentigines on sun-exposed skin and multiple skin cancers), and Cronkhite-Canada syndrome (buccal, facial, and palmoplantar lentigines, alopecia, nail dystrophy, and intestinal polyps).

Histopathology

Lentigo simplex shows mild elongation of the epidermal rete ridges with variable basal cell hyperpigmentation. The elongated rete ridges are either thin or club shaped. Some authors accept that there may be an increased number of single melanocytes in the basal layer devoid of cytologic atypia. In some cases there are giant melanosomes as in lentigines. Papillary dermis is often fibrotic; however, in contrast with dysplastic rarely is there concentric and lamellar fibroplasia. Also in the papillary dermis, there may be a subtle lymphohistiocytic infiltrate with scattered melanophages. While the majority of lentigo simplex are stable, some may develop junctional nests and melanocytes may descent into papillary dermis. Thus, lentigos and junctional nevi may coexist and can be designated as lentiginous junctional nevus (jentigo) [9–11]. Because of that apparent capacity to progress, lentigo simplex is being conceived by some authors as embryonic junctional melanocytic nevi, and that such distinction is arbitrary (Fig. 1.2a–c).

Differential Diagnosis

Lentigo simplex is often biopsied to rule out melanoma in situ, especially if the lesion is located in the head and neck of an older individual. In most cases, this differential diagnosis is straightforward. However, in some instances, lentigo simplex may display isolated melanocytes at and above the basal layer. This represents a rare occurrence, and its distinction with melanoma in situ can be problematic if the specimen is small and the complete architecture of the lesion cannot be evaluated. Lentigo simplex located in special sites (such as umbilical, genital, and axillary areas) can also show irregular distribution of the pigment. Close attention to the cytology of the cells is very important to make a distinction from melanoma, as these melanocytes do not differ from those seen in the basal layer of the epidermis, and cytologically they have small nuclei with compact chromatin and scant cytoplasm. Upwardly scattered melanocytes can also be seen in cases of lentigo simplex that have been traumatized. The presence of parakeratosis, spongiosis, extravasated red blood cells, dyskeratotic keratinocytes, and the melanin pigment above the suprabasal layer is a hint that a lesion has been traumatized. The presence of melanocytes with vesicular nuclei and abundant cytoplasm along with signs of solar damage, pagetoid spread of melanocytes, irregular distribution of melanin pigment in epidermis and dermis, and a dense lichenoid inflammatory infiltrate in superficial dermis (especially underneath the area of the lesion) raises the possibility of melanoma in situ. A diagnostic hallmark of melanoma in situ (especially lentigo maligna) is the extension of neoplastic melanocytes down the adnexal epithelial structures, a phenomenon not seen in lentigo simplex (Fig. 1.2a–c).

Actinic Lentigo (Pigmented Early Actinic Keratosis, Solar Lentigo)

Clinical Features

Actinic lentigines are common, macular, hyperpigmented lesions that range in size from a few millimeters to more than a centimeter in diameter. They tend to be multiple with individual lesions gradually increasing in size to larger macules or patches. Synonyms for this condition include solar lentigo, liver spots, age spots, and sun spots. Most commonly it appears on the face, upper extremities, dorsa of the hands, and upper part of the trunk. The incidence increases with age, affecting more than 90 % of white persons older than 50 years of age; however, they are now seen in younger patients likely because of their common exposure to sun and the use of artificial sources of UV light. Clinically, the lesions are usually small, slightly scaly, tan brown, macules, or thin papules on sun-damaged skin. In some cases the color may range from yellow tan to black and many lesions eventually coalesce to form larger patches. These enlarged solar lentigines correspond to evolution into standard actinic keratosis or seborrheic keratosis and may simulate clinically melanoma in situ [2, 12].

Histopathology

The lesions tend to have elongated rete ridges and a proliferation of pigmented basaloid cells, which form buds and strands (bulb-like). Overlying epidermis shows hyper/compact keratosis indicating an abnormal pattern of keratinocytic maturation. In some cases, the rete ridges form large fingerlike projections in a reticulated pattern; however, in lesions from the face, the rete ridge hyperplasia is less prominent and almost absent [13]. Melanocytes can be mildly increased in number, do not have a confluent pattern, and are not cytologically atypical. In rare cases, melanocytes can be seen above the basal cell layer. There are melanophages

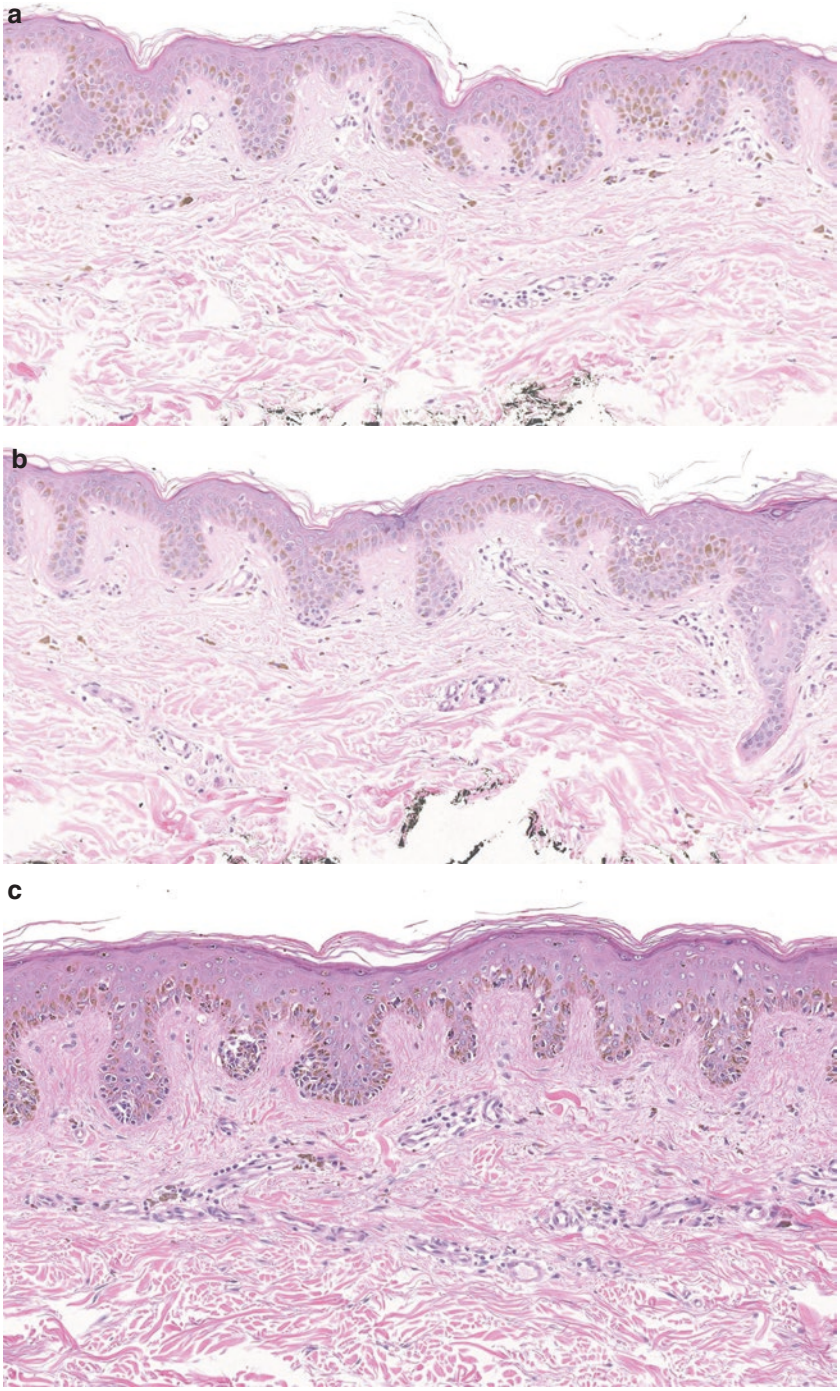

Fig. 1.2 Lentigo simplex. The lesion shows elongation of rete ridges and pigmented keratinocytes with absence of solar damage (**a**). The pigment varies within epidermis and can be prominent in some cases (**b**). An early transition into an early junctional nevus (jentigo) (**c**)

(secondary to pigment incontinence) in superficial dermis. Solar elastosis is invariably present.

Solar lentigines may progress to standard seborrheic keratosis, thus showing progressive elongation and interanastomosis of rete ridges and horn pseudocysts. At any point in the evolution of a solar lentigo into a seborrheic keratosis, there may be a dense lichenoid inflammatory response along with an interface vacuolar damage of the dermal epidermal junction, known as benign lichenoid keratosis. Actinic lentigo may also undergo regression and it will also show lichenoid changes. In some other cases, there may be progressive architectural disarray of the epidermis with increased cytologic atypia, i.e., standard actinic keratosis. In cases in which there is severe actinic damage, it is not unusual to observe the coexistence of pigmented actinic keratosis and solar lentigo (Fig. 1.3a–c).

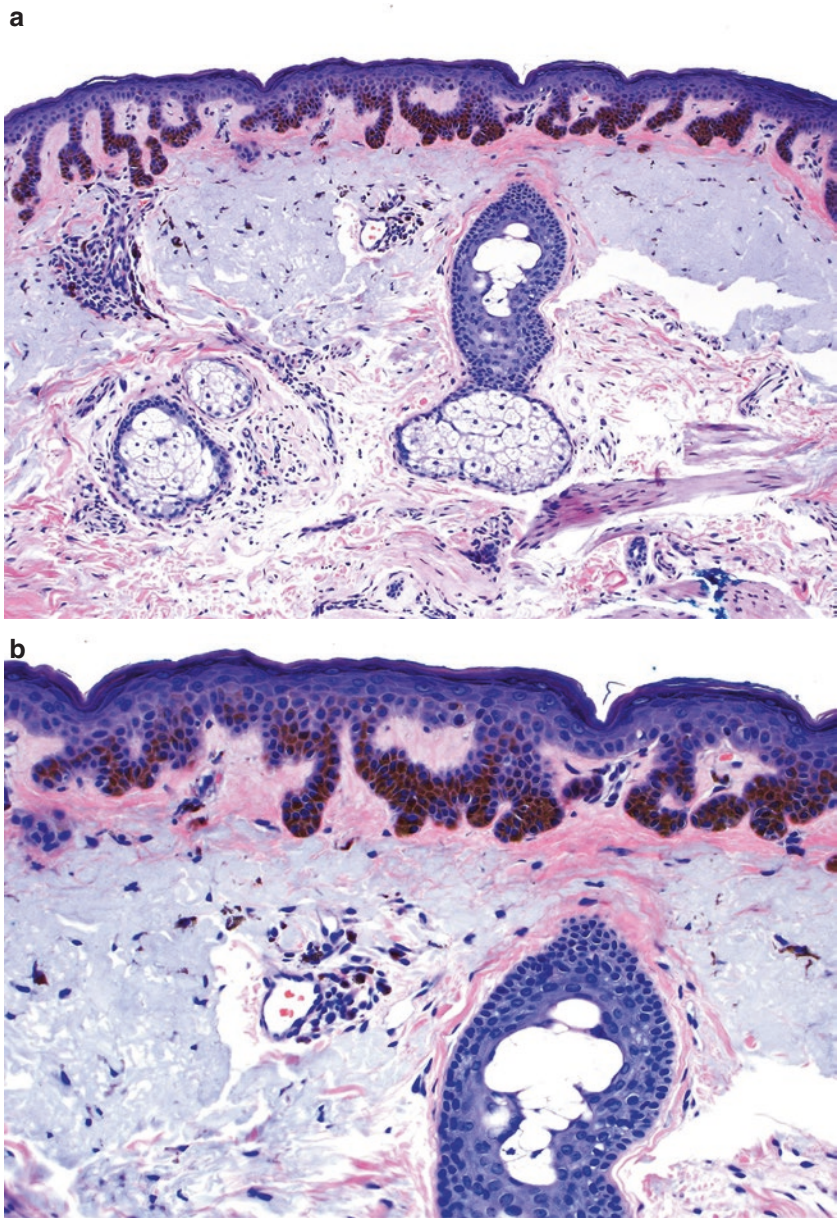

Fig 1.3 Solar lentigo. Elongated and pigmented rete ridges with prominent solar elastosis (**a**). High power showing pigmented retes and the lack of melanocytes (**b**)

Differential Diagnosis

In some cases, one may notice enlarged and cytologically atypical isolated melanocytes in the basal layer of the epidermis in an otherwise standard solar lentigo. This phenomenon is usually seen when there is severe solar damage. These melanocytes slightly vary in size and shape and may have enlarged and irregularly shaped vesicular nuclei with abundant cytoplasm. Therefore, at times it can be quite difficult to distinguish sun-damaged intraepidermal melanocytic hyperplasia in a solar lentigo versus incipient melanoma in situ (lentigo maligna type), particularly in small biopsies of a larger lesion. Both disorders will show an increased number of cytologically atypical melanocytes in the basal layer of epidermis. A useful feature to make a distinction would be to identify the presence of junctional nests, which will favor a melanocytic lesion (in this case melanoma in situ). Also, if there are solitary melanocytes in a confluent pattern of growth replacing the basal layer of epidermis and with periadnexal distribution, this is indicative of melanoma in situ (see also below in melanoma in situ, lentigo maligna type). If the dominant lesion is a solar lentigo, and there is low density

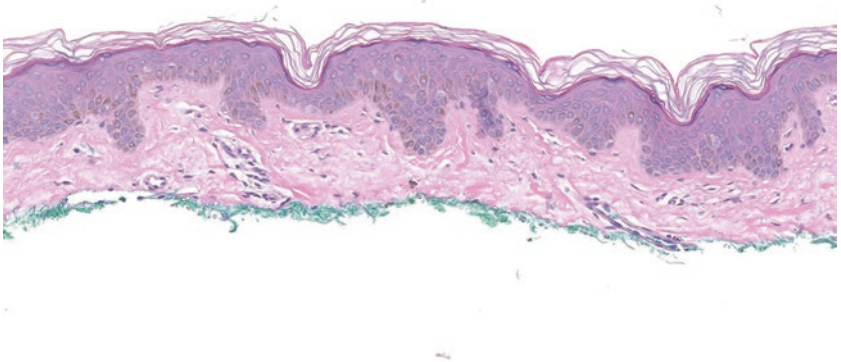

Fig 1.4 Solar lentigo with subtle intraepidermal melanocytic hyperplasia. Note the focal intraepidermal melanocytic hyperplasia most compatible with chronic sun damage

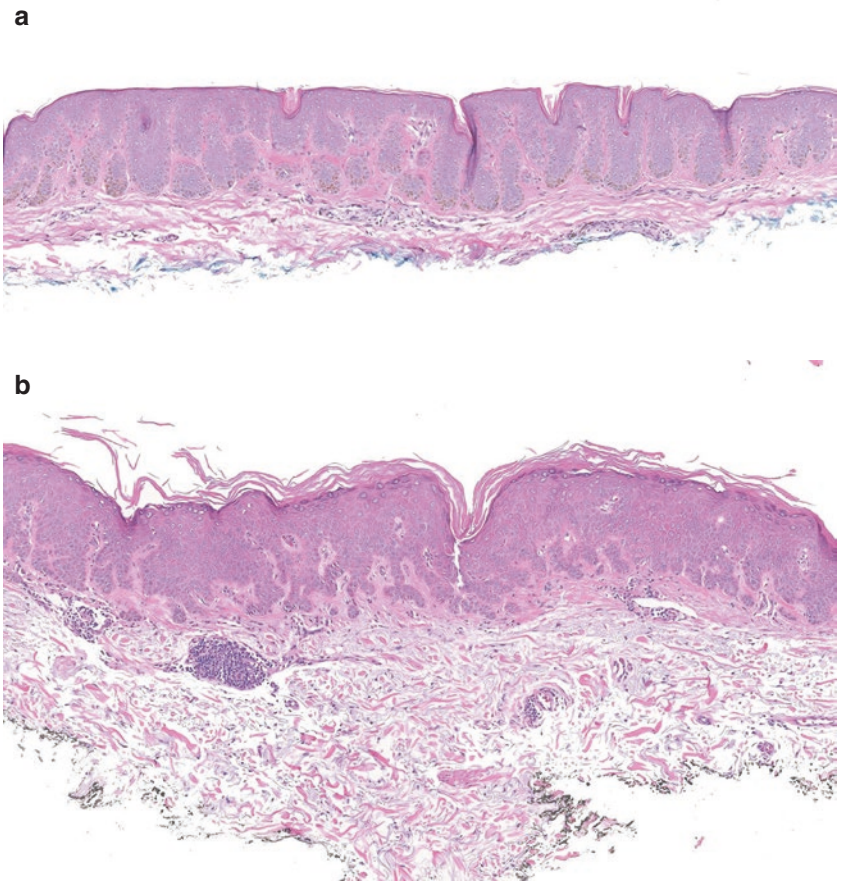

Fig 1.5 Solar lentigo with early progression to seborrheic keratosis. The lesion shows elongated rete with acanthosis in the background of solar damage (**a**). The retes are elongated and have pigmented keratinocytes in the basal layer. Prominent solar elastosis is present (**b**)

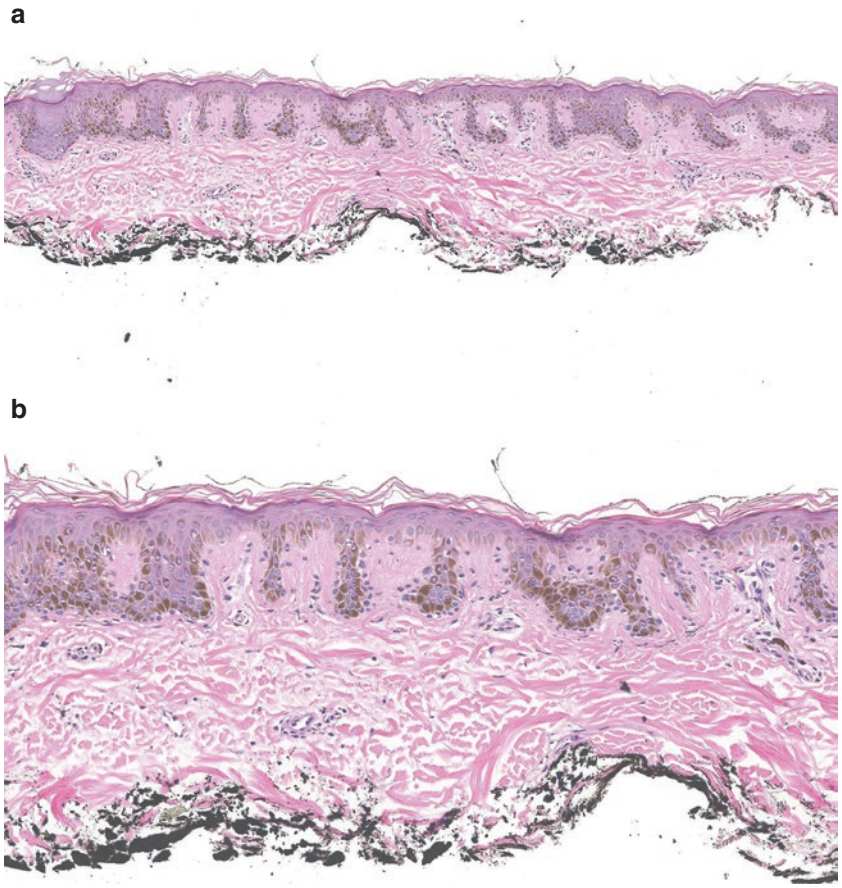

Fig 1.6 Solar lentigo with early junctional nevus ("jentigo"). This lesion shows classic features of a solar lentigo along with superimposed melanocytes forming small nests in the junction (**a**). High power showing fusion of the rete along with rare melanocytes within epidermis ("jentigo") (**b**). The presence of these nests represents early transformation into a junctional nevus

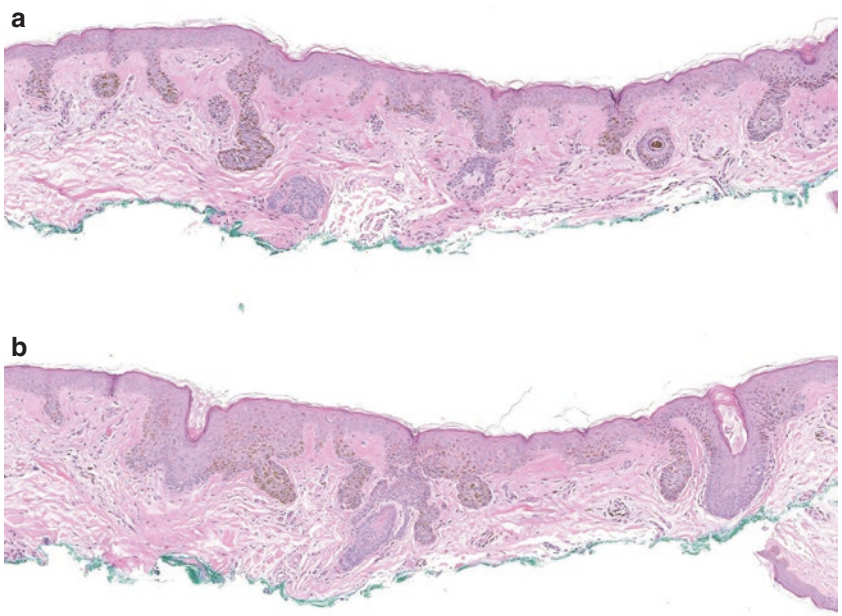

Fig 1.7 Solar lentigo with early junctional nevus. Another example with slight higher density of intraepidermal melanocytes and forming small nests (**a**). Higher magnification showing the rare and banal-appearing nests (**b**)

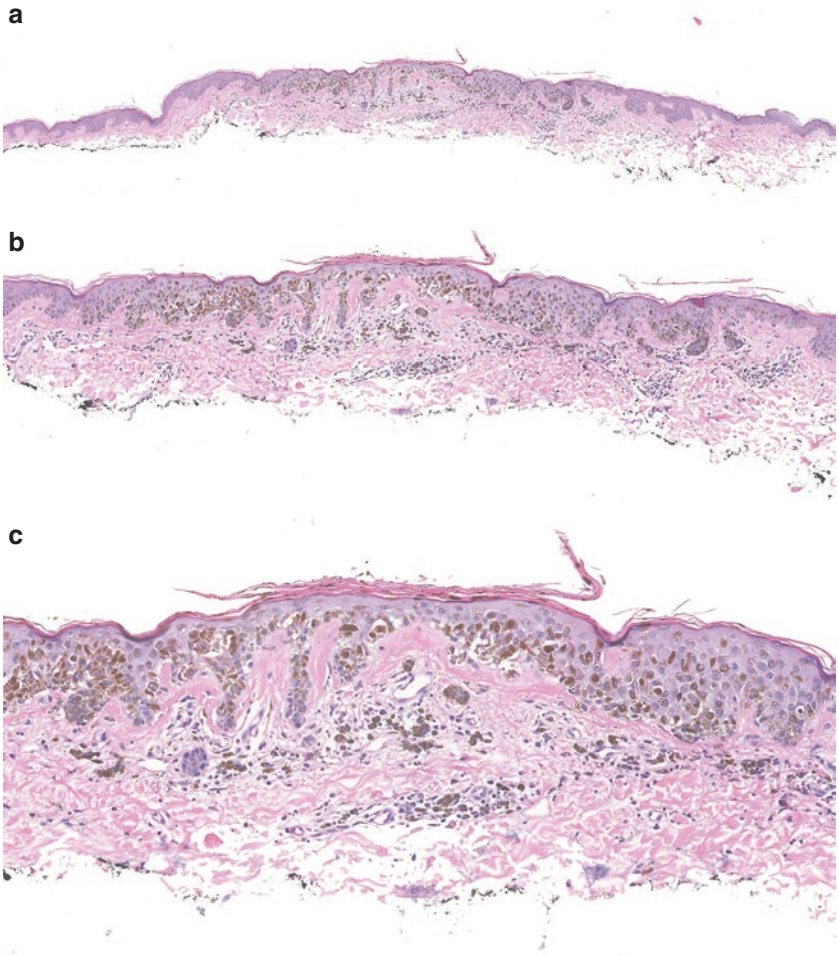

Fig 1.8 Ink-spot lentigo. Small lesion with pigmented epidermis and melanophages in dermis (**a**). Note the lentiginous hyperplasia of the epidermis and marked skipping hyperpigmentation of the basal layer (**b**). There is minimal increase in the number of melanocytes along with scattered melanophages in dermis (**c**). The papillary plates are less pigmented than the tips of rete ridges

of melanocytes at the basal layer, no lentiginous growth, and no melanocytic nests or pagetoid spread of melanocytes, these features will be in favor of sun-damaged intraepidermal melanocytic hyperplasia in a solar lentigo. Nonetheless, in certain cases it will be impossible to unequivocally separate the two by light microscopy in small samples, thus needing additional biopsies to establish the correct diagnosis.

Ink-Spot Lentigo

Clinical Features

Ink-spot lentigo (reticulated solar lentigo of the back) is a variant of solar lentigo. It affects fair-skinned individuals and usually presents on a background of solar-damaged skin as a solitary, reticulated, black macule with a wiry, markedly irregular outline (reminiscent of an ink spot). The distribution is limited to sun-exposed areas of the body, usually on the upper back. Most commonly, it presents as one ink-spot lentigo among an extensive number of solar lentigines. Ink-spot lentigines can initially suggest melanoma because of their dark color and irregular borders [17].

Histopathology

Ink-spot lentigines are also similar to solar lentigines. However, the rete ridges appear less blunted and more tortuous (elongated and clubbed); there is epidermal hyperplasia with marked basal, suprabasal, and corneal cell hyperpigmentation. Melanocytes may be normal or mildly increased in number, but without cytologic atypia. The superficial dermis has melanophages.

Large Cell Acanthoma

Large cell acanthoma is a pigmented, epidermal lesion that shares clinical and histopathologic features with solar lentigo and actinic keratosis. Some authors consider large cell acanthomas to be an evolutionary phase of solar lentigo to a reticulated seborrheic keratosis or established pigmented actinic keratosis, in which the keratinocytes show uniform enlargement, but the clinical appearance and the biologic potential are the same as conventional solar lentigo. The clinical presentation of the large cell acanthoma is primarily that of a large, flat, slightly scaly, tan macule on sun-damaged skin, i.e., indistinguishable clinically from a solar lentigo [14, 15]. There is a verrucous variant [16].

Histopathology

Large cell acanthoma shows keratinocytes that are uniformly enlarged without a significant increase in the nuclear to cytoplasmic ratio. Some cases may show a slight increased number of melanocytes. These changes can be confused with squamous cell carcinoma in situ, but the uniformity of the keratinocytes and the lack of other cytologic features allow a precise identification. As opposed to solar lentigo, there is no elongation of rete ridges.

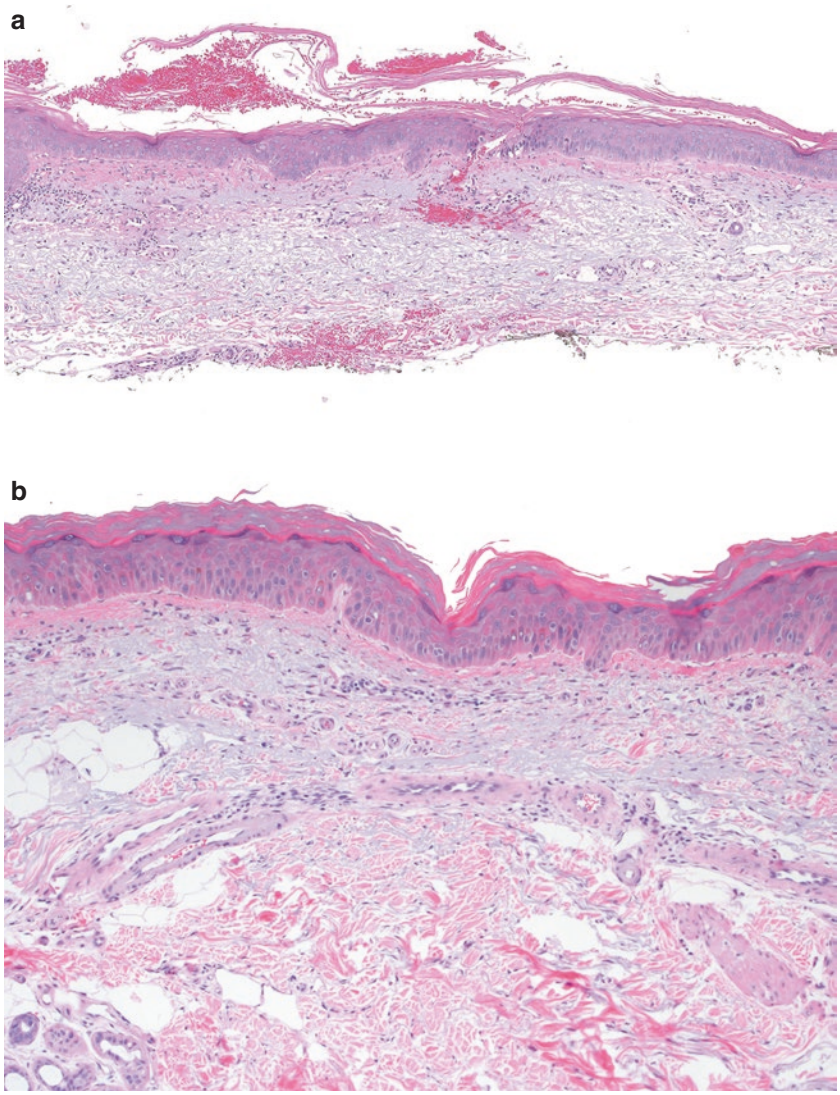

Fig. 1.9 Large cell acanthoma. The lesion is composed of large uniform pigmented keratinocytes (**a**). High power shows lack of elongated retes and the uniform pigmented keratinocytes (**b**).

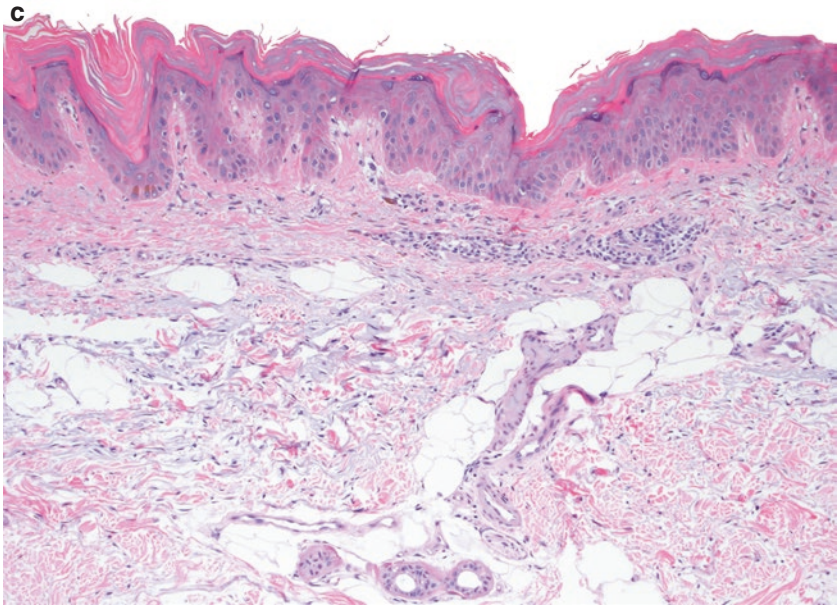

Fig. 1.9 (continued) Note the large keratinocytes (**c**)

Melanotic Macules

Clinical Features

Benign melanotic macules can be considered as the mucosal counterpart of lentigos. They present clinically as flat, smooth-bordered, well-defined pigmented lesions. Many variants can be included in this category including oral (labial) melanotic macule, genital melanotic macule, melanosis of the areola, melanosis of acral sites, and melanotic macules of the nail bed. They may be solitary of multiple, occasionally associated with complex syndromes.

Oral/labial melanotic macules: More commonly seen in the inferior lip; however, they can also be seen in the palate and tongue. When they present on the lip, the lower vermilion border is the most commonly affected area, although they can be seen anywhere in the oral mucosa [17–19]. Oral and labial melanotic macules appear to be more common in patients infected with the human immunodeficiency virus [19, 20]. Multiple lesions can be seen in genetic syndromes including Hunziker-Laugier syndrome, Albright syndrome, neurofibromatosis, and familial polyposis syndrome [21].

Genital melanotic macules: Rare pigmented lesions, more commonly seen on the penis and vulva [22]. In the vulva they are more commonly located in the labia minora but also can be seen in the labia majora, introitus, and perineum. In the vulva they are usually multiple and can be large in size (up to 5 cm in diameter). On the penis, melanotic macules are usually located on the shaft. Lesions can also occur on the glans, and in this location they tend to be more irregular and larger in size. Lesions can also be seen in the scrotum. Melanotic macules on genital areas are clinically indistinguishable from melanoma in situ; however, lesion stability maintained after the phase of initial growth will favor benign over malignant.

Acral melanotic macules: On the volar surface of palms and soles of African American individuals. These lesions tend to be larger and multiple, although usually less than 5 mm in diameter.

Nail bed melanotic macules: Regular, delineated, and elongated pigmented stripes also known as melanonychia striata. Nail bed melanotic macules are the most common cause of melanonychia striata; however, melanomas, nevi, postinflammatory hyperpigmentation, and some complex syndromes can also cause melanonychia striata. Nail bed melanotic macules are usually multiple and randomly distributed as opposed to subungual melanoma which occurs on the thumb or great toe in most cases (90 %).

Histopathology

All forms of melanotic macules will show similar histologic features. These lesions are characterized by prominent uniform melanin pigmentation in the basal cell layer of the epithelium, usually accentuated at the tips of the rete ridges

(in some occasions it can be distributed homogenously along the epithelium). There is only mild hyperkeratosis and acanthosis. Melanocytes may be normal or mildly increased in number, and when present they are equidistant from each other and separated by normal keratinocytes (without pagetoid migrations). Melanotic macules lack confluent lentiginous growth or junctional nests. Melanocytic atypia should not be observed; if atypia is observed, other diagnoses should be entertained such as atypical genital melanocytic hyperplasia (this lesion may actually be a precursor of melanoma) [23]. The presence of dendrites entrapping keratinocytes at the basal layer of the epithelium is a characteristic feature of melanotic macules. When one encounters an increased number of melanocytes within epithelium, this should be used against the diagnosis of a simple form of melanotic macule, and in some occasions this may represent an incipient form of melanoma in situ [24–27]. There are usually in the lamina propria/superficial dermis in most cases.

Differential Diagnosis

The most important differential diagnosis of melanotic macules is with incipient melanoma in situ, especially when lesions are localized in the volar surface of acral sites, nail matrix, and mucosa. Melanotic macules and incipient melanoma in situ will show many similarities at the histologic level. However, melanoma in situ shows crowding and lentiginous growth of melanocytes along the basal layer of epidermis along with cytologic atypia, irregular pigmentation, gradual elongation of interpapillary rete ridges, irregular pigment distribution, and melanocytes in the uppermost layer of epidermis. In melanotic macules, when melanocytes are present, they are separated by keratinocytes (equidistant), and there is no obvious cytologic atypia (inconspicuous nuclei). Aggregations of melanocytes in nests and lentiginous pattern are against the diagnosis of melanotic macules, as these lesions tend to be paucicellular. Thus, increased density of melanocytes should not be seen in a melanotic macule. Melanotic macules do not evolve into melanoma; however, in certain circumstances melanotic macules and incipient melanoma in situ can be indistinguishable from each other. If the biopsy is from the edge of a melanoma in situ (either oral or genital), these peripheral areas can look histologically very similar to benign melanotic macules, thus representing a possible diagnostic pitfall. In some occasions the clinical data may be of aid, as melanomas are usually found in older patients (rare exceptions), and melanotic macules appear in young adults. The location of the lesion will also be of help in certain instances, for example, melanomas of the nail will almost always be located in the thumb or large toe. At any rate, clinical-pathologic correlation is essential to determine the extent of the lesion and if the sample is actually representative.

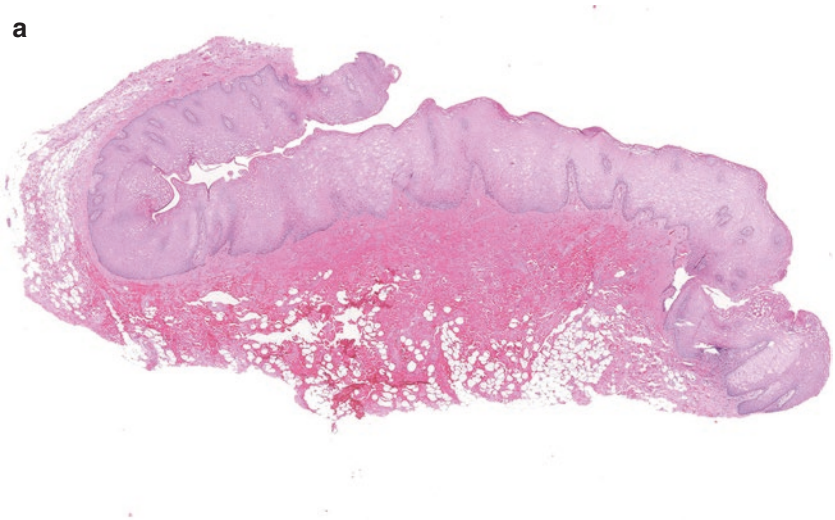

Fig. 1.10 Melanotic macule. This lesion is located in the lip of a 55-year-old female. Note the acanthotic epithelium with pigmented keratinocytes at the basal layer (**a**).

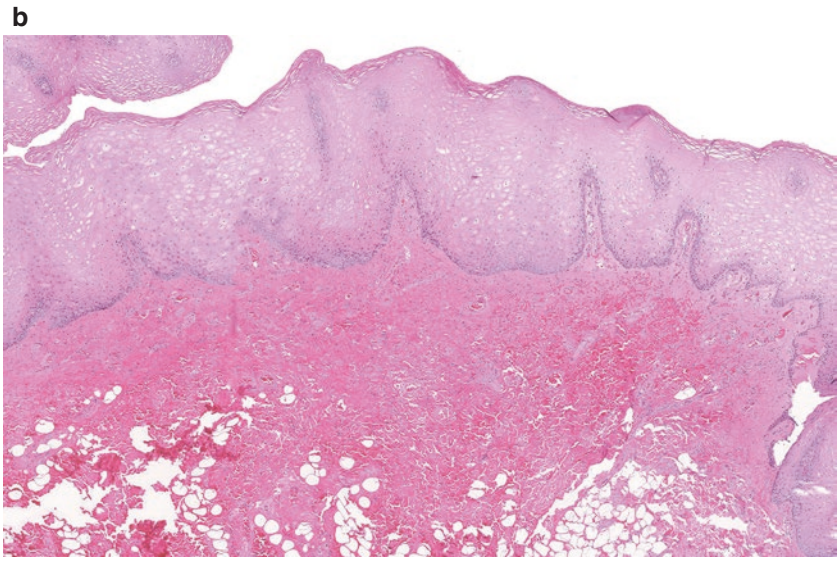

Fig. 1.10 (continued) High power showing the acanthotic epithelium with lack of cytologic atypia (**b**)

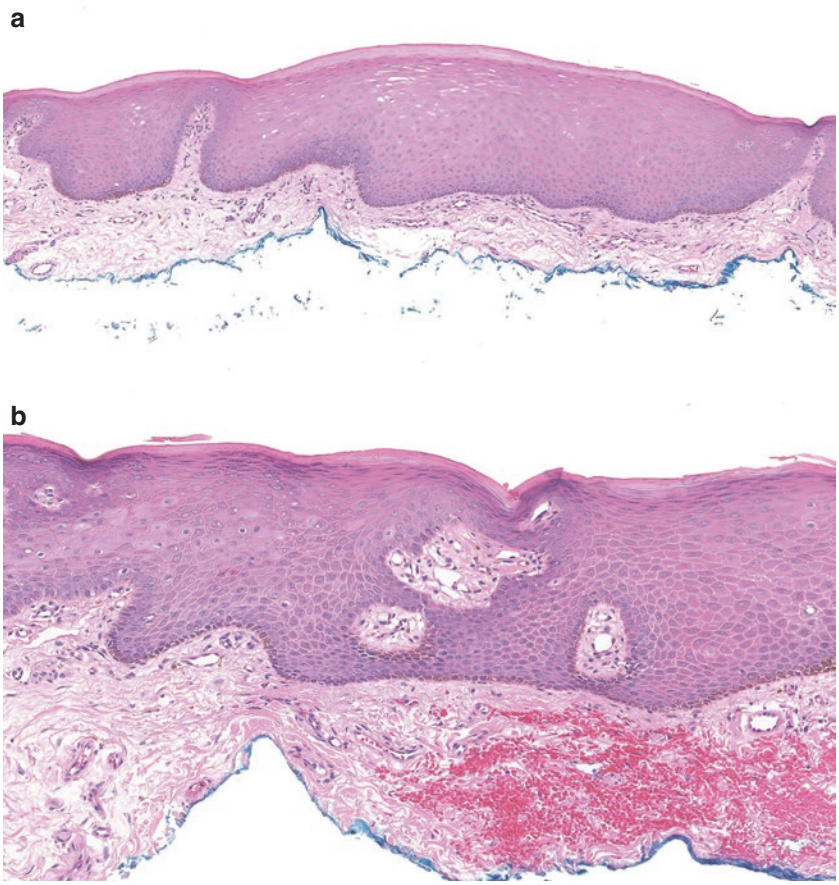

Fig. 1.11 Melanotic macule (lip). This case shows marked acanthosis with basal layer hyperpigmentation (**a**). At high magnification note the lack of melanocytes within the epidermis and rare pigmented melanophages in superficial dermis (**b**)

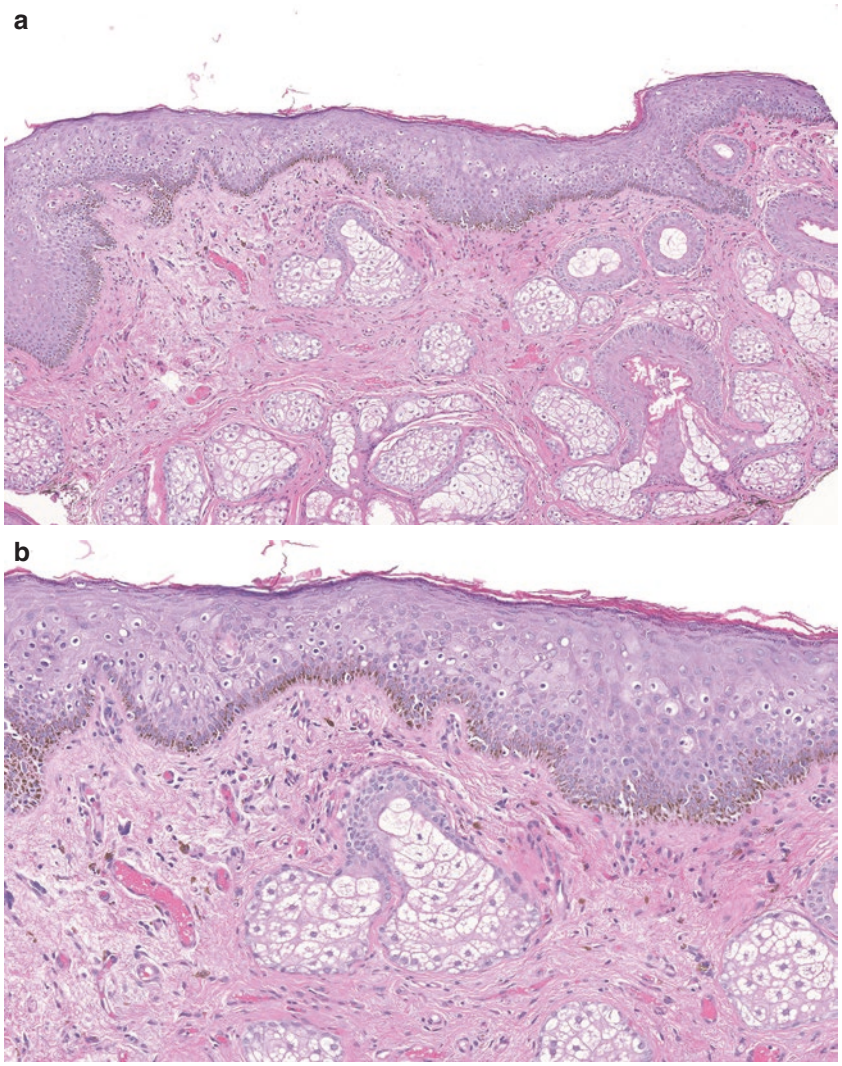

Fig. 1.12 Melanotic macule (vulva). This lesion is located in the vulva of a 28-year-old female. This example shows increase pigmentation in the basal layer, predominantly at the tips of the rete (**a**). Higher magnification showing the increase pigmentation in the basal layer (**b**)

PUVA Lentigo

Clinical Features

Psoralens and ultraviolet-A radiation (PUVA) are widely used for a number of skin disorders including psoriasis, vitiligo, mycosis fungoides, etc. [28, 29]. The presence of acquired lentigines has been reported in patients treated with PUVA. PUVA lentigines have been shown to develop in 40–50 % of patients after long-term PUVA treatment [30, 31]. Clinically, the lesions are usually multiple and have a dark pigmented color resembling solar lentigines, but they often have more irregular borders with speckled lentiginous/nevus spilus-like morphology. The lesions range in size from 3 to 8 mm in diameter; however, some may measure up to 3 cm. The occurrence of lesions is associated with cumulative doses of PUVA, and the lesions may occur on all treatment sites. The most common areas involved by PUVA lentigines include the upper part of the chest, back, buttocks, and penis. Some lesions may regress within 6 months after stopping the treatment. Similarly, sunbed lentigines are related lesions which are encountered after exposure to UVA (no psoralens involved) for tanning purposes. The most common site of tanning-bed lentigines is primarily the anterior aspects of the arms and legs [31, 32].

A concern that PUVA lentigines could be the precursors of melanocyte dysplasia or malignancy has been increased by the fact that PUVA is known to be an effective proliferative stimulus for melanocytes. A recent study has demonstrated the presence of T1799 BRAF mutations in 33 % of PUVA lentigines indicating that PUVA lentigines might be precursors of melanoma [32].

Histopathology

In PUVA and sunbed lentigines, the lesions are architecturally very similar to actinic lentigines; however, in contrast to actinic lentigines, PUVA lentigines often display an increased size of melanosomes, irregular elongation of rete ridges, irregular basal layer and stratum corneum hypermelanosis, and mild atrophy of epidermis between rete ridges. The majority of these lesions do not show increased intraepidermal melanocytes; however, in some cases there is mild increase with clustering and binucleation with nuclear hyperchromatism and cellular pleomorphism [30, 31, 33]. One study showed melanocytic atypia consisting of large or angular hyperchromatic nuclei in up to 57 % of PUVA lentigines [31]. Similar changes can be observed in PUVA-exposed skin without clinical evidence of actinic lentigines.

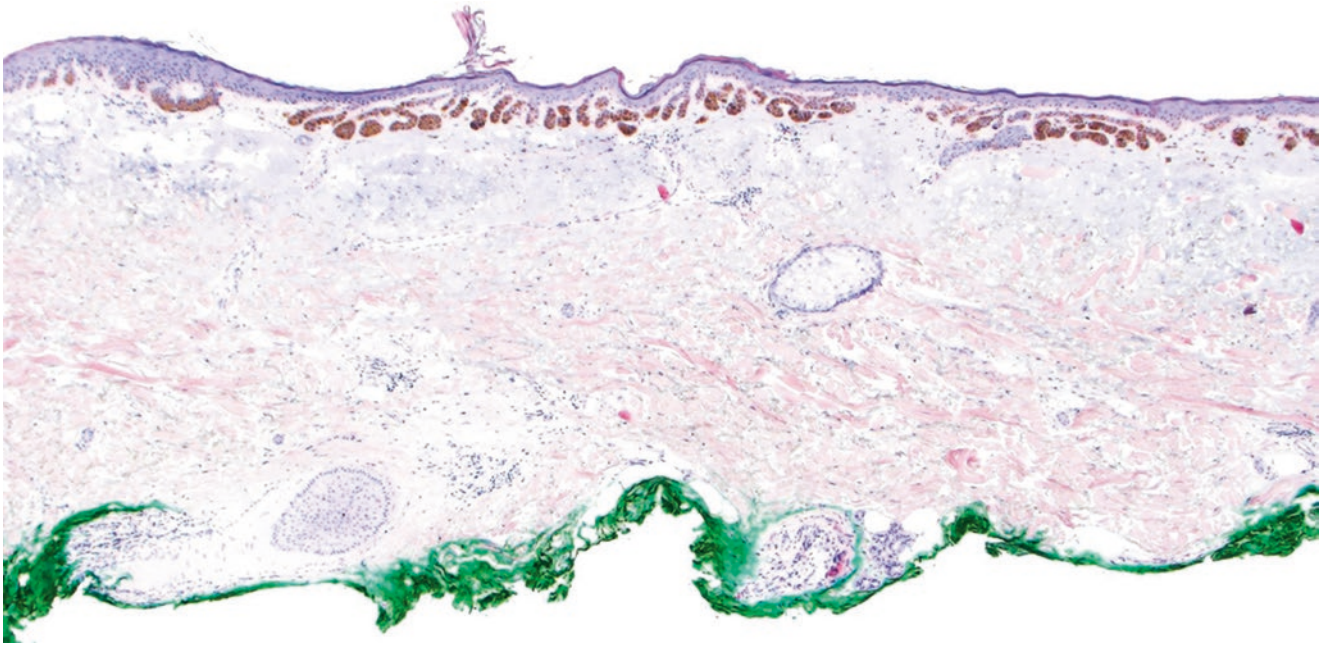

Fig. 1.13 PUVA Lentigo. Patients with history of psoriasis treated with PUVA can develop lentigines. Histology is identical to solar lentigo

Becker Nevus

Clinical Features

Becker nevus is a rare, benign, hamartomatous lesion characterized by one or more hyperpigmented patches that do not follow the lines of Blaschko lines but are instead arranged in a checkerboard pattern [34, 35]. The lesions have an onset during or after puberty and are more common in males than in females. It presents initially as a unilateral, uniform, well-demarcated, tan to dark-brown enlarging macular lesion, which subsequently develops hypertrichosis. The androgen dependence of this nevus results in a preponderance of cases in males and a characteristic hypertrichosis after puberty. Very rarely can it be congenital (autosomal dominant inheritance) or may present within the first years of life [36]. All races may be affected; however, there appears to be a predilection for non-white patients. Most frequently they are located in the upper half of the thorax, but all regions of the body may be affected. They may enlarge slowly within a few years but then remain stable in size (they can measure up 20 cm in size). Association of Becker nevus and melanoma is exceedingly rare [37]. Becker nevus syndrome refers to cases in which there is the presence of Becker nevus in addition to cutaneous, skeletal, and muscular abnormalities such as ipsilateral breast hypoplasia, supernumerary nipples, scoliosis, vertebral defects, limb asymmetry, spina bifida, or pectus excavatum [38, 39].

Histopathology

The epidermis shows mild hyperkeratosis, hyperplasia, and acanthosis with regular elongation of the rete ridges and variable hypermelanosis of the basal cell layer. The rete ridges can be elongated, fuse to each other, or can be flat. Intraepidermal melanocytic hyperplasia is focally seen but without confluent pattern of growth [40]. In the superficial dermis, there may be melanophages and a superficial perivascular lymphohistiocytic infiltrate. In some cases there are increased numbers and enlarged hair follicles and sebaceous glands along with a hamartomatous proliferation of smooth muscle bundles. These bundles of smooth muscle lie haphazardly within the superficial and mid-dermis and are unassociated with follicular units (clue to diagnosis). Occasionally there are increased numbers of terminal hair. As expected, Becker nevus shows increased expression of androgen receptors [35].

Differential Diagnosis

The main differential diagnosis of Becker nevus is with café au lait macule. The clinical appearance of the lesions will allow rapid discrimination as Becker nevi usually are raised and with hypertrichosis, and café au lait macules are flat lesions. However, histologically, these two conditions may show overlapping features; Becker nevi are distinguished by the presence of epidermal papillomatosis, marked pilosebaceous unit, and smooth muscle bundles in dermis, all of which are absent in café au lait macules. Both conditions can have mild basal melanocytic hyperplasia.

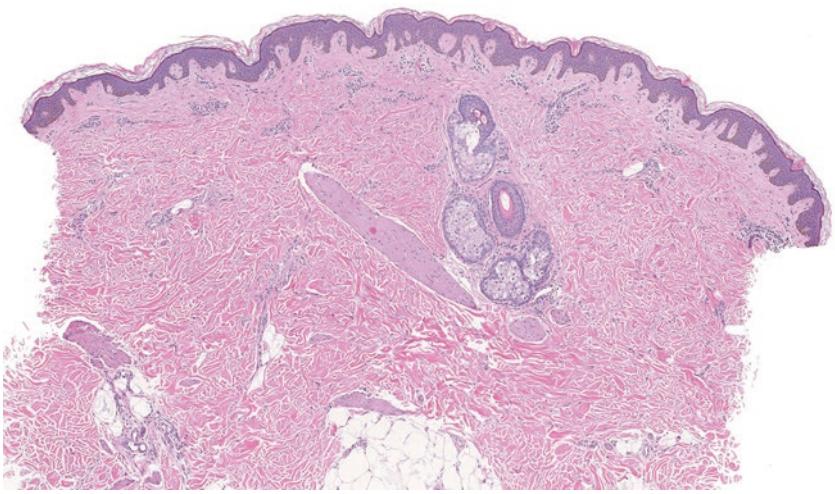

Fig. 1.14 Becker nevus. Low power showing epidermal hyperplasia and acanthosis

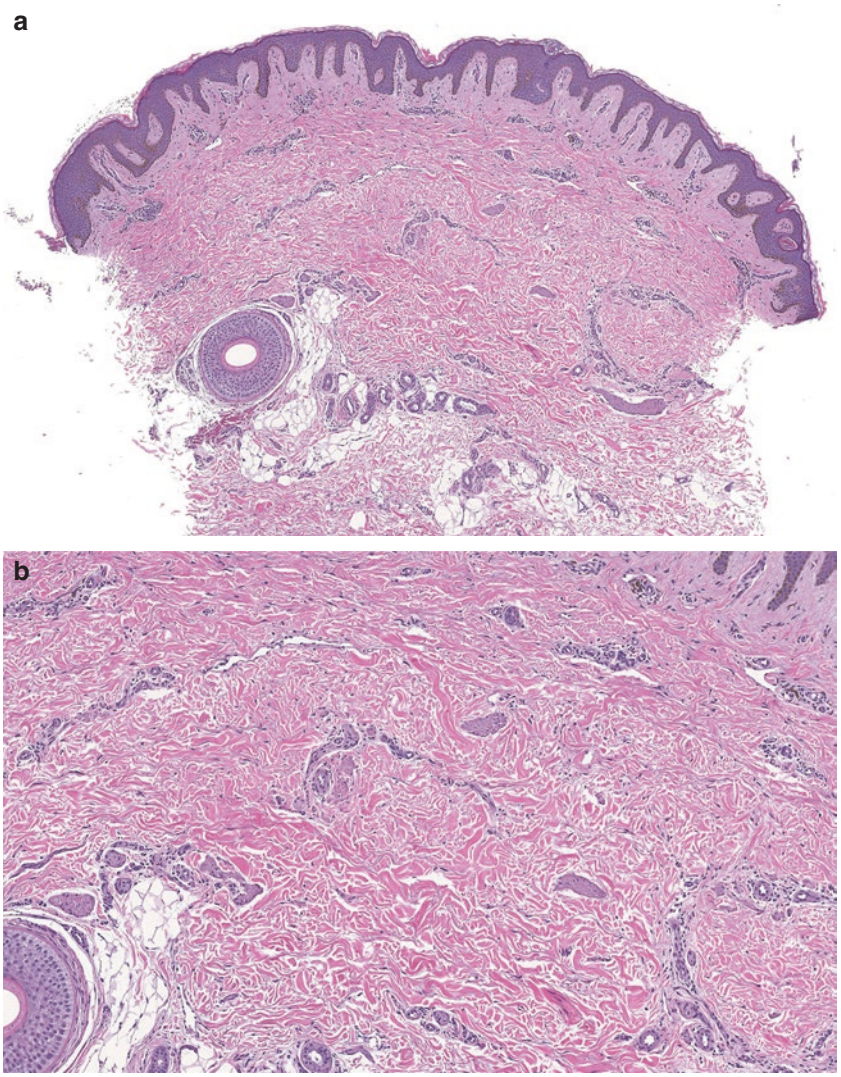

Fig. 1.15 Becker nevus. Another example showing regular epidermal hyperplasia with areas of hypermelanosis (**a**). Note the smooth muscle hyperplasia in dermis that is not associated with follicular units (**b**)

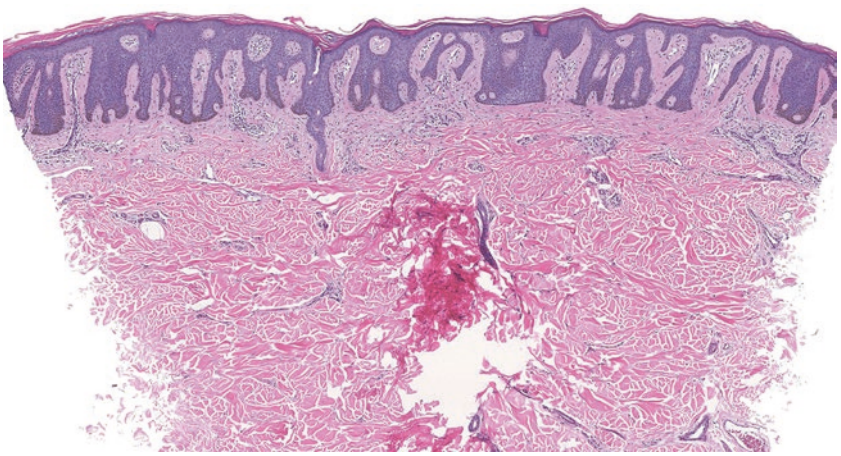

Fig. 1.16 Becker nevus. This example shows the characteristic irregular elongation of rete, increased basal layer pigmentation, mild acanthosis, and hyperkeratosis

Café-au-lait Macule

Clinical Features

Café au lait macules (CALM) are discrete benign pigmented patches. Despite the analogy of the color to coffee with milk, the pigmentation varies from light to dark brown. These lesions are common in the pediatric population and in most children represent a normal finding (10–20 % of normal population); however, it is important to recognize whether the presence of multiple CALMs in a particular patient is normal or indicates an association with a multisystem disorder such as neurofibromatosis. They may be present at birth but more commonly develop in early childhood and tend to increase in size with age. In newborns these lesions are commonly located on the buttocks, whereas in older children the trunk is the most common anatomic site [41]. Clinically, they usually have a uniform color that varies from light to dark brown. These lesions are flat and the borders are usually smooth and regular, but in some lesions these borders can be ill defined. In newborns, the size ranges from 0.2 to 4.0 cm in diameter and increases proportionately with body growth, whereas in older children and adults the diameter ranges from 1.5 to 30 cm [41–43].

CALMs are observed in 95 % of patients with neurofibromatosis type 1 (NF1), which is the most frequently occurring neurocutaneous syndrome. CALMs are one of the cardinal criteria in diagnosing NF-1. Additional criteria for diagnosis include multiple neurofibromas, plexiform neurofibroma, Lisch nodules, osseous lesions, axillary or inguinal freckling (Crowe sign), optic gliomas, and a family history of NF-1 in a first-degree relative. CALMs occur at birth, increase in number until 4 years of age, and are distributed randomly over the body, with relative sparing of the face. The "natural history" of CALMs associated with NF-1 differs from sporadic cases. Although sporadic CALMs increase in number in childhood and fade in adulthood, the macules associated with NF-1 become more numerous in adulthood and do not fade later in life [44]. CALMs may be present, but are not a diagnostic criterion, in some other categories of neurofibromatosis. Thus, in NF-2 and NF-3, CALMs tend to be large, pale, and fewer in number than in NF-1. Although approximately 60 % of patients with NF-2 have at least one CALM, the presence of more than five macules is unusual in this disorder [45].

Other conditions in which CALMS may be observed include Bloom syndrome, McCune-Albright syndrome, Cowden disease, tuberous sclerosis, Bannayan-Riley-Ruvalcaba syndrome, Watson syndrome, and Fanconi anemia [46–50].

Histopathology

The epidermis shows normal contour with mild basilar hyperpigmentation. In some occasions one can observe suprabasal hyperpigmentation in a pattern similar to that in dark-skinned individuals. The number of melanocytes is usually normal, but in some occasions, it may be slightly increased. Giant melanosomes are commonly observed in melanocytes and at times in basal keratinocytes, especially in patients with neurofibromatosis [51]. However, the presence of giant melanosomes (melanin macroglobules) is not specific for lesions seen in NF-1 as they are sometimes seen in isolated CALMs without underlying disease and in several other pigmented lesions including dysplastic nevi, congenital nevi, lentigo simplex, and Becker nevi [51–53].

Differential Diagnosis

As mentioned above, CALMS share multiple features with Becker nevi. The clinical features should permit an accurate separation between the two in most instances. The histologic differences include the presence of epidermal papillomatosis, elongation of rete ridges, and presence of smooth muscle hyperplasia in dermis in Becker nevus and not in CALMs.

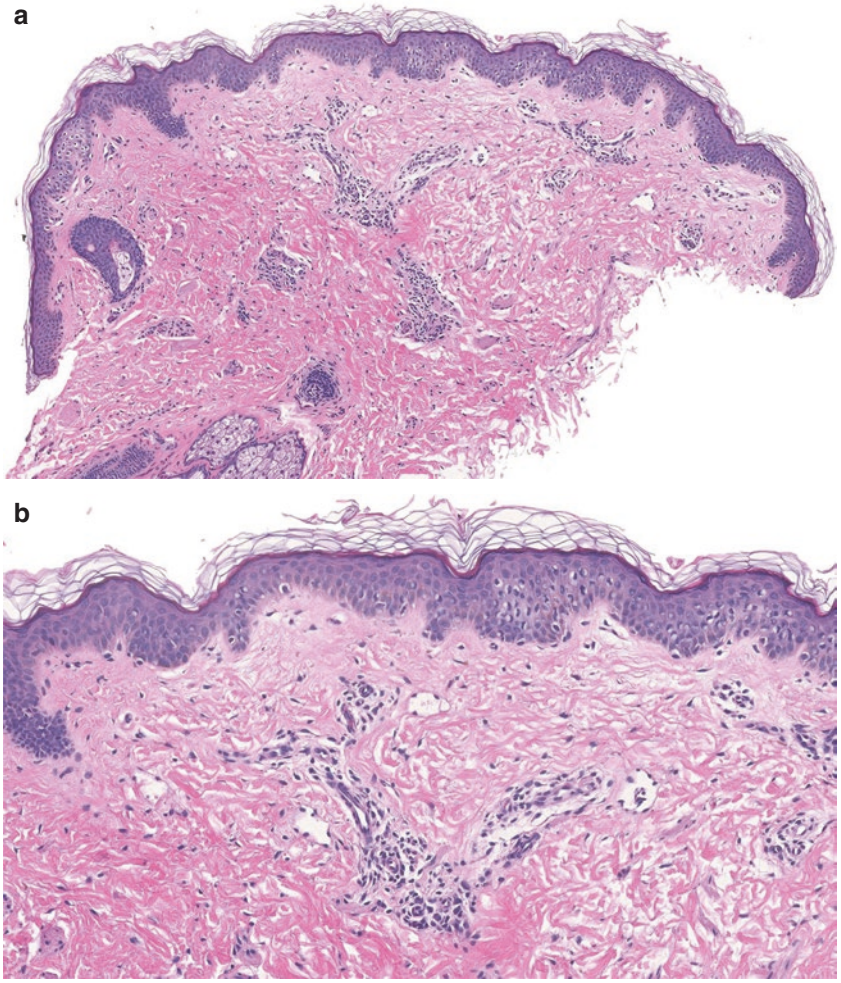

Fig. 1.17 Café au lait macule. Epidermal shows normal architecture with scattered basal hyperpigmentation (**a**). Note the focal and subtle melanocytic hyperplasia (**b**)

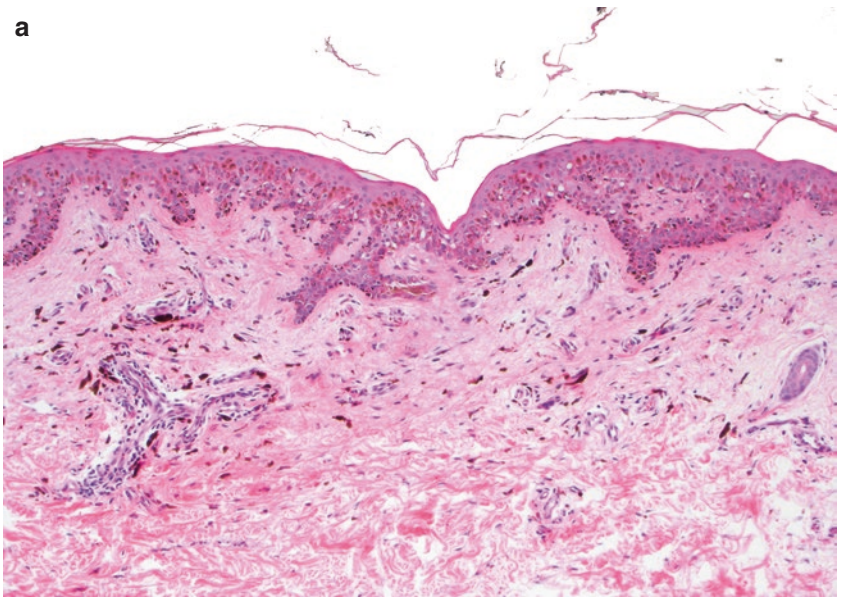

Fig. 1.18 Café au lait macule. Some examples show increased number of melanosomes (**a**).

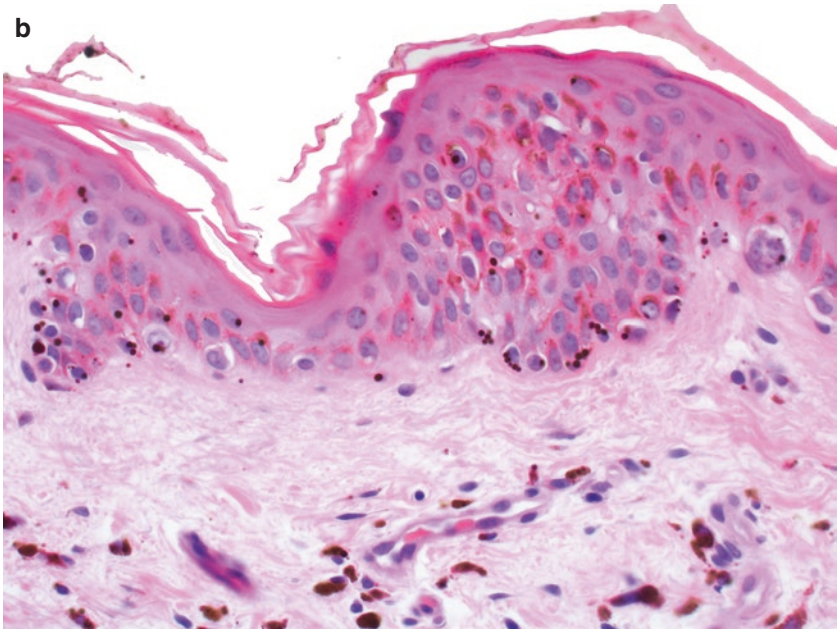

Fig. 1.18 (continued) High power showing the giant melanosomes (**b**)

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Dermal Melanocytoses

2

Nevus of Ota and Ito

Clinical Features

Nevus of Ota: Also known as oculodermal melanocytosis or nevus fuscoceruleus opththalmomaxillaris, it presents as a diffuse, slightly speckled, unilateral macular lesion of bluish to dark-brown pigmentation of the skin in the area of the ophthalmic and maxillary divisions of the trigeminal nerve. The conjunctiva and sclera can be involved in more than half of the cases and occasionally the mucous membranes of the nose, ear, and oral cavity. Nevus of Ota can be bilateral in up to 10 % of cases [1, 2]. Other affected areas include the forehead, the temple, the cheeks, and the nose. The cutaneous and mucosal discolorations in nevus of Ota are present throughout life and do not usually fade away with time; however, color can vary in intensity. These lesions are most commonly seen in Asians and in darker-skinned individuals and are uncommon in white patients. Most nevi of Ota present at birth (60 % of cases) and the second peak is seen during adolescence with a female predominance (4:1 ratio). Rare acquired cases with adult onset are sometimes considered as a separate disease, such as Hori nevus (acquired bilateral nevus of Ota-like facial macules). Malignant degeneration in a nevus of Ota is extremely rare [3–6]. The choroid is the most common site affected, but the uvea, iris, and optical tract can also be involved. Although nevus of Ota is much more prevalent in Asians, malignant change appears to be much more common in white patients [5, 6]. Nevus of Ota can be associated with meningeal melanocytosis, Sturge-Weber disease, Klippel-Trenaunay syndrome, and spinocerebellar degeneration.

Nevus of Ito: Also known as nevus fuscoceruleus acromiodeltoideus, it is a very rare dermal melanocytosis that clinically is characterized by heavy macular pigmentation in the distribution of the posterior supraclavicular and lateral brachial cutaneous nerves (shoulders and upper back). Nevus of Ito differs from the nevus of Ota only by its area of distribution and lower incidence. Clinically, it presents as a subtle, light gray, mottled, macular pigmentation. Similar to nevus of Ota, lesions do not regress with time. These lesions more commonly appear in the first to second decades of life, but are possibly congenital in nature. Nevus of Ito often occurs in association with nevus of Ota in almost half of patients [7]. Also, rarely can melanoma develop [8].

"Mongolian" Blue Spot

Clinical Features

"Mongolian" spot was the old terminology used for blue-gray macules and patches frequently located on the sacral region (including gluteal and lumbar regions). These lesions should be named "blue nevi" or "dermal melanocytoma." Some lesions can be occasionally found at extra-sacral locations, including posterior thighs, legs, thorax, back, and shoulders [9]. Most lesions are a few centimeters in diameter (3–5 cm), but in some patients, they are large enough to cover the entire lower back and buttocks (>10 cm in diameter). They usually are present at birth or soon afterward and are most commonly seen in Japanese, Chinese, and dark-skinned individuals (more common in males). Most lesions undergo spontaneous

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regression during infancy or childhood and generally disappear by puberty (in contrast with nevus of Ito and Ota, which do not regress). Persistence of the lesion into adulthood is rare and has been associated primarily with extrasacral locations. These lesions have not been associated with melanoma. They can be a marker of an underlying storage disease, such as Hurler syndrome, GM1 type I gangliosidosis, and mucolipidosis type I [10–12]. The coexistence of widespread capillary malformations (nevus flammeus) along with this type of blue nevi, nevus spilus, nevus of Ota, and nevus anemicus is referred as phacomatosis pigmentovascularis [13].

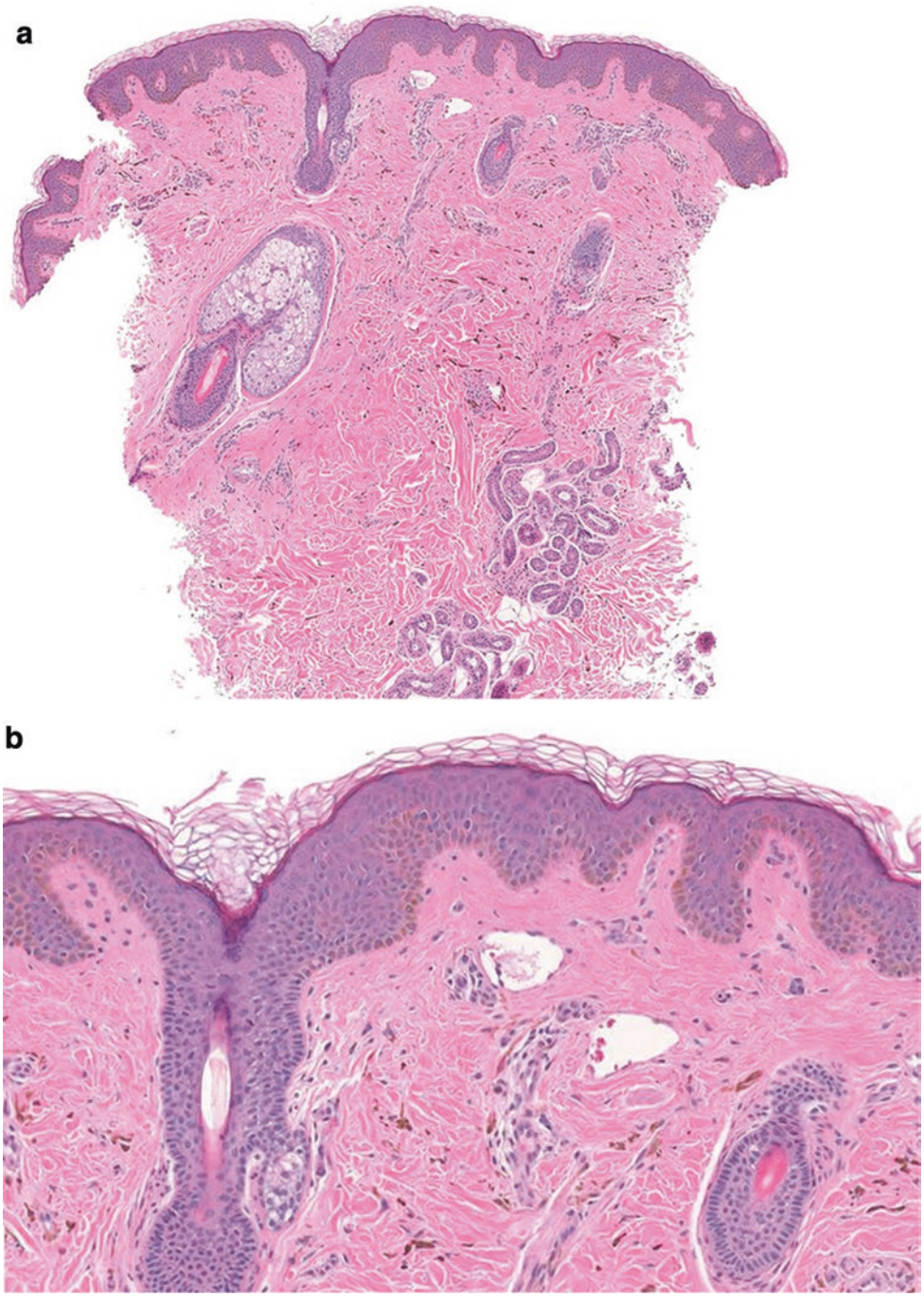

Fig. 2.1 Nevus of Ota. Note the very subtle population of dendritic melanocytes in superficial and reticular dermis depicted in this image (**a**). These changes can be overlooked easily if adequate clinical information is not provided (**b**).

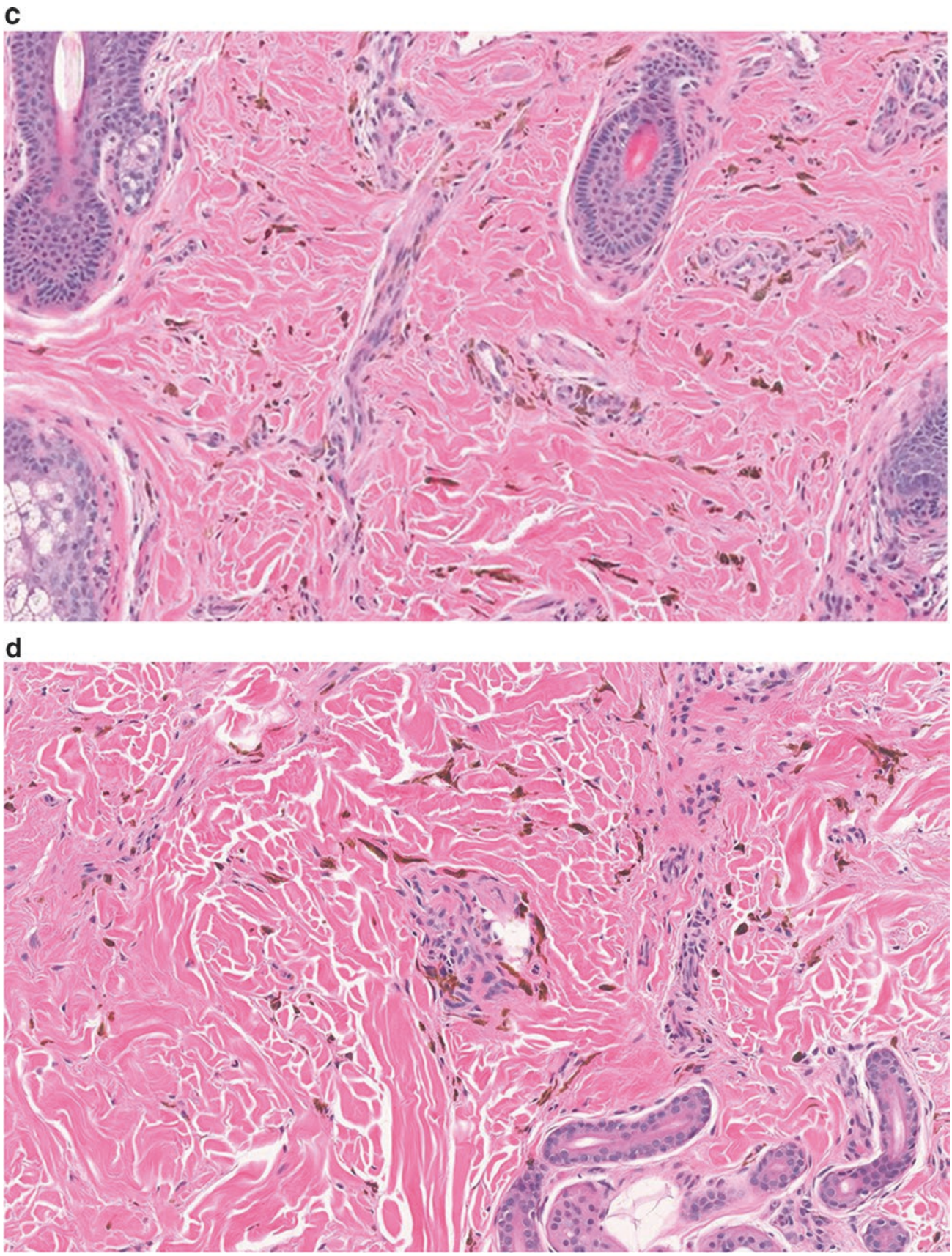

Fig. 2.1 (continued) Higher magnification shows the elongated and pigmented dendritic melanocytes (**c, d**)

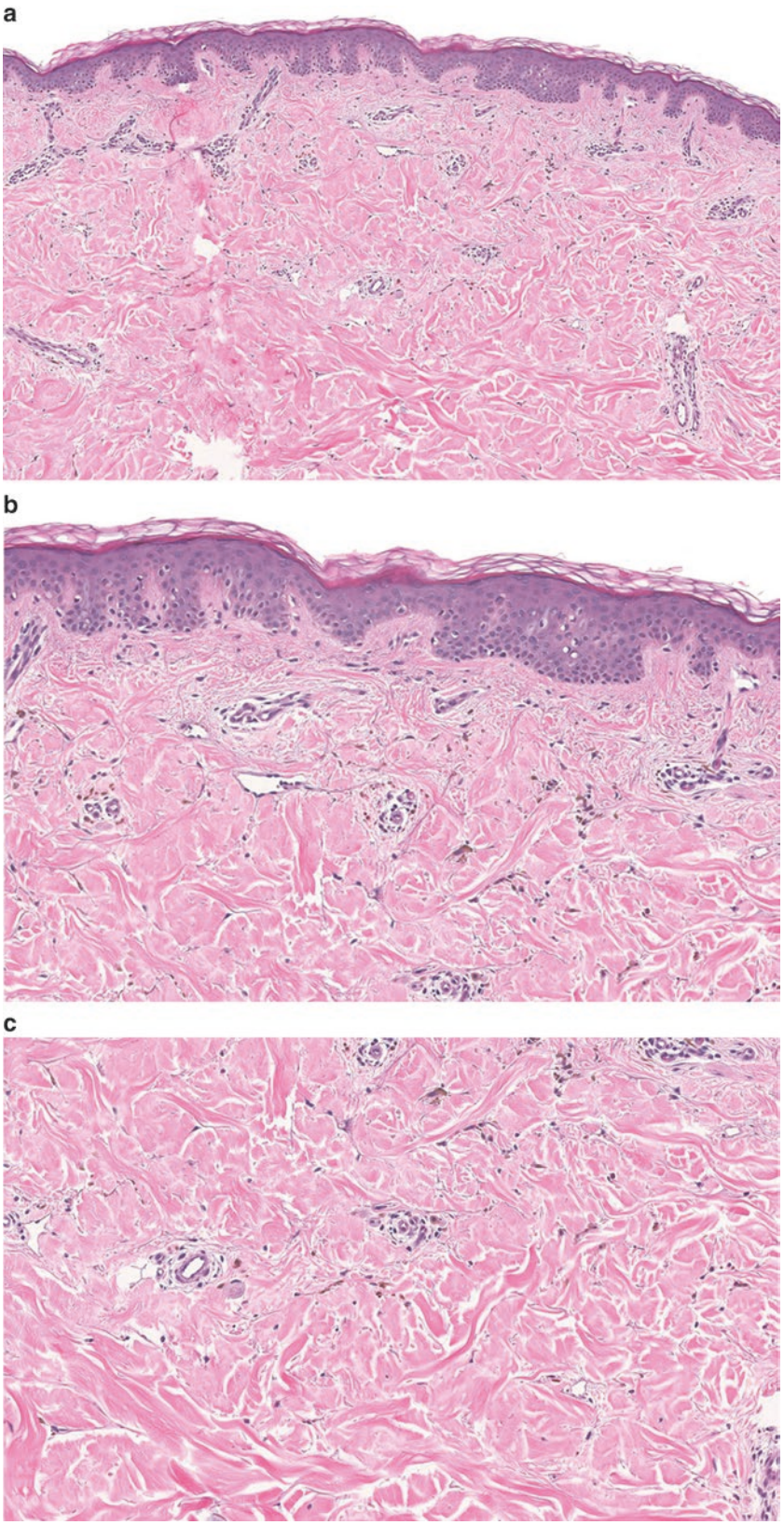

Fig. 2.2 Mongolian spot. The lesion illustrates the rare dendritic melanocytes in the dermis (very scarce) (**a**). Higher magnification showing the rare dendritic cells interspersed among the collagen bundles (**b**, **c**)

Nevus of Sun and Nevus of Hori

Clinical Features

Nevus of Sun, also known as nevus fuscoceruleus zygomaticus, is a rare melanocytosis that represents an acquired form of nevus of Ota. Nevus of Hori is a rare acquired bilateral nevus similar to a nevus of Ota. Nevus of Sun has a similar distribution as nevus of Ota; however it is more commonly located in the zygomatic branch area. Nevus of Sun, contrary to nevus of Ota, never involves the eye and never is congenital. Hori nevus presents as bilateral and symmetrical bluish macules in the malar region of the cheek but also can affect the forehead, temples, and nose. Both of these melanocytoses exclusively affect Asians and there is a predilection for females [14]. Malignant degeneration has not been described.

Histopathology

The histologic changes in these melanocytoses are very similar. In the papillary and upper reticular dermis, there is a band-like distribution of isolated, pigmented, spindled, bipolar, or dendritic melanocytes surrounded by fibrous sheaths. These pigmented dendritic cells are very similar in morphology to those observed in blue nevi. Thus they have oval nuclei with fine and evenly distributed chromatin with inconspicuous nucleoli. The cytoplasm has characteristic long and thin dendrites speckled with fine granules of melanin. These spindle cells are evenly distributed throughout the dermis with occasional crowding around adnexal and/or neurovascular structures. In some instances these cells can involve the deep dermis and subcutaneous fat. Dermal melanophages associated with dendritic cells are uncommon (as opposed to blue nevi). In most cases, the melanocytes are separated from each other without formation of cellular aggregates; however, rarely can they conglomerate in a pattern similar to a blue nevus. In some occasions these melanocytes can be scarce and thus special stains (Fontana Masson) can be of help.

In cases of nevus of Ota and Ito, the melanocytes are commonly located in superficial dermis in contrast to other melanocytoses. Also, in nevus of Ota and Ito, there is epidermal hyperpigmentation and normal to focally increased numbers of intraepidermal melanocytes without forming a junctional component.

Differential Diagnosis

Sometimes these dermal melanocytoses can show inconspicuous histology; thus, if the clinical picture of a pigmented lesion is unknown to the pathologist, the histopathology can be easily overlooked. The clinical presentation is more obvious than the histological one, and when in doubt, immunostains for melanocytic antigens (MART-1, gp100 [HMB-45]) or special stains (Fontana Masson) can be very helpful to highlight the dendritic melanocytes. In addition, in cases where the lesions are aberrantly located, the histology can be missed and sometimes confused with normal skin. Also, cases of exogenous or endogenous dermal hyperpigmentation (from hemosiderin deposition) can look very similar to dermal melanocytoses; however, if one looks closely, the hemosiderin pigmentation should be located within macrophages and not within melanocytes. In cases in which the distinction is problematic, special stains can be handy as hemosiderin will be highlighted with iron stains (Perl stains), such as in minocyclin pigmentation.

Blue Nevus

Clinical Features

Blue nevus is a common benign dermal dendritic melanocytic proliferation that was first described by Jadassohn-Tièche in 1906. These nevi most commonly arise in children and young adults (more common in females) but can occur at any age or can present as congenital lesions. Common locations are the dorsal aspects of the hands and feet (most common location), head and neck, and trunk and buttocks [15]. Rarely have they been described in extracutaneous locations, such as the subungual region, the orbit and conjunctiva, oral cavity, sinonasal mucosa, meninges, and internal organs [16–20]. When they present as congenital lesions, they are usually found on the scalp; however, other sites can also be involved such as the thorax and distal extremities [21]. Many different clinical forms of blue nevi have been reported; the most frequent consists of a well-demarcated, slightly raised papule, often <1 cm in diameter, ranging in color from blue/gray to black. Blue nevi more commonly affect dark-skinned adolescent or adult females. Lesions usually remain static throughout life but may undergo change in color and gradual involution. Congenital lesions present as large nodules that involve the deep dermis and in some occasions the subcutaneous fat; these lesions remain stable until adolescence then gradually enlarge.

Rarely may multiple blue nevi occur in a familial setting. They may be associated with LAMB syndrome (lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi), NAME syndrome (atrial myxomas, myxoid neurofibromas, ephelides), or present sporadically in a diffuse distribution or grouped in a circumscribed anatomic area (so-called agminated blue nevi) [22, 23].

Blue nevi may rarely involve the lymph nodes, usually in the capsular region, sometimes with an extension into perinodal adipose tissue. Their distinction from metastatic

melanoma may be problematic, particularly in sentinel lymph node specimens [24, 25]. In contrast with metastatic melanoma, nodal blue nevi are located in the fibrous capsule of the lymph node and are composed of a combination of subtle elongated spindle cells with dendritic processes and pigment-laden melanophages and histologically resemble their cutaneous counterparts [26, 27].

Histopathology

Blue nevi are composed by a somewhat symmetrical upper and/or mid-dermal proliferation of bipolar, spindle-shaped cells, sometimes arranged in short fascicles. The melanocytes show elongated and slender dendritic processes and contain variable amounts of melanin pigment in their cytoplasm. Their nuclei are small, elongated, and hyperchromatic. Cellular atypia is minimal and mitotic figures are almost never seen. Most blue nevi are relatively small and located within the superficial dermis; however, they may extend deep into reticular dermis along adnexal structures, arrector pili muscle, and/or neurovascular structures (~perineural invasion, an occasional pitfall in the interpretation of this lesions). These dendritic melanocytes are frequently arranged around hair follicles in a densely cellular sheath of cells and often separated from the follicular epithelium by a thin rim of collagen. The involved hair follicles are frequently dysmorphic and undergo atrophy and in some cases may be entirely replaced by bundles of pigmented melanocytes. The dendritic melanocytes are associated with some degree of stromal fibroplasia, sclerosis, and scattered melanophages; however, the neoplastic cells do not alter the normal dermal architecture and distribution of skin adnexa. Not uncommonly, the dendritic cells seen in blue nevi are intermixed with oval and spindle melanocytes reminiscent of type B or type C (neurotized) melanocytes. The maturation gradient in blue nevi is absent since all the neoplastic cells within the lesion are similar; thus, there is no zoning/maturation pattern. In most cases, there is a grenz zone of uninvolved papillary dermis that separate the lesion from the overlying epidermis. The overlying epidermis lacks a junctional component, unless when blue nevi are part of a combined nevus (see below) [28]. Also, it is not unusual to observe hyperpigmentation of the basal layer of the epidermis and mild melanocytic hyperplasia along the epidermis and the follicular infundibulum. Some lesions may show intermediate histologic features between a nevus with congenital pattern and common (or cellular) blue nevus; such lesions can be designated as combined nevus with intradermal nevus with congenital pattern and blue nevus.

While most of blue nevi are stable lesions, over time the dendritic and spindle/oval melanocytes tend to decrease in number and the collagen production is more pronounced. In more advanced stages, the dendritic cells are localized in the periphery of the lesion, and in the center the oval cells are intermixed with thickened collagen bundles. In the final stages of blue nevi, the lesion may be almost entirely replaced by dense compact collagen with melanin interspersed between the collagen bundles, either lying free or within macrophages (sclerotic blue nevi).

Differential Diagnosis

Blue nevi depicting classical histomorphological features are not usually difficult to diagnose and most of the time are accurately interpreted. However, certain histologic variants such as amelanotic (hypopigmented) blue nevi may appear similar to other spindle cell proliferations, such as dermatofibroma (see below). Immunohistochemistry usually clarifies the diagnosis in morphologically equivocal lesions. Sclerosing blue nevi may resemble desmoplastic melanoma or other dermal spindle cell proliferations, but can be distinguished by its negligible cytologic atypia and the characteristically diffuse expression of HMB45 antigen and usually S-100p expression, which is different from desmoplastic melanoma (see below) [29–31]. Another important differential diagnosis is a subtype of metastatic melanoma to the skin that mimics blue nevus due to the dendritic morphology of the tumor cells. However, this rare form of metastatic melanoma typically displays severe cytologic atypia and mitotic figures are easily found [32].

Immunohistochemistry and Molecular Findings

By immunohistochemistry the cells of blue nevi are positive for S100p, MART-1, and HMB-45 antigen; however, the intensity of the labeling is highly variable. Many nevi and melanomas show oncogenic mutations in signaling components of the mitogen-activated protein kinase pathway, in particular BRAF and NRAS. However, blue nevi less frequently exhibit mutations in these pathways, with BRAF mutations reported in 12 %, NRAS in 11 %, GNA11 in 7 %, and KRAS in 11 % of lesions [33, 34]. Recent studies reveal an increased frequency of somatic mutations of heterotrimeric G-protein α subunit (GNAQ) in up to 83 % of blue nevi. In addition, GNAQ or GNA11 mutations have been found in uveal melanomas (46 %) as well as in blue nevus-like melanoma (50 %) [35]. These findings support the interpretation that blue nevi and variants represent a distinct type of melanocytic neoplasms.

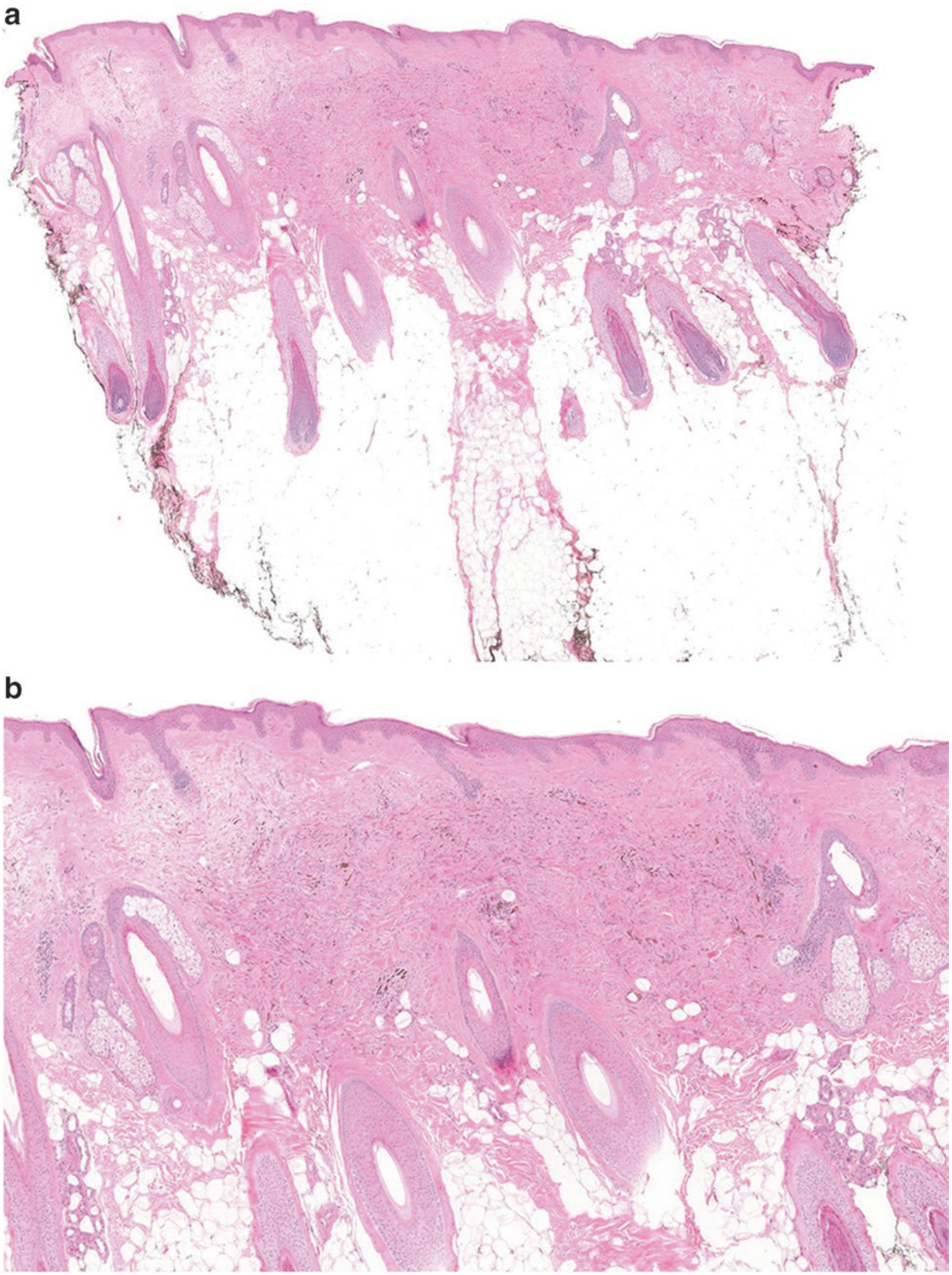

Fig. 2.3 Conventional blue nevus. The lesion depicts a small and symmetric proliferation of dendritic melanocytes occupying reticular dermis (**a**). Dendritic melanocytes arranged around hair follicles and the overlying epidermis lack a junctional component (**b**).

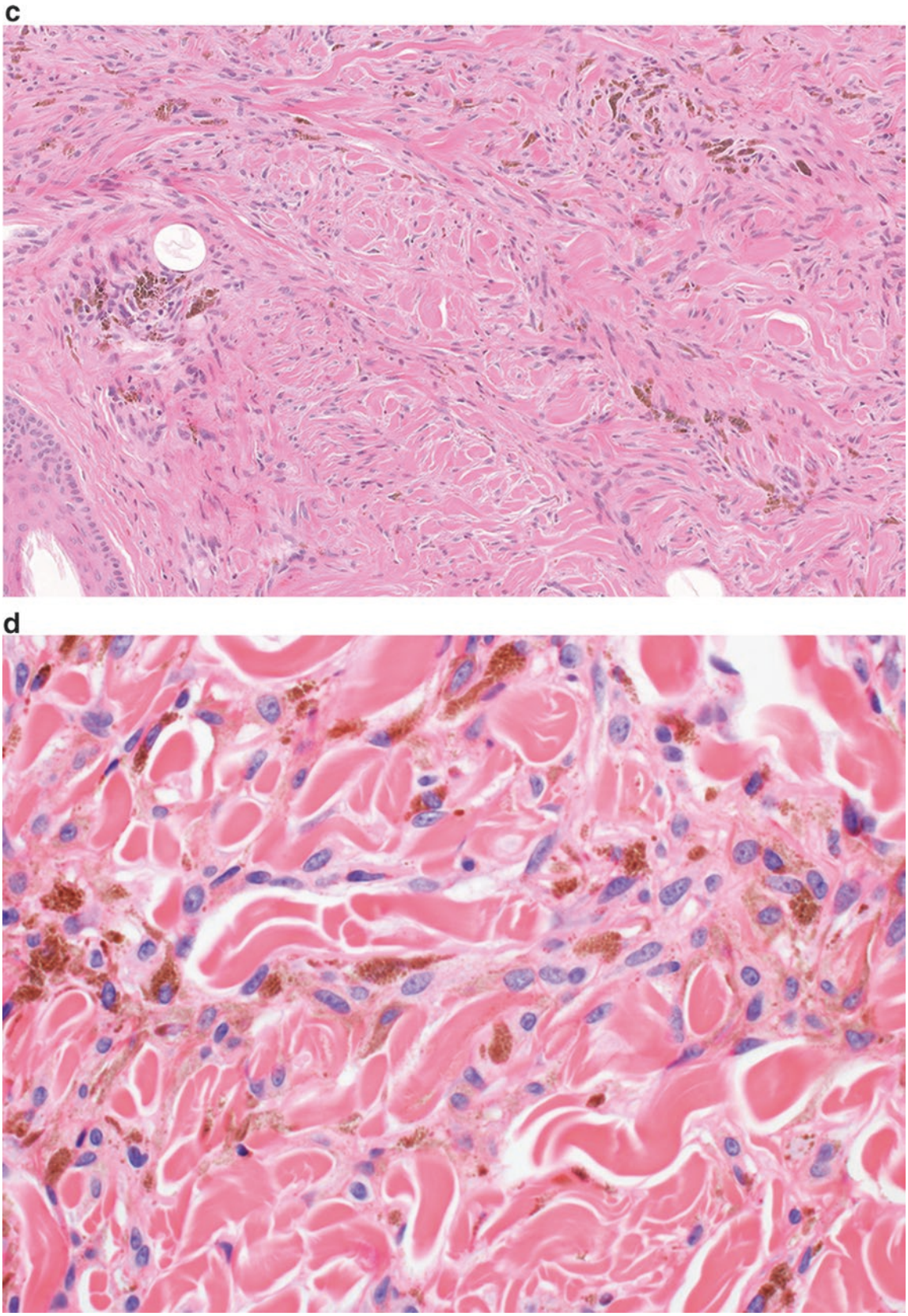

Fig. 2.3 (continued) Note the increased number of dendritic melanocytes interspersed among the thickened collagen fibers (**c**). Higher magnification shows the bipolar melanocytes with elongated dendritic processes containing cytoplasmic melanin pigment, along with scattered melanophages (**d**)

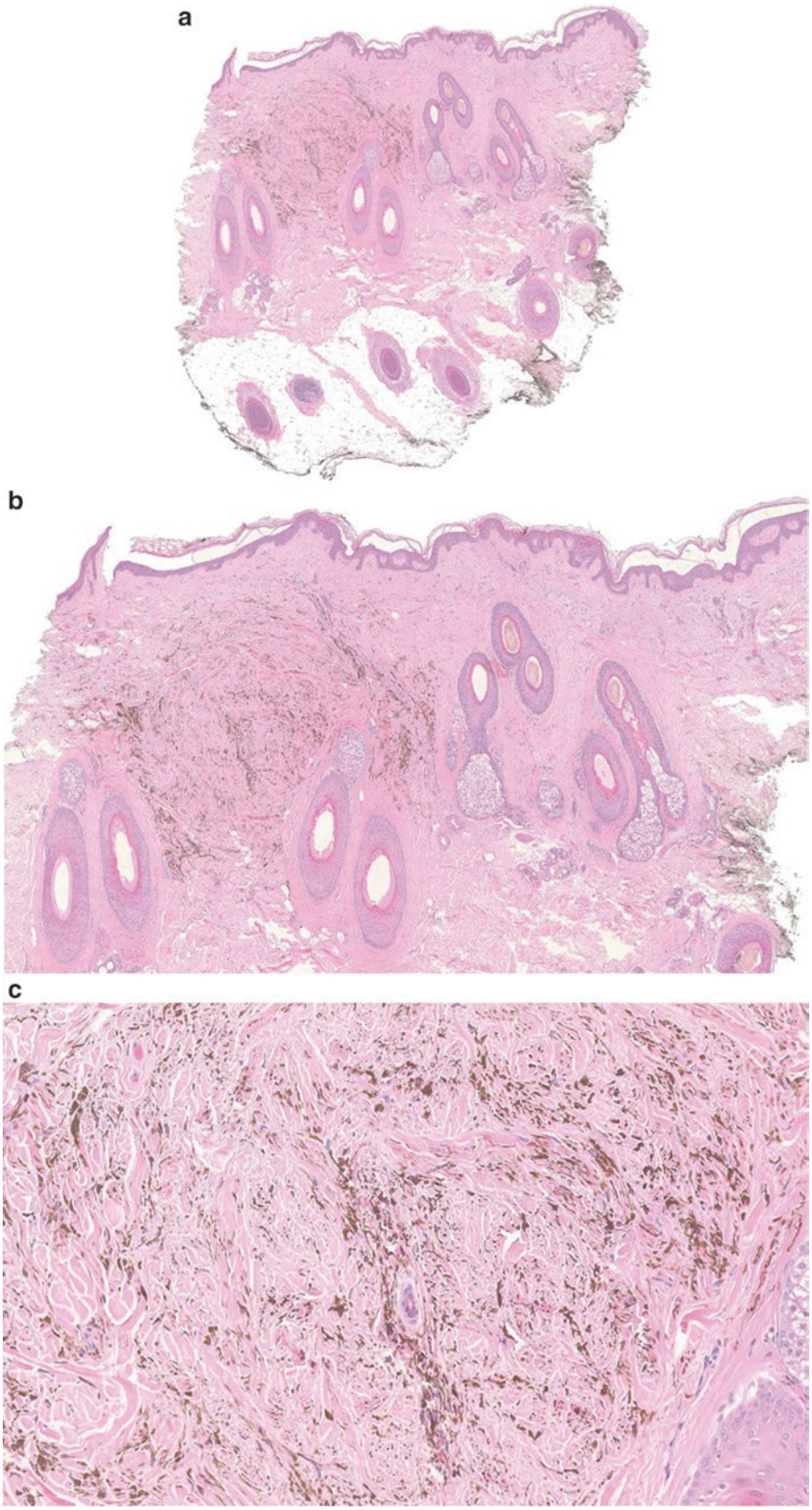

Fig. 2.4 Conventional blue nevus. This image depicts a small pigmented papule in the dermis with banal appearance. Note the abundant and evenly distributed pigment in the lesion (**a**). Note the propensity of dendritic cells to surround hair follicles (**b**). The cells are elongated and the cytological details have been partly obscured by the abundant pigment (**c**).

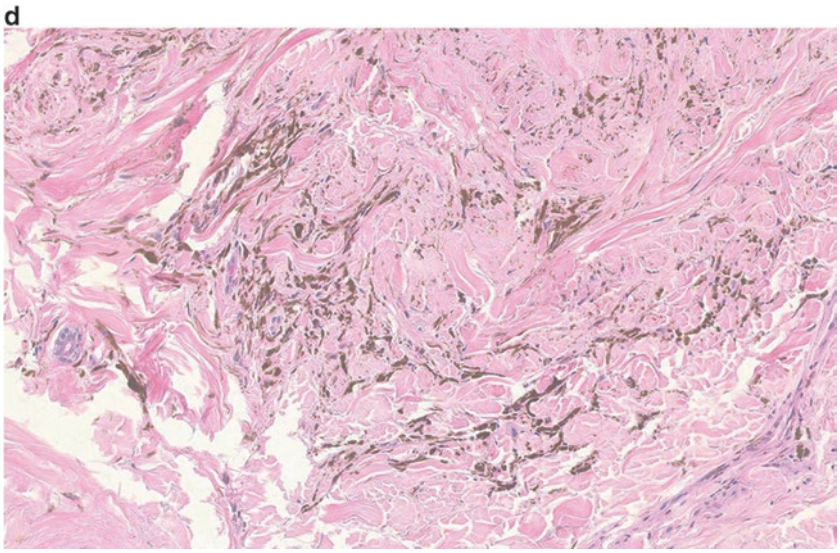

Fig. 2.4 (continued) Higher magnification displays the bipolar dendritic melanocytes associated with stromal fibroplasia (**d**)

Histologic Variants of Blue Nevus

Combined Blue Nevus

Combined nevi are composed of more than one nevus type in a single lesion. They may be composed of any combination of common acquired nevi, blue nevus variants, or Spitz nevi. Some authors have proposed the term "nevus with phenotypic heterogeneity" for this group of melanocytic lesions. However, the terminology has not been widely accepted, possibly because the term "phenotypic heterogeneity" may instigate clinical concern about the nature of the lesion. The most common combination is a compound nevus with congenital pattern along with a group of dendritic melanocytes in the center (blue nevus). This focus of blue nevus can be very small and composed only of few dendritic melanocytes and melanophages (in some occasions can be large and occupy most of the lesion).

Compound Blue Nevus

This is a rare variant of blue nevus defined by the presence of an intraepidermal component. It shows all the features of a common blue nevus but with an obvious junctional component. The lesions are symmetrical with slight epidermal hyperplasia and basal layer hyperpigmentation along with a junctional component of heavily pigmented dendritic melanocytes arranged as solitary units at the dermal epidermal junction. In rare occasions, these dendritic melanocytes can reach the upper layers of epidermis. Junctional nests are absent. The dermal component shows pigmented dendritic melanocytes arranged singly and in fascicles, similar to classic blue nevus [28, 36, 37]. In some cases, the dermal component can be heavily pigmented and so rich in melanophages that the cellular details of the melanocytes are barely distinguishable. Removal of pigment with special techniques such as potassium permanganate helps to identify the cellular component.

Amelanotic Blue Nevus

It may be considered either a variant of or be the same as desmoplastic nevus (see below). Clinically, this variant is usually either white or skin colored. Histologically, it shows a poorly defined, dermal proliferation of spindle cells associated with variable desmoplastic stroma (very similar to the classic variant) with thick collagen bundles in a scar-like pattern. In contrast to classic blue nevi, they are characterized by absent or minimal melanin pigment within the spindle melanocytic cells. When pigment is present, it is usually located at the edges of the lesion. The tumor cells have indistinct eosinophilic cytoplasm and fusiform hyperchromatic nuclei often containing small nucleoli. Intranuclear cytoplasmic pseudoinclusions are occasionally present, and mitotic figures are exceptional. The diagnosis can be challenging as lesions can mimic a scar, neurofibroma, dermatofibroma, or even desmoplastic melanoma. In difficult cases, immunohistochemistry can be of aid as the cells usually express HMB-45 antigen. S100 and MART-1 are also expressed.

Desmoplastic (Sclerosing) Blue Nevus

This variant of blue nevus is very important to be aware of as in some instances it may mimic a desmoplastic melanoma. Histologically, it shows features of classic blue nevi but associated with marked dermal fibrosis and sclerosis. Diagnostic clues include the presence of a symmetrical and inverted wedge-shaped configuration of the lesion and extension into deep dermis along adnexal structures and neurovascular bundles. The diagnosis can be established by the proper identification of dermal dendritic melanocytes; however, in some cases the lesions are quite paucicellular which makes difficult to identify them appropriately. The dendritic cells tend to be more abundant and easier to identify at the periphery of the lesion. As with other nevi, there may be neurotropism, but, in contrast with desmoplastic melanoma, there is no involvement of the endoneurium. This desmoplastic variant may indeed represent the later stages of some blue nevi. In some cases, immunohistochemistry is required to confirm the melanocytic cell population (S100p, MART-1, and HMB-45).

The differential diagnosis of this variant is primarily with desmoplastic melanoma. The distinction can be achieved in adequate excisional biopsies that permit evaluation of all the factors relevant for the diagnosis. However, both lesions will display spindled melanocytes and desmoplastic stroma. Diagnostic clues favoring desmoplastic melanoma include infiltrative, asymmetric silhouette, amelanotic appearance, obvious cytologic atypia (prominent nucleoli, hyperchromasia, and pleomorphism), and lymphoid aggregates. If the desmoplastic dermal melanocytic proliferation is accompanied by obvious melanoma in situ, the diagnosis is straightforward; however, in one third of desmoplastic melanomas, there is no in situ component detectable within the epidermis. Desmoplastic melanoma only rarely shows increased mitotic activity, but this is never seen in desmoplastic blue nevus. Intraneural invasion is present in desmoplastic melanoma and absent in sclerosing blue nevi. Ancillary immunohistochemistry studies have been used for problematic sclerosing melanocytic proliferations, such as the use of Ki-67, HMB-45, and MART-1. Desmoplastic melanoma tends to have a higher Ki-67 labeling index than melanocytic nevus, patchy HMB-45 labeling, and minimal expression of MART-1, while sclerosing blue nevi usually show a low cell proliferation index with Ki-67 and diffuse labeling with HMB-45 and anti-MART-1 [31, 38]. Also, it has been proposed that immunohistochemical staining for p16 may be helpful in such distinction, as the majority of desmoplastic melanomas lack p16 expression; however, in our experience desmoplastic melanoma commonly expresses p16 at least focally; thus it is not a valid marker for such distinction [39]. Occasional cases of desmoplastic melanoma may have a very low Ki-67 labeling index or may be immunoreactive for MART-1; thus, these markers should be used with caution. A recent study using a four-probe fluorescence in situ hybridization (FISH) assay targeting RREB1, MYB, Cep6, and CCND1 showed that 47 % of desmoplastic melanomas had detectable aberrations in the probe sites by FISH, while none of sclerosing melanocytic nevi (including sclerosing blue nevi) showed any level of chromosomal aberrations that met FISH criteria for melanoma [40]. This study concluded that a positive FISH test strongly supports the diagnosis of melanoma in this context; however, in this setting a negative FISH test was of limited diagnostic value.

Blue Nevus with Atypical Cells

In certain occasions common blue nevi can show cellular atypia. This cytologic atypia is usually focal and not extensive but can be striking as cells may show ample cytoplasm with large hyperchromatic nuclei and conspicuous nucleoli (similar to the cellular atypia noted in benign Spitz nevi). However, these lesions are small in size, symmetric, and wedge shaped and lack mitotic figures.

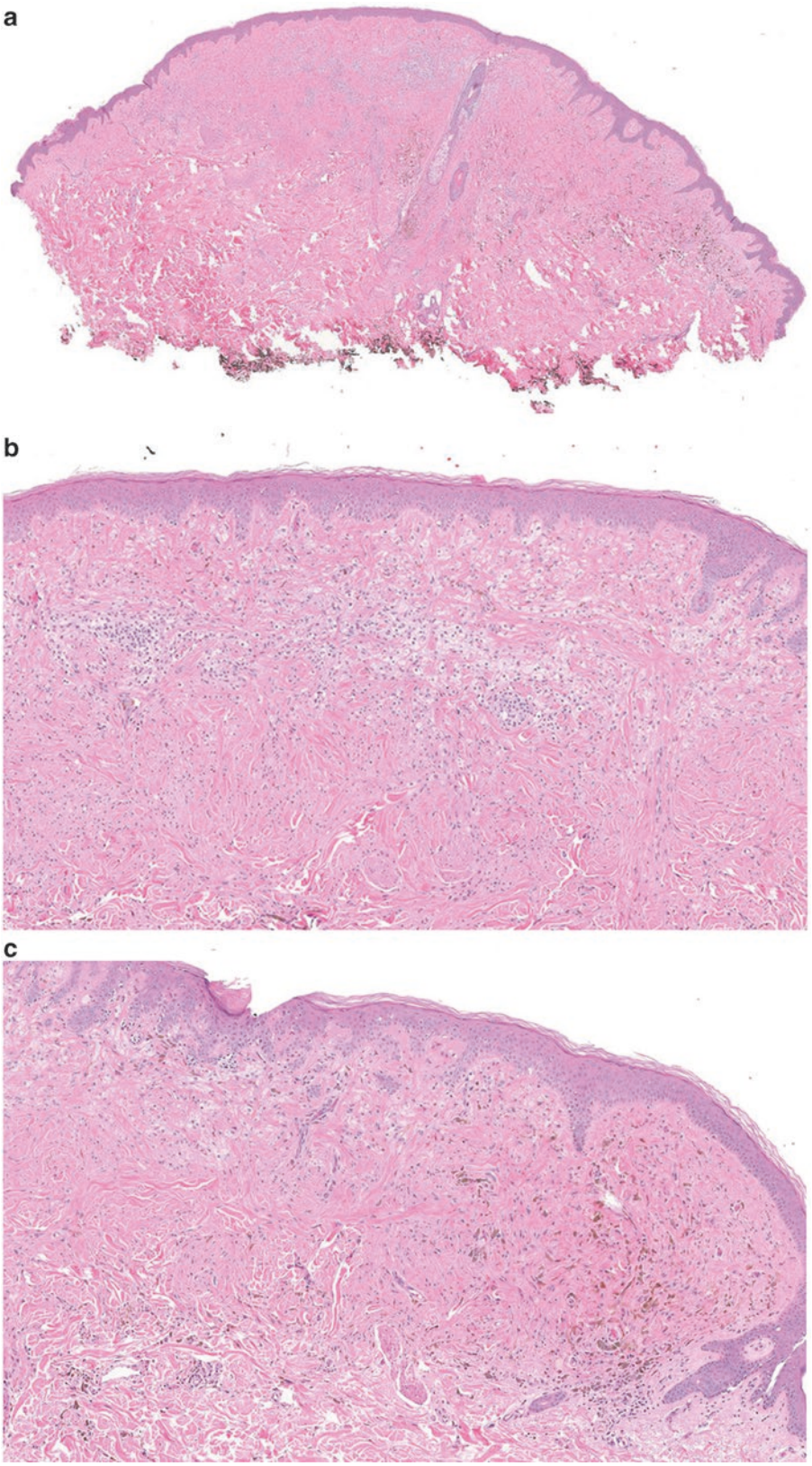

Fig. 2.5 Combined blue nevus. The pigmented lesion is located in the arm of a 32-year-old male. This lesion is composed of two components; there is an intradermal nevus in the center of the lesion and on the sides the lesion clearly depicts a blue cell component (**a**). The center of the lesion shows the intradermal component. Note the balloon cell changes in some of the cells (**b**). Note the blue cell component clearly illustrated at the lateral side of the lesion (**c**)

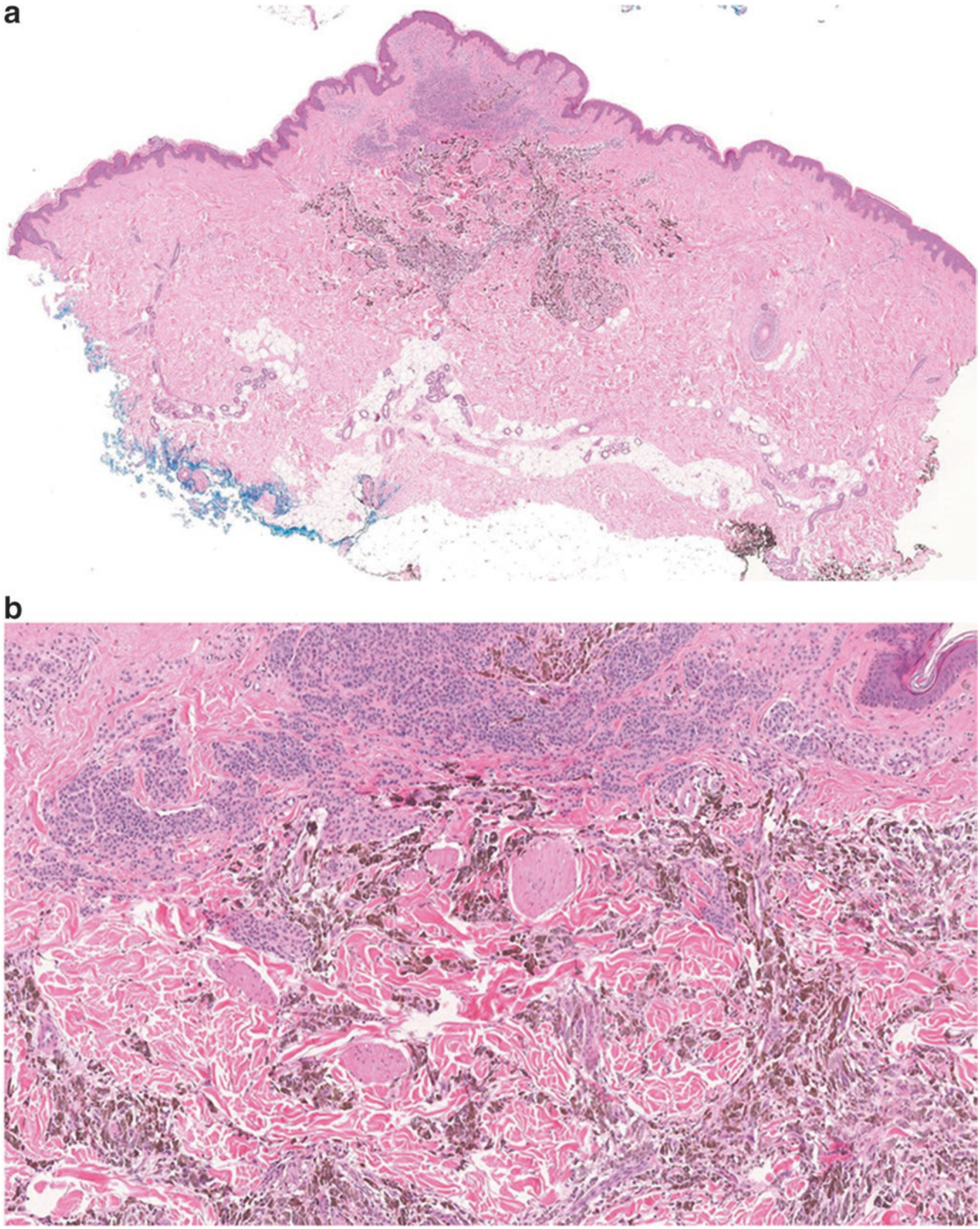

Fig. 2.6 Combined blue nevus. The lesion is located in the buttock of a 65-year-old male. The blue nevus component is located at the base of the lesion and above it is the intradermal component (**a**). The lesion displays aggregates of dendritic melanocytes at the base of the lesion. Note the absence of atypia and mitotic figures (**b**).

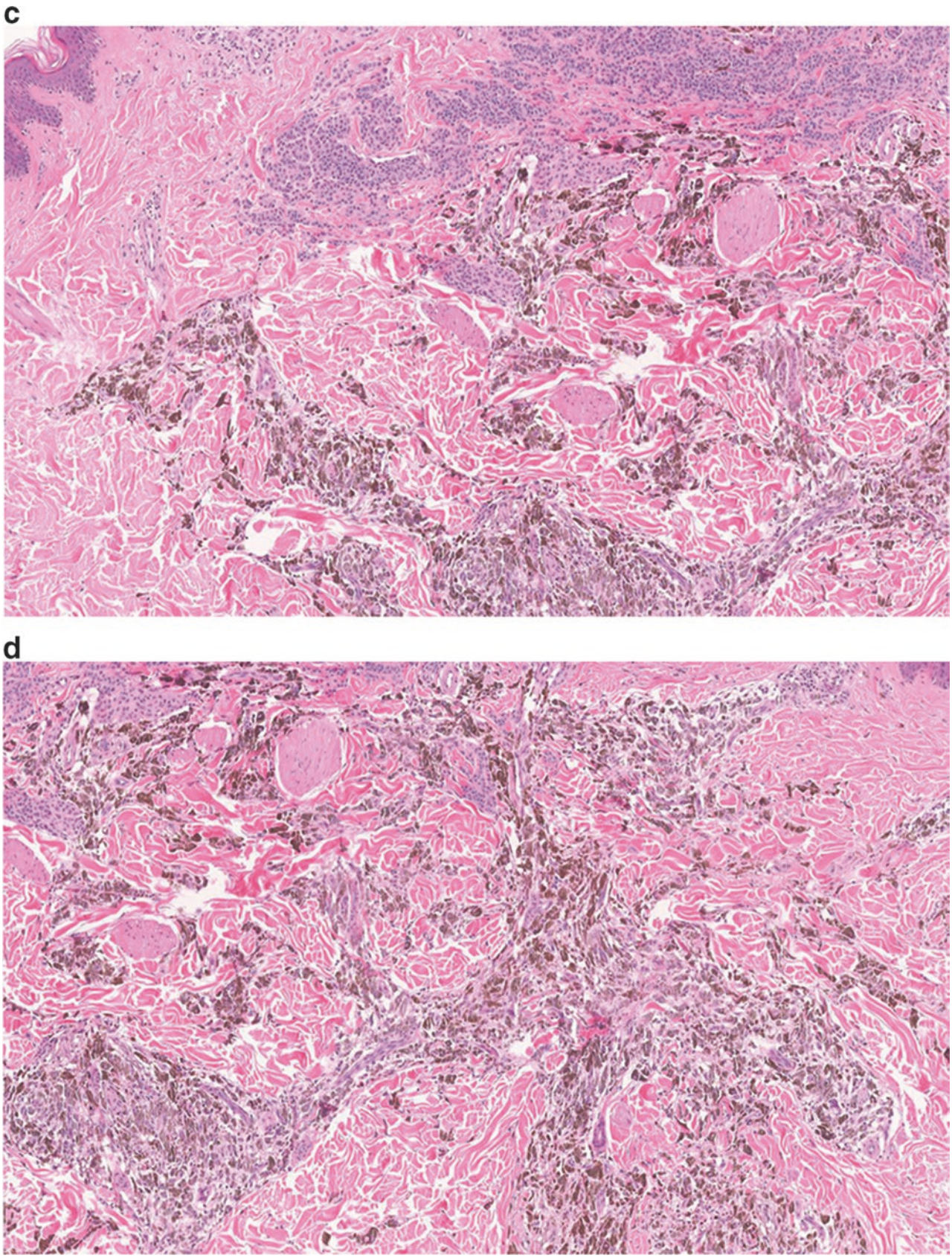

Fig. 2.6 (continued) Observe the aggregates of dendritic melanocytes in the dermis and focally around the erector pili muscle (**c**). Higher magnification showing marked hyperpigmentation (*blue color* clinically) (**d**)

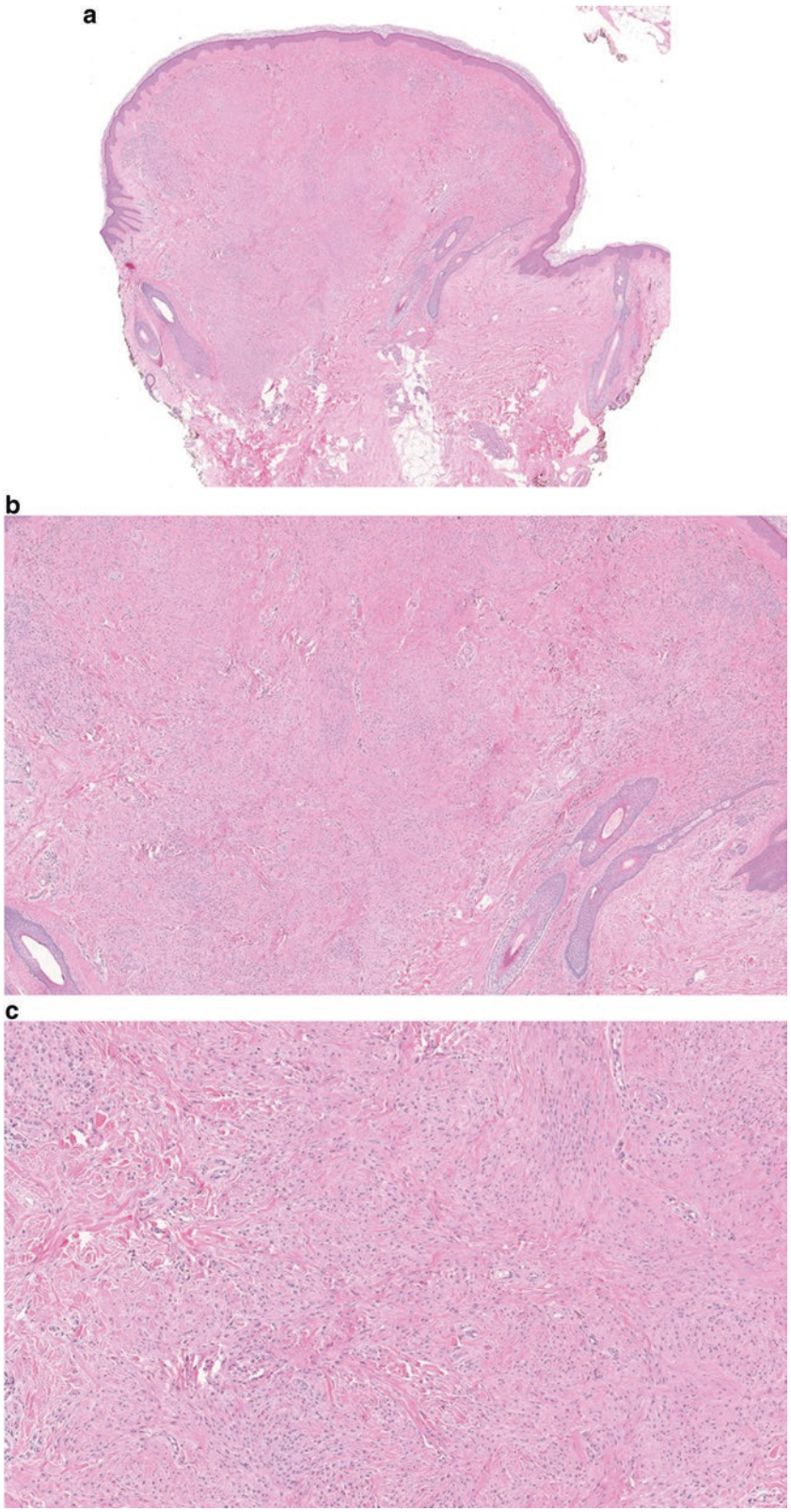

Fig. 2.7 Combined blue nevus. This image shows a polypoid lesion with a clear amelanotic blue cell component in the background and admixed with an intradermal nevus (**a**). The lesion depicts normal maturation toward the base and lack of cytologic atypia (**b**). The lesion shows dendritic melanocytes devoid of pigment (**c**)

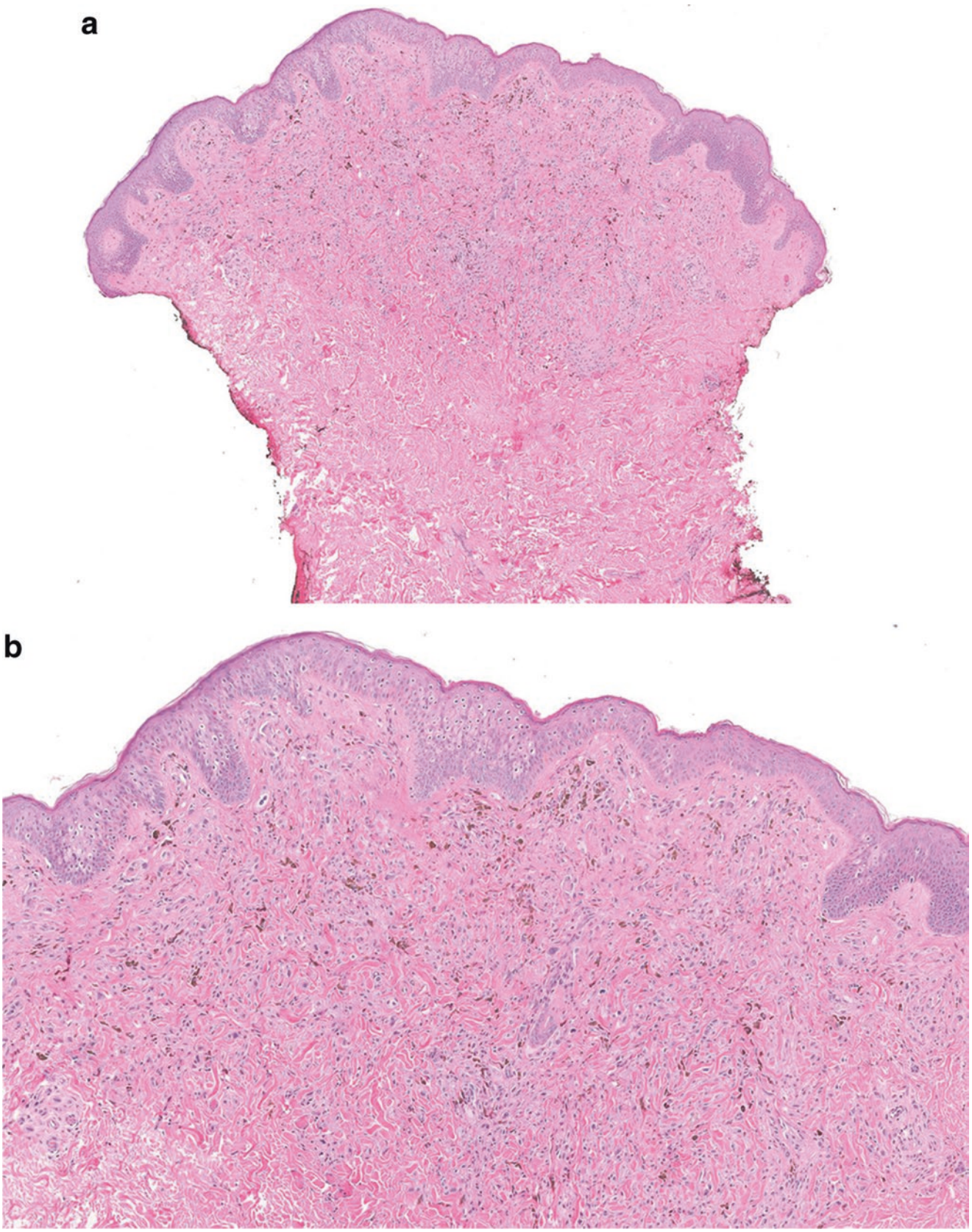

Fig. 2.8 Combined blue nevus. This lesion shows blue nevus admixed with many spitzoid melanocytes (**a**). The spitzoid component is composed of small- and medium-sized epithelioid melanocytes admixed with many scattered pigmented dendritic melanocytes (**b**).

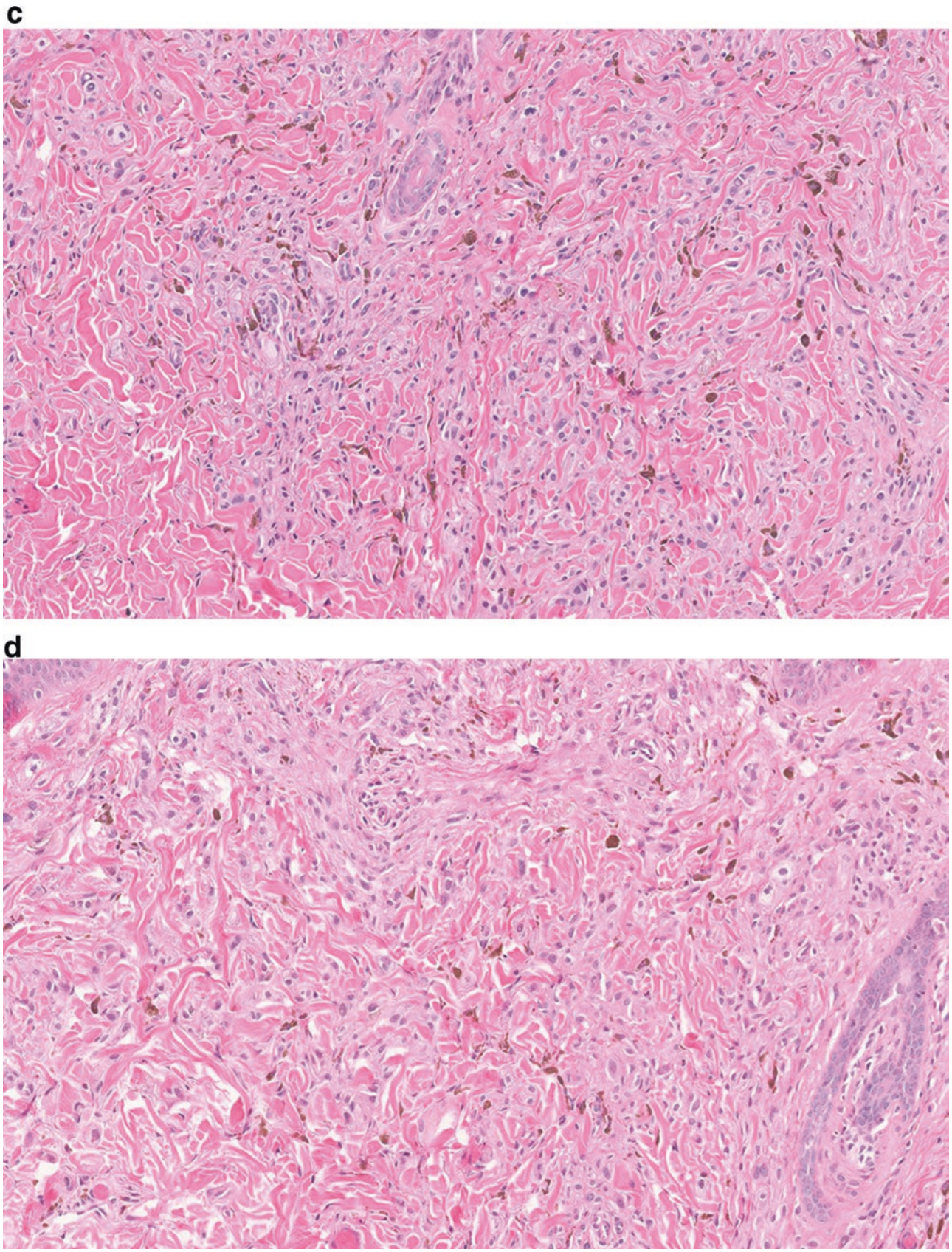

Fig. 2.8 (continued) Note the normal maturation toward the base. The melanocytes lack cytologic atypia and devoid of mitotic figures (**c**). High power shows the spitzoid melanocytes interspersed between the collagen bundles (**d**)

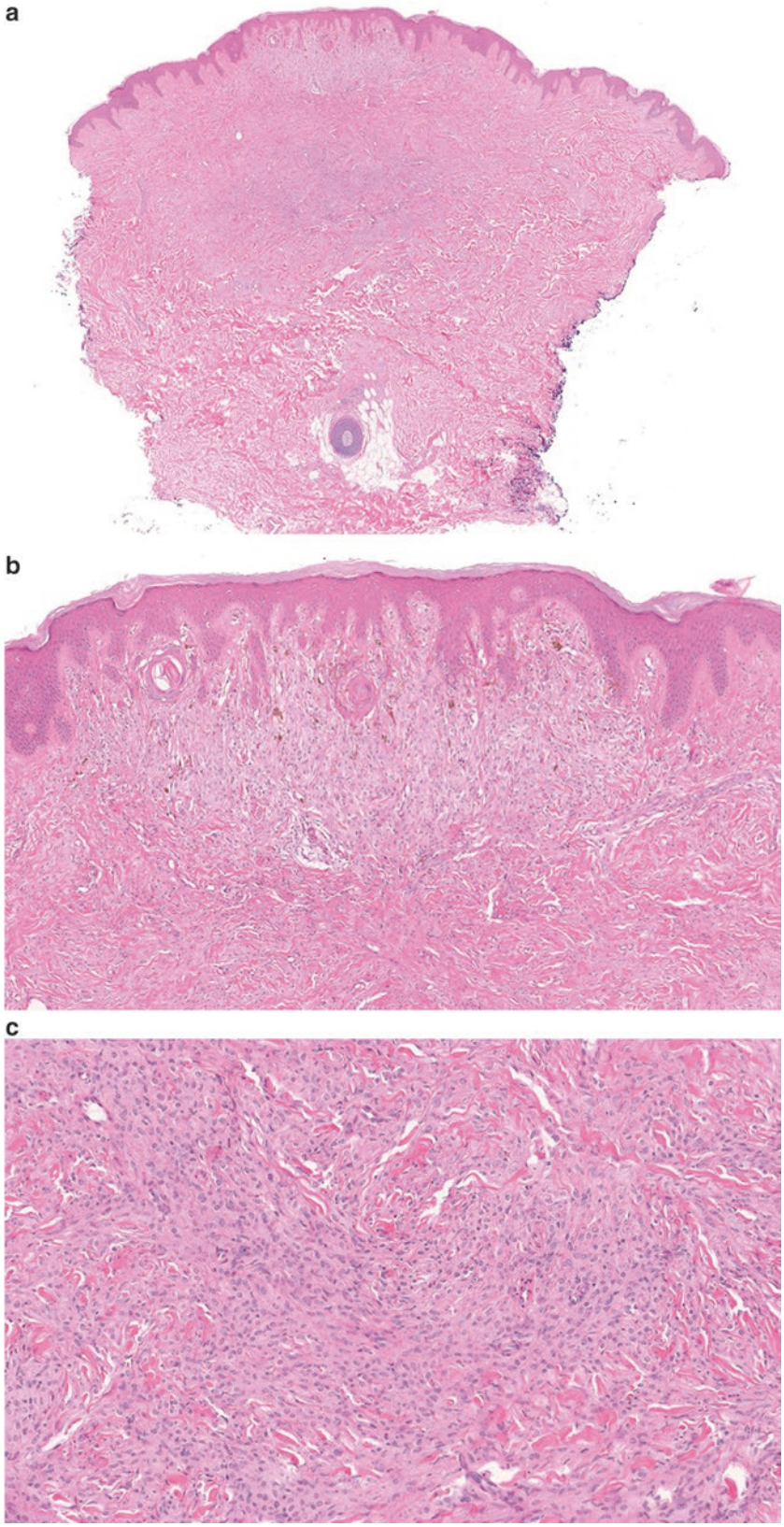

Fig. 2.9 Compound blue nevus. This example has an amelanotic blue component with an overlying junctional component (**a**). Note the basal layer hyperpigmentation along with single melanocytes in the epidermis (**b**). Normal maturation of melanocytes (**c**)

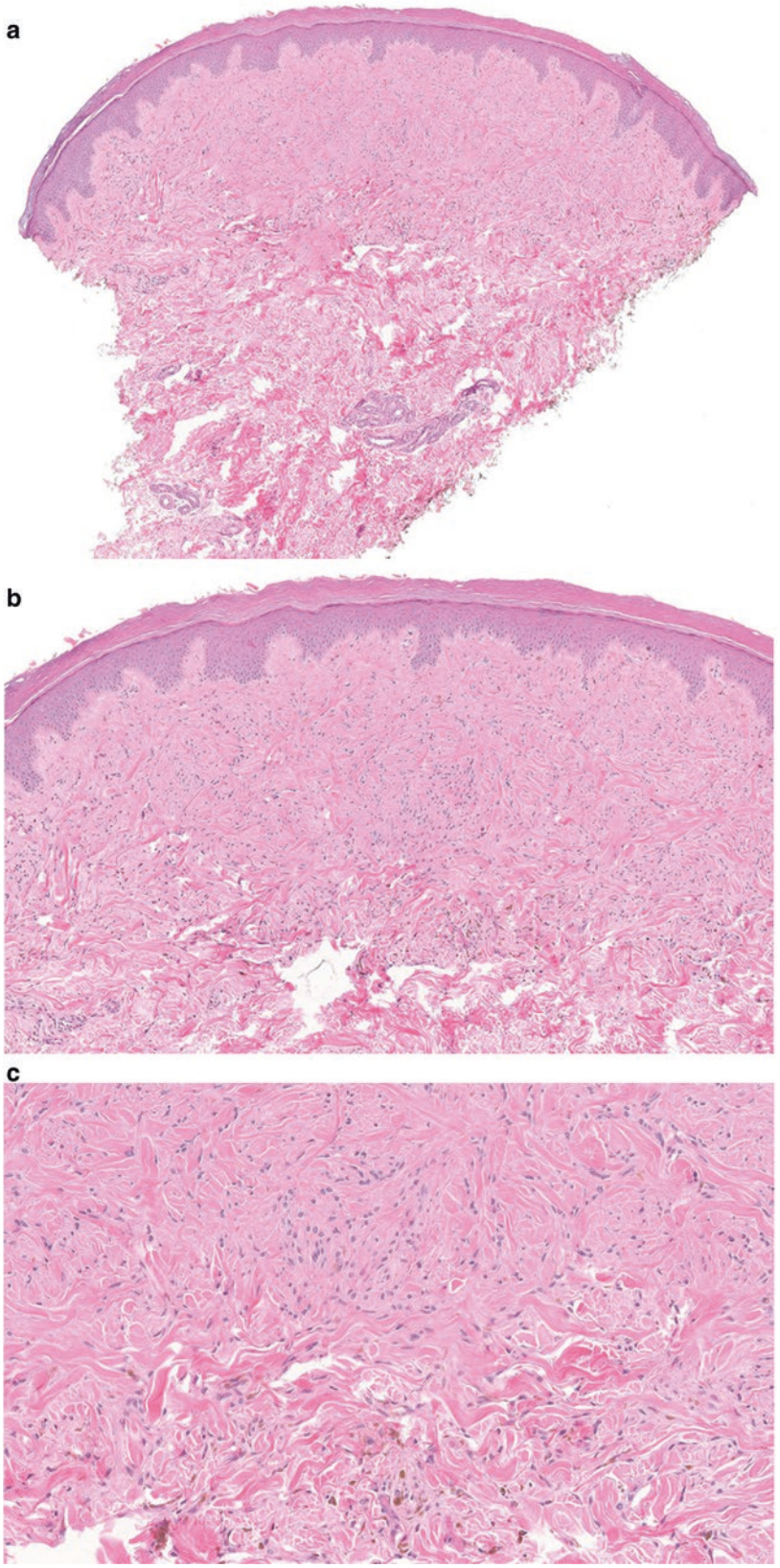

Fig. 2.10 Amelanotic blue nevus. This case shows the dendritic spindle cells in superficial and reticular dermis. Note the scant pigment throughout the lesion (**a**). The center of the lesion is devoid of pigment with only minimal pigment observed in the deep component of the lesion (**b**). High power of the deep portion shows only rare pigmented dendritic cells (**c**)

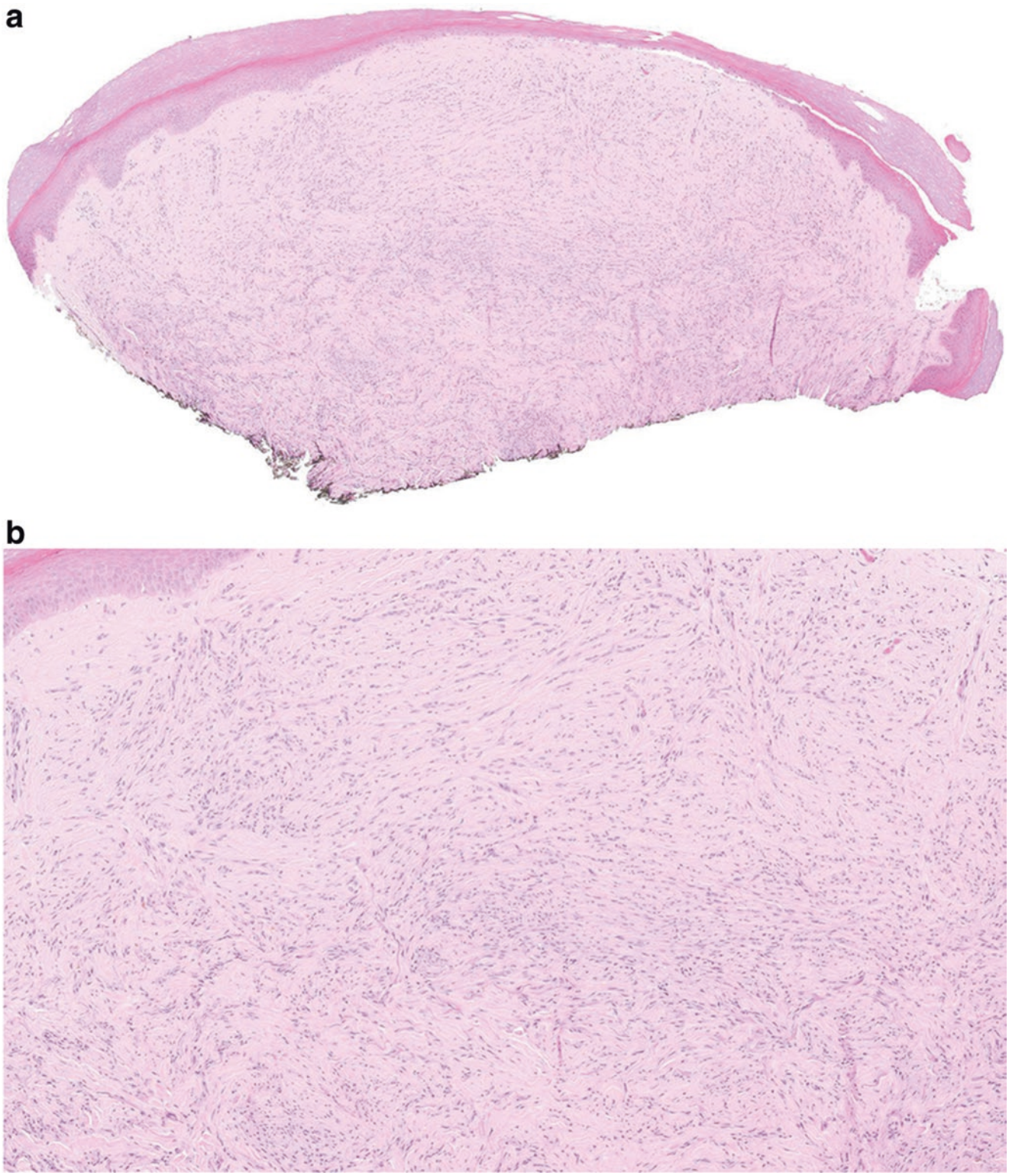

Fig. 2.11 Amelanotic blue nevus. The low-power magnification shows a papule composed of spindle melanocytes admixed with many dendritic cells (**a**). Note increased thickening of the collagen bundles and melanocytes interspersed in between them (**b**).

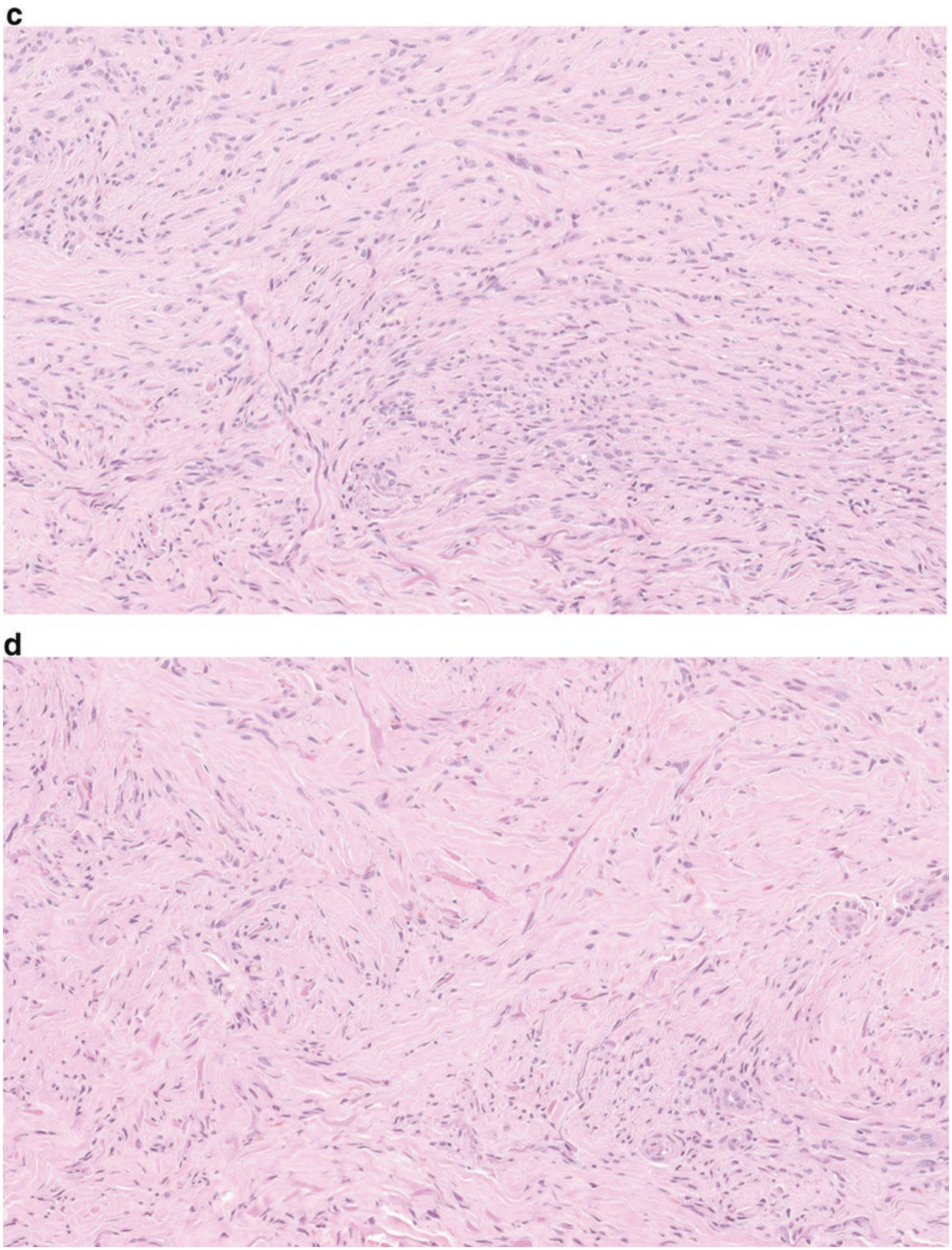

Fig. 2.11 (continued) Higher magnification shows banal appearance of the melanocytes along with lack of mitotic figures (**c**). Note the homogeneity of the spindle cell melanocytes (**d**)

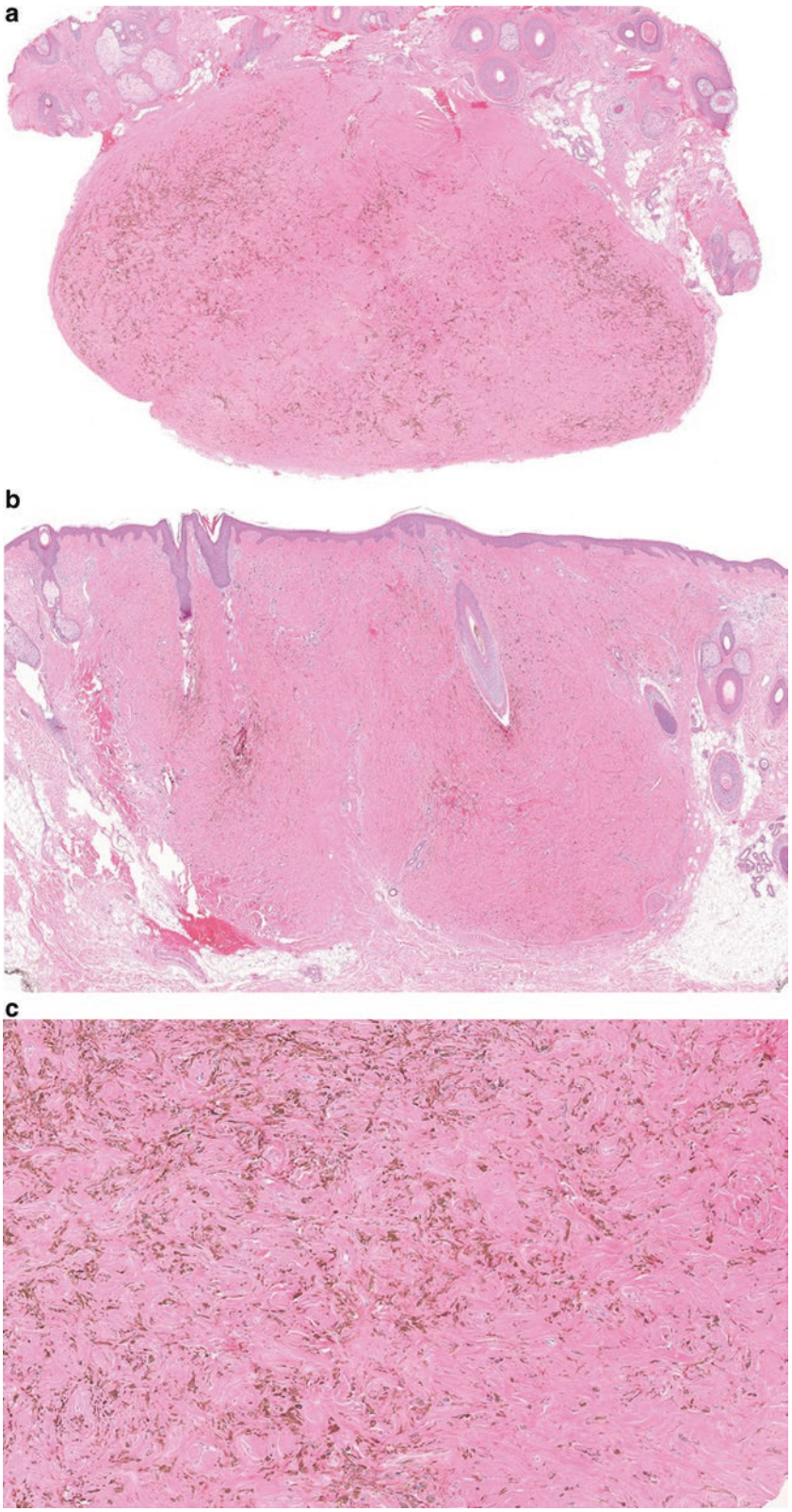

Fig. 2.12 Sclerotic blue nevus. Scalp of a 48-year-old female. The biopsy shows a pigmented nodular and symmetric lesion extending deep into the dermis. There is increased fibrosis and sclerosis. Note the *bottom* of the lesion shows bulbous aggregations (**a**). A different area of the same tumor showing a wedge-shaped nodular growth with marked fibrosis and sclerosis. There are heavily pigmented dendritic melanocytes arranged in small fascicles within a sclerotic stroma (**b**, **c**).

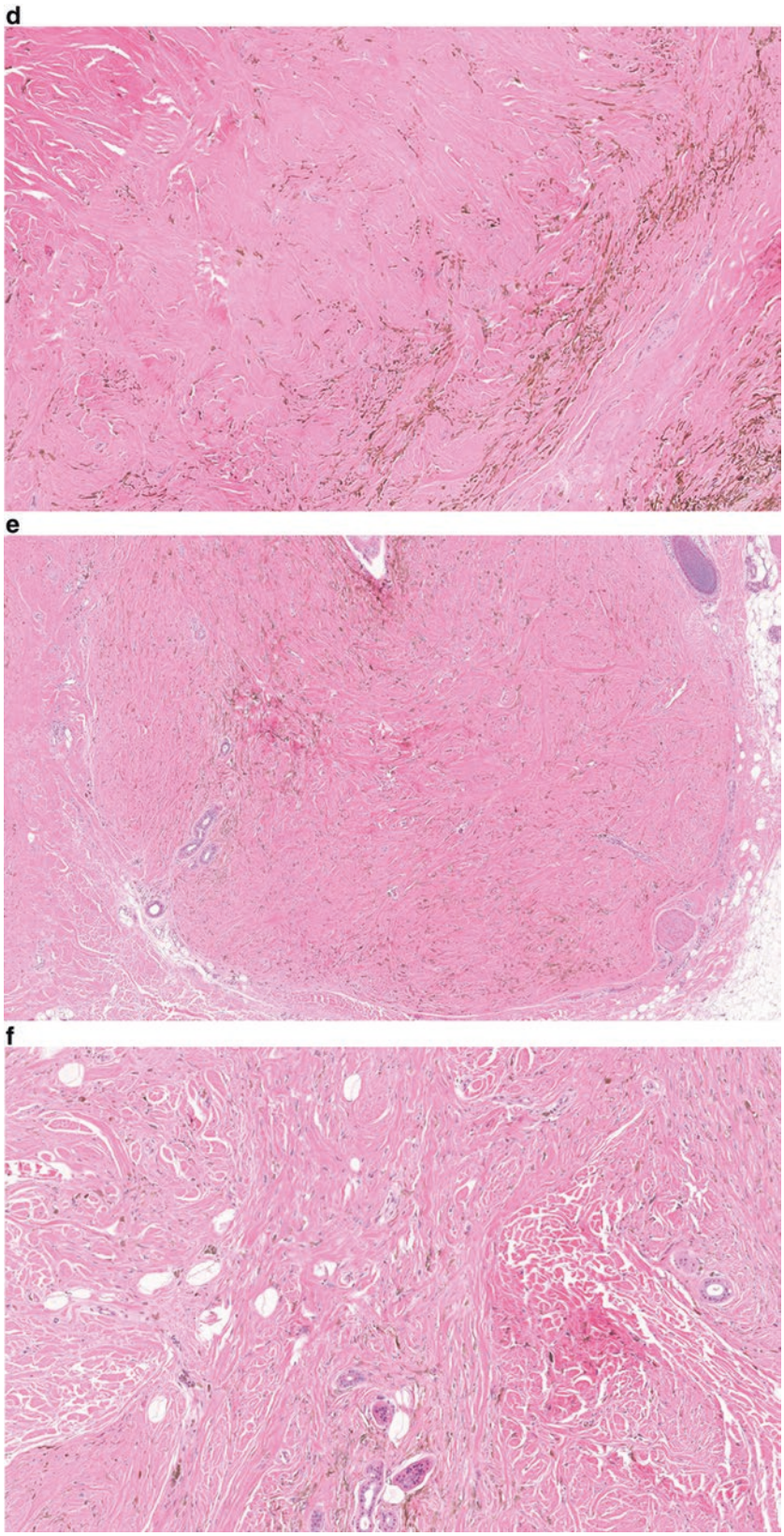

Fig. 2.12 (continued) A more paucicellular area and with more pronounced sclerosis and fibroplasia (**d**). Note the deep extension along adnexal structures (**e**). The propensity of the dendritic cells to wrap around the adnexal structures (**f**)

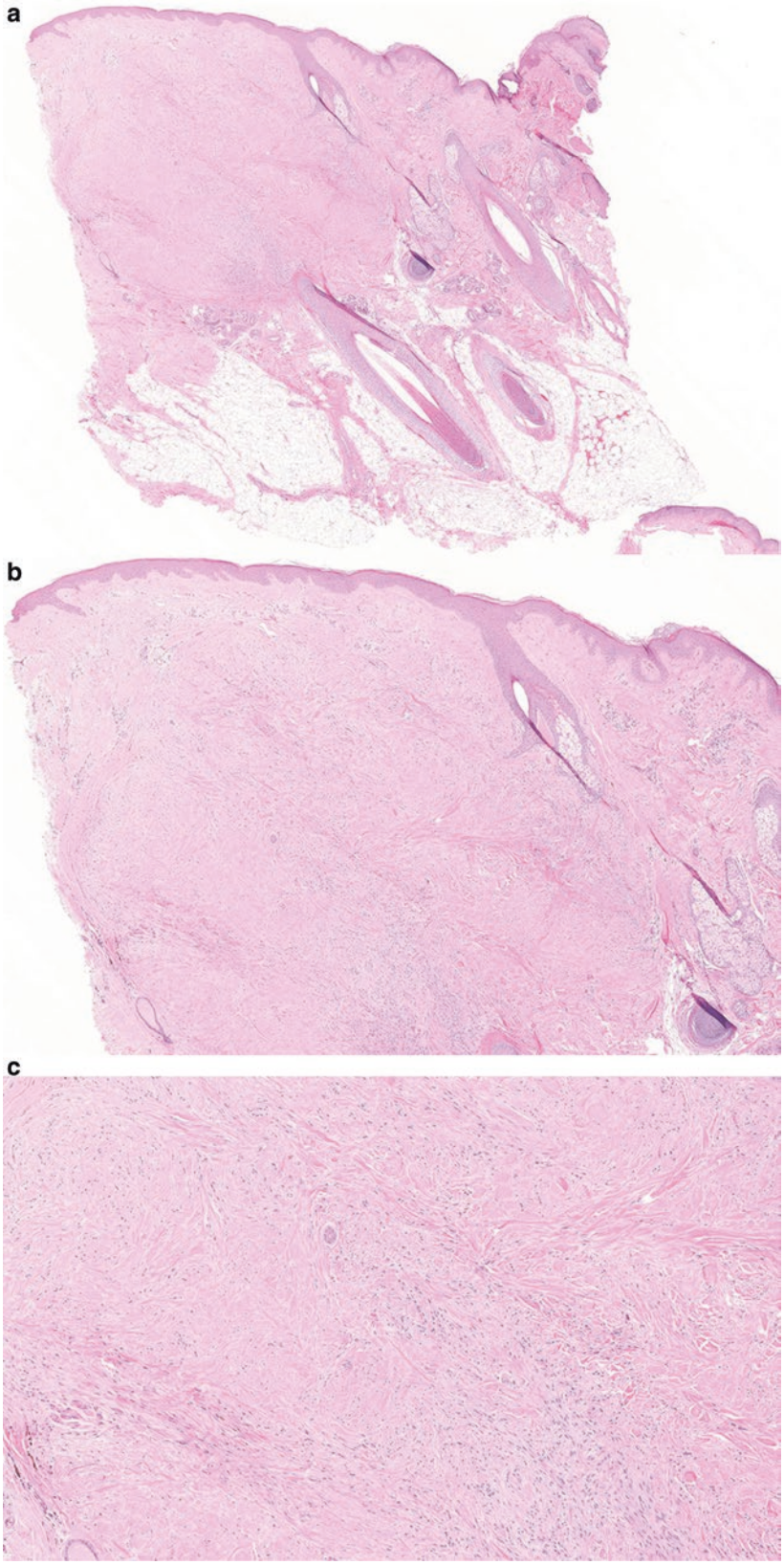

Fig. 2.13 Sclerotic amelanotic blue nevus. The lesion shows a well-delineated nodule in reticular dermis composed of spindle dendritic cells and devoid of pigment (**a**). The spindle cells are arranged in small fascicles (**b**). The dendritic nature of the spindle cell melanocytes without pigmentation (**c**, **d**). In cases wherein there is doubt about the etiology of the spindle cells, MART-1 is a helpful marker to stain the cells

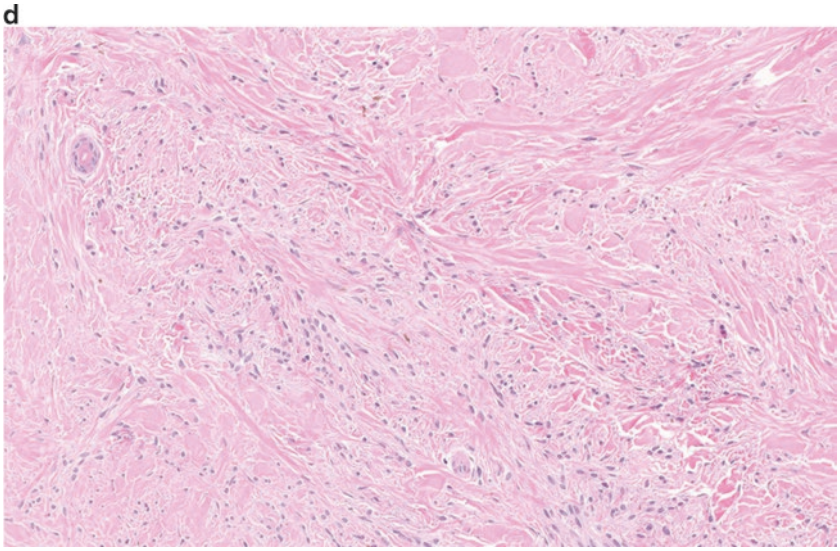

Fig. 2.13 (continued)

Epithelioid Blue Nevus (Pigmented Epithelioid Melanocytomas)

Clinical Features

Epithelioid blue nevus is a rare histologic variant of blue nevus that was first introduced in patients with Carney complex (myxomas, endocrine overactivity, spotty skin pigmentation, psammomatous melanotic schwannomas, thyroid neoplasms, etc.). Nonetheless, there are sporadic lesions that are histomorphologically indistinguishable from epithelioid blue nevi of Carney complex and have been referred to as pigmented epithelioid melanocytomas (PEMs) or animal-type melanoma (pigment synthesizing melanoma). The current preferred term is PEM as it may reflect the intermediate malignant potential of this tumor.

These neoplasms have a predilection for children, adolescents, and young adults, but they occur over a broad age range. The most common location includes trunk and extremities; however, it can have a wide distribution, including mucosal sites, and thus suggesting that sun exposure is unlikely to be a major factor in its pathogenesis. The majority of tumors apparently arise de novo, but occasional lesions can be associated with a dermal nevus. These neoplasms are currently referred as low-grade melanocytic tumors since they may involve regional lymph nodes but have limited ability to spread beyond lymph nodes. Lymph node metastasis was detected in 46 % of cases in one series [22, 41–43]. However, they have a favorable clinical outcome in most cases [43], and the prognosis is significantly more favorable than that of conventional melanoma. It is questionable whether epithelioid blue nevus patients would benefit from sentinel lymph node (SLN) biopsy as positivity does not seem to predict the outcome of the disease [44–47].

Histopathology

Histologically, epithelioid blue nevus is composed of a poorly defined, heavily pigmented, dermal melanocytic proliferation with infiltrative or pushing borders, and not uncommonly these lesions may invade the subcutaneous fat. The dermal proliferation often but not always abuts the epidermis and in some examples may even show a grenz zone. The overlying epidermis in some occasions may show hyperplasia and elongated rete ridges. Some lesions may show a minor junctional component, as rare intraepidermal melanocytes are usually dendritic.

The lesions tend to be more cellular in the center, while in the periphery the tumor cells permeate between preexisting collagen fibers. The tumor is composed of a mixture of epithelioid and spindled, heavily pigmented melanocytes. The epithelioid cells range in size from medium to large and contain moderate to abundant amounts of coarsely granular, cytoplasmic melanin pigment and dispersed uniform nuclear chromatin and small distinct nucleoli. In some epithelioid cells, the pigment is dispersed evenly throughout the cytoplasm, but in other cells, the pigment is located at the periphery, leading to a pigment-free perinuclear zone. Nuclear atypia is generally more pronounced in the larger cells. The spindled cells are present singly or forming small groups and

more commonly seen at the periphery of the lesion (checkerboard pattern). These spindle cells have the same nuclear features as those seen in the epithelioid cells; however, some of them show similar features to those observed in common blue nevus (pigmented cells with delicate dendrites). Melanocytes can infiltrate the adnexal epithelium, pilar erector muscles, perivascular spaces, and perineurium. The neoplastic cells lack maturation with depth and mitotic activity is occasionally seen (mostly ranging from 0 to 2 mitotic figures/mm^2), *without* atypical forms. Tumor necrosis is rarely seen [23].

Also, there have been reported cases of epithelioid blue nevi occurring in chronically sun-damaged skin with a predominance of epithelioid morphology but also containing a component of fusiform and conventional blue nevus cells, which has been termed "epithelioid and fusiform blue nevus of chronically sun-damaged skin" [48]. These lesions are more commonly seen in older patients, obviously with a predilection for sun-exposed areas. Distinguishing histopathologic features of epithelioid and fusiform blue nevus of chronically sun-damaged skin from PEMs include the presence of solar elastotic bundles and a higher frequency of an associated conventional blue nevus component. A small subset of cases has marked pleomorphism and nuclear atypia with rare mitotic activity and with the accompanying solar elastosis, thus raising concern for the possibility of melanoma.

Differential Diagnosis

The epithelioid blue nevus seen in Carney syndrome is histologically identical to the sporadic counterpart. The differential diagnosis of epithelioid blue nevus is primarily with deep penetrating nevus (DPN). DPN causes significant histologic confusion due to its resemblance to epithelioid blue nevus, as they are deeply pigmented dermal tumors with wedge-shaped architecture, show subcutaneous fat involvement, and both have pigmented spindle cells with common periadnexal or perivascular extension. Furthermore, several authors, among them are one of us, consider DPN a variant of cellular blue nevi. In the classical description, in DPN the melanocytes are arranged in a plexiform pattern with large nests and fascicles and are not as uniformly pigmented as in epithelioid blue nevus. Also, in DPN the cells have smudged nuclear chromatin (open vesicular nuclei in epithelioid blue nevus) and variable nuclear atypia and pleomorphism with prominent intranuclear inclusions. Also, the presence of prominent nucleoli is a characteristic finding in epithelioid blue nevus. DPNs are benign melanocytic neoplasms and only rarely recur.

Epithelioid blue nevus can have similar architectural features to cellular blue nevi, including periadnexal and subcutaneous extensions and a dumbbell architecture on low-power magnification. In our opinion, one of the most specific differentiating features between epithelioid blue nevus and cellular blue nevi is the presence of epithelioid cells in the former, which are absent in cellular blue nevi. Dermal sclerosis, common in blue nevi, is only rarely observed in epithelioid blue nevus. Also, epithelioid blue nevus tends to have infiltrating borders while cellular blue nevi do not, as the cellular nodules tend to be well circumscribed. The differential diagnosis between epithelioid blue nevus and blue nevus-like melanoma (BNLM) may be challenging because of the at least focal presence of severely atypical epithelioid cells in both neoplasms. The most important differentiating features are the presence of cellular blue nevus component, monotonous high-grade cytological atypia, high mitotic activity (atypical mitotic figures), and tumor necrosis in BNLM.

Immunohistochemistry and Molecular Testing

A recent study analyzed mutations of the protein kinase A regulatory subunit 1 alpha (PRKAR1A) gene, loss of heterozygosity (LOH) at the gene locus 17q22-24, and expression of PRKAR1A by immunohistochemistry in PEMs, in a variety of nevi and in melanomas [49]. This study showed that there are no PRKAR1A gene mutations, a protein that is mutated in 50 % of patients with Carney complex [49], in PEMs, in nevi, or in melanomas; however, most PEMs (up to 82 %) and Carney complex-associated epithelioid blue nevi lose expression of PRKAR1A by immunohistochemistry. Also, five of the seven PEMs studied in that series showed 17q22-24 LOH. PRKAR1A protein is expressed in virtually all melanomas and some melanocytic nevi [49]; thus, loss of expression of PRKAR1A may offer a useful diagnostic test that helps to distinguish PEM from its histologic mimics including conventional, cellular and malignant blue nevi, and deep penetrating nevi. Also, these findings provide a molecular basis supporting the common phenotype of Carney complex-associated and sporadic cases of PEMs. Additionally, a recent study showed the presence of GNAQ mutations (20 % of cases) and the absence of HRAS and GNA11 mutations in PEMs; thus, these studies provided molecular support for the classification of these tumors as variants of blue nevi [50]. In contrast, the "epithelioid and fusiform blue nevus of chronically sun-damaged skin" seems to represent a unique subtype of blue nevus without association with Carney complex or loss of PRKAR1A expression (by IHC) typically found in PEMs and Carney complex-associated epithelioid blue nevi [48].

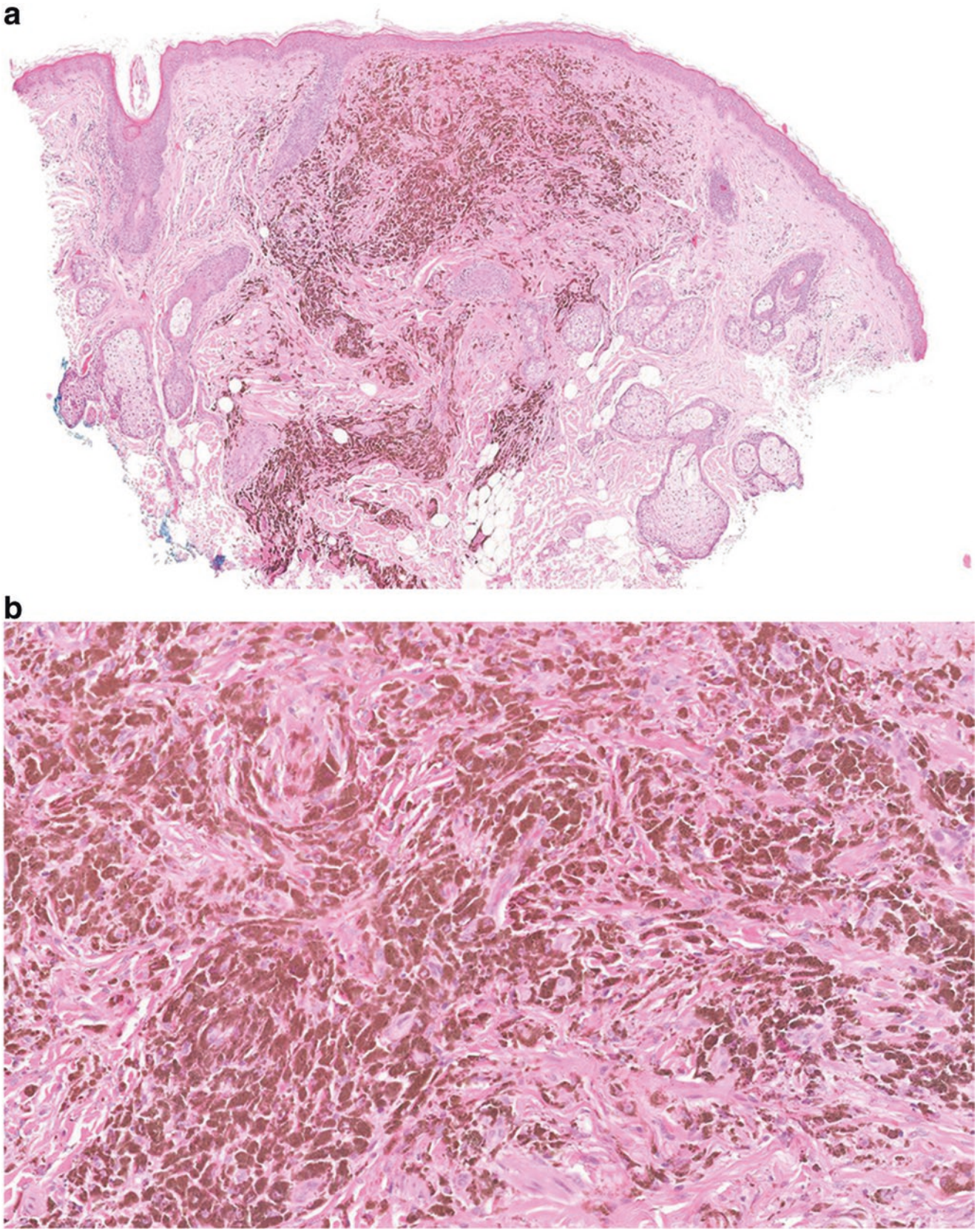

Fig. 2.14 Pigmented epithelioid melanocytoma (PEM). This lesion is composed of heavily pigmented dermal melanocytes with infiltrative borders (**a**). The cells are mostly epithelioid and with abundant heavily pigmented cytoplasm and forming cohesive sheets of closely packed uniform cells (**b**)

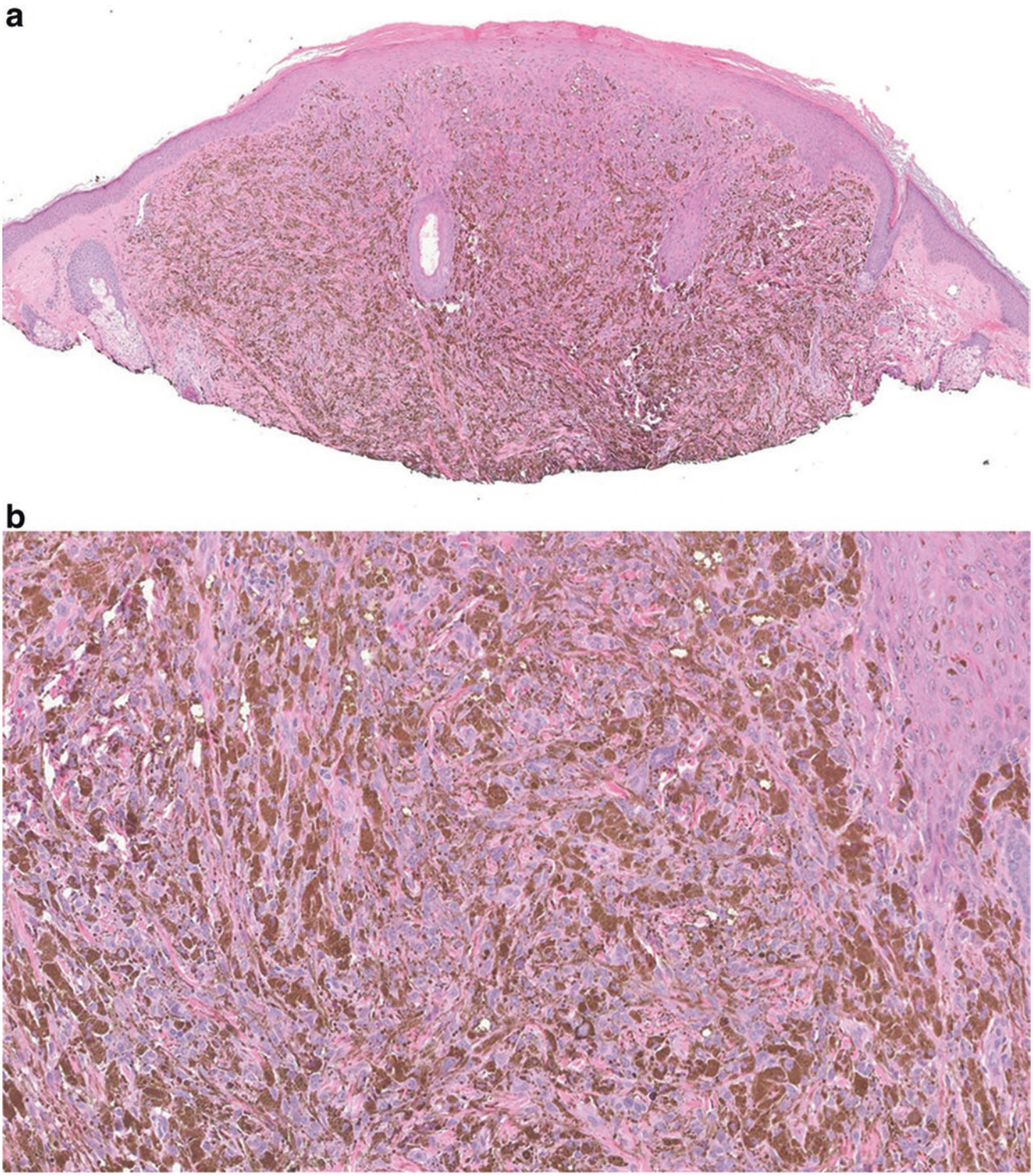

Fig. 2.15 Pigmented epithelioid melanocytoma (PEM). This example shows a heavily pigmented dermal lesion with an inverted wedge-shaped architecture abutting the epidermis and inducing mild epidermal hyperplasia (**a**). This tumor is composed of variably pigmented epithelioid and spindle cells with prominent nucleoli, interspersed with many melanophages (**b**).

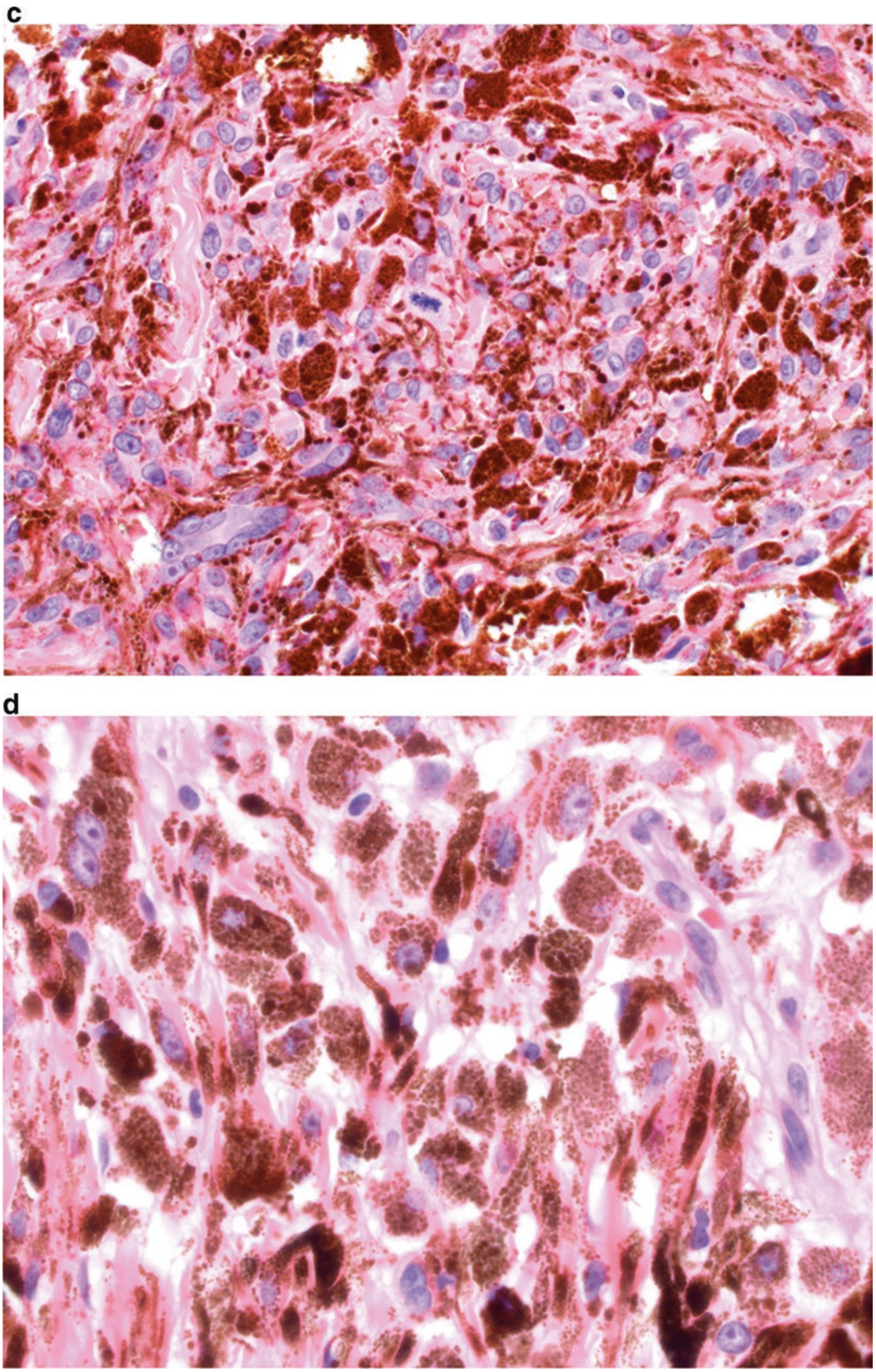

Fig. 2.15 (continued) Rare mitotic figures can be present (usually <2 mitoses per mm2) (**c**). Note the dot-like melanin granules at the periphery of the cell (**d**)

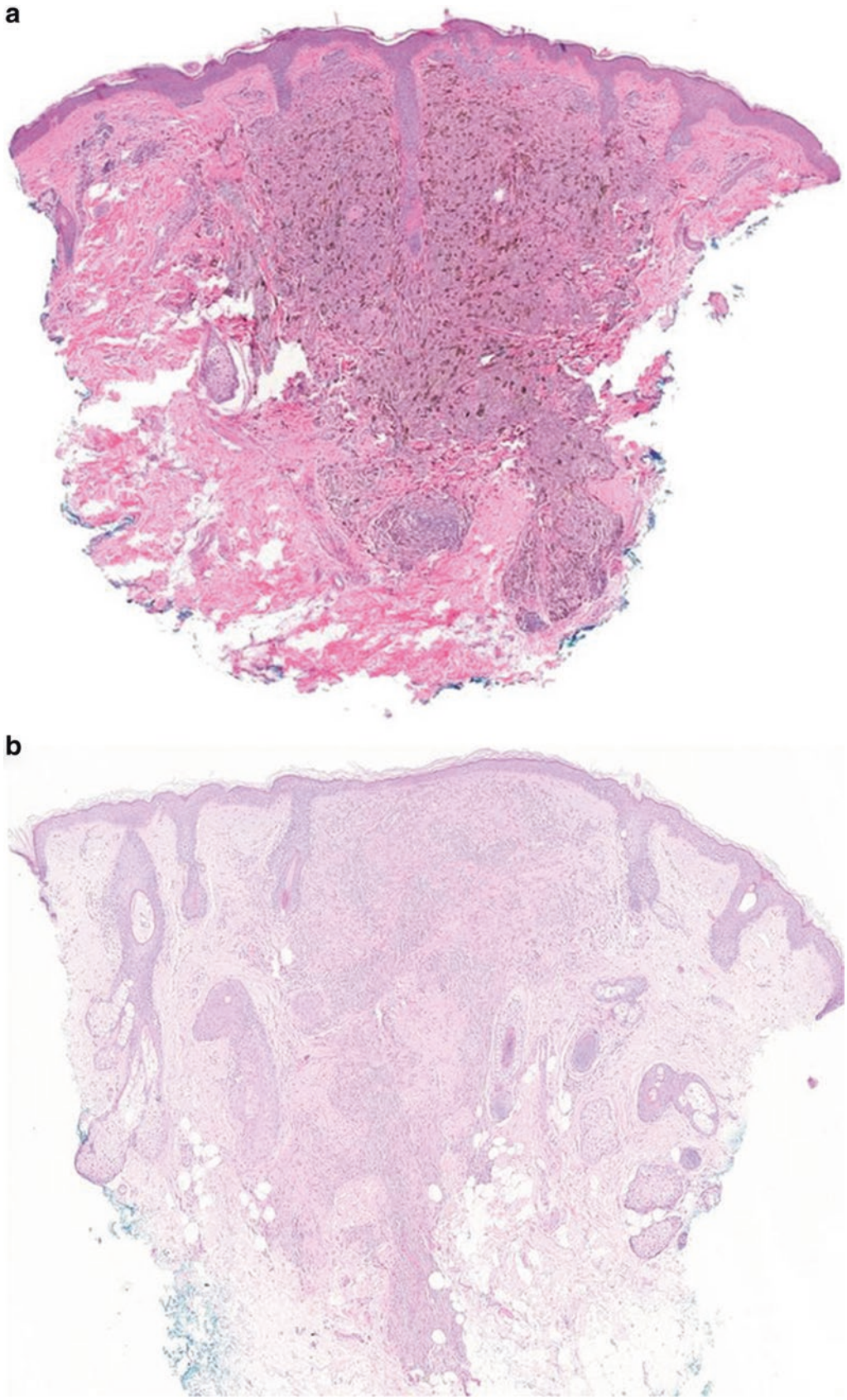

Fig. 2.16 Pigmented epithelioid melanocytoma (PEM). Another example of PEM showing a heavily pigmented dermal melanocytic tumor with infiltrative borders. The figure below represents a bleached slide to visualize better the tumor cytology

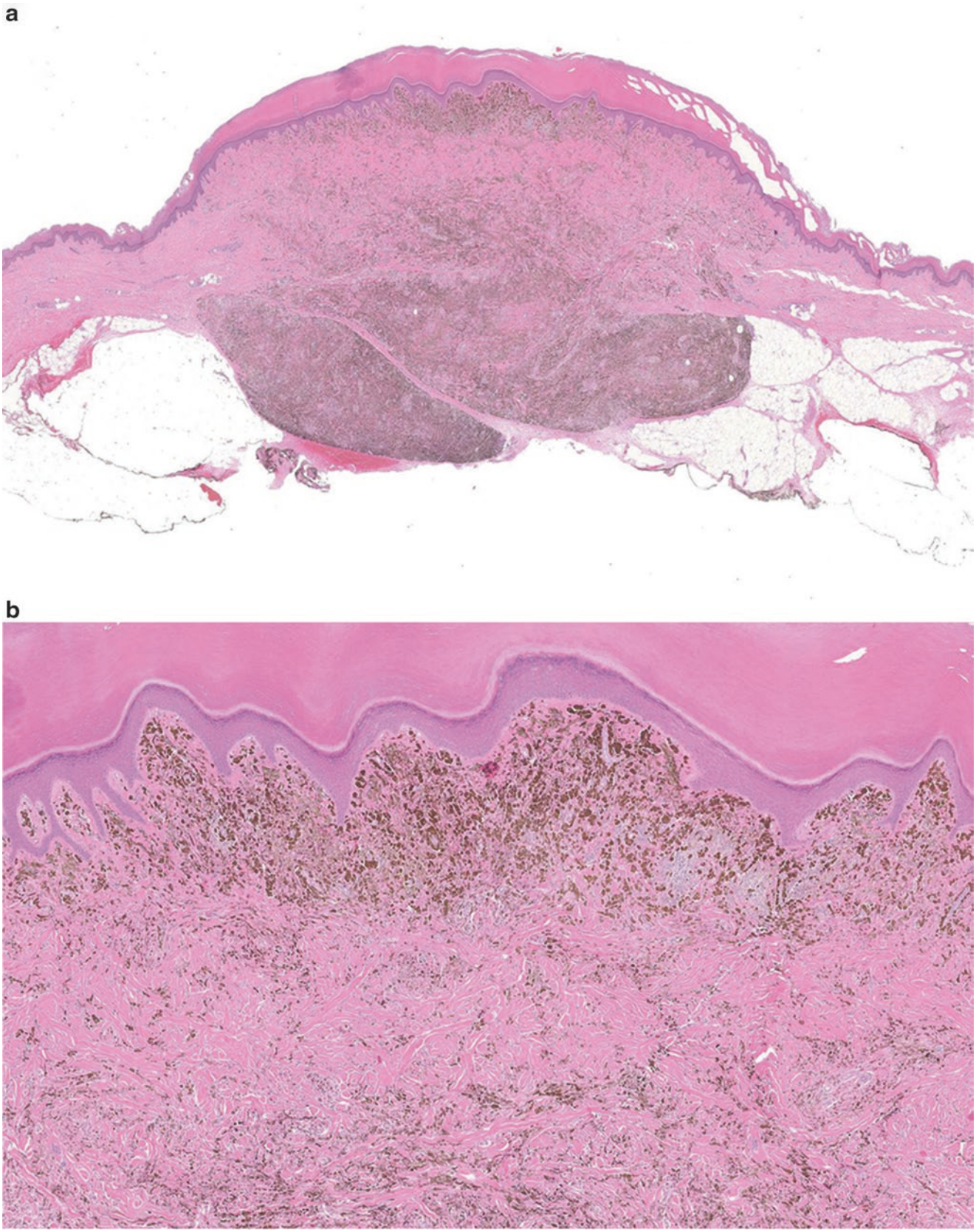

Fig. 2.17 Pigmented epithelioid melanocytoma (PEM). Scanning magnification shows a heavily pigmented dermal melanocytic tumor extending into the subcutaneous tissue along eccrine coils (**a**). The epithelioid cells are intermixed with a variable number of spindled cells. The spindle cells penetrate between the surrounding stromal collagen bundles (**b**).

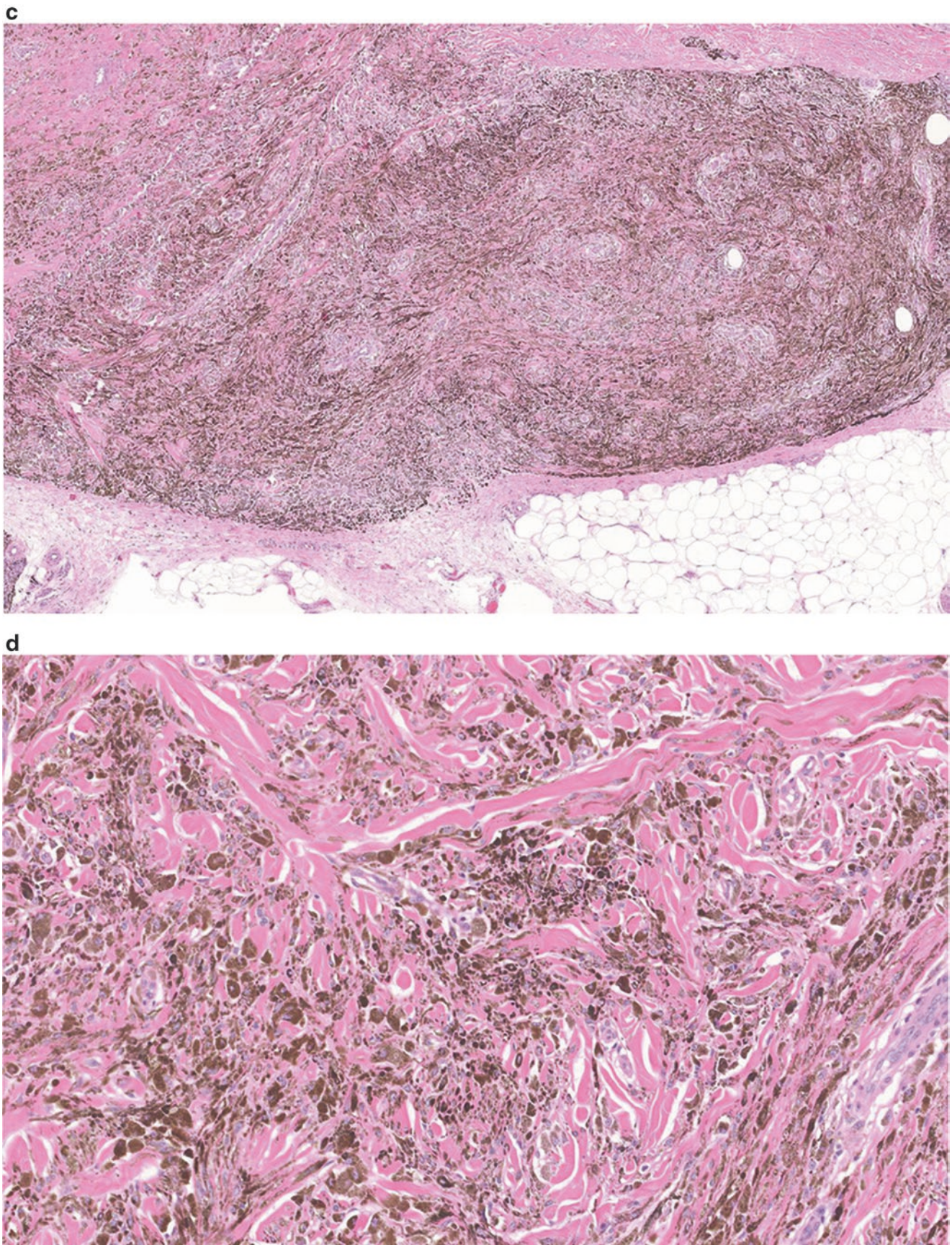

Fig. 2.17 (continued) The spindle and epithelioid cells are infiltrating along the eccrine ducts in the deep dermis (**c**). The melanocytes have a heavily pigmented cytoplasm forming cohesive sheets of closely packed uniform cells (**d**)

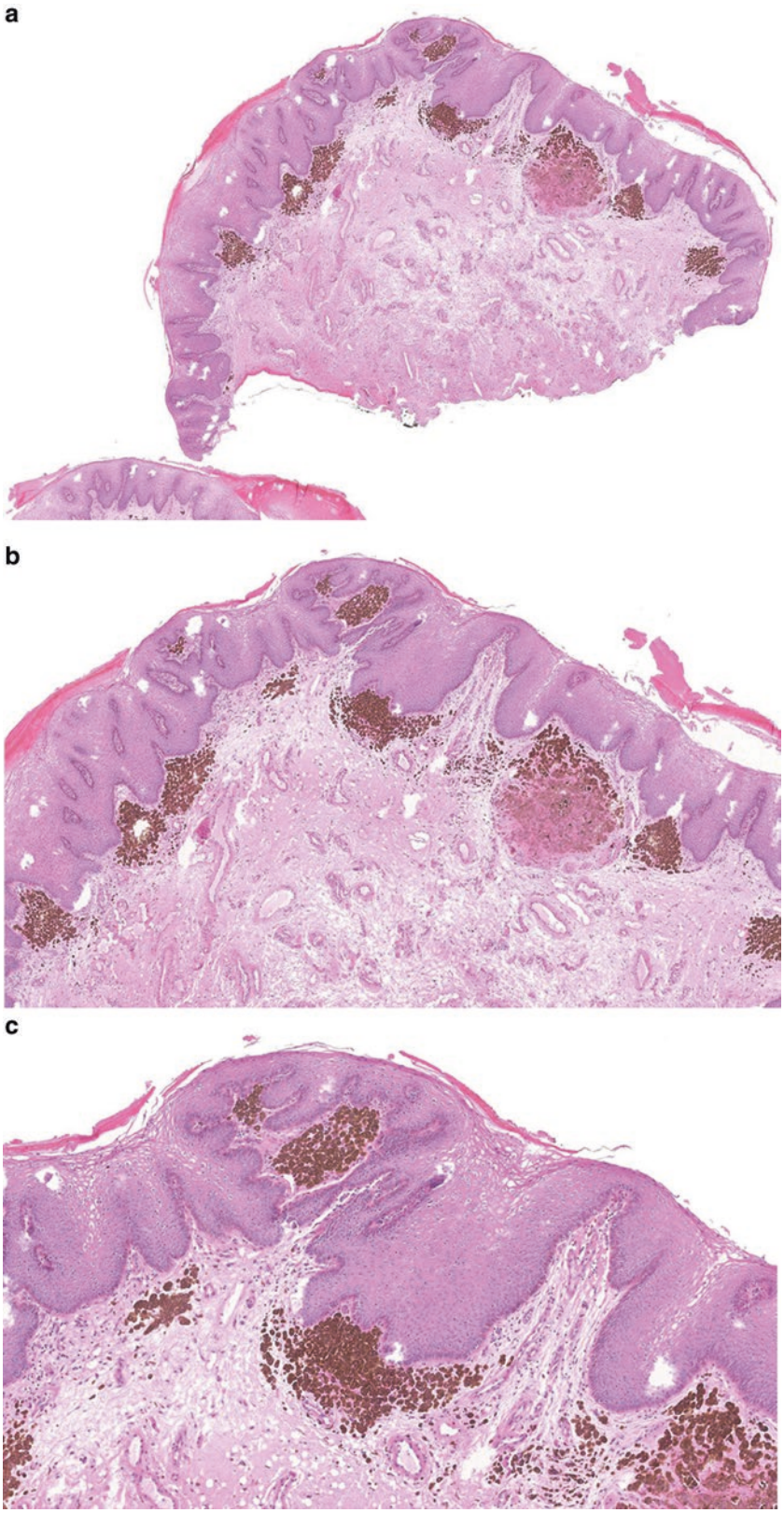

Fig. 2.18 Pigmented epithelioid melanocytoma (PEM) of the vulva. The lesion is composed of discrete aggregates of epithelioid heavily pigmented melanocytes (**a**). Some authors may consider this lesion as epithelioid blue nevus. These lesions are common on genital areas and show aggregates of epithelioid pigmented melanocytes (**b**–**d**)

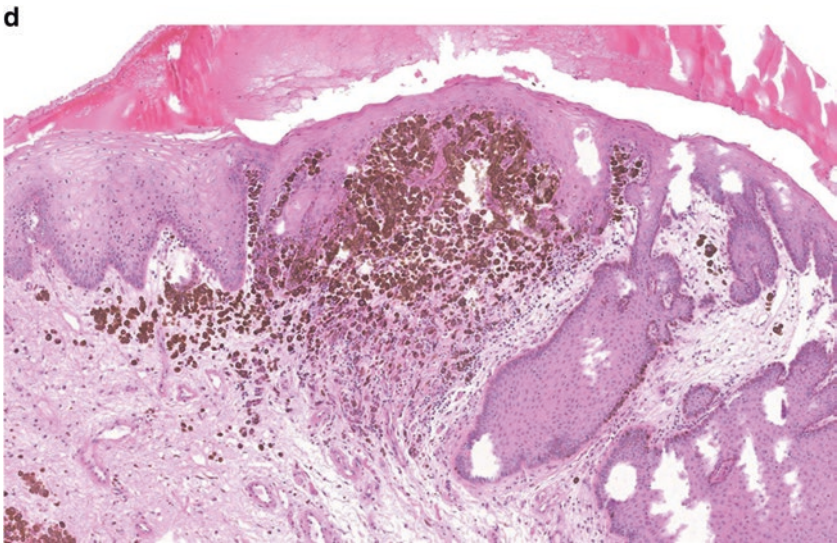

Fig. 2.18 (continued)

Cellular Blue Nevus

Clinical Features

Cellular blue nevi (CBN) are dermal melanocytic neoplasms that are present at all ages, but are most commonly seen in young adults with slight female predominance. Rarely, they may have a congenital onset. The most common sites of involvement include the buttocks/sacrococcygeal region and the scalp, also the face, extremities, genital tract, breast, subungual region, intraocular, and conjunctiva. It presents as a large, pigmented, multinodular mass that ranges in size from few millimeters to up to 6 cm (most lesions measure between 1 and 3 cm) [22, 23, 51, 52].

CBN may involve the subcapsular sinuses and even the parenchyma of regional lymph nodes, but the latter is an exceedingly rare phenomenon [53–55]. Such deposits of CBN in lymph nodes may pose difficulties when trying to distinguish CBN from BNLM [53]. Comparison with the histology of the primary cutaneous tumor may help to arrive at the correct diagnosis and prevent inappropriate treatment. This phenomenon does not appear to represent true metastases as it seems not to alter the prognosis of CBNs. The few previous reports of patients affected by CBN with lymph node metastases reported survival without recurrence of the disease for 5, 10, and 22 years after conservative surgery [55]. The risk for malignant transformation and developing melanoma in cellular blue nevi has been estimated to be between 5.2 and 6.3 % [56, 57].

Histopathology

Histologically, most lesions appear well defined and extend deeper into the dermis and/or subcutis in a typical dumbbell pattern. At low magnification the tumor shows pigmented alternating zones of hypercellularity with collagenous hypocellular pigmented foci. It may present as a pigmented biphasic tumor with a component of a common blue nevus and distinct cellular areas comprised of larger, plump oval to fusiform spindle cells with small monomorphous nuclei with speckled chromatin, small nucleoli, and more abundant, clear, or finely pigmented cytoplasm. In the more superficial and peripheral aspects of the lesion, the appearance is often of a classic blue nevus with varying amounts of stromal fibrosis and desmoplasia, and in the center and deeper portions, the cellularity is increased. The cellular areas are arranged in short fascicles or nests, in solid sheets, or in a plexiform pattern. Around the periphery of the nested pattern, there is a wreath of dendritic pigmented melanocytes admixed with pigmented melanophages. Most of the pigment observed is in the macrophages (i.e., melanophages) and the pigmented dendritic cells, whereas the melanocytes are usually only lightly pigmented or amelanotic. In many cases an alveolar growth pattern is seen, which is predominantly characterized by a small, well-defined, nested arrangement of epithelioid, amelanotic melanocytes surrounded by dense collagen, pigmented dendritic melanocytes, and melanophages. Also, there are commonly elongated slender melanocytes resembling Schwann cells in a neurotized pattern (similar to ordinary nevi). Mitotic figures should be absent or only focal; up two per ten high-power fields may be considered the upper limit in CBNs.

The stroma in these lesions is sclerotic. Sometimes there are multinucleated wreath-like giant cells and balloon cells, but nuclear pleomorphism is rare. A characteristic feature of cellular blue nevi is the presence of central, cystic degeneration. Myxoid degeneration, hemorrhage, and stromal hyalinization can also occur. Nerve hypertrophy is often present with perineural aggregation of cells. Not unusually cellular blue nevi may display balloon melanocytes [58]. Kazakov et al. [59] reported the presence of “ball in mitts” structures in

cellular blue nevi, which are composed of a single centrally placed rounded melanocyte (ball) encircled by a single dendritic cell (mitt). They also reported "microalveolar structures," composed of two to ten central rounded cells surrounded by one or more dendritic cells similar to those seen in the "ball in mitts" structures. The same authors noted that similar structures may occur in combined nevi, deep penetrating nevi, acquired melanocytic nevi, and classic blue nevi.

Cellular blue nevi may show unusual features such as the presence of rare mitotic figures, focal nuclear pleomorphism, and focal necrosis, but not all three features simultaneously. These cases have been named atypical cellular blue nevi (see below) [60, 61]. When seen, mitotic figures can even be present in the deeper aspect of the tumor; however, atypical forms are not observed. We report the presence of isolated mitotic activity or focal necrosis in the absence of other atypical findings (such as nuclear atypia or expansile growth pattern) is indicative of atypical cellular blue nevus although the possibility of aggressive behavior appears to be low [61, 62].

Different thresholds exist as to what is the amount of cellular areas allowed within a common blue nevus. We use the term CBN in lesions with cellular areas noticeably present and particularly if the lesion is large enough (>1 cm). Cellular blue nevi have a greater potential for recurrence and local aggressive growth than do common blue nevi; thus, correct identification is advised. Furthermore, the risk of malignant transformation is significantly higher for the cellular blue than common blue nevus, although still quite rare. Ideally, all cellular blue nevi should be completely excised.

Differential Diagnosis

The main differential diagnosis of cellular blue nevi is with blue nevus-like melanoma (BNLM). Like BNLM, CBN is usually composed of large epithelioid and/or spindle cells, lacks maturation with depth, may extend deeply, may be pigmented, and may contain occasional mitotic figures. The distinction will be made based on the proper identification of severe cytologic atypia, obvious tumor necrosis, high mitotic count (>2/mm^2), atypical mitotic figures, large expansile nodules, and diffuse infiltrative borders; all these will favor the diagnosis of BNLM. Other histologic findings that favor BNLM over CBN include the presence of large pleomorphic epithelioid cells, cell crowding, an "infiltrating" growth pattern (margins of the tumor are irregular, as opposed to the pushing margins of CBN), and expansile growth. The cells in CBN have bland nuclear qualities in most cells as opposed to BNLM which show marked variability of nuclear chromasia, size, and shape. Also, the architectural disposition of the biphasic elements seen in CBN is not observed in BNLM; in contrast, there is effacement of the dermal architecture by a densely cellular proliferation. Neurotropism can be observed in both cellular blue nevi and BNLM. BNLM may show multiple chromosomal aberrations with FISH or CGH analysis.

DPN also enters in the differential diagnosis of cellular blue nevi, but the presence of orderly oriented fascicles of pigmented spindle cells following neurovascular bundles and adnexal structures (sometimes with plexiform arrangement), nests of epithelioid cells (resembling type A melanocytes of common nevus) surrounded by macrophages and extending into deep dermis or subcutis, a wedge-shaped architecture, and a minor component of dermal nevus without dendritic cell differentiation will favor the former.

Immunohistochemistry and Molecular Testing

The tumor cells in cellular blue nevi usually express S-100p, MART-1, and HMB-45 antigen, although some cases may be negative or have variable expression of S-100p or HMB-45 antigen, especially in cases that have prominent desmoplasia and/or neurotization. CD34 and cytoplasmic bcl-2 can be expressed in a subset of lesions [5]. The use of a red chromogen should allow an easier distinction between melanin pigment and the immunoreaction.

IHC evaluation of proliferative activity has been shown to help discriminate nevi from melanoma [31]. The most commonly used proliferative marker, MIB-1 (ki-67), identifies cells in G1, G2, S, or M phase and is frequently elevated in melanomas but rarely in benign nevi, including cellular blue nevi. Also, phosphohistone H3, a marker of cells in mitosis, has been evaluated in the distinction of melanoma from benign nevi. Studies have revealed phosphohistone H3-positive nuclei in almost 100 % of all melanomas as opposed to cellular blue nevi which show negative to sparse positivity [63].

CGH is a powerful ancillary test that analyzes the entire genomic DNA of a melanocytic neoplasm. Many studies using CGH have shown clear differences between atypical nevi and melanoma indicating that dermal melanocytic proliferations that by histopathology are unequivocally benign or malignant have a nonoverlapping chromosomal aberration pattern [64, 65]. Studies have demonstrated that unequivocal cellular blue nevi show no chromosomal aberrations, whereas obvious BNLM showed multiple chromosomal aberrations [66]. Other studies have shown that most of blue nevi have normal chromosomal copy numbers, but a subset may display chromosomal abnormalities [63]. In one study an unequivocally benign cellular blue nevus demonstrated unusual clinical behavior (recurrence) and harbored copy number aberrations detected by CGH [63], thus underscoring the importance of correlating in the molecular and histopathology data. In our experience, patients with histologically ambiguous blue nevus tumors should undergo complete excision and careful clinical follow-up.

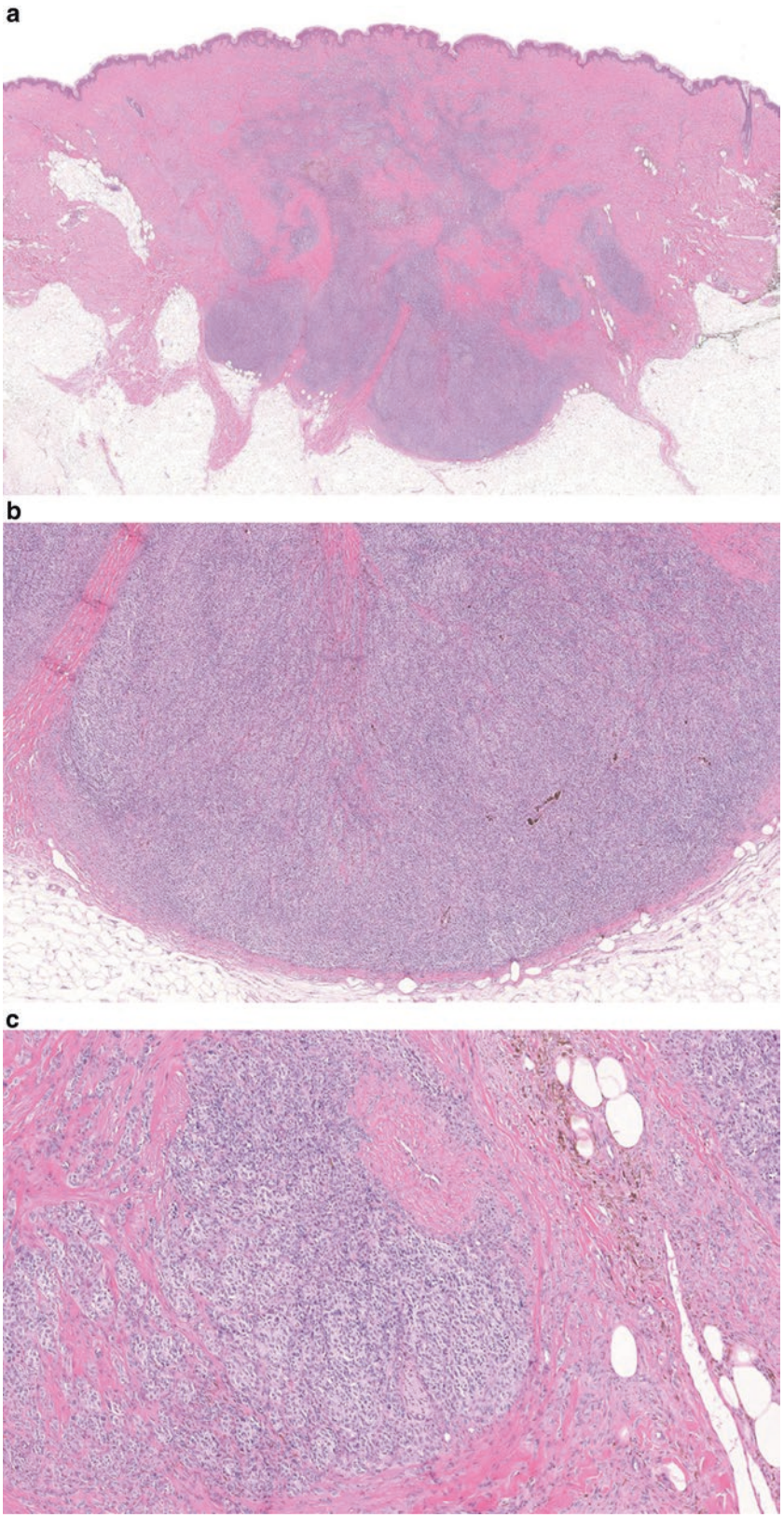

Fig. 2.19 Cellular blue nevus. Scanning magnification shows a well-defined nodular mass in the dermis that has a somewhat dumbbell architecture. Note the alternate zones of hypercellularity and hypocellularity (**a**). The base of the lesion is composed of characteristic hypercellular areas composed of spindle and epithelioid melanocytes with pale cytoplasm (**b**). Note the nests and fascicles of epithelioid and spindle cells surrounded by a sclerotic stroma (**c**).

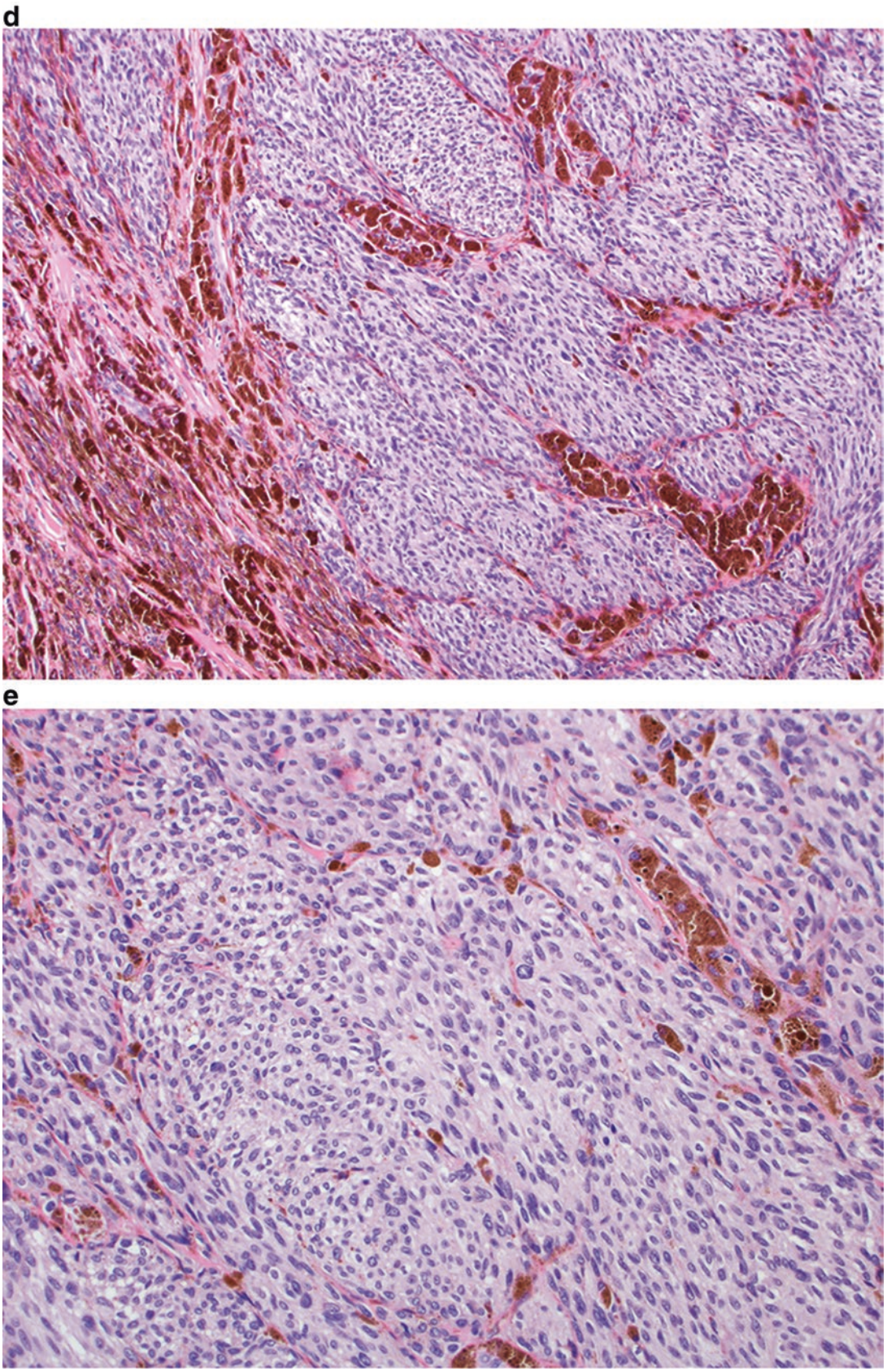

Fig. 2.19 (continued) This image depicts both the cellular areas and the blue nevus-like changes (**d**). Masses of spindle and epithelioid cells surrounded by a wreath of dendritic pigmented melanocytes and pigmented melanophages (**e**).

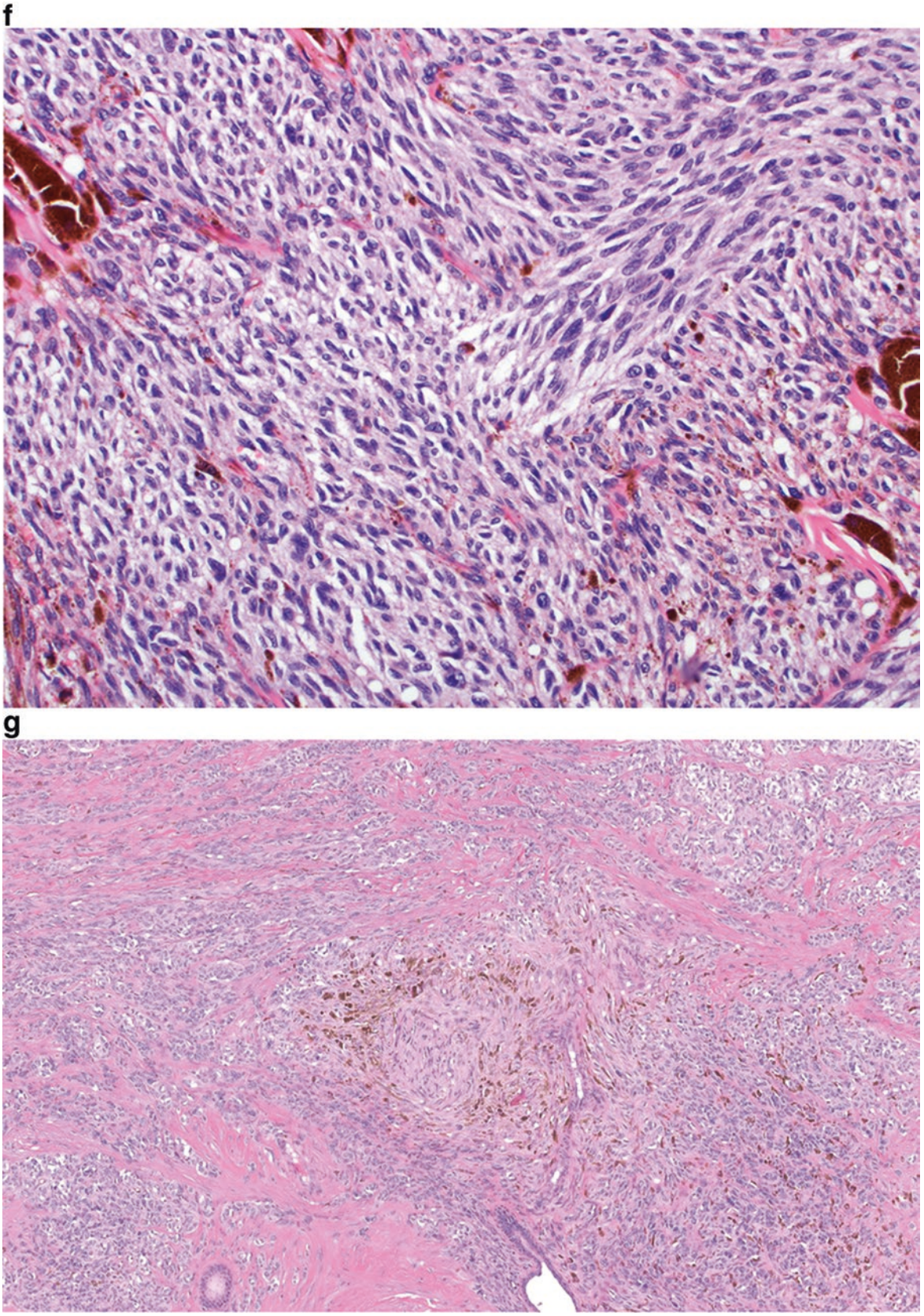

Fig. 2.19 (continued) Higher magnification of the spindle cells with small monomorphous nuclei, small nucleoli, and a characteristic clear cytoplasm (**f**). The propensity of melanocytes to wrap nerves (**g**).

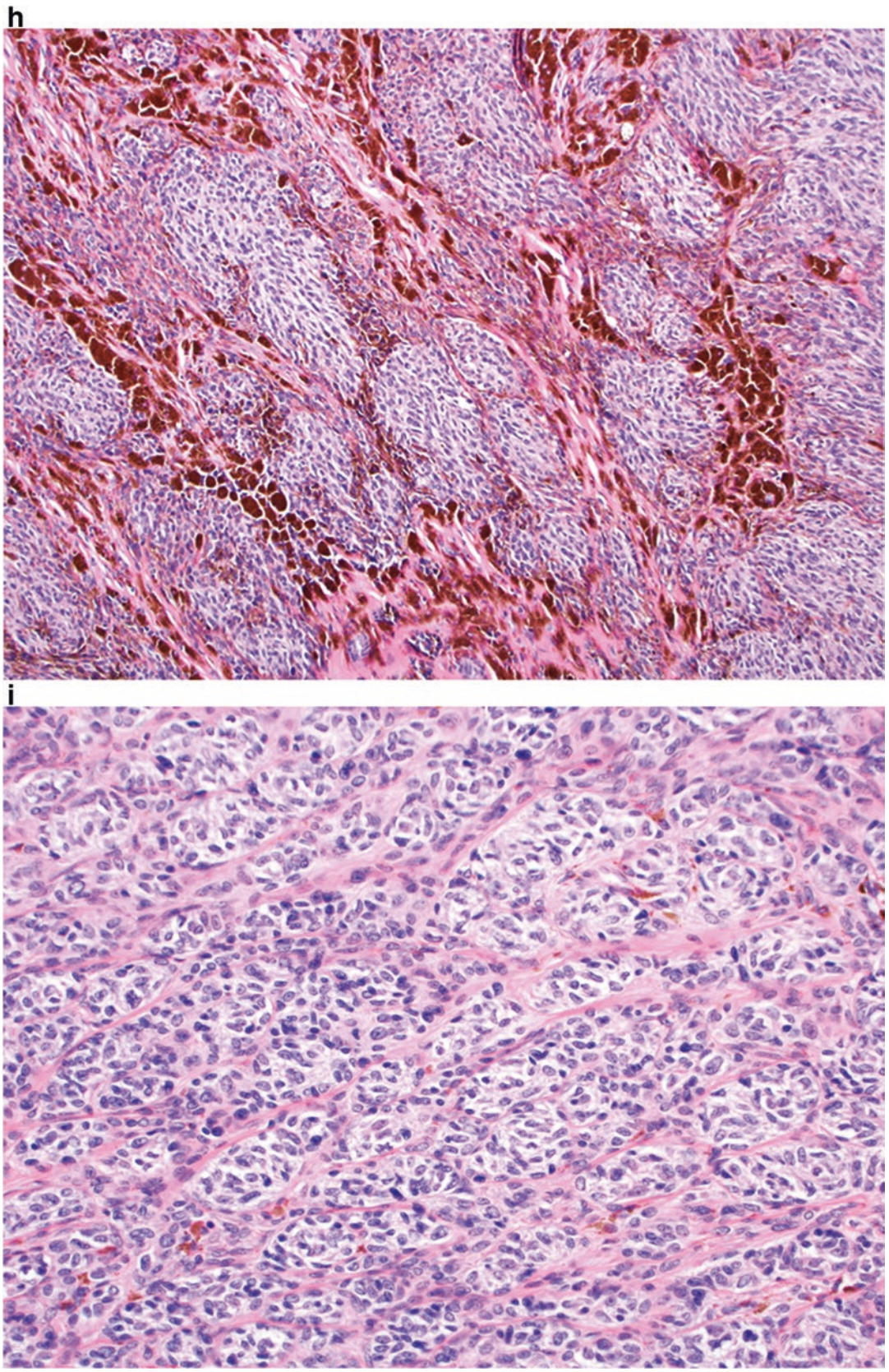

Fig. 2.19 (continued) The alveolar pattern characterized by small nodules of plump or spindle-shaped nonpigmented or clear melanocytes surrounded by dense collagenous septa, pigmented dendritic cells, and melanophages (**h**). The alveolar growth pattern devoid of surrounding pigmented dendritic cells and melanophages (**i**)

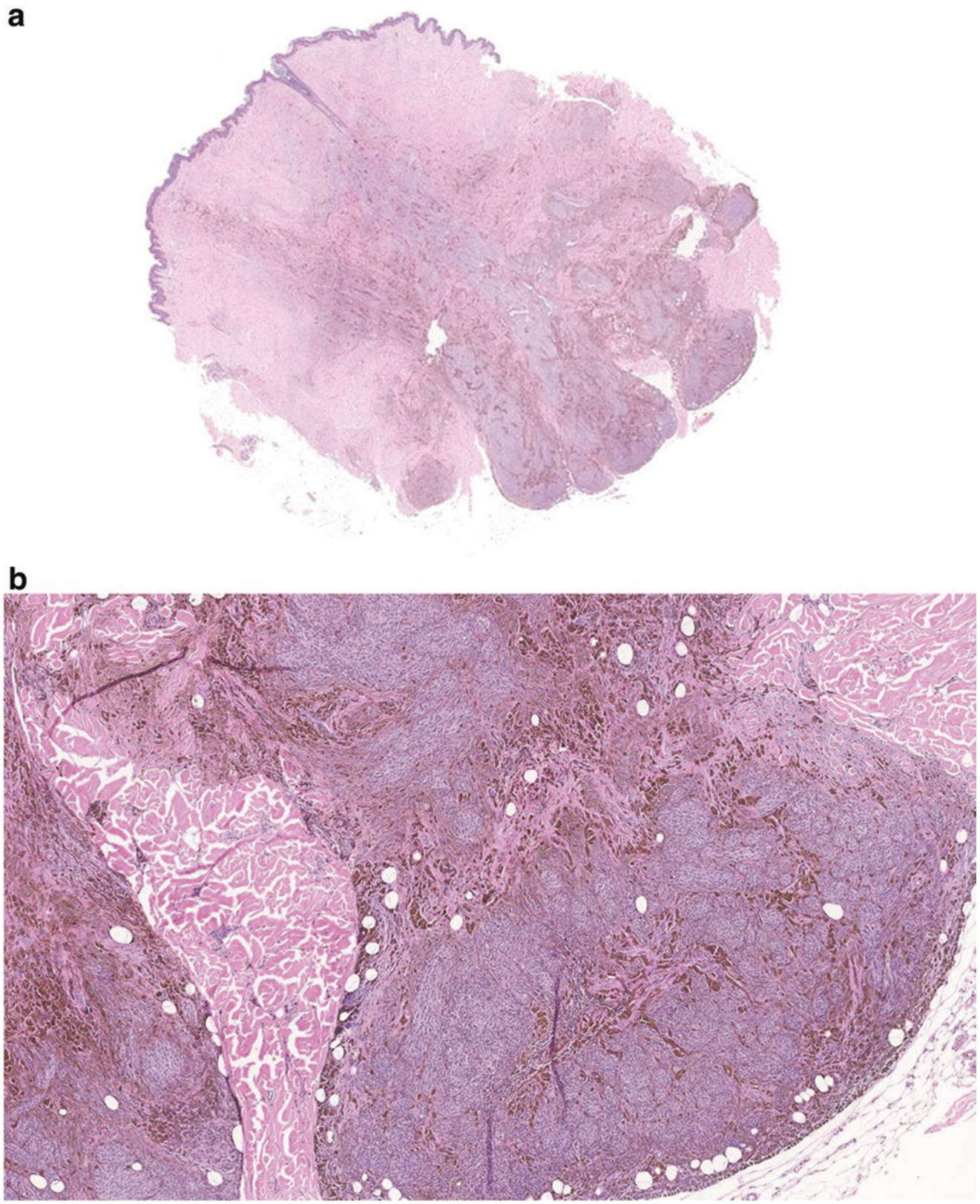

Fig. 2.20 Cellular blue nevus. In this example one can appreciate the dermal growth of melanocytes along the follicular structures. The follicles are not clearly noted; however, there is an elongated silhouette (**a**). The base of the lesion is characteristically hypercellular. The base of lesion shows bulging areas into the subcutis (**b**).

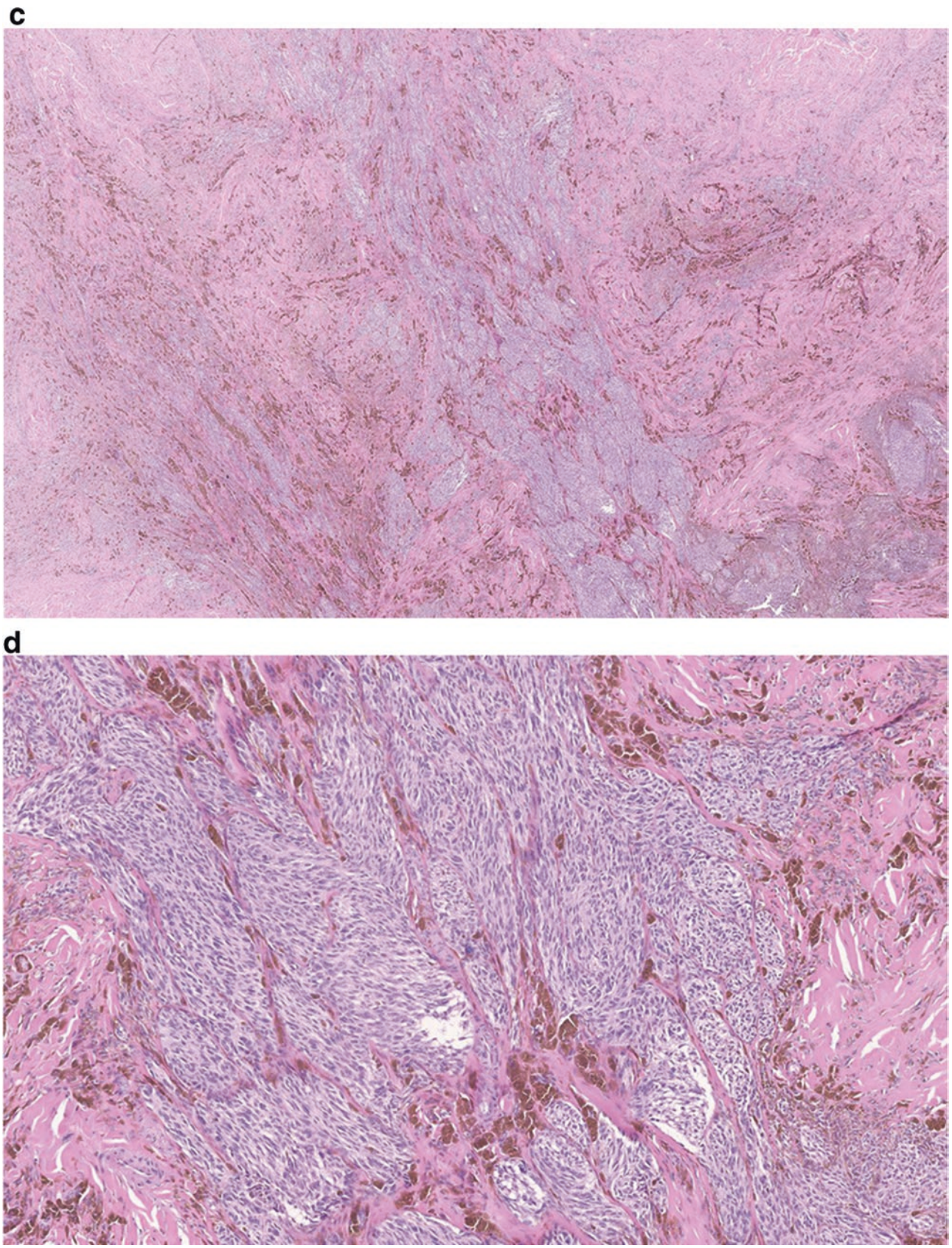

Fig. 2.20 (continued) Masses of ovoid melanocytes surrounded by heavy hyperpigmentation (**c**). Note the monomorphic nests composed of mature pale (or minimally pigmented) melanocytes (**d**)

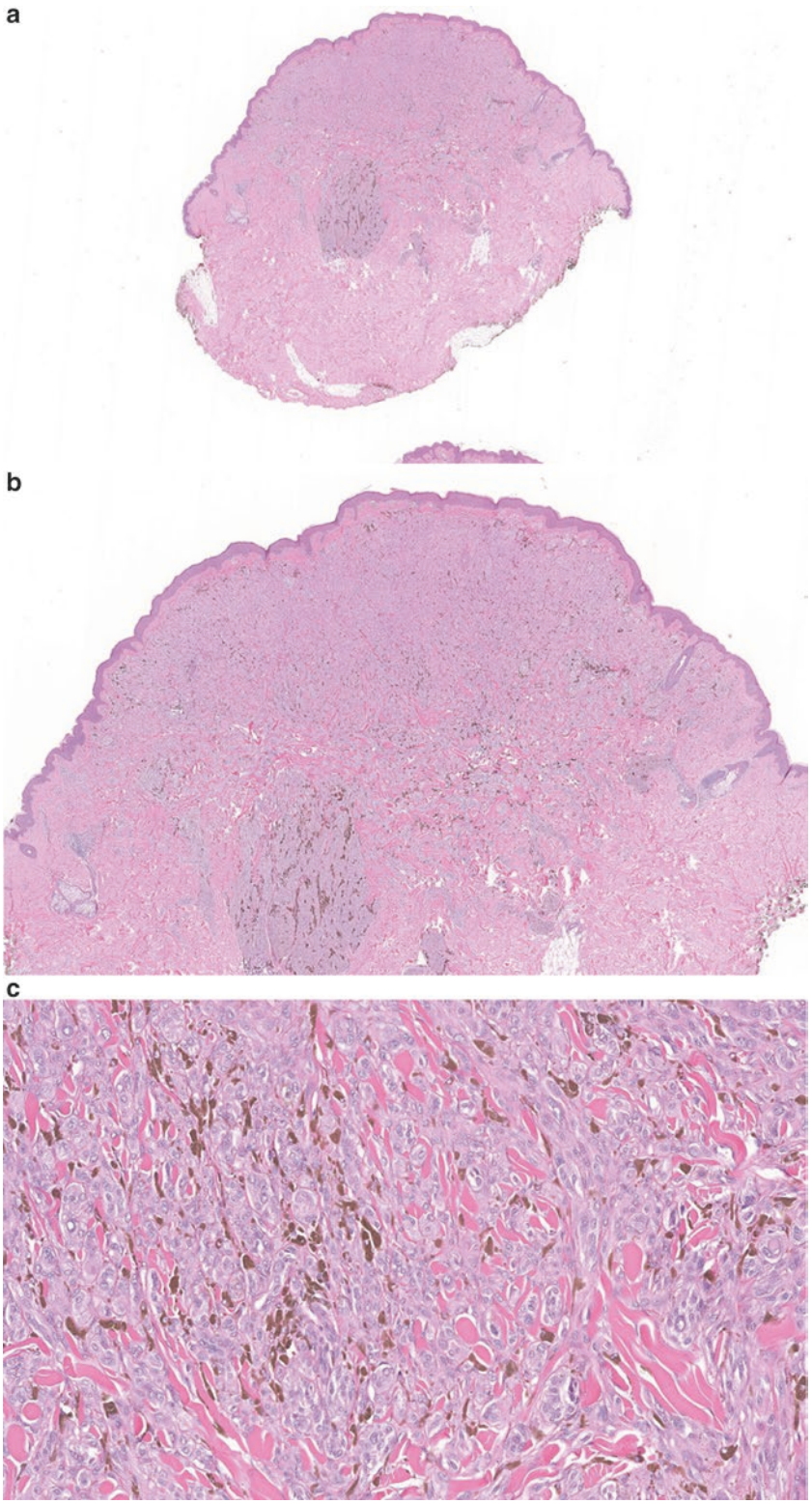

Fig. 2.21 Epithelioid cellular blue nevus. This is a polypoid lesion composed of epithelioid melanocytes with scattered areas of hyperpigmentation (**a**). Note the wedge-shaped growth in the dermis (**b**). The melanocytes are epithelioid and surrounded by scattered pigmented dendritic melanocytes (**c**, **d**).

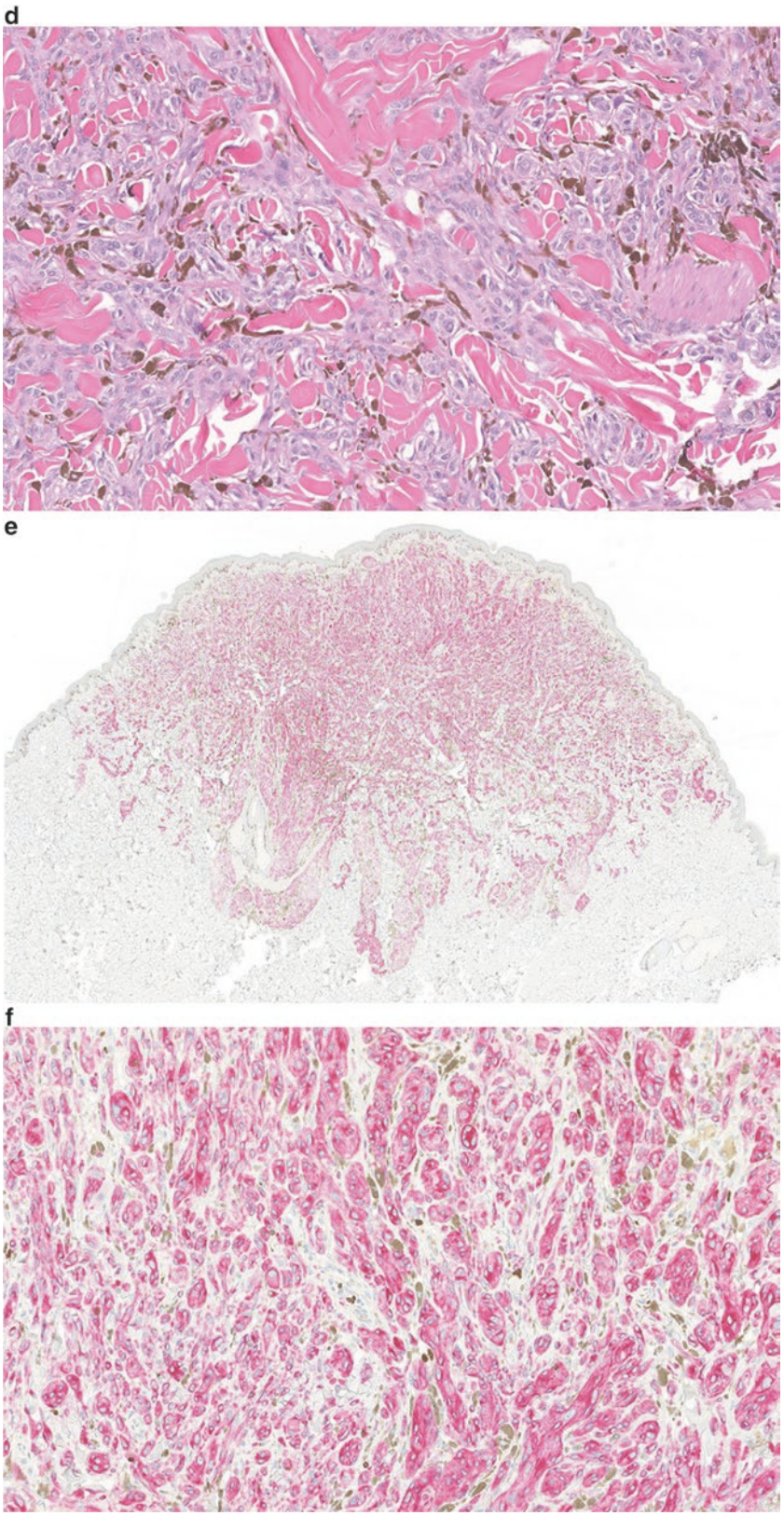

Fig. 2.21 (continued) A MART-1/Ki-67 dual stain. This cocktail is helpful to determine the proliferation rate of the lesion, which shows a low proliferation rate within the lesion (**e**, **f**)

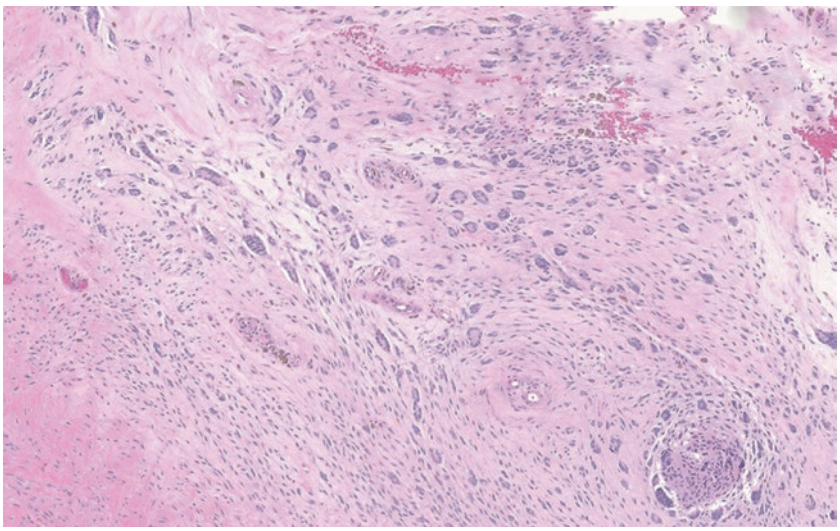

Fig. 2.22 Cellular blue nevus with multinucleated wreath-like giant cells. This example of cellular blue nevus is composed of multinucleated cells

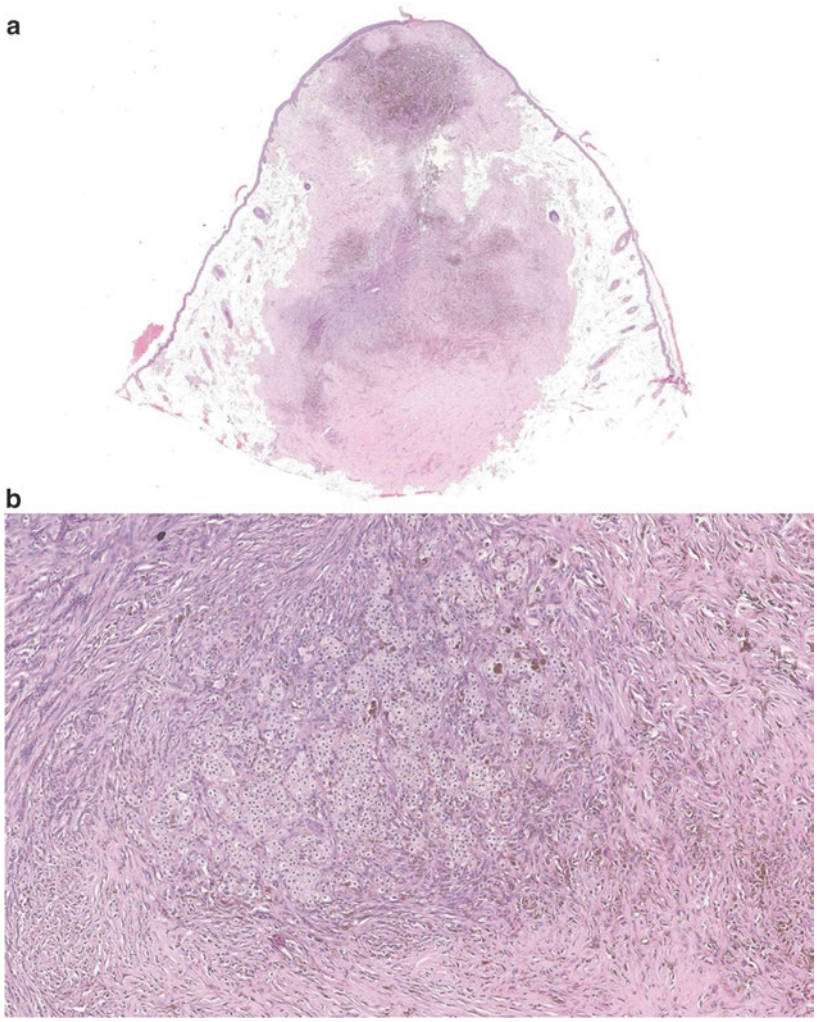

Fig. 2.23 Cellular blue nevus with balloon cell changes. This case is a rare form of cellular blue nevus. It shows a prominent balloon cell degeneration of melanocytes (**a**). The periphery of the lesion is composed of more typical areas of cellular blue nevus, but the center of the lesion shows increased number of melanocytes with balloon cell changes (**b**).

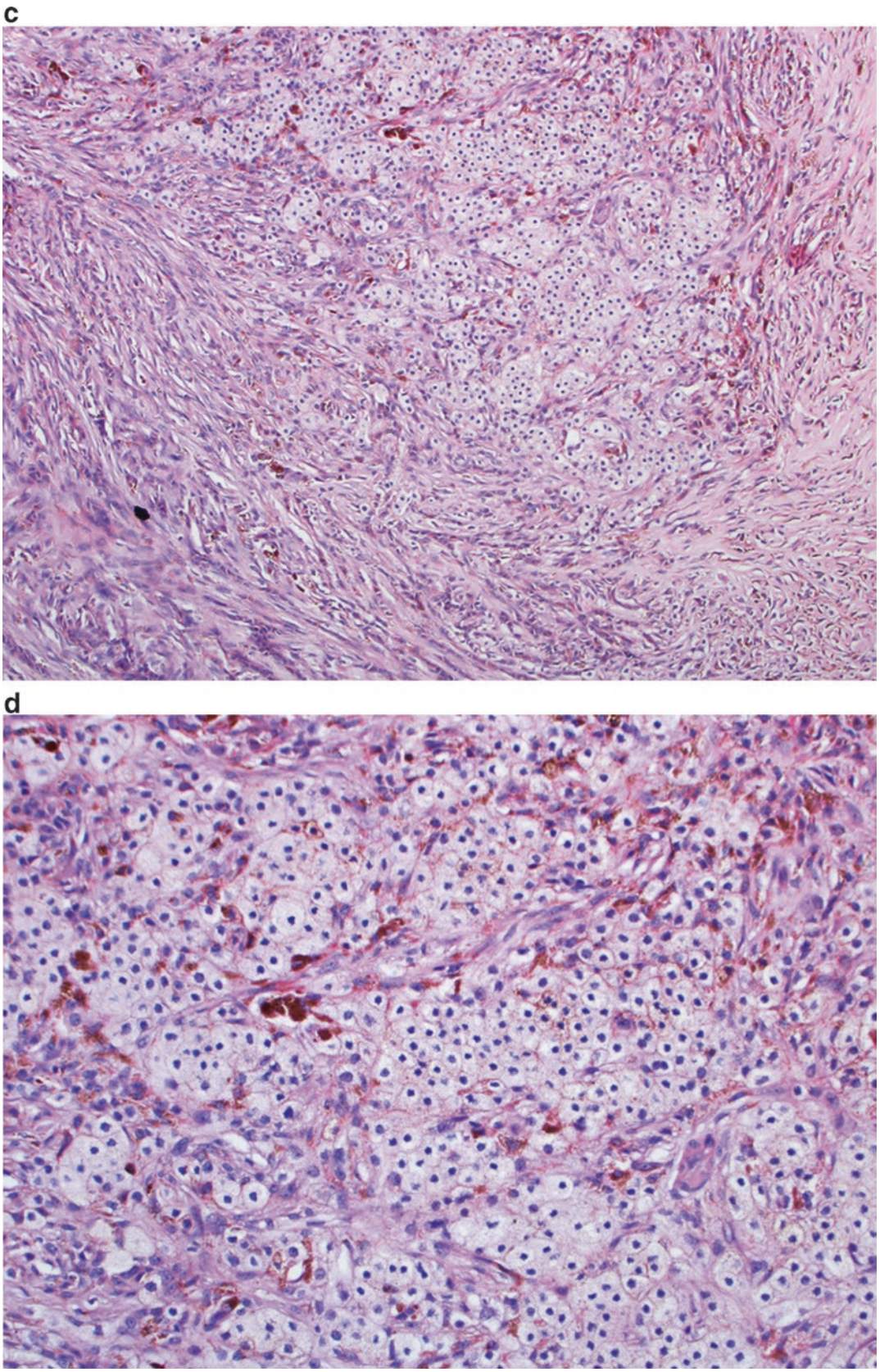

Fig. 2.23 (continued) Higher magnification showing the epithelioid melanocytes with ample clear and bubbly cytoplasm (**c**, **d**)

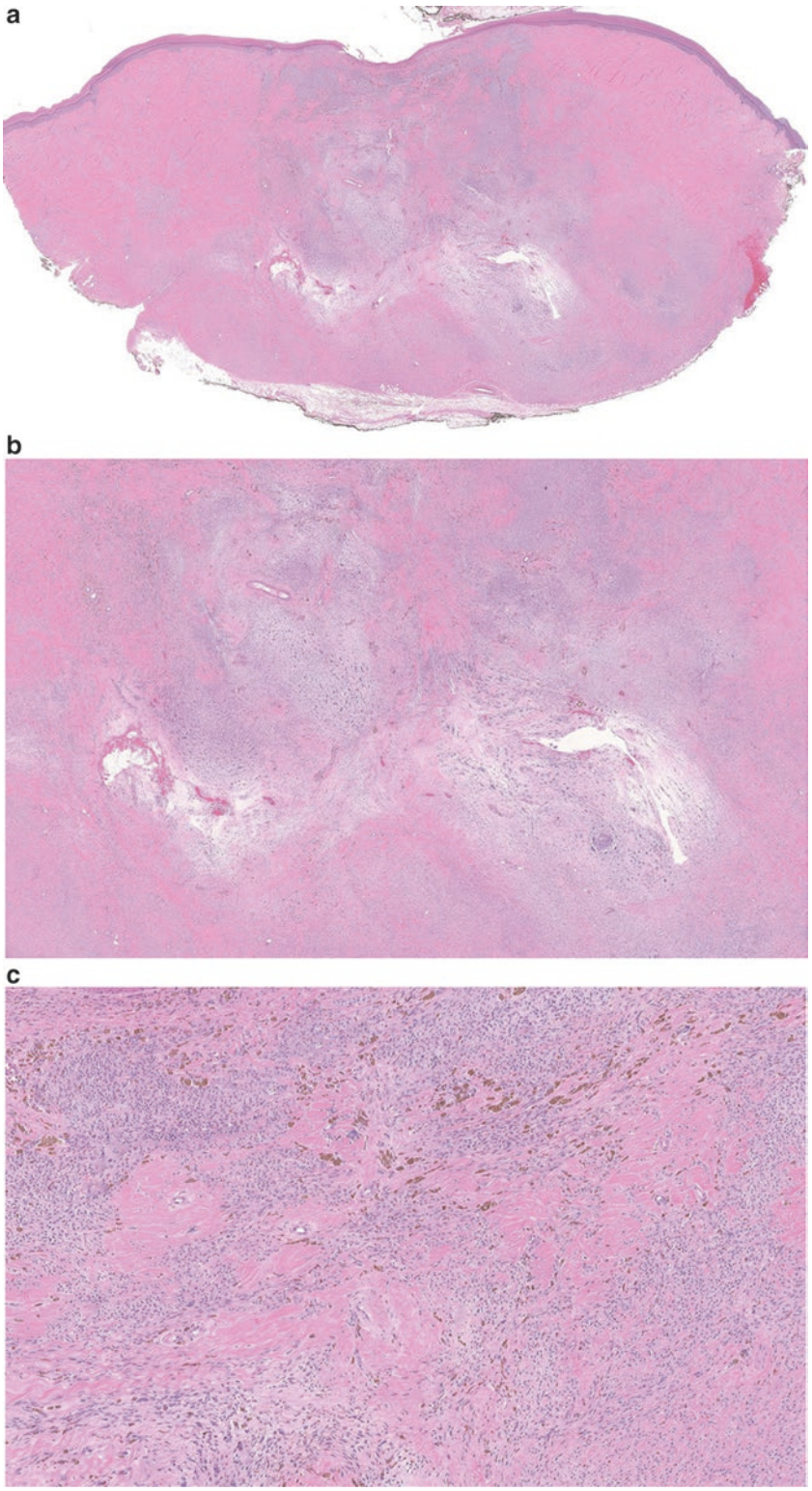

Fig. 2.24 Cellular blue nevus with myxoid and cystic degeneration. This example shows a clear cellular blue nevus with extensive areas of degeneration in the center of the lesion. Note the increased amount of hyalinization, fibrosis, and hemorrhage (**a**). Note the myxoid areas in the dermis along with cystic changes (**b**). The adjacent areas show clear-cut cellular blue nevus (**c**)

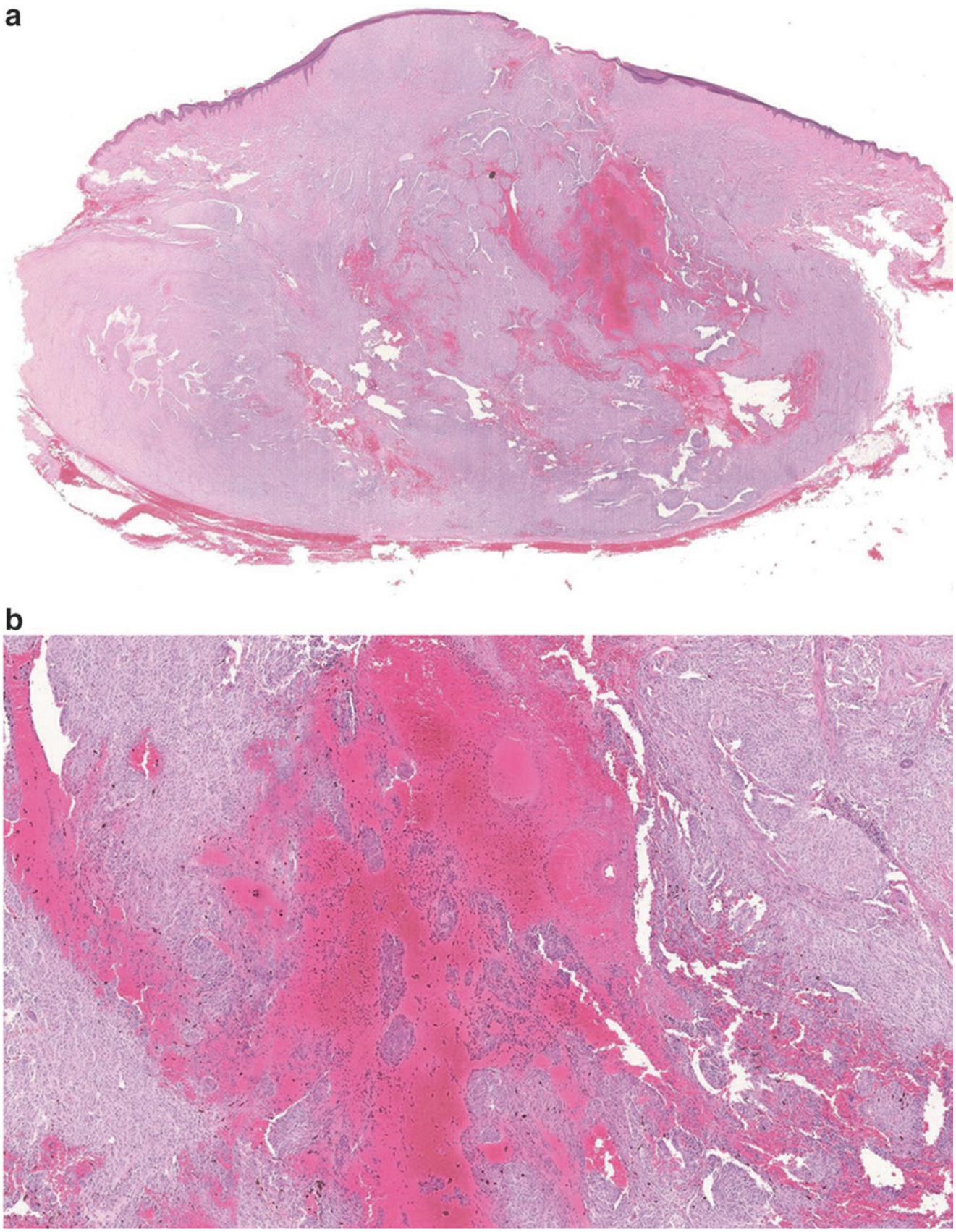

Fig. 2.25 Cellular blue nevus with marked stromal hemorrhage. This example displays a cellular blue nevus with areas of extensive hemorrhage (**a**). The diagnosis can be made by recognizing the surrounding areas of cellular blue. Note the hemorrhagic areas in between the cellular areas (**b**).

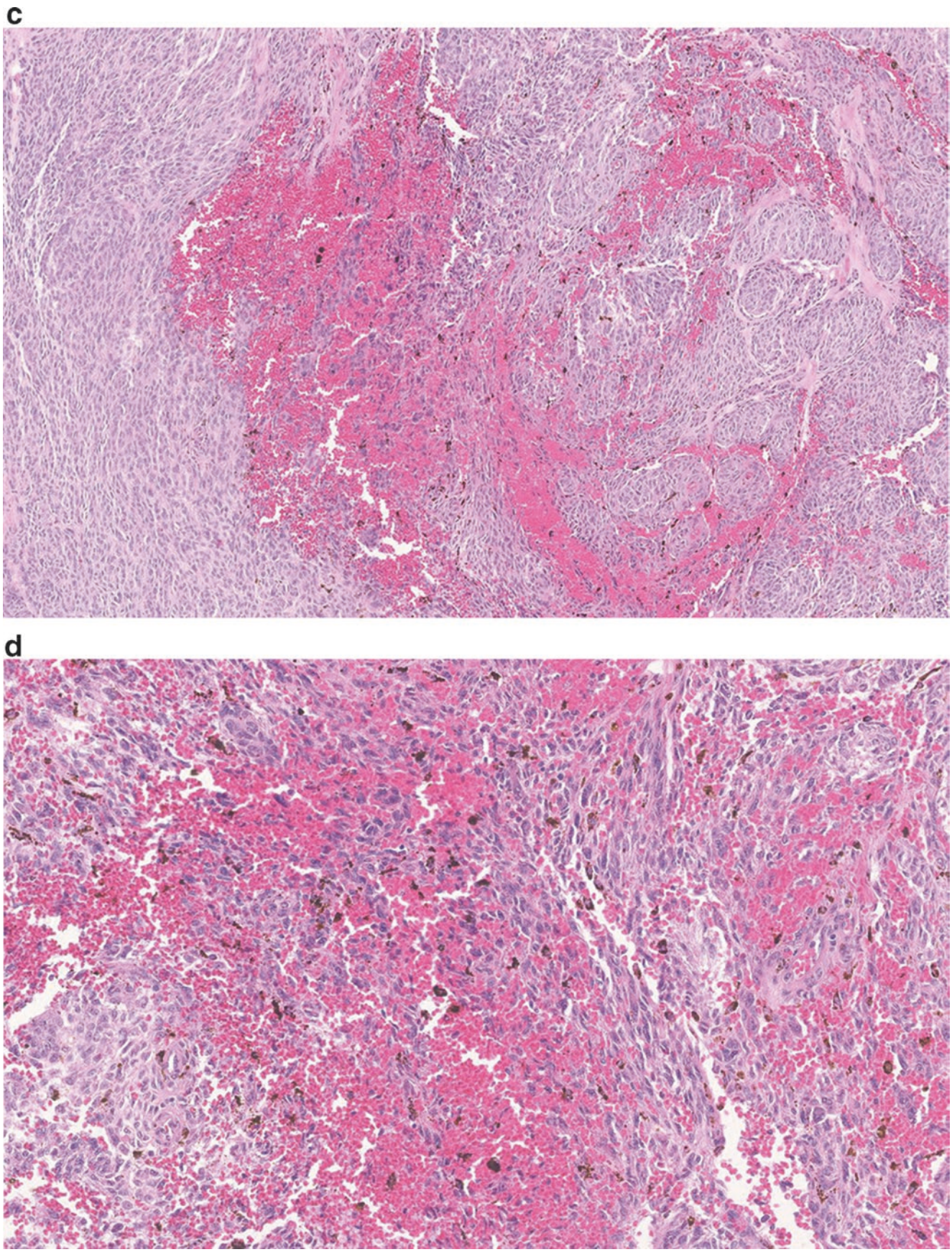

Fig.2.25 (continued) Higher magnification showing the small fascicles and nests of spindle and epithelioid melanocytes along with hemorrhage in the stroma (**c**, **d**)

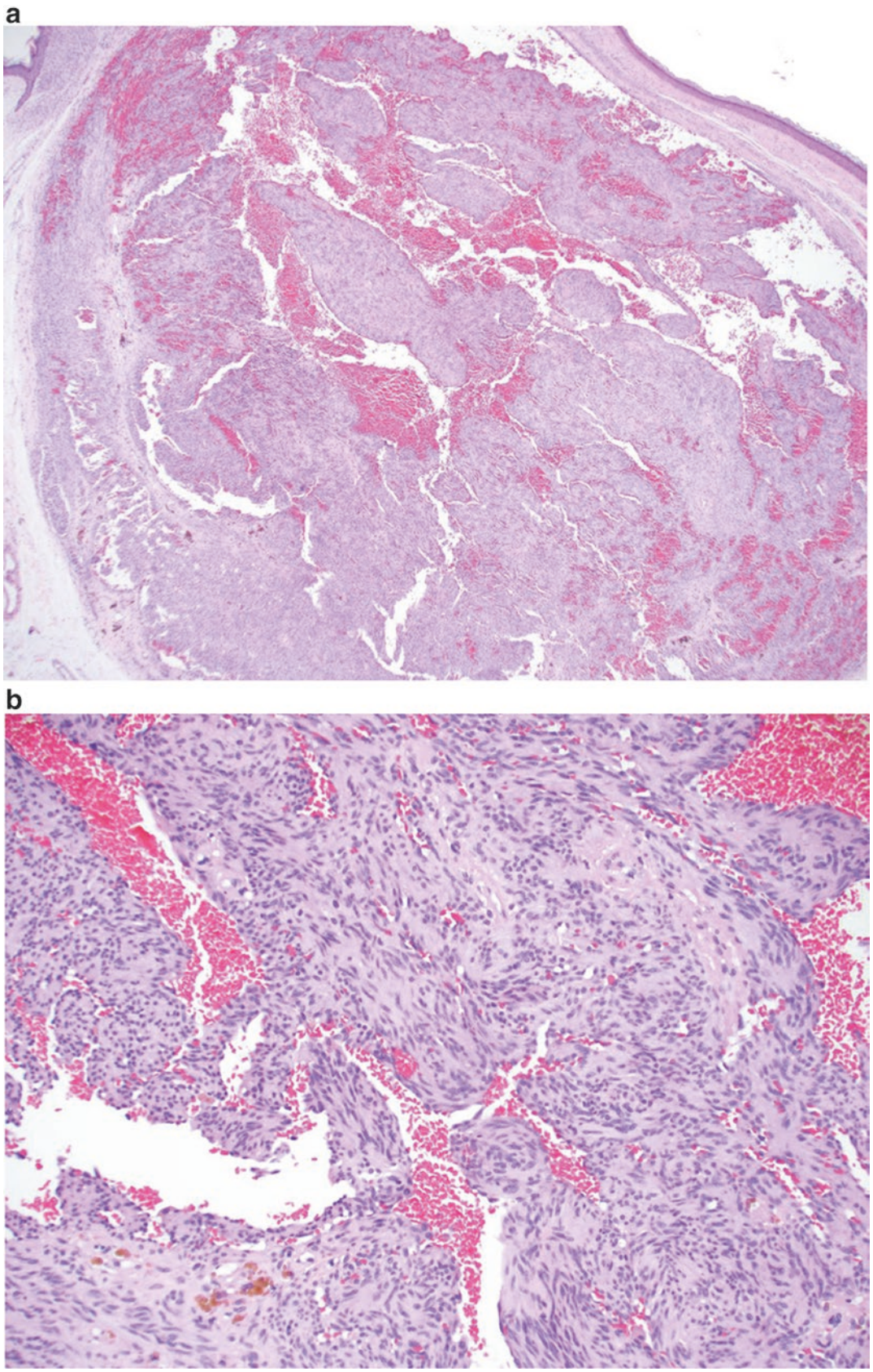

Fig. 2.26 Aneurysmal cellular blue nevus. This is a rare variant of cellular blue nevus (**a**). The lesion shows a nodular neoplasm in the dermis along with cystic areas filled with hemorrhage and with pseudovascular spaces lined by the lesional melanocytes (**b**).

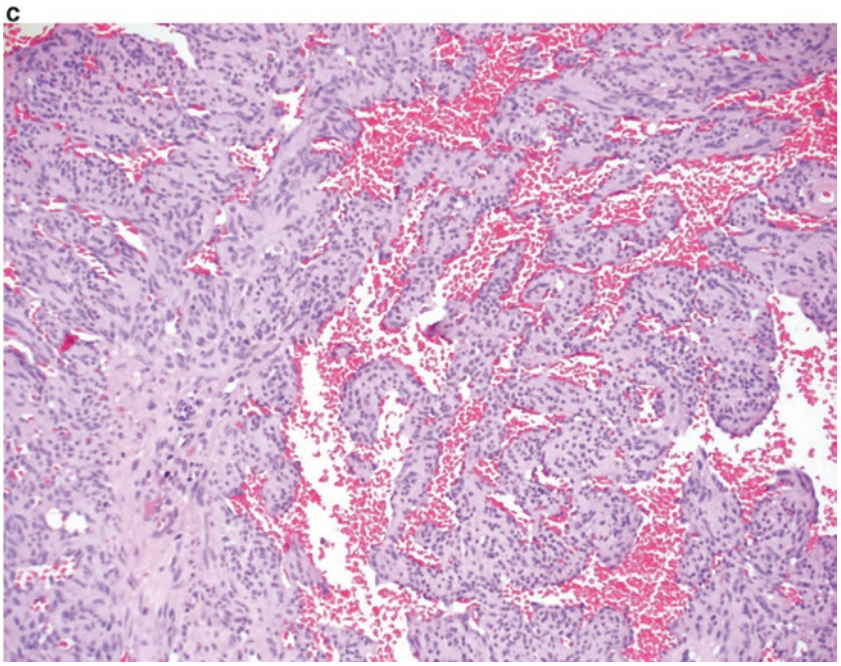

Fig. 2.26 (continued) High power of the blood-filled, nonendothelial lined pseudovascular spaces surrounded by the dendritic melanocytes (**c**). Courtesy of Kiran Motaparthi, MD (Miraca Life Sciences)

Variants of Cellular Blue Nevus

Amelanotic Cellular Blue Nevus

This variant is histologically similar to classical cellular blue nevus but with only minimal cytoplasmic pigment or melanophages [67]. The histologic diagnosis of amelanotic cellular blue nevus requires careful evaluation of the typical architectural and cytologic features of cellular blue nevus and may be very challenging to make an unequivocal diagnosis on a small biopsy. A diagnostic clue will be the proper identification of the biphasic nature of the tumor with classic blue nevus spindle and dendritic cell proliferation in the superficial dermis and cellular expansile nodules or sheets of round cells. By definition, there is minimal or no pigment visible in addition to only some pigmented melanophages in the septa between the cellular nodules. The majority of lesions have uniform cytologic features with little atypia, although in some cases, there may be mild nuclear pleomorphism. Features that are indicative of the malignancy include a sheet-like growth pattern, nuclear hyperchromasia and pleomorphism, tumor necrosis, numerous mitotic figures, and infiltrative borders. Due to lack of pigment, this variant poses a significant diagnostic challenge, and immunohistochemical studies can be used to confirm the melanocytic nature of the tumor and to highlight dendritic morphology of dendritic cells (S100p, HMB-45 antigen & MART-1) [67].

Plaque-Type Blue Nevus

This type of blue nevus is considered a variant of a cellular blue nevus since it contains significant areas that overlap with cellular blue nevi [68]. This rare variant poses also a significant diagnostic and therapeutic challenge due to its large size (up to 24 cm in diameter). The clinical presentation is of an ill-defined plaque with blue-gray pigmentation, often containing multiple papules and nodules more commonly seen in the scalp and trunk. The age range at presentation is wide, but congenital or childhood onset is most commonly seen with change in appearance and growth during and after puberty. Histologically, the tumors show varying cellularity with areas reminiscent of common blue nevus, dermal melanocytoses, and cellular blue nevus. These tumors are multinodular and show a diffuse growth pattern involving the dermis, subcutaneous fat, and muscular fascia but without a destructive growth pattern. They show multiple foci, similar to common blue nevus. The tumor nodules are localized mainly in subcutaneous fibrous septa and in fascia. Mitotic figures can be observed but are rare (2/50 HPF); however, necrosis, cytologic atypia, or nuclear pleomorphism should be absent [68, 69]. The cells are uniform, ovoid to spindled, in a background of pigmented dendritic cells, separated and surrounded by loose aggregates of clusters of heavily pigmented dendritic melanocytes and melanophages in a fibrous stroma. Similar to cellular blue nevi, there may be neurotropism and angiotropism.

Features that favor a plaque-type blue nevus and not melanoma include the lack of cytologic atypia and low mitotic and proliferative index, which is similar to what is seen in cellular blue nevus. What is different and set them apart from most cellular blue nevus and atypical cellular blue nevus (see below) are the presence of multinodularity, a deep growth component in the subcutis (even in fascia) and the background setting of a large lesion with multiple foci of common blue nevus and melanocytoses. Cases of melanoma arising in a plaque-type blue nevus have been described; thus, we recommend careful inspection of the entire lesion when analyzing such neoplasms [70].

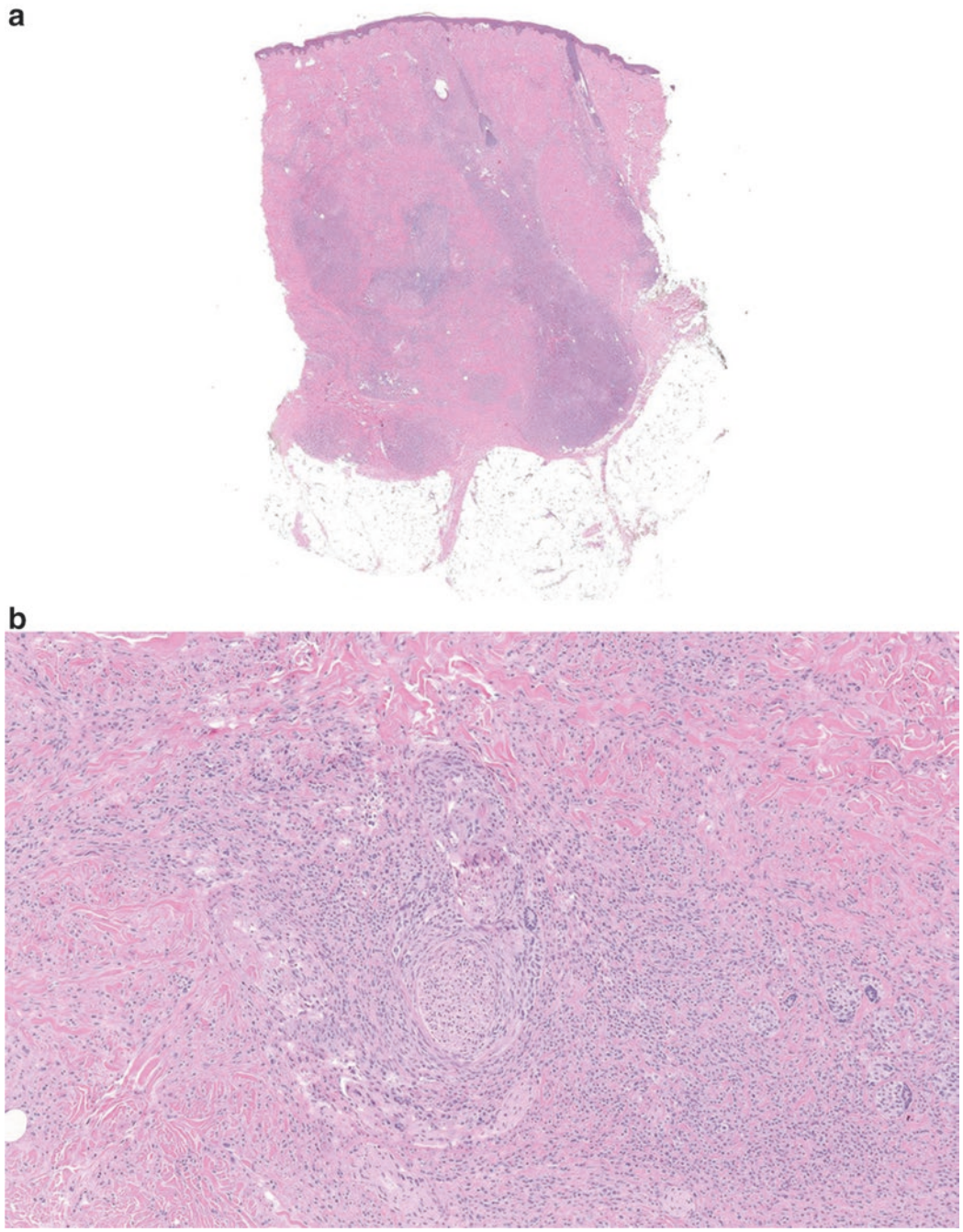

Fig. 2.27 Amelanotic cellular blue nevus. Scanning magnification shows a cellular melanocytic dermal neoplasm with dumbbell architecture and a clear lack of pigmentation (**a**). There is no pigment visible and there is lack of pigmented melanophages in the septa between the spindle cells (**b**).

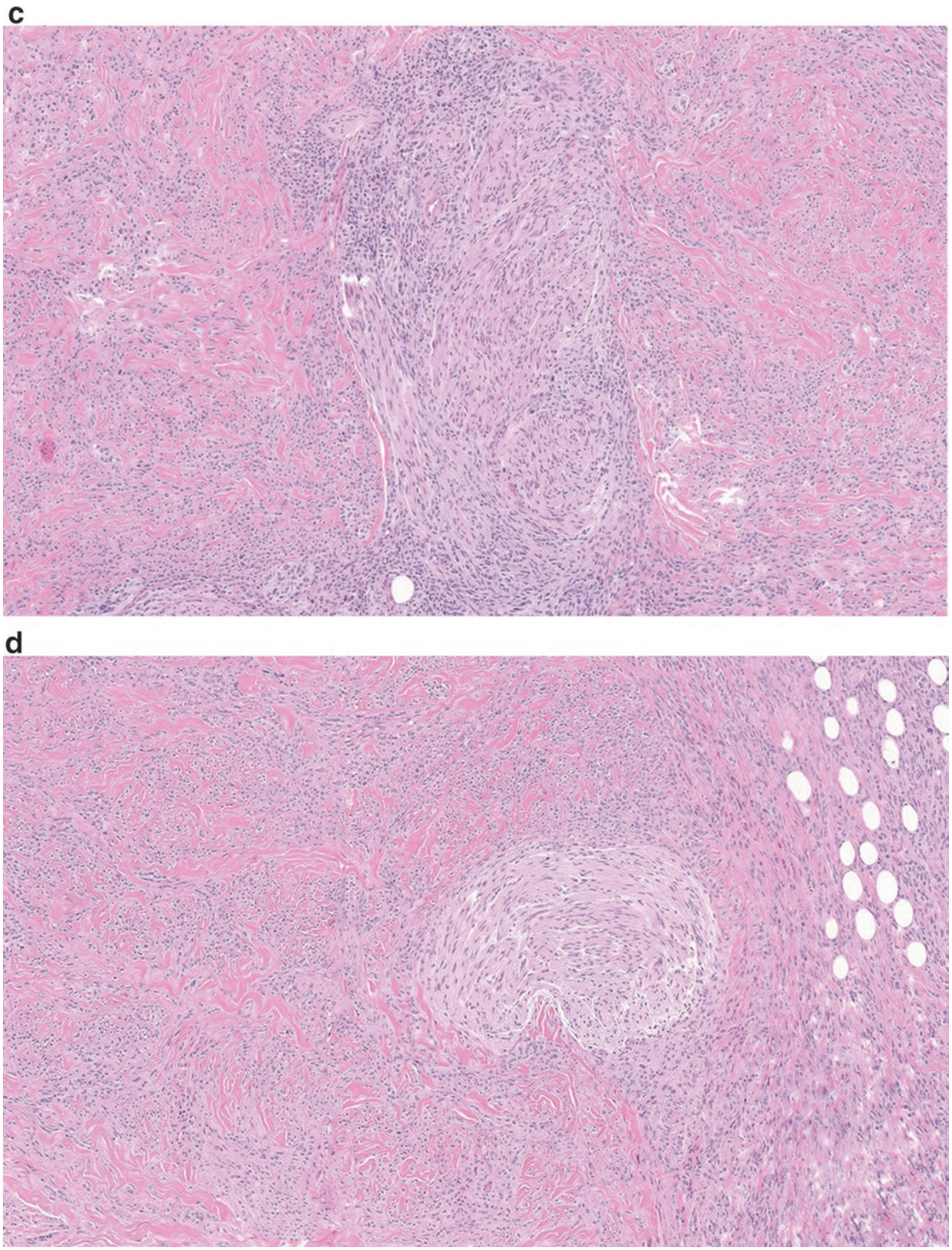

Fig. 2.27 (continued) Note that some spindle cells are wrapping some nerves bundles. Note the nerve hypertrophy that is not unusually observed in cellular blue nevi (**c**). Characteristic uniform cytologic features with little to minimal cytologic atypia (**d**)

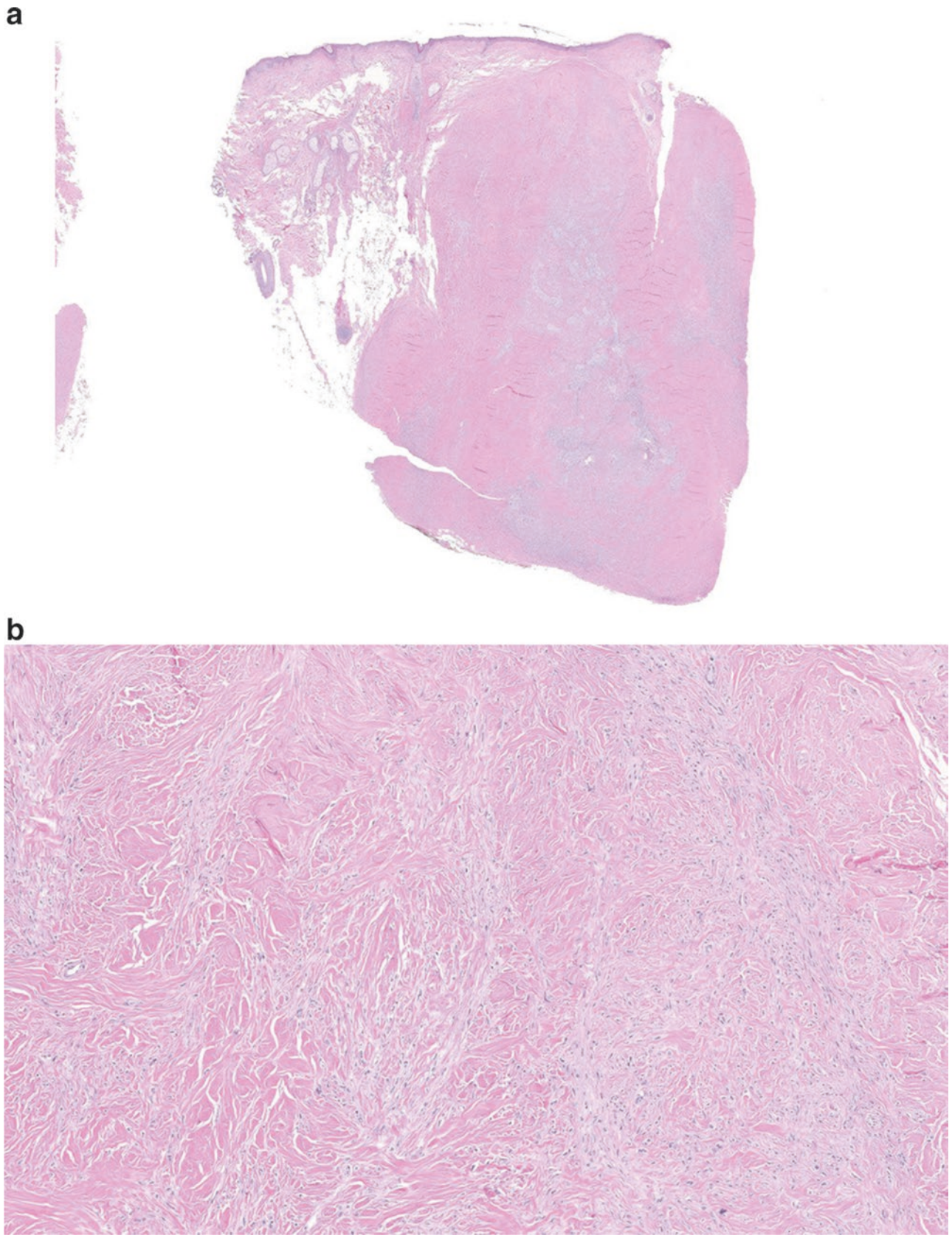

Fig. 2.28 Amelanotic cellular blue nevus. This example shows areas that have a scar-like growth in the dermis along with increased density of melanocytes and elongated distribution. Note the clear lack of pigmentation (**a**). The cells are arranged in long fascicles and dissecting the collagen bundles (**b**).

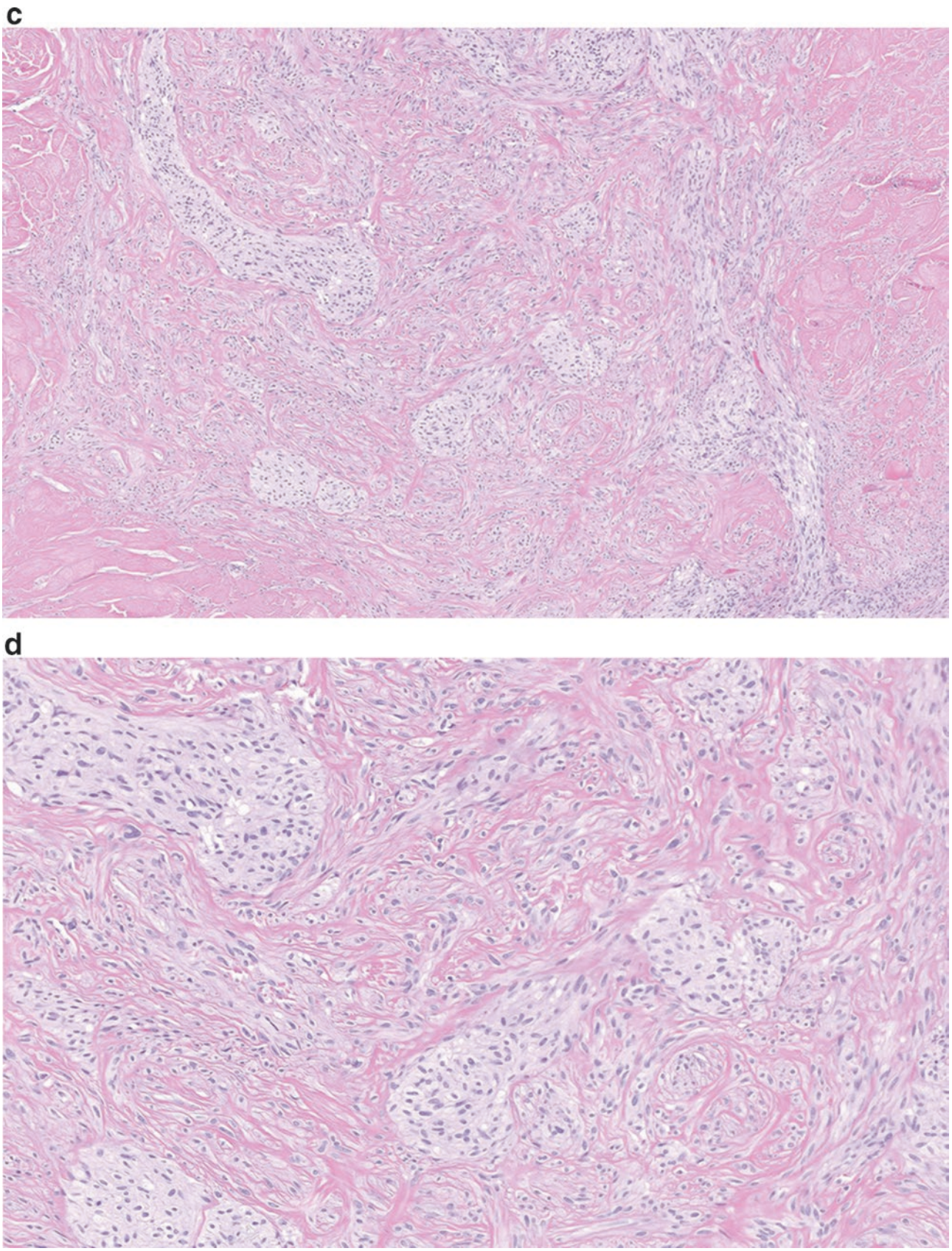

Fig. 2.28 (continued) In other areas the lesion is composed of masses of monomorphic melanocytes surrounded by mature collagen (**c**). The nests are composed of mature pale melanocytes with a monomorphic appearance. There are no mitotic figures (**d**)

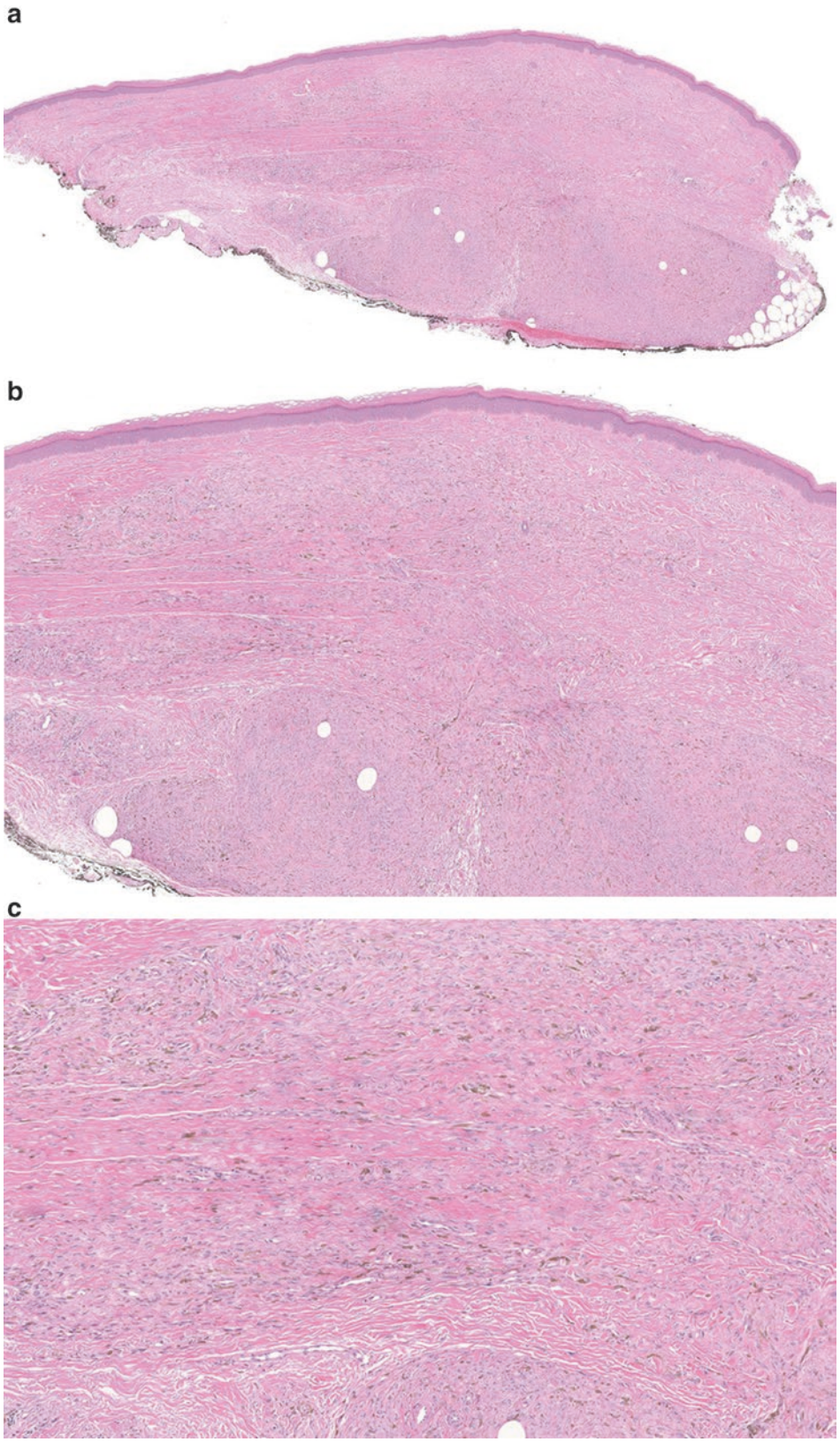

Fig. 2.29 Plaque-type cellular blue nevus. Scanning magnification shows a multinodular lesion with a diffuse growth pattern involving subcutaneous fat (**a**). Note the varying cellularity with areas reminiscent of conventional blue nevus and cellular blue nevus (**b**). Uniform spindle melanocytes associated with pigmented dendritic cells and by loose aggregates of pigmented dendritic melanocytes in a fibrous stroma (**c**).

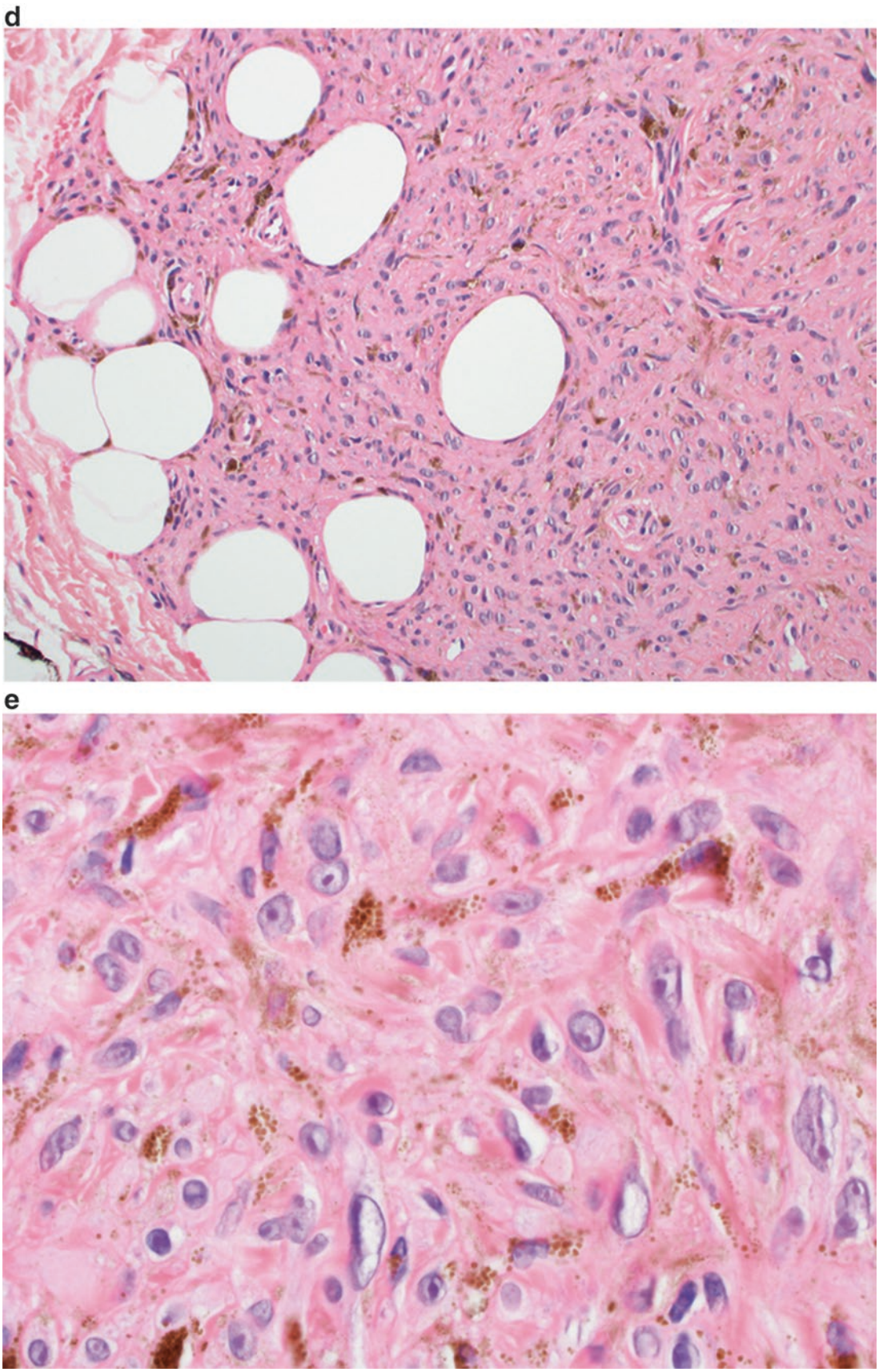

Fig. 2.29 (continued) Higher magnification of the uniform melanocytes and dendritic cells (**d**). Note the uniformly atypical cells with similar sizes and shapes of single, central nucleoli (**e**)

Atypical Cellular Blue Nevus

Clinical Features

Atypical cellular blue nevus (ACBN) (also known as cellular blue nevus-like melanocytic tumor of uncertain malignant potential) is a rare histologic variant of cellular blue nevus with atypical features but without clear-cut histologic evidence of malignancy. Histopathologic criteria for the distinction of CBN from BNLM have been proposed in the literature; however, such criteria are not reliable in some cases, because some CBNs demonstrate characteristics overlapping those of malignant lesions. As a result, this intermediate category of tumors (ACBN) has been introduced to accommodate these controversial or borderline neoplasms [62]. Some authors define these lesions as showing focal areas of cytologic atypia, dermal mitotic figures, or focal necrosis but not being present in the same lesion [23, 62, 71, 72]. Similarly to CBN, these tumors are more commonly seen in the buttock or sacral region of young or middle-aged adults. These tumors are usually solitary, predominantly dermal nodules, and some extending into the superficial subcutis. Some studies have shown that these neoplasms can recur and may progress to a more aggressive phenotype if incompletely excised, whereas other authors found no evidence of recurrence or metastasis in such cases [61]. In our opinion, when confronted with a case that is difficult to classify as benign or malignant, the pathology report should reflect this uncertainty (indeterminate malignant potential), the lesion should be excised completely, and the patient should be observed carefully for evidence of recurrence.

Histopathology

There is substantial disagreement among pathologists about the definitions and biologic nature of the spectrum of cellular blue melanocytic neoplasms. The difficulties are possibly due to several factors including their low frequency and that there appears to be a continuum of overlapping features between atypical and malignant forms. ACBN is very similar histologically to CBN, but they show asymmetry, hypercellular foci, focal cytologic atypia, and occasional dermal mitotic figures (<2/mm^2). ACBN may be considered when the lesion is large (size >3 cm), ulceration, increased cellularity, focal cellular pleomorphism, and dermal mitotic figures (≤2/mm^2) [72]. As a general rule, atypical mitotic figures are not seen in ACBN. However, there is no clear consensus among experienced dermatopathologists [71]. These results highlight the lack in poor interobserver reproducibility. ACBNs may show other histologic features, including the presence of degenerative changes and hemorrhage, which can be misinterpreted as tumor necrosis. As delineated in this text, it is difficult to define the limits of atypicality that are acceptable in CBN on the one hand and the minimal essential criteria for diagnosis of BNLM.

Differential Diagnosis

The differential diagnosis of ACBN is primarily with CBN and BNLM. BNLM has at least some of the following: large size (>6 cm), high mitotic activity (>2/mm^2), atypical mitotic figures, marked cytologic atypia, increased cellular density, cell crowding, expansile growth, and necrosis [73, 74]. In our opinion, of all these features mentioned, atypical mitotic figures and geographic necrosis may be the most helpful distinguishing feature.

ACBN is distinguished from CBN by the presence of asymmetric growth, hypercellular foci, focal cytologic atypia, and occasional dermal mitotic figures (<2/mm^2). Available follow-up data on ACBN suggest that most of these tumors have a favorable outcome; however, local recurrence may occur [61, 62]. Rare cases of ACBN have shown lymph node deposits; however, it is not completely clear if the presence of this indicates true malignancy or, as in cases of PEM, is just an indication of intermediate malignant potential, similar to the reported lymph node involvement in pigmented epithelioid melanocytoma.

Immunohistochemistry and Molecular Testing

Immunohistochemistry has been used in the histologic differential diagnosis between CBN, ACBN, and BNLM. Ki-67 has its limitations to unequivocally separate cellular blue nevus and ACBN since there is no clear cutoff among the three diagnostic categories. Lost expression of HMB-45 antigen and increased expression of Ki-67 favor BNLM.

Using comparative genomic hybridization (CGH), one study showed that ACBN has more chromosomal aberrations (copy number increases in chromosome 6p, 8, and 9q and deletions in chromosome 3 and 15) than unequivocally benign CBN, but are less frequent in number than unequivocal BNLM [66]. In that study, authors concluded that the presence of at least three chromosomal aberrations in dermal melanocytic proliferations was suggestive of melanoma. These authors also stated that ACBN can be separated into lesions with and without chromosomal aberrations thus suggesting that studies with clinical follow-up may be able to determine which aberrations are prognostically most informative. Studies have shown a strong association of FISH positivity with adverse outcome in some other types of ambiguous melanocytic tumors [75].

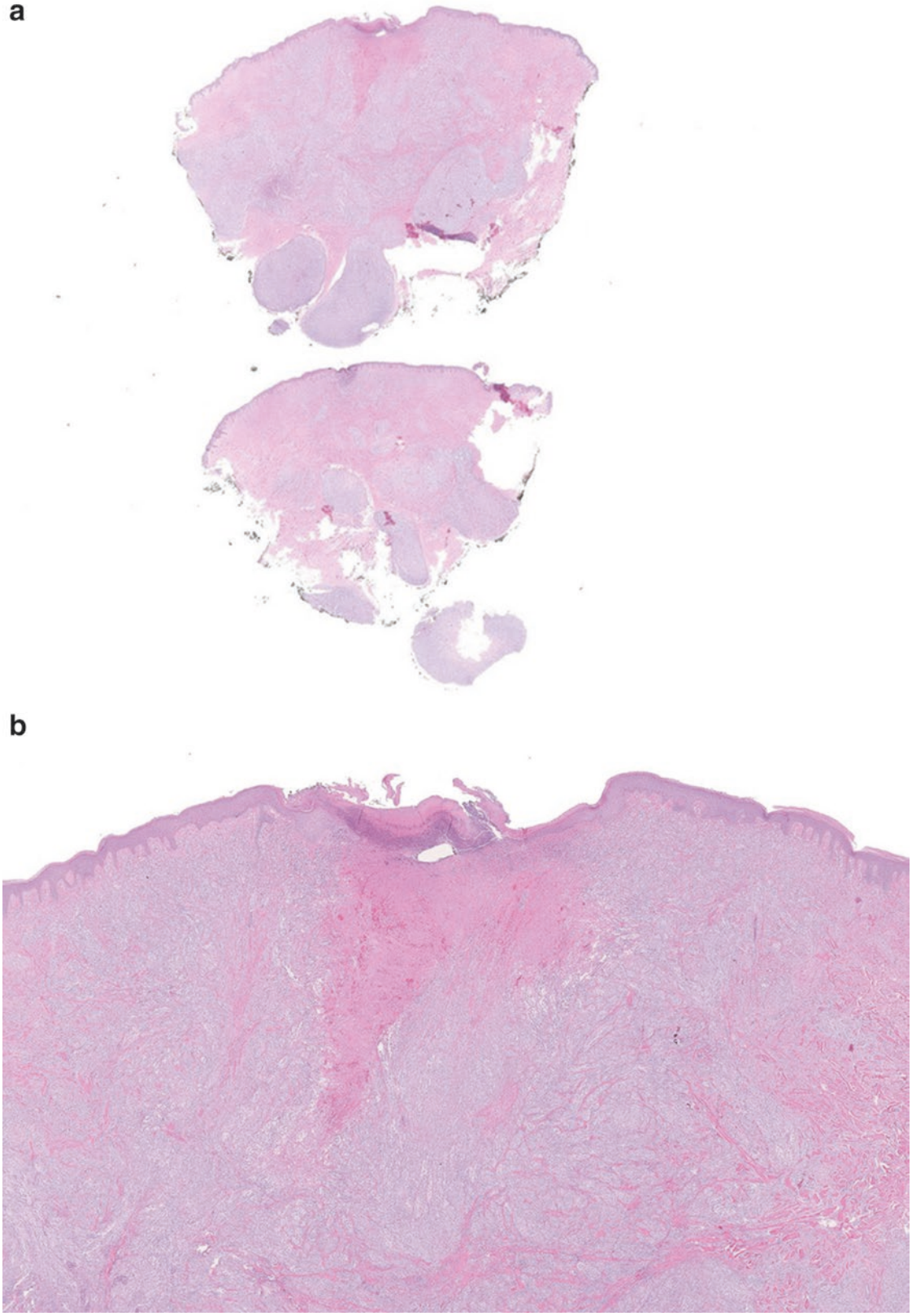

Fig. 2.30 Atypical cellular blue nevus. This is a challenging case as it shows many features similar to cellular blue nevus (**a**). However, the lesion was large, ulcerated, and with increased cellularity and dermal mitotic figures (2 per mm2). In these cases, CGH can represent a useful adjunct test to confirm the benign nature of the lesion. Note the areas of ulceration along with increased density of melanocytes in the dermis (**b**).

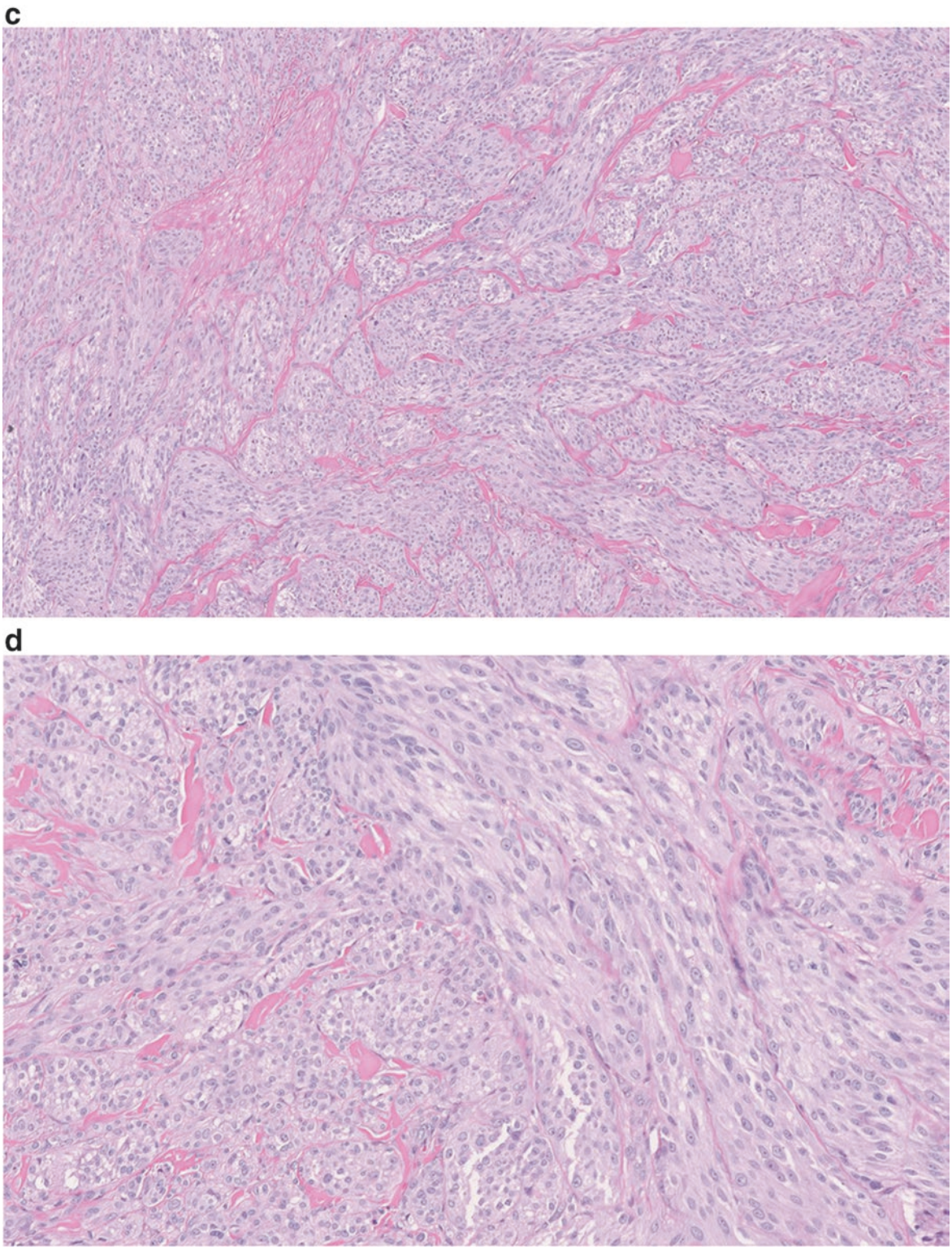

Fig. 2.30 (continued) Note the large nests of melanocytes with an expansile growth pattern (**c**, **d**)

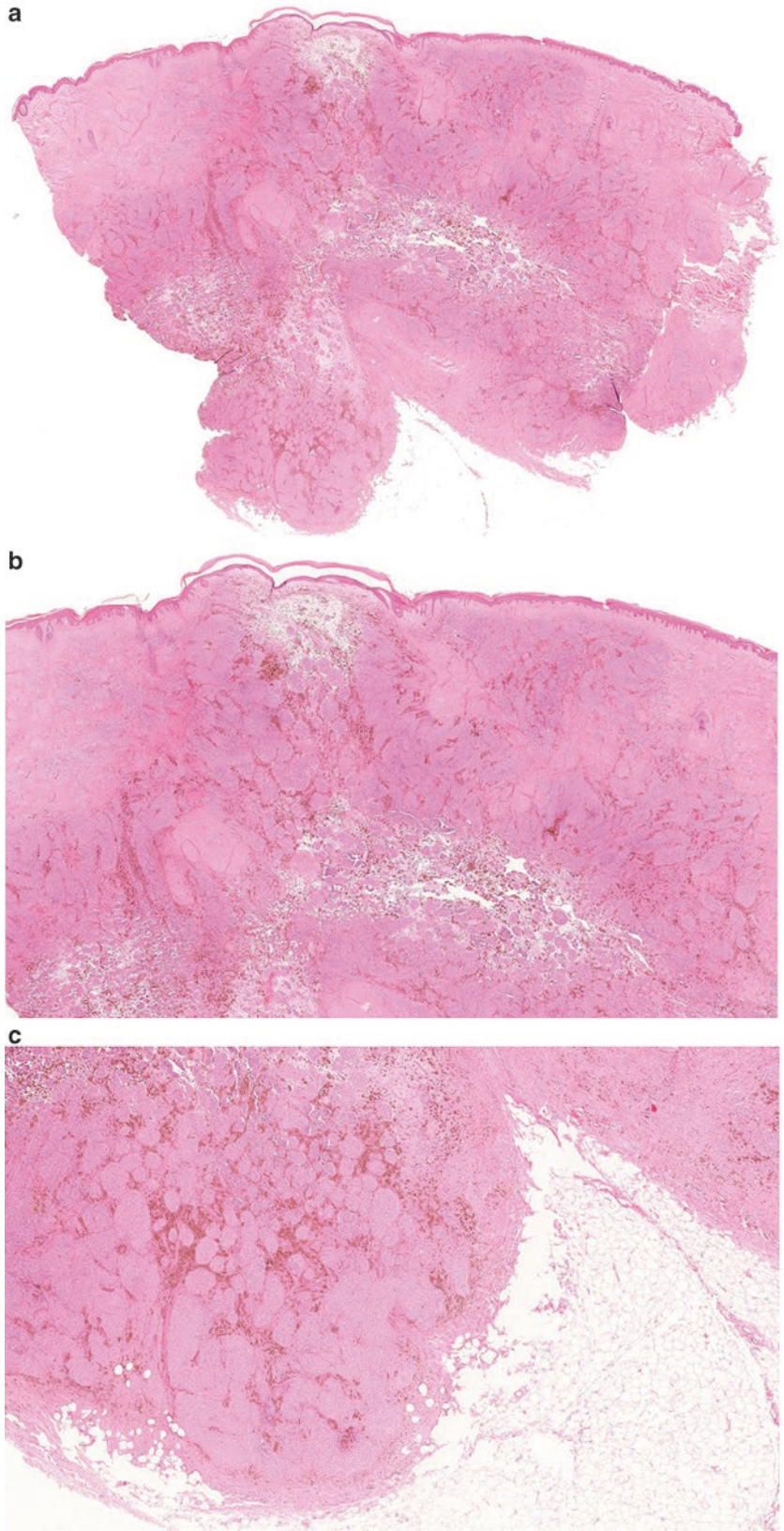

Fig. 2.31 Atypical cellular blue nevus. This is another challenging case as it does show unusual features and does not fit perfectly into the cellular blue nevus category. Scanning magnification shows an asymmetric lesion in the dermis composed of hypercellular areas reminiscent of a cellular blue nevus. The lesion is composed by large and confluent nests of melanocytes in the dermis (**a**). Note the degenerative changes in the background (**b**). Hypercellular nests pushing into deep dermis similar to what is observed in a cellular blue nevus (**c**).

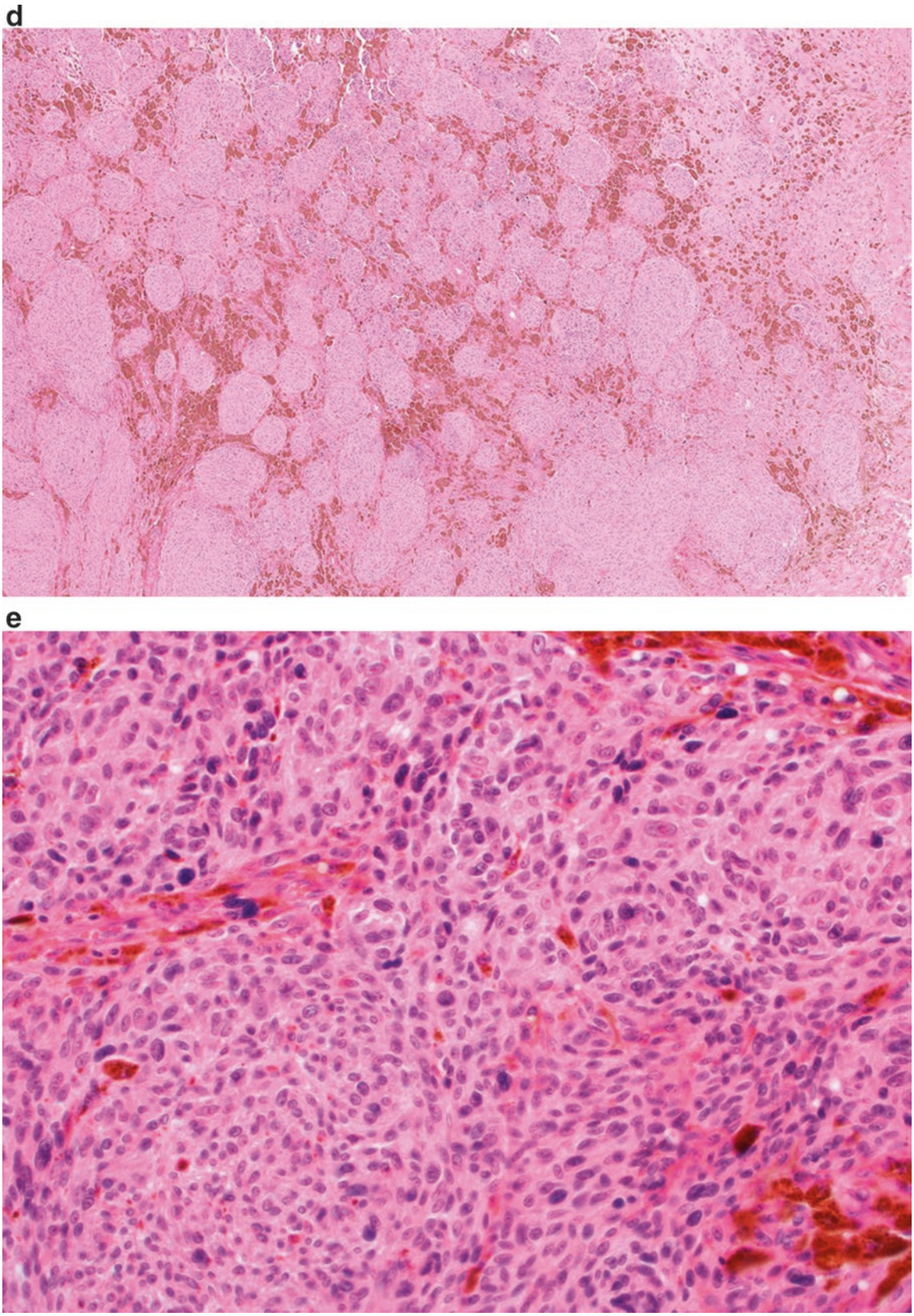

Fig. 2.31 (continued) Note the variable size of nests in the dermis along with the presence of heavily pigmented melanophages (**d**). Higher magnification displays focal cytologic atypia (**e**).

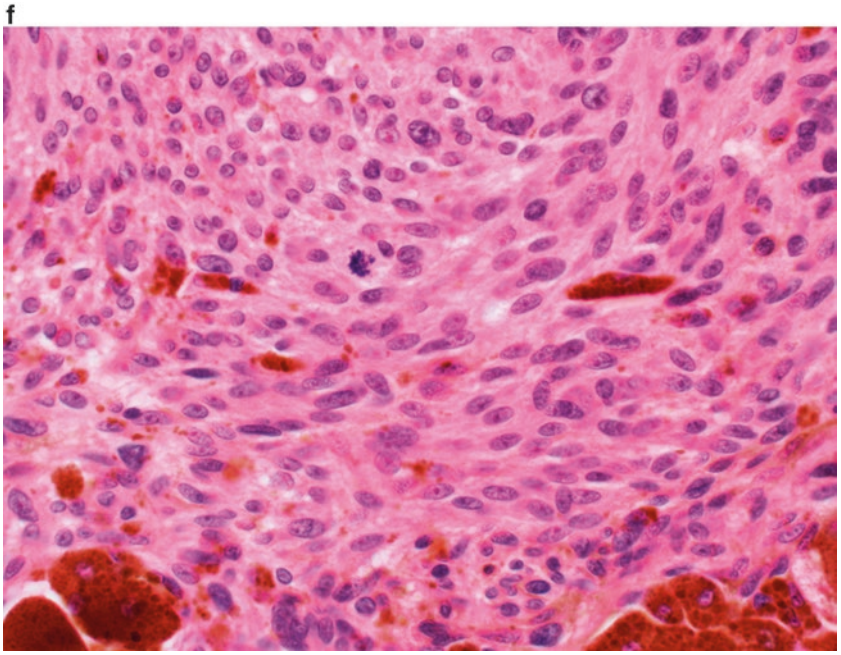

Fig. 2.32 (continued) Note the mitoses in this field (this case showed 2 mitoses per mm^2) (**f**)

Blue Nevus-Like Melanoma (Malignant Blue Nevus)

Clinical Features

Blue nevus-like melanoma (BNLM) is a rare and aggressive type of melanoma that was first described by Allen and Spitz under the name malignant blue nevus [76]. They described lesions that had features similar to blue but resulting in metastasis and death. This term has been used to describe malignant change arising in a preexisting cellular blue nevus, melanoma arising at the site of a blue nevus, melanoma with architectural features resembling cellular blue nevus, or melanoma with an admixed, benign, cellular blue nevus component [60, 73, 74, 77]. However, as with others, we discourage the use of the term "malignant" blue nevus for the contradiction of using "malignant" and "nevus" (connoting a benign tumor) in the same description.

Many BNLMs arise in association with a cellular blue nevus but can also be associated with other melanocytoses including blue nevi, nevus of Ota, and nevus of Ito [78, 79]. The diagnosis of BNLM may be easily rendered when there is high mitotic rate (>2/mm^2) or when there are atypical mitotic figures, tumor necrosis, or a nodular proliferation of atypical epithelioid cells [80]. These tumors are more commonly seen in the fourth decade of life and in men. Clinically they are usually large (range in size 3–13 cm). In some cases, there is satellitosis around the primary tumor. They have even distribution among several body sites (face, buttocks, chest), but have a predilection for the scalp. BNLMs tend to present at relatively high stage (high Breslow thickness, median 5.5 mm) and have a metastatic pattern comparable to other types of melanoma [81]. BNLM are aggressive neoplasms with frequent metastases to regional lymph nodes and distant sites. In addition to the Breslow thickness, other possible prognostic factors that are indicative of a poor prognosis include the presence of a congenital lesion, older age, and high mitotic count. BNLMs should be treated in the same way as any other melanoma variants based on clinical staging and pathologic prognostic indices. Sentinel lymph node biopsy may provide prognostic information similar to conventional melanoma [82, 83].

Histopathology

As mentioned above, there are no absolute histologic criteria to distinguish BNLM from other pigmented melanocytic lesions. Among helpful features is the biphasic architecture showing a benign component typified usually by the presence of a standard or cellular blue nevus (in many cases there is a combination of both cellular blue and a conventional blue nevus components); however, some cases apparently arise de novo. The areas of cellular blue nevus show solid aggregates of monomorphous ovoid cells with round vesicular nuclei with inconspicuous nucleoli and ample pale cytoplasm containing only minimal melanin pigment. The areas of conventional blue nevus are composed of spindle bipolar melanocytes with long dendritic cell processes (most of them filled with

granular melanin pigment). A common feature is the presence of abundant, pigmented melanophages and prominent sclerosis among the fascicles of dendritic melanocytes.

The malignant component is usually located in the reticular dermis and subcutaneous fat as a deep-seated, asymmetric, and expansile nodule. The surrounding benign component usually displays an abrupt transition with the malignant component. The malignant component is characterized by sheets of atypical melanocytes that have pushing borders and involve diffusely the deep dermis and destroy the adjacent structures. These atypical melanocytes are large with a combination of epithelioid and spindle shapes. They have abundant cytoplasm and pleomorphic and hyperchromatic nuclei with prominent nucleoli and usually only minimal melanin pigment. There is rarely striking vacuolization of the cytoplasm. The presence of widespread necrosis is sometimes seen in the malignant component (1/3 of cases); however, focal necrosis has also been reported in classical cellular blue nevus [60]. In our opinion, in the absence of prior biopsy or trauma, the presence of necrosis is highly concerning for malignancy and should be used as a red flag. Also in our experience, the vast majority of BNLM have high mitotic rate (>2/mm^2), atypical mitotic figures, vascular invasion, expansile/destructive growth, marked cytologic atypia, and infiltrative margins [77]. Occasional cases of BNLM may, however, be associated with a negligible mitotic rate. Some studies have shown that the presence of atypical mitotic figures and tumor necrosis correlates best with malignant behavior; however, they should always be interpreted in the context of other features.

Differential Diagnosis

BNLM should be distinguished from cellular blue nevus with or without atypical features (ACBN). In addition to the lack of absolute distinguishing criteria, the observation that CBN may commonly involve regional lymph nodes only increases the diagnostic difficulty. Clinically, BNLM are usually >3 cm in size, whereas cellular blue nevi are usually <2 cm. Also, BNLM are much more irregular and asymmetric and with a more nodular architecture than cellular blue nevus. Microscopically, BNLM can generally be distinguished from cellular blue nevus by the presence of a frankly malignant component. Unequivocal BNLM are characterized by widespread necrosis in many cases, although focal necrosis has been reported in cellular blue nevi. Also, the presence of necrosis must be distinguished from the areas of liquefactive degeneration common in some cellular blue nevi, especially those found in sites of pressure, such as the buttock or foot. Compared with tumor necrosis in melanomas, the liquefactive necrosis seen in some cellular blue nevi tends to be associated with cystic degeneration, myxoid change, and edema (see above). Other criteria supportive of a diagnosis of BNLM include high mitotic rate, abnormal mitotic figures, vascular invasion, expansile or destructive growth, marked cytologic atypia, and infiltrative margins [81]. Since cellular blue nevi can have rare dermal mitotic figures, mitotic rate cannot be used as a sole or even major histologic criterion of malignancy. However, any cellular blue nevus with mitotic activity should be examined carefully for other features of malignancy. And since the distinction between BNLM and ACBN sometimes can be exceedingly difficult, all cases of ACBN should be completely excised with long-term follow-up.

Due to the markedly difference in prognosis, it is very important to distinguish BNLM from a metastatic melanoma mimicking blue nevus [56]. These metastases can occur in the same anatomic site as BNLM and may show very similar histologic features. However, metastatic melanoma mimicking blue nevus will lack the presence of a benign cellular blue or conventional blue nevus component [84]. Correlation with clinical details is also of paramount importance if a diagnosis of metastatic melanoma is being entertained, particularly to know whether the patient has a prior history of melanoma and whether there is evidence of metastatic disease elsewhere [32].

Immunohistochemistry and Molecular Testing

BNLM is positive (the benign and the malignant component) for S100, HMB-45 antigen, and MART-1. The proliferation index, measured with ki-67 expression (with MIB1), is significantly higher in the malignant component than in the benign component. As stated above, while the majority of CBN can be readily distinguished from BNLM by conventional histology, there is a subset of cases where this distinction may be exceedingly difficult. Loss of BAP1 expression has been recently described as a feature of BNLM [85]. Ancillary molecular testing has been suggested to be helpful in this differential diagnosis. Studies using FISH have found copy number aberrations within chromosome 6 or 11, commonly seen in melanoma, in BNLM [86]. Same studies have shown that cases of unequivocal cellular blue nevus lack significant aberrations in chromosome 6 or 11 [86]. Other studies using CGH have found similar results by showing a uniform presence of copy number aberrations in chromosome 6 and 11q in unequivocal melanomas and uniform lack of such changes in cellular blue nevi [66].

As mentioned above, one study found that histopathologically ambiguous or indeterminate cases (possibly best classified as atypical cellular blue nevi) may show intermediate levels of chromosomal aberrations [66]. These intermediate lesions show intermediate levels of copy number aberrations in chromosome 6. Thus, it is possible that there is a continuum from CBN to BNLM and that intermediate lesions may be best qualified as borderline in behavior (atypical cellular blue nevus) and that FISH may provide additional findings with prognostic value. A recent gene signature test (MyPath) appears to be able to distinguish between BN and BNLM (Personal communication, Lauren Clarke, MD).

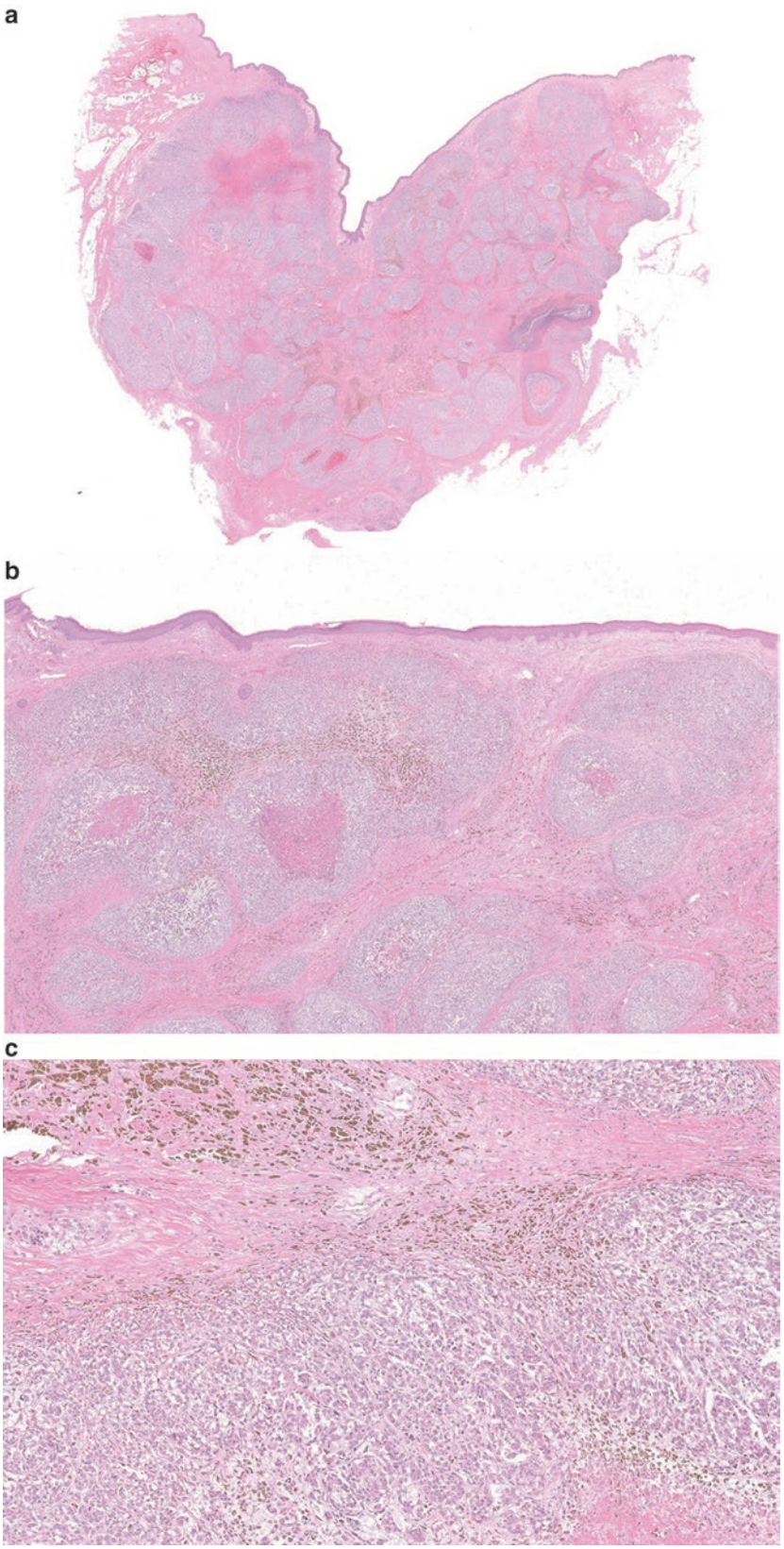

Fig. 2.32 Blue nevus-like melanoma. Low power depicts a biphasic neoplasm composed of cellular areas (reminiscent of cellular blue nevus) and conventional blue nevus component (**a**). Note the areas of necrosis in the tumor nodules (**b**). This image shows the transition between the blue nevus component and the malignant component which is characterized by diffuse sheets of malignant large, epithelioid cells (**c**).

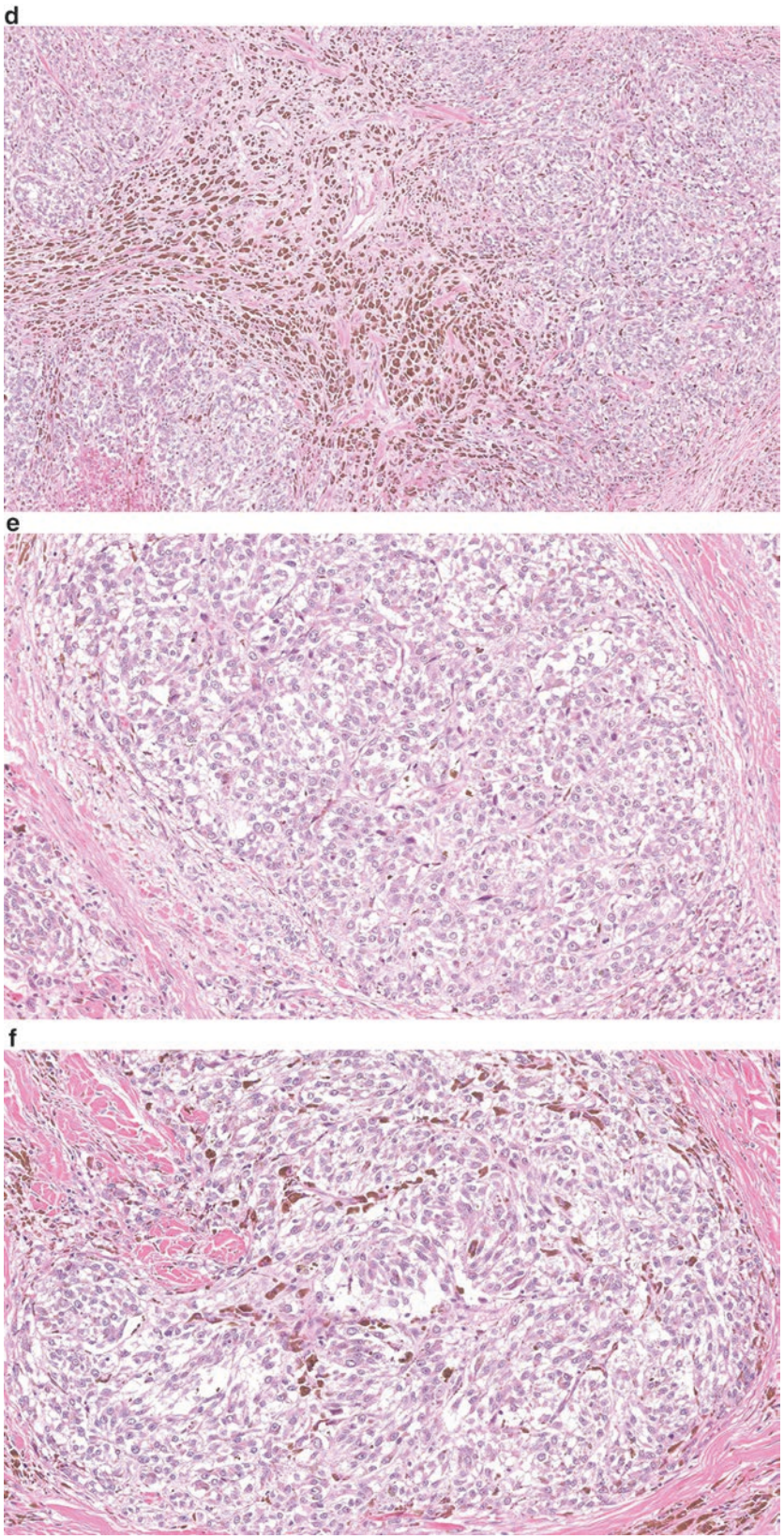

Fig. 2.32 (continued) Sheets of epithelioid melanocytes surrounded by pigmented melanophages (**d**). This image displays the cytologic features of the malignant component with large epithelioid melanocytes that have an abundant cytoplasm and pleomorphic and hyperchromatic nuclei (**e**). High-power image of the tumor cells depicting ample clear cytoplasm and pleomorphic and hyperchromatic nuclei (**f**)

Deep Penetrating Nevus

Clinical Features

Deep penetrating nevus (DPN) is a distinctive melanocytic neoplasm that was first described by Seab et al. [87] that may simulate melanoma both clinically and histologically. The term is not accepted by all authors, since due to their similarities with cellular blue nevi, they can be interpreted to be a variant of cellular blue nevi. Clinically, it presents as a solitary, deeply pigmented, light-brown to dark-blue papule (<1 cm in diameter) in adolescents and young adults (first four decades of life) with a slight female predominance. There is a strong predilection for the upper half of the body, in particular the head and neck area. As opposed to cellular blue nevi, DPN does not involve the buttocks or scalp. Lesions are present up to several years. While a majority of DPNs are acquired and usually diagnosed after puberty, there are rare congenital cases [87, 88]. DPN is mostly a benign melanocytic neoplasm that only rarely recurs after histologically incomplete excision; thus, conservative and complete local excision appears to be the best treatment option for DPNs.

Histopathology

At lower magnification DPN has a sharply demarcated, often symmetrical and usually wedge-shaped configuration (the base toward the epidermis and the tip toward the reticular dermis/subcutis). The distribution of melanocytes in the dermis can be either compact or plexiform. The compact variant is more common; cells are arranged in nests sometimes separated by a thin rim of dermal collagen. The plexiform variant shows well-defined cellular cords and nests with normal dermis in between. There are extensions along the skin adnexa or neurovascular bundles into the deep reticular dermis and/or subcutis, also sometimes giving the lesion a plexiform appearance. The epidermis overlying a DPN may show a generally inconspicuous junctional melanocytic component in up to 60–85 % cases [88–90]. Such epidermal melanocytic component usually consists of focal, lentiginous hyperplasia and nests of melanocytes with uniform nuclei, indistinct nucleoli, and mild to moderately abundant cytoplasm containing mild amounts of melanin. The junctional component is usually located immediately above the intradermal component (there is no "shoulder"). Only rarely is there pagetoid proliferation of melanocytes into the upper layers of the epidermis [88].

The dermal component, mostly located in the reticular dermis, consists of nests and vertically oriented fascicles of epithelioid and, less frequently, spindle-shaped melanocytes. The proportion of both epithelioid and spindle-shaped cells can vary greatly among lesions, but the epithelioid cell component usually predominates. The epithelioid morphology is more frequently observed in upper parts of the lesion and the spindle cell morphology is more common in the deeper areas. The epithelioid cells differ from those seen in acquired melanocytic nevi by displaying more pronounced, pale, pink cytoplasm and by having larger nuclei and melanin pigment. The nuclei are hyperchromatic, with variation in size and shape (from round to oval). Nuclear contours may be irregular. Mild to moderate nuclear pleomorphism is a constant feature in DPN and may be marked, but usually in a focal and random manner. Nuclear pseudoinclusions may be present. The spindle cell component is very similar to that observed in cellular blue nevus, and there may be dendritic melanocytes similar to those seen in common blue nevus. Dermal maturation with depth may be incomplete, with only focal mitotic activity (usually 1/mm^2, rarely in the deeper half of the tumor); atypical mitotic figures should not be observed. Heavily pigmented melanocytes grow along the skin adnexa and neurovascular bundles without destroying them.

Commonly there are melanophages and a subtle mononuclear inflammatory cell infiltrate. Melanophages can be sparse to abundant and characteristically dispersed evenly throughout the lesion. They usually surround nests and fascicles of melanocytes and are especially prominent at the periphery of the lesion. Sometimes these melanophages can be dispersed throughout the lesion in a net or chessboard pattern. The mononuclear inflammatory cell infiltrate (composed predominantly of mature lymphocytes) can be sparse and focal and only rarely diffuse. In some DPNs, pigmented dendritic melanocytes can be seen and in such cases a distinction from blue nevi may be difficult (especially if the tissue sample is limited). These features have prompted some experts to suggest that DPN is part of the spectrum of PEMs.

Atypical Histologic Features in DPN

Rarely, DPNs may display concerning histologic features: asymmetry, expansile melanocytic nests, obvious cytologic atypia with nuclear pleomorphism, absence of maturation, presence of dermal mitotic figures, and inflammation. These concerning histologic features can be expected in about 40 % of DPNs and should not be regarded as a sign of malignancy [88, 90].

Rarely, DPNs may with more pronounced cytologic atypia, in a diffuse manner, as single or small groups of melanocytes with larger nuclei, prominent eosinophilic nucleoli, and increased mitotic activity (>2/mm^2). Such lesions usually display other histologic features otherwise typical of DPN. On the basis of diffuse cytologic atypia and mitotic figures, such lesions have been designated as atypical DPNs with uncertain malignant potential.

Differential Diagnosis

CBN can be difficult to separate from DPNs. As stated above the clinical distribution of CBN and DPN differs (acral/buttocks vs. upper trunk) and is slightly different histologically. DPNs usually demonstrate a junctional component and lack stromal fibrosis. CBN may tend to have areas of common blue nevi at the periphery. In addition, CBN is composed of prominent nests of nonpigmented or scantily pigmented, uniform, ovoid to spindled cells, unlike DPN.

Rarely, metastatic melanoma can sometimes simulate DPNs, given the main intradermal location of the lesion. Metastatic melanomas usually display a high degree of cytologic atypia and mitotic rate along with a high proliferative rate (high Ki-67). In problematic cases, CGH studies can be helpful to demonstrate the genomic mutations of both the primary and metastatic melanoma. In some occasions melanoma can display a plexiform architecture simulating DPNs; however, DPNs can be reliably separated by the presence of wedge-shaped configuration, symmetry, and the lack of or very limited mitotic activity with an absence of atypical shapes. As mentioned above, the detection of numerous mitotic figures, either in the superficial or deep portion of the tumor, will favor the diagnosis of melanoma. Other features that favor a primary melanoma include the presence of an overlying obvious melanoma in situ, the absence of grenz zone, and clusters of atypical melanocytes arranged in nodules or sheets.

PEMs can also be difficult to separate from DPNs (see above) since both may display dome-shaped proliferations of heavily pigmented epithelioid and spindle melanocytes with abundant cytoplasm, large vesicular or hyperchromatic nuclei, and single, eosinophilic nucleoli. Although cytologic atypia is invariably present, tumor cells are fairly homogeneous throughout the lesion. Commonly there are nuclear pleomorphism and occasional mitotic figures (0–2/mm^2). Melanocytes show variable extension along the adnexal structures, but also display more diffuse growth in the dermis, with frequent infiltration into the subcutis.

Immunohistochemistry and Molecular Testing

Immunohistochemical analysis usually shows expression of both S-100 and HMB-45 antigen; thus, there is no value in differentiating DPN from melanoma. A recent study suggests that DPN, in addition to sharing some morphological similarity to Spitz nevus, also shares similarities at the molecular level, showing HRAS mutations, and appears to be unrelated to blue nevi based on the absence of QNAQ and QNA11 mutations in DPNs [50]. In challenging cases, in which the differential diagnosis of DPN includes melanoma, CGH studies can be of help as DPNs usually show no chromosomal aberrations. DPN show a gene signature similar to CBN (MyPath, personal communication, Lauren Clarke, MD).

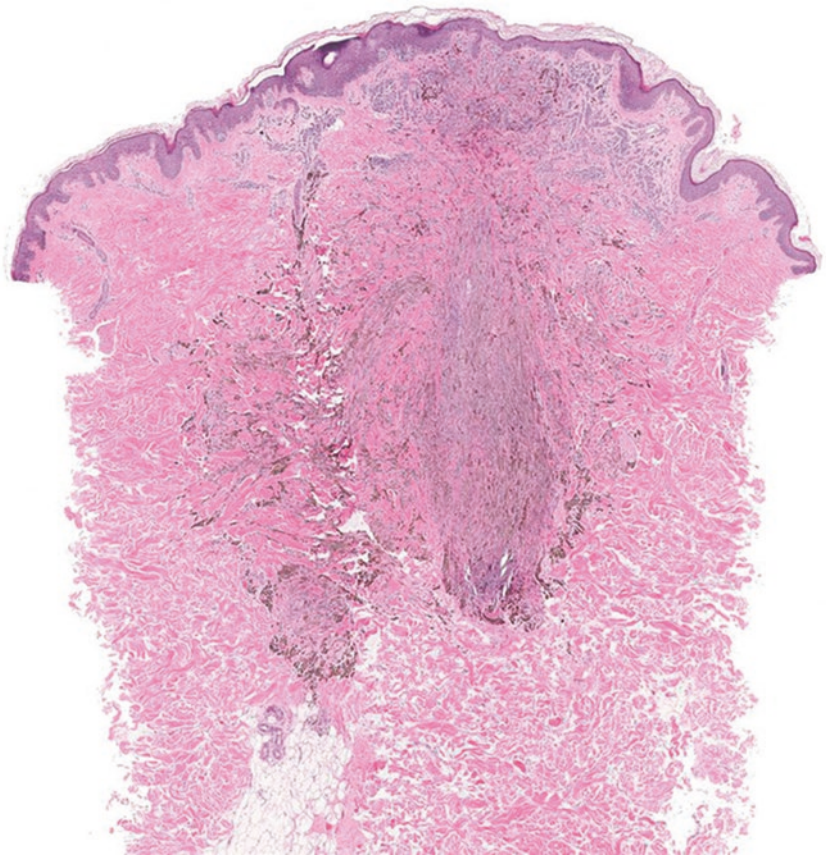

Fig. 2.33 Deep penetrating nevus. Low-power view showing an inverted wedge-shaped architecture lesion with periadnexal extension

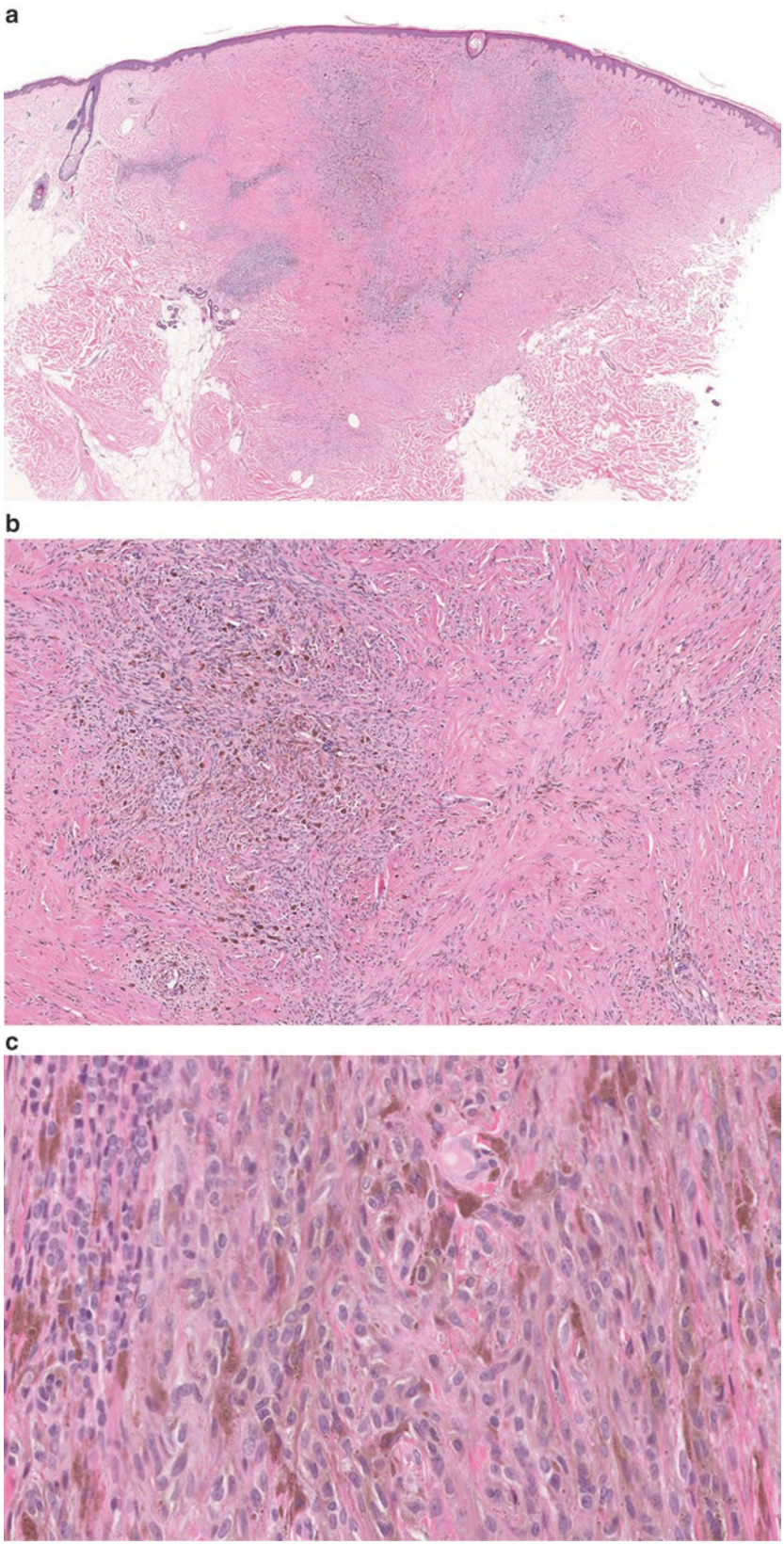

Fig. 2.34 Deep penetrating nevus. This image shows a larger lesion with characteristic inverted wedge-shaped architecture (**a**). Note the fascicles of spindle and epithelioid melanocytes (**b**). Note the spindle and epithelioid cells with characteristic dusty melanin pigment and mild cytologic atypia (**c**).

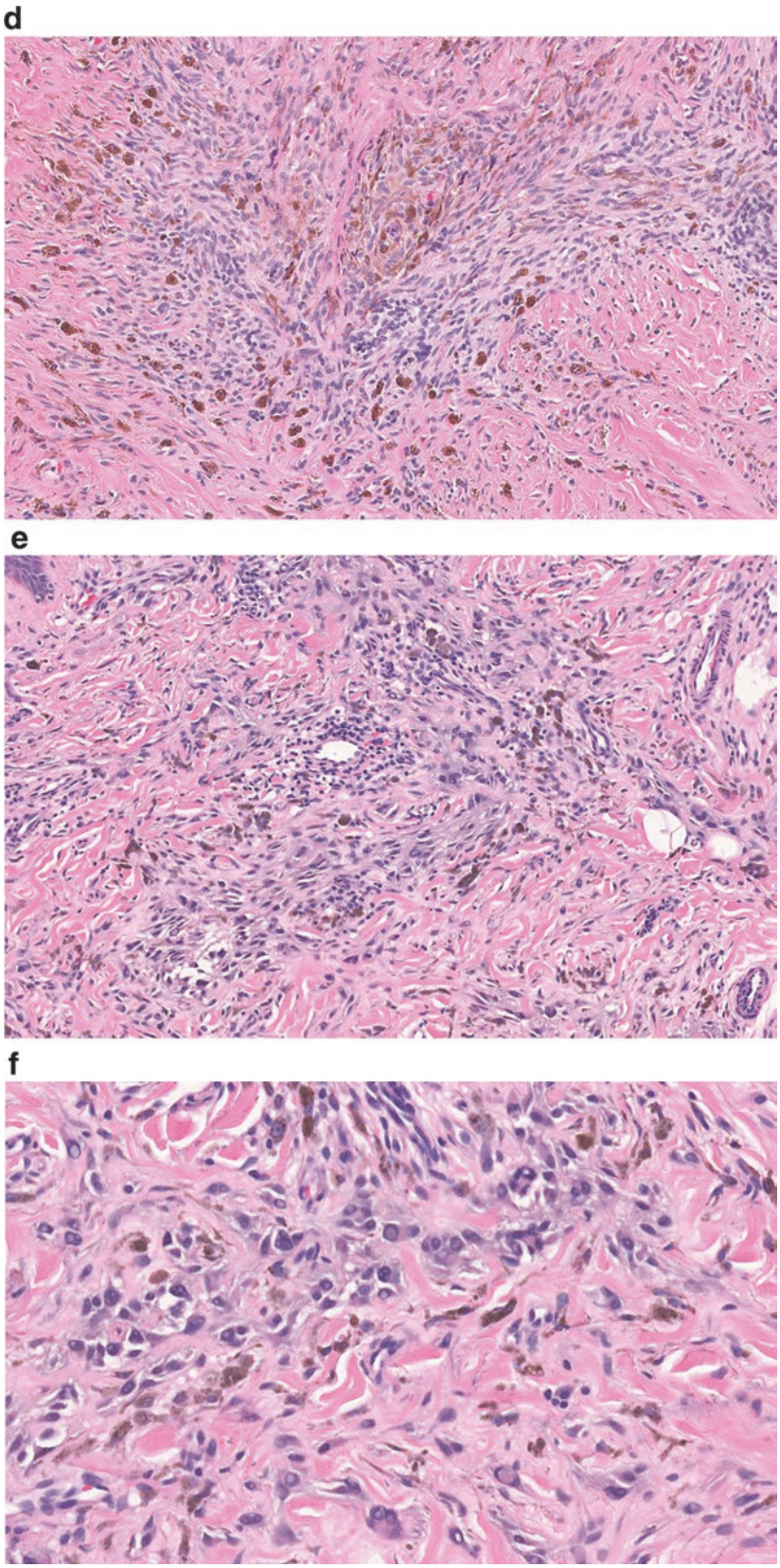

Fig. 2.34 (continued) These images show the presence of intranuclear inclusions which is characteristic findings in DPNs (can be numerous in some cases) (**d**–**f**)

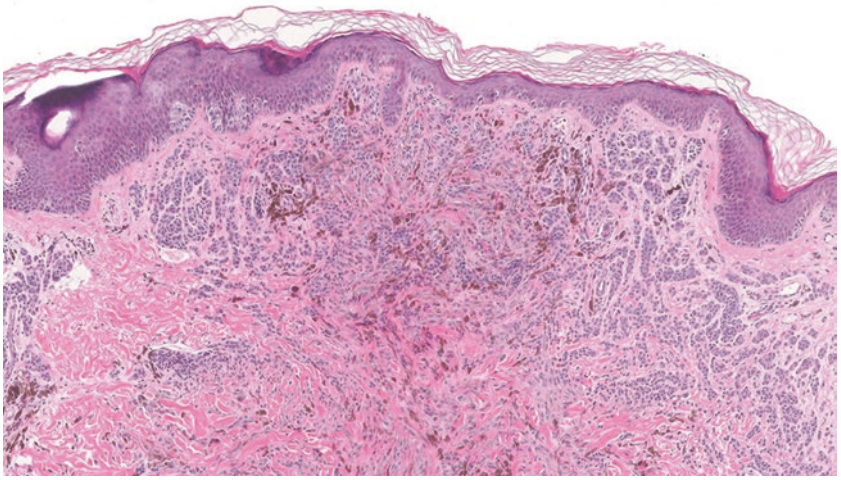

Fig. 2.35 Deep penetrating nevus. This image depicts a junctional component which consists of mild lentiginous hyperplasia and uniform nests of melanocytes

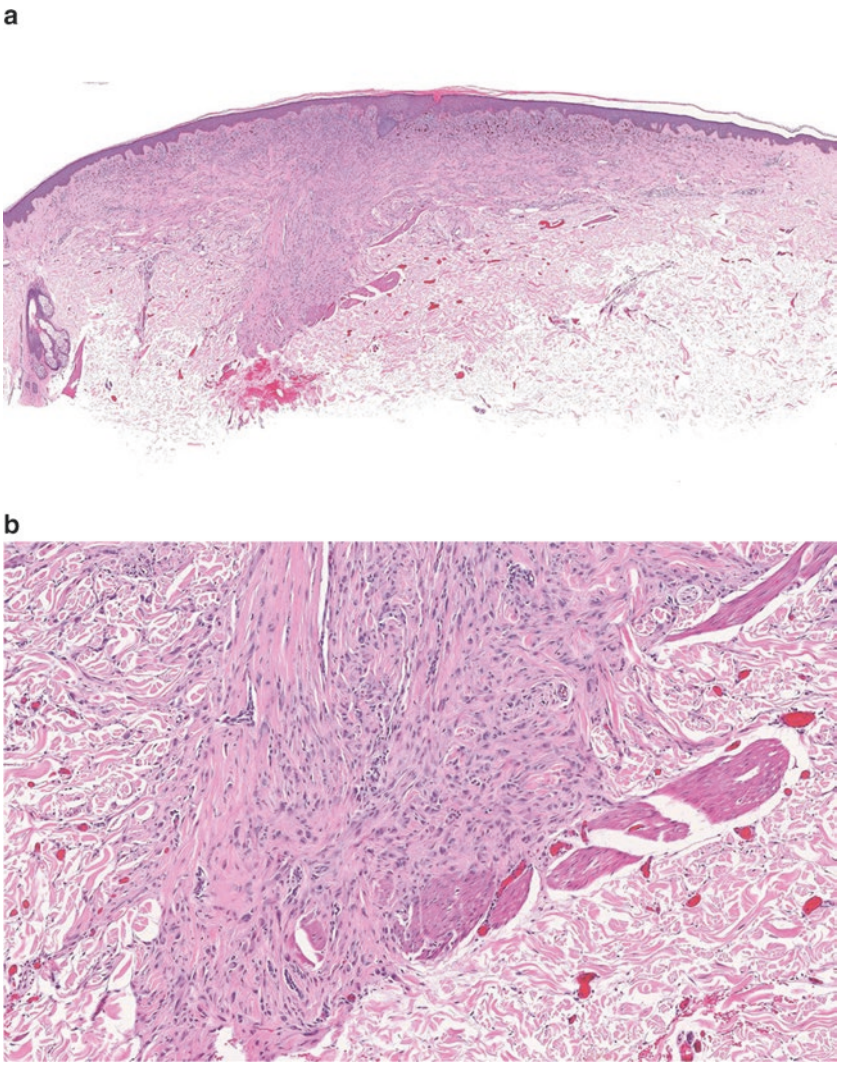

Fig. 2.36 Deep penetrating nevus. This case of DPN is smaller in size and shows wedge-shaped silhouette in which most of the lesion is located in the upper half of reticular dermis. Note the epithelioid and spindle melanocytes with a fine dusty cytoplasmic pigment (**a**). Some melanocytes are wrapping the erector pili muscle (**b**).

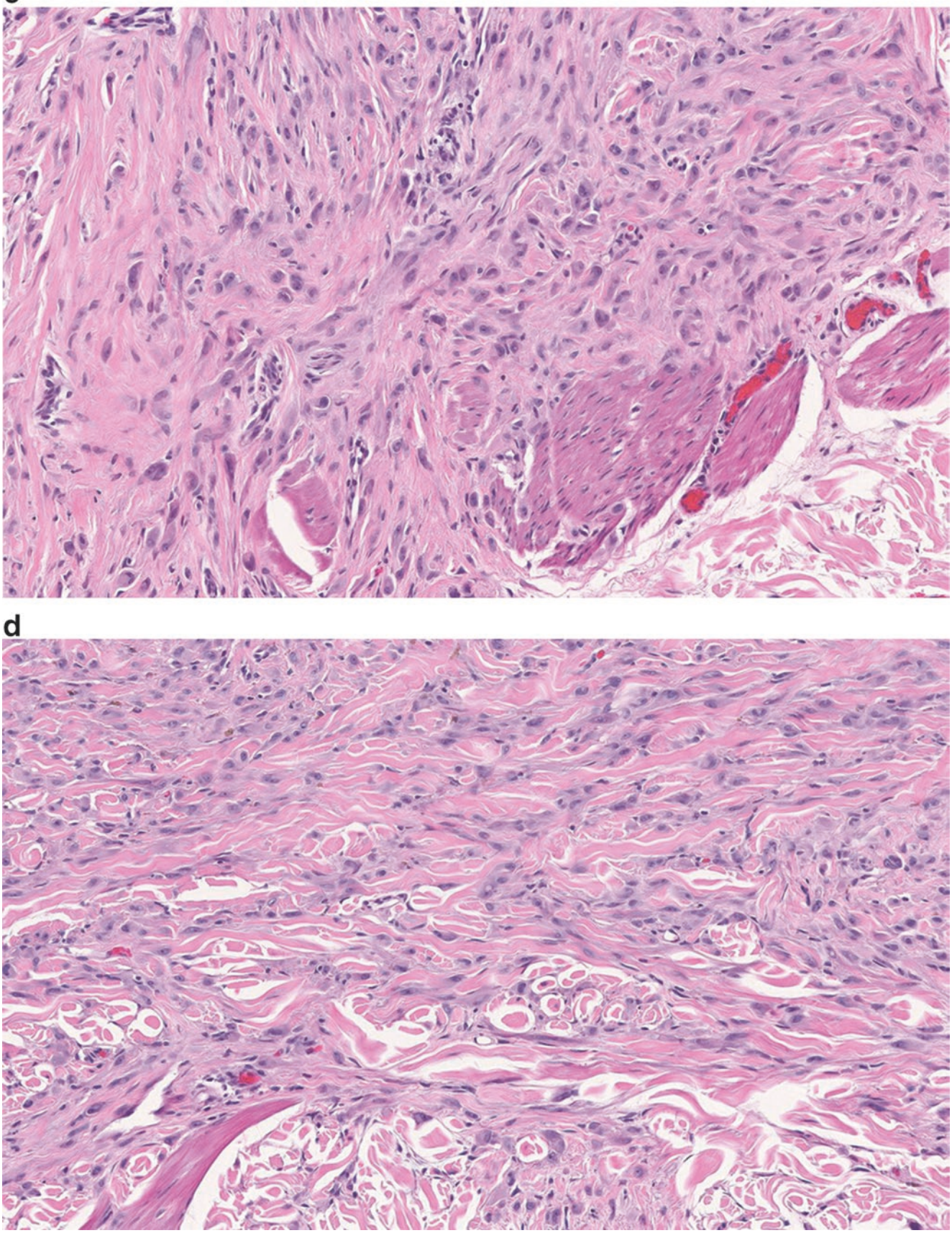

Fig. 2.36 (continued) Higher magnification showing the uniform population of melanocytes with minimal cytologic atypia (**c**, **d**)

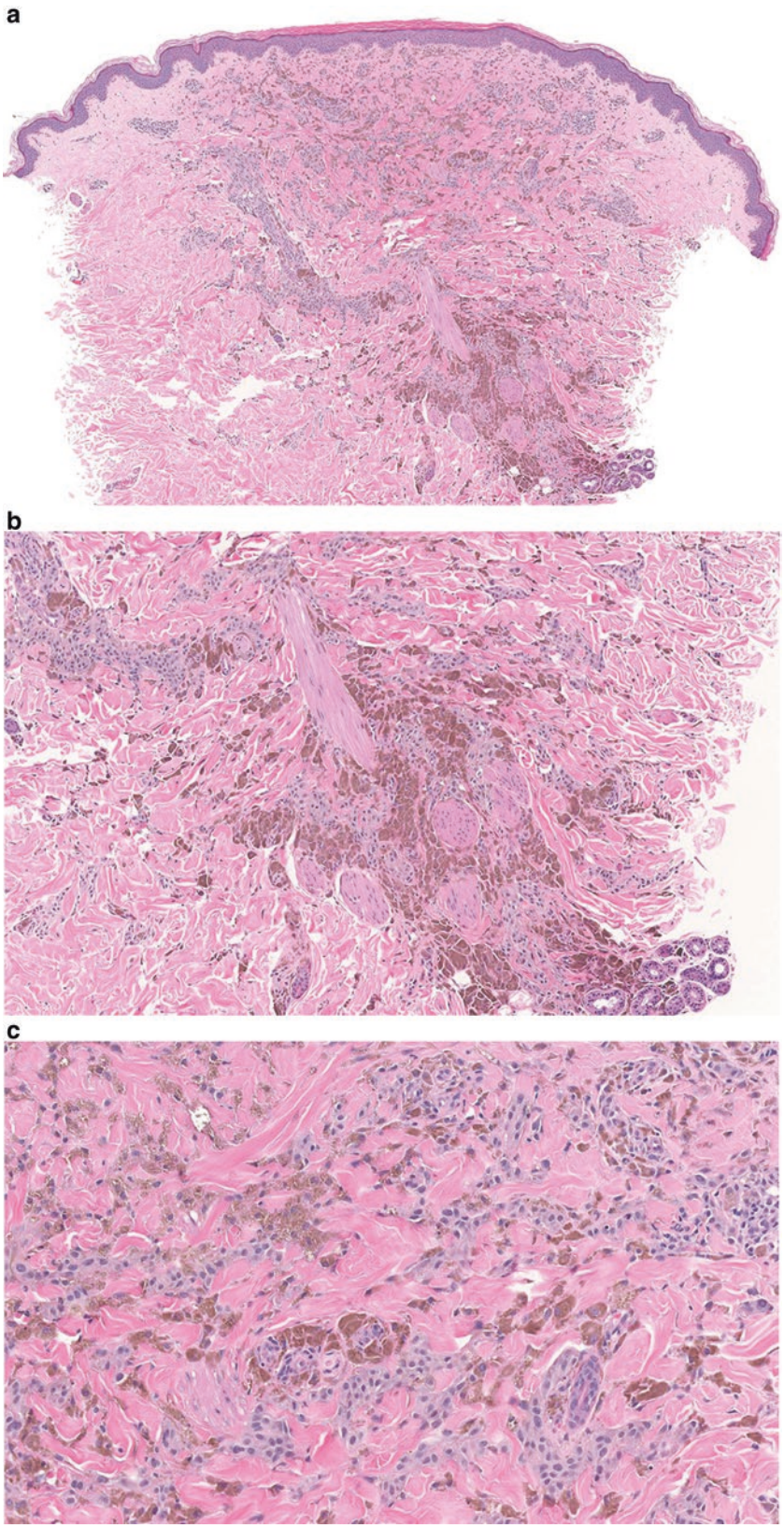

Fig. 2.37 Deep penetrating nevus. This case shows a wedge-shaped growth in the dermis with pigment also observed in the deeper part of the lesion (**a**). Note the distribution of epithelioid melanocytes around eccrine and erector pili muscle (**b**). There are an increase number of uniform epithelioid melanocytes with dusty cytoplasmic pigment (**c**)

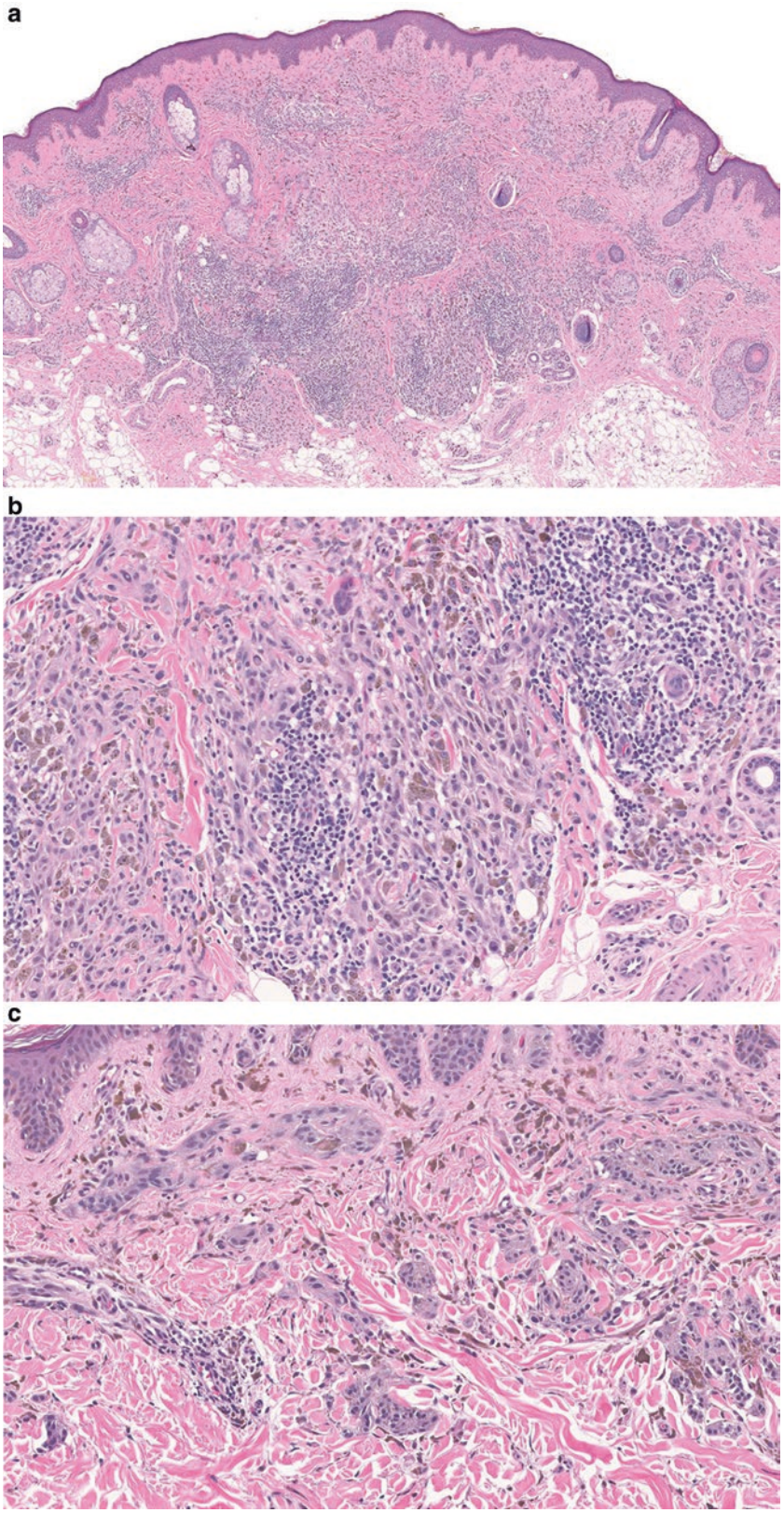

Fig. 2.38 Deep penetrating nevus. This example of DPN shows a roughly wedge-shaped architecture with sparse chronic inflammatory response (**a**, **b**). The epithelioid melanocytes are intermingled with the lymphocytes (**c**)

Cutaneous Neurocristic Hamartoma

Clinical Features

Cutaneous neurocristic hamartoma (CNH) was first described in 1982 and was referred as pilar neurocristic hamartoma [91]. It represents a rare, developmental hamartomatous lesion of neural crest origin exhibiting divergent differentiation along melanocytic, neural, and pigmented dendritic cell lines. The majority of CNH lesions are congenital; however, there are some acquired variants [30]. Clinically, it generally presents as a slow-growing, localized collection of often folliculocentric keratotic macules, papules, and nodules, sometimes with associated alopecia. The lesions often involve the scalp, face, neck, buttock, and back. These tumors exhibit low-grade behavior, and the clinical course is characterized by slow progressive growth with numerous recurrences [92–94]. Cases of melanoma have been reported in association with CNH; however, these melanomas tend to follow a more indolent course than conventional melanomas [95, 96]. Because of this possible occurrence, CNH is sometimes regarded as a low-grade melanocytic tumor with a low but definite risk of malignant behavior, and some experts classify this neoplasm as borderline melanocytic tumor.

Histopathology

CNH shows a combination of differentiation including melanocytic (nevoid, spindled, and dendritic components), neurosustentacular (Schwann and perineural cells and), mesenchymal fibrogenic elements. These tumors are composed of infiltrating, multinodular clusters of cells involving the deep dermis and subcutis. They lack a junctional component, but the overlying epidermis may show hyperpigmentation and seborrheic keratosis-like features. In the superficial dermis, there may be collections of benign, standard intradermal and blue nevus. In the reticular dermis, characteristically, pigmented spindled cells surround the lower segments of hair follicles and adjacent eccrine sweat glands resembling blue nevus, cellular blue nevus, and PEM. These spindle cells may infiltrate along nerves. The interfollicular dermis contains scattered, pigmented spindled, and dendritic cells with a background of spindled cells showing well-defined Schwann cell nodules (pilar neurocristic hamartoma). There is no cytological atypia or mitotic figures. Skeletal muscle or bone involvement has been reported in some cases. Occasionally there is bizarre architecture such as trabecular pattern, perivascular cuffing, tactile body differentiation, and pseudorosette formation, patterns not seen in blue or congenital nevi. As mentioned above, there may be malignant transformation, sometimes referred as malignant neurocristic tumors (MNT) [37, 38]. It appears that malignant transformation more commonly occurs on the head and neck. In all the few cases of MNT reported, there is a background of neurocristic hamartoma in addition to discrete expansile nodules of cytologically atypical epithelioid and spindled cells with prominent eosinophilic nucleoli, mitotic activity, and tumor necrosis.

Immunohistochemistry and Molecular Testing

CNH can express S-100, CD57, HMB-45 antigen, MART-1, NSE, collagen 4, and CD34. The surrounding stroma in CNHs shows numerous CD34-positive cells. Anti-EMA highlights the Schwann and perineural cells. Congenital nevi do not usually show stromal expression of CD34, and although congenital nevi may have melanocytic clones positive with HMB-45, the pattern is not diffuse, as in CNH.

As stated above, mutations in GNAQ or GNA11 have been reported in dermal melanocytoses and they are frequently detected in blue nevi (83 %) and uveal melanoma. Despite the prominent pigment noted in MNT and foci resembling blue nevus and cellular blue nevus in the background of neurocristic hamartoma, GNAQ mutations have not been detected, possibly suggesting that the background neurocristic hamartoma and the malignant component are distinct from blue nevus and blue nevus-like melanoma, respectively [97]. The lack of GNAQ, NRAS, BRAF, and KIT mutations in cases of MNT seems to support the notion that these tumors may be distinct from conventional melanoma, blue nevus-like melanoma, or melanoma arising in congenital nevi.

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Acquired Melanocytic Nevus

3

Common Acquired Melanocytic Nevi

Introduction

Melanocytic nevi are defined as benign hamartomatous lesions composed of melanocytes. Melanocytes are derived from the neural crest and migrate during embryogenesis to selected ectodermal sites, primarily the skin and the central nervous system, including the eyes and the ears; however, ectopic melanocytes have been found in other organs such as multiple locations of the gastrointestinal tract. Acquired melanocytic nevi commonly form during early childhood and their onset is believed, at least in some cases, to be a response to sun exposure. However genetic factors are also involved in the development of some types of acquired nevi. Melanocytic nevi are biologically stable, benign lesions but in some occasions they can be associated with melanoma. The frequency of transformation of a melanocytic nevus into melanoma varies widely in the literature, with some data suggesting that up to 40 % of melanomas are associated with a precursor nevus.

Melanocytic nevi are more common lesions in patients with light skin. As mentioned above, some melanocytic nevi are likely stimulated by exposure to sunlight; thus, individuals with dark skin might have fewer nevi because of the protective properties of melanin. There is no clear sex predilection for the development of nevi; however, melanocytes have shown to exhibit some degree of sex hormone responsiveness and the fact that nevi may enlarge and darken during pregnancy supports this relationship with gender.

Clinical Features

Common acquired nevi are usually smaller than 1 cm in diameter and evenly pigmented. They are most commonly tan to brown, but coloration can be variable, ranging from skin colored to black. It is believed that some acquired nevi tend to follow an orderly process of progression from junctional to compound nevus and then intradermal nevus and gradual involution. Nonetheless, at any of these stages, the nevus may arrest its growth.

Junctional nevi tend to be macular and uniformly pigmented, dark brown to black, but minor degrees of color variegation are not uncommon, especially if they have a lentiginous component. Junctional nevi are typical in young patients but can be seen at any age; however, they clearly decrease with age and thus, in old patients, melanoma should always be considered in the differential diagnosis of junctional melanocytic lesions. Compound nevi are elevated relative to the surrounding uninvolved skin. Compound nevi are often lighter in color than junctional nevi, but those that have been recently irritated may show areas of dark pigmentation. Intradermal nevi are often elevated and since they lose most of their pigmentation, they usually appear as skin-colored papules. Nonetheless, it should be emphasized that there is clinical overlap among these three categories of nevi. Additionally, the development of a new area of hyperpigmentation within a long-standing compound or intradermal melanocytic nevus should be taken as a red flag for the possibility of development of melanoma. Although these hyperpigmented areas could be due to incidental inflammation or recent trauma, the possibility of melanoma should be always considered.

Histologic Features of Melanocytes in Common Acquired Melanocytic Nevi

Nevi have three types of melanocytes: type A, type B, and type C. Type A melanocytes tend to show an epithelioid configuration with uniformly dispersed chromatin with a ground-glass basophilic appearance and delicate nuclear membranes. Nucleoli can be noted, however, as usually small in size. Some of these type A melanocytes can be pigmented, and when present the pigment is evenly distributed

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in the cytoplasm. Type B melanocytes tend to be arranged in compact cords and small nests. These melanocytes are round and nonpigmented, with a round nucleus and inconspicuous nucleoli. The cytoplasm is small and the histomorphology of these melanocytes is reminiscent of lymphocytes. Type C melanocytes have spindle cell configuration begriff with fibrillary elongate cytoplasmic processes that are reminiscent of a Schwann cell. These melanocytes lack nuclear pleomorphism and show only small, inconspicuous nucleoli. Melanocytes in the dermis show maturation; this implies a change of morphology from the epidermis to the deeper dermis, i.e., diminished size of those melanocytes in deeper aspects of the lesion and change from epithelioid to spindle, i.e., A to C. This change has been identified as similar to the changes from neurons to Schwann cells ("schwannian metaplasia"). However, one needs to be aware of the fact that schwannian maturation is not only seen in benign lesions but can also be present in melanoma, so-called pseudo-maturation [1].

Histology of Junctional Melanocytic Nevi

This type of nevus refers to restriction of melanocytes almost exclusively located within the epidermis. These intraepidermal melanocytes are present in single cells or forming nests. The proliferation of single junctional melanocytes is present at the basal layer of the epidermis, usually at the tips of rete ridges. The junctional nests aggregate more frequently in the tips and the basilar region of the rete ridges. These nests are uniform in size and evenly distributed with variable degrees of pigmentation (when present the pigment is fine and uniformly distributed in the cytoplasm). Within the nests, melanocytes are cohesive, homogeneous, and surrounded by a clear space. The cells tend to have ample cytoplasm with small dendrites and round nucleus, with delicate nuclear margins and small amphophilic nucleoli. Melanocytes within the nests have similar size and shape and tend to have either type A or B morphologies. The dermal stroma underneath a junctional nevus may show scattered melanophages, but it is usually identical to that seen in the uninvolved skin.

Histology of Compound Melanocytic Nevi

Compound melanocytic nevi contain melanocytes in both the epidermis and dermis. The proliferation of melanocytes in the junctional component in compound nevi is the same as seen in junctional nevi; thus, melanocytes are distributed either in nests or single cells. The junctional component usually does not extend at the lateral edges beyond the nested component; however, some nevi with lentiginous pattern (i.e., single cells along the rete ridges) may extend beyond the nested component. The intradermal component in the papillary and reticular dermis has nests and cords of melanocytes, sometimes arranged in a coalescent, band-like pattern. Nonetheless, these nests are equidistant rather than forming expansile nodules; thus, when large and confluent nests are seen in the dermis, this finding should raise suspicion for melanoma, similarly if nests at the deep aspect of the lesion are larger than the ones superficially. The majority of acquired compound nevi do not extend beyond the papillary-reticular dermis junction. The exception is nevi on the head and neck, since they commonly extend around hair follicles and in reticular dermis mimicking the pattern seen in congenital nevi. As mentioned above there is a change in morphology with depth. The melanocytes in superficial dermis show a similar morphology as those seen in the junctional component, i.e., epithelioid cells with round nuclei and abundant cytoplasm with variable pigmentation; single nucleoli can be seen in the center of the nuclei (type A melanocytes). The melanocytes deeper in the lesion are smaller and with minimal cytoplasm (type B melanocytes) or can be spindle with schwannian differentiation (type C melanocytes).

The stroma in the dermis is composed of collagen fibers arranged among single melanocytes and small nests. Large, irregular, and confluent sheets of melanocytes in the dermis without the presence of interposed collagen in between them are not a characteristic feature of a common nevus and should raise suspicion for melanoma. As described above, most nevi show maturation as characterized by the presence of progressive reduction of the size of melanocytes as well as by the decrease in size of the intradermal nests in the deeper aspects of the lesion. Also, the cells adopt spindle cell morphology and there is decreased pigmentation at the base of the lesion.

Histology of Intradermal Melanocytic Nevi

In this type of nevus, the melanocytes are almost exclusively confined to the dermis, as there are no or very few melanocytes in the overlying epidermis. The dermal component of a compound nevus is identical to the dermal component seen in an intradermal nevus (see above). Thus, these lesions show the normal maturation pattern as described above.

Differential Diagnosis

The diagnosis of a junctional nevus is most of the times straightforward; however, there are some occasions in which the single-cell component (lentiginous growth) predominates, and the distinction with melanoma in situ can be a difficult one, especially in limited tissue samples. There are certain histologic features that will favor a diagnosis of

melanoma such as the presence of irregularly distributed nests, large size, and irregular distribution of melanin pigment. The presence of pagetoid upward migration should be carefully inspected and only accepted when nevi are localized in special sites (genital areas, acral sites) or when there has been previous trauma. Furthermore, melanoma pagetoid upward migration, if present, is usually seen beyond the dermal nests at the periphery of the lesion. In small biopsies, sometimes immunohistochemical studies may be helpful to highlight the degree of single-cell proliferation above the basal layer and beyond the dermal component. We prefer MITF-1 over MART-1, since the former provides a nuclear pattern. Also, MART-1 may label some pigmented keratinocytes, thus giving a false-positive reaction. In general, mitotic figures seen in the junctional component are not a criterion for a diagnosis of melanoma; however, if these mitotic figures are atypical or numerous, such finding should be considered a red flag. The age of the patient is also very important to take into account as melanoma in situ in young patients is exceedingly rare. Junctional nevi in older patients with severe actinic damage should always be carefully inspected as may represent part of a melanoma in situ.

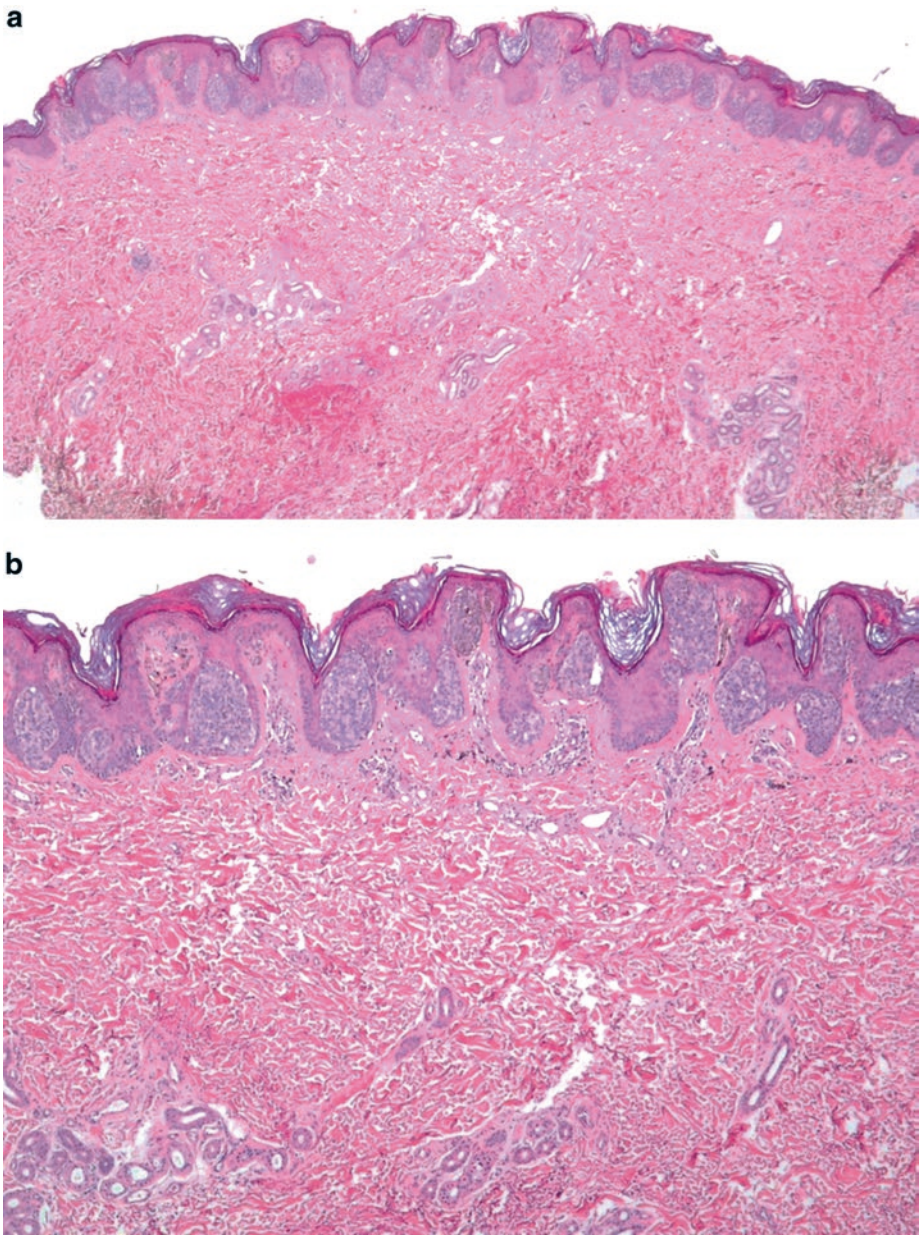


Fig. 3.1 Junctional nevus. Note the symmetrical elongation of rete ridges and the similar size of nests located in the epidermis (**a**). There is no evident dermal component, fibrosis, inflammation, or vascular proliferation (features of dysplastic nevi). Uniformly sized intraepidermal nests (**b**).

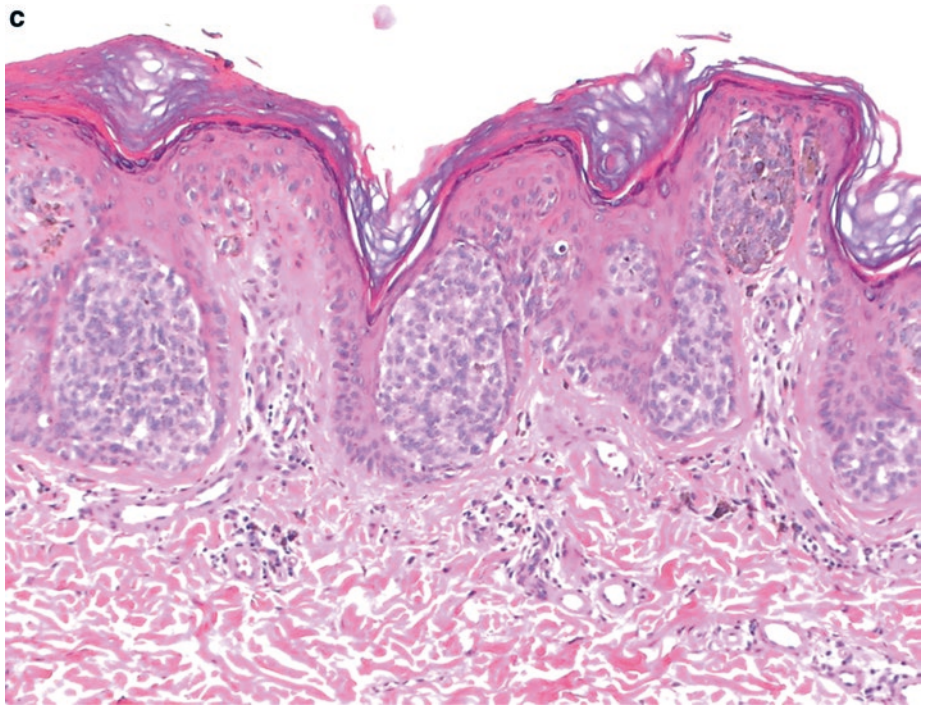


Fig. 3.1 (continued) Only rare melanophages in the dermis without significant fibrosis (main difference with dysplastic nevus) and lack of pagetoid upward migration (**c**)

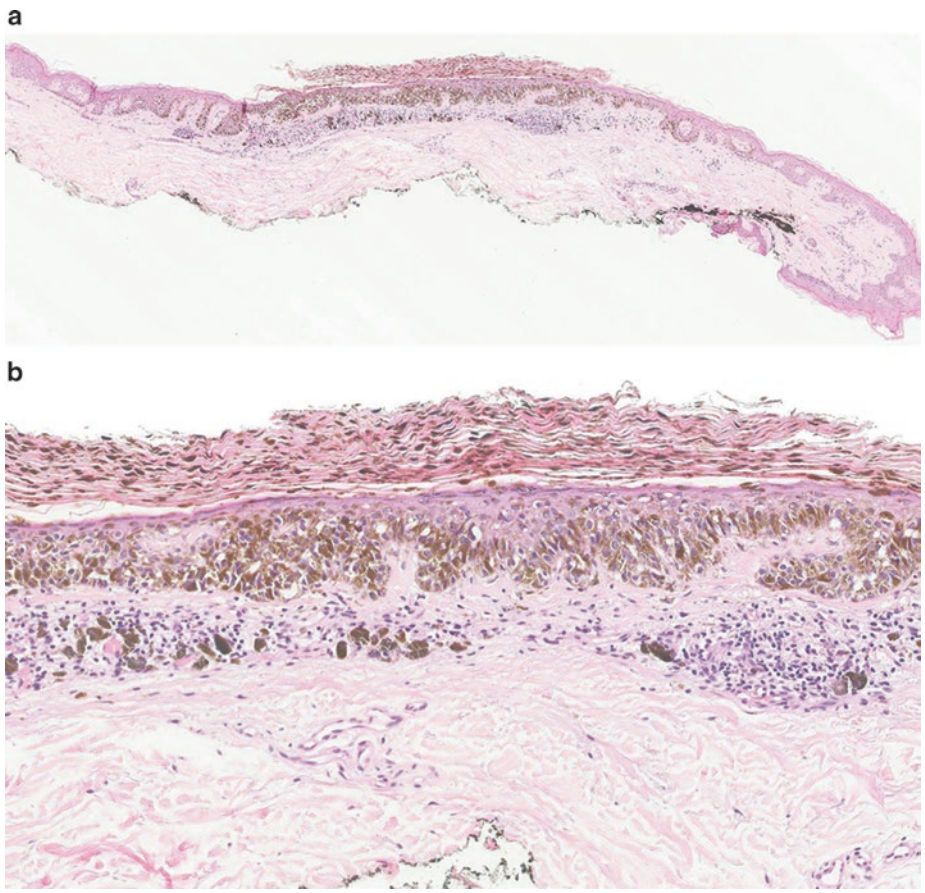


Fig. 3.2 Hypermelanotic lentiginous junctional nevus. This example is irritated and pigmented. Note the symmetry and the small size of the lesion, as well as the marked pigmentation of the epidermis (especially the stratum corneum) (**a**). Higher magnification showing single cells melanocytes located lower in the epidermis with minimal pagetoid upward migration. The marked amount of melanin in the stratum corneum is consistent with a prior trauma (**b**)

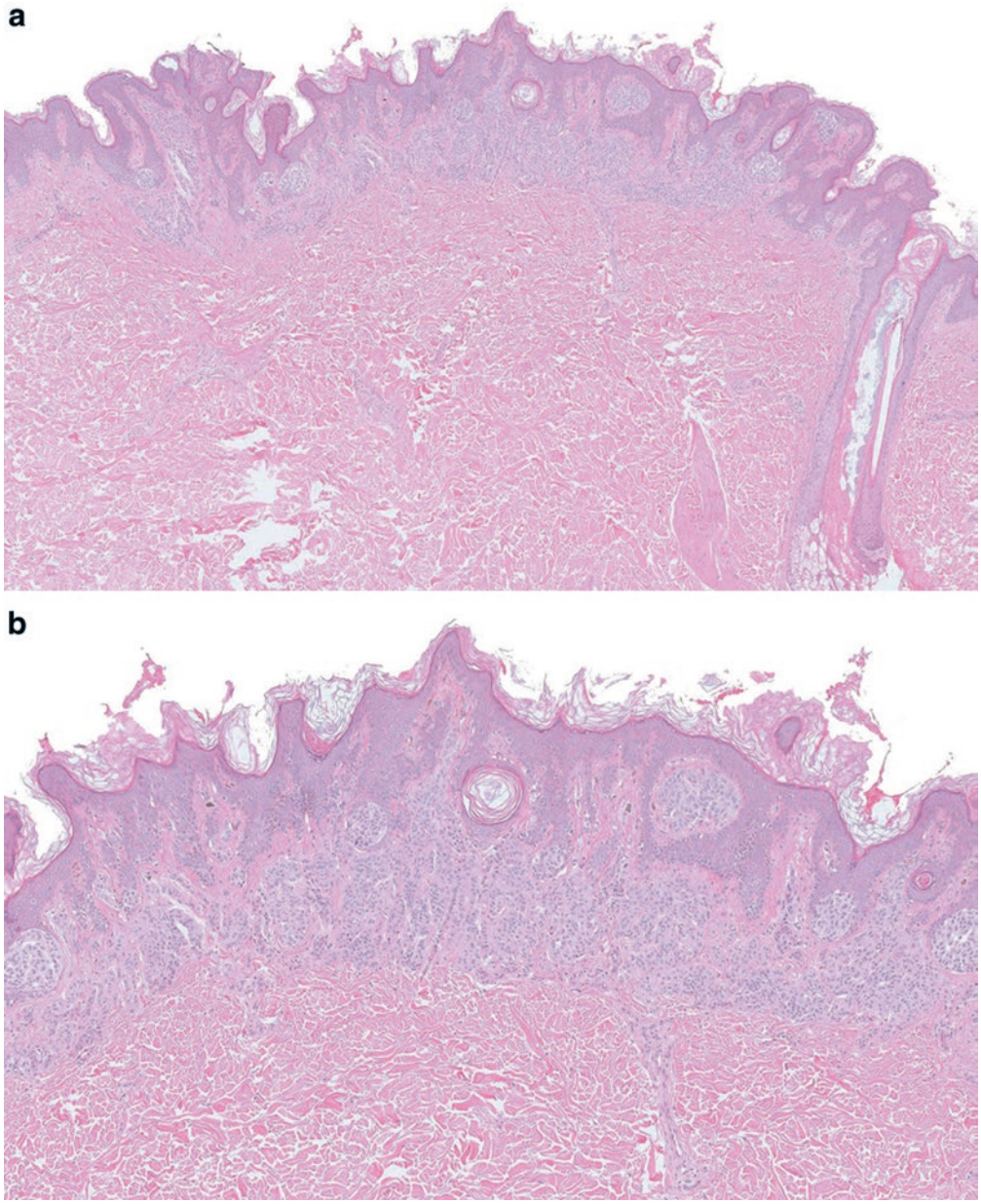


Fig. 3.3 Compound nevus. The lesion is symmetric and with normal maturation (decrease in size of nests with depth in the dermis) (**a**). Higher magnification showing small nests of melanocytes lacking cytologic atypia (**b**)

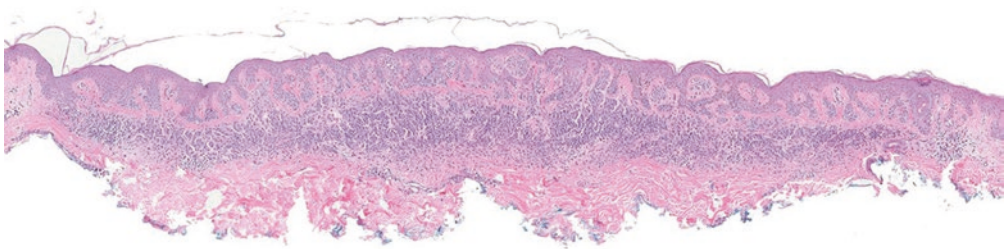


Fig. 3.4 Lentiginous compound nevus: Note symmetry of the lesion with regular elongation of rete ridges

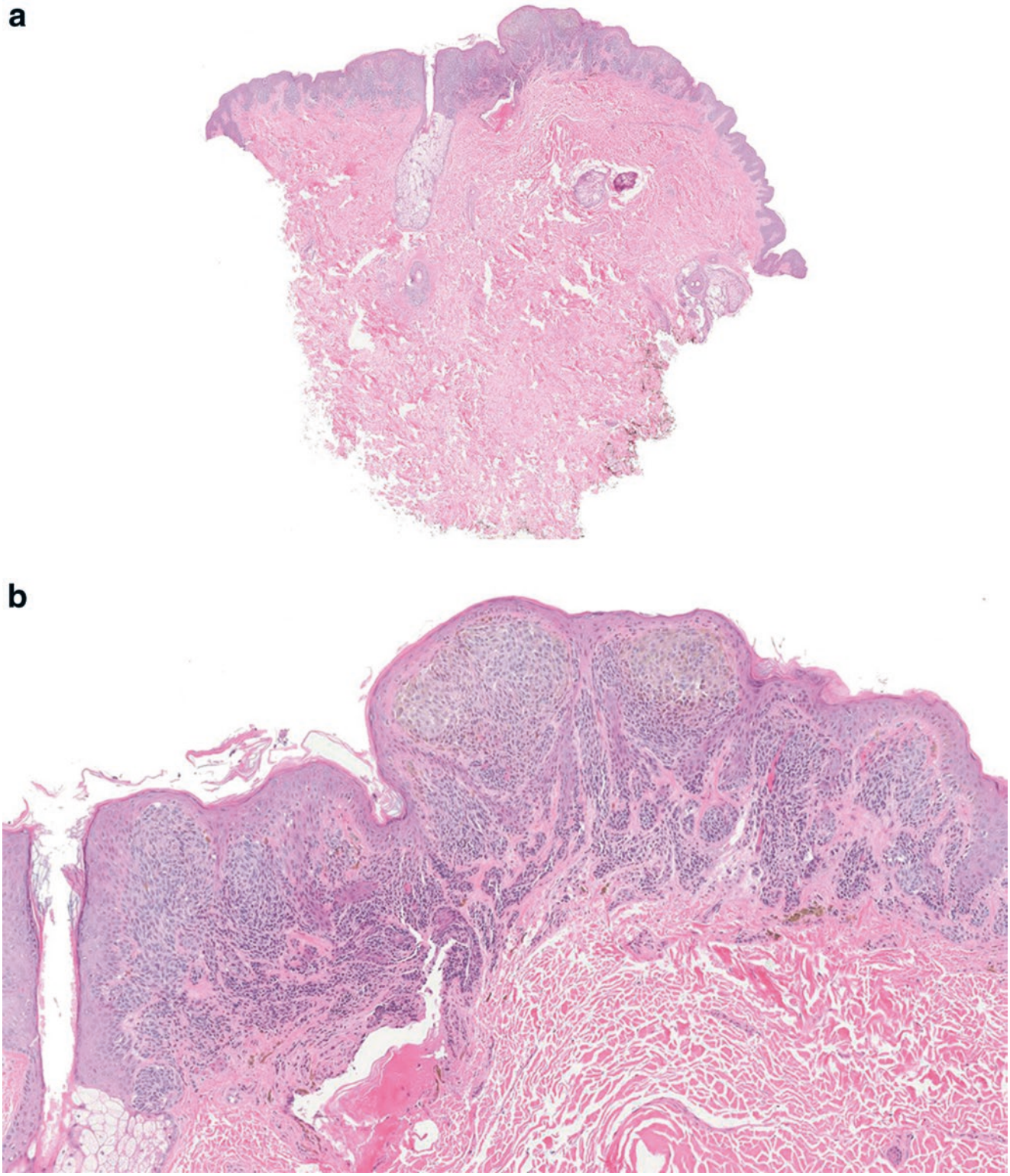


Fig. 3.5 Compound nevus. Wedge-shaped lesion with uniform elongation of the rete ridges (**a**). Maturation pattern with decreased pigmentation and size of nests with depth (**b**)

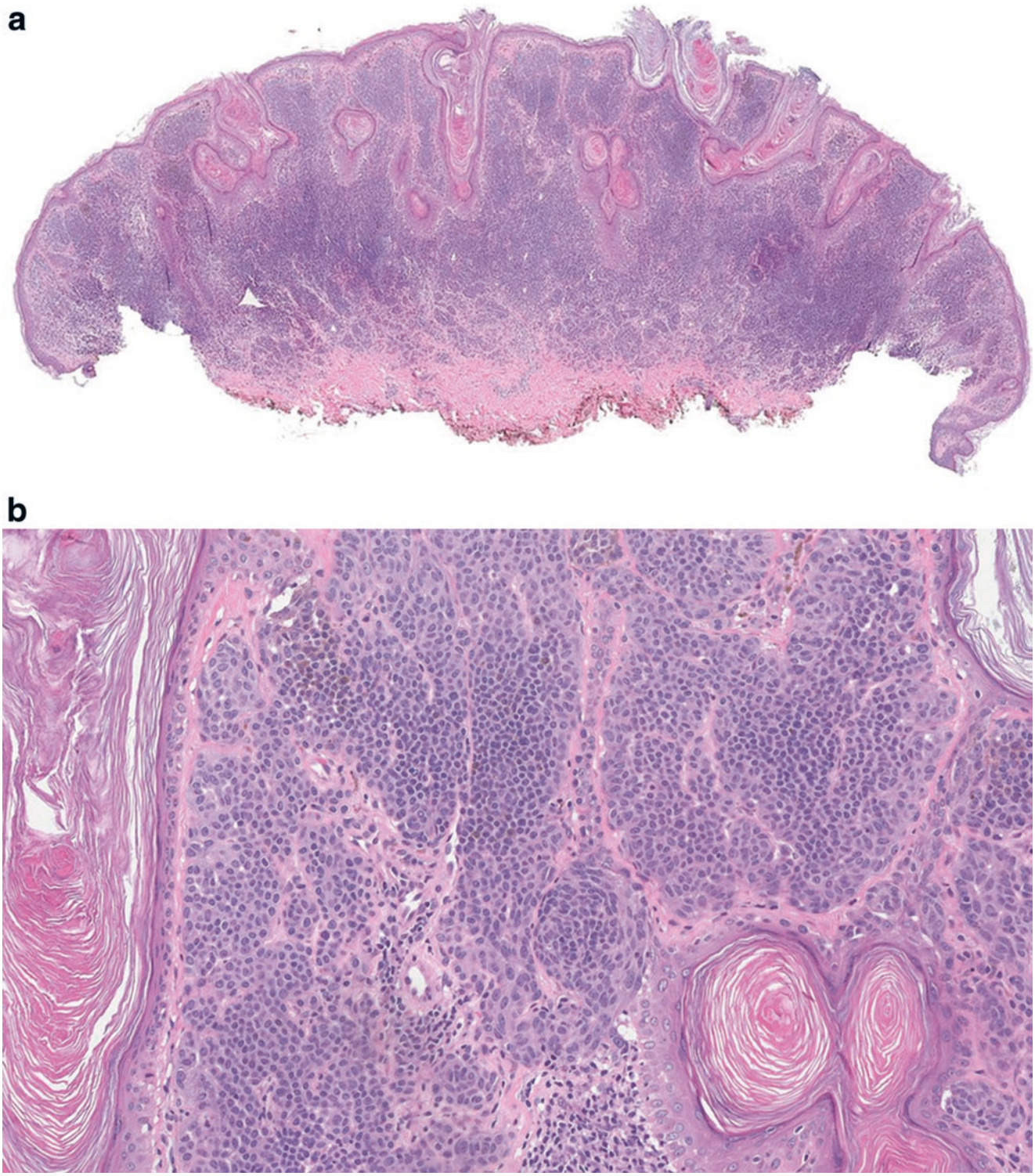


Fig. 3.6 Intradermal nevus. Note the lack of a visible junctional component and the large intradermal component extending well into the reticular dermis (**a**). Higher magnification showing small, uniform melanocytes with delicate, intervening stroma (**b**)

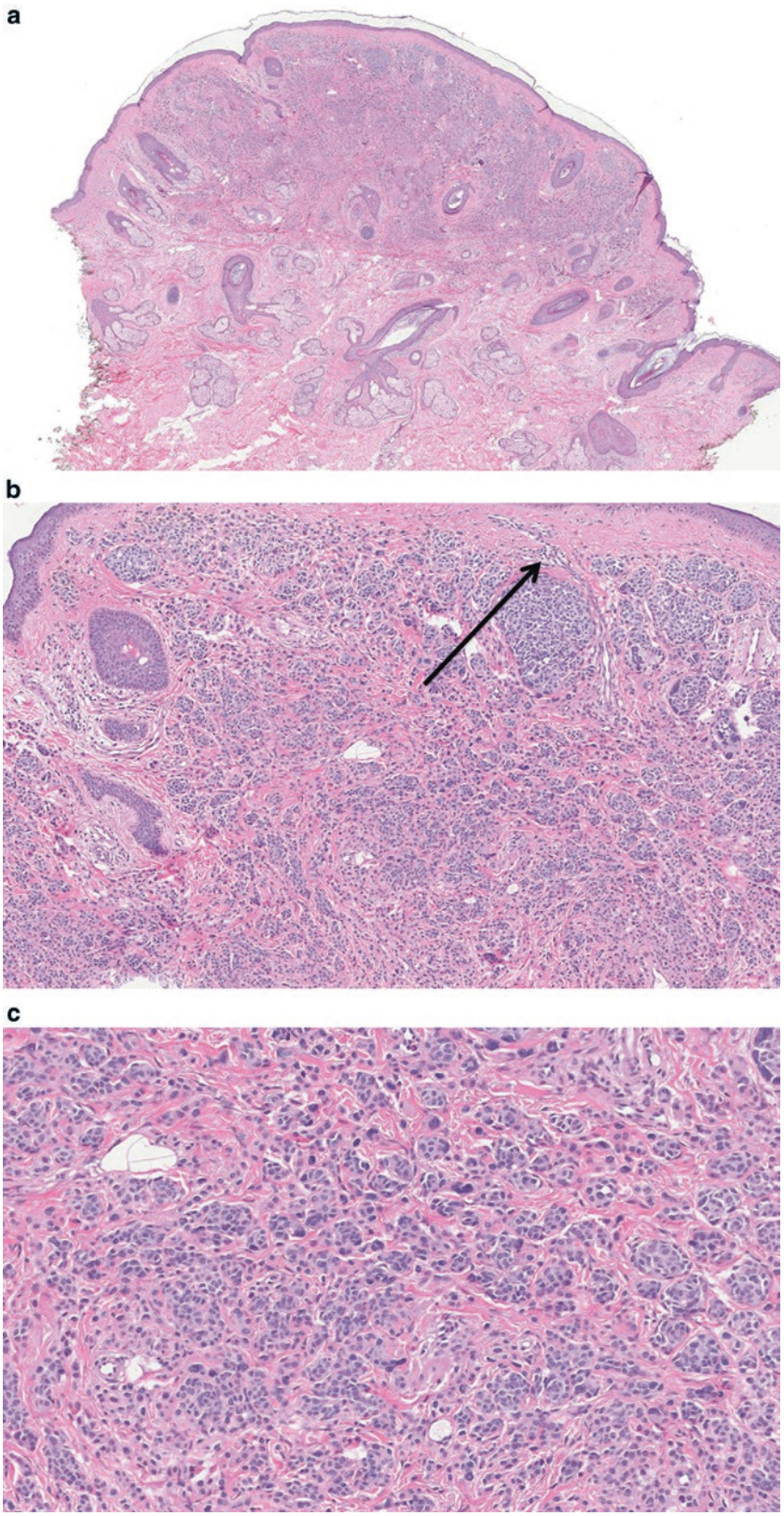


Fig. 3.7 Intradermal nevus. Note the melanocytes surrounding the adnexal structures, consistent with a congenital onset (**a**). There are signs of chronic irritation such as the presence of fibrosis in superficial dermis (*arrow*) (**b**). The cells are epithelioid (type A melanocytes) and with uniform nuclei without cytologic atypia (**c**)

Melanocytic Nevi Variants

Unna Melanocytic Nevi

These nevi are more commonly seen on the neck, extremities, and trunk, with some predisposition in the flexural areas, thus similar to skin tags [2, 3]. These nevi have a characteristic exophytic and pedunculated architecture and present as a dark papule that sometimes shows an umbilicated appearance. Unna nevus is a predominantly intradermal melanocytic nevus that is mainly exophytic and wholly adventitial; thus, all melanocytes are located within an expanded papillary dermis and frequently within perifollicular adventitial dermis. Histologically, these nevi can be either compound or intradermal. The overlying epidermis tends to be flat; however, in some occasions it is papillated simulating a seborrheic keratosis. The melanocytes in dermis mostly occupy the papillary dermis and tend to wrap the perifollicular adventitial dermis while sparing the reticular dermis. The nevus cells aggregate in dermis to form radial nests, resembling the sticks of a fan [2]. This configuration is more frequently noted on the periphery of the lesion. Another characteristic feature of Unna nevi is the presence of pseudovascular spaces lined by nevus cells. The melanocytes mature following the pattern above described showing lymphocyte-like melanocytes in the reticular dermis (type B) and spindle cell melanocytes toward the deeper portion of the lesion (type C). Mitotic figures in the Unna nevus are very rare, and when seen they are isolated. Although exceptional there may be a rare, deeply located mitotic figure. The junctional component when present is sparse; however, in some cases the junctional component can show asymmetric growth mimicking a melanoma. However, it should not extend beyond the dermal component. Rare cases of melanoma have arisen in the junctional component of an Unna nevus.

Miescher Melanocytic Nevi

Miescher nevus presents clinically as a dome-shaped papule with light brown color mostly found on the face and neck [2, 3]. Histologically, Miescher nevus is a predominantly intradermal melanocytic lesion with a smooth, slightly convex to semispherical surface and intradermal nevus cells infiltrating diffusely both the adventitial and the reticular dermis in a V-shaped (wedge) pattern. These nevi are mostly intradermal (few nests can be seen in epidermis). The melanocytes in the dermis form small nests in the upper part of the lesion and toward the base form cords separated by collagen bundles. In Miescher nevi, nevus cells almost never aggregate in radial nests, and pseudovascular spaces are present only exceptionally, as opposed to Unna nevi. Multinucleated melanocytes and adipocytes in between nevus cells are frequent and much more commonly seen than in Unna nevi. Cytologically melanocytes in dermis are banal appearing; however, some cases may show mild cytologic atypia possibly related to senescence or to actinic damage. As long as there is no expansile growth in the dermis, these changes should not be interpreted as nevoid melanoma. Also, melanocytes in Miescher nevus have an indistinct nucleoli as opposed to nevoid melanoma in which melanocytes have prominent nucleoli (sometime can show multiple nucleoli). Dermal mitotic figures are exceedingly rare. Large, dilated follicular structures and/or follicular cysts are not an uncommon finding in this type of nevus. In some cases, these follicular cysts can rupture and develop a granulomatous reaction. When the junctional component is noted, it is usually mildly cellular with a lentiginous pattern and only rare small nests; however, in some cases these junctional melanocytes can be asymmetrically arranged and melanocytes can have a large in size with epithelioid morphology. These large, isolated melanocytes in the epidermal basal layer are more commonly seen in Miescher nevi than Unna nevi. In such cases, this atypical junctional component does not extend lateral to the dermal component. It is important to be aware of this possible finding so it is not misinterpreted as melanoma in situ.

Meyerson Melanocytic Nevi

Meyerson nevus is generally caused by an eczematization of the center and/or the periphery of a melanocytic nevus [4–7]. This nevus is mostly found in male young adults (only rarely seen in children) and is more commonly located on the trunk or proximal extremities, although it can present on virtually any location of the skin. Clinically, it presents as a symmetrical area of erythema encircling a central melanocytic nevus. The phenomenon spontaneously resolves in months, although the nevus usually persists. Sometimes, Meyerson nevus can progress to a standard halo nevus or vice versa [8, 9]. In most cases, Meyerson nevi represent an isolated event; however, in some cases they can be associated with atopic dermatitis [10]. Meyerson phenomenon has been associated with congenital or acquired nevi, dysplastic nevi, and other cutaneous non-melanocytic lesions, such as seborrheic keratoses, basal cell carcinomas, squamous cell carcinomas, etc. [11–13]. Histologically, beyond the standard nevus, the adjacent epidermis shows spongiosis, acanthosis, and parakeratosis, and depending on the stage of the eczematous component, there may be frank vesiculation (acute phase). In the dermis, there is a superficial perivascular lymphohistiocytic infiltrate, and in some cases, there is eosinophilia. Of note, the lymphocytic infiltrate in Meyerson nevi is mainly CD4+ T cells, with a small population of CD8+ T cells, as

opposed to the inflammatory reaction seen in halo nevi, which are predominantly CD8+ T cells [13, 14].

Cockarde Melanocytic Nevi

Cockarde nevus, also known as speckled lentiginous nevus, is a rare, benign, acquired targetoid nevus characterized by a distinct variegated pattern of pigmentation (compound nevus bordered by a junctional nevus) [7, 15–17]. Cockarde nevus is most commonly seen in children and young adults and the most common location is the trunk. Clinically, it presents as a central, dark papule with an intervening, nonpigmented zone and peripheral stippled pigmented papules arranged in a circle [18]. Histologically, the central area is usually a junctional or compound nevus, and the periphery is composed of junctional theques with variable pigmentation. The periphery of the lesion may show pigmented melanophages in the superficial dermis.

Spilus Melanocytic Nevi

Nevus spilus it is a benign, large, lightly brown, pigmented macular lesion that usually presents at birth or in infancy, although it can appear at any age. This nevus commonly appears as a solitary lesion made of multiple pigmented macules, or papules, within a lightly pigmented macular background [7, 19]. It commonly progresses to more noticeable red-brown macules and papules over the years. This nevus can occur anywhere on the body, although it is more common on the trunk and extremities. The risk of melanoma seems to be higher in congenital cases and in cases where the lesions have a large diameter [20, 21]. Histologically, the background of the lesion shows mild pigmentation of the basal layer similar to a lentigo simplex, but in some cases, there may be slightly increased melanocytes or even frank nests. The darker speckled areas show either a junctional or a compound nevus. There are cases of nevus spilus with a blue or Spitz nevus component [22–24].

Inverted Type A Melanocytic Nevi (Clonal Nevi)

Inverted type A nevus is a variant of melanocytic nevus that histologically exhibits a localized proliferation of pigmented, epithelioid, dermal melanocytes within an otherwise ordinary nevus [25, 26]. It most commonly affects young adults and is more commonly located on the head and neck but can be seen at any anatomic site. This type of nevus can be either dermal or compound and shows no cytologic atypia or architectural changes. The pattern is that of a banal nevus admixed with the "clonal" cells. These clonal cells are located near the horizontal center of the nevus, arranged in nests, strands, and cords. Characteristically, these cells are large epithelioid pigmented melanocytes that are associated with occasional melanophages [27, 28]. The nuclei are usually small or slightly enlarged (severe cytologic atypia is not a feature). Mitotic figures are rarely present.

"Ancient" Melanocytic Nevi

This term was coined by Kerl et al. to describe a simulator of melanoma [7, 29, 30]. The designation "ancient" was chosen because of histopathologic similarities with ancient schwannoma. Recently, the term "pleomorphic melanocytic nevus with degenerative changes" has been used to delineate these nevi. Ancient nevi are found most commonly on the face, especially the cheek or ear, in middle-aged and older patients. Other sites include the trunk and extremities. These nevi are usually dome shaped, either skin-colored or reddish-brown papule.

Histologically, ancient nevi are well circumscribed, are exoendophytic, and involve most or all of the dermis. These lesions tend to lack a junctional component. In the dermis there are two populations of melanocytes, one with large pleomorphic nuclei and the other with small monomorphous ones. The large melanocytes are epithelioid or spindled and tend to be arranged in nests and sheets, cytologically reminiscent of the cells of a Spitz nevus; their nuclei are pleomorphic and hyperchromatic with sometimes prominent nucleoli; their cytoplasm tends to be abundant. The smaller melanocytes may be arranged in a congenital pattern and are situated above, underneath, or at the lateral margins of where the larger melanocytes are situated. These smaller melanocytes have scant cytoplasm. If any mitotic figure is identified, they usually are in the superficial portion of the large cell component. In addition, there are other senescent changes that include degenerative stromal changes, including thrombi, hemorrhage, pseudoangiomatous spaces, perivascular rims of sclerosis (hyaline rings), edema, and mucin [30].

Differential Diagnosis: Ancient nevus can be misdiagnosed as dermal melanoma. The distinction from melanoma should be based on the presence of only rare atypical melanocytes restricted to one area of the lesion. Also, the architecture in ancient nevus is not affected by the presence of these atypical melanocytes, which do not conglomerate in solid nests, pushing outward the small cell population, as happens in melanomas arising in nevi. Also, melanoma lacks the presence of degenerative stromal changes, which is a clue to the diagnosis of ancient nevus. In summary, dermal melanoma shows marked cytologic atypia of melanocytes, frequent mitotic figures, absence of degenerative changes (only the presence of necrosis), and large nodules and sheets of atypical melanocytes. It is unknown the relationship between ancient nevi and BAP1-deficient nevi (see also below).

Table 3.1 Ancient melanocytic nevi vs. dermal melanoma

• Degenerative stromal changes, such as the presence of a vascular component, are a diagnostic clue of ancient nevus. Melanoma usually does not display degenerative changes
• Two populations of melanocytes are characteristically observed in ancient nevus (large- and small-sized melanocytes)
• In melanoma, the atypical melanocytes are arranged in expansile, large nodules and sheets
• Rare mitotic figures in dermis in ancient nevus. Melanoma usually shows frequent mitotic figures

Balloon Cell Melanocytic Nevi

Balloon cell nevus is a rare variant that is characterized histologically by a predominance or complete occurrence of large, vesicular, clear cells, known as balloon cells [31, 32]. The most common site appears to be the head and neck area, followed by the trunk and extremities, and most commonly under the age of 30. Clinically, these nevi do not have any specific features but are generally asymptomatic, are brown in color, and may appear as a smooth papule [31, 33–35]. Histologically, they can be either compound or intradermal. By definition, the balloon cell component involves more than 50 % of the lesion in balloon cell nevi; however, focal balloon cell change (balloon cell melanocytes in <50 % of the lesion) can be seen in any benign and malignant melanocytic lesions [32, 36–39]. The classic pattern is that of balloon cells admixed with ordinary melanocytes. Balloon cell nevus is composed of melanocytes that have ample cytoplasm which is finely vacuolated and have small hyperchromatic wrinkled nuclei with scalloped contour. Sometimes these balloon cell melanocytes can have scarce melanin pigment. While the majority of these balloon melanocytes are seen in the intradermal component, in some occasions they may be seen in the dermal-epidermal junction. Within the dermal component, these balloon cell melanocytes merge with the type A, type B, and type C melanocytes. In only rare occasions, balloon cell nevi are composed solely of balloon cell melanocytes without the presence of more typical melanocytes. Multinucleated melanocytes with balloon cell change may be seen. Maturation is seen as in ordinary acquired nevi.

Differential Diagnosis: The main differential diagnosis of balloon cell nevus is with balloon cell melanoma. Balloon cell melanoma displays melanocytes with nuclear pleomorphism (irregular distributed chromatin) and prominent nucleoli throughout the neoplasm [40]. In balloon cell nevi, the melanocytes appear rather small and monomorphous. Also, mitotic figures are virtually absent in balloon cell nevus, thus any mitotic figure should alert the possibility of melanoma. Clinically, balloon cell nevus is usually seen in younger patients, whereas melanomas are more common in older patients.

Neurotized Melanocytic Nevi

Neurotized nevus refers to a nevus which histologically is composed of spindle-shaped melanocytes arranged in cords or fascicles resembling neuroid structures in the dermis which reportedly represent the end of development of an intradermal nevus [41–43]. The predominant melanocytic type in neurotized nevus is the type C, which in some occasions may organize into neuroidal structures resembling Meissner corpuscles. Schwannian and perineurial differentiation may be identified. This nevus in some occasions may look very similar to a neurofibroma, although it usually preserves a few nests of melanocytes in the papillary dermis. Neurotization can also be observed at the base of many other melanocytic neoplasms including Unna nevus, congenital nevus, and even melanomas (especially desmoplastic type).

Melanocytic Nevi with Adipose Metaplasia

Nevus with mature adipose tissue is a common histologic change related to senescence. The etiology is likely to be multifactorial. In addition to advancing age, the degree of body fat may contribute to the pathogenesis of these lesions. Clinically, these nevi are most commonly located in the head and neck area and resemble a skin tag [42, 44, 45]. It may occur in all age groups; however, they are observed most commonly in middle-aged persons (>50 years of age). Histologically, nearly 90 % are intradermal nevi.

Melanocytic Nevi with Pseudovascular Spaces

Melanocytic nevus may be histologically associated with clefts or slits of nests, resembling lymphatic or vascular spaces (pseudovascular spaces). This unique histologic feature might be due to an artifact during tissue processing or perhaps it is an involutional event [46–48]. The pseudovascular spaces may resemble lymphatic invasion of melanoma; however, one can easily make a distinction by identifying the regular contour and the presence of flattened endothelial cells in real vascular spaces, while the cells lining the pseudovascular spaces are similar in morphology to the adjacent melanocytes. Most nevi with pseudovascular spaces are intradermal or congenital; this phenomenon has not been identified in cases of dysplastic nevi, Spitz nevi, or melanoma. An important point to remember is that melanocytes can be identified within the dermal lymphatics in a nevus, and this should not be interpreted as melanoma.

Melanocytic Nevi with Dermal Mitotic Figures

The presence of dermal mitotic figures is an important diagnostic criterion for differentiating melanoma from melanocytic nevi. However, mitotic activity can be identified in some examples of benign intradermal or compound melanocytic nevi [48–52]. While the presence of dermal mitotic figures in a nevus should alert the pathologist to the possibility of melanoma, it is important to be aware that they can be identified in histologically and clinically banal-appearing nevi [53]. In these nevi the cytology and the architecture of the lesion are identical to standard melanocytic nevi, and there are no changes that indicate the histologic diagnosis of melanoma.

In a recent study, authors revealed that up to 8 % of benign melanocytic nevi had one or more mitotic figures. In this study the great majority of mitotically active nevi contained a single mitotic figure (>80 % of cases); however, some cases contained more than one mitotic figure, highlighting the potential for multiple mitotic figures in otherwise banal lesions [53]. An important point to remember is that nevi exhibiting mitotic figures are significantly more frequent in the youngest age group (0–20 years) than in patients older than 50 years [49]. Polypoid or verrucous configuration of the nevus and signs of traumatization are associated with higher mitotic activity [49, 54, 55]. When mitotic figures are present, they are located usually in superficial dermis, but in cases where multiple mitotic figures are seen within a single nevus, they are usually distributed far from one another and in some cases even distributed in the deeper parts of the lesion but never forming clusters [49–52]. The most common nevus type that is more commonly to show mitotic activity cases is a compound nevus. Some studies have found the highest incidence in special sites, including the genitals, perineum, groin, and acral regions. Some other studies have shown that most nevi with mitotic activity are located on the head and neck [50]. In addition, exposure to ultraviolet radiation has been shown to increase proliferative activity in nevi, which may explain the increased incidence of mitotic figures in sun-exposed areas, such as the head and neck [56]. Nevi in pregnancy may show an increase number of mitotic figures and modest ki-67 proliferation index [57].

It is very important to identify where the mitotic figures are located, as some of them may actually correspond to inflammatory cells. Some studies had recommended to try to separate those proliferating cells by using immunohistochemistry studies, including dual anti-Ki-67/MART-1 [58] or mitotic markers phosphohistone H3 (PHH3) and MPM2 [49, 59]. This particular study [49] identified that mitotic figures in inflammatory cells were present in 35.4 % of the PHH3 and 42.2 % of the MPM2-stained sections, respectively. Mitotic figures were more frequently identified in heavily inflamed lesions in which proliferative active melanocytes and inflammatory cells were intermixed and could hardly be distinguished from each other concluding that the number of mitotic figures in melanocytes may be overestimated by the application of immunohistochemistry. In our experience, immunohistochemistry studies to detect mitotic figures are usually not needed for the diagnosis of banal melanocytic nevi; however, mitotic markers may be a very helpful ancillary tool for the evaluation of suspected nevoid melanomas, spitzoid melanocytic neoplasms, and cellular blue nevi as they give an overall impression of the distribution and the degree of proliferation and approximate number of mitotic figures at a low magnification. In heavily pigmented melanocytic lesions, mitotic figures can be easily overlooked on H&E stain but are well identifiable by immunohistochemistry.

Table 3.2 Melanocytic nevi with mitotic figures vs. melanoma

• Melanocytic nevi with mitotic figures are more commonly seen in young patients
• Polypoid or verrucous architecture and signs of trauma are associated with higher mitotic activity
• Mitotic figures in banal melanocytic nevi are never atypical or clustered together; this finding is very supportive of a diagnosis of melanoma
• The distribution of dermal mitotic figures in melanoma is highly heterogeneous. In nevi, mitotic figures are evenly distributed

Traumatized Melanocytic Nevi

Melanocytic nevi when they are traumatized undergo changes in their clinical appearance and can clinically mimic atypical melanocytic lesions and in some cases even melanoma. This phenomenon causes clinical concern because a small percentage of nevi with such clinical features (e.g., ulceration or bleeding) show an associated melanoma.

Although one of the most useful histologic features in making a diagnosis of melanoma is the presence of pagetoid upward migration of melanocytic cells, such phenomenon is not specific to melanoma and can be seen in Spitz nevi, congenital nevi, recurrent nevi, acral nevi, and genital nevi [60, 61]. In traumatized nevi, the melanocytes underneath the ulcer can show pagetoid upward migration, mild cytologic atypia, and focal confluent growth pattern. In fact, one study found that up to 20 % of nonsurgical traumatized nevi can show pagetoid upward migration [62], but that should be limited to the area of trauma (parakeratosis, irregular flattening of the epidermis). The presence of ulceration is another histologic feature that is commonly seen in traumatized nevi and can easily raise concern for malignancy.

Histologically, traumatized nevi show evidence of trauma including ulceration, parakeratosis, presence of melanin within the stratum corneum, hemorrhage, dermal inflammation, granulation tissue in the dermis, and, depending on the stage of the lesion, dermal fibrosis. Pagetoid upward migration can be observed and is usually limited to the site of trauma. In addition, traumatized nevi with pagetoid spread can be separated from melanoma based on the cytologic features of the cells and knowledge of the clinical scenario including age and anatomic site. The presence of dermal mitotic figures can be identified in traumatized nevi, but the presence of more than one or two mitotic figures in the entire lesion should be a red flag for melanoma [49]. Atypical melanocytes are usually absent but when noted are located in superficial dermis and are entrapped in the fibrotic dermis. Thus, in our opinion, caution should be used when purported traumatized nevi display significant cytologic atypia, marked pagetoid spread (lateral to the traumatized epidermis), or atypical dermal mitotic figures.

One study showed that while aberrant HMB-45 labeling (i.e., absence of maturation) is observed in the region of trauma in cases of late traumatized nevi, the overall assessment of the lesions shows both histologic and immunohistochemical maturation [63]. In this same study, authors showed that low MIB-1 labeling (<5 %) in traumatized nevi is an additional reassuring finding as higher MIB-1 immunoreactivity is usually seen in melanoma.

Table 3.3 Traumatized melanocytic nevi vs. melanoma

• In ulcerated melanocytic lesions, it is always advised to inspect the adjacent non-ulcerated epidermis for signs of melanoma
• Pagetoid spread in traumatized nevi is usually seen underneath the area of trauma; pagetoid spread seen lateral to the area of trauma is usually indicative of melanoma
• In traumatized nevi, dermal mitotic figures are not uncommonly identified. These dermal mitotic figures are not clustered or atypical
• In traumatized nevi, melanocytic atypia when seen is usually mild

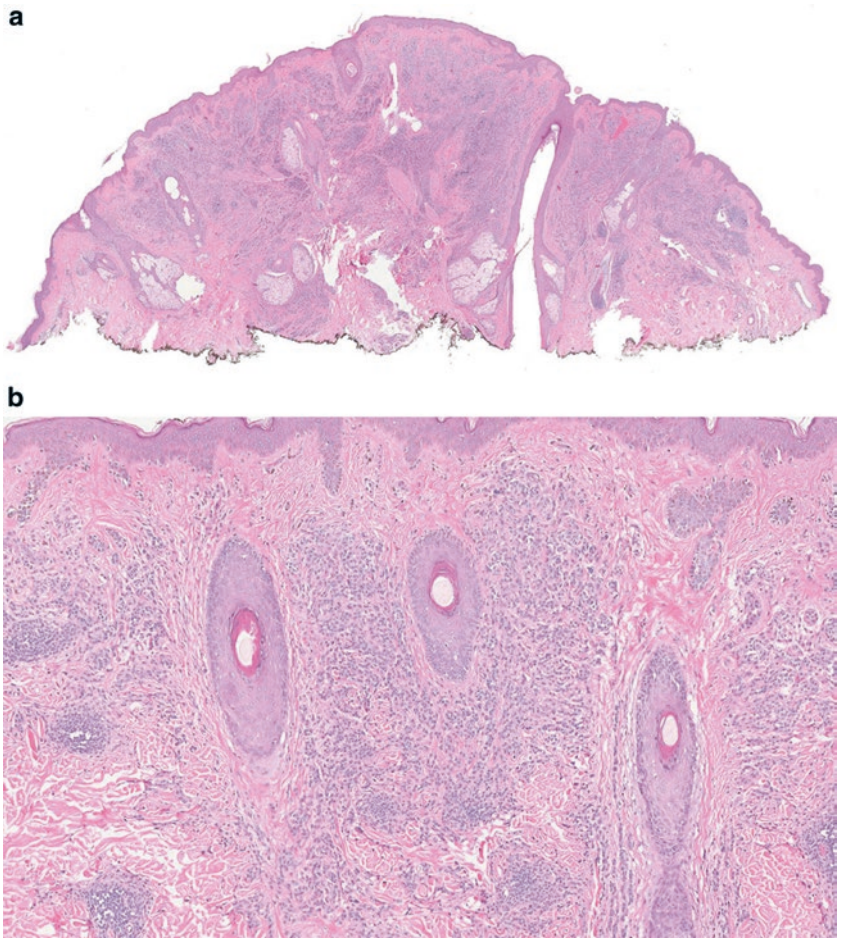


Fig. 3.8 Nevus with congenital features. This is an intradermal nevus with a congenital pattern that includes melanocytes surrounding the adnexal structures and arrector pili muscle (**a**). Upper portion with nests of small melanocytes (**b**).

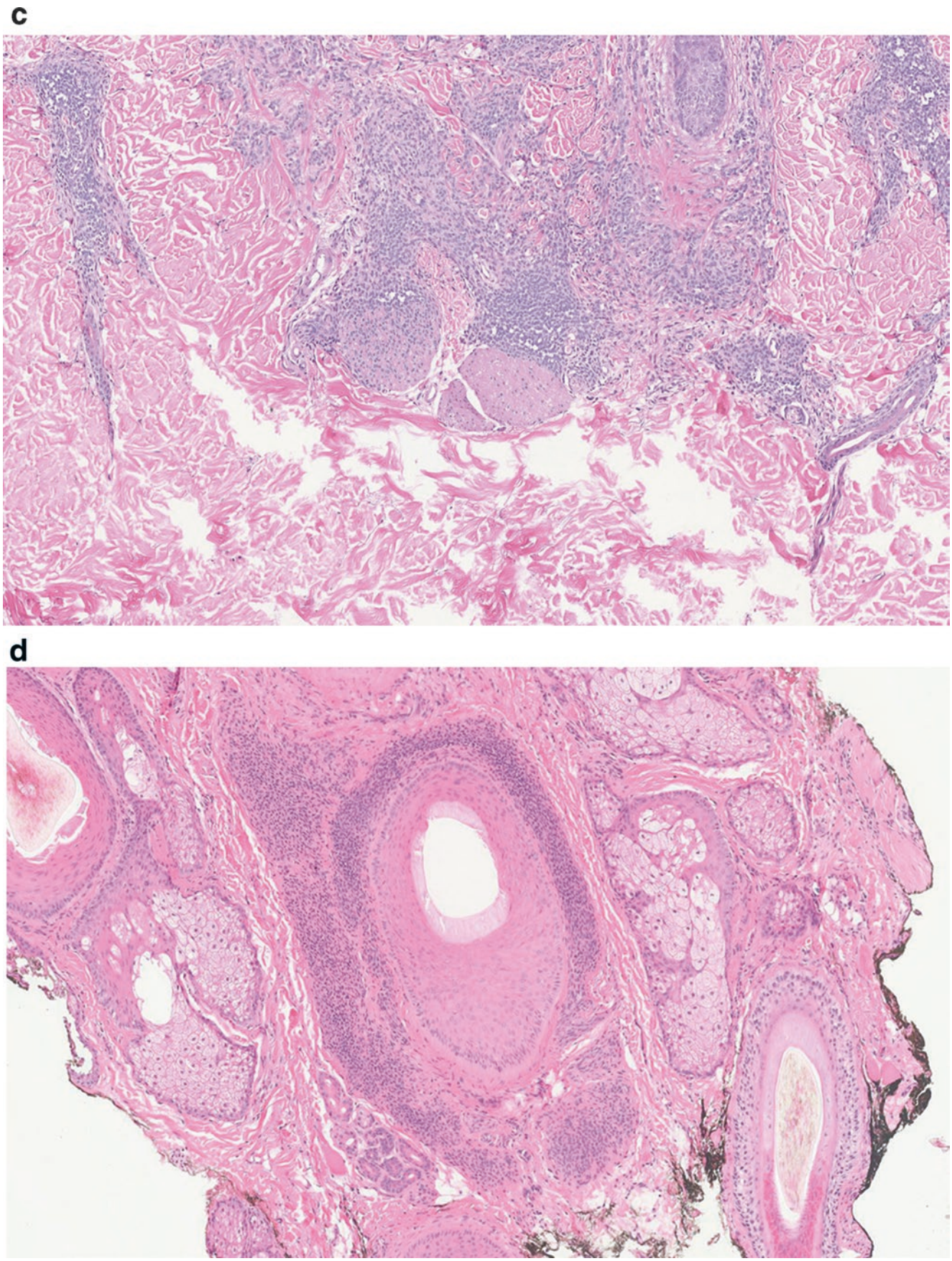


Fig. 3.8 (continued) Involvement of the arrector pili muscles (**c**). Periadnexal arrangement of melanocytes (**d**)

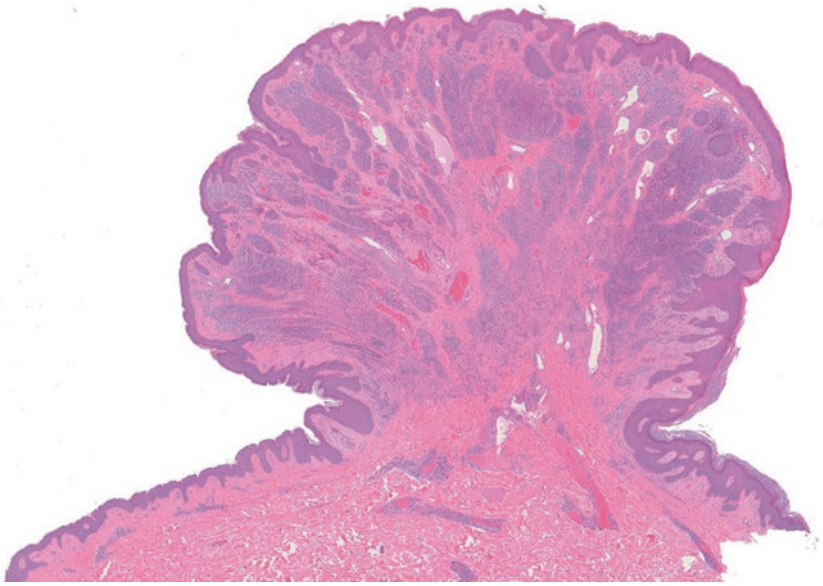


Fig. 3.9 Predominantly intradermal exophytic nevus (Unna nevus). Note the exophytic and pedunculated architecture of this nevus

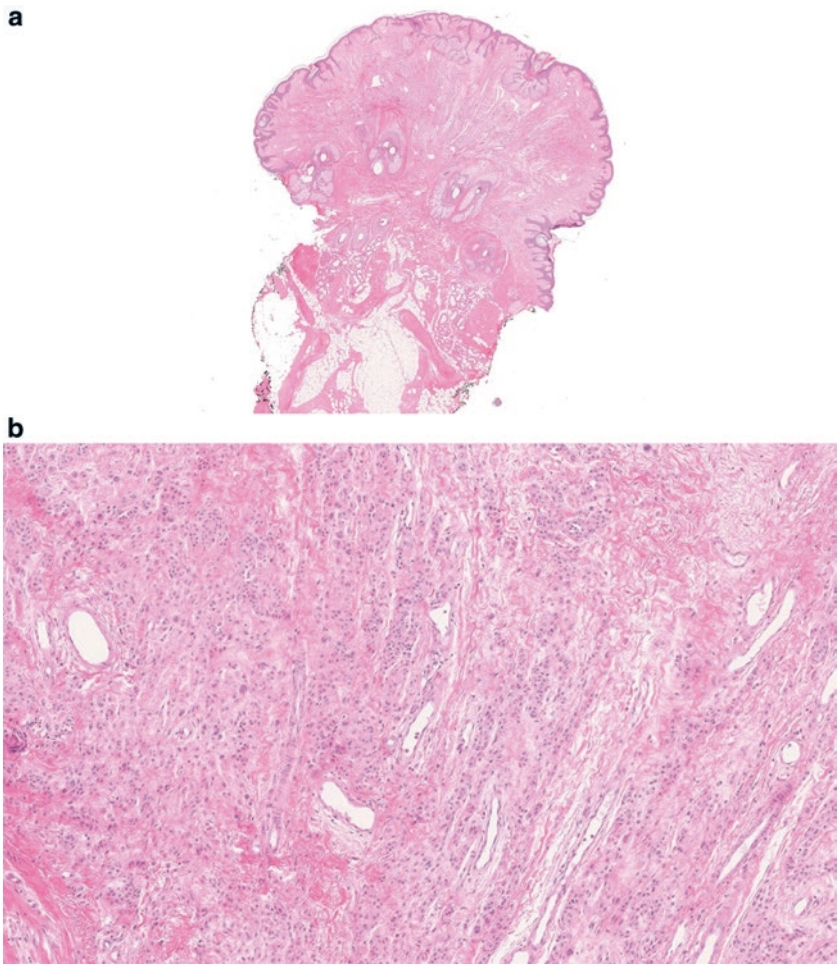


Fig. 3.10 Unna nevus. Another classic example showing polypoid architecture (**a**). Note the interstitial disposition of the small melanocytes leaving collagen fibers among them (maturation) (**b**)

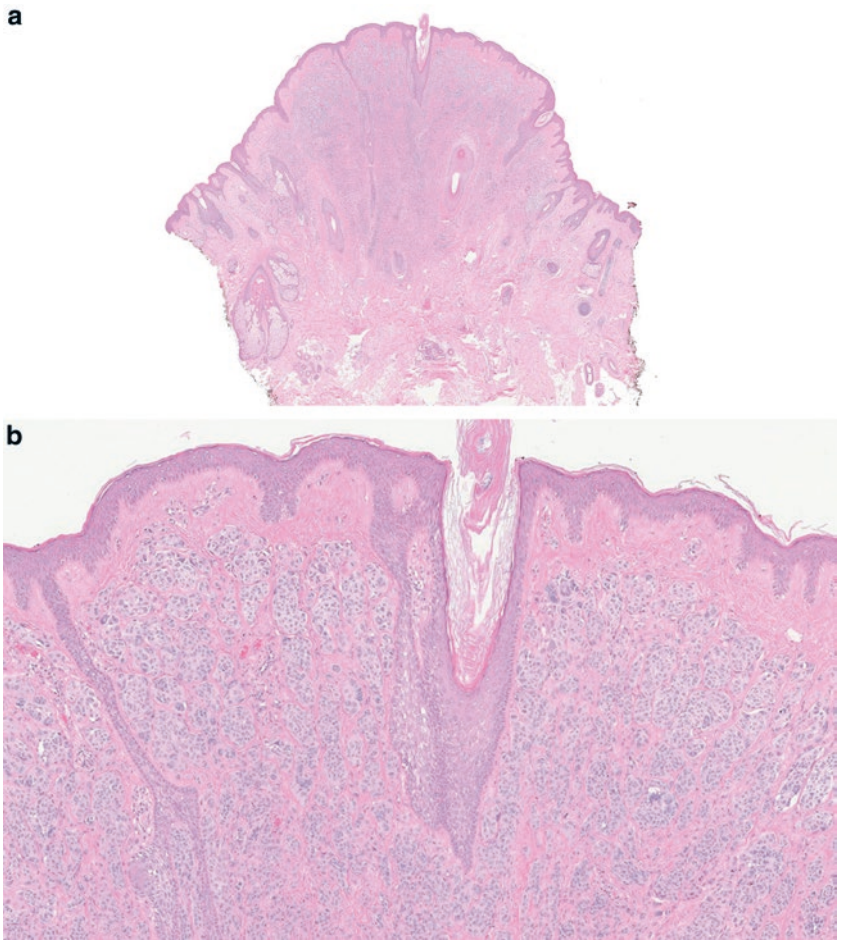


Fig. 3.11 Predominantly intradermal endophytic (Miescher) nevus: note the V-shaped infiltrate of melanocytes in dermis (**a**). Miescher nevus: note the small melanocytic nests in the upper part of the lesion (**b**)

Fig. 3.12 Predominantly intradermal endophytic (Miescher) nevus: another example showing the wedge-shaped arrangement in the dermis

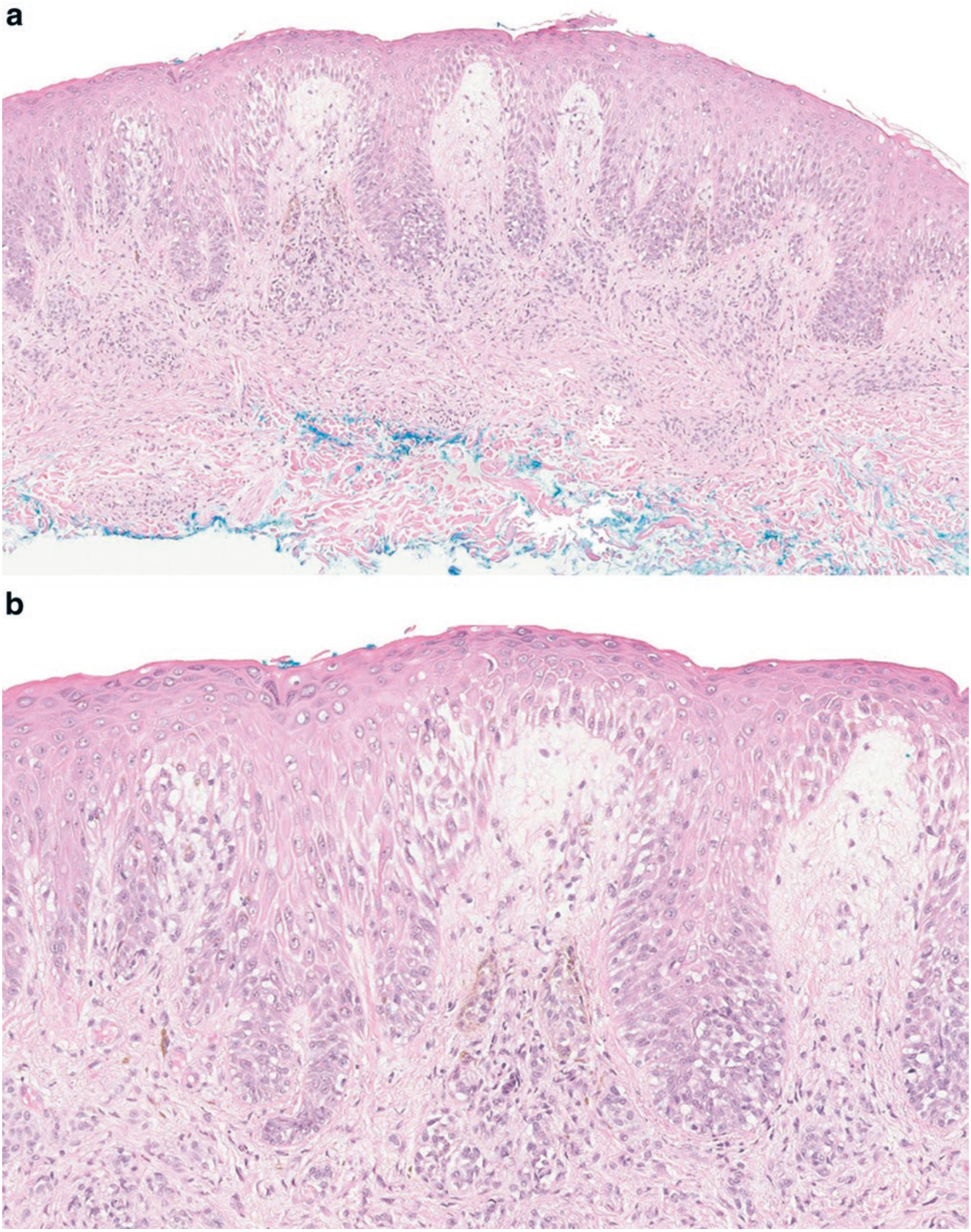


Fig. 3.13 Inflamed (Meyerson) compound nevus. Note this compound nevus with marked epidermal spongiosis along with perivascular lymphohistiocytic infiltrate (**a**). The associated lymphocytic infiltrate may result in focal, mild cytologic atypia (hyperchromasia and pleomorphism of melanocytes) (**b**).

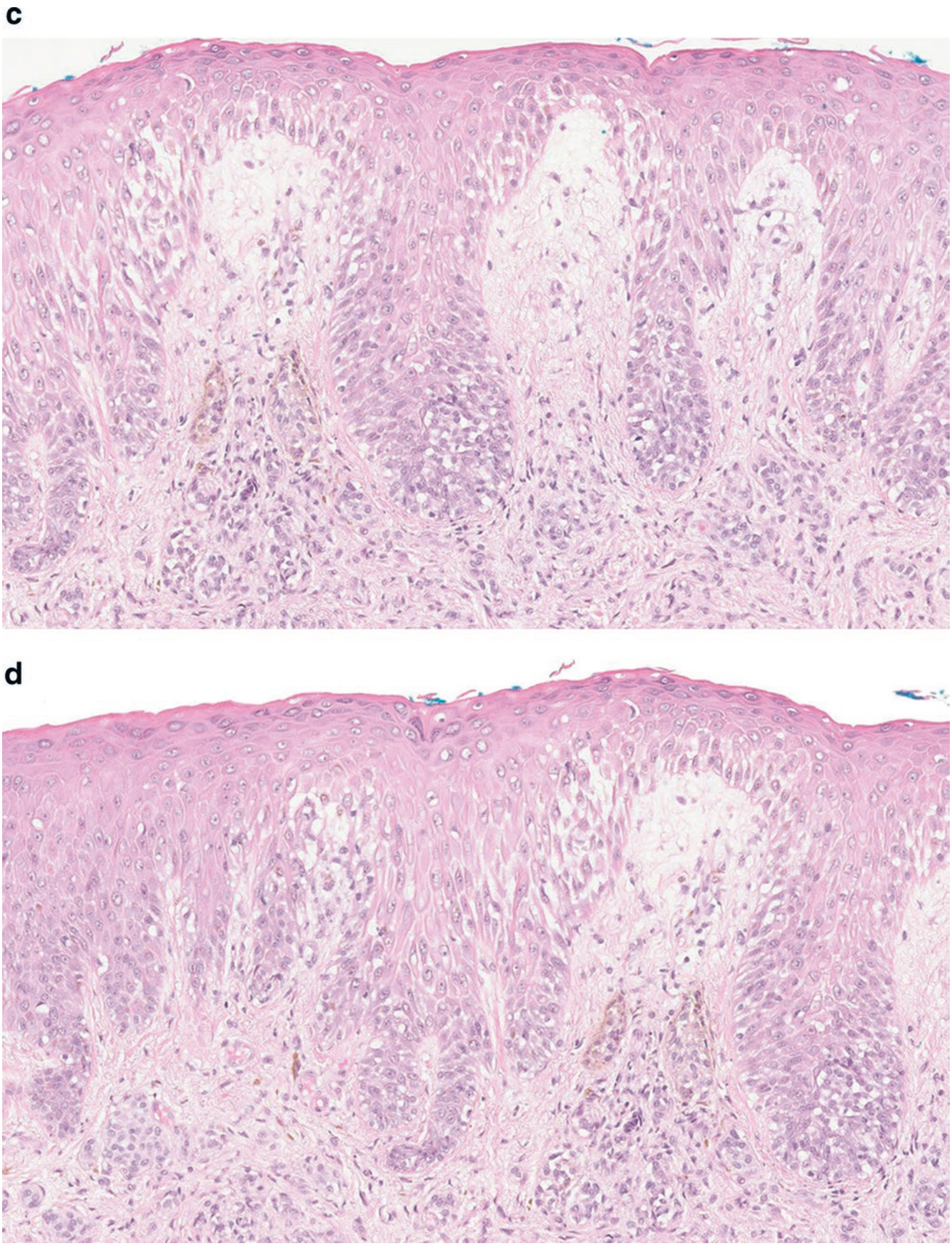


Fig. 3.13 (continued) Lymphocytic infiltrate and focal cytologic atypia of melanocytes. Note the absence of significant pagetoid migration (**c**). Lymphocytic infiltrate and focal cytologic atypia of melanocytes (**d**)

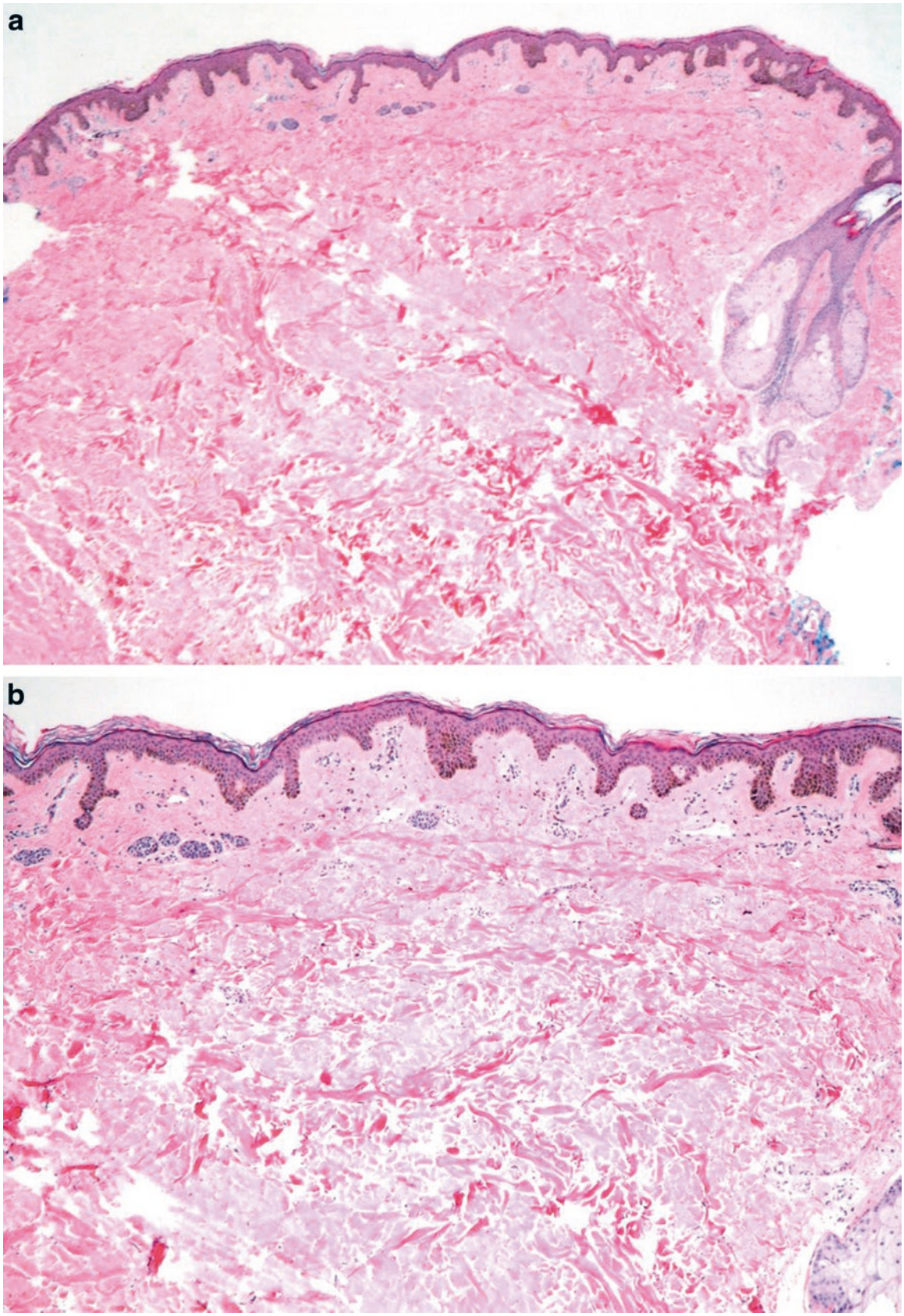


Fig. 3.14 Compound nevus (Speckled/spilus). Note a few intradermal nests alternating with areas of hyperpigmentation in the epidermis (**a**). Elongation and hyperpigmentation of some of the rete ridges. Scattered, small dermal nests (**b**).

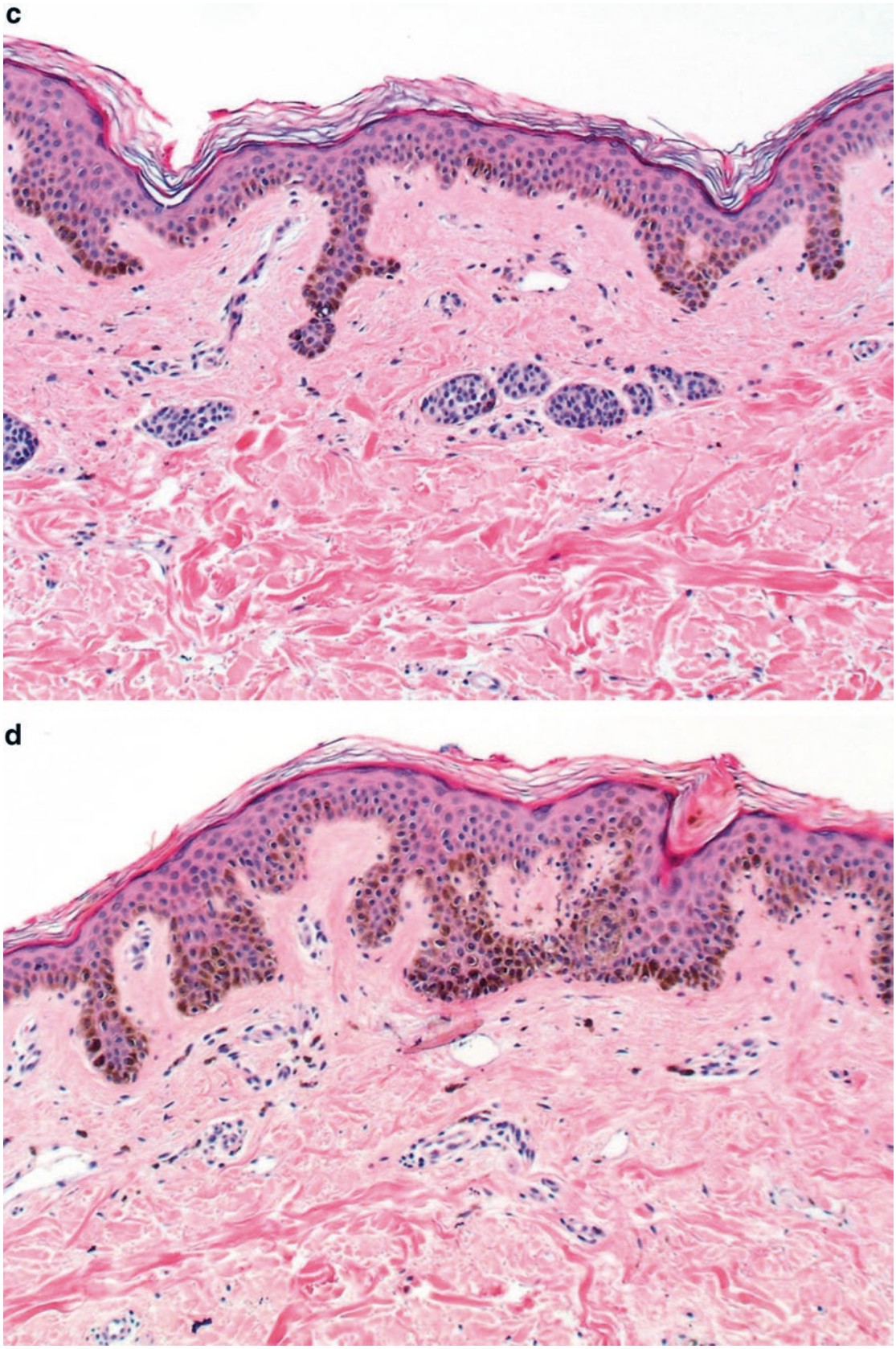


Fig. 3.14 (continued) Small intradermal nests with minimal junctional component (**c**). Subtle junctional component with small melanocytes in a lentiginous pattern (**d**).

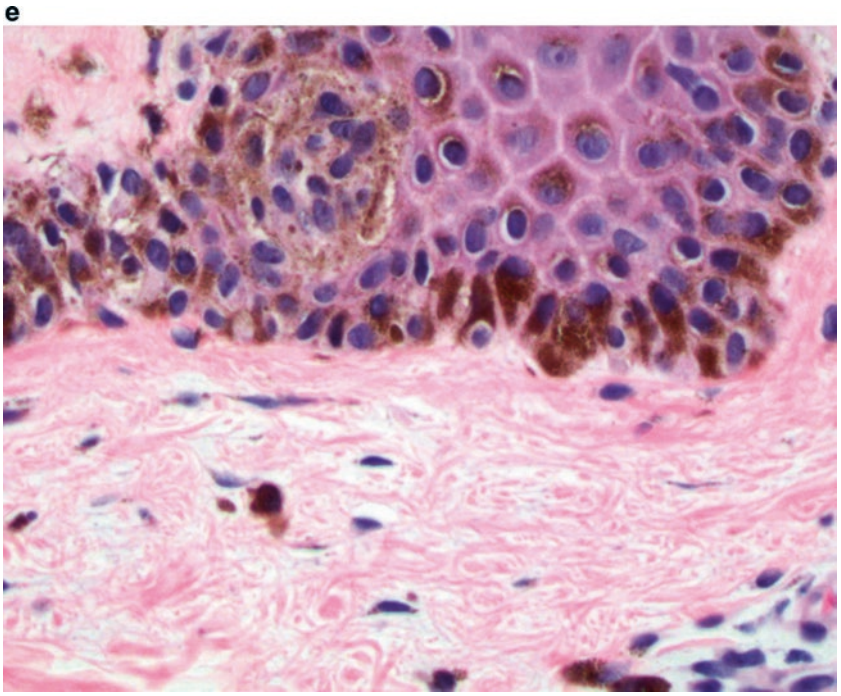


Fig. 3.14 (continued) Small junctional melanocytes, mostly as single cells but with occasional nests (**e**)

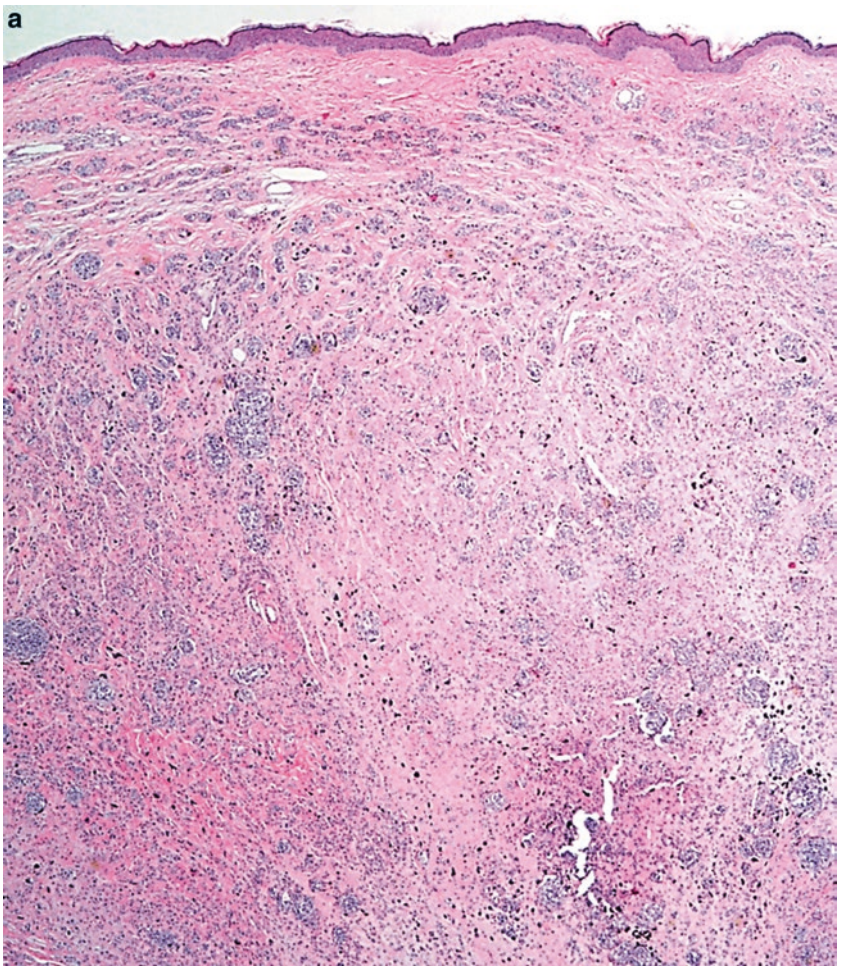


Fig. 3.15 "Ancient" nevus. Large intradermal lesion with two distinct areas. Top with small nests of melanocytes (standard intradermal nevus) and a large area in the center with hyper- and hypocellular areas and small clusters of melanin (**a**).

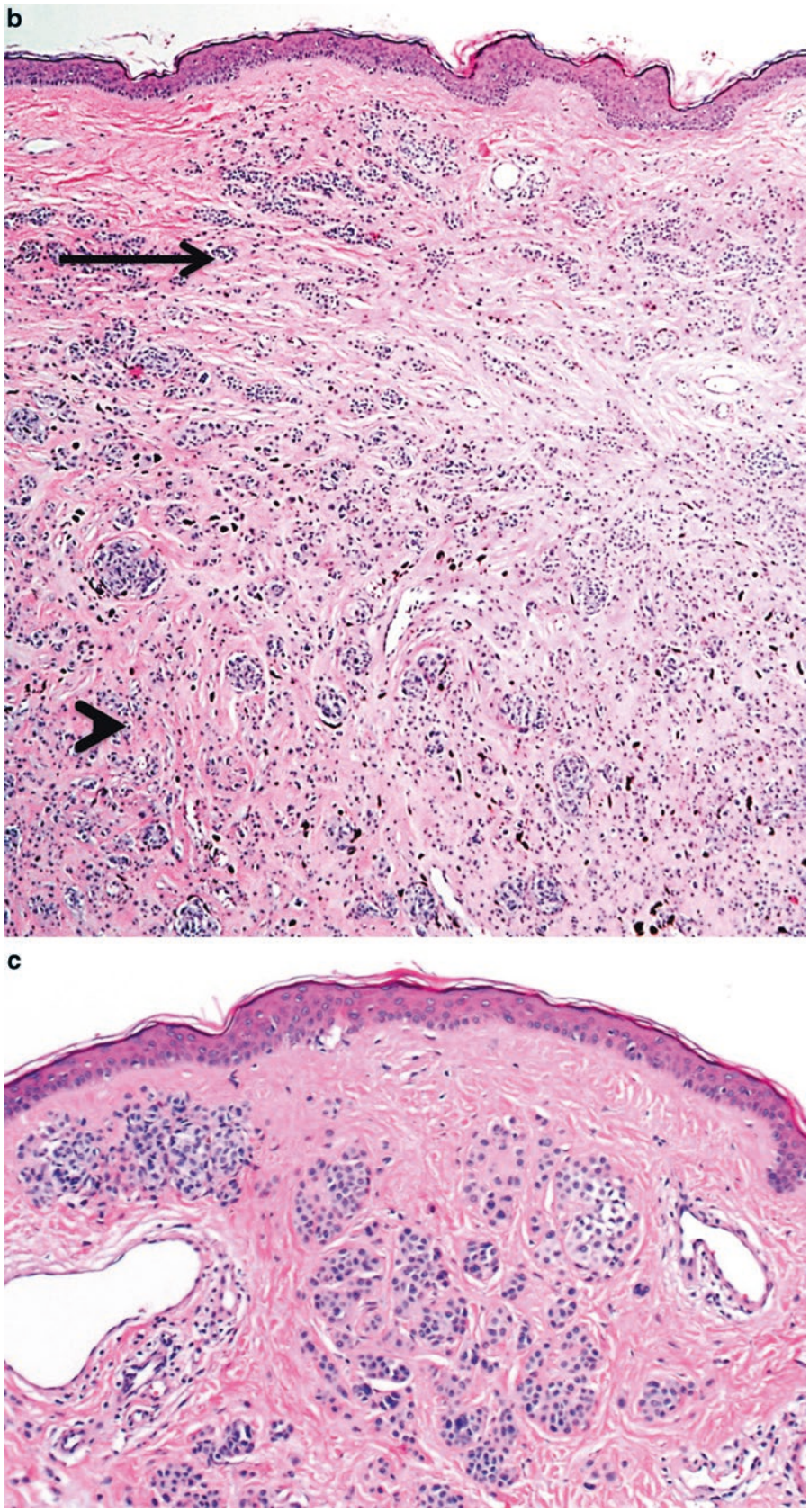


Fig. 3.15 (continued) Standard intradermal nevus on the top (*arrow*) and ancient area (*arrow head*) underneath (**b**). Standard intradermal nevus in the upper dermis (**c**).

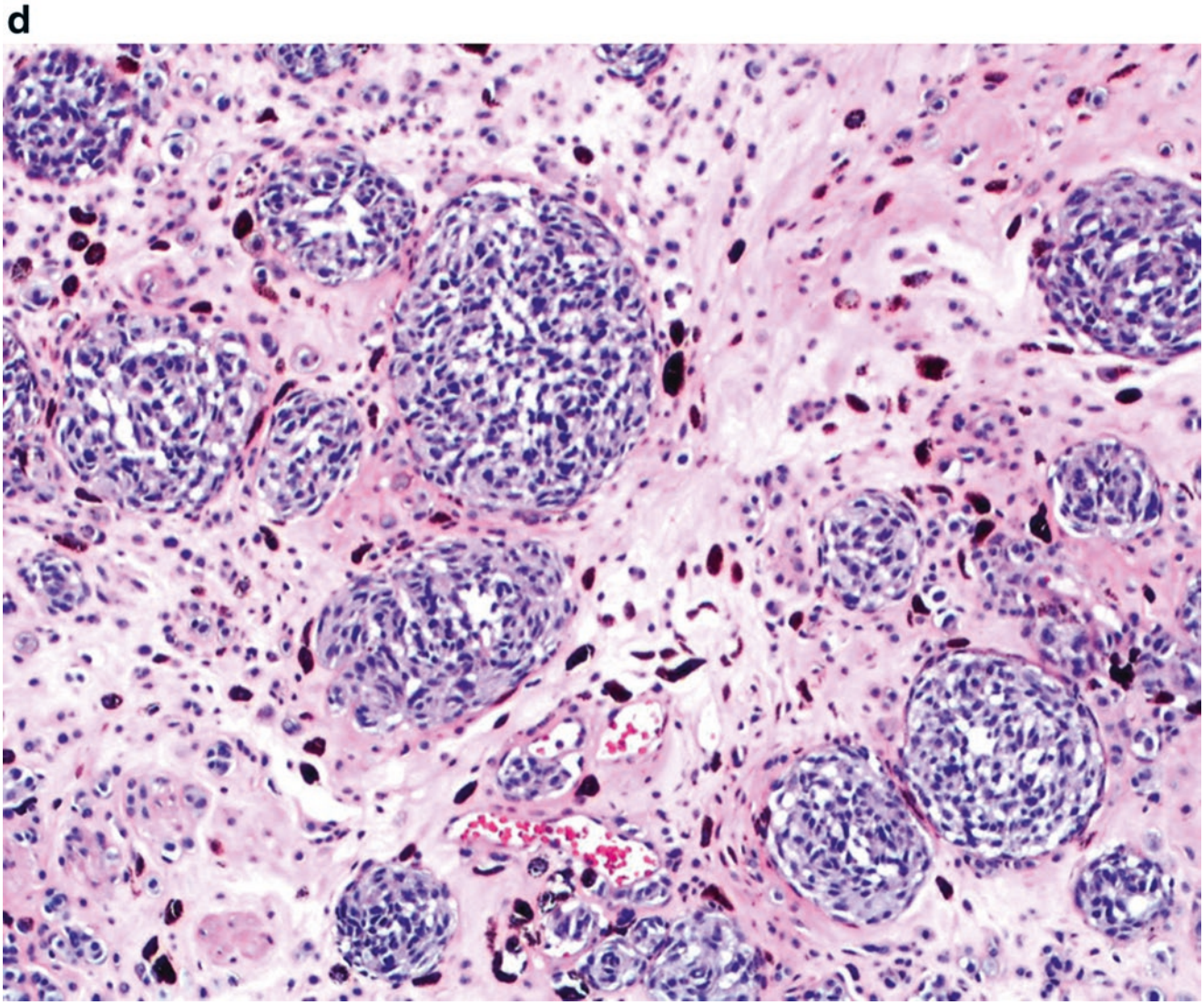


Fig. 3.15 (continued) Area with edematous stroma, dilated vessels, and epithelioid melanocytes with focal melanin pigment (**d**)

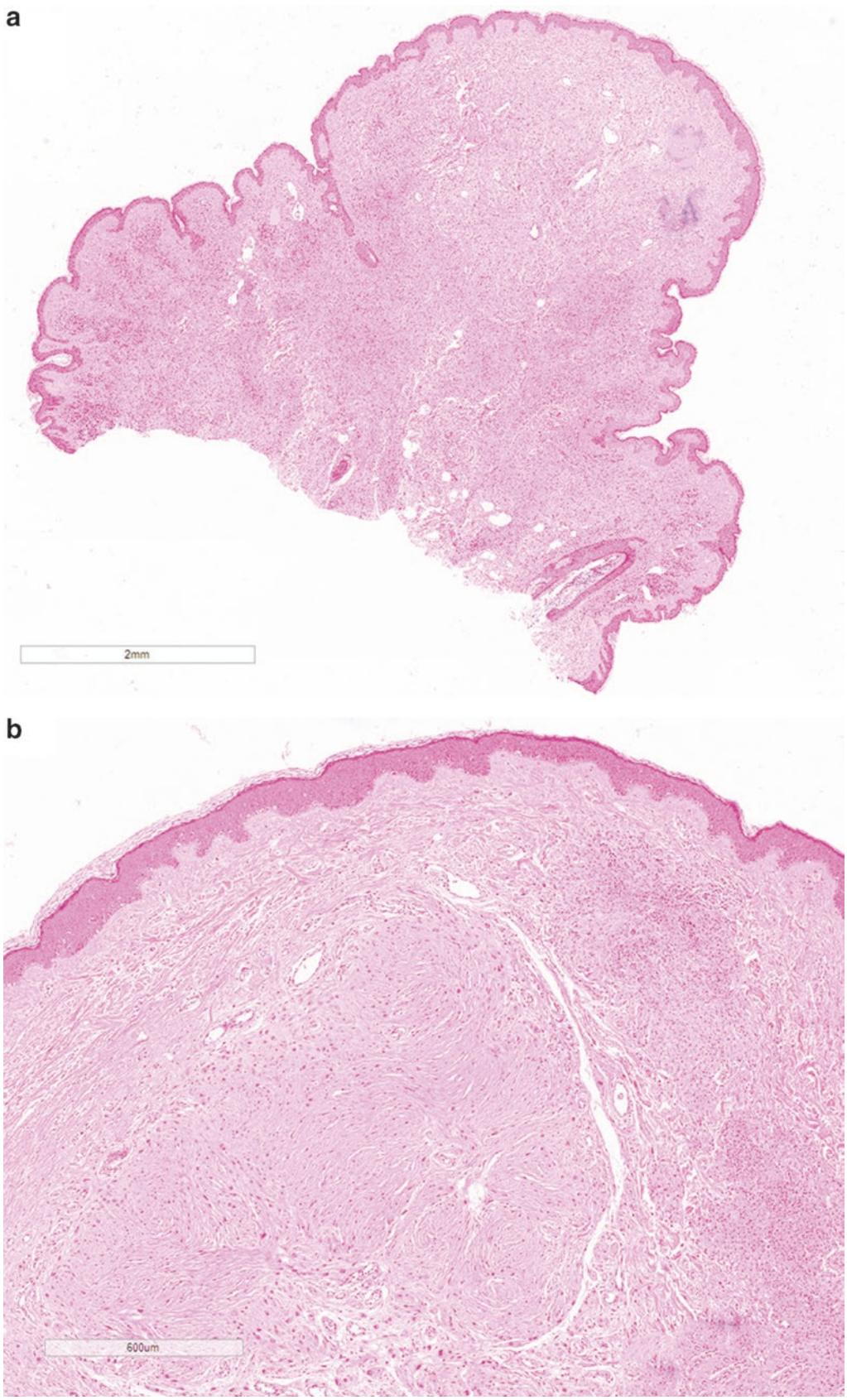


Fig. 3.16 Another example of "Ancient nevus". Predominantly intradermal nevus with a congenital pattern (deep infiltration with arrangement around skin adnexa) (**a**). Note the standard intradermal nevus with small melanocytes to the *right* and the dermal nodule to the *left* with a few dilated vessels (**b**).

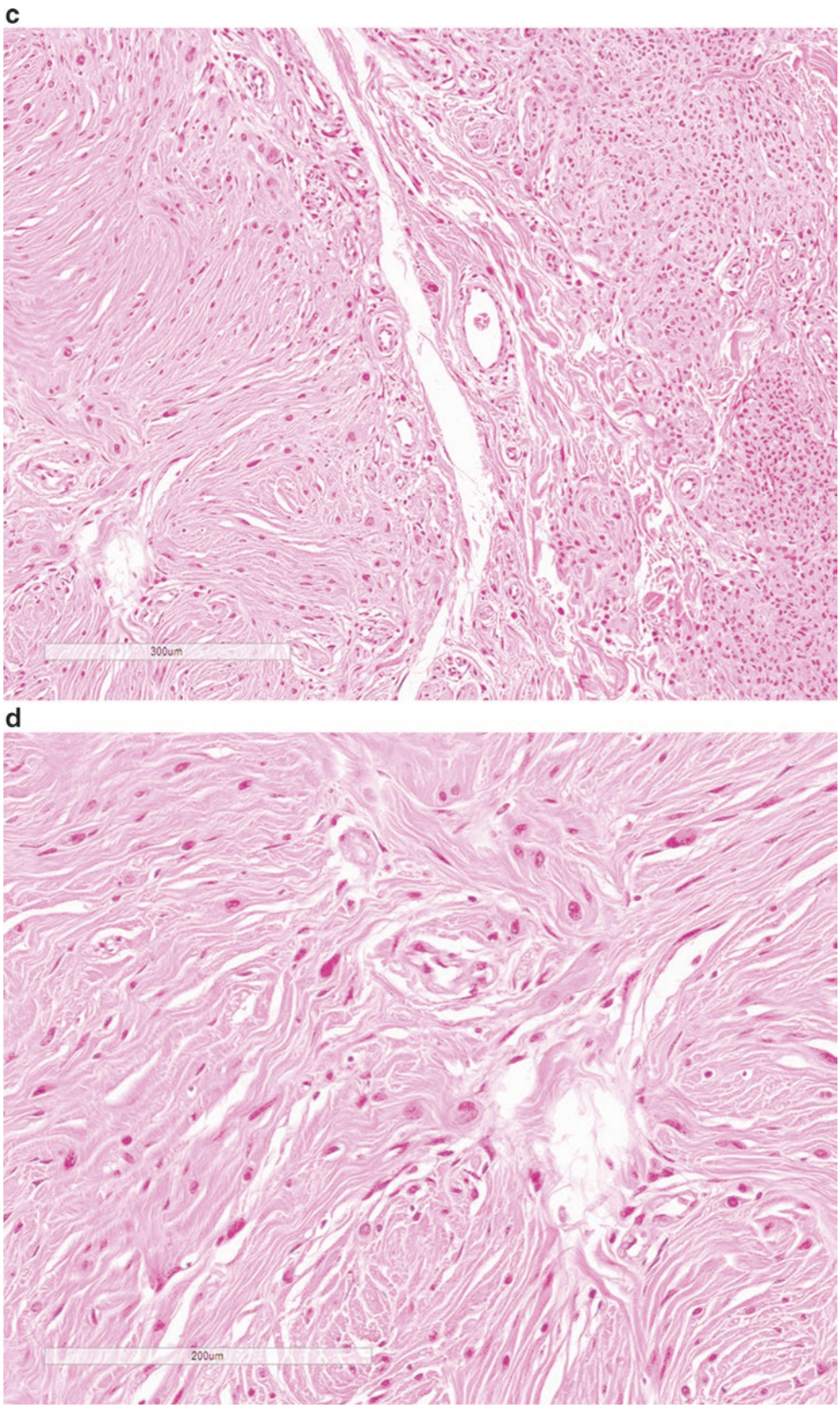


Fig. 3.16 (continued) Note the contrast between the standard nevus cells (to the *right*) and the large, epithelioid cells in the nodule to the *left* with a few thick vessels (**c**). Large, epithelioid cells in the nodular area. Although they are cytologically atypia, the type of nuclei resembles those seen in "ancient" schwannomas. Mitotic figures are not evident (**d**).

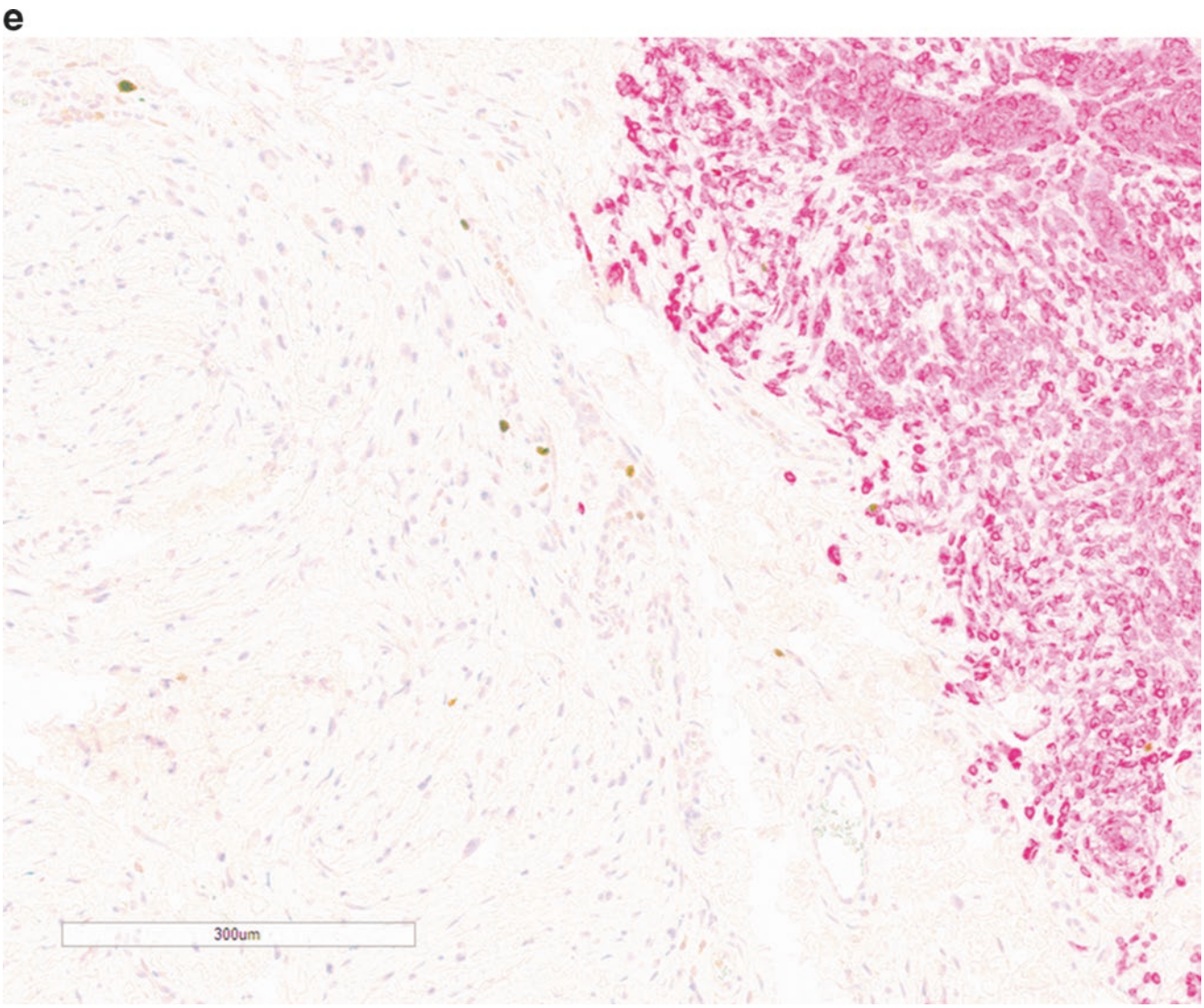


Fig. 3.16 (continued) A double immunostudy with anti-MART1 (*red*) and anti-Ki67 (*brown*) shows minimal proliferation in the dermis, supporting the diagnosis of nevus (**e**)

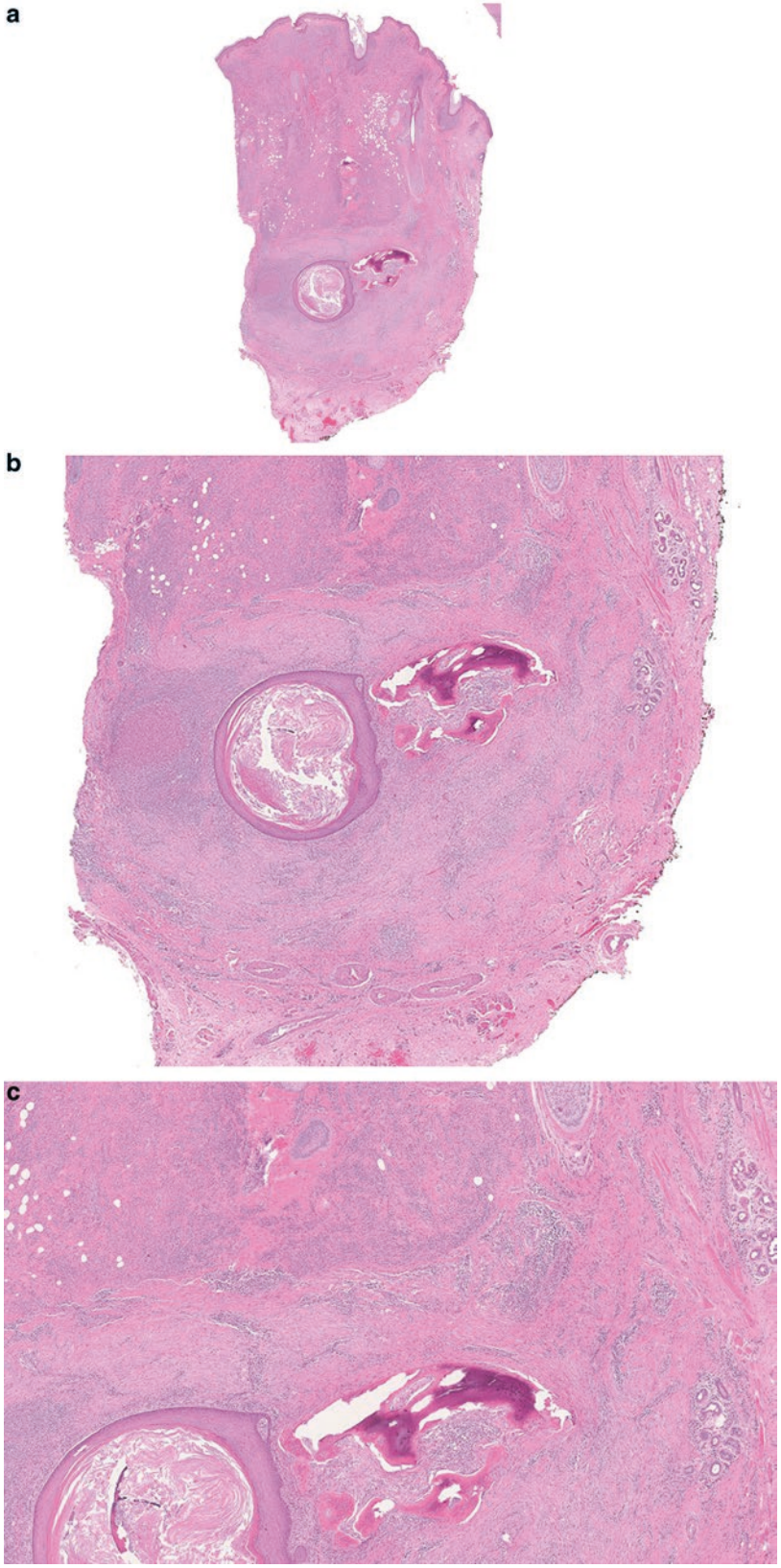


Fig. 3.17 Nevus with bone metaplasia. Note the ruptured follicle with adjacent mature bone formation (**a**–**c**)

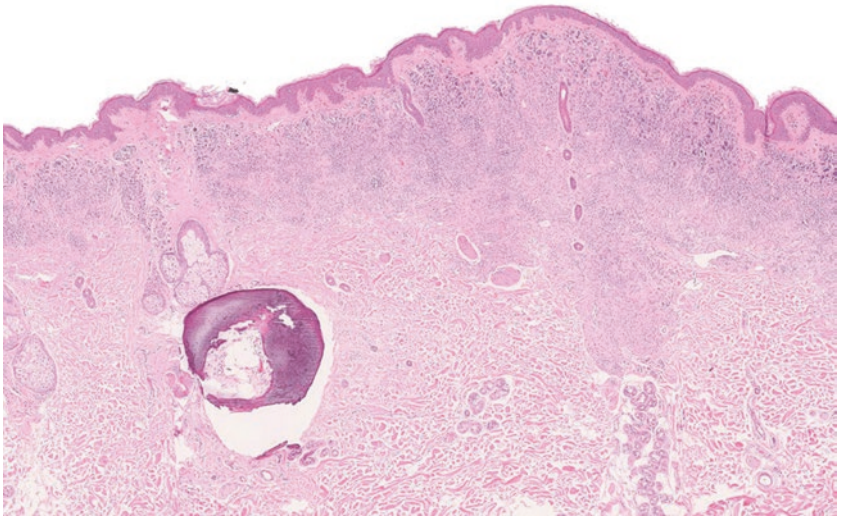


Fig. 3.18 Nevus with bone metaplasia. This particular case also shows a congenital nevus

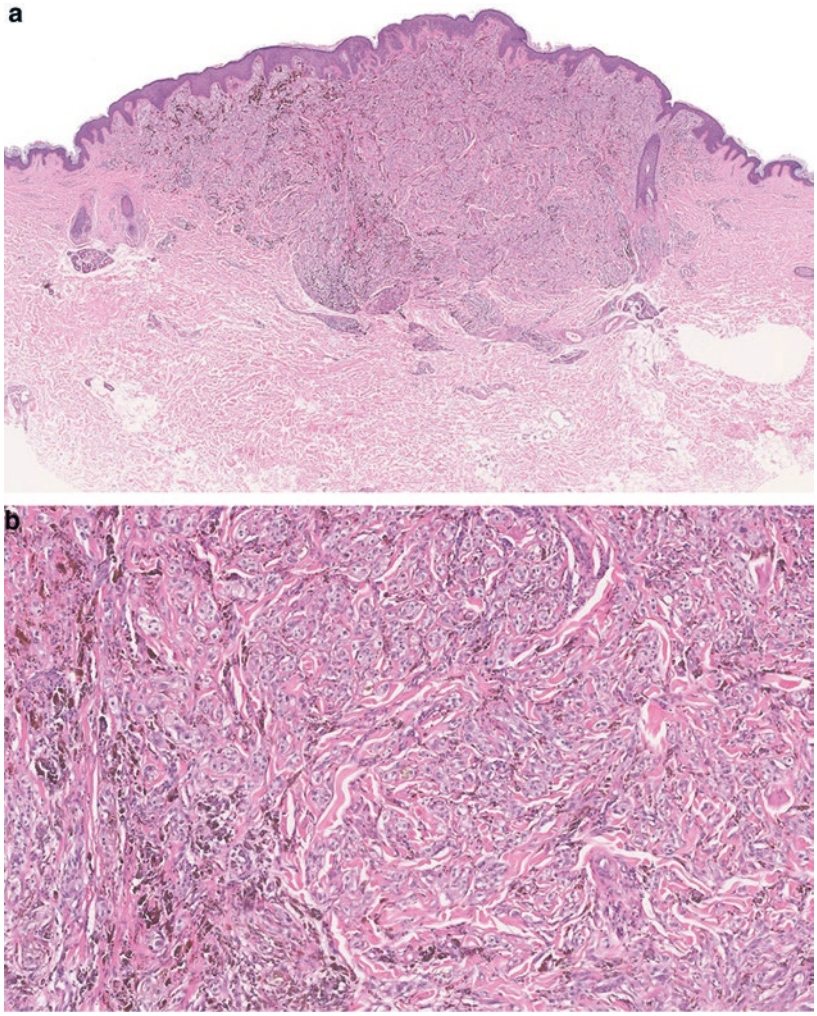


Fig. 3.19 Balloon cell nevus. Intradermal melanocytic lesion composed of melanocytes that have ample cytoplasm (**a**). Melanocytes with ample cytoplasm admixed with pigmented melanophages (**b**).

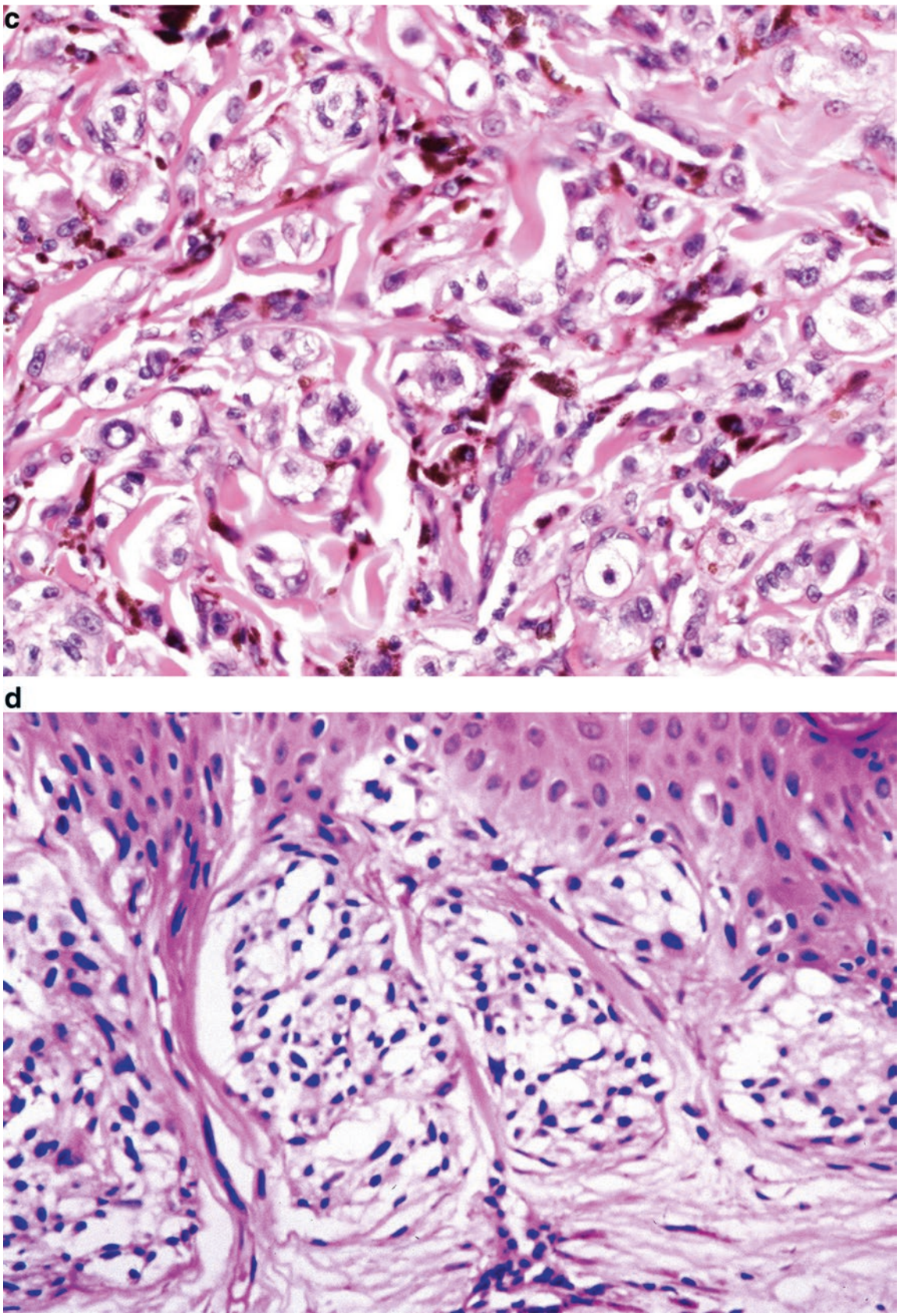


Fig. 3.19 (continued) Deeply located dermal melanocytes with interspersed melanin pigment (**c**). Junctional component with vacuolated melanocytes (corresponding to markedly dilated melanosomes) (**d**)

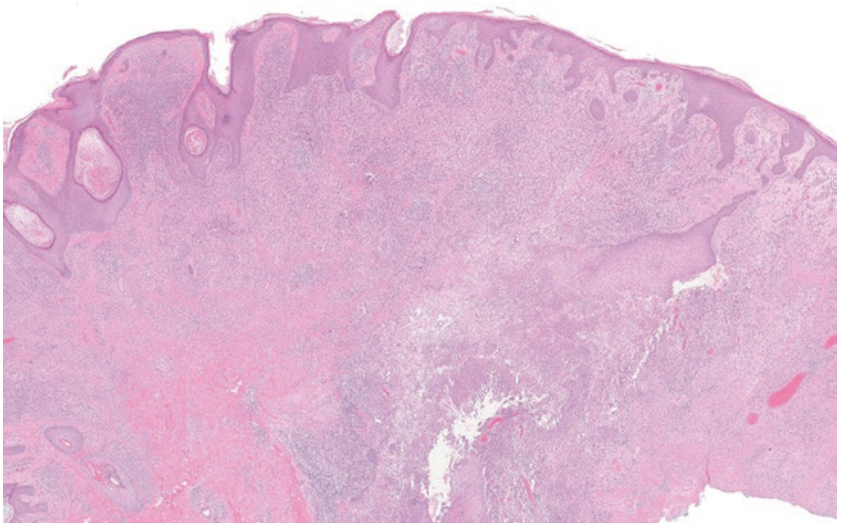


Fig. 3.20 Nevus with ruptured folliculitis. Such situation may be interpreted as a "changing" nevus and thus may raise the clinical suspicion of melanoma arising in a nevus

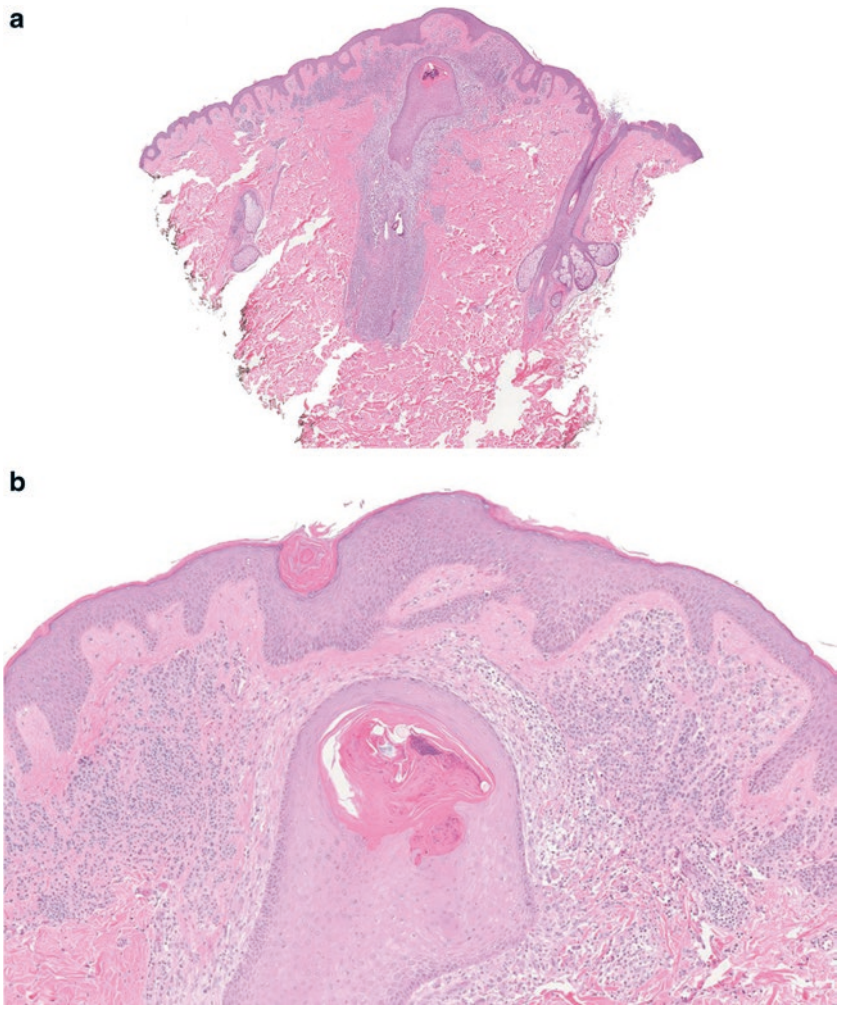


Fig. 3.21 Nevus with ruptured folliculitis. Note the nevus cells surrounding the inflamed hair follicle. The patient possibly pulled a hair from the nevus (**a**). Higher power view of the distorted hair follicle (**b**)

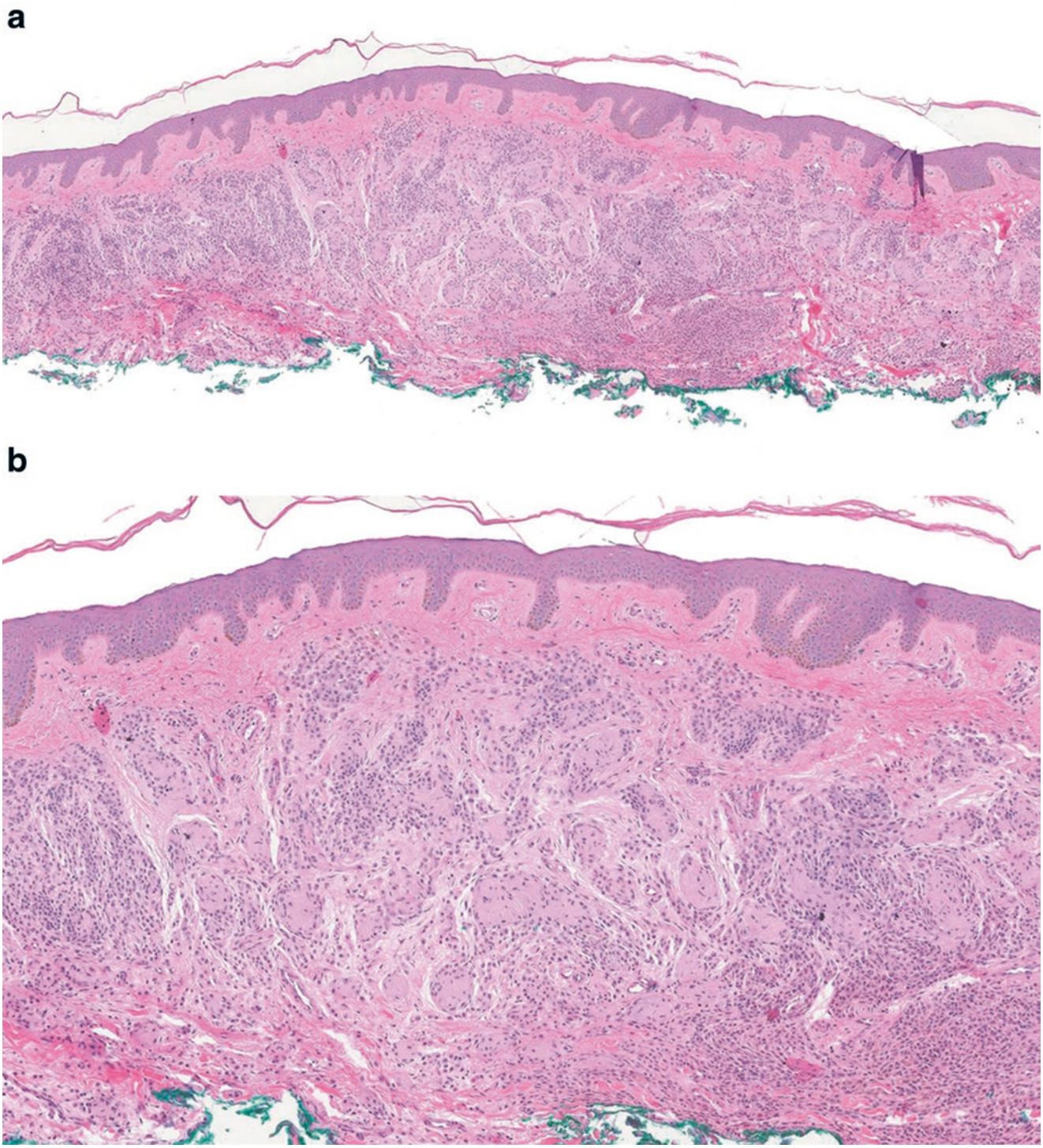


Fig. 3.22 Neurotized nevus. Intradermal nevus with neuroid-like structures (**a**). Note the type C melanocytes arranged in neuroidal structures (**b**).

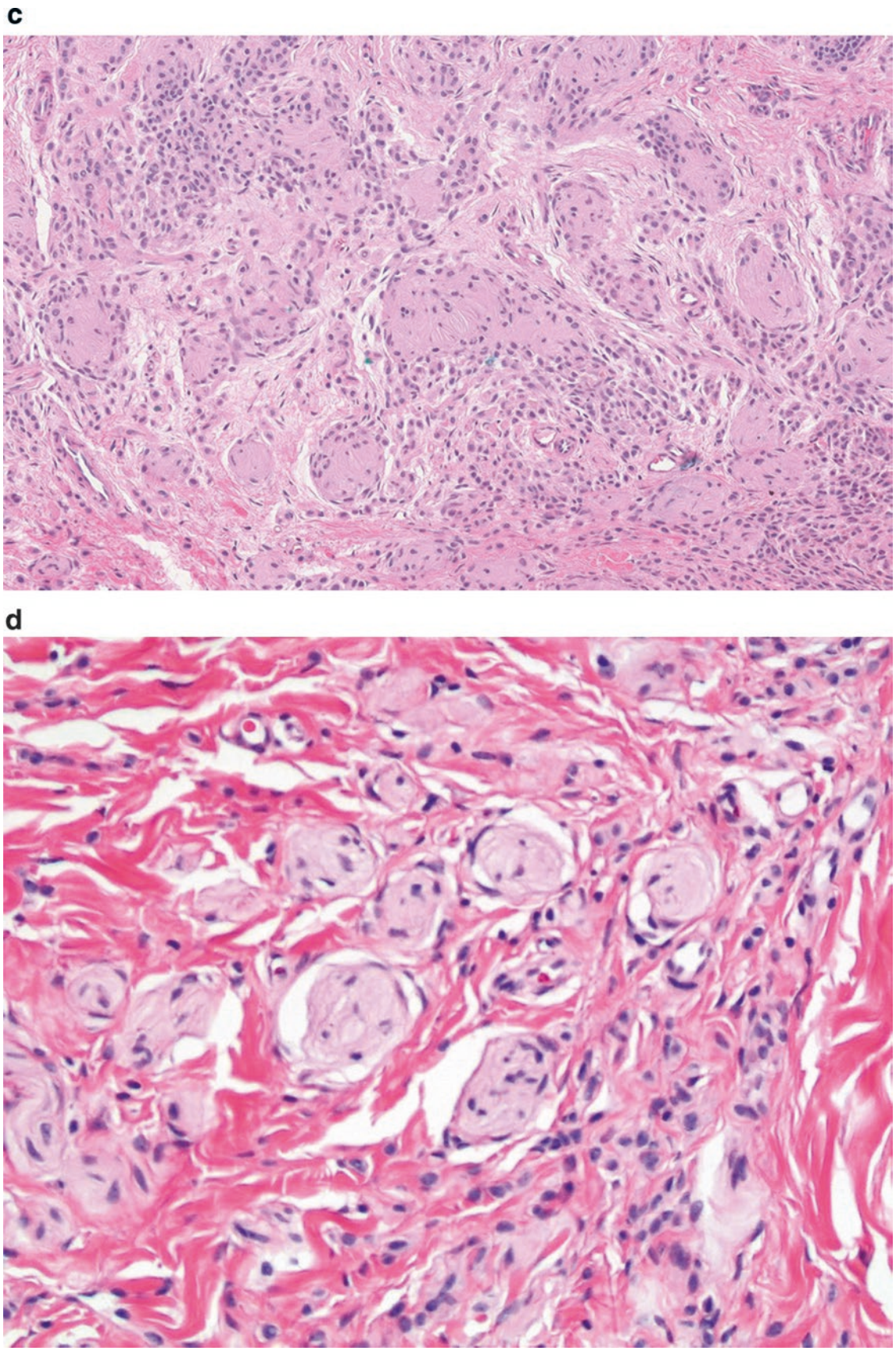


Fig. 3.22 (continued) High power of the neuroidal structures (**c**). Meissner-like corpuscles (**d**)

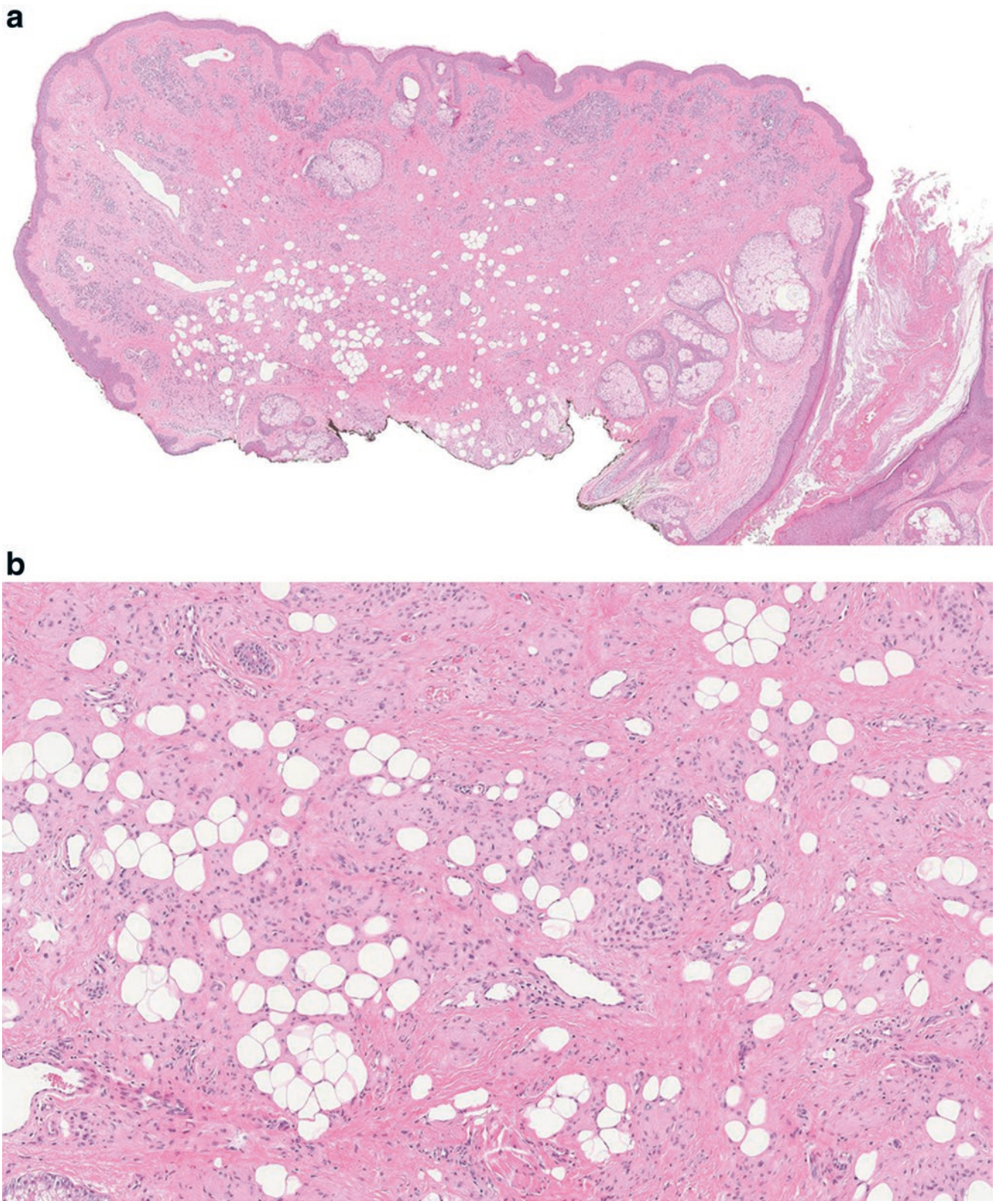


Fig. 3.23 Nevus with lipomatous metaplasia (**a**). Note the adipocytes arranged within the lesion (**b**)

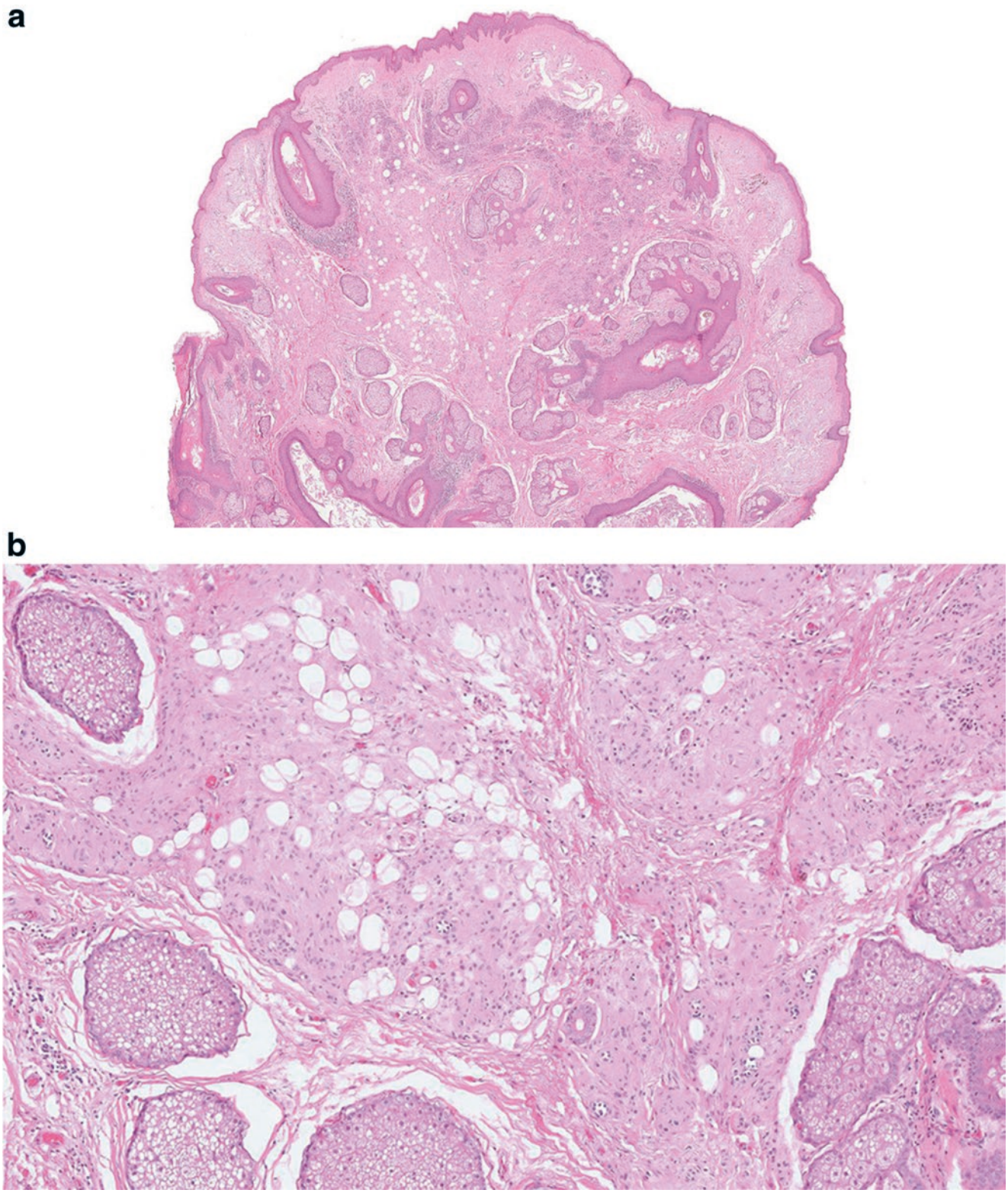


Fig. 3.24 Nevus with lipomatous metaplasia. This is the face of a 32-year-old male with an intradermal nevus with congenital pattern. Note the numerous adipocytes at all levels of the lesion (**a**, **b**)

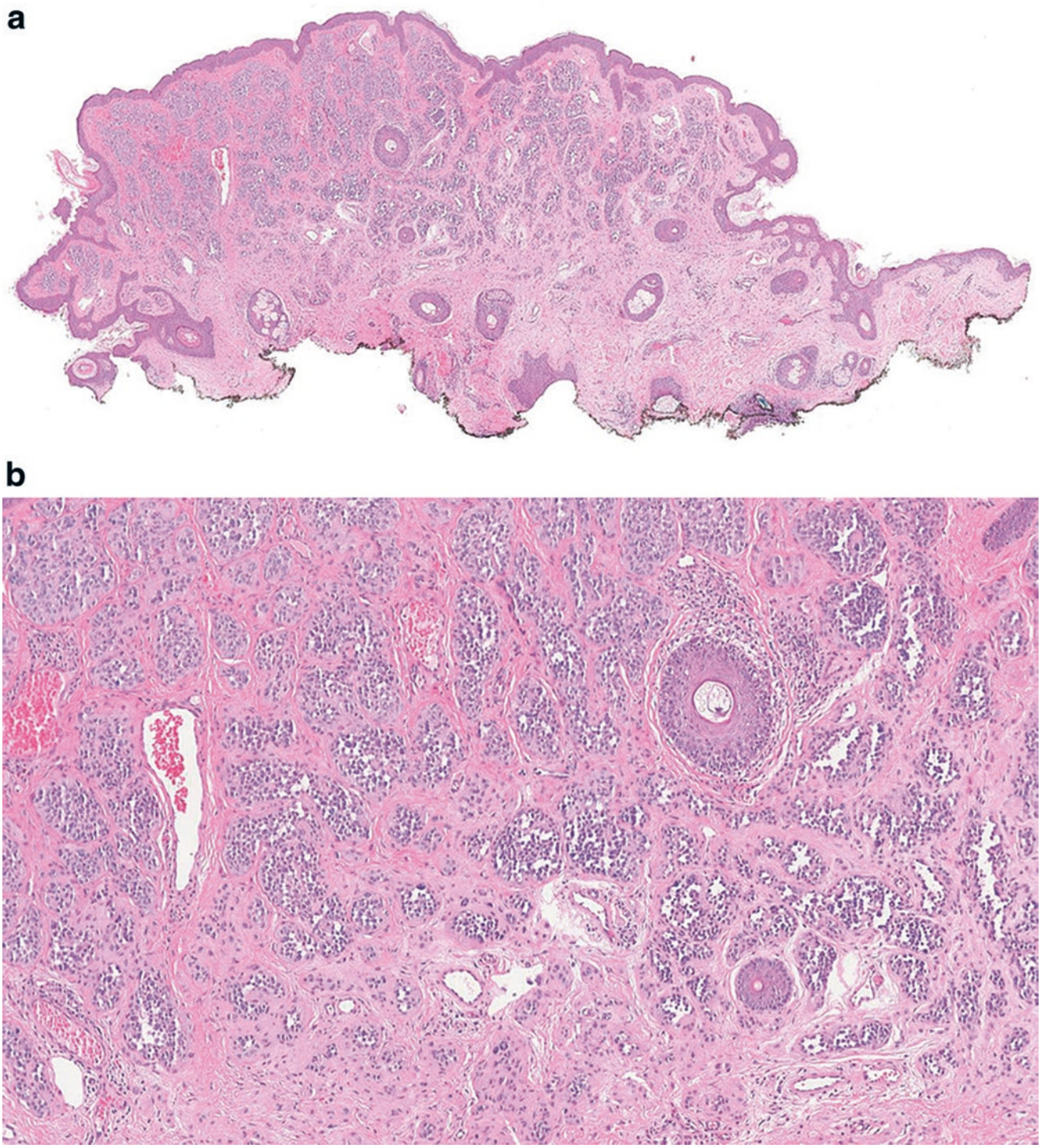


Fig. 3.25 Intradermal nevus with pseudovascular spaces (**a**). Clefts within the melanocytic nests, resembling vascular spaces (pseudovascular spaces) (**b**)

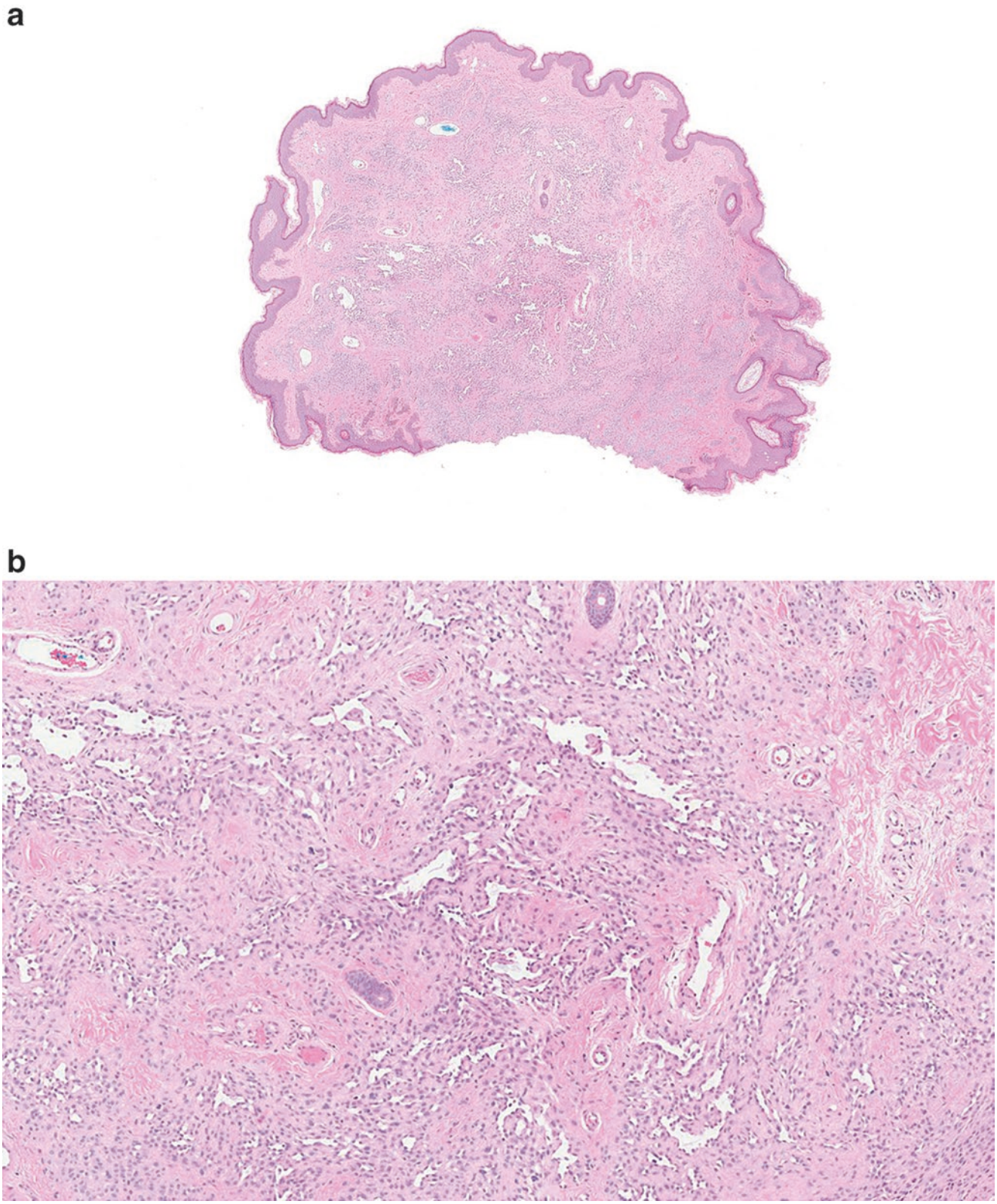


Fig. 3.26 Melanocytic nevus with pseudovascular spaces. These spaces are lined by melanocytes and not by endothelial cells (hence the term "pseudovascular") (**a**, **b**)

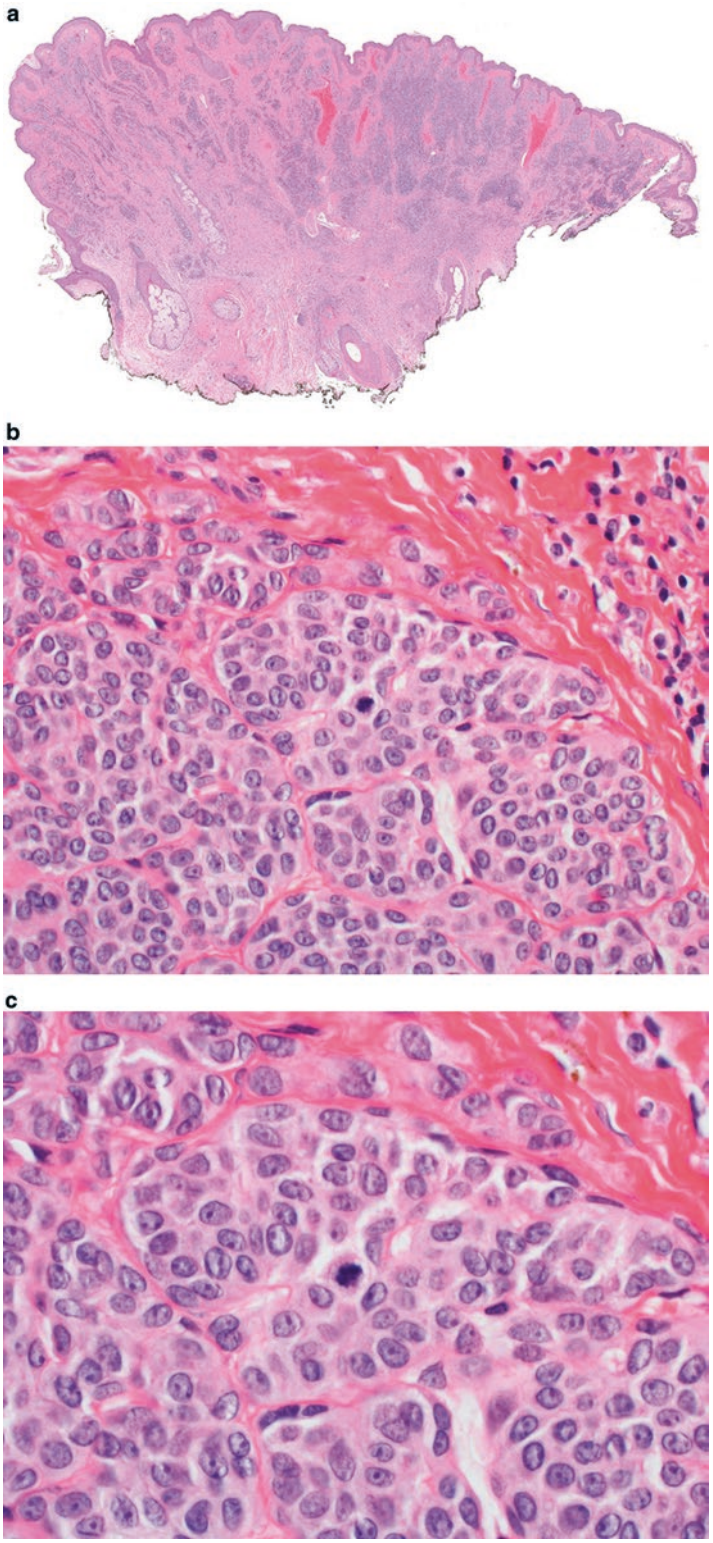


Fig. 3.27 Predominantly intradermal nevus with mitotic figures. This otherwise standard nevus shows rare mitotic figures in the upper half of the lesion (**a**). Some of these patients may have hormonal changes (e.g., pregnancy) resulting in this histologic feature (**b**). High-power view of the mitotic figures (**c**)

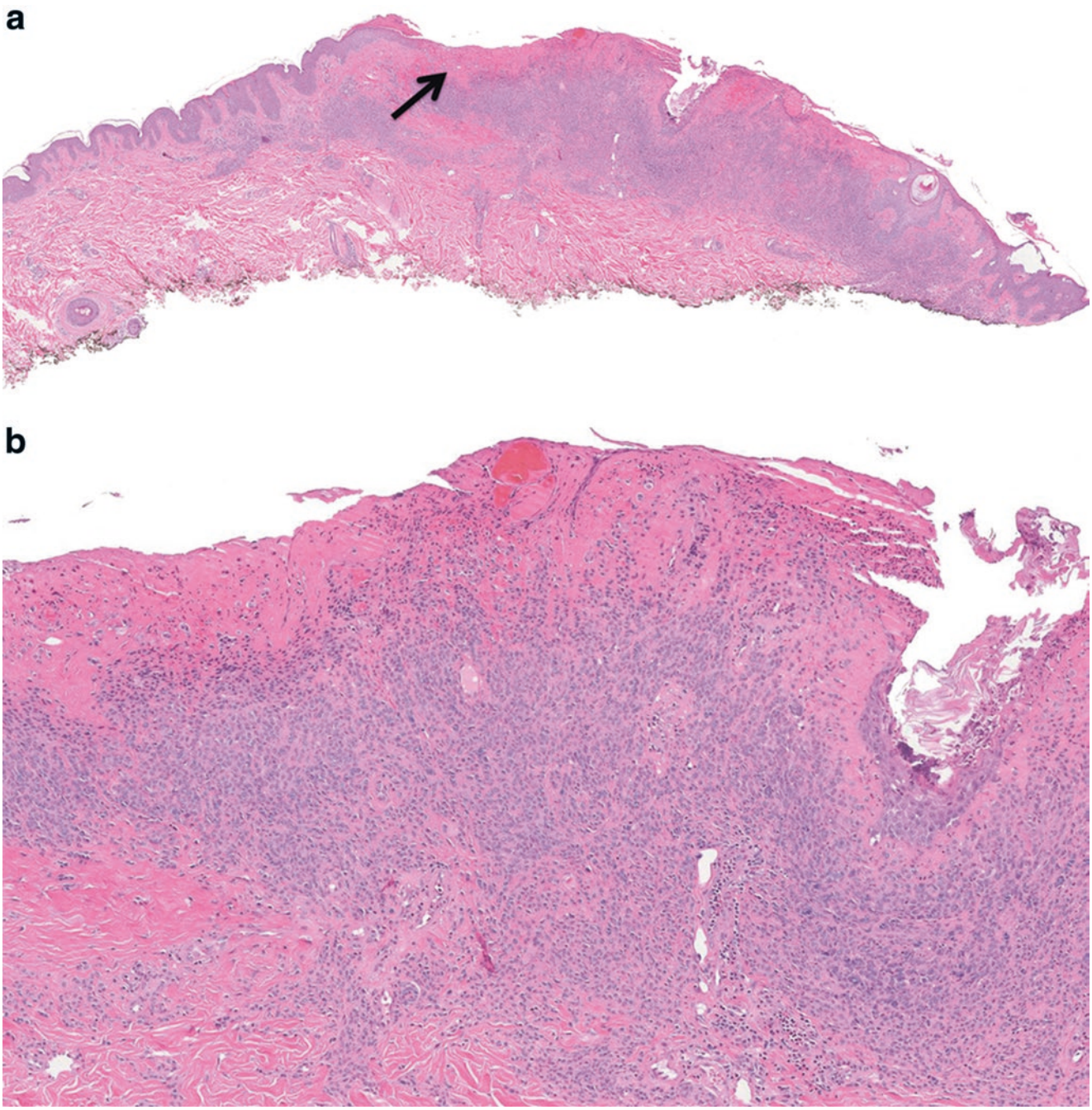


Fig. 3.28 Traumatized nevus. Note the ulcerated epidermis (*arrow*) (**a**). Melanocytes located in the dermis display small nuclei and appear to mature with depth (**b**)

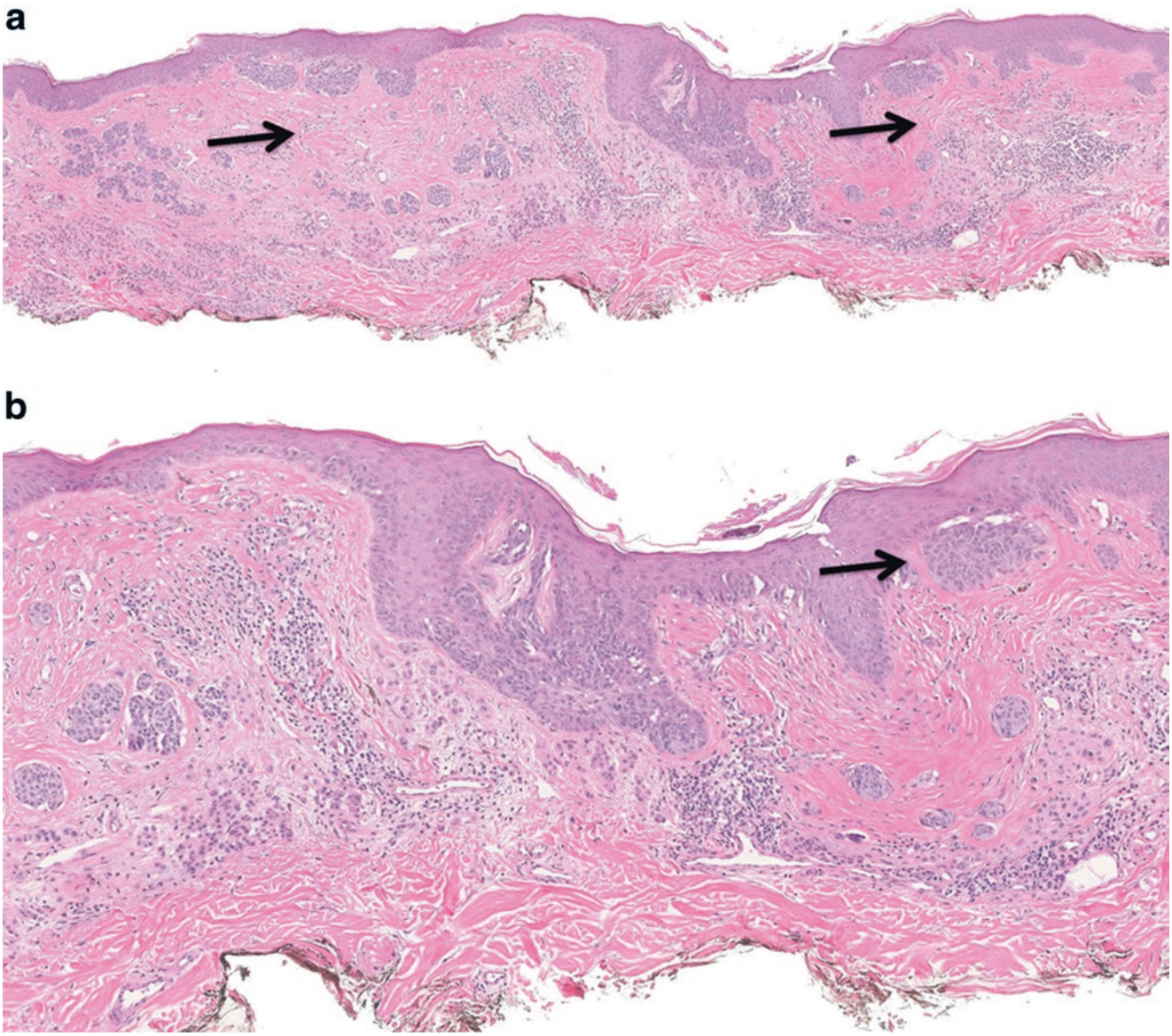


Fig. 3.29 Traumatized nevus. Note the scar in the upper dermis (*arrows*) above the dermal nests of melanocytes (**a**). Irregular junctional component with large nests (*arrow*) and single melanocytes. Melanocytes mature normally toward the base of the lesion (**b**)

Combined Melanocytic Nevi

Combined melanocytic nevi are composed of two or more distinct melanocytic populations in a single lesion. The constituent components may include any combination of benign acquired nevi (with or without dysplasia) or congenital nevi with blue nevus, cellular blue nevus, or Spitz nevus [64, 65]. It is not clear whether combined nevi represent the coexistence of two discrete nevus cell populations or whether they reflect divergent terminal differentiation of a single-cell population. Combined nevi may occur at any age but are most commonly observed in children and young adults and slightly more common in women than in men [66]. The most common type of combined nevus is a blue nevus and a nevus with an intradermal component which is histologically readily identified as a standard benign nevus. In contrast, those tumors with deeply pigmented or Spitz nevus elements often have atypical features; thus, it is very important to distinguish these lesions from melanoma.

Clinically, combined nevi present as small, dark, papules with regular, well-circumscribed borders but with focal variegation in pigmentation. While it is the presence of the latter feature that may provide a clinical clue to the diagnosis, it may also raise the clinical suspicion of malignancy and thus

usually prompts surgical excision. Also, some patients have a history of rapid growth or change in a long-standing lesion, which may cause alarm to expert dermatologists. Combined nevi with blue nevus component are more commonly located in the face, back, and shoulders. Combined nevi including a Spitz nevus component are more commonly located in the extremities.

Histologic Features of Combined Nevus

As discussed above combined nevi may potentially display the entire spectrum of melanocytic nevi. When two distinct melanocytic cell populations are identified histologically within a nevus, the differential diagnosis is between a combined melanocytic nevus and a melanoma arising in association with a nevus. A combined nevus could be misdiagnosed as melanoma if it is not recognized that the dual cell populations identified are benign [67, 68]. The difficulty for the pathologist relies if one of the melanocytic cell populations shows an infiltrative growth pattern, has large atypical melanocytes, displays occasional dermal mitotic figures, or is associated with a lymphocytic response. Unfortunately, all of these histologic features can be seen in both nevi and melanomas, and thus careful inspection is necessary when these features are encountered. In particular, it is the Spitz nevus component that is most likely to be responsible for a misdiagnosis of melanoma because the histologic features may include large epithelioid cells and dermal mitotic figures [69]. Below we highlight the most common combinations seen in combined nevi.

Blue and Common Intradermal Nevus: This is the most common combination seen in combined nevi. In the majority of cases, the ordinary nevus overlies or is adjacent to the blue nevus component. The blue nevus consists of a dermal proliferation of dendritic, evenly pigmented melanocytes with small, round-to-oval nuclei. Some cases show scattered melanin-laden macrophages and variable fibrosis. The ordinary melanocytic population is usually a common intradermal nevus; however, it can be a compound nevus or a dysplastic nevus (junctional or compound). In cases with atypia, those atypical features most often represent cytologic atypia of the intraepidermal component of a dysplastic nevus. The presence of mitotic figures in this type of combined nevus is exceedingly rare, if ever identified. The histopathology of this type of combined nevus is benign appearing; thus, the differential diagnosis of melanoma is usually not a consideration.

Spitz and Common Nevus: This combination is unusual and is more commonly seen in female adults. Histologically, combined nevi with Spitz elements usually display a characteristic dermal proliferation of large epithelioid cells that is usually more nested in the superficial dermis and extends as individual cells among the deep reticular dermal collagen bundles, alongside an ordinary intradermal or compound nevus, dysplastic nevus, or blue nevus. Cytologically the spitzoid cells show similar features to that observed in ordinary Spitz nevi, i.e., epithelioid cells with large monomorphous and vesicular nuclei with prominent nucleoli. As mentioned above, the combination of Spitz and common nevus type is the one that most often displays atypical features. In one study it was found that significant atypical features were seen in nearly half of the cases of combined nevi that had Spitzoid elements [66]. Atypical features in this type of combined nevi usually manifest as lack of symmetry and presence of hypercellularity, cytologic atypia, and increased numbers of mitotic figures. In addition, combined nevi with Spitz elements may display dermal sclerosis, which may contribute to a diagnostic consideration of melanoma. In order to differentiate them from melanoma, the most important feature in combined nevi is the almost universal absence of deep dermal mitotic figures.

Spitz and Blue Nevus: This variant of combined nevus is rare and some authors have used the term "BLITZ" (blue + Spitz) for such neoplasms [70]. Histologically, they usually show a clear component of Spitz and blue nevus, and in some cases on low magnification, they can be confused with pigmented epithelioid melanocytoma or epithelioid blue nevus. Most cases show a symmetrical lesion in dermis with wedge-shaped architecture. The overlying epidermis usually shows acanthosis and hyperplasia and there may be a focal junctional component. The Spitz component shows epithelioid and spindle cell melanocytes with large vesicular nuclei, prominent nucleoli, and variable pigmented cytoplasm. Intranuclear cytoplasmic inclusions are commonly seen. These lesions are associated with scattered, heavily pigmented, dendritic melanocytes and melanophages and, at times, slight fibroplasia, in a pattern similar to a blue nevus. These lesions are essentially indistinguishable from an intradermal Spitz nevus.

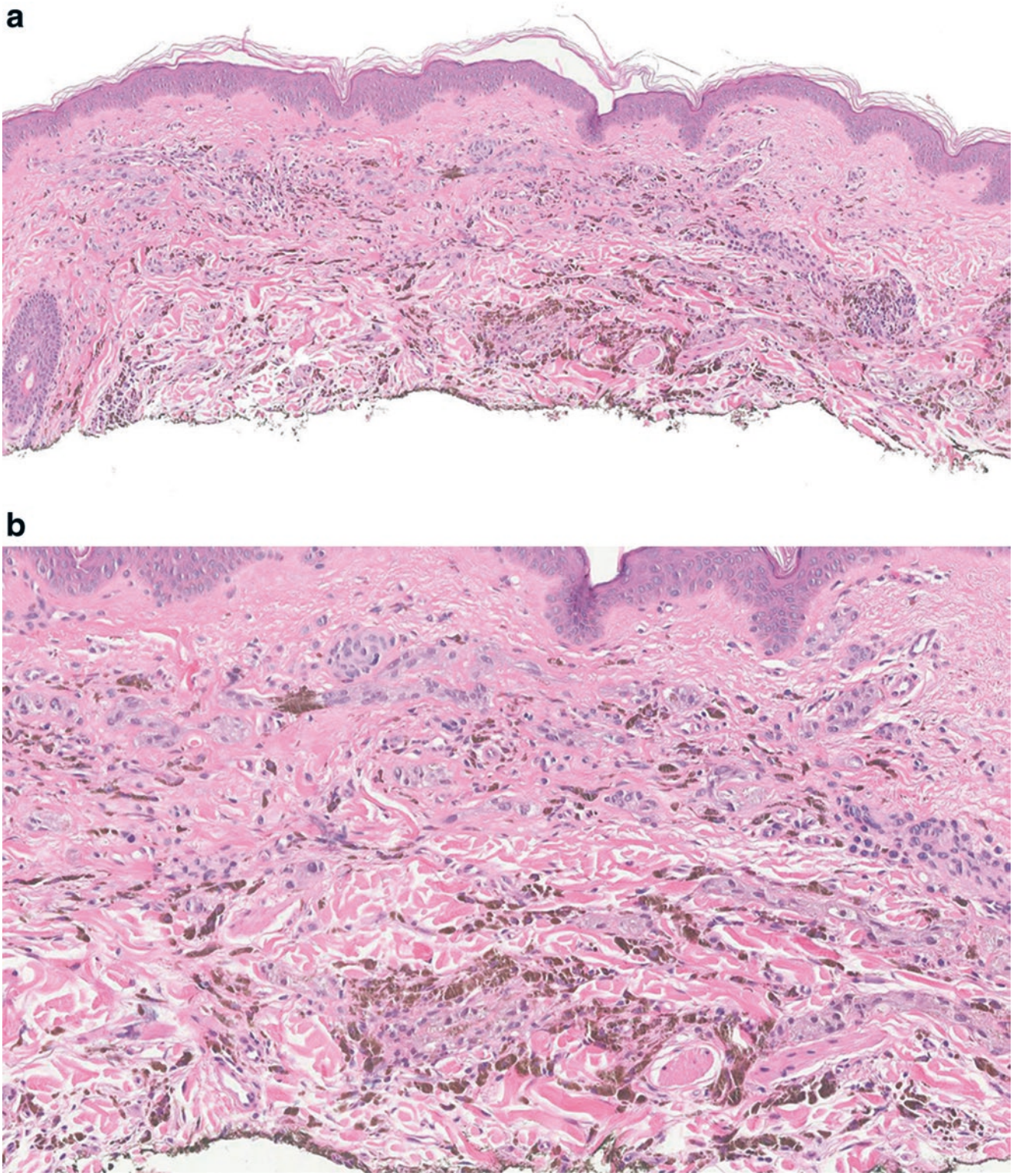


Fig. 3.30 Combined melanocytic nevi (intradermal + blue). Note the epithelioid melanocytes admixed with a subtle dermal proliferation of dendritic pigmented melanocytes (**a**, **b**).

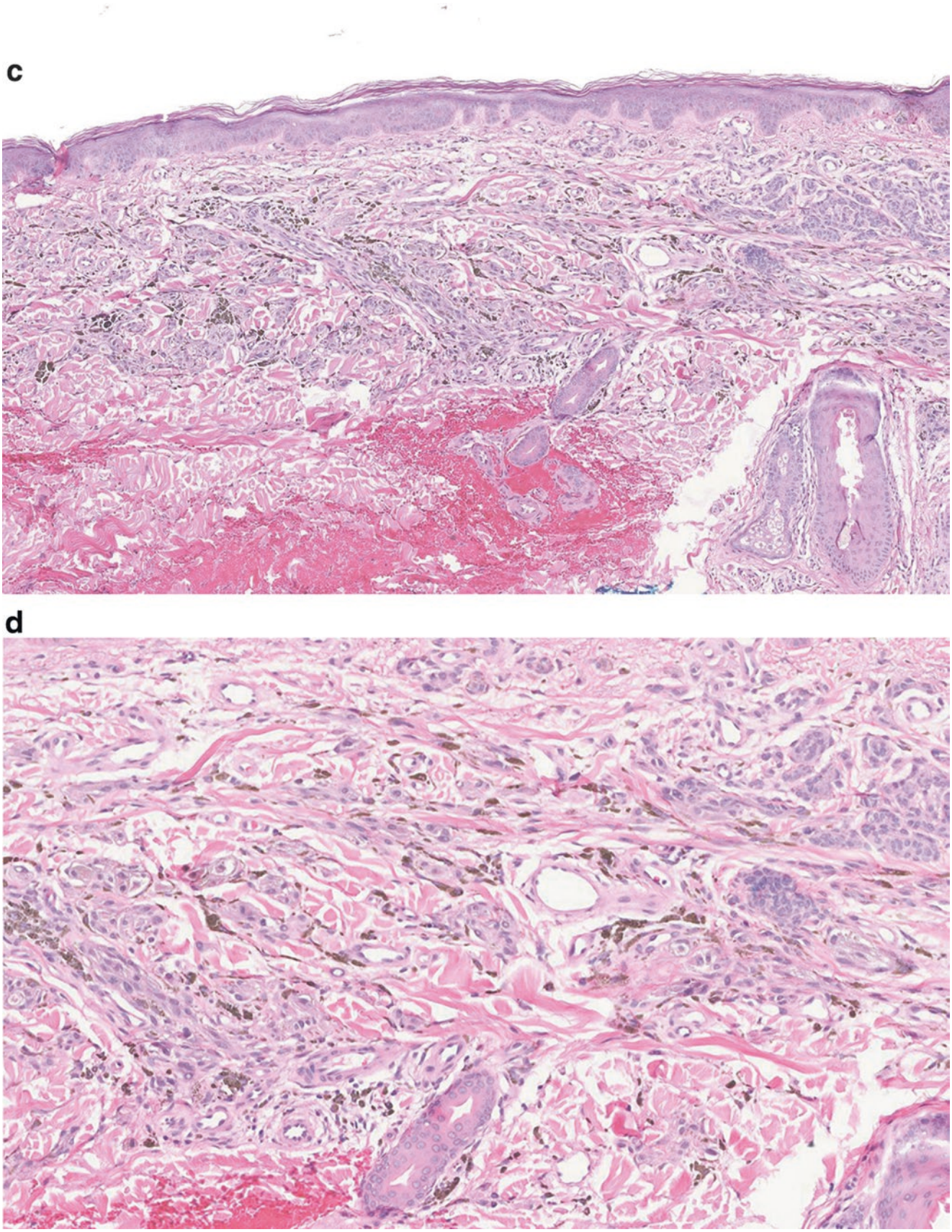


Fig. 3.30 (continued) High power showing the mixture of both standard intradermal and dendritic, pigmented melanocytes (**c**, **d**)

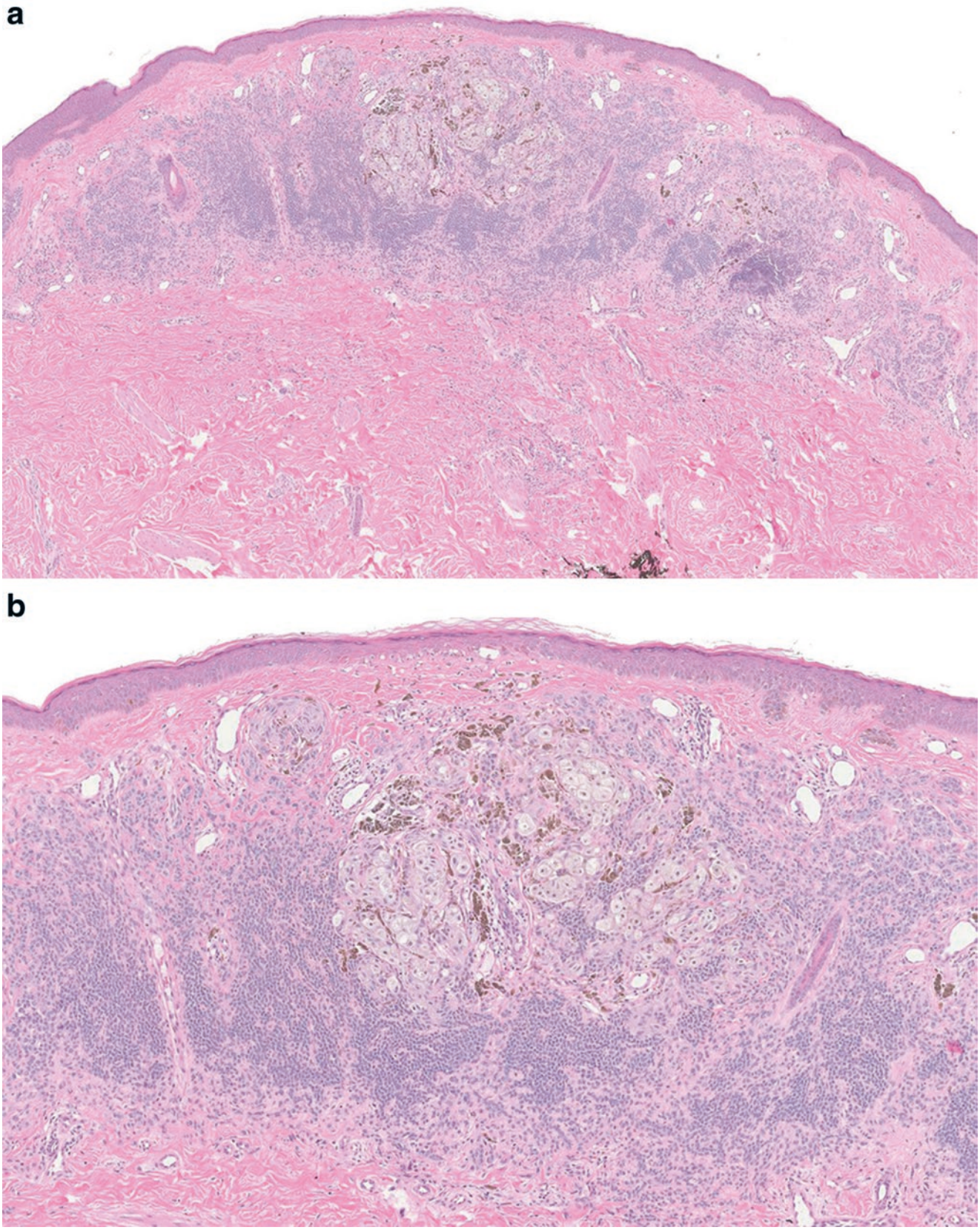


Fig. 3.31 Combined nevus (intradermal and Spitz). A 17-year-old male, back, with recent change in color. The low power of the lesion shows a conventional intradermal nevus with epithelioid melanocytes located in the center of the lesion (**a**). The melanocytes in the central region are epithelioid, have an ample dusky cytoplasm, and abundant melanin pigment (**b**).

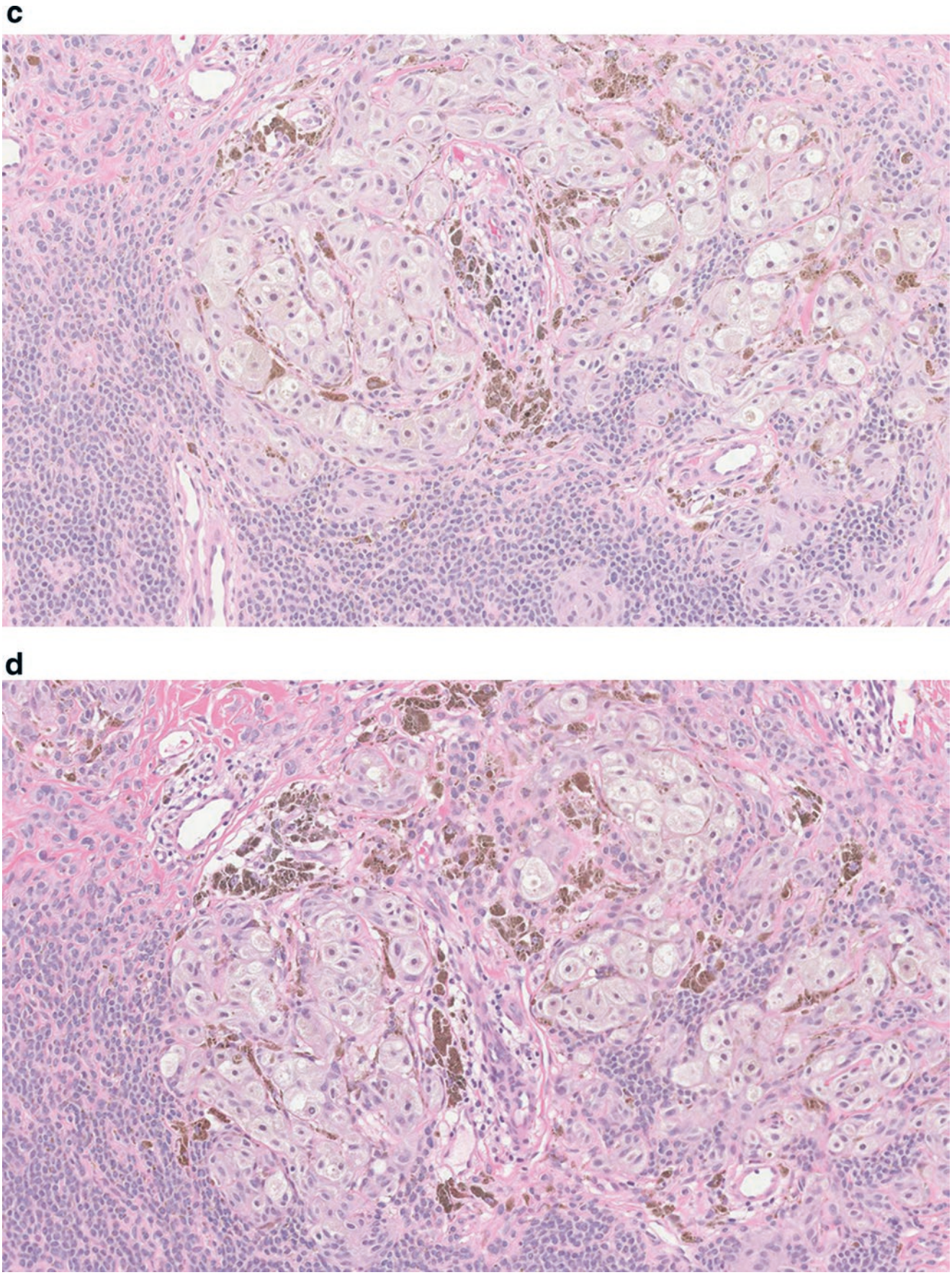


Fig. 3.31 (continued) Note the central cells with ample cytoplasm and melanin pigment (Spitz cells) surrounded by standard intradermal melanocytes (**c**). The cells in the center lack mitotic figures (**d**)

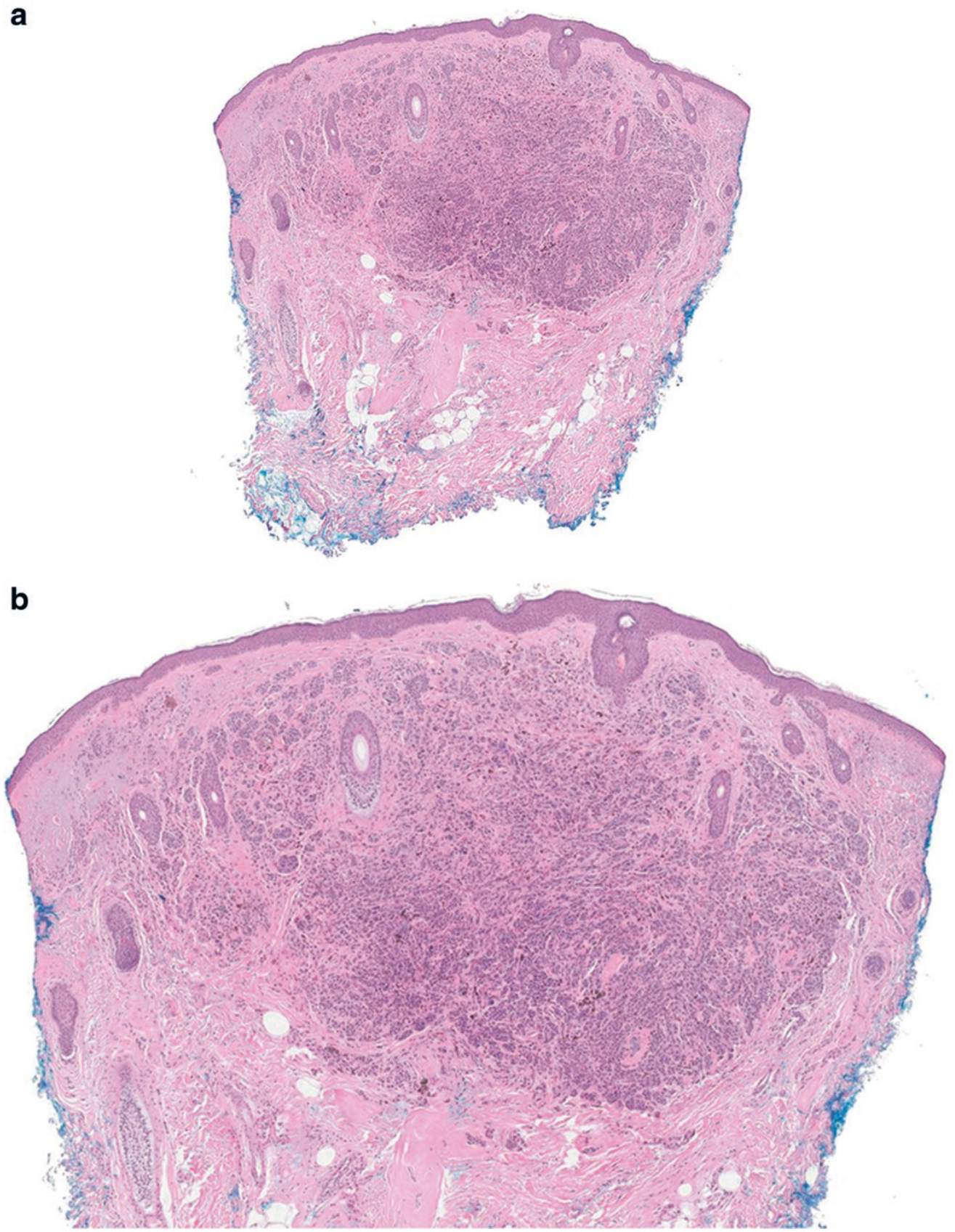


Fig. 3.32 Combined melanocytic nevi (Spitz + blue). Wedge-shaped lesion with minimal junctional component. In this example, there is a dual population of melanocytes (**a**). Note the normal maturation toward the base of the lesion. No mitotic figures were noted in this lesion (**b**).

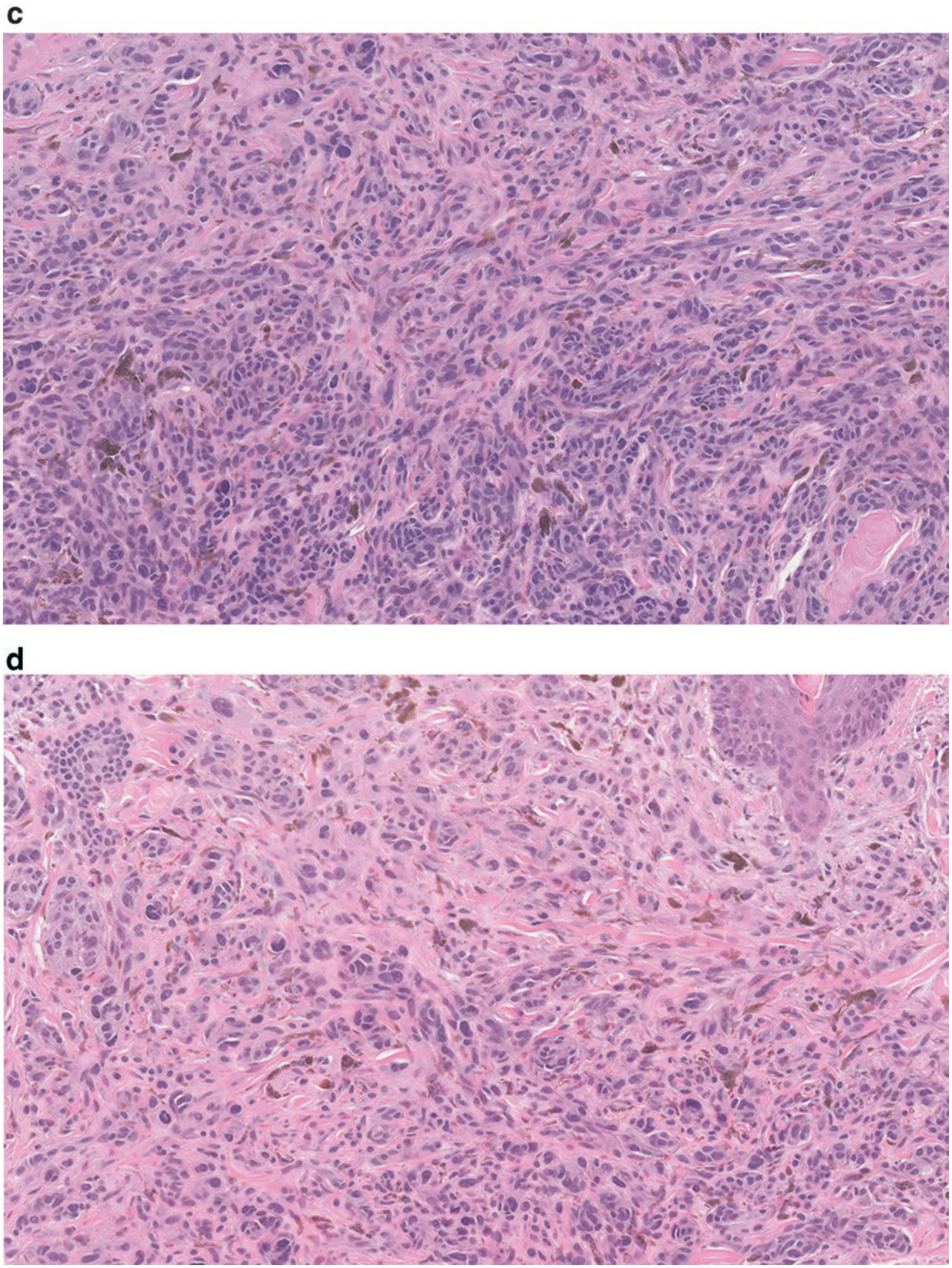


Fig. 3.32 (continued) Area with dendritic, pigmented cells (blue-nevus type) (**c**). Larger cells with spitzoid morphology (**d**)

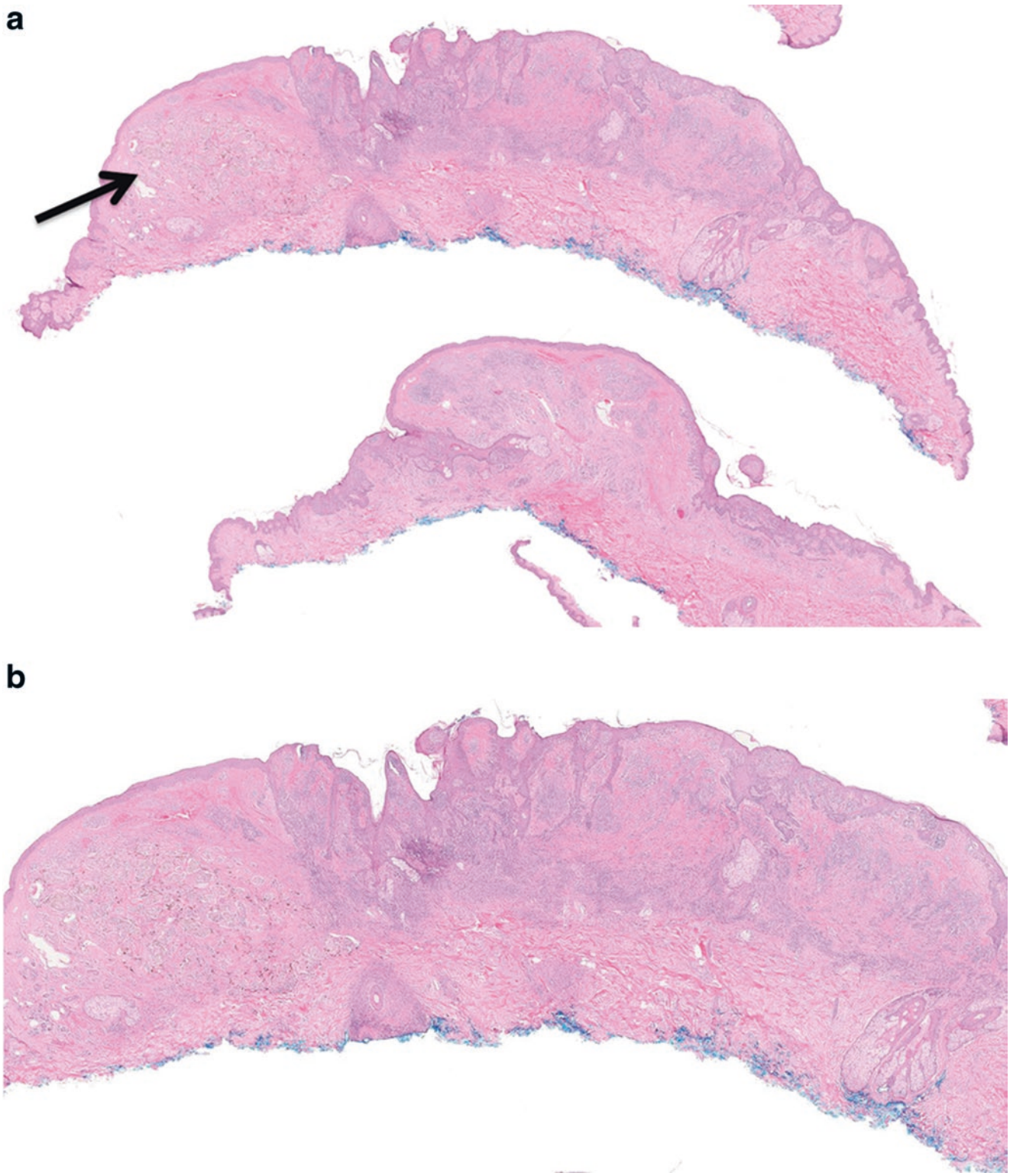


Fig. 3.33 Combined melanocytic nevi (pigmented Spitz + standard compound). A 16-year-old male, arm. The spitzoid component is located at the *left* (*arrow*) while the standard compound nevus occupies the rest of the lesion (**a**). The Spitz area has single cell junctional component without evident pagetoid component (**b**). The intradermal Spitzoid component is composed of large epithelioid nests. The cells have an ample dusky cytoplasm without evidence of mitotic activity.

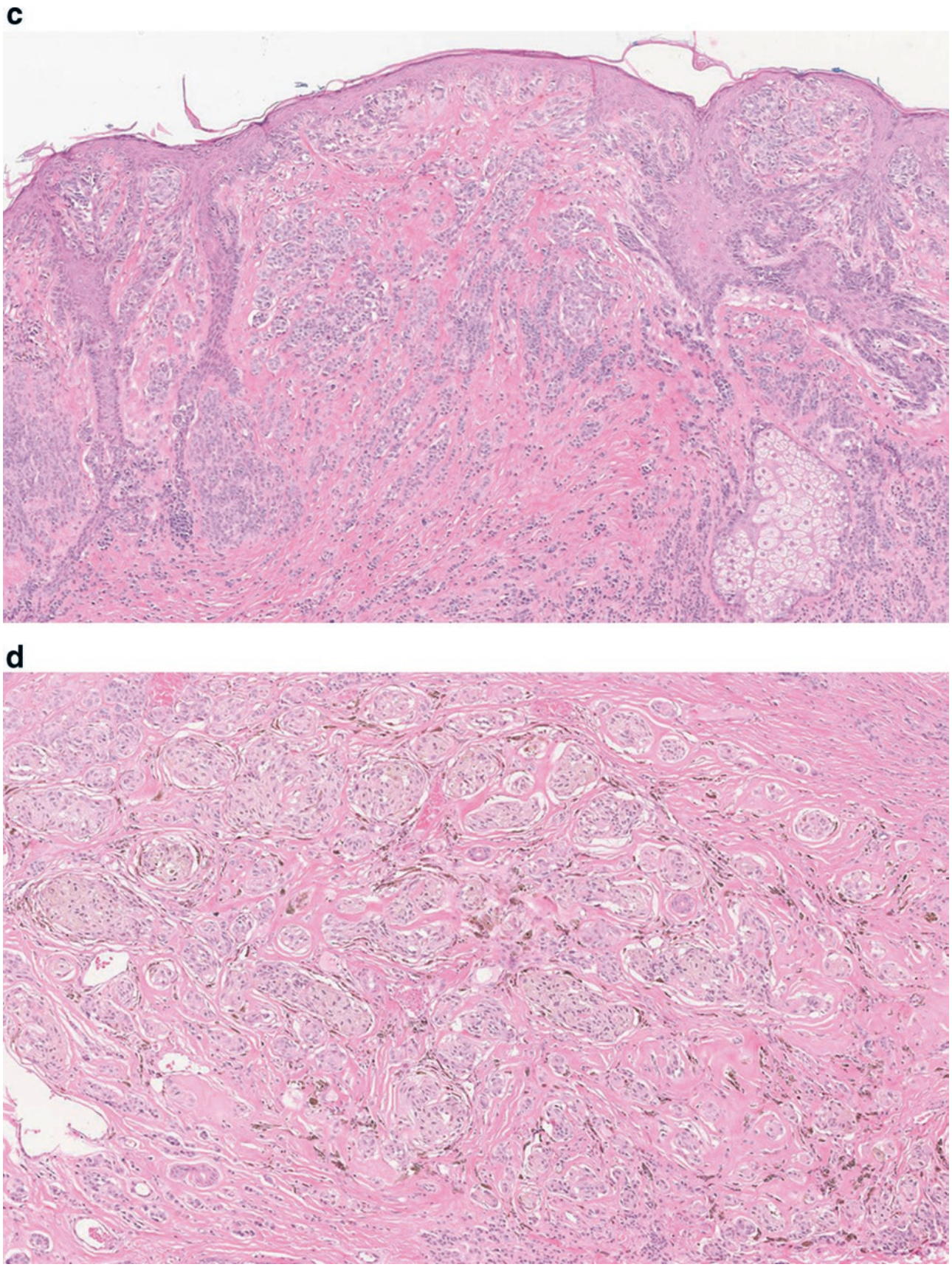


Fig. 3.33 (continued) The large, spitzoid cells show abundant melanin pigment (**d**). Mitotic figures were not identified in the lesion (**c, d**)

Halo Nevi

Halo nevus, also known as Sutton nevus or leukoderma acquisitum centrifugum, is a benign melanocytic nevus that is surrounded by a halo of depigmentation. This halo of depigmentation is represented histologically in most cases by a dense inflammatory infiltrate; however, the relationship between the area of depigmentation (halo) and the inflammatory infiltrate is inconsistent as some nevi that display an inflammatory infiltrate do not show clinically this area of depigmentation or vice versa [71–73]. This phenomenon usually indicates the beginning of involution and subsequent regression of a melanocytic nevus, a process that extends over a period of several months. Some authors prefer to use the term "halo nevus" only for melanocytic nevi that clinically show a depigmented area (halo). We, as others, use the term "nevus with halo phenomenon" when we identify a dense lymphocytic infiltrate within the lesion, in those cases in which there is no clear clinical description of a halo.

Halo nevus is more commonly observed on the back during childhood or adolescence (mean age of onset is 15 years); however, lesions can be seen in older patients too and they occur equally in males and females. Clinically, the center of a halo nevus is a pigmented macule or papule that varies in color from skin colored to dark brown and is surrounded by an area of symmetric depigmentation. The size ranges from 3 to 6 mm in diameter and the borders are usually well defined. The area of depigmentation (halo) is white in color and varies in size (usually measures few millimeters but in rare instances can measure several centimeters). Multiple lesions are found in about 50 % of cases, occurring either simultaneously or successively. The nevus itself is most commonly acquired but rarely develops around congenital nevi. Halo nevi may be seen more frequently in patients with Turner syndrome and vitiligo. About 20 % of children and adults with vitiligo have halo nevi, and those with multiple halo nevi are more likely to have concurrent vitiligo. It is thought that the halo in these nevi results from either an immune response against nevus cells expressing neoantigens associated with tumor progression or a cell-mediated reaction targeting melanocytes [74–77]. One should be aware that this halo phenomenon may also be observed around some other benign or malignant neoplasms such as blue nevi, neurofibromas, flat warts in regression, seborrheic keratoses, dermatofibromas, basal cell carcinomas, and melanomas [78].

Halo nevi have different clinical stages of development. In lesions with the characteristic area of depigmentation surrounding the lesion, the center of the nevus then loses its pigmentation, leaving a skin-colored macule or papule with a surrounding halo. Subsequently, the papule or macule in the center vanishes completely, with only an oval or round patch of depigmentation remaining. Finally the depigmented area undergoes repigmentation, with no trace of its prior existence over a time-span of months or even years [79]. Each halo nevus may go through these stages or may cease development at any stage.

Histologic Features

Halo nevus is characterized by an inflammatory, destructive reaction against melanocytes which progressively regress. On low magnification, it usually shows a small and symmetric compound nevus that expands papillary dermis. It characteristically displays a dense lymphocytic infiltrate within the dermis, with nests or single melanocytes admixed among the lymphocytes [80]. The number of melanocytes within the lesion depends on the stage at which the biopsy is taken. The lesions are usually compound, but halo nevi can be junctional or predominantly intradermal. Fully evolved lesions are associated with a dense homogeneous lymphohistiocytic infiltrate that fills the entire papillary dermis and sometimes shows a lichenoid pattern. In the majority of cases, this infiltrate is sharply defined in the lateral and deep aspects of the lesion and often blurs the dermal-epidermal junction (in some cases these infiltrate can invade into the junctional nests). In some occasions the density of the infiltrate in dermis is so striking that melanocytes are not readily visible on H&E sections, thus requiring immunohistochemistry studies (S100p or MART-1) to assist in the identification of residual melanocytes [81]. Cases with granulomatous inflammation have been reported [82]. In some cases, there is thinning of the epidermis especially in the center of the lesion along with the presence of dyskeratotic keratinocytes. This thinning (consumption) of the epidermis is a characteristic histologic feature of melanoma; thus, it is very important to be aware of this possible occurrence in halo nevi. The melanocytes in halo nevi may appear swollen with variable size and shape, which can be quite alarming to the pathologist analyzing the lesion. The dermal melanocytes are epithelioid and in some cases arranged in large nests in the papillary dermis. Epidermal melanocytes may show a confluent growth pattern in the dermal-epidermal junction and sometimes forming dishesive nests with peripheral clefting artifact. When cytologic atypia is observed, it is usually seen in the upper part of the lesion; these atypical melanocytes are scarce and usually admixed in the background of an ordinary nevus. One study showed that half of halo nevi had melanocytes with some degree of cytologic atypia, ranging from minimal to moderate severity [78]. Mitotic figures can be rarely encountered in halo nevi, and when seen they are usually located in the upper part of the lesion and they are not arranged in clusters as one would see in cases of melanoma. Halo nevi usually show maturation toward the base of the

lesion. The area of depigmentation toward the periphery of the lesion shows a diminished number of melanocytes, and the papillary dermis may show mild fibrosis and minimal lymphocytic infiltrate. In cases in which there is partial regression, the nests of melanocytes are isolated by the dermal fibroplasia. However, there may be total regression with complete loss of melanocytes. The center of the lesion is replaced by fibrosis with vascular ectasia, melanophages, and variable number of inflammatory cells.

Differential Diagnosis

The most important differential diagnosis of halo nevus is with a regressing melanoma. Clinically, halo nevi are characteristically seen in younger patients and most melanomas are restricted to the adult population. The histologic distinction should primarily rely on evaluating the lesion on low magnification. The architecture of halo nevi is symmetric and well delineated, as opposed to regressing melanoma in which most examples tend to show clear asymmetric borders. Halo nevi are mostly small in size and melanomas tend to be larger and quite irregular. Histologically, most cases of halo nevi only show minimal cytologic atypia, and when atypical melanocytes are present, they tend to be isolated and admixed with ordinary melanocytes. Regressing melanoma tends to show diminished number of melanocytes in dermis, but a clue to the diagnosis is the presence of conglomerates of atypical melanocytes which are always absent in halo nevi. The lymphocytic infiltrate in halo nevi is homogeneous and evenly distributed, while in melanoma the infiltrate is uneven and irregularly distributed. Also, melanophages in halo nevi are evenly distributed, while in melanoma there are large numbers clustered together and have an irregular disposition throughout the lesion. The identification of mitotic figures in the deep part of the lesion and in clusters will favor a diagnosis of melanoma. In order to distinguish proliferating melanocytes from inflammatory cells, melanocytic studies may be helpful (see above). The presence of ulceration and melanoma in situ overlying the lesion should point toward the diagnosis of melanoma.

Table 3.4 Halo nevus vs. regressing melanoma

• Age: halo nevi are most commonly seen in younger patients while melanomas in adults
• Symmetry: halo nevi are symmetric lesions, while regressing melanomas are wide and asymmetric
• Inflammatory infiltrate: the inflammatory infiltrate in halo nevi is well delineated, evenly dispersed, and homogeneous. Melanomas have a sparse and scattered lymphocytic infiltrate throughout the lesion
• Cytologic atypia: halo nevi show isolated atypical melanocytes admixed with conventional ones, while regressing melanoma characteristically displays aggregates of atypical melanocytes
• Macrophages: in halo nevi melanophages are evenly distributed throughout the lesion while in melanomas are haphazardly arranged

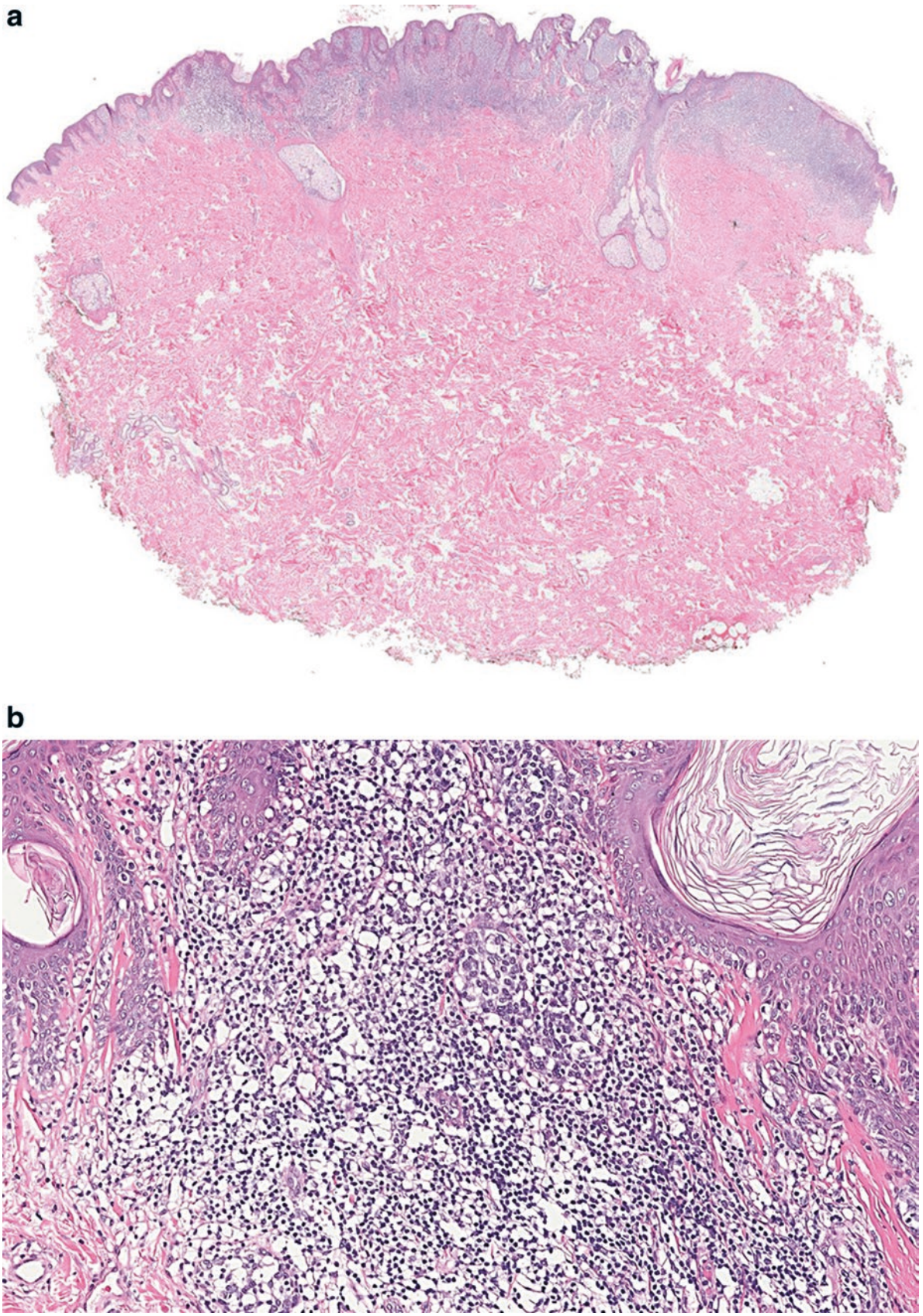


Fig. 3.34 Halo nevus. Low power of this compound nevus with dense inflammatory reaction (**a**). Note the dense lymphocytic infiltrate surrounding the dermal melanocytes (**b**).

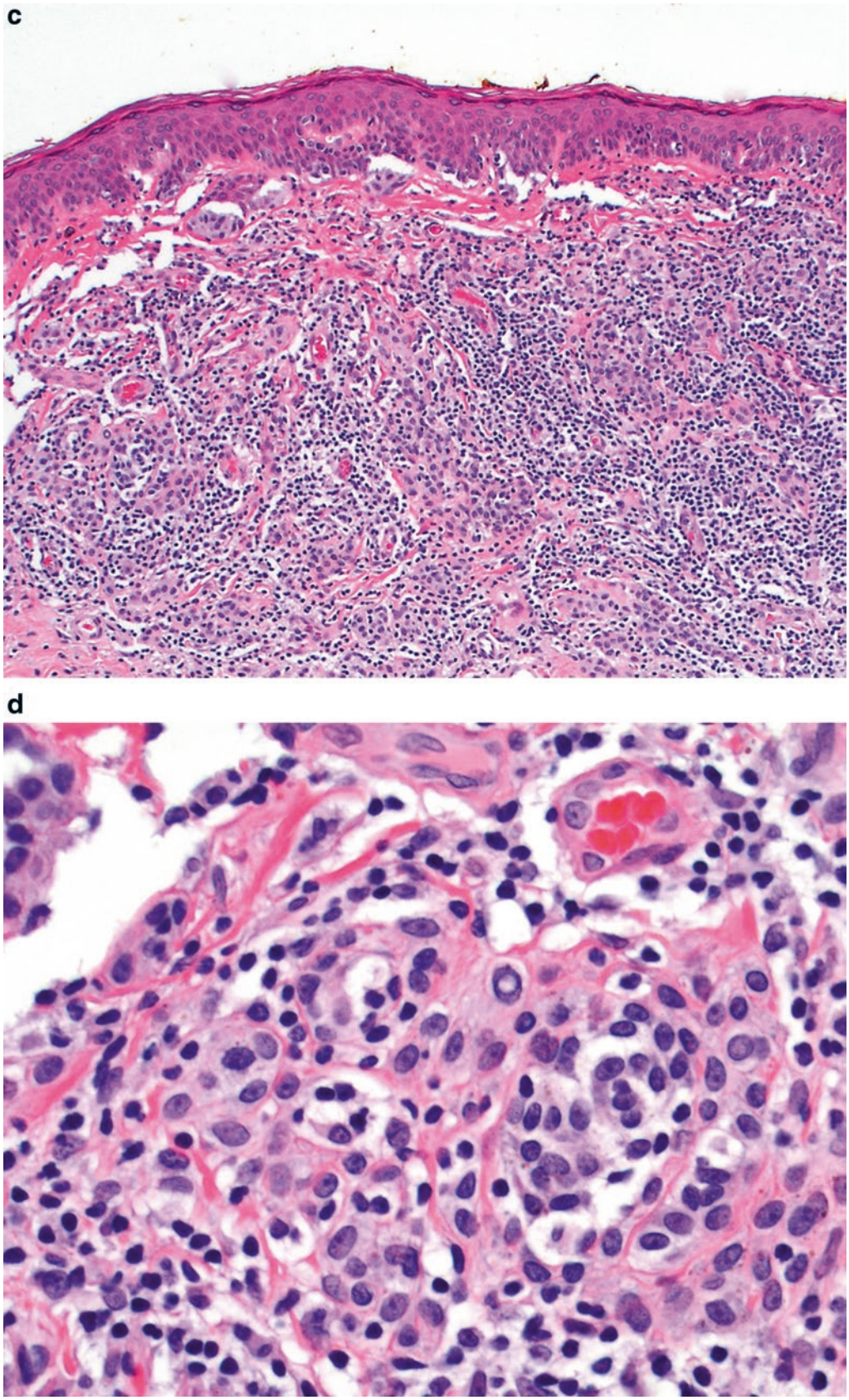


Fig. 3.34 (continued) Higher magnification shows a mixture of melanocytes and lymphocytic infiltrate (**c**). Usually, there is mild to moderate cytologic atypia of the junctional and dermal melanocytes induced by the inflammatory response (**d**).

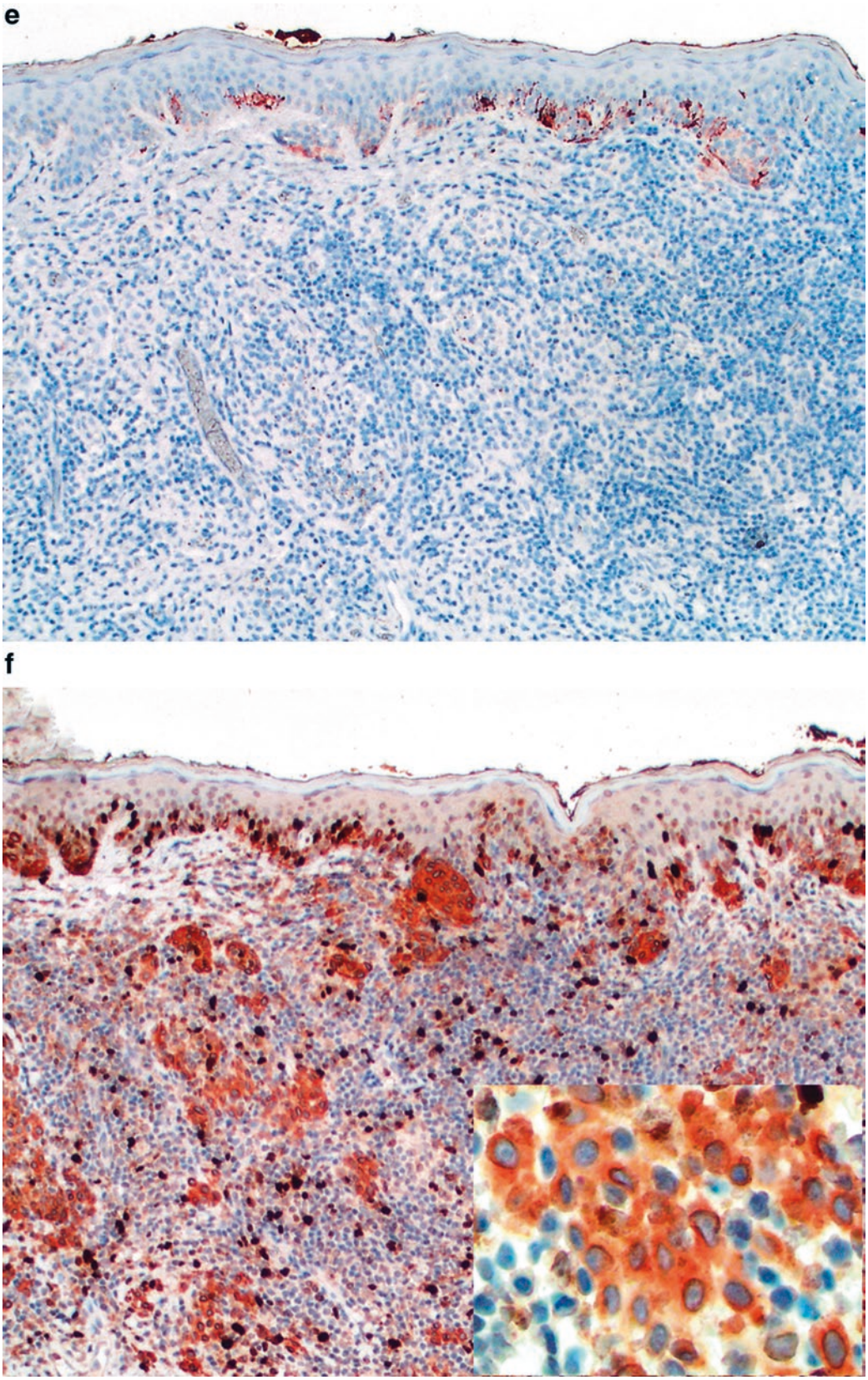


Fig. 3.34 (continued) HMB45 shows maturation in the lesion (labeling of the junctional melanocytes but minimal labeling of the dermal melanocytes) (**e**). A double immunostudy (with anti-MART1 [*red*] and anti-Ki67 [*brown*]) shows little proliferation in the dermal melanocytes (*inset*). Note the number of proliferating lymphocytes (*brown* nuclei not associated with *red* immunolabeling) (**f**)

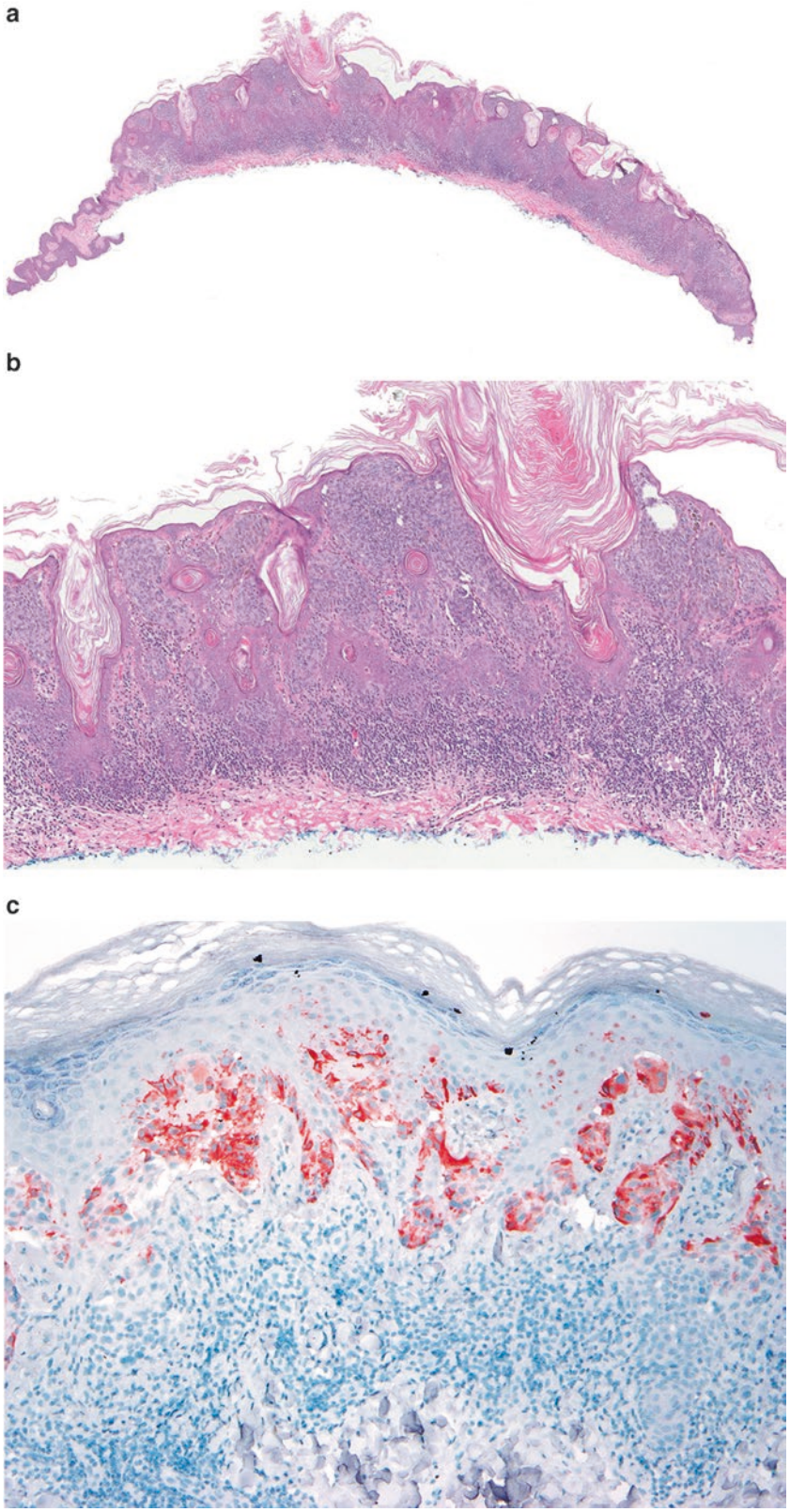


Fig. 3.35 Halo nevus. This example shows a dense lymphocytic infiltrate mimicking a lichenoid keratosis (**a**). The dense lichenoid infiltrate makes it difficult to identify the melanocytes (**b**). An immunohistochemical study with HMB45 highlights the presence of scattered melanocytes in the epidermis, and rare in the dermis (**c**)

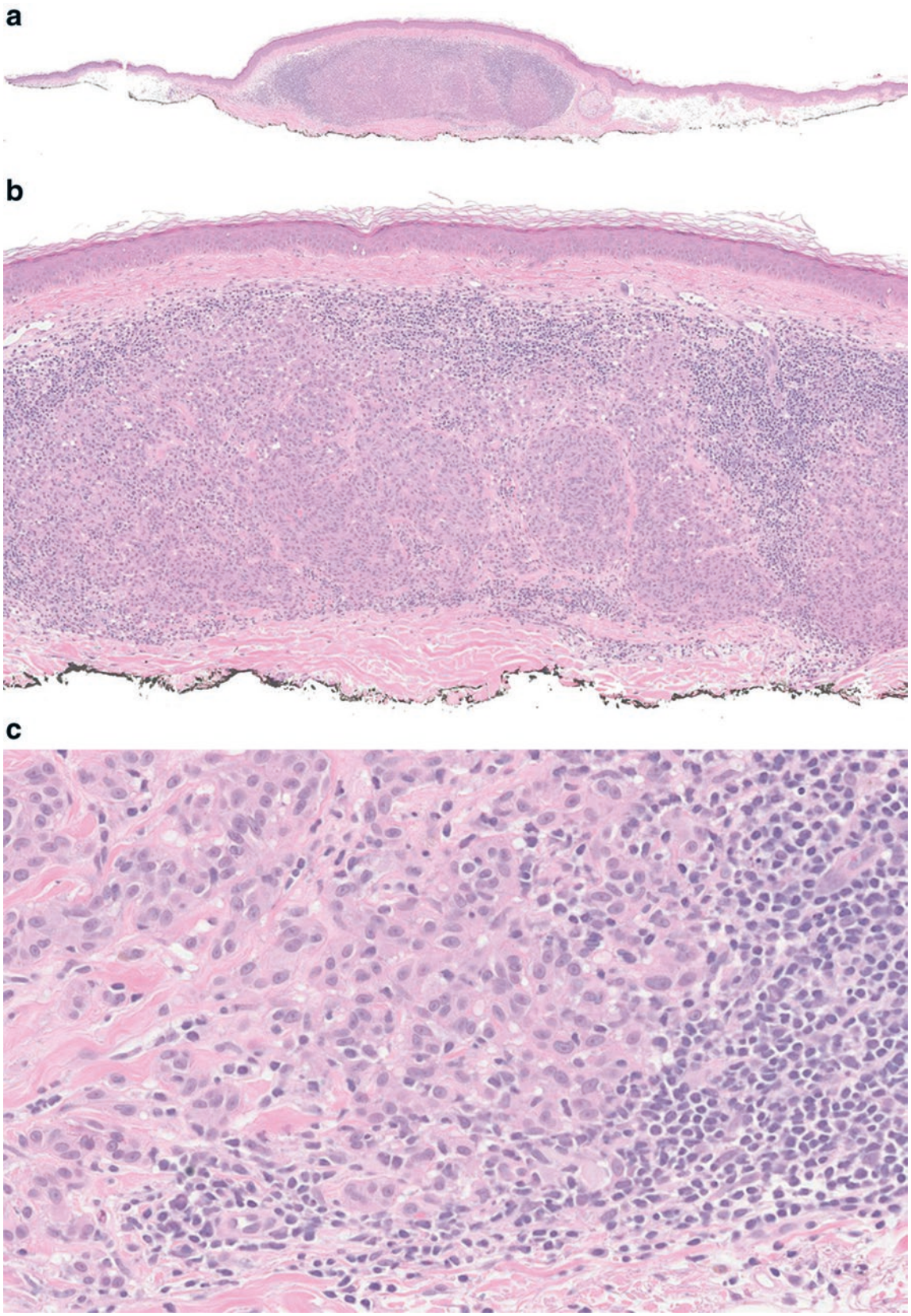


Fig. 3.36 Halo nevus. This example shows a melanocytic intradermal component surrounded by dense lymphocytic infiltrate (**a**). In this case, there is clear-cut demarcation between the melanocytes and lymphocytes (**b**). There is focal atypia of the dermal melanocytes but mitotic figures are not evident (**c**)

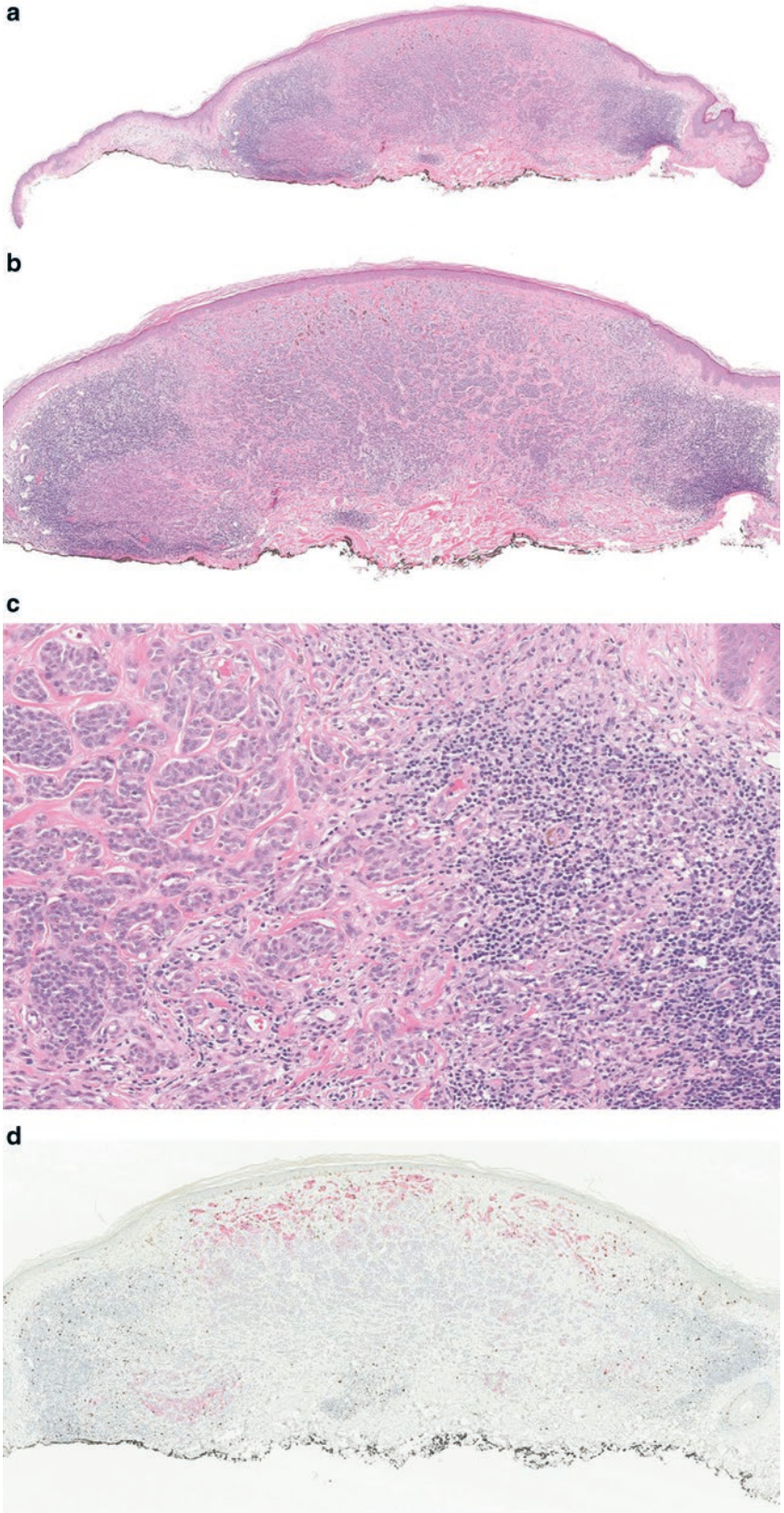


Fig. 3.37 Halo nevus. This is an example of a lesion with cytologic atypia of melanocytes (**a**). Flat epidermis with minimal junctional component. Although the dermal component appears to be expansile in the center, cells disperse in the deep dermis (maturation) (**b**). Area with melanocytes admixed with lymphocytes. Some of the melanocytes display large, hyperchromatic nuclei but mitotic figures are not evident (**c**). HMB-45 showing normal maturation of melanocytes (strong labeling of those melanocytes located close to the epidermis) (**d**)

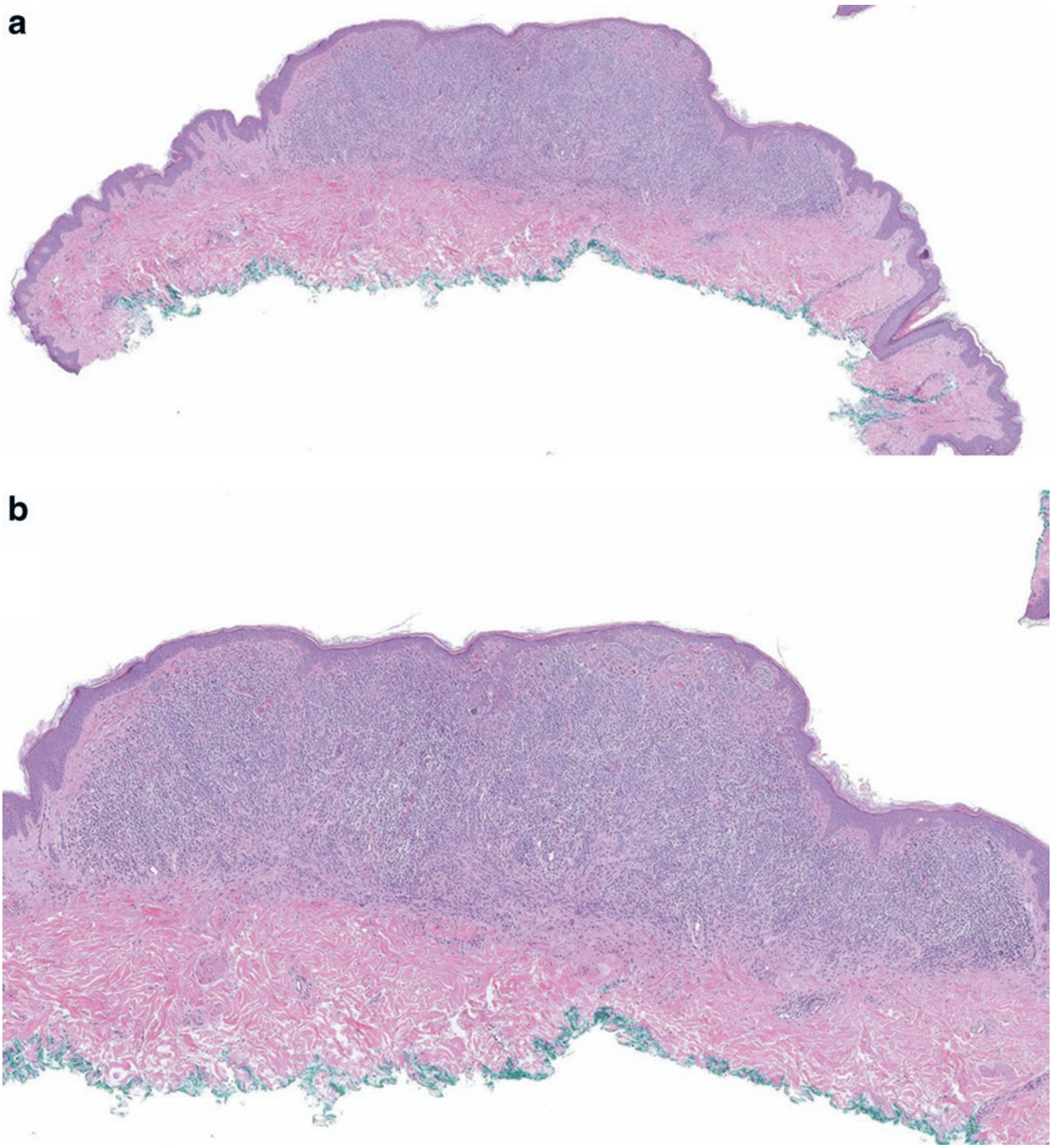


Fig. 3.38 Halo nevus. Note the symmetry of the lesion along with maturation toward the base (**a**). Minimal junctional component. Melanocytes disperse at the base of the lesion (**b**).

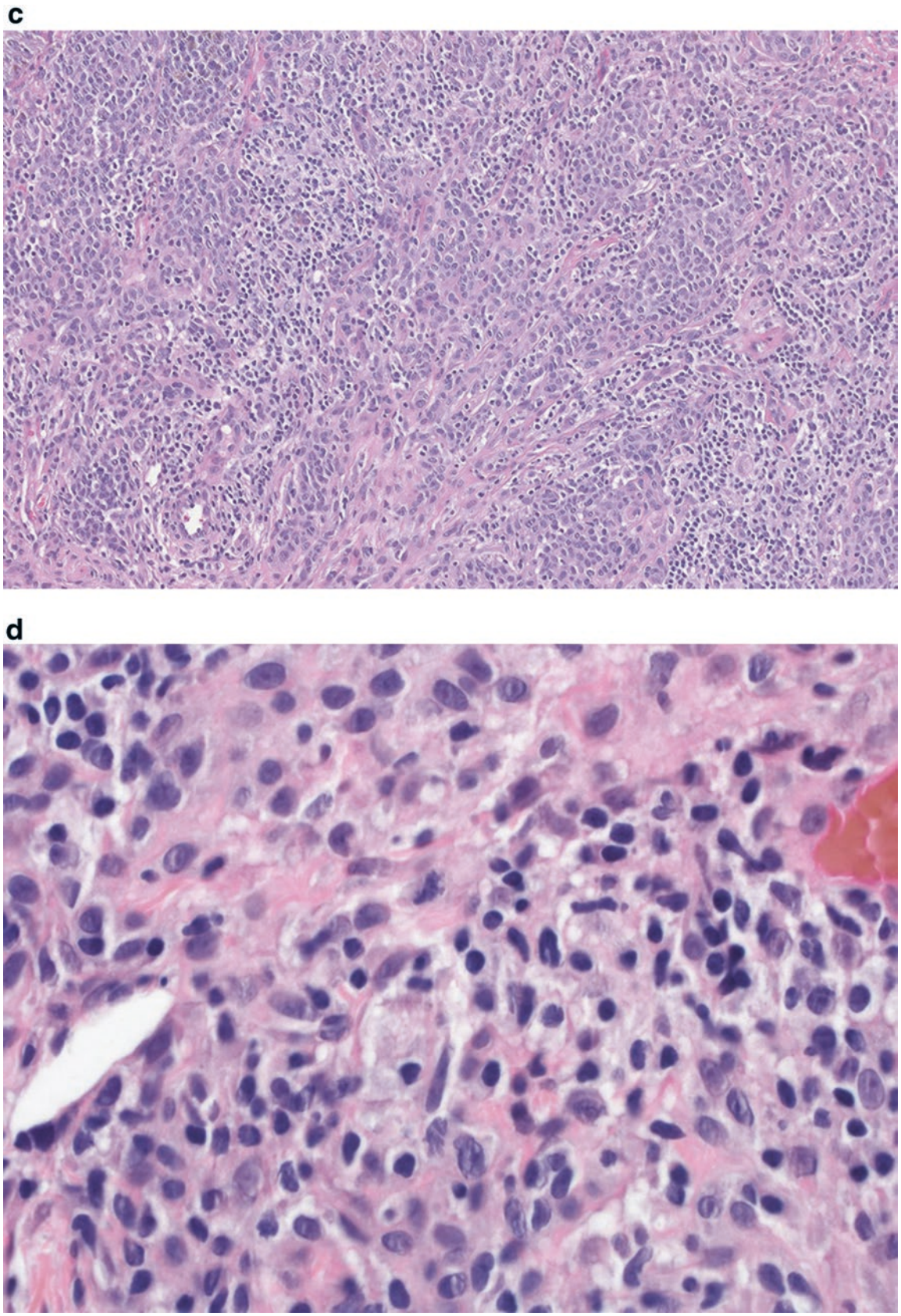


Fig. 3.38 (continued) At this power the lesion shows intermixed melanocytes and lymphocytes (**c**). Cytologic atypia of melanocytes with a rare mitotic figure in the upper dermis (**d**)

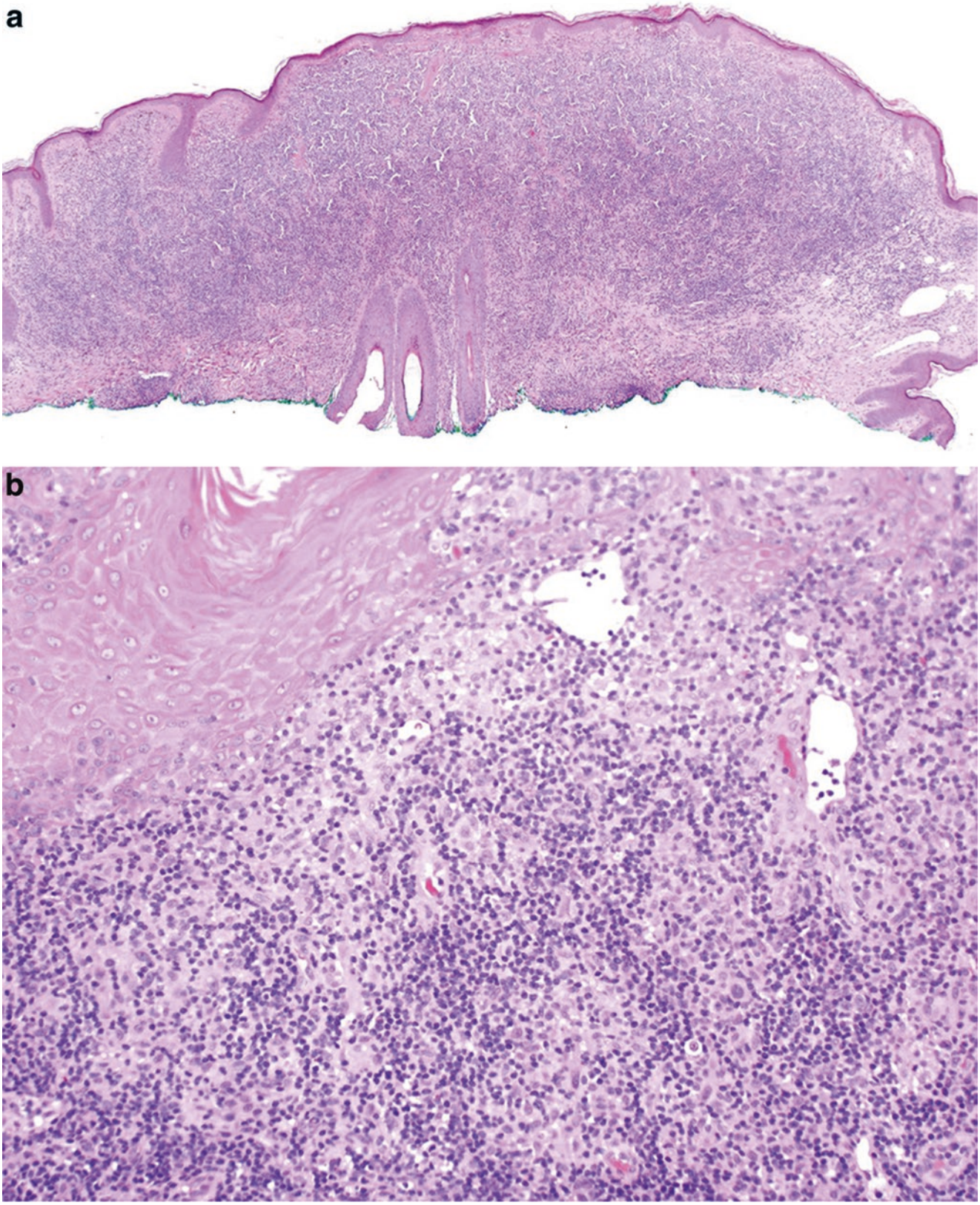
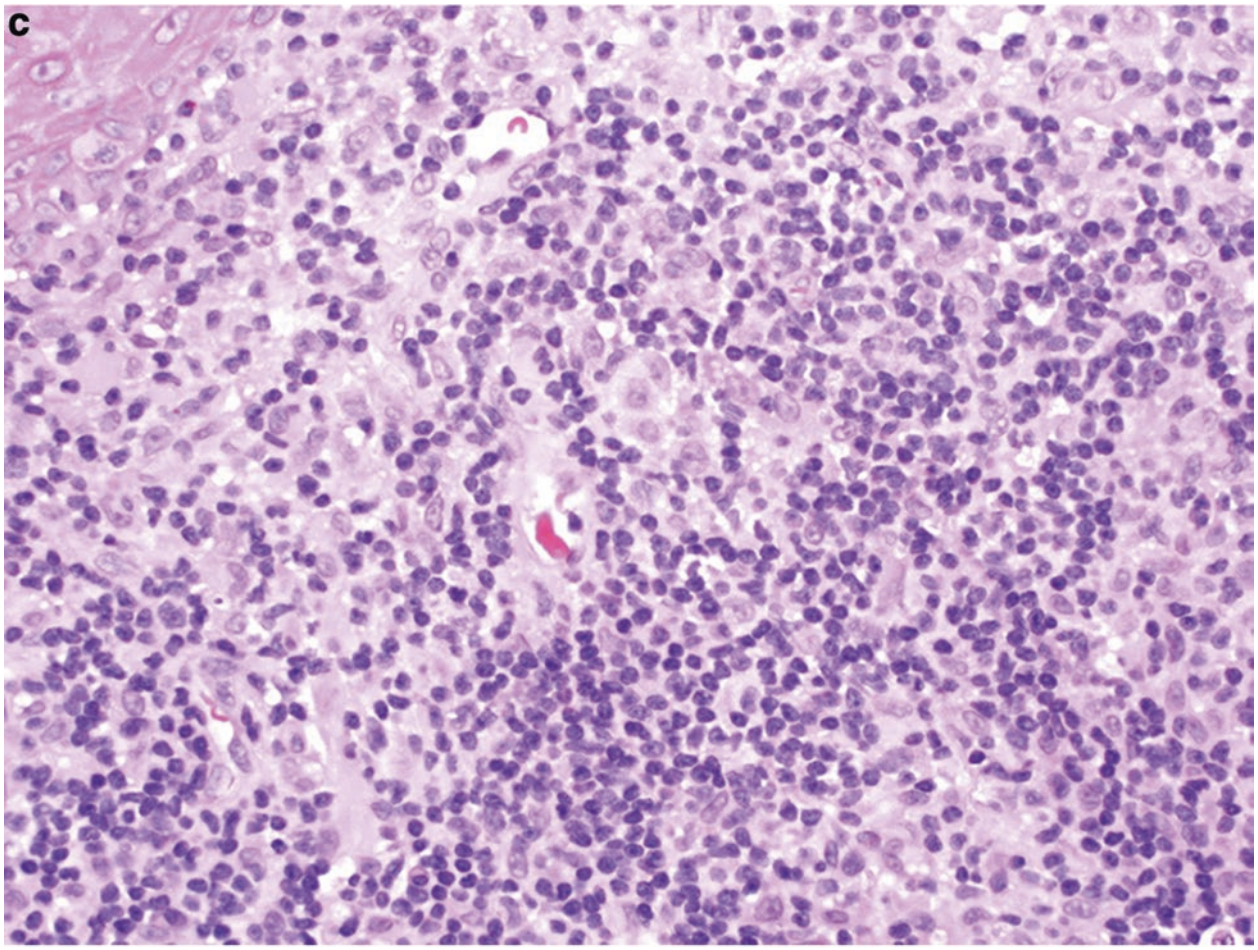


Fig. 3.39 Halo nevus. A 35-year-old female, abdomen. This example shows a predominant lymphohistiocytic infiltrate that simulates a lymphocytic process on low magnification (**a**). On higher magnification one can see that there are scattered, small type B melanocytes admixed with lymphocytes (**b, c**).



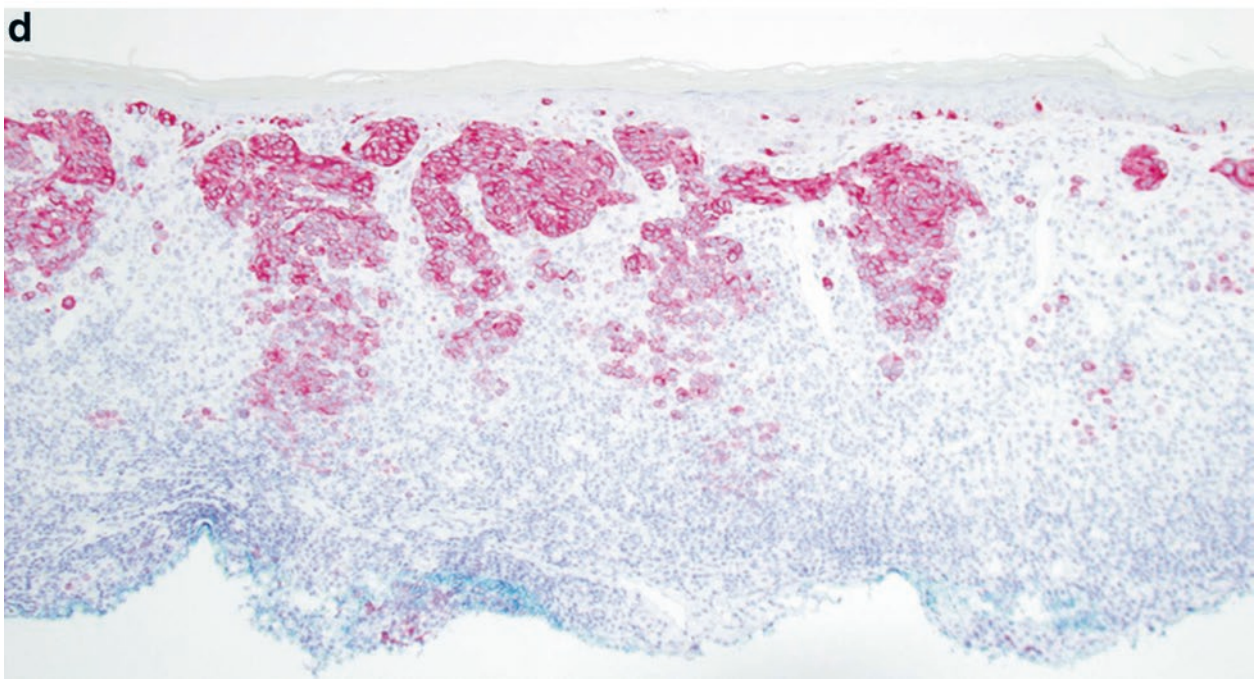


Fig. 3.39 (continued) Anti-MART-1 highlights only scattered cells in the epidermis with minimal pagetoid migration (**d**). There is labeling of superficial melanocytes with decrease with depth (maturation). These findings support the diagnosis of halo nevus (**d**)

Nevi in Pregnancy

During pregnancy, the clinical appearance of pigmented skin lesions undergoes morphological changes, possibly related to the influence of pregnancy-related hormones [83–86]. Despite the term "of pregnancy," actually these features can be seen in nonpregnant patients under hormonal treatment [87]. It has been shown that hormonal influences normally cause melanocytic nevi to darken or enlarge during pregnancy [88]. Immunohistochemical studies have shown an increase in estrogen receptor β expression in nevi excised from pregnant women, suggesting an increased responsiveness of melanocytes to estrogen during pregnancy [87, 89–92]. Some studies have shown significant clinical and histologic changes in nevi during pregnancy; while, some other studies have shown no significant differences [85, 93, 94]. Pregnancy was once regarded as a risk factor and a poor prognostic indicator of melanoma; however, to date, no studies have been able to definitively link the development or progression of melanoma in pregnancy [92, 95–97].

Histologic Features

As explained above nevi in pregnancy may increase in size and become darker. Histologically, these changes may correlate with polypoid architecture, prominent lentiginous junctional component, dermal mitotic figures, and superficial micronodules of pregnancy (SMOP). The junctional changes show scattered, large, single, or nested melanocytes arranged in an irregular lentiginous pattern, focally confluent. As a possible diagnostic pitfall, dermal melanocytes in nevi of pregnancy appear "crowded" with an expansile pattern of growth. These nevi are more likely to have dermal mitotic figures, with an average number greater than dermal nevi in nonpregnant patients (62.5% vs. 13.3%) [57]. The mitotic figures are usually limited to the superficial aspect of the lesion; however, in some cases mitotic figures may be more deeply located. SMOPs are rounded clusters of large epithelioid melanocytes with prominent nucleoli; abundant pale, eosinophilic cytoplasm; and occasional visible finely distributed cytoplasmic melanin. It was recently shown that these foci were more commonly found in nevi of pregnancy (81.3%) as compared to the controls (26.7%) [57]. The presence of SMOPs may alert the dermatopathologist that they are dealing with a nevus under the influence of pregnancy-related hormonal changes. These nevi show normal maturation toward the base of the lesion.

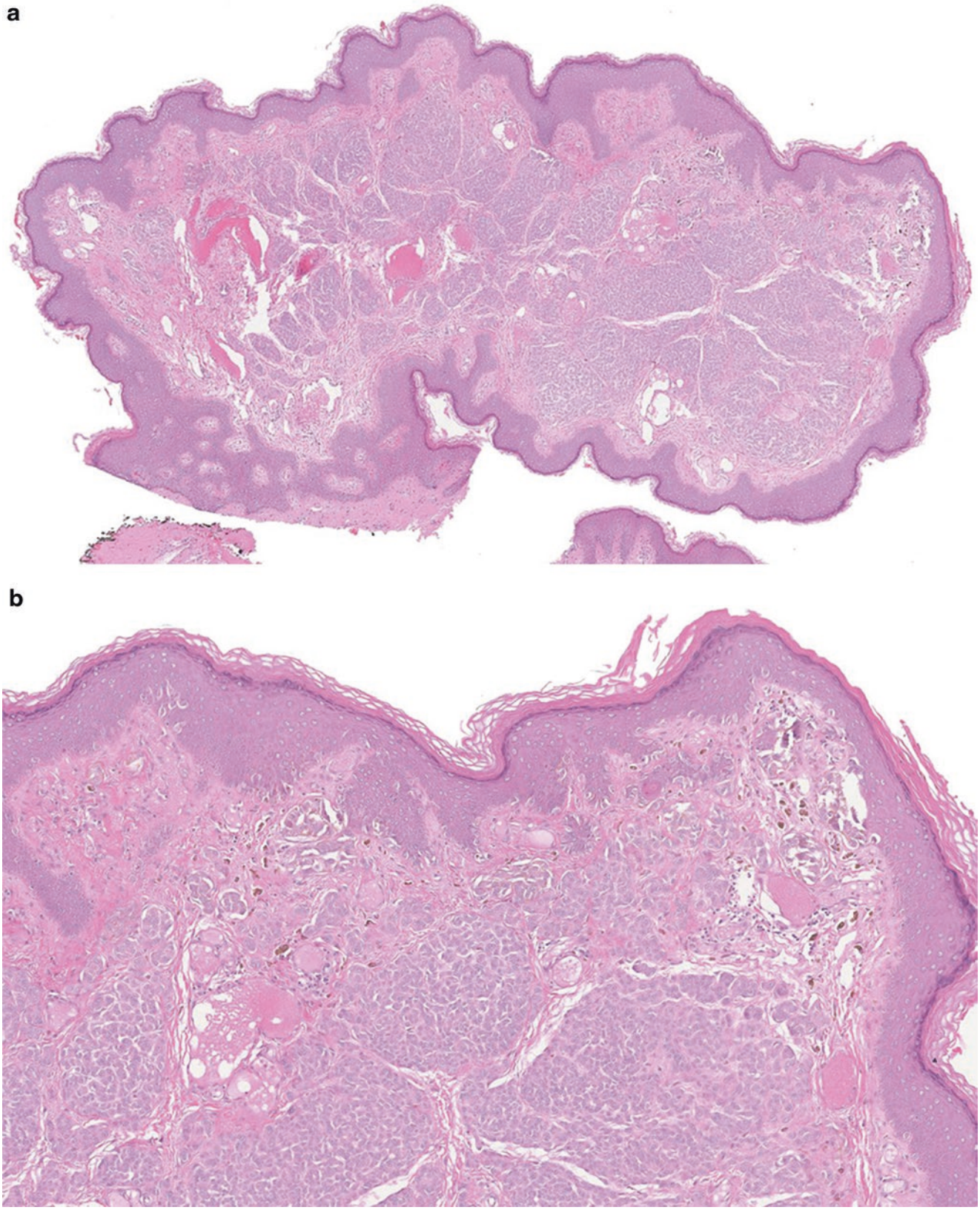


Fig. 3.40 Nevus of pregnancy. Note the polypoid architecture of this compound nevus (**a**). There is focal junctional component, which displays a lentiginous growth pattern (**b**).

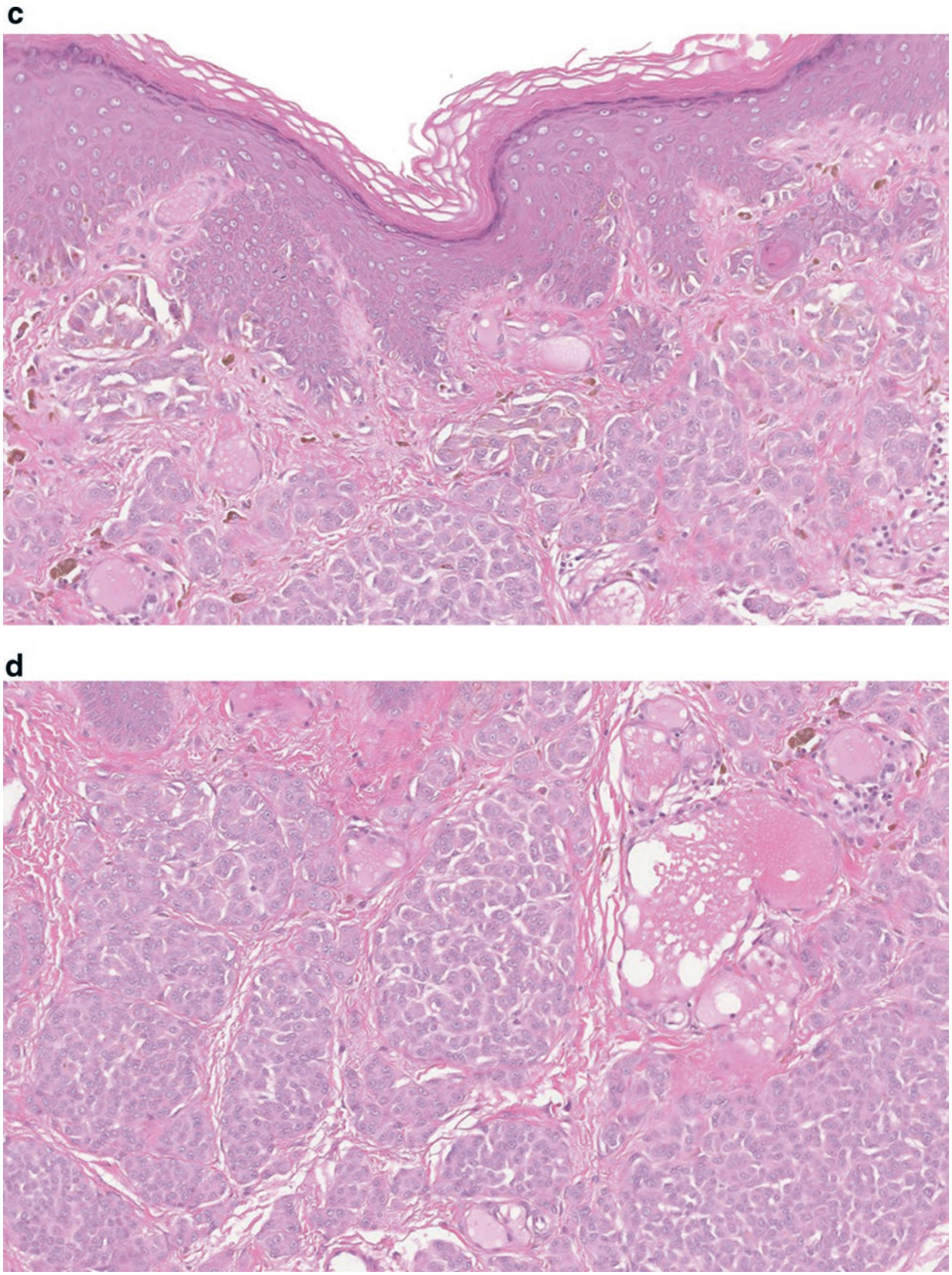


Fig. 3.40 (continued) Note the single cell, lentiginous pattern with minimal pagetoid upward migration (**c**). There is focal expansile pattern of growth but cells disperse at the base of the lesion (**d**)

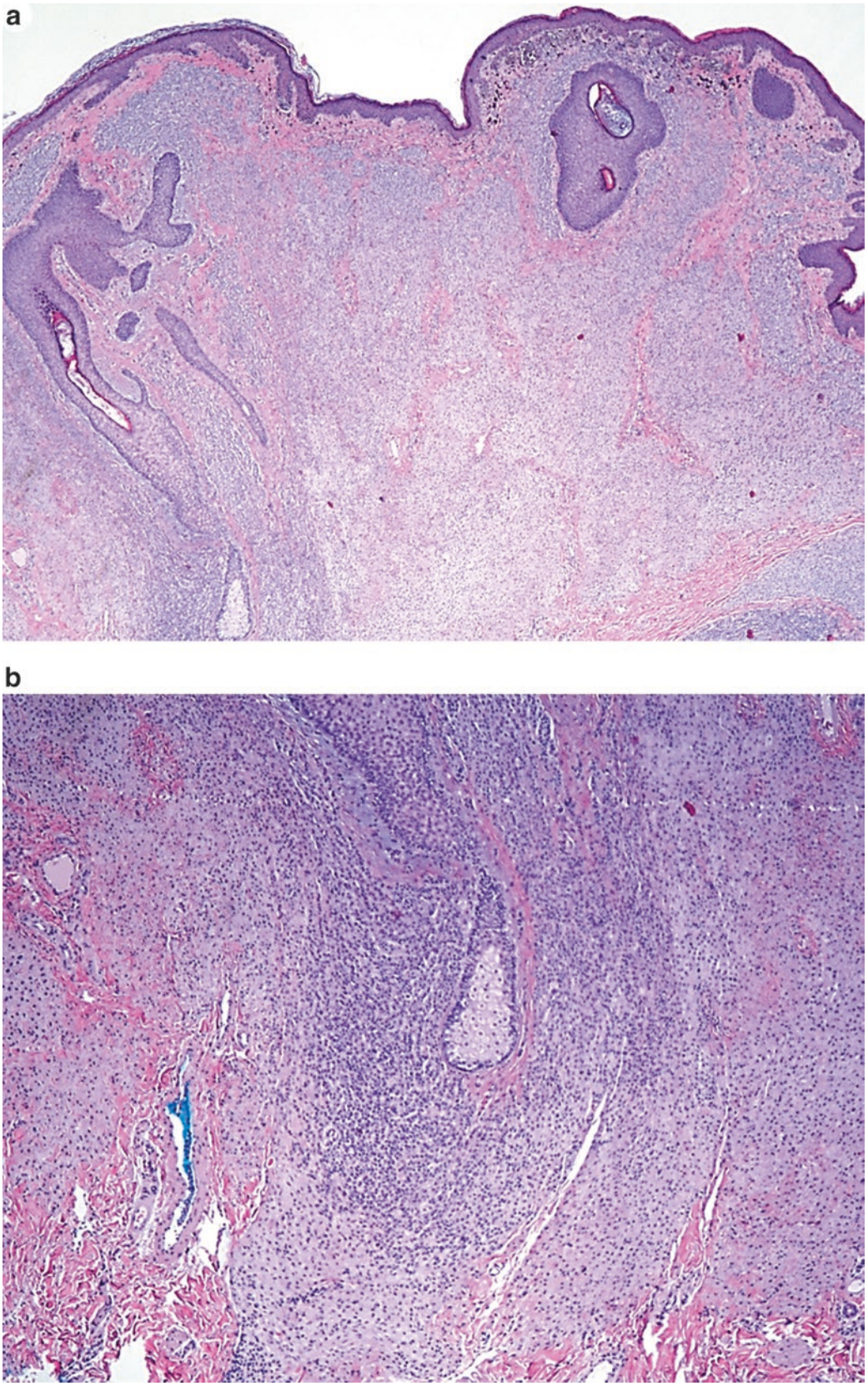


Fig. 3.41 Nevus of pregnancy. A 38-year-old pregnant woman with a large pigmented lesion in the *right* labium. Note the focal intraepidermal component associated with pigmentation to the *right*. Focal periadnexal arrangement in the dermis (*left*) (**a**). Periadnexal arrangement (congenital pattern) (**b**).

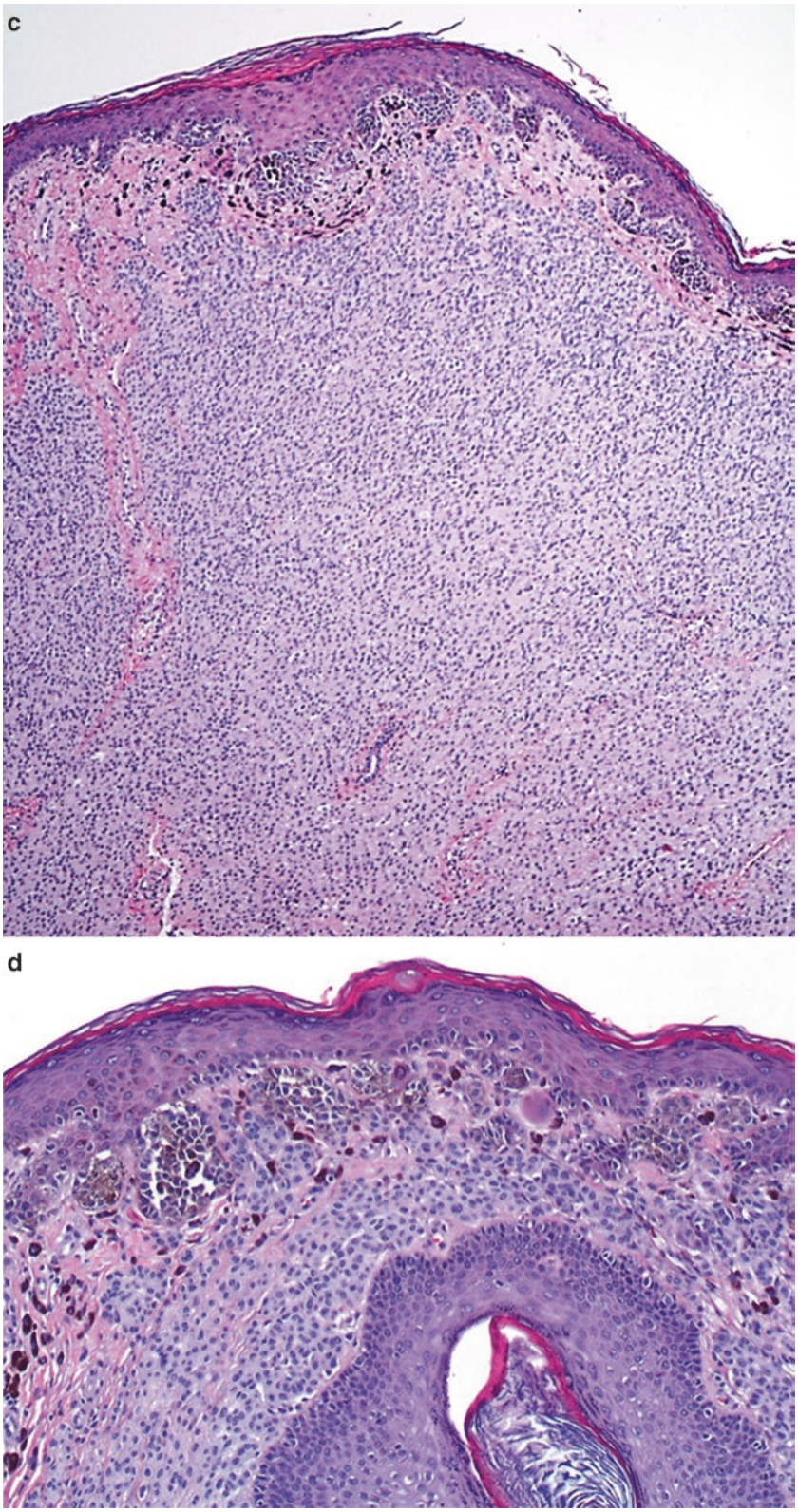


Fig. 3.41 (continued) Intermediate power view of the junctional component. Note the relatively dense dermal component (**c**). Lack of pagetoid upward migration. Pigmentation mostly limited to the upper components of the lesion (**d**).

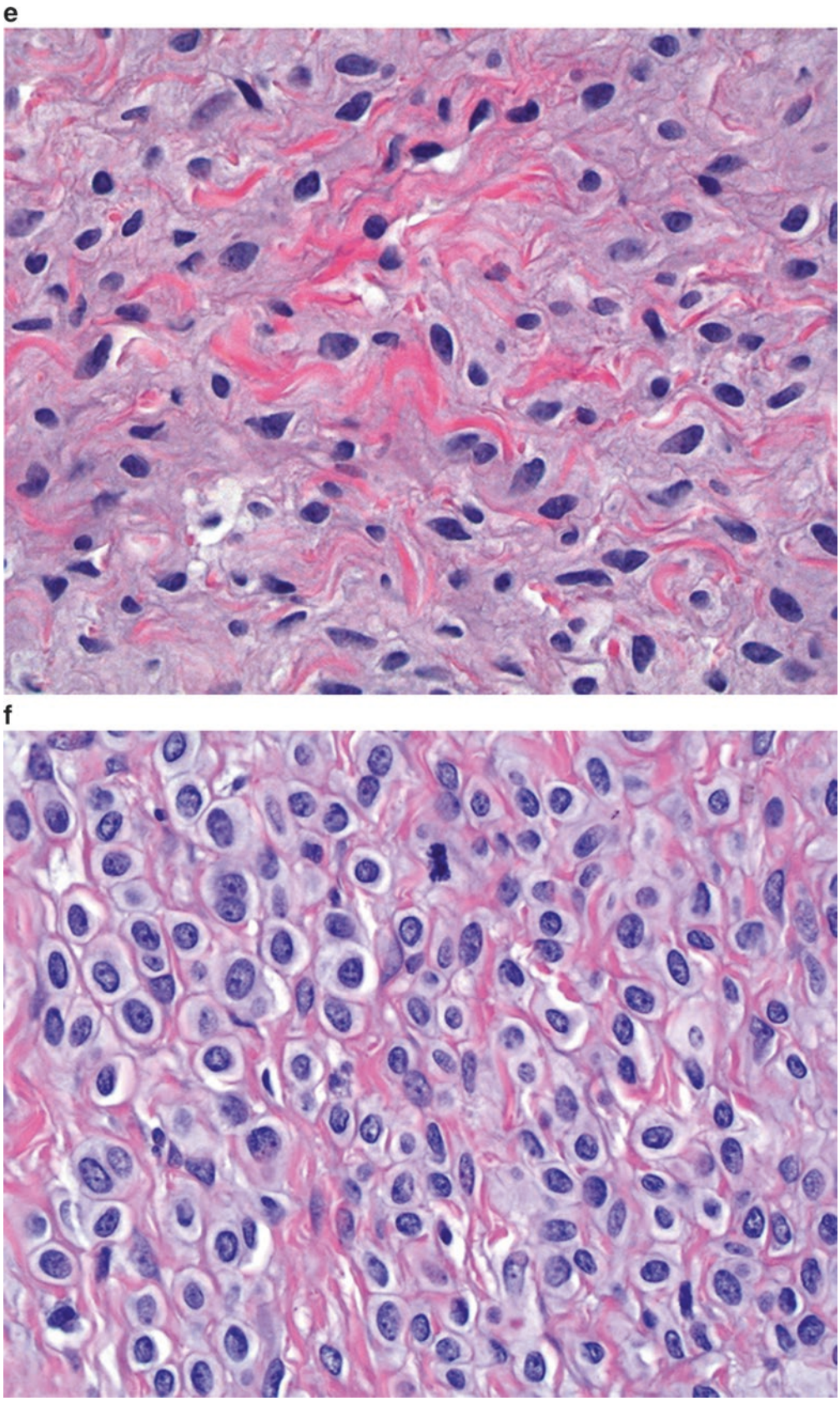


Fig. 3.41 (continued) Dermal component with epithelioid melanocytes with small nucleus and central, small nucleolus (**e**). Mitotic figure in the upper half of the lesion (**f**).

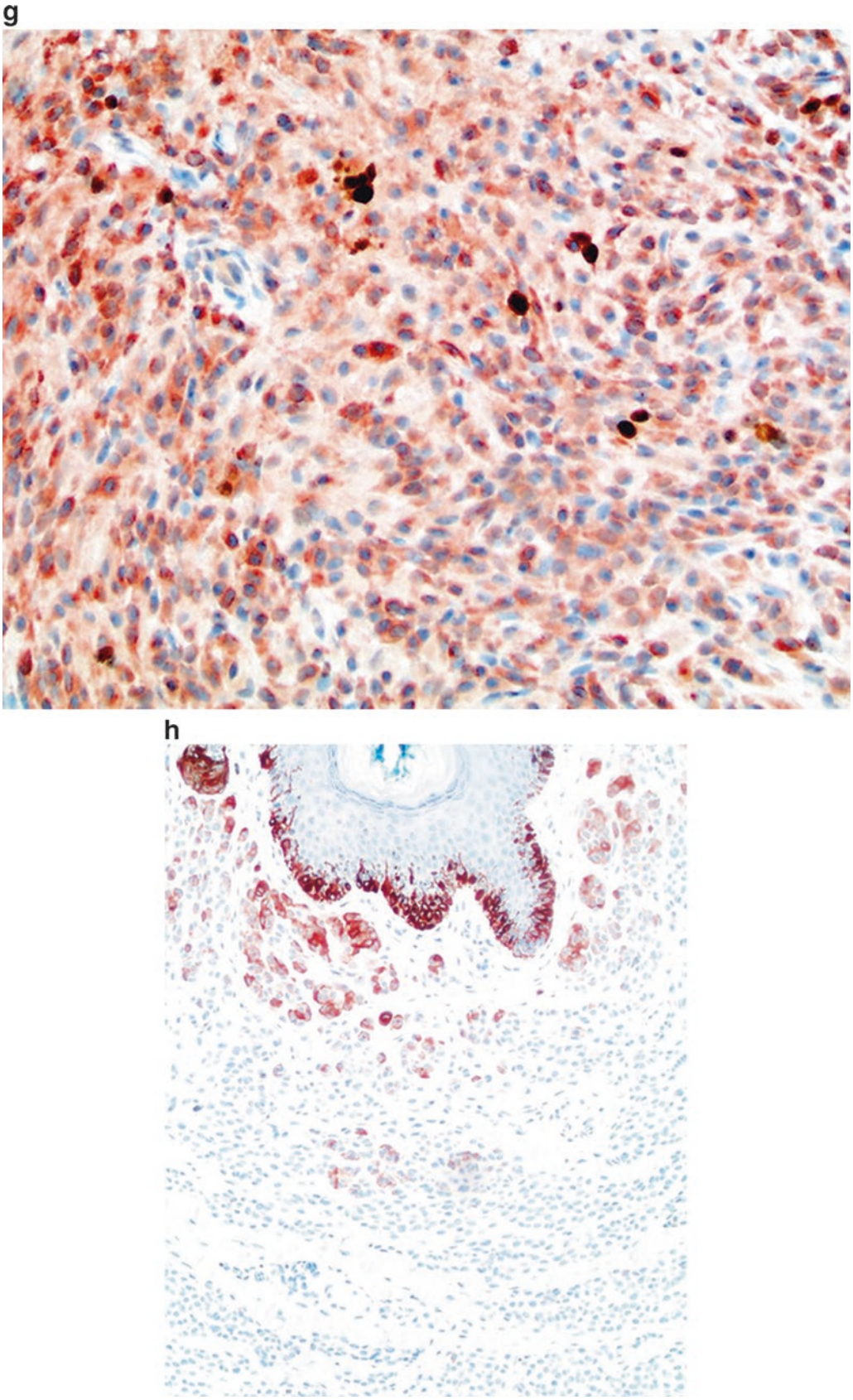


Fig. 3.41 (continued) A double immunostudy against MART1 (*red*) and Ki67 (*brown*) highlights some melanocytes predominantly located in the upper half of the lesion of positive melanocytes in the dermis (**g**). HMB45 highlights a decreased expression with depth in the dermis (maturation), thus supporting the diagnosis of nevus (**h**)

Recurrent/Persistent Nevi

Recurrent/persistent nevi arise after partial removal of a nevus. Clinically, it presents as an area of repigmentation in the scar at the site of a previous biopsy. This repigmentation usually appears within weeks to months after the initial surgery. Sometimes the recurrence simply represents epithelial hyperpigmentation associated with an underlying scar, but the repeat biopsy may actually show focal melanocytic nevus either in the epidermis or dermis and associated with the scar. Recurrent/persistent melanocytic nevi may raise clinical concern when they show irregular pigmentation and asymmetry, as these features are worrisome for melanoma. The lesions can be irregular with jagged borders and variegated pigmentation that ranges from tan to black; this pigment can be seen within or adjacent to the scar. Recurrent/persistent melanocytic nevi are most commonly seen in young patients, usually in females. The most common site for persistence is the back, followed by the abdomen and chest [98, 99]. The most common nevi that recur are congenital and dysplastic nevi. In benign acquired nevi, the recurrence usually takes place in a month; however, dysplastic nevi tend to recur later and on average is about 2 years, a finding also seen in recurrent melanomas. Recent studies on rates of recurrence/persistence of dysplastic nevi after biopsy have found a low rate of clinical recurrence (3.6 % at 2 years of follow-up) but also found that the recurrence of both dysplastic and conventional melanocytic nevi was significantly associated with performance of shave biopsy as the original procedure [100]. Recurrent/persistent melanocytic nevi may also mimic melanoma microscopically, as the intraepidermal melanocytes may show nuclear atypia, involvement of adnexal structures, and prominent lentiginous growth. This histopathological overlap between recurrent/persistent melanocytic nevus and melanoma led Ackerman to coin the term "pseudomelanoma" [101].

Histologic Features

Histologically, recurrent nevi show a characteristic trizonal pattern (epidermal melanocytic proliferation, scar in dermis from previous biopsy, and residual nevus at the bottom). The epidermis typically shows a proliferation of melanocytes overlying the area of dermal scar. This epidermal growth shows lateral circumscription in which the edges are defined by the presence of scar from the prior biopsy [102]. In some cases this junctional proliferation can be broad and may extend beyond the scar in the dermis, but this finding is exceptional, and it is much more likely to be associated with a recurrent/persistent melanoma. Melanocytes at the dermal-epidermal junction are arranged in single cells with only focal nest formation and with variable confluent growth pattern. When nests are present, they tend to show atypical features such as irregular shape and size and dyshesion mimicking dysplastic nevi. In fact, the distinction of a recurrent dysplastic nevus from acquired recurrent nevus might be impossible, unless there is residual dysplastic or acquired nevus for review peripheral to the scar; in any case, examination of the original biopsy is highly encouraged. Intraepidermal melanocytes show epithelioid features with round to oval nuclei and abundant cytoplasm, and in some instances the nucleus can be hyperchromatic with cytologic atypia [103]. The intraepidermal growth of melanocytes is mostly in single cells with lentiginous pattern; in some instances there may be focal pagetoid upward migration [61], not extending beyond the dermal scar. This proliferation of melanocytes can involve the intradermal portion of follicular and sweat gland structures. Another characteristic feature is the presence of a somewhat atrophic epidermis with loss of the retiform architecture secondary to the healing wound process. In most examples, there is heavy melanin pigmentation within keratinocytes giving a hypermelanotic appearance of the epidermis. In fact, recurrent nevi tend to be darker than the original nevus.

In the dermis, there is a band of scar tissue that replaces the papillary dermal collagen with characteristic neovascularization. In some occasions, melanocytes similar to those seen in the epidermis can be present in the scar but are confined to the papillary dermis, and the density is not as prominent as seen in the intraepidermal component. These cells in the papillary dermis can be large in size with ample cytoplasm but display normal maturation pattern with descent. The dermis underneath the scar shows remnants of the benign nevus if the previous lesion was not entirely excised.

An important, potential diagnostic pitfall is the detection of mitotic figures in the dermal component. In our experience, if they are detected, they are rare and are located in the upper dermis [99]. Another possible pitfall is that, in contrast with most nevi, there may be abnormal labeling with HMB-45 in traumatized/recurrent nevi, with patchy labeling of the dermis, similar to melanoma [63].

Differential Diagnosis

Recurrent nevi often may mimic melanoma histologically; thus, the epidermal melanocytic proliferation is often called "pseudomelanoma" [101]. It is very important that, in addition to histologic evaluation, clinical-pathologic correlation and review of the material form the initial biopsy. Histologically, there are certain features that help distinguish recurrent nevi from melanoma. Recurrent nevi tend to show lateral circumscription and the intraepidermal melanocytes arranged in an irregular, confluent pattern, are located above the scar and do not involve the epidermis beyond the scar. If pagetoid upward migration beyond the center of the scar is prominent, a diagnosis of melanoma should be entertained. A benign melanocytic component in reticular dermis is present in a recurrent nevus, as opposed to melanomas in which there

is an atypical proliferation of melanocytes that lack maturation. Obviously, a similar finding is theoretically possible in cases of recurrence in a melanoma associated with a nevus. However, in such cases the junctional component should still extend *beyond* the dermal scar. In certain occasions, recurrent nevi may show an atypical proliferation of melanocytes within the scar that have similar histologic appearance to those seen in the overlying epidermis. These melanocytes can show atypical features (large size and ample cytoplasm) but with cells mature with descent; while melanocytes in melanoma do not mature. This phenomenon is more commonly seen in recurrent dysplastic nevi. One last point to consider is the presence of solar elastosis in dermis; such finding is more commonly seen in cases of recurrent melanoma, whereas recurrent nevi tend to occur more commonly in younger patients, and thus solar elastosis would be unusual. Melanoma with regressive changes can simulate a recurrent nevus. In a recurrent nevus, the scar is composed of laminated, thick bundles of collagen arranged parallel to the epidermis with interspersed vessels arranged perpendicular to the epidermis. In regressed melanoma, there are areas of inflammation sometimes in a lichenoid pattern along with conspicuous melanophages. Another feature to look for is the presence of an atypical proliferation of melanocytes outside the areas of regressive stromal fibrosis. As explained above, in recurrent nevus the atypical intraepidermal growth does not extend beyond the area of the scar, and the intraepidermal growth beyond this point displays a standard melanocytic growth, mostly as junctional nests. Immunohistochemistry could be potentially useful. HMB-45 usually demonstrates a gradual decrease in staining intensity and number of labeled cells toward the base of the lesion, which would support the diagnosis of recurrent nevus. Also, Ki-67 shows a low proliferation rate [103]. A possible pitfall is the irregular pattern of HMB-45 labeling sometimes seen in traumatized nevi [63].

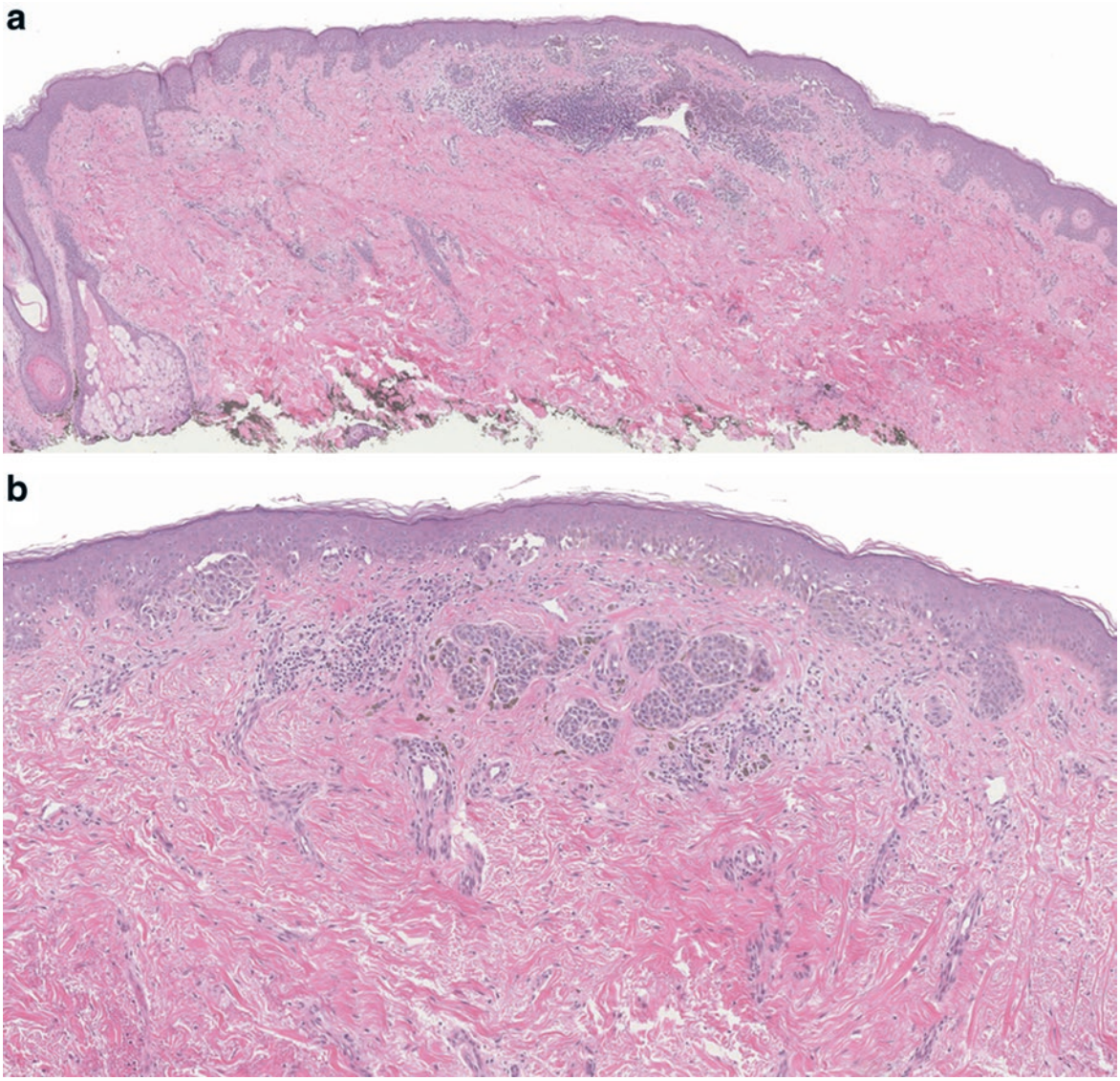


Fig. 3.42 Recurrent/persistent nevus. This lesion was previously biopsied and diagnosed as a dysplastic compound nevus recurred 4 months after the initial biopsy. A clue to its recognition is the presence of scar in dermis (**a**). Note the flat epidermis with intraepidermal melanocytic proliferation, the scar in dermis, and the residual nevus deeper in dermis (**b**).

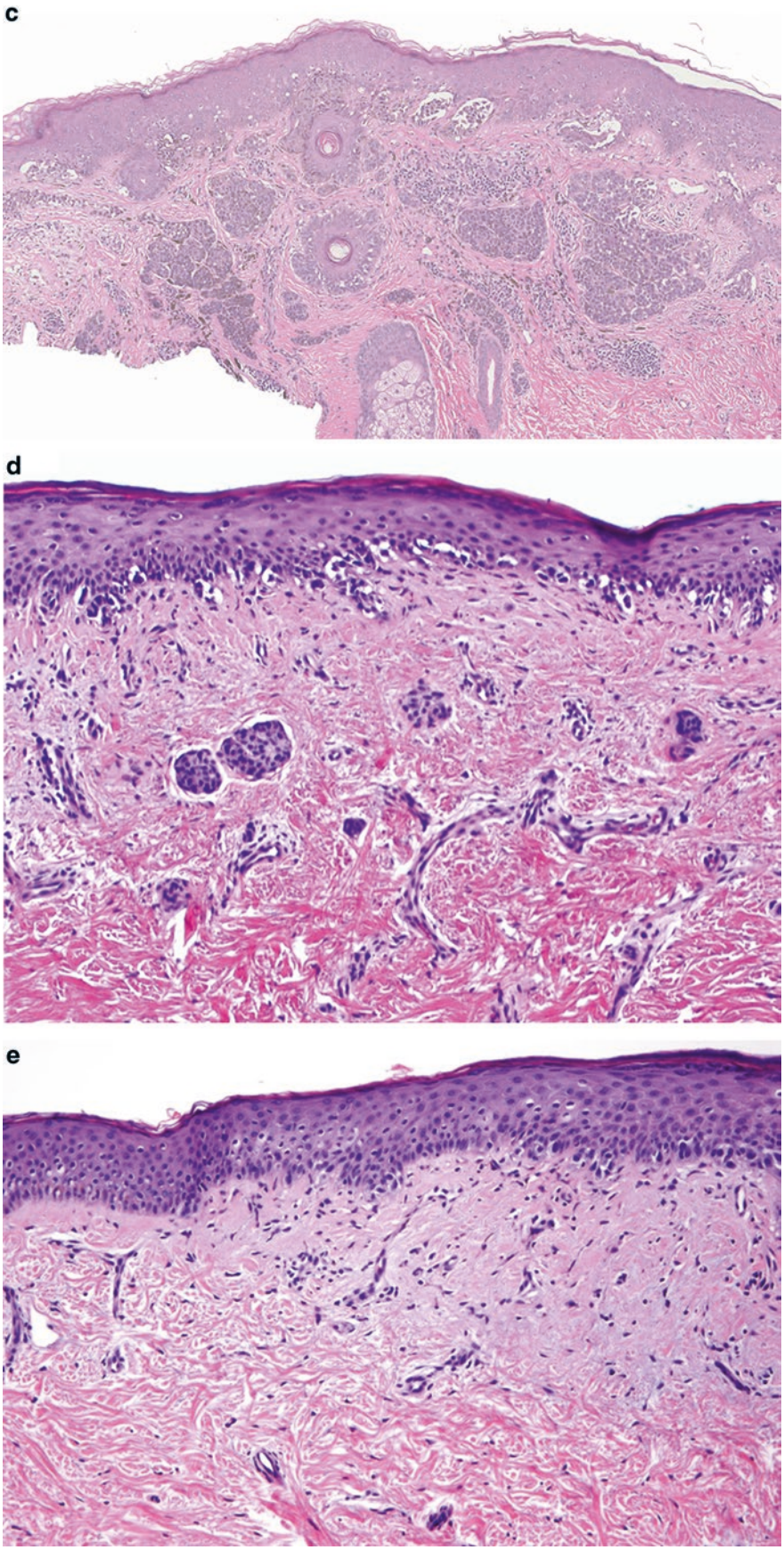


Fig. 3.42 (continued) Another area shows the irregular intraepidermal nests (**c**). Poorly cohesive intraepidermal nests and isolated melanocytes ("pseudomelanoma") with a few, remaining dermal nests (**d**). The atypical intraepidermal proliferation extends only in the area above the scar ("pseudomelanoma") thus consistent with a recurrent/persistent nevus (**e**)

Nevi of Special Site

A relatively common and widely accepted group of nevi that may simulate both dysplastic nevi and melanomas have been recognized and termed "nevi of special sites." Nevi in special sites (particularly breast, milk line, flexural, scalp, and auricular areas) and also in physiological states such as old or young age or pregnancy (see above) may show histologic patterns of that may deviate from ordinary acquired nevi and cause diagnostic confusion as they can exhibit features that overlap with dysplastic nevi and melanomas. In our opinion, nevi of special sites appear to represent an isolated event and are not associated with an increased risk of developing melanoma; however, it is important to recognize that the existence of a special site nevus category does not preclude the presence of authentic dysplastic nevi and melanomas on these special sites. In addition to the above list, some authors may include thighs, ankles, and knees. In our opinion, these anatomic sites deserve a separate description as their histologic features differ somewhat from the prevalent features seen in acral and genital lesions (which are discussed in a separate section, see below).

While nevi from special sites may show unusual histologic features, they are clinically unremarkable. Therefore, it is always important to compare the clinical features of the lesion for an appropriate assessment. The vast majority of these nevi are seen in young patients; however depending on the anatomic location, nevi of special site can also be observed in older patients, such as around the ear [104].

Histologic Features

The majority of cases of nevi of special site will display features of a conventional acquired nevus. In this section we will focus on nevi of special site with atypical and unusual features which can be misinterpreted as melanoma or dysplastic nevus. In our experience, these nevi have variable histologic features that will depend on the anatomic location of the lesion.

Scalp: The scalp is a common anatomic site which has a predilection for benign but histologically atypical nevi, especially in young patients [105–109]. Many of these nevi share features that are commonly seen in dysplastic nevi such as the presence of lentiginous growth melanocytes aligned in single units, bridging of the adjacent ridges, dermal inflammatory infiltrate, and lamellar fibroplasia. Characteristically, they show large and confluent nests at the junction usually distributed at the edge of the rete ridges and not only at their tips. Large, bizarrely/pleomorphic-shaped nests with a discohesive cellular pattern can be also present at the junction. In some cases, this junctional component extends beyond the dermal component (shouldering). Hair follicles are also involved commonly by the presence of a lentiginous growth of melanocytes. In some cases, the presence of scattered atypical melanocytes with hyperchromatic large nuclei can be identified at the junction. There may be pagetoid upward migration of melanocytes above the dermal-epidermal junction in the center of the lesion. A dermal component is almost always seen, and despite the occasional presence of rare large melanocytes at the surface, there is always normal maturation toward the base of the lesion. Mitotic figures are unusual outside the upper dermal component.

Breast: Breast is another location which has a predilection for benign but histologically atypical nevi [110, 111]. They may occur anywhere in the breast including on and around the nipple in both male and in female patients and more commonly seen in the youngsters. Histologically, nevi of this location show variable-sized nests at the junction with loose interconnecting melanocytes. The melanocytes are enlarged but uniform and have a characteristic clear-to-dusty cytoplasm. There are single melanocytes and small nests with variable degree of cytologic atypia within papillary dermis; however, normal maturation toward the base is seen. In some cases there are papillary dermal fibroplasia and the presence of suprabasal melanocytes. Nevi located on the milk line show similar histology to nevi on the scalp.

Flexural: Flexural sites include axillary, umbilical, inguinal, antecubital, and popliteal fossae and pubic, scrotal, perineal, and perianal locations. Histologically, they often show papillomatous features similar to what is seen in Unna nevus. The junction shows variable-sized nests with cellular dyshesion located along the tips and sides of the rete. Cytologic atypia is minimal and restricted to junctional and papillary dermal portions of the nevus.

Ear: Nevi on the ear can represent a diagnostic challenge. At this anatomic region, the skin is variably thin and rich in lymphatics; thus, it is common that nevi from the ear have unusual histologic changes. Another problem is that adequate biopsies from the ear pose difficulties to clinicians and tend to be small and superficial, resulting in an inadequate overall inspection of the lesion. One study showed that 41.6 % of nevi from the ear had atypical histologic features including poor lateral circumscription, lateral extension of the junctional component, elongation of rete ridges, junctional bridging, a dermal lymphocytic infiltrate, and cytologic atypia with variable pleomorphism [104]. In our experience, these nevi may show large nests that are widely spaced and composed of spindle pigmented melanocytes (Spitzoid appearance). It is very important to recognize this subset of histologically atypical but benign nevi from the ear and not to confuse them with melanoma; however,

sometimes due to the small samples received, it is difficult to assess the full architecture of the lesion. In our opinion, the presence of severe melanocytic atypia and solar elastosis should be interpreted cautiously as they may indeed represent melanoma. In cases in which an adequate tissue sample is received, helpful features for distinction from melanoma include lack of a well-developed in situ component and presence of symmetry and maturation of the dermal component, without mitotic figures.

Thigh and Ankle: In our experience, we have identified a subset of melanocytic nevi on the thigh and the ankle that are benign but exhibit histologically atypical and unusual changes, especially in young female patients [112, 113]. Sometimes nevi on this location may show overlapping features with dysplastic nevi and melanoma, requiring particular attention to avoiding misinterpretation. On the thigh, some of these nevi show both dysplastic and spitzoid features and are characterized by elongated rete ridges with bridging, papillary fibroplasia, junctional nests of variable size and shape, and intraepidermal epithelioid spitzoid melanocytes with focal (centrally located) suprabasilar upward migration. In some cases there are no dysplastic architectural features except for suprabasilar spread of these large epithelioid melanocytes. Features favoring nevus over melanoma include small size, circumscription, symmetry, even distribution of cells, and lack of marked cytologic atypia. On the ankle, we have identified lesions that have histologic and cytologic features intermediate between common nevi and melanoma. These nevi tend to show moderate to severe architectural disorder (prominent single-cell proliferation with lack of circumscription) but usually with mild cytologic atypia and lack features of dysplastic nevi (no host response, namely, lamellar or concentric fibrosis and dermal vascular proliferation). The differential diagnosis of these nevi would be with early melanoma in situ. Although the presence of severe architectural disorder may suggest that diagnosis, the low degree of cytologic atypia and relative symmetry of the lesions argue against it, also supported by the relatively long clinical follow-up of our cases indicating no recurrence or progression after conservative excision [113].

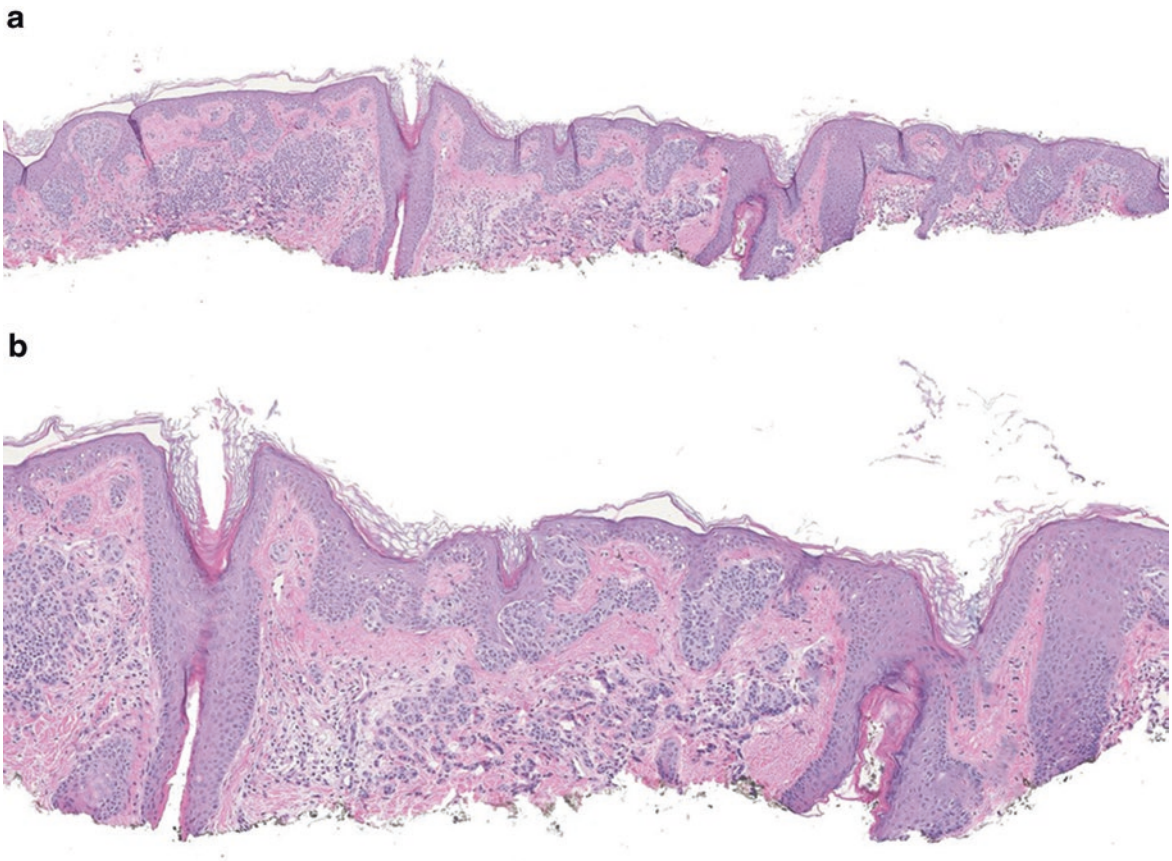


Fig. 3.43 Scalp nevus. Nevi in this location share features with dysplastic nevi such as the presence of lentiginous growth of melanocytes, bridging of the adjacent ridges, and dermal inflammatory infiltrate (**a**). Note the bridging and confluence of nests in the dermal epidermal junction. There is no significant pagetoid migration or evident inflammatory infiltrate in the dermis (**b**)

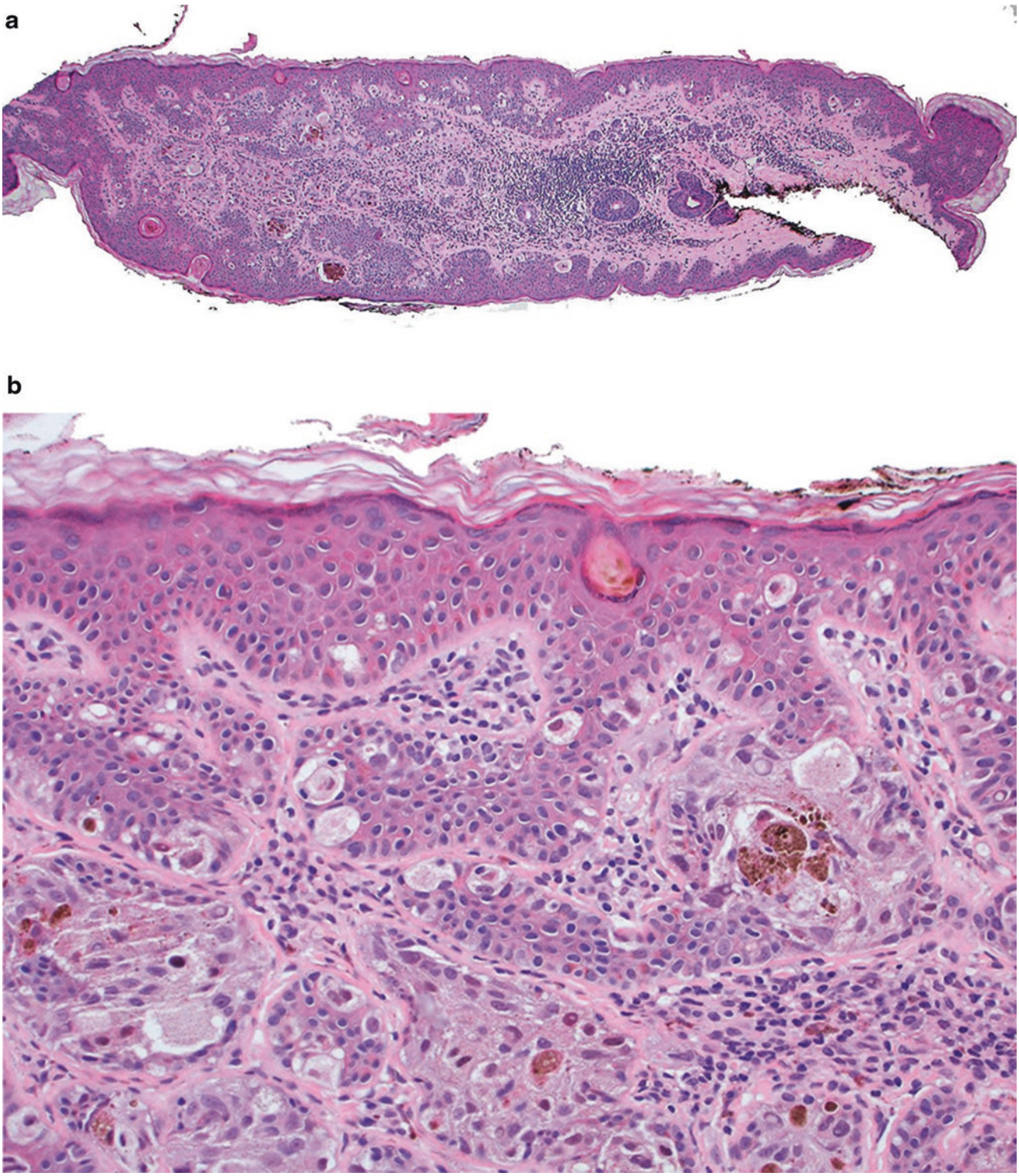


Fig. 3.44 Scalp nevus. This is a long-standing scalp mole on a 15-year-old male showing focal bridging and single cells (**a**). This case shows single cells and focal upward migration limited to the center of the lesion. The cells also show ample and dusky cytoplasm (**b**)

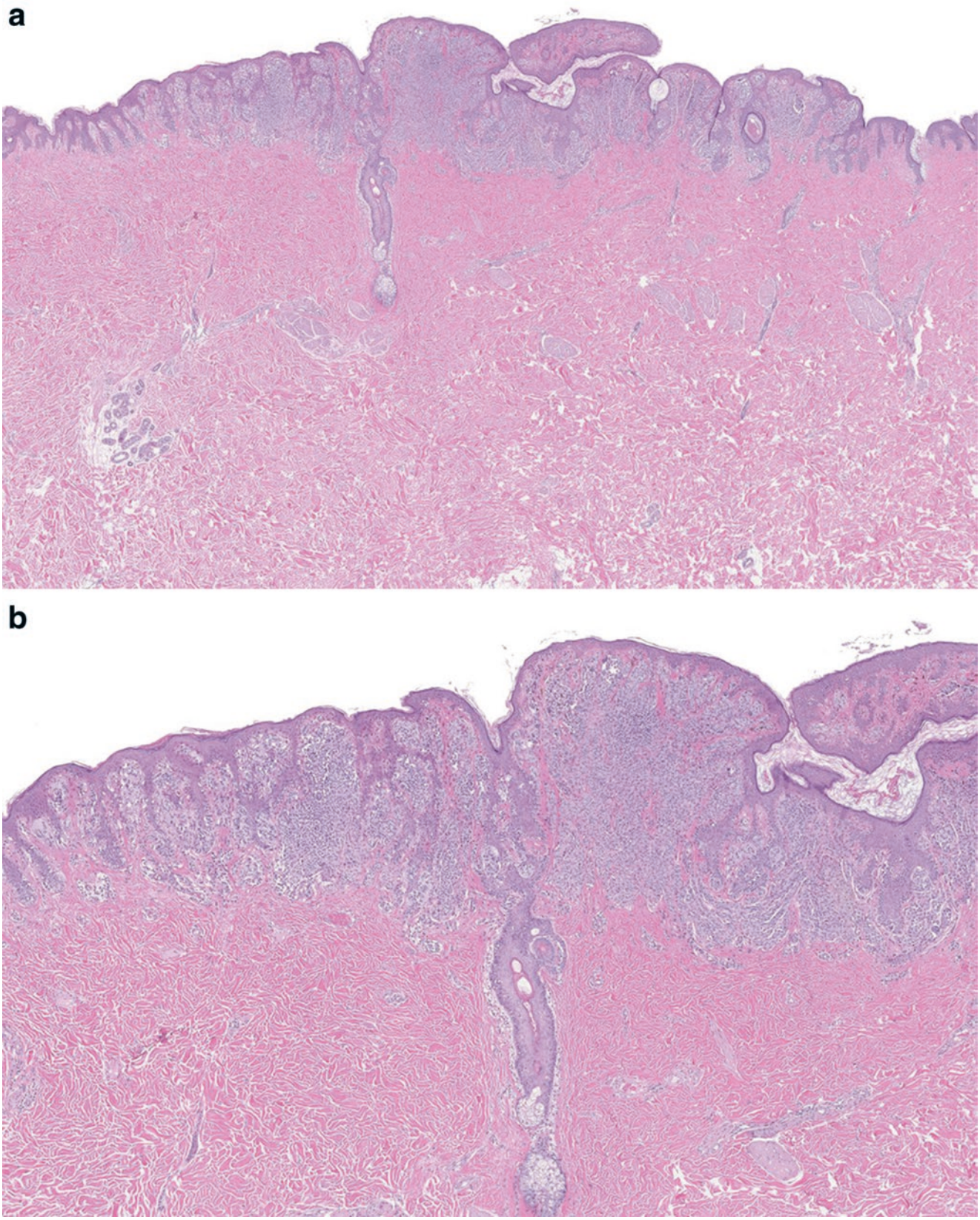


Fig. 3.45 Breast nevus. These nevi tend to show variable sized nests at the junction with loose, dishesive melanocytes (**a**). Low power view still shows a wedge-shaped growth (**b**).

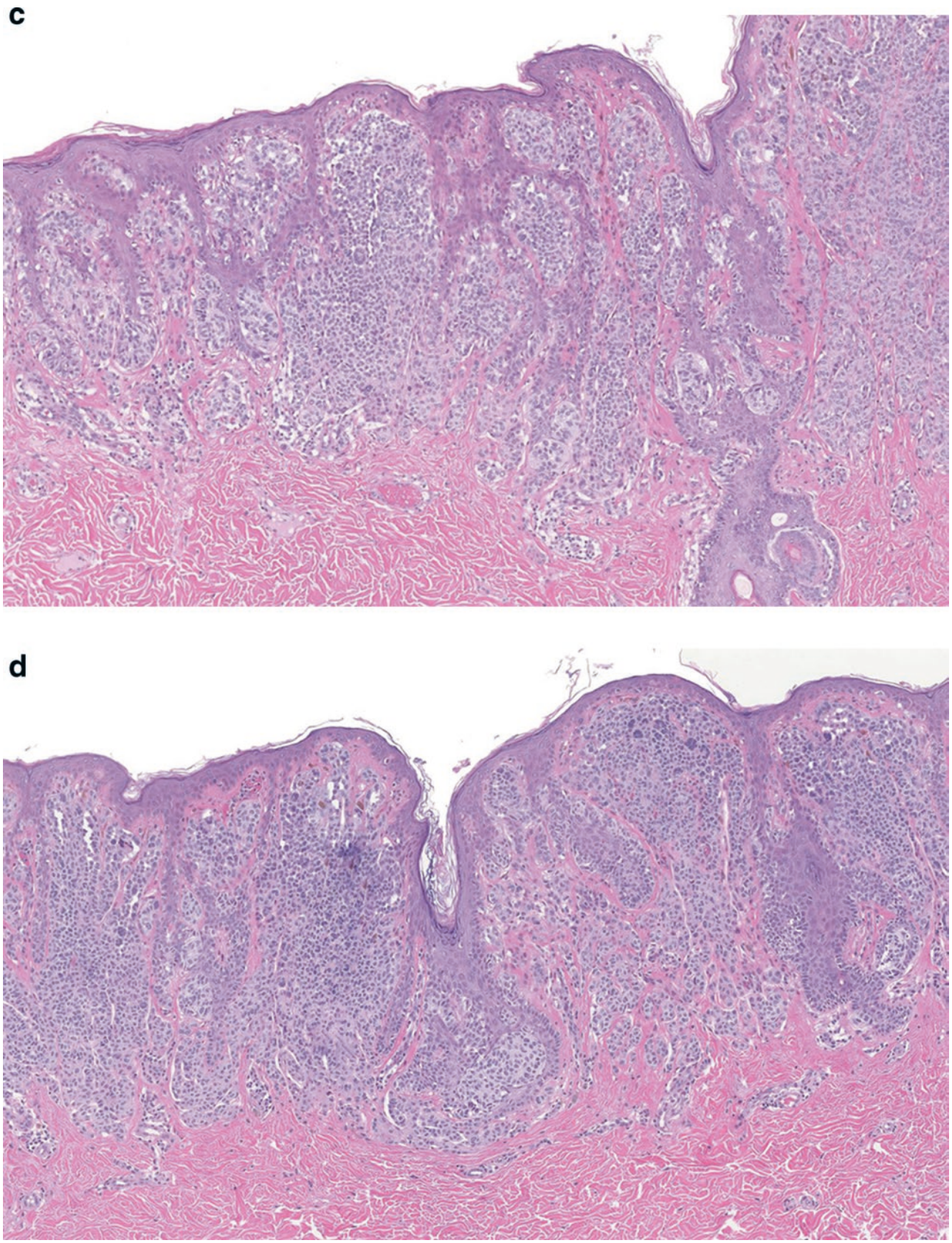


Fig. 3.45 (continued) Bridging of rete ridges with lentiginous pattern of growth (**c**). Lack of pagetoid upward migration and dispersion of melanocytes in the dermis, both features supporting the diagnosis of special site nevus (**d**)

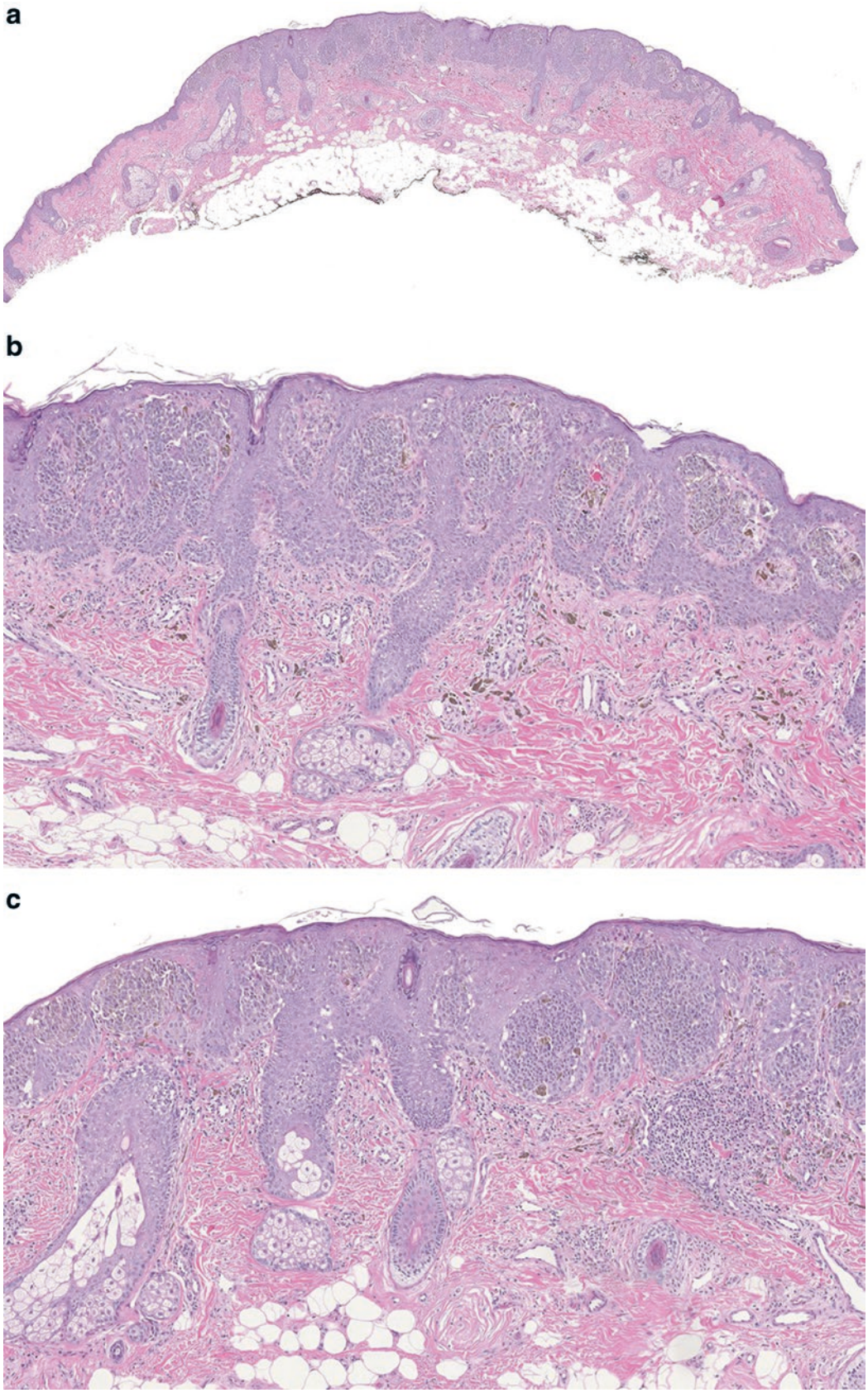


Fig. 3.46 Ear nevus. This is a more conventional example showing large nests and symmetric growth (**a**). These nevi tend to have large junctional nests (**b**). Periphery of the nevus with large nests (**c**)

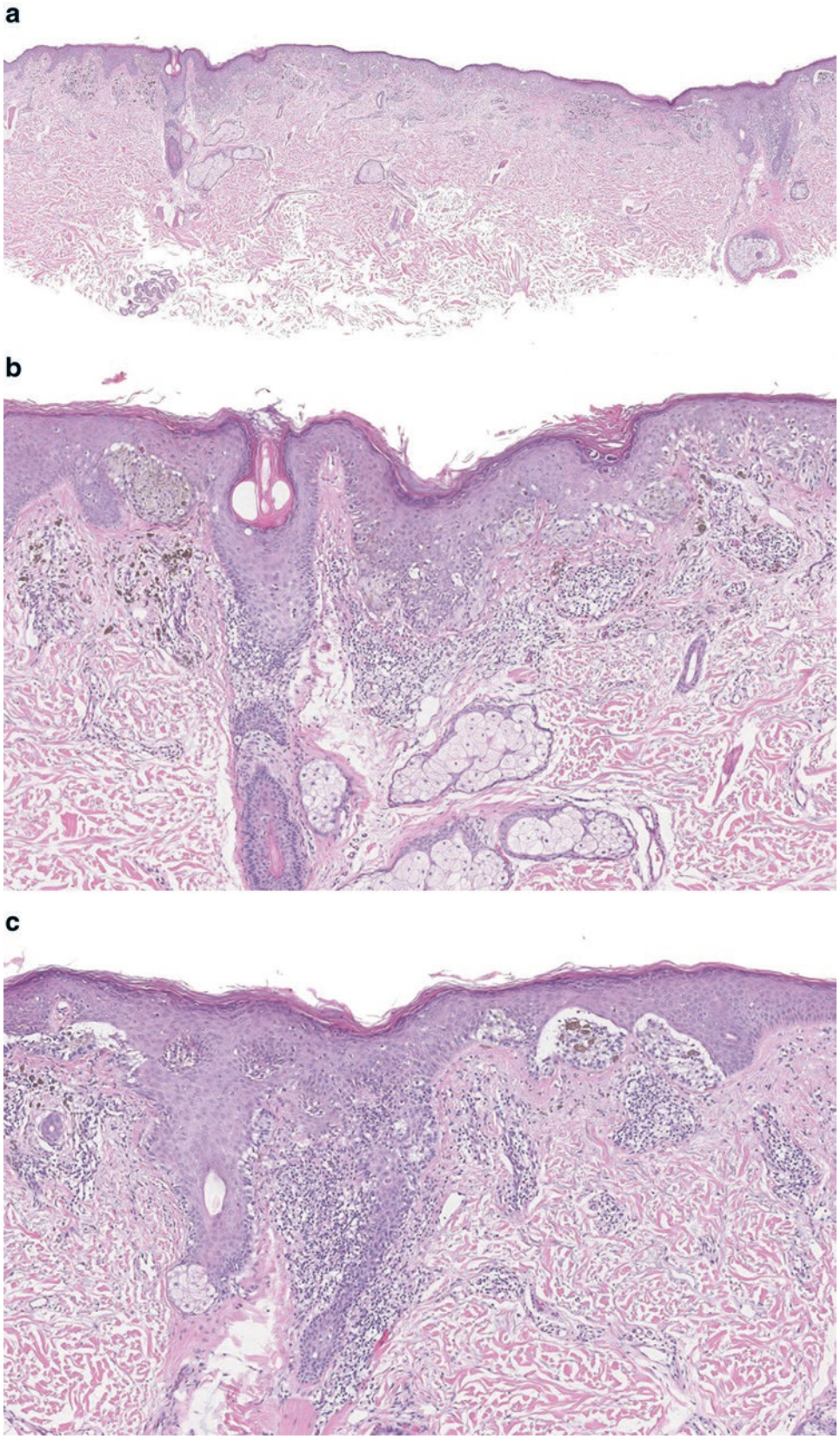


Fig. 3.47 Ear nevus with dysplastic features. A 41-year-old male. The lesion shows shoulder and focal confluence. There is no solar damage (**a**). Note the focal single-cell growth and the presence of fibrosis and dermal melanophages (**b**). Another area with dishesive nests and focal dermal infiltrate. Still the lesion appears circumscribed and lacks pagetoid upward migration (**c**)

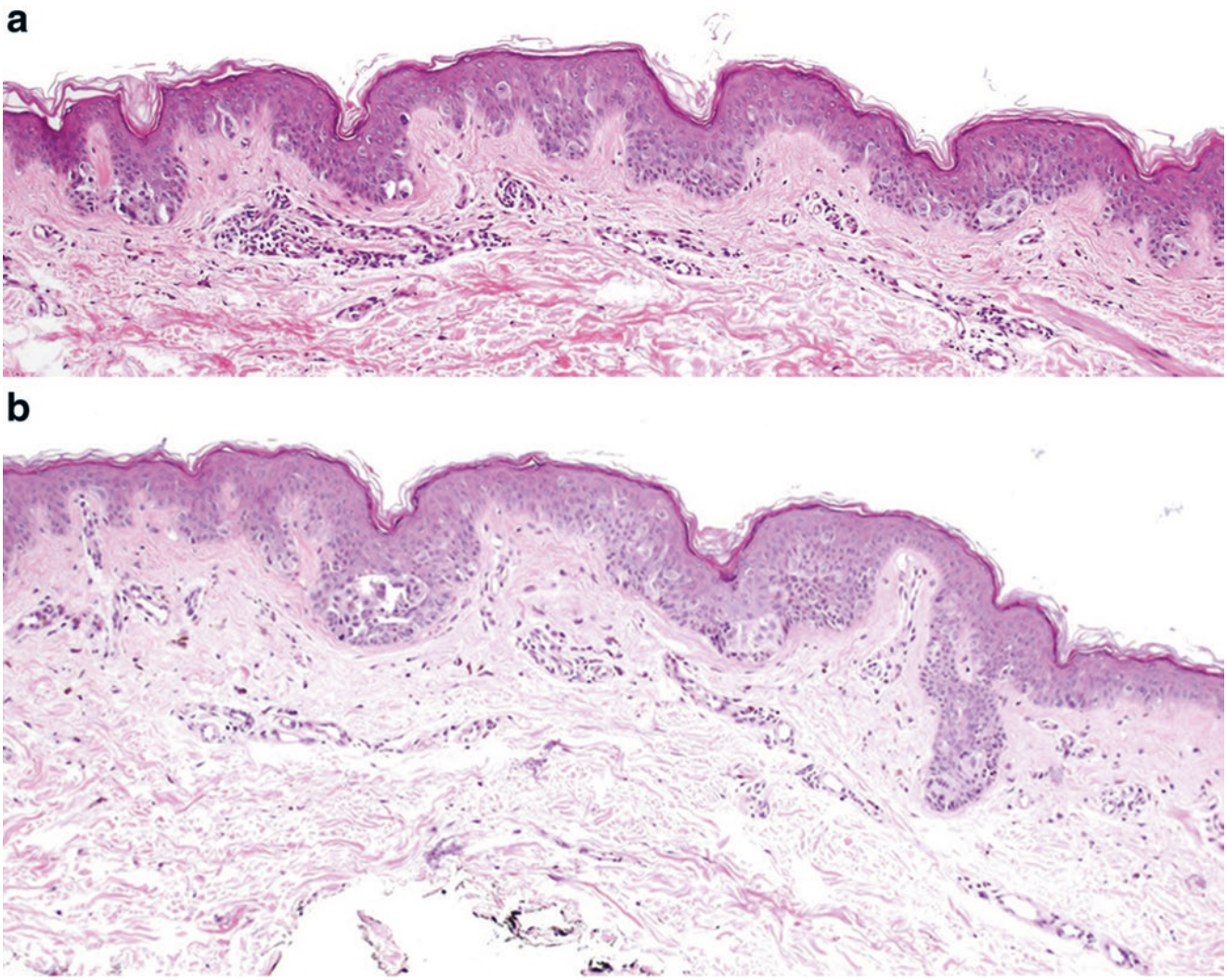


Fig. 3.48 Leg nevus with spitzoid features. A 19-year-old female, thigh mole (5.0 mm) (**a**). The intraepidermal component shows both single melanocytes and nests (**b**).

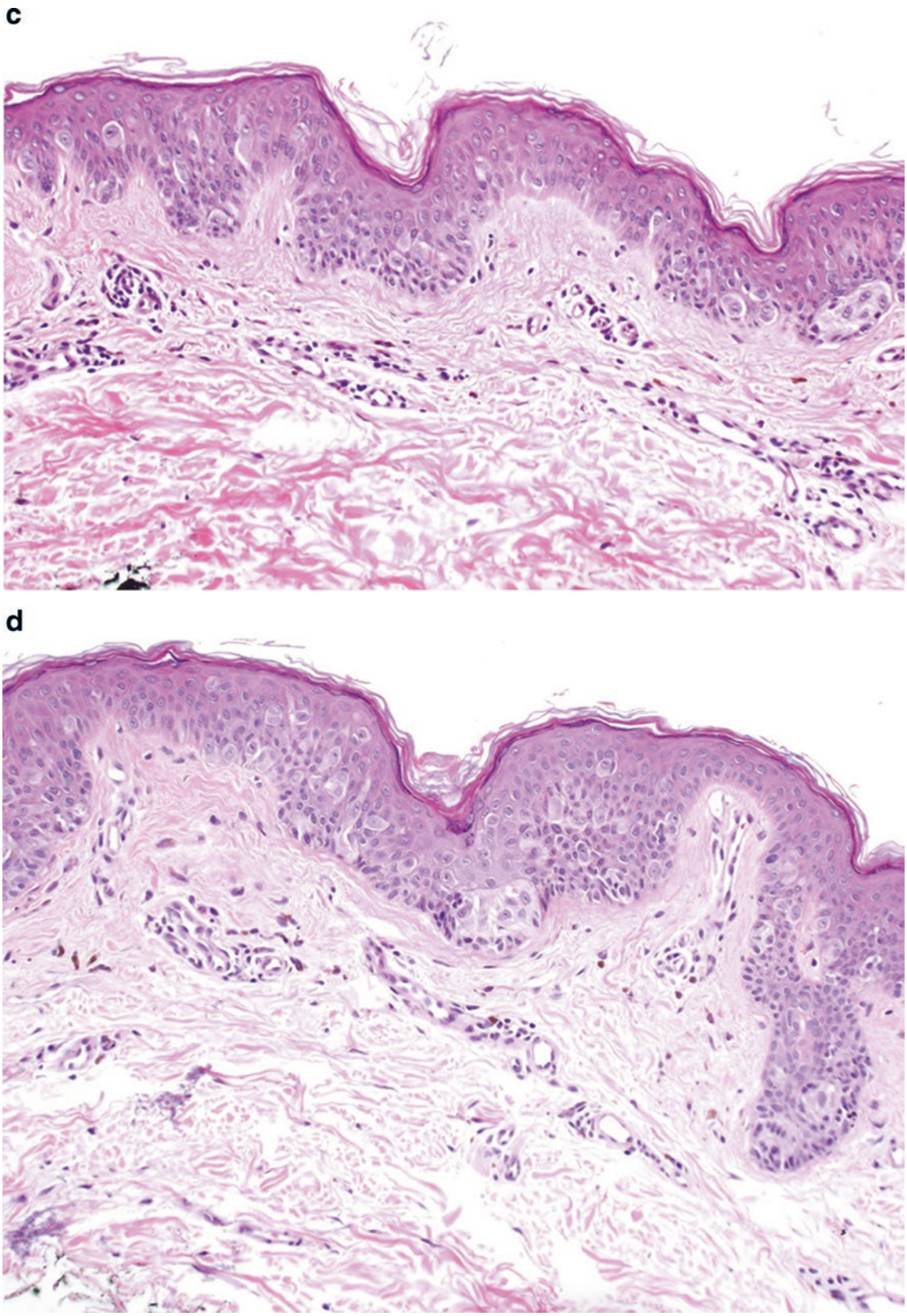


Fig. 3.48 (continued) Elongation of rete ridges with focal pagetoid upward migration of large, epithelioid melanocytes (**c**). In this anatomic site, it is not unusual for junctional nevi to have epithelioid melanocytes with focal pagetoid upward migration (spitzoid features). Separate area with similar spitzoid cells (**d**)

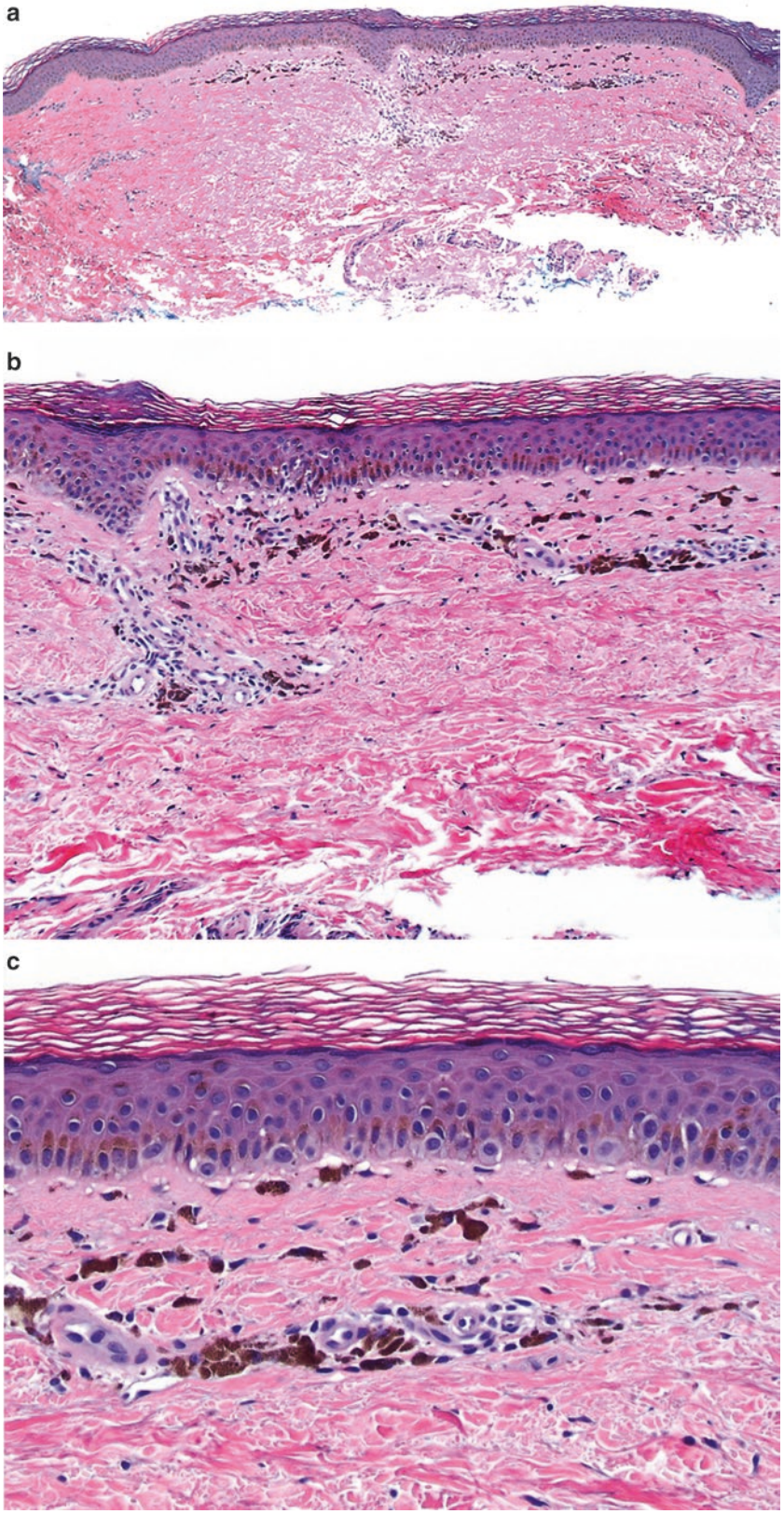


Fig. 3.49 Ankle nevus. A 44-year-old woman. On low power, the lesion shows a flat epidermis showing the presence of single melanocytes with an epithelioid configuration. Note also the presence of a dermal lymphoid infiltrate with melanophages (**a**). High-powered view of the flat epidermis with the single, large, intraepidermal melanocytes and the dermal infiltrate (**b**). Single cell melanocytes with absence of pagetoid upward migration (**c**).

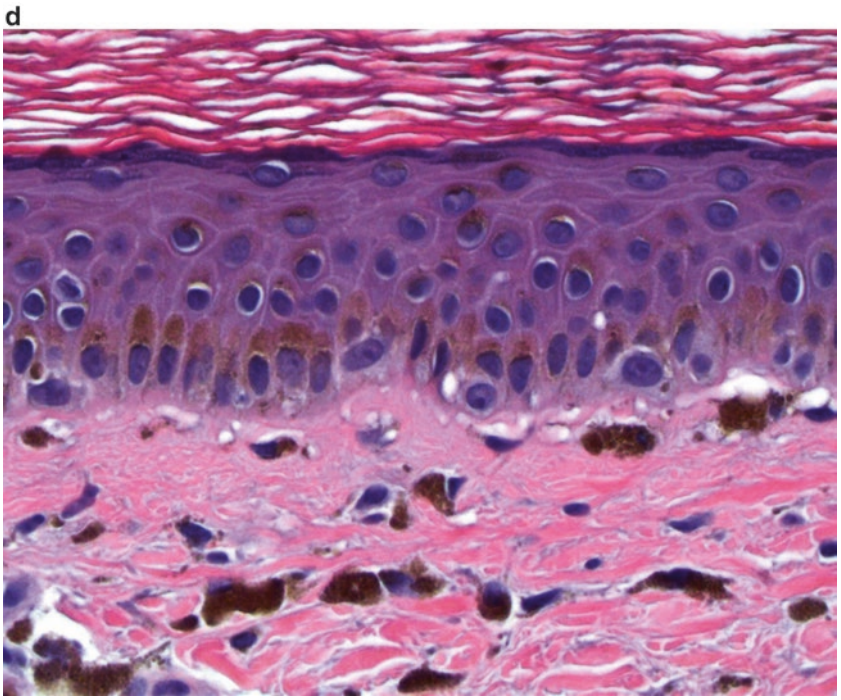


Fig. 3.48 (continued) Moderate degree of cytologic atypia of the intraepidermal melanocytes (**d**)

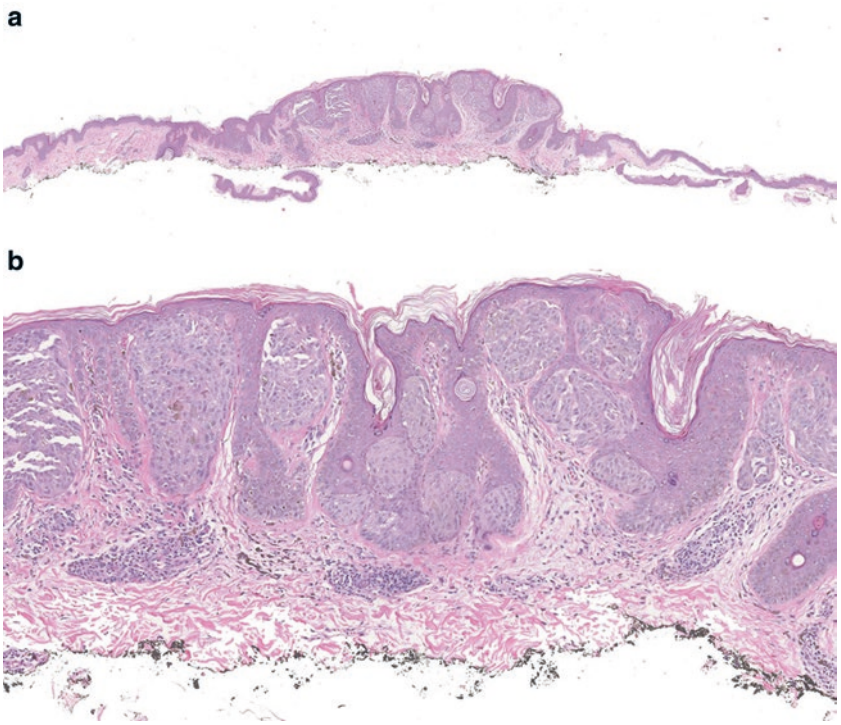


Fig. 3.50 Axillary nevus. The lesion is symmetric and composed of large confluent nests at the junction with elongated rete ridges (**a**). The shape and size of nests is variable and located not only at the tips but in the lateral sides of the rete ridges (**b**).

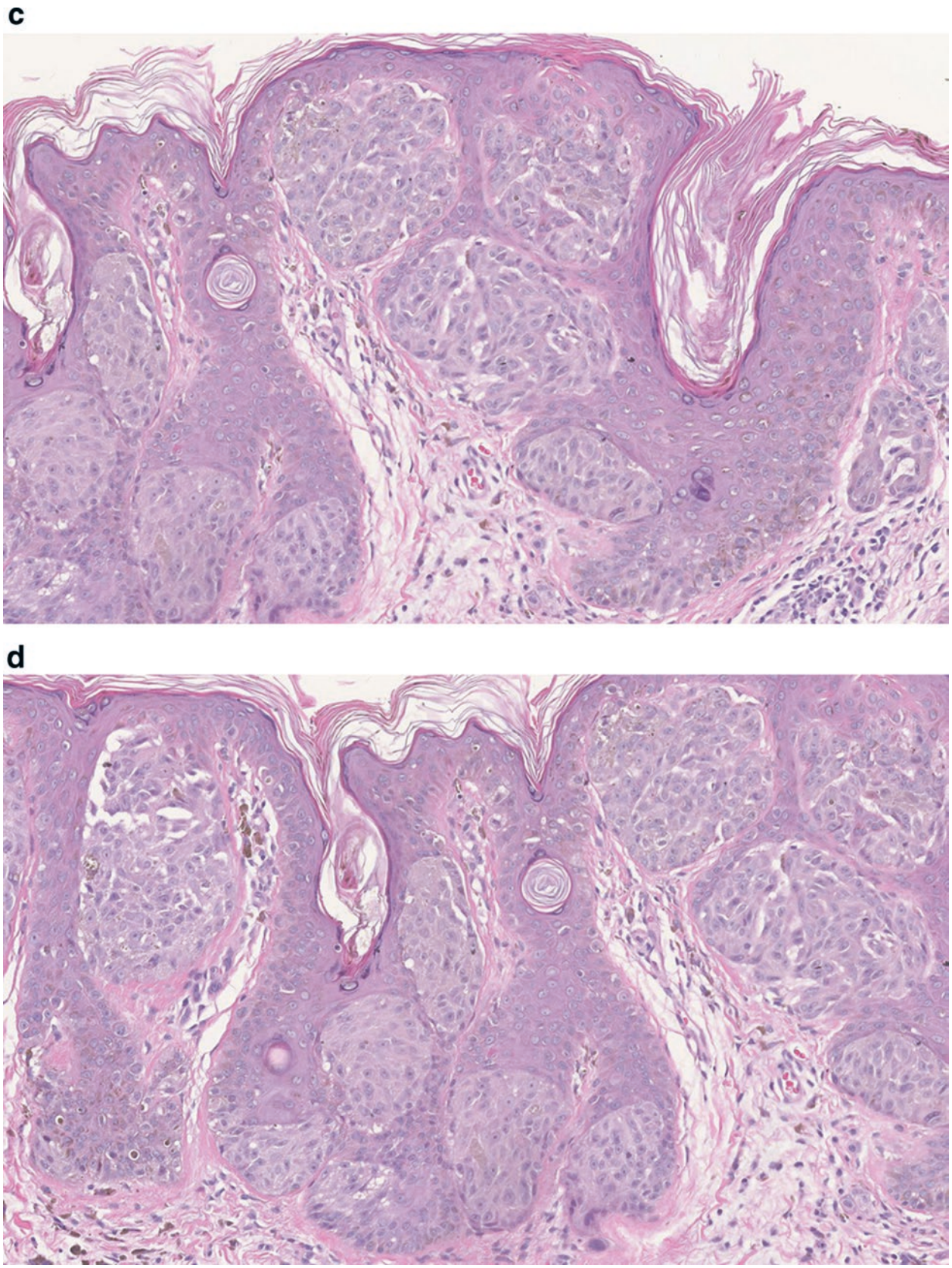


Fig. 3.50 (continued) There is variable cytologic atypia (large, epithelioid melanocytes) but pagetoid upward migration is not evident (**c**). Higher magnification showing moderate cytologic atypia of melanocytes that is primarily nested without pagetoid upward migration (**d**)

Acral Melanocytic Nevi

Acral melanocytic nevi represent a frequent diagnostic challenge because in some occasions it may show histologic features that overlap with melanoma, such as asymmetry, poor circumscription, and scatter of melanocytes at all levels of the epidermis [61, 114–118]. Acral melanocytic nevi encompass lesions on the palms and soles, nail matrix/bed, knees, and elbows. Acral skin is characterized by the presence of skin markings (dermatoglyphics) which are formed by bundles of parallel ridges and furrows forming loops, whorls, and arches. In acral nevi, the pigment tends to be mostly concentrated in furrows; thus, this particular distribution might also account for some peculiar architectural features seen in histologic sections of acral melanocytic nevi [119].

Clinically, acral melanocytic nevi usually present as small and dark brown macular or slightly elevated lesions with irregular margins [120, 121]. These nevi tend to be almost always less than 5 mm in size (unless when they are congenital in which they may be larger). The pigment in these nevi usually follows the furrows and this result in a clinical appearance of dark brown lines that spare the rete ridges. In acral melanoma, the furrows and the ridges are involved resulting in complete pigmentation of the lesion along with irregular borders and diffuse variegations of light and dark brown discoloration. After the initial growth, acral nevi usually follow stability; therefore any subsequent increase in size of an acral-pigmented lesion in an adult should be a red flag. The age is very important when inspecting these nevi, as acral melanoma is almost always seen in adults and the elderly and is extremely rare in very young patients. Regarding clinical changes in a preexisting area, in our experience, it is exceptional for acral melanoma to arise in association with a nevus.

Histologic Features

The majority of acral nevi will show benign, unequivocal features, i.e., either a junctional, compound, or intradermal nevi, as seen in other anatomic sites. As mentioned above, it is very important to bear in mind that when analyzing acral nevi, the age of the patient needs to be always taken in consideration. However, in some occasions acral melanocytic nevi may represent a diagnostic challenge for dermatopathologists as they can display morphological similarities to acral melanomas. This appears to be related, at least in part, due to the presence of dermatoglyphics in acral sites. If the histologic sections are cut perpendicular, rather than parallel to the dermatoglyphics, symmetry and circumscription are seen more frequently [122]. Histologically, the typical acral melanocytic nevi are characterized by a symmetrical, lentiginous, and nested melanocytic proliferation along the dermoepidermal junction. The nests are variable in size, well-formed, with round to oval melanocytes, and often vertically orientated. The nevus cells have an epithelioid appearance with inconspicuous vesicular nuclei. In cases wherein there is a dermal component, the melanocytes are round and normally mature toward the base, identical to what one would expect in ordinary melanocytic nevi. These melanocytes in dermis tend to frequently surround the upper portion of the eccrine ducts and vessels. The dermal component will show bland cytology and will lack fibrosis, lymphocytic infiltrates, or mitotic figures.

As stated above, acral melanocytic nevi may adopt atypical features. Such nevi have a propensity to show a lentiginous pattern of growth with single melanocytes along the basal layer of the epidermis. This lentiginous growth is observed even when the lesions have also junctional nests. Thus, the nests can be arranged irregularly in the dermoepidermal junction, and in between them, it is not unusual to find single-cell proliferation of melanocytes, usually located in and between the acrosyringia. This latter feature is a major clue in the diagnosis of acral nevi. In some cases, there is a striking, pigmented dendritic cell component within the lentiginous growth. The presence of well-defined, symmetrically distributed nests should be used as a criterion in favor of acral nevus and against the diagnosis of acral melanoma; however, many times, acral nevi do not form nests until they reach 2 or 3 mm in diameter, and the entire lesion will be composed of a proliferation of single melanocytes along the dermoepidermal junction. Also, acral congenital nevus tends to show a proliferation of individual melanocytes that is clearly greater than the nest proliferation. In some congenital lesions (>6 mm in size), they are composed of single-cell melanocytes in a lentiginous pattern, sometimes with a complete absence of nest formation [123]. In such cases, it is exceedingly difficult to evaluate the symmetry or circumscription in the absence of nesting. In our opinion, when dealing with small, flat, pigmented lesions on acral locations that are suspicious clinically for acral melanoma, clinicians should be advised that the best sampling method is an excisional biopsy with adequate margins.

Another interesting histologic feature that can be observed in acral nevi is the presence of scatter melanocytes throughout the entire thickness of the epidermis, giving the impression of pagetoid spreading. Sometimes these scatter melanocytes can be observed in the granular layer, and sometimes they can even be seen in the corneal layer and may extend laterally beyond the limits of the intradermal component. This phenomenon is most commonly seen in youngsters and has been referred as “MANIAC” nevus (melanocytic acral nevus with intraepidermal ascent of cells) [124]. These pagetoid melanocytes are more commonly

accentuated around the acrosyringium, while the melanocytic nests are situated at the tips of the rete ridges; in some instances, these melanocytes may extend into the stratum corneum forming parakeratotic tiers. It is important to mention that these pagetoid melanocytes demonstrate banal cytomorphology. In fact, these pagetoid cells tend to decrease in size as they migrate in the upper layers of the epidermis. It is important to remember that this pagetoid spread of melanocytes has been observed in up to 61 % of acral nevi from the palms and soles [61]. Spotty pigment in the stratum corneum is a common finding and may be physiologically related to the upwardly migrating cells as a transepidermal elimination pattern, given the constant trauma to these sites. This spotty pigmentation is frequently seen as the presence of pigmented columns and oval globules of melanin, in contrast with acral melanomas in which the pigmentation of the stratum corneum tends to be irregular and confluent. In some occasions, the lateral margins of the nevi are not sharply delineated, and this will depend on the plane of section, whether the lesion has been cut perpendicular or parallel to the dermatoglyphic markings.

Cytologically, the cells in acral nevi (especially in the intraepidermal and dermal nested component) have an epithelioid morphology with round or oval nuclei with conspicuous nucleoli and variable hyperchromasia. Some cells may show an open chromatin pattern while other may appear hyperchromatic. The cytoplasm of these cells is lightly pigmented, and the nuclei are usually larger than the adjacent keratinocytes, thus giving the impression of cytologic atypia as one can observe in dysplastic nevi. However, these nevi lack other signs seen in dysplastic nevi such as inflammation, lamellar fibrosis in papillary dermis, and bridging of rete ridges.

The aforementioned atypical histologic features seen in some acral nevi should be evaluated carefully, and one should be cautious not to overdiagnose melanoma. There is scant evidence that acral lesions with one or more of the above atypical histologic features connote the same increased risk for a patient developing melanoma as true nevi with architectural disorder at other anatomic sites [111].

Differential Diagnosis

As stated above, the majority of acral nevi show typical features, thus they are unequivocally recognizable by most dermatopathologists. However, in some instances acral melanocytic nevi may show atypical or unusual features that pose diagnostic difficulties to even experienced pathologists, especially when dealing with small and superficial biopsies. In such cases, acral melanoma enters in the differential diagnosis as both conditions may show pagetoid upward migration, lentiginous features, and poor circumscription [125].

Acral melanoma is commonly seen in older patients in which presents as a pigmented variegated lesion that measures >8 mm in size. The intraepidermal pagetoid melanocytes in acral melanoma have a haphazard, single-cell pattern of growth rather than having a nested pattern at the junction as seen in acral nevi (clue to the diagnosis of acral melanoma). The presence of a predominant single-cell pattern of growth with effacement of the epidermis should favor a diagnosis of acral melanoma since in acral nevi there is a predominant nested junctional component that has a preserved and often hyperplastic epidermis. The melanocytes in acral melanoma are cytologically atypical as they tend to show marked hyperchromasia with high nuclear to cytoplasmic ratio. The presence of irregular pigmented dendritic cells is easily identified in acral melanoma and in some cases they can reach the corneal layer. Acral melanoma tends to show a host response which translates into the presence of a patchy lymphohistiocytic infiltrate in dermis along with areas of regression. The dermal component of acral melanoma shows atypical features, such as the presence of mitotic figures, spindle/desmoplastic cell component, and neurotropism. A very important point that needs to be stressed is the age of the patient. Acral melanocytic lesions in youngsters (<32 years of age) with atypical features will most likely represent acral melanocytic nevi; however, acral melanocytic lesions in older and elderly patients with atypical features will most likely represent acral melanoma.

Table 3.5 Acral melanocytic nevi vs. acral melanoma

• Age of the patient: acral melanoma is almost always seen in adult and elderly patients. In our experience, acral melanoma in young patients is an exceedingly rare event
• Pagetoid spread and lentiginous growth is seen in acral nevi of young patients. Acral melanoma shows pagetoid spread at all levels of epidermis with confluent growth
• Size: acral nevi are <5 mm in size, unless is a congenital acral nevus which are larger. Acral melanomas are always >8 mm in size
• Patchy and irregular dermal lymphohistiocytic infiltrate in dermis favors melanoma
• Pigment in stratum corneum: the presence of regular pigmented columns (vertically oriented) in sulci and the cristae profundae limitantes favor acral nevi (although not always present). Acral melanoma shows columns with dispersed pigment and located above the dermatoglyphics

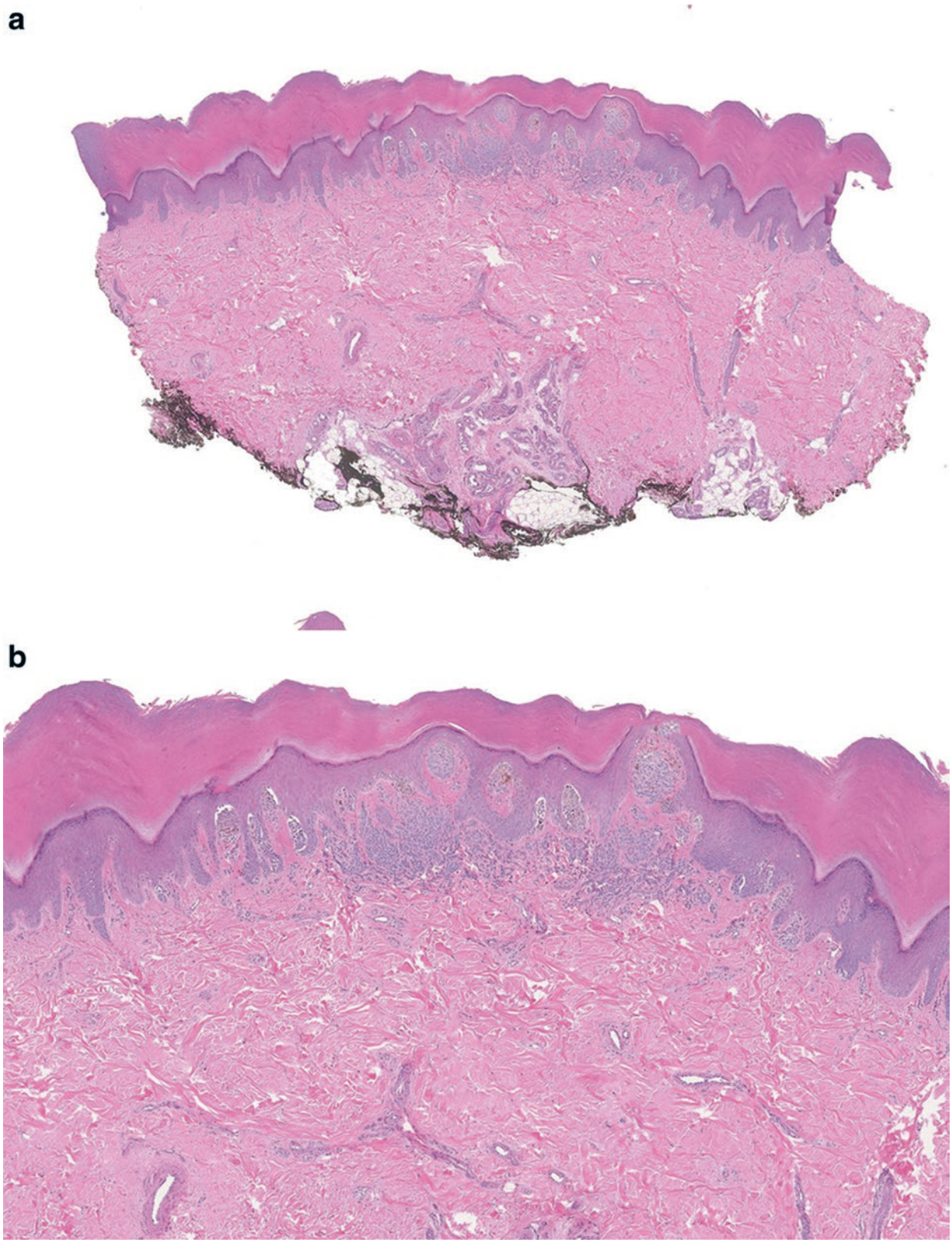


Fig. 3.51 Acral nevus. Note the small size and circumscription of the lesion (**a**). The lesion is symmetric and composed of well-defined nests along the dermoepidermal junction (**b**).

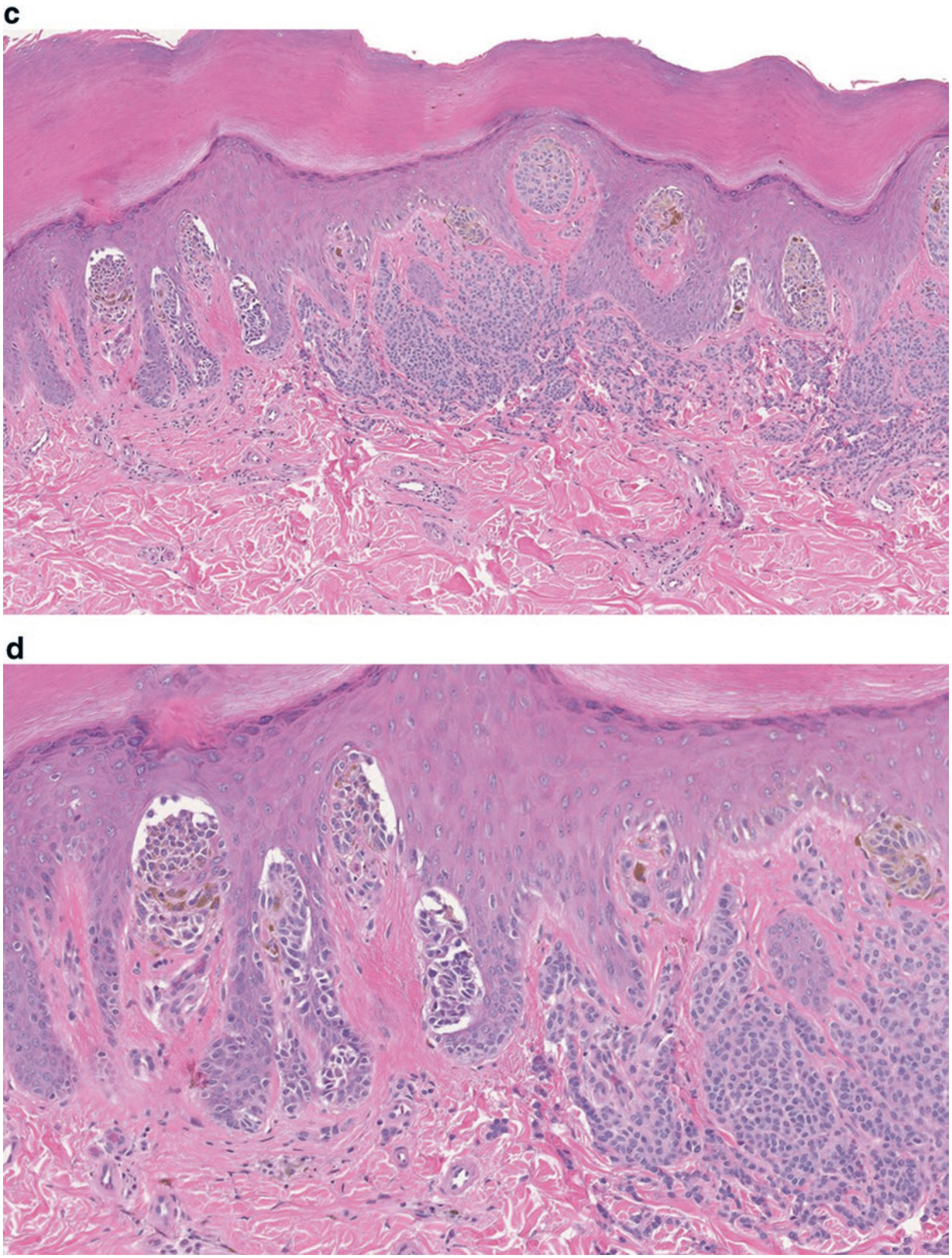


Fig. 3.51 (continued) The lesion shows normal maturation in dermis (**c**). Mixture of nests and single cells in the epidermis without pagetoid migration (**d**)

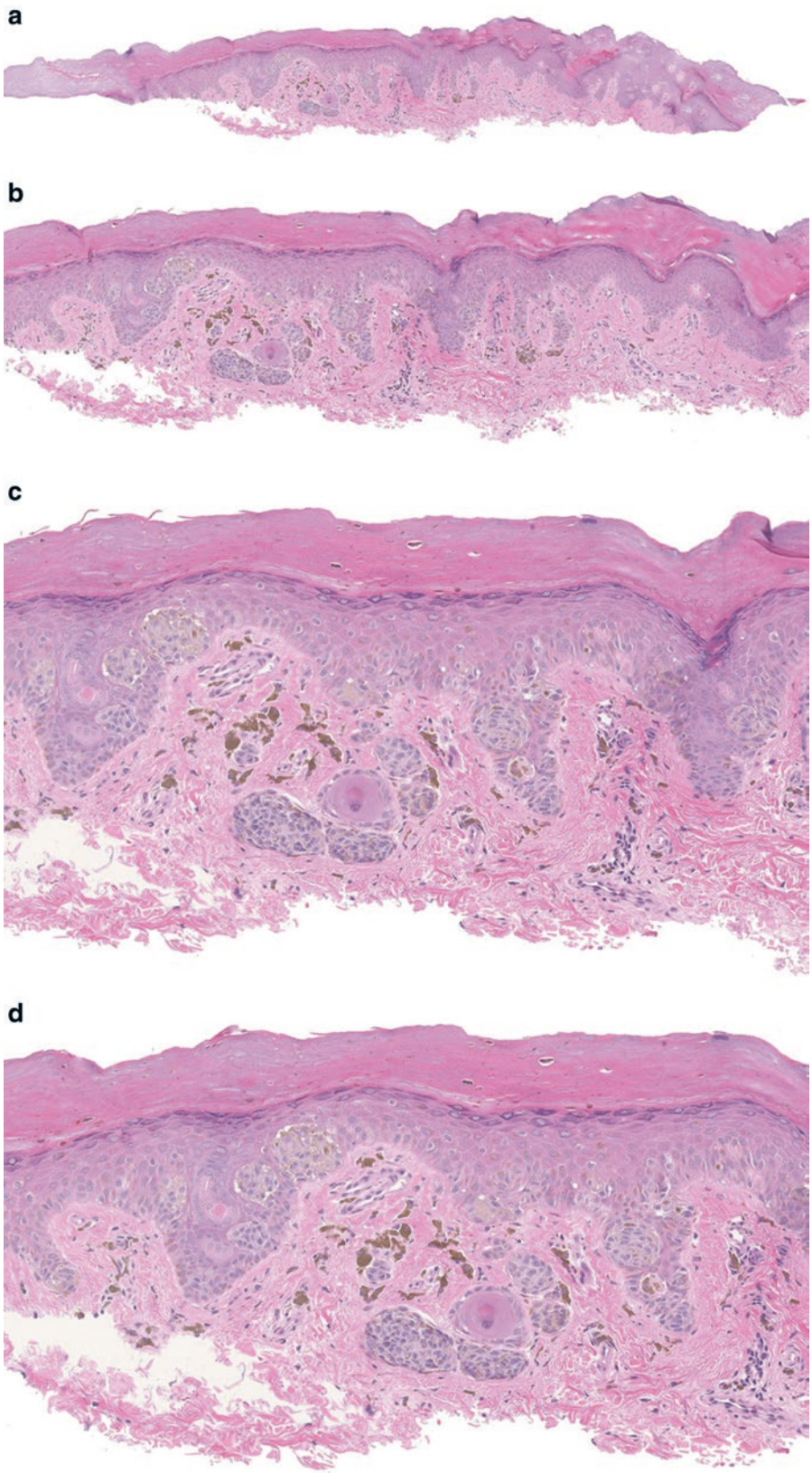


Fig. 3.52 Acral nevus. A 48-year-old male, foot. Note the small size and symmetry of the lesion (**a**). Some examples like this one can show a lentiginous and nested growth along the dermal-epidermal junction (**b**). The nests are variable in size, well formed, with round to oval melanocytes (**c**). There may be focal pagetoid upward migration but it should be located in the center of the lesion (in rare occasions acral nevi show pagetoid upward migration at the periphery of the lesion) (**d**)

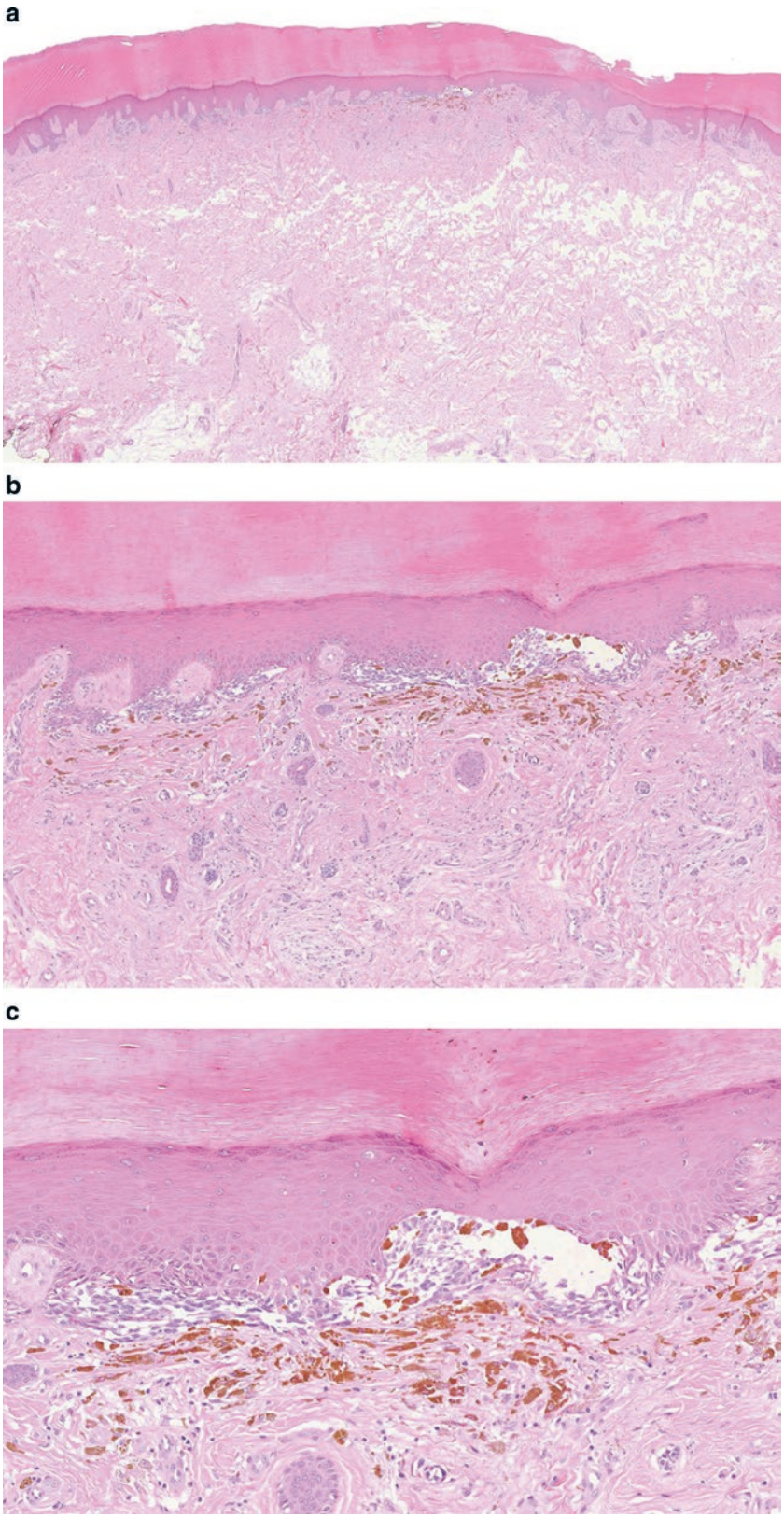


Fig. 3.53 Acral nevus. This example shows a lentiginous pattern of growth with single melanocytes along the basal layer of the epidermis (**a**). Nests located at the dermal epidermal junction, focally dishesive, but showing minimal pagetoid upward migration (**b**). Note that there is just a column of melanin in the stratum corneum instead of the irregular "peppering" of melanin common in acral melanomas (**c**)

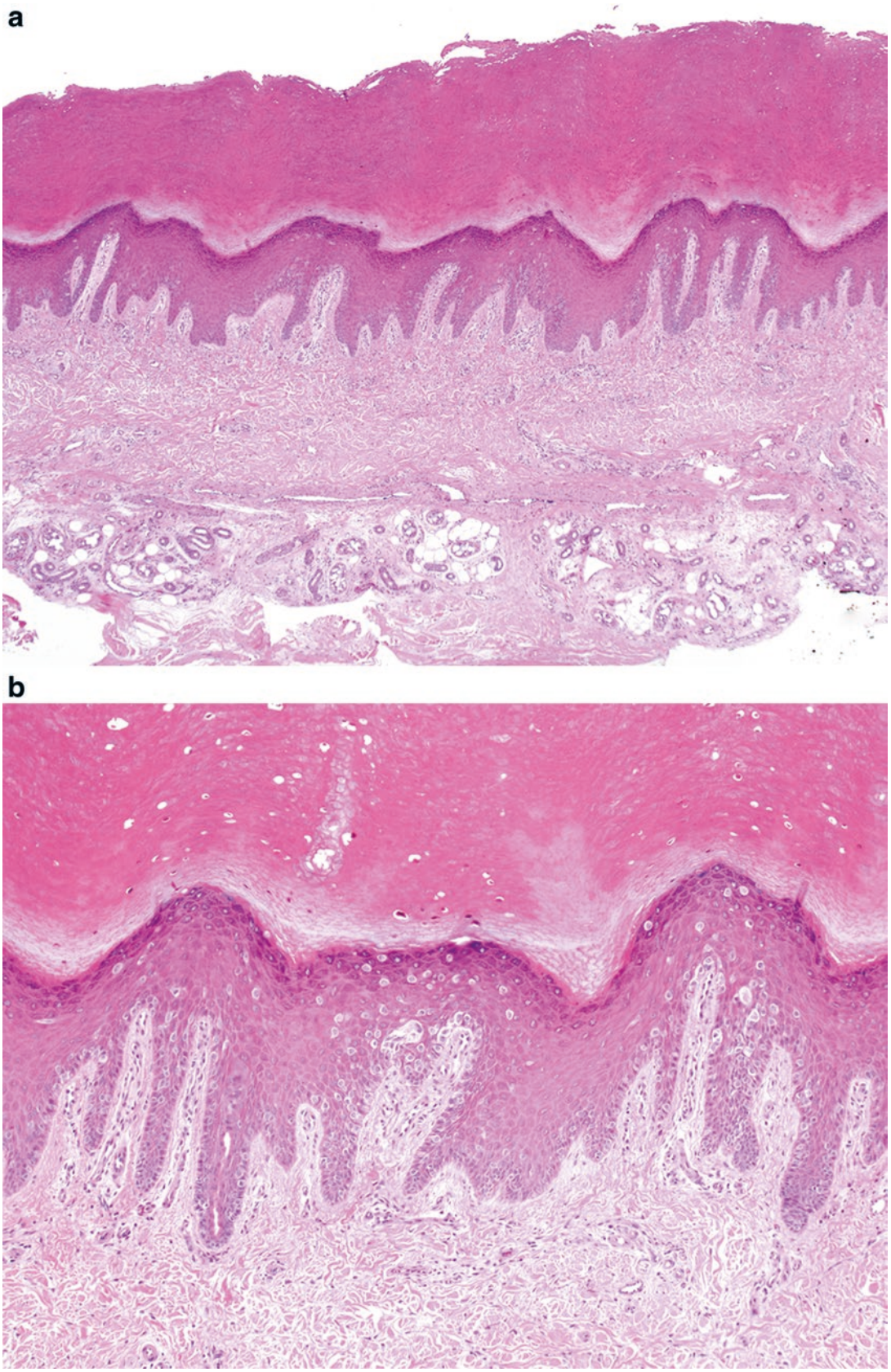


Fig. 3.54 "MANIAC" nevus. A 26-year-old male, sole, clinically 6 mm in size. The lesion is subtle and composed of scatter melanocytes throughout the entire thickness of the epidermis (**a**). The pagetoid melanocytes extending focally into the stratum corneum forming parakeratotic tiers (**b**).

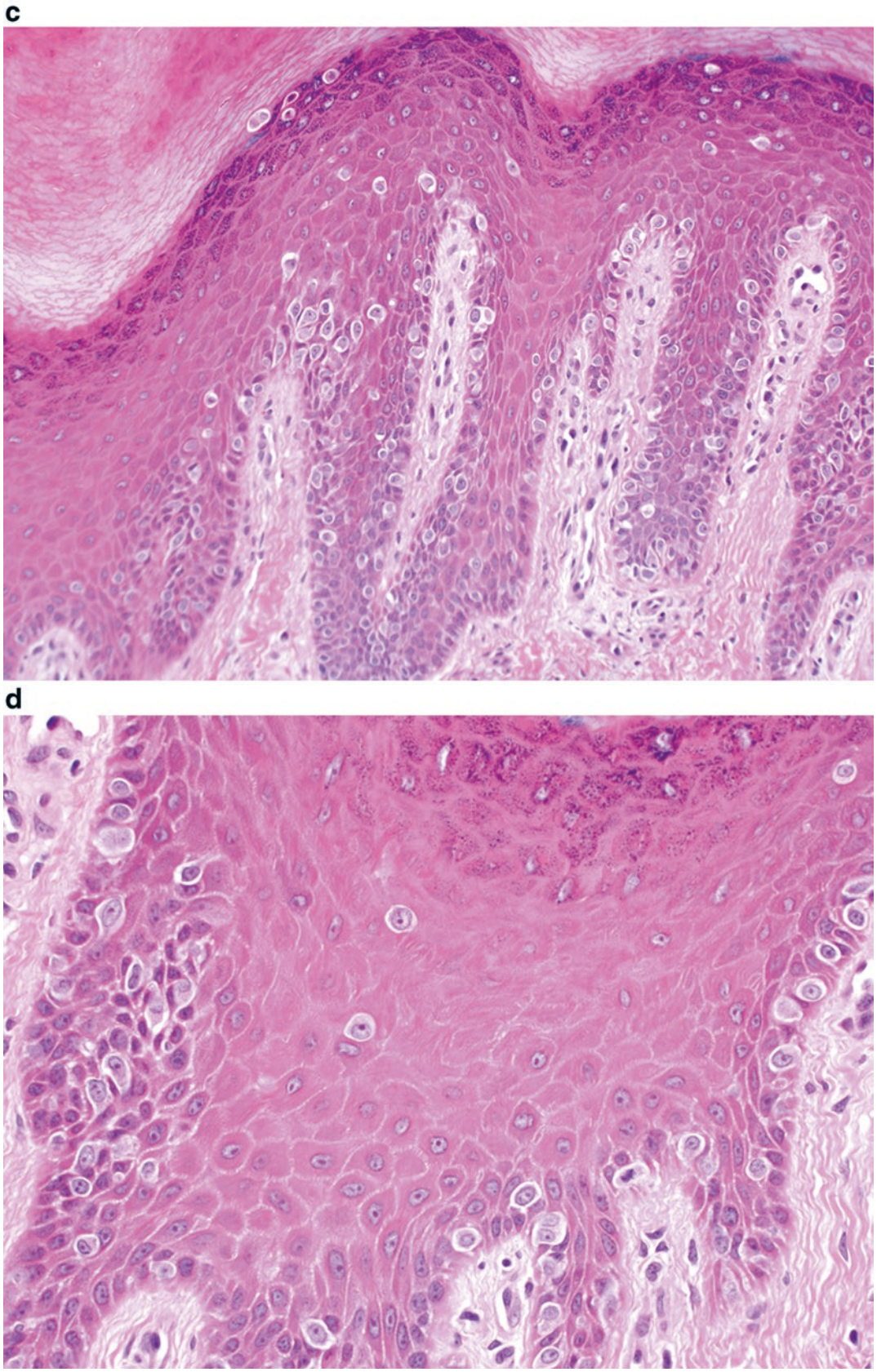


Fig. 3.54 (continued) Note the uniformity of size and shape of the intraepidermal melanocytes (**c**). An important clue is the decrease in the size of melanocytes toward the upper layers of the epidermis (**d**)

Genital Nevi

Melanocytic lesions of the genital area may present great difficulty in histologic interpretation. They are most often seen in female patients, usually young women but they are sometimes seen in children. They arise mainly in the vulva although they can also occur less frequently in the perineum, mons pubis, and male genitalia [126–128]. Most pigmented lesions on genital skin show no peculiar histopathology and will show identical features to conventional acquired nevi; however, a few of them will show atypical features that can simulate melanoma, especially in young women [129, 130]. Obviously, overdiagnosing melanoma in the vulvar region can potentially lead to unnecessary disfiguring surgeries.

Clinically, nevi of the genital areas have a banal appearance and are typically symmetrical papular lesions, most often smaller than a centimeter in diameter, usually uniformly pigmented with discrete well-circumscribed borders (even nevi that have atypical histology). The vulva, including labia majora, labia minora, and clitoris, is most frequently affected, followed by the mons pubis and perineum [54, 130–132]. Presentation in childhood is common, and more than 50 % of patients are younger than 20 years [129]. Hormonal changes can cause nevi on the genitalia to increase in size and to darken. Most of these atypical pigmented lesions are biopsied or removed from young women during routine gynecologic examinations and are unaware of their presence. These nevi are most often seen in young women, but similar lesions also occur on the male genitalia (less frequently involved).

Histologic Features

Only the histologic features of genital nevi with atypical features will be discussed in this section. In our opinion, the features of these nevi are characteristic and reproducible in most cases. Most of these nevi are compound, polypoid, and with well-demarcated and symmetric contours, with architectural features similar to those of a dysplastic nevus or a nevus with congenital pattern. In some instances, these nevi may be purely junctional. On low magnification, the lesion may appear nodular in configuration and may be of concern because of the increased cellularity and the variable but striking pigmentation. The junctional component is florid and composed of large nests with variable size and shape without clear relationship with the rete ridges (cellular dyshesion within the nests is commonly seen). The nests are distributed haphazardly along the epidermal rete (originating from the sides as well as the tips of rete), often oriented parallel to the surface. There may be confluence of nests along with prominent retraction artifact. These nests can form thick ribbons at the base of the epidermis and can be so prominent and confluent that obscure the dermal-epidermal junction. Single melanocytes and nests of nevus cells may occasionally be seen within the epithelia of skin adnexa. Lentiginous growth and pagetoid spread into the granular cell layer are typically only a focal finding confined to the center of the lesion; thus there should be a predominance of a nested pattern. The atypical melanocytes are predominantly epithelioid, containing abundant pale cytoplasm with dust fine pigmented granules and vesicular nuclei with variably prominent nucleoli; however, in some occasions they are spindled shaped. The intradermal component of the nevus is often prominent. In some cases, the atypical features noted in the junctional component are frequently present in the superficial aspect of the dermal component. However, the melanocytes in the deep dermis are uniform and small and demonstrate maturation with descent into the deeper dermal layers. Importantly, these melanocytes in deep dermis are cytologically different from the junctional melanocytes which are a diagnostic clue to the diagnosis. Mitotic figures are rare in these nevi, and when present they are located in the upper part of the lesion. Deep dermal or atypical mitotic figures are not a feature. An important histologic finding is the presence of concentric and lamellar fibroplasia or diffuse fibrosis of the superficial dermis as well as coarse melanin pigmentation of the junctional and superficial dermal melanocytes, in addition to the presence of melanophages.

Differential Diagnosis

The most important differential diagnosis of atypical genital nevi is with dysplastic nevus and vulvar melanoma. While dysplastic nevi are rare in the genital area, they have been very well documented in the literature [127, 128]. Histologically dysplastic nevi have a more pronounced lentiginous component and a well-formed shouldering phenomenon overlying the dermal component. Melanocytic atypia is random, rather than uniform, and melanocytes have intracytoplasmic melanin pigment that is fine and evenly distributed, compared with the coarse and prominent pigmentation seen in atypical genital nevi.

The most important differential diagnosis of atypical genital nevi is with melanoma. In our opinion, the age of the patient should always be considered, as genital melanomas are much more common in older patients as opposed to atypical genital nevi which are more common in young individuals. There are some histologic features that can be seen in atypical genital nevi that may overlap with melanoma such as the large size of the lesion, the variable pigment on low magnification, the presence of a prominent junctional component with large and confluent nests, pagetoid spread, and extension of melanocytes along the adnexal structures. In addition, cytologic atypia and the presence dermal mitotic

activity might create diagnostic confusion. Atypical genital nevi tend to be symmetric and well defined as opposed to melanomas that tend to show a more asymmetric growth with poorly delineated borders. The presence of dermal maturation should clinch the diagnosis of genital nevi, as melanomas almost always lack maturation; instead, melanoma shows highly atypical cells with pleomorphic and hyperchromatic nuclei of variable size and shape and with deep dermal mitotic figures. The invasive component in melanoma lacks maturation with depth and may be characterized by expansile growth. Genital nevi may show pagetoid extension; however, it is centrally located and not as prominent as one would expect in melanomas. The "shouldering" effect in genital nevi is minimal and in the dermis there is no evidence of an expansile, pushing, or infiltrating lesion. Melanomas show a broad radial growth phase and more prominent and irregular pagetoid spread.

Molecular studies could be helpful in certain settings. Studies have found that BRAF V600E mutations are common in both genital nevi without atypia and in atypical genital nevi [133, 134]. A recent study showed that a higher incidence of BRAF V600E was present in 75 % of genital nevi with atypia and 100 % of genital nevi without atypia [134]. Some other studies have shown variable results on vulvar melanomas with BRAF mutation, suggesting that BRAF mutations are uncommon in melanomas of the female genital tract [134, 135]. These studies support that the prevalence of BRAF V600E in atypical genital nevi suggests that UV exposure is not essential for generating the BRAF V600E mutation. The results of the literature review show that gynecologic melanomas most frequently feature KIT mutations (26 %), less frequently NRAS (15 %), and uncommonly BRAF mutations [134, 136–138].

Table 3.6 Atypical genital melanocytic nevi vs. melanoma

• Age: atypical genital nevi are seen in younger patients, while melanomas are almost always seen in elderly patients
• Symmetry: atypical genital nevi have a preserved symmetry while melanomas asymmetric silhouette
• Shouldering: atypical genital nevi have a small shouldering effect, while melanomas have a broad radial growth
• Pagetoid spread: atypical genital nevi have a focal and centrally located pagetoid cells, while melanomas have extensive and prominent pagetoid upward migration

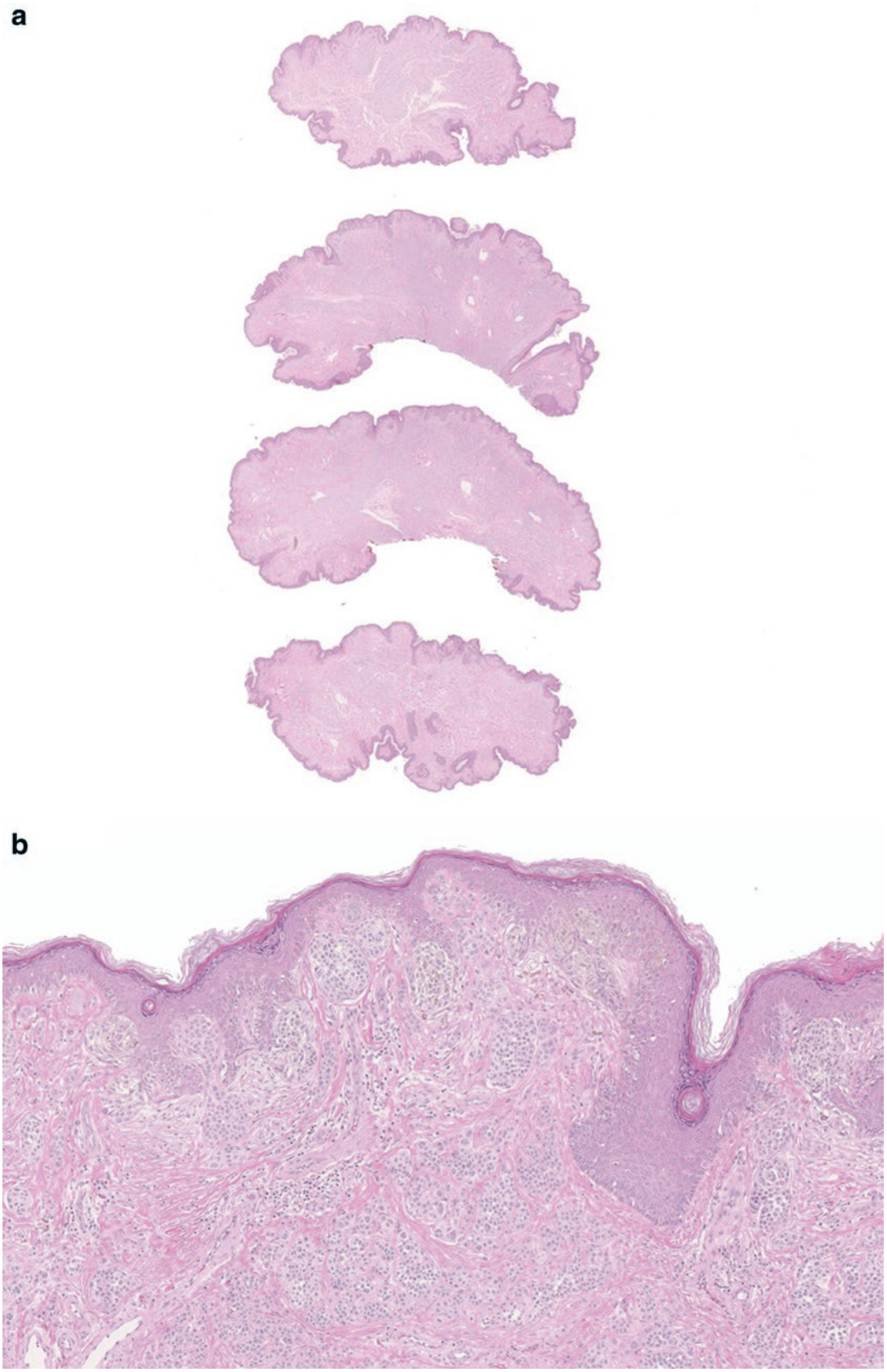


Fig. 3.55 Genital nevus. A 30-year-old female, mons pubis. Note the polypoid architecture of the lesion (**a**). Note the florid junctional component in the center of the lesion, composed of nests with variable size and shape (**b**).

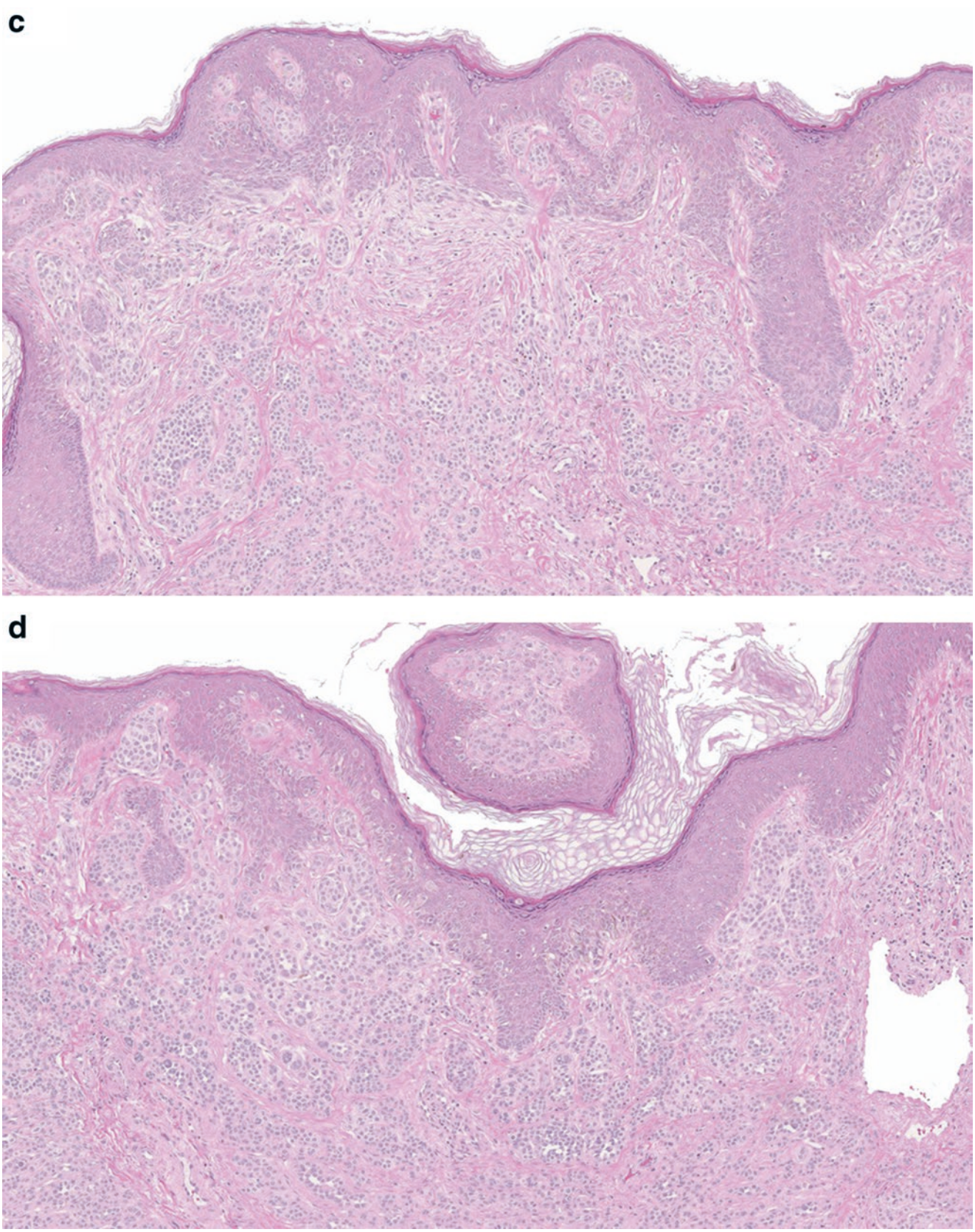


Fig. 3.55 (continued) The nests are arranged haphazardly and often oriented parallel to the surface (**c**). Note the presence of single melanocytes and nests located in the center of the lesion. Mitotic figures are not identified in the dermis (**d**)

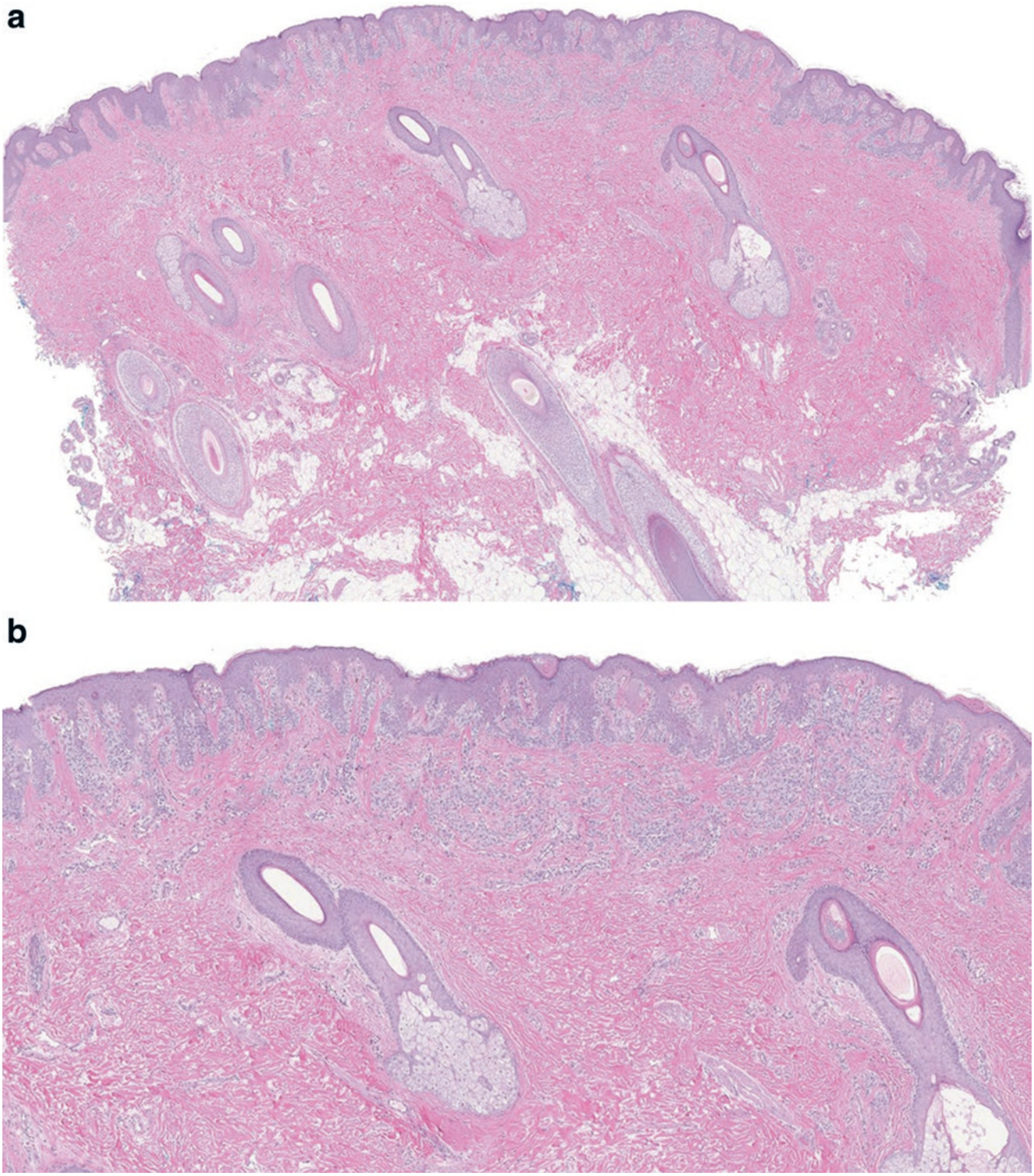


Fig. 3.56 Genital nevus. Symmetrical lesion composed of nests with focal confluent growth that obscure the dermal-epidermal (**a**). Lentiginous growth with focal confluence of nests mimicking dysplastic nevus (**b**).

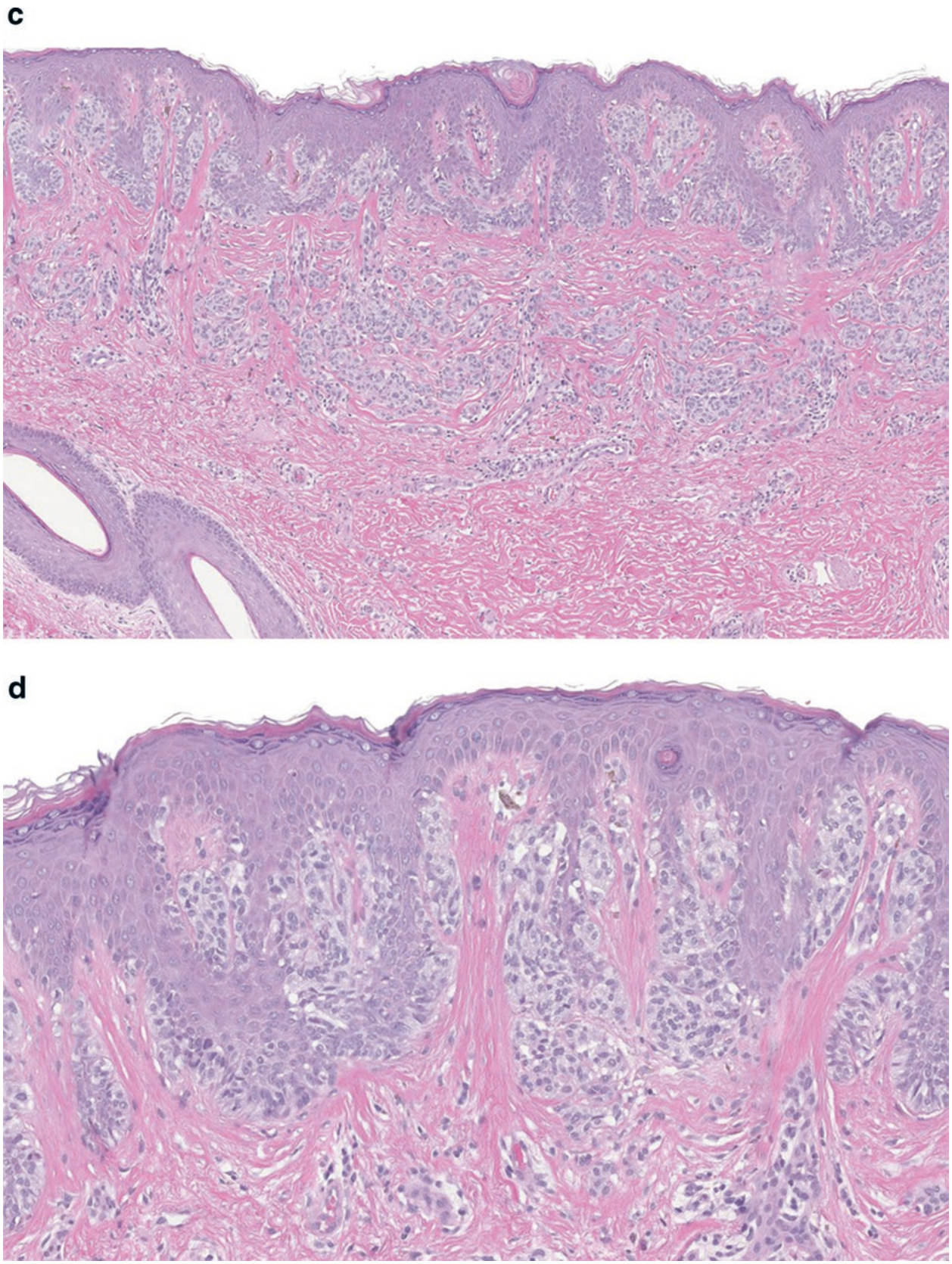


Fig. 3.56 (continued) The atypical junctional melanocytes are epithelioid with pale cytoplasm and vesicular nuclei (**c**). Despite the focal degree of cytologic atypia there is no pagetoid upward migration and the lesion lacks mitotic figures in the dermis (**d**)

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Spitz Nevi

4

Spitz Nevus

Spitz nevi are benign, acquired, melanocytic proliferations, which generally develop in children and adolescents, although it also occurs in adults. Spitz nevus was first described by Sophie Spitz in 1948, and it was regarded as a juvenile melanoma, with the implication of being a malignant lesion but noting that these lesions were less aggressive than the majority of adult melanomas [1]. Subsequently, to distinguish them from obviously malignant lesions, these lesions were designated as Spitz nevi. Since their description, the histologic diagnosis has been a cause for controversy because in some instances, it is not possible to render an unequivocal diagnosis of Spitz nevus versus melanoma and thus predict the biologic behavior. However, since currently there are no definitive immunohistochemical or molecular ancillary techniques that can reliably distinguish between the benign and malignant lesions, in our opinion the histopathologic evaluation continues to be the gold standard.

While there are certain histologic features that have been systematically evaluated to distinguish between Spitz nevi and spitzoid melanomas, experts' opinions vary in defining the relative importance of the criteria to diagnose these tumors. As a matter of fact, we and others consider these entities to belong to a histologic spectrum suggesting stratifying those entities that fall in the gray zone between the two extremes [2]. This lack of objective criteria for predicting the biologic behavior of such lesions may result in a misdiagnosis with the potentially aggressive nature of an untreated spitzoid melanoma.

Clinical Features

Spitz nevi more commonly arise during childhood; however, they can occur at any age [3], thus underscoring the concept that Spitz nevus is "not" only a pediatric melanocytic nevus. However, it is still true that at a young age, most of the lesions are benign, while in older adults, the proportion of malignant to benign is the opposite. Nonetheless, we believe that a diagnosis should not be changed because of the patient's age. In rare occasions, Spitz nevi may be congenital or arise associated with a conventional nevus [4–7]. Spitz nevi are slightly more common in females, but cosmetic considerations may skew the proportion of patients seeking medical attention [3]. Spitz nevi can occur at any anatomic site; however, the most common locations include the face and head in children and the lower extremities and the trunk in young adults [8]. There are rare cases arising in mucous membranes such as the conjunctiva or oral mucosa.

Clinically, Spitz nevus most commonly presents as a single, dome-shaped, nonpigmented papule or nodule, usually less than 0.8 cm in diameter; however, exceptionally it has been reported to reach several centimeters in size. In rare occasions, Spitz nevi can present as multiple lesions, which can show an agminated (grouped together) or disseminated pattern [9–12], and thus may closely mimic the development of multiple satellites/in-transit metastases of melanoma [13]. Multiple Spitz nevi have been reported after sunburn, radiotherapy, or a variety of traumas including biopsy or excision of a previously solitary Spitz nevus [13–16]. In younger patients, Spitz nevi are pink or red in color, due to the limited melanin content and the presence of numerous capillaries; in fact, some cases are clinically diagnosed as hemangioma or pyogenic granuloma. Pigmentation in Spitz nevi is more commonly seen during adolescence and adulthood; this pigmentation is uniform and evenly distributed, with colors ranging from tan to brown to black [17]. Some Spitz nevi are tender or pruritic; ulceration and bleeding can be seen after trauma. Even though the gross features of Spitz nevi are not distinctive to allow a precise clinical diagnosis, it should be emphasized that Spitz nevi are usually not diagnosed clinically as melanoma.

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Histologic Features

Like other melanocytic nevi, Spitz nevi are thought to evolve through all three distinct junctional, compound, or intradermal phases [3]. Spitz nevi exhibit a wide spectrum of histologic appearances, following a purported pattern of maturation, starting with intraepidermal lesions trough a junctional, compound, and intradermal stages. In all these stages, Spitz nevi display the same cytomorphology that is typified by the presence of round/polygonal (epithelioid), oval/spindled, or both cells. Some cases have a predominance of spindled or epithelioid cells, and other cases have an admixture of both. Based on our observations, the predominant cell type is spindle regardless of the age of the patient. The presence of a junctional component is significantly associated to spindle cell type, pagetoid extension, and epidermal hyperplasia. In contrast, the presence of a predominantly intradermal component is more commonly associated with epithelioid cell type, hyalinization, and desmoplasia.

Intraepidermal/Junctional Spitz Nevus

As mentioned above, Spitz nevus presents as an intraepidermal lesion, in which the dominant pattern of growth is single cells with pagetoid distribution [18]. Junctional Spitz nevi show symmetrical and sharply demarcated intraepidermal nests that are composed of spindle cells (in some cases, they may show an admixture of epithelioid cells) located mostly at the base of epidermis. The epidermis shows mild hyperplasia with elongated rete ridges, which characteristically stops at the edge of the lesion (clue to the diagnosis). The lateral borders of intraepidermal Spitz nevi often consist of a nest rather than of a gradual diminution of solitary melanocytes (demarcation). These epithelioid and/or spindle melanocytes are large in size with abundant eosinophilic cytoplasm, well-defined cytoplasmic borders, and vesicular nuclei with evenly distributed chromatin and prominent nucleoli. In some occasions, the cytoplasm might show light pigmentation. The intraepidermal nests tend to be vertically oriented and characteristically separated from the adjacent epidermis ("hanging bananas"), features also that helps in the diagnosis. The melanocytes are uniformly scattered throughout the lesion either singly or forming small nests within epidermis. In some cases, the melanocytes within the epidermis may show a lentiginous pattern of growth with focal pagetoid growth, in which the melanocytes are characteristically distributed along the sides of rete ridges, particularly near the center of the lesion and not at the periphery. In some cases, melanocytes display a dendritic morphology. Some examples of junctional Spitz nevi may show transepidermal elimination of nevus cell nests and can be associated with pagetoid upward spread of single melanocytes. This pagetoid upward spread of solitary melanocytes is generally focal and centrally located, and the number of ascending melanocytes is relatively small compared to the richly cellular junctional component. Pagetoid migration across the entire width of the lesion is not characteristic of Spitz nevi and its presence should raise the diagnosis of melanoma. These ascending melanocytes often diminish in size in Spitz nevi, whereas ascending melanoma cells often retain their original size and appearance [18].

An additional diagnostic clue of Spitz nevi is the presence of Kamino bodies, which are seen in most Spitz nevi. Kamino bodies are collections of amorphous, PAS-positive and diastase-resistant, eosinophilic globules and are found in about 60 % of Spitz nevi [19]. Although Kamino bodies resemble apoptotic cells, they are rather formed of basement membrane material, including collagens IV and VII, fibronectin, and laminin [20–22]. These bodies may be found at, or immediately subjacent to, the dermal-epidermal junction and sometimes within the nests; when they are numerous, they represent an important diagnostic clue in the diagnosis of Spitz nevi. Kamino bodies are more commonly seen in cases in which nests are well formed and the cellular density is high. Although more common in Spitz nevi, they can be seen in melanomas.

The differential diagnosis of junctional Spitz nevi, especially when dealing with a limited tissue sample, is with melanoma in situ. The presence of a small-sized lesion, lateral circumscription, and symmetry and the uniform distribution of melanocytes within epidermis are very important clues to the correct diagnosis. Also, the presence of "spitzoid" cell type (large, uniform nuclei with prominent, central nucleoli), the predominance of small nests surrounded by shrinkage artifacts, the relative paucity of pagetoid cells, and the absence of changes in cell type or lesional architecture from area to area are characteristic features of junctional Spitz nevi. In some cases, the distinction between junctional Spitz nevus and in situ melanoma may be impossible; however, this possible uncertainty has less of a clinical implication since both may be handled by simple, complete excision (a different situation from that of the distinction between a compound Spitz nevus and invasive melanoma). Particularly for this reason, complete excision is recommended when dealing with spitzoid lesions.

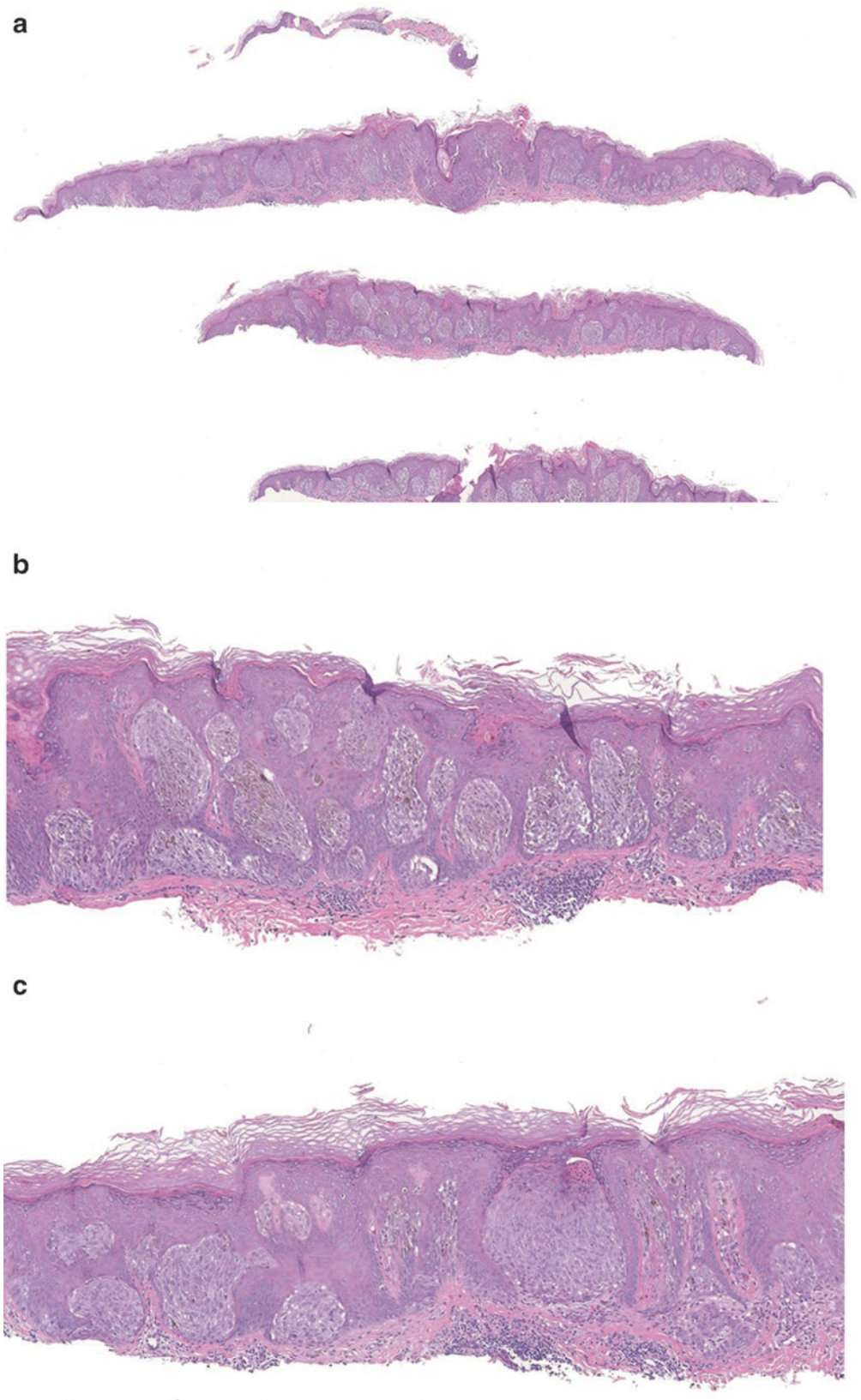

Fig. 4.1 Junctional Spitz nevus. This example is located in the arm of a 21-year-old female. Note the symmetry and predominant nested component of the lesion (**a**). The lesion shows marked hyperplastic epidermal changes which are characteristic for Spitz nevi (**b**). Note the scattered Kamino bodies throughout the epidermis (**c**).

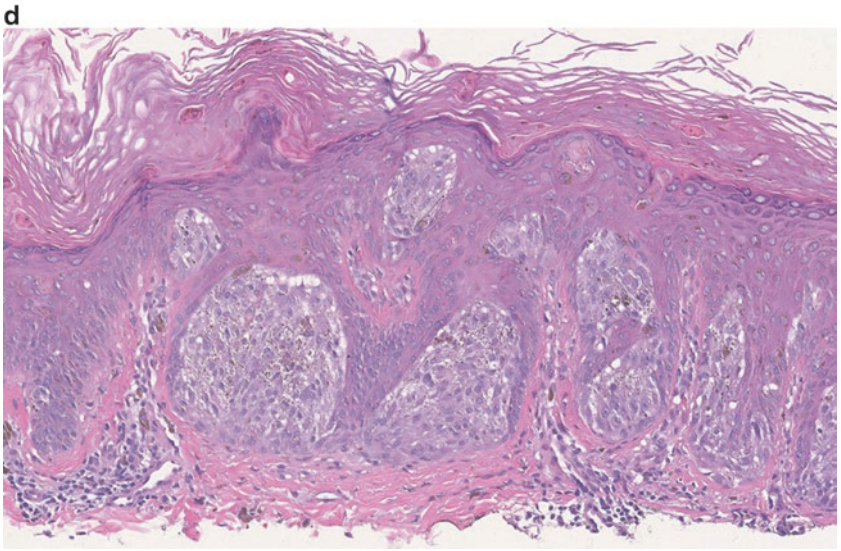

Fig. 4.1 (continued) These lesions tend to show increased number of dendritic cells and melanophages (**d**)

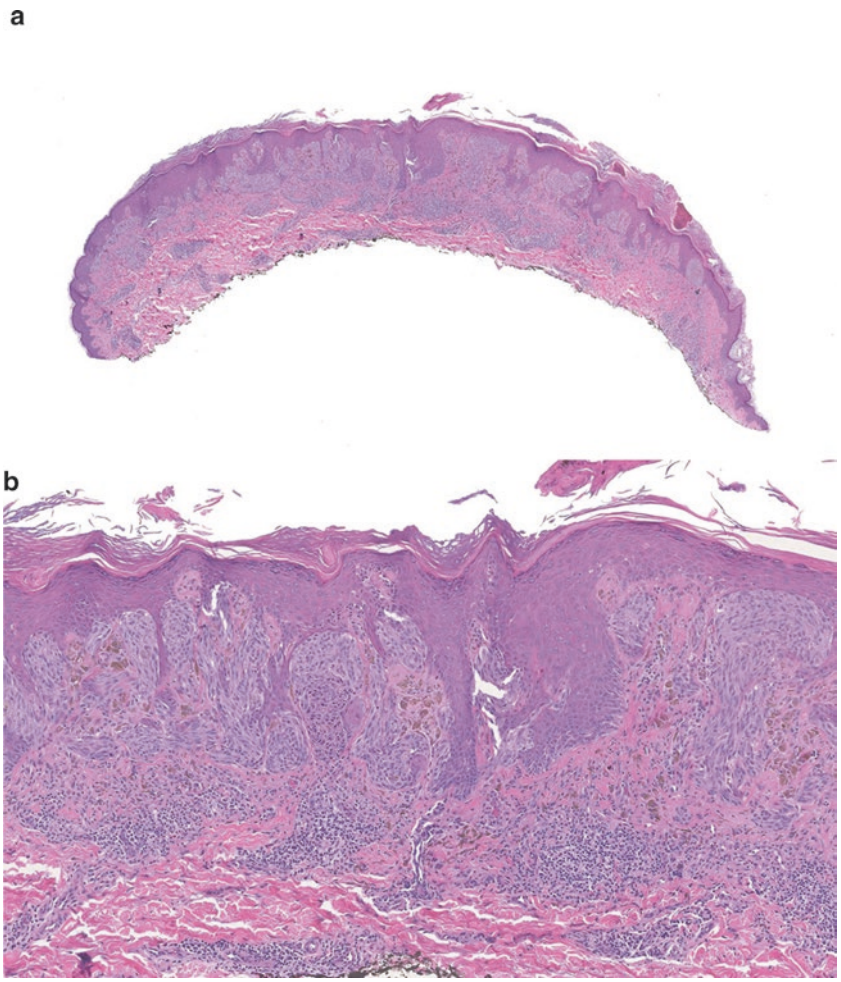

Fig. 4.2 Spitz nevus. This is another example showing a mixture of epithelioid and spindle melanocytes. Note the large size of nests, focal clefting around the nests, and scattered Kamino bodies (**a**). The nests are composed of a monomorphic population of spindle melanocytes (**b**).

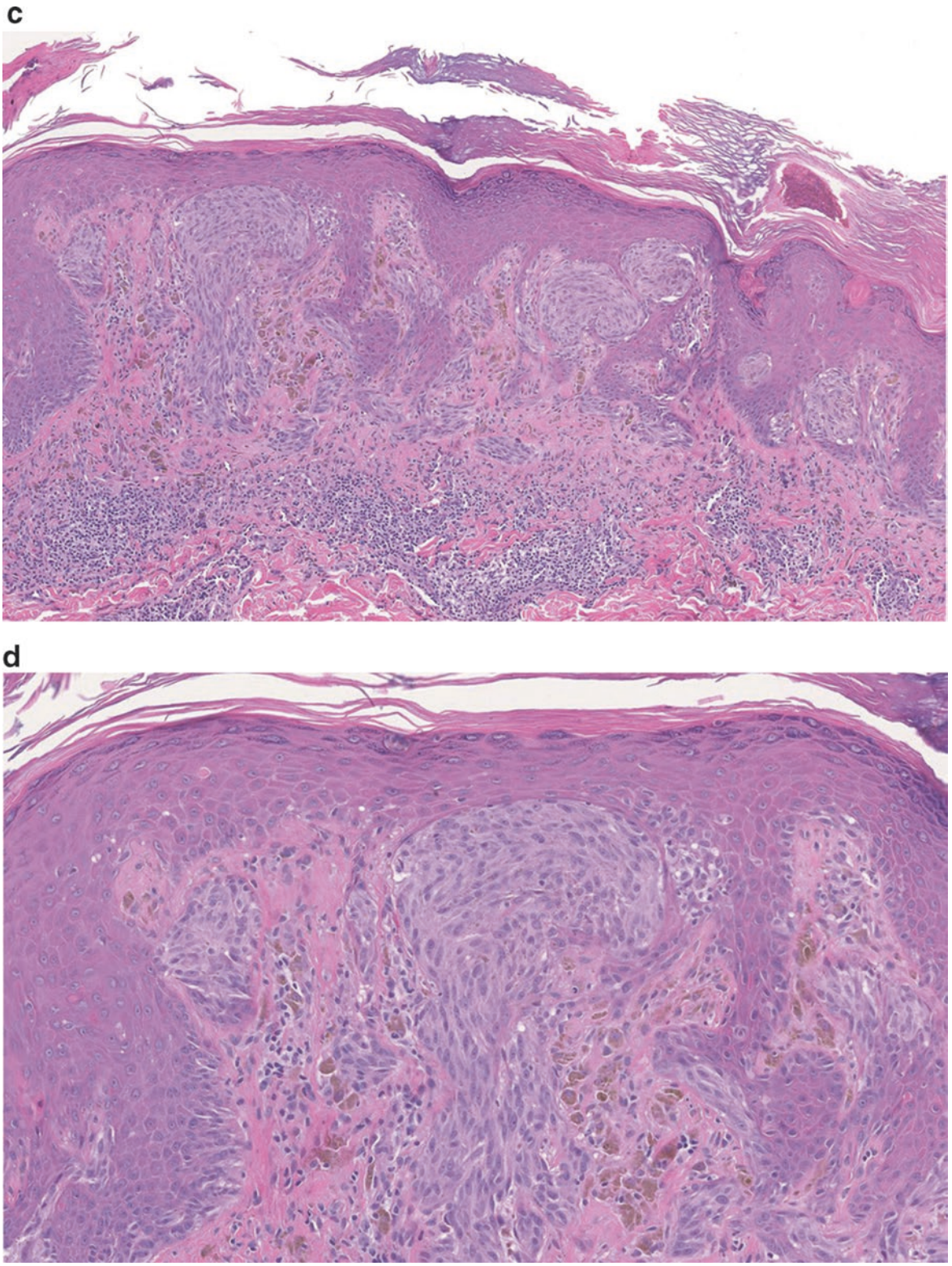

Fig. 4.2 (continued) There is a prominent host response in dermis (**c**). Monomorphic melanocytes with oval nuclei and small nucleoli (**d**)

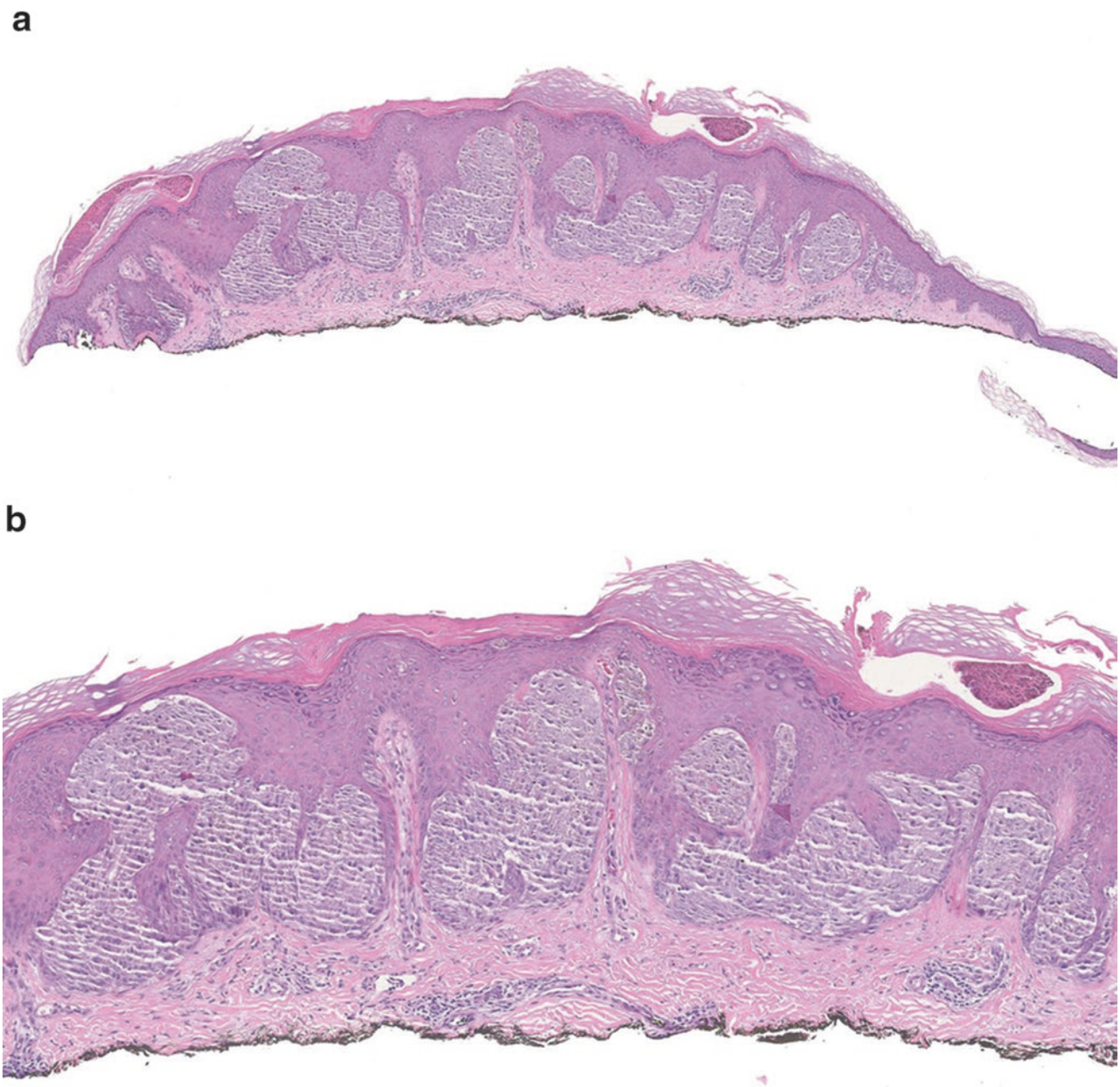

Fig. 4.3 Junctional Spitz nevus. This case is predominantly composed of large monomorphic nests. The melanocytes have an ample dusky cytoplasm but note the symmetry of the lesion which is key to diagnose this lesion accurately (**a**). Note the epidermal hyperplasia along with the lack of cytologic atypia. Focal transepidermal elimination of nests is noted (**b**).

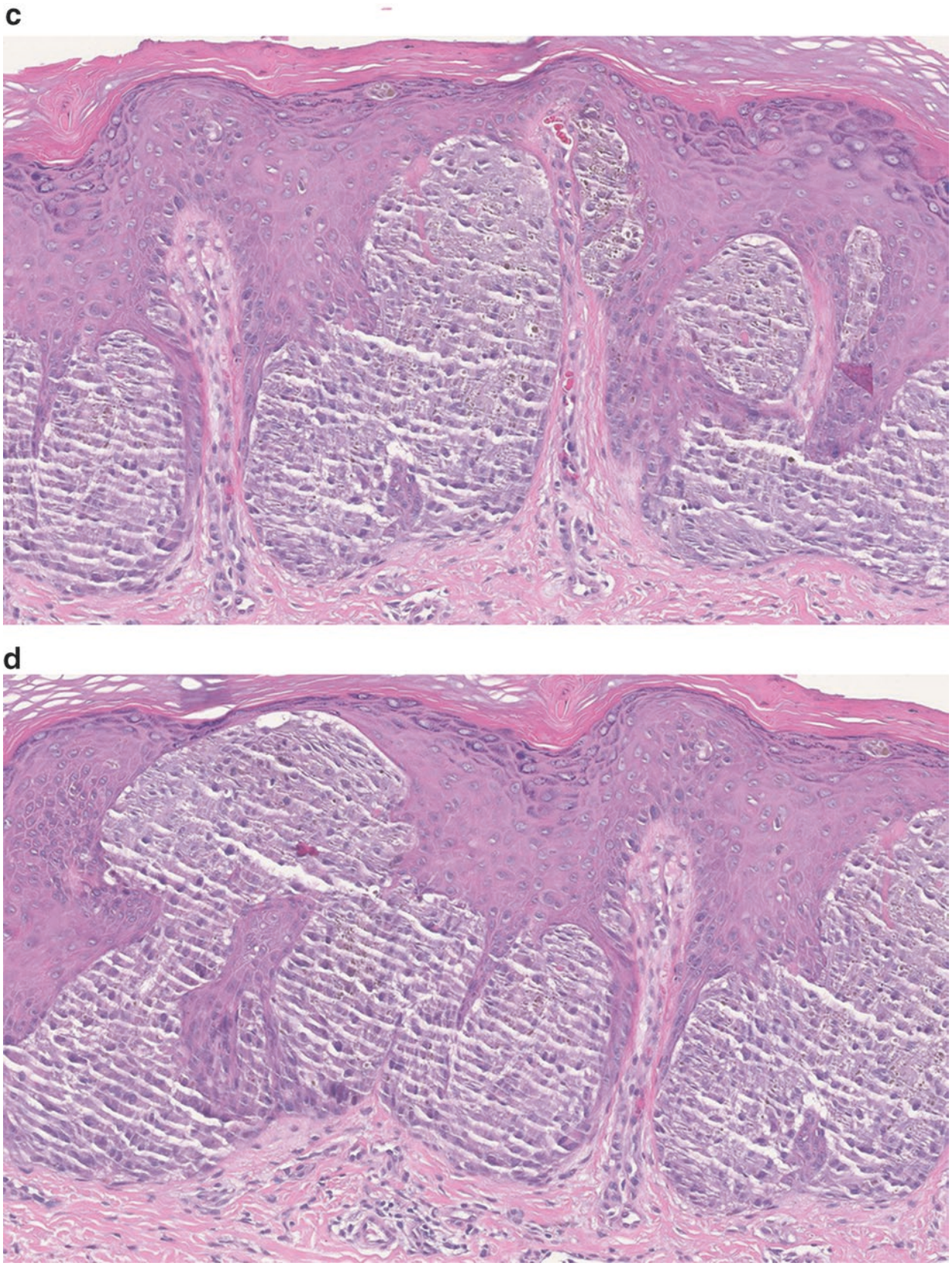

Fig. 4.3 (continued) In this example, the melanocytes have ample dusky cytoplasm and small nuclei (**c**). High power showing the well-delineated nests (**d**)

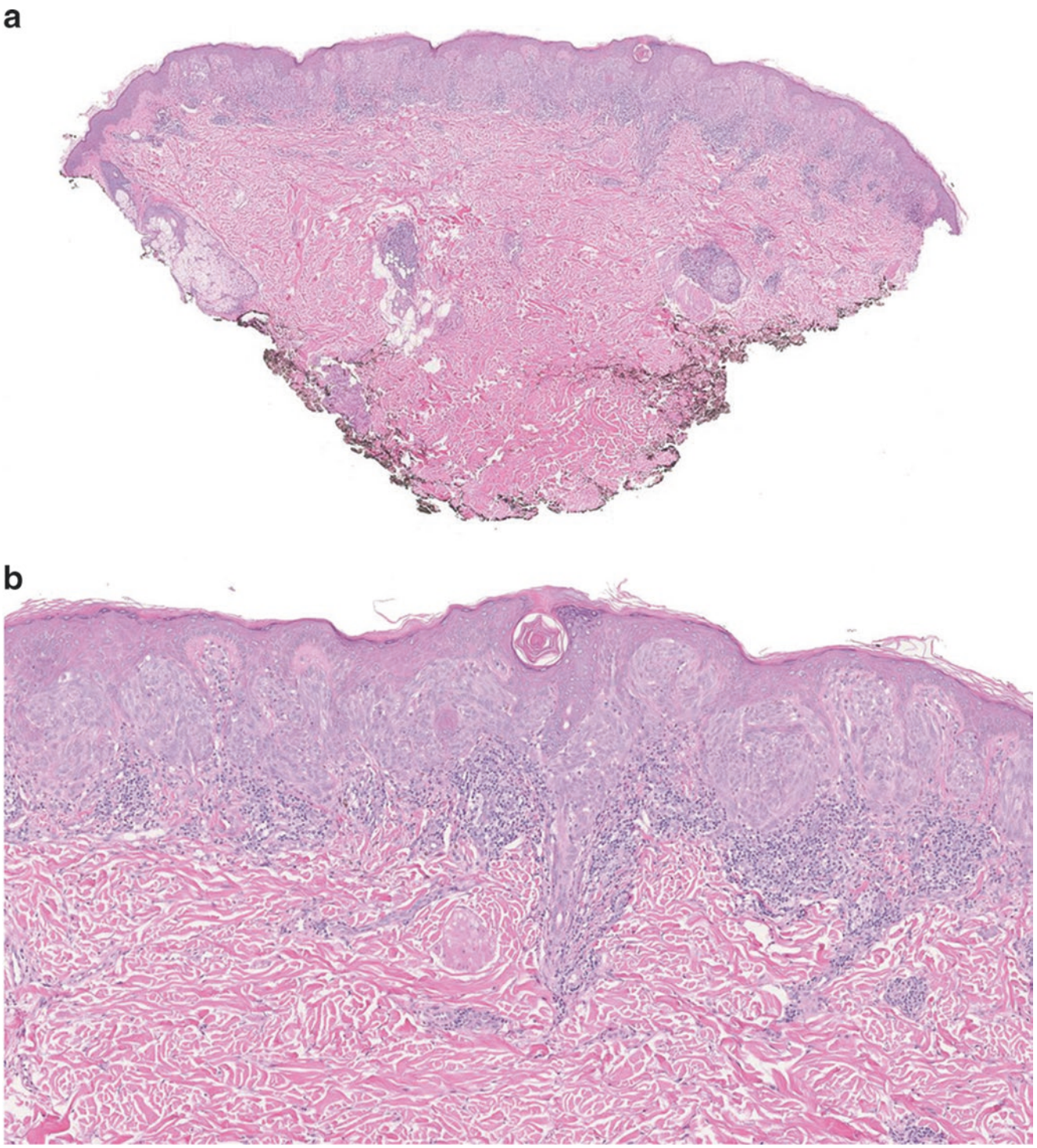

Fig. 4.4 Junctional Spitz nevus. This lesion is located in the back of a 19-year-old female (**a**). The lesion is hypercellular, symmetric, and with many dendritic cells. It is common to see host response in superficial dermis as noted in this example (**b**).

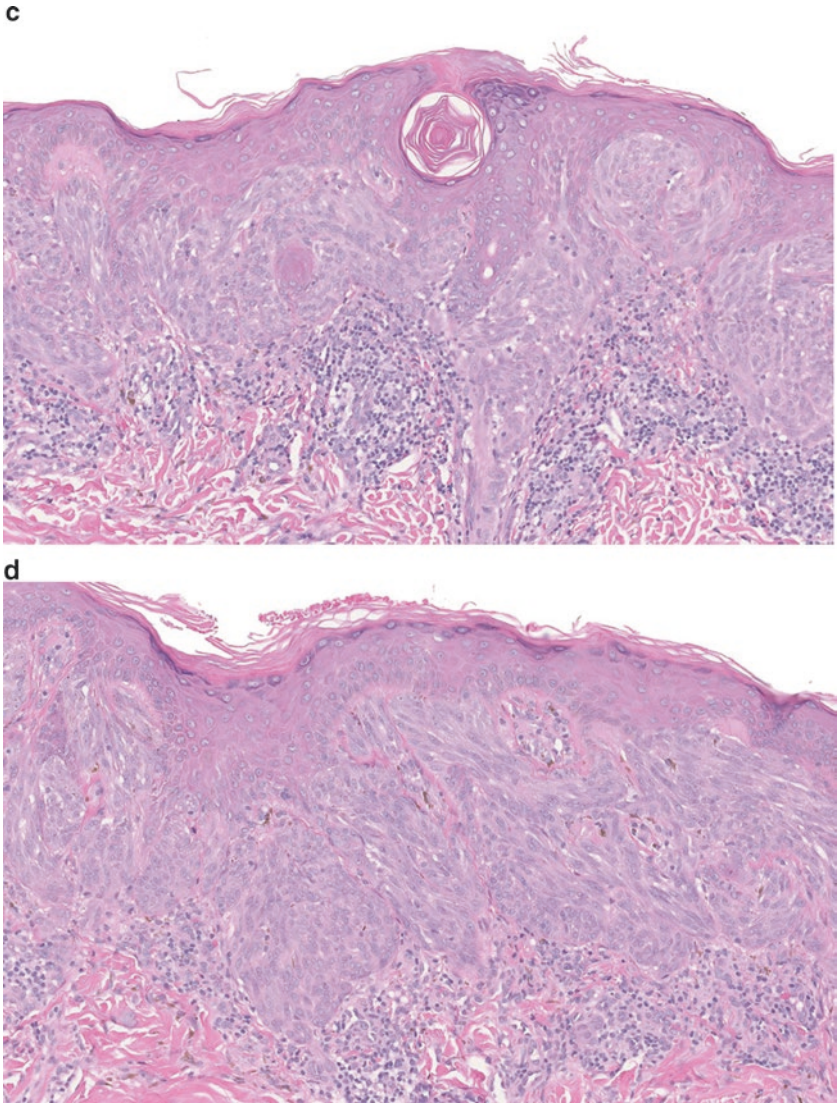

Fig. 4.4 (continued) Mixture of spindle and epithelioid melanocytes (**c**). Note the vertically oriented nests (*hanging bananas*) (**d**)

Compound Spitz Nevus

The vast majority of Spitz nevi are excised while in the compound stage when melanocytes are detected in the dermis. The majority of compound Spitz nevi are symmetric, well circumscribed with sharp lateral demarcation, and often wedge shaped; however, in some cases the architecture of Spitz nevi can exhibit a wide spectrum of appearances (such as a flat base or a dome, papillomatous or verrucous surface). In most cases, the epidermis exhibits distinctive epidermal changes including hyperplasia and elongated rete ridges including occasional frank pseudoepitheliomatous hyperplasia. It is not unusual to see expansion of the papillary dermis and vascular ectasia. In our experience, the presence of flattening of rete ridges (consumption of the epidermis) is considered a red flag, because it is much more commonly observed in spitzoid melanomas. The melanocytes within epidermis are arranged in nests that are relatively uniform in size and shape. The junctional nests are typically vertically oriented, and retraction artifact typically surrounds the junctional nests. Some of these nests show the "hanging-banana" pattern into papillary dermis, as the spindle cells run along the rete ridges perpendicular to the stratum corneum. As mentioned above, Kamino bodies can be seen in up to 60 % of Spitz nevi.

Pagetoid spread of melanocytes in the overlying epidermis can be seen either as single cells or forming small nests, although in most cases, it is limited to the central portion of the lesion and confined to the lower half of epidermis [23, 24];

however, in some rare occasions, they can even reach the stratum corneum. This phenomenon is more commonly seen in younger patients and suggests a diagnosis of melanoma in spitzoid lesions in adult. Since there is overlap in the amount of pagetoid migration in Spitz nevi and in melanoma, this is only one of many parameters that need to be assessed to make the diagnosis. In melanoma the pagetoid spread of melanocytes usually involves the entire epidermis (including the epidermis lateral to the dermal component). Also, it should be noted that pagetoid melanocytes can be seen not only in Spitz nevi but also acral nevi, congenital nevi, traumatized or recurrent nevi, etc. The presence of mitotic figures is uncommon in Spitz nevi and when encountered are more commonly observed in childhood cases and located in the junctional component and in mid- to upper dermis (very rarely grouped). Some authors suggest a cutoff number of up to two mitotic figures per lesion; however, we have rarely encountered lesions with more mitotic figures but located in the upper dermis, in some rapidly growing Spitz nevi as well as in recurrent or regressing lesions [25, 26]. The presence of atypical mitotic figures is exceedingly rare in these nevi and should definitely prompt for a search of other possible histologic features of melanoma.

As mentioned above, a very important histologic feature of Spitz nevi is their cytomorphology. Melanocytes are large, epithelioid, and spindle and have a variably enlarged vesicular nucleus, often with a central plump but regularly shaped monomorphous nucleolus (melanocytes). The color of the nucleoli may vary depending on stain of hematoxylin and eosin; in general most nucleoli will be blue/purple. The cytoplasm is generally ample and pale with a ground-glass appearance and distinct cell borders; the cells with the largest nucleus generally have the most abundant cytoplasm. Multinucleated epithelioid and giant melanocytes may be present and are numerous in some cases. Based on our experience, these multinucleated melanocytes are more commonly observed when the lesion is primarily composed of epithelioid melanocytes. Some lesions have large nuclei, but it is usually observed in the upper part of the lesion while the lower parts show cells with smaller nuclei (maturation). In some cases, there is shrinkage of melanocytes, resulting in irregular intercellular slit-like spaces, most prominent around the junctional nests. This is an important diagnostic clue, because melanomas tend to show much less cellular shrinkage. Melanin pigment is usually absent and if present the pigment is symmetrically distributed. The presence of melanin pigment is in fact a valuable diagnostic criterion for the distinction of Spitz nevi versus spitzoid melanoma, since the latter has irregularly distributed melanin and may be bottom heavy.

The dermal component of compound Spitz nevi varies as some cases are composed of just single cells in dermis, while some other lesions may extend deeply into the underlying subcutaneous fat. Melanocytes in dermis are mostly nested or arranged in fascicles. The dermal component of Spitz nevi shows gradual diminution of the cellularity, and nests decrease in size toward the base, which is associated with diminution in cell size and loss of proliferative activity (maturation). Lesions that show disproportionately large nests at the base should be carefully scrutinized. In general, the melanocytes in deep dermis infiltrate between collagen bundles; this is a very important diagnostic feature because spitzoid melanomas commonly show compact cell groups at the base, and these nests are horizontally arranged. Also, if melanocytes in Spitz nevus are large and pleomorphic at the base of the lesion, the degree of this enlargement and pleomorphism is similar throughout at any given level and is less pronounced than in the upper dermis. A superficial biopsy that does not contain the base of the lesion cannot be fully evaluated. For those lesions a possible diagnosis is that of spitzoid lesion and a complete excision is recommended. When the subcutaneous fat is involved, only the upper part is usually affected in the form of a nodule. If a spitzoid lesion involves the entire subcutaneous fat, this feature should be analyzed in conjunction with other histologic features as may represent a melanoma. Lymphocytic inflammatory infiltrate is often seen around perivascular spaces and at the base of deep compound lesions, but rarely intermixed with melanocytes. In thin or superficial compound Spitz nevi, the lymphocytic infiltrate can be distributed in a lichenoid fashion. The stroma of Spitz nevi in young patients has prominent edema and ectatic vessels in papillary dermis. In rare cases there may be lymphatic invasion or perineural invasion; however, its presence should prompt the pathologist to carefully inspect the lesion. In addition, melanocytes can be seen within the adnexal epithelium especially within eccrine ducts. In some occasions, melanocytes can be observed within the arrector pili muscle, and its presence could be useful for its diagnosis since only rarely do melanomas show these features.

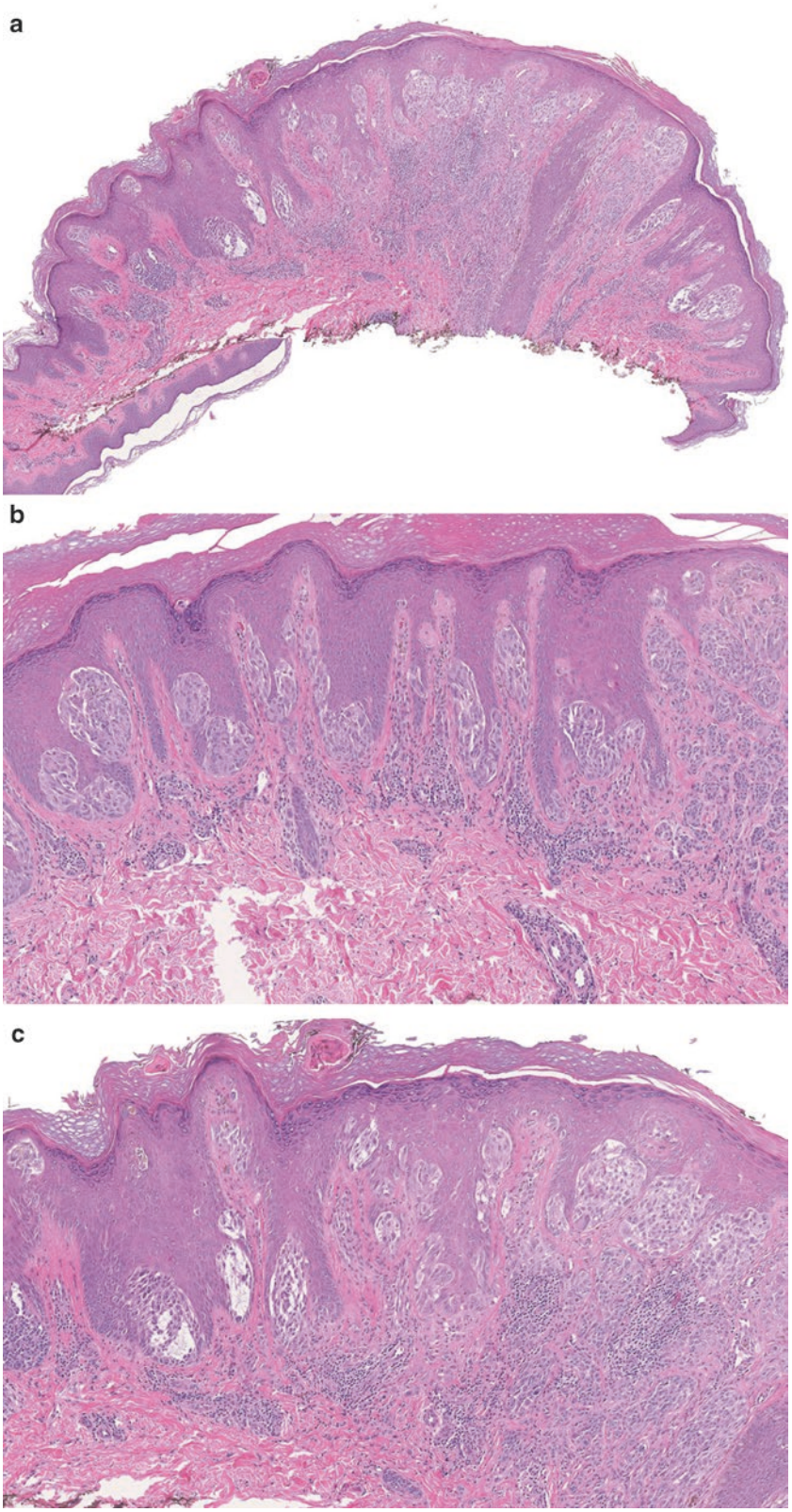

Fig. 4.5 Compound Spitz nevus. This pigmented lesion was taken from a 30-year-old male (**a**). The lesion is symmetric and displays marked cellular monomorphism (the lesion starts with a nest and end with a nest). Large nests mostly located at the tips of the rete ridges. Many Kamino bodies are noted (**b**). The centers of the lesion displays rare single and upward melanocytes (**c**).

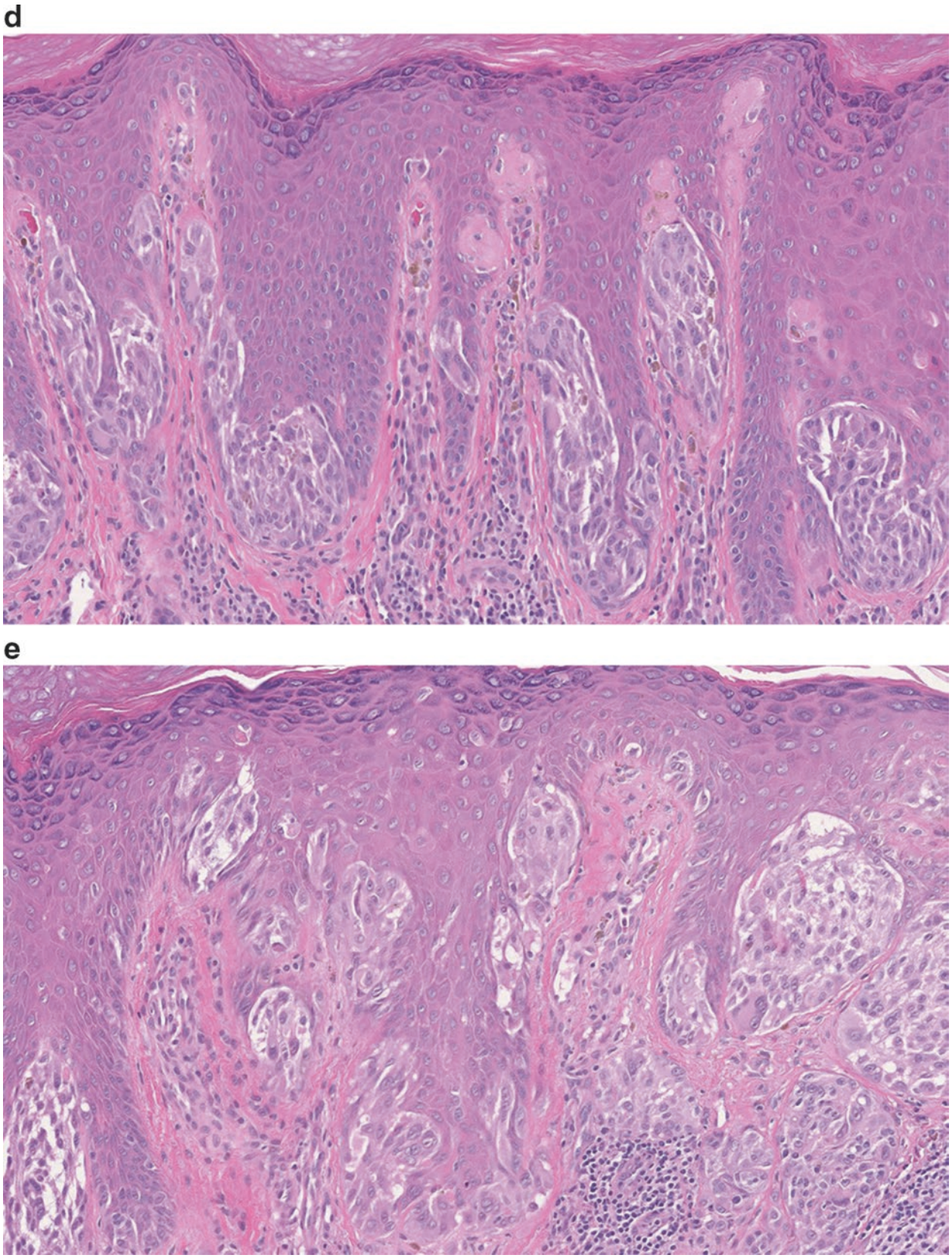

Fig. 4.5 (continued) Vertically oriented nests with scattered Kamino bodies. Note the subtle clefting around the melanocytic nests (**d**). High power showing the nests along with scattered single melanocytes (**e**)

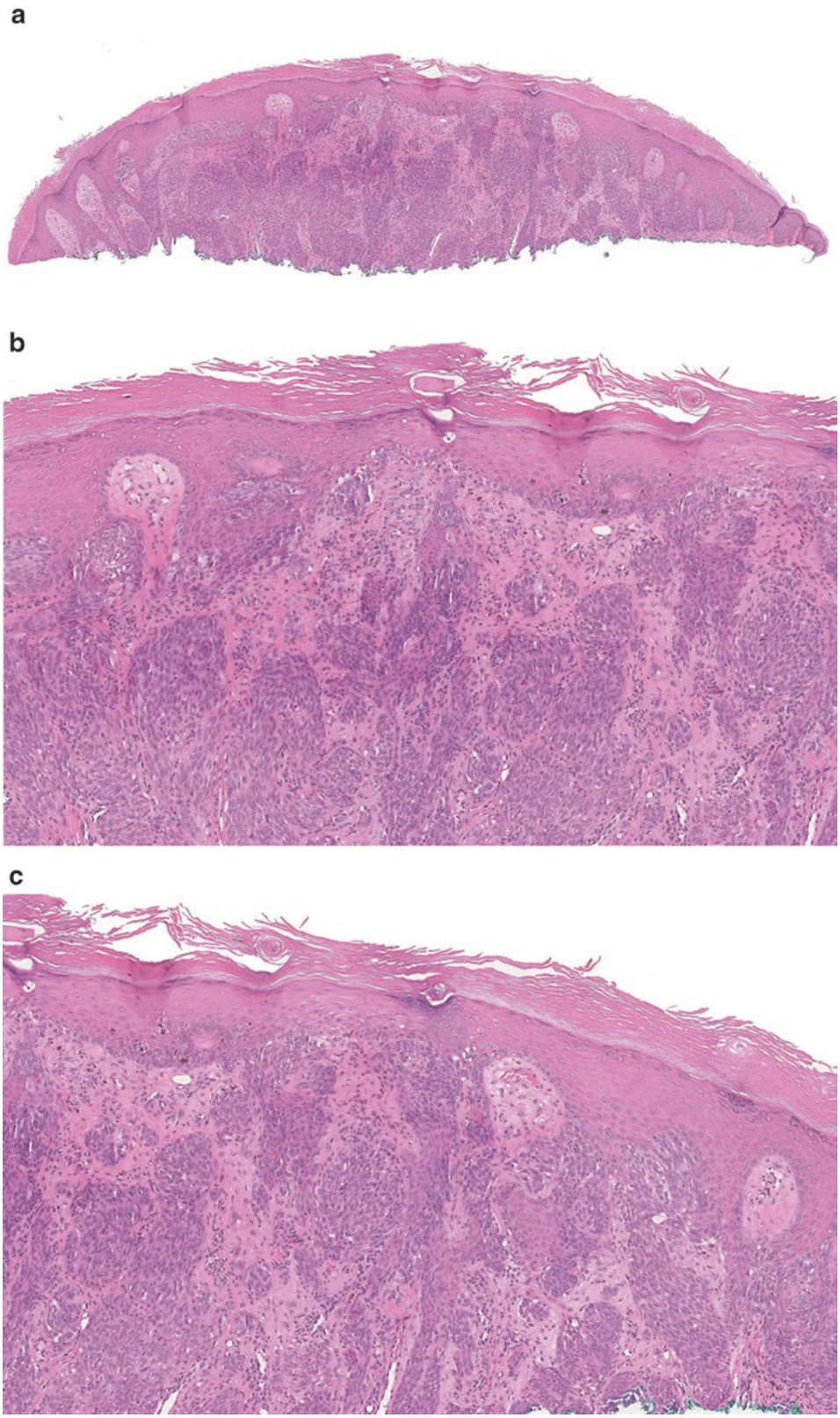

Fig. 4.6 Compound Spitz nevus. A 39-year-old female with a pigmented lesion on the forearm. This example displays a more prominent growth in dermis. Note the large nests in the center of lesion (toward the periphery the size of nest diminishes) (**a**). Despite the presence of large nests, there is lack of mitotic activity and cytologic atypia (**b**). Note the increased number of dendritic cells and pigmented melanophages in epidermis. The melanocytes in dermis show a homogeneous growth and display thin nuclear membranes, vesicular nucleus, and pinpoint nucleoli (**c**)

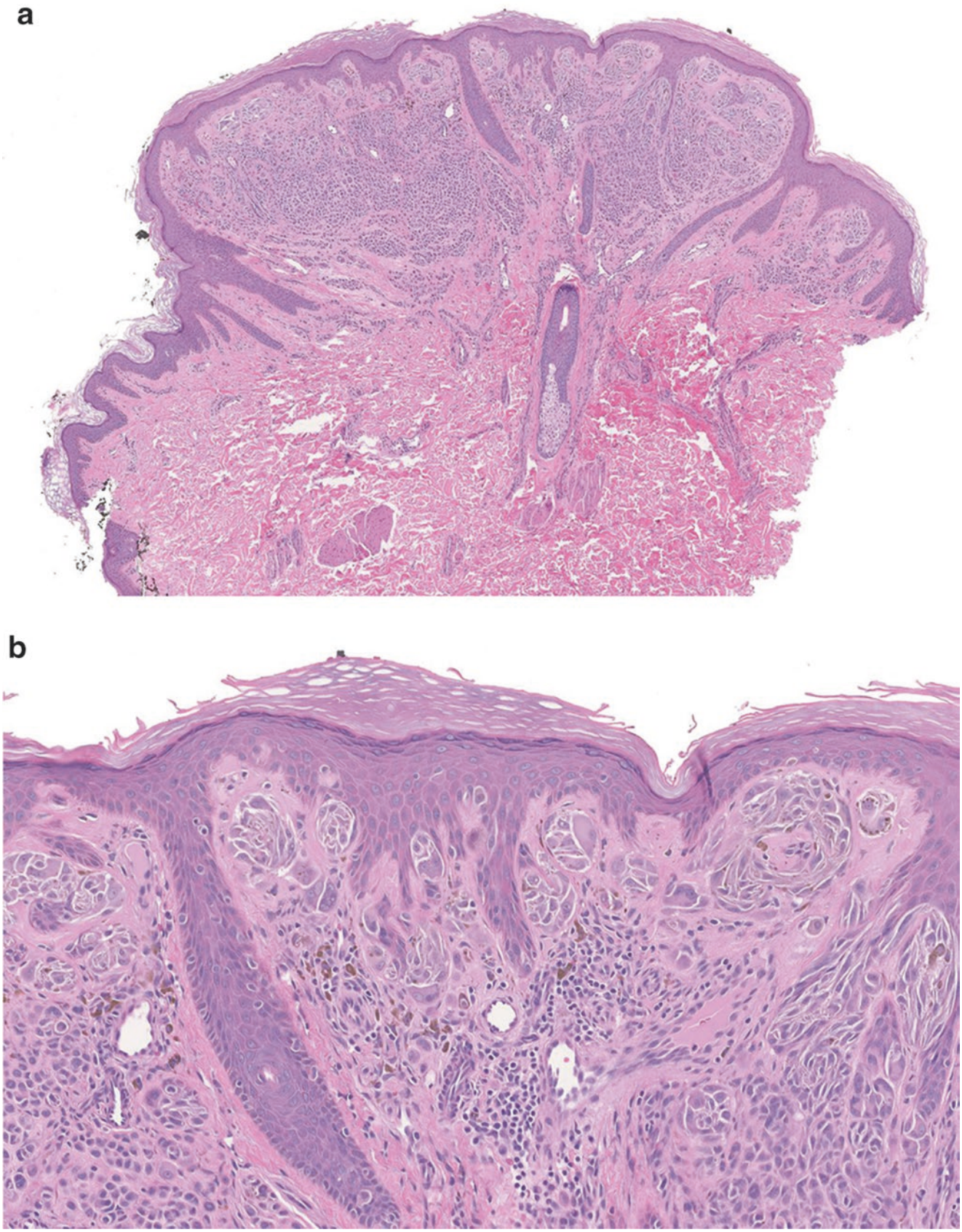

Fig. 4.7 Compound Spitz nevus. A 42-year-old male with a lesion on the trunk. This lesion is polypoid and melanocytes decreased in size and number toward the base of the lesion (**a**). The nests are predominantly composed of epithelioid melanocytes (**b**).

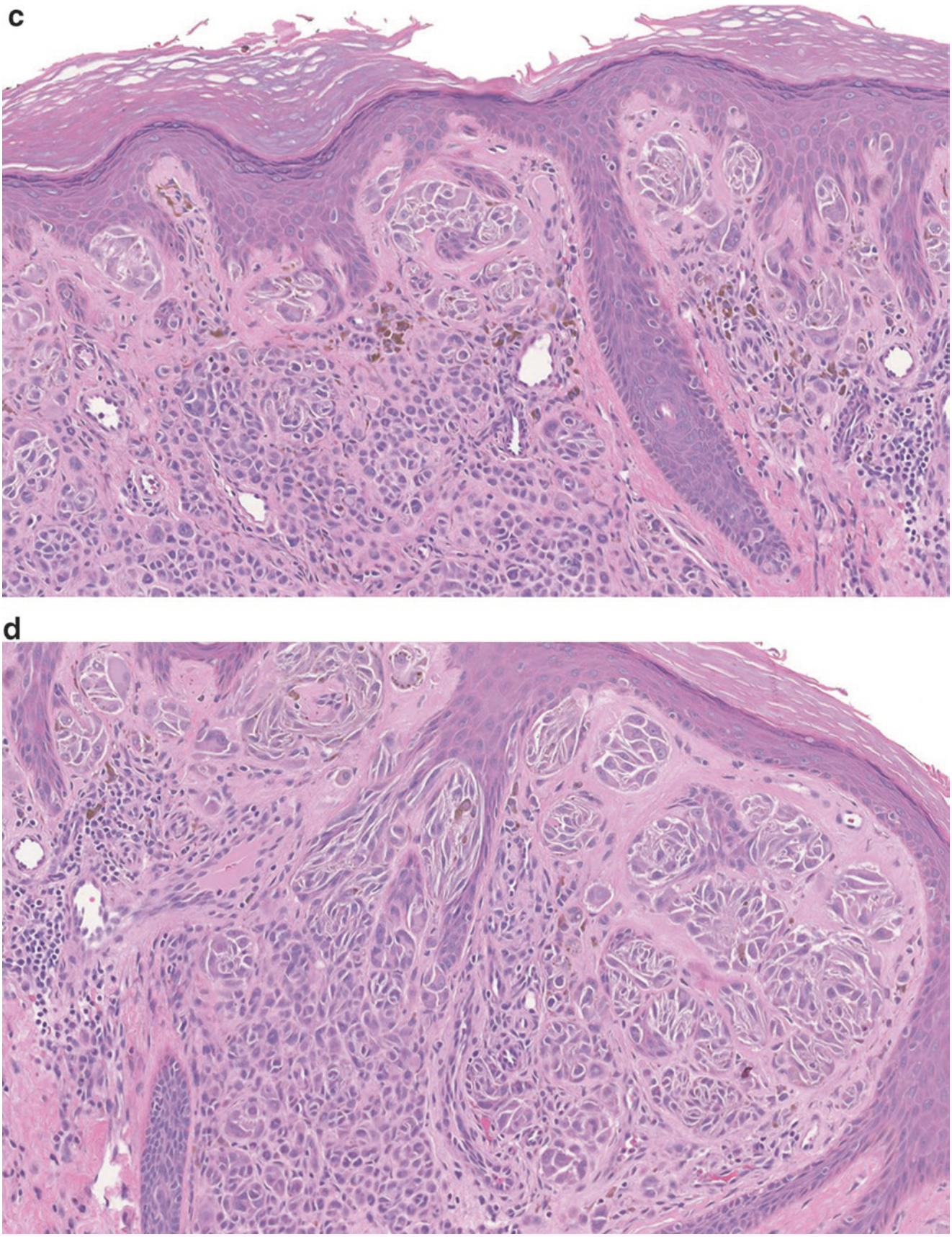

Fig. 4.7 (continued) The melanocytes in dermis are uniform with normal maturation and lack atypical changes (**c**). At higher magnification, the melanocytes are banal with typical nucleoli. Rare multinucleated melanocytes are noted (**d**)

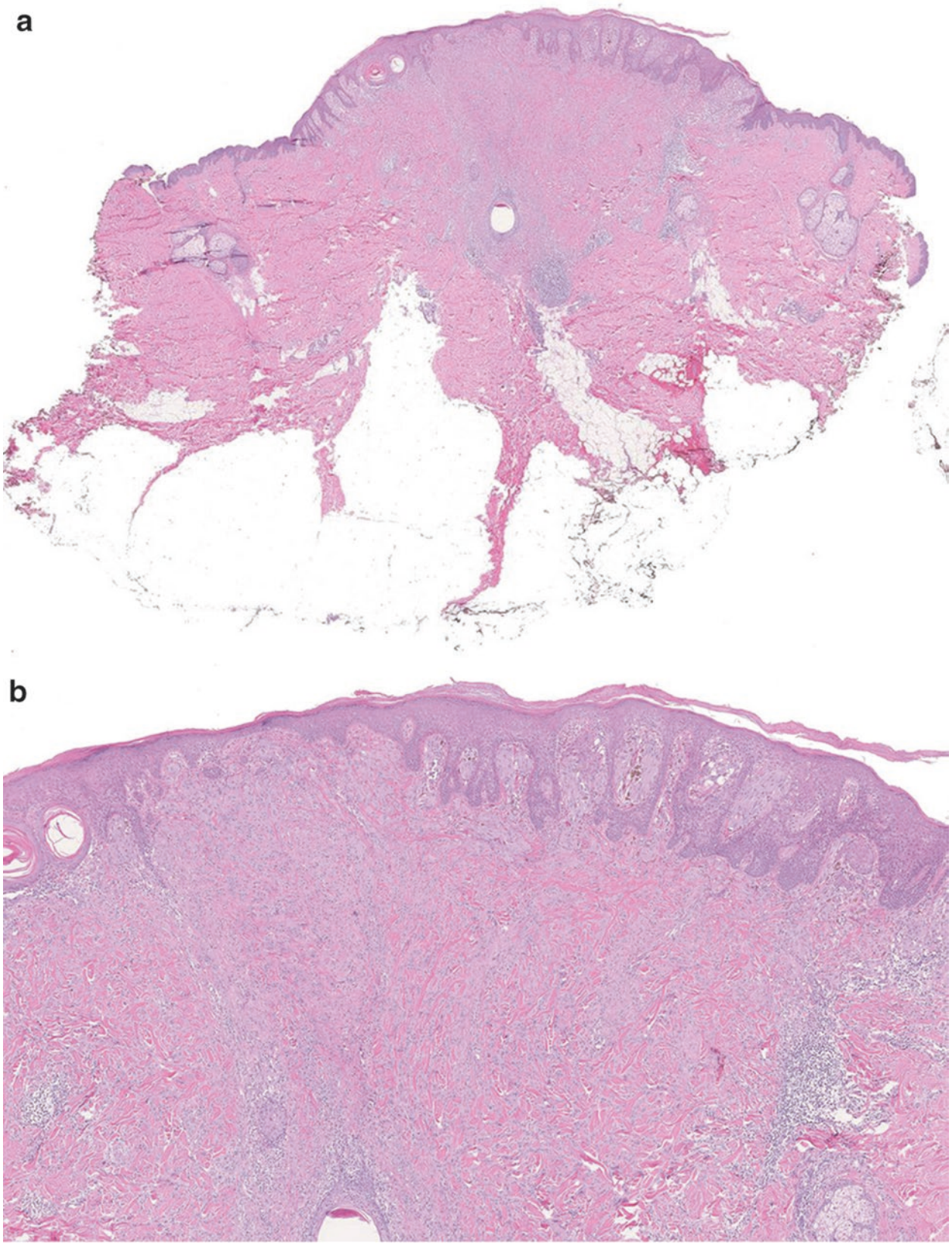

Fig. 4.8 Compound Spitz nevus. This example shows a wedge-shaped growth in dermis (**a**). Note the epidermal hyperplasia and the large nests in the upper part of the lesion (**b**).

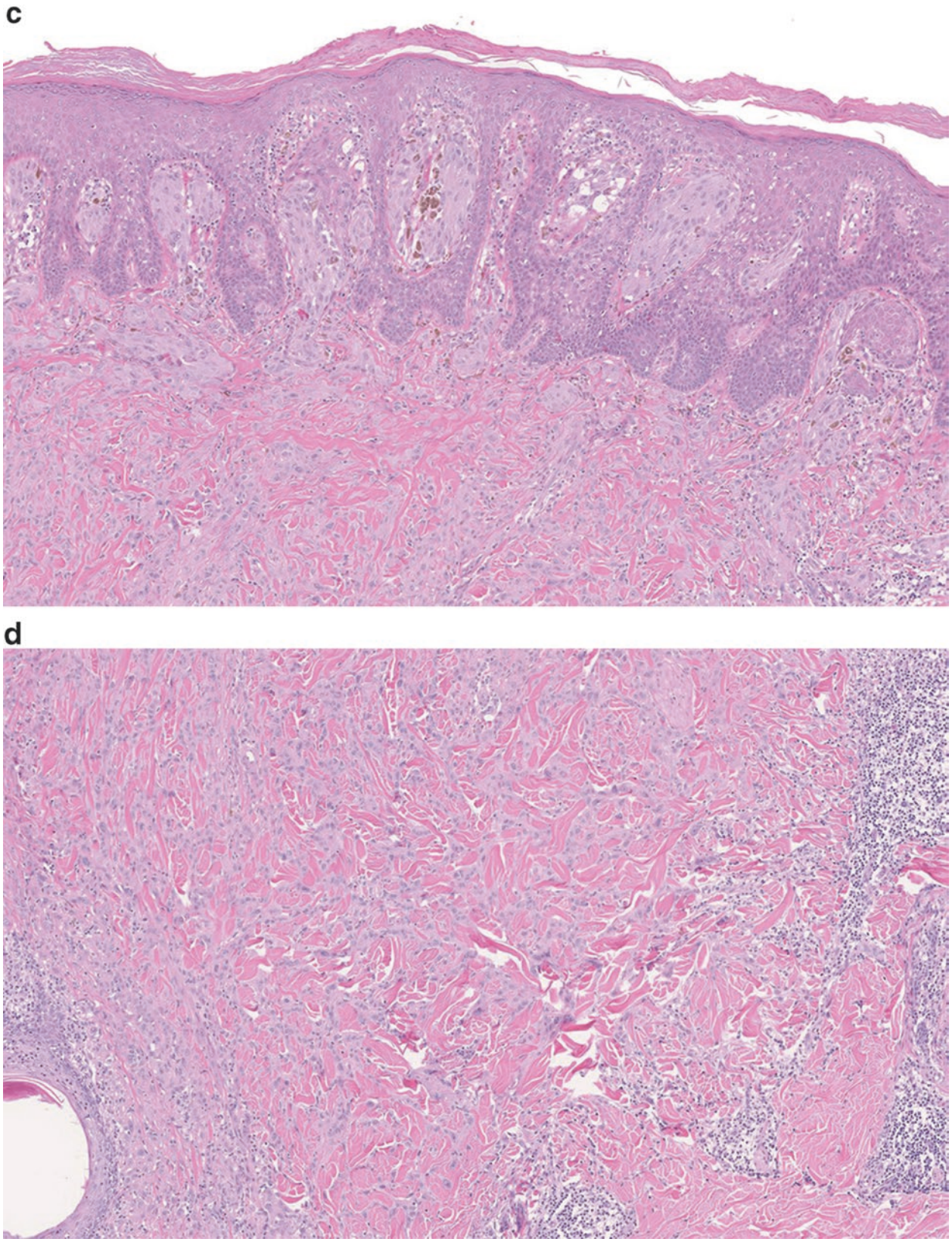

Fig. 4.8 (continued) The melanocytes in this case have an ample, pale with a ground-glass appearance and distinct cell borders (**c**). This case shows gradual diminution of cellularity with a decrease in nest size toward the base with characteristic infiltration in between collagen bundles (**d**)

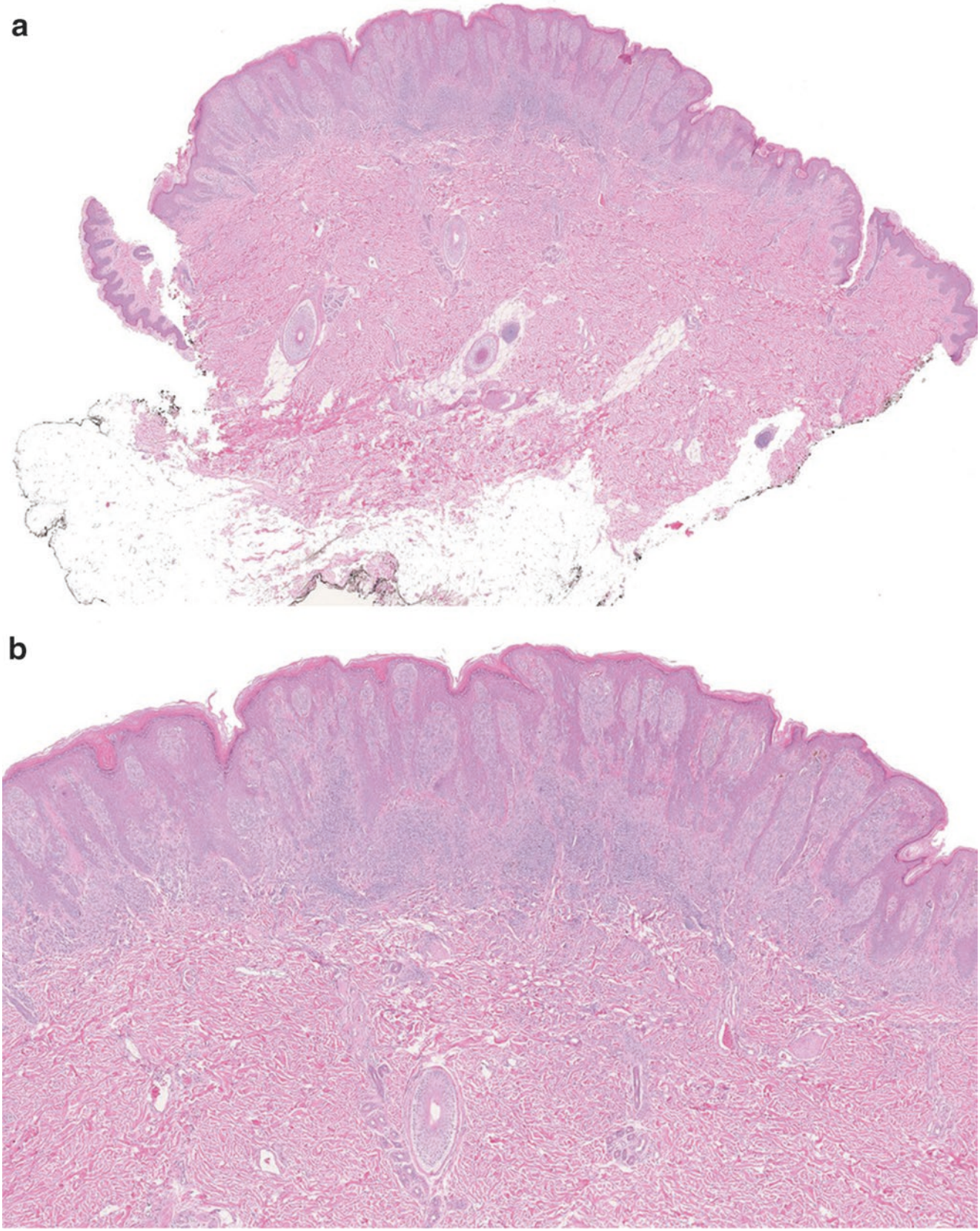

Fig. 4.9 Compound spitz nevus. 15-year-old male with a pigmented lesion on his shoulder. This example shows marked epidermal hyperplasia, large nests and maturation in single cell at the base of the lesion (**a**). The upper part of the lesion is hypercellular. Note the cells in reticular dermis that infiltrate in single cells (diagnostic clue) (**b**).

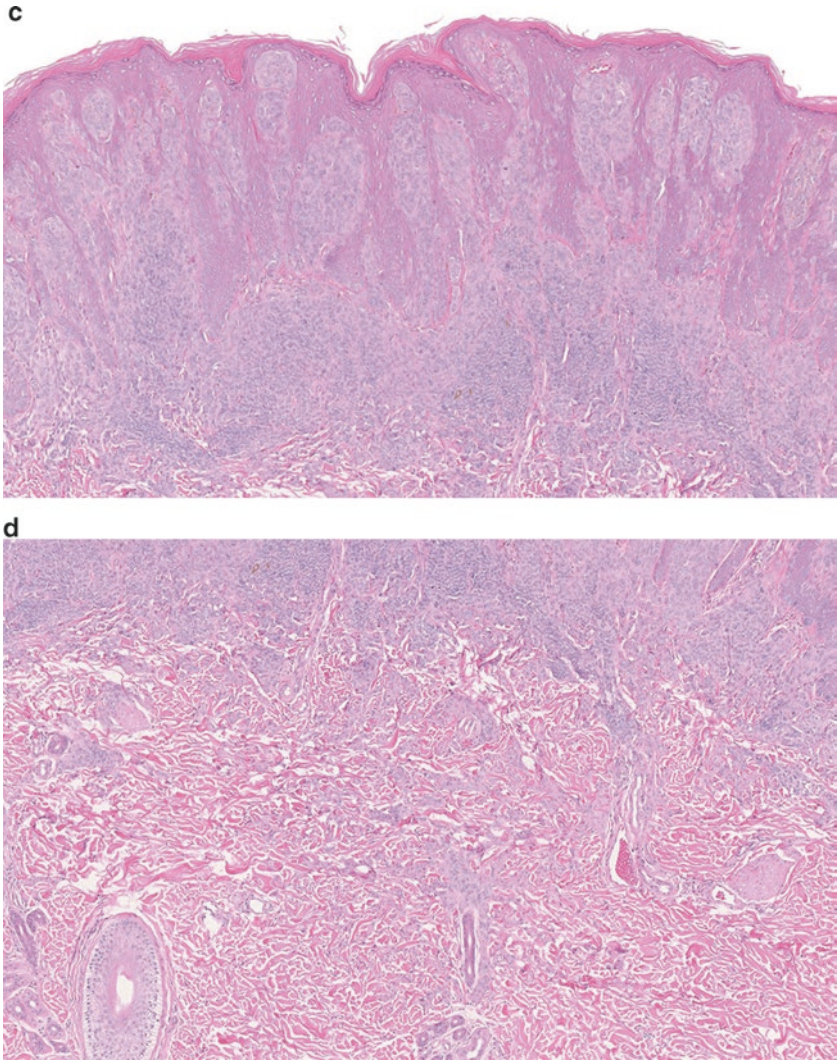

Fig. 4.9 (continued) The center of the lesion showing single cells and focal pagetoid upward migration (**c**). Note the base of the lesion infiltrating the deeper dermis in single cells (**d**)

Intradermal Spitz Nevus

Intradermal Spitz nevi have a symmetrical architecture. The overlying epidermis can show epidermal hyperplasia but is not as common as that seen in compound Spitz nevi. This lack of epidermal changes is most likely due to the absence of a junctional component [27]. As opposed to cases of intraepidermal and compound Spitz nevi, Kamino bodies are only rarely observed [19, 27]. In some cases, one can find rare isolated melanocytes within the epidermis (these melanocytes show spitzoid features such as large epithelioid cells with well-defined cell borders). Also, deeper sections in such lesions may reveal rare junctional nests with the same cytomorphology as junctional or compound Spitz nevi. There may be a grenz zone right beneath the epidermis. The predominant cell in intradermal Spitz nevus is the epithelioid type; however, some cases may show a mixture of both epithelioid and spindle cell melanocytes or being purely composed of spindle cell melanocytes (rare) [27]. The melanocytes usually show mild hyperchromasia with irregular chromatin distribution and have prominent nucleoli. The cytoplasm of these melanocytes is abundant, eosinophilic, and devoid of pigment. Multinucleated giant melanocytes can be seen, especially in cases in which the epithelioid cell type predominates. In some cases there is a chronic inflammatory lymphocytic infiltrate, and the distribution of the infiltrate is perivascular and/or interstitial; rare examples show a dense, halo-like pattern. In intradermal Spitz nevi, the presence of melanin pigmentation is more commonly seen when lesions are composed primarily of epithelioid melanocytes. Marked pigmentation has been reported in Spitz nevi with epithelioid cell type, known as pigmented epithelioid Spitz nevus [28, 29]. Mitotic figures may be seen in intradermal Spitz nevus, up to 38 % of cases. These mitotic figures are located in the

superficial portion of the lesion (superficial dermis) and are not seen in the deeper aspect of the lesions. Atypical mitotic figures are not identified in any of our cases. The presence of atypical mitotic figures, especially located at the base of the lesion, should be a red flag for melanoma.

Most Spitz nevi show maturation in the dermis; however, some lesions, usually in adults, lack this phenomenon. In our experience, the absence of maturation in intradermal Spitz nevi should not be used as a single criterion to establish a diagnosis of melanoma, especially if other histopathologic features are present such as symmetry, the absence of mitotic figures at the deep portion of the tumor, and lack of severe pleomorphism throughout the lesion.

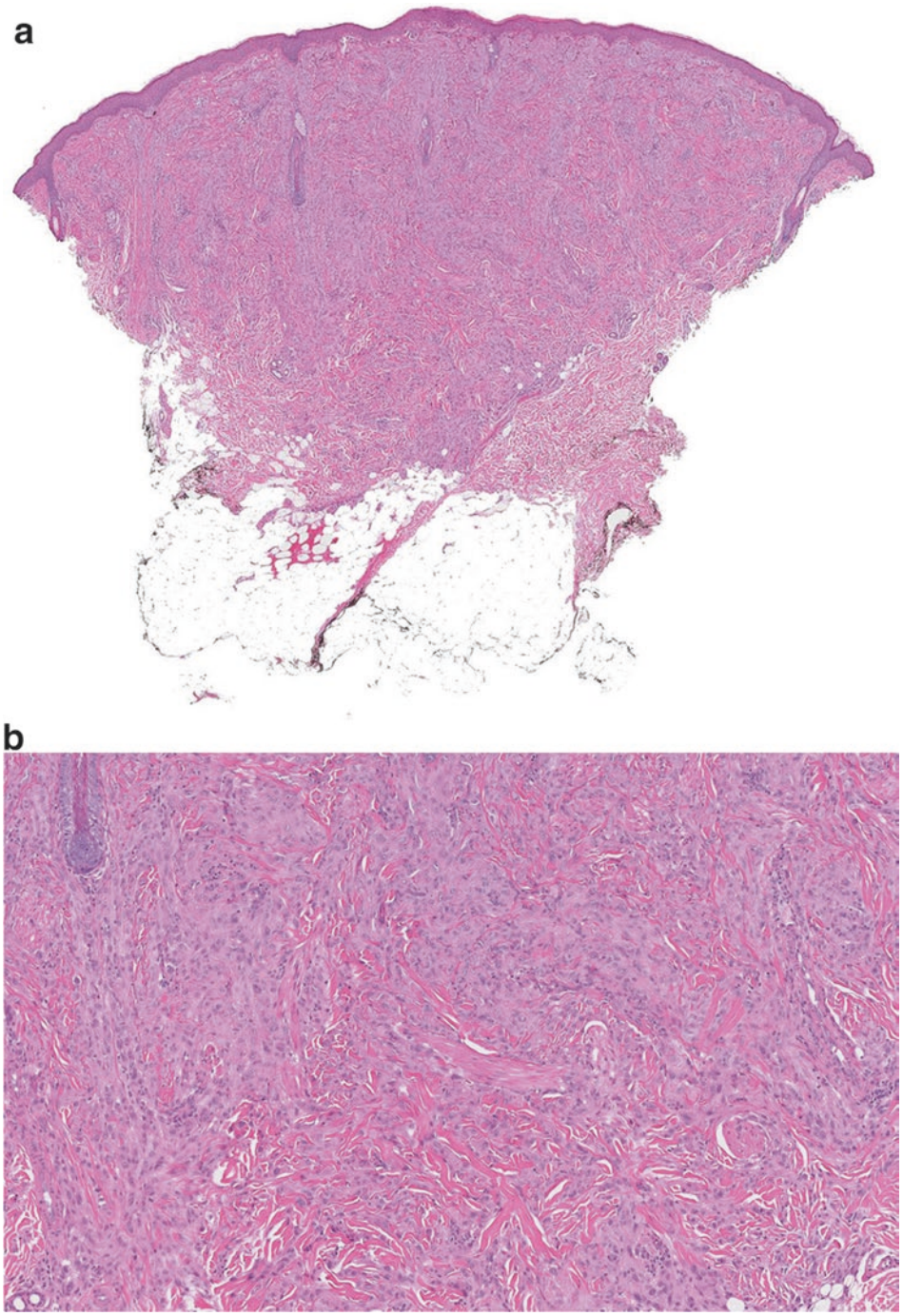

Fig. 4.10 Intradermal Spitz nevus. The lesion is composed of an intradermal component only (**a**). The melanocytes are epithelioid and have an ample eosinophilic cytoplasm (**b**).

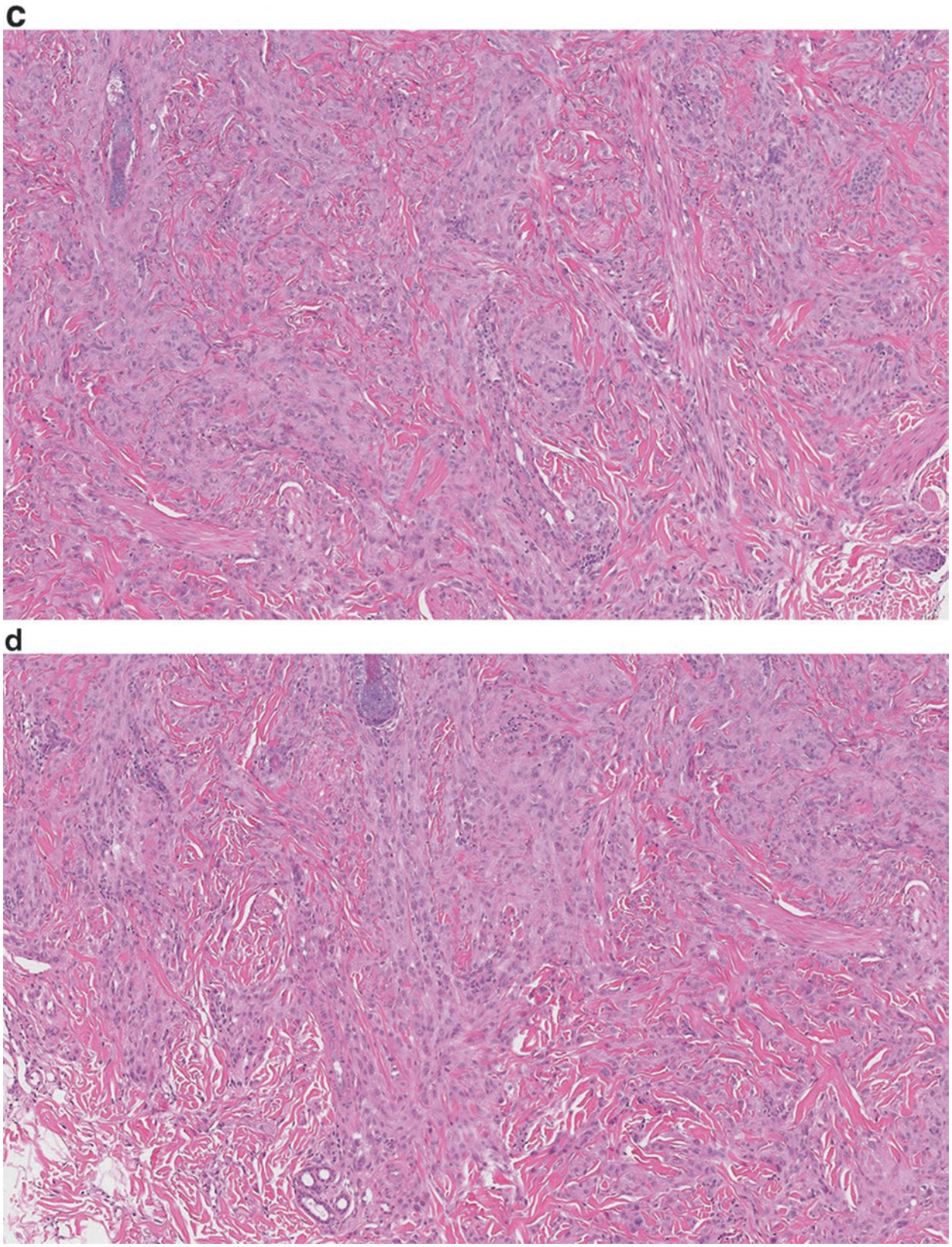

Fig. 4.10 (continued) The melanocytes are arranged in nests and large fascicles (**c**). The base of the lesion shows a clear decrease in cellular density (characteristic feature) (**d**). This lesion showed no mitoses

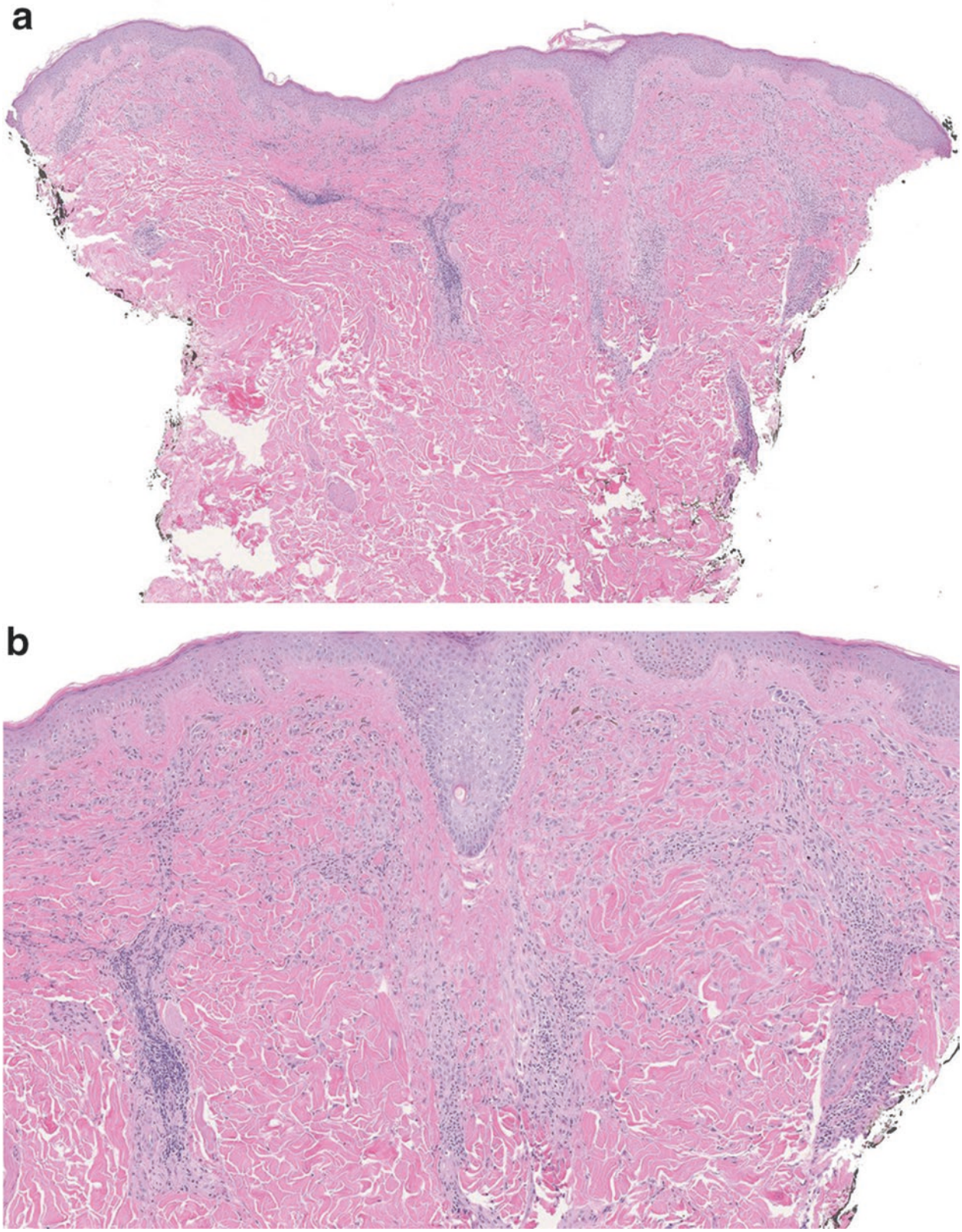

Fig. 4.11 Intradermal Spitz nevus. This lesion is located in the neck of a 25-year-old male. This example of intradermal Spitz nevus shows an interstitial growth pattern. Note the absence of an epidermal component (**a**). The melanocytes in dermis show even maturation toward the base of the lesion (**b**).

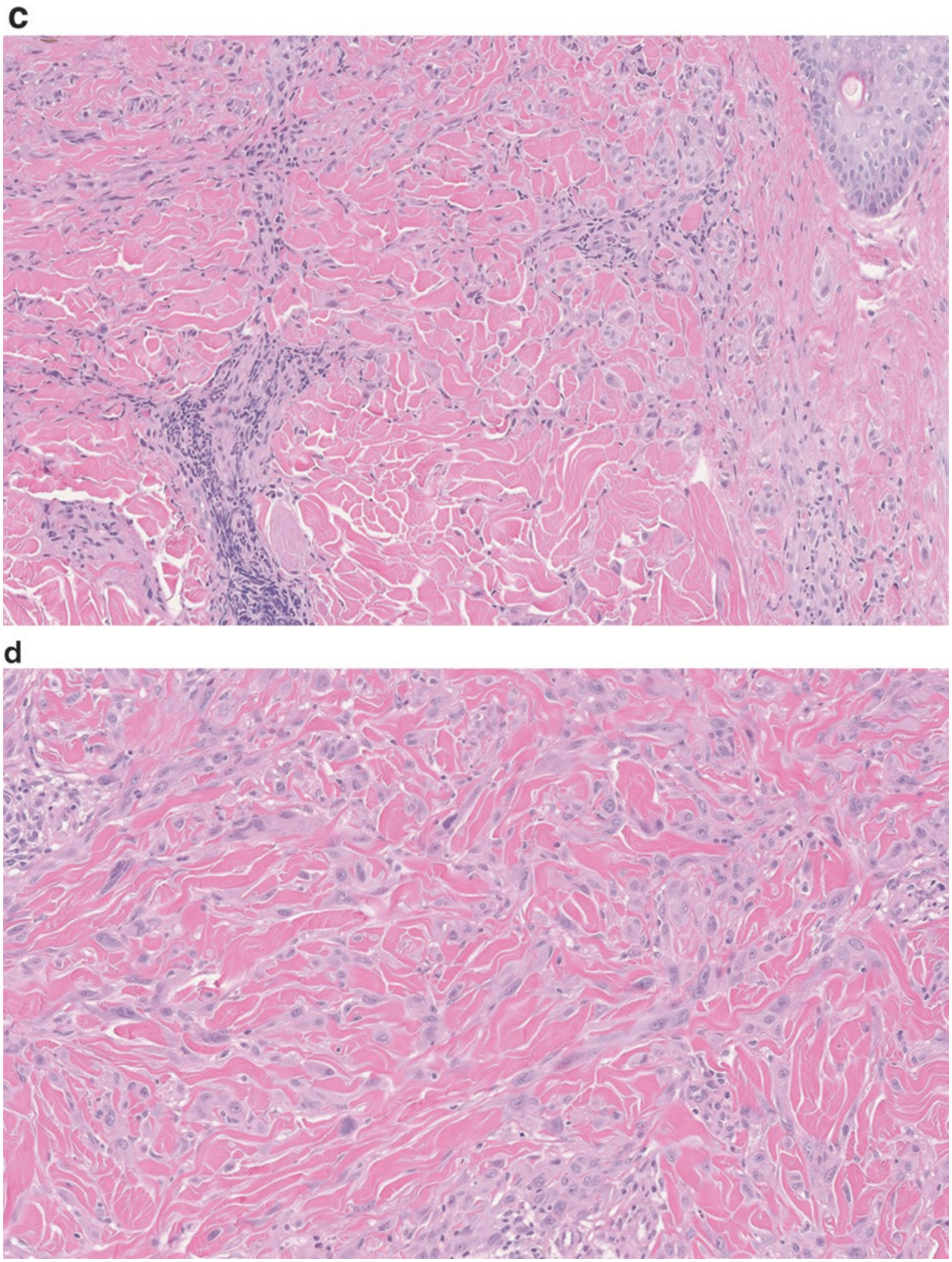

Fig. 4.11 (continued) The large epithelioid spitzoid melanocytes are arranged interstitially in dermis. The deeper dermis shows decreased number of melanocytes (**c**). High power showing large epithelioid cells with defined cell borders and with a prominent nuclei (**d**). The lesion showed no mitotic figures

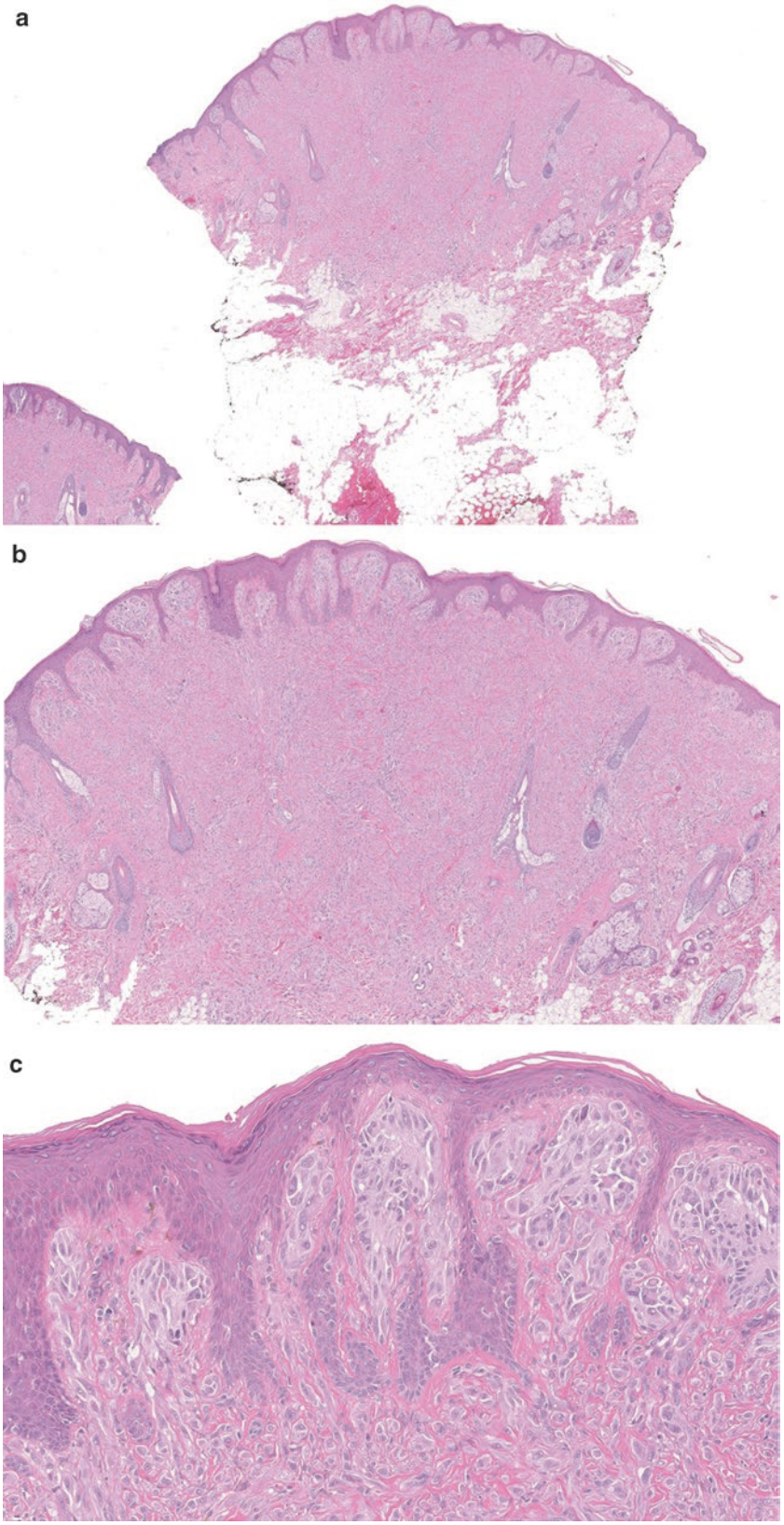

Fig. 4.12 Intradermal Spitz nevus. This is a lesion in a 31-year-old male. The lesion is intradermal with normal maturation, but it shows scattered epithelioid melanocytes with atypia (**a**). The nests in dermis abut the epidermis and spare the adnexal structures (**b**). On higher magnification, the melanocytes are epithelioid, large, with atypical nuclei and with a prominent nucleoli (**c**).

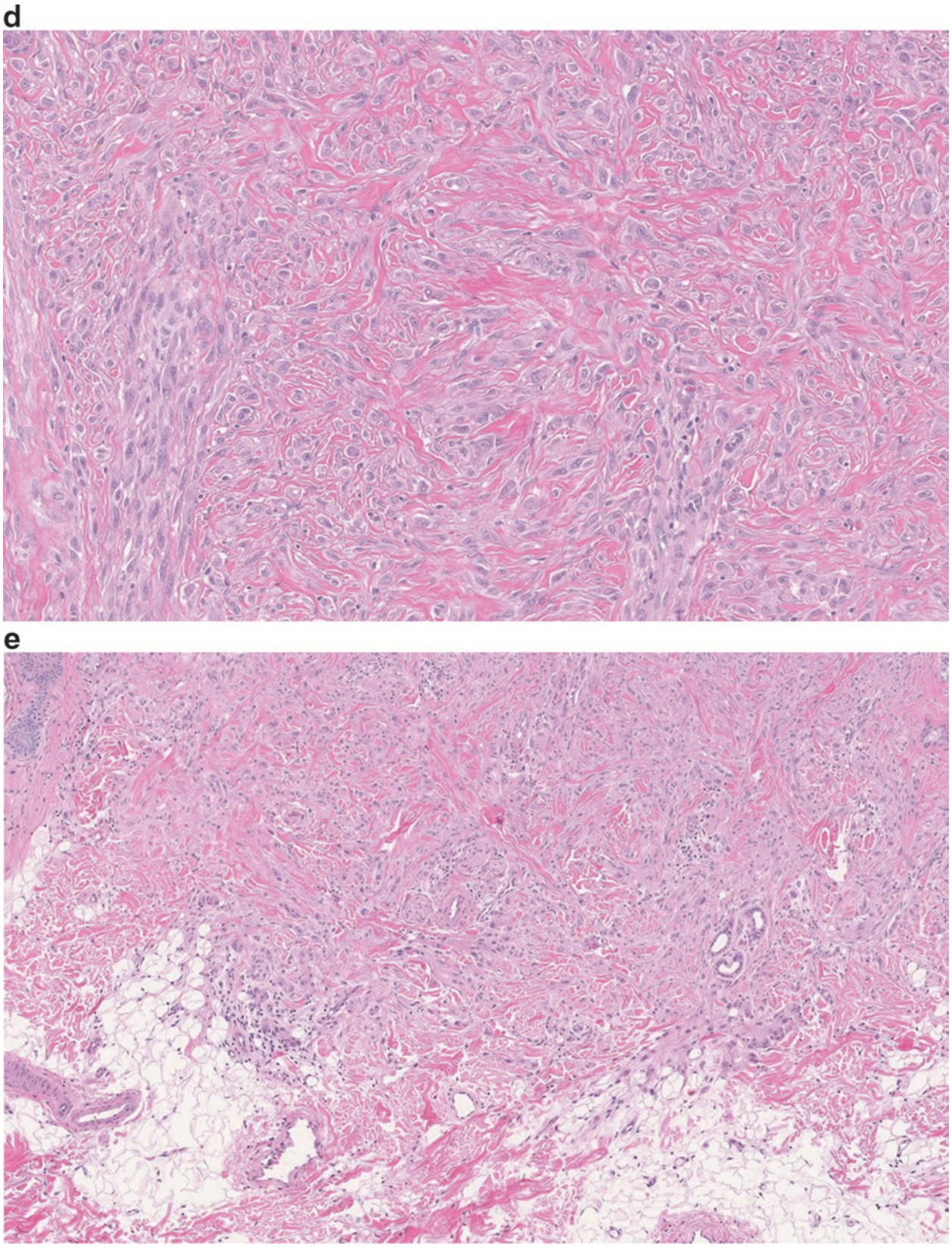

Fig. 4.12 (continued) Note the large epithelioid melanocytes; however, the monomorphism is preserved in this lesion (**d**). The base of the lesion shows maturation and lack deep mitoses (dispersed melanocytes at the base) (**e**)

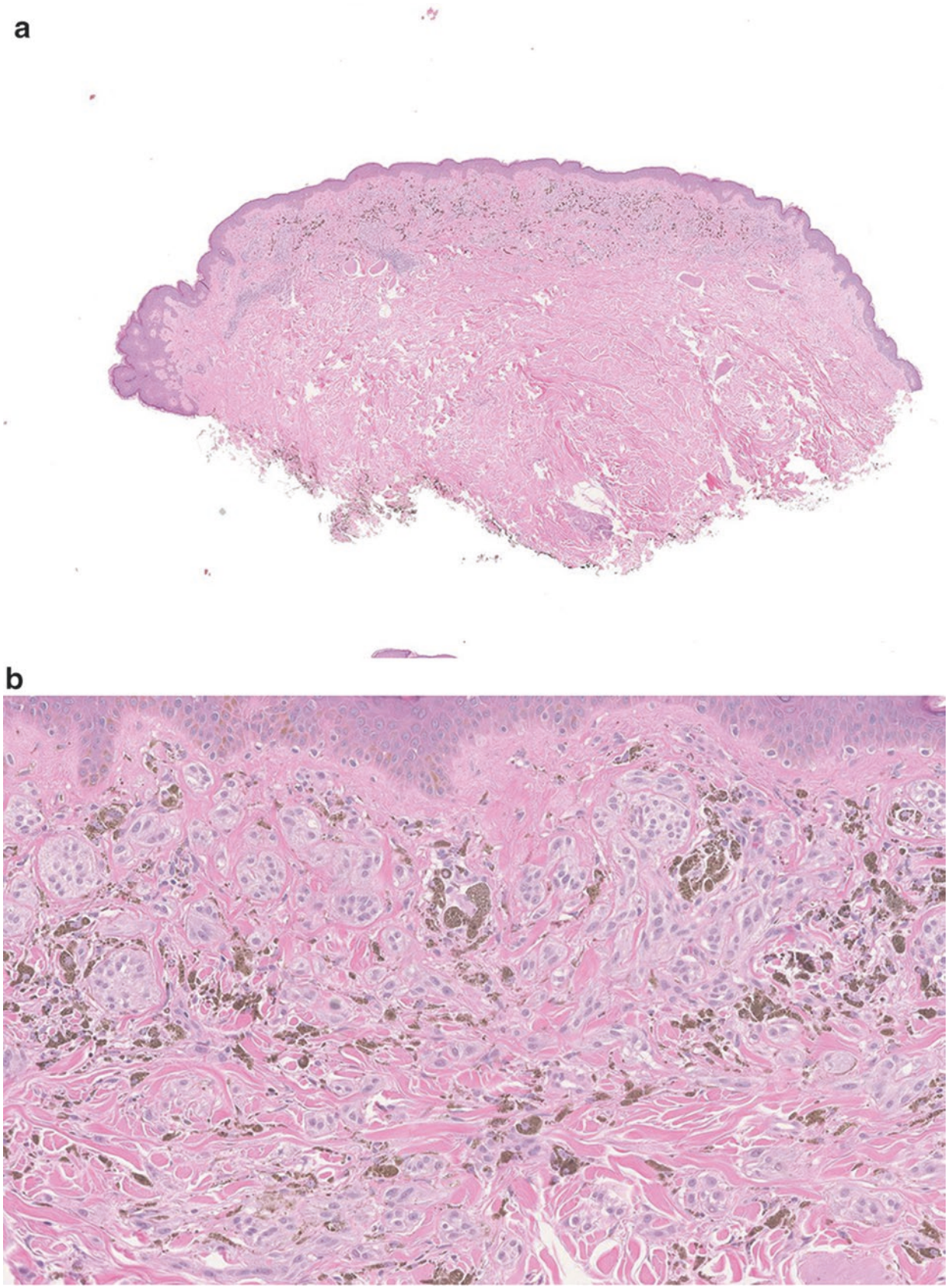

Fig. 4.13 Intradermal Spitz nevus. This is an example of a pigmented intradermal Spitz. Notice the increased number of pigmented melanophages admixed with the nests of epithelioid (spitzoid) melanocytes (**a**). There is no epidermal component (**b**).

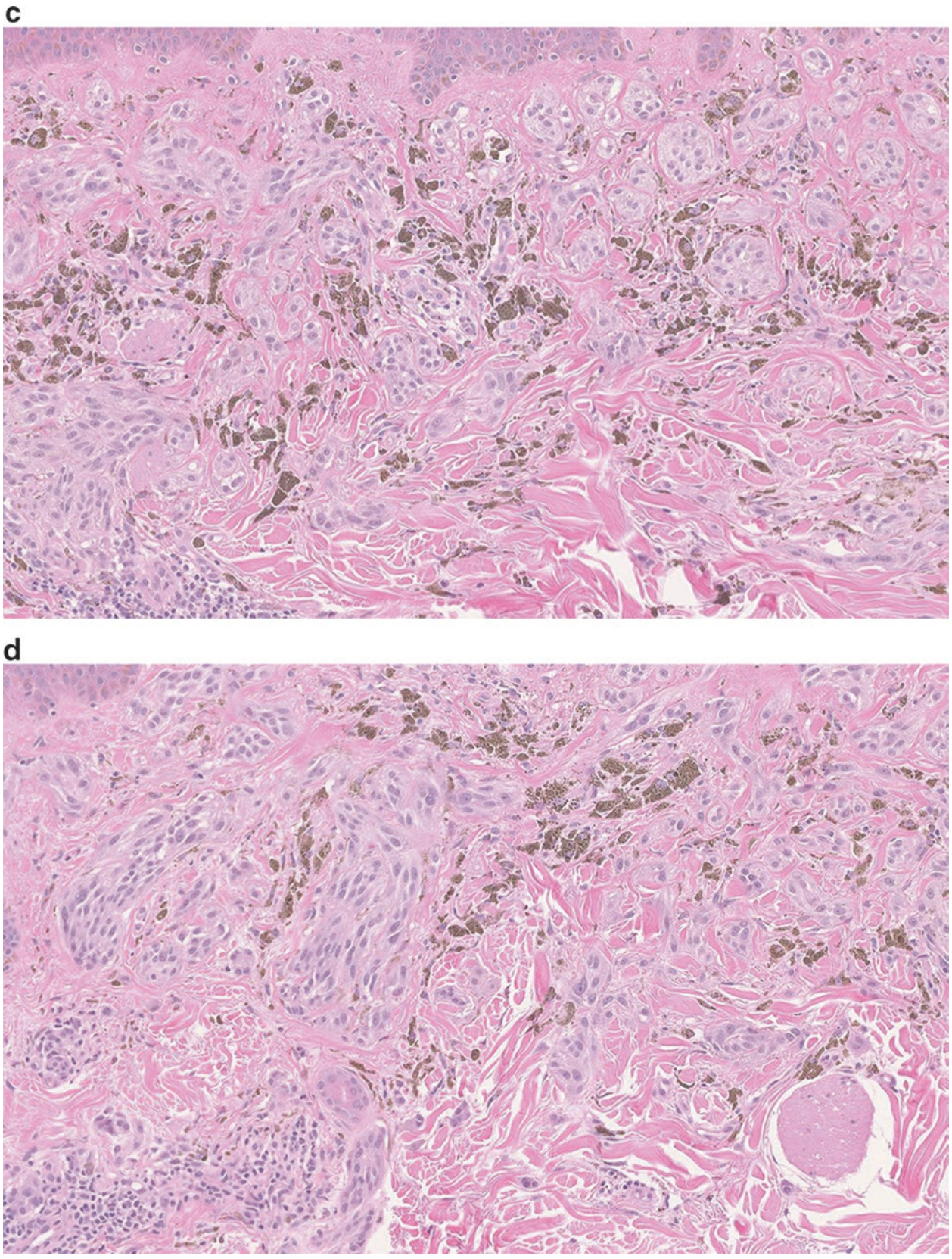

Fig. 4.13 (continued) The lesion is composed of nests and single epithelioid melanocytes dispersed in reticular dermis (**c**). Scattered dendritic melanocytes are seen in dermis (**d**)

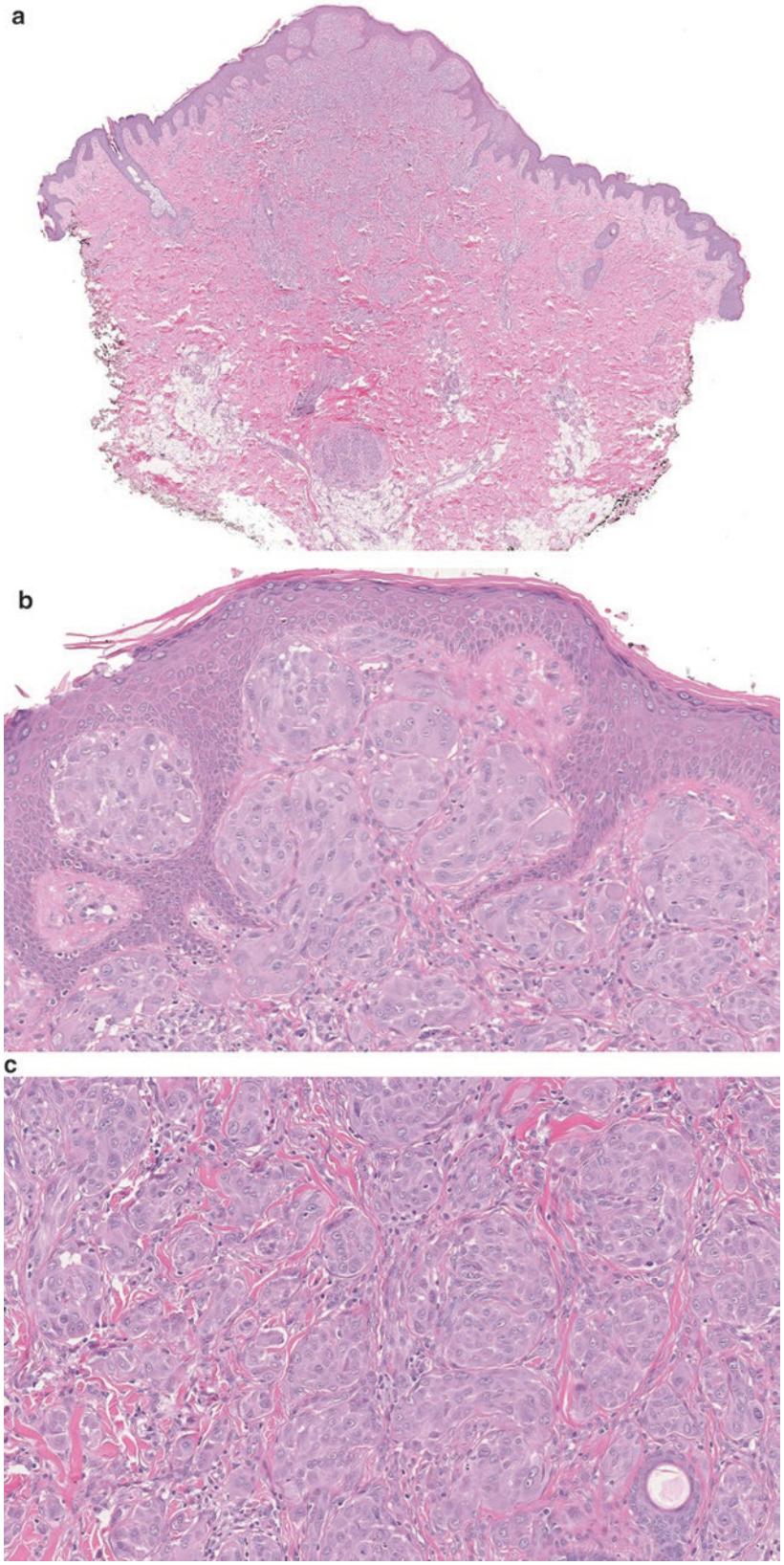

Fig. 4.14 Intradermal Spitz nevus. This example of intradermal Spitz nevus shows a deep dermal component with involvement of the sweat duct structures (**a**). At higher magnification, note the large and pleomorphic epithelioid cells in dermis (**b**). However, note the homogeneity in the melanocytes and there is lack of atypical mitotic figures, necrosis, and ulceration. In reticular dermis, the melanocytes show a nested arrangement (**c**).

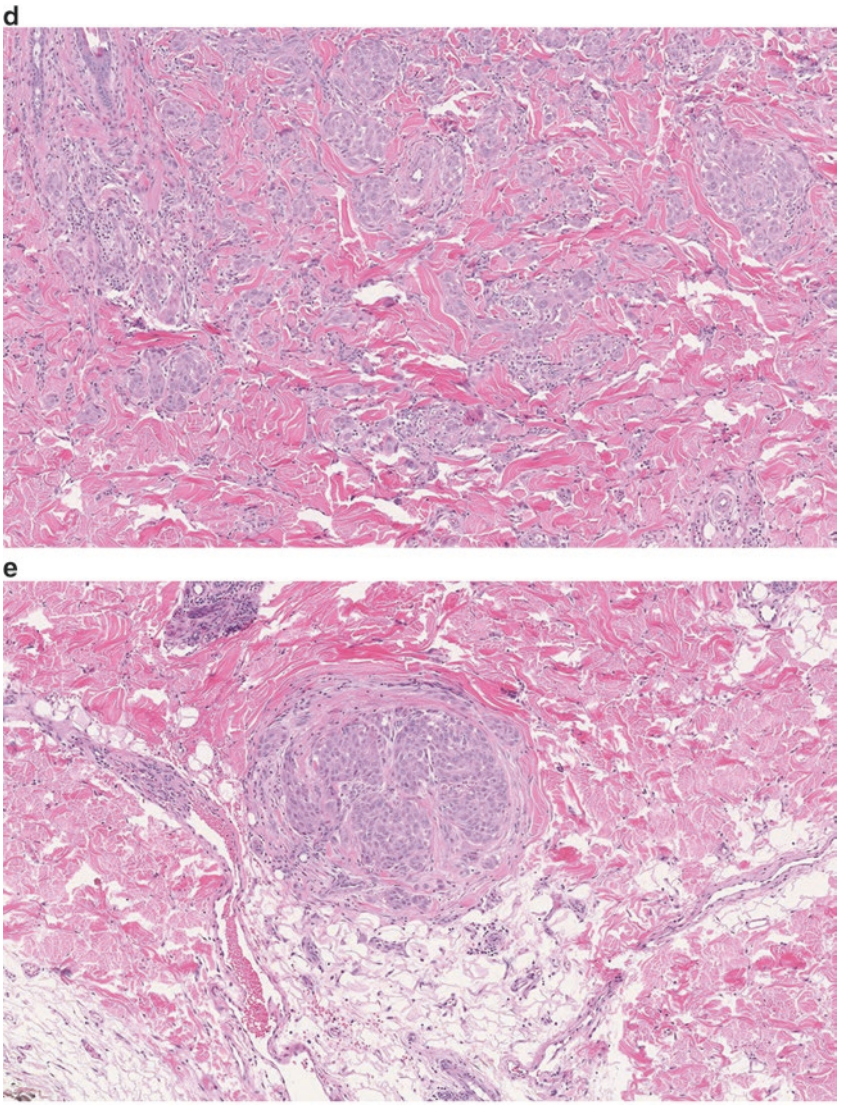

Fig. 4.14 (continued) In the base of the lesion, the melanocytes are dispersed and are present in isolated and small aggregates (**d**). In this case, there is involvement of the deep sweat duct structures (**e**)

Differential Diagnosis of Spitz Nevi

The main differential diagnosis of Spitz nevi is with spitzoid melanoma. While it is fairly easy to distinguish conventional Spitz nevi from conventional melanomas, not all cases fall under this category. In our opinion, unified interpretation of histopathologic criteria for distinguishing such cases is lacking. On the other hand, to make a distinction between these entities is of crucial importance due to the marked difference in management and prognosis. Since most of the developed diagnostic criteria derive from conventional Spitz nevi and melanomas and not from the unusual variants of these neoplasms, it can be quite difficult to arrive to the correct diagnosis in some occasions. The tumors that deviate from the classic description can cause difficulties in diagnosis particularly since these lesions are relatively infrequently encountered. In addition, there are many factors such as age, trauma, pregnancy, and exposure to sunlight that are well known to alter the microscopic appearances of melanocytic lesions and may contribute to cause pitfalls in diagnosis.

Clinically, spitzoid melanomas occur rarely in younger patients and thus are more commonly seen in adults, whereas Spitz nevi are common in young patients. While we agree with many authors that Spitz nevi in adults are rare, we do not believe that all Spitz nevi in adults should be diagnosed as melanoma. Rather, all spitzoid lesions in adults should be carefully inspected and always keeping in mind the possibility of melanoma.

The clinical presentation of the lesion may be extremely important. Spitz nevi tend to have an initial brisk growth with further stabilization and are uniform in size and shape, whereas spitzoid melanomas tend to grow rapidly and keep increasing in size. Thus, when a lesion either in adults or children has been present for a long time without clinical change, it most likely represents a Spitz nevus (exceptions do exist). Size of the lesion is also an important consideration as only 10 % of Spitz nevi are larger than 1 cm in size; thus, larger lesions more likely represent melanoma (although spitzoid melanomas can be smaller than 1 cm in size). A recent study showed that the mean size of spitzoid melanoma cases was 7.27 mm [30]. The presence of ulceration in Spitz nevi is usually secondary to trauma; thus, not all lesions that show ulceration represent melanoma. The presence of severe, sun-damaged skin will favor the diagnosis of melanoma, especially if the lesion is junctional in nature (in general junctional nevi tend to appear at young age). In our experience, a diagnosis of unequivocal Spitz nevus in an elderly adult should only be made when the lesion shows the classic, conventional histologic features of Spitz nevus.

Histologically, Spitz nevi are symmetric and more often have either a wedge-shape or a flat-based dome shape. It is always very important to assess the lateral margins of the lesion. In Spitz nevi the nests at the junctional edges are similar in shape, size, and number, the lateral borders are clear-cut, and the junctional nests end abruptly. In some cases, especially in growing lesions and in lesions located in acral locations, the lateral borders may show single melanocytes rather than nests at the edges. On the other hand, in spitzoid melanoma the edges are asymmetric with single melanocytes extending beyond the last nest at the edge. These atypical melanocytes progressively decrease toward the periphery of the lesion and do not show the uniformity that one observes in Spitz nevi. Also, some cases of cutaneous metastatic melanoma may show spitzoid features with symmetric borders and thus can be exceedingly difficult to separate from intradermal Spitz nevus. When this problem arises, clinical history usually helps clarify the correct diagnosis.

Classic Spitz nevi display zonation with depth (uniformity of size, shape, and spacing of melanocytic nests and fascicles within the same horizontal plane); deeper cells should exhibit greater maturation as reflected in decreasing cellular density, progressively smaller nests with transition into single cells, and the infiltration of these individual melanocytes among collagen bundles. Therefore, marked lateral heterogeneity and persistence of deep nests of considerable size and a pushing deep border all represent red flags for the diagnosis of melanoma. While most Spitz nevi show a flat or a wedge-shaped base, in some occasions Spitz nevi can show irregular and infiltrative margins at the base of the lesion. In such cases, melanocytes tend to be arranged in an interstitial pattern, as linear clusters or isolated cells, and distributed among thickened collagen bundles. The presence of large nests of melanocytes or confluent fascicles in deep reticular dermis is a feature more characteristic of melanoma. Maturation is not always present in Spitz nevi and some melanomas may show "pseudo" maturation. Another important point to always assess is the depth of the lesion as Spitz nevi usually should not involve the deep subcutaneous fat (some cases may show superficial involvement of the subcutaneous tissue). Thus, the presence of a spitzoid lesion that involves the subcutis should be carefully scrutinized as probably it will represent melanoma.

The presence of Kamino bodies is a helpful clue. When Kamino bodies are confluent, numerous, and large, such finding is almost diagnostic of Spitz nevus; however, we seem to have melanomas with Kamino bodies developing metastasis. Unfortunately, Kamino bodies are more commonly seen in conventional Spitz nevi than in ambiguous, more challenging cases.

In Spitz nevi, the cells tend to be monomorphous despite the presence of cytologic atypia ("uniformly atypical"). Spitz nevi, especially in children, may display severe cytologic atypia, i.e., large cells with hyperchromatic nuclei and prominent eosinophilic nucleoli; however, such melanocytes tend to also show a large homogeneous cytoplasm. On the other hand, spitzoid melanomas tend to show cells with variable size and including large nuclei and prominent nucleoli with minimal or vacuolated cytoplasm. Also, the presence of prominent nucleoli is usually restricted to the epithelioid cells in the surface of the lesion in Spitz nevi. On the other hand, the presence of prominent eosinophilic nucleoli in the deep portion of the lesion, especially if a lesion is composed of primarily of spindle cells, is more indicative of melanoma. The melanocytes in Spitz nevi tend to show clear-cut borders, whereas in melanomas the cytoplasmic borders are blurred. Cellular density is a good discriminator between nevi and melanoma, as spitzoid melanoma tends to have a much higher cellular density, especially in cases in which the cells have minimal cytoplasm. Another important clue is the presence of expansile nodules, more commonly seen in melanomas. Spitz nevi can show a nodular appearance in dermis; however, the surrounding tissue is not compressed, whereas in melanomas the dermal nodules tend to have pushing, compressive margins.

Spitz nevi are well known to have mitotic figures, particularly in lesions that are growing. Mitotic figures in Spitz nevi range from 10 to 58 % [3, 27, 31–33]. They are scarce and typically located in the superficial areas of the neoplasm. When located in the deep aspect of the lesion (marginal mitotic figures), the likely diagnosis will be an atypical Spitz tumor or melanoma. In addition, if mitotic figures are arranged in clusters even if they are located in the surface of

the lesion are features of melanoma. We consider this criterion very important in the differential diagnosis of Spitz nevus and spitzoid melanoma; thus, the presence of mitotic figures in the lower portion or many grouped in an area of a spitzoid lesion must be considered highly indicative of melanoma.

Pagetoid spread of melanocytes in the overlying epidermis or within epithelium of the intraepidermal portions of the adnexa (infundibula and acrosyringia) can be observed in Spitz nevi. Because both melanomas and Spitz nevi share this feature, there are certain points that need to be remembered when evaluating such tumors. In melanoma, the presence of pagetoid spread usually is seen beyond the dermal component (shouldering effect), since melanocytes are scattered throughout the entire lesional epidermis. Those melanocytes located in the adnexa are grouped as single melanocytes, and the epidermis lacks hyperplasia. In Spitz nevi, the pagetoid cells are usually located in the center of the lesion, the epidermis shows hyperplasia, the melanocytes in adnexal structures are arranged in nests, and the melanocytes are uniform and homogenous (similar to those observed in the junctional nests). In addition, one should keep in mind that irritated lesions (trauma) can induce pagetoid spread of melanocytes beyond the center of the lesion.

Epidermal hyperplasia is a feature seen in Spitz nevi. The epidermis shows rete ridges with pointed bases with uniform size and shape. In melanoma, the epidermis shows atrophic changes that alternate with irregular epidermal hyperplasia (in some cases there is even ulceration). In some cases of Spitz nevi, there is even pseudoepitheliomatous hyperplasia [19].

Table 4.1 Spitz nevi versus spitzoid melanoma

• Age: Spitz nevi are more common in young patients and spitzoid melanomas are more common in adults
• Symmetry: Spitz nevi are symmetric (starts with a nest and ends with a nest). Most spitzoid melanomas are usually asymmetric (starts with a nest and ends in single cells)
• Mitotic figures: When located in the deep portion of the lesion or grouped in an area, they must be considered highly indicative of melanoma
• Cellular atypia: Spitz nevi can show prominent nuclei and nucleoli but the cytoplasm tends to be ample too. In melanomas, the cells show large nuclei and prominent nucleoli with minimal or vacuolated cytoplasm
• Pagetoid spread: In Spitz nevi the pagetoid cells are usually located in the center of the lesion, and in melanoma the pagetoid spread goes beyond the dermal component, scattered throughout the entire lesional epidermis
• Kamino bodies: In Spitz nevi Kamino bodies are confluent, numerous, and large as opposed to melanomas, in which Kamino bodies are smaller in number and size

Immunohistochemistry

As explained above, the diagnosis of Spitz nevus and spitzoid melanoma can be exceedingly difficult in some cases as there are lesions with features of both benignity and malignancy. Immunohistochemistry has been used widely in the evaluation of melanocytic lesions and may play a role in the distinction between Spitz nevus and spitzoid melanoma. Spitz nevi usually show a stratified pattern of HMB-45 labeling, similar to ordinary acquired nevi; a second pattern is that of homogeneous labeling throughout the lesion, similar to that seen in blue nevi [34]. However some cases may show patchy labeling in deeper melanocytes similar to what is seen in melanoma [35]. Ki-67 (MIB-1) can help when there are positive cells throughout the lesion [34]. In contrast, in Spitz nevi, anti-Ki-67 shows a stratified pattern with positive cells in the upper portion of the tumor and decreased expression toward the bottom. In cases with significant lymphoid infiltrate, a double immunostudy (MIB-1 and anti-MART-1) may help detect if the proliferating cells are melanocytes [34]. Immunodetection of phosphohistone H3 has been shown to increase the sensitivity and accuracy for detection of mitotic figures; it improves interobserver variability and may reduce the time required to identify mitotic figures in melanomas. Because it is of paramount importance to find and evaluate the number of mitotic figures in Spitz nevi, this marker can be used for this purpose. A cocktail against MART-1 and phosphohistone H3 may be helpful as it would identify the proliferating cells as melanocytes and not lymphocytes [36].

Spitz Nevi Variants

Pigmented Spindle Cell Nevus of Reed

Clinical Features

Pigmented spindle cell nevus of Reed (PSCN) was first described by Reed et al. in 1975 as a distinctive, benign, acquired melanocytic nevus [37]. This lesion has been widely considered as a variant of Spitz nevus [38–40] and thus it is discussed in this chapter. Clinically, it presents as an intensely pigmented lesion that frequently acquires a dark color and displays rapid growth. PSCN is usually symmetric, is well delineated, and presents as a dark brown or a pitch black macule or thin plaque; however, in some cases it may present as a papule. Lesions are uniform in appearance, typically small (<6 mm), and well circumscribed. Most common locations include proximal extremities (especially the thigh), back, and abdomen, most commonly in young women, although it may occur in children and adults [41, 42].

Histologic Features

Histologically, the lesion is characterized for its spitzoid morphology, prominent pigmentation with numerous melanophages, horizontal fascicular growth pattern restricted to the epidermis and papillary dermis, and predominance of spindled melanocytes. On low magnification, the benign nature of the lesion is assessed by the recognition of a small size, sharp circumscription and symmetry. The vast majority of cases are junctional; however, there are also compound lesions. In such cases, the melanocytes in the papillary dermis are in direct connection with the junctional nests. Such lesions usually involve only the superficial papillary dermis, although they may infiltrate the superficial reticular dermis. When the reticular dermis is fully involved, those lesions should probably be called conventional compound Spitz nevus. In our experience, the epidermis of most PSCN has a uniform thickness throughout; however, marked epidermal hyperplasia can be present (especially in older stages of the lesion). In early stages, PSCN may show at their periphery a lentiginous growth pattern. There are usually numerous melanophages in the papillary dermis, lined up in a band parallel to the epidermis along with granulation tissue-like stroma (resembling dermal regression). A diagnostic clue to PSCN would be the presence of the preserved nested architecture in the junctional component.

The lesion is mainly composed of tightly packed melanocytic nests or fascicles with uniformly sized and distributed. The nests and fascicles are vertically oriented, but in some cases, they have concentric arrangement and are disposed horizontally. They are usually located close to each other and in the lower epidermis, with a peripheral cleft separating them the thinned suprapapillary plate. The spindled melanocytes show large, oval nuclei with speckled chromatin and small, centrally located inconspicuous nucleoli. The cytoplasm is scant with variable amount of granular melanin pigment. Heavy pigmentation can also involve the adjacent keratinocytes, stratum corneum, and papillary dermis. Some cases show scattered atypical melanocytes with indented nuclei and prominent nucleoli but always in the background of monomorphous melanocytes. Epithelioid and multinucleated giant melanocytes are seen in some cases but represent only a minor cell population. Pagetoid ascent of cells is often seen and is classically in a nested rather than single-cell pattern. Pagetoid melanocytes are more commonly seen in the center of the lesion, usually associated with numerous junctional nests (typically in children). In contrast, spitzoid melanoma shows pagetoid migration also at the periphery of the lesion. Normal-appearing mitotic figures can be seen in the intraepidermal and upper dermal component; however, atypical mitotic figures gathered in clusters are diagnostic clues for melanoma. Similar to what can be identified in conventional Spitz nevi, melanocytes in PSCN can involve the eccrine ducts. Kamino bodies can be seen in PSCN but tend to be smaller than those seen in conventional Spitz nevi. Cases with a thick dermal component should show decrease in the size of melanocytes and more rounded shape with depth in the dermis (maturation). There is commonly perivascular dermal inflammation, although regression is not a feature of PSCN.

Differential Diagnosis

The main differential diagnosis is melanoma in situ [43]. Both lesions are composed of spindle melanocytes arranged in junctional nests that can involve the skin appendages. One point to consider is that PSCN is only rarely seen in sun-damaged skin of older patients. The uniformity of the lesion, the small size and symmetry, and the benign silhouette with lack of "shoulder" favor a diagnosis of PSCN. On the other hand, melanoma is asymmetrical and shows irregular pigmentation, melanocytes with ample pale cytoplasm and dusty melanin, deep dermal mitotic figures, and lack of maturation. Some lesions of PSCN may show marked pagetoid upward migration, but it should be limited to the center of the lesion.

Table 4.2 Pigmented spindle cell nevus of Reed

• Symmetric lesions with lateral circumscription
• Marked monomorphism of melanocytes
• Most cases are junctional (compound lesion are confined to papillary dermis)
• Melanocytes are arranged in nests always predominate over single cells
• Nests are large and confluent with parallel or vertical orientation
• Maturation of melanocytes
• Frequent mitotic figures within epidermis (only rarely seen in dermis)
• Solar damage is usually absent

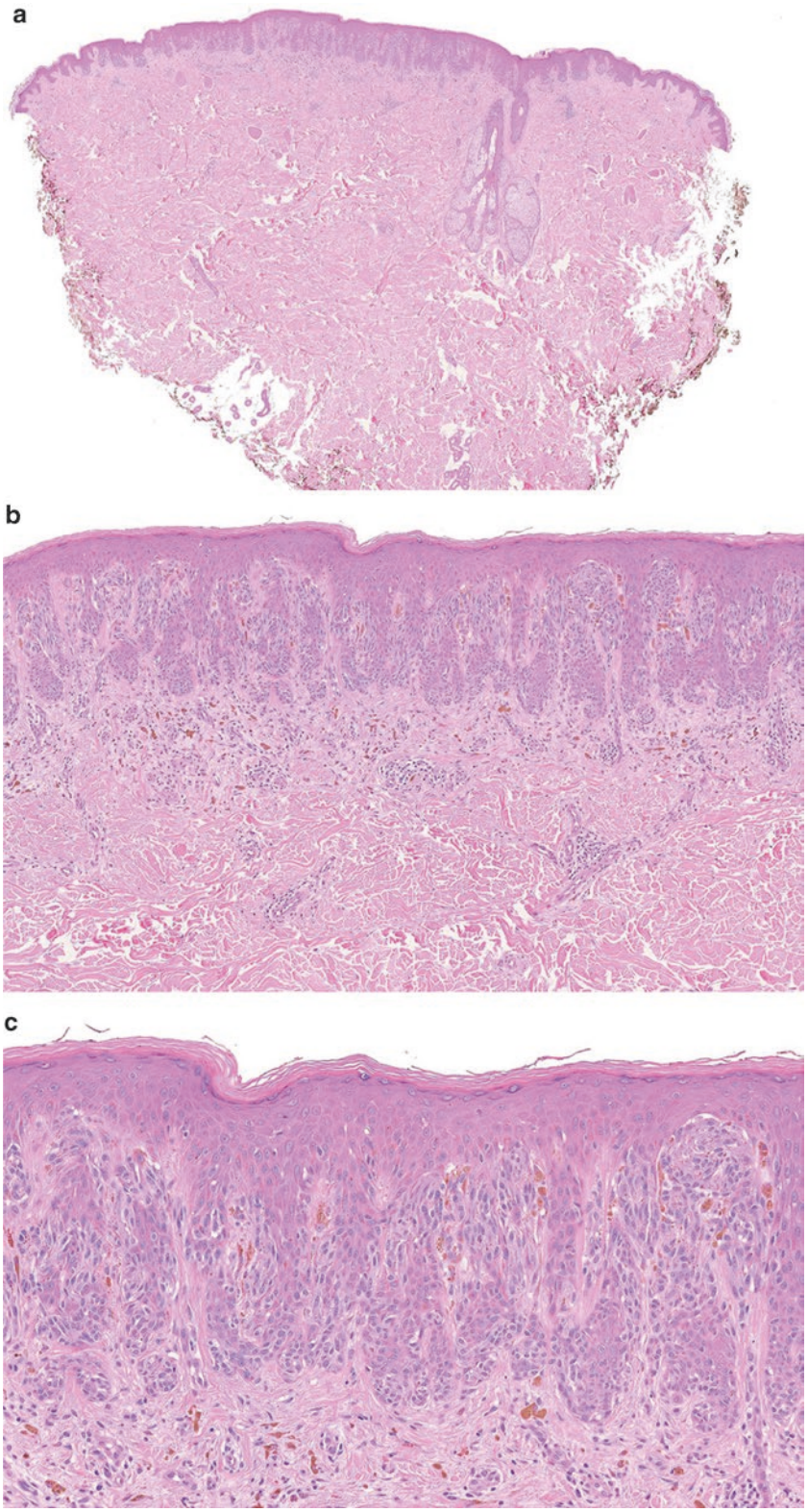

Fig. 4.15 Early phase of pigmented spindle cell nevus of Reed. The lesion is symmetric and composed of homogeneous nests with lentiginous growth and many dendritic cells the single and small nests of melanocytes are aligned along the junction (**a**). Note the preserved architecture in the epidermis (**b**). Higher magnification showing single elongated melanocytes, nests, and dendritic cells (vertically oriented). This example shows focal host response in papillary dermis (**c**)

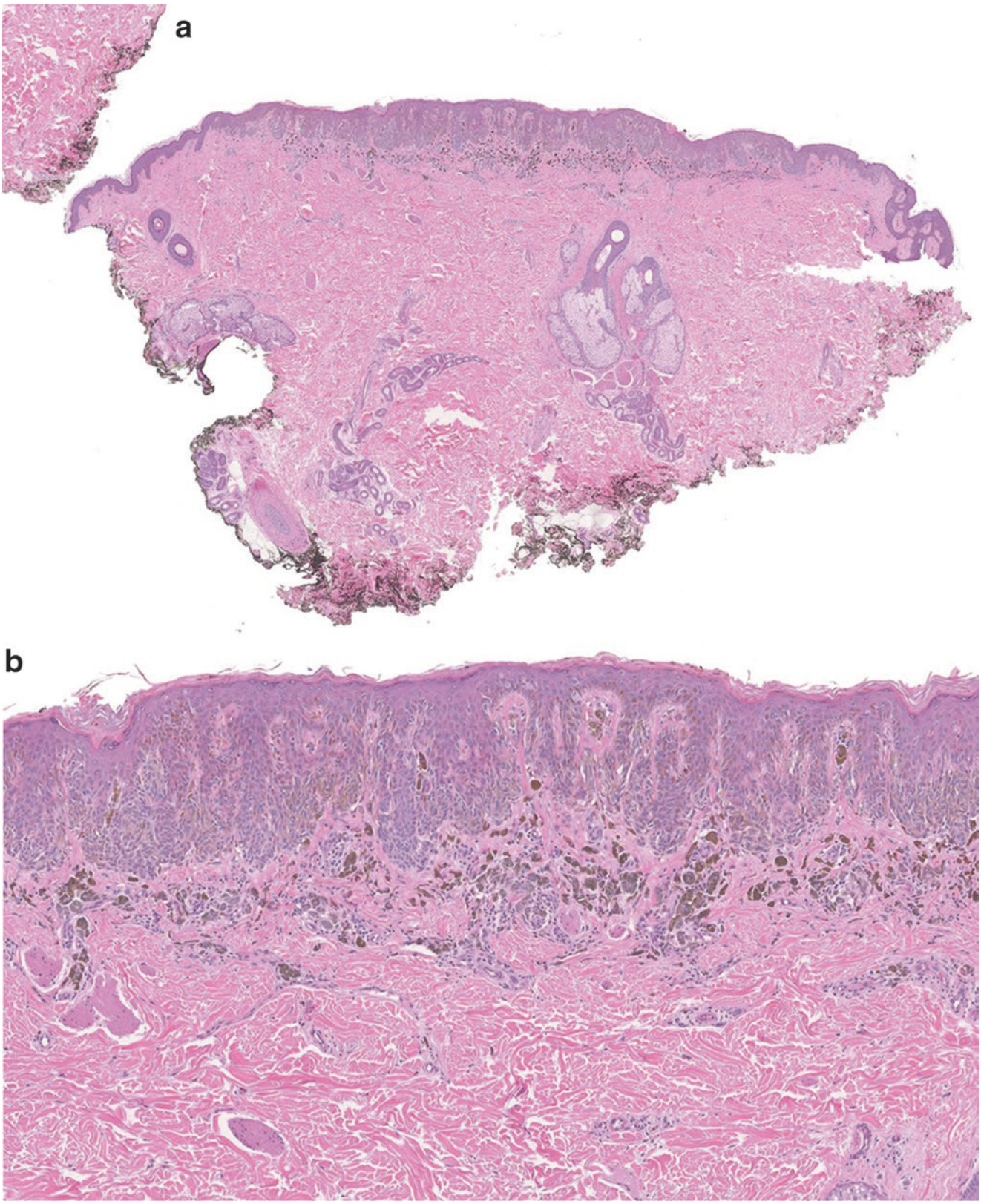

Fig. 4.16 Early phase of pigmented spindle cell nevus of Reed. This example shows elongated and dendritic melanocytes gathered in irregular small nests (**a**). Most of junctional nests are located at the base of the rete ridges. The pigment is distributed throughout the lesion (**b**).

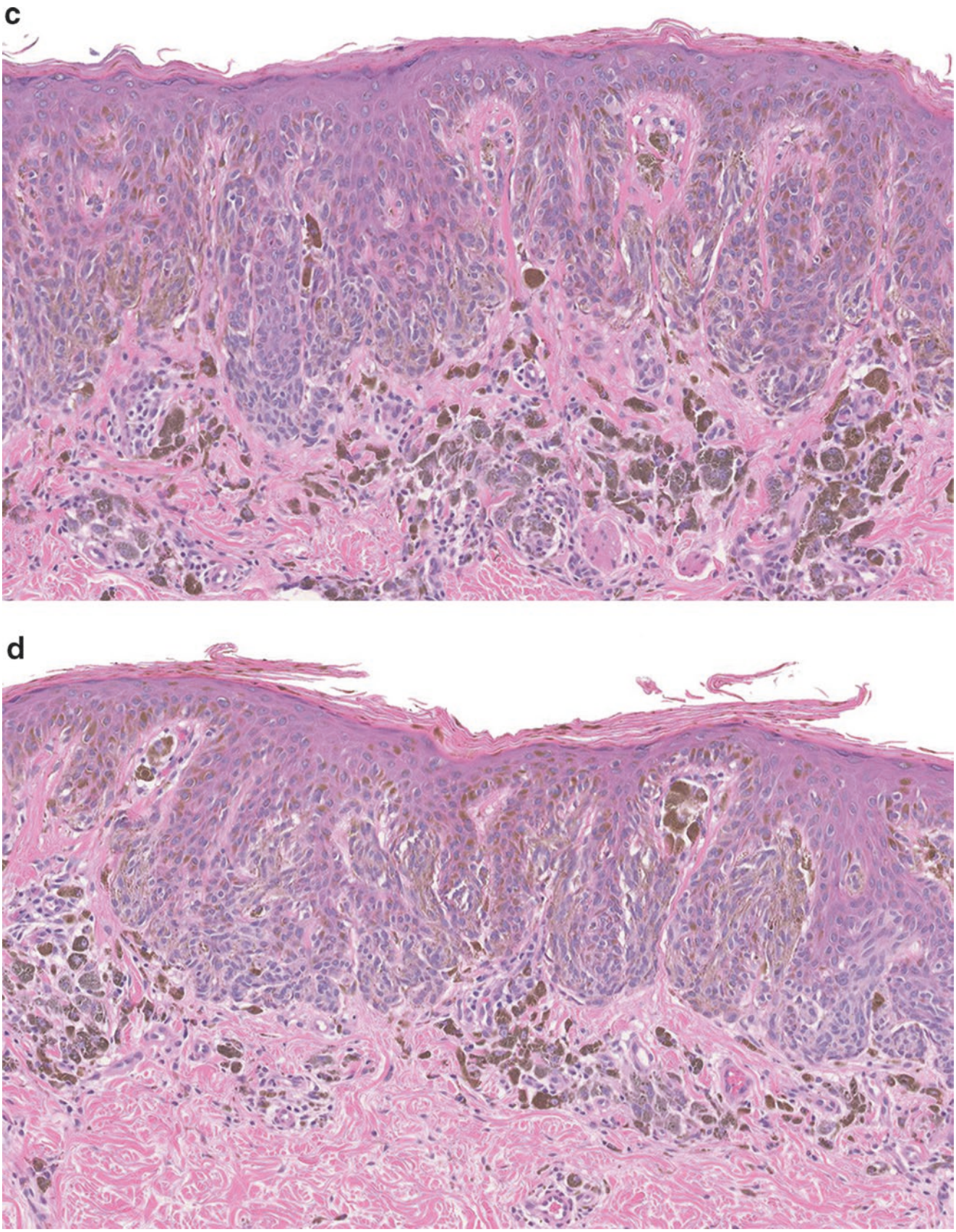

Fig. 4.16 (continued) The lesion shows increased number of single melanocytes but lack cytologic atypia. In the early stages, single melanocytes can predominate at the edge of the lesion (**c**, **d**)

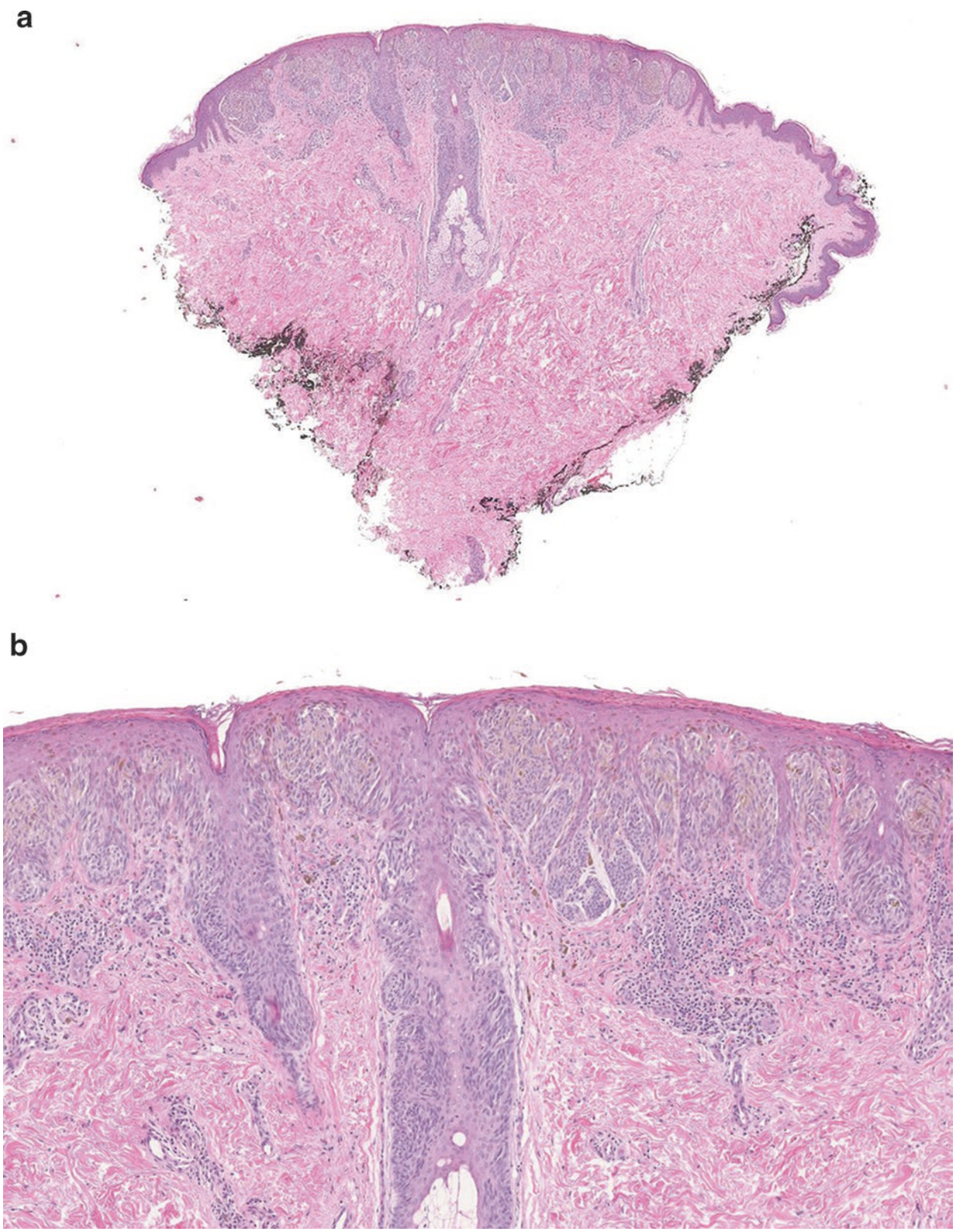

Fig. 4.17 Pigmented spindle cell nevus of Reed. This is a classic example showing symmetry, tightly packed melanocytic nests and fascicles with uniform size. The nests are vertically oriented (**a**). Pigmentation is noted in the stratum corneum, epidermis, and melanocytic nests. There is characteristic compact hyperkeratotic stratum corneum (**b**).

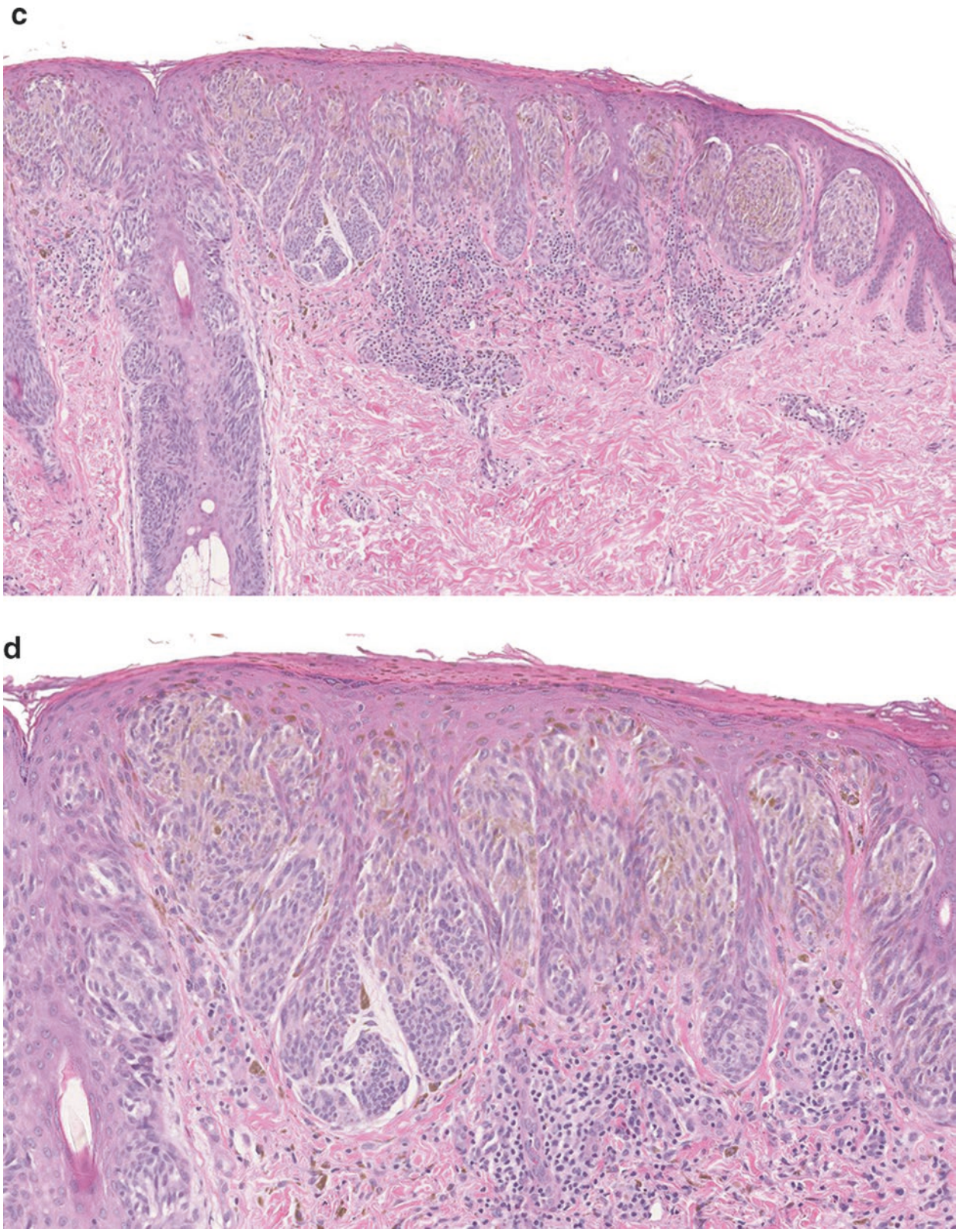

Fig. 4.17 (continued) There are melanocytic nests that are located close to each other and in the lower epidermis. Some nests show a focal peripheral clefting (**c**). The melanocytes are large, oval nuclei with speckled chromatin. The cytoplasm is scant with variable amount of granular melanin pigment (**d**)

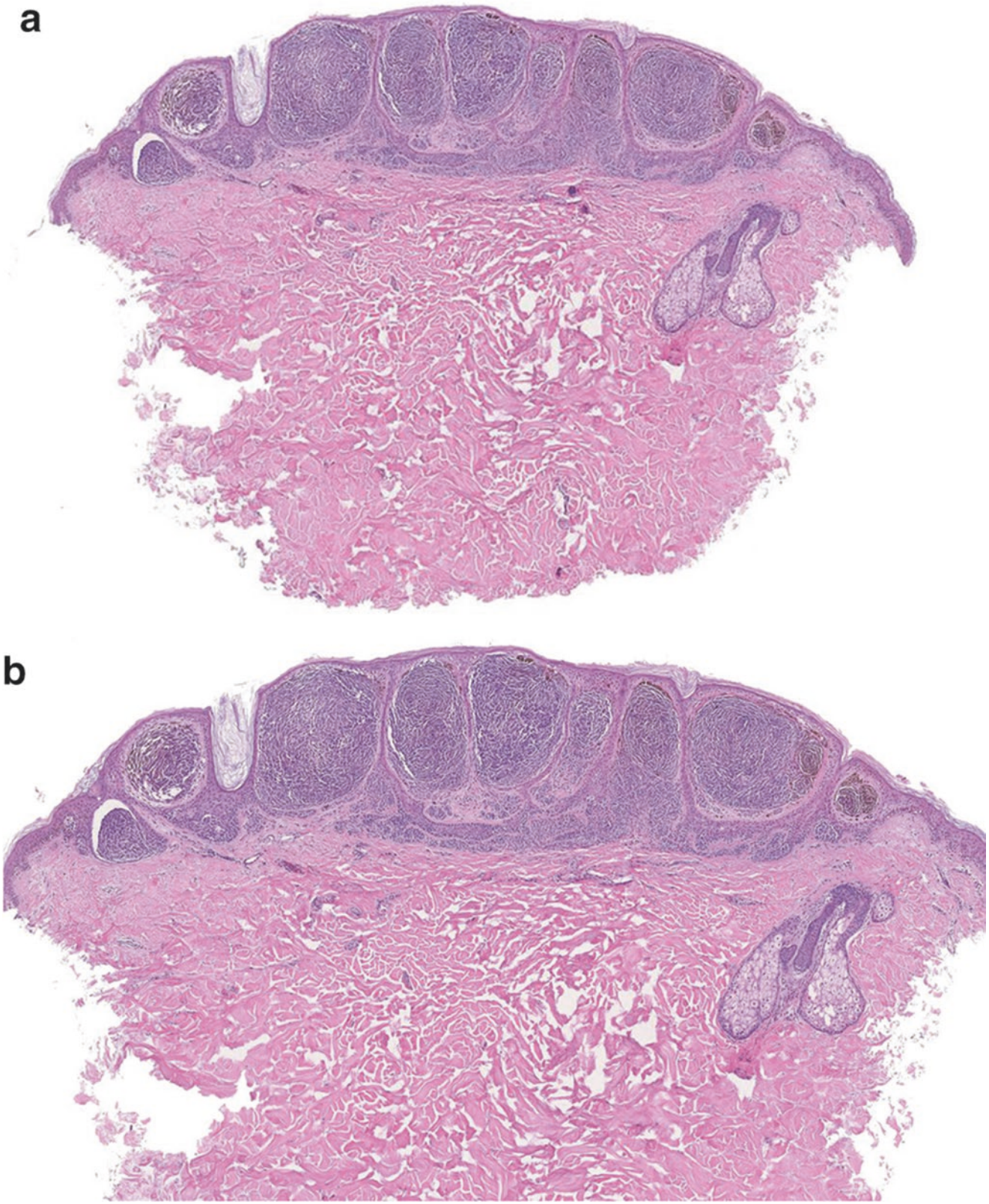

Fig. 4.18 Pigmented spindle cell nevus of Reed. This example is composed of large nests with heavy pigmentation (**a**). The lesion is symmetric with a flat base and composed of vertically oriented monomorphous spindle melanocytes (**b**).

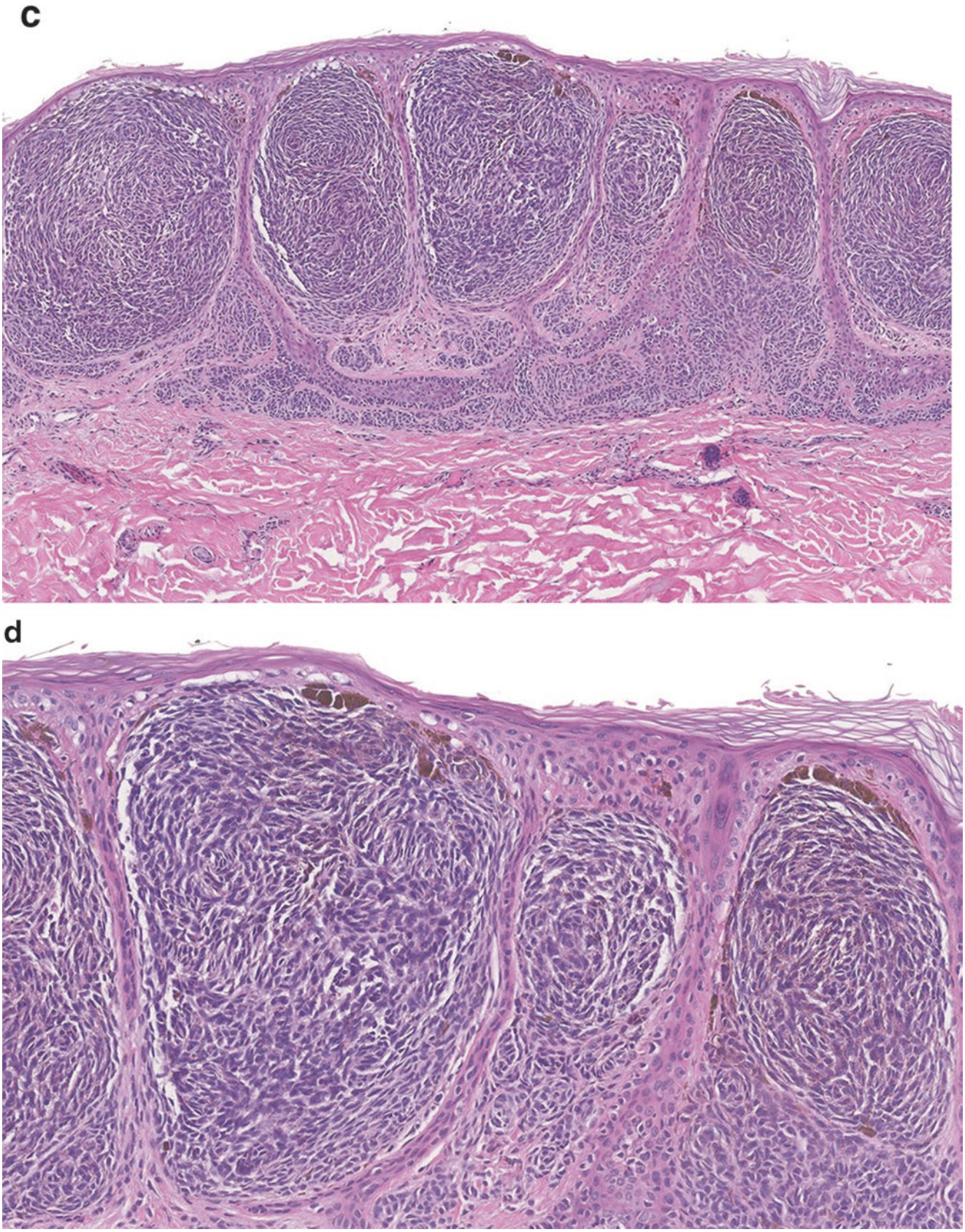

Fig. 4.18 (continued) Note the increase amount of pigment in the large nests (**c**). There is minimal clefting around the melanocytic nests (**d**)

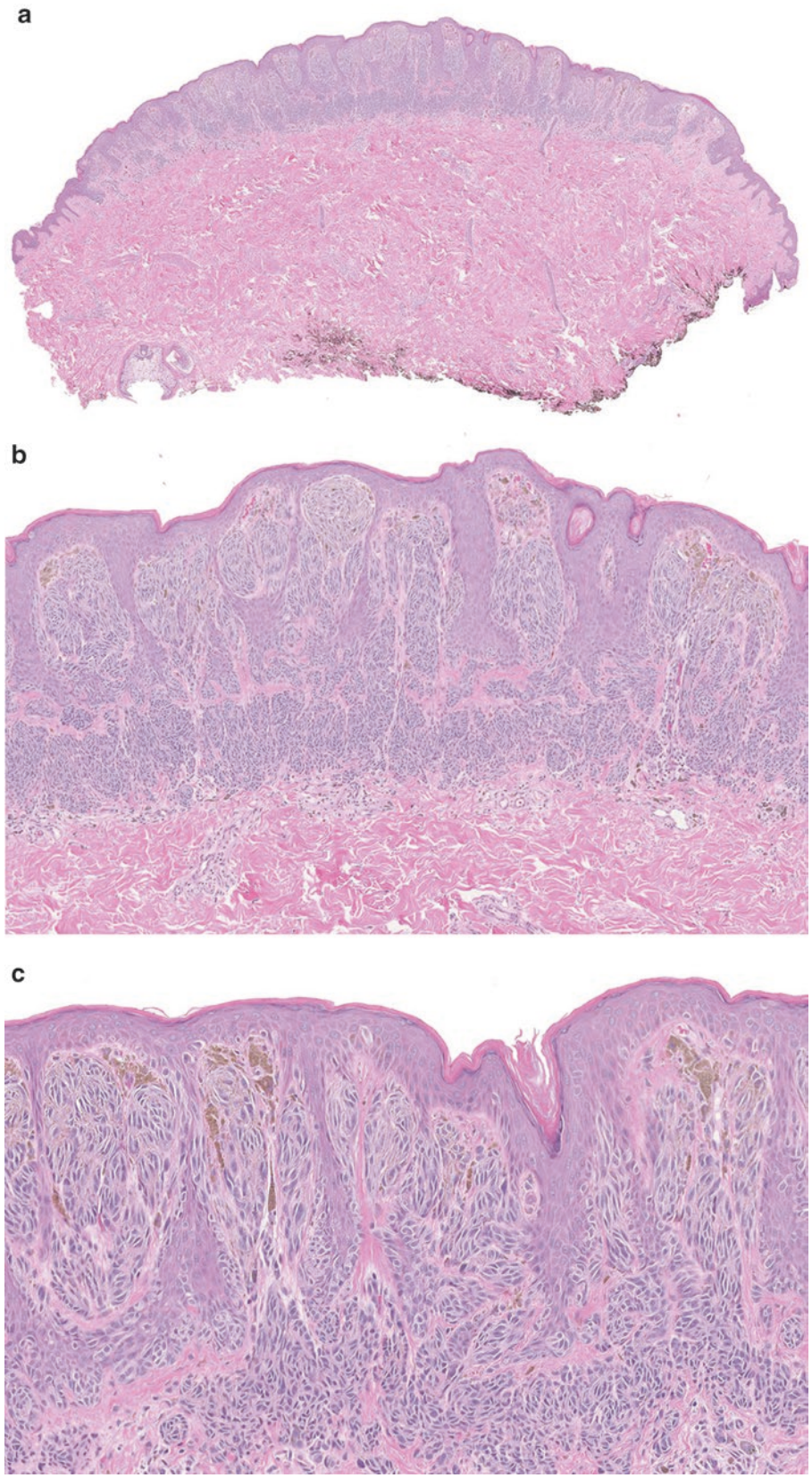

Fig. 4.19 Pigmented spindle cell nevus of Reed. This example is compound. The intradermal component expands in papillary dermis (**a**). Note the characteristic nests at the junction and the preserved mature collagen bundles in dermis in between the dermal nests (**b**). Vertically oriented melanocytes in the junction and more epithelioid melanocytes in dermis (**c**)

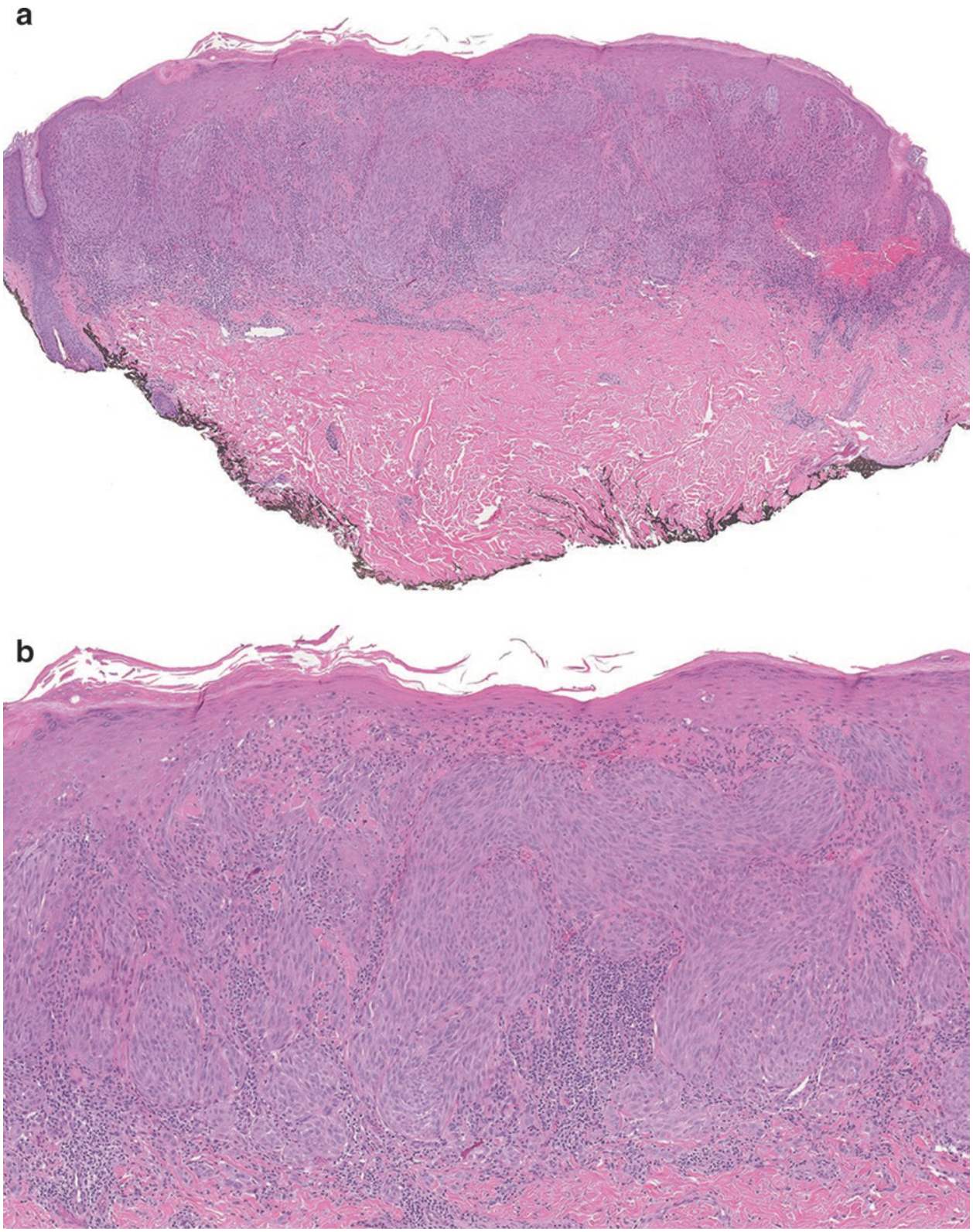

Fig. 4.20 Amelanotic spindle cell nevus of Reed. This is a 16-year-old male with a lesion on his thigh. This example is compound and amelanotic. Note that the spindle cell melanocytes are devoid of pigment. Note the compact and well delineated growth of the lesion along the nested component at the periphery (**a**). Note the lack of pigment, the fascicular growth of the spindle cell melanocytes, and the preserved monomorphism throughout the lesion. The center of the lesion has a flat base (**b**).

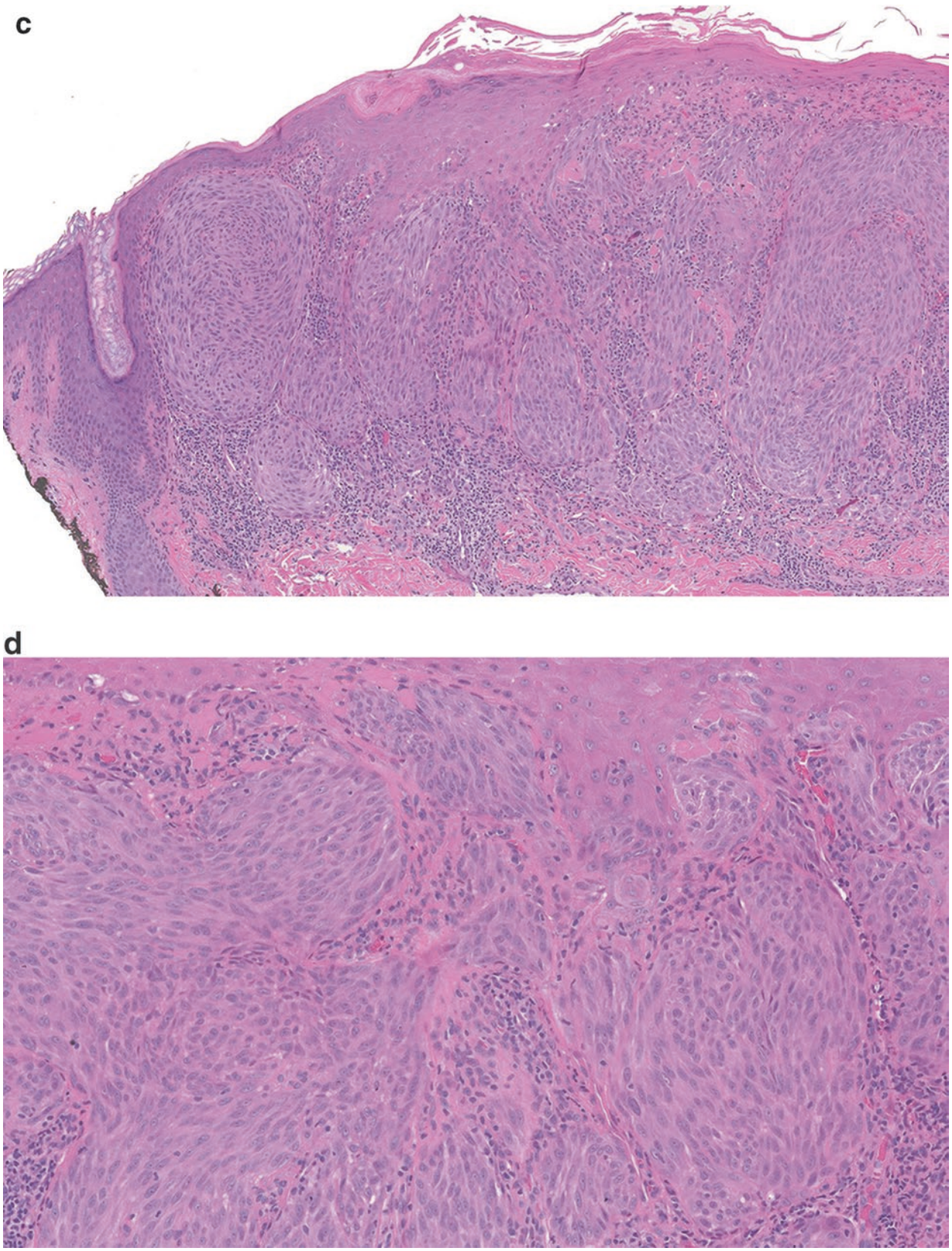

Fig. 4.20 (continued) The lesion ends with abrupt nest formation (**c**). High power of the monomorphic melanocytes showing banal cytologic features (**d**)

Atypical Pigmented Spindle Cell Nevus of Reed

Atypical pigmented spindle cell nevus is a term used to raise clinical concern about the biological potential of a lesion consistent with a PSCN, but that demonstrates further atypical features [39] including some of the following: larger size (>6 mm), involvement of reticular dermis, loss of the benign silhouette, cytologic atypia with high cellularity, lack of symmetry with lentiginous growth at the periphery of the lesion, and large, epithelioid melanocytes with ample cytoplasm and prominent nucleoli. These atypical features warrant caution in the biological behavior of the lesion, and thus a diagnosis of atypical pigmented spindle cell nevus would be appropriate. In general, clinical follow-up of these cases has not suggested aggressive behavior in such lesions.

Spitz Nevus with Dysplastic (Clark) Features ("Spark")

Clinical Features

In practice, one may occasionally encounter hybrid melanocytic lesions with features of both dysplastic and Spitz nevus. Thus, the term Spark nevus that combines cytomorphologic features of Spitz nevi with the altered architectural pattern commonly associated with dysplastic nevi. Some authors refer them by a more descriptive term "spitzoid dysplastic nevi." These lesions are often difficult to diagnose as they may exhibit unusual features that may overlap with melanoma. Clinically, these nevi are more frequently seen on the thighs and trunk of young woman [44–46] and are usually small in size (one series documented <5 mm in size) [45].

Histologic Features

Histologically, the lesions are either junctional or compound and superficial and horizontally oriented. Spark nevi are composed of variable proportions of spindled and epithelioid spitzoid-appearing melanocytes, which are large in size and generally monomorphic in appearance. These melanocytes are disposed in oblong, regularly sized nests on the sides and tips of often hyperplastic rete ridges along the dermal-epidermal junction, with extensive bridging of nests between rete ridges in a horizontal or plaque-like pattern. This extensive bridging occasionally gives an asymmetric appearance of the lesion. Also, the presence of underlying fibroplasia gives a flat appearance to the base of the junctional component. The junctional component extends laterally ("shoulder") beyond the dermal component in compound lesions. Foci of small clusters and single isolated melanocytes (pagetoid upward migration) can be found in the epidermis primarily within the center of the lesion. There are variable numbers of Kamino bodies. In compound lesions, the dermal component is usually small and limited to the papillary dermis. There is maturation of the dermal component with descent into the dermis. Mitotic figures are only rarely seen in (upper) dermal component.

Differential Diagnosis

The differential diagnosis of this lesion is primarily with melanoma. The presence of excessive pagetoid upward migration (especially at the lateral edges), enhanced atypia, broad zones of epidermal effacement, dermal mitotic figures, and an expansile growth pattern in the papillary dermis favors a diagnosis of melanoma. Spark nevi generally lack significant melanocyte involvement of suprapapillary plates and are symmetrical, laterally circumscribed, and typically smaller than superficial spreading melanomas. There is not enough documentation on whether these lesions may undergo malignant degeneration, thus underscoring the importance of achieving complete excision of these lesions. If only a portion of the lesion is present for histologic interpretation in the initial biopsy and diagnostic uncertainty exists as to whether the lesion is a melanoma or not, then it is advisable to recommend complete excision for accurate histologic examination. The differential diagnosis of this lesion also includes a dysplastic nevus and Spitz nevus. The parallel and superficial arrangement of spindled cell melanocytes in epidermis gives Spark nevi a characteristic histologic appearance that differs from that of conventional Spitz nevi. In addition, in cases where cytologic atypia is not as pronounced, Spark nevi could be considered a form of dysplastic nevus.

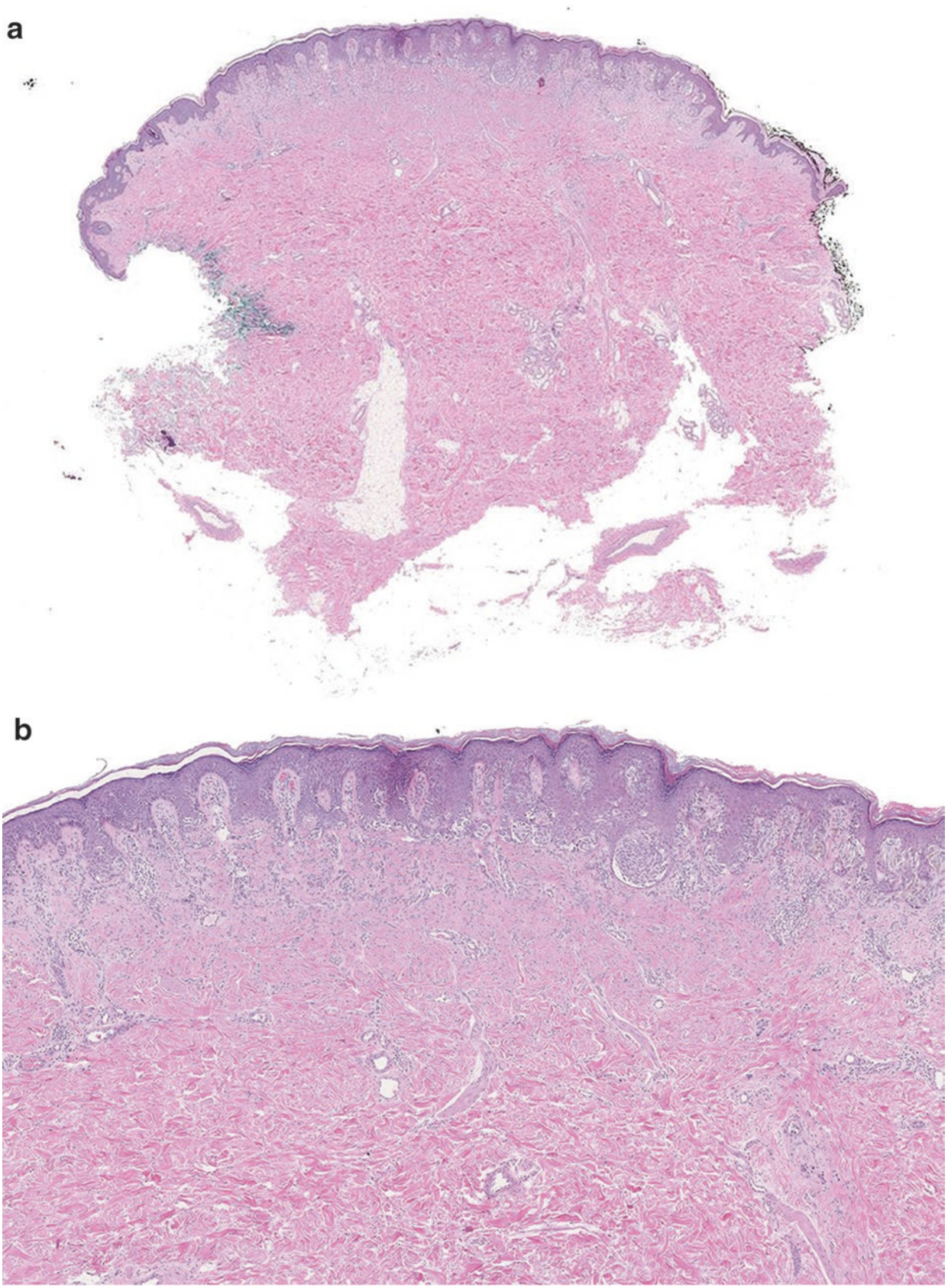

Fig. 4.21 Spitz nevus with dysplastic (Clark) features (Spark). Note on low power the symmetric appearance of the lesion (**a**). The lesion is composed of elongated nests arranged parallel to the epidermis. Note the bridging of the rete ridges (as seen in dysplastic nevi) (**b**).

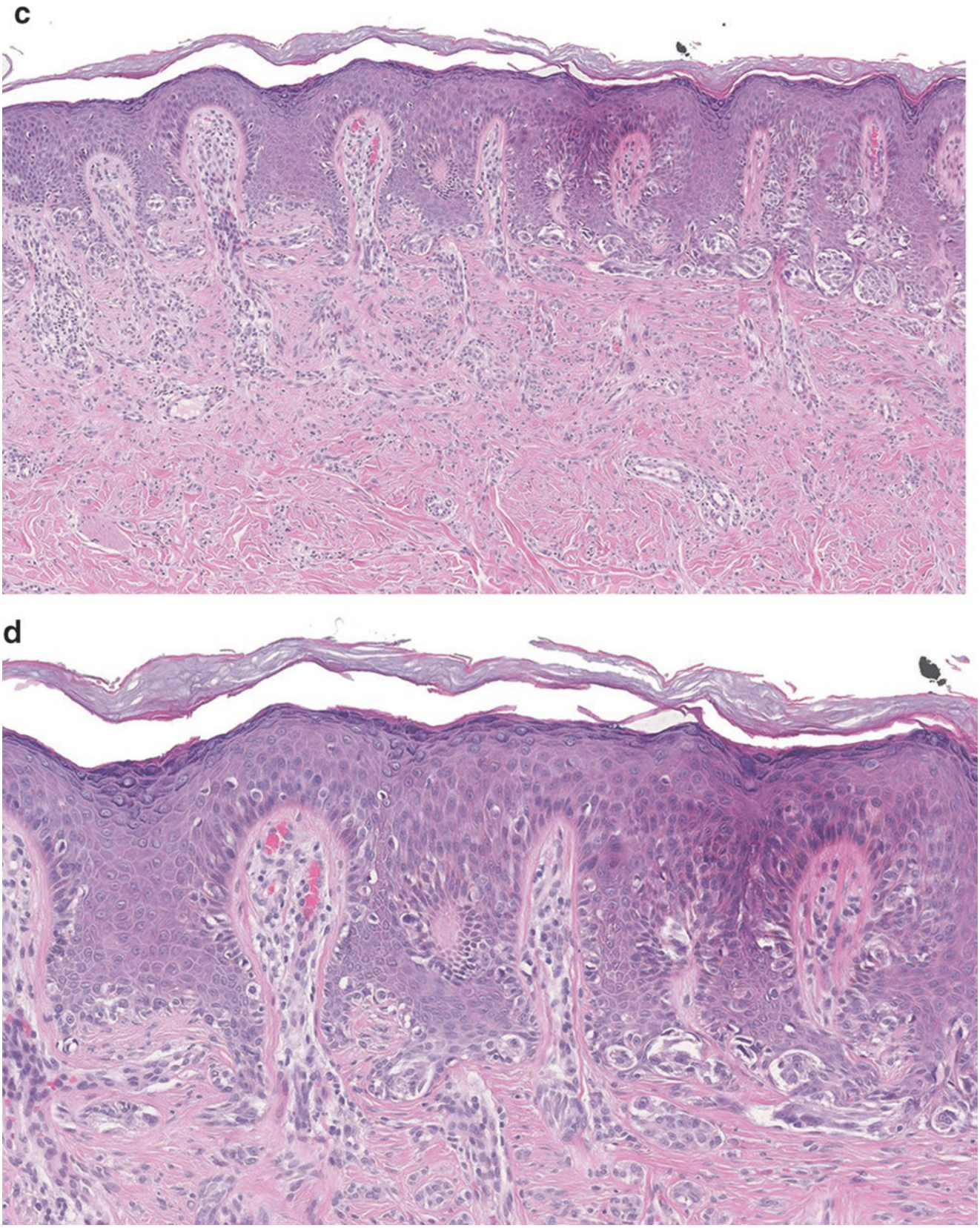

Fig. 4.21 (continued) Note the cells in the junction and in dermis with spitzoid cytomorphology (**c**). The nests have a similar size and shape with only rare melanocytes above the basal layer (**d**)

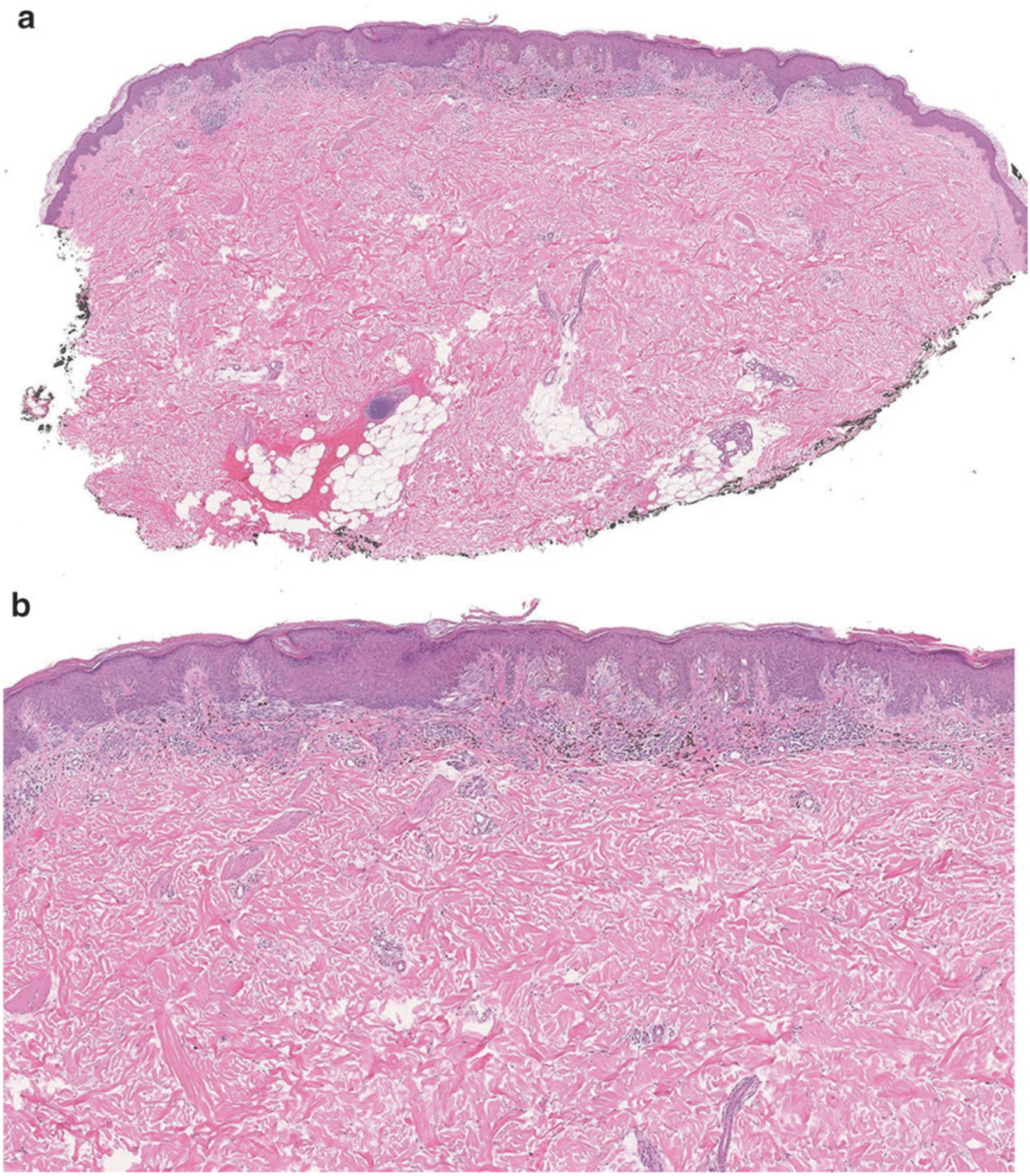

Fig. 4.22 Spitz nevus with dysplastic (Clark) features (Spark). Another example showing a flat and symmetric growth (**a**). The nests in this example are parallel to epidermis and composed predominantly of spindle cell melanocytes (**b**).

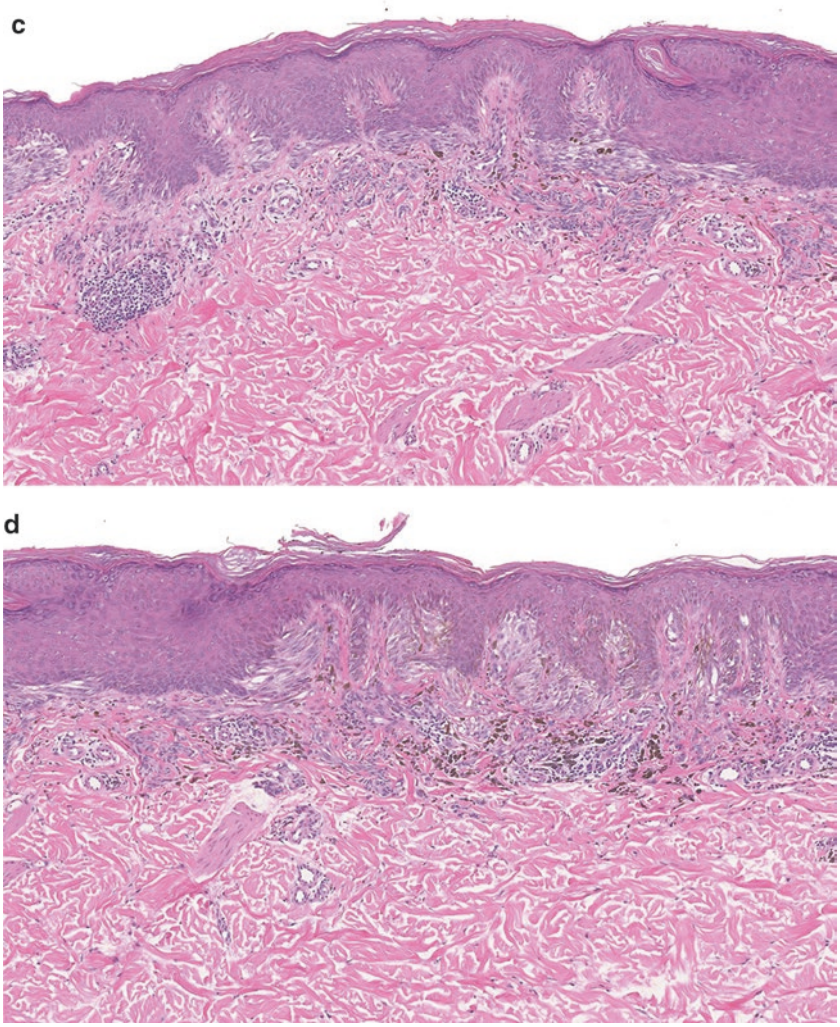

Fig. 4.22 (continued) In addition to the spitzoid cytomorphology of the lesion, there is extensive bridging of rete ridges (**c**). This example shows some host response in papillary dermis (**d**)

Desmoplastic Spitz Nevus

Clinical Features

Desmoplastic nevus was originally characterized by Reed et al. in 1975 as an end-stage spindle and epithelioid cell nevus that had lost continuity with the epidermis and had undergone marked fibroplasia within the reticular dermis [37]. Clinically, desmoplastic Spitz nevi present as erythematous or red-brown papules of several years duration and may be confused with atypical melanocytic proliferations including melanoma. These nevi are more commonly seen in young adults and children and exhibit a predilection for the limbs [3, 27, 47–49]. However, rare cases of desmoplastic nevi have been documented in chronic sun-damaged skin [50].

Histologic Features

Histologically, these nevi are symmetric with a wedge-shaped growth pattern [51]. Due to the associated prominent sclerosis, some cases have a pink appearance at scanning magnification. Most lesions are intradermal; however, some cases show small, junctional nests and/or a lentiginous melanocytic proliferation of epithelioid melanocytes. The dermal component has a distinctive zonal configuration extending to the reticular dermis, which has greater cellularity superficially. The dermal component is characterized by a proliferation of epithelioid cells with visible nucleoli (usually 5–10 % of the lesion), fusiform melanocytes, and dendritic melanocytes, in addition to conventional melanocytes, which are usually present superficially and arranged in nests. These melanocytes are dispersed in a desmoplastic

stroma that is composed of thick, eosinophilic collagen bundles. In most of cases, the cellularity diminishes toward the edges of the lesion with the most peripheral melanocytes dispersed in between collagen bundles. Usually, epithelioid melanocytes predominate superficially and demonstrate a nesting pattern, similar to an acquired nevus, blending imperceptibly with the underlying spindle portion of the lesion, and the amount of stroma increases with dermal depth. Melanin pigment is generally sparse and when present is finely granular and mostly found in the ovoid melanocytes. Mitotic figures are exceptional. A recent study highlighted the presence of lymphoid aggregates thus mimicking desmoplastic melanoma [52].

Differential Diagnosis

The main differential diagnosis of desmoplastic Spitz nevi is with desmoplastic melanoma. Their distinction usually can be made with confidence if one is provided with adequate tissue that permits the evaluation of features that are relevant for the diagnosis. If one is dealing with a small tissue sample, the distinction is often challenging requiring additional tissue to make a diagnosis. Clinically, desmoplastic Spitz nevi are more commonly seen in younger patients and located on limbs and trunk, whereas desmoplastic melanomas are usually seen in older patients and located in sun-exposed areas. Although both conditions may demonstrate junctional melanocytes, spindled dermal melanocytes, and desmoplastic stromal change, desmoplastic melanoma tends to be more deeply invasive and often demonstrates perineural invasion. If the desmoplastic dermal melanocytic proliferation is accompanied by melanoma in situ, the diagnosis is straightforward; however, in approximately one third of desmoplastic melanomas, there is no obvious in situ melanoma. Desmoplastic melanoma typically displays an infiltrative asymmetric silhouette that often extends into the subcutaneous fat. Desmoplastic Spitz nevi tend to be symmetric, broader than deep, and confined to the dermis. The finding of any dermal mitotic figures should raise the possibility of desmoplastic melanoma [51]. The presence of solar elastosis will favor the diagnosis of desmoplastic melanoma over desmoplastic Spitz nevus. Lymphocytic aggregates are commonly mentioned as a helpful diagnostic feature for the diagnosis of desmoplastic melanoma but can also be seen in desmoplastic nevus [52].

Immunohistochemical studies may be useful in this differential diagnosis. Desmoplastic Spitz nevus demonstrates S-100 protein, MART-1, and HMB-45 expression, the latter demonstrating stronger staining in the superficial portions of the lesion with diminution upon dermal depth [53]. The numbers of proliferating cells are few, and this low proliferative activity, as assessed by mitotic count and/or Ki-67 expression (fewer than 10 cells/mm^2), helps confirm a diagnosis of desmoplastic Spitz nevus [51]. Both desmoplastic melanoma and desmoplastic Spitz nevus are positive for S-100p; however, rare cases of desmoplastic melanoma can be negative for this marker. HMB-45 and MART-1 are almost exclusively negative in desmoplastic melanoma (positive if epithelioid melanocytes are seen), whereas positive in desmoplastic nevus. In our experience, p16 has limitations in the diagnostic value of desmoplastic melanocytic proliferations, as immunohistochemical labeling is not restricted to desmoplastic Spitz nevi, but can also be found in desmoplastic melanoma. This limitation in the diagnostic use of p16 is not surprising, as it has been previously documented that the expression of p16 alone does not reliably distinguish Spitz nevi from spitzoid melanoma or common nevi from conventional melanoma [54–56]. Spitz nevi with overlapping features with desmoplastic Spitz nevi have been found to have gains in chromosome 11p and HRAS mutations in exon 3 [57].

Table 4.3 Histologic features of desmoplastic Spitz nevus

• Desmoplastic Spitz nevi are small and symmetrical
• Most examples are intradermal
• Distinctive zonal configuration of the dermal component
• Epithelioid melanocytes predominate superficially and spindle cell melanocytes predominate in the deeper portion of the lesion
• The stroma increases with depth
• Spitzoid melanocytes (epithelioid cells with visible nucleoli) are present (represent 10–15 % of the lesion)
• Absent mitotic figures and low proliferation rate

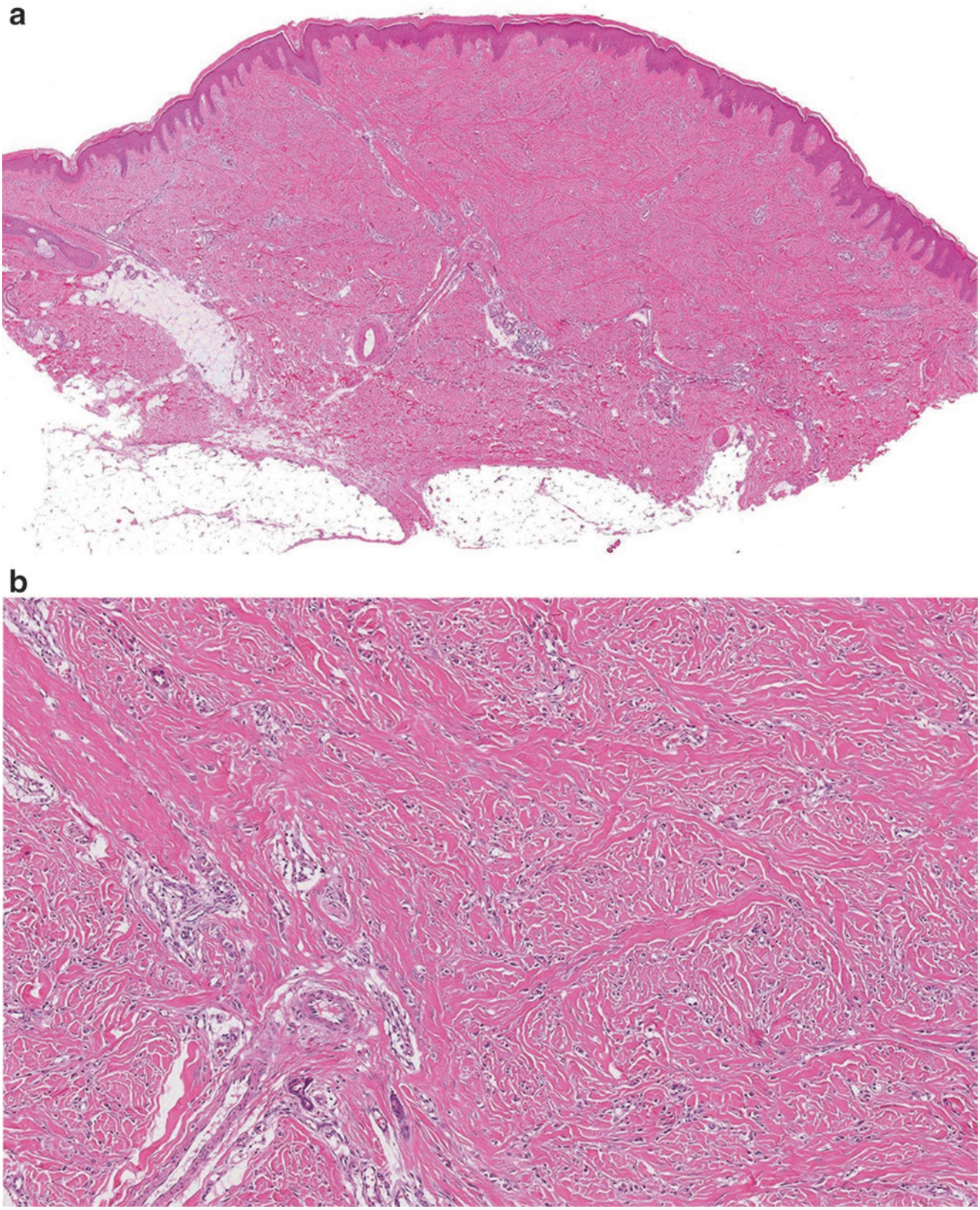

Fig. 4.23 Desmoplastic Spitz nevus. This case shows a symmetric dermal proliferation of epithelioid and spindle melanocytes within a desmoplastic stroma (**a**). Note the paucicellular hyalinized stroma (**b**).

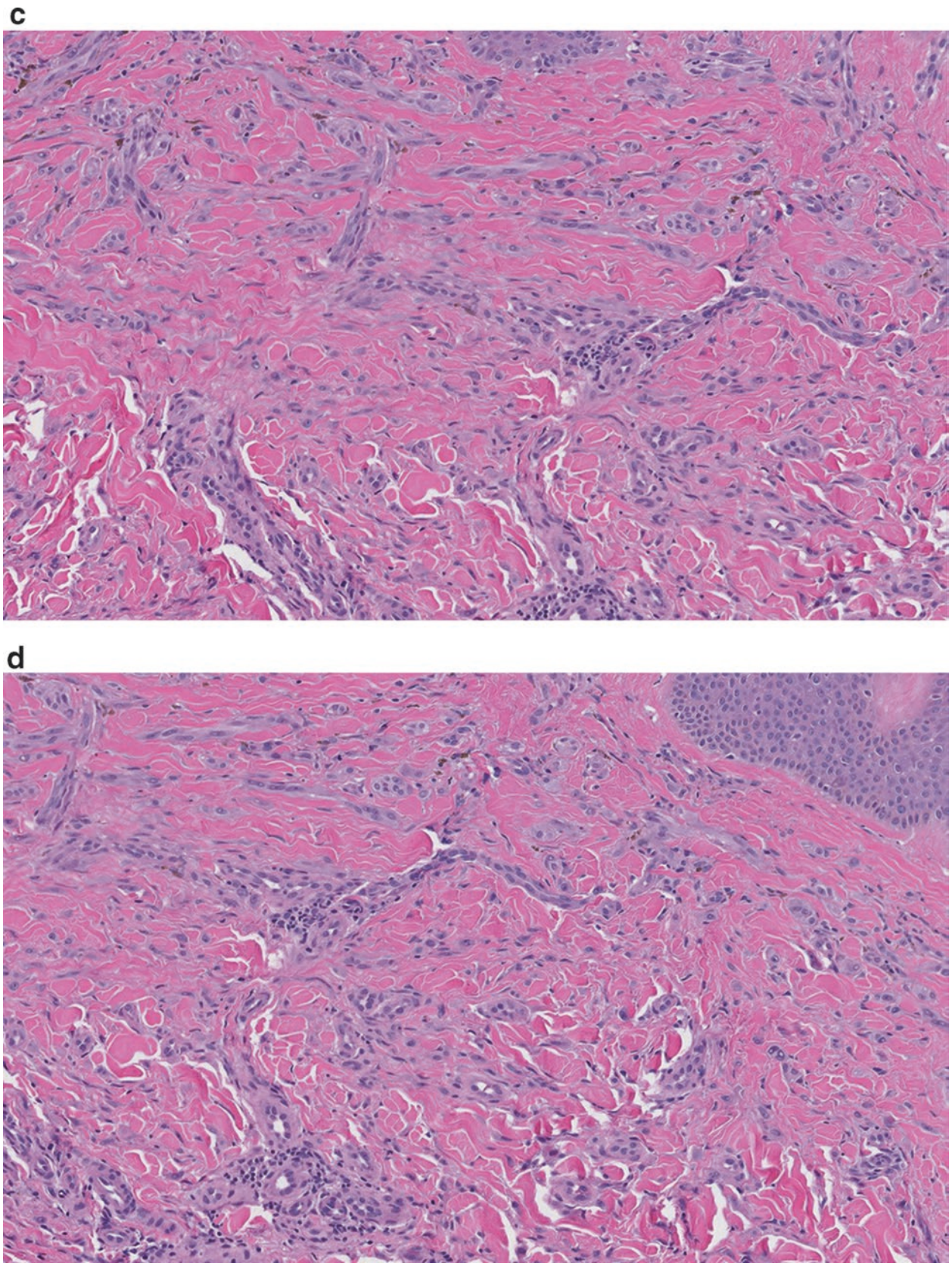

Fig. 4.23 (continued) The melanocytes are isolated and arranged in small nests (**c**). The cells have a fibroblast-like appearance and lacks cytologic atypia. There is slight lymphocytic infiltration (**d**)

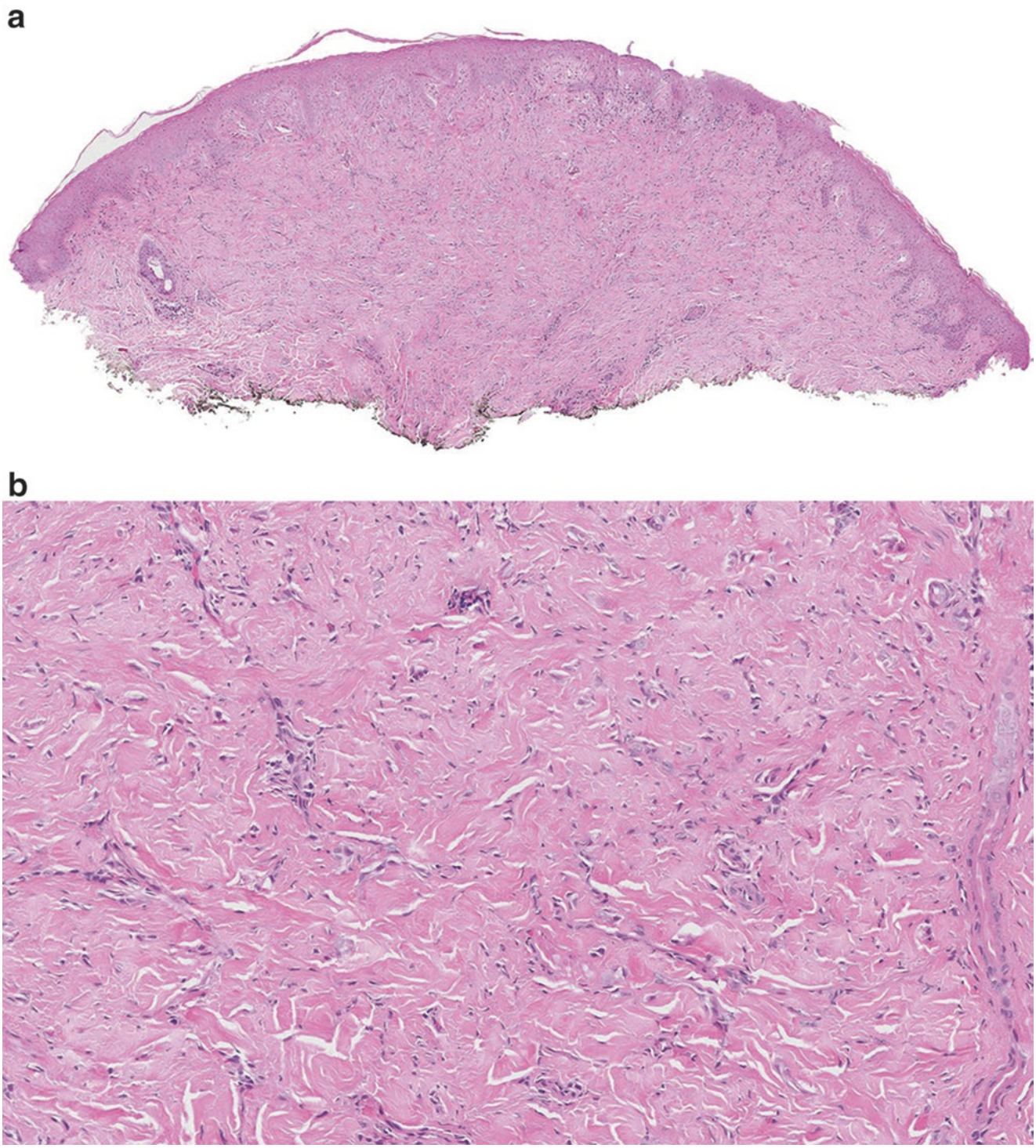

Fig. 4.24 Desmoplastic Spitz nevus. This case shows a wedge-shaped architecture in dermis. Note the decrease in density of cellularity in the base of the lesion (**a**). The cells are very small and in some cases it may mimic a scar (**b**)

Angiomatoid Spitz Nevus

Clinical Features

The angiomatoid Spitz nevus was initially described as a histopathologic variant of desmoplastic Spitz nevus. Clinically, these nevi typically present as solitary papules on the extremities of young women [58].

Histologic Features

Histologically, angiomatoid Spitz nevi are relatively symmetric and well circumscribed. Most cases are confined to dermis; however, an epidermal component is not unusual, and in some cases, there are solitary melanocytes at the base of the epidermis. The density of melanocytes varies as some cases show only relatively few melanocytes, while other cases contain moderate to numerous melanocytes in dermis. Neoplastic melanocytes show epithelioid features, typical of conventional Spitz nevi, but other cases show a predominance of spindled melanocytes. In all cases epithelioid melanocytes predominate over the spindle cell melanocytes. These large epithelioid melanocytes show voluminous, pale, eosinophilic to amphophilic cytoplasm, enlarged oval nuclei with evenly distributed pale chromatin, and a prominent, centrally placed nucleolus. Intranuclear cytoplasmic pseudoinclusions are identifiable in the epithelioid melanocytes. Numerous binucleated and some multinucleated melanocytes are present in some cases. These melanocytes are distributed in the dermis as solitary units or, less commonly, in small nests and cords. Melanocytes are embedded in a dense fibrous stroma with thick bands of collagen throughout the dermis. Characteristically there are large numbers of small thick-walled blood vessels with rounded lumina, lined by plump endothelial cells with conspicuous oval-shaped nuclei devoid of cellular atypia. Some cases may show a variable, mild to moderate, lymphoplasmacytic infiltrate surrounding these blood vessels. Mitotic figures are usually absent, but if present they are seen in the superficial portion of the lesion.

Differential Diagnosis

The differential diagnosis of angiomatoid Spitz nevus is primarily with regressing melanoma. Many histologic features of angiomatoid Spitz resemble a regressing melanoma such as the presence of prominent vasculature throughout the papillary and reticular dermis, with an associated perivascular lymphocytic infiltrate in a background of diffuse fibrosis. However, angiomatoid Spitz nevus is symmetric and composed of uniform, large epithelioid melanocytes distributed symmetrically throughout the lesion as single cells or in small clusters and essentially devoid of pleomorphism. These epithelioid melanocytes are composed of relatively monotonous cells, uniform from side to side at each level of the dermis, and maturation is usually present, typically with dispersion of single cells into the reticular dermis collagen at the base. In addition, mitotic figures are exceedingly rare to absent, and expanding nodules in the form of large clusters of dermal melanocytes are not seen in this type of nevus. Also, the inflammatory infiltrate in these nevi is almost always perivascular rather than the asymmetric, band-like type of inflammatory infiltrate directed toward the melanocytes that would be expected in a regressed melanoma. The dermal fibrosis within a regressed melanoma is usually composed of fine, thin bands of collagen, whereas the dermal collagen in angiomatoid Spitz nevi assimilates into large thickened bands in the papillary and reticular dermis. Most angiomatoid Spitz nevi lack nested epidermal involvement, prominent cellular atypia, and mitotic figures at the base of the tumor (features that are almost always seen in melanoma).

Table 4.4 Angiomatoid Spitz nevus versus regressing melanoma

• Angiomatoid Spitz nevi are symmetrical lesions and regressing melanomas are asymmetric
• Melanocytes in angiomatoid Spitz nevus lack cytologic atypia and show maturation. Melanocytes in regressing melanoma tend to show significant cytologic atypia and to cluster at the base
• Mitotic figures in angiomatoid Spitz are exceedingly rare (when present they are located superficially), as opposed to melanoma in which mitotic figures are common
• Angiomatoid Spitz shows thick band of collagen and regressing melanoma usually shows fine, thin bands of collagen
• Angiomatoid Spitz nevi show thick-walled vasculature with perivascular inflammation and regressing melanomas prominent vasculature and asymmetric band-like inflammation with many melanophages

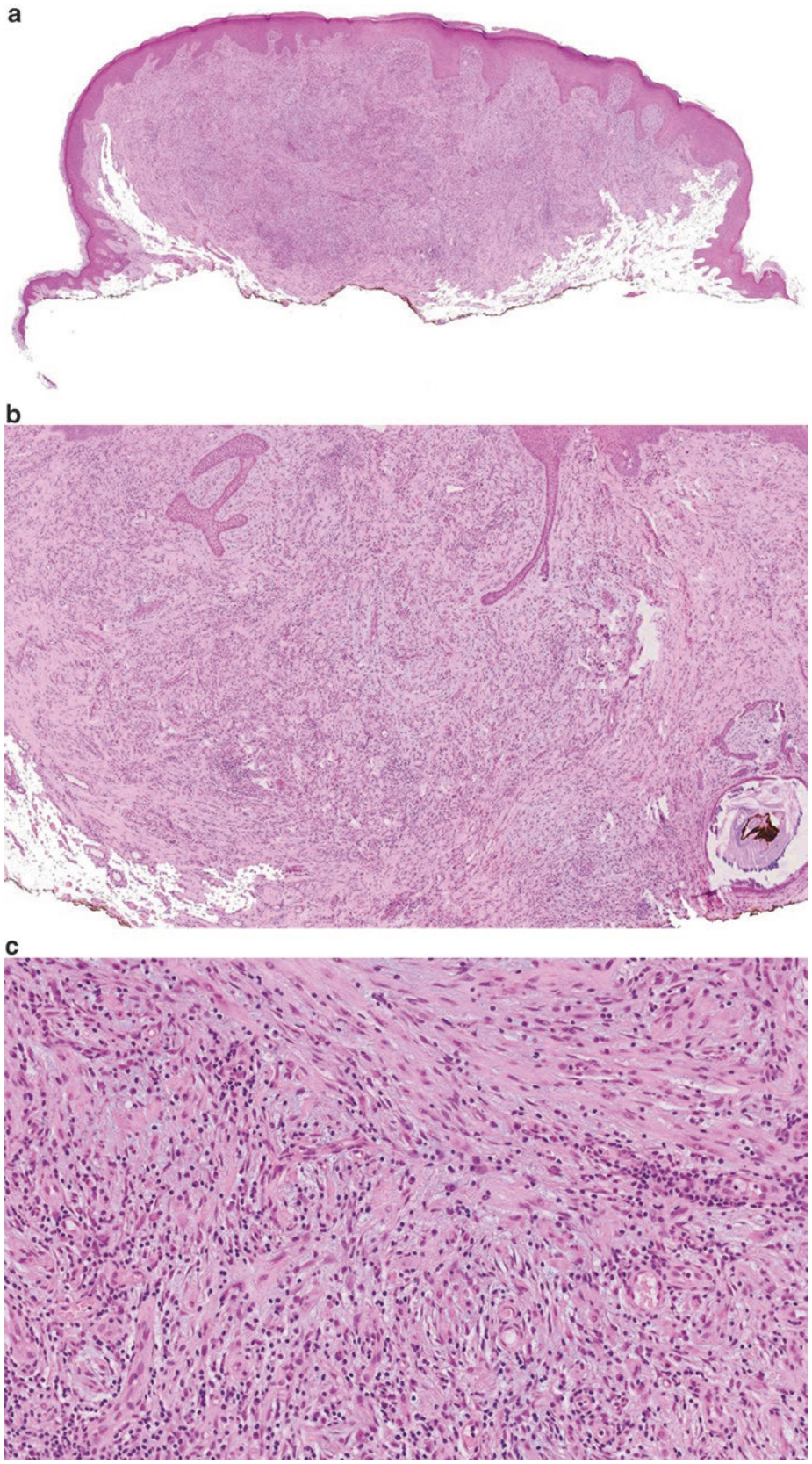

Fig. 4.25 Angiomatoid Spitz nevus. This lesion is located in the leg of a 37-year-old female. The lesion is symmetrical and well circumscribed. The lesion is composed of a high density of melanocytes (**a**). Note the conspicuous blood vessels and melanocytes are embedded in a fibrous stroma (**b**). Increased number of vessels is characteristic of this type of nevus (**c**).

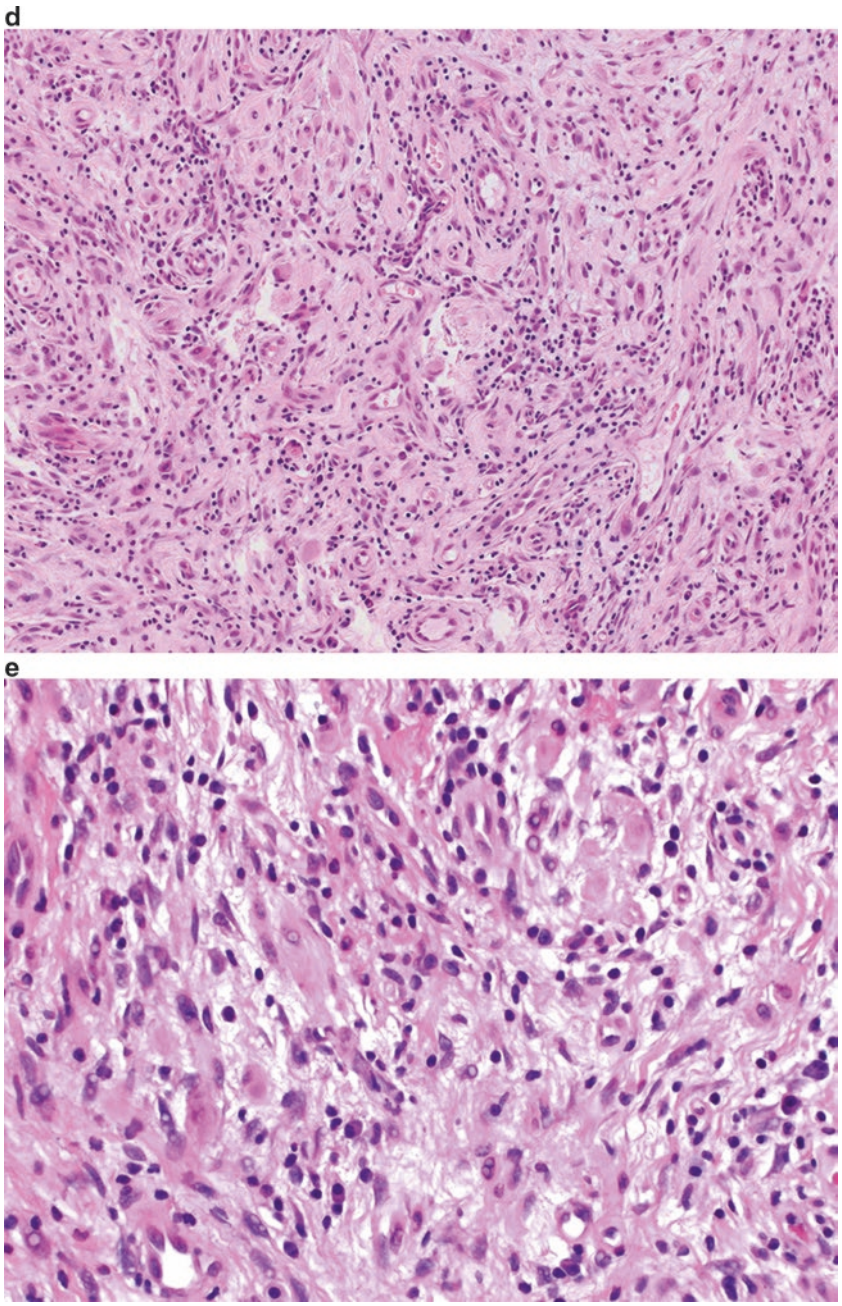

Fig. 4.25 (continued) The lesion is composed of large spindled and epithelioid melanocytes. The melanocytes have an oval, normochromatic nuclei with prominent nucleoli and abundant eosinophilic cytoplasm. Intranuclear cytoplasmic pseudoinclusions are easily identifiable (**d**). High power of the epithelioid cells and vascular spaces (**e**)

Hyalinizing Spitz Nevus

Hyalinizing Spitz nevus is an uncommon variant. These lesions are more commonly seen in adults and possibly represent the end stage of a long-standing Spitz nevus. Histologically, the lesions are dermal, are symmetrical, and typically lack a junctional component. Usually they have a characteristic dishesive growth pattern of large epithelioid and/or spindle melanocytes arranged as isolated individual melanocytes, single melanocytes in a linear pattern, small nests, and fascicles. These epithelioid and/or spindle cell melanocytes tend to have prominent eosinophilic nucleoli and are evenly exhibited from the superficial to deep dermis. The melanocytes are separated by an abundant paucicellular hyalinized or collagenous stroma [27, 59–62].

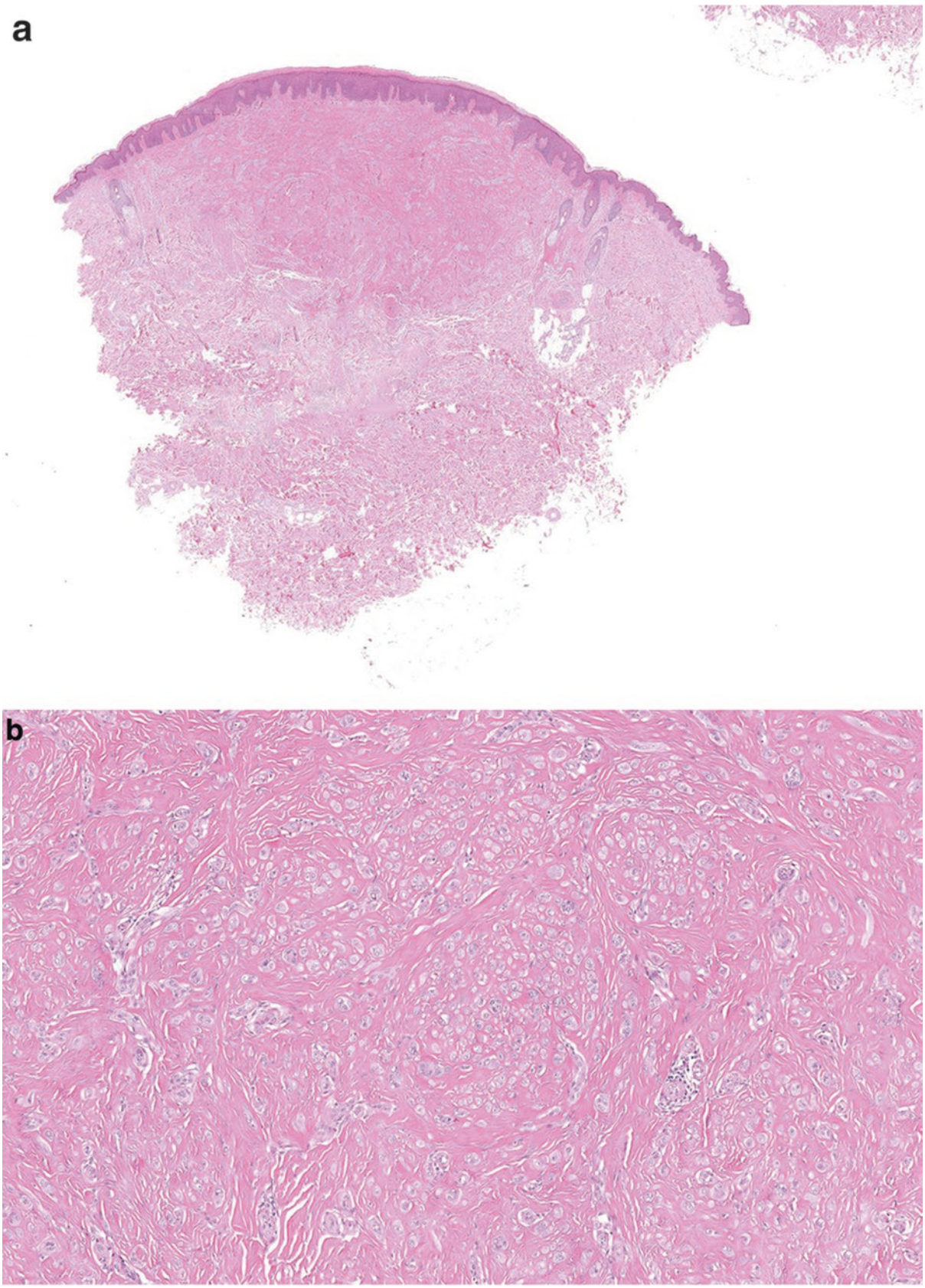

Fig. 4.26 Hyalinizing Spitz nevus. The lesion is dermal, symmetrical, and lacks a junctional component (**a**). Note the large epithelioid melanocytes arranged in small nests and as isolated individual cells (**b**).

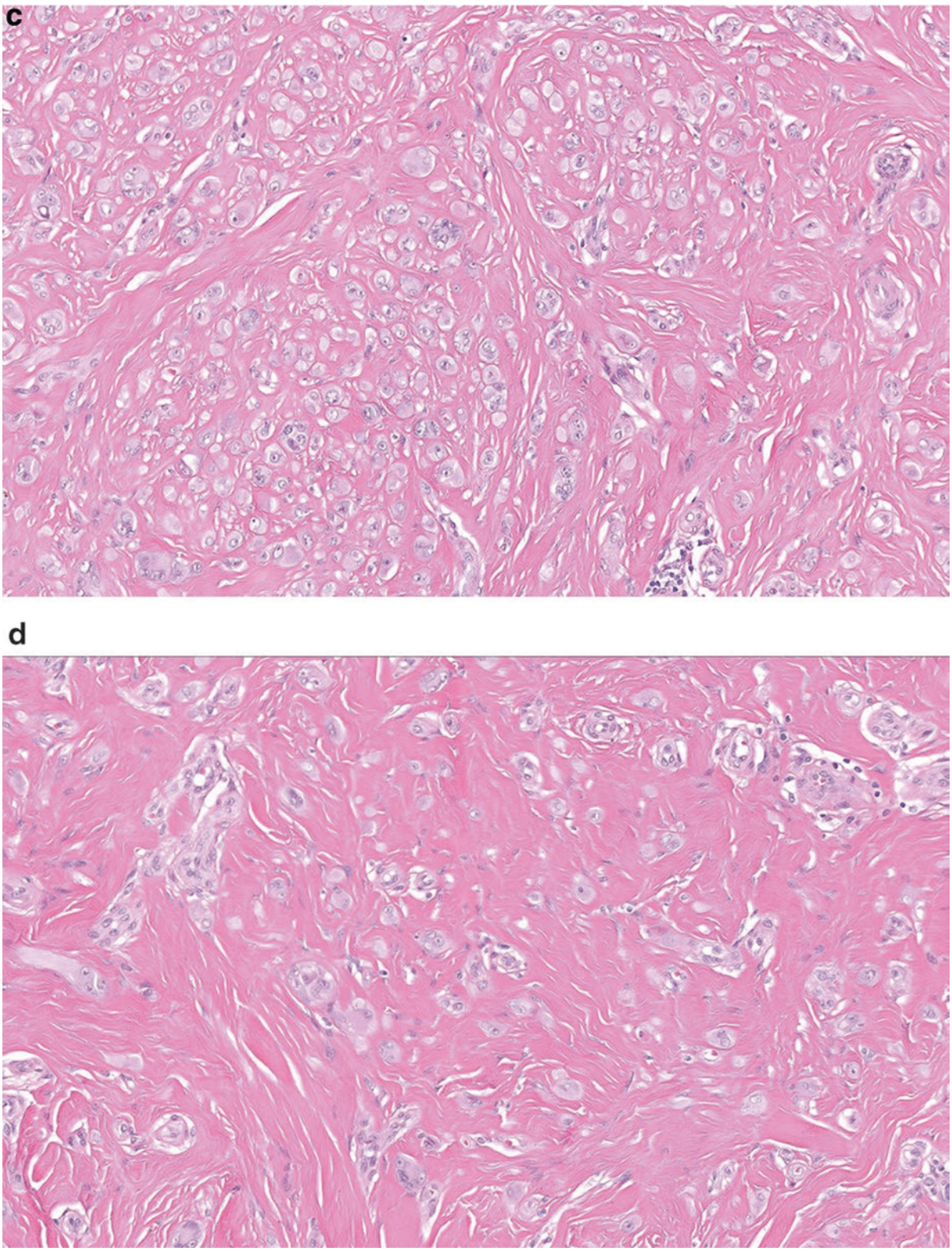

Fig. 4.26 (continued) The melanocytes are separated by abundant paucicellular hyalinized stroma (**c**). High power of epithelioid melanocytes embedded in a collagenous stroma (**d**)

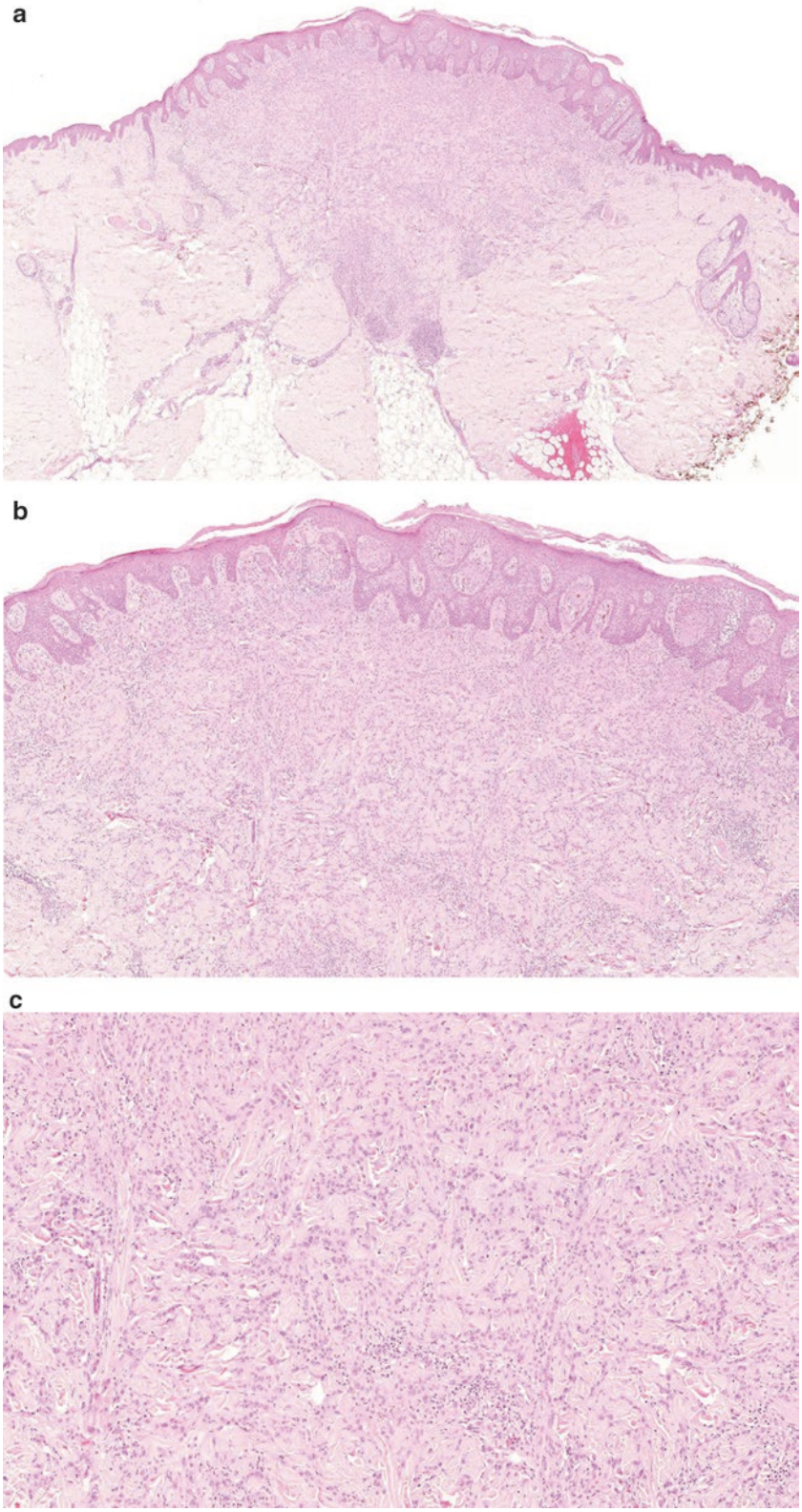

Fig. 4.27 Hyalinizing Spitz nevus. This is a different example that is mostly dermal and with a small junctional component (**a**). In this case, the lesion is composed of spindle and epithelioid melanocytes arranged in linear pattern, small nests, and fascicles (**b**). Note the linear arrangement of melanocytes embedded in a hyalinizing stroma (**c**)

Spitz Nevus with Halo Reaction

Clinical Features

Halo reactions refer to melanocytic nevi that show a dense lymphocytic infiltrate on histology. This phenomenon often indicates the onset of involution and regression of the nevus and may correspond to the observation of a clinical halo in the lesion. In addition to acquired melanocytic nevi, other nevi can show this halo reaction including dysplastic, congenital, Spitz, etc. [63–65]. These nevi may or may not demonstrate clinical evidence of a surrounding hypopigmented area. Thus, in cases with no clinical description, it is preferable to use the term "halo reaction."

Histologic Features

Histologically, these nevi are characterized by a diffuse lymphocytic infiltrate throughout the lesion that permeates the full thickness of the nevus up to the dermal-epidermal junction. These lymphocytes are homogeneously and symmetrically distributed and are in direct contact with melanocytes in the dermis and epidermis. The melanocytes in dermis tend to show an epithelioid appearance with ample eosinophilic cytoplasm. It is worth to mention that Spitz nevi with halo reaction may have striking cytologic atypia above and beyond what is seen in conventional Spitz nevi. Also, most cases show pyknosis/karyorrhexis of the nuclei, likely secondary to a cytotoxic effect of the lymphocytic infiltrate. Mitotic figures when identified are located in the superficial portion of the lesion. In some cases (especially when lesions are purely intradermal and have a dense band of lymphocytes at the base), there may not be obvious maturation. One has to remember that most conventional Spitz nevi display a lymphocytic infiltrate; however, this infiltrate is different from the halo reaction. The infiltrate in standard Spitz nevi is superficial perivascular or lichenoid pattern in contrast with the dense infiltrate intermixed with melanocytes in the halo reaction.

Differential Diagnosis

The distinction of Spitz nevus with halo reaction from melanoma with regression can be exceedingly difficult. It requires assessing the architecture and cytologic features of the lesion. Spitz nevi with halo reaction are for the most part symmetric lesions, which often have all the features of a conventional Spitz nevus in addition to the presence of a dense lymphocytic reaction throughout the entire lesion (full thickness). Melanomas with regression show an uneven and irregularly distributed lymphocytic infiltrate with large and confluent sheets of epithelioid melanocytes and possibly with (atypical) mitotic figures located in deep part of the lesion. These mitotic figures should be carefully scrutinized as Spitz nevi with halo reaction may show lymphocytes or macrophages with mitotic figures. In such cases, examination of a MART-1/phosphohistone H3 double immunostudy may be helpful in identifying if the mitotic figures as in melanocytes [36, 66].

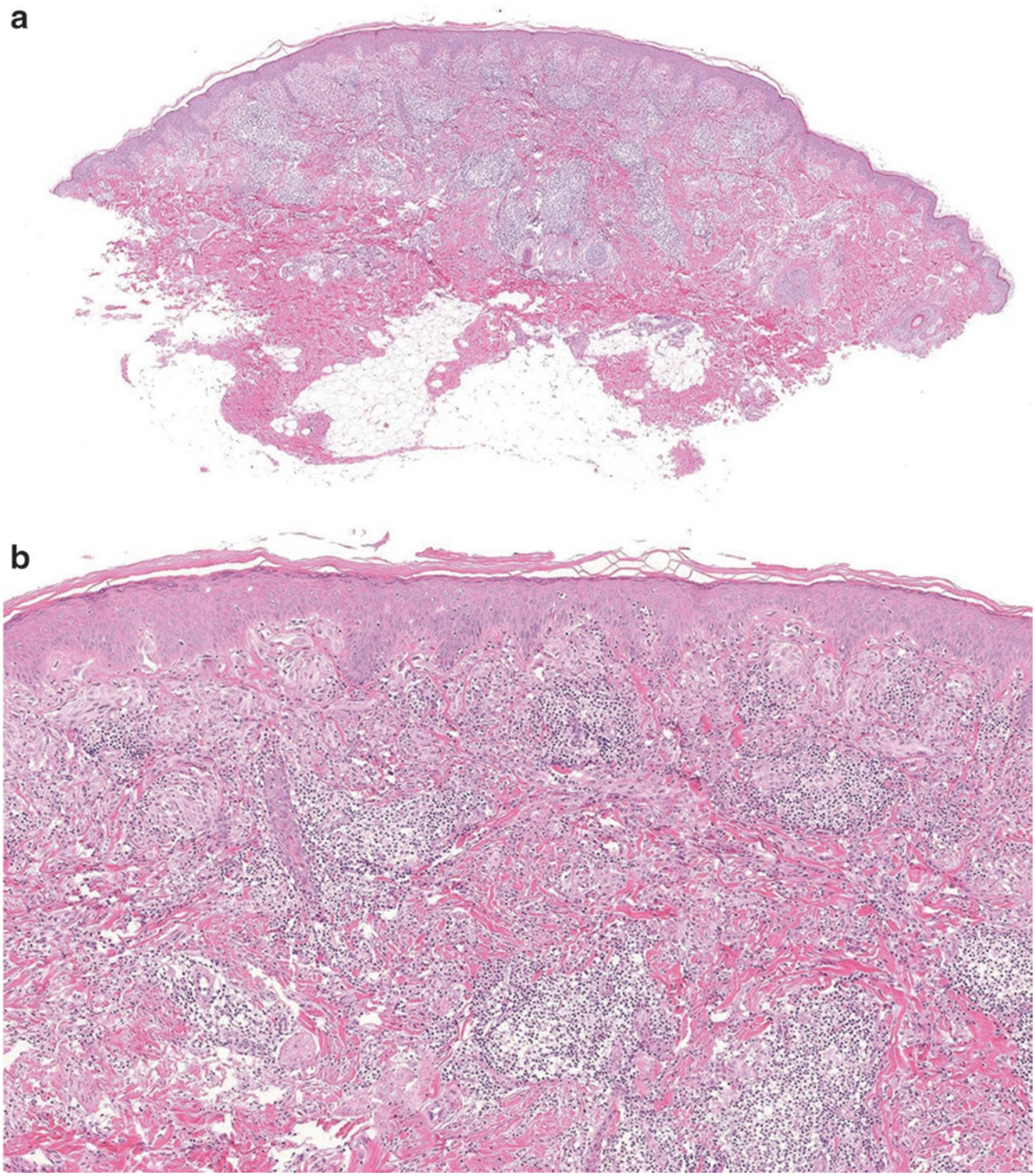

Fig. 4.28 Spitz nevus with Halo Reaction. This lesion is predominantly intradermal and composed of a dense lymphocytic infiltrate throughout the lesion (**a**). Note the spitzoid melanocytes in dermis admixed with a chronic lymphocytic infiltrate (**b**).

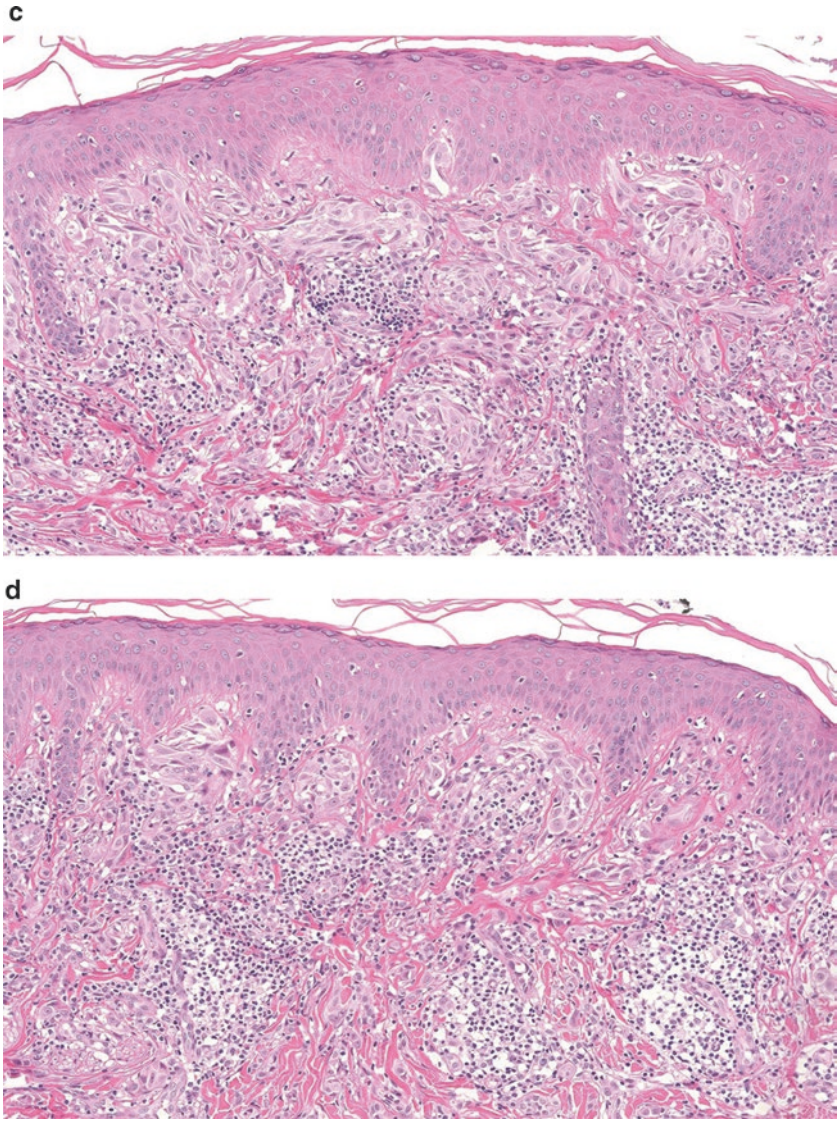

Fig. 4.28 (continued) Note the cellular atypia in dermis (not unusual in these types of lesions) (**c**)

Polypoid Spitz Nevus

This variant of Spitz nevus has a prominent, pedunculated architecture. In the dermis, the melanocytes are arranged mostly in nests, files, and single units. Even though the dermal component expands the dermis, it does not compress or destroy the surrounding normal structures. Also, between the nests of melanocytes, there is usually a smaller and more benign-appearing melanocytes than those found in the center of the nests. Although this biphenotypic morphology may raise the possibility of a melanoma associated with a nevus, the intimate relationship between both types of cells supports the diagnosis of nevus. As any type of Spitz nevi, mitotic figures can be identified but always in the superficial upper portion of the tumor. Also, some cases may display areas with thick bundles of mature collagen fibers interposed among the epithelioid cells [27, 67, 68].

The diagnosis of polypoid Spitz nevus can be challenging, especially when the lesions are large and when there are biopsied in adults. This variant can be mistaken for a polypoid melanoma, but they can be distinguished from each other with confidence if careful attention is devoted to the histologic details, such as lack of deep mitotic figures and the presence of abundant mature collagen fibers. Also, the nests of epithelioid cells seen in cases of polypoid Spitz nevi do not show compression or destruction of the adjacent structures as usually seen in polypoid melanoma.

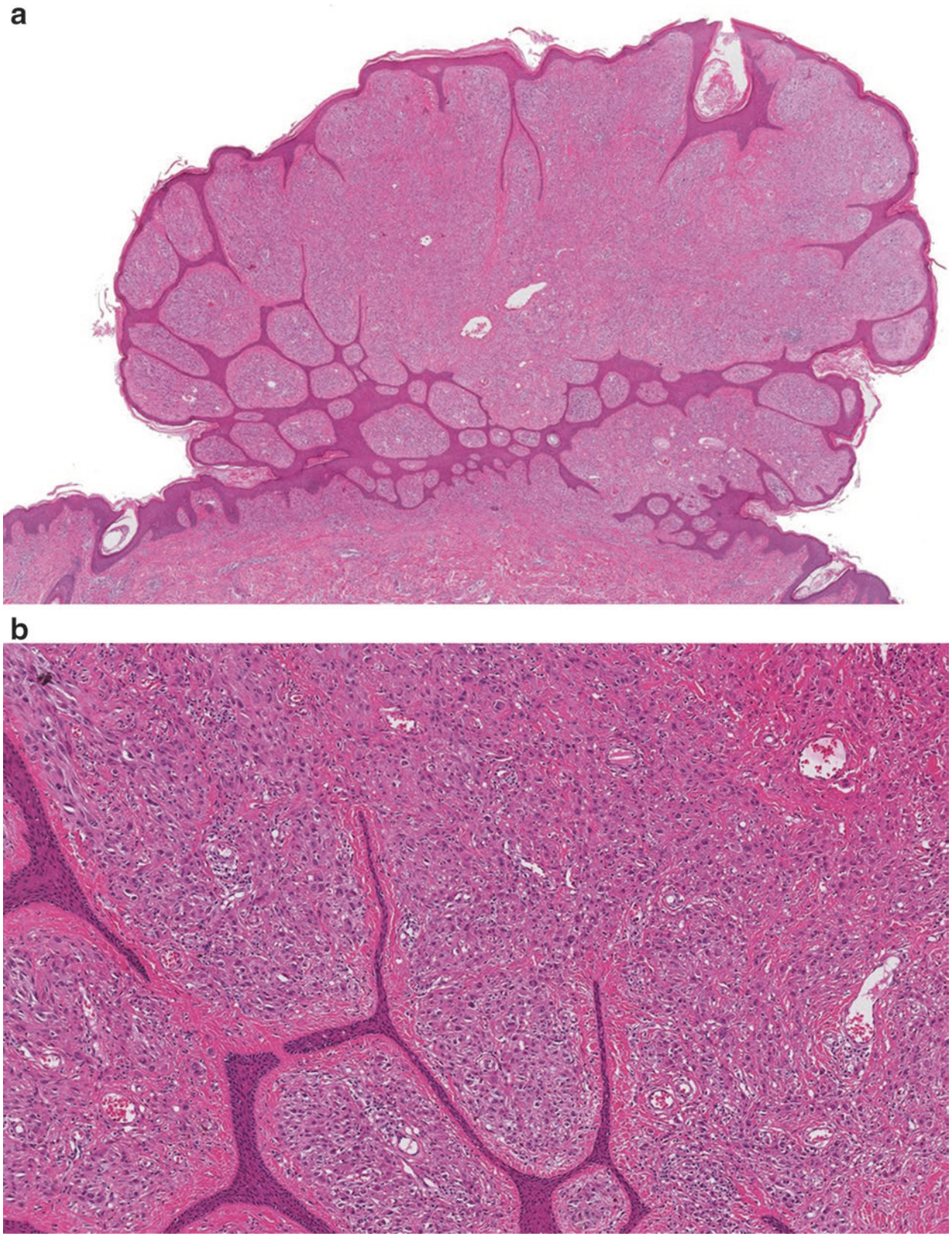

Fig. 4.29 Polypoid Spitz nevus. This is a lesion in the arm of a 12-year-old male. Note the pedunculated architecture of the lesion (**a**). The lesion is composed predominantly of an intradermal component. Note the large sheets of epithelioid cells in dermis (**b**).

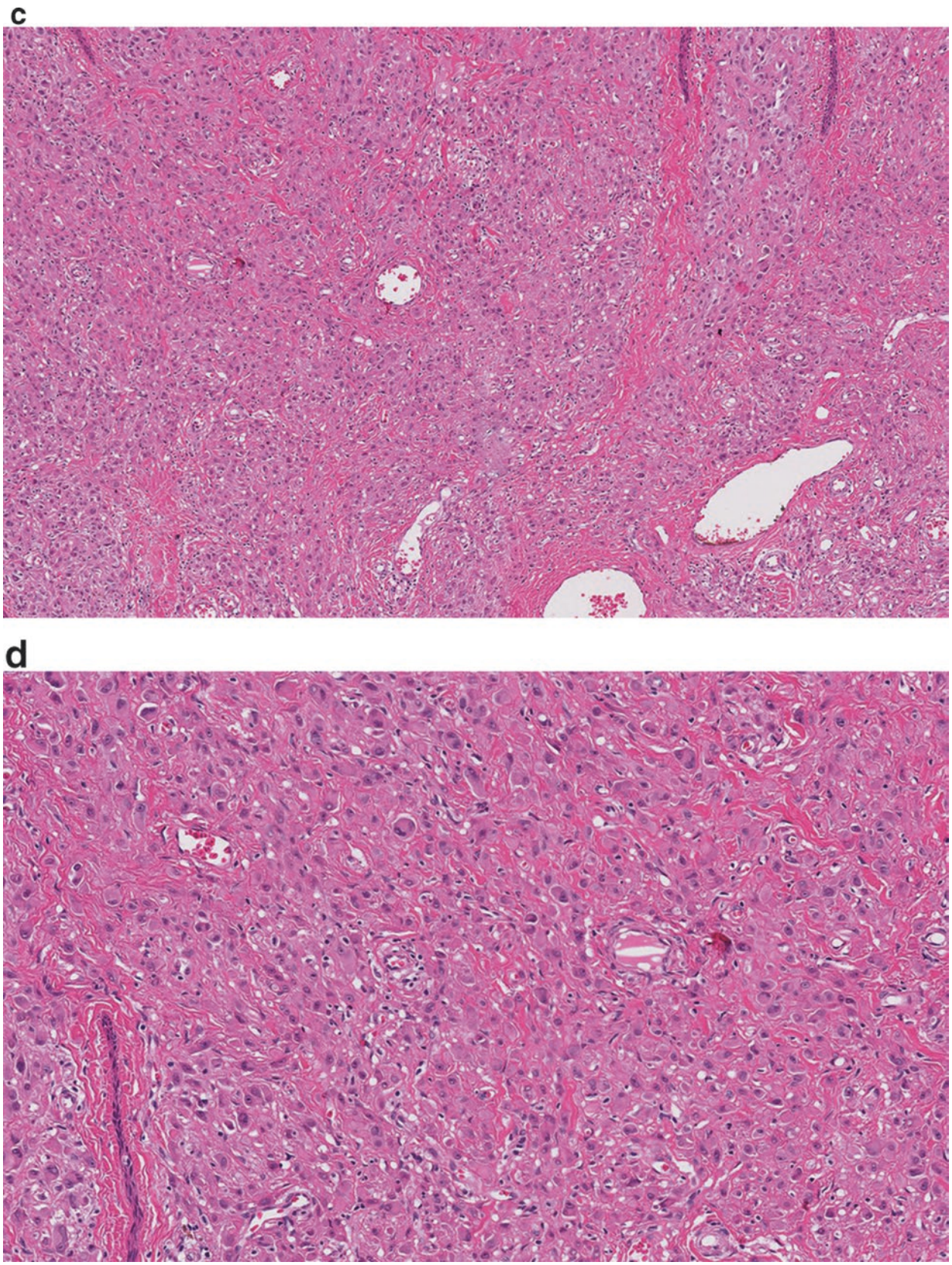

Fig. 4.29 (continued) The lesion does not show the selective advantage of growth seen in melanoma and do not compress or destroy the surrounding normal structures (**c**). At higher magnification, the cells have ample eosinophilic cytoplasm with large nuclei. There were no mitotic figures. FISH studies were negative in this particular case (**d**)

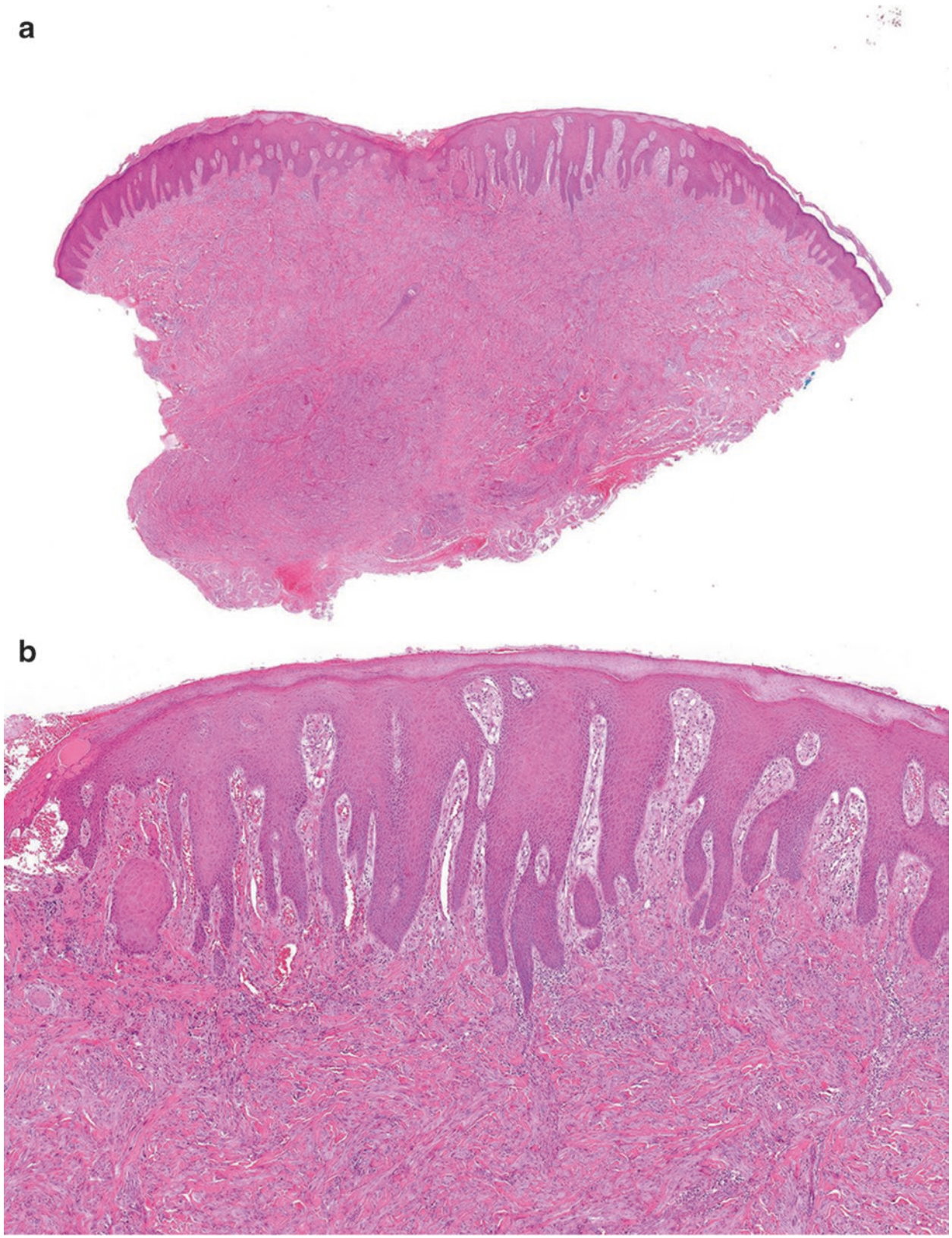

Fig. 4.30 Spitz nevus with pseudoepitheliomatous hyperplasia. Note the intradermal melanocytic lesion along with prominent epidermal changes (**a**). In dermis, the lesion is composed of epithelioid and spindle cell melanocytes among collagen bundles (**b**, **c**).

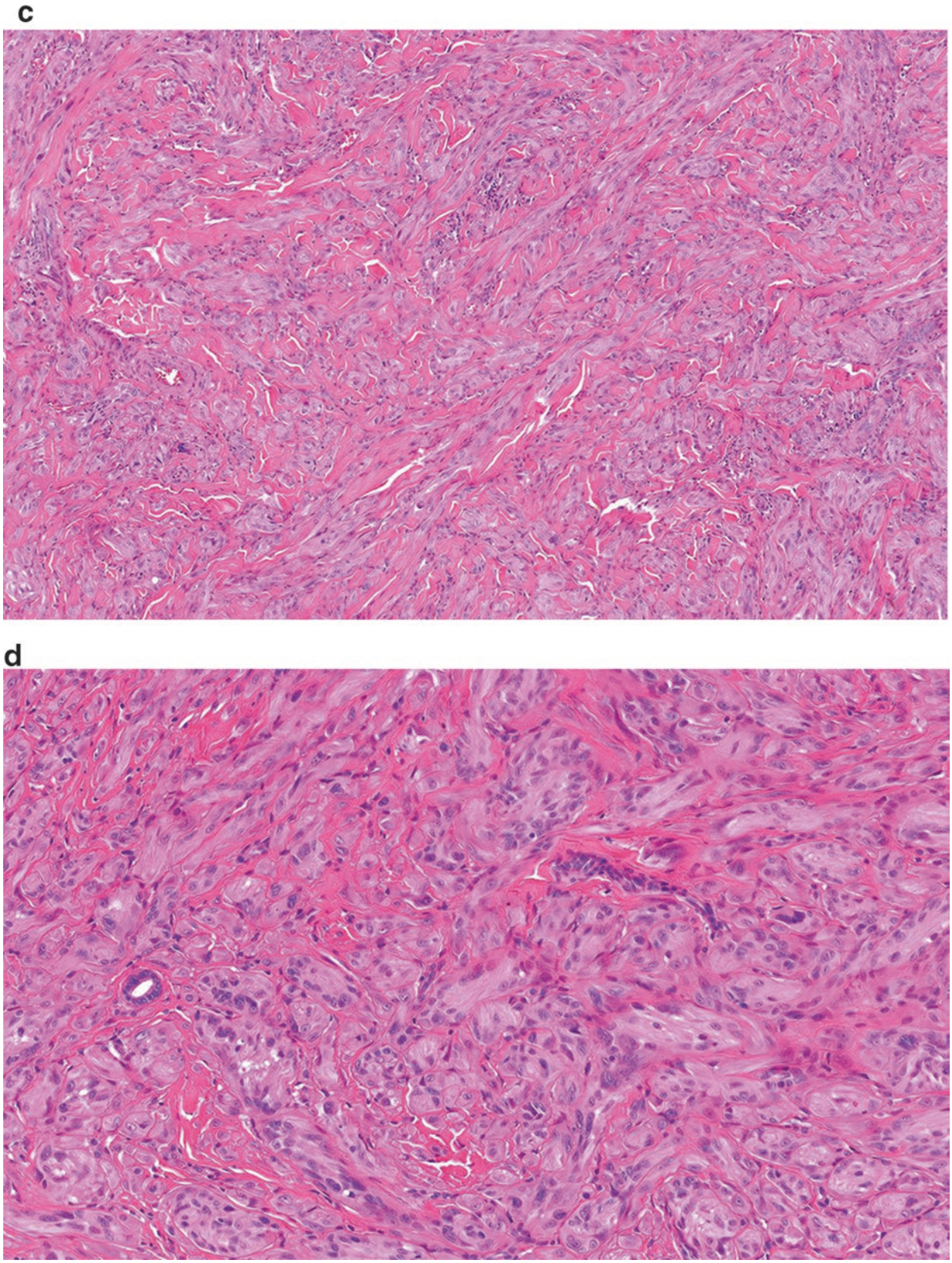

Fig. 4.30 (continued) Higher magnification of the melanocytes. No mitotic figures were identified (**d**)

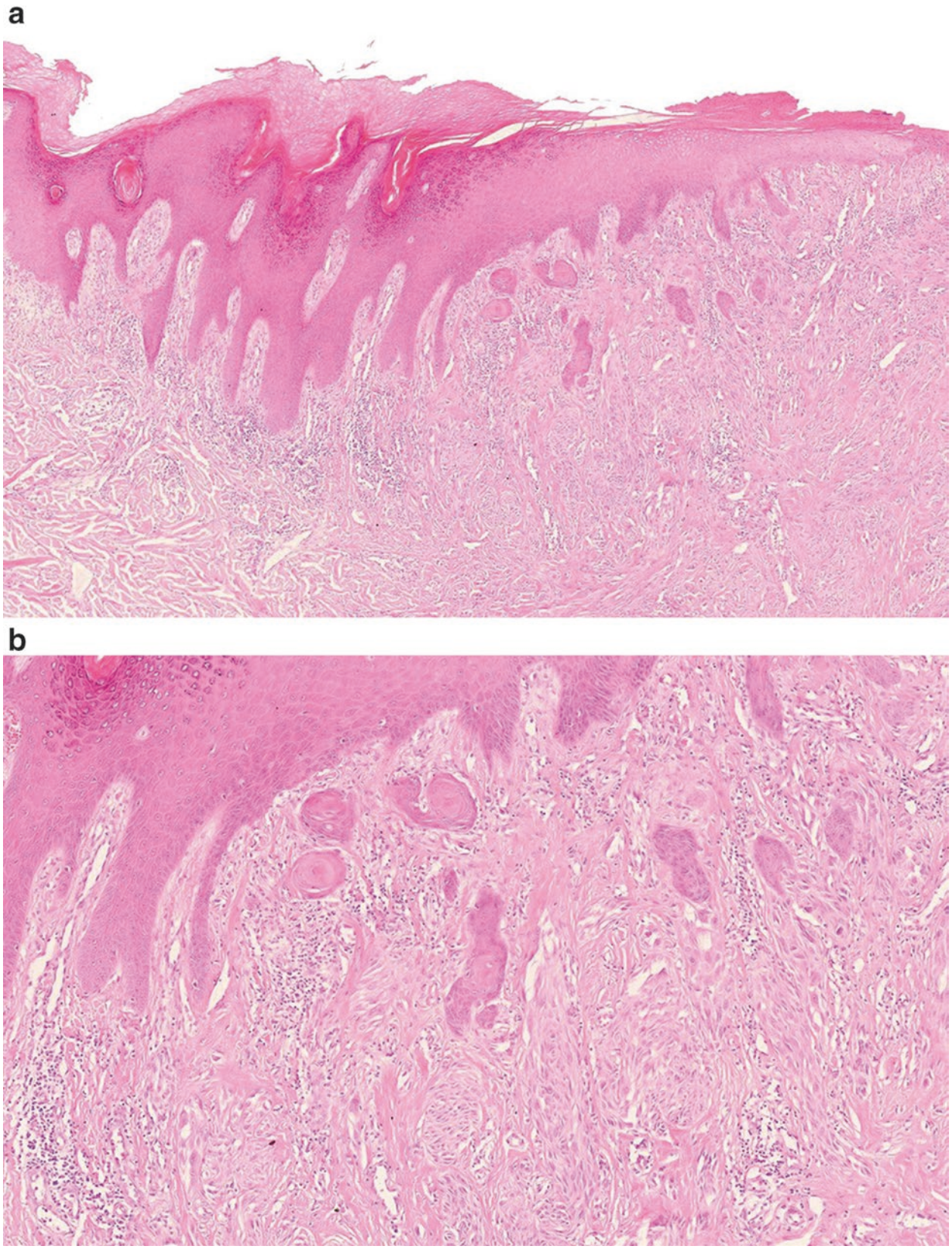

Fig. 4.31 Spitz nevus with pseudoepitheliomatous hyperplasia. This lesion in located in the arm of a 27-year-old female. Another example with prominent pseudoepitheliomatous hyperplasia (**a**). The melanocytes in dermis show normal maturation and lack mitotic figures (**b**)

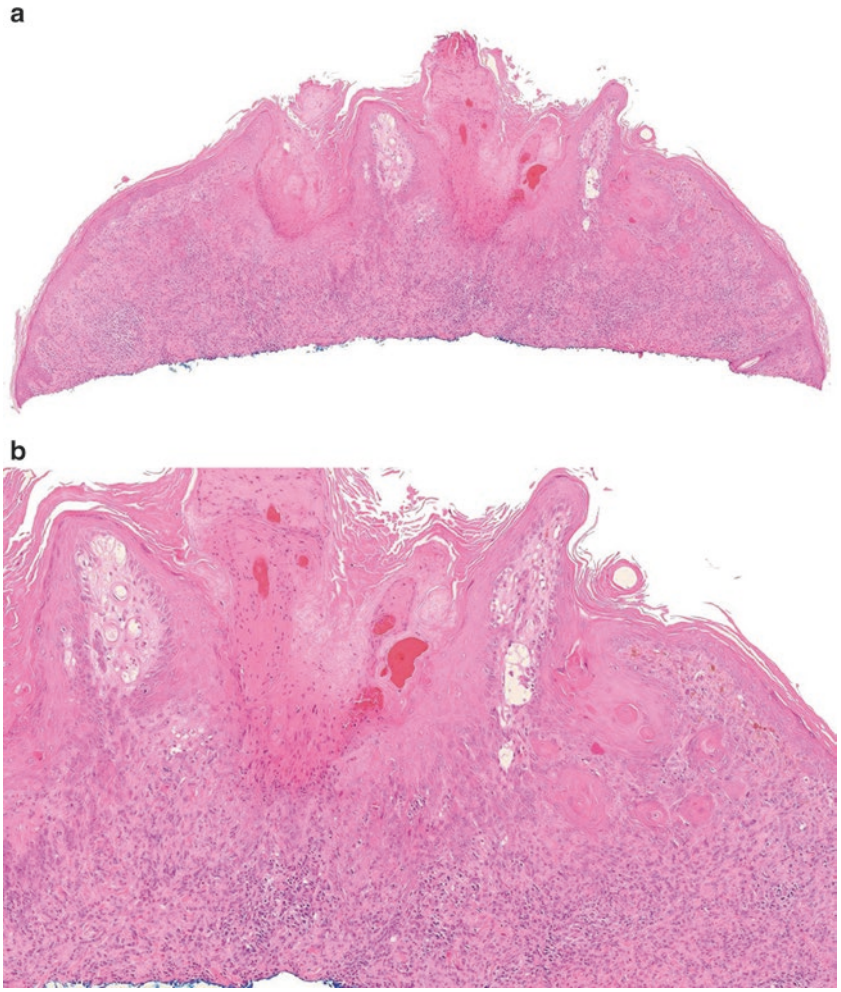

Fig. 4.32 Spitz nevus with pseudoepitheliomatous hyperplasia. This lesion is located on the trunk of a 14-year-old male. Note the prominent hyperplasia mimicking an epidermal neoplastic process (**a**). Note spitzoid melanocytes in dermis with normal maturation (**b**)

Plexiform Spitz Nevus (See Section of Spitz Nevi with ALK Fusion)

This is a rare variant of Spitz nevus [69, 70]. Histologically, it is composed by a symmetric and plexiform arrangement of well-defined bundles and lobules of enlarged, spindle to epithelioid melanocytes throughout the superficial and deep dermis. There is usually no infiltration of the surrounding dermis and no clear maturation with depth. The melanocytes have moderate eosinophilic cytoplasm with vesicular nuclei and prominent nucleoli and occasional intranuclear inclusions. The tumor nodules are usually embedded in a myxoid stroma with intralesional and perilesional lymphocytes. Cases may show multinucleate giant cells similar to what is observed in conventional Spitz nevi.

Pagetoid Spitz Nevus

This is a rare variant [18]. Histologically, it shows single growth of melanocytes within the epidermis with pagetoid upward migration. There are intraepidermal nests; however, they are not the dominant pattern in the lesion. These lesions are symmetric and well defined at the borders. The melanocytes are monomorphous in appearance with epithelioid features. These melanocytes have an oval nucleus, inconspicuous nucleoli, and ample lightly eosinophilic cytoplasm. The main distinction with melanoma is the circumscription and the symmetrical pattern of pagetoid migration, most prominent in the center of the nevus.

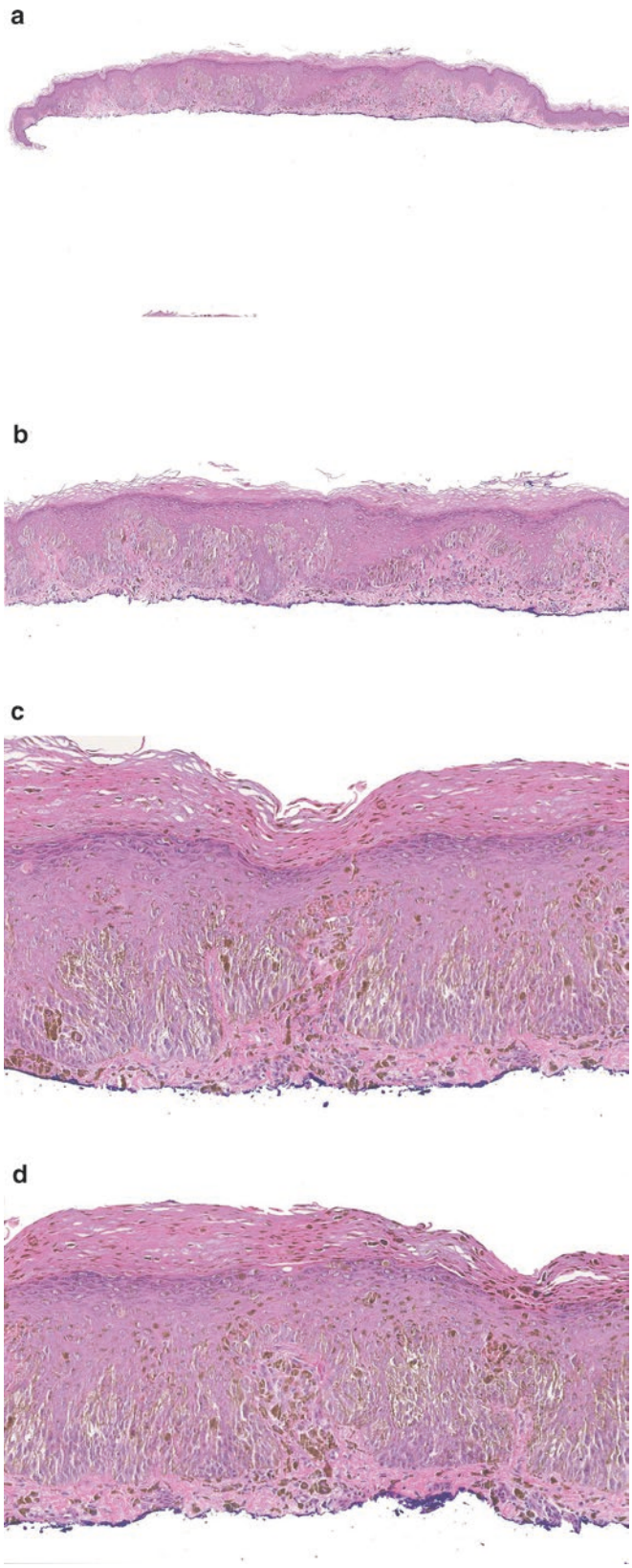

Fig. 4.33 Pagetoid Spitz nevus. This is a pigmented lesion located in the forearm of a 24-year-old female. Note the small size, the symmetry and the degree of irritation (**a**). While most of the lesion is composed of nests, there are scattered pagetoid cells (**b**). Note the upward single melanocytes (**c**). Note the areas of irritation that are associated with the presence of single upward melanocytes (**d**)

Recurrent/Persistent Spitz Nevus

Clinical Features

Spitz nevi only rarely recur, even in cases that have not been completely removed [71]. One study showed that there were no clinical recurrences, despite the fact that more than half of those biopsies exhibited positive margins histologically [72]. When they occur, these recurrences are more commonly seen in young individuals, particularly on the extremities and head and neck. The interval to recurrence ranges from weeks to 5 years after the previous surgical procedure. Clinically, the recurrence presents as a raised pink papule associated with a scar. However, some cases may present as large nodular lesions extending beyond the scar area.

Histologic Features

In our opinion, a recurrent lesion needs always to be reviewed along with the slides of the previous biopsy to confirm the diagnosis of Spitz nevus and to exclude melanoma. Cases of recurrent melanomas that have been incorrectly diagnosed as recurrent Spitz nevus are seen not uncommonly in our practices. Histologically, the recurrent/persistent lesions tend to show residual typical features of Spitz nevus, such as the presence of spindle or epithelioid melanocytes, maturation with dermal depth, an infiltrative pattern of melanocytes as either small nests or individual melanocytes at the base of the lesion, clefting between the individual melanocytes within nests, and a low mitotic rate (and when present restricted to the superficial portion of the lesion). One the most striking histologic features of recurrent Spitz nevi is the architectural growth pattern. One pattern is similar to what is observed in conventional persistent melanocytic nevus. This pattern shows a junctional lesion that resembles the "pseudomelanoma" pattern seen among persistent acquired melanocytic nevi. Overlying the scar, there is a junctional proliferation of single and nested melanocytes, sometimes with pagetoid scatter, occurring in an epidermis with loss of rete ridges. As seen in conventional recurrent melanocytic nevi, the intraepidermal melanocytes of the recurrent growth do not extend beyond the scar. In cases of recurrent compound Spitz nevi, the recurrent lesion is very similar to the original nevus showing a scar adjacent to or admixed with the residual/persistent Spitz nevus. Some cases may show large nodules of melanocytes that appear to compress adjacent structures within and next to the scar in the superficial reticular dermis. In such cases, without reviewing the prior biopsy, these lesions can be misinterpreted as melanoma. Another pattern observed in these recurrent lesions is the desmoplastic Spitz nevus pattern. These cases exhibit marked desmoplasia with melanocytes located in between thick collagen bundles. Melanocytes in recurrent Spitz nevi show atypical features such as large size and large nuclei with conspicuous nucleoli. Also, while most recurrent lesions do show maturation, not always this phenomenon is noted. As a final comment, due to the possibly very challenging histologic diagnosis of recurrent Spitz nevi, most authors recommend complete excision of Spitz nevi at the time of diagnosis.

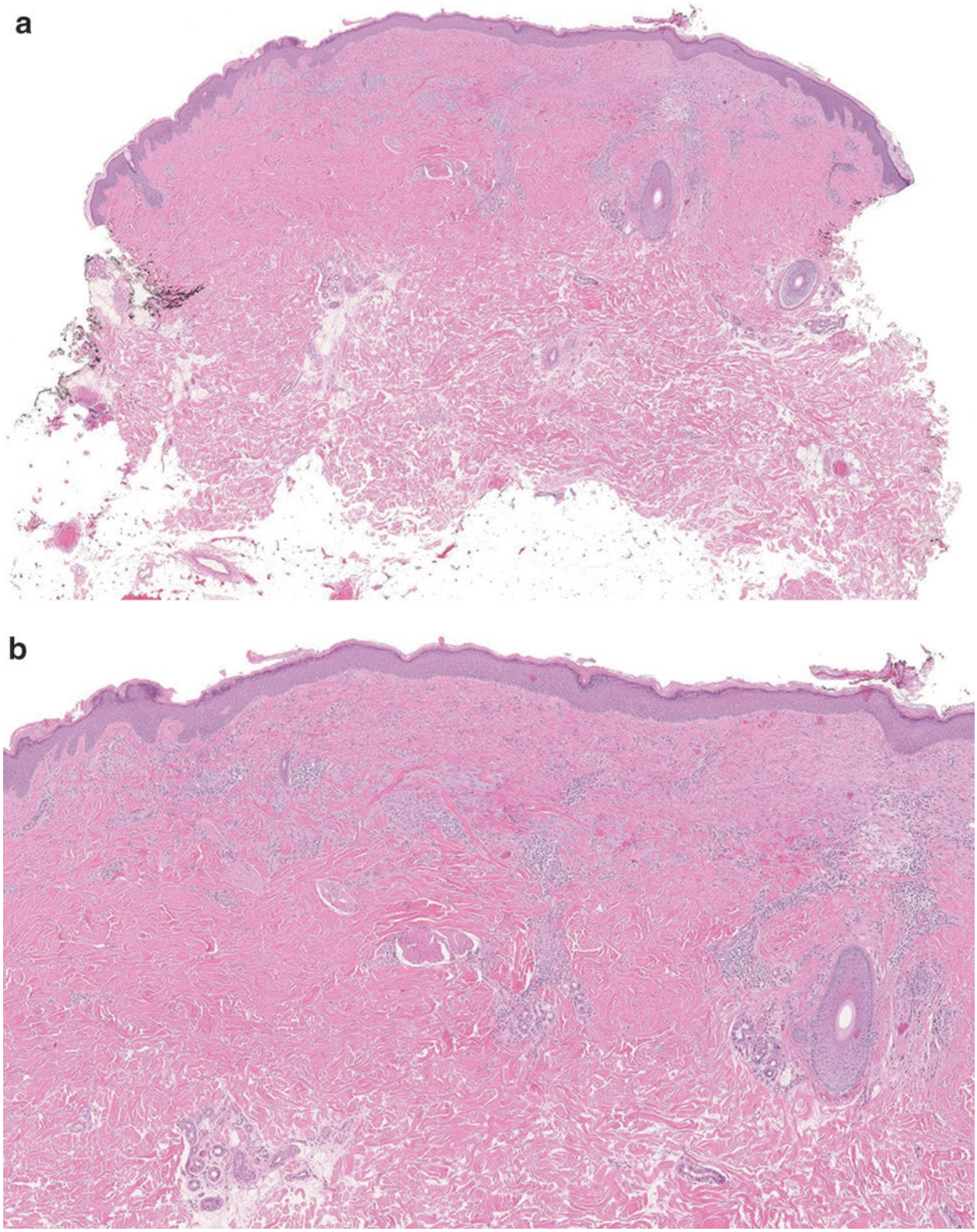

Fig. 4.34 Recurrent Spitz nevus. This is a 33-year-old male that was diagnosed with Spitz nevus 6 months prior to this biopsy. Note the dermal scar along with a proliferation of single and nested melanocytes (**a**). Note that the epithelioid melanocytes do not extend beyond the dermal scar (**b**).

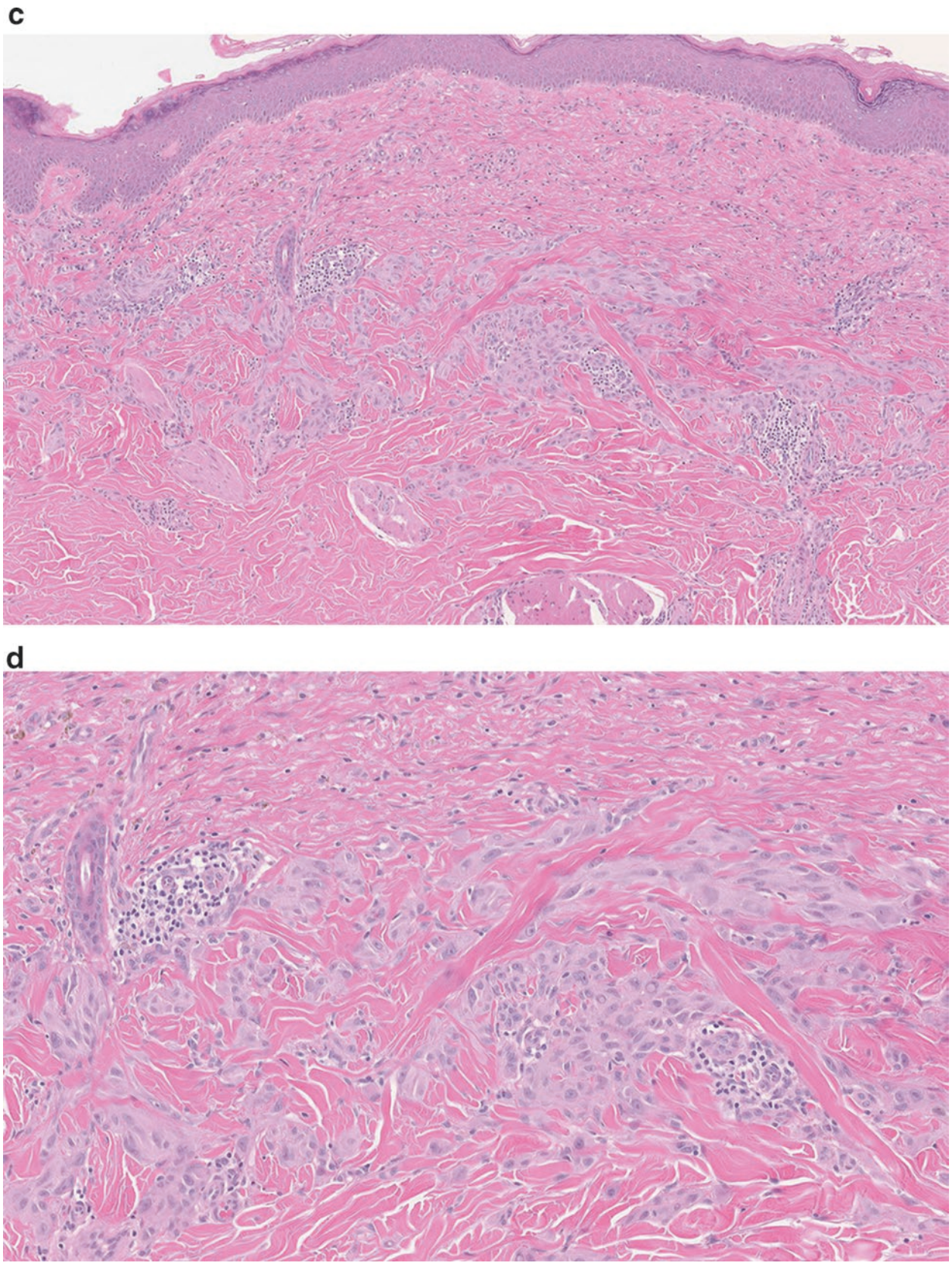

Fig. 4.34 (continued) There is a mixture of spindle and epithelioid melanocytes in dermis (**c**). Higher magnification showing the melanocytes dispersed in dermis (**d**)

Spitzoid Lesions with BAP-1 Loss

BAP1 (BRCA1-associated protein 1) is a tumor suppressor gene that plays a role in controlling cell cycle progression at the G1/S checkpoint. Mutation of this gene have recently been reported to increase susceptibility for the development of many neoplasms including cutaneous melanocytic lesions, uveal melanoma, lung adenocarcinoma, meningioma, clear cell renal cell carcinoma, mesothelioma, etc. [73–76]. There is an autosomal dominant tumor syndrome caused by inactivating germ-line mutations of the BAP1 gene, in which patients are at high risk for developing the abovementioned tumors with varying degrees of penetrance [77]. Involving the skin, mutations and losses involving the BAP1 gene have been found in lesions within the spectrum of atypical Spitz lesions, a heterogeneous group of melanocytic neoplasms sharing some resemblance with Spitz nevi but also displaying atypical features overlapping with melanoma. Affected individuals developed multiple spitzoid lesions that clinically have a skin-colored, dome-shaped, well-circumscribed papular appearance and histopathologically composed of large epithelioid (spitzoid) melanocytes. Subsequently, morphologically similar melanocytic tumors were recognized in a sporadic setting [75]. These sporadic lesions also lack BAP1 expression (by immunohistochemistry), but in contrast to most Spitz nevi, they harbor BRAFV600E mutations.

Histologically, these spitzoid lesions have a characteristic histopathologic appearance. They are composed predominantly of dermal aggregates of epithelioid melanocytes that are arranged in nests or sheets, often forming a dermal nodule. The melanocytes have amphophilic to pale eosinophilic cytoplasm, well-defined nuclear membranes, and large pleomorphic vesicular and conspicuous nucleoli. There may also be multinucleate/giant melanocytes and an associated lymphocytic infiltrate. Some other lesions appear to represent combined melanocytic nevi containing both a spitzoid and ordinary melanocyte population. Although these melanocytic tumors are considered spitzoid because of their cytologic appearance (abundant amphophilic cytoplasm with pleomorphic nuclei and prominent nucleoli), they lack other classical histologic features of Spitz nevi, such as epidermal hyperplasia, clefting between melanocytes, and Kamino bodies.

The use of two antibodies, one for BAP1 and another for BRAFV600E (VE1), represents a simple, quick, and highly sensitive way to confirm the diagnosis of a BRAFV600E-BAP1-loss spitzoid lesion [78, 79]. Immunohistochemistry detects lack of nuclear labeling for BAP1 with diffuse cytoplasmic expression of BRAFV600E (VE1) in the large epithelioid melanocytes.

While limited clinical follow-up information is available on the BAP1loss/BRAFV600E Spitz tumors, preliminary data suggest that most lesions are clinically indolent and most likely represent combined spitzoid melanocytic nevi. However, until more long-term follow-up data are reported, conservative excision seems adequate for patients with an isolated individual lesion. In our practice, we have seen at least one lesion with loss of BAP1, expression of BRAF V600E, and metastasis to the sentinel lymph node. In addition, patients with multiple lesions should undergo clinical follow-up for detection of additional neoplasm and should probably receive genetic counseling (search for germ-line mutations) and evaluate their relatives.

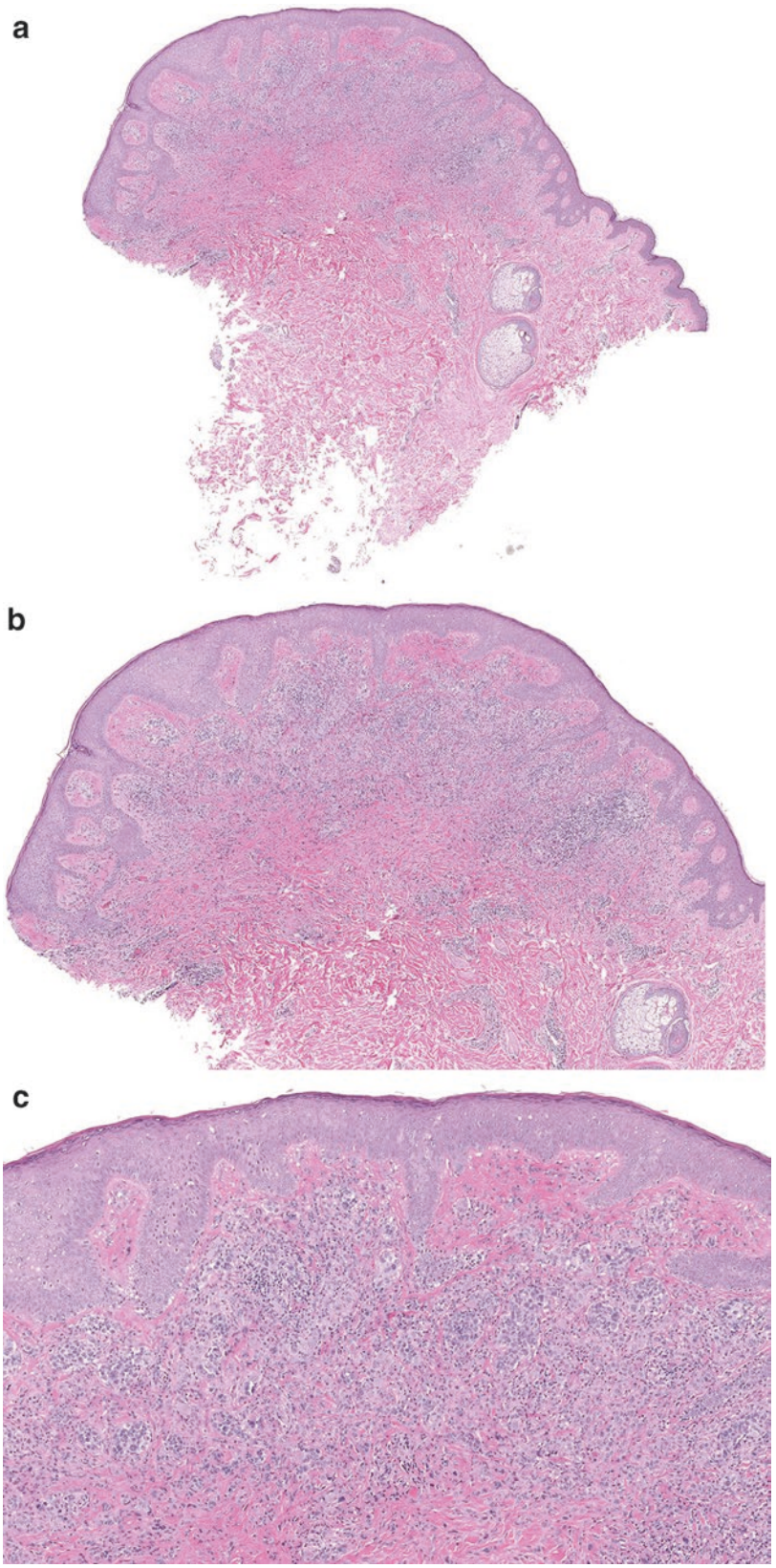

Fig. 4.35 Spitzoid lesion with BAP-1 loss. The lesion is composed predominantly of aggregates of epithelioid melanocytes arranged in nests, often forming a dermal nodule (**a**). Note the sheets and nests of epithelioid melanocytes admixed with chronic inflammatory response (**b**). These lesions usually lack an epidermal component (**c**).

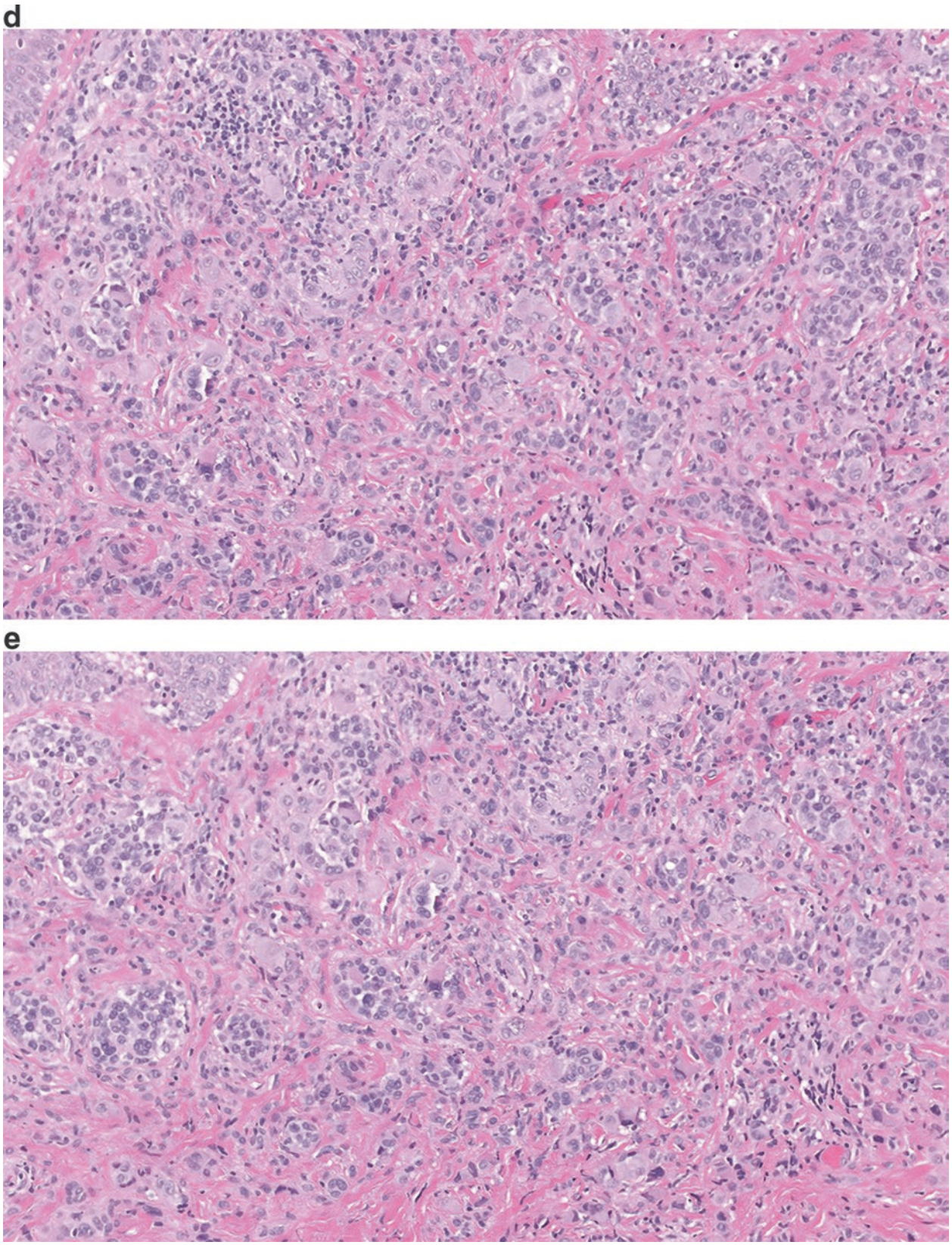

Fig. 4.35 (continued) The epithelioid melanocytes have amphophilic eosinophilic cytoplasm and large pleomorphic vesicular and conspicuous nucleoli (**d**). Note the scattered multinucleate melanocytes and associated lymphocytic infiltrate (**e**)

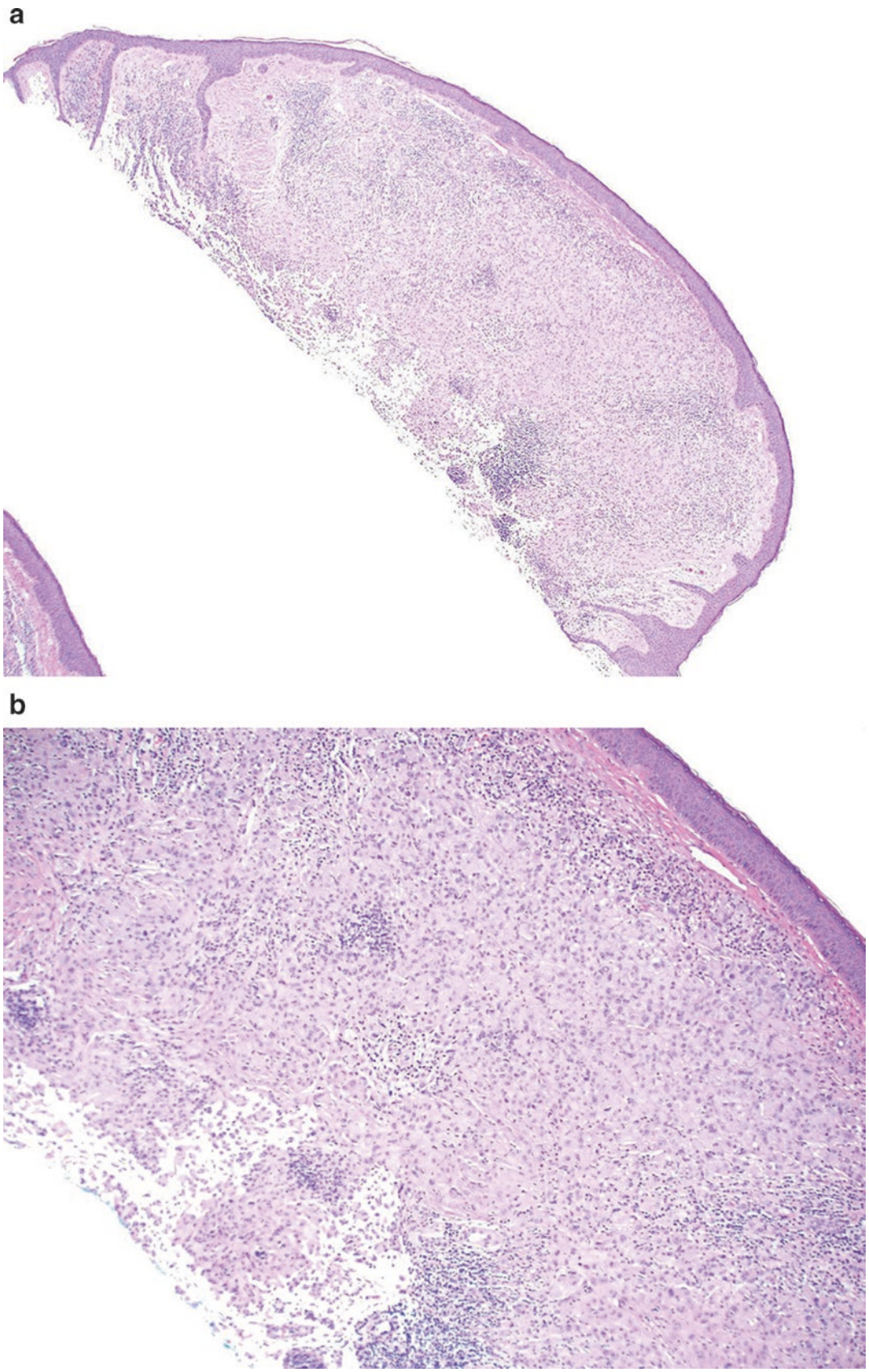

Fig. 4.36 Spitzoid lesion with BAP-1 loss. The lesion is located in the trunk of a 41-year-old female (**a**). The lesion is primarily intradermal and composed of epithelioid melanocytes with sparse chronic inflammatory infiltrate (**b**).

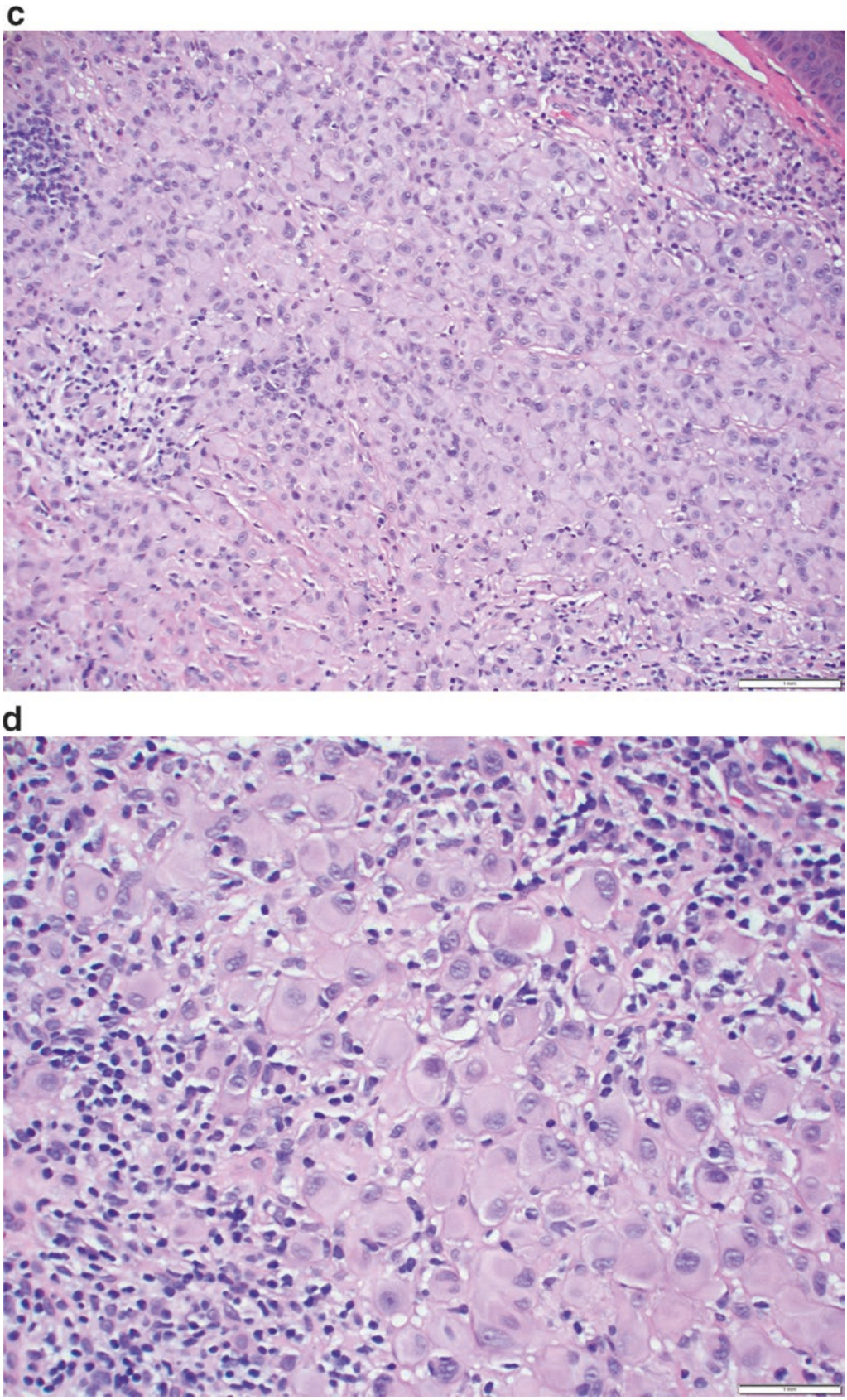

Fig. 4.36 (continued) Note the polypoid architecture of the lesion (**c**). The melanocytes are spitzoid and with mild to moderate cytologic atypia. There were no mitoses seen in this lesion (**d**).

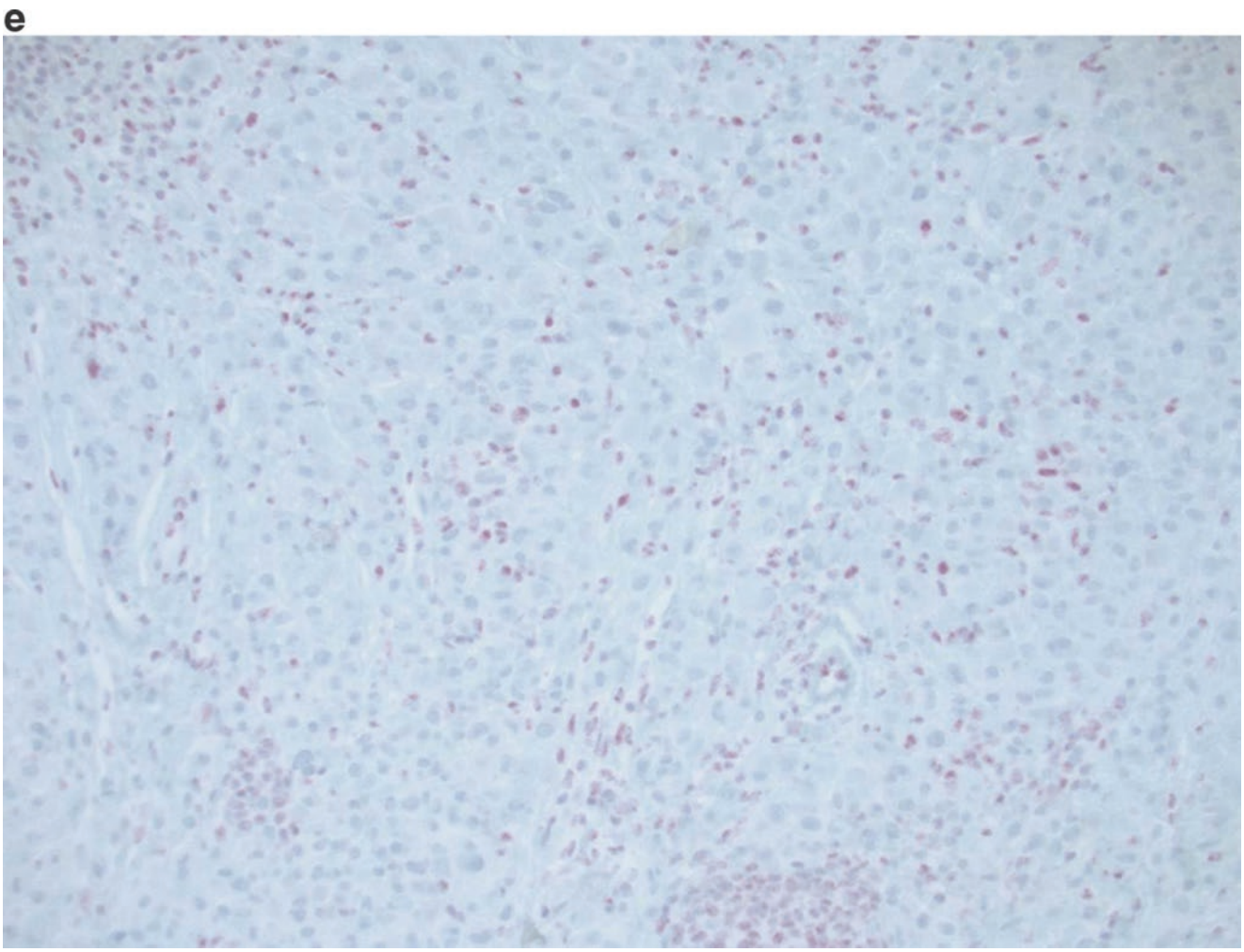

Fig. 4.36 (continued) BAP-1 stain shows loss of nuclear staining in the spitzoid epithelioid melanocytes (positive test) (**e**)

Spitz Nevi with HRAS Mutations

As explained throughout this chapter, diagnostic uncertainty rises if the cases of Spitz nevus in which the histology deviates by one or more criteria from the conventional depiction of Spitz nevus. It is well known that about 15 % of Spitz nevi harbor an activating HRAS mutation [57, 80–82]. As of now, no HRAS mutations have been found in spitzoid melanomas, and so far no malignant progression of a Spitz tumor with a HRAS mutation has been described to the best of our knowledge. Thus, the presence of a HRAS mutation in a Spitz tumor seems to point to a good prognosis [57].

After integration of histologic and molecular data and review of all HRAS-mutated cases, there are remarkable histomorphological similarities between all HRAS-mutated Spitz neoplasms [57, 80]. These Spitz nevi are significantly thicker and larger in diameter. Typically, they are predominantly intradermal, with relatively low cellularity and with a pronounced desmoplastic stromal reaction. The melanocytes are large, with pleomorphic nuclei, and they have an infiltrating pattern of growth at their base, characterized by extensive zones of single cells situated among collagen bundles with fine eosinophilic rims surrounding their cytoplasm. The tumor cell nuclei in cases with gains in 11p tend to exhibit greater pleomorphism than Spitz nevi diploid for 11p. These lesions tend to have no or very little melanin pigment. Some cases may have more than two dermal mitotic figures per mm^2 and rarely deep mitotic figures. Despite the presence of these mitotic figures, most studies have found these lesions to behave in an indolent fashion.

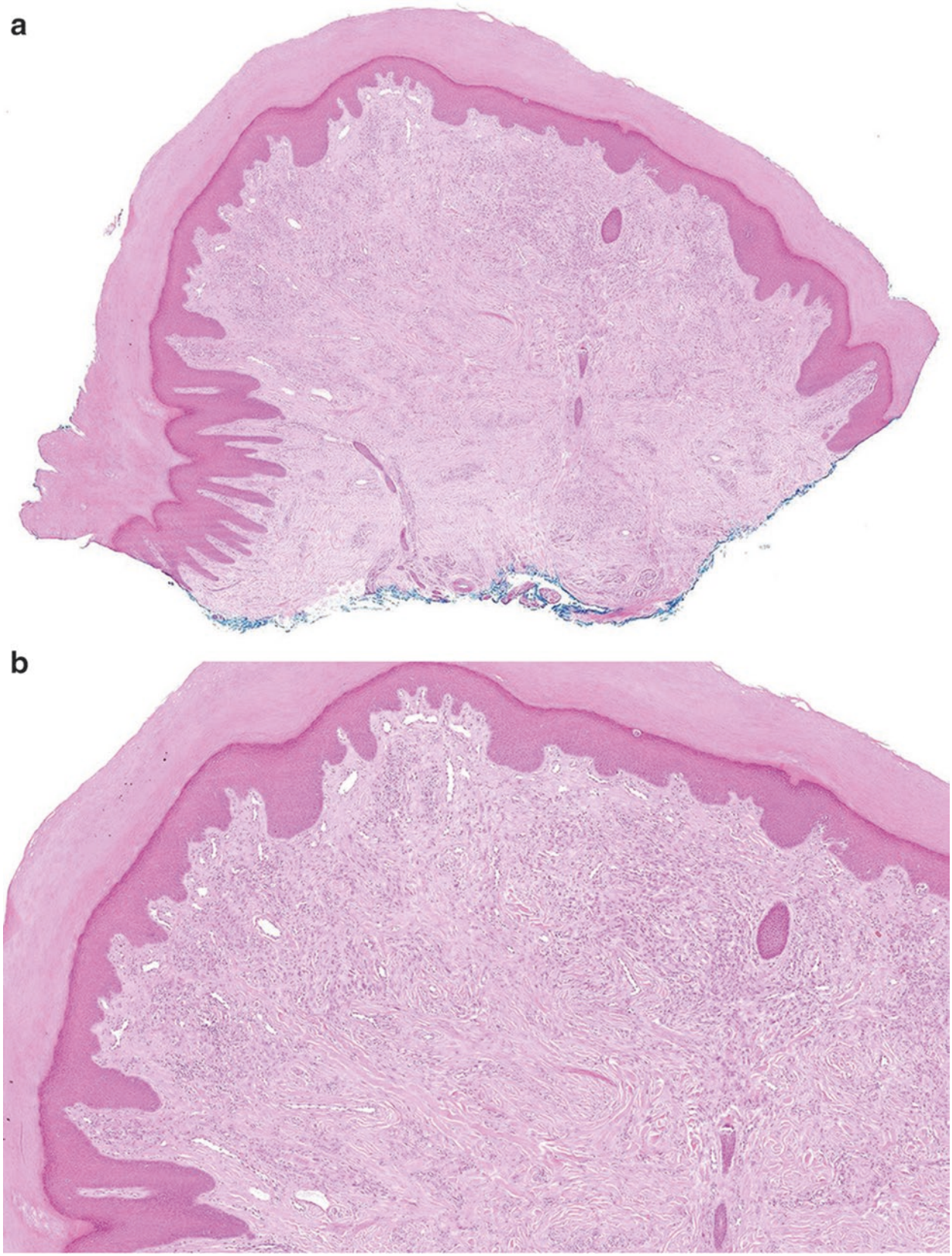

Fig. 4.37 Spitz nevi with HRAS mutation. Note predominant intradermal component with low cellularity (**a**). The presence of desmoplastic stromal reaction is characteristic in this variant (**b**).

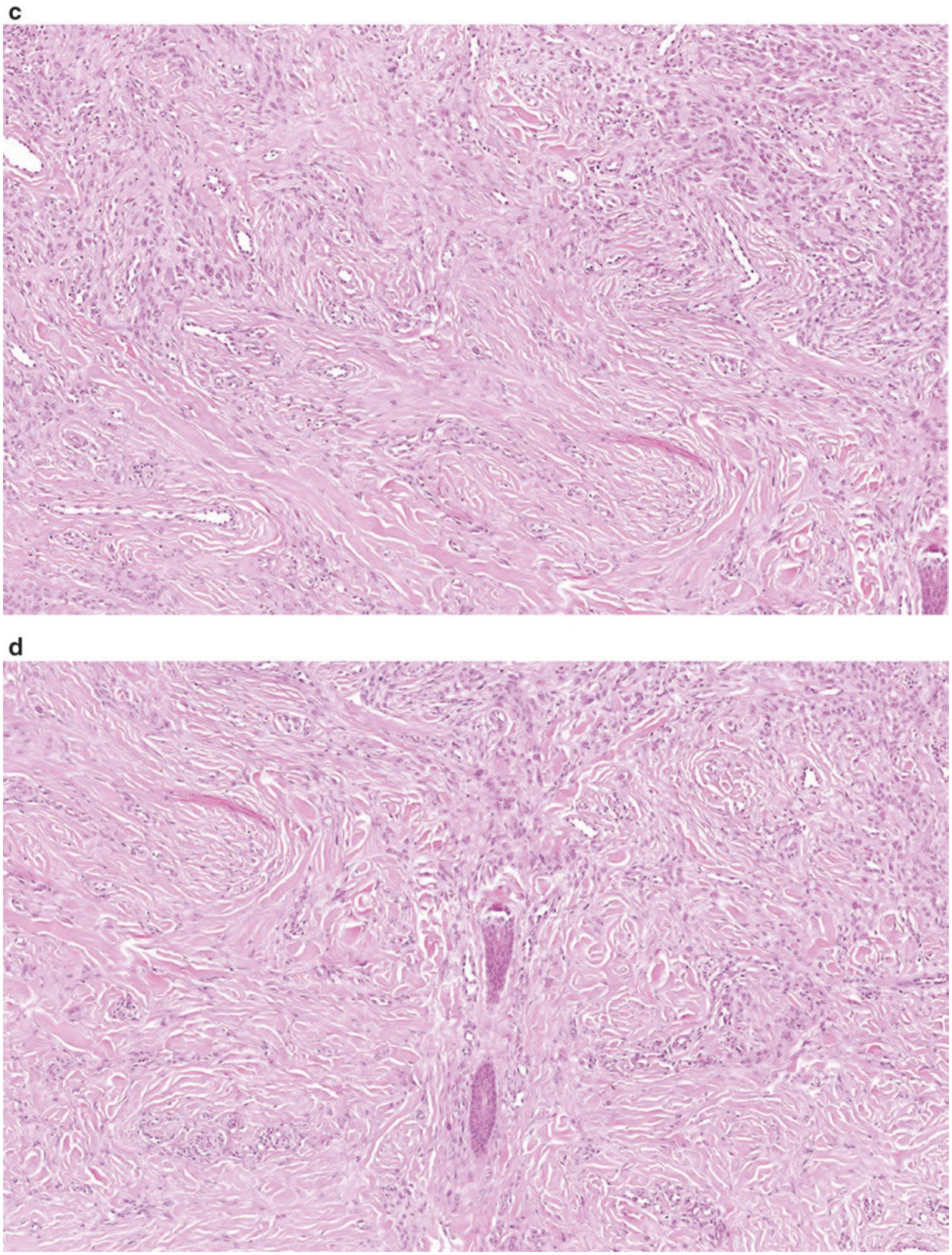

Fig. 4.37 (continued) The melanocytes are large and have an infiltrating pattern of growth at their base (**c**). Note the zones of single cells in between collagen bundles (**d**)

Spitz Nevi with ALK Fusions

A recent study highlighted the discovery of cytogenetic abnormalities of spitzoid melanocytic neoplasms by the presence of various types of kinase fusions, involving ROS1, NTRK1, ALK, RET, and BRAF [83]. Current studies suggest that these fusions occur in a mutually exclusive pattern, do not overlap with HRAS mutations or loss of BAP1 (see above), and are seen across the biological spectrum of Spitz lesions. In a recent study, authors documented the morphologic spectrum associated with Spitz lesions with ALK rearrangements to explore a possible association between histopathologic appearance and fusion partner subtype [84]. All Spitz nevi in this study were immunohistochemically positive for ALK and showed TPM3-ALK fusions by quantitative PCR and sequencing methods. Spitz nevi with ALK fusions in this study were polypoid and amelanotic and with a plexiform growth of intersecting fascicles of fusiform melanocytes. This fascicular growth displays a pattern of melanocytes streaming in large confluent nests or sheets that is often oriented in a radial pattern, converging towards the base of the tumor. Most lesions are amelanotic, but focal pigmentation can be identified. The majority of lesions display a marked infiltrative growth pattern with deep dermal invasion. The nuclei of the cells had a smooth nuclear contour and a slightly vesicular chromatin pattern. Authors of this study concluded that future studies are needed to determine the association between the histologic features of the lesion and the type of kinase fusion and, most importantly, to learn more about the possible biological and clinical significance of kinase fusions in spitzoid melanocytic lesions.

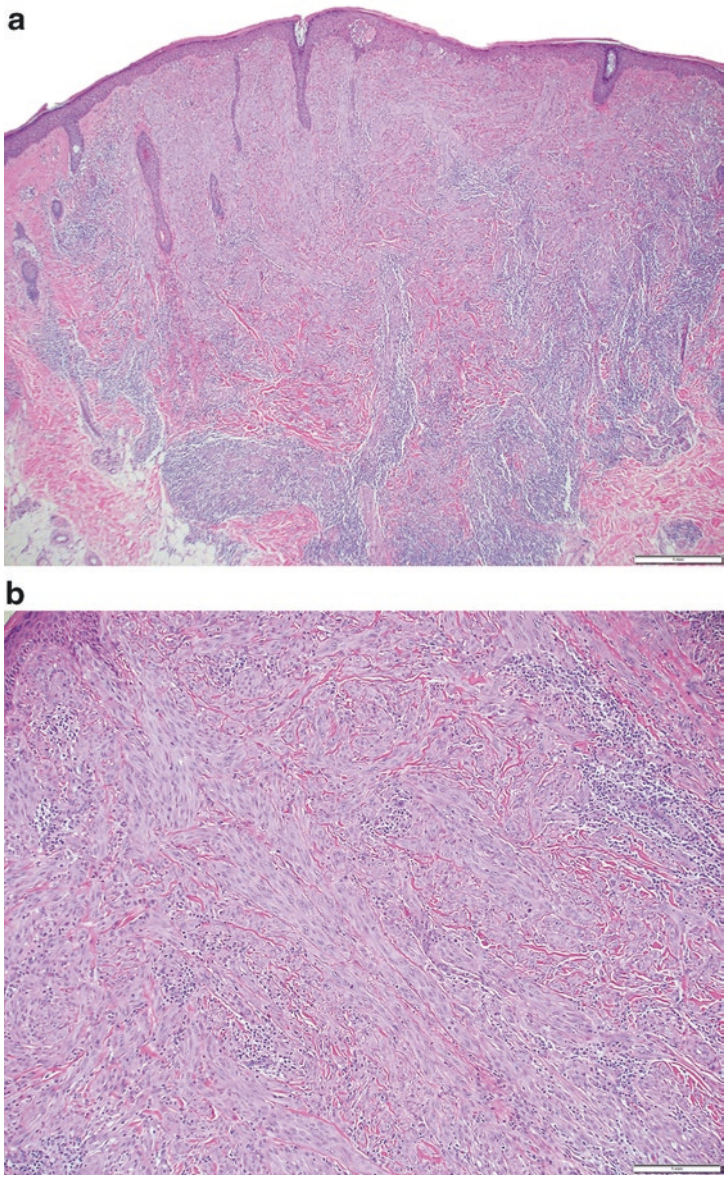

Fig. 4.38 Spitz Nevus with ALK fusion. This example shows a somewhat polypoid lesion forming a compound melanocytic lesion. The tumor is composed of a fascicular growth pattern with melanocytes streaming in large confluent nests/sheets that is characteristically oriented in a radial pattern (**a**). The lesion is clearly amelanotic and with a pronounced infiltrative growth pattern with deep dermal invasion (**b**, **c**).

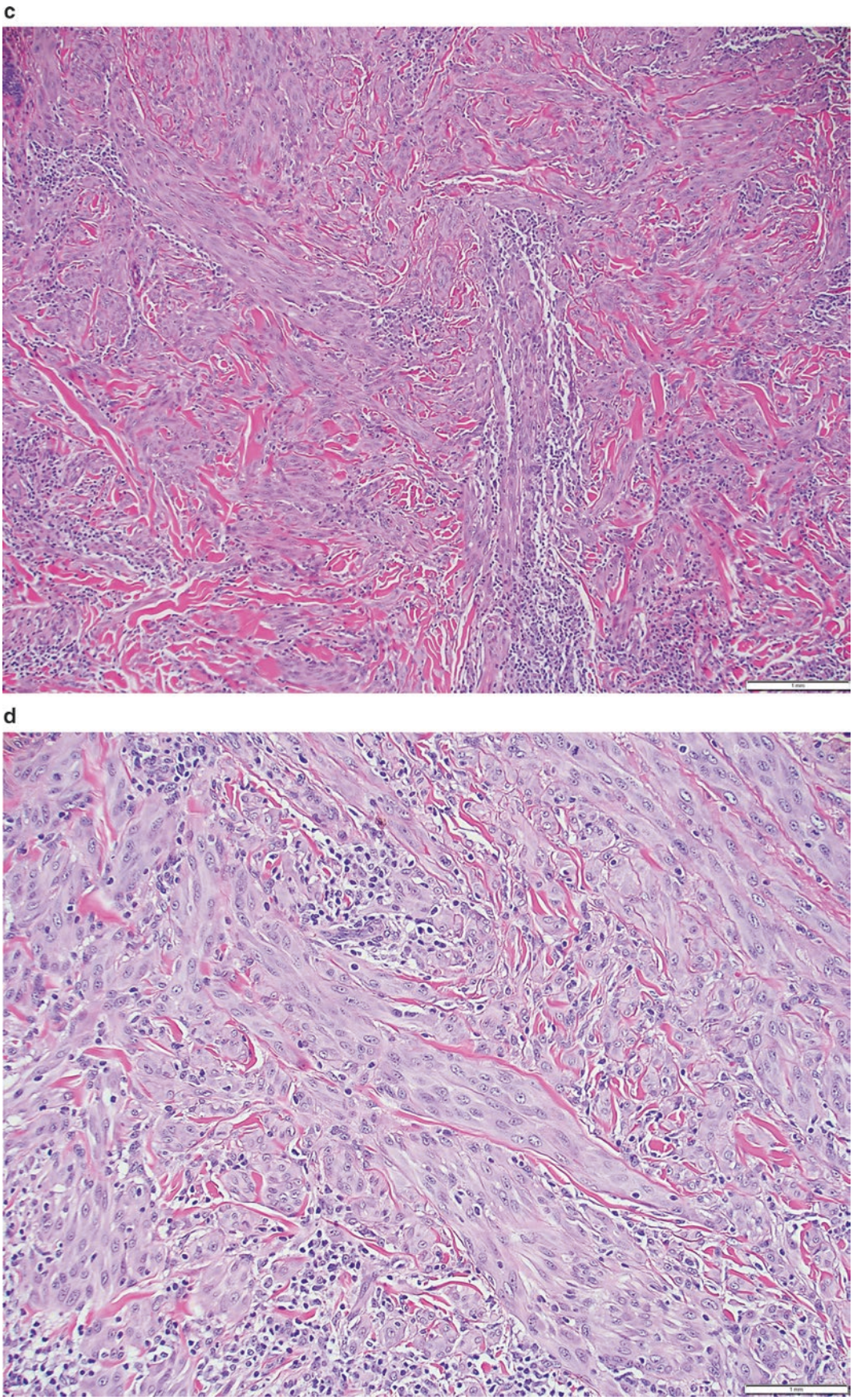

Fig. 4.38 (continued) Higher magnification shows fusiform to polygonal melanocytes with an amphophilic cytoplasm with a fibrillar quality (**d**).

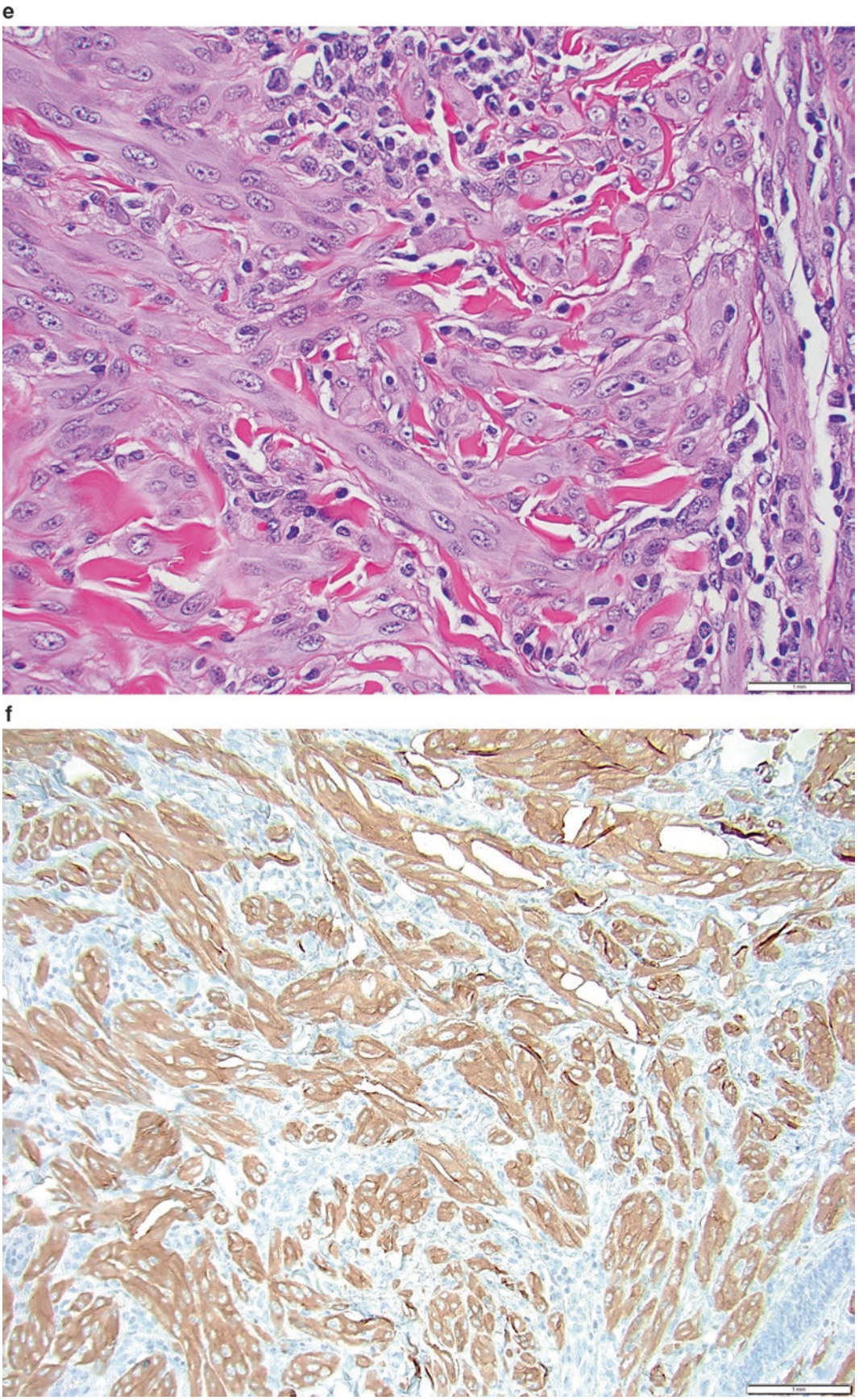

Fig. 4.38 (continued) The melanocytes display an enlarged nuclei and prominent nucleoli with only rare mitoses noted in superficial dermis (**e**). ALK stain showing a strong expression (**f**). Courtesy of Dr. Darren Whittemore (Miraca Life Sciences)

Atypical Spitz Lesions

Atypical Spitz lesions (atypical spitzoid neoplasms or atypical Spitz tumors) represent a controversial and poorly defined group of lesions that have an intermediate architecture and cytologic features between a Spitz nevi and melanoma. Thus, in practice the use of this term conveys a degree of uncertainty or unpredictability regarding their biologic behavior. Clinical and particularly histologic features deviate significantly from those attributed to the conventional Spitz nevus and can overlap with those of melanoma. Lesions that fall under this category are diagnostically controversial and lack sufficient atypicality to make an unequivocal diagnosis of spitzoid melanoma, especially in young patients. In our experience, such tumors when seen in children are likely to behave indolently; however, there are cases in which metastasis may occur, but it tends to be localized to regional lymph nodes [85, 86]. Particularly in patients younger than 11, even with positive sentinel lymph nodes, they tend to behave in a benign fashion although longer follow-up may be needed to elucidate if such lesions should be labeled nevus or melanoma.

The morphologic features for atypical Spitz lesions have been recognized for years but how one subjectively group them results in high interobserver disagreement, which may be reflected in the final diagnosis. Thus, it should be acknowledged that when dealing with atypical spitzoid neoplasms, histomorphology alone might not be sufficient to predict the biological behavior of such neoplasms. Thus, adjunct tests have been proposed to screen atypical Spitz lesions such as fluorescence in situ hybridization (FISH), comparative genomic hybridization, mutational analyses, and mass spectrometry.

Atypical Spitz tumors usually are larger than conventional Spitz tumors (>1 cm) and have abnormal gross morphologic features such as irregular borders and/or ulceration. Histologically, while most atypical Spitz tumors share some histologic features with Spitz nevus, they often demonstrate asymmetry and lack of circumscription. These tumors display greater than expected cytologic atypia in the form of large, pleomorphic cells with prominent nucleoli and high nuclear-to-cytoplasmic ratios including nuclear pleomorphism. In some case the melanocytes are arranged in sheet-like growth resulting in a dense compact cellularity that distorts the dermal architecture. Maturation with dermal descent is lacking and mitotic activity is often present, including the deep dermis. Other features that can be noted in these tumors include ulceration, pagetoid upward migration, high cellular density with nodular architecture, irregular distribution of melanin pigment, the presence of deep mitotic figures, and subcutaneous involvement with pushing borders at the base. One particular study found that the presence of numerous mitotic figures, mitotic figures near the base, and an inflammatory reaction are significant histomorphologic features that are more frequently observed in cases with unfavorable behavior [87]. Other studies have found that lesions >1 cm, the presence of ulceration, subcutaneous fat involvement, and mitotic figures (>6 per mm^2) correlate with a likelihood of metastatic behavior [2].

As the histomorphologic features of atypical Spitz lesions are also seen in melanomas, and such cases do not appear overtly malignant, dermatopathologists are faced with a diagnostic challenge to classify with certainty. In many cases, due to the uncertain histologic nature of these neoplasms, patients are often treated as melanoma, with sentinel lymph node biopsies. Many studies have shown a relatively high proportion of positive sentinel lymph nodes (up to 40 %) in cases of atypical Spitz lesions [88, 89]. Initially, the presence of any atypical cells in sentinel lymph nodes was interpreted as strong evidence of aggressive behavior, and the primary skin lesions were retrospectively diagnosed as melanoma; however, subsequent studies have demonstrated that a number of these lesions with positive sentinel lymph nodes do not seem to show the aggressive behavior seen in conventional melanoma [90–92]; it has been suggested that such unusual behavior may be due to the development of a strong immune response that results in the destruction of the metastatic spitzoid cells [88]. Recent molecular studies, such as comparative genomic hybridization or FISH, may provide additional information to better classify these neoplasms (see below).

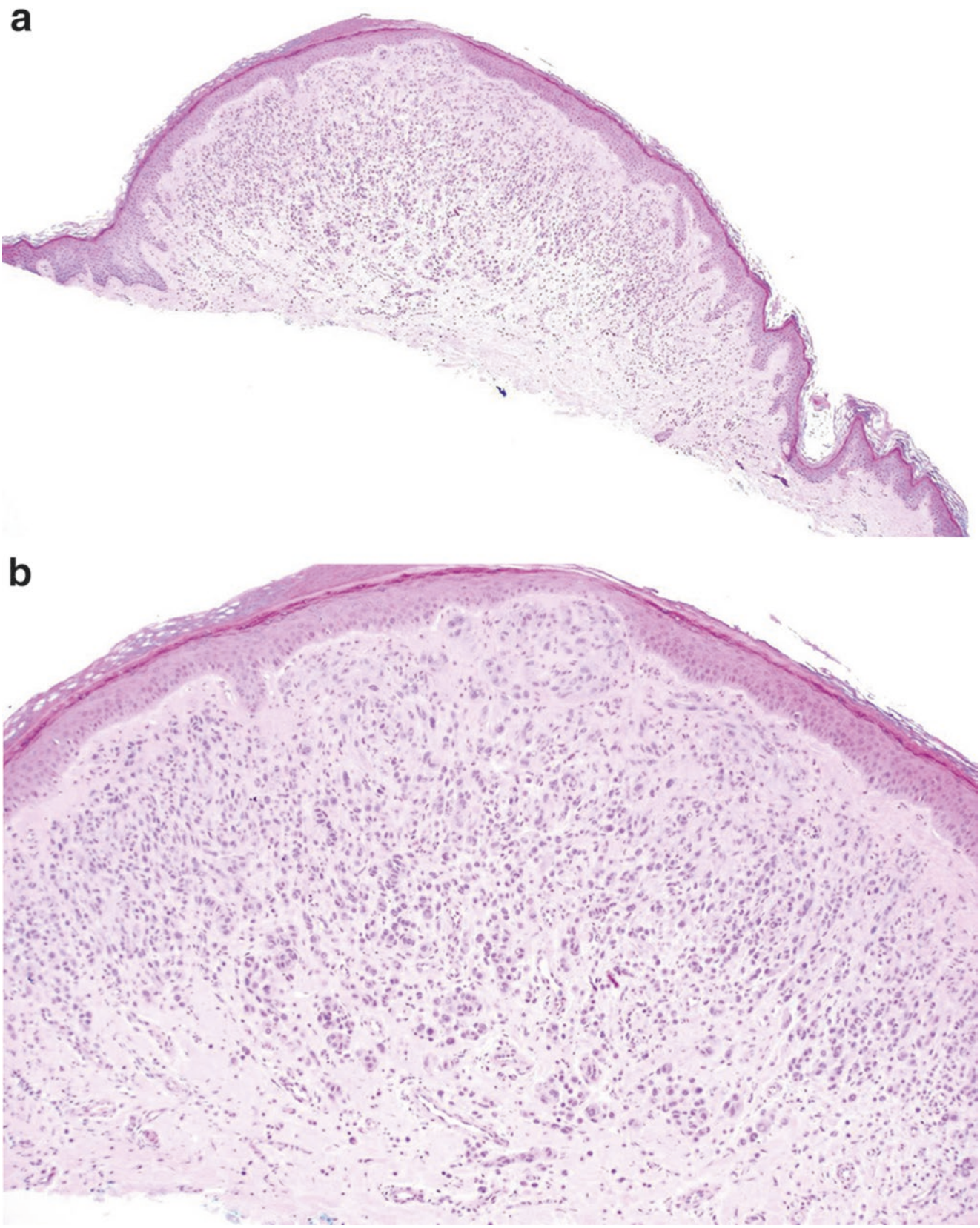

Fig. 4.39 Atypical Spitz nevus. This is a 29-year-old male that presents with a pigmented lesion on his distal leg (**a**). The lesion is small and clearly spitzoid (**b**).

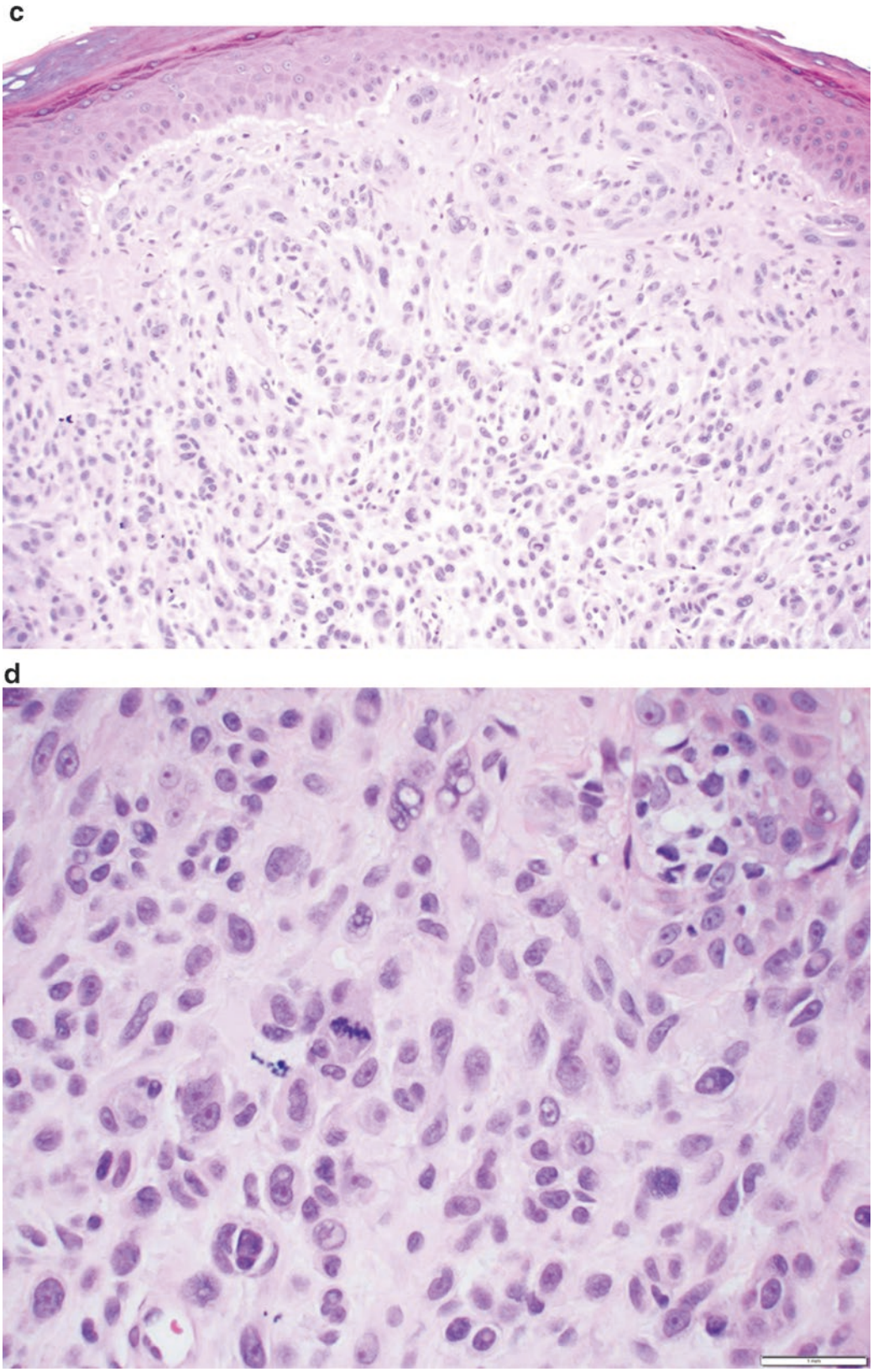

Fig. 4.39 (continued) There were some unusual features including the presence of deep atypical mitoses (2/mm2) (**c**). FISH studies were performed and the results showed gains in RREB1 and CCND; however, there was evidence of tetraploidy which can be seen in benign (5–10 % of Spitz nevi), borderline, and malignant melanocytic tumors, and therefore it is considered a nondiagnostic finding and explains the RREB1 gain (see images below) (**d**).

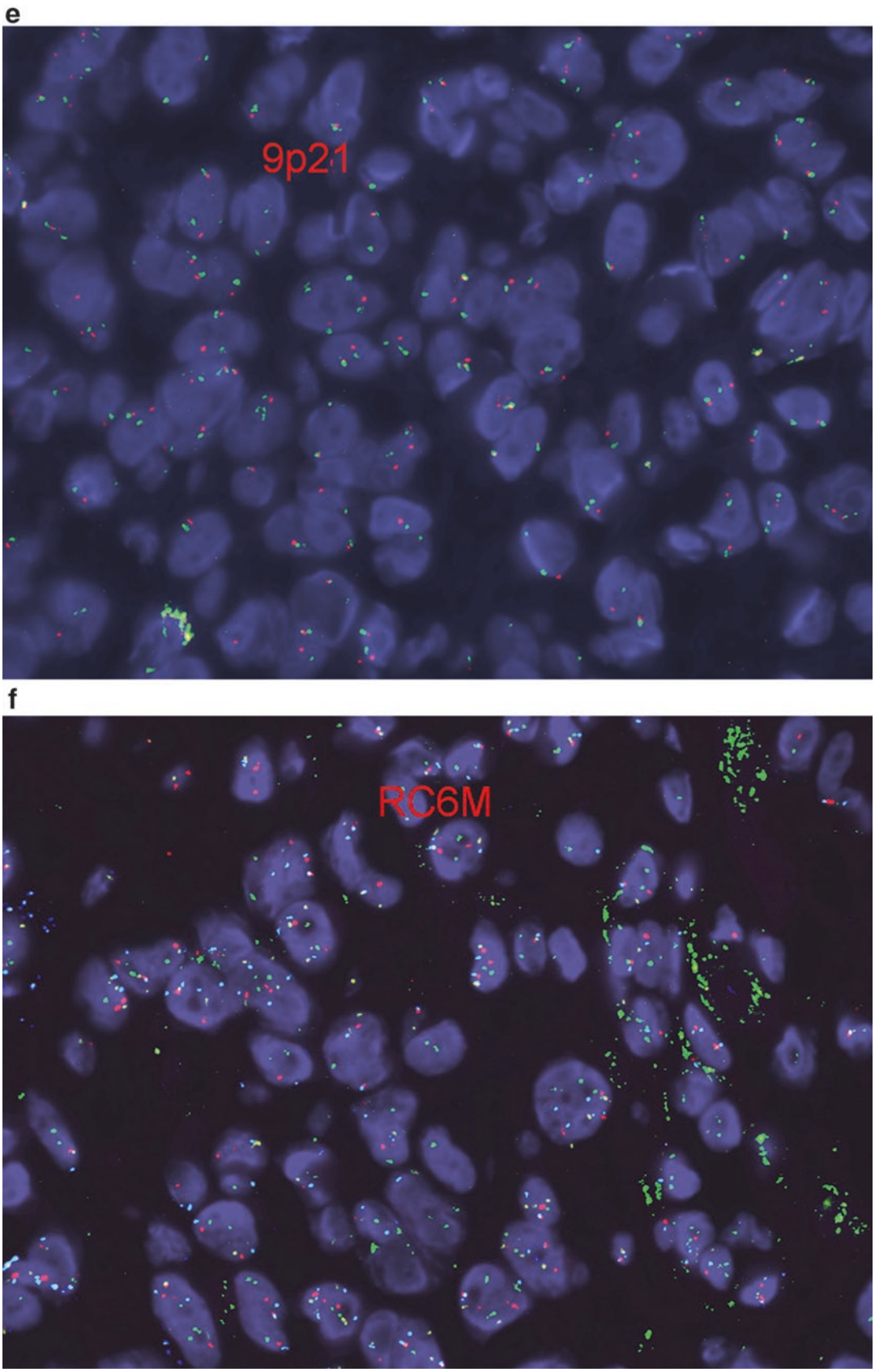

Fig. 4.39 (continued) FISH: There is no homozygous loss of 9p21 (**e**, **f**). Courtesy of Julie Reimann MD, Miraca Life Sciences

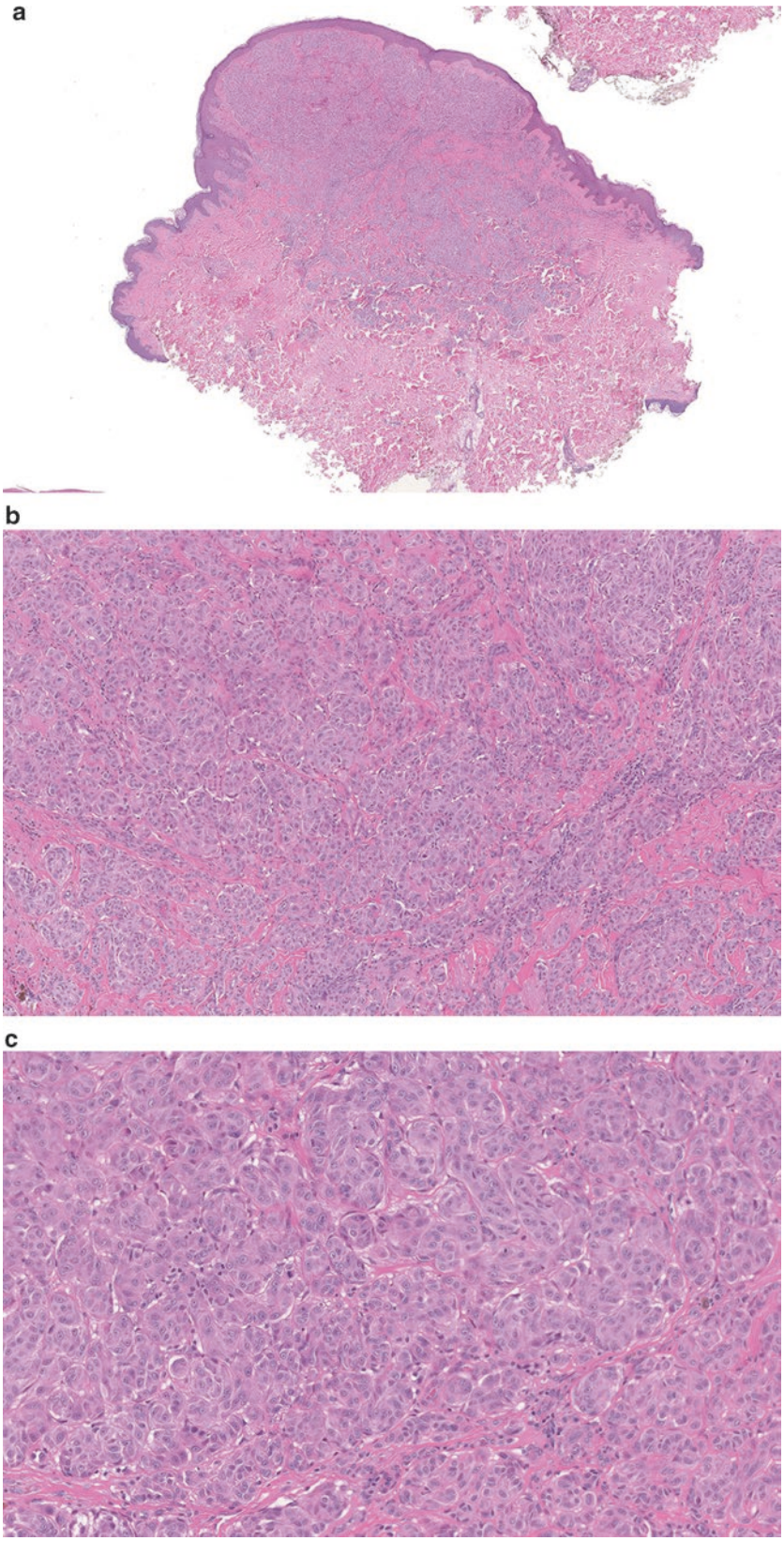

Fig. 4.40 Atypical Spitz nevus with 6q23 deletion. This case presented as pigmented nodule in a 7-year-old male. The lesion displays many atypical features including large sheets of epithelioid melanocytes, absence of maturation, and rare mitoses in deep dermis (2/mm2). Due to the inherent limitations in the ability of morphologic assessment to accurately predict clinical behavior in Spitzoid lesions, the tumor was submitted for the melanoma fluorescence in situ hybridization test to further assess the potential for aggressive behavior (see images below) (**a**). Note the high cellular density in this lesion along with cytologic atypia and lost of maturation (**b**).

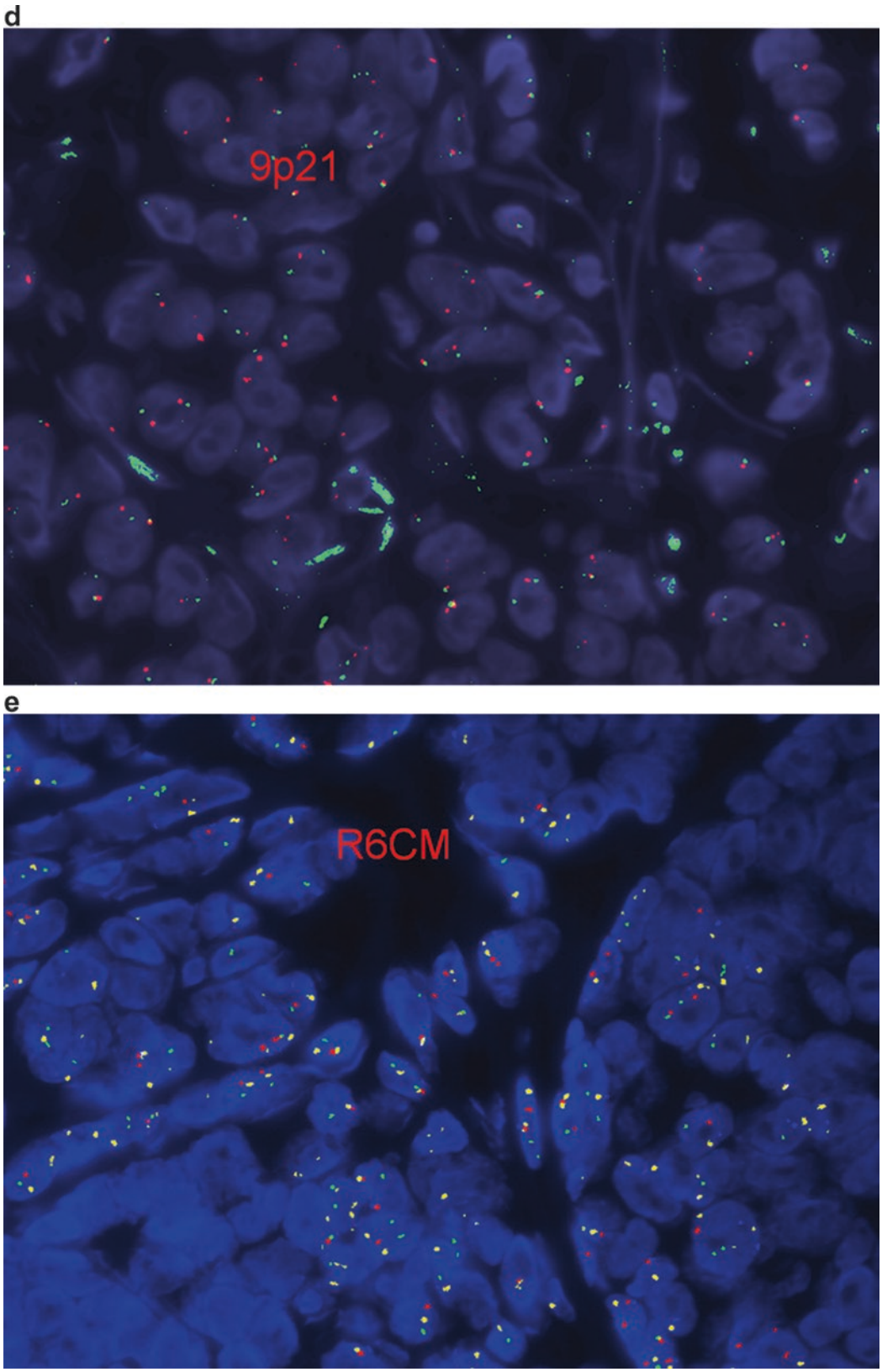

Fig. 4.40 (continued) FISH: There is no homozygous loss of 9p21 (CDKN2A). FISH: MYB (6q23)/CEP6 shows more than 40 % of nuclei with less 6q23 (MYB) than CEP 6 signals. There is preliminary data to suggest that atypical Spitz tumors with isolated MYB (6q23) loss show less evidence of aggressive behavior (e.g., advanced regional spread, distant metastases, or death) than atypical Spitz tumors with gains in RREB1 or CCND1 or 9p21 deletion (**c**–**e**). Courtesy of Julie Reimann MD, Miraca Life Sciences

Immunohistochemistry and Molecular Studies Advances in Atypical Spitz Lesions

As explained throughout this chapter, the majority of Spitz nevi can be accurately diagnosed on histomorphologic grounds, but a number of cases (atypical Spitz lesions) may raise concern and pose a diagnostic challenge because of a confusing combination of histologic features making it difficult to classify them as benign or malignant. Many studies have demonstrated lack of consensus in the precise diagnosis and classification of atypical Spitz lesions and spitzoid and conventional melanomas in children [90, 93–96], thus the need to develop additional ancillary techniques to aid in this distinction.

There have been attempts to use special techniques to distinguish between benign and malignant spitzoid lesions. AgNOR (argyrophilic nucleolar organizing regions) had significantly different sizes in nevi and melanoma although this technique has fallen in disuse. Immunohistochemistry also reveals differences between Spitz nevus and spitzoid melanoma. In our experience, Spitz nevi reveal maturation with HMB-45 and anti-Ki-67. Most Spitz nevi display labeling with HMB-45 in the intraepithelial and periepithelial melanocytes, while the deeply located cells are negative, although some cases may show strong, diffuse labeling similar to blue nevi. Ki-67 is expressed by superficially located melanocytes while deep cells are negative [97]. p16 has been suggested to be differentially expressed in spitzoid lesions, since it is usually preserved in nevi [98]. However, recent studies indicate that the differences are not significant since Spitz nevi may lack p16 and spitzoid melanomas may preserve it [55].

There has been accumulating evidence that molecular techniques that detect chromosomal copy number aberrations may be used in conjunction with standard histology as a method of improving diagnosis in ambiguous atypical spitzoid melanocytic neoplasms [99, 100]. It has been shown that spitzoid melanomas and atypical Spitz lesions in children have a different clinical course and different molecular aberrations than conventional melanoma [101]. Determining risk assessment for aggressive behavior of spitzoid lesions remains a significant challenge for pathologists. Despite the presence of concerning histologic features such as tumor ulceration, large dermal growth, dermal mitotic figures, and cytologic atypia, the majority of these atypical Spitz lesions tend to behave in an indolent fashion. In addition, as mentioned above, while the prognostic value of sentinel lymph node biopsy in conventional melanoma is very well known and accepted, sentinel lymph node biopsy in atypical spitzoid neoplasms in children carries a different prognostic value. Spitzoid melanomas frequently have a prolonged phase of aggressive local disease occurring with significantly less frequency or with a significantly greater latency period than in conventional melanoma [90, 92, 102, 103].

Several FISH assays have been developed to differentiate conventional melanoma from nevi. Some studies have suggested a relatively high sensitivity and specificity for conventional FISH in differentiating spitzoid melanomas from Spitz nevi [104, 105]. The first developed FISH assay focused on chromosomal aberrations of chromosome 6, including copy number gains in 6p25, deletions in 6q23, and gains in 11q13. One of the primary goals of these molecular assays is to be able to predict prognosis of intermediate-grade lesions (such as atypical spitzoid lesions). The identification of potential chromosomal aberrations seen in atypical Spitz lesions with favorable outcome demonstrates the importance of evaluating the prognostic significance of individual or combinations of chromosomal aberration in this setting.

One important limitation of the first-generation FISH assay is the presence of polyploidy/tetraploidy in some Spitz nevi. From a diagnostic standpoint, the presence of tetraploidy favors a benign diagnosis (tetraploid melanomas have been described, but they are rare) [106]. From a genomic standpoint, melanomas are more typically aneuploid, characterized by amplifications or deletions in discrete regions of chromosomes. Since the FISH assay does not differentiate between gains in all of the chromosomes from gains in discrete regions of chromosomes (it detects changes in copy numbers at specific loci), tetraploidy is the most common source of false positivity among benign lesions [107]. Due to the relatively low sensitivity of conventional first generation of FISH for ambiguous lesions (especially in atypical spitzoid tumors) and the compromised specificity due to the relatively high frequency of tetraploidy, it prompted the development of a new FISH assay that improved the diagnostic sensitivity and specificity of such neoplasms [108]. This second-generation FISH included 6p25, 8q24, 9p21 (the locus of p16), and 11q13. The cutoffs determined for these probes to indicate a positive result were >29 % of tumor cells with either gains at 6p25, 8q24, or 11q13 or homozygous deletion at 9p21. This new probe set demonstrated a sensitivity of 94 % and a specificity of 98 %, whereas the first generation of FISH assay showed a sensitivity of 75 % and a specificity of 96 % in the same set of lesions. In this second generation of FISH, the problem of tetraploidy was largely eliminated. However, we have seen examples of spitzoid lesions with tetraploidy in patients referred to us incorrectly labeled as "positive FISH results."

FISH studies have been proposed to be used as a surrogate of clinical outcome. A recent study showed that a variety of chromosomal aberrations may be seen in conventional melanomas in children including 6p25 gain, 11q13 gain, 8q24 gain, 6q23 deletion, and homozygous 9p21 deletions [99]. Same authors have shown that atypical Spitz lesions with homozygous 9p21 deletions, 6p25 gains, and/or 11q13 gains all had a statistically significant relationship with

tumor progression beyond the sentinel lymph node when compared with FISH-negative atypical Spitz lesions. On the other hand, cases with "isolated" 6q23 deletions had the same outcome as those with a negative FISH result [100]. In this study, the histologic features of atypical Spitz lesions with 6q23 deletions were not entirely specific, but they did identify a trend toward certain histomorphological patterns including the absence of pagetoid spread or only focally seen. The presence of micro ulceration (extending 2–3 rete ridges in length) was also commonly present, and in dermis these cases had large nests with expansile nodular growth. This same study found patients with isolated 6q23 deletions, despite having a positive sentinel lymph node concluding that atypical Spitz lesions with isolated 6q23 deletion represent a subset of atypical Spitz lesions with relatively high incidence of sentinel lymph node involvement but only rarely if ever develop disease beyond the sentinel lymph node. Based on these results, spitzoid melanocytic neoplasms in children as in adults can be classified into specific risk categories on the basis of the cytogenetic changes determined by FISH. Cases with homozygous deletions of 9p21 tend to show the greatest risk for potential aggressive behavior associated with adverse prognosis, including increased risk for metastasis and death of disease, whereas those with isolated 6q23 deletions or no copy number aberrations have significantly less risk of aggressive behavior [99, 100]. Also, spitzoid melanomas with homozygous 9p21 deletion tend to have frequent involvement of sentinel lymph nodes and a prolonged phase of advanced local-regional disease with frequent in-transit metastasis. Further studies are necessary to determine how to incorporate this information in the diagnosis of spitzoid lesions. Also, other techniques have been reported to provide high sensitivity and specificity in differentiating between Spitz nevi and spitzoid melanomas, namely, mass spectrometry [109] and gene signatures [110].

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Dysplastic Nevi

5

Dysplastic Melanocytic Nevi

Introduction

Dysplastic melanocytic nevi are common acquired melanocytic proliferations with distinct clinical and histologic features. This category of melanocytic lesions has been one of the most controversial terms introduced into dermatopathology and has resulted in completely divergent entrenched opinions as to its existence, diagnostic criteria, prevalence, and its significance [1–5]. Since dysplastic melanocytic nevi were first reported in 1978 by Wallace Clark and colleagues as histologically defined lesions in melanoma-prone families, there has been extensive debate about the definition, classification, and biologic importance of these lesions [6–8]. And although a number of authors object to the use of the term "dysplastic," we think that it has been so much popularized that it is probably best to continue using it. The most important point that has been debated is whether dysplastic nevi represent premalignant lesions that will progress to melanoma or not. There are authors who view dysplastic nevi as a discreet entity of clinical significance and others who dismiss the concept entirely [4, 9–11]. It is unknown the probability of a particular dysplastic nevus to become melanoma; however, patients with a diagnosis of dysplastic nevus are more likely to have had or to have in the future a diagnosis of melanoma in some other area of their bodies (see also below).

The precise definition of these melanocytic nevi has been a source of great controversy, as many synonyms have been proposed such as atypical nevus, Clark nevus, melanocytic nevus with architectural disorder, cytologic atypia, etc. First, Wallace H. Clark and colleagues described distinctive nevi in 37 patients from six melanoma families with "B-K mole syndrome" (B and K were the first letters of the names of two patients) [6]. These melanocytic nevi exhibited variable clinical appearance (>5 mm in size with variable color and borders). Second, Henry T. Lynch and colleagues reported a similar nevus phenotype in a melanoma-prone family. These phenotypic "syndromes" were referred to, respectively, as B-K mole syndrome and familial atypical multiple-mole melanoma (FAMMM) syndrome [8]. Then, David Elder and colleagues coined the term "dysplastic nevus syndrome" (DNS) and postulated the existence of sporadic and familial variants [1]. The term "dysplastic nevus" was proposed as these benign melanocytic nevi are characterized histologically by architectural disorder and cytologic atypia, similar to dysplastic lesions in other organs, such as the cervix, uterus, or esophagus [12]. These investigations of melanoma kindreds suggested a close relationship with these clinically atypical and histologically dysplastic nevi. However, it was noted early on that this nevus phenotype was not required for melanoma development in these kindreds, given that Clark and colleagues described two family members who developed melanoma without having clinically dysplastic nevi. An autosomal dominant mode of inheritance of the nevus phenotype has been described in melanoma-prone families, and it has been reported that up to 40 % of these families harbor a mutation in the CDKN2A locus, which encodes the p16 and ARF tumor suppressor proteins [13, 14].

The term "dysplastic nevus" remains the most commonly used name; an alternative term was proposed by the National Institutes of Health (NIH) consensus group as "nevus with architectural disorder and cytologic atypia"; however, it has been used less often as it is not very well accepted by many authorities in the field [15]. Some dermatopathologists have promoted using the term "Clark nevus" instead of dysplastic nevus to honor Dr. Clark as being the researcher that popularized the concept. Despite the NIH consensus conference and multiple studies to assess reproducibility of dysplastic melanocytic nevi, no single definition for these melanocytic nevi has yet been accepted by all [12, 16–21]. Some authors suggest that the term "dysplasia" requires histologic evaluation, and thus the term "atypical" is considered more appropriate for any clinical classification. In our view, the problem with using "atypical" is that "atypical nevi" include a broad range of different types of nevi with unusual morphology. Thus, the lack of clarity could create not only diagnostic confusion but also unnecessary treatment.

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The etiology of dysplastic nevi is not well defined. In general, the major environmental risk factor for melanoma is ultraviolet radiation but the presence of an increased number of melanocytic nevi is another major host risk factor. Other host factors include increased freckling, poor tanning ability, fair complexion, light hair and eye color, and family history of melanoma. The major genetic risk factors for melanoma include the high-risk susceptibility genes CDKN2A and CDK4 as well as numerous low-risk susceptibility loci. Similar to melanoma, dysplastic nevi seem to result from genetic, host, and environmental factors. Evidence suggests that sun exposure, in addition to genetic susceptibility, can affect the development of dysplastic nevi. The incidence of dysplastic nevi among patients with fair skin types is higher compared with those with darker skin, which might explain the increased risk of melanoma in these individuals [22]. At the molecular level, common nevi and dysplastic nevi have proven some differences. Dysplastic nevi tend to display mutation-deletion of p16 gene, altered expression of p53, and increased microsatellite instability [23]. Familial melanoma and dysplastic nevi were originally thought to be pleiotropic effects of a single gene, but subsequent studies have shown that the genetics are more complex and that the genetic causes of familial melanoma and dysplastic nevi are not the same. There is not much evidence that dysplastic nevi are caused by mutations in the major melanoma susceptibility genes CDKN2A or CDK4; however, similar to dysplastic nevi in unselected patients with melanoma, dysplastic nevi are risk factors for melanoma in melanoma-prone families independent of CDKN2A mutations [24–28].

Dysplastic Nevi as a Risk Factor and Precursor of Melanoma

There is a general consensus that increased number of melanocytic nevi is associated with melanoma risk and that the association is strongest if those are dysplastic. The frequency of clinically dysplastic nevi among patients with a history of melanoma has been reported to range from 34 to 59 % [29, 30]. Patients with dysplastic nevi and two or more family members with melanoma seem to be at the highest risk of melanoma. Patients with a family history of melanoma but lacking dysplastic nevi have only an average risk for the development of melanoma; thus, a patient's risk of developing melanoma increases with the number of dysplastic nevi.

Most studies that have evaluated dysplastic nevi as a risk factor for melanoma have used clinical criteria primarily or exclusively to classify these melanocytic lesions rather than histologic examination of their nevi. Rarely has there been an attempt to correlate the presence of dysplastic nevi confirmed histologically with melanoma risk. One study retrospectively reviewed a large number of cases of nevi with architectural disorder that were classified as mild, moderate, and severe cytologic atypia. Then the clinical chart was reviewed for the presence of a melanoma diagnosis whether prior or after the diagnosis of that dysplastic nevus. The incidence of melanoma was 5.7 %, 8.1 %, and 19.7 % for those patients with nevi with mild, moderate, and severe atypia, respectively, thus suggesting that the risk of melanoma is higher for patients with dysplastic nevi having higher grades of histologic atypia [31]. Another study generated a scoring system to grade the level of atypia in dysplastic nevi and correlated the scores with clinical parameters and outcomes. Patients with dysplastic nevi with moderate or severe dysplasia had an increased risk of having melanoma (odds ratio (OR) 2.60, 95 % confidence interval (CI) 0.99–6.86) [32]; however, interobserver variability associated with grading dysplasia was relatively poor (kappa 0.28), similar to other studies.

Other authors doubt that dysplastic nevi are risk factors for melanoma based on the fact that dysplastic nevi are highly prevalent in the population. Dysplastic nevi with mild dysplasia are reportedly very common (present in 7–32 % of population), suggesting that dysplasia is a relatively common phenomenon and thus not a strong predictor of melanoma [19]. One study found that a high number (88 %) of clinically benign nevi that were biopsied from healthy individuals showed at least one feature of dysplasia and that up to 30 % of them had three features of dysplasia (pattern atypia, cytologic atypia, and host response) [33]. From a more mechanistic point of view, other studies have shown that mildly dysplastic nevi lack DNA aneuploidy as opposed to the presence of DNA aneuploidy in dysplastic nevi with at least moderate atypia, thus suggesting that mildly dysplastic nevi are not associated with increased melanoma risk [34].

Clinical Features

Dysplastic nevi are acquired atypical melanocytic lesions that oftentimes share some of the same clinical features as melanomas, including one or more of the ABCDs (asymmetry, border irregularity, color variability, and a diameter which may be >6 mm). Although these criteria are useful for recognizing suspicious lesions, there is often great difficulty in differentiating dysplastic nevi from melanoma.

Clark and colleagues initially defined dysplastic nevi as a nevus >5 mm in diameter with variegation in its pigmentation and irregular borders; however, since this morphologic description, there have been proposed further criteria [6]. Tucker et al. clinically defined dysplastic nevi as being >5 mm in size and having “flatness” (being entirely flat or having a flat component). In addition, two of three characteristics were also necessary: variable pigmentation, irregular and asymmetric outline, and having indistinct

borders [30]. Kelly and colleagues classified dysplastic nevi as lesions with a macular component that showed at least three of five criteria: irregularly distributed pigmentation, ill-defined or irregular border, background of erythema, and >5 mm [35]. The Dutch Working Group has used the following criteria for atypical nevi: ≥5 mm in diameter, vague border, asymmetric shape, irregular pigmentation, and red hue [36].

Dysplastic nevi differ from melanomas in situ clinically, as they tend to be symmetrical. The common appearance of a dysplastic nevus is that of a "fried egg," where there is a central papular component ("the head") and an adjacent macular component ("shoulders"). Some dysplastic nevi are entirely junctional, and thus they usually lack this fried egg appearance. The borders of dysplastic nevi are less irregular than those of melanomas, and perhaps paradoxically they are often ill defined compared with the sharper border of most melanomas. Lentigo maligna melanoma can have an ill-defined border, similar to that of a dysplastic nevus; however, these lesions are usually much larger and show greater pigmentary variegation and asymmetry. The color of dysplastic nevi is usually less variable (uniform color) than that of melanomas and does not usually include the red, white, and blue colors that may signify partial regression in a melanoma. Dysplastic nevi, by definition, are >5 mm; however, it has been proven that dysplastic nevi <5 mm may be also associated with melanoma risk. Dysplastic nevi are most often seen on the trunk, especially the upper back, although they can appear anywhere on the skin, including sun-protected areas such as the scalp, breasts, and buttocks.

It is also important to remember that small nevi have been reported to cover the same histopathological spectrum as large lesions and to show a high proportion of atypical features (this is not the exception with dysplastic nevi). Most of the studies about dysplastic nevi concentrate on lesions larger than 5 mm in diameter, mostly because it is relatively uncommon for clinicians to biopsy lesions of smaller size. One study focused on small lesions, measuring less than 3 mm, and concluded that small junctional melanocytic lesions may display severe architectural disorder, which might be related to active melanocytic proliferation [37]. In such lesions it is important to know how to interpret the severe architectural disorder when lesions are small in size and with features of dysplastic nevi, in order to avoid overdiagnosis of melanoma.

Dysplastic Nevi Syndrome

The current definition of dysplastic nevus syndrome has been a source of controversy due its nomenclature and definition. Dysplastic nevus syndrome has also been referred as atypical mole syndrome, FAMMM syndrome, B-K mole syndrome, etc. Although originally described as a familial condition, there are also sporadic cases. Familial cases were originally called the B-K mole syndrome and the FAMMM syndrome (see above) [6, 8, 38]. In familial cases the melanoma trait is inherited as an autosomal dominant with incomplete penetrance. As explained above, the dysplastic nevus trait has a more complicated inheritance, occurring more commonly than it would be expected for a dominant inheritance. Mutations of the CDKN2A gene on 9p21–22 have been found in patients with familial melanoma (in approximately 40 % of families), but these mutations are uncommon in dysplastic nevi themselves [39–41]. CDKN2A encodes the tumor suppressor gene products p14ARF and p16INK4a. Patients with dysplastic nevus syndrome have also been associated with partial deletion of chromosome 11 and with deletion of 17p13 (p53) [42, 43]. Patients with dysplastic nevus syndrome have increased risk of developing other neoplasms, especially pancreatic cancer [44, 45].

The importance of the dysplastic nevus syndrome is that it identifies an at-risk population group for the development of melanoma. The sporadic dysplastic nevus syndrome is characterized by the presence of 2–5 dysplastic nevi on sun-exposed areas, patients have no personal or family history of melanoma, and the nevi first appear at puberty and then develop new lesions during adult life (only 20 % of these nevi appear after 50). The familial dysplastic nevus syndrome is characterized by multiple nevi (>100 melanocytic), one or more large nevi (>6 mm), and one or more clinically atypical nevi (ABCD rule), and the nevi are distributed all over the body including sun-exposed and sun-protected areas (involvement of face and scalp). The risk of developing melanoma in melanoma-prone families with the dysplastic nevus syndrome varies in the literature, and some studies have suggested that it exceeds 50 %, being highly positively correlated with higher number of nevi [46].

Histologic Features

Dysplastic nevi, whether familial or sporadic, show identical histologic features. The changes seen in dysplastic nevi can be divided into architectural, cytological, and host responses. Dysplastic nevi by definition should display melanocytic proliferative changes (intraepidermal, at least focally lentiginous, hyperplasia of melanocytes), cytologic and architectural atypia, and a stromal response [9, 47, 48].

Architecture: Dysplastic nevi are either junctional or compound. The surface of these nevi is flat and mildly papillated. As mentioned above, compound lesions usually tend to show an extension of the epidermal component beyond the dermal component ("shoulder"). The main architectural feature of dysplastic nevi is the irregular intraepidermal melanocytic proliferation. The junctional component generally displays

nests as well solitary melanocytes arranged in a lentiginous pattern. In cases in which a lentiginous pattern predominates, the melanocytes are arranged as variable nests and single cells along the basilar aspect of elongated, club-shaped rete. The rete ridges tend to be irregularly elongated. The junctional melanocytic nests are irregularly sized and shaped and often have a horizontal orientation. These junctional melanocytic nests are found near the tips and laterally to the elongated rete ridges and above the dermal papilla. Melanocytic nests connect the bases of the rete and fuse to the adjacent rete ("bridging"). This bridging is more prominent when the nests are not uniform in size and shape. The junctional component is characteristically hypercellular in areas replacing the vast majority of basal keratinocytes, and in some cases, there is marked lentiginous melanocytic hyperplasia in which single melanocytes predominate at the side of the rete ridges. Both nests and lentiginous proliferations can extend somewhat along the epithelium of cutaneous adnexa. Melanocytes within the junctional nests tend to show a dyshesive pattern with shrinkage artifact with scant cytoplasm and a spindle-shaped pattern, but in some lesions, there are epithelioid melanocytes with dusty pigment. In advanced lesions, there can be confluence of nests which may involve three or four rete ridges. In some cases, melanocytes can display retraction spaces, which give a vacuolated appearance to the basal layer. While pagetoid upward migration is not common in dysplastic nevi, there may be focal or limited suprabasal extension of melanocytes (see below).

The intradermal component, if present, often is focal and located in the central part of the lesion with the junctional component extending beyond the dermal component ("shoulders"). In most cases, there are well-defined nests and strands of melanocytes underneath the epidermis, along with sclerotic changes (fibroplasia, see "host response). Deeper areas of the nevus consist of ill-defined aggregates or compact small groups of melanocytes. The dermal component appears cytologically banal with small, round melanocytes. However, some nevi show superficial cytologic atypia comparable to the junctional component. The dermal component routinely lacks mitotic figures; therefore, the presence of a single mitotic figure in the dermal component should be a red flag to further evaluate the lesion to rule out melanoma.

Cytology: Dysplastic nevi show a variation in morphology of melanocytes including epithelioid, spindle cell, vacuolated, small melanocytes, etc. In cases in which a lentiginous pattern predominates, melanocytes tend to have a retracted cytoplasm giving a vacuolated appearance. Those cases with a predominantly nested pattern usually have epithelioid melanocytes (advanced cases may show spindle morphology). A very important criterion in the diagnosis of dysplastic nevi is the characteristic discontinuous cytologic atypia of the intraepidermal melanocytes (the degree of atypia varies from melanocyte to melanocyte).

Some melanocytes show with large, hyperchromatic, and pleomorphic nuclei; some authors considered them a requisite for the diagnosis of dysplastic nevus. In our opinion, cytologic atypia occurs along a continuum characterized by nuclear pleomorphism, chromatin variation, and presence of nucleoli, as previously described [48]. The low-end of spectrum tends to show only very minimal cytologic atypia that is almost imperceptible. Some cases may display a vacuolated cytoplasm with only mild enlargement of the nuclei (similar to the size of the adjacent keratinocyte nuclei). In this category, the chromatin is evenly dispersed with inconspicuous nucleoli. In advanced lesions, cytologic atypia is characterized by the presence of melanocytes with large oval shape with abundant pale cytoplasm with large central vesicular and hyperchromatic nuclei and prominent eosinophilic nucleoli. The nuclei are larger in size than the nucleus of the overlying keratinocytes. In some cases, the cytoplasm is ample with granular appearance or filled with dusty pigment. These atypical melanocytes may be present singly or in small clusters. These atypical melanocytes do not represent the majority, and in any one nevus, there is an admixture of normal and atypical melanocytes (random/discontinuous cytologic atypia). Mitotic figures are very rarely seen, and they should be located in the upper dermis near the epidermis. Although rare melanocytes may be seen in the suprabasal epidermis, any significant degree of pagetoid spread or its presence at the periphery of the lesion should raise the possibility of melanoma.

Host response: Host response is referred to as the presence of eosinophilic lamellar and concentric fibroplasia of the papillary dermis, mononuclear cell infiltrate, and prominent vascularity. In some cases, there is fibrosis in the upper reticular dermis, resulting in widely spaced nests.

The inflammatory lymphocytic infiltrate varies from sparse to dense. When sparse, the lymphocytes are arranged along the perivascular spaces in the superficial dermis, while in cases where there is dense inflammation, there is a band-like distribution that fills the papillary dermis. Melanophages (pigment incontinence) are usually present along with lymphocytes in the papillary dermis. Dermal fibroplasia is observed as lamellar or concentric. Lamellar fibroplasia is characterized by horizontally dispersed collagen subjacent to the epidermal rete ridges. Concentric fibroplasia is characterized by hyalinized collagen that is compactly disposed around a rete ridge. Dysplastic nevi usually show prominent vascularity in the papillary dermis, represented by the presence of ectatic vessels.

Table 5.1 Histologic features of dysplastic nevi

Architecture:
1. Nested and lentiginous melanocytic proliferation
2. Variable size and location of nests
3. Junctional bridging
4. Lack of cellular cohesion within nests
5. Later extension (shouldering phenomena)
6. Asymmetric intraepidermal component
Stroma:
1. Concentric fibroplasia/lamellar pattern
2. Lymphocytic infiltrate with melanophages
3. Marked vascularity
Cytology:
1. Epithelioid and/or spindle melanocytes
2. Melanocytes with variable cytologic atypia (nuclear pleomorphism and hyperchromasia)
3. Melanocytes with pale of dusky cytoplasm

Table 5.2 Duke University grading system for dysplastic nevi

(A)	Architectural disorder
	– Junctional component nested at both edges (both edges nested = 0; single cells = 1)
	– Overall symmetry (symmetrical = 0; asymmetrical = 1)
	– Cohesiveness of junctional nests (≥50 % of nests = 0, <50 % = 1)
	– Suprabasal spread (focal or absent = 0, prominent or at edge of the lesion = 1)
	– Confluence of rete ridges ("bridging"; ≥50 % of rete = 0, <50 % = 1)
	– Ratio of nested vs. single-cell proliferation (nested in ≥50 % equals 0, <50 % = 1)
(Grading score: mild 0–1, moderate 2–3, severe 4–6)	
(B)	Cytologic atypia (as established after evaluating two high-power fields with the most atypia of the lesion)
	– Nuclear shape and chromasia (≥50 % of cells with nuclei round/oval and euchromatic = 0; else = 1)
	– Nuclear size (≥50 % of cells with nucleus smaller or equal to the size of basal cell keratinocyte nuclei = 0; larger = 1)
	– Cellular size (≥50 % of cells smaller or equal to twice the size of basal cell keratinocyte nuclei = 0; other = 1)
	– Nucleolar size (≥50 % of cells with small, inconspicuous = 0; visible = 1)
(Grading scores: mild 0-1, moderate 2, severe 3–4)	

Grading Dysplastic Nevi

There have been many studies that have tried to consolidate histologic criteria; however, great controversy still surrounds the histopathological diagnosis of dysplastic nevi, and the possible usefulness of histological grading have raised interest in assessing the reproducibility of grading criteria.

Differences between the degree of cytologic atypia and architectural disorder have been noted in dysplastic nevi; however, in our opinion significant correlation exists between these two parameters. Several groups have proposed that dysplastic nevi be graded using architectural and cytologic features. To make dysplasia grading more objective and reproducible, a semiquantitative scoring system (the Duke criteria) was proposed and validated by Shea et al. [48]. This scoring system assessed both the architecture and the cytologic atypia of dysplastic nevi. Other authors have recommended the distinction between low-grade and high-grade dysplastic nevi using slightly different histologic criteria [49]. One study used a system for grading melanocytic dysplasia and concluded that severe dysplasia could be reliably distinguished from mild and moderate dysplasia; thus, these authors recommended a two-grade system (low and high grade) for classifying dysplastic nevi [49]. Some authors recommend not to try to grade dysplastic nevi and rather establish a diagnosis of "atypical" or "dysplastic" or "Clark" for these lesions. However, as discussed above, patients with lesions with high degree of dysplastic seem to have a higher risk of developing melanoma.

In our practice, we use the Duke system, to grade dysplastic nevi (see Table 5.2). Using this method the architectural disorder is graded as measuring the junctional component at both edges (both edges nested equal 0; single cells equal 1), the overall symmetry of the lesion (symmetrical equals 0; asymmetrical equals 1), cohesiveness of junctional nests (>50 % of nests equals 1), suprabasal spread (prominent or at edge equals 1), confluence of rete ridges (>50 % equals 1), and single-cell proliferation (>50 % equals 1). Lesions are then graded as mild (scores of 0 and 1), moderate (scores of 2 and 3), and severe (scores of 4–6) architectural disorder (see Table 5.2).

Cytologically, lesions are evaluated in the two most atypical high-powered fields. The points are given if more than 50 % of the melanocytes in those two fields show the studied criterion: 1) shape and chromasia of melanocytes (round/oval, euchromatic equals 0; else equals 1), 2) nuclear size (smaller or equal to basal cell keratinocyte nuclei equals 0; larger equals 1), cellular size (cells smaller or equal to twice the size of basal cell keratinocyte nuclei equals 0; larger equals 1), and nucleolus (small, inconspicuous equals 0; visible equals 1). Lesions are then graded as mild (score of 0), moderate (scores of 1 and 2), and severe (scores of 3 to 4) (see Table 5.2).

Although we do not grade the amount of alteration of the dermal stroma, we consider that dysplastic nevi have some degree of host response against the atypical melanocytes and thus will show different degrees of lymphocytic and macrophage infiltrate, dermal fibrosis, and vascular proliferation (see Table 5.2).

Dysplastic Nevi Variants

Dysplastic (Atypical) Nevus of the Elderly

Dysplastic (atypical) lentiginous nevus of the elderly is a relatively newly described lesion that represents a peculiar variant of dysplastic nevi that shows overlapping histologic

features with both lentiginous nevi and dysplastic nevi. Clinically, these nevi are seen in chronic sun-damaged skin and usually present as a pigmented solitary lesions that vary in size (0.3–1.0 cm or more in diameter). These nevi are primarily located on the back or the proximal parts of the limbs in individuals aged 50–70 years but may be seen in younger individuals who have sun-damaged skin. This lesion was first described by Kossard et al., who observed clinically atypical pigmented lesions with histologic features conforming to the histopathology of dysplastic melanocytic nevus with a lentiginous pattern [50]. Because these atypical lentiginous nevi manifest clinically as pigmented, asymmetric, multicolored lesions in areas of chronic sun damage, this condition can be confused with melanoma. In our opinion, the appropriate classification of these nevi is a subject of some debate as the histopathologic findings do not always completely resolve clinical uncertainties as they can be indicative of both dysplastic nevus and melanoma. Some authors have suggested that these atypical lentiginous dysplastic nevi of the elderly indeed represent potential precursors of melanoma [51]. This is particularly relevant when analyzing partial samples of large, junctional, pigmented melanocytic lesions in the elderly in which deeper skin sections, additional tissue samples, or removal of such lesions may be required to exclude the presence of melanoma [52].

Histologically, atypical (dysplastic) lentiginous nevus of the elderly is characterized by an irregular lentiginous epidermal hyperplasia that is unevenly spaced and of different sizes. In the epidermis there are melanocytic nests within the rete ridges with increased numbers of isolated or nested melanocytes, irregularly distributed along the basal layer. These nests may form bridges between rete ridges, and the suprapapillary plates between the ridges are associated with focal confluence of melanocytes. The papillary dermis shows the characteristic concentric papillary fibroplasia and lymphocytic inflammation with pigment incontinence of dysplastic nevi.

A very interesting and controversial topic is the possible existence of this type of lesions within the face and its distinction with lentigo maligna. In general, lesions with cytologic atypia occurring in the skin with actinic damage are usually considered to be melanoma. However, humans develop dysplastic nevi throughout their lives, and thus there is no obvious reason why dysplastic nevi cannot appear on solar-damaged skin (e.g., face) of elderly individuals. Thus we consider that as long as there are other features of a dysplastic nevus (elongation of rete ridges, bridging, host response in the dermis), such lesions may be considered to be dysplastic nevi and be graded according to the same criteria described above.

Dysplastic Nevi with Pagetoid Melanocytes

Dysplastic nevi may occasionally display alarming histologic features, such as pagetoid upward migration of melanocytes, which can easily simulate melanoma. Pagetoid melanocytosis has been very well described in a variety of other melanocytic nevi including congenital nevi in early infancy, Spitz nevi, pigmented spindle cell nevi of Reed, acral nevi, genital nevi, scalp nevi, recurrent and traumatized nevi, and nevi following ultraviolet exposure. Typically, in these lesions the melanocytic ascent is confined to the center of the lesion and does not show the uniform cytologic atypia seen in melanomas; in melanomas, the pagetoid spread is typically more extensive and is present at the periphery of the lesion, with the individual melanocytes showing marked cytologic atypia. Limited pagetoid upward migration of melanocytes into the lower layers of the epidermis is acceptable in dysplastic nevi; however, the spread of large numbers of melanocytes is not, and thus it raises suspicion for melanoma [53–55]. In our experience, dysplastic nevi with pagetoid melanocytes show a low level ascent of melanocytes and confined to the center of the lesion; anything beyond the center of the lesion should be cautiously inspected as it may indicate melanoma in situ (possibly melanoma in situ arising in association with a dysplastic nevus).

Differential Diagnosis of Dysplastic Nevi

The main differential diagnosis of dysplastic nevi is with early melanoma, as these lesions are characterized histopathologically by the presence of architectural disorder and cytologic atypia. This distinction can be quite challenging especially when dysplastic nevi are fully developed and display severe architectural disorder and cytologic atypia (such as the presence of architectural disorder, cytologic atypia, nested and a lentiginous pattern of growth). Unfortunately, in many cases the separation of these two lesions can be disturbingly arbitrary and subjective, as there are not well-established criteria to separate these lesions. Furthermore, the NIH consensus conference of 1992 recommended treating severely dysplastic nevi as melanomas in situ. The presence of marked pagetoid upward migration (especially at the border of the lesion), prominent asymmetry, diffuse continuous high-grade cytologic atypia, and atypical mitoses in dermis are useful criteria for rendering a diagnosis of melanoma.

Some dysplastic nevi are predominantly lentiginous and appear to form a continuous spectrum with early melanoma in situ (lentiginous melanoma or lentigo maligna). Dysplastic nevi with lentiginous features are distinguished

from early melanoma in situ by their lack of epidermal atrophy, marked solar elastosis, skin adnexal involvement, and pagetoid spread; however, extreme caution should be taken in cases of junctional dysplastic nevi in severe sun-damaged skin (especially when located in the face) (see above). These lesions tend to be composed of single-cell growth with lentiginous pattern and lack of cytologic atypia, which can overlap with lentiginous melanomas (dysplastic nevi-like melanoma) [50, 52, 56, 57]. Dysplastic nevi with a lentiginous component show melanocytes that are gathered in bizarrely elongated nests; however, a lesion with large prevalence of the lentiginous organization throughout the lesion along with the flat epidermis is more characteristic of melanoma. In addition, in melanoma the junctional nests are widely confluent to each other and seem to form one single aggregate of melanocytes at the junction as opposed to dysplastic nevi in which nests are mostly located at the tips of rete ridges. Lentiginous melanomas do not show architectural alterations of the dermal-epidermal junction, such as lamellar fibroplasia typical of dysplastic nevi. In our experience, dysplastic nevi with lentiginous growth located on sun-exposed areas need to be entirely removed and treated similarly as melanomas, as some of these lesions may in fact represent early melanomas when they regrow. In addition, lentiginous melanomas differ from lentiginous dysplastic nevi by their ability to attain large size, by the presence of confluent growth of atypical melanocytes spanning the entire lesion, and by pagetoid spread. Lentiginous melanoma and lentigo maligna patients are usually older, and the clinical picture is always worrying; furthermore, melanomas may display areas of regression, a feature relatively rare in dysplastic nevi.

Junctional dysplastic nevi with severe architecture and cytologic atypia can be difficult to separate from lentigo maligna melanoma as both can show histologic similarities and might be difficult to distinguish (see also dysplastic nevi of sun-damaged skin). Lentigo maligna is usually seen in older patients and commonly located in sun-exposed anatomic areas (face, scalp). Lentigo maligna shows a dense proliferation of basilar melanocytes in single cells and with rare nest formation. The melanocytes have the propensity to spread along hair follicles and eccrine structures, which would be unusual in dysplastic nevi. The rete ridges are flat and effaced and solar elastosis is easily seen in the dermis. On the other hand, dysplastic nevi are characterized by elongated rete ridges with high density of melanocytes along the lateral aspect of the rete. Nonetheless, there are cases in which such distinction is very difficult, especially when the architecture of the epidermis is partially preserved (lack of prominent effacement of rete ridges). In such cases, the presence of a predominant lentiginous pattern, marked involvement of follicular structures, and solar elastosis should favor the diagnosis of lentigo maligna.

In some occasions, dysplastic nevi show effacement of epidermal rete and confluence of melanocytes along the dermal-epidermal junction along with a mononuclear cell infiltrate. While these changes may highly suggest melanoma, these findings must be carefully interpreted in the overall context of the lesion. Dysplastic nevi tend to have variable or discontinuous cytologic atypia, and this finding is quite helpful to distinguish dysplastic nevi from melanoma. Melanoma usually shows a homogenous, continuous, and uniform cytologic atypia. Also, in some cases of dysplastic nevi, there are entrapments of atypical melanocytic nests in the fibrotic papillary dermis, suggesting the possibility of melanoma with regression. The diagnosis of melanoma in such instances should be based on a systematic evaluation of the lesion including the cytologic and architectural features. Nonetheless, it is important that the dermal melanocytes in the fibrotic papillary dermis lack the marked and uniform and marked cytologic atypia usually seen in melanomas.

An important point to remember is that dysplastic nevi that have been traumatized may show atypical changes such as the presence of pagetoid upward migration within the epidermis. Traumatic effects at the periphery of the lesion may be more difficult to recognize than in the center of the nevus. The histologic spectrum of alterations may include any of the following: parakeratosis, hypergranulosis, pagetoid upward migration (commonly beneath parakeratosis and focal), ulceration, poor circumscription, and irregular and disordered proliferation of melanocytes along the dermal-epidermal junction and in the dermis.

Table 5.3 Dysplastic nevus vs. melanoma

Junctional dysplastic nevi (severe architectural)	Melanoma in situ
Poorly defined with asymmetric borders	Asymmetric and poorly defined
Focal preservation of the nested pattern	Disordered nesting pattern
Lentiginous melanocytes predominate in rete	Confluent growth of melanocytes throughout the epidermis
Minimal pagetoid upward migration	Marked pagetoid upward migration
Discontinuous cytologic atypia	Continuous cytologic atypia

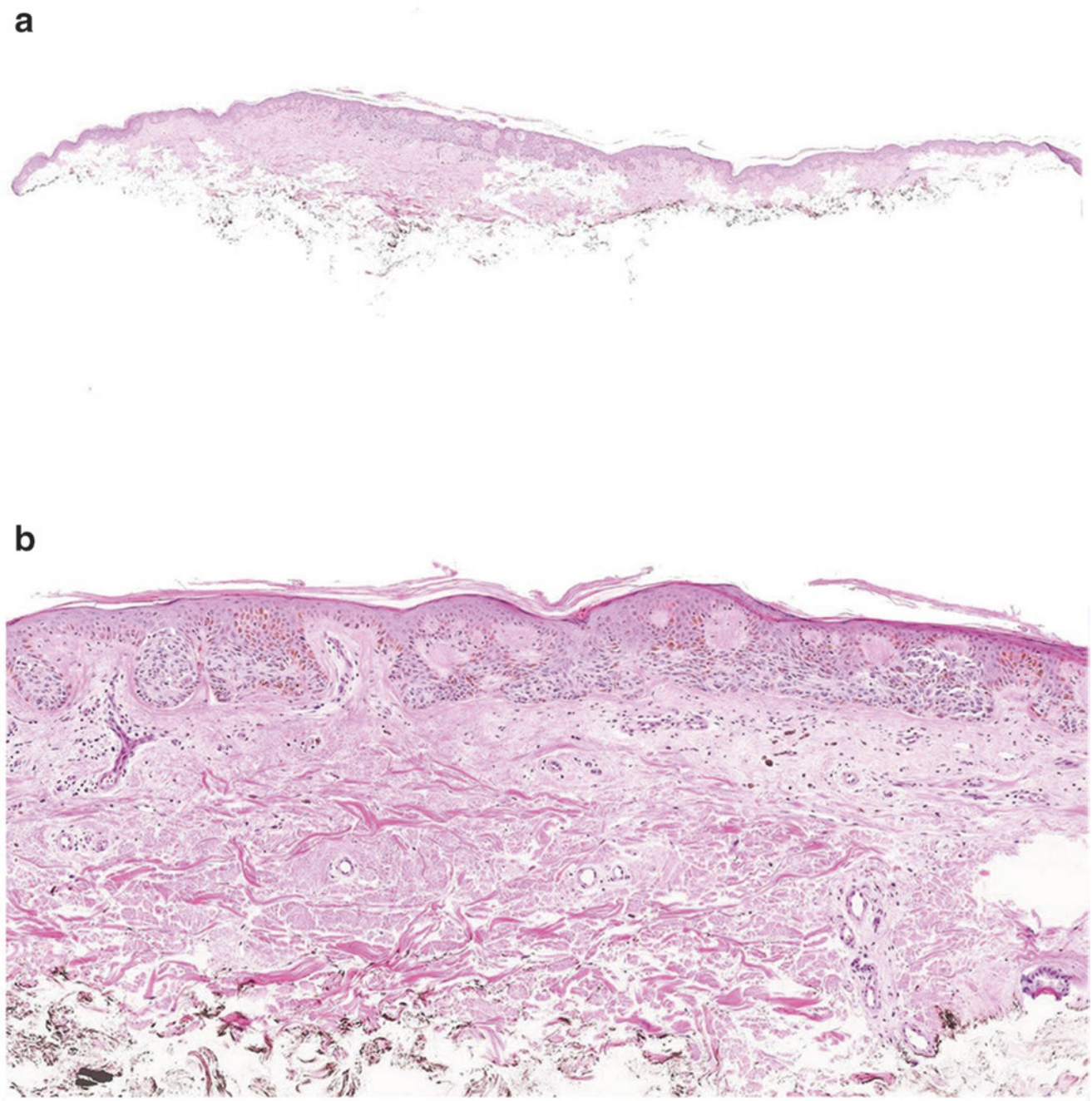

Fig. 5.1 Junctional dysplastic nevus with mild architecture disorder and cytologic atypia. The lesion is symmetric and composed of bridging of nests, and elongated rete ridges (**a**). Note the bridging of melanocytes with lamellar fibroplasia (**b**).

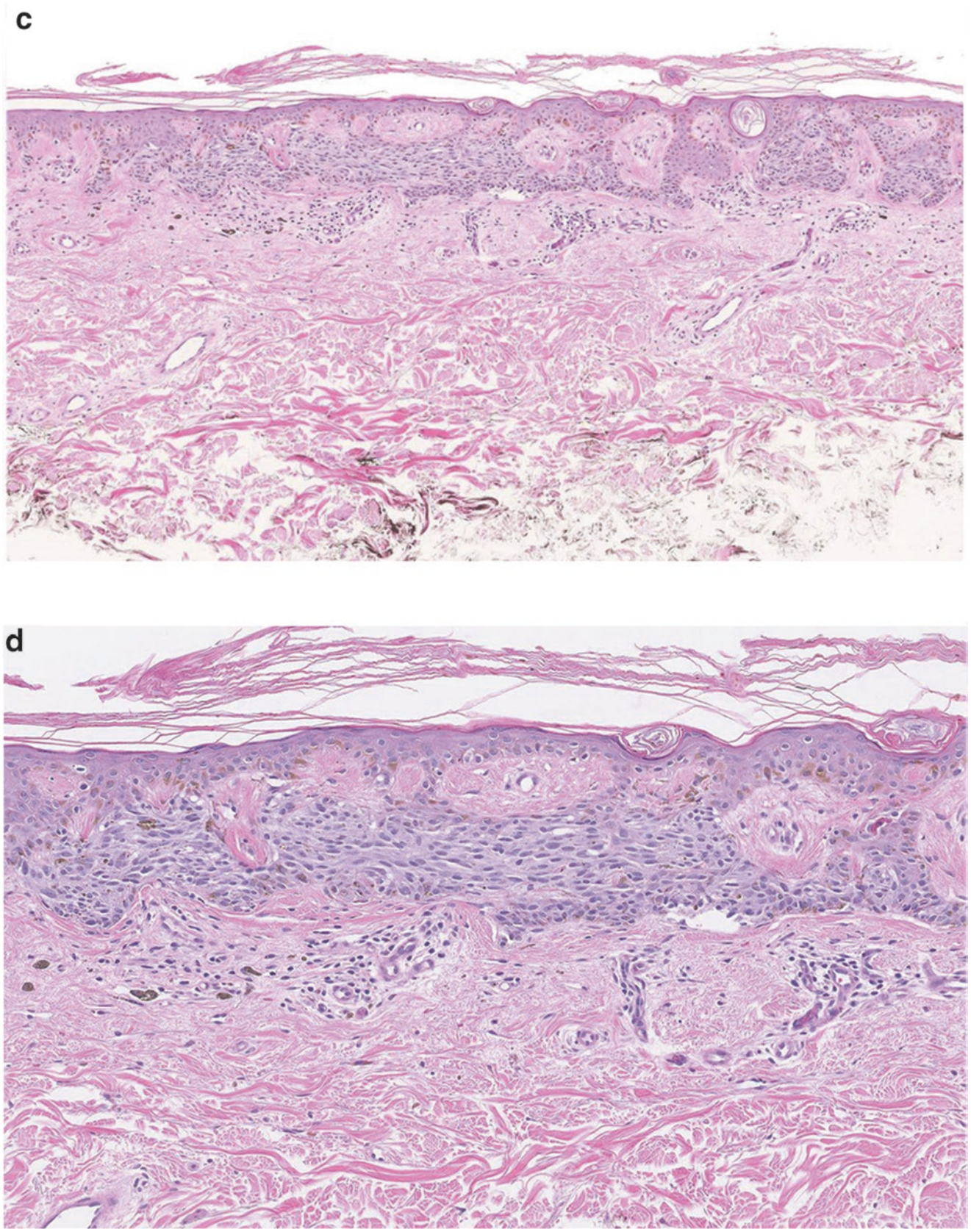

Fig. 5.1 (continued) Papillary dermis shows host response composed of mild chronic inflammation and pigmented melanophages (**c**). Note the lack of cytologic atypia only with mild pleomorphism and rare hyperchromatic melanocytes (**d**)

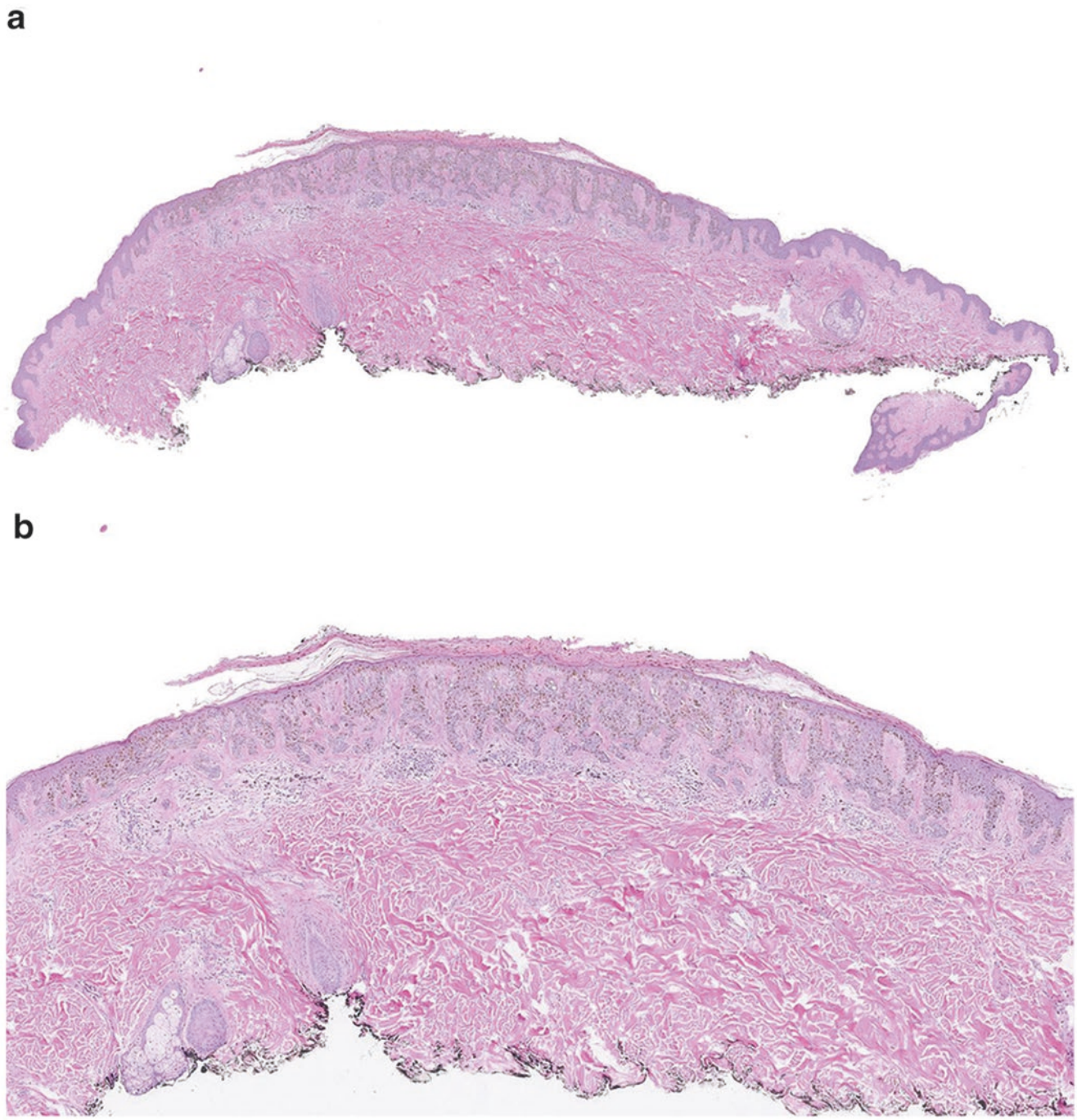

Fig. 5.2 Irritated junctional dysplastic nevus with mild architectural disorder and cytologic atypia. This example is irritated and it shows a little more lentiginous changes compared to the previous example (**a**). In addition to the features of a dysplastic nevus (elongated rete ridges, bridging and fibrosis), there is a central area of hyper/parakeratosis. Note the areas of parakeratosis with the uniform bridging (**b**).

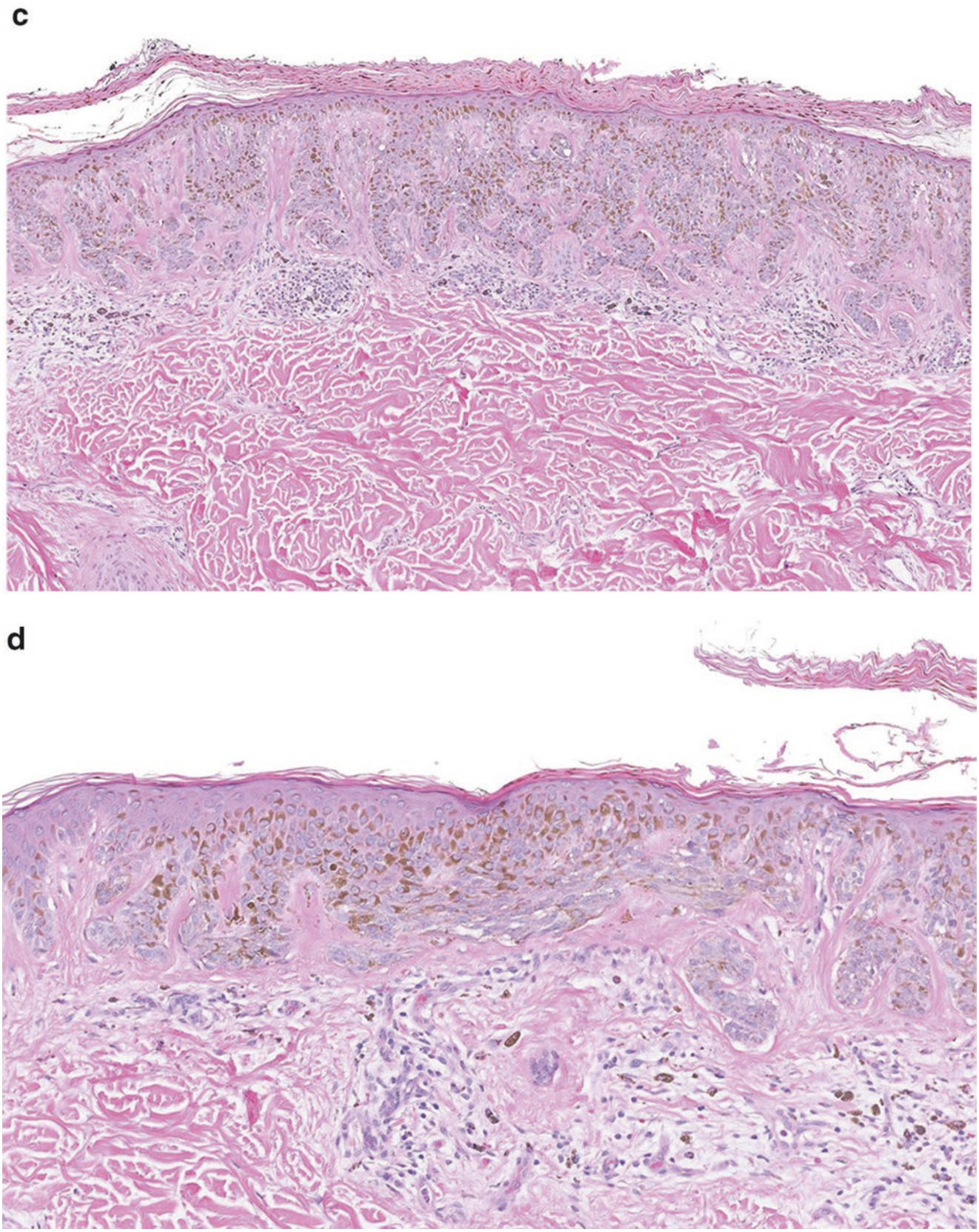

Fig. 5.2 (continued) The melanocytes in epidermis are mostly located at the tips of the rete ridges (**c**). There is transepidermal pigmentation noted in the stratum corneum. Junctional nests with bridging, pigmentation, and lentiginous changes. Marked host response in dermis (**d**)

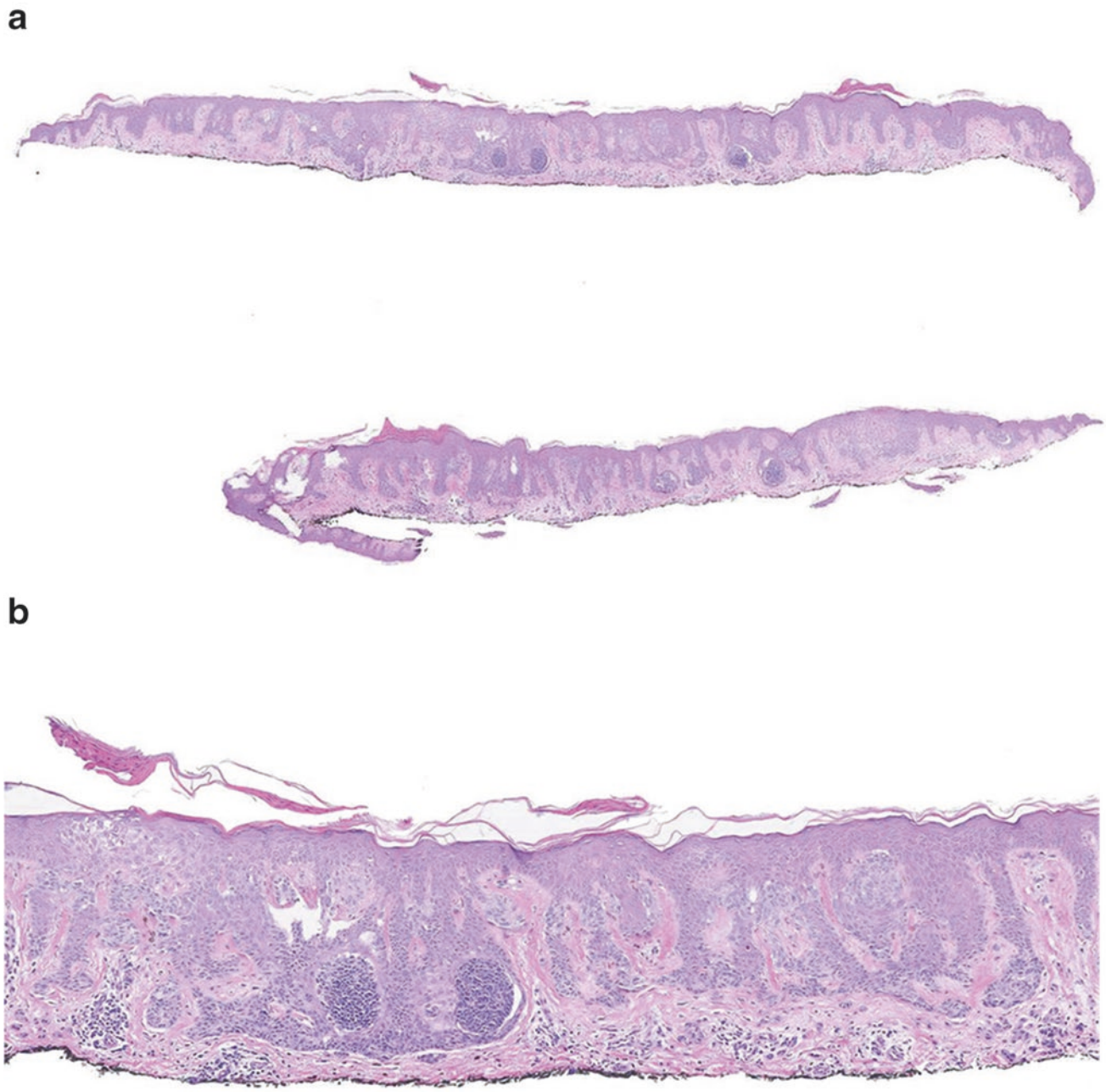

Fig. 5.3 Compound dysplastic nevus with mild architectural disorder and cytologic atypia. This example shows architectural changes with elongation of rete ridges, bridging of nests, lamellar fibroplasia, and host response (**a**). This example shows a clear "shouldering" phenomenon. Most melanocytes are located at the tips of rete ridges, with only rare melanocytes in between rete ridges (**b**).

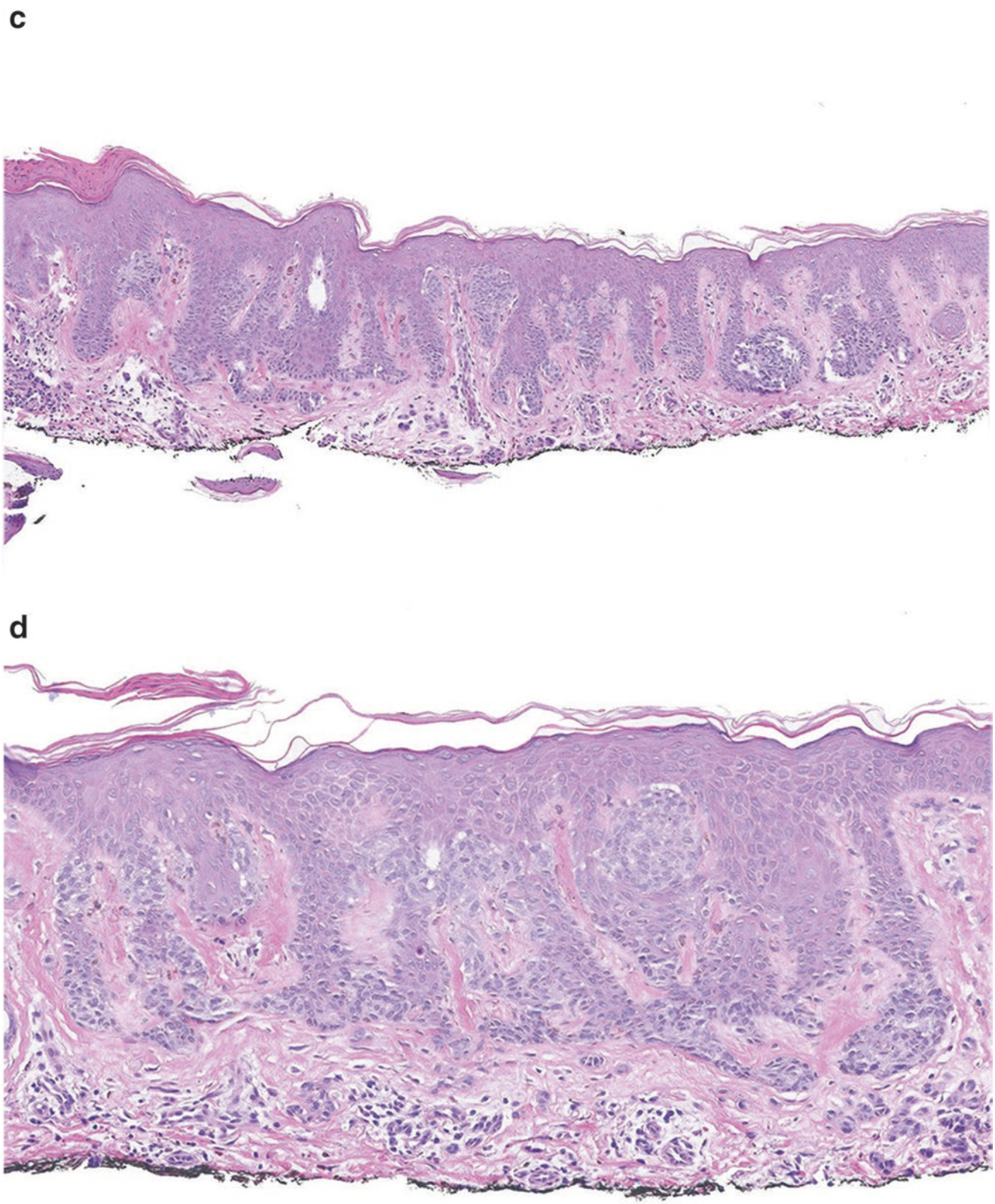

Fig. 5.3 (continued) Note how the melanocytic nests vary in size and are dispersed haphazardly (**c**). Higher magnification confirms pleomorphism of melanocytes with more than 50 % of them having large cytoplasm and large nuclei (**d**)

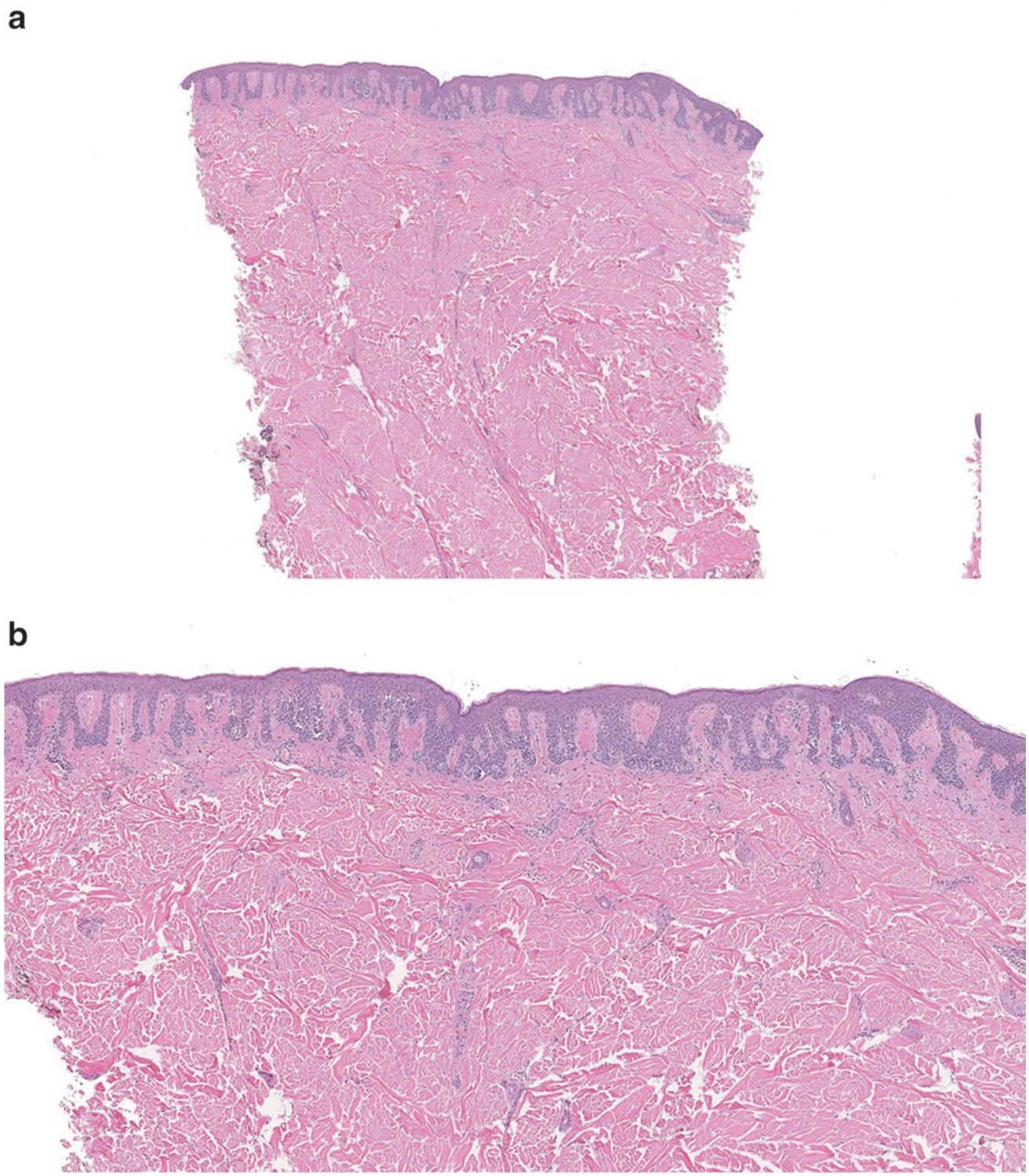

Fig. 5.4 Junctional dysplastic nevus with moderate architectural disorder and cytologic atypia. The architecture disorder of this lesion is more extensive along with cohesive nests and single melanocytes in the junction (**a**). There is bridging in more than 50 % of the lesion. Note the host response in dermis. More than 50 % of the lesion shows single melanocytes (**b**).

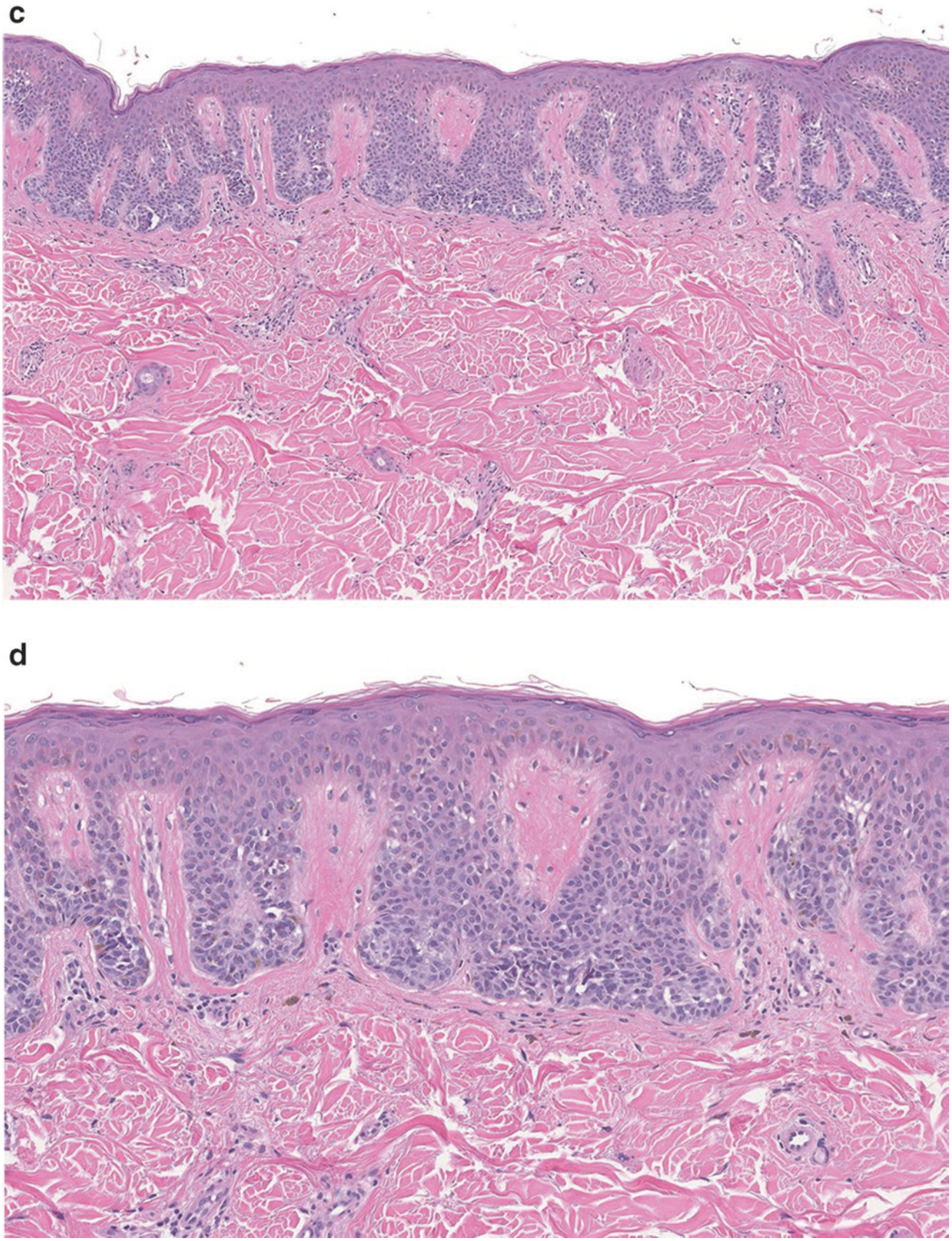

Fig. 5.4 (continued) Note that the single cells are increased but keeping cohesive nests in the tips of the rete ridges (**c**). Increase number of atypical melanocytes with hyperchromatic nuclei. Note the melanocytes are not only at the tips of the rete but also located at the sides of the rete (**d**)

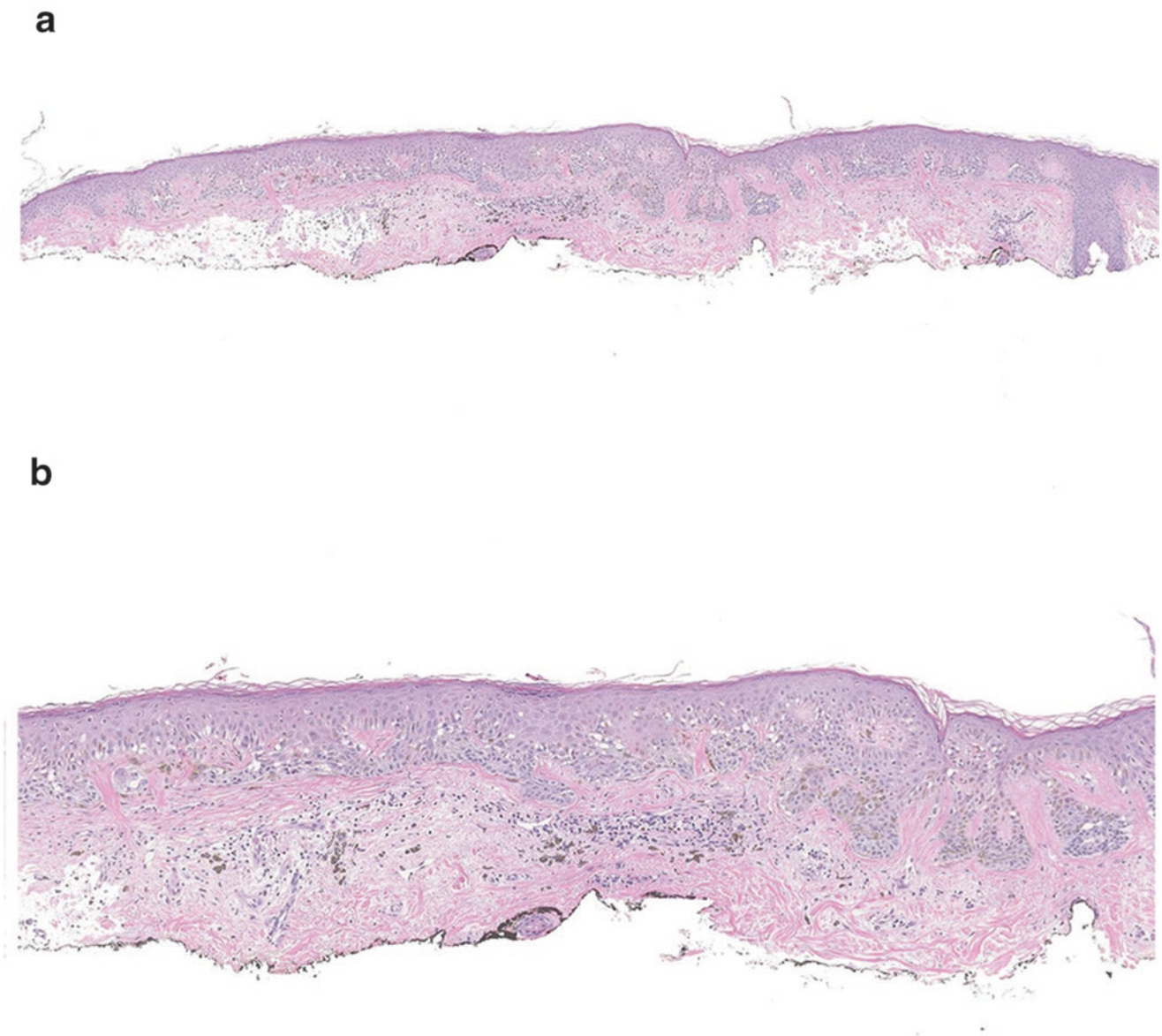

Fig. 5.5 Junctional dysplastic nevus with moderate architectural disorder and cytologic atypia. This lesion is located in the back of a 65-year-old male. The lesion shows marked bridging of nests, variability in nest size, areas of discohesion, and focal confluence (**a**). Note the melanocytic nests at the arch of the dermal papillae and sides of the rete (**b**).

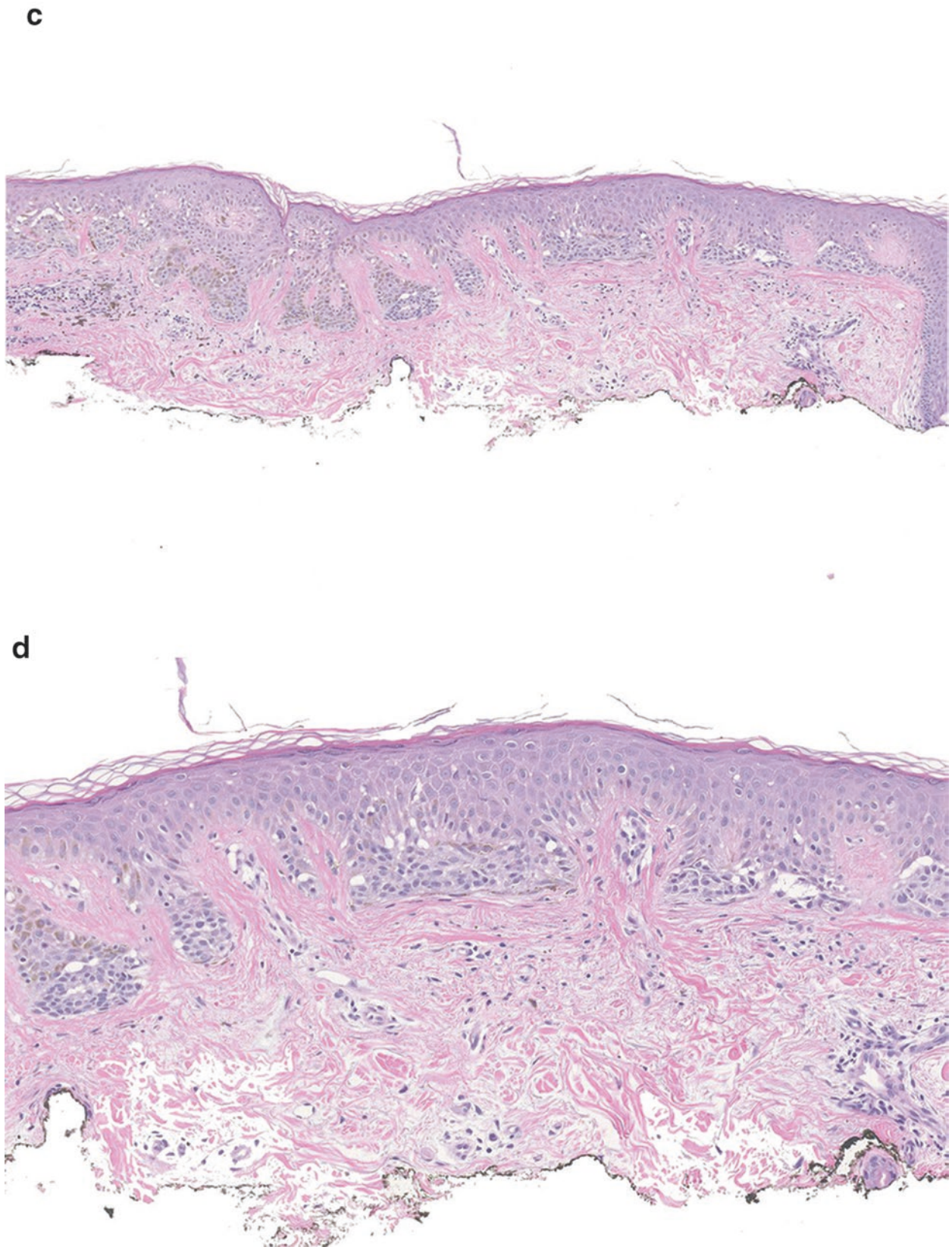

Fig. 5.5 (continued) This example shows marked solar damage and prominent host response (**c**). Higher magnification showing hyperchromatic melanocytes. Compare the adjacent melanocytes are smaller than the junctional melanocytes (**d**)

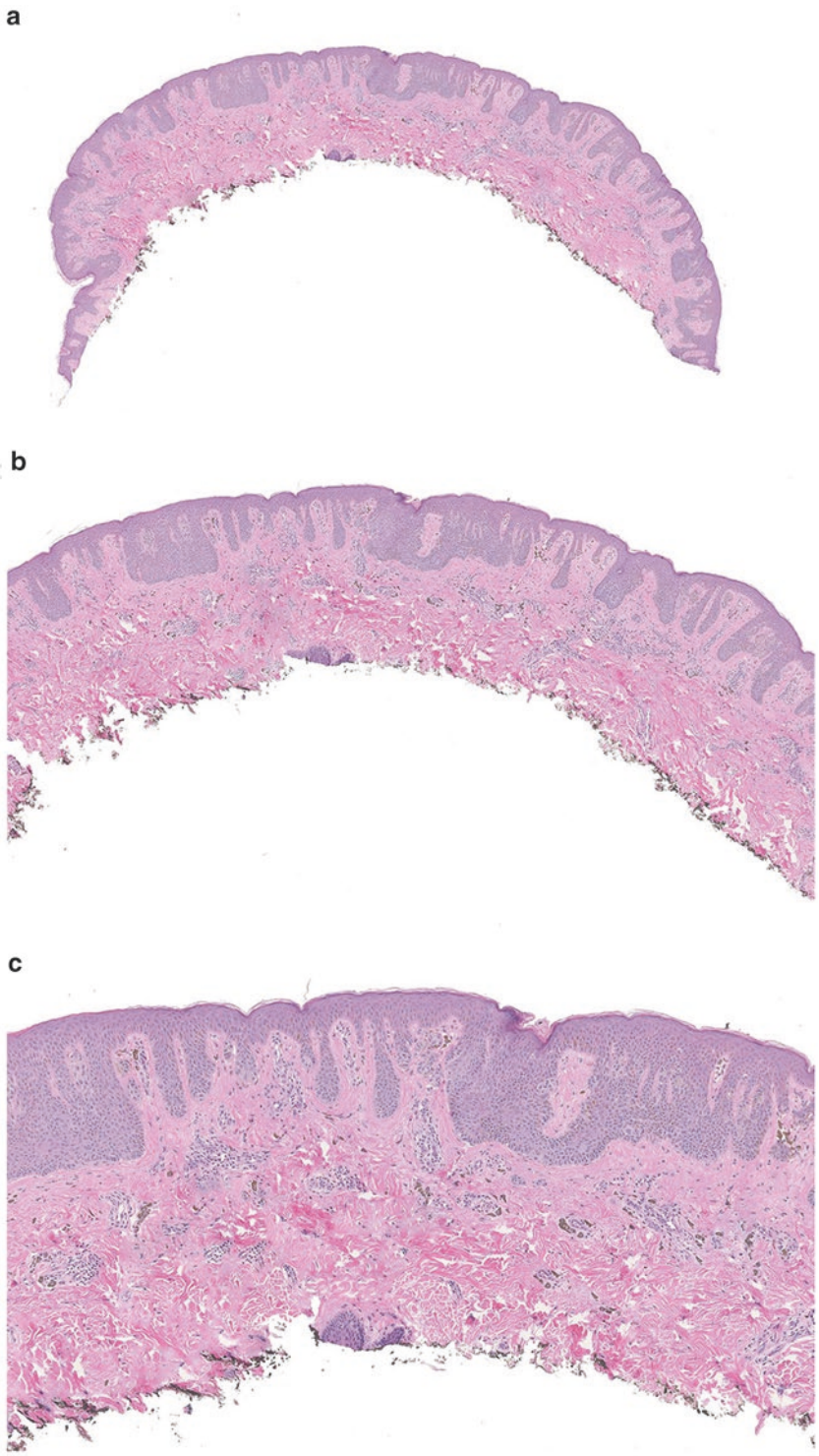

Fig. 5.6 Junctional dysplastic nevus with moderate architectural disorder and cytologic atypia. This is a broad melanocytic lesion that extends to the lateral edges (**a**). Note the prominent bridging formation along the fibroplasia hugging the rete (**b**). There is an asymmetric basilar proliferation of melanocytes along the dermal epidermal junction. There is an increased number of melanocytes both at the tips and shoulders of the rete (**c**)

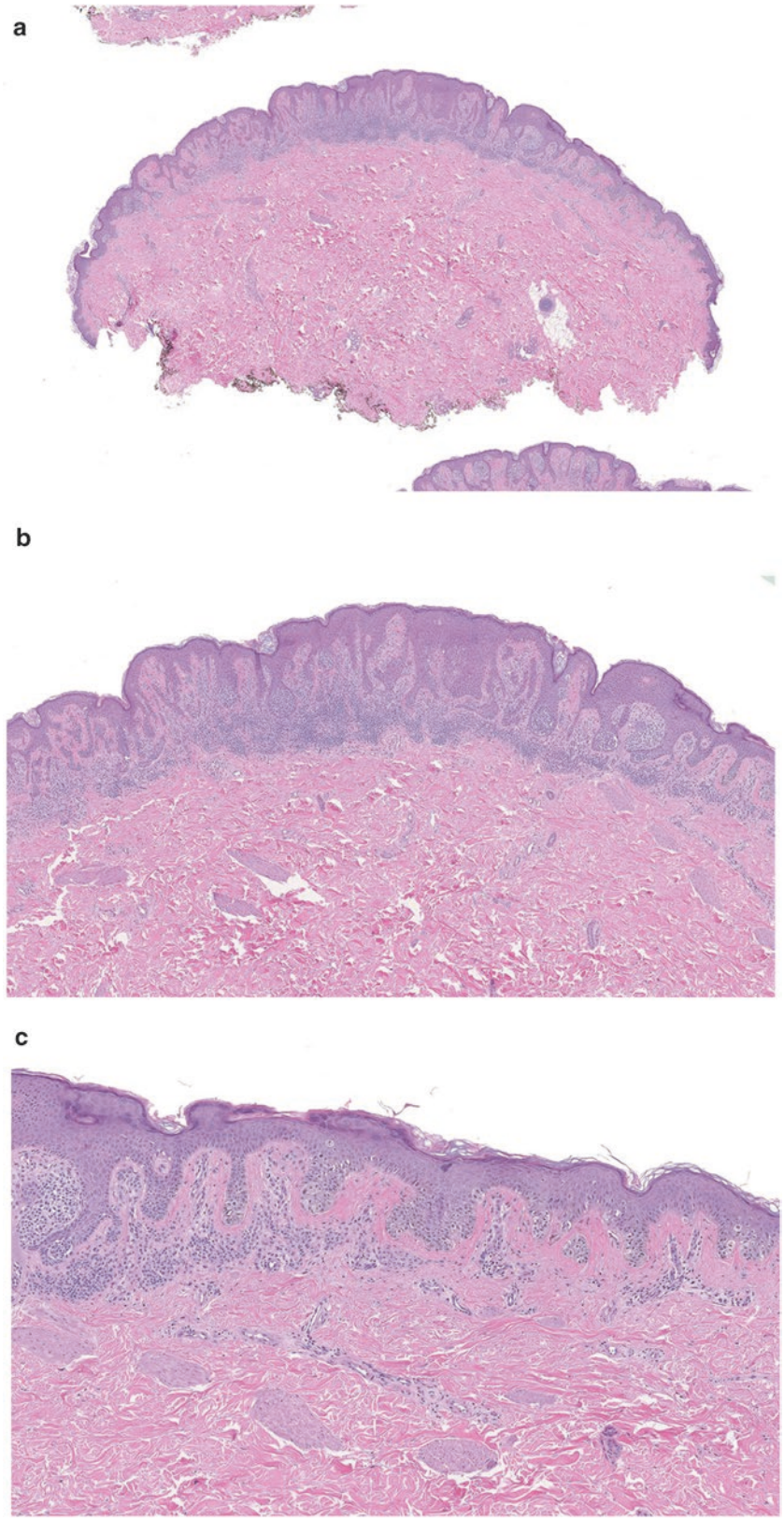

Fig. 5.7 Compound dysplastic nevus with moderate architectural disorder and cytologic atypia. This example shows features reminiscent of an acquired nevus; however, note that there is a shouldering growth at the sides of the lesion, along with host response (fibrosis, melanophages, lymphocytic infiltrate) (**a**). If only the center of the lesion is inspected, cases like this could easily be diagnosed as compound nevus. Some of the more deeply located nests resemble the pattern seen in superficial congenital nevi (**b**). Note the shoulder composed of single melanocytes, lentiginous growth, abnormal orientation of nests at the junction, irregular size and shape of nests, discohesion, and host response (**c**)

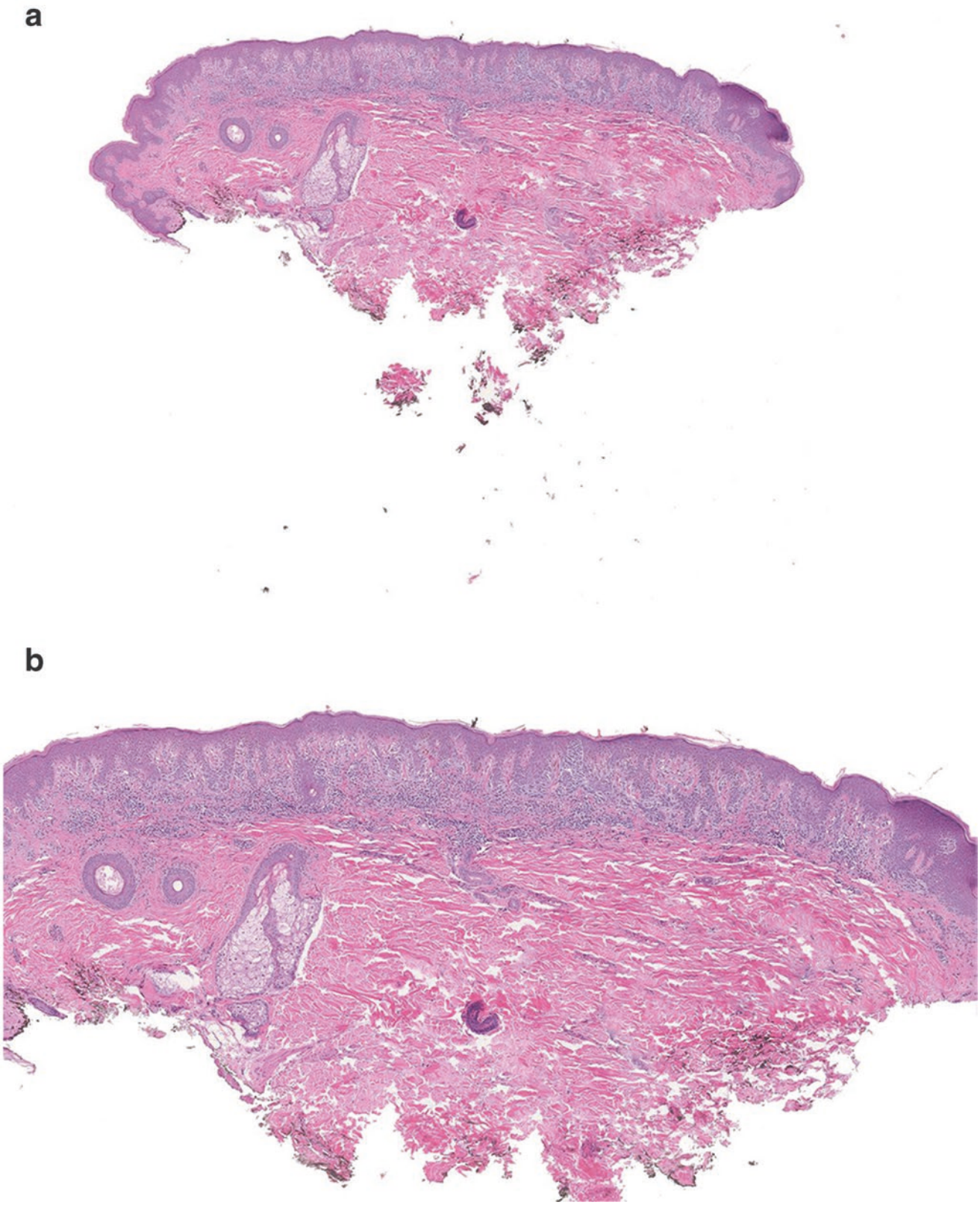

Fig. 5.8 Compound dysplastic nevus with moderate architectural disorder and cytologic atypia. Note the symmetry of the lesion along with variable nest size and dyshesion. This example depicts a prominent host response (**a**). The lesion is composed predominantly of epithelioid melanocytes that have noticeable heterogeneity of nuclear size and shape (**b**).

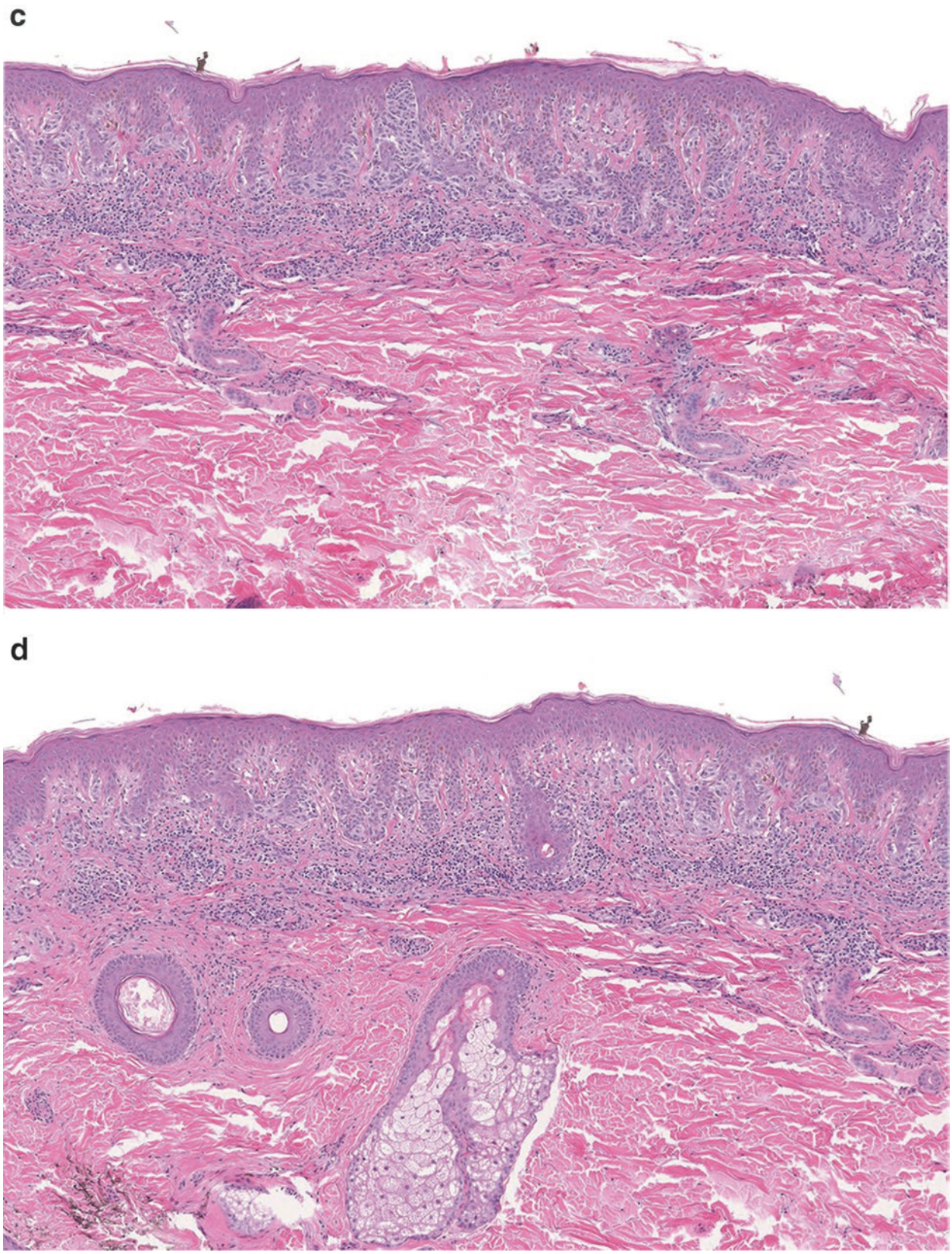

Fig. 5.8 (continued) The junctional component shows a prominent lentiginous growth (**c**). Note the lack of pagetoid upward migration of melanocytes (**d**)

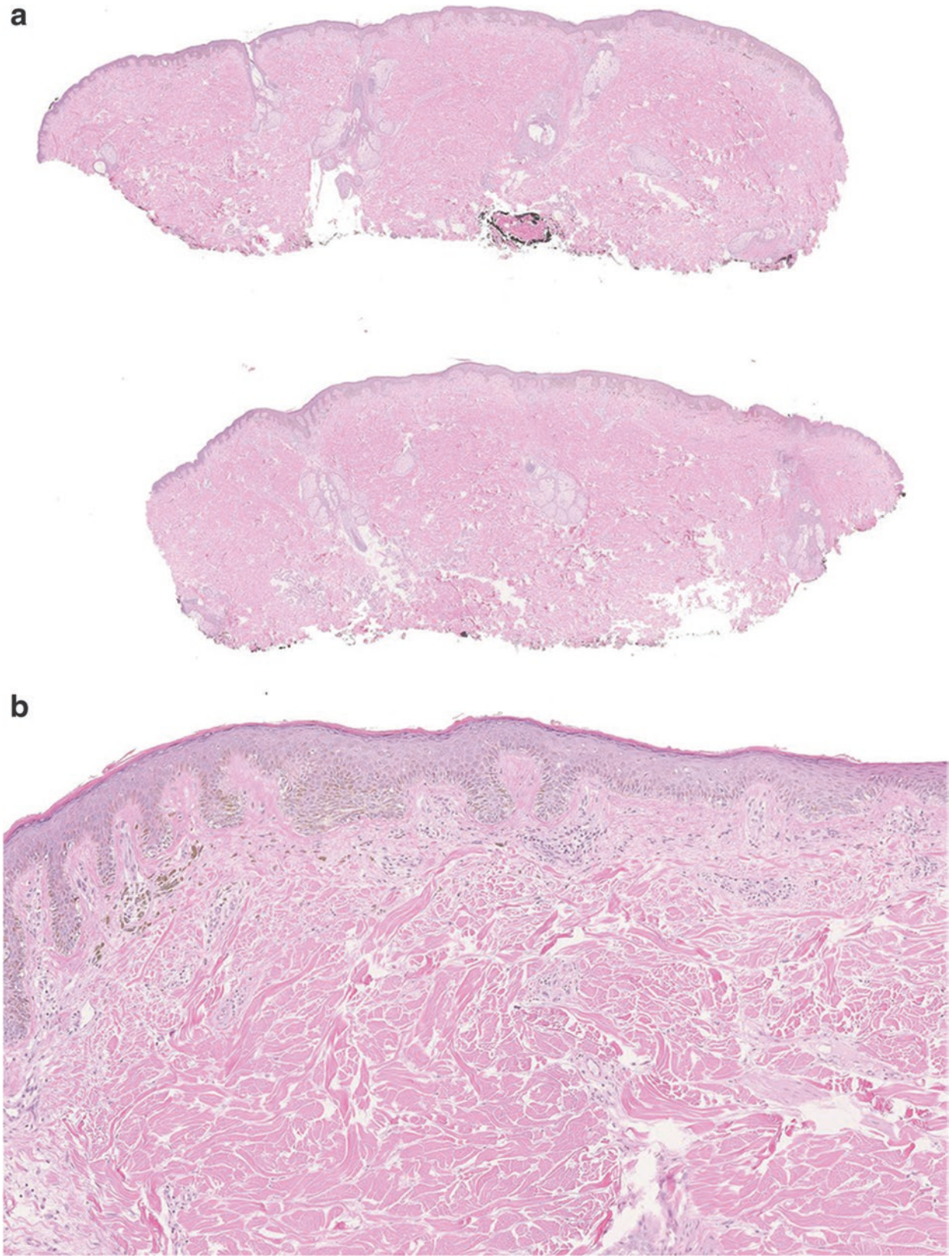

Fig. 5.9 Junctional dysplastic nevus with severe architectural disorder and cytologic atypia (**a**). This lesion is on the back of a 54-year-old male. The lesion is composed of a confluent nested and single population of melanocytes at the dermal epidermal junction. Note the effacement of the epidermis and the lentiginous appearance of the lesion (**b**).

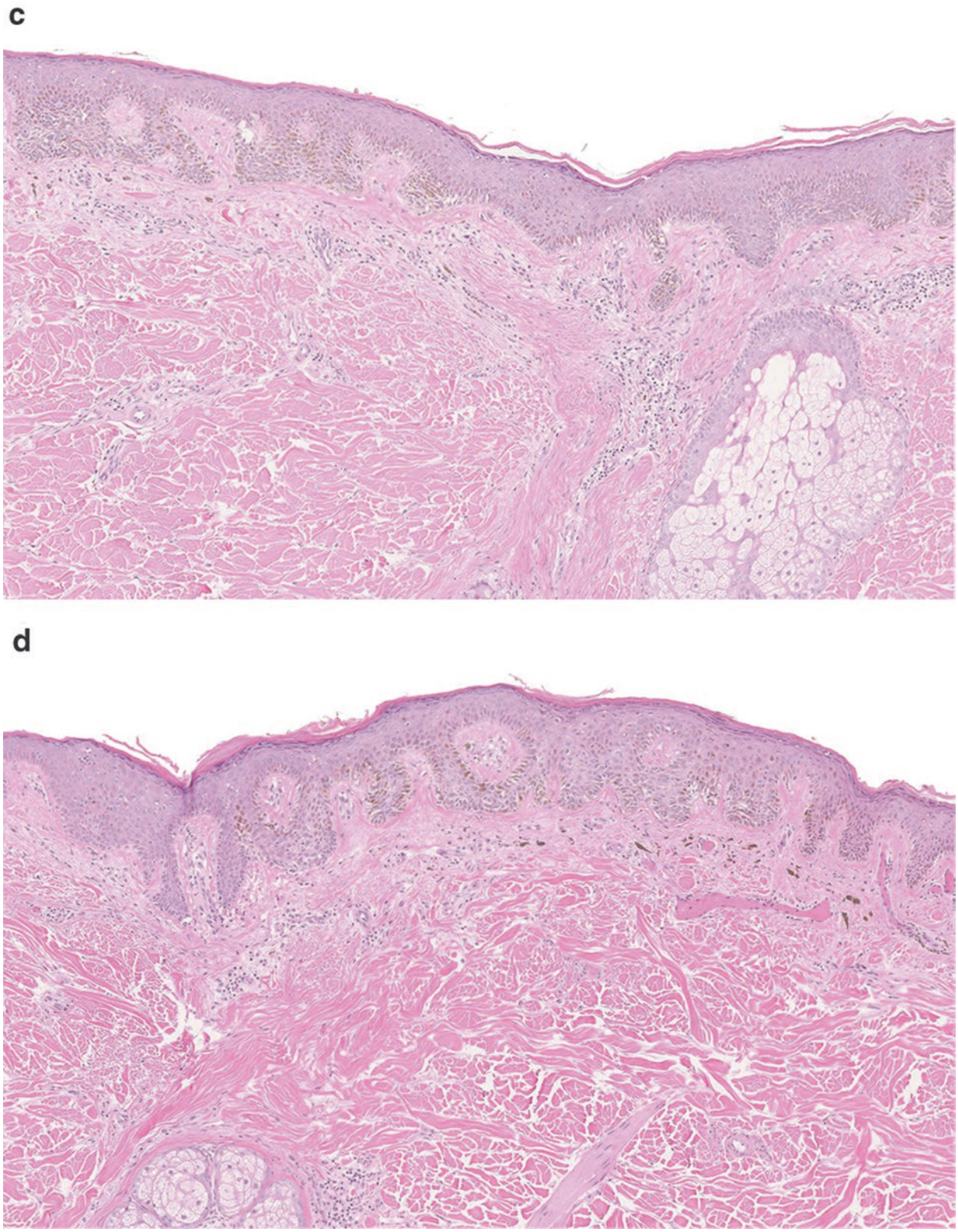

Fig. 5.9 (continued) Cases in which there is a prominent effacement, it may indicate that there is early transition into melanoma in situ. Despite the prominent effacement and confluent growth there is lack of pagetoid upward migration (**c**). The edge of the lesion shows less confluence and effacement (**d**)

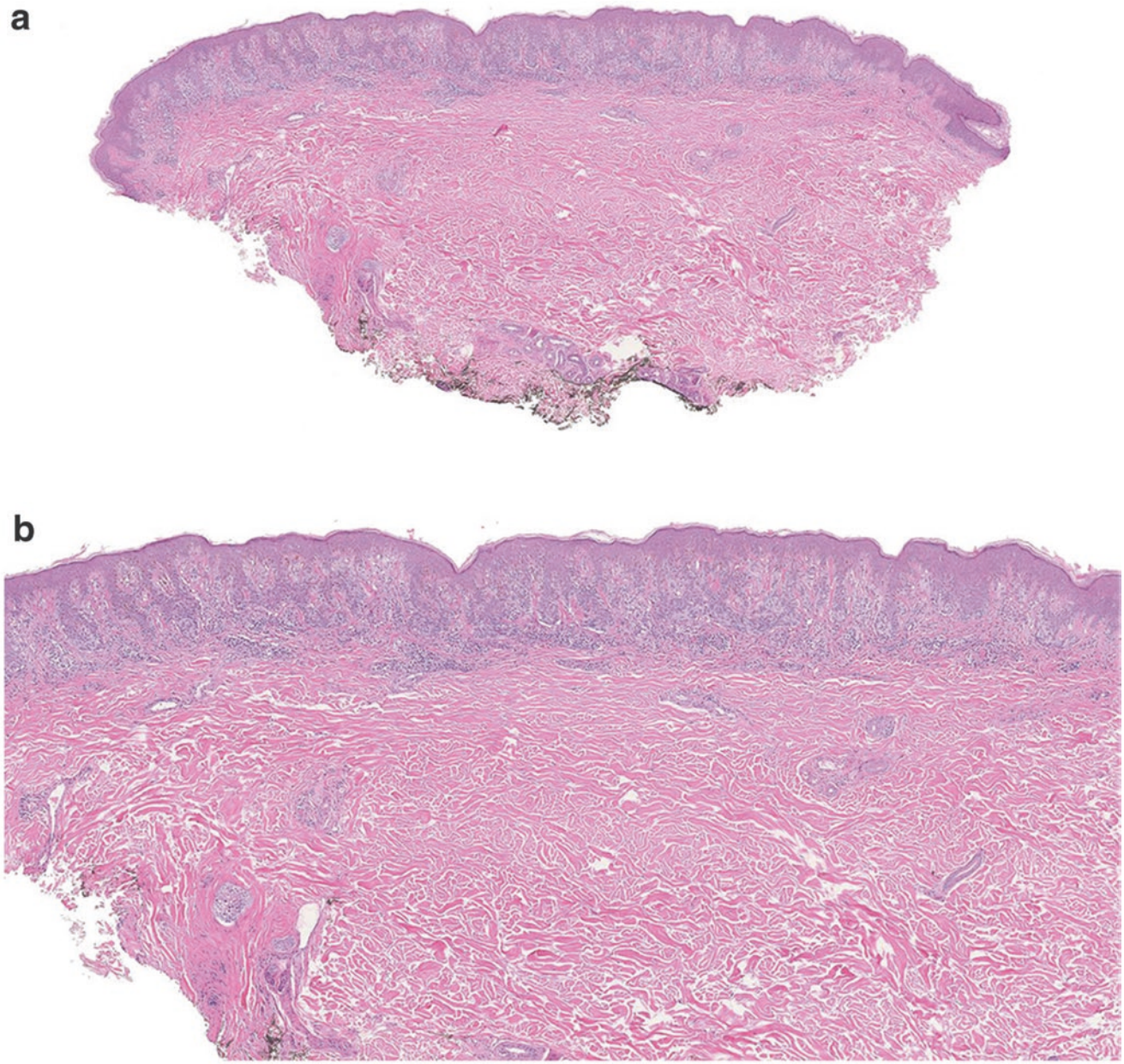

Fig. 5.10 Junctional dysplastic nevus with severe architectural disorder and cytologic atypia. This example shows bridging, extensive proliferation of melanocytes forming nests and in single cells (**a**). Note the prominent single-cell lentiginous growth along with preservation of the epidermal architecture of dysplastic nevus (**b**).

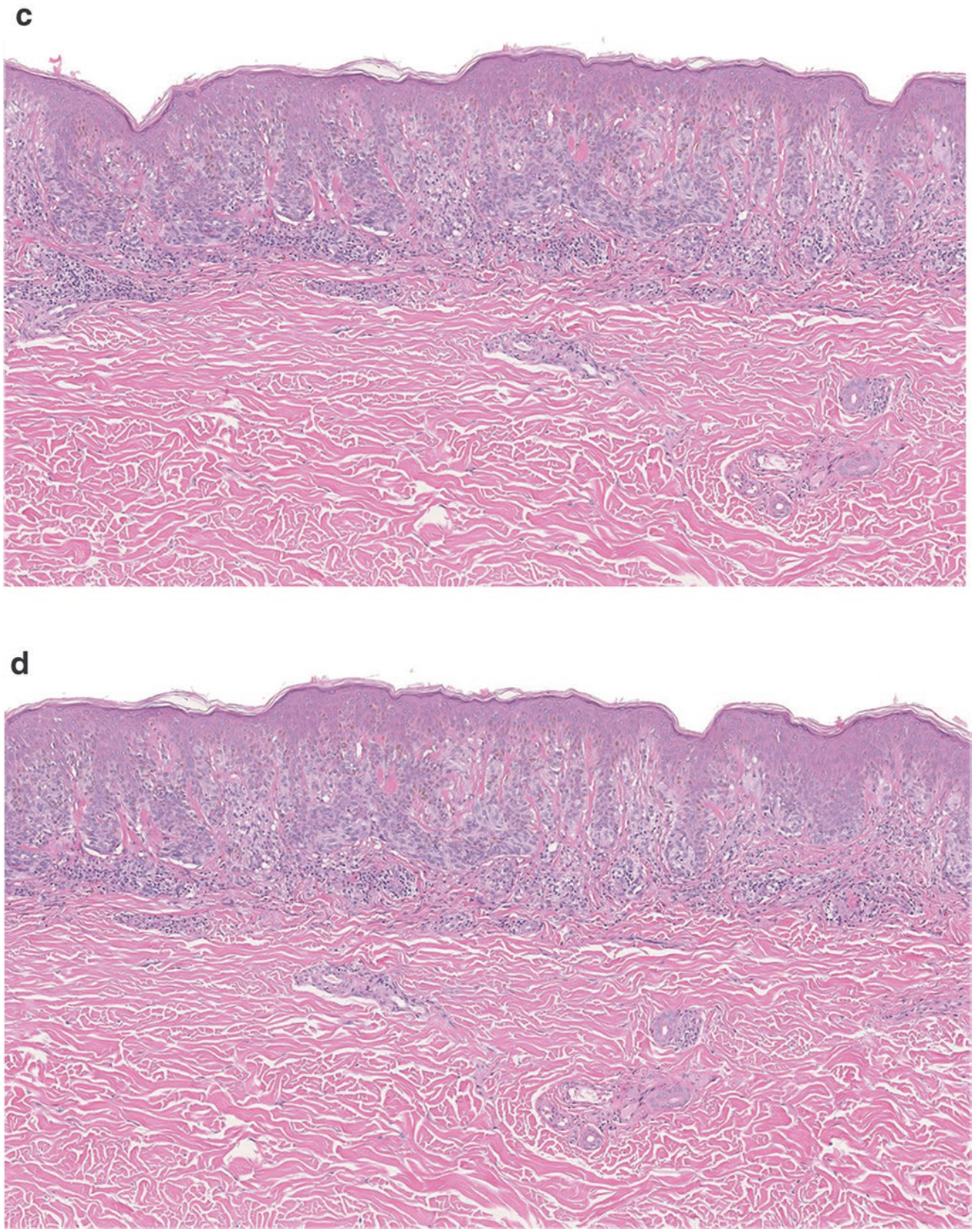

Fig. 5.10 (continued) Note the large epithelioid melanocytes with marked nuclear pleomorphism (**c**). There is minimal pagetoid upward migration in the center of the lesion that is insufficient to warrant a diagnosis of melanoma. Even at this power, melanocytes have hyperchromatic nuclei with angulated contours and ample dusky cytoplasm (**d**)

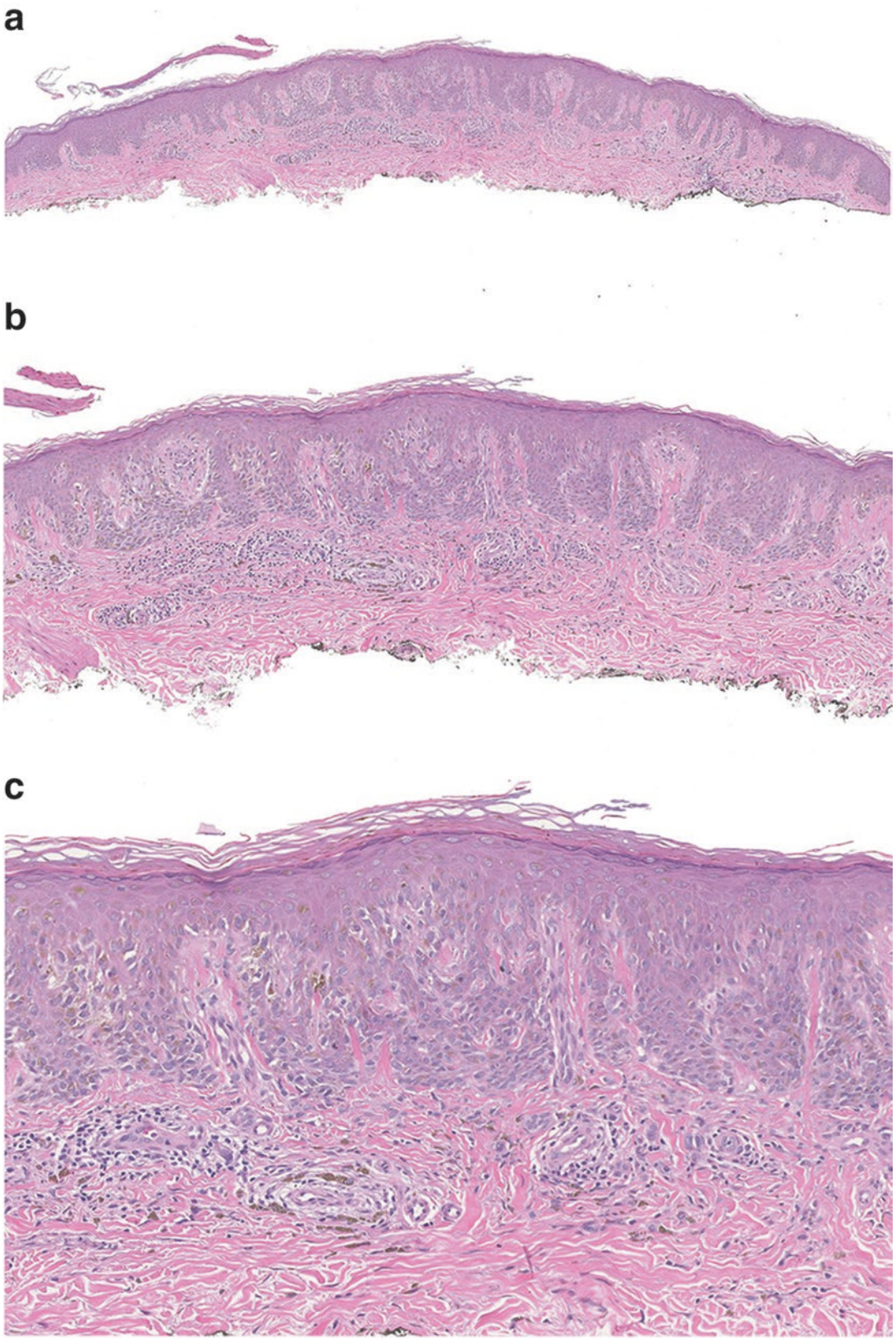

Fig. 5.11 Compound dysplastic nevus with severe architectural disorder and cytologic atypia. This example is not as broad as the previous examples; however, it shows prominent single cell growth with severe cytologic atypia (**a**). Note the prominent lentiginous growth along with marked inflammation in dermis. The dominant melanocyte is epithelioid in configuration (**b**). Note that the dominant lentiginous melanocytes have a dark angulated nucleus with scant cytoplasm. There is minimal pagetoid upward migration of melanocytes (**c**)

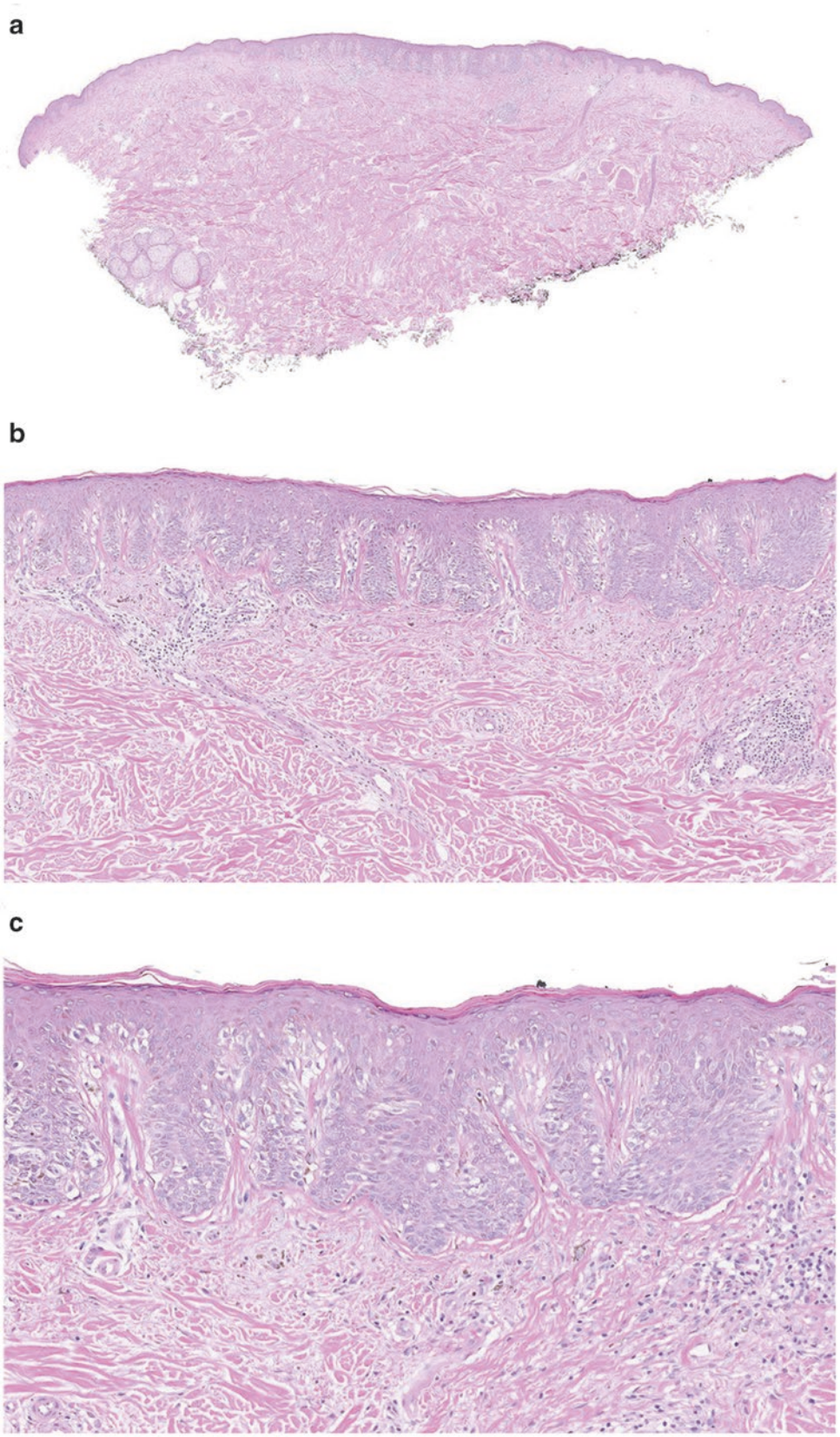

Fig. 5.12 Junctional dysplastic nevus with severe architectural disorder and cytologic atypia. This example is located in the scapula of a 72-year-old female (**a**). The melanocytes are spindle and epithelioid in shape and arranged in a predominantly lentiginous growth (**b**). There is a preserved dysplastic architecture despite the presence of severe cytologic atypia (**c**).

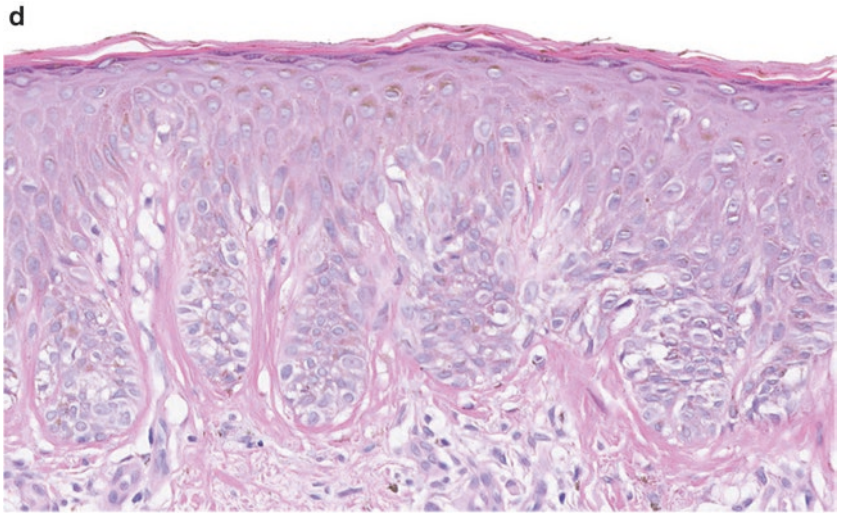

Fig. 5.12 (continued) Note the poorly formed nests with prominent intercellular dyshesion. There is heterogeneity of nuclear size and nuclei overlap (**d**)

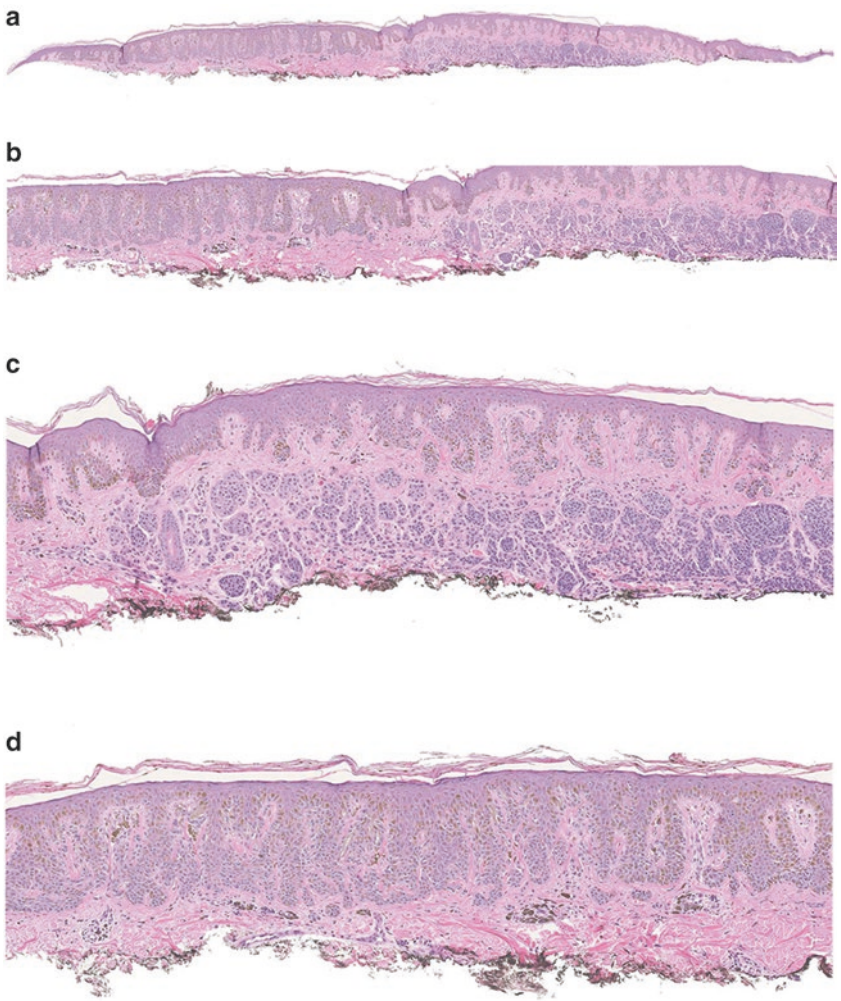

Fig. 5.13 Dysplastic nevus associated with an acquired nevus. Note the left side of the image showing a lentiginous dysplastic architecture and the right side shows a compound nevus (**a**, **b**). Higher magnification showing a lentiginous compound nevus with normal maturation toward the base (**c**). This is the dysplastic component of the lesion with marked bridging, lentiginous growth, and host response (**d**)

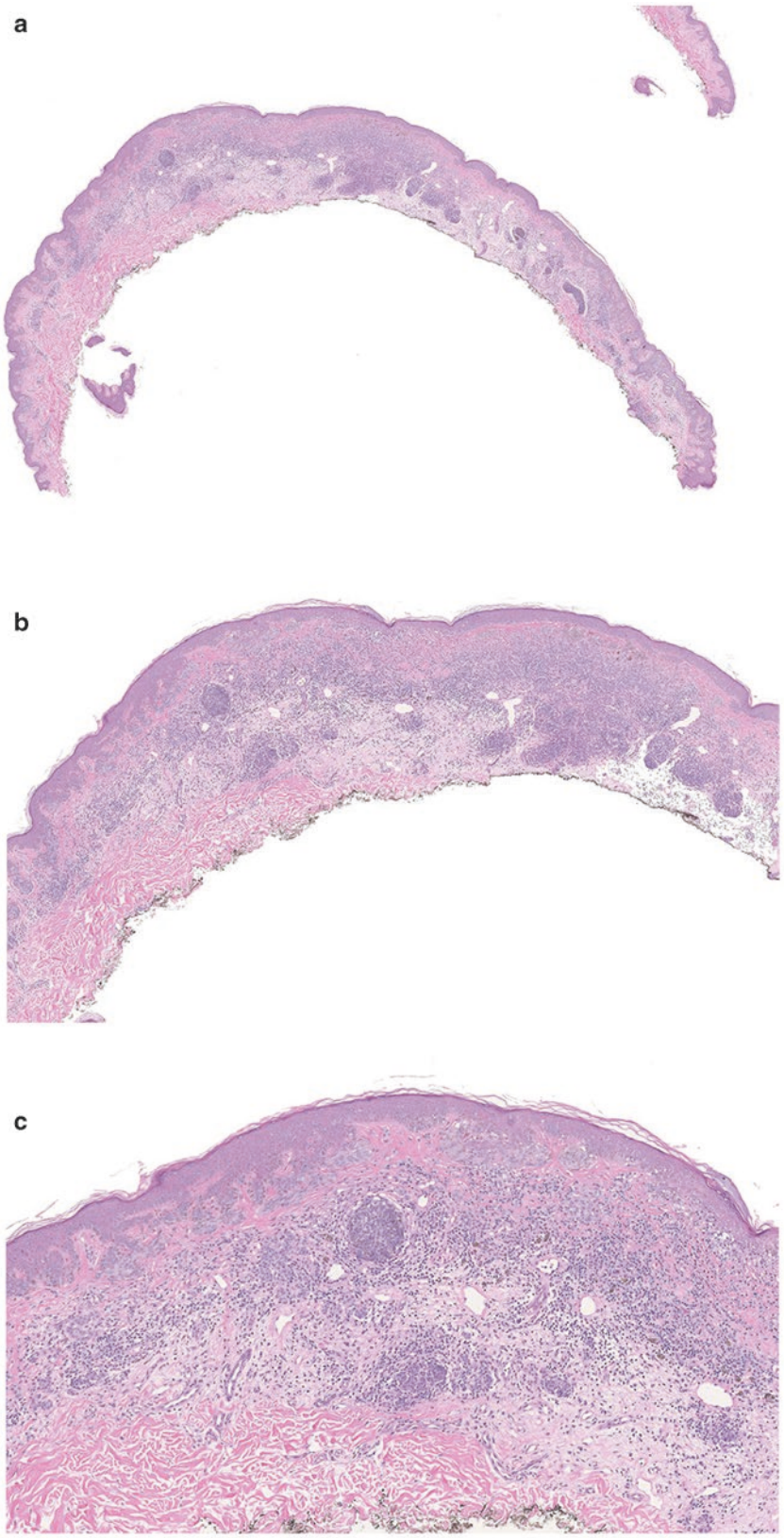

Fig. 5.14 Dysplastic nevus with regression. This compound dysplastic nevus shows coalescing dermal nests and prominent inflammation, fibrosis, melanophages, and vascular ectasia (**a**). Inflammation is prominent and associated with stromal regressive changes. Note the decrease number of junctional nests (**b**). This area of the lesion shows a more preserved architecture of the junction with clear dysplastic features (**c**)

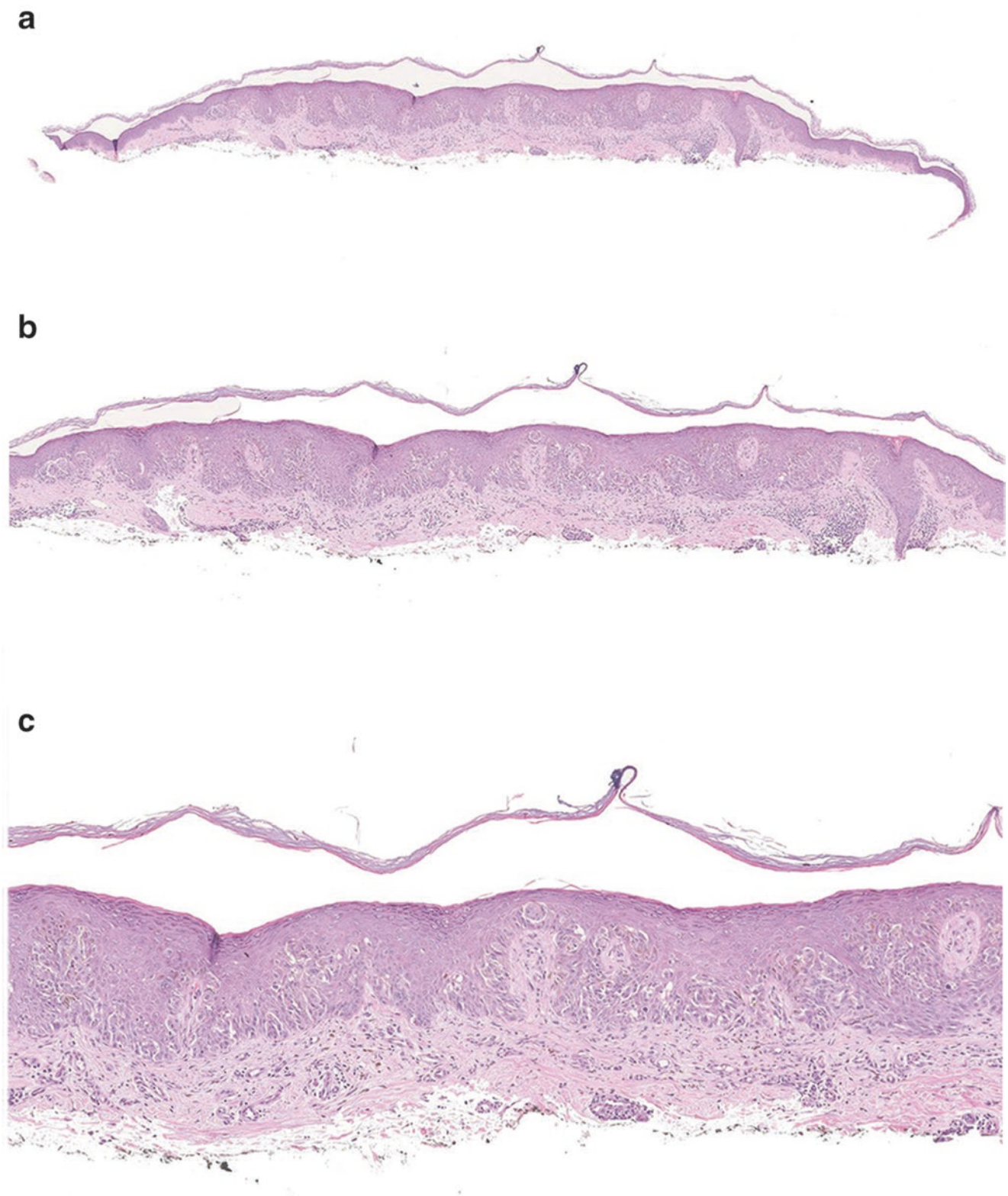

Fig. 5.15 Melanoma arising in a dysplastic nevus. This lesion is located in the arm of an 85-year-old male that presents with a long-standing lesion that recently has changed in color and shape. This example shows a broad lesion that on low magnification shows dysplastic changes (**a**). The center and the lateral edges of the lesion show a prominent confluence and haphazard distribution of nests (**b**). Higher magnification shows confluence of melanocytes, discohesive nests and areas with prominent pagetoid upward migration not only at the center but at the periphery of the lesion (**c**).

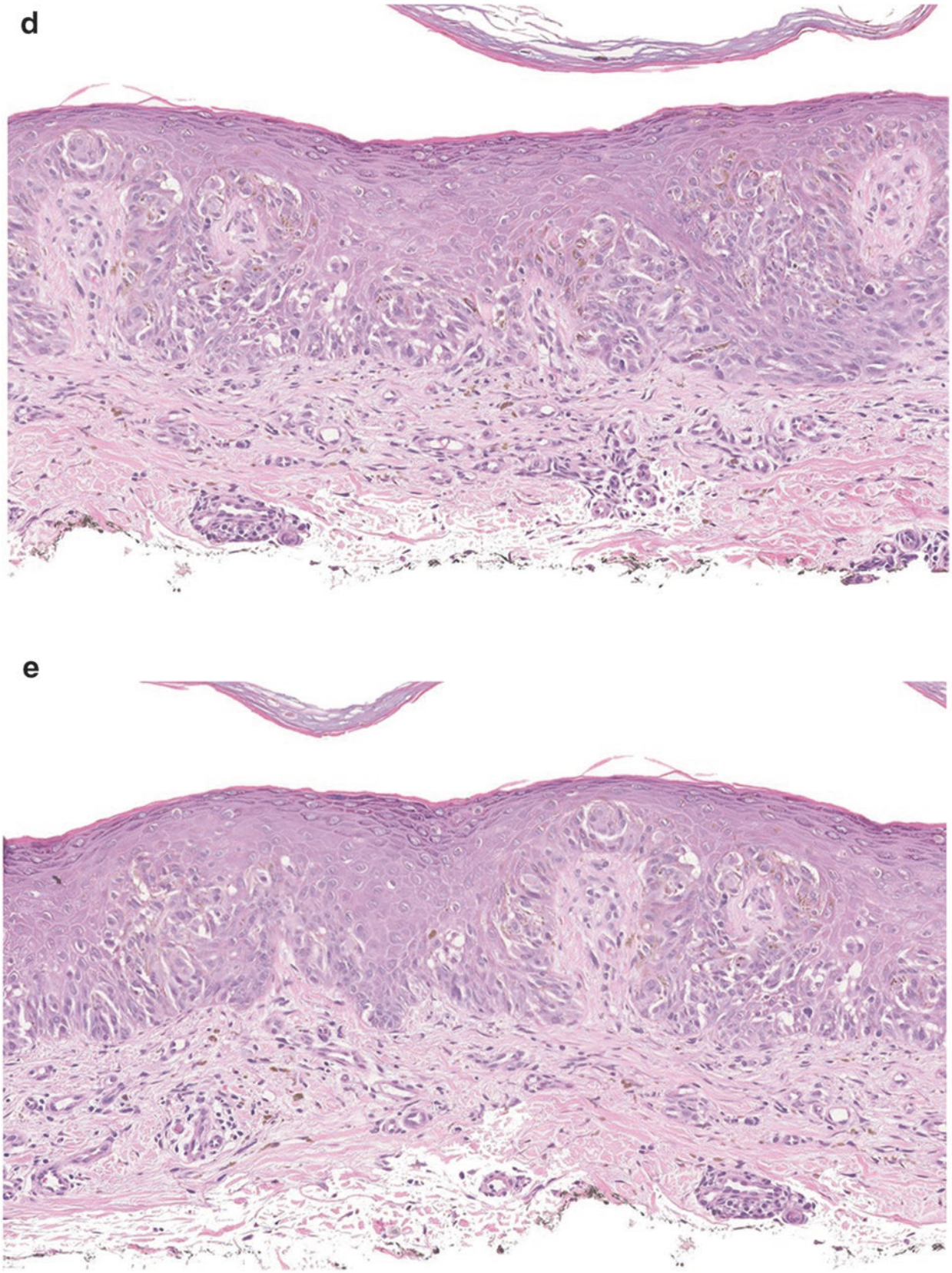

Fig. 5.15 (continued) Note the extensive pagetoid spread of melanocytes (**d**). Different view of the marked cytologic atypia along with pagetoid upward migration (**e**)

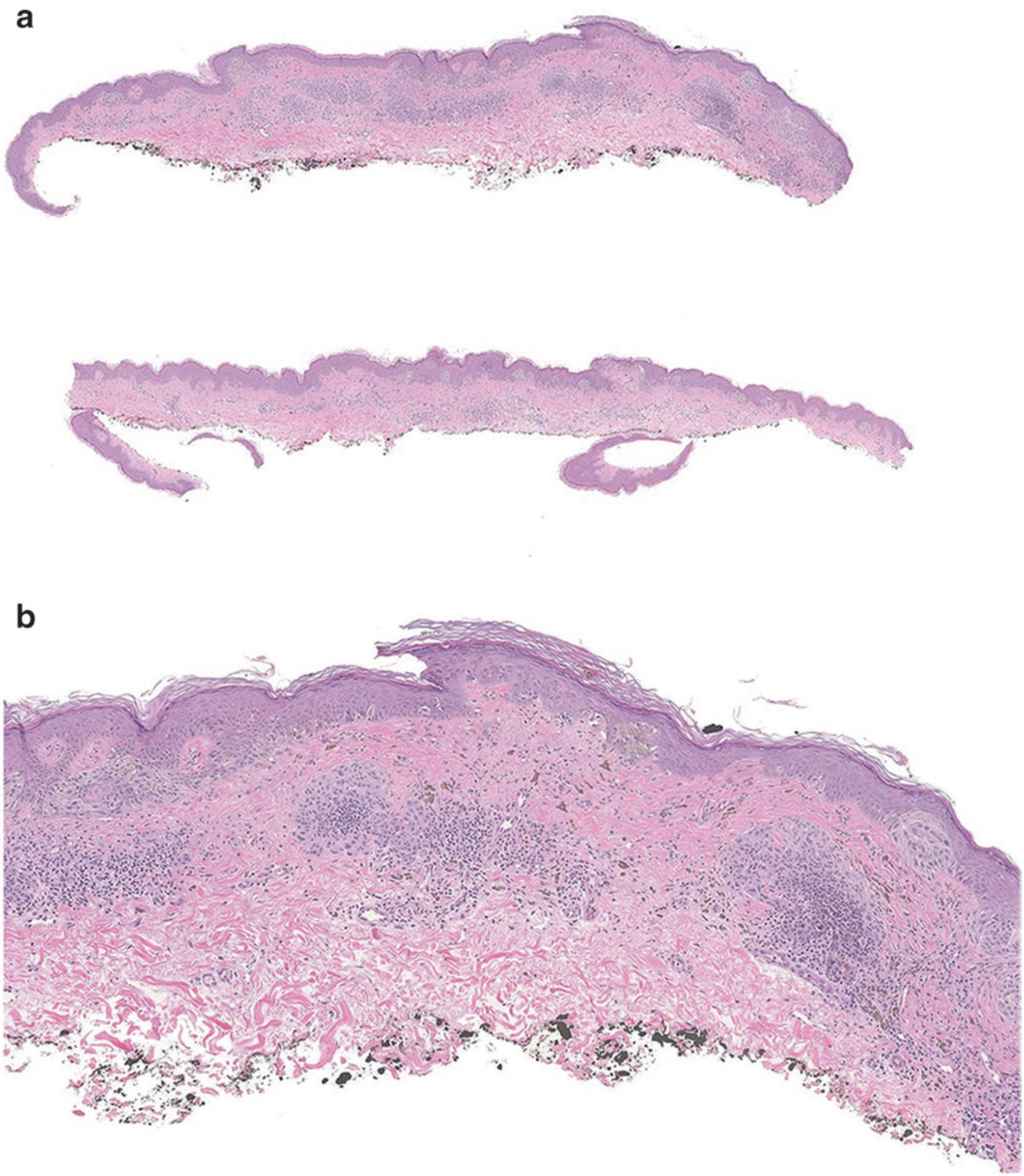

Fig. 5.16 Dysplastic nevus after cryotherapy. This is the case of a 36-year-old male that presents with an atypical mole after it was initially treated with cryotheraphy (**a**). The lesion is asymmetric and composed of atypical features including melanocytic atypia, large confluent growth, pigmented melanocytes, and marked host response. In addition, there is scar which should always be thoroughly analyzed (**b**).

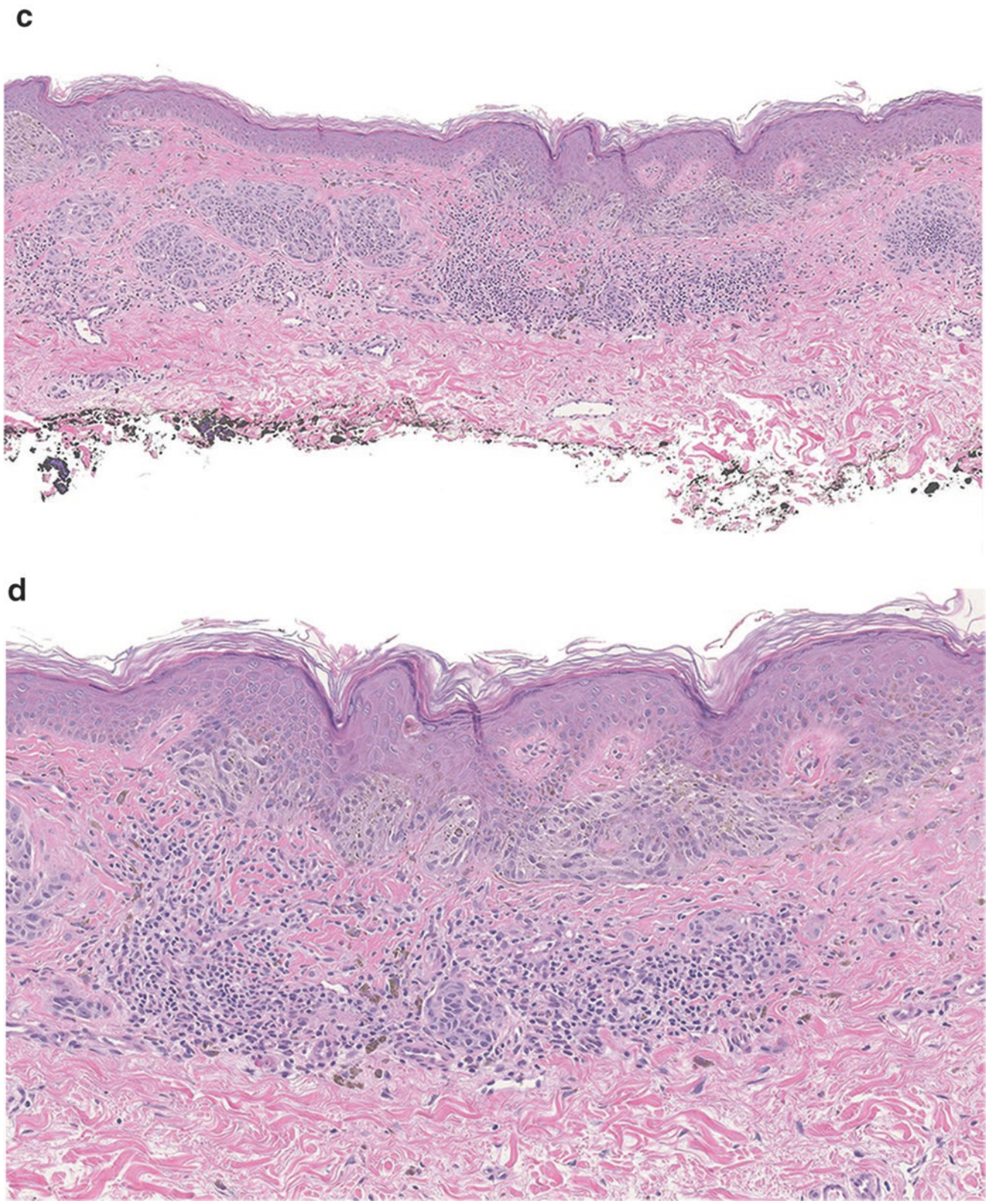

Fig. 5.16 (continued) Note the atypical and asymmetric growth in epidermis; however, these atypical features are localized in the area of trauma (look at the scar). Traumatized dysplastic nevi may show histomorphologic features similar to melanoma (**c**). This is the lateral area of the lesion and the changes are that of a dysplastic nevus (**d**)

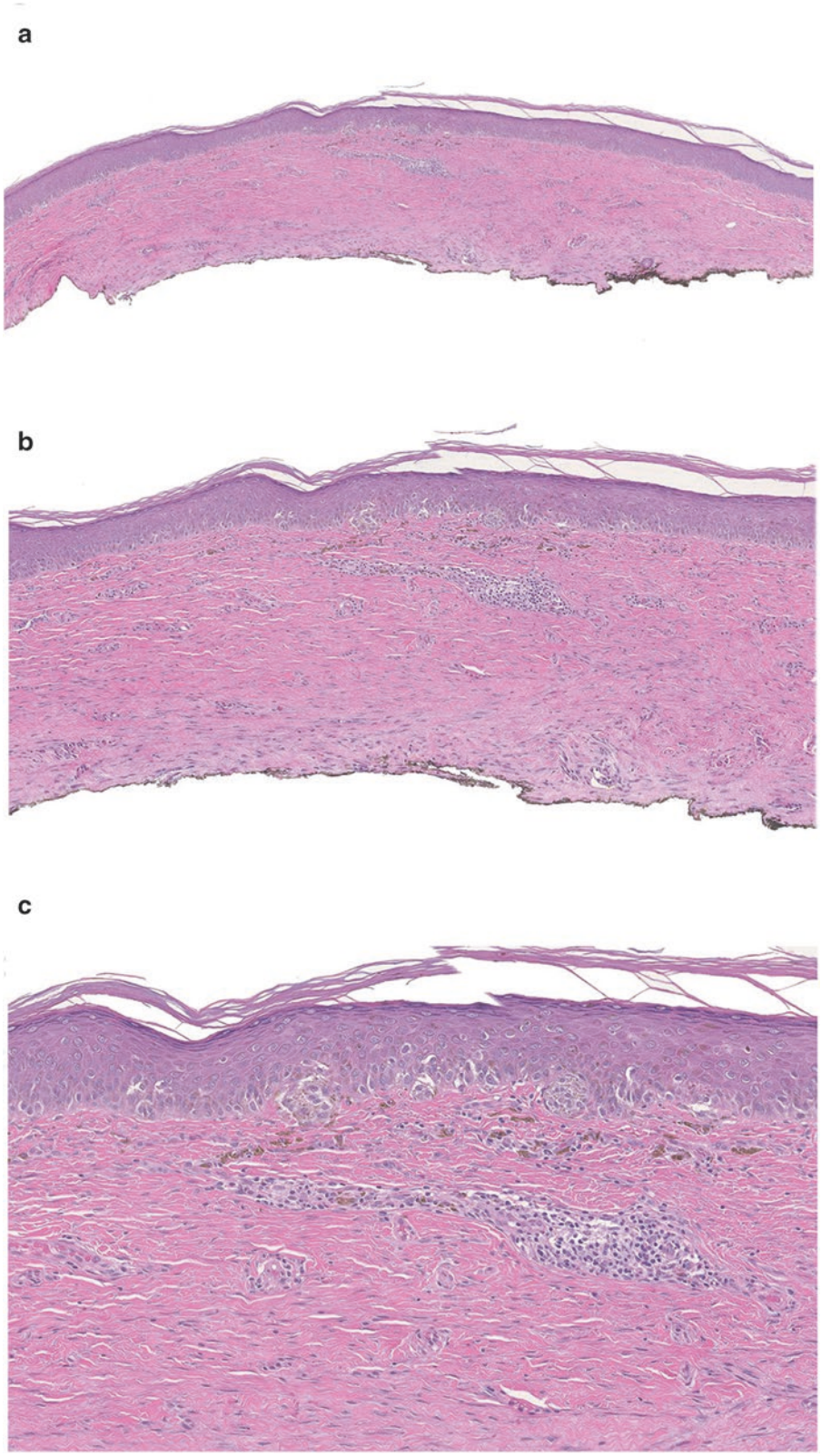

Fig. 5.17 Recurrent dysplastic nevus. This lesion is located in the leg of a 31-year-old male; this lesion was previously biopsied 7 months prior and was diagnosed as a mildly dysplastic nevus. Note the scar in dermis along with scattered atypical junctional nests. Note the confluent growth of junctional melanocytes above the scar in dermis (**a**, **b**). Higher magnification showing the lentiginous and nested proliferation in the dermal epidermal junction (pseudo melanoma). Note the atypical melanocytes in the junction. This particular case can easily be mistaken by a melanoma if the scar and the prior biopsy are overlooked (**c**)

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Congenital Nevi

6

Congenital Melanocytic Nevi

Introduction

Congenital melanocytic nevi are benign melanocytic proliferations that are present at birth or, according to some authors, arise within the first few weeks of life. These nevi are one of the most common cutaneous lesions in a newborn. The terms "tardive" congenital melanocytic nevus has been used to represent nevi with clinical and histologic features of congenital melanocytic nevi that were not clinically apparent at birth but were detected within the first 2–3 years of life. Prevalence of congenital melanocytic nevi ranges from 0.2 to 2.7 % for lesions less than 1.5 cm in greatest diameter to 0.005 % for lesions greater than 10 cm in greatest diameter [1–4]. Most congenital melanocytic nevi occur sporadically but there may be familial clustering. These melanocytic lesions may pose considerable clinical dilemma given their frequency, wide variation in presentation, and potential for medical significance. The medical significance of these newborn skin lesions is that over a lifetime they can be a marker for increased risk of malignancy, may be associated with rare syndromes, or themselves can transform into melanoma. Furthermore, while small lesions are most often inconsequential, large nevi can carry a devastating psychosocial burden and increased risks of melanoma, since the relative risk for melanoma arising within a congenital nevus is directly related to the size of the lesion.

Several developmental abnormalities are associated with congenital nevi, especially with giant congenital nevi. These associations include scoliosis, spina bifida, atrophy, asymmetry, clubfoot, or cranial bone hypertrophy [5, 6]. In addition, patients with large congenital melanocytic nevi are at increased risk to develop neurocutaneous melanocytosis, in which collections of melanocytes are present in the leptomeninges. Neurocutaneous melanocytosis is a rare congenital disorder characterized by the presence of giant or multiple melanocytic nevi associated with benign or malignant melanotic tumors of the central nervous system. Neurocutaneous melanosis can occur in both patients with large nevi or with multiple small- or medium-sized congenital nevi. Patients with large congenital nevi located on the posterior axis have greater risk for neurocutaneous melanocytosis, particularly those patients with large congenital nevi and multiple satellite nevi [7]. Malignant transformation can also occur in neurocutaneous melanosis and result in primary melanoma of the central nervous system. Even without malignant transformation, neurocutaneous melanosis can carry significant morbidity and mortality, often from seizures, hydrocephalus, and other signs of irritation of the central nervous system.

Congenital nevi can be also associated with café au lait spots, mucosal nevi, fascicular schwannoma, lipoma, lymphangioma, capillary hemangioma, fibroepithelial polyp, ectopic mongolian spot, atopic dermatitis, vitiligo, neurilemmomas, perinevic leukoderma, and cartilaginous hamartomas [6, 8, 9]. Extracutaneous associations include limb hypertrophy, electroencephalography abnormalities, and cryptorchidism.

Etiology and Pathogenesis

The etiology of congenital melanocytic nevi remains unclear. Its development is determined in utero between the 5th and 24th weeks of gestation. An important theory of melanocyte differentiation is that the neural tube develops during early embryogenesis; melanoblasts migrate from the neural crest along the leptomeninges to the embryonic dermis. From the embryonic dermis, the progenitor melanocytic cells migrate into the epidermis, where they differentiate into dendritic melanocytes.

Congenital melanocytic nevi have somatic mutations in either NRAS codon Q61 or BRAF codon V600. Particularly, giant congenital nevi and neurocutaneous melanocytosis exhibit a high frequency of NRAS mutations [10–12]. Some studies have supported that the same Q61 NRAS mutation is

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present in the central nervous system and affected skin lesions, and patients with multiple cutaneous lesions harbor the same mutation in each lesion. This finding supports the existence of multiple pathways of melanocytic tumorigenesis with NRAS mutations perhaps exerting a stronger growth signal or having different consequences during embryogenesis when compared with BRAF mutations. On the other hand, BRAF mutations have a higher prevalence in small- and medium-size congenital nevi and have been considered to be associated with a more benign clinical phenotype.

A recent study demonstrated in some patients with neurocutaneous melanocytosis the BRAF V600E mutation instead of NRAS Q61 [13]. In addition, BRAF V600E somatic mosaicism was also associated with giant congenital nevi. This same study found that congenital nevi with BRAF V600E mutation had more dermal/subcutaneous nodules and less hypertrichosis than those with NRAS Q61 mutation. Overall, this study concluded that NRAS mutations should not be considered exclusive of giant congenital nevi or neurocutaneous melanocytosis and also that BRAF mutations cannot be taken as responsible for a more benign disease [13].

Clinical Features

Congenital nevi change of appearance with age. At birth, the lesions may appear to be lightly pigmented macules that in some cases mimic café au lait spots. They are usually small and oval, but also round, linear, curvilinear, geographic pattern [14, 15]. Multiple lesions can be found, coalescing on one anatomic area, discontinuous in a geographic area, or randomly scattered. The lesions may change during the first few years of life and vary greatly from patient to patient. A common change is the presence of flat or elevated small, dark brown macules or papules within the parent lesion; this change may remain static into adult life. Once fully developed, the typical clinical features are those of a pigmented, brown plaque with regular, smooth, and well-demarcated borders. Formation of terminal hairs within the plaque and verrucous changes may be seen in older nevi, and some studies have even suggested that congenital nevi may lighten with age [16]. Congenital nevi located on the scalp have a peculiar tendency to gradually lighten and regress over time. As such, medium-sized to large congenital nevi on the scalp may undergo complete or almost complete clinical resolution [17, 18].

Congenital nevi can involve almost any location including the mouth, palms and soles, and nails. When located in the mouth and nails, the lesions adopt a macular appearance. On the other hand, when located on the scalp, the lesion commonly displays a central area of coloration that is a different shade or color than the periphery.

Several methods have been used to classify congenital melanocytic nevi. The most common classification defines melanocytic nevi on the basis of their size (small, medium, and large/giant) [19]; small congenital nevi are <1.5 cm, medium are 1.5–19.0 cm, and large are those >20 cm (as defined by the largest dimension diameter achieved in adulthood). The distinction between large and giant congenital nevi has been much debated [20]. The term "giant" congenital nevus is sometimes used for nevi covering large segments of the body; however, some authors have defined giant congenital nevi as those with >20 cm or body surface area [21–23]. In this chapter we will use the above described classification [19]

Small and medium congenital nevi: These nevi are often tan to brown in color and oval shaped with well-defined borders. Lesions may develop a mammillated surface and hypertrichosis over time. The risk of melanoma development in these nevi is thought to be less than 1 % over a lifetime and when it happens is usually seen after puberty [9, 16, 24–26]. Melanomas arising in small and medium congenital nevi tend to develop at the dermal-epidermal junction and at the peripheral edge of the congenital nevus; such changes make a clinical morphologic change readily recognized by patients and clinicians [27].

Giant congenital melanocytic nevi: These nevi are always present at birth; however, some congenital nevi are better visualized within the first years of life and are referred to as "tardive" nevi. Giant congenital melanocytic nevi can occupy large areas of the skin surface and most often occur on the trunk, followed by the extremities and the head and neck [28]. The clinical presentation often changes with age; a hairless, light brown, flat lesion at birth may evolve over months and years to develop areas of hyperpigmentation and color variegation, hypertrichosis, erosion or ulceration, a verrucous texture, and nodularity usually representing "neurotization" changes (see histology below). The majority of patients with giant congenital melanocytic nevi have also solitary or multiple satellite nevi associated with them and dispersed over the extremities, trunk, or head and neck.

The absolute risk of melanoma development in giant congenital nevi is approximately 2–5 % over one's lifetime, considering prospective and retrospective cohort studies with significant follow-up [26]. About half of these melanomas occur in the first 5 years of life and tend to arise deep in the dermis or subcutaneous tissues, making early detection difficult [29, 30]. The number of satellite nevi does not

portend a higher risk for developing cutaneous melanoma but having >20 satellite lesions increases the risk for neurocutaneous melanocytosis and melanoma of the central nervous system. Other malignancies such as liposarcomas, rhabdomyosarcomas, and malignant peripheral nerve sheath tumors have been associated with giant congenital nevi [31].

Melanoma Associated with Congenital Melanocytic Nevus

The risk of melanoma in patients with congenital melanocytic nevi increases with the size of the nevus. When considering malignant transformation, it is essential to distinguish between small and large congenital melanocytic nevi. This risk has ranged from 1.1 % to as high as 45 % [21, 32–35]; however, recent data suggest that the risk of melanoma ranges from 2.8 to 8.5 %. The risk for transformation of small congenital nevi is controversial and is thought to be between and 0 and 5.0 % and for those with large or giant congenital nevi between 4.5 and 10.0 %. In larger congenital melanocytic nevi, melanoma usually develops deep to the dermal-epidermal junction or occurs extracutaneous (e.g., the central nervous system, gastrointestinal tract, or retroperitoneum), usually in the first decade of life. In such patients, melanoma most commonly begins in the deeper dermis or subcutaneous tissue; thus, it often presents as a palpable deep nodule.

As mentioned above, tumors other than melanoma associated with congenital nevi include rhabdomyosarcoma, malignant peripheral nerve sheath tumor, and other sarcomas [6, 9, 36–38].

Clinically, malignant transformation may manifest as increasingly dark pigmentation, accelerated growth, change in shape, appearance of nodularity, pain, ulceration with or without bleeding, or pruritus; however, many of these features are also common to the benign course of congenital nevi [24]. Transformation may occur later in life and underscores the importance of long-term follow-up, even after surgical intervention.

Histopathologic Features

Congenital melanocytic nevi may be junctional, compound, or intradermal in type, depending on the phase at which they are removed. Congenital nevi have variable appearance, and in some cases, the histology is identical to their conventional acquired variant as some of the clues present in congenital nevi can also be noted in some examples of acquired melanocytic nevi. Of interest, there are some congenital nevi that do not show histologic features that indicate their congenital origin, and some small congenital nevi can be histologically indistinguishable from common acquired melanocytic nevi [2, 39, 40]. It has also been proven that congenital melanocytic nevi in infants have the pattern of distribution of melanocytes and the depth of the melanocytic proliferation established very early in life.

Junctional congenital nevi are rare and more commonly seen in small lesions in neonates. Some cases of junctional congenital nevi may display prominent melanocytic hyperplasia in the epidermis and adnexal epithelium. These junctional nevi are more commonly seen after birth and clinically present as small macular brown lesions. Congenital nevi are more commonly compound or intradermal. At low power, congenital melanocytic nevi are usually symmetric with a wedge-shaped or platelike dermal component. When a junctional component is present, it is usually well circumscribed with nests of melanocytes positioned at the side and base of rete ridges and relatively uniform in size and shape. The melanocytes are typically small to medium sized and monomorphous in appearance. One of the most common atypical features and possible pitfalls seen in congenital nevi is the presence of a lentiginous melanocytic proliferation, which may or may not be associated with variation in the size and shape of the melanocytic nests and cytologic atypia. The junctional component of congenital nevi, especially in patients younger than 10 years of age and in certain anatomic locations (e.g., scalp), may show large nests of melanocytes that vary in size and shape and that are not uniformly distributed. Single melanocytes may predominate over nests in some areas, and the melanocytes may be large and show mild degree of pleomorphism. Cases in which these findings are present may be misinterpreted as melanoma. However, such changes in congenital nevi are located in the center of the lesion, while most melanomas developing in the epidermis over a congenital nevus do extend *beyond* the dermal component.

In compound congenital nevi, in addition to a junctional component, there are melanocytes in the dermis which tend to be aggregated in nests. Melanocytes are typically larger in the superficial portion of the dermis. They are uniform, with minimal cytoplasm, and show maturation from the superficial to the deep aspect of the lesion with nests and individual melanocytes gradually diminishing in size with descent into the dermis. With increasing depth, the melanocytes often demonstrate less crowding and greater splaying of the collagen. Occasional mitotic figures may be noted in congenital nevi and when seen they are located in the superficial portion of the lesion.

Congenital melanocytic nevi usually reach the lower aspect of the dermis with a characteristic perivascular, perineural, and periadnexal distribution; however, aggregates of melanocytes can be seen located far away from the main

dermal lesion giving a patchy pattern. In some examples melanocytes can be predominantly located around eccrine ducts in nests or single melanocytes (usually around the external end of the duct or in the intradermal portion).

The dermal component may reach the subcutaneous fat, and in such cases, melanocytes often extend along fibrous septa of the subcutaneous fat and, in some instances, may infiltrate the fat lobules, similar to diffuse neurofibromas. The presence of scattered single melanocytes infiltrating the subcutaneous fat is a clue to the congenital nature of the lesion. In some giant congenital nevi, the melanocytes can reach the fascia and skeletal muscle.

In those predominantly intradermal congenital nevi, there is often a grenz zone separating the dermal melanocytes from the overlying epidermis, although it is frequent to see slightly prominent junctional melanocytes with a lentiginous pattern. There may be superficial pigmented dermal melanocytes, but there is typical diminution or absence of pigment in deeper portions of the lesion. Congenital nevi characteristically show melanocytes that appear to splay the dermal collagen in aligned rows between collagen fibers. Spindled melanocytes and neuroid elements can be seen at the base of the lesion. The scalp is a common anatomic site in which these neuroid elements resemble the histologic pattern of a neurofibroma.

Some congenital nevi display pigmented melanocytes aligned in the junction of the follicular infundibula and within the sebaceous lobules, follicular sheath, epithelium of eccrine glands, and arrector pili muscle. In general, it is considered that the identification of melanocytes within the sebaceous glands, nerves, and blood vessels in the deep reticular dermis is highly specific for a diagnosis of congenital onset. Also the presence of large number of hair follicles within the lesion usually indicates a congenital origin. There may be intraepidermal pagetoid spread of melanocytes, especially in patients during their first year of life. These pagetoid cells often display no or slight cytologic atypia and are usually confined to the center of the lesion (along with a nested junctional component) and are restricted to the lower half of the epidermis, in contrast to melanoma in which the pagetoid growth is observed as lateral spread beyond the nested areas [41–43].

Table 6.1 Histologic features of congenital melanocytic nevi

• Presence of melanocytes within the lower two thirds of the dermis and within the subcutaneous tissue
• Melanocytes splaying between the collagen bundles of the reticular dermis as single or cords of cells
• Melanocytes extending around and within hair follicles, sebaceous glands, eccrine apparatus, vessel walls, and nerves
• Perivascular and perifollicular distribution of melanocytes simulating an inflammatory dermatosis
• Arrector pili that may be enlarged and infiltrated by melanocytes

Differential Diagnosis

Diagnosing a congenital nevus is not a challenging process especially when all histologic features are present, such as circumscription, uniform melanocytic nests within the epidermis that are equidistant from each other, nests and individual melanocytes that mature with their descent, wrapping of melanocytes around vessels and adnexal structures, and splaying of melanocytes among collagen bundles. However, these histopathologic findings are not always clear-cut. There are some possible pitfalls, namely, intraepidermal lentiginous melanocytic proliferation, pagetoid spread of melanocytes, and proliferative nodules.

The most important differential diagnosis in congenital nevi is to rule out the development of melanoma. When melanomas originate in small- and medium-sized congenital nevi, they usually appear after puberty and often develop at the periphery of the preexisting nevus. Most of these melanomas have an intraepidermal origin (clear in situ component) and are usually of the conventional type (superficial spreading) [36]. As explained above, pagetoid change can occur in congenital nevi, particularly in neonates and young children, but in contrast to melanoma, those isolated cells tend to involve the lower half of the epidermis and display a limited degree of atypia.

Histologically, melanomas that are observed in giant congenital nevi are morphologically different to the melanomas seen in small- and medium-sized congenital nevi as the majority of such melanomas are intradermal without an obvious intraepidermal component. Melanomas in giant congenital nevi present as cohesive nodules that are distinctly different and clearly delimited from the surrounding nevus. These nodules tend to demonstrate marked cellularity, are composed of epithelioid melanocytes, and often have prominent nuclear pleomorphism and atypical mitotic figures. The malignant melanocytes can also be spindled or small and round in shape. Furthermore, these dermal nodules of melanoma show a pushing border against the surrounding melanocytes of the congenital nevus; in contrast, the benign proliferative nodules tend to be smaller, and the cells blend with the surrounding melanocytes.

Nevoid melanoma may resemble a compound or intradermal melanocytic nevus with features of congenital nevi. There are certain architectural features that should raise suspicion of a nevoid melanoma including asymmetry and prominent cellular density. At high power, the melanocytes of a nevoid melanoma show high degree of cytologic atypia with subtle pleomorphism, nuclear hyperchromasia, prominent nucleoli, dusty pigmentation of the cytoplasm, and absence of dermal maturation. Also, mitotic figures (some of atypical shape) in the deep aspects of the lesion favor the diagnosis of nevoid melanoma.

The distinction between congenital nevi and acquired nevi is very important for obvious reasons. However, as explained above, the histologic clues described in congenital nevi can also be shared with some acquired nevi. A good number of acquired nevi that appear in infancy have histologic features that are encountered in congenital nevi, and some examples of congenital nevi do not show any histological clues that indicate their congenital origin. Important information to rely on includes detection at birth; presence of melanocytes in the lower two thirds of the dermis and subcutaneous tissue; arrangement of melanocytes as isolated elements or single lines among the collagen bundles in the reticular dermis; the involvement of sebaceous glands, arrector pili muscles, eccrine glands, and lymphatic vessels; and the presence of melanocytes around perivascular, perifollicular, and/or around the eccrine gland distribution.

An important distinction is between congenital and dysplastic nevi. Congenital nevi can have a pattern reminiscent of dysplastic nevi (in compound and junctional nevi), and thus the distinction can be a challenging one. In addition, one study showed that up to 8.3 % of compound dysplastic nevi can show features of congenital nevi [44]. Congenital nevi can show junctional nests that are confluent and irregular with bridging between the rete ridges, lentiginous hyperplasia, extension of junctional component beyond the dermal component (shoulder phenomenon), and variable cytologic atypia. Importantly, it should be kept in mind that none of these features is by itself diagnostic of dysplasia or congenital nevi with dysplastic features, and it should always be interpreted in the clinical context. Classifying a nevus as congenital with dysplastic features or as a true dysplastic nevus with features of a congenital nevus can in some cases be arbitrary.

Histologic Variants

Recurrent Congenital Nevus with "Pseudomelanoma" Features

In occasions congenital nevi that have been previously biopsied may show irregular pigmentation confined to this area and can be clinically worrisome for melanoma. Histologically, recurrent congenital nevi show an irregular intraepidermal melanocytic proliferation confined to the area above a dermal scar with some effacement of the rete ridges. There is usually minimal cytologic atypia, and melanocytes may be seen above the dermal-epidermal junction (pagetoid spread), but confined to the lower half of the epidermis. In such cases, there is a visible remnant of the nevus present underneath the scar or peripherally, if the nevus was not completely removed previously. It is of paramount importance to be aware of any prior biopsy at this anatomic site, in order to evaluate appropriately the lesion. This will allow a distinction from melanoma and therefore to render a correct diagnosis of recurrent/persistent congenital nevus.

Congenital Nevus with Neurofibromatosis-like Features

In some congenital nevi, melanocytic elements may take on the histologic appearance of a neurofibroma [45–48]. In addition, neurofibromatosis type 1 may occur in patients with congenital melanocytic nevi, and giant pigmented nevi have been reported in about 5 % of patients with neurofibromatosis type 1 [49, 50]. Their coexistence can be explained by the fact that both melanocytes and Schwann cells originate from the neural crest. Yet, neurofibromatosis is an autosomal dominant trait, whereas congenital nevi have a multifactorial inheritance.

Histologically, melanocytes show neuroid differentiation showing as spindled wavy nuclei with tapered ends embedded in a delicate, fibrillary, fibrous stroma and forming nevic structures that resemble neuroid tubes and Meissner corpuscles. Furthermore, there may be sheetlike arrangements of melanocytes, mastocytes, and neuroid-like Verocay bodies. The histological distinction of congenital nevi with neural features and neurofibroma can be exceedingly difficult, and some cases will require the use of immunohistochemistry studies to elucidate further the diagnosis. And to further complicate the issue, neurofibromas, particularly those associated with NF-1, may display melanin pigment and express melanocytic markers [51].

Congenital Blue Nevus

Congenital blue nevus is rare; the scalp and face are common locations. These lesions are large in size and may behave in an aggressive fashion with involvement of the underlying skull and dura mater or may remain superficial [52, 53]. Some cases may evolve into melanoma. Histologically, congenital blue nevus may acquire the appearance of common blue nevus or cellular blue nevus (see Chap. 3). In the spindle and epithelioid cell nevus type, the deep reticular dermis is infiltrated by epithelioid and spindle cells often mixed with small banal melanocytes or neuroid elements (combined nevus).

Congenital Spitz Nevus

Congenital Spitz nevus is extremely rare with only a few sporadic cases reported [54, 55]. Histologically, congenital Spitz nevi display the same histologic features as the acquired

type including the presence of large epithelioid or spindle-shaped melanocytes with abundant cytoplasm, well circumscribed, a variable number of multinucleate melanocytes, downward maturation of melanocytes, scatter of individual and nests of melanocytes above the dermoepidermal junction for compound cases, and melanocytes present far down the epithelial structures of adnexa [56–58]. Some cases may show histologic features that would classify them as congenital melanocytic nevi, such as angiocentricity, adnexocentricity, splaying of melanocytes between collagen bundles, and nests varying in size and shape.

Congenital Nevus with Dysplastic Features

As mentioned above, congenital nevi can show an intraepidermal component that is reminiscent to what is observed in dysplastic nevi. These histologic features include the presence of a lentiginous melanocytic proliferation, slight to severe cytologic atypia, variable junctional nesting, confluence of nests, and lamellar fibroplasia, and in some cases, there is even single melanocytic proliferation in the epidermis. In our practices, we refer these nevi as congenital nevi with dysplastic features. In addition, dysplastic nevi might show a congenital pattern histologically. Studies have found an incidence of up 8.3 % of compound dysplastic nevi showing congenital features [44].

Proliferative Nodules in Congenital Nevi

Proliferative nodules are discrete dermal nodular proliferations that are particularly seen in giant congenital nevi but occasionally in smaller lesions as well. They can occur congenitally or present as new pigmented papules within the nevus in infancy and early childhood. Nodules excised in teenager and adults are rare but still possible. There is little data about the frequency of proliferative nodules but some series have reported them in 2.9–19 % of congenital nevi [9, 59, 60]. The clinical appearance of the proliferative nodules varies but when clinically identified, the lesions are usually noted as soft nodules arising de novo in an existing congenital nevus. They usually develop slowly and when they reach a certain size, they tend to remain stable in growth. Occasionally, especially in newborns, proliferative nodules may exhibit worrisome clinical features such as rapid growth, hemorrhage, and ulceration [61, 62]; and thus these clinical features often raise suspicion for melanoma. Despite their alarming clinical and histological appearance, proliferative nodules are often self-limited and may occasionally regress spontaneously [63, 64]. The biologic course of proliferative nodules arising in congenital nevi is believed to be banal as most proliferative nodules become static after reaching a certain size and involute/regress with age [64].

Histopathologic Features

Proliferative nodules are composed by a nodular population of melanocytes in the reticular dermis which on low power show clear-cut borders that contrast with the adjacent melanocytic nevus. Most proliferative nodules are small in size but some cases may reach several centimeters in diameter. The cellular density of melanocytes in the proliferative nodule differs with that of the adjacent nevus. At higher magnification, proliferative nodules show gradual intermixing between the large melanocytes of the nodule and the small benign appearing melanocytes of the rest of the nevus, i.e., melanocytes in proliferative nodules merge and blend with the surrounding melanocytes. Proliferative nodules can display atypical changes including melanocytes with prominent nucleoli, higher cellularity than the surrounding nevus, and focal areas of hemorrhage and ulceration. Furthermore, some of these cases can show chromosomal aberrations. These atypical proliferative nodules can show a high proliferative rate with ki-67 along with expression with bcl-2 and p53. However, they reportedly behave in a benign fashion.

Some proliferative nodules may show a population of melanocytes in the epidermis, which is frequently seen in the area above a proliferative nodule; the pattern is similar to the pseudomelanoma intraepidermal proliferation seen in congenital nevi in young patients. The melanocytes are gathered in irregular confluent nests at the junction and scattered throughout the epidermis. In a few cases, especially in young patients, an atypical melanocytic proliferation can also be present in the epidermis with important pagetoid spread of melanocytes above the junction. Such proliferation is unrelated to the proliferative nodule itself, but these features may raise the diagnosis of melanoma.

Histologic Variations in Proliferative Nodules

Proliferative Nodules with Epithelioid Melanocytes

This pattern is seen more commonly in newborns; however, it can also be identified later in life. Clinically, these nodules present in giant congenital nevi and can have a worrisome presentation such as ulceration, multinodularity, and rapid growth.

Histologically, melanocytes within the nodule are more cellular than the background lesion but also blend focally with the surrounding melanocytes. These are large

melanocytes that can be heavily pigmented and predominantly composed of epithelioid cells, showing low-grade cytologic atypia and minimal pleomorphism. The cytoplasm of these epithelioid melanocytes is often ample and eosinophilic, and when pigmented the distribution of the pigment can be irregular. Mitotic rate is usually low with <1/mm^2; however, in some cases there are numerous mitoses, particularly in very young patients. The overlying epidermis can be involved by melanocytes and small nests. In some cases, the nodule can extend into the upper subcutis with well-demarcated, pushing borders but in some cases the nodules can have irregular, infiltrative borders. The histological distinction with melanoma can be supplemented with the clinical information. Thus, in newborn patients with giant congenital nevi, it is highly likely that any nodules represent proliferative nodules and not melanoma. However, melanomas can rarely arise in newborn patients, and it is our experience that intradermal melanomas arising in a giant congenital nevi show a quite striking degree of cytologic atypia. Signs that favor melanoma are a sharp demarcation of the nodule, lack of maturation, and atypical mitotic figures. Melanoma should also be suspected when the features otherwise accepted for proliferative nodule are too exaggerated, that is, when there are large zones of necrosis, extremely atypical melanocytes, and numerous mitoses. Immunohistochemistry may also be helpful since proliferative nodules show either diffuse HMB-45 labeling or only positivity in the most superficial cells.

Proliferative Nodules with Small Round Blue Cell-like Pattern

This variant is composed by tightly packed population of small round blue cells with very coarse chromatin and with inconspicuous nucleoli and scant cytoplasm. These cells are arranged in sheets and in some cases there are ectatic blood vessels. Some of these cases can mimic histologically lymphomas or Merkel cell carcinomas. In our experience, this variant can rarely display a high mitotic count especially in young and newborn patients. The distinction from melanoma is based on the lack of nuclear pleomorphism and presence of maturation at the periphery of the nodule. In cases, in which there are high mitotic counts, the distinction with melanoma can be difficult but, as explained above, the clinical presentation should be taken into consideration. Criteria indicating a melanoma are mostly pleomorphism and high mitotic rate with atypical mitotic figures and necrosis. Also, the size of the nodule should be considered as large, and deeply sited nodules are most probably melanoma, whereas small, circumscribed, and superficial collections of small and round melanocytes are most likely benign.

Proliferative Nodules with Spitzoid Pattern

This variant shows nodules with features of Spitz nevus and characterized by a monomorphous population of epithelioid melanocytes. Melanocytes tend to be atypical (large nuclei and prominent nucleoli) but are uniform in size and shape. In some atypical cases, the melanocytes display exuberant cytologic atypia as epithelioid cells with large hyperchromatic nuclei and clumped chromatin. Some cases show scattered mitotic figures but they tend to be superficial. In such cases, these nodules tend to have a clear-cut edge abutting the adjacent nevus and in some cases may also have a thin layer of collagen around the nodule. This distinction from melanoma can be a difficult task especially those cases with cytologic atypia. In our experience, low mitotic count, homogenous population of epithelioid melanocytes, and circumscription of the nodule favor a diagnosis of a proliferative nodule. On the other hand, melanomas may show variable cytoplasmic shapes that range from cells with abundant cytoplasm to cells with only a rim of pale cytoplasm or naked nuclei.

Overall Differential Diagnosis Between Intradermal Melanoma and Proliferative Nodule

Differentiating proliferative nodules in congenital nevi from melanomas arising in congenital nevi may be a diagnostic challenge for dermatopathologists. While cases of melanomas arising in the dermis of congenital nevi in children are exceedingly rare, there are a few reported cases [65–69]. It is important to remember that large benign proliferative nodules arising in the midst of a large congenital nevus are much more frequent than a melanoma in the same site. Thus, based on statistical considerations, a nodule in the center of a congenital nevus is most likely benign, in both children and in adults. This is even truer in very young patients (<2 years of age) where benign nodules can have remarkable cytologic atypia and a very high mitotic rate (atypical proliferative nodules). In this group of very young patients, pathologists should always be reluctant in giving a straightforward diagnosis of melanoma despite striking atypical features. Proliferative nodules in patients older than 2 years of age usually have low mitotic activity, whereas melanomas developed in the dermal portion of a nevus show obvious mitotic figures. In addition, such mitotic figures observed in melanomas are often atypical, a feature not observed in proliferative nodules. Many histologic features typically seen in melanomas can be also seen in proliferative nodules such as high mitotic count, sheets of large atypical melanocytes with epithelioid morphology, nuclear atypia, and necrosis. This is further complicated by the fact that congenital nevi may also have intraepidermal single cells that can mimic melanoma in

situ (see above). To further complicate the diagnosis, clinically proliferative nodules may also have many worrisome features such as rapid growth, change in color or shape, and ulceration that can bias a diagnosis of melanoma [61, 63].

Histologically, proliferative nodules can show a wide range of different histologic patterns including expansile nodules of epithelioid melanocytes with low number of mitotic figures, a small round blue cell pattern with many mitotic figures, blue nevus-like pattern, a nevoid melanoma-like pattern, etc. (see above). Proliferative nodules that are composed of epithelioid cells tend to have sharp demarcation of the nodule and are characterized by low mitotic counts, as well as mild to moderate nuclear atypia. This pattern is not difficult to separate from melanoma and in our experience is the most commonly encountered. Conversely, the small round blue cell-like pattern usually shows high mitotic counts as well as a higher degree of nuclear atypia, representing a diagnostic pitfall in certain cases. The morphologic distinction of a proliferative nodule arising in the dermis of a congenital nevus from melanoma can be complicated due to the frequent atypical junctional proliferations seen in congenital nevi in children. Also, cases of proliferative nodules can have some degree of junctional component in the epidermis regardless of the size of the congenital nevus, including frequent lentiginous and pagetoid growth as well as effacement of the epidermis. One recent study found that 68.2 % of cases of proliferative nodules may show this finding [70]. Melanomas arising in congenital nevi usually form expansile nodules of epithelioid melanocytes with high mitotic counts that range from 5 to 20 mitoses/mm^2. Other features include the presence of focal necrosis within the nodule or a lack of circumscription, with nests of cells infiltrating into the adjacent nevus. These nodules tend to demonstrate marked cellularity, and melanocytes often have prominent nuclear pleomorphism and atypical mitotic figures. The overlying epidermis can show changes that include effacement of the epidermis, extensive pagetoid, and lentiginous spread. A characteristic clue of melanoma in this setting is that it is clearly delimited from the surrounding nevus. The age of the patient can be crucial for such distinction as melanoma arising in a congenital nevus usually develops between 2 years of age and puberty (before this age range, the lesion most likely represents a proliferative nodule). Congenital melanomas and melanomas in the first 2 years of life are exceedingly rare. In adulthood, melanomas in congenital nevi usually develop at the junction and not in the intradermal portion of the lesion. In an adult, a melanoma in the intradermal component of a congenital nevus is very rare.

Table 6.2 Features that help to differentiate a proliferative nodule from melanoma

• There is not well-defined interface between the nodule and the adjacent nevus
• Melanocytes within the nodule blend with the surrounding melanocytes
• Exceptional necrosis
• Lack of homogeneous cytologic atypia
• Lack of destructive expansile growth
• Rare mitotic figures (atypical proliferative nodules can show obvious, scattered mitotic figures)

A recent study showed that by FISH, proliferative nodules have mostly whole chromosomal copy number aberrations, with rare partial chromosomal aberrations, whereas melanomas show highly elevated copy number aberrations involving 6p25 without gains of the long arm of the chromosome. This same study concluded that the presence of expansile nodular growth of severely atypical "epithelioid-shaped" melanocytes with high mitotic count (>5 mitoses/mm^2), ulceration, and partial chromosomal copy number changes by molecular studies are the features that suggest melanoma [70]. Other studies, using comparative genomic hybridization (CGH), have shown chromosomal aberrations between melanoma and proliferative nodules [71]. In such studies, CGH detected numerical aberrations of entire chromosomes in the great majority of the atypical proliferative nodules in congenital nevi with a specific pattern that is distinct from that of melanoma, which mostly showed aberrations involving parts of chromosomes. In contrast, bland congenital nevi with foci of increased cellularity typically did not show any abnormalities by CGH. The numerical aberrations in most atypical proliferative nodules position them in the spectrum between benign melanocytic nevi that tend to have no chromosomal aberrations and melanoma in which regional gains and losses are commonly found.

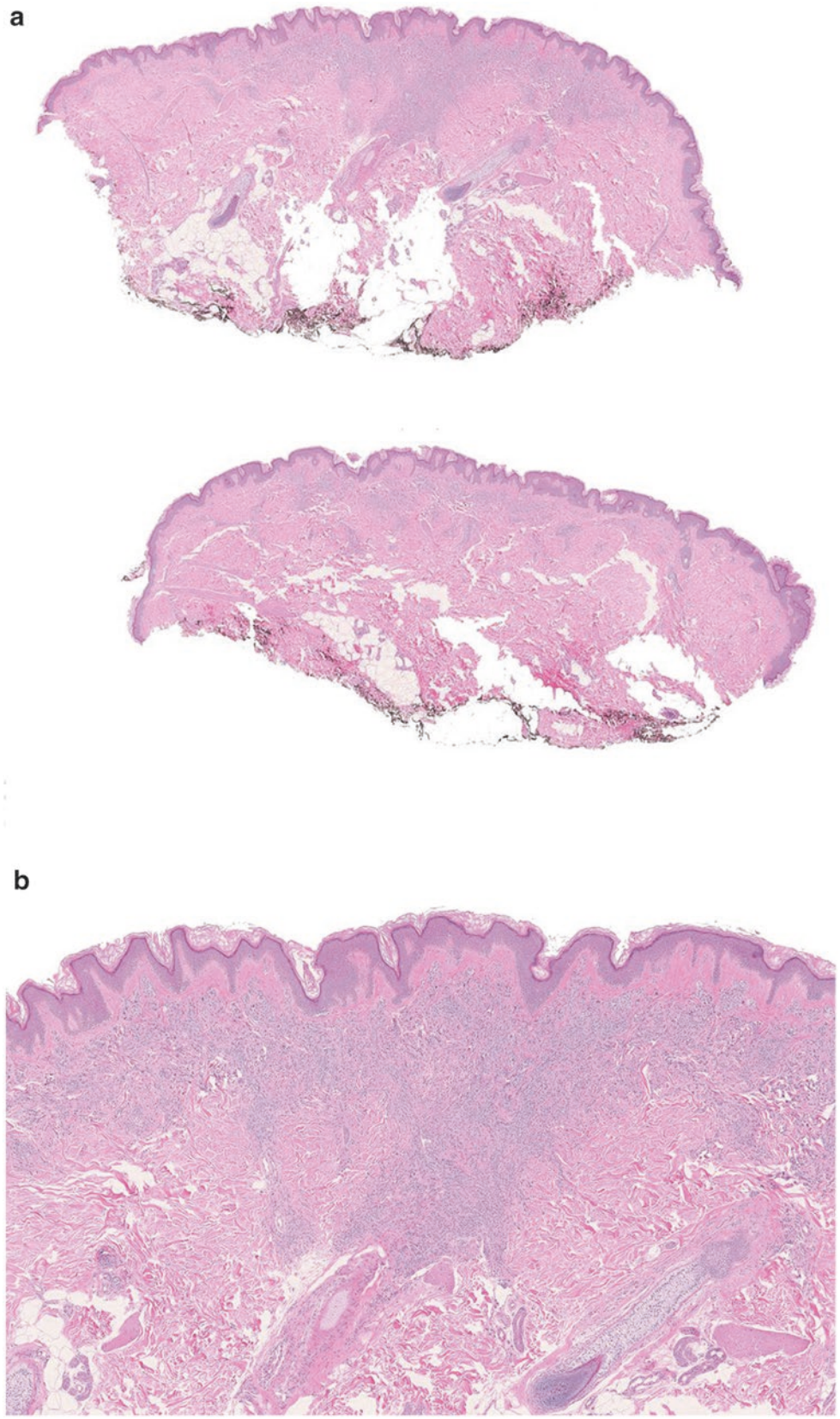


Fig. 6.1 Congenital nevus involving the mid and deep reticular dermis. Note the overlying papillomatous epidermis, which is a characteristic feature of congenital nevi (**a**). Note the sheets of small, hyperchromatic type B melanocytes in the reticular dermis, arranged in a broad-band pattern, with accentuation around skin adnexa (note the central follicle surrounded by melanocytes) (**b**).

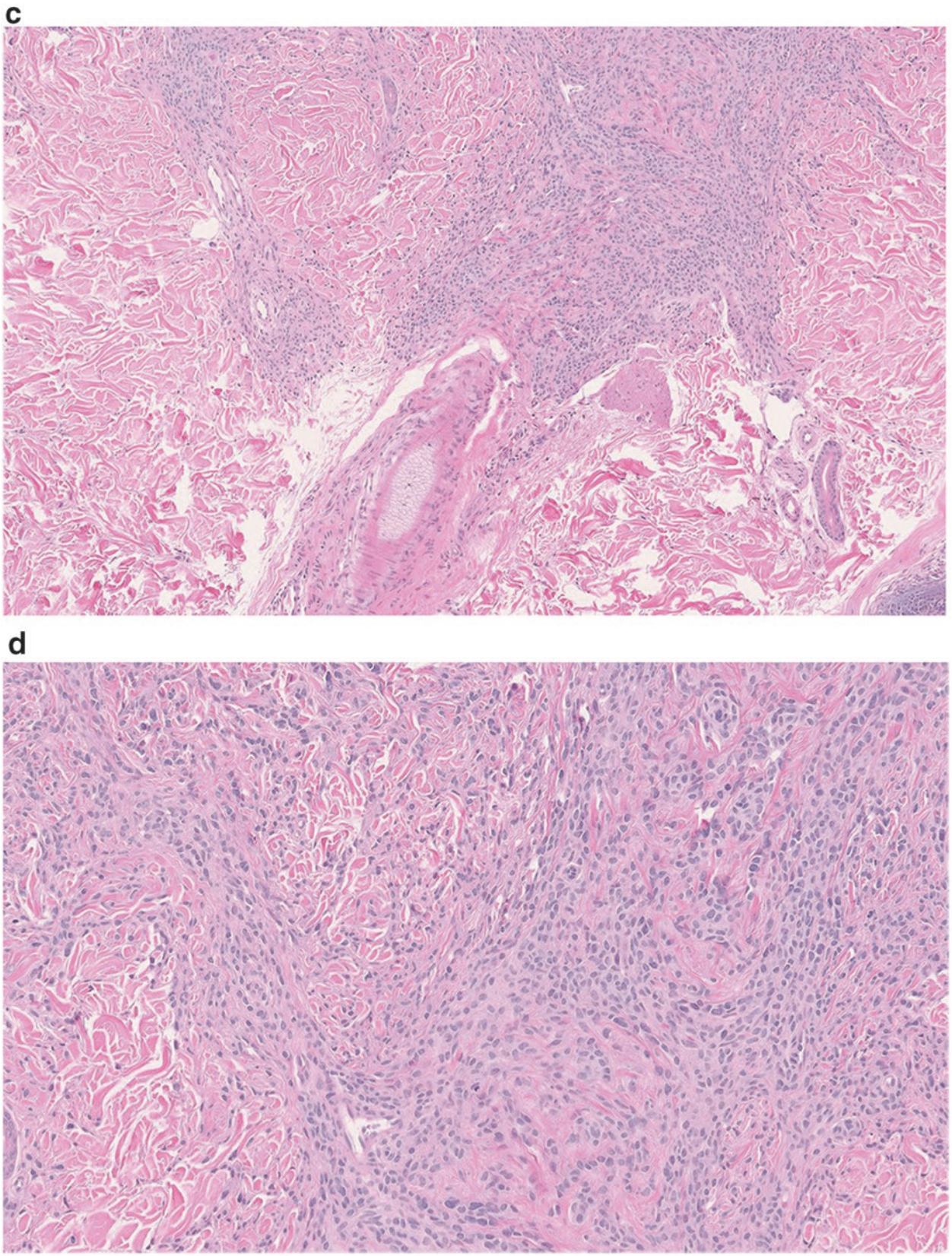


Fig. 6.1 (continued) Melanocytes extend away from the adnexa in single units among collagen fibers (**c**). Note the monomorphism of melanocytes among delicate, pink collagen fibers in the dermis (**d**)

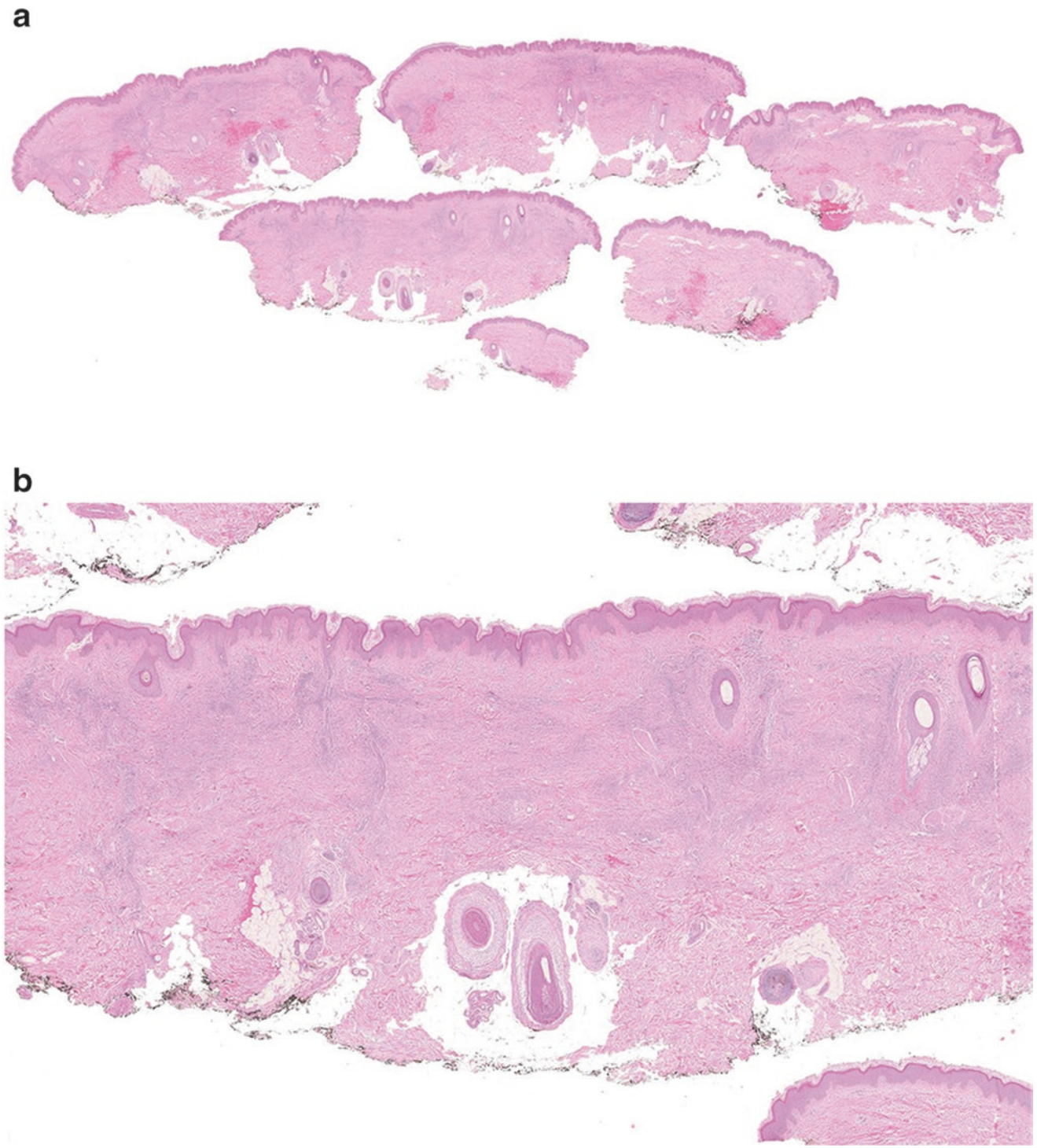


Fig. 6.2 Low-powered view of a lesion in a 10-year-old boy. Diffuse involvement of the reticular dermis and subcutaneous tissue (**a**). The melanocytes infiltrate throughout the dermis. Note the prominent periadnexal involvement. The involvement of the subcutaneous tissue resembles, at this power, the pattern of growth of large neurofibromata (**b**).

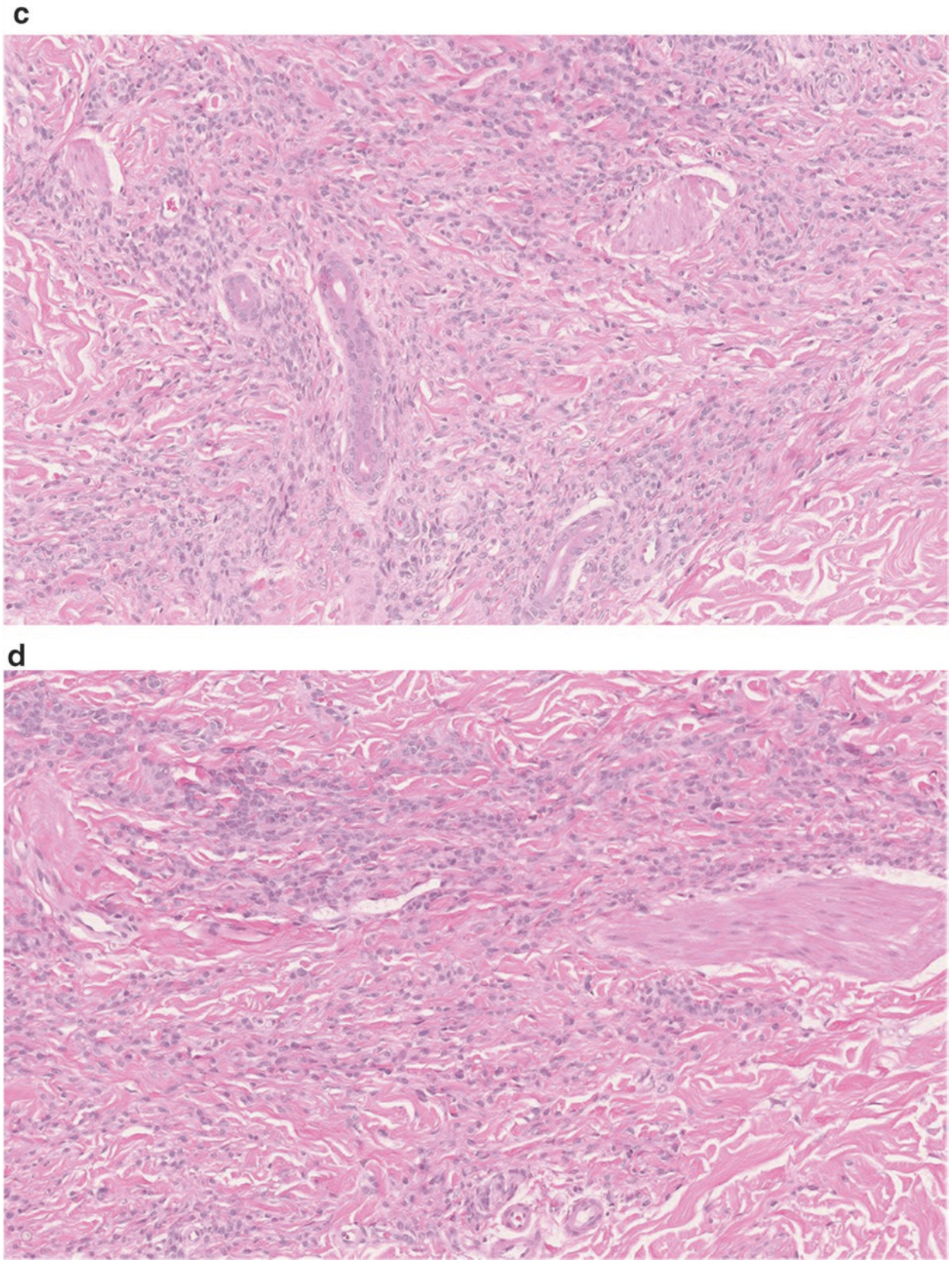


Fig. 6.2 (continued) Note the characteristic splaying of cords and strands of melanocytes in between collagen bundles (**c**). Note the monomorphic melanocytes surrounding erector pili muscle (**d**)

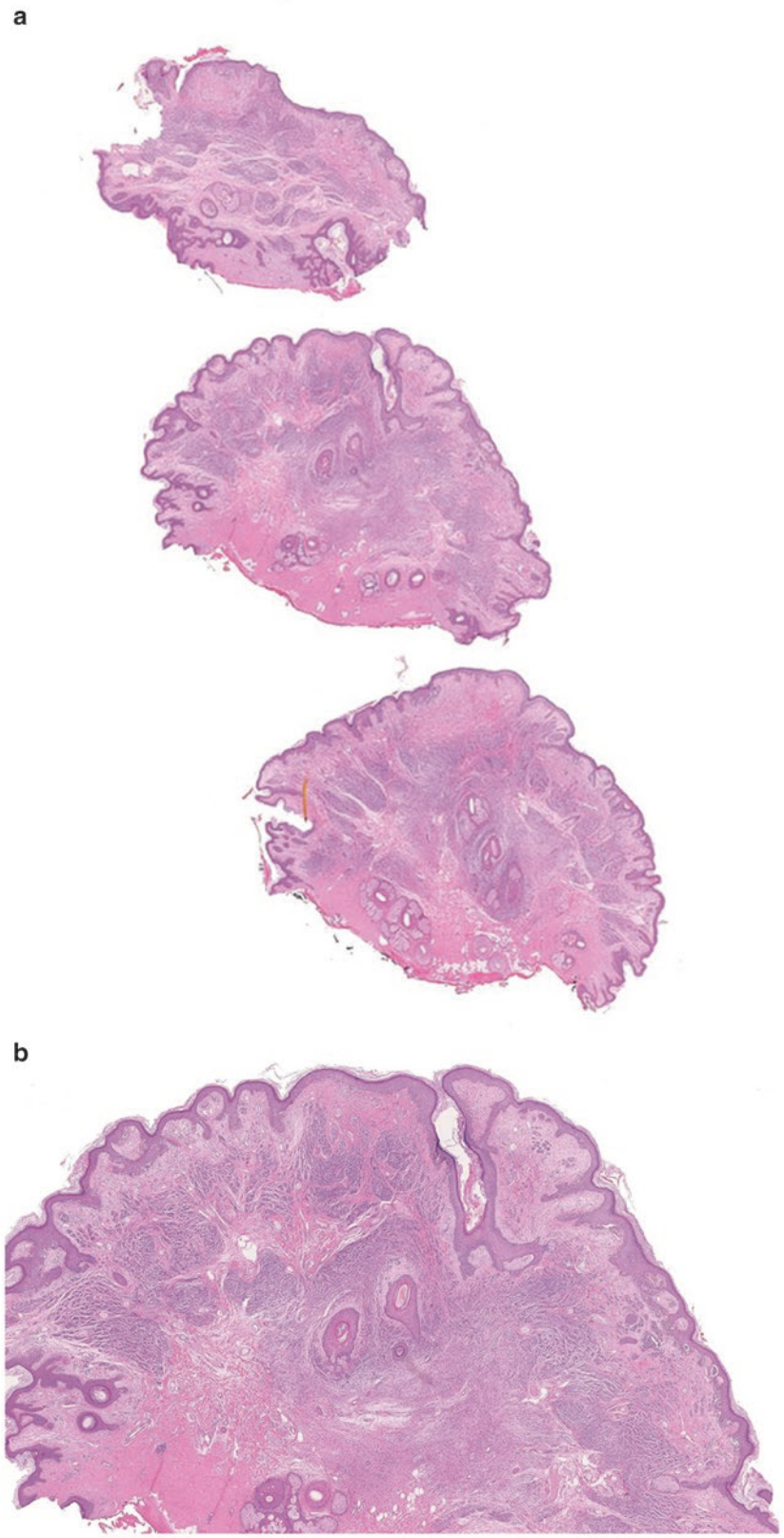


Fig. 6.3 Compound congenital nevus. Note the classic dermal component with periadnexal distribution (**a**). There are characteristic single cells and nested melanocytes around the hair follicles (**b**).

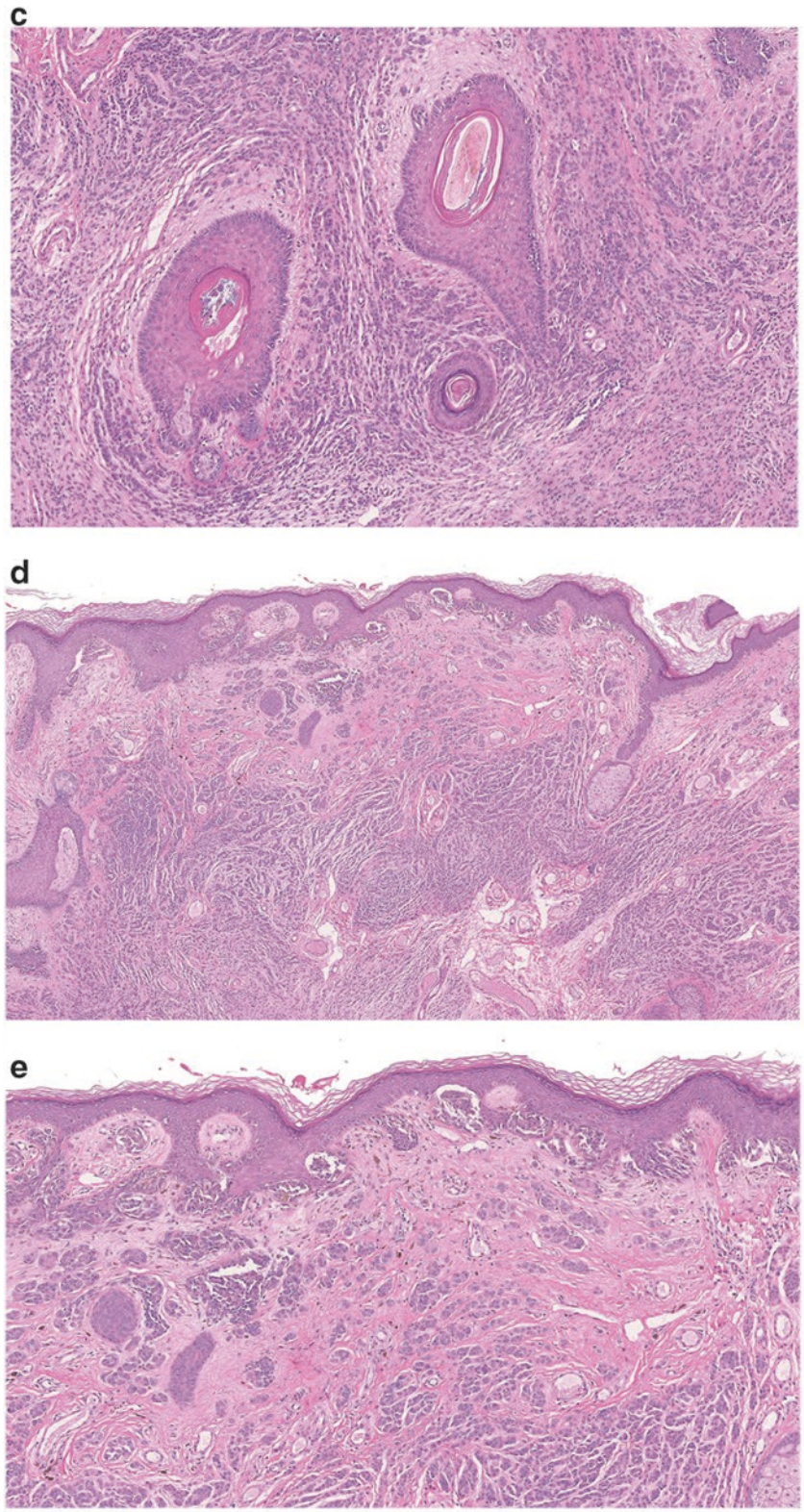


Fig. 6.3 (continued) Also, rare nests are seen in the follicular epithelium (**c**). Note the junctional component with nests of variable size as well as with a lentiginous growth (thus resembling that of a dysplastic nevus) (**d**). Higher magnification showing the asymmetric junctional component composed of a high density of melanocytes, fusion of rete ridges, and fibrosis in upper dermis (**e**)

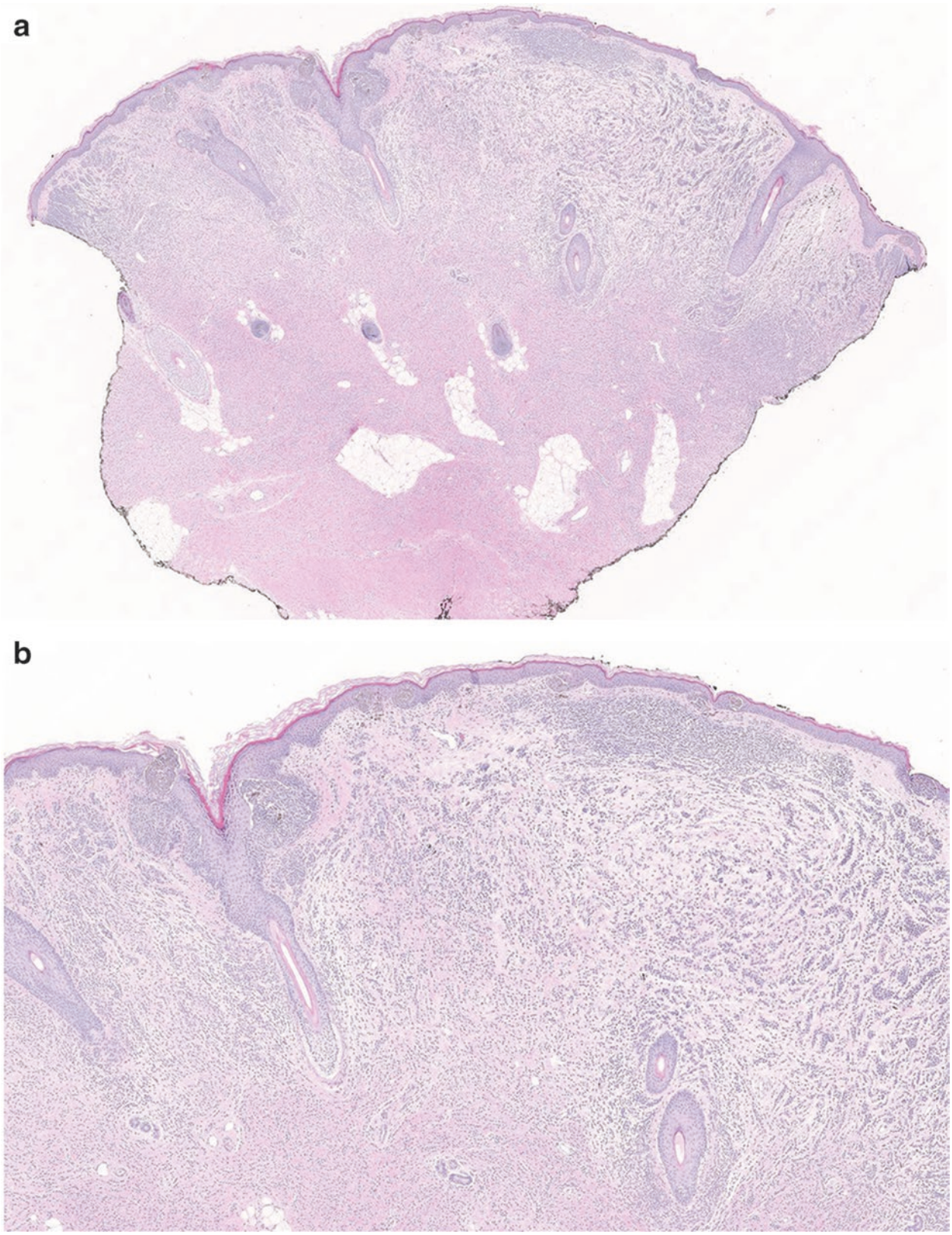


Fig. 6.4 This is a 5-year-old girl with a large congenital nevus. This example shows a more prominent involvement of the subcutaneous adipose tissue (**a**). There are characteristic monomorphic melanocytes in dermis with single cell pattern among collagen fibers. The density of the proliferation is higher near the epidermis and less in the deeper regions of the lesion (maturation) (**b**).

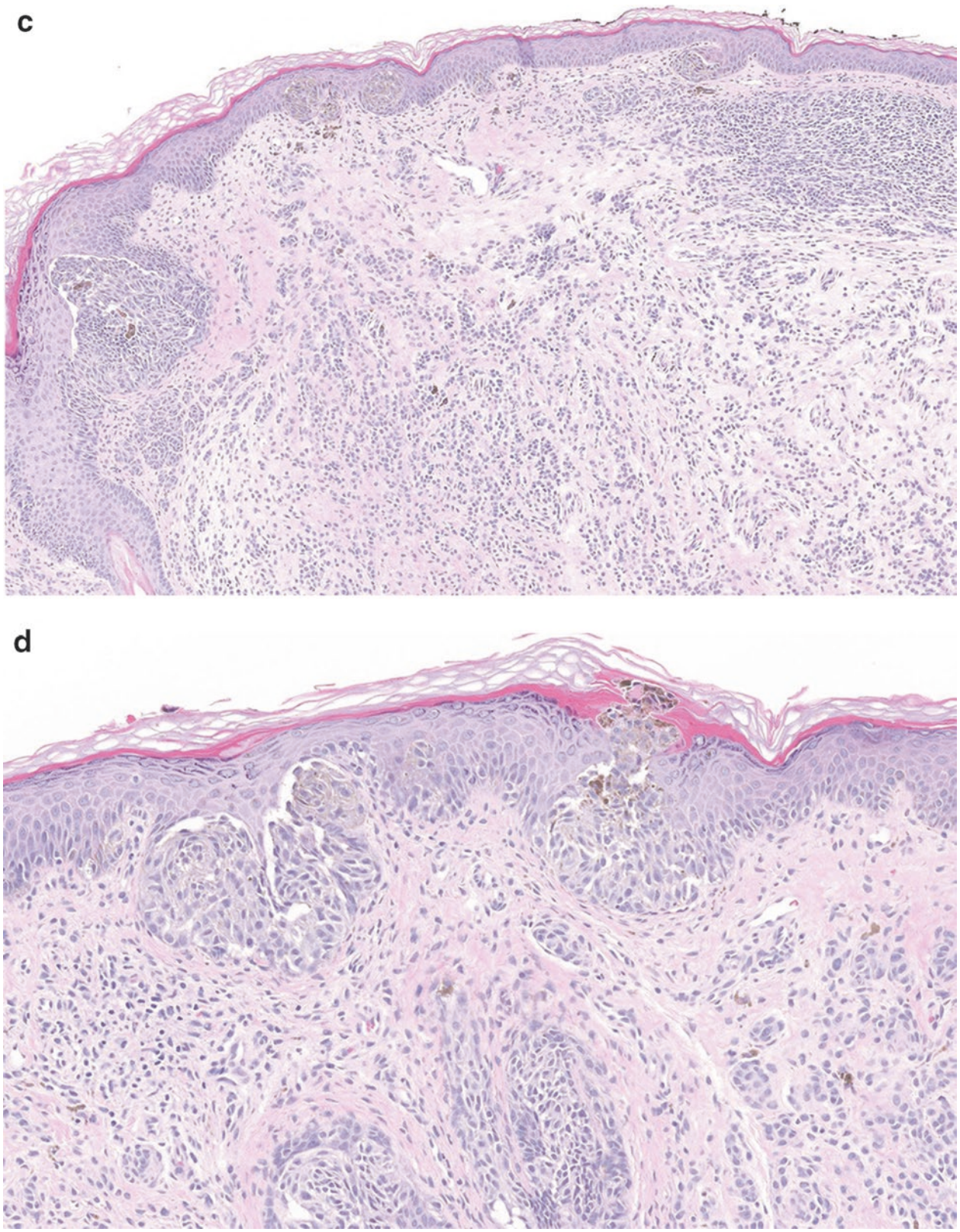


Fig. 6.4 (continued) Note the large junctional nests with minimal pagetoid migration (**c**). Note the large junctional nests with focal transepidermal elimination. The nests are composed of epithelioid melanocytes and some with peripheral cleft (spitzoid morphology) (**d**)

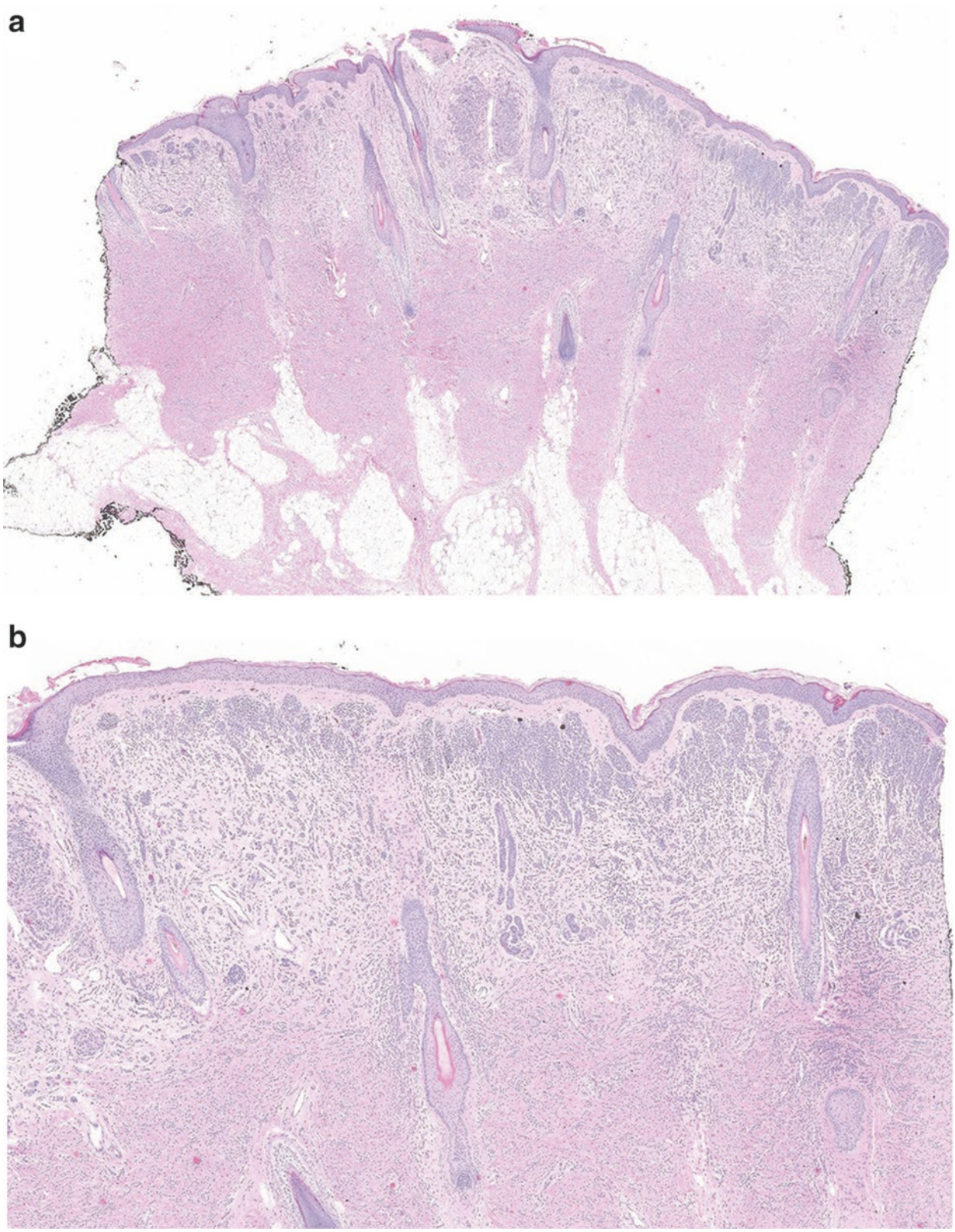


Fig. 6.5 This example shows a diffuse proliferation of melanocytes in reticular dermis with involvement of the deep subcutaneous tissue (**a**). The surface of the lesion shows minimal junctional component. In the dermis, there is a superficial predominantly nested component and a deeper, single-cell component infiltrating extensively the reticular dermis. Note the classic splaying of collagen bundles by single melanocytes (**b**).

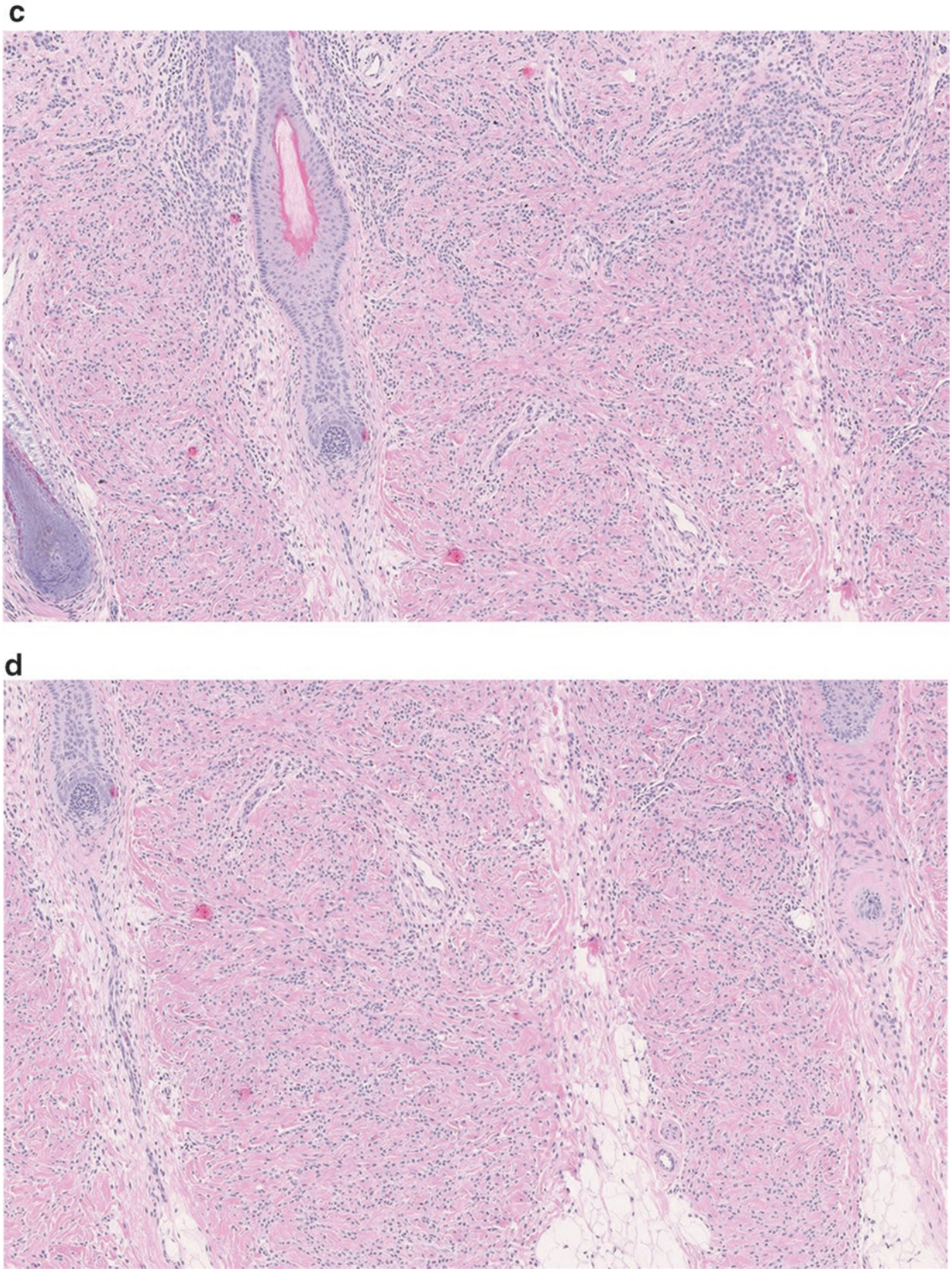


Fig. 6.5 (continued) Higher magnification of melanocytes infiltrating among collagen bundles (**c**). Note the infiltration of single cells into the subcutaneous fat, similar to the pattern seen in diffuse neurofibroma (**d**)

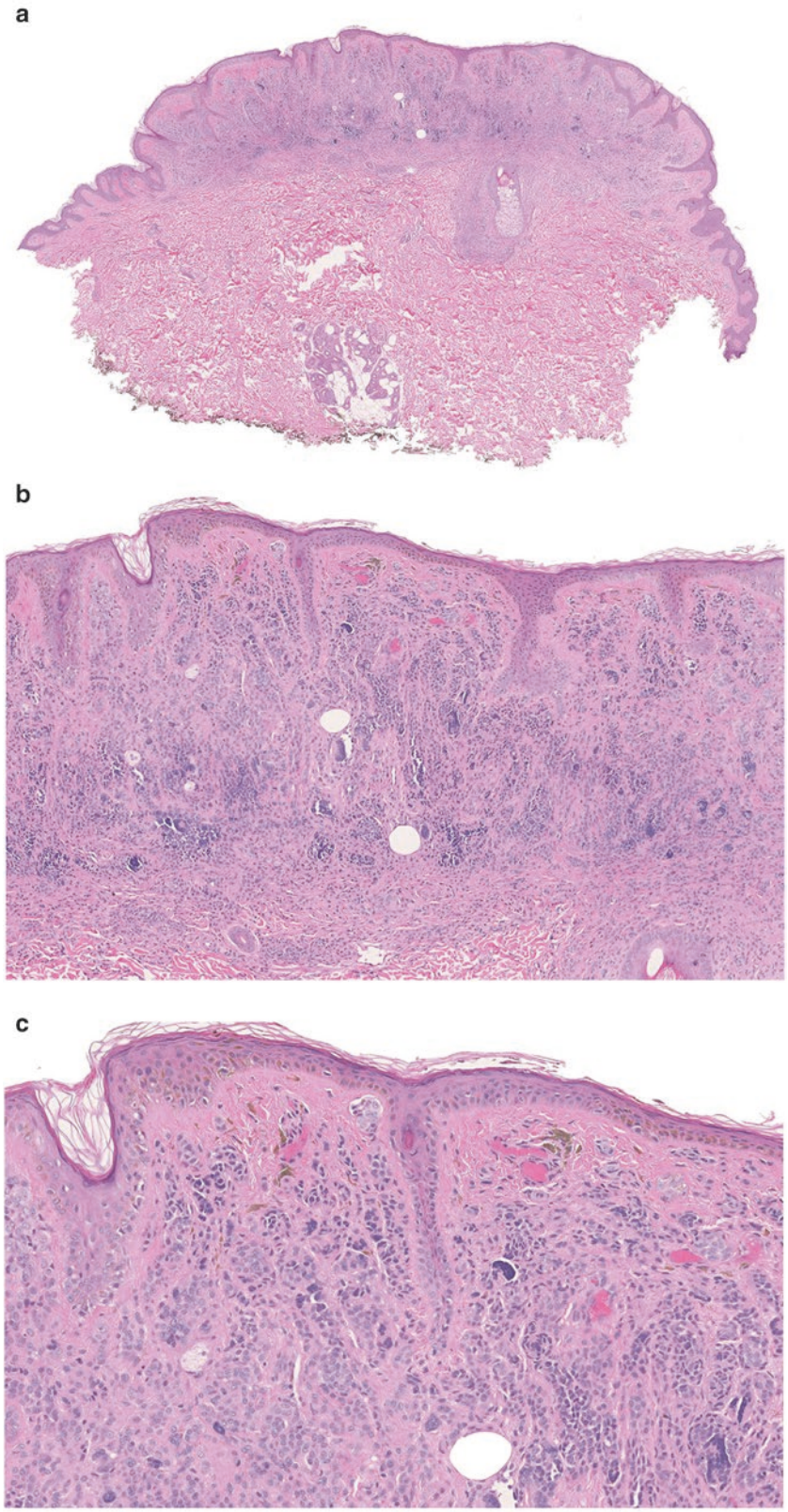


Fig. 6.6 Predominantly Intradermal Congenital Nevus. This example of congenital nevus displays many multinucleated giant melanocytes (**a**). Note the multiple nests, the perivascular and periadnexal infiltrate of melanocytes, and single sparse melanocytes in deep dermis. Note the presence of multinucleated giant cell melanocytes (*darker areas*) (**b**). Higher magnification of scattered multinucleated, giant melanocytes. Only the most superficial melanocytes show evident melanin pigment (**c**)

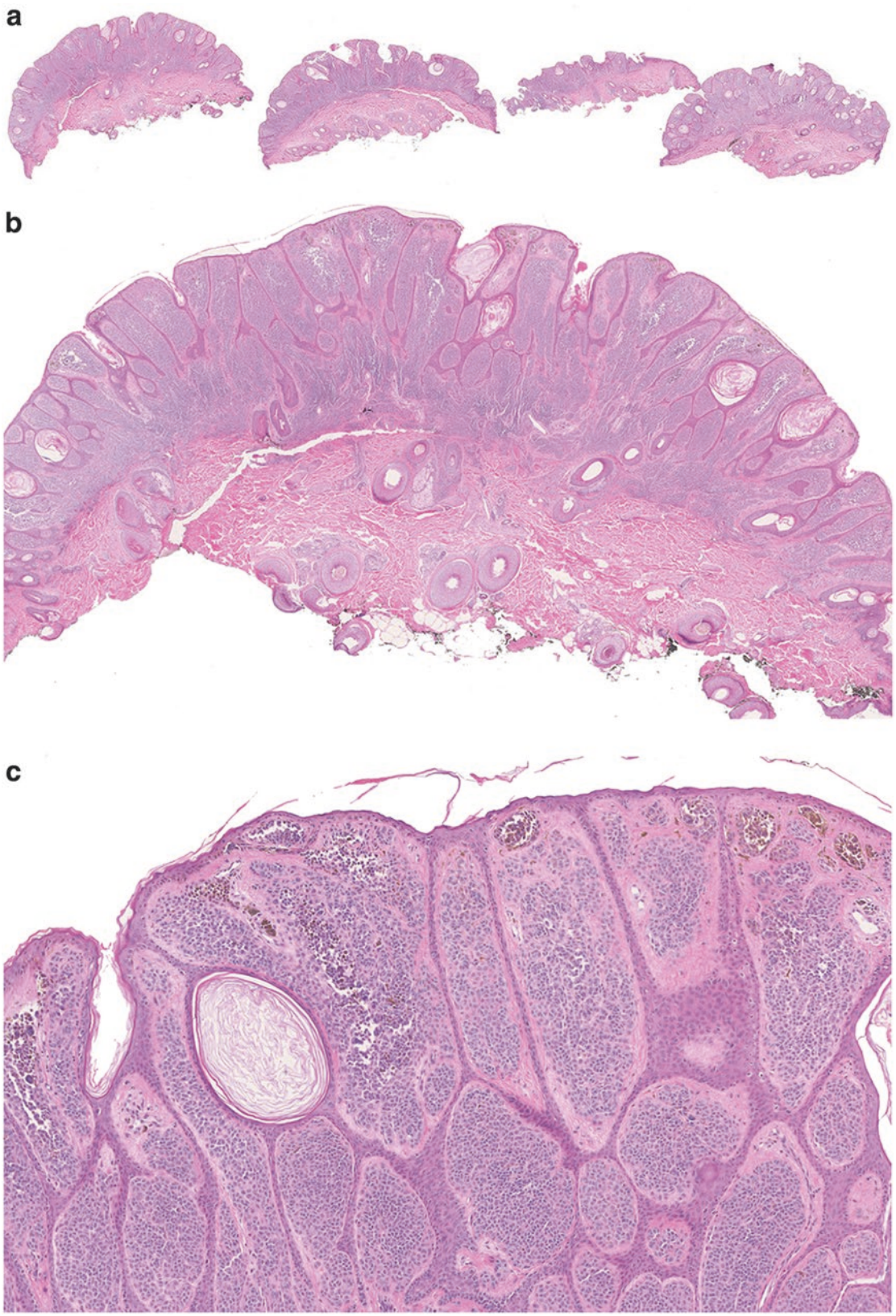


Fig. 6.7 This lesion is a congenital nevus from an 11-year-old male. The biopsy was taken from a nodular area in the nevus that was clinically concerning for the possibility of a melanoma arising in a nevus (**a**). Note the large nests of melanocytes that abut the epidermis; the latter shows marked hyperplasia (**b**). Note the expansion and distortion of papillary dermis with the very prominent elongation of the epidermal rete ridges. The melanocytes show small size, only focally present in the epidermis (**c**)

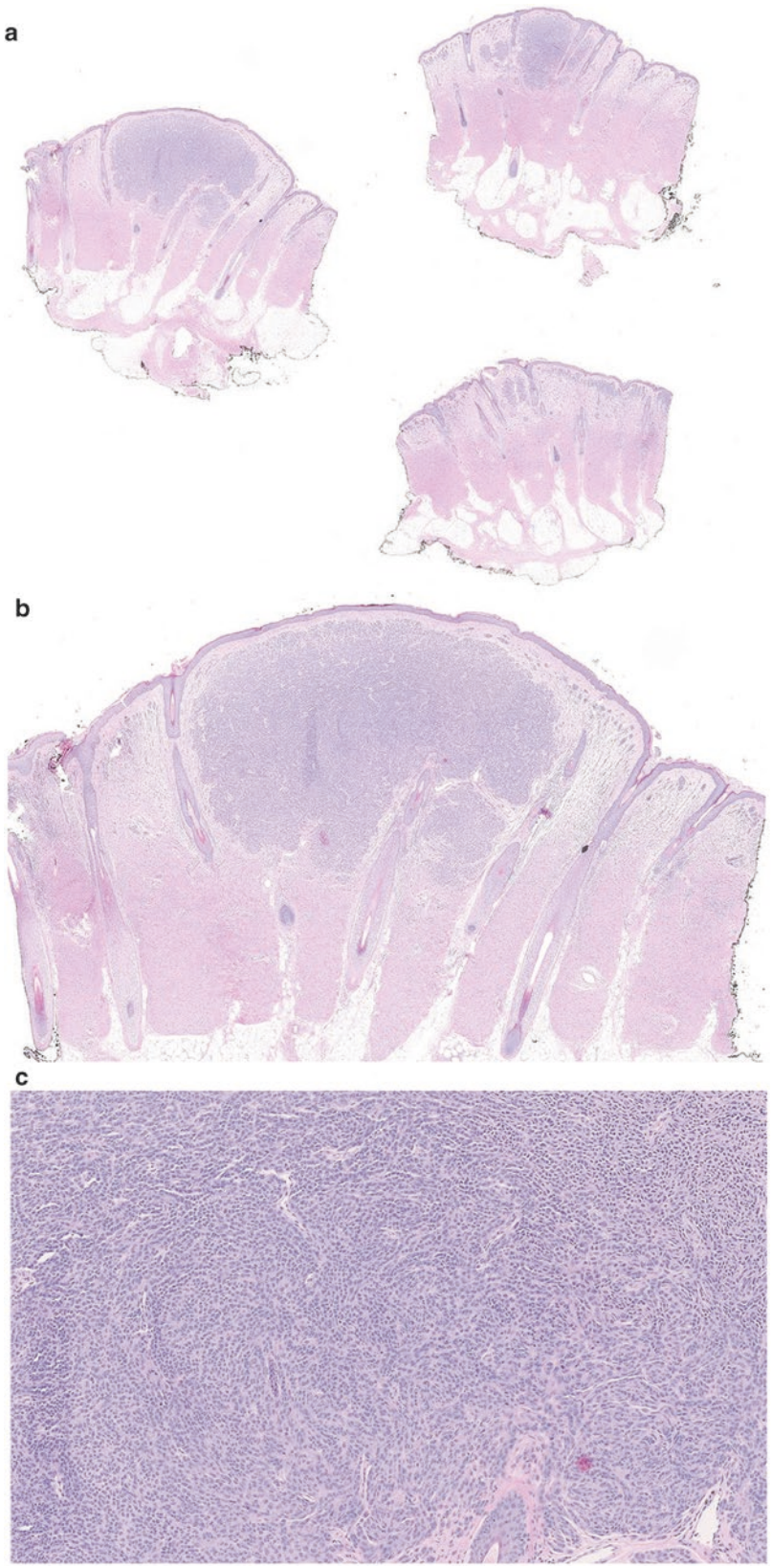


Fig. 6.8 Proliferative nodule in a congenital nevus. A 7-year-old girl with a congenital nevus that clinically had changed recently. The lesion shows a central nodule (**a**). The nodule in dermis is discrete and symmetrical (**b**). Note the monotonous appearance of melanocytes (**c**).

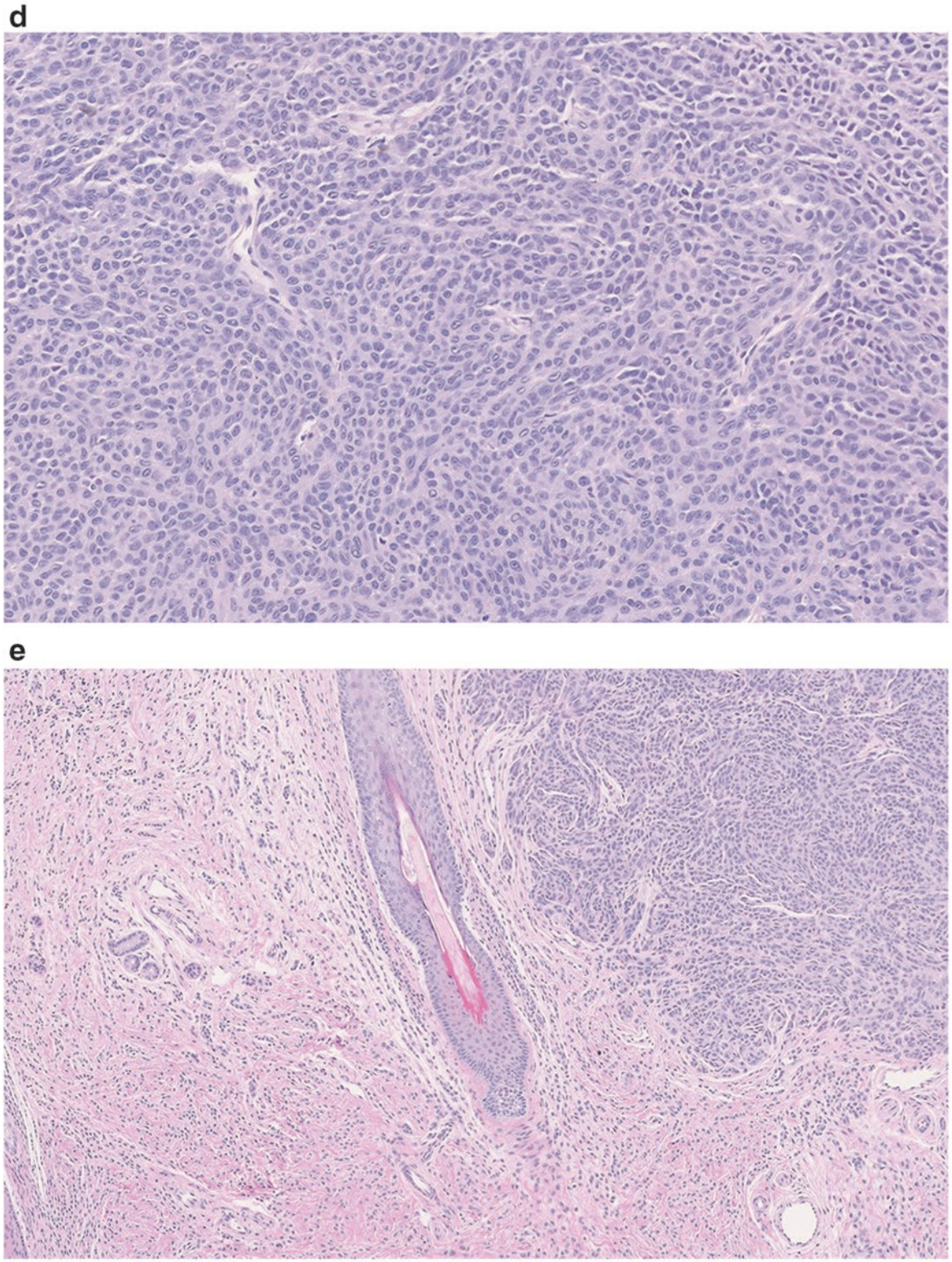


Fig. 6.8 (continued) Higher magnification of monomorphous melanocytes with round nuclei and evenly distributed chromatin (**d**). Note that melanocytes in the proliferative nodule merge and blend with the surrounding melanocytes rather than having an expansile pattern replacing the nevus component (**e**)

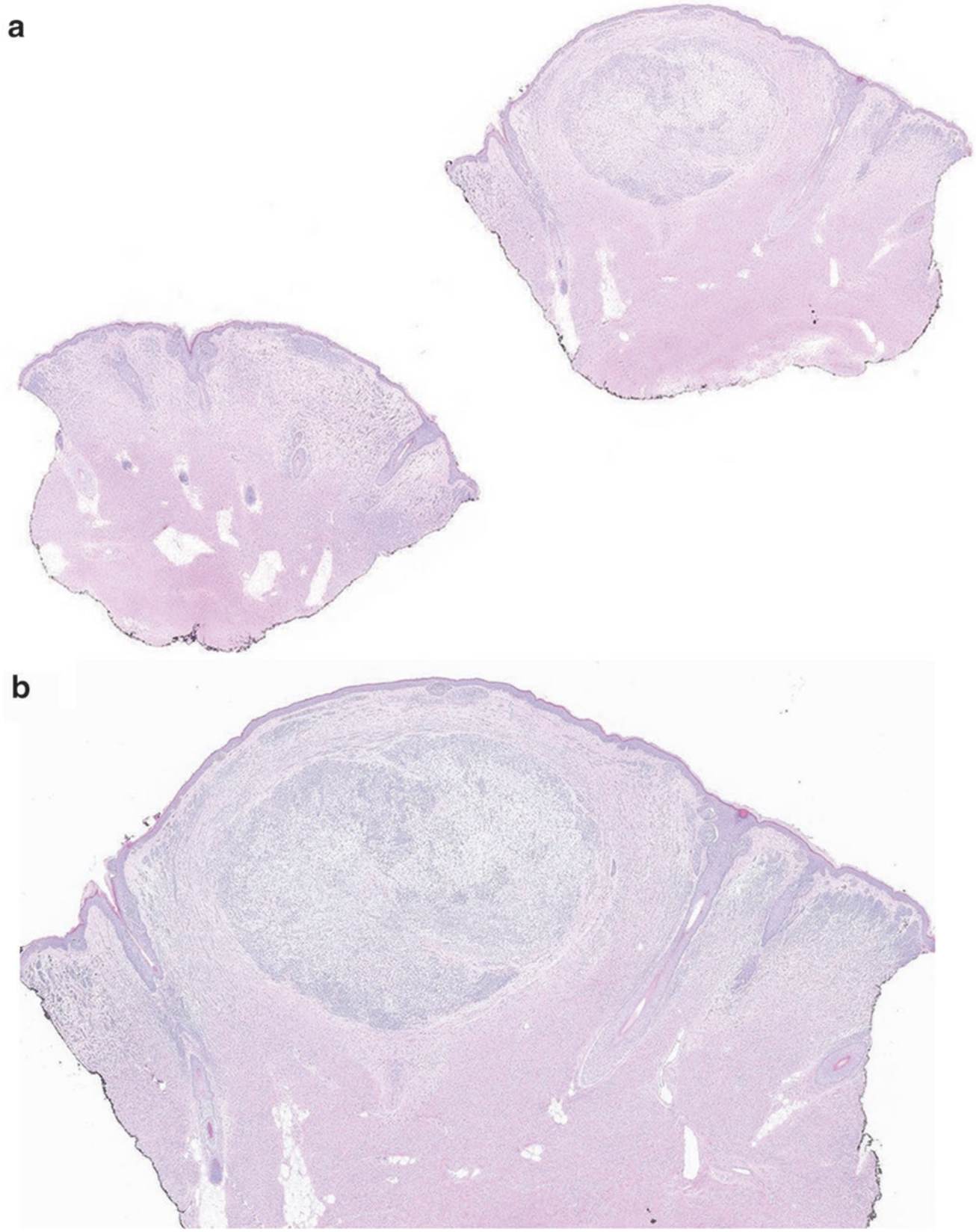


Fig. 6.9 Proliferative nodule. On low magnification, there is a nodule in the dermis arising in the background of a congenital nevus (**a**). The lesion is hypercellular and the lesion blends with the surrounding nevus (**b**).

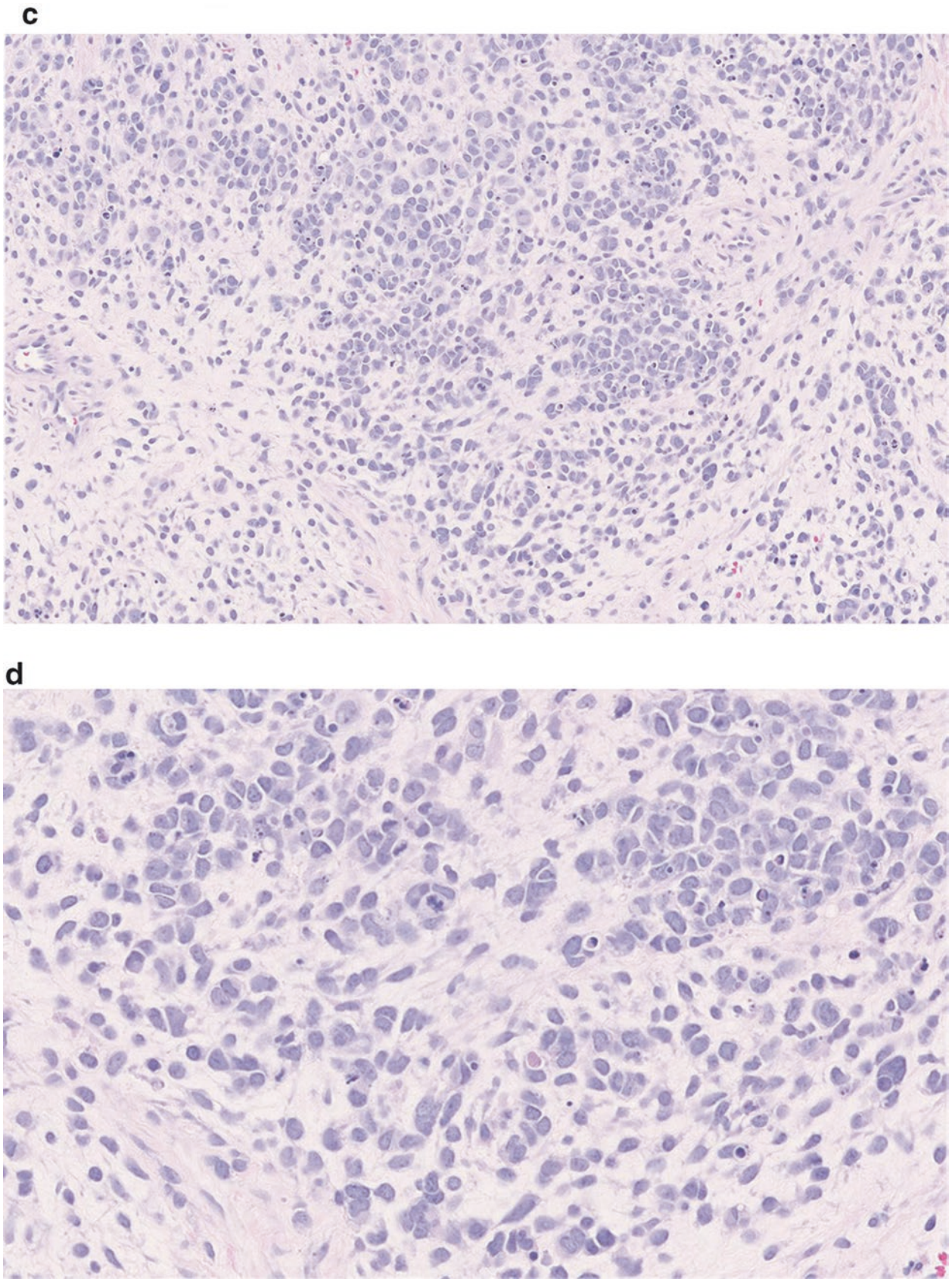


Fig. 6.9 (continued) Higher magnification shows focal melanocytes with atypical, pleomorphic nuclei, prominent nucleoli, and scattered mitotic figures (**c**). Note the occasional mitotic figures within the nodule (**d**)

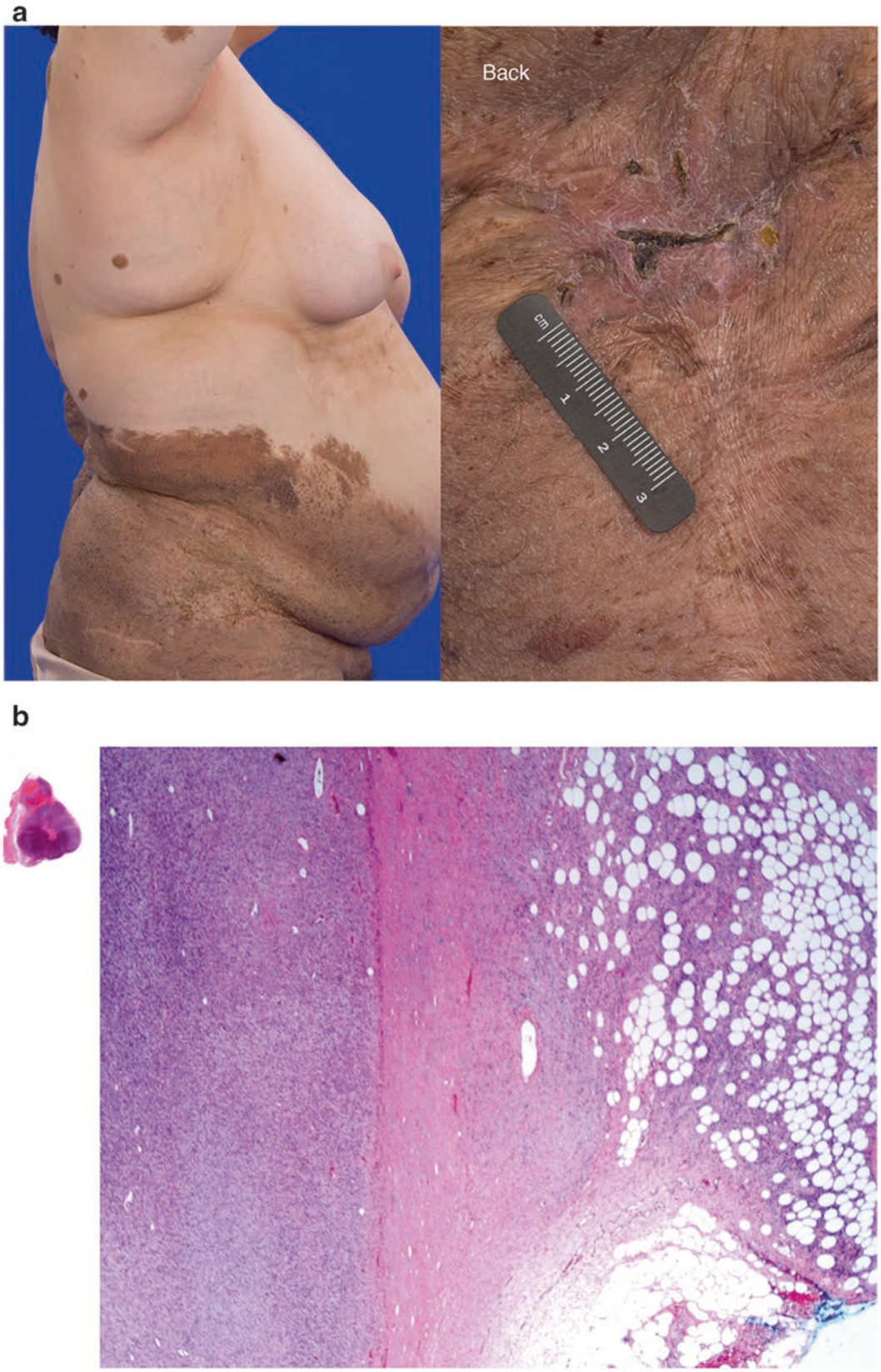


Fig. 6.10 Melanoma arising in a congenital nevus. A 44-year-old woman with a giant nevus. Nodule on the back with a biopsy in a recently detected growing nodule (**a**). Section of the large, expansile nodule. Notice the hypercellularity to the left (melanoma), clearly demarcated from the small cells admixed with the subcutaneous tissue corresponding to the congenital nevus (**b**).

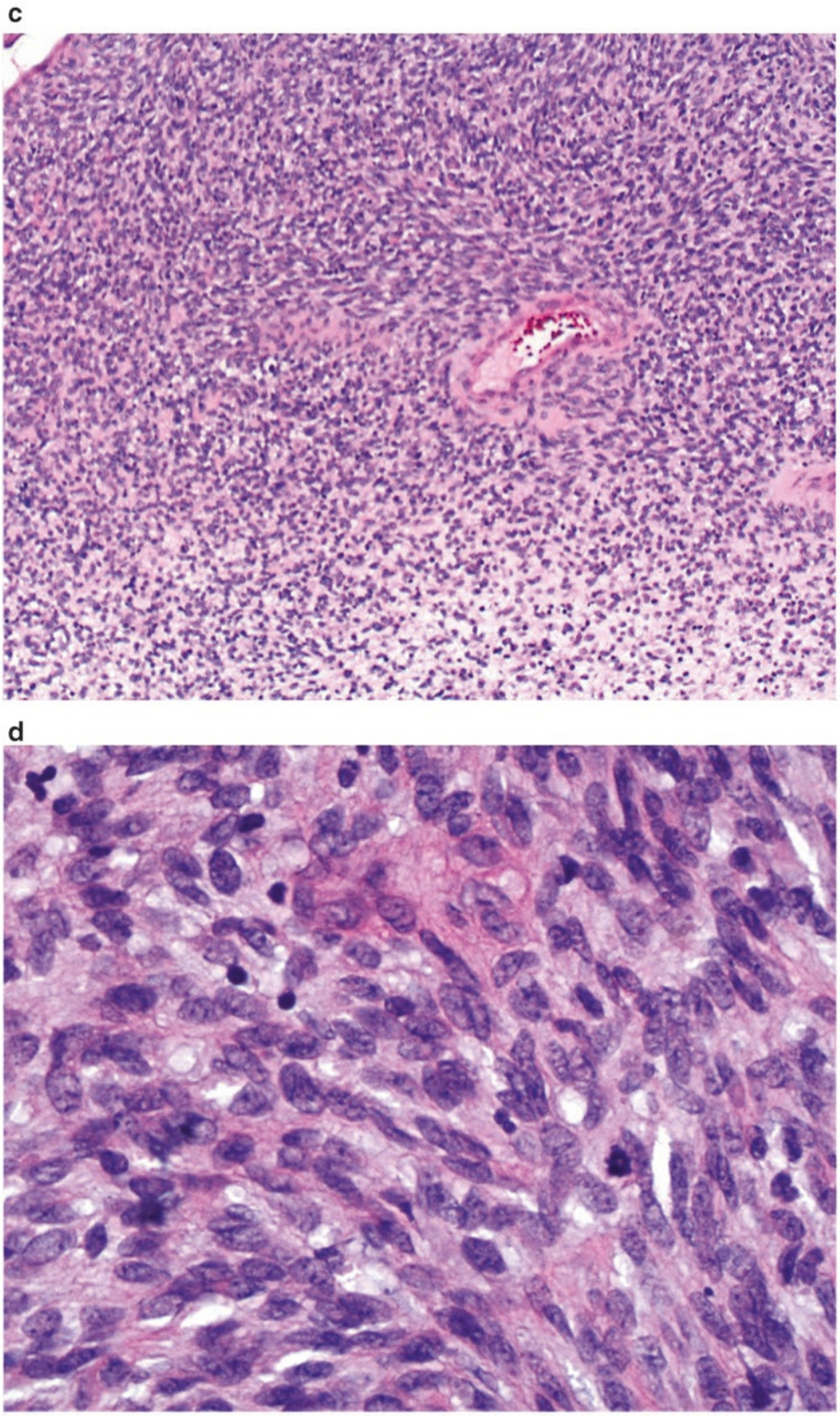


Fig. 6.10 (continued) Melanoma. Hypercellular area with minimal intervening stroma. Slightly dilated vessels with prominent endothelial cells; this finding is relatively commonly seen in high-grade, malignant neural and glial neoplasms (**c**). Pleomorphic cells, with hyperchromatic nuclei and numerous mitotic figures (**d**).

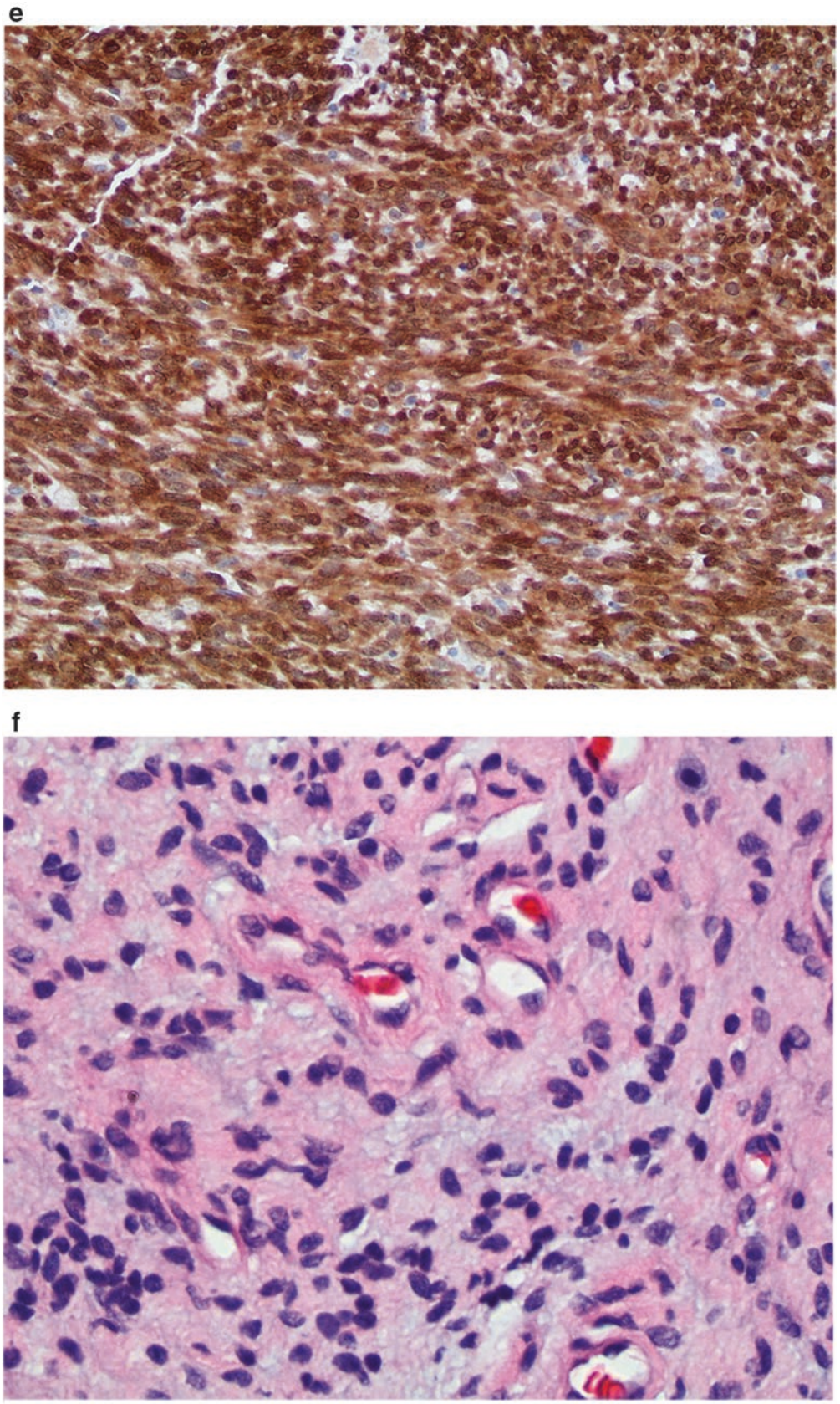


Fig. 6.10 (continued) Strong expression of S100 by most tumor cells (**e**). Congenital nevus located in an area adjacent to the hypercellular nodule. Small cells with delicate, fibromyxoid stroma (**f**)

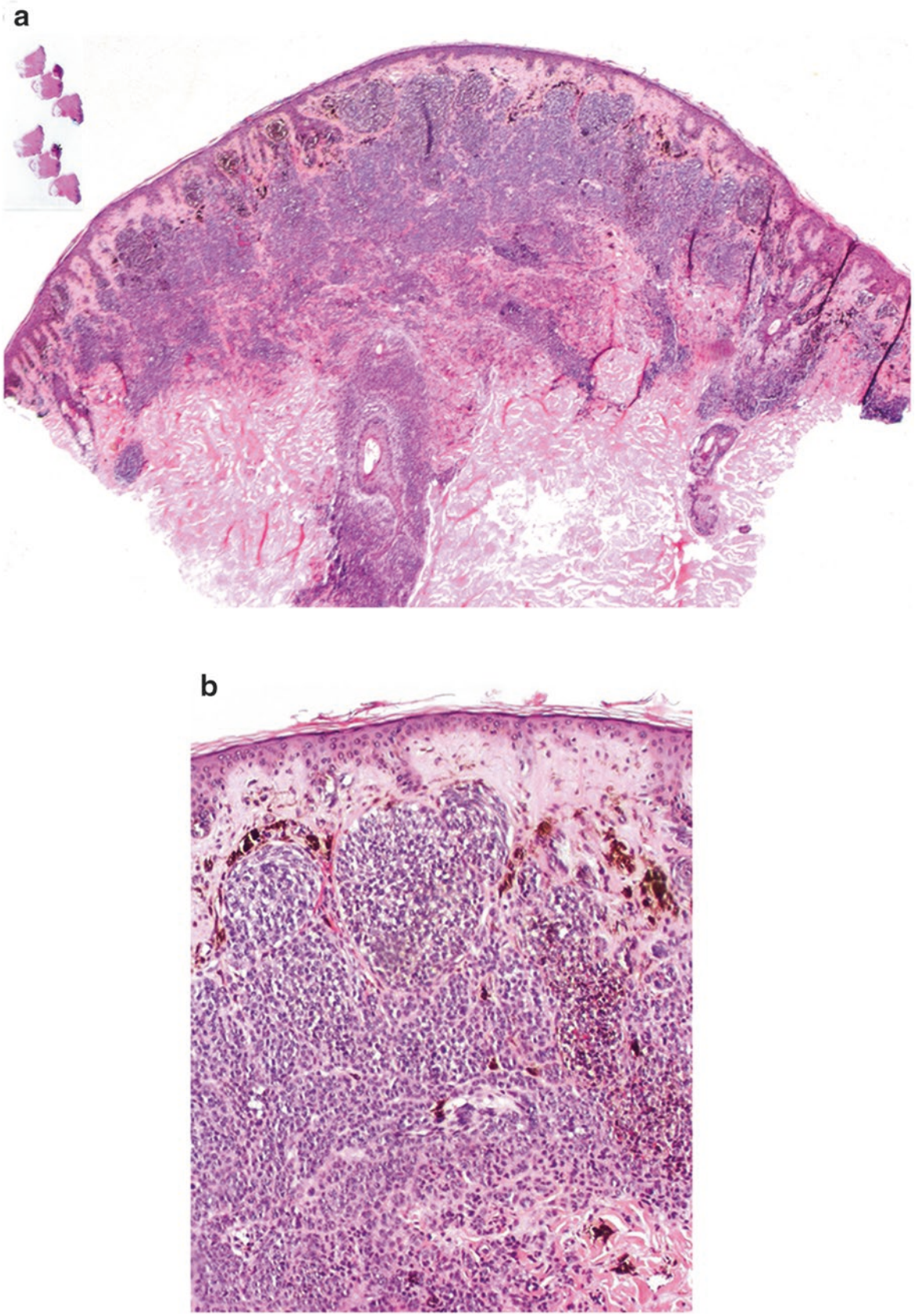


Fig. 6.11 Melanoma arising in a congenital nevus. Large lesion on the trunk with recent change (**a**). Superficial portion of the lesion with large nests of epithelioid melanocytes and abundant melanin pigment. There is no obvious junctional component (**b**).

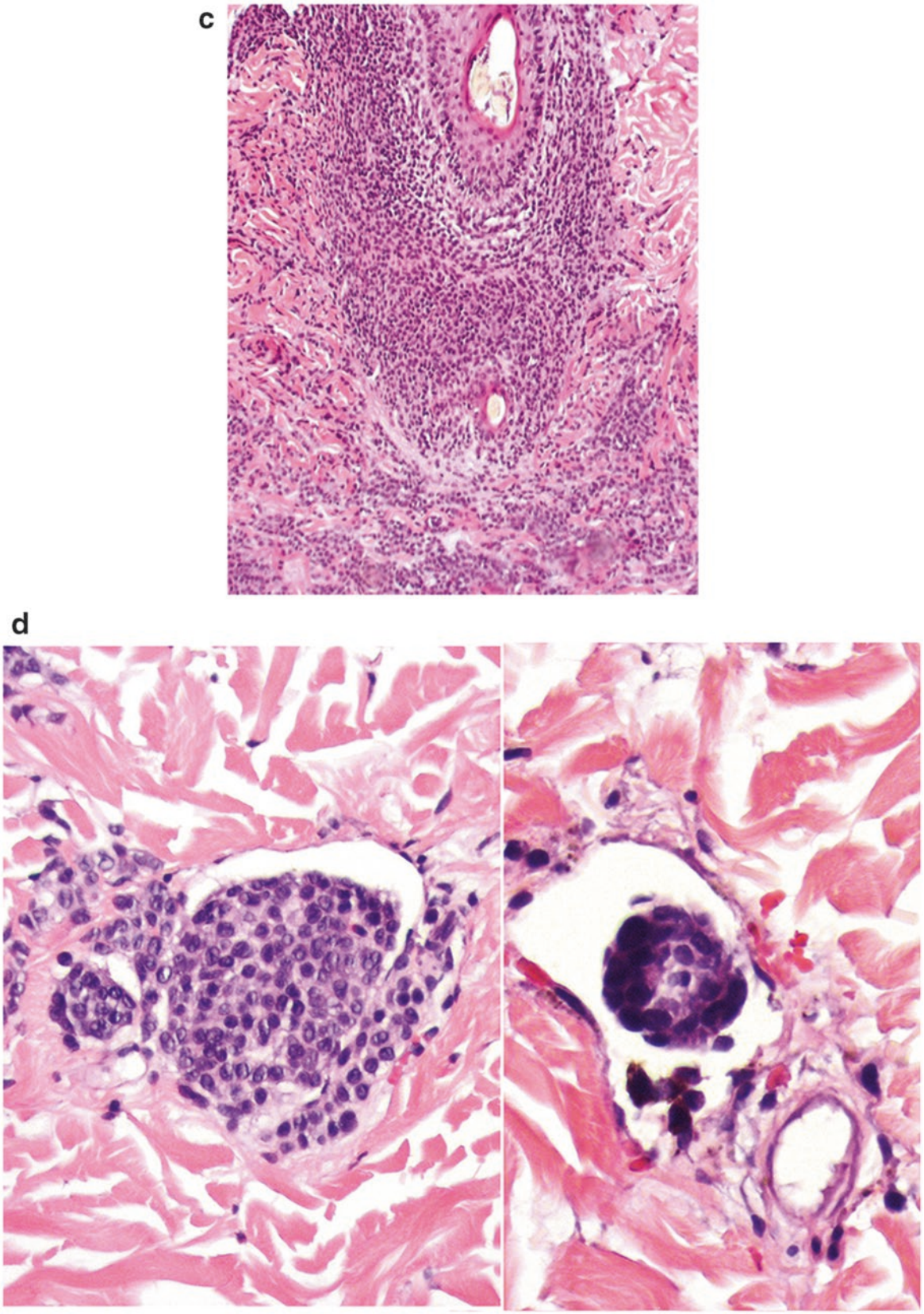
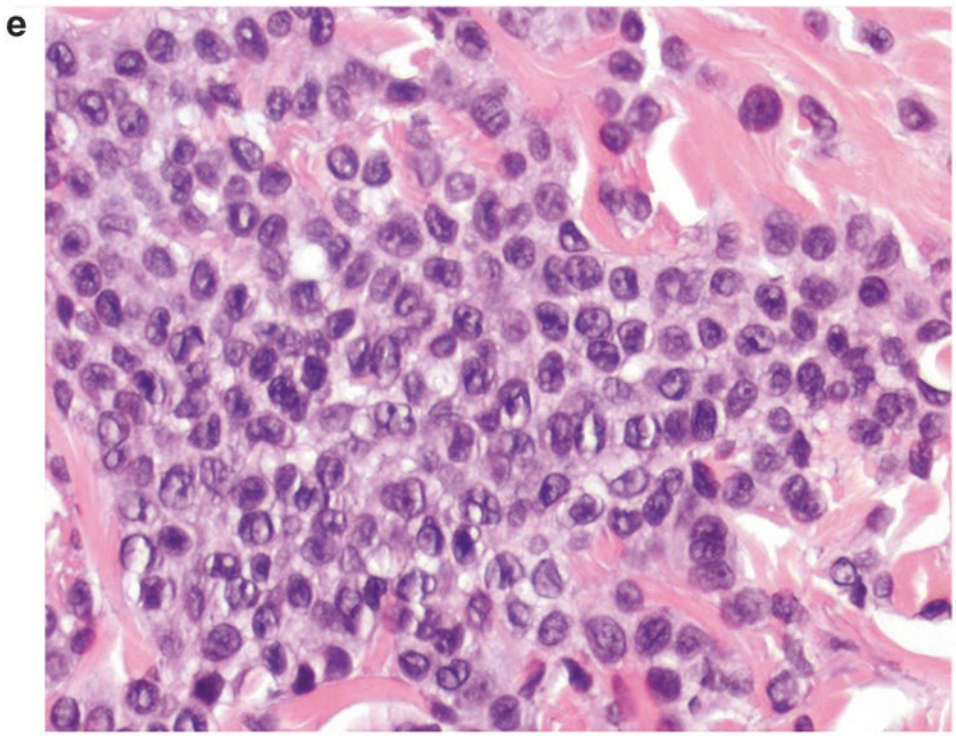


Fig. 6.11 (continued) Characteristic perifollicular arrangement (**c**). Presence of benign melanocytes within a vascular space, likely source of capsular nevus (benign, intranodal melanocytes) (**d**).



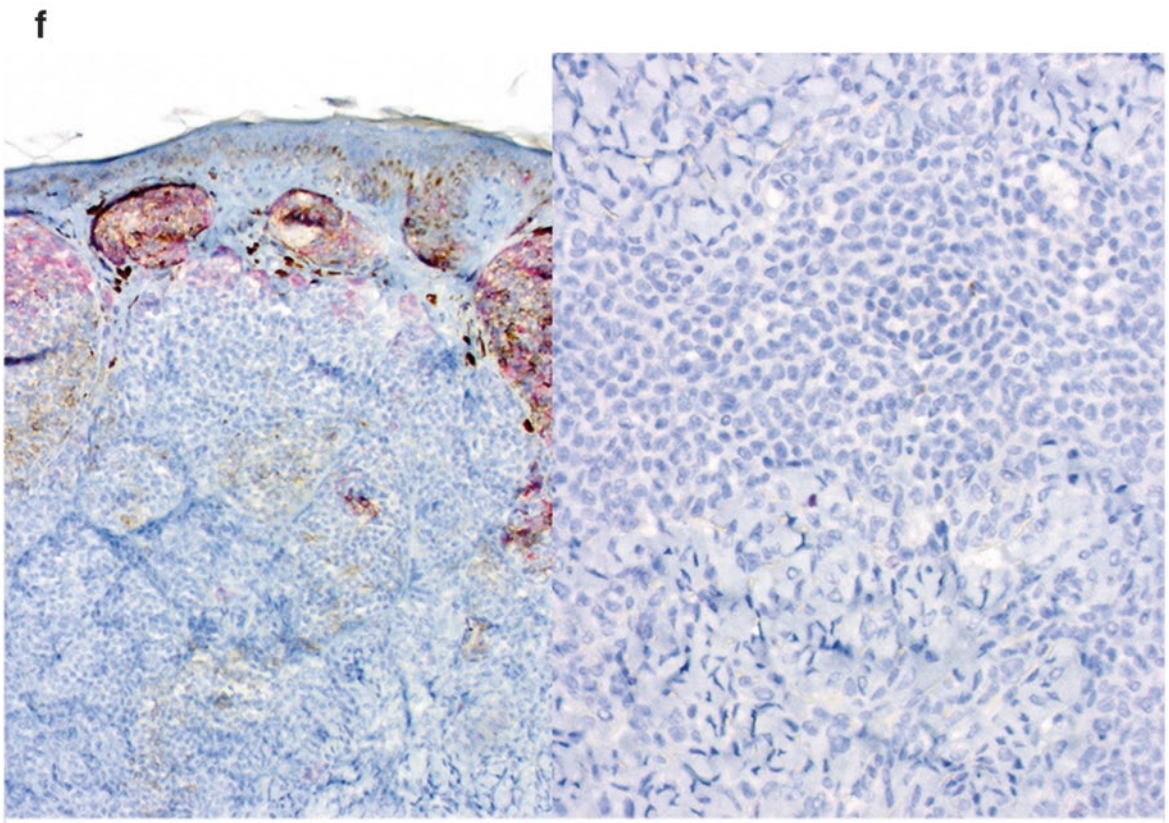


Fig. 6.11 (continued) High-powered view of uniformly shaped melanocytes with small nucleoli. Mitotic figures are not evident (**e**). Maturation pattern with HMB45 (decreased intensity with depth) and Ki67 (no evident proliferation in the dermal melanocytes) (**f**)

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Melanoma

7

Introduction

Melanoma is a relatively common malignant neoplasm that arises from melanocytes and is most commonly cutaneous in origin; however, it can arise in the eye, mucosae, and internal organs [1, 2]. Melanoma is one of the most common forms of cancer in young adults and thus it represents a major public health problem. Overall, melanoma is the fifth most common cancer in men and the sixth in women in the United States. The incidence of cutaneous melanoma has increased dramatically in the last years and remains to be the leading cause of death in cutaneous malignancies [3–6]. The Surveillance, Epidemiology, and End Results (SEER) Program reports an increase of more than 600 % in the diagnosis of cutaneous melanoma from 1950s to 2000s [7], with an average increase of 2.9 % each year between 1985 and 2009. Overall, the lifetime risk for developing melanoma in patients born in 2012 is 2.62 for men and 1.63 for women (SEER data). The increased incidence varies by age, gender, ethnicity, and histologic subtype. Before the age of 40, the incidence is higher in women, with most melanomas located on the lower extremities and exhibiting the superficial spreading histology. After the age of 40, the incidence is much higher in men, with most melanomas presenting on the head and neck and back. Also, incidence increases are most pronounced in white populations, particularly elderly individuals, whereas the incidence among darkly pigmented populations has risen only slightly or remained stable. The incidence of melanoma in children is increasing [8–10], which can be associated with risk factor such as xeroderma pigmentosum, familial dysplastic nevus syndrome or familial melanoma, and possibly immunosuppression.

Interestingly, there appears to be discordance between incidence and mortality trends in melanoma. While mortality rates increased slightly in the United States and Europe during the 1970s and 1980s, a stabilization of mortality rates was observed in most countries during the 1990s and 2000s. This difference in incidence and mortality trends may be due to the fact that more patients present at an earlier stage with smaller lesions that are potentially curable although it is also possible that changes in histologic criteria may have resulted in overdiagnosis of melanoma [11–16]. While these factors likely play some role, they certainly cannot explain entirely the observed incidence rise in patients presenting with advanced tumors suggesting a true increase in melanoma incidence [17, 18].

Risk Factors

Understanding the risk factors for the development of melanoma is important. Individual risk assessment influences clinical decision-making including the threshold for performing a biopsy, prevention counseling, and surveillance. The etiology of melanoma is multifactorial including demographic, environmental, and genetic risks. However, the majority of melanomas are likely related to ultraviolet radiation, since UV-related mutations are relatively common in melanoma [19].

Demographic Risk Factors: Age is a well-known risk factor for the development of melanoma as its incidence increases with age [20]. Although the median age of melanoma patients is about 50 years, it occurs in a wide age distribution [21]. The incidence is greatest in older patients, but it is also one of the most common cancers in young adults and adolescents. When compared to other cancers, due to the relatively young median age of melanoma patients, melanoma ranks among the worst in terms of lost productive years. The risk for melanoma is greatest in ethnic groups with lighter skin types, with the majority of melanomas in the United States diagnosed in non-Hispanic, white patients. On the other hand, in the United States, African Americans and Hispanics present with higher-stage melanomas and have a worse 5-year survival compared to white populations. The lifetime

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risk for melanoma is higher in men than in women, but it is also affected by sex. Before age 40, incidence rates are higher in women than in men; after age 40 years, rates are almost twice as high in men as in women.

A personal history of melanoma confers an increased risk for developing an additional melanoma. Patients with a prior melanoma have an approximately 2–5 % chance of developing a subsequent melanoma. Regarding histologic subtypes, patients whose first melanoma is lentigo maligna melanoma or nodular melanoma have a higher risk of a subsequent primary melanoma, compared with superficial spreading melanoma. A personal history of squamous cell carcinoma or basal cell carcinoma triples or doubles (respectively) the risk of developing melanoma. The risk is slightly lower in patients with actinic keratosis.

Environmental Risk Factors: It is well accepted that exposure to ultraviolet (UV) radiation is a major risk factor, especially among those with fair skin who are more susceptible to sunburns. As such, individuals who are most susceptible to the effects of excessive sunlight (e.g., blond or red haired, blue eyed, or with fair complexions) that tan poorly and tend toward sunburn have an increased risk of melanoma [22, 23]. While UVB has been regarded as the causative agent, UVA radiation is also carcinogenic and can induce melanoma [24, 25]. There is an increased incidence of melanoma in people that live close to the equator or at high altitudes and, in general, in persons who report increased exposure to UV radiation. The risk from UV radiation varies according to intensity, frequency, and age at the time of exposure. Intermittent and intense UV radiation exposure and sunburns are risk factors. Studies have shown UV radiation exposure during childhood is particularly associated with increased risk; however, sunburns occurring during any period of life also increase the risk of melanoma. The most common anatomic location of melanoma for men is the back and in women the legs, finding that has been suggested to be due to intermittent and intense UV radiation in each sex. Exposure to artificial UV radiation also increases melanoma risk, particularly tanning salons [26].

Presence of Nevi and/or Dysplastic Nevi: Large numbers of standard nevi, of large size, and presence of dysplastic nevi are risk factors for melanoma [27]. The presence of >10 clinically dysplastic nevi confers a 12-fold increased risk. Also increased numbers of conventional nevi and nevi greater than 6 mm in diameter are independent risk factors for the development of melanoma [27–30]. However, although the presence of non-dysplastic and dysplastic nevi predicts an increased risk for melanoma, only a small percentage of nevi progress to melanoma; approximately 25 % of melanomas arise in association with a melanocytic nevus [31]. Some authors have observed that younger age, superficial spreading histologic subtype, and trunk location are predictors of a melanoma being histologically associated with a melanocytic nevus [31].

Family History: A prior family history of melanoma increases the risk for acquiring melanoma. The risk of developing melanoma is 2.62 times higher when a parent has had melanoma and is 2.94 times higher if the melanoma was in a sibling. Overall, about 8 % of people newly diagnosed with melanoma have a first-degree relative with melanoma, and about 1–2 % has two or more close relatives with melanoma. Fewer than 10 % of patients present with true familial or hereditary melanomas in which there is a strong family history or a documented melanoma-related, germline mutation. These families have autosomal dominant inherited susceptibility mutations and develop single or multiple melanomas at early age [32].

Several genetic loci determine susceptibility to melanoma, with the most important of these being CDK4 and p16/CDKN2A located on chromosome 9p21, both being high-risk genes [33]. Both CDNKN2A and CDK4 are highly penetrant, susceptibility genes and result in the majority of familial melanomas. The CDKN2A gene encodes two proteins, p16 and p14 ARF, which are cell cycle inhibitors and are potent tumor suppressors. The CDKN2A mutation is present in up to 40 % of families with three or more cases of melanoma, whereas CDK4 mutations are present in far fewer families. The risk of developing melanoma in a patient who is a CDKN2A mutation carrier is between 30 % by age of 5 years and 67 % by age of 80 years. This risk varies by geographic location due to environmental factors, such as UV radiation, since the latter appears to play a significant role in susceptible families [34]. In addition, the same risk factors that influence the incidence of melanoma (such as increased number of nevi, sunburn, etc.) also increase the penetrance in CDKN2A mutation carriers. Melanoma-prone families with CDKN2A germline mutations have an increased risk of developing other neoplasms, primarily pancreatic cancer, with variable penetrance [33]. Germline CDK4 mutations in familial melanoma account for approximately 1 % of all familial melanomas [33]. While less frequent than CDKN2A mutations, CDK4 mutations carry an equally high risk for the development of melanoma and show a similar clinical phenotype [35]. In contrast to CDKN2A and CDK4, heritable mutations in the melanocortin-1 receptor (MC1R) gene have low penetrance [36]. MC1R mutation is commonly associated with a red hair phenotype, but it confers an increased risk of developing melanoma even in non-red-haired individuals. The risk of developing cutaneous melanoma lies between 1.5-fold and 3-fold for patients with MC1R variants, but when both alleles are mutated, it increases 17-fold for development of BRAF mutant melanomas. Some familial melanomas occur in the setting of dysplastic nevus syndrome. A family history of melanoma in multiple first-degree relatives and younger age at diagnosis are important features of this syndrome. Families who present with the dysplastic nevus syndrome may also have

CDKN2A mutations. Other heritable disorders that predispose patients to melanoma include xeroderma pigmentosum, Li-Fraumeni syndrome, BRCA2, or familial retinoblastoma.

Histologic Parameters Reported in Melanoma

Accurate and thorough histopathological diagnosis of melanocytic lesions is essential for the clinical management of the patients, since the reporting of these histopathologic parameters, especially in the initial biopsies, is a critical component of both diagnosis and staging [37]. Institutions and dermatopathologists have different styles and variables in regard to the routine reports of histologic parameters in invasive melanomas. Some of these reports have only minimal information (such as Breslow thickness), while others reports are quite comprehensive. The information in those detailed reports might not be of immediate relevance, but its importance might become apparent later, when analyzed in prospective or retrospective studies. As an example of this, mitotic activity count is now included as a histopathologic element in the AJCC melanoma staging and classification system [37]. In our practices, we provide a report that includes all the histologic parameters that have been proved to be significant for staging and prognosis, as well as additional histologic features that may potentially be helpful (see Table 7.1).

Cutaneous melanomas are classified into four histologic subtypes: superficial spreading, lentigo maligna, acral lentiginous, and nodular type. While technically speaking the histologic subtype classification does not seem to affect prognosis, its proper classification is important for other reasons. One benefit of histologic classification is to provide subtyping for epidemiologic studies. Also, there are emerging genetic studies that show distinctive patterns of chromosomal aberrations in melanomas arising on chronically sun-exposed skin versus melanomas arising in areas with intermittent sun exposure or acral/mucosal areas. These heterogeneous molecular changes in melanoma are of clinical relevance because they are likely to result in different targeted therapies; acral lentiginous and mucosal melanomas can harbor KIT gene mutations and can potentially respond to targeted therapies with tyrosine kinase inhibitors [38–40]. It is also important to recognize that desmoplastic melanomas have higher propensity for neurotropism with high local recurrence and that in cases of pure desmoplastic melanoma, there is a lower incidence of lymph node metastasis and with an outcome different from conventional melanomas [41].

Table 7.1 Synoptic report of melanoma

Malignant melanoma, invasive, type
Clark level
Breslow thickness, mm
Radial (non-tumorigenic) growth phase
Vertical (tumorigenic) growth phase
Mitotic figures/mm^2
Ulceration
Regression
Vascular invasion
Perineural invasion
Microscopic satellitosis
Tumor-infiltrating lymphocytes
Associated melanocytic nevus
Predominant cytology
Surgical margins

Breslow Thickness

Numerous prognostic models have been developed in an attempt to predict which patients ultimately will develop advanced disease [42–45]. Identification of patients at high risk for advanced melanoma can help physicians plan appropriate surgery and possible adjuvant therapy. Virtually all studies conducted on primary cutaneous melanomas that have analyzed prognostic factors have shown that the most significant prognostic variable is Breslow thickness [46], which measures the vertical thickness of melanoma. The revised American Joint Committee on Cancer (AJCC) staging criteria accurately predict sentinel lymph node positivity in clinically node-negative melanoma patients. When grouped by AJCC cutoff points, there was an increased incidence of positive sentinel lymph nodes with increasing tumor thickness: 4 % in melanomas smaller than 1.00 mm, 12 % in melanomas 1.01–2.00 mm, 28 % in melanomas 2.01–4.00 mm, and 44 % in melanomas exceeding 4.00 mm. However, the correlation between thickness and prognosis is not perfect; occasionally thin melanomas are capable to metastasize, and occasionally patients with thick melanomas have long survival periods.

The Breslow thickness is measured from the top of the epidermal granular layer to the deepest point of dermal invasion. It is important to mention, when present, the involvement of adnexal structures by melanoma in situ. Even though it should not be measured as part of the Breslow thickness, it may result in a positive deep margin by melanoma in situ. At our institutions, the areas of perineural invasion by melanoma are measured. If such measurement is larger than the thickness elsewhere in the tumor, we report the Breslow thickness as including the area of perineural invasion; note this situation in the diagnosis and also provide the thickness of the tumor *without* including the area of perineural invasion. On the other hand, Breslow thickness should not include areas of vascular invasion or satellitosis. In cases in

which there is ulceration, the measurement should be made from the base of the ulcer to the deepest point of invasion. In some cases there is extensive follicular involvement by melanoma and the invasive component is identified only by surrounding those structures; in such cases, the thickness of melanoma should be measured from the central portion of the follicular structure to the adjacent invasive component.

Clark Level

Dr. Clark in 1969 introduced a histopathologic classification of melanoma based on the level of invasion, demonstrating that the level of invasion was closely related to survival. The anatomic levels of melanoma invasion proposed were level I (melanoma in situ), level II (invasion into superficial papillary dermis), level III (invasive melanoma that fills and expands the papillary dermis), level IV (invasion "well" into the reticular dermis), and level V (infiltration into subcutaneous adipose tissue). After this, many studies have compared Breslow thickness and Clark level by multivariate analysis, and the results have shown that Breslow thickness retains a high level of prognostic significance, whereas Clark level does not [44, 47–49]. These results led to the elimination of Clark level from the melanoma staging protocol of the American Joint Committee on Cancer (AJCC) as a stand-alone criterion. In the current classification, Clark level is considered in those stage 1 cases (thinner than 1 mm in Breslow thickness) in which mitotic counts are not available [37].

Radial and Vertical Growth Phase

Most melanomas evolve through a stepwise process of tumor progression that results in histologic changes associated with prognostic information [50–53]. Tumor progression is considered to be the result of sequential acquisition of genetic abnormalities and modulated by host factors in the microenvironment. The histologic criteria of radial and vertical growth phases were first developed by Dr. Clark based on the concept of staged tumor progression and correlation between the histologic features and the survival rate [54]. Melanomas that are diagnosed in the early stage of tumor progression present clinically as patches or plaques and have thus been termed radial growth phase melanomas. Histologically, the radial growth phase is defined as a lesion in which neoplastic melanocytes are mostly present in the epidermis "melanoma in situ" but may be present in the superficial papillary dermis. Such superficially located melanoma cells usually lack the capacity for proliferation in the dermis, i.e., they are not mitotically active and they do not form tumor nests. These non-tumorigenic invasive melanomas typically have the capacity for local persistence and regrowth if not completely excised, and they also have the capacity for progression. At this stage melanoma lesions do not have the capacity for metastasis. In the vertical growth phase (tumorigenic phase), the neoplastic melanocytes have acquired capacity for proliferation in the dermis (which typically occurs vertically, separating from the epidermis, and has therefore been termed the vertical growth phase). Histologically, vertical growth phase is defined as presence of dermal nests that are larger than any nest in the junctional component or when mitotic figures can be identified within the dermal melanocytes. One study showed that the metastatic potential of a melanoma highly correlates with the presence of vertical growth phase [55].

Mitotic Figures

Tumor mitotic rate was recently introduced as a major criterion for melanoma staging and prognosis. Detailed analysis of the AJCC Melanoma Staging Database showed a significant inverse correlation between primary tumor mitotic rate and survival as an independent predictor of survival (as the number of mitoses/mm^2 increases, melanoma survival decreases) [37, 56]. Studies have shown that mitotic rate is the second most powerful predictor of survival outcome after tumor thickness in patients with localized melanoma and fourth after the number of positive lymph nodes, age, and tumor ulceration in patients with regional node micrometastases [37, 57]. Due to these, primary melanoma mitotic rate was incorporated into the seventh edition of the AJCC Cancer Staging Manual as a required element for melanoma staging in T1 patients (Breslow thickness smaller than 1 mm). As such, the mitotic rate replaced the level of invasion (Clark) in defining T1 categories (see above). Either ulceration or presence of any mitotic figure per square millimeter in the dermis is used as a primary criterion for defining T1b-stage melanoma. The upcoming 8th edition of the AJCC will modify the pT1 classification to pT1a (<0.80 mm, no ulceration), pT1b (ulceration or 0.8–1.0 mm).

Although there is no universally accepted method for counting mitotic figures in melanoma, the seventh edition of the AJCC Cancer Staging Manual recommends employing the so-called hot spot, to count them in the tumoral areas in the dermis containing the most mitotic figures. In other fields of pathology, the reported mitotic rate is expressed as the number per 10 high-power fields, but since different microscopes have different field sizes, newer protocols recommend reporting the mitotic count per 1 mm^2. After detecting the area with the most dermal mitotic figures, with the ×40 lens or at ×400 magnification, the count is then extended to adjacent contiguous fields until examining an area corresponding to 1 mm^2 (usually about 4 1/2 high-power fields). If mitotic figures are sparse and randomly scattered throughout the lesion, any mitotic figure is chosen, the field containing it becomes the first field, and then additional contiguous fields are counted to achieve the equivalent of 1 mm^2.

Ulceration

The presence of ulceration should be evaluated in every primary cutaneous melanoma. Ulceration is characterized by full-thickness, epidermal defect, evidence of fibrin deposition and neutrophils, and thinning, effacement, or reactive hyperplasia of the surrounding epidermis in the absence of trauma or a recent surgical procedure. Ulceration is an independent prognostic factor for melanoma-associated survival. Survival rates of patients with an ulcerated melanoma are lower than those of patients with a non-ulcerated melanoma of similar thickness [37]. It has been reported that extent of ulceration provides more accurate prognostic information than the mere presence of ulceration [58]. Due to its preeminence in the AJCC staging classification, it is very important to recognize the difference between tumor-related ulceration and ulceration secondary to trauma or recent surgery. Clinical correlation may be required to determine the cause of ulceration [59].

Regression

Regression is the replacement of melanoma cells by fibrosis, melanophages, lymphocytic infiltrate, and telangiectases with or without residual intraepidermal component. The regression changes can range from focal to extensive. The correlation of regression with prognosis is controversial. One possibility for this controversy is that among different studies, there is lack of consensus on the exact definition and measurement of regression. Some studies have defined regression as complete absence of melanoma cells, whereas others have included areas of partial regression and the active phase of host cell interaction with tumor tissue in their measurements of regression. Some studies have reported that the presence of regression indicates a worse prognosis especially in thin melanomas [60–62]. One study analyzed thin melanomas with evidence of regression and demonstrated only one melanoma that metastasized [63]. Another study analyzed a large number of stage I melanomas and although almost half of melanomas 0.75 mm or smaller had regression compared with only 12 % of melanomas exceeding 3 mm, there was no significant difference between mean disease-free survivals. Furthermore, metastases developed in 19.4 % of patients with regressing tumors compared with 29.85 % of patients with non-regressing tumors [64]. At our institutions, we define the presence of extensive regression in cases in which there is regression in more than 50 % of the invasive component. In contrast, the CAP classification uses 75 % as the cutoff between focal and extensive; therefore, our reports include both cutoffs for the evaluation of regression.

Lymphovascular Invasion

Vascular invasion is identified by the histopathological demonstration of melanoma cells within the lumina of blood vessels and/or lymphatics and is generally regarded as a marker of poor prognosis. It is considered a major prerequisite for metastatic spread. Several reports have shown that vascular invasion significantly increased the risk of relapse, lymph node involvement, distant metastases, and death, and its impact on melanoma outcomes was similar to that of ulceration [65–67]. One study analyzed 476 patients with melanoma and found a 5-year survival rate of 27.3 % in patients with vascular invasion versus 76.1 % in those without vascular invasion [68]. Another study analyzed patients with nodular melanoma, of which 15 % had vascular invasion. Vascular invasion was present in more than half of the patients who had lymph node metastases at the time of diagnosis compared with 12 % of the patients without nodal involvement and, similarly, in 75 % of the patients with distant metastases compared with 12 % of the patients without metastatic dissemination. Survival at 5 years in the patients with vascular invasion was 38 % versus 68 % for those without vessel involvement [69]. However, some studies have shown that vascular invasion does not represent an independent factor in predicting prognosis [67, 70–72]. Regarding histologic assessment of vascular invasion, there are potential artifacts such as tissue shrinkage that can result in the false appearance of a vascular space. Thus some studies have evaluated the detection of lymphovascular invasion by IHC and tried to correlate it with metastasis or survival. One study showed that IHC can reliably identify lymphatic vessel distribution and can detect melanoma cells within lymphatic vessels, but it was highly unreliable in predicting melanoma metastasis, since it failed to detect metastatic spread in more than two thirds of patients with regional node metastasis [73]. On the other hand, one study showed that lymphovascular invasion detected by IHC with D2-40 (podoplanin) in melanomas thicker than 1 mm correlated with sentinel lymph node status and survival [71]. Evaluation of vascular invasion is currently being considered for possible inclusion in the AJCC classification.

Perineural Invasion

Perineural invasion is defined as melanoma infiltration of nerve fibers with subsequent extension of the tumor along the surrounding nerves. At our institutions, we record the presence of perineural infiltration in our reports. The inclusion of this piece of information is very important as some types of melanomas, such as desmoplastic, spindle cell, and acral lentiginous, have a high propensity for perineural inva-

sion. In addition, some studies have shown that neurotropism appears to worsen melanoma prognosis. One study analyzed 190 patients with desmoplastic melanoma and 90 patients with desmoplastic neurotropic melanoma. The 5- and 10-year overall survival rates for all desmoplastic melanoma and desmoplastic neurotropic melanoma patients were 75.2 % and 52 %, respectively [74]; thus, neurotropism appears to be a poor prognostic factor. However, since a strict histologic definition of desmoplastic is not universally accepted, it is possible that some of those neurotropic melanomas were actually only "mixed" and not "pure" desmoplastic lesions. Although metastases are less frequent with neurotropic melanomas, they do have high local recurrence rates, which likely derive from their deep infiltration and extension along nerve sheaths [75, 76].

Microscopic Satellitosis

Microsatellites are defined in the current CAP recommendations as microscopic and discontinuous cutaneous and/or subcutaneous metastases having a diameter larger or equal to 0.05 mm in largest dimension, adjacent to a primary melanoma [77]. At our institutions we use a slightly different definition, i.e., clusters of tumor cells separated from the main invasive component by normal dermal collagen or subcutaneous fat. The presence of microsatellites increases from 4.6 % in tumors less than 1.5 mm to 65 % in those greater than 4 mm [77, 78]. Only few studies have evaluated the role of microsatellites as a prognostic factor in cutaneous melanoma. Although it is difficult to predict whether their presence represents an independent prognostic factor, satellites in tumors thicker than 1.5 mm do appear to correlate with a higher risk of local recurrence and with an increased frequency of regional lymph node metastasis [78]. Microsatellites are also associated with an increased frequency of regional lymph node metastasis in tumors greater than 1.5 mm.

Tumor-Infiltrating Lymphocytes

Tumor infiltrating lymphocytes (TILs) are believed to represent the degree of immune response to melanoma cells. They are measured by assessing the extent of lymphocytic infiltrate surrounding the invasive dermal component of melanoma, categorized as brisk, non-brisk, or absent (minimal). The role of TILs as prognostic factors has been suggested by several reports, although with conflicting data [79–81]. These differences may be due to different reasons such as the difficulty to grade a TILs infiltrate using the brisk and non-brisk categories that studies may be underpowered to demonstrate that TILs are an independent prognostic factor or that there is still scarce information regarding the immunology and pathobiology of TILs. The presence of a brisk inflammatory infiltrate has been reported to correlate with improved survival; however, this is observer dependent, mainly owing to the lack of a uniform definition of host response in terms of type and location of the infiltrate. Studies have shown 5- and 10-year survival rates for melanomas with a brisk infiltrate of 77 % and 55 %, respectively, compared to 53 % and 45 % for tumors with a non-brisk infiltrate and 37 % and 27 % for those with absent TILs [82].

Subtypes of Melanoma

The initial classification of primary cutaneous melanoma was based on observations and descriptions of the clinical and histopathological features, which was first described over four decades ago [54, 83]. Lately, there have been some minor changes to the classification scheme, but the basic findings as described over 40 years form the foundation for the currently recognized subtypes of cutaneous melanoma [53, 84]. These authors started by describing the clinical appearance of the lesion, the anatomic site, the presence or absence of sun damage, and the patient's demographics. All these features were considered alongside the histologic features of the tumors, including intraepidermal and dermal patterns of growth, cytology, epidermal changes, the presence of solar elastosis, the anatomic level of invasion into the dermis, the maximal tumor thickness, vascular invasion, mitotic activity, and the pattern and density of lymphocytic host response. Using these variables, the authors recognized four major subtypes: superficial spreading, lentigo maligna, nodular, and acral lentiginous melanoma.

Lentigo Maligna

Clinical Features

Lentigo maligna was first described by Sir John Hutchinson in 1892 as a "senile freckle." The Hutchinson melanotic freckle was originally thought to be infectious because of its slow, yet progressive, growth. Some authors refer to it as lentigo maligna when it is confined to the epidermis and lentigo maligna melanoma when it invades into the dermis, but in our opinion, there is no need to distinguish in situ and invasive melanoma with two different names. Lentigo maligna originates on chronically sun-exposed skin, particularly the head and neck although less common sites include the arm, leg, and trunk, in general after chronic exposure to ultraviolet light. Patients with lentigo maligna tend to be older than those with superficial spreading or nodular melanoma. Usually, patients with lentigo maligna are older than

40 years, with a mean age of 65 years and the peak incidence occurs in the seventh to eighth decades of life. The majority of patients with lentigo maligna present with a slowly enlarging, pigmented macule that may remain stable or enlarge slowly or rapidly. Lentigo maligna can be present for long periods, usually between 5 and 15 years, before it invades into the dermis; however, there are reported cases of rapid progression. The risk for progression to invasion appears to be proportional to the size of the lesion of lentigo maligna [85]. The fact that lentigo maligna lacks some of the histopathologic characteristics ascribed to other types of melanoma in situ (particularly pagetoid upward migration and prominence of intraepidermal nests) and may remain stable for years, progress or even regress spontaneously, has led some authors to suggest that lentigo maligna is a precursor or dysplastic lesion rather than being an in situ melanoma [86, 87]. Clinically, individual lesions are characterized by asymmetry, irregular border, heterogeneous color, enlarging diameter, and change in appearance over time. Areas of partial regression within the lesion are not uncommon, and they appear as gray discoloration. It should be recognized also that the clinical extent of lentigo maligna may be difficult to determine based on visual inspection alone. In rare occasions, lentigo maligna can present as a hypopigmented, scaly patch that can mimic squamous cell carcinoma in situ or basal cell carcinoma [88–90]. The clinical diagnosis of lentigo maligna can be difficult particularly in early lesions. The differential diagnosis includes solar lentigo and macular seborrheic keratosis. Dermoscopy and in vivo confocal microscopy have been used to help with diagnosis; however, the gold standard of diagnosis continues to be histopathology [91, 92].

Histopathologic Features

Lentigo maligna goes through different phases. At its early stage, the histologic features of lentigo maligna are subtle and can be confusing due to the apparent bland nature of the intraepidermal melanocytes. Histologically, it is composed of single melanocytes located at the basal layer of epidermis, often with only minimal atypical features (such as mild nuclear enlargement and with or without hyperchromasia). These melanocytes tend to lose polarity of nuclei against the basement membrane, and in some cases, they show a clear halo with a moth-eaten appearance of the nuclei. This bland population of melanocytes is consistently accompanied by solar damage. A diagnostic clue at this early stage is the presence of asymmetric and confluent disposition of melanocytes in the basal layer and the involvement of hair follicles. One needs to keep in mind that the architectural changes may be much more pronounced than the degree of cytologic atypia at this stage. Importantly, smaller atypical melanocytes of lentigo maligna may be partially obscured by surrounding enlarged pigmented basal keratinocytes. Unfortunately, the presence of an early, pigmented actinic keratosis or of a pigmented macular seborrheic keratosis on chronically sun-damaged skin does not preclude concurrent lentigo maligna. The difficulty on making an unequivocal diagnosis at this stage is accentuated especially when the pathologist is dealing with a small tissue sample. As most lesions are located on the head and neck, small biopsies are usually taken to make the diagnosis before definitive treatment is given. Small tissue samples often pose diagnostic difficulty as the biopsy may not be representative of the entire lesion thus resulting in underdiagnosis of lentigo maligna.

As the lesion of lentigo maligna progresses, the histologic features are more pronounced and better appreciated on light microscopy. At this intermediate stage, lentigo maligna shows a confluent lentiginous and sometimes unevenly distributed, nested proliferation of enlarged melanocytes involving the basal layers of the epidermis and extending down appendageal epithelium, again associated with epidermal atrophy and solar elastosis. Melanocytes are commonly hyperchromatic and small with dense nuclear chromatin and unapparent nucleoli. Multinucleated melanoma cells (including "starburst" forms) are often present, but their presence is not specific for lentigo maligna since they can be seen also in benign lesions. There is often a variable superficial dermal inflammatory response with pigment incontinence. In our experience one of the most reproducible histological parameters that is used to confirm a diagnosis is the proliferation of atypical melanocytes at the dermal-epidermal junction in small nests or single cells, with involvement of the skin adnexa and coupled with underlying solar damage. Pagetoid spread of melanocytes is unusual in this type of melanoma and is generally seen later in the progression of the disease, often when there is dermal invasion. The distinction from actinic intraepidermal melanocytic hyperplasia (increased intraepidermal melanocytes secondary to chronic sun exposure) can be exceedingly difficult (also see differential diagnosis below). This reactive condition is also characterized by increased numbers of single basilar melanocytes occurring in the setting of an atrophic epidermis, with diminished rete ridges. The melanocytes tend to be hyperchromatic and slightly enlarged and do not significantly differ from those seen in lentigo maligna. The main distinguishing features are numbers of melanocytes (higher density in melanoma in situ), presence of pagetoid extension (when present in the later stages), and extension down cutaneous appendages. Immunohistochemistry may be helpful to highlight the numbers and size of intraepidermal melanocytes. Since anti-MART-1 is very sensitive, it may prominently label the cytoplasmic dendrites of melanocytes thus resulting in a relatively large area of the epidermis labeled with the immu-

nodye (e.g., DAB), thus resulting in an overdiagnosis of melanoma [93]. HMB-45 is usually less sensitive than anti-MART-1 and thus the area covered by the immunodye is less extensive. At any rate, rather than evaluating the "positive area" highlighted by the dye, it is better to determine how many nuclei are surrounded by immunodye since such quantification will be closer to the actual number of melanocytes present in the epidermis [94].

When lentigo maligna becomes invasive in the dermis, melanoma cells are usually arranged in dermal nests and single cells, and there is frequent vascular ectasia in the superficial vascular. The dermal melanocytes most commonly display an epithelioid or spindle-shaped morphology. Melanocytes are hyperchromatic and atypical, but frequently lack the vesicular nuclei and prominent eosinophilic nucleoli that are seen in other subtypes of melanoma (such as superficial spreading or nodular melanoma). Also, in cases of early invasive lesions with only a few single cells or small nests within a fibrous or inflamed superficial dermis, these invasive cells may be difficult to identify. Immunohistochemistry (IHC) may be used to highlight the focal dermal invasion in cases with only individual invasive melanocytes or small nests admixed with inflammatory cells [94]. The most sensitive immunohistochemistry marker for melanocytes is probably S-100 protein; however, this marker has relatively low specificity, as dermal dendritic cells are positive for S-100, making specific identification of individual melanocytes in the dermis somewhat difficult. Although anti-MART-1 is more specific than anti-S100, it may be still positive in pigmented dermal macrophages [95]. Thus, HMB-45 or antibodies against some nuclear melanocytic markers (MITF or SOX10) may be more helpful in detecting dermal invasion.

As seen in other melanoma subtypes, dermal maturation in lentigo maligna is not apparent, and mitotic figures may be observed, but these are usually few in number. Melanocytes can be found individually throughout the dermis or seen along the skin adnexa. The spindle-shaped melanocytes have a predilection for nerves within the reticular dermis, and perineural invasion is relatively often in lentigo maligna. Some cases of lentigo maligna can be associated with desmoplastic melanoma, and the invading spindle tumor cells are very subtle, bearing a striking resemblance to a dermal scar. In such cases, anti-S100p, anti-MITF1, or anti-SOX10 is very helpful to make such distinction (since other markers such as MART-1 or HMB-45 antigen are often negative in desmoplastic melanoma).

Differential Diagnosis

Lentigo maligna has traditionally been difficult to diagnose, especially in its early stage or when a limited tissue sample is provided. Recent studies about the molecular pathogenesis of melanoma revealed that melanomas occurring on the sun-exposed skin show a distinct pattern of chromosomal instability sometimes related to UV DNA damage and are less frequently associated with BRAF mutations than superficial spreading melanoma (i.e., occurring on intermittently sun-exposed skin).

The main differential diagnosis of lentigo maligna is with lesions associated with sun damage such as early lesions of seborrheic keratosis, lichen planus-like keratosis, pigmented actinic keratosis/solar lentigo, and junctional melanocytic nevus. However, differentiating lentigo maligna from a background of increased melanocytes on chronically sun-damaged skin is one of the most difficult diagnostic challenges in diagnostic dermatopathology. In its earliest stages, lentigo maligna shows a single-cell, lentiginous proliferation of atypical melanocytes at the dermal-epidermal junction with only minimal cytologic atypia. It is well known that benign reactive melanocytic hyperplasia in sun-exposed areas or in the vicinity of surgical scars can exhibit histologic patterns similar to early lentigo maligna. In fact, the classic morphologic depiction of chronic photoactivation of melanocytes includes lentiginous melanocytic proliferation with the potential for nuclear hyperchromasia, binucleation and multinucleation, and low-level pagetoid ascent. Thus, a proliferation of melanocytes with slightly atypical nuclei in skin severely UV damaged is not sufficient for a diagnosis of lentigo maligna. Sun-exposed epidermis shows approximately twice as many melanocytes as non-sun-exposed, covered skin, and the density of melanocytes has been said to be proportional to cumulative sun exposure. As the lesion of lentigo maligna progresses, the histologic changes are more obvious, including coalescence of single melanocytes along the dermal-epidermal junction, extension into skin adnexa, focal pagetoid spread, and obvious junctional nest formation. Indeed, a very important and useful feature for the diagnosis of lentigo maligna is the presence of intraepidermal melanocytic nests. Furthermore, some authors have suggested that, if there are melanocytic nests in an entirely intraepithelial lesion on the skin in the head and neck area with severe solar elastosis, the diagnosis almost always is lentigo maligna. However, we consider that patients may develop junctional dysplastic nevi during all their life, and therefore some may occur on the face after sun damage has started.

The in situ component of lentigo maligna is usually wide and poorly circumscribed, with individual neoplastic melanocytes extending beyond the last melanocytic nest; thus, the absence or presence of melanocytic nests does not always help differentiate lentigo maligna from melanocytic hyperplasia in sun-damaged skin and is only rarely helpful in delineating the borders of a melanoma. The distribution of pigment is relevant in distinguishing these two conditions, as in cases of solar lentigo with melanocytic hyperplasia, there is an even distribution of melanin in basal keratinocytes, as opposed to the irregular distribution of pigment noted in len-

tigo maligna [96]. An important diagnostic clue is the presence of preserved elongation of rete ridges that are relatively uniform and relatively equidistant from each other in cases of solar lentigo/pigmented actinic keratosis, in contrast to lentigo maligna in which the rete ridges tend to be flattened. In cases of lentigo maligna in which there is focal preservation of rete ridges, they tend to be usually irregular and not equidistant from one another.

As mentioned above, immunohistochemistry plays an important role to separate incipient lentigo maligna from intraepidermal melanocytic hyperplasia on sun-damaged skin. Mere close inspection of H&E-stained section does not always allow an unequivocal diagnosis, because it is sometimes difficult to distinguish pigmented keratinocytes from melanocytes. Anti-MART-1 may overestimate the number of melanocytes because it labels the melanocytic dendrites and might also label pigmented keratinocytes, including structures mimicking junctional melanocytic nests in the setting of a lichenoid infiltrate [97–99]. This lack of specificity may result in false-positive result in the assessment of difficult intraepidermal melanocytic lesions. Both MITF-1 and SOX10 are nuclear makers that facilitate the diagnosis [100] since they avoid the cytoplasmic labeling seen with anti-MART-1 or HMB-45.

A similar challenge may occur when evaluating the peripheral margins of a melanoma in situ in a re-excision specimen, since epidermal melanocytes are usually increased in number as a reaction to the prior trauma (biopsy). Among the criteria that can be used for delineating the borders of a melanoma are presence of melanocytes above the junction, pleomorphism or hyperchromasia of melanocytes, and a high density of melanocytes with a confluent pattern.

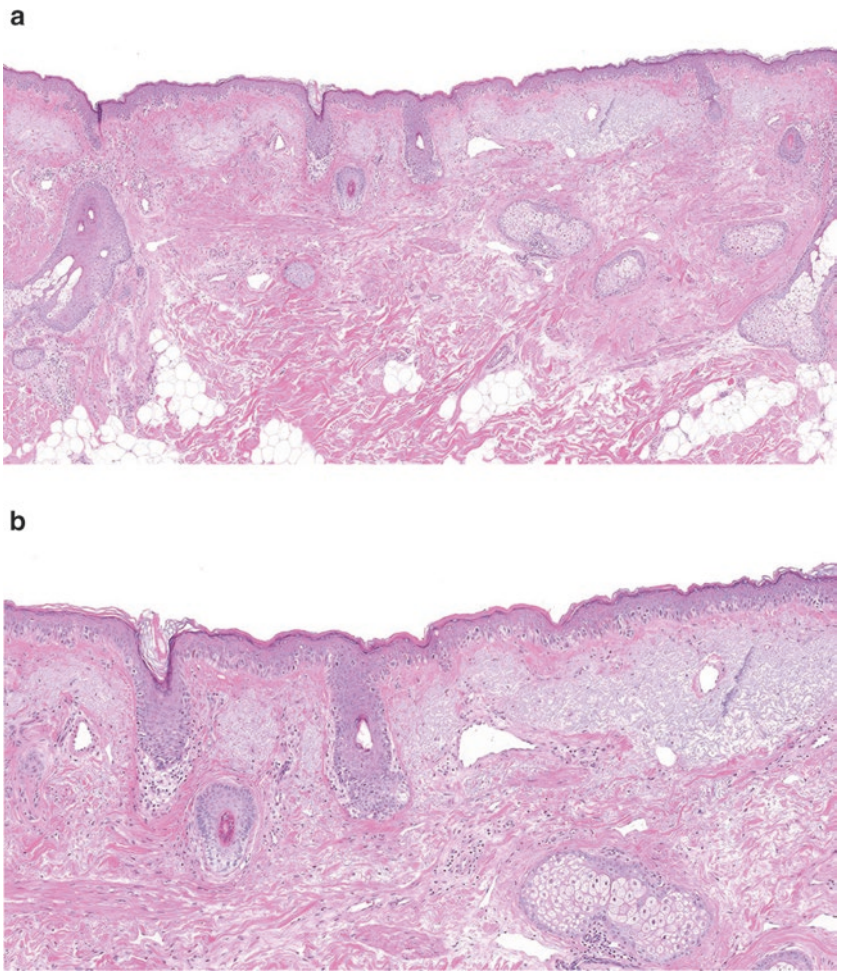
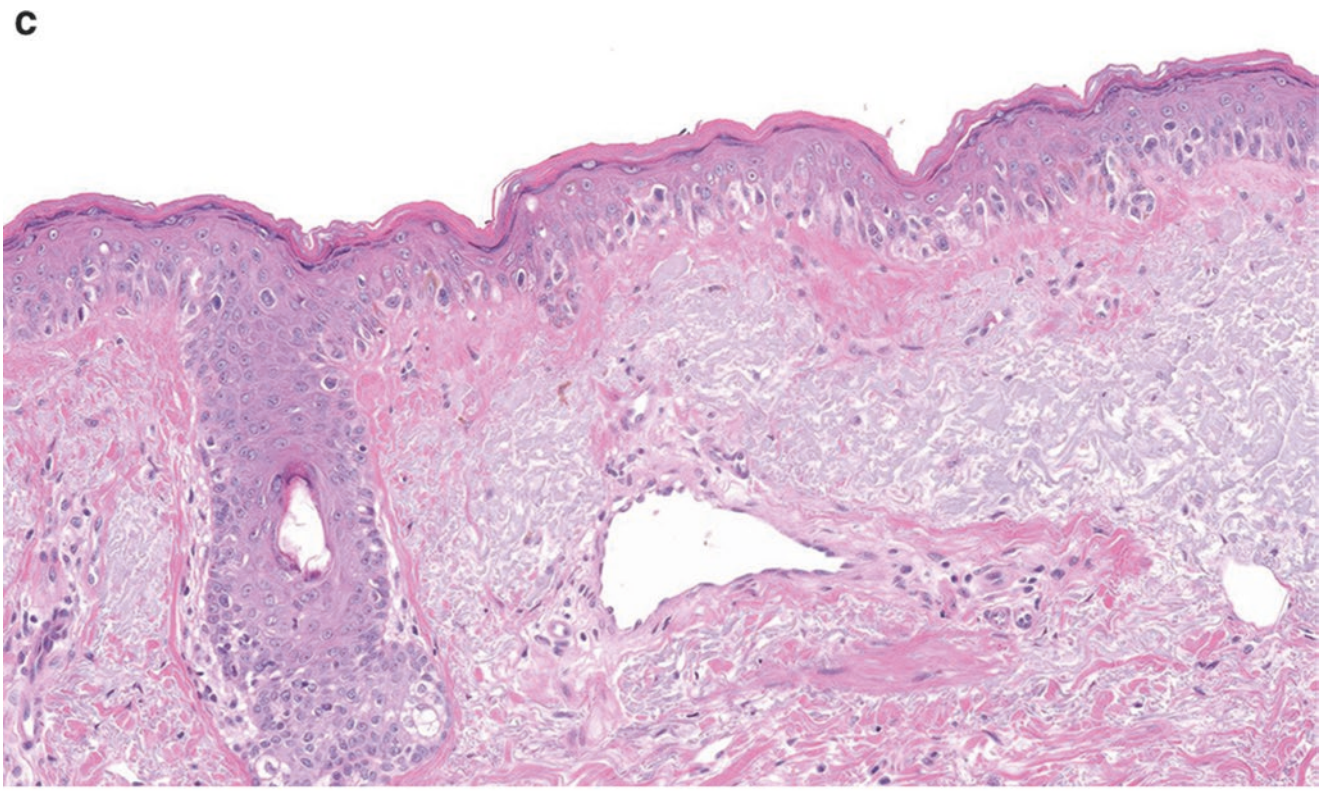


Fig. 7.1 Early lentigo maligna melanoma in situ. This lesion is located in the forehead of a 53-year-old male. The lesion is composed of a subtle increase of intraepidermal melanocytes accompanied by flattening of the epidermis and diffuse solar elastosis (**a**). Single-cell proliferation of melanocytes in the epidermis with focal extension into skin adnexa. As characteristically observed in lentigo maligna lesions, there is no prominent pagetoid extension (**b**).



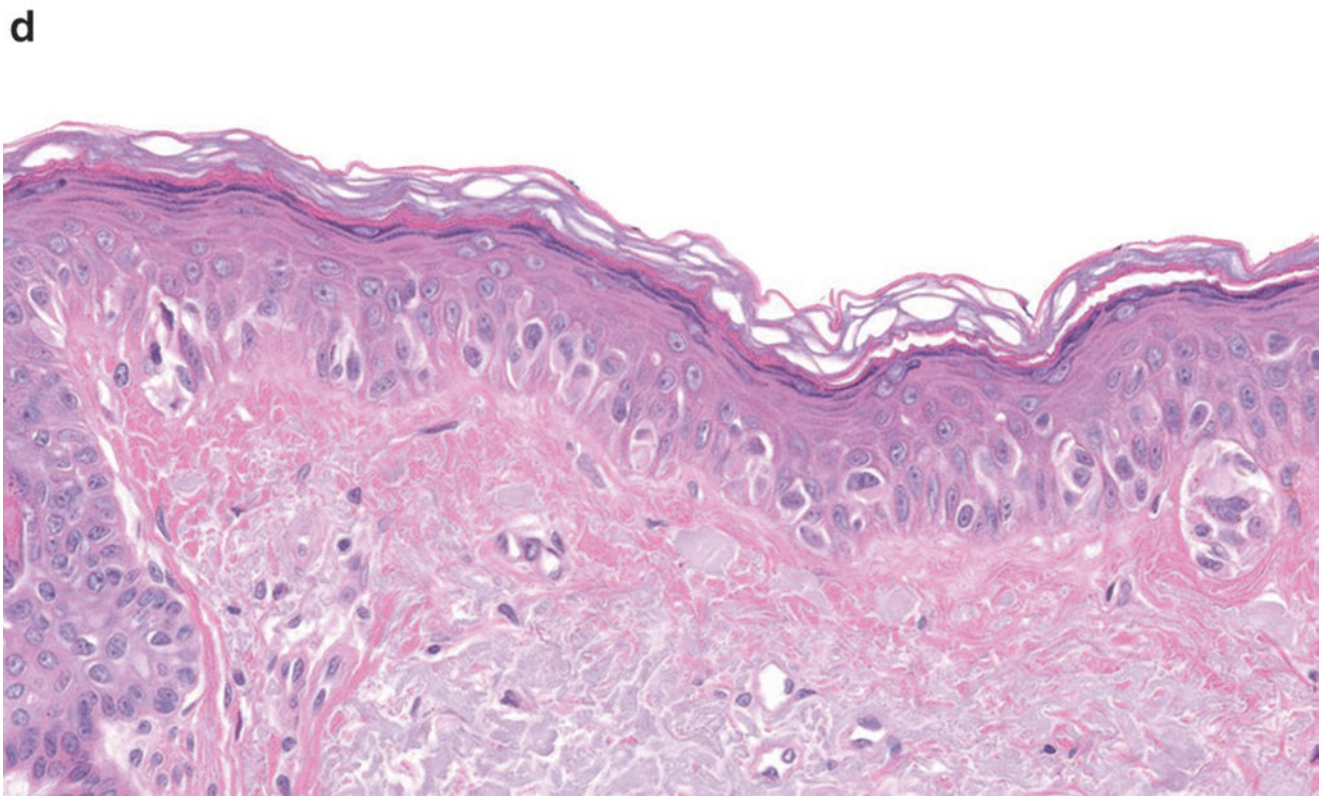


Fig. 7.1 (continued) Increased numbers of large-sized melanocytes along the dermal-epidermal junction and into a hair follicle (**c**). Early note the large size of melanocytes with visible nucleoli. Single nest (*right*) (**d**)

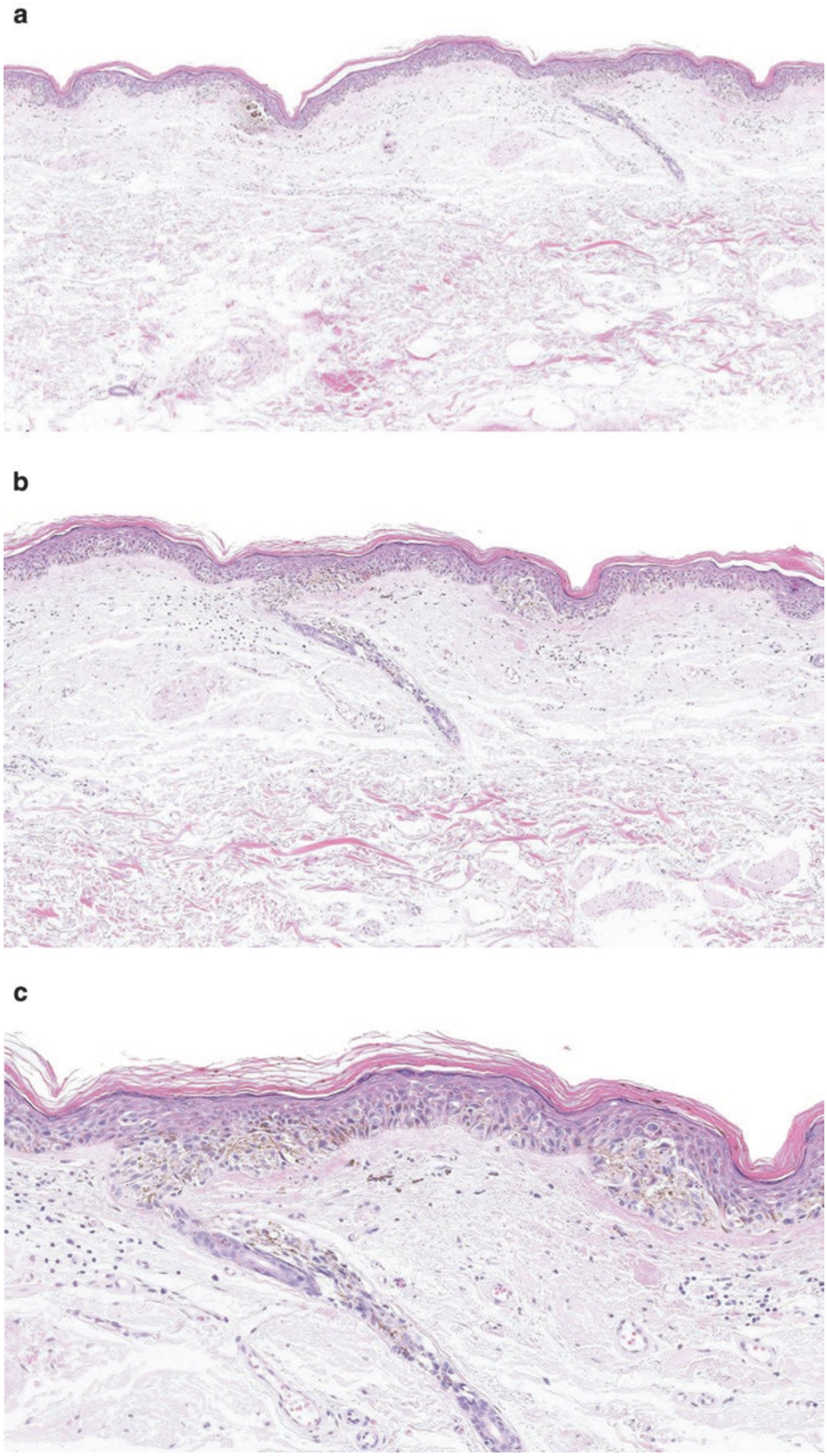


Fig. 7.2 Lentigo maligna melanoma in situ. This lesion is located on the neck of an 83-year-old male. Flattening of rete ridges and solar elastosis (**a**). Diffuse and confluent proliferation of melanocytes along the dermal-epidermal junction (**b**). Higher power highlights the increased number of melanocytes in the epidermis. There is follicular extension of the atypical melanocytes (**c**)

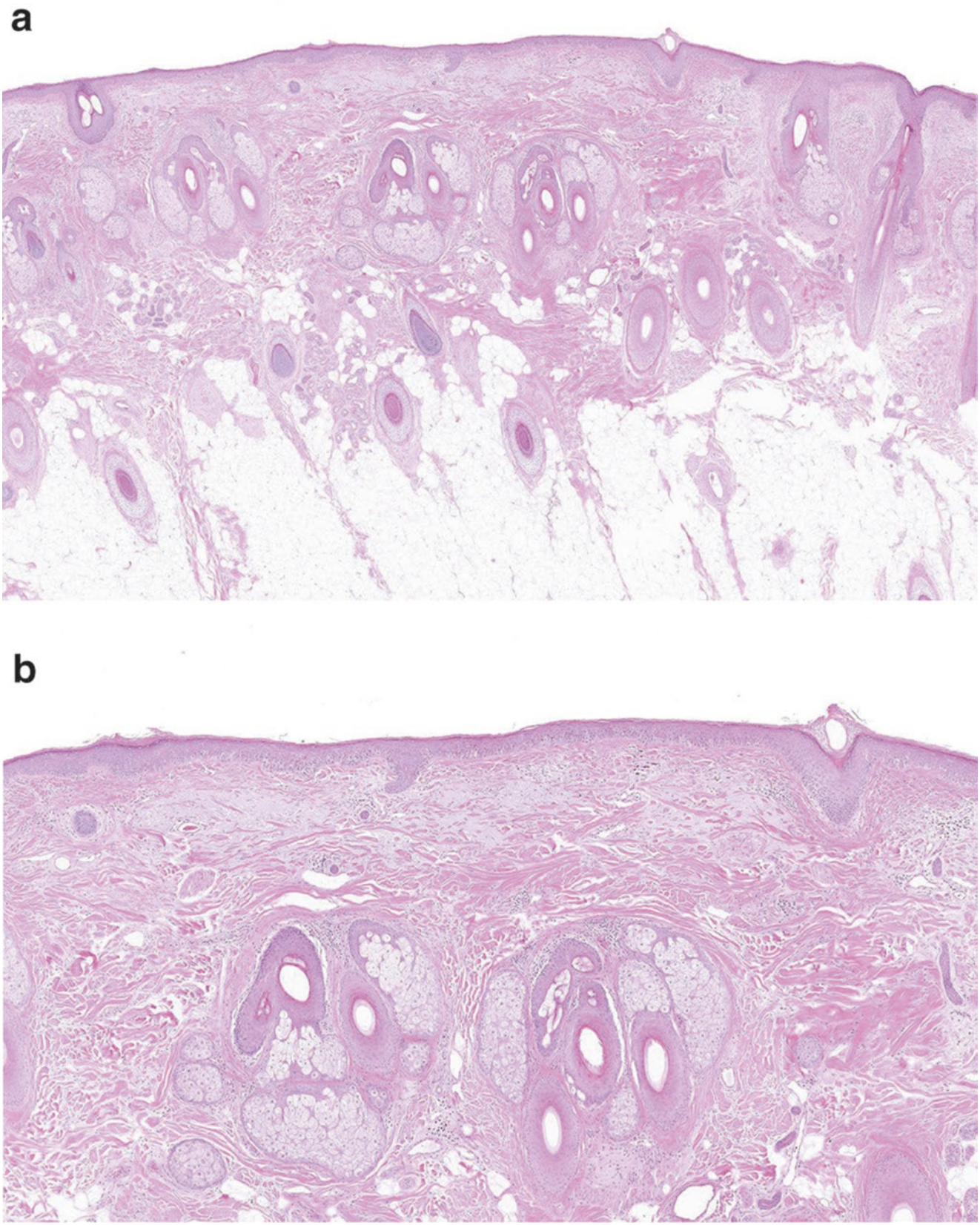


Fig. 7.3 Lentigo maligna melanoma in situ. This lesion is located in the scalp of a 70-year-old male. Depending on how the lesion is sampled, it can be difficult to interpret (specially in small biopsies, where the edge of the lesion can simulate intraepidermal melanocytic hyperplasia in sun damage) (**a**). On low magnification, there is an abnormal effacement of the epidermis along with prominent solar elastosis (**b**).

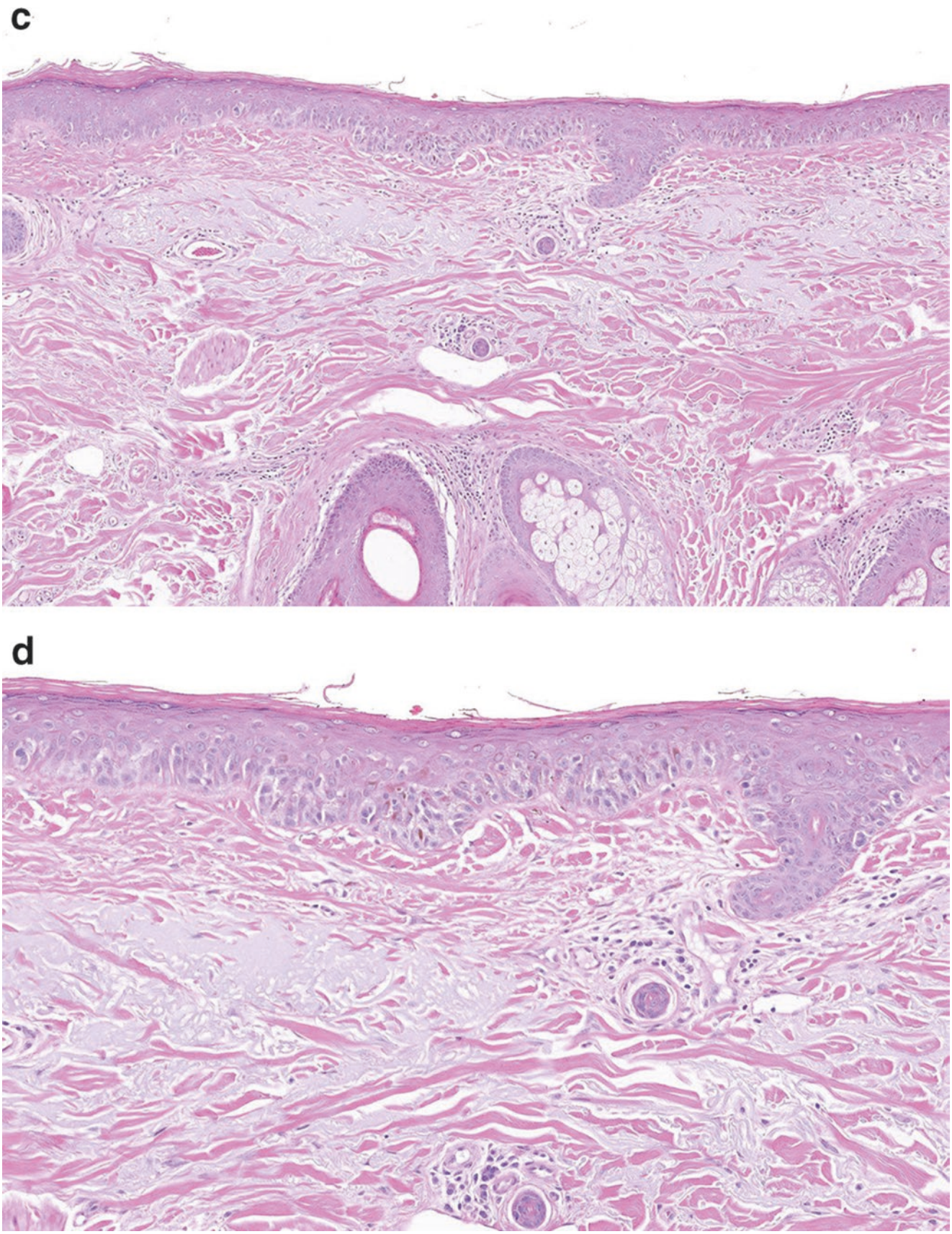


Fig. 7.3 (continued) Confluent single-cell melanocytes without nest formation (**c**). The melanocytes have prominent nuclear pleomorphism (**d**)

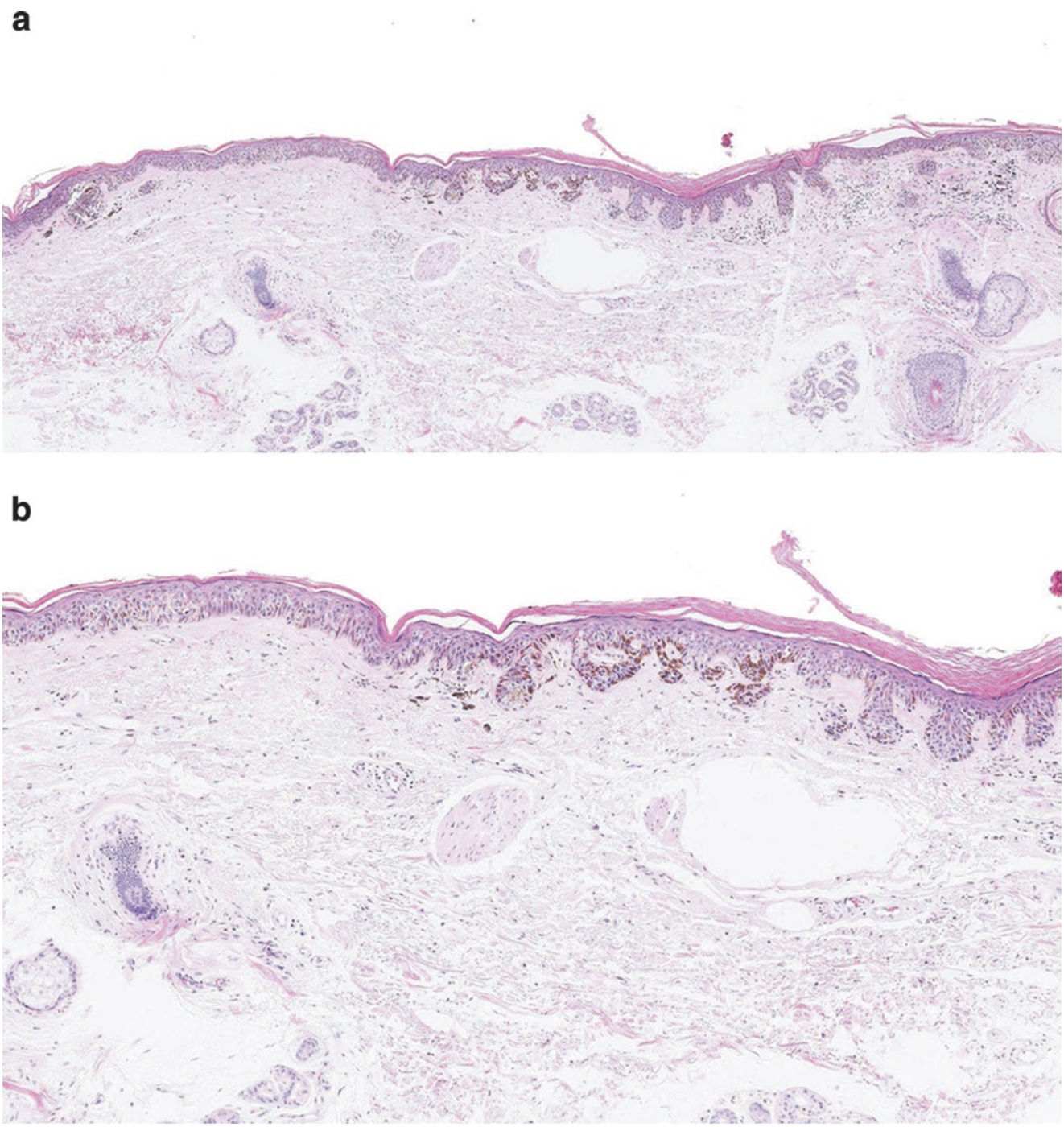


Fig. 7.4 Lentigo maligna melanoma in situ. In contrast with Figs. 7.1–7.3, in this example the lesion is more asymmetric, with areas of epidermal hyperplasia and focal host response (**a**). There is effacement of the rete ridges and isolated vacuolated cells (melanocytes) at the dermal-epidermal junction (**b**).

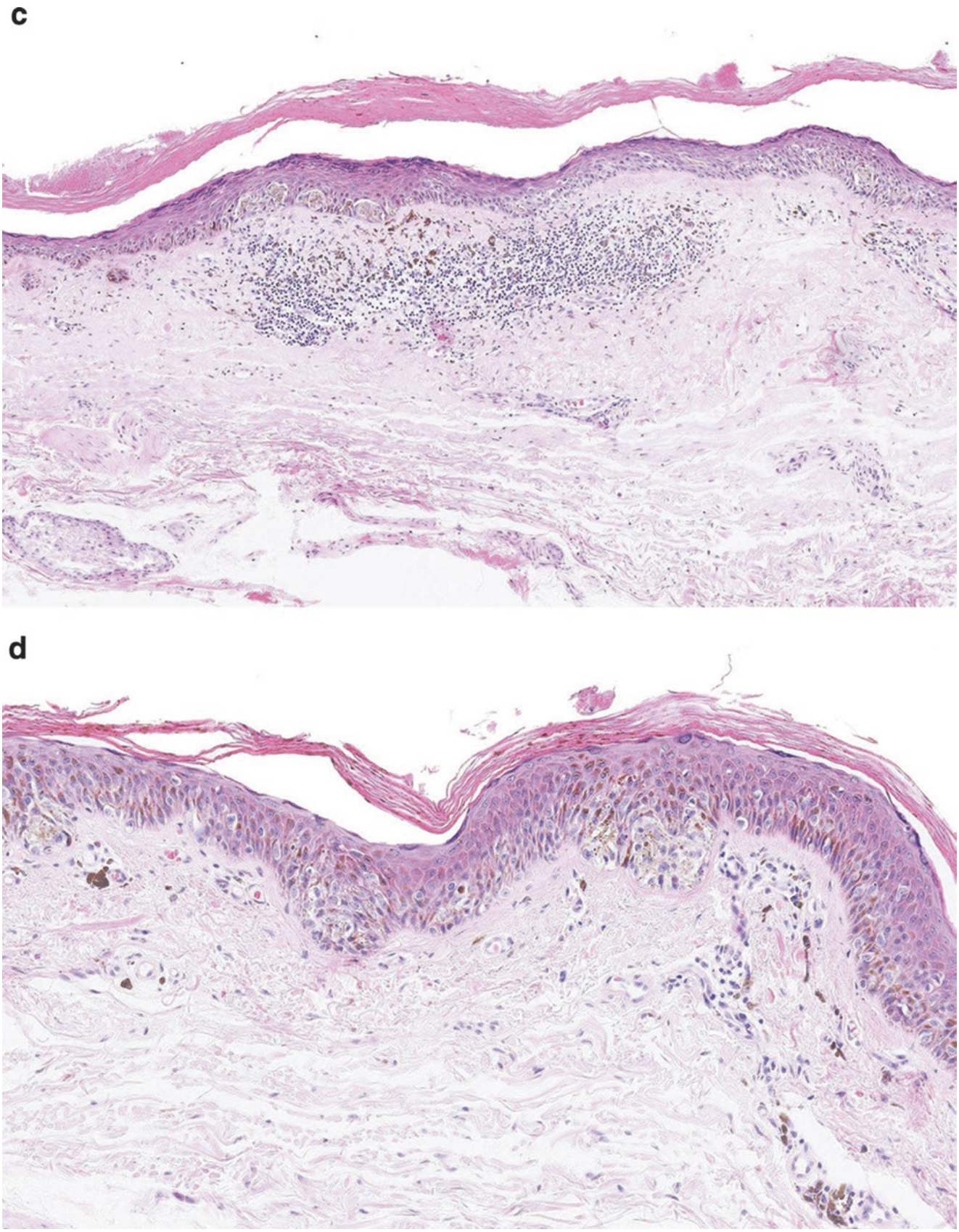


Fig. 7.4 (continued) Nests and single cells in the epidermis. Note the areas of fibrosis, inflammation, and pigment incontinence in the superficial dermis (**c**). High-power view of large, hyperchromatic melanocytes at the dermal-epidermal junction (**d**)

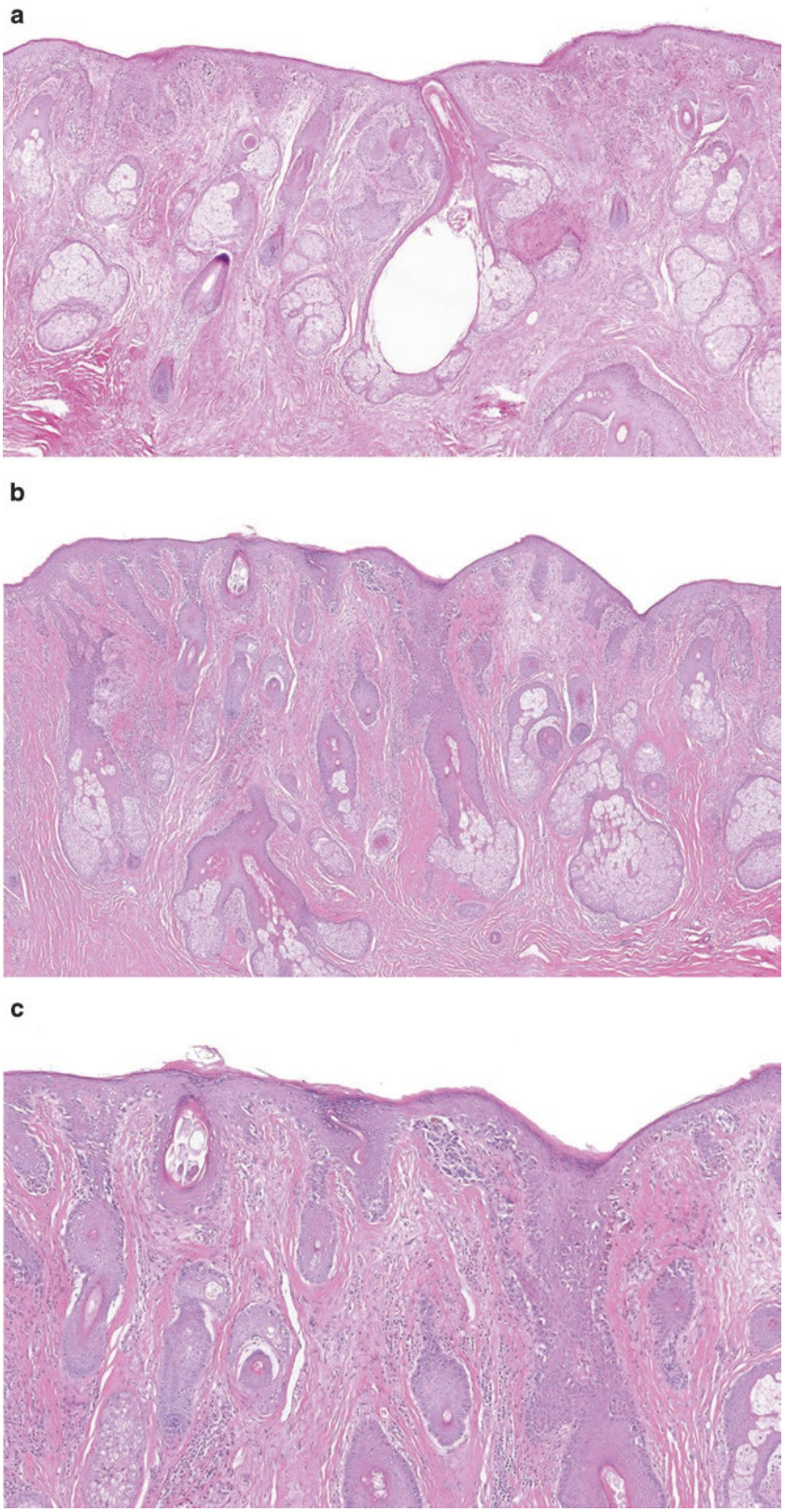


Fig. 7.5 Lentigo maligna melanoma in situ, with adnexal extension. There is diffuse proliferation of melanocytes along the dermal-epidermal junction (**a**). The follicular structures are involved by atypical melanocytes. An important point to remember (specially in small biopsies) is that intraepidermal melanocytic hyperplasia induced by chronic sun damage can also involve the adnexal structures but usually only involve the follicular infundibulum and acrosyringia. Note in this case that the extension of the hair follicles is deep (**b**, **c**)

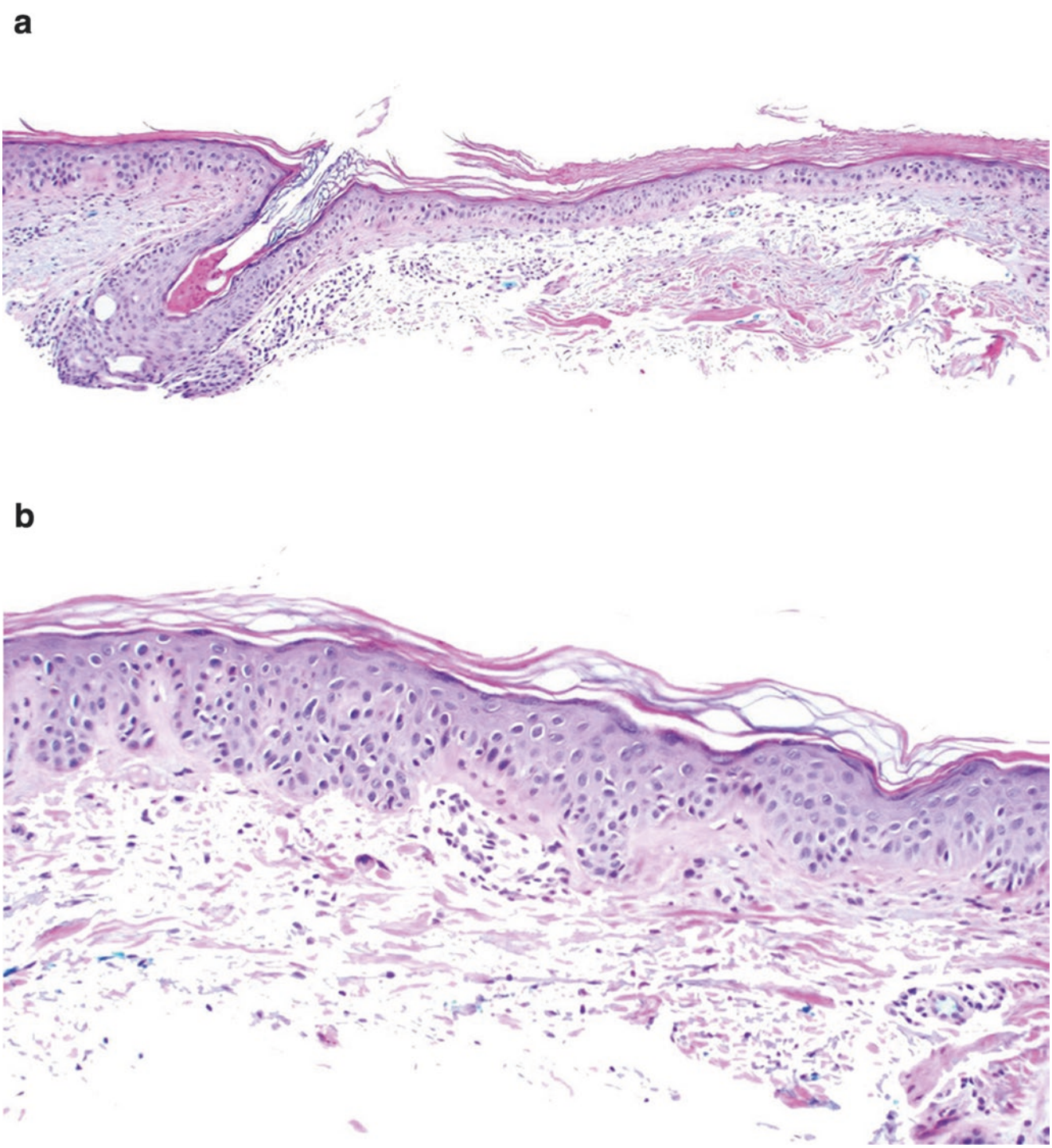


Fig. 7.6 Solar lentigo with intraepidermal melanocytic hyperplasia. This is a 56-year-old female that presented with a light pigmented lesion on her cheek (**a**). The melanocytes are present in single units, however, distant from each other and without a confluent growth (**b**).

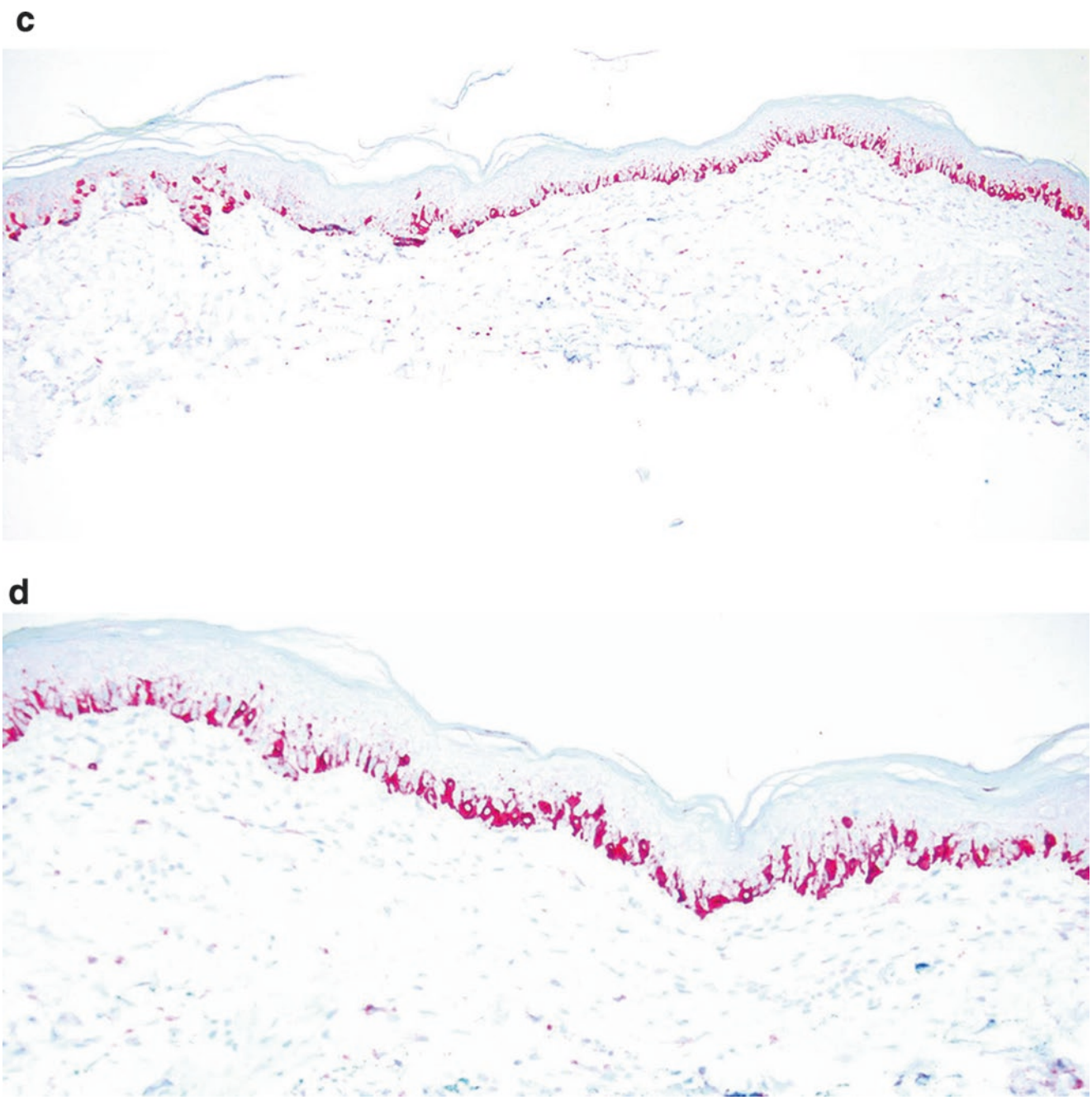


Fig. 7.6 (continued) Anti-MART-1 shows increased number of melanocytes but without a confluent growth (equidistant melanocytes) (**c**). Higher-power view of MART-1 expression showing melanocytes as single units (not nested or confluent) (**d**)

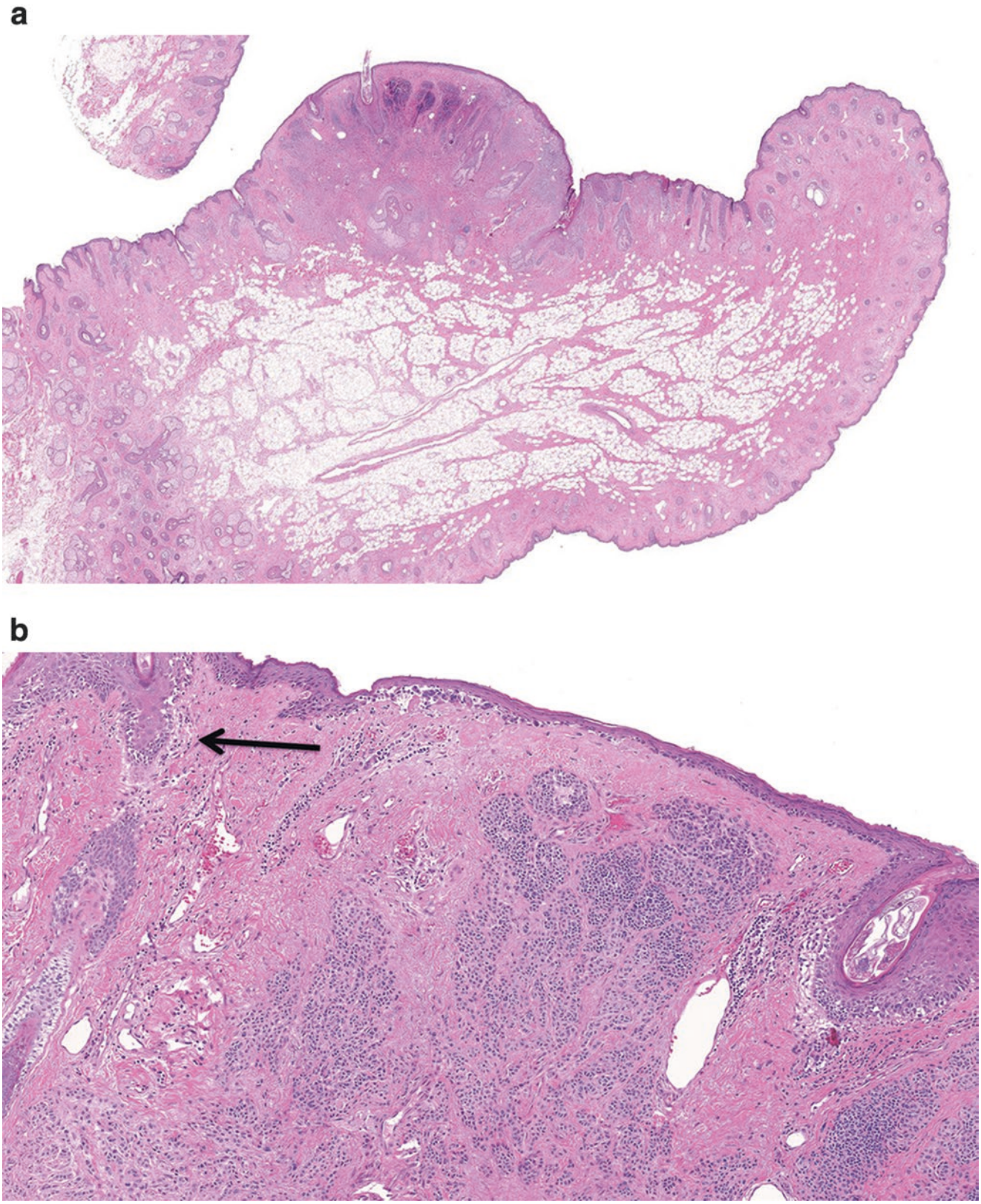


Fig. 7.7 Lentigo maligna melanoma of the ear associated with a congenital nevus. This case is located in the ear of a 61-year-old male. The patient had a nevus in this location and recently the lesion increased in size, shape, and color (**a**). The image depicts an intradermal nevus with congenital pattern, and the overlying epidermis shows a confluent growth of melanocytes (more prominently seen in the hair follicle (*arrow*)) (**b**).

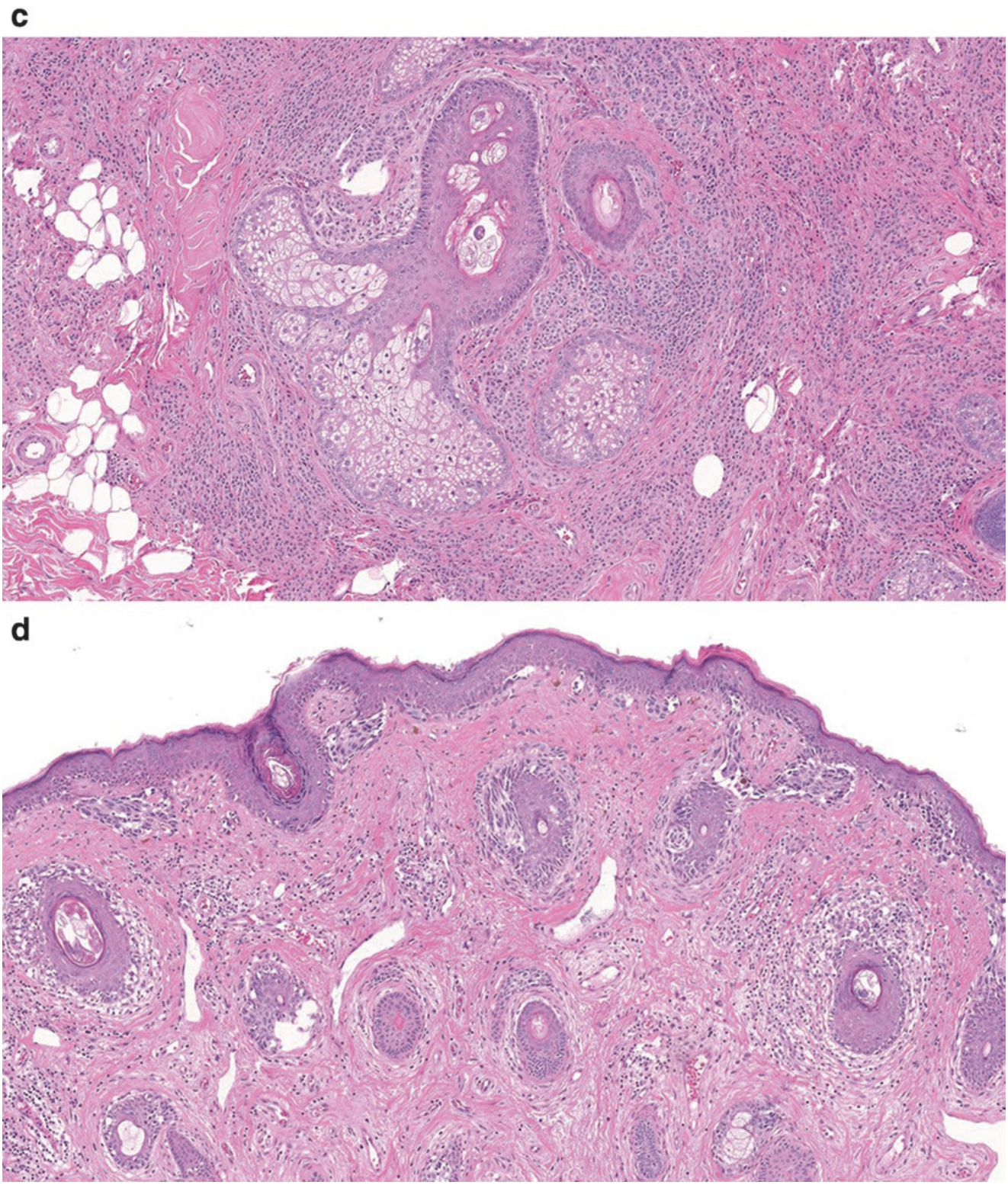


Fig. 7.7 (continued) The nevus cells in the dermis show periadnexal pattern, consistent with a congenital onset (**c**). Note the characteristic confluent pattern of growth of melanocytes along the dermal-epidermal junction and skin adnexa (**d**)

Superficial Spreading Melanoma

Clinical Features

The term superficial spreading melanoma was first coined by Dr. Clark, as a melanoma that grows primarily on the trunk and proximal extremities, with a nested, intraepidermal pattern of growth and prominent pagetoid upward migration. This type of melanoma accounts for around 70 % of all melanomas. The prevalence of superficial spreading melanoma has increased in the last few years. Apart from a possible connection with increased exposure to UV light, it is possible that this increase may be due to a lower threshold for its diagnosis. It has been suggested that many cases that were previously identified as dysplastic nevi are now being classified as melanomas [101]. The first clinical sign is the appearance of a flat or slightly raised discolored, asymmetrical patch that has variable pigmentation and with irregular and indurated borders. The color varies, with areas of tan, brown, black, red, blue, or white, with sometimes protruding blue-black papules/nodules. The histologic correlates of these variations in color are the presence of dermal inflammation, regression, and the deep dermal melanin pigment in macrophages. Small, notch-like indentations may be noted at the edge of the lesion. Ulceration is sometimes seen, a finding rarely seen in nevi and also associated with impaired prognosis. Lesions are usually larger than 10 mm (average 15 mm), but in rare occasions superficial spreading melanoma can present as a smaller lesion. Superficial spreading melanoma can be found almost anywhere on the body, but is most likely to occur on the trunk in men, the legs in women, and the upper back in both.

Histopathologic Features

The in situ component of superficial spreading is characterized by an asymmetrical proliferation of atypical melanocytes scattered singly and in clusters throughout all levels of the epithelium giving an appearance reminiscent of Paget disease (pagetoid upward migration or "buckshot" scatter). These pagetoid melanocytes are scattered throughout the epidermis giving a moth-eaten appearance and sometimes even infiltrating the stratum corneum. Melanocytes are epithelioid in appearance with abundant cytoplasm, often showing fine or dusty melanin pigmentation, and pleomorphic vesicular nuclei with prominent, eosinophilic nucleoli. There may be necrotic melanocytes and scattered mitotic figures including atypical forms. Melanocytic nests within epidermis tend to be irregularly distributed and have a confluent growth. An important diagnostic clue is that the amount of cellularity, pigment, and size of melanocytes vary from to nest. These melanocytic nests are large in general and have irregular contours; in occasions this pattern predominates over pagetoid melanocytes. Most of such cases of superficial spreading melanoma composed predominantly of large nests have only scant intraepidermal or junctional single melanocytes; thus, histologic recognition can be difficult [102, 103]. "Consumption" of the epidermis is present in approximately half of cases of superficial spreading melanoma. This epidermal consumption is defined as thinning of the epidermis with attenuation of basal and suprabasal layers and loss of rete ridges adjacent to collections of melanocytes. The epidermis may become separated from the dermis by an artefactual cleft ("zipper" sign; Christopher R. Shea, personal communication). Some authors believe that this consumption of the epidermis appears to represent a precursor to ulceration. In contrast to lentigo maligna, there is often little visible evidence of actinic damage. Also, in some cases there is lymphocytic infiltration in the papillary dermis and this may herald the presence of rare invasive cells. There may be fibroplasia of the papillary dermis; however, the organized (lamellar or concentric) stromal response observed in dysplastic nevi is not seen in such cases.

As per the original description by Dr. Clark, extension of the intraepidermal component for more than three rete ridges past the dermal component is a must to classify the lesion as superficial spreading (or acral lentiginous or lentigo maligna) melanoma. Progression of the radial growth phase starts with the development of a microinvasive component as single cells or small nests in the papillary dermis. These melanocytes have a similar cytomorphology as the intraepidermal component. When these dermal melanoma cells display either nests larger than observed in the overlying epidermis or have mitotic figures, these are the features of vertical growth phase. The invasive component in the dermis may be arranged in single melanocytes and solid nests or may have a fascicular growth pattern. Melanocytes may be epithelioid, spindle-shaped, small (nevus-like), and vacuolated (balloon cell-like). These melanocytes are pleomorphic and have irregular nuclei with irregular, hyperchromatic chromatin and thick nuclear membrane. The nuclei have an irregular outline that can be indented. The melanocytic density in melanomas is high, and the cells seem to overlap one to another. Melanocytes can form expansile nodules, which usually compress the adnexal structures. The presence of irregular distribution of pigment in the dermis is another diagnostic clue of melanoma. Detection of dermal mitotic figures in melanoma is a very important finding to confirm the diagnosis; however, absence of dermal mitotic figures should not be considered sufficient to exclude a diagnosis of melanoma. Particularly relevant is the presence of mitotic figures in the deeper portion of the lesion, since such a finding is only exceptionally seen in nevi. Recent studies have used immunodetection of phosphohistone H3 to facilitate the identification of mitotic figures in various neoplasms, including

melanomas [104–106]. One study in particular provided definite support for the application of MART-1/phosphohistone H3 immunohistochemistry as an adjunctive test in the evaluation of primary melanomas [107]. This study concluded that adding this ancillary test could potentially add important value to the analysis and characterization of primary cutaneous melanoma, especially this is particularly true for the description of thin melanomas (≤1.0 mm) where mitotic figures can be difficult to identify and for which the identification of a mitotic figure would have the most profound implications for staging and patient management. In our practice, we apply dual immunohistochemical staining for MART-1 and phosphohistone H3 in cases where mitotic figures are seen in the infiltrate, but it is unclear if they represent melanocytes or other cells (e.g., macrophages, endothelial cells) or it is unclear if a cell is on mitosis or apoptosis.

Differential Diagnosis

Superficial spreading melanoma can mimic other melanocytic and non-melanocytic neoplasms. The main melanocytic lesion that needs to be considered in the differential diagnosis of melanoma is dysplastic nevus. In occasions, the distinction can be difficult and somewhat subjective, especially if the dysplastic nevus has severe architectural and cytologic features. Features that favor melanoma over a dysplastic nevus are the presence of significant pagetoid upward migration especially at the lateral borders of the lesion, diffuse and even cellular atypia, and the presence of deep-seated mitotic figures in the dermal component (see also the dysplastic nevus chapter). Another important clue is the presence of confluent nests in the dermal-epidermal junction, as it tends to abut the undersurface of the epidermis in between the rete ridges. In the differential diagnosis between melanoma and dysplastic nevi, it must be considered that focal areas of pagetoid upward migration in a nevus can be a sign of melanoma in situ originating in a dysplastic nevus. On the other hand, trauma to a nevus can induce focal pagetoid upward migration and this should not be interpreted as melanoma in situ. An important feature to distinguish between focal melanoma and prior trauma in a nevus is the presence of pigmented parakeratosis in the latter. Both melanoma and dysplastic nevus may show regression; however, in dysplastic nevi regression is usually focal as opposed to cases of melanoma in which the regressive changes are usually more widespread.

Recurrent/persistent nevi may simulate superficial spreading melanoma. The most important piece of information to make such distinction is to review the previous specimen. Histologic features that favor nevus include the sharp circumscription of the lesion, as recurrent nevi tend to preserve circumscription as opposed to melanomas, which are asymmetric. A banal intradermal component supports the diagnosis of recurrent nevus, as in melanomas the dermal component shows an atypical growth along with the presence of deep mitotic figures. In recurrent nevi, the intraepidermal growth is above the scar, while the epidermis beyond the scar is uninvolved. The presence of pagetoid upward migration beyond the area of scar in the dermis is almost always diagnostic of melanoma.

Non-melanocytic skin lesions can also mimic superficial spreading melanoma. Merkel cell carcinomas can be easily confused with melanoma, especially in superficial shave biopsies, since they can show an intraepidermal growth with marked pagetoid upward spread and forming small nests. If the tissue sample allows inspection of the dermis, it will become obvious the characteristic round blue cell morphology of Merkel cell carcinoma. Immunohistochemistry will allow easy recognition of both of these entities (keratin and CK20 in Merkel cell carcinoma, both unlikely to be seen in melanoma). Paget and extrammamary Paget disease can also mimic superficial spreading melanoma. Both of these conditions form nests and single cells with pagetoid growth in the epidermis and thus can look almost identical to superficial spreading melanoma. Cells in Paget disease tend to be located above the dermal-epidermal junction (so-called “eyeliner” sign). Paget cells express keratins, including CK7, and only rarely can they express S100 (other melanocytic markers are consistently negative in Paget disease). Examples of metastatic gastrointestinal, prostate, and lung carcinoma can occasionally invade the epidermis and thus can easily simulate melanoma. In general such lesions have widespread vascular invasion or glandular arrangement. Also, immunohistochemistry will allow a more specific distinction depending on the type of lesion. Epidermotropic metastatic carcinomas can mimic superficial spreading melanoma; in such cases, clinical-pathologic correlation will be essential (i.e., history of prior melanoma of similar morphology and located nearby).

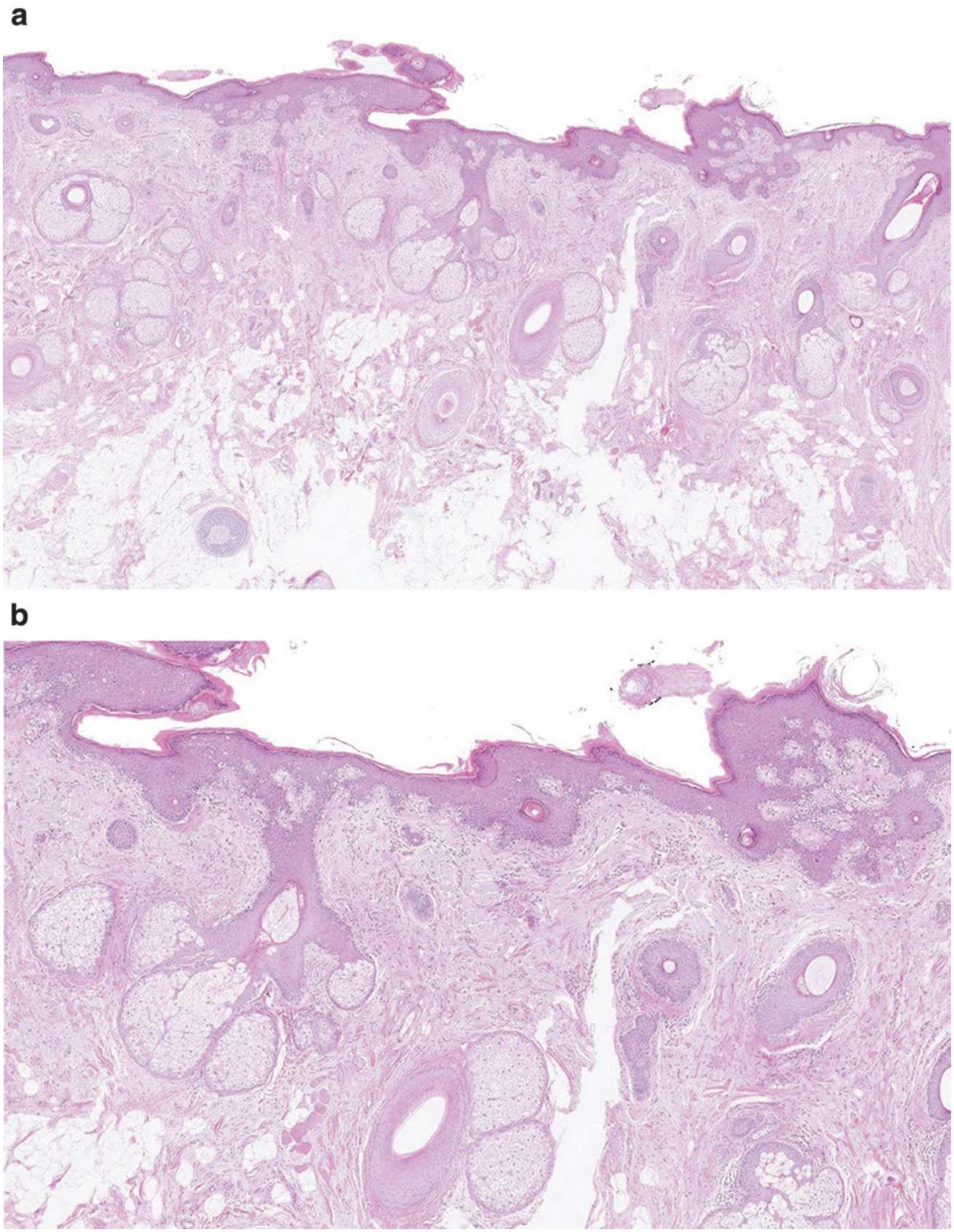


Fig. 7.8 Superficial spreading melanoma in situ. This case is composed of an irregular junctional growth of melanocytes mostly aligned in the dermal-epidermal junction in single cells (**a**, **b**).

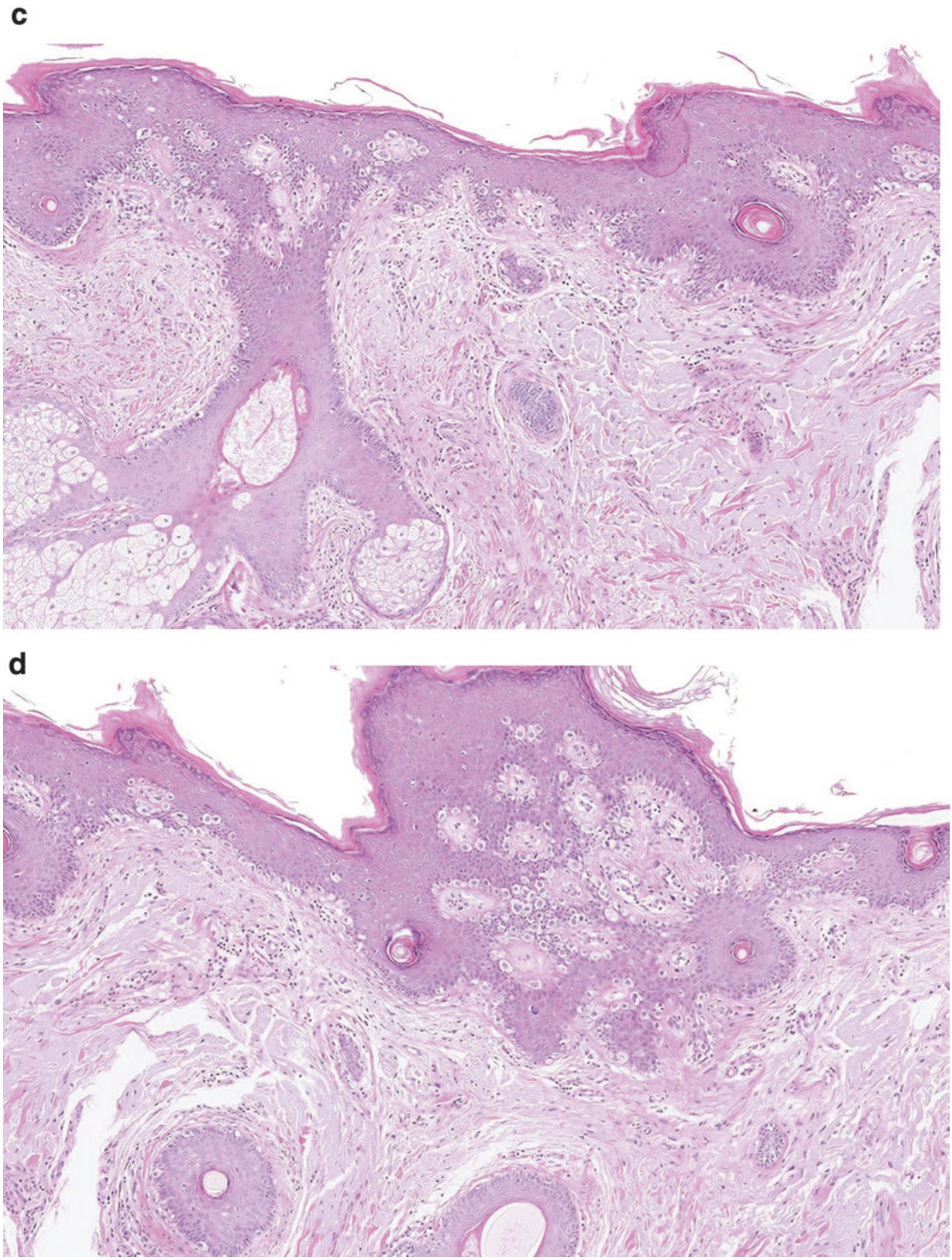


Fig. 7.8 (continued) The melanocytes are epithelioid and display a single-cell pattern in which they are close together and in some other areas they are far apart. There is increase pagetoid upward migration throughout the lesion (**c**). The cells have variable nuclear pleomorphism and irregular thick membrane and are surrounded by clear halos (**d**)

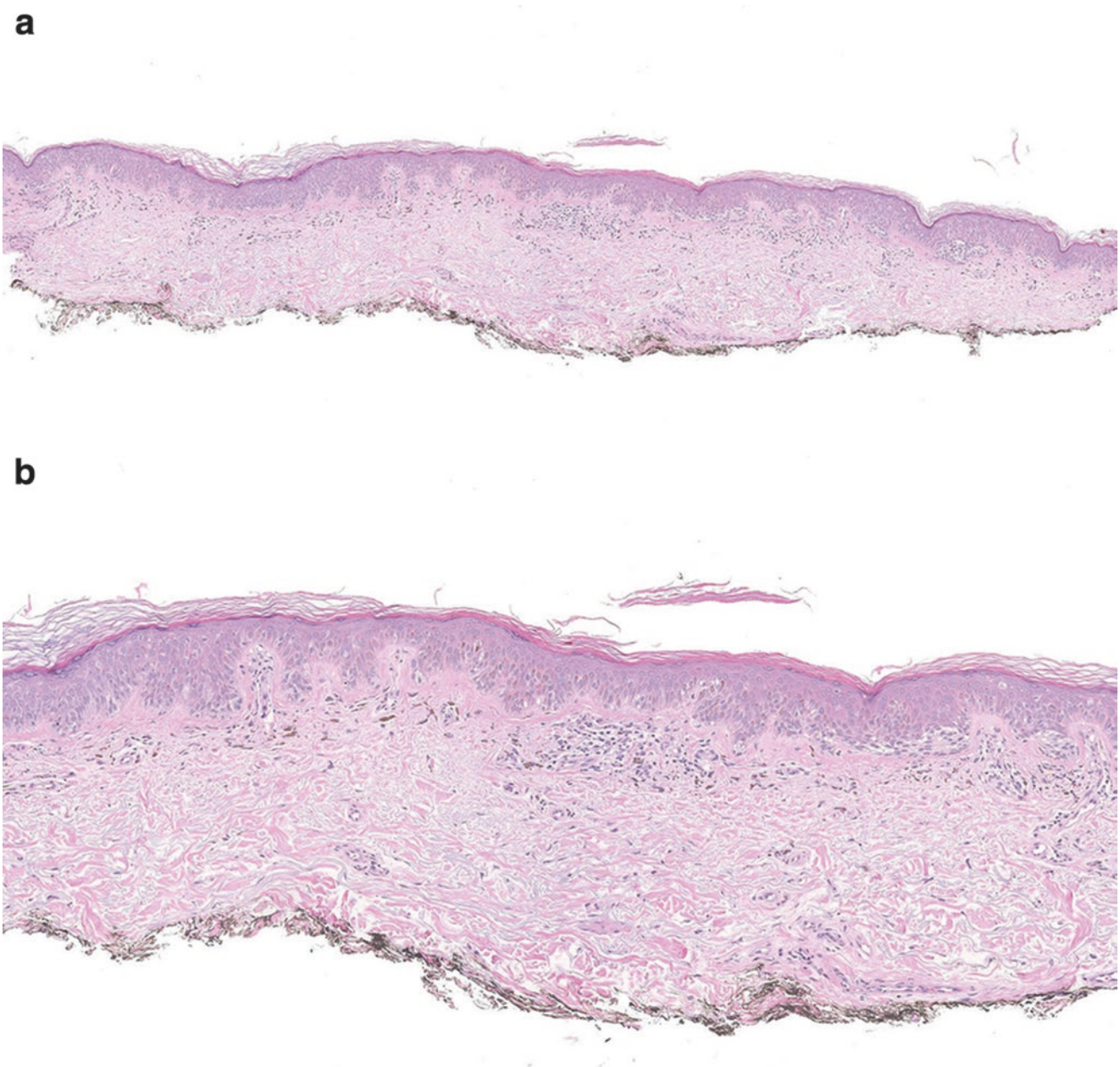


Fig. 7.9 Lentiginous superficial spreading melanoma in situ. This is an example of superficial spreading melanoma in which the cells have a predominant lentiginous growth (**a**). The low-power image shows a lentiginous nevus-like growth; however, the degree of cellular density and the asymmetry of the lesion are clues to the diagnosis of melanoma (**b**).

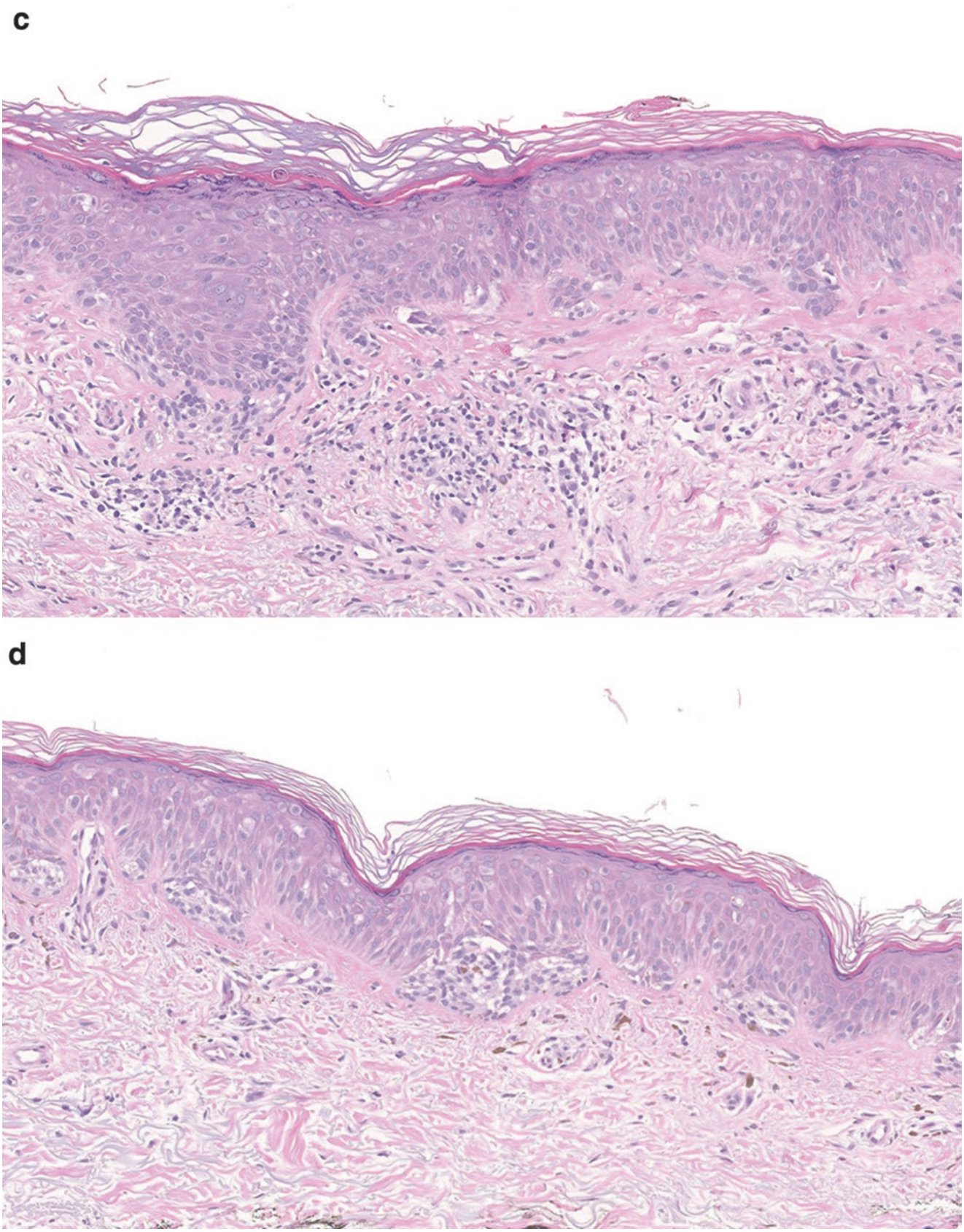


Fig. 7.9 (continued) On higher magnification, the lesion shows atypical nests along with an increased number of atypical melanocytes with prominent pagetoid upward migration (**c**, **d**)

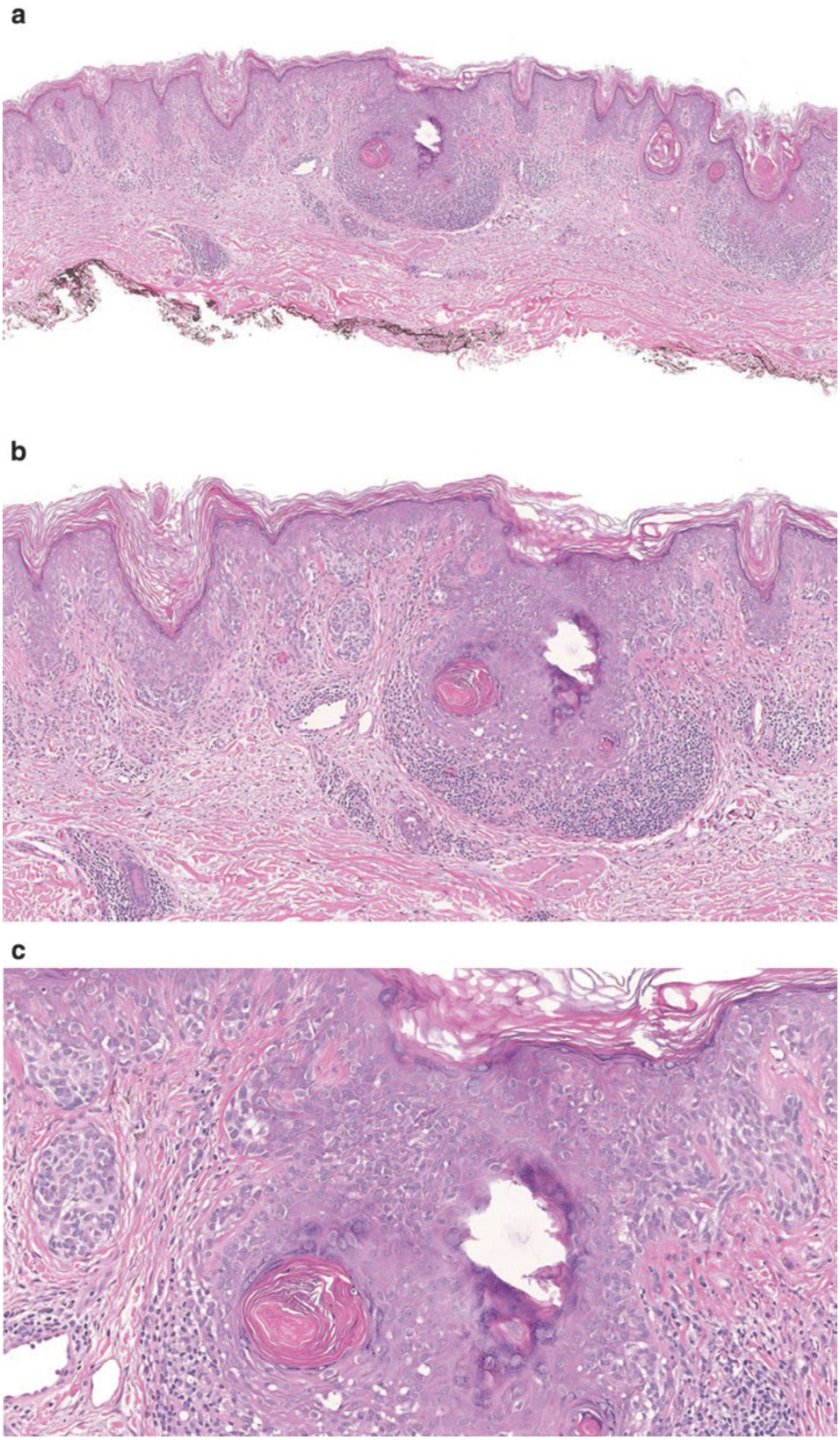


Fig. 7.10 Superficial spreading melanoma in situ with adnexal extension. This example shows a clear melanoma composed of single and nested melanocytes seen at the bases and the flanks of the rete ridges (**a**). On low magnification, one can see the irregularly shaped nests (**b**). This example shows extensive adnexal extension. On higher magnification, the melanocytes have an ample pale cytoplasm with pleomorphic nuclei (**c**)

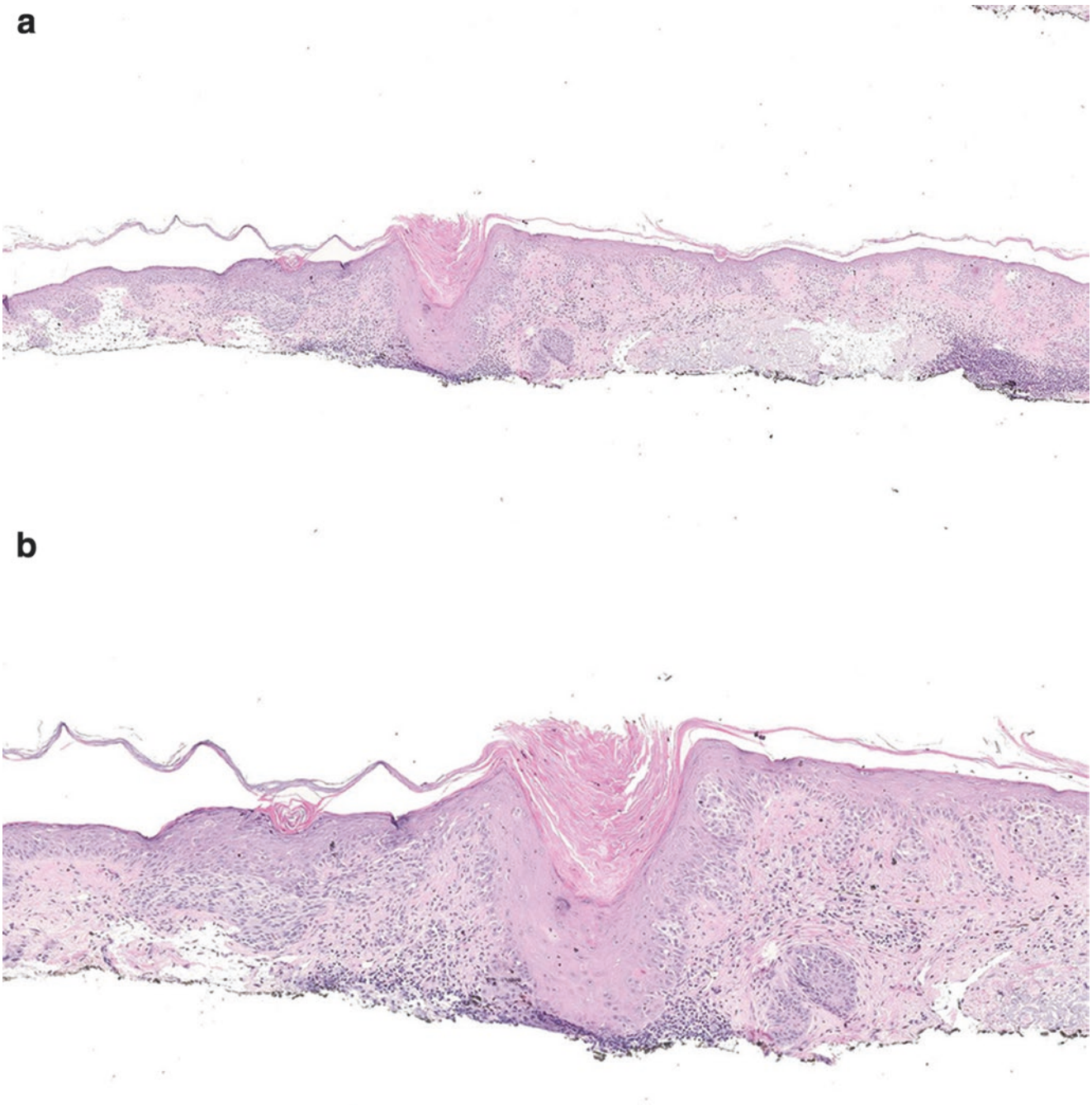


Fig. 7.11 Superficial spreading melanoma in situ with adnexal extension and prominent host response. This lesion is composed of atypical bizarre-shaped nests with increase confluent of growth (**a**). Areas with early epidermal consumption are noted (**b**).

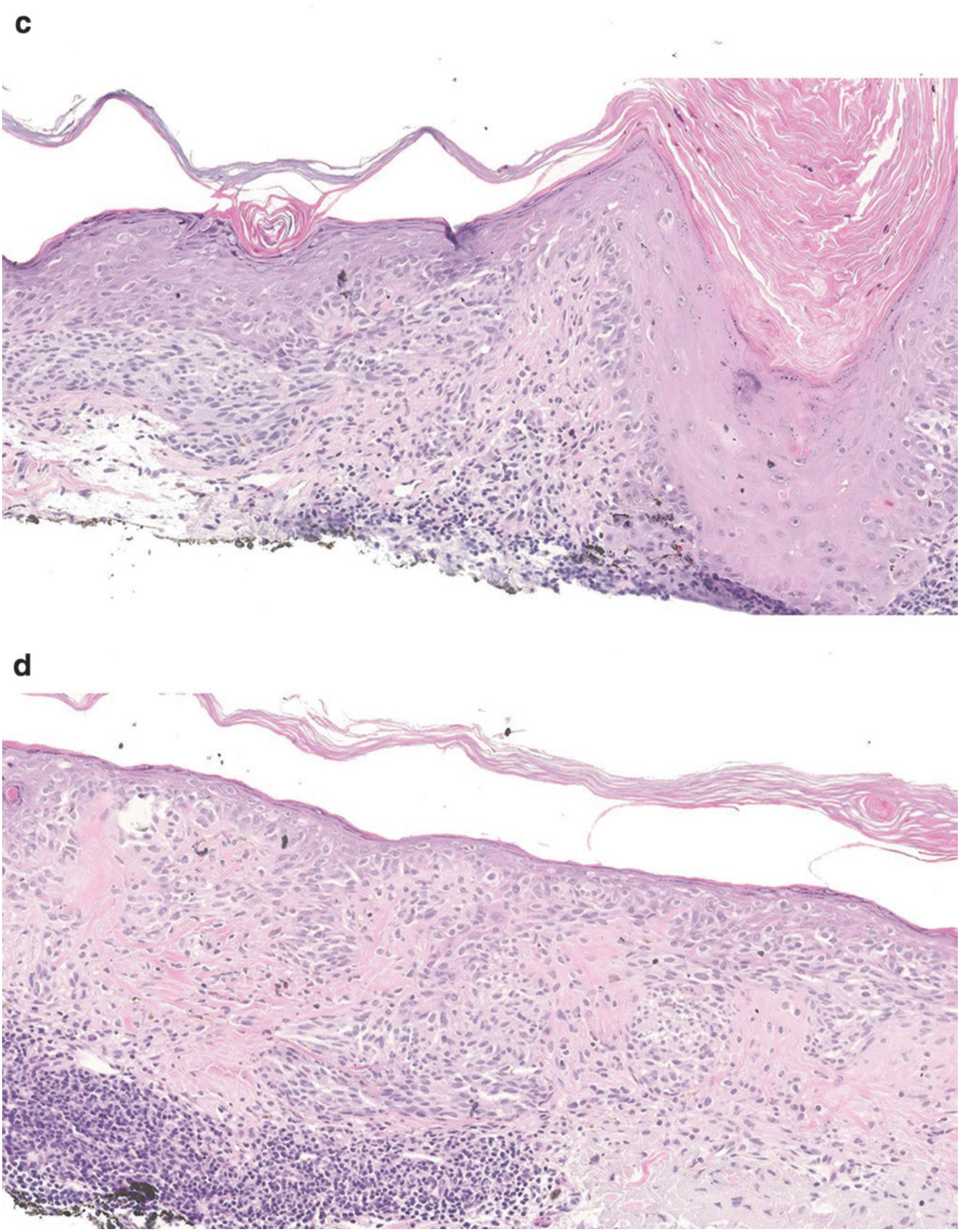


Fig. 7.11 (continued) The lesion shows extensive adnexal extension and increased host response in the dermis (**c**). Areas of superficial invasion are noted in the papillary dermis (**d**)

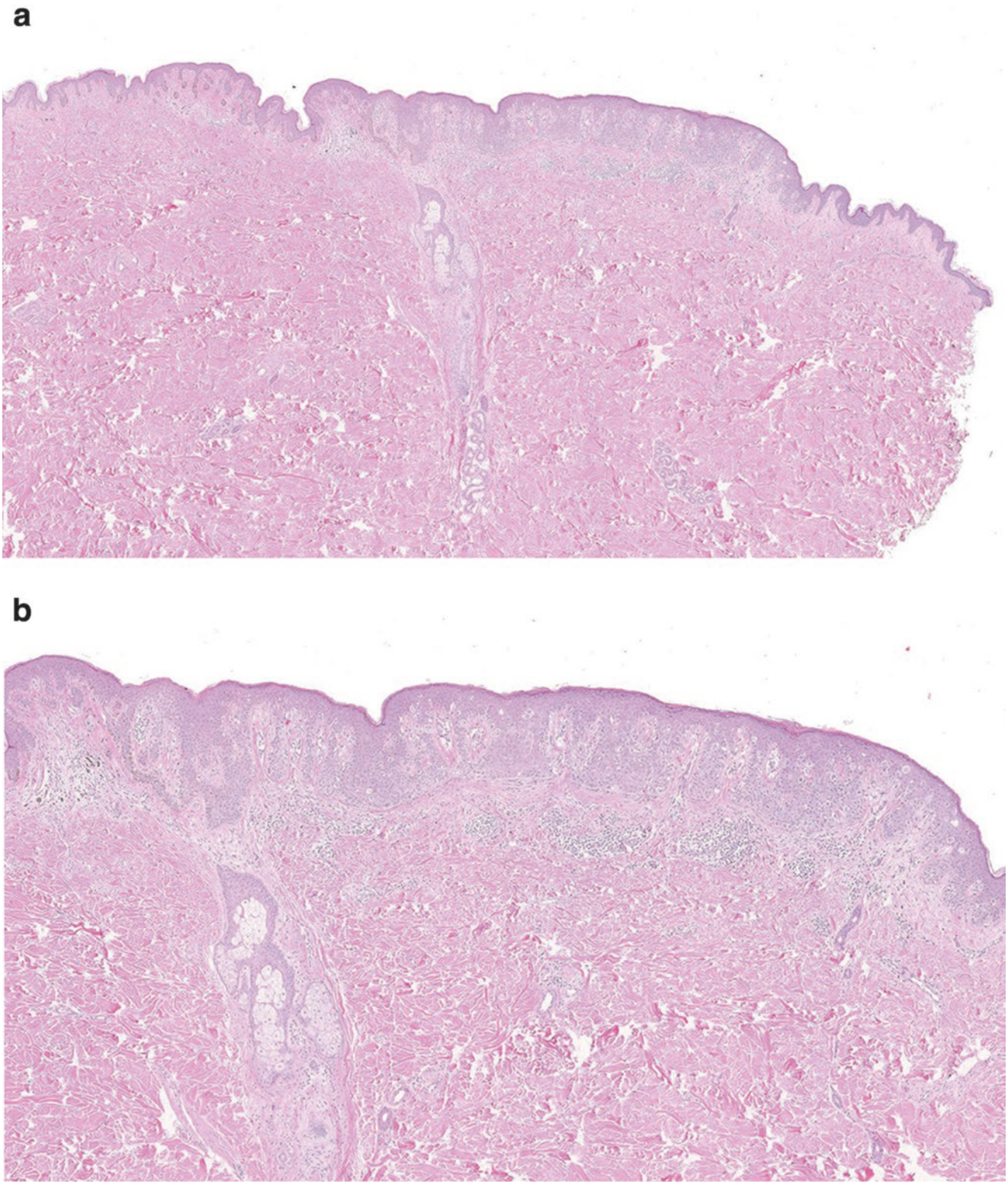


Fig. 7.12 Superficial spreading melanoma in situ. This example shows on low magnification a dysplastic-like architecture, including bridging of rete and fibroplasia of the papillary dermis (**a**, **b**).

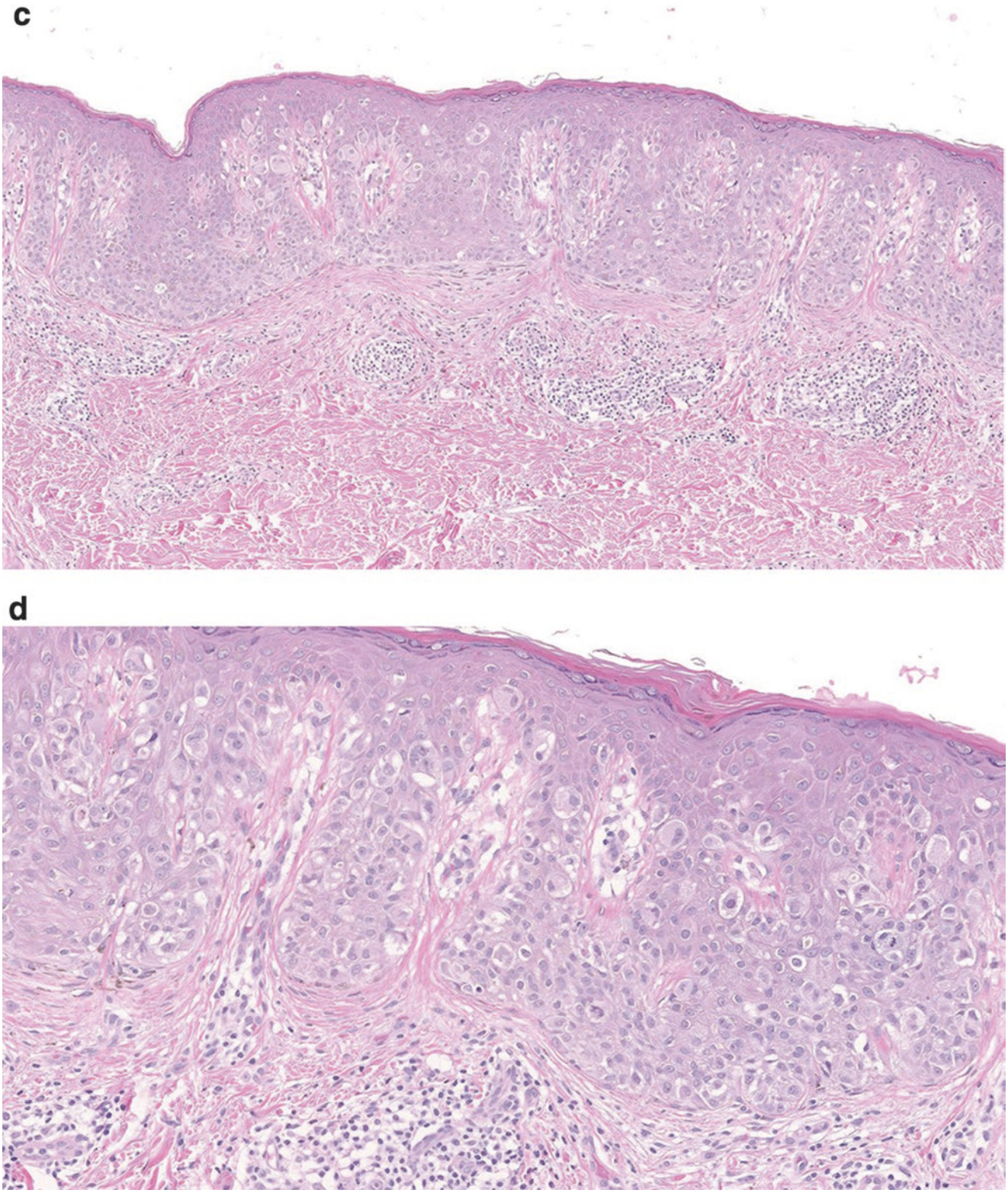


Fig. 7.12 (continued) However, one can clearly identify the increase density of melanocytes in the dermis along with increase number of atypical epithelioid melanocytes with prominent pagetoid spread throughout the thickness of the epidermis. Note the atypical melanocytes involve the rete ridges not only at the tips but the lateral sides and the suprapapillary plates (**c**, **d**)

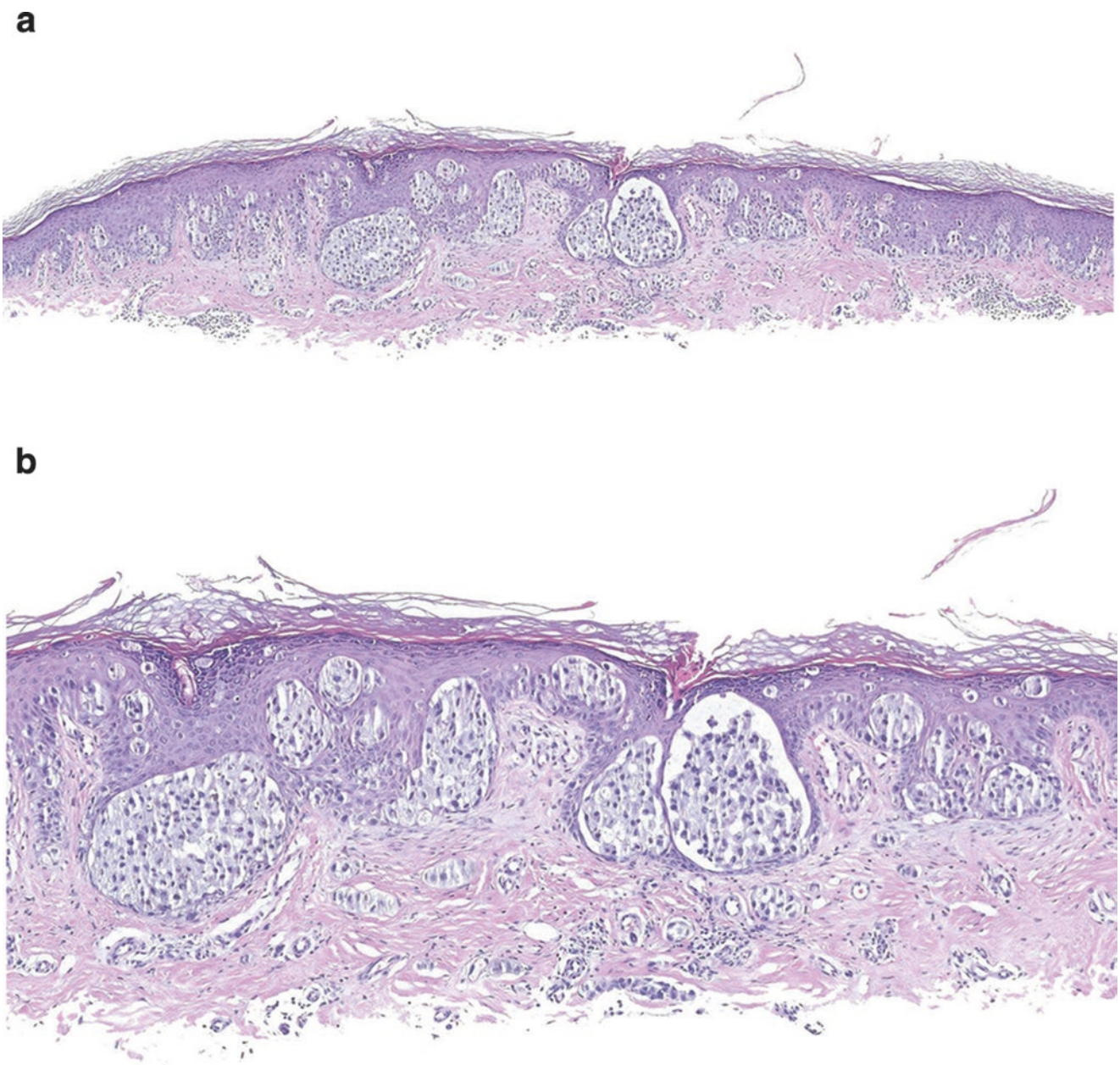


Fig. 7.13 Superficial spreading melanoma with superficial invasion. This example displays a lesion that is primarily composed of nests in the epidermis. Note variable size and shape of nests with areas. Areas with pagetoid growth (**a**, **b**).

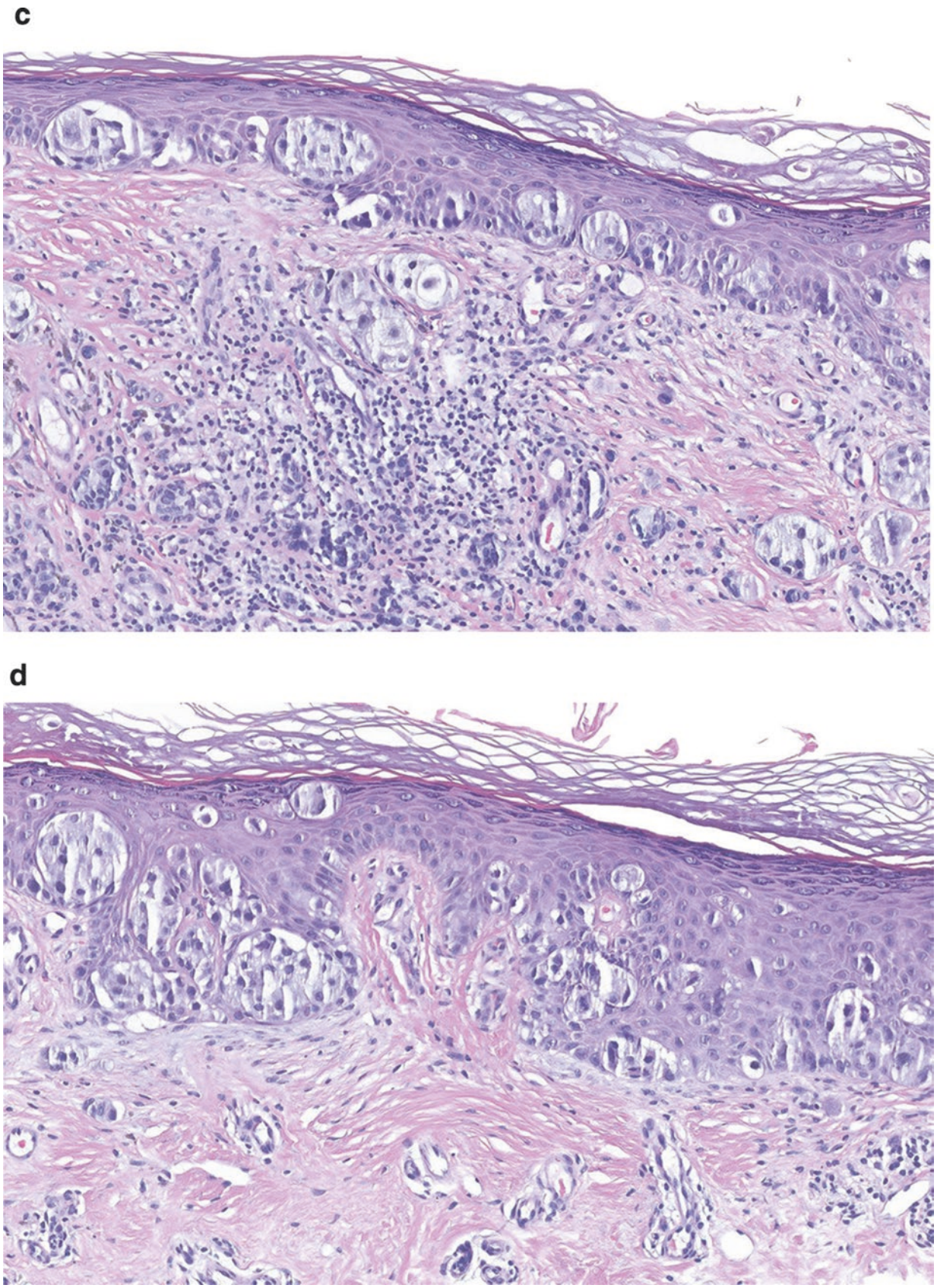


Fig. 7.13 (continued) The cells are round, with pleomorphic nuclei, and have a characteristic ample pale cytoplasm. Note that early invasion is seen in the papillary dermis (**c**, **d**)

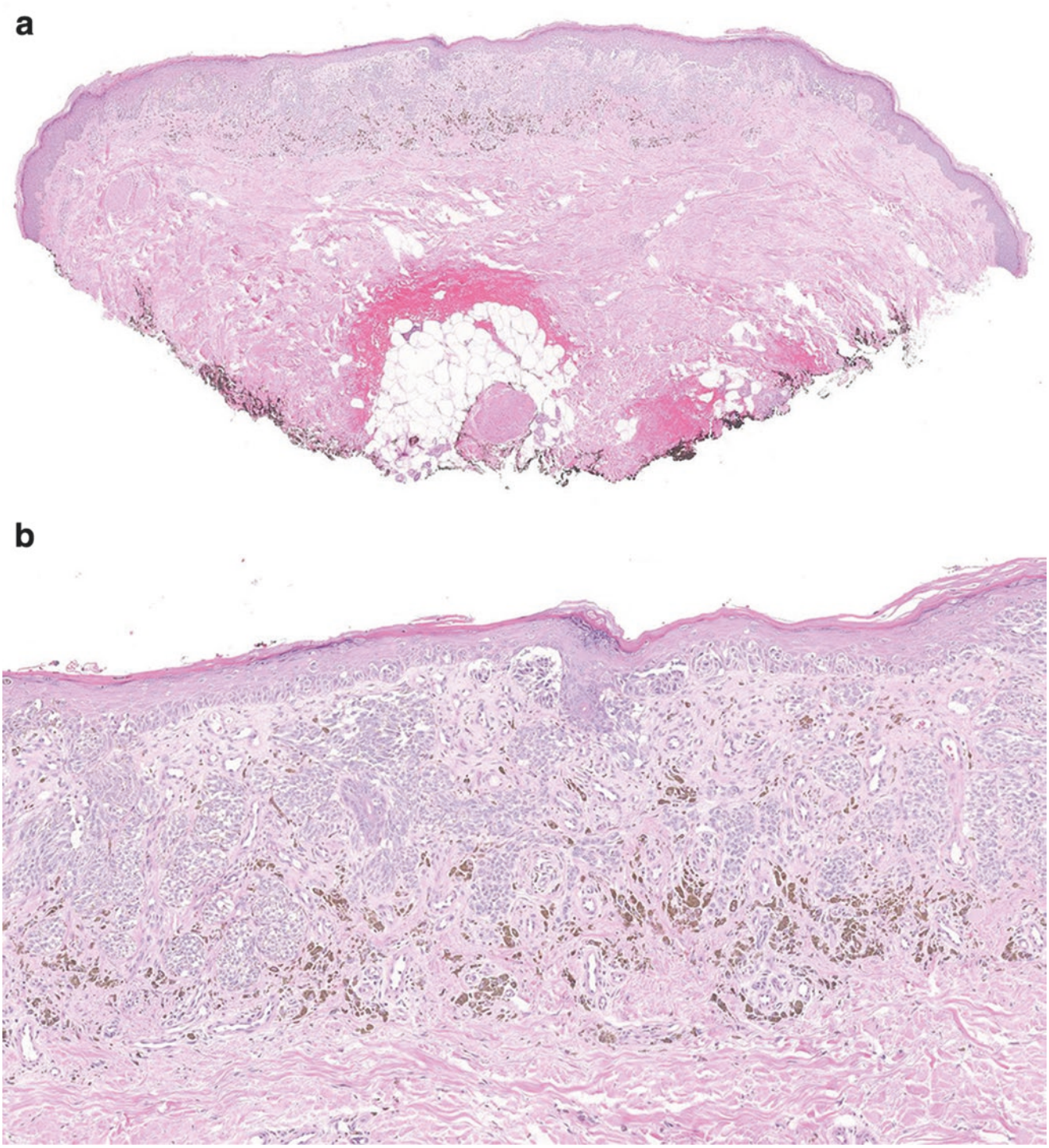


Fig. 7.14 Invasive superficial spreading melanoma. This example shows areas of clear invasion along with areas of early regression. The in situ component of the lesion has a single-cell growth with nested formation and pagetoid growth. In the dermis, the atypical melanocytes involve the reticular dermis (**a**, **b**).

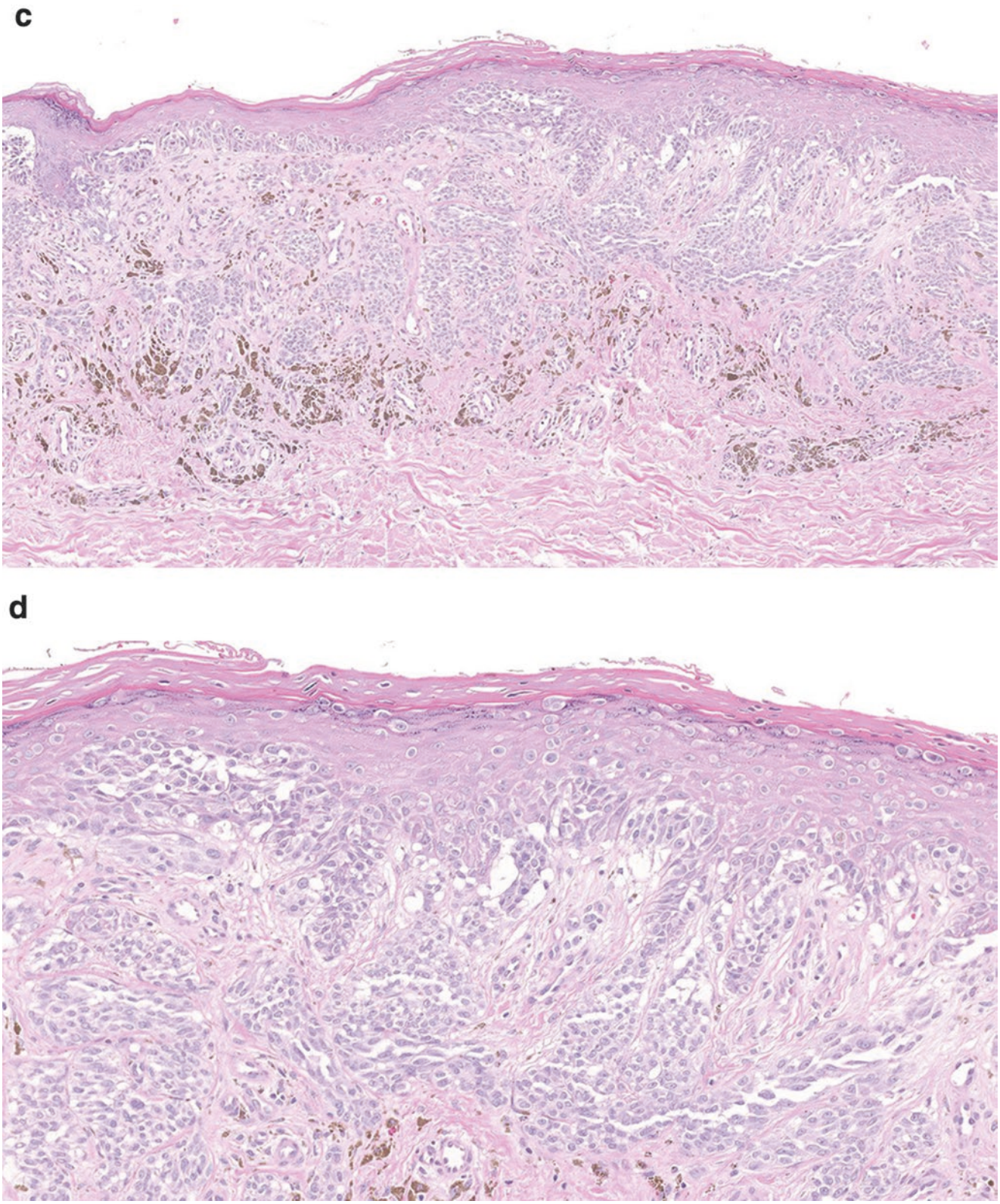


Fig. 7.14 (continued) On high magnification, the melanocytes in the dermis are pleomorphic, lack maturation, and have similar morphology to those seen in the overlying epidermis. There are early areas of regression composed of pigment incontinence, angiogenesis, and minimal dermal fibrosis (**c**, **d**)

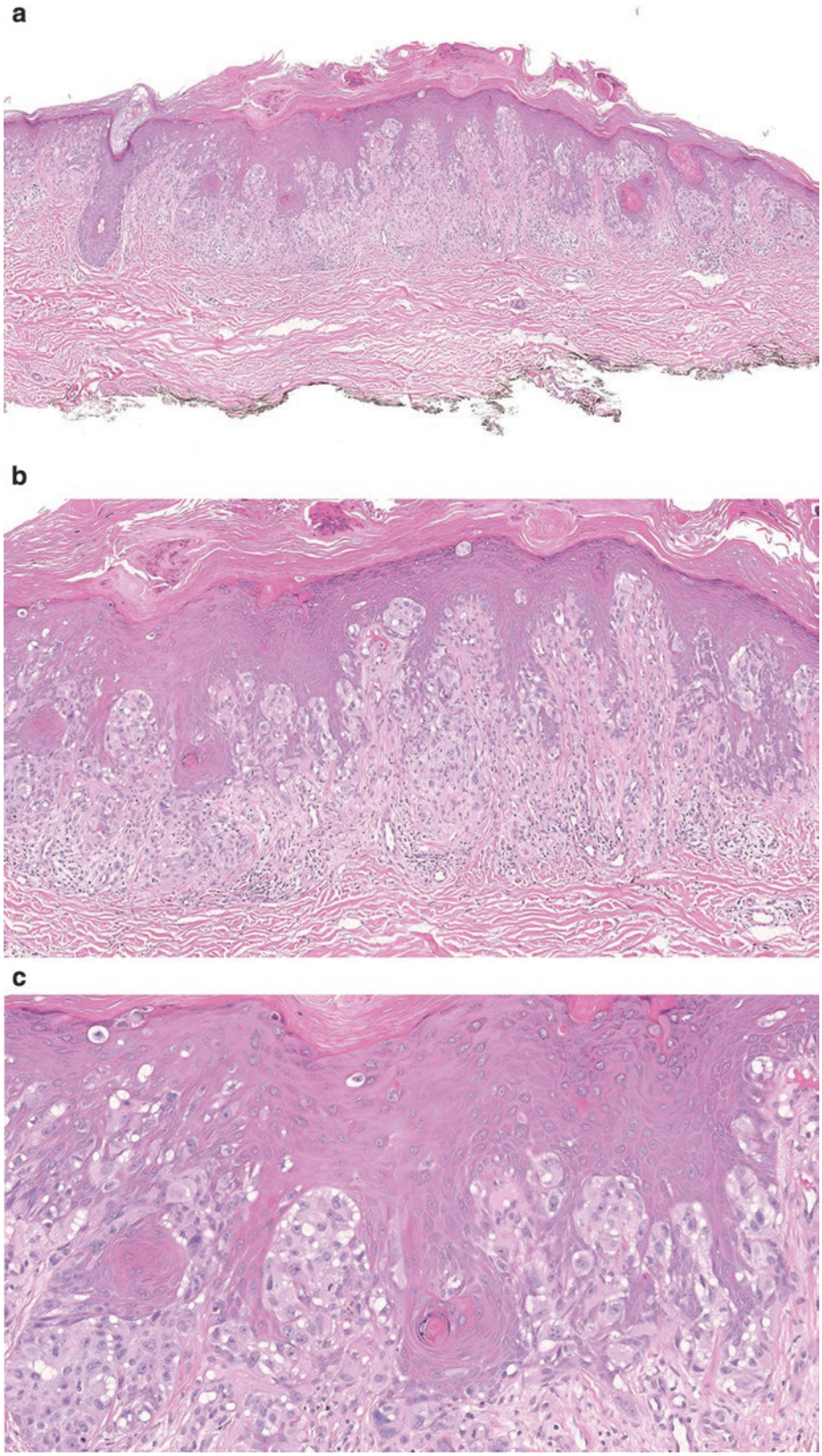


Fig. 7.15 Superficial spreading melanoma with pseudoepitheliomatous hyperplasia. This example shows epidermal hyperplasia (which is not unusually seen in melanoma) along with an atypical growth of melanocytes in both the epidermis and dermis (**a**, **b**). The cells in the epidermis have a single-cell growth with pagetoid growth. The cells in the dermis are reminiscent to those seen in the epidermis. The melanocytes are epithelioid in shape and display an ample eosinophilic cytoplasm (**c**)

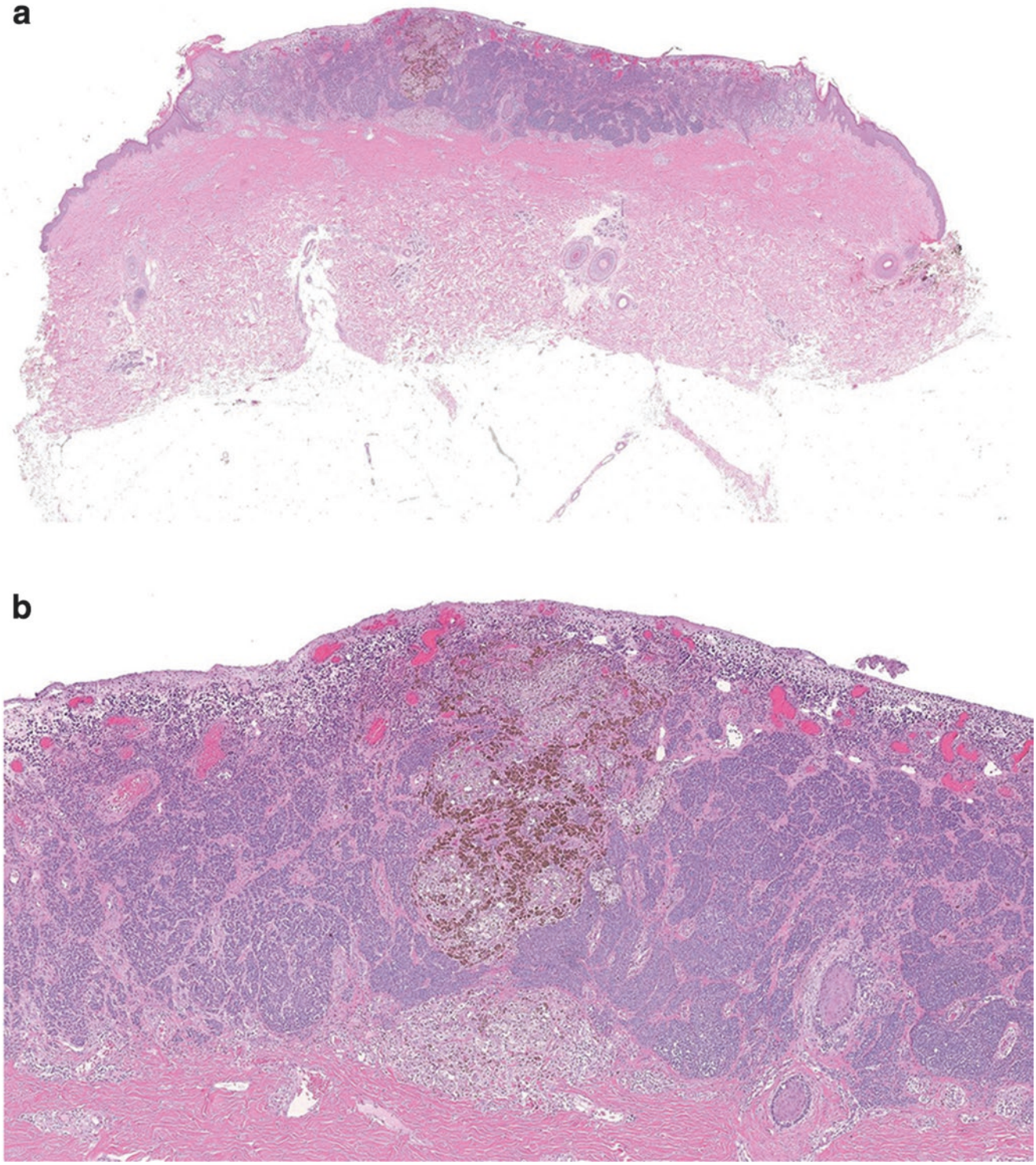


Fig. 7.16 Ulcerated superficial spreading melanoma composed of epithelioid pigmented and nonpigmented melanocytes. This example of invasive melanoma shows ulceration, but the viable epidermis shows a massive growth of atypical intraepidermal melanocytes with pagetoid growth (**a**, **b**).

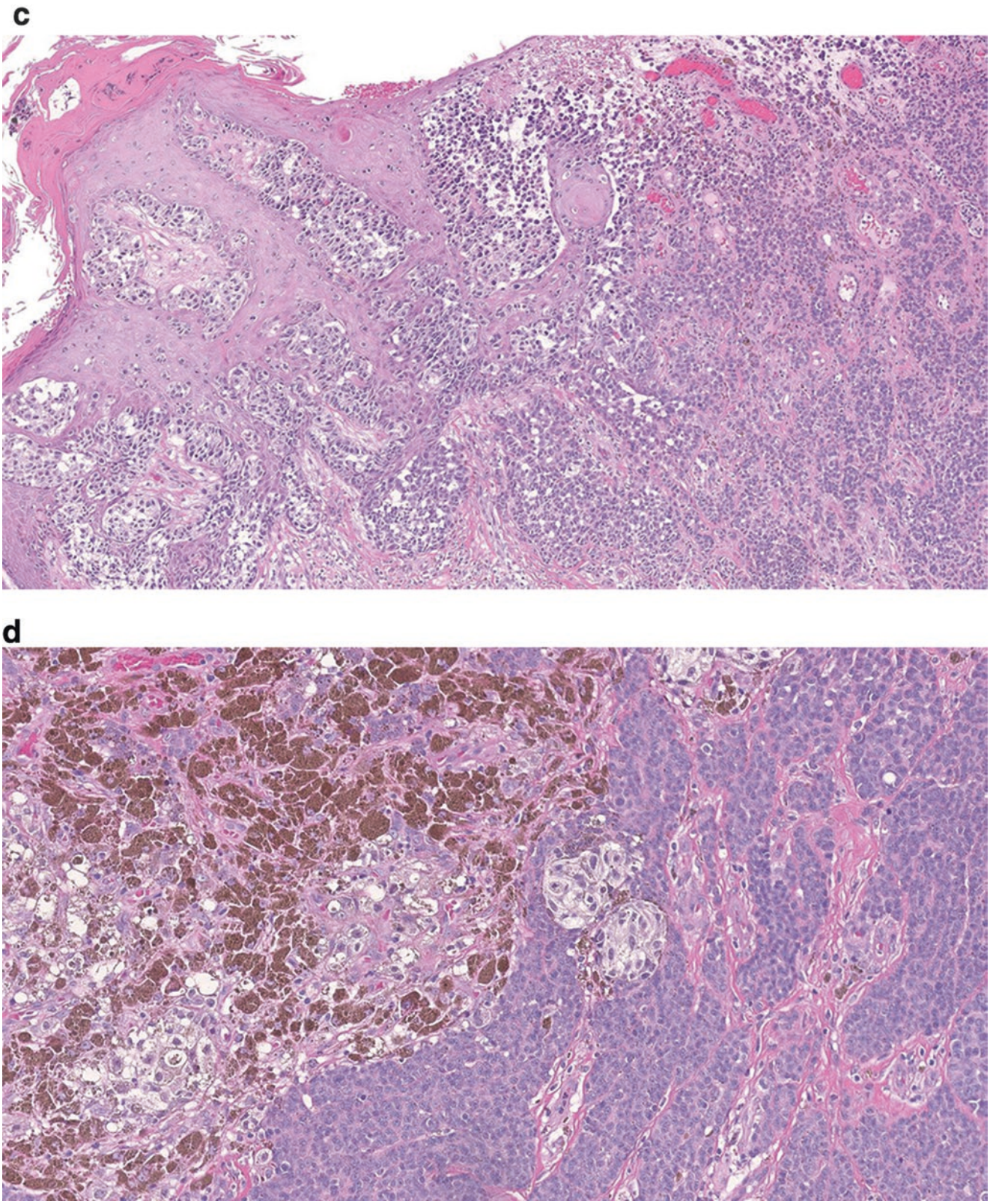


Fig. 7.16 (continued) The dermal component shows a biphenotypic component. Most of the dermal component is composed of lymphocyte-like melanocytes with a small to medium hyperchromatic nuclei; however, the center of the lesion shows pigmented epithelioid cells with ample dusky to pale cytoplasm with prominent nuclear pleomorphism (**c**, **d**)

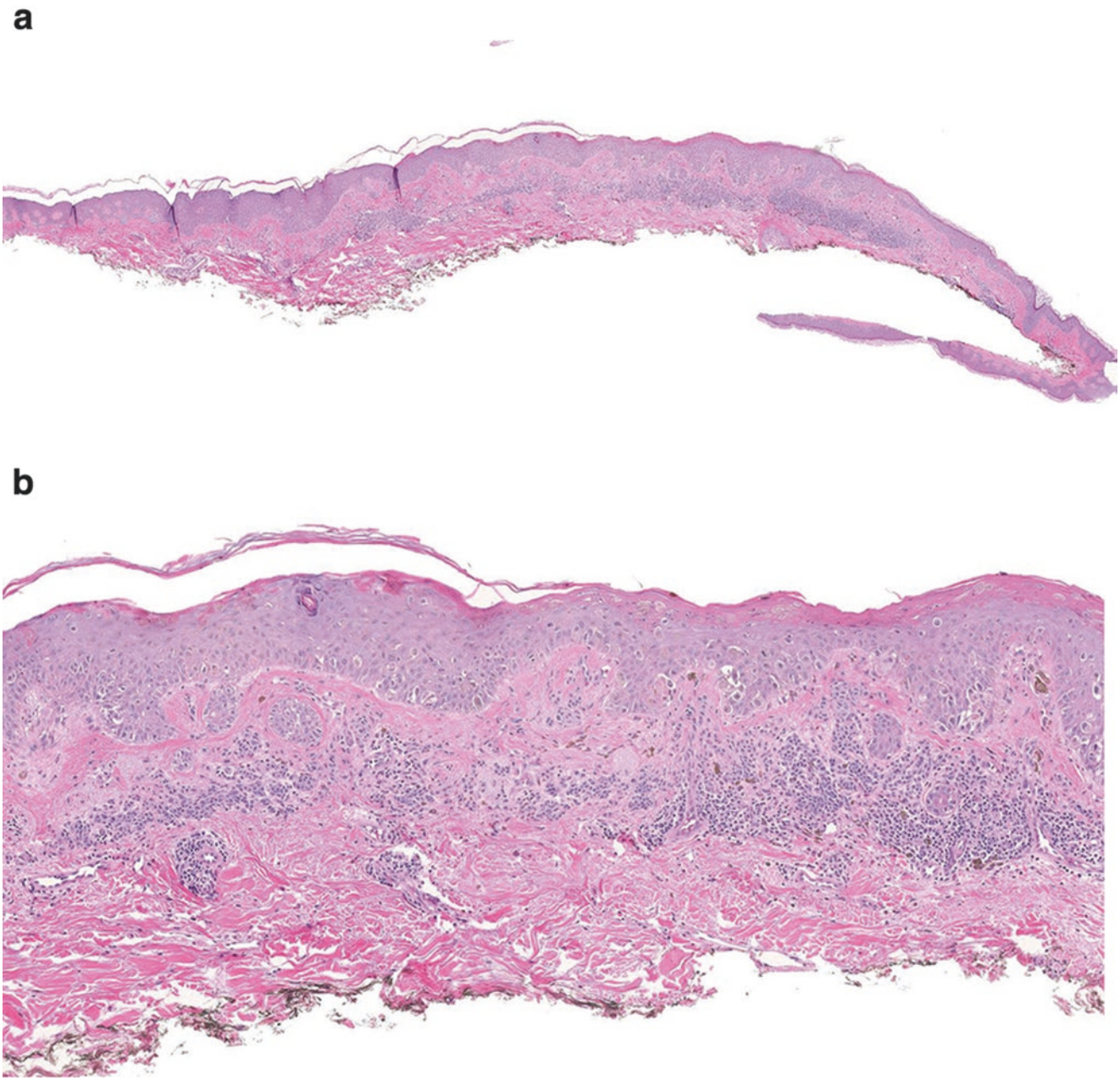


Fig. 7.17 Superficial spreading melanoma associated with nevus. This example shows melanoma in situ composed of atypical intraepidermal growth composed of single and nested melanocytes with pagetoid growth. In the dermis, there is a nevus that is cytologically different from the growth in the overlying epidermis (**a**, **b**).

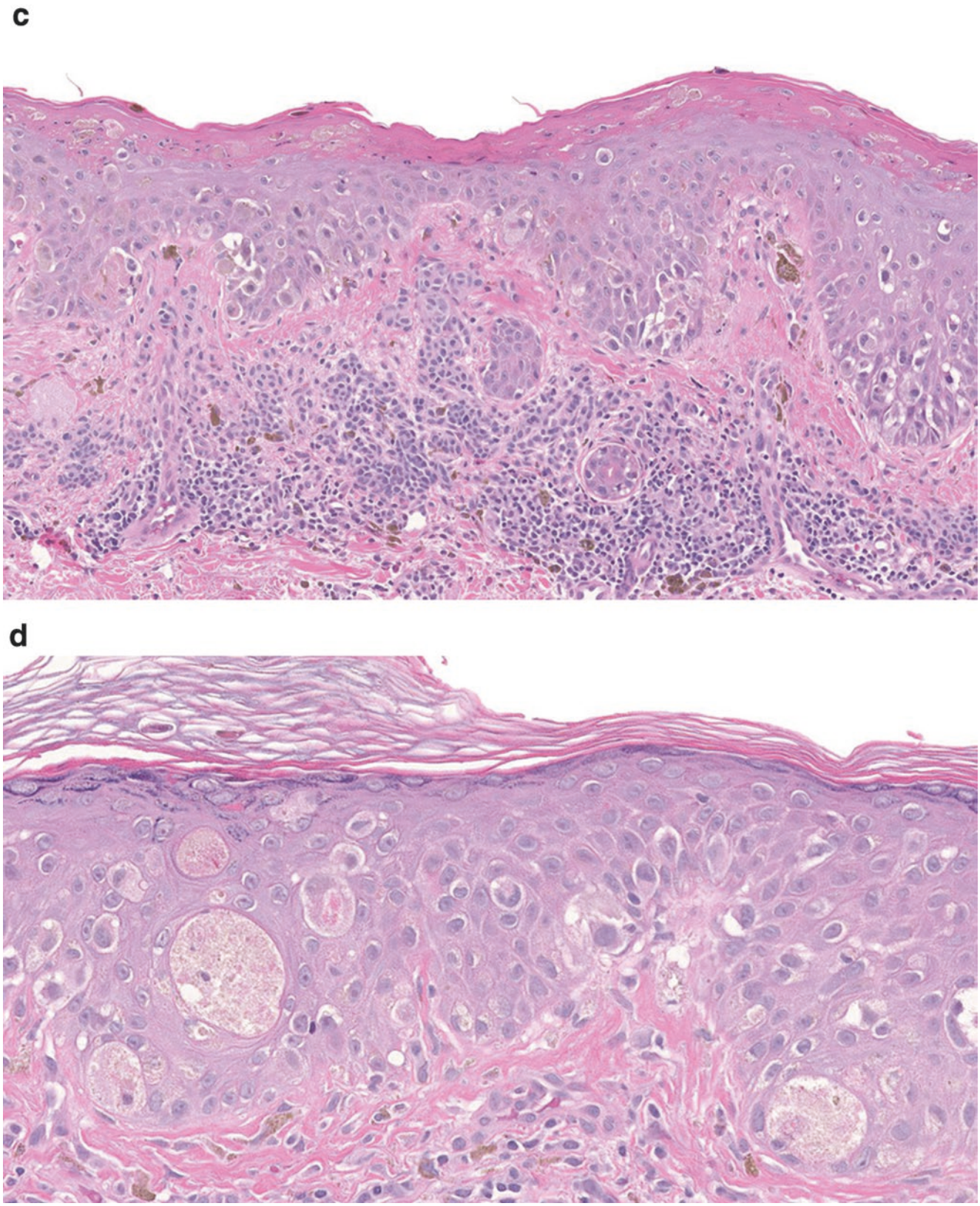


Fig. 7.17 (continued) Per the patient, he observed a pigmented lesion on his arm since he can remember but recently the lesion has grown in size. Note that the melanocytes in the dermis show no cytologic atypia and normally mature toward the base. Also, the dermal stroma surrounding the dermal melanocytes shows normal collagen without the presence of desmoplasia or fibrosis (which is commonly seen in invasive melanomas) (**c**, **d**)

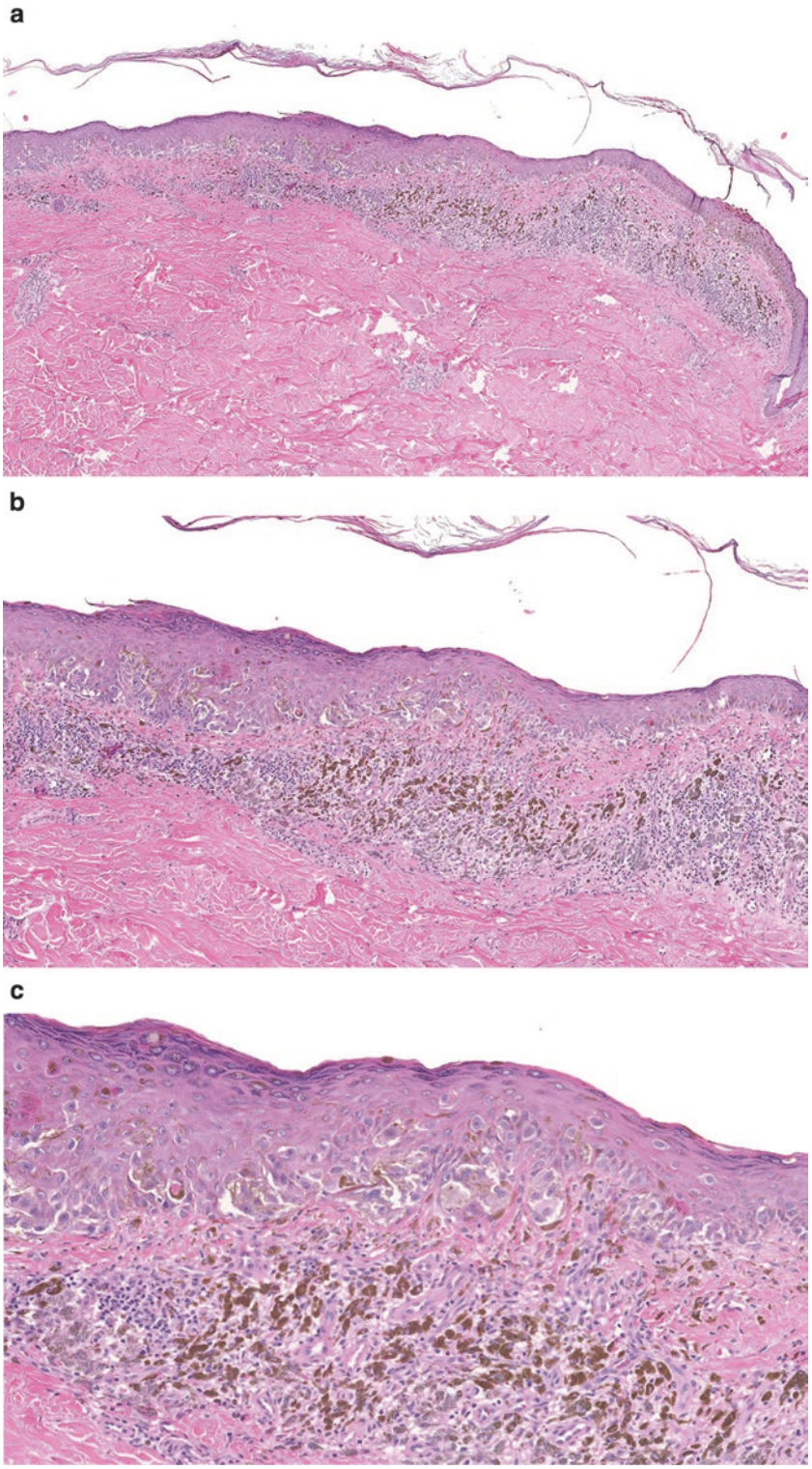


Fig. 7.18 Superficial spreading melanoma with dermal regression. This case shows a melanoma in situ along with dermal fibrosis and pigment incontinence (**a**). Also, note the early vacuolar damage of the epidermis with rare dyskeratotic cells which is not unusually seen in regressing melanomas (**b**). The overlying epidermis displays severe cytologic atypia of the melanocytes along atypical nests that have confluent growth and single-cell melanocytes with pagetoid upward migration (**c**)

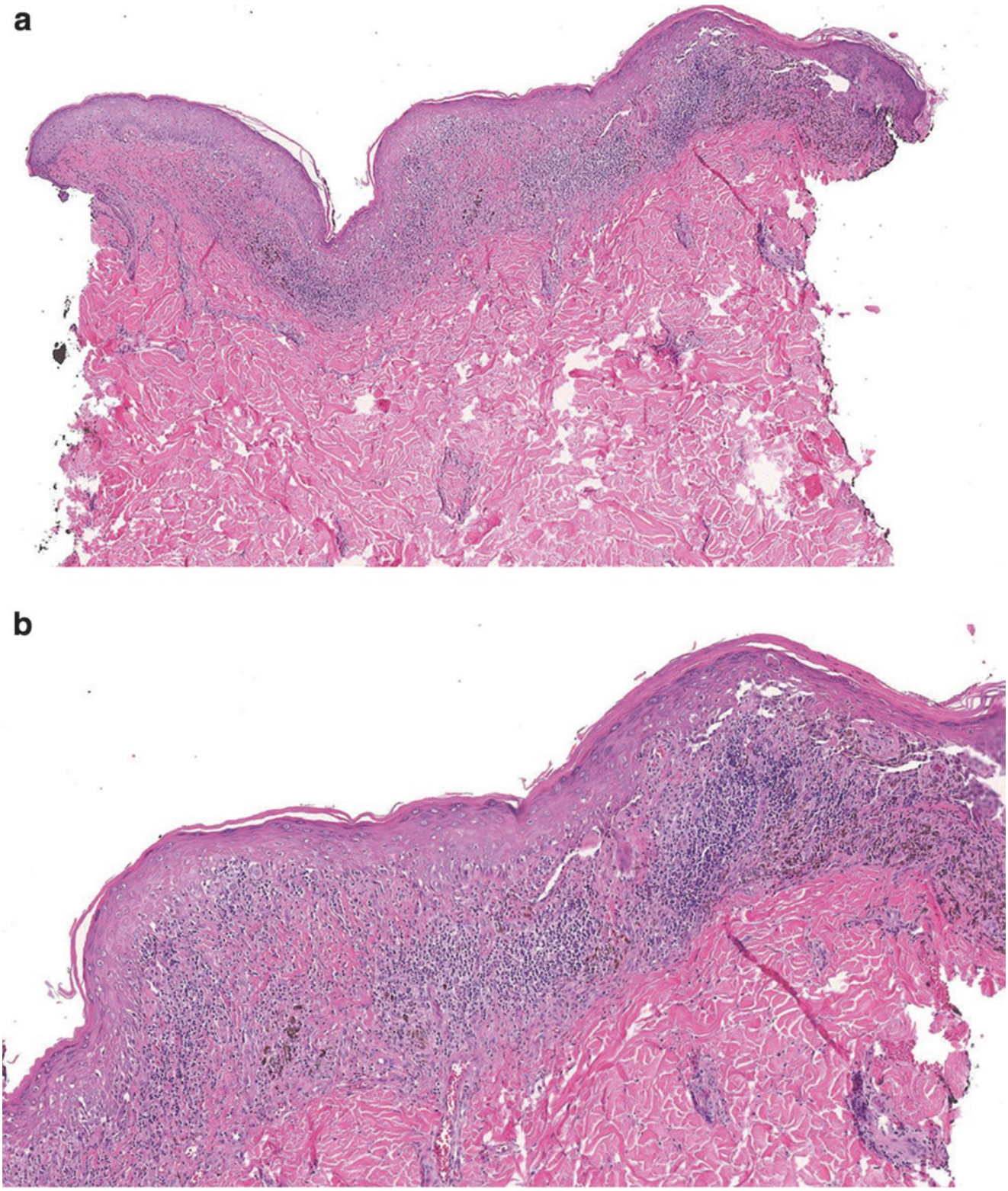


Fig. 7.19 Superficial spreading melanoma with lichenoid tissue reaction. This is a challenging case as it can mimic lichenoid keratosis or lichenoid dermatitis. Note the epidermal acanthosis, thickened granular layer, vacuolar alteration of the dermal-epidermal junction, and clear lichenoid inflammation in the dermis (**a**, **b**).

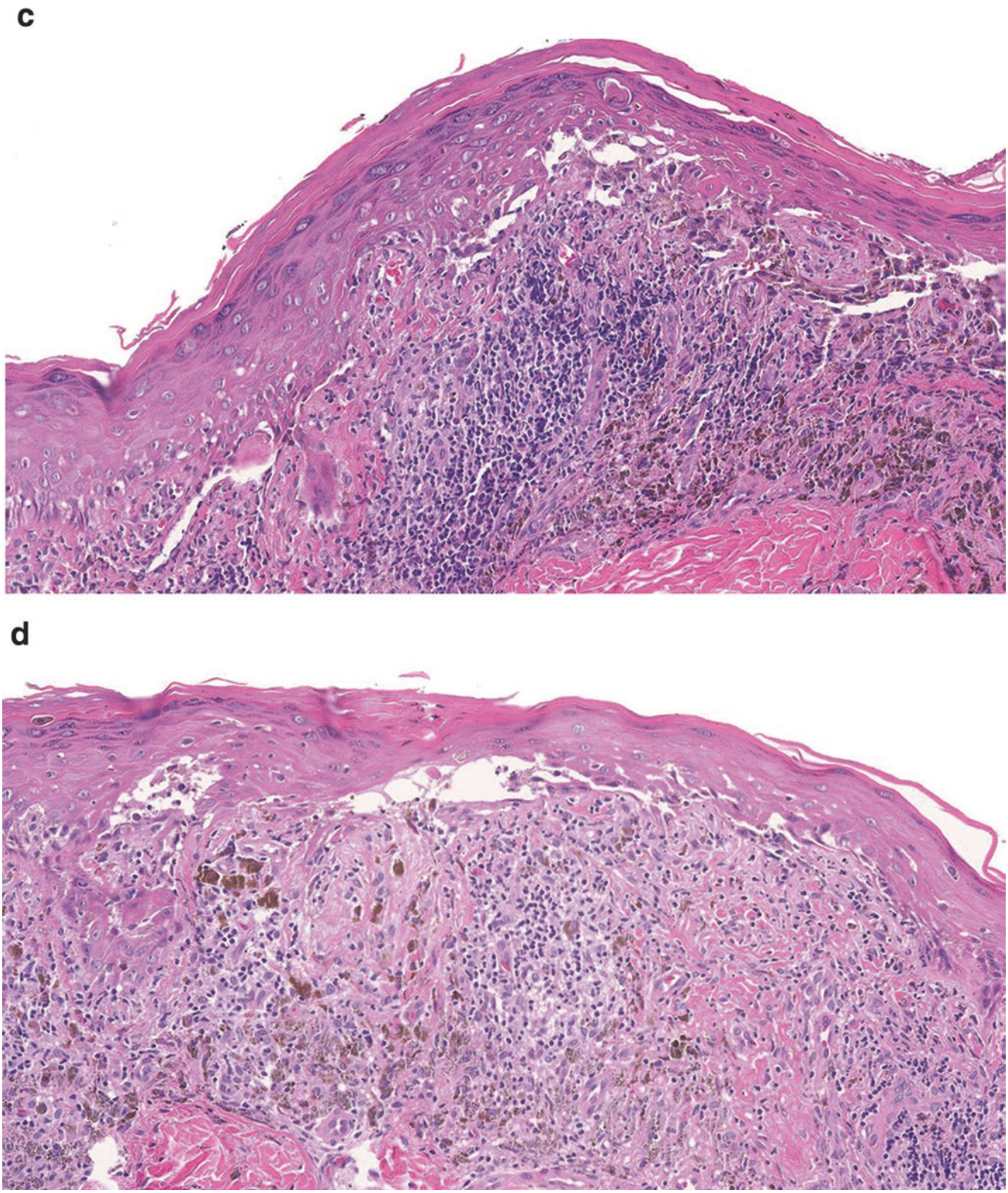


Fig. 7.19 (continued) After careful inspection, one can identify the atypical population of melanocytes that is located at the edge of the biopsy and forming an atypical confluent growth of intraepidermal melanocytes (**c**, **d**). Remember that lichenoid keratosis can show pseudomelanocytic nests; however, in this example the nests are larger and broader than those seen in cases of lichenoid keratosis. In cases like this, immunostains (MART-1, SOX10, or MITF-1) are an important ancillary test as it can help to delineate the atypical junctional component (keep in mind that pseudonests in lichenoid keratosis can also be highlighted with immunostains)

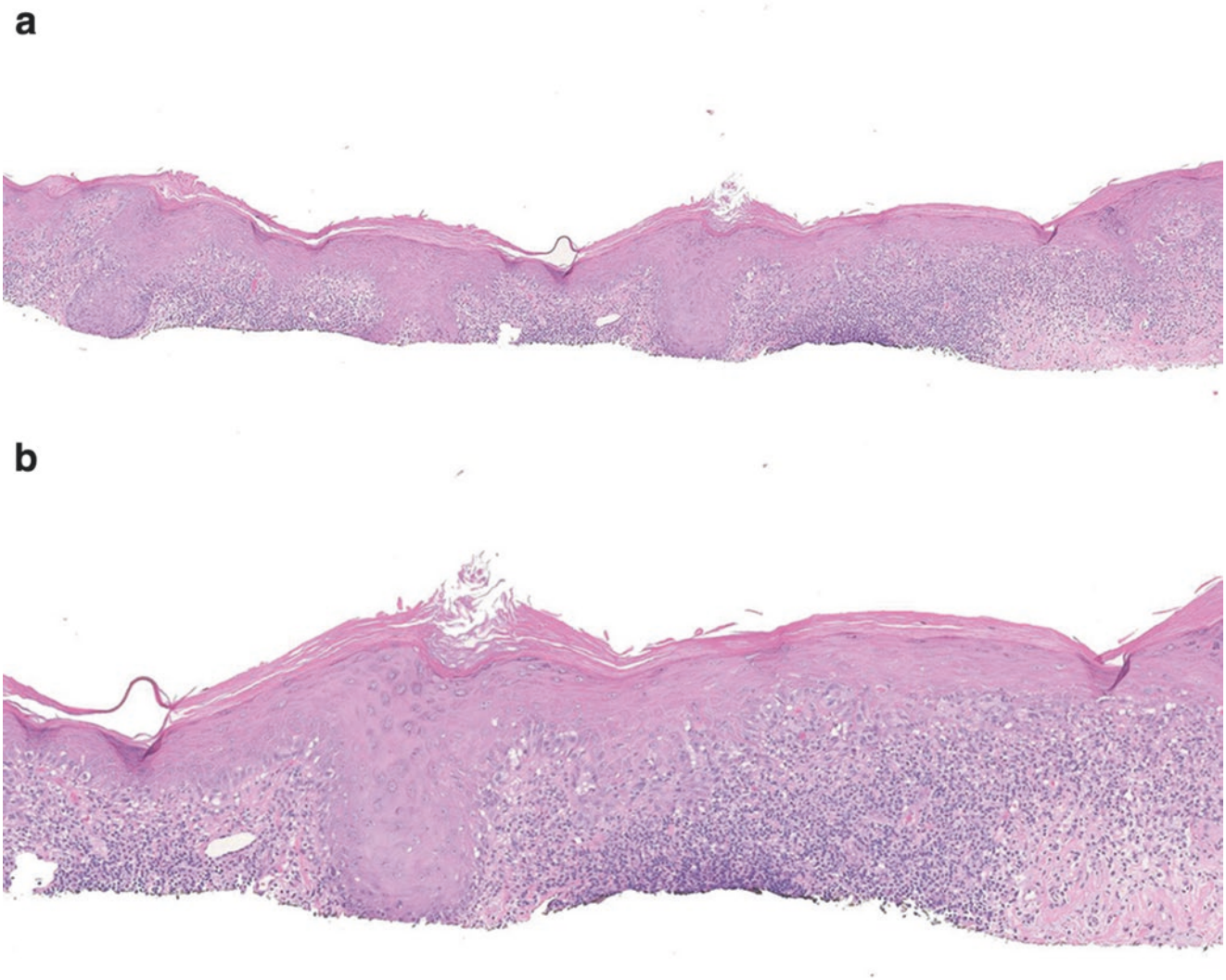


Fig. 7.20 Superficial spreading melanoma with lichenoid tissue reaction. This example also shows a lichenoid inflammatory reaction in the dermis (**a**, **b**).

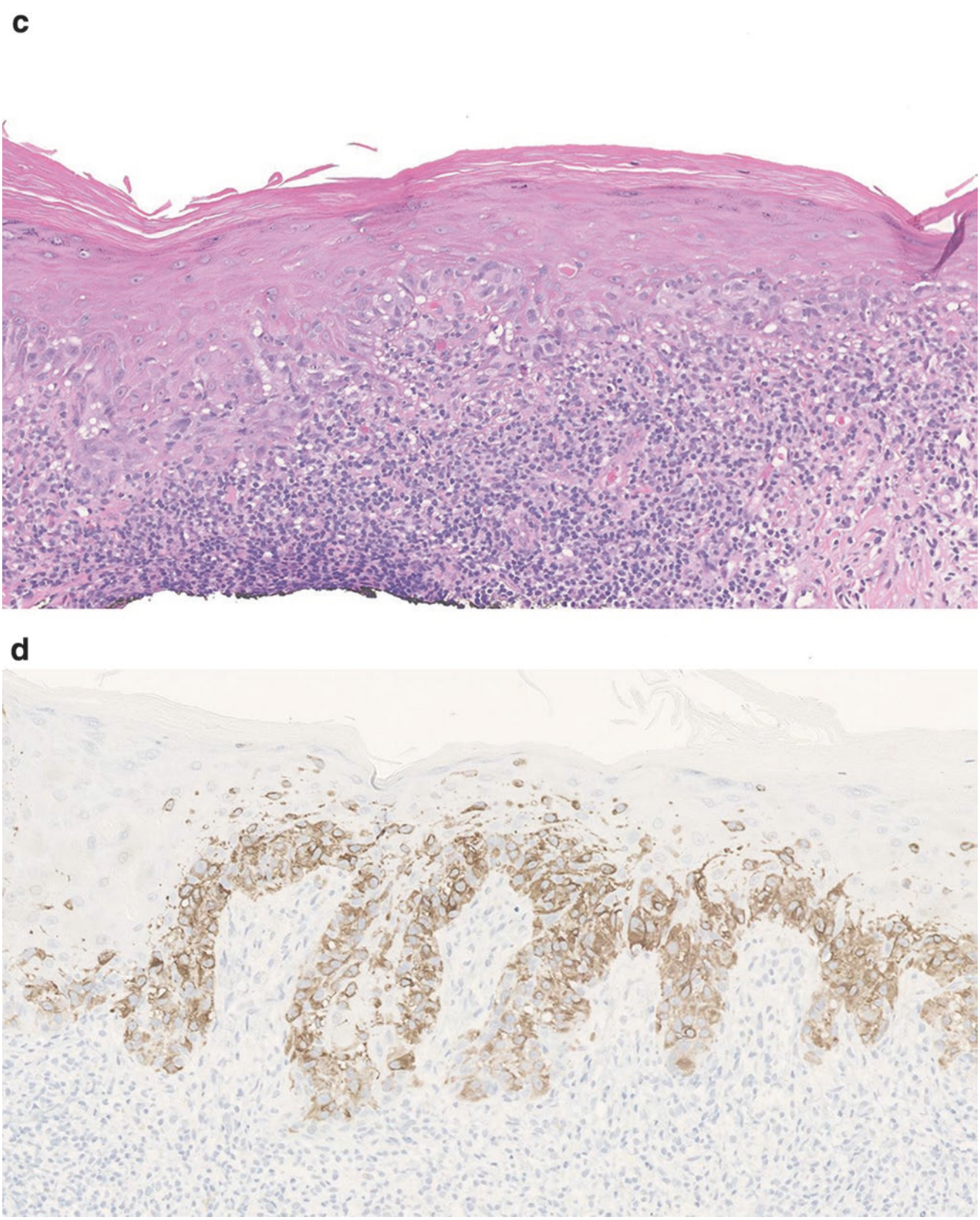


Fig. 7.20 (continued) Note the subtle epidermal component that shows atypical melanocytes in a confluent growth along with focal pagetoid upward migration (**c**). Note the presence of scattered dyskeratotic cells and vacuolar damage of the dermal-epidermal junction. MART-1 is helpful, as it delineates clearly the atypical population of melanocytes within the epidermis (**d**)

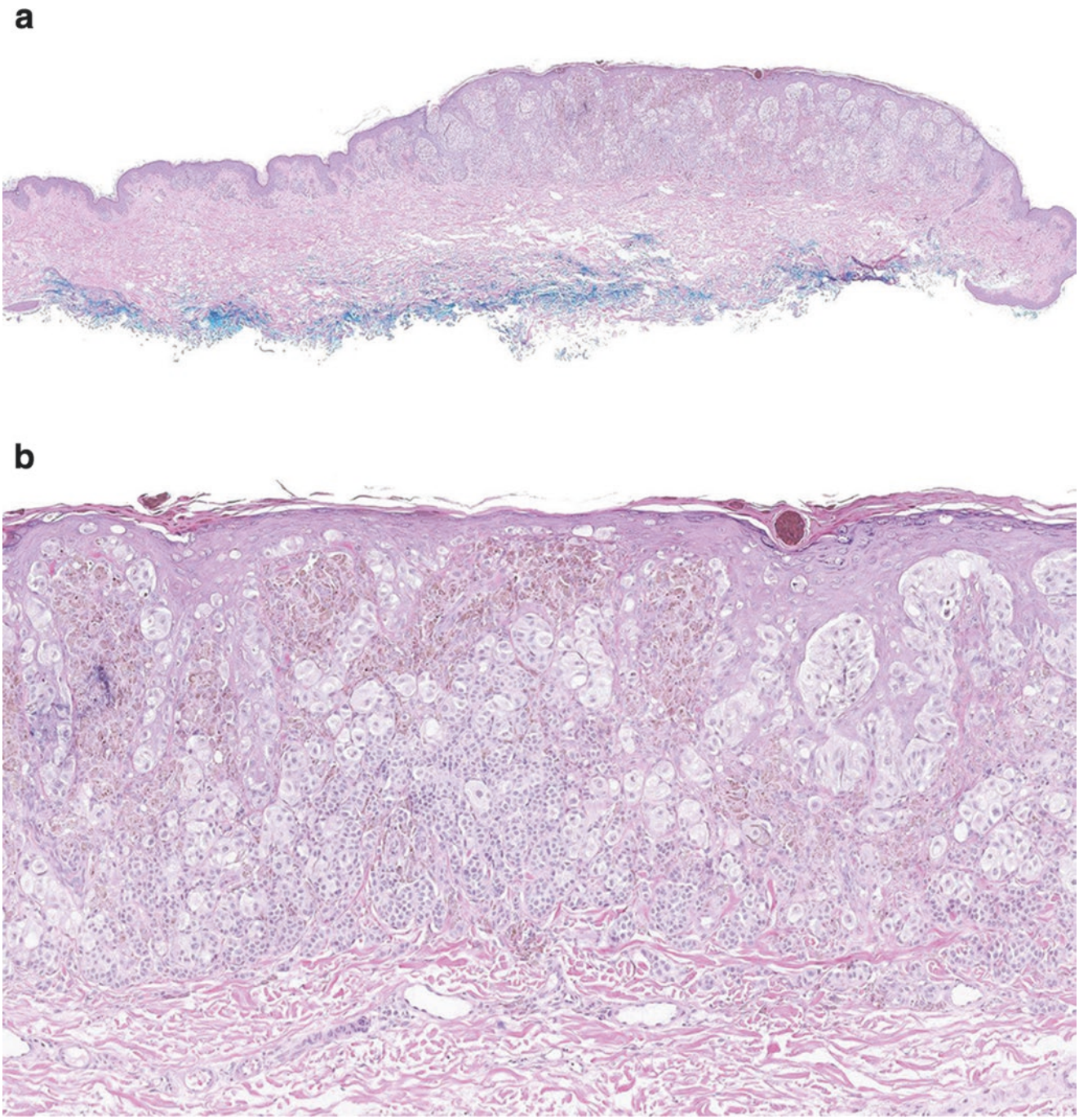


Fig. 7.21 Superficial spreading melanoma with epithelioid melanocytes. This lesion is primarily composed of epithelioid melanocytes. The epidermis shows scattered nests with single pagetoid melanocytes (**a**). Most melanocytes have an epithelioid morphology with clear/pale cytoplasm, severe cytologic atypia, and nuclear pleomorphism (**b**).

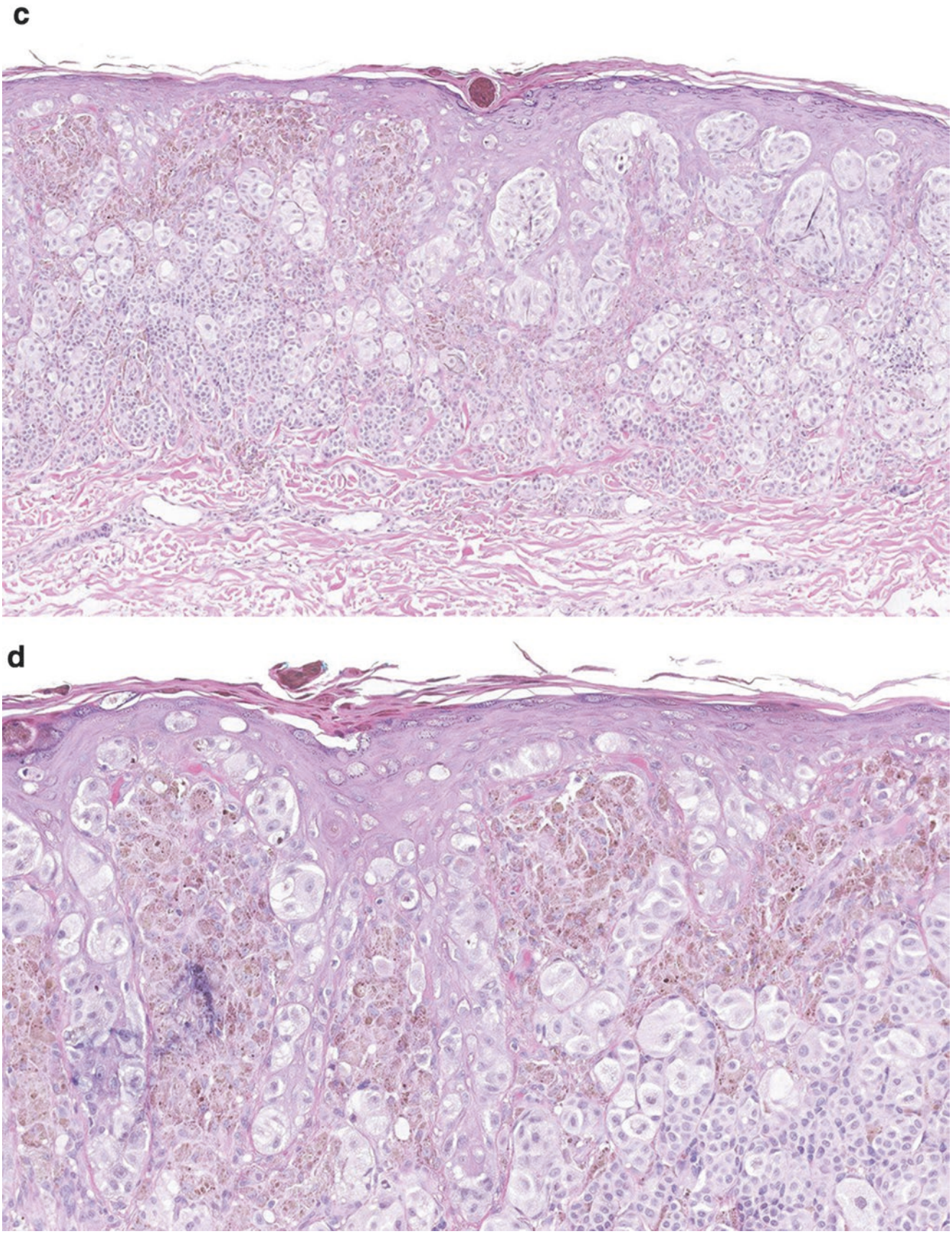


Fig. 7.21 (continued) The dermal component shows similar cytomorphology (**c**). The epithelioid melanocytes have a dusky cytoplasm (**d**)

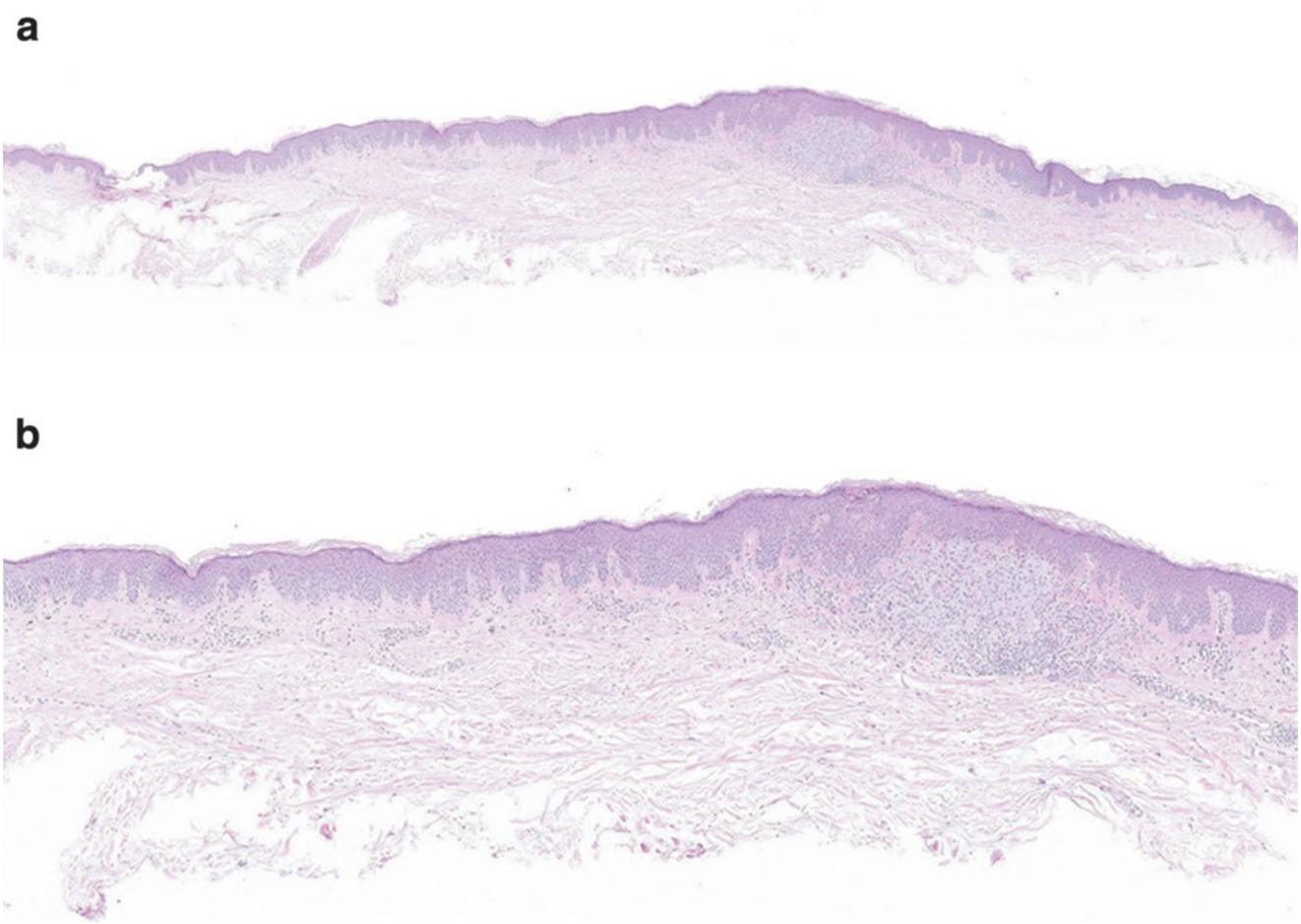


Fig. 7.22 Superficial spreading melanoma with invasive nevoid component. This a challenging case, as on low power the lesion is quite subtle (**a**). At medium magnification, one can identify the increase number of intraepidermal melanocytes in a single-cell pattern without nest formation (**b**).

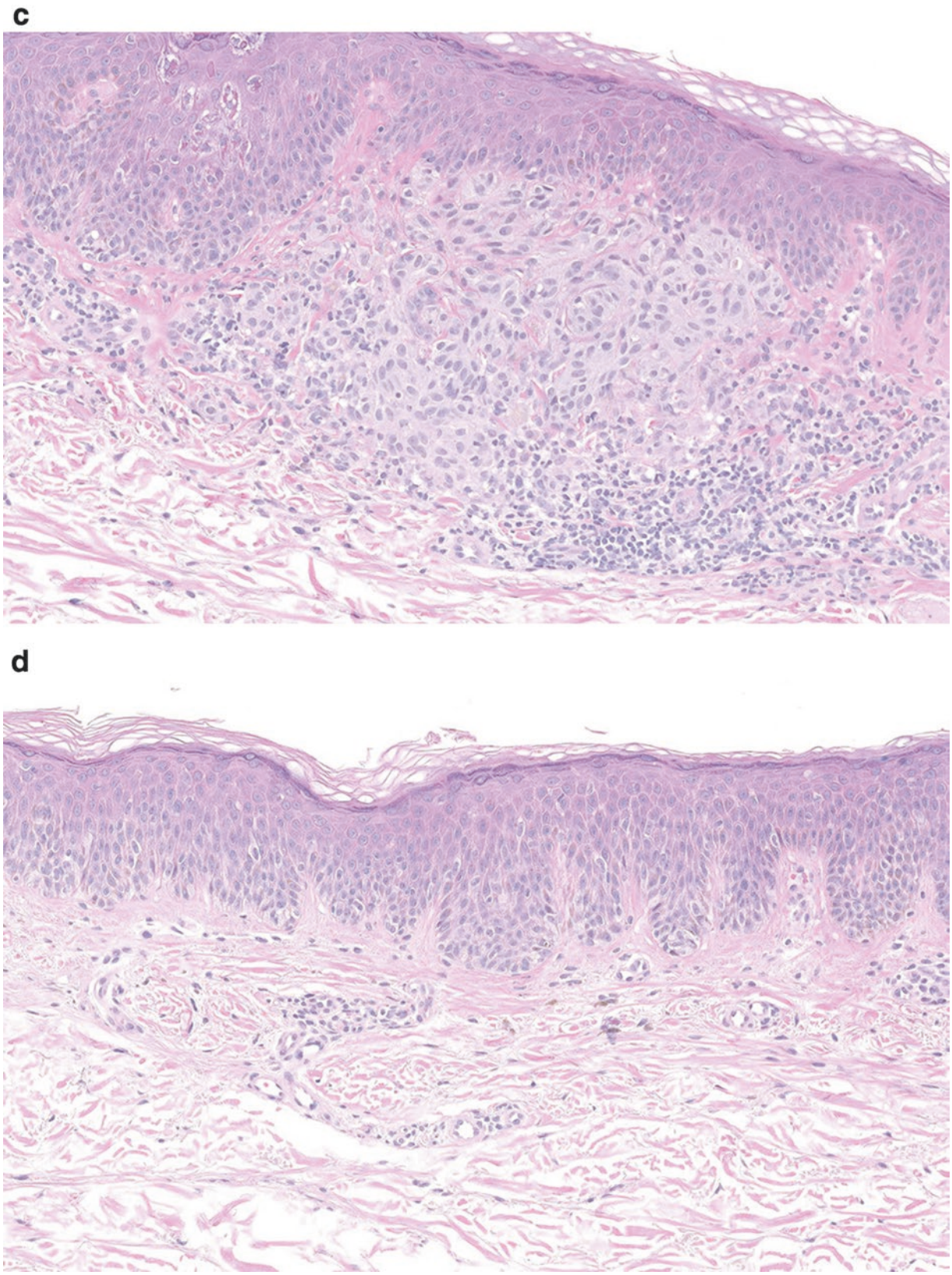


Fig. 7.22 (continued) The intraepidermal growth is subtle; however, there is prominent pagetoid growth throughout all levels of the epidermis (immunostains can be helpful in such cases, as it delineates clearly the atypical melanocytes). There is a small invasive component in which the melanocytes have a nevoid growth; however, there is lack of maturation and presence of enough cytologic atypia to interpret this as invasive component (**c**, **d**)

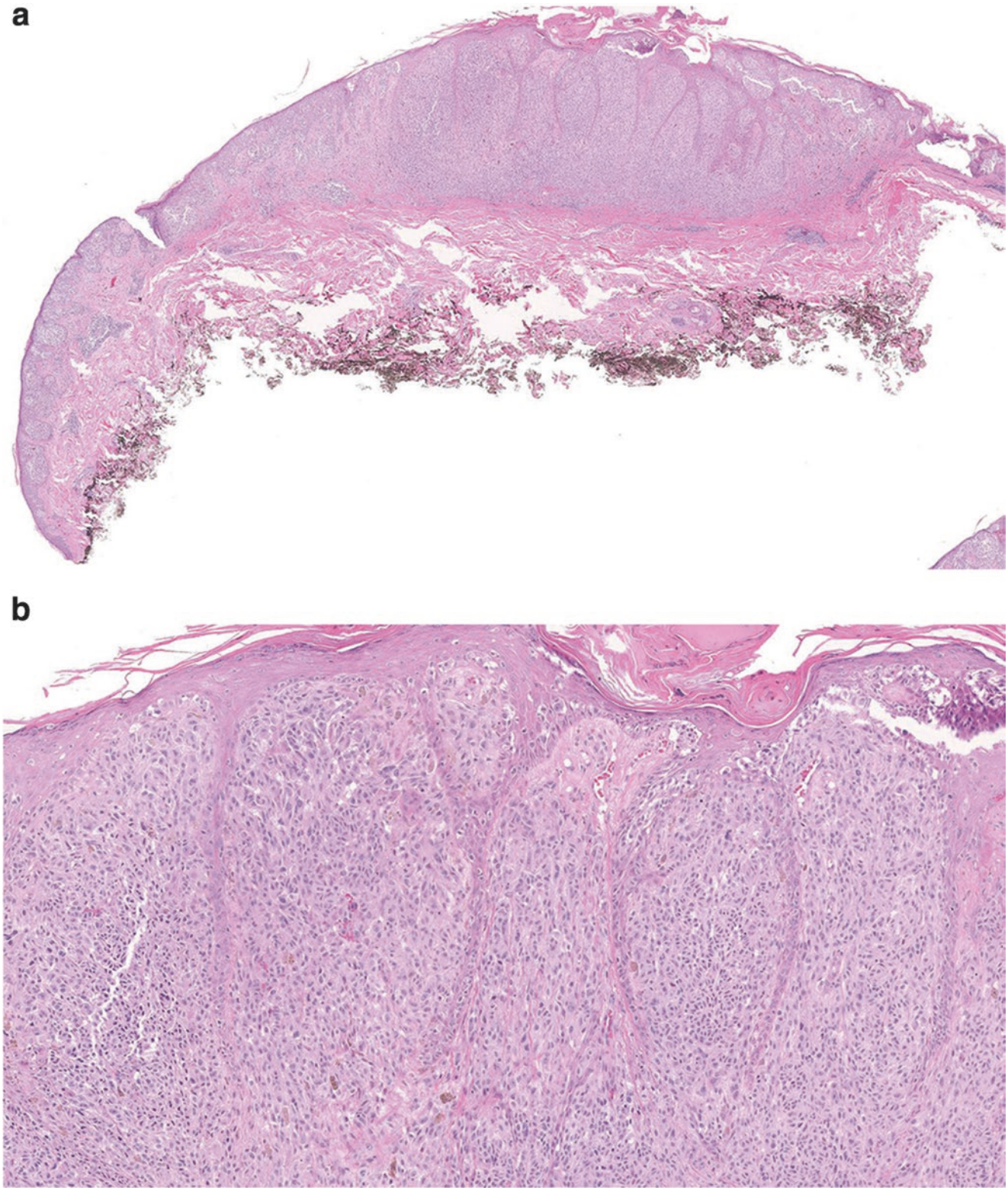


Fig. 7.23 Superficial spreading melanoma. This case shows on the *left side* of the image an in situ component and the *right side* shows epidermal hyperplasia with invasion (**a**). The invasive component shows atypical melanocytes with epithelioid cytomorphology (**b**).

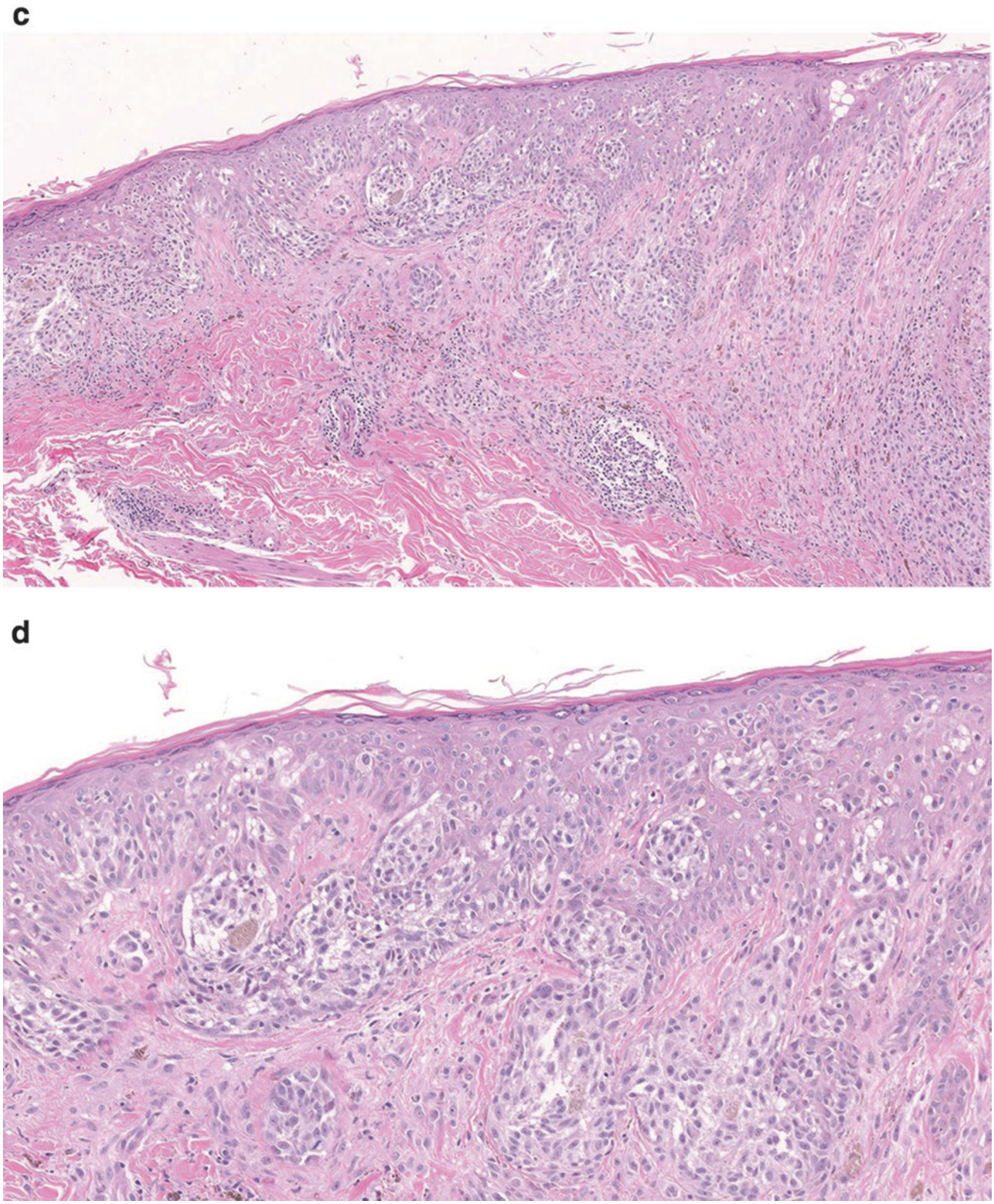


Fig. 7.23 (continued) The epidermis overlying the invasive component does not show a clear in situ growth (**c**, **d**)

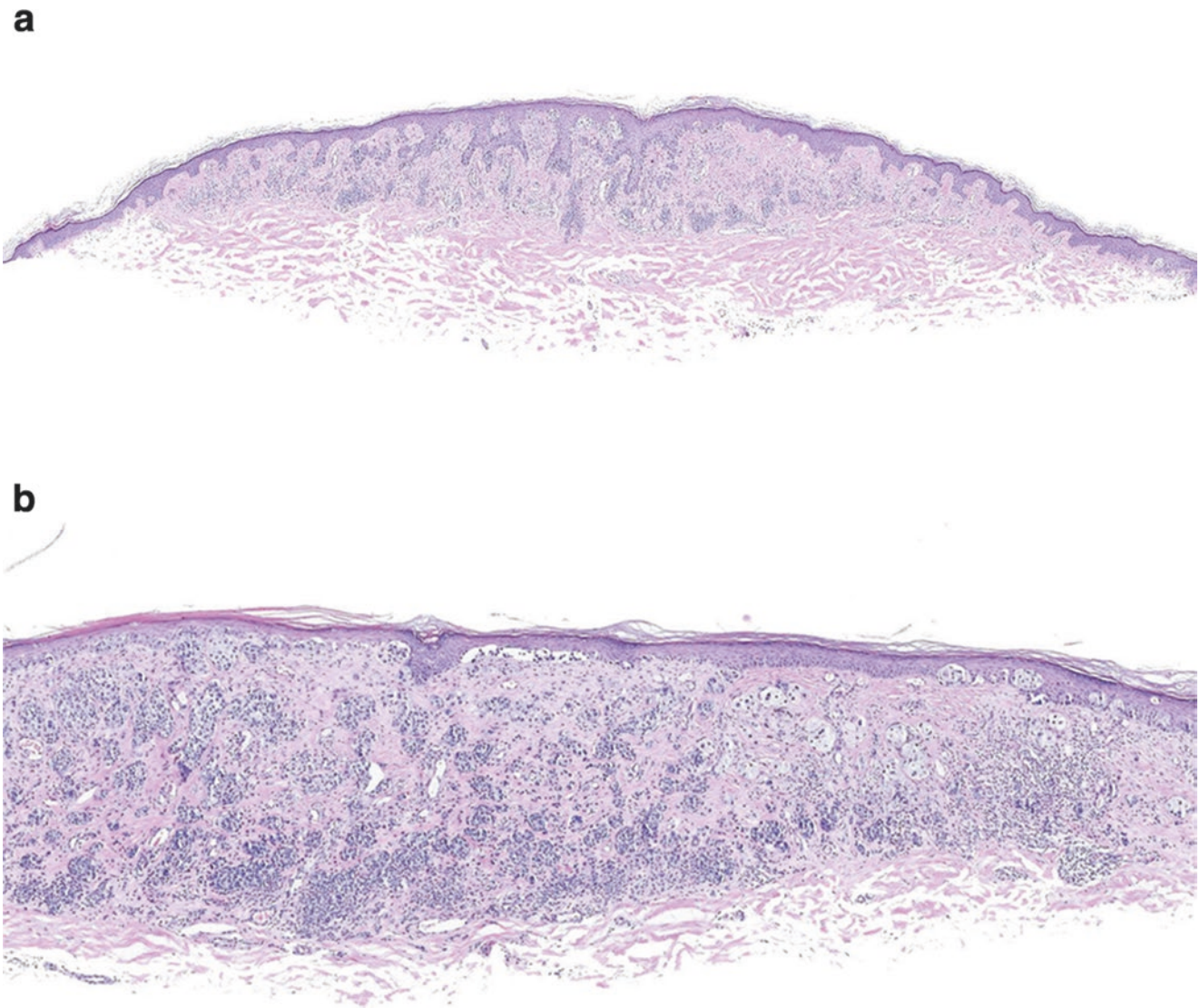


Fig. 7.24 Superficial spreading melanoma with balloon cells. The lesion shows characteristic features of melanoma including the atypical intraepidermal growth, including nests with heterogeneous size and shape (**a**). The lesion also shows areas of clear epidermal consumption. Many of the nested and single melanocytes have balloon cell melanocytes (cells with ample and bubbly cytoplasm) (**b**–**d**)

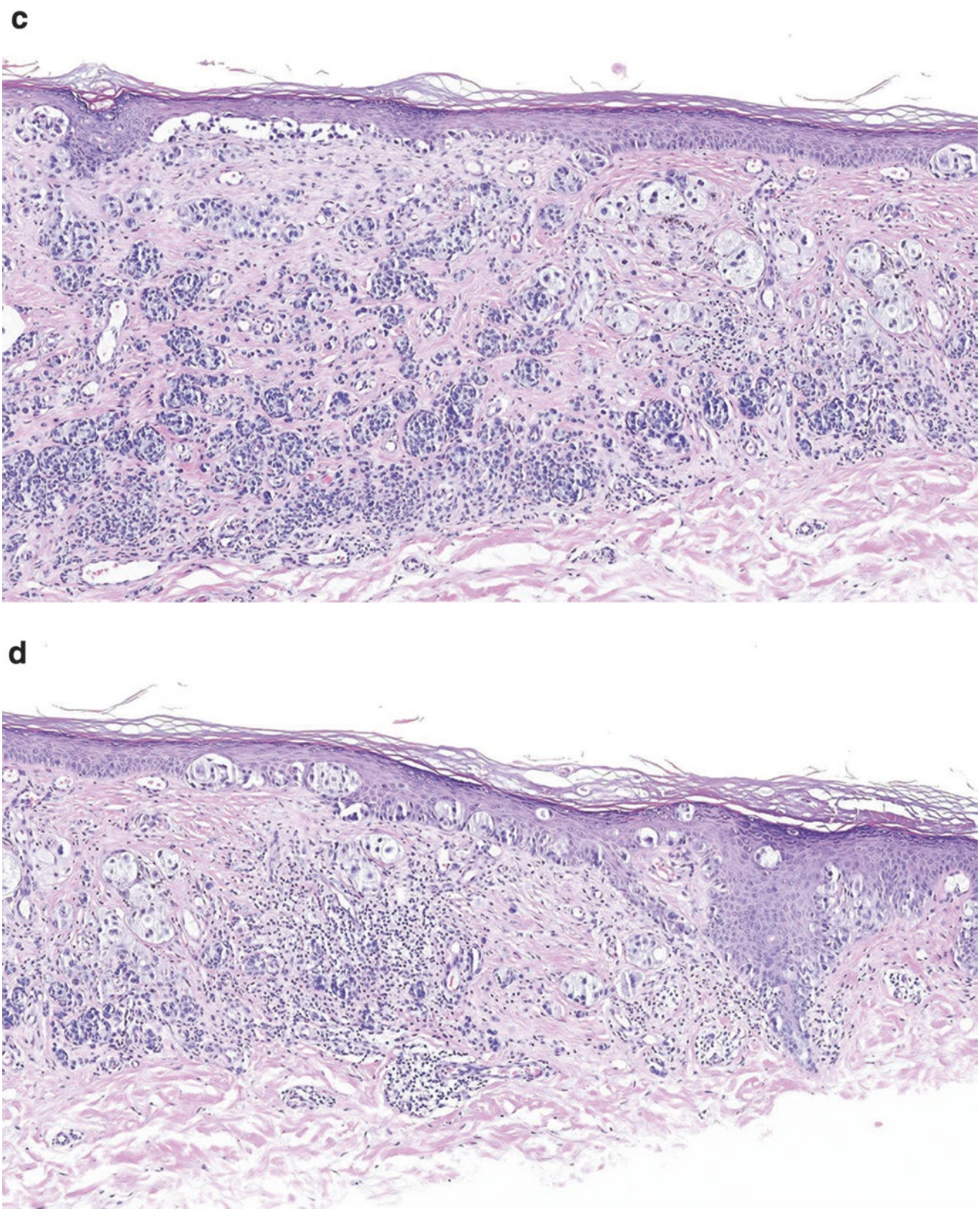


Fig. 7.24 (continued)

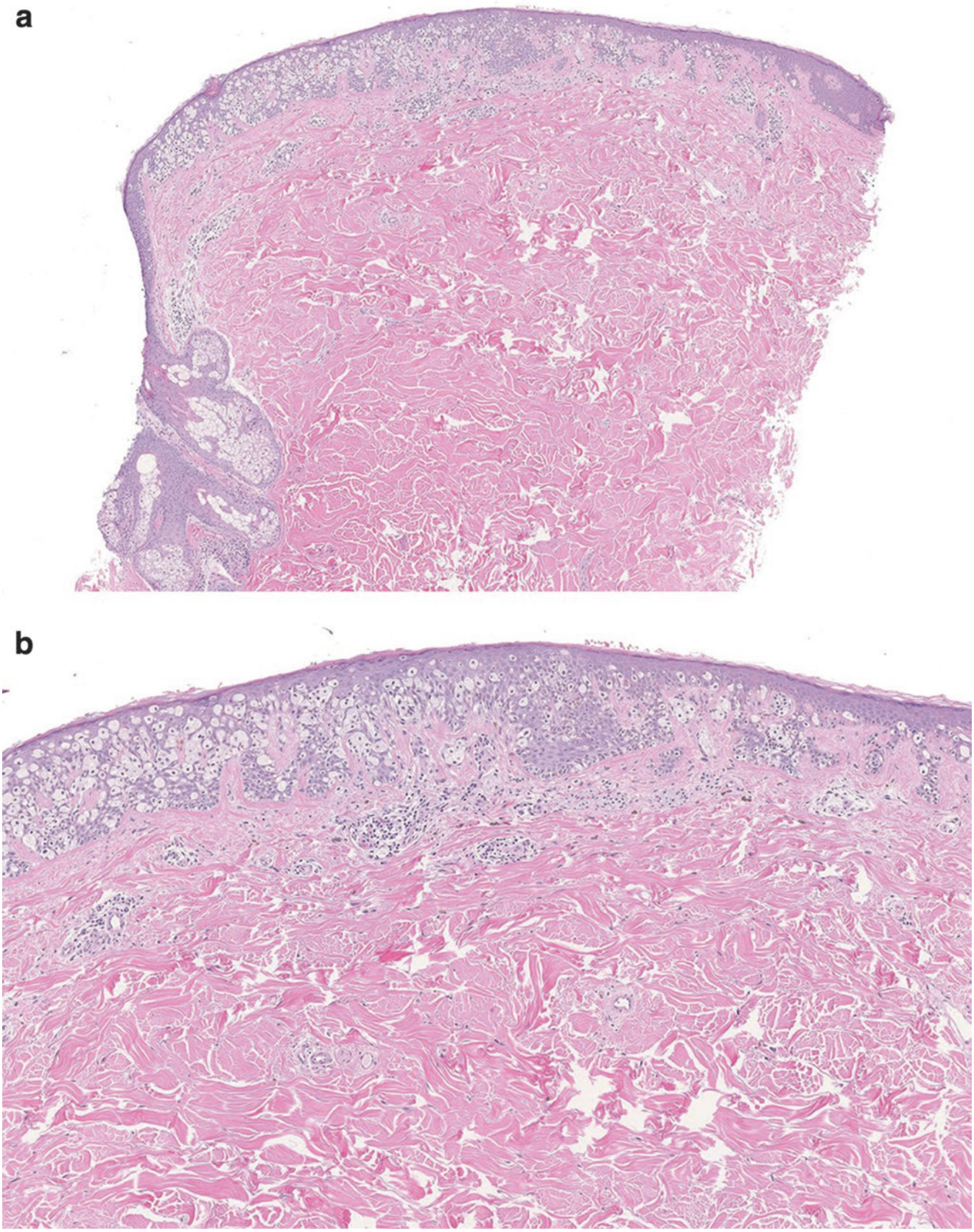


Fig. 7.25 Superficial spreading melanoma with extensive balloon cell changes. This is a 45-year-old male with a lesion on his arm; the patient has a prior history of melanoma. This is an extraordinary case of melanoma in situ composed of balloon cell melanocytes. One can clearly identify the atypical intraepidermal growth with massive confluence, pagetoid growth, and extension down the adnexa (**a**, **b**).

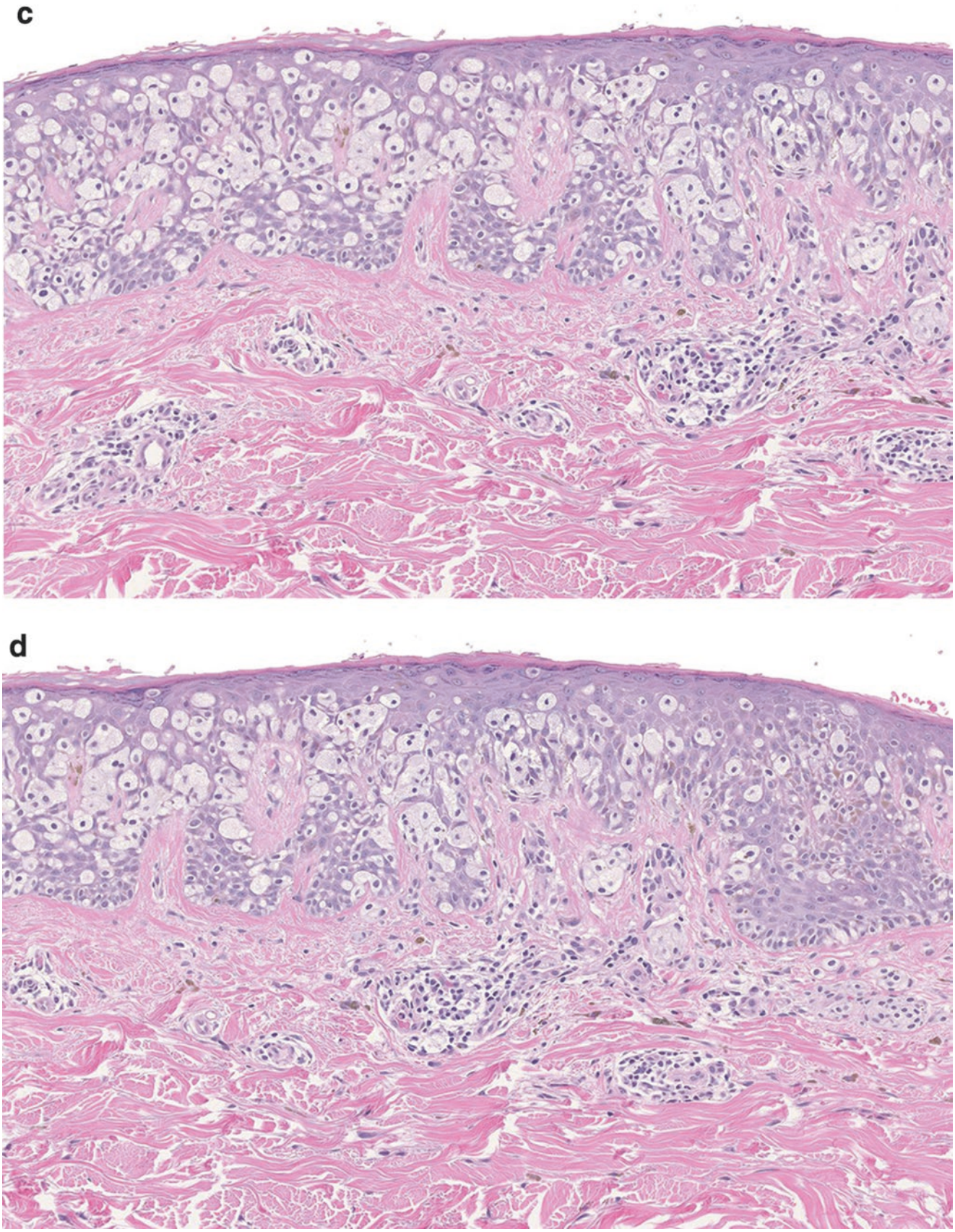


Fig. 7.25 (continued) Note that all melanocytes have an ample, watery clear cytoplasm with bubbly appearance (**c**, **d**)

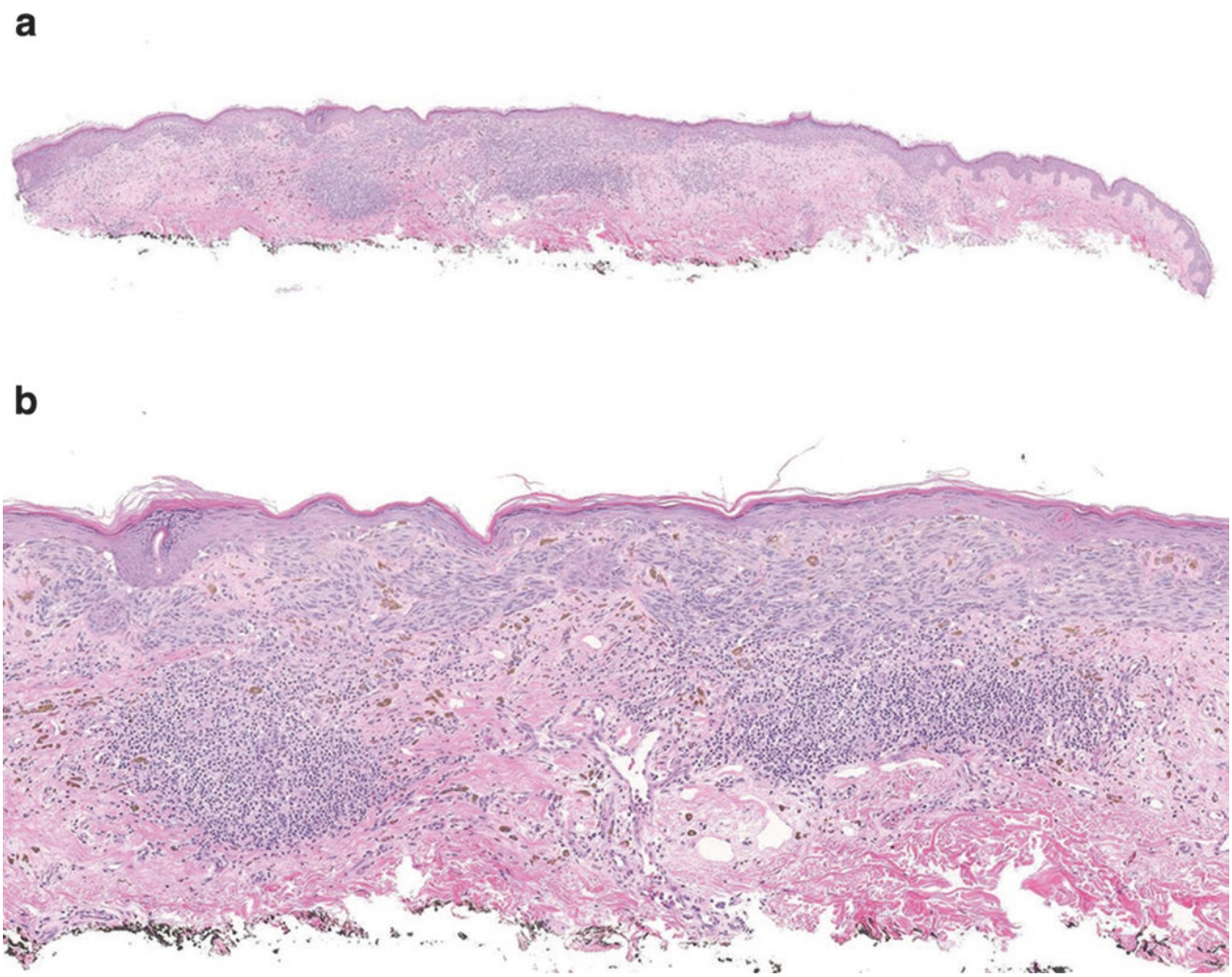


Fig. 7.26 Superficial spreading melanoma composed of spindle melanocytes. The lesion is located in the trunk of an 84-year-old male. This is an example of in situ melanoma composed primarily of spindle cells. The lesion is composed of an atypical confluent growth of melanocytes within the epidermis (**a**). The melanocytes are spindle and arranged in confluent nests that are parallel located to the epidermis (**b**).

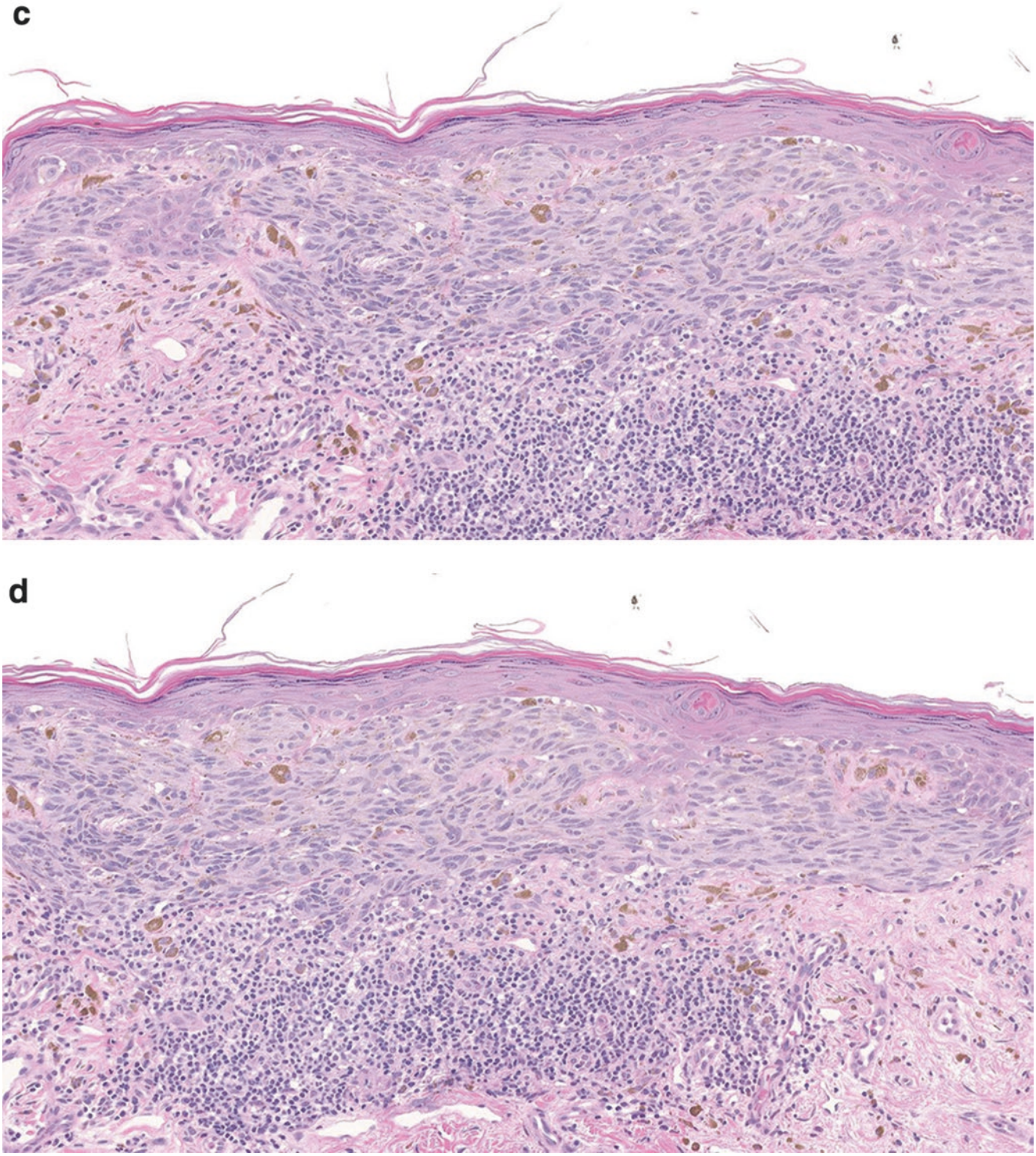


Fig. 7.26 (continued) On high magnification, the spindle cells have only minimal cytoplasm and there is nuclei overlapping with marked pleomorphism. Areas of epidermal consumption are noted (**c**, **d**)

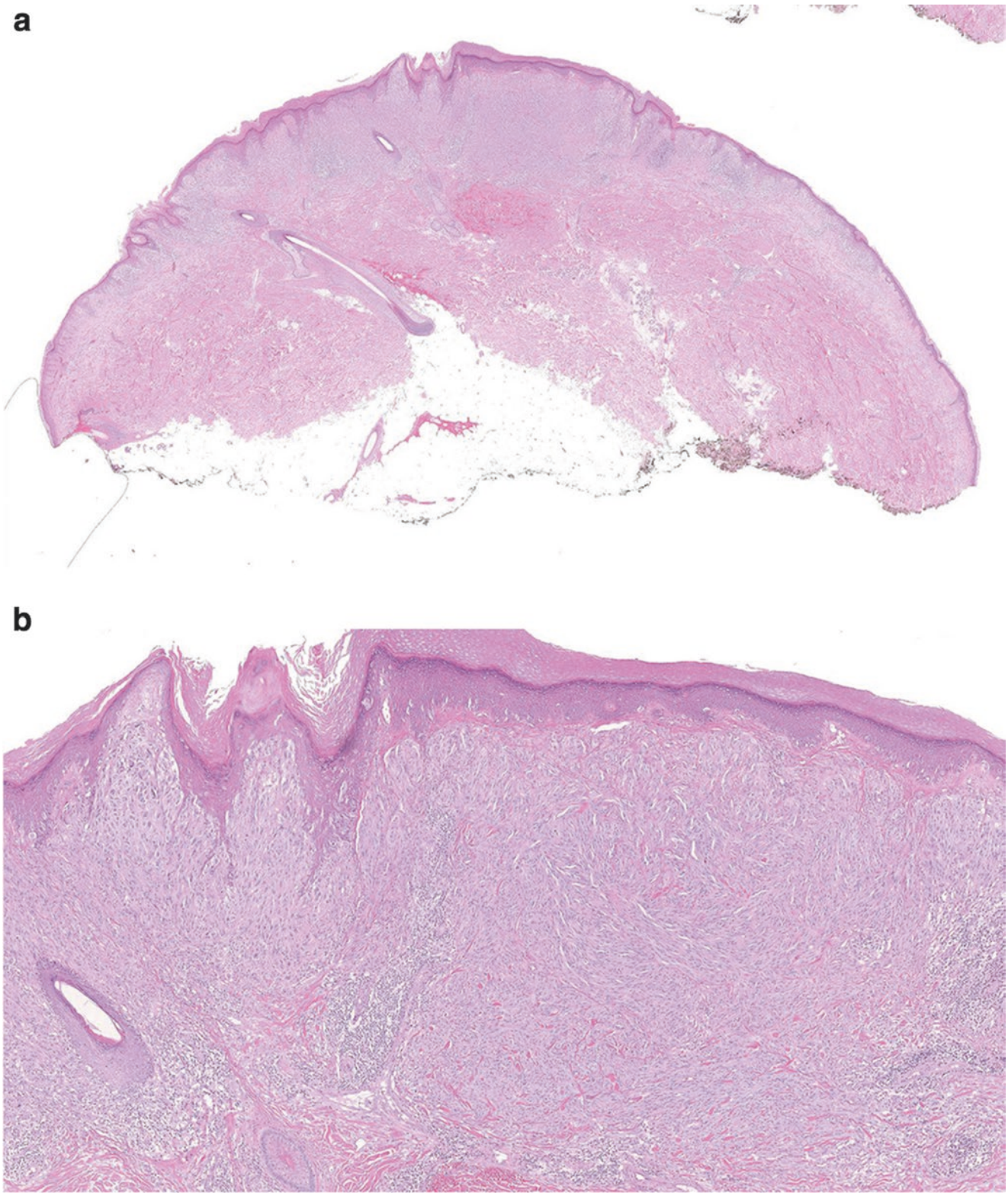


Fig. 7.27 Superficial spreading melanoma composed of spindle melanocytes. This case shows minimal in situ component composed of scattered single irregular melanocytes. In the dermis, prominent sheets of melanocytes underneath the consumed epidermis are seen. The solid growth pattern in the dermis shows a fascicular growth (**a**, **b**).

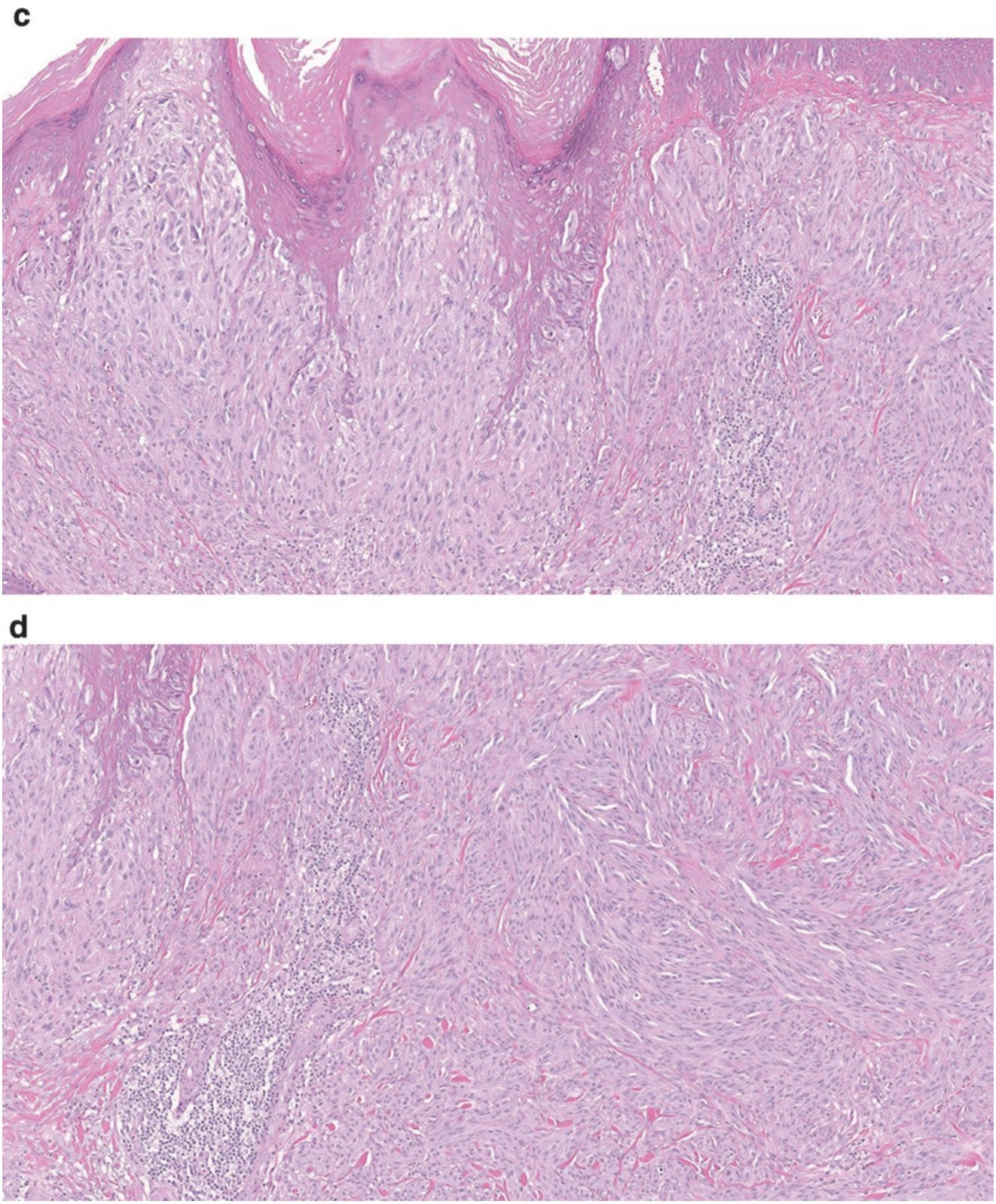


Fig. 7.27 (continued) The spindle cell melanocytes have an eosinophilic cytoplasm, severe cytologic atypia, and a large prominent nucleoli. This case showed scattered atypical mitoses that were easily identifiable (including the base of the lesion) (**c**, **d**)

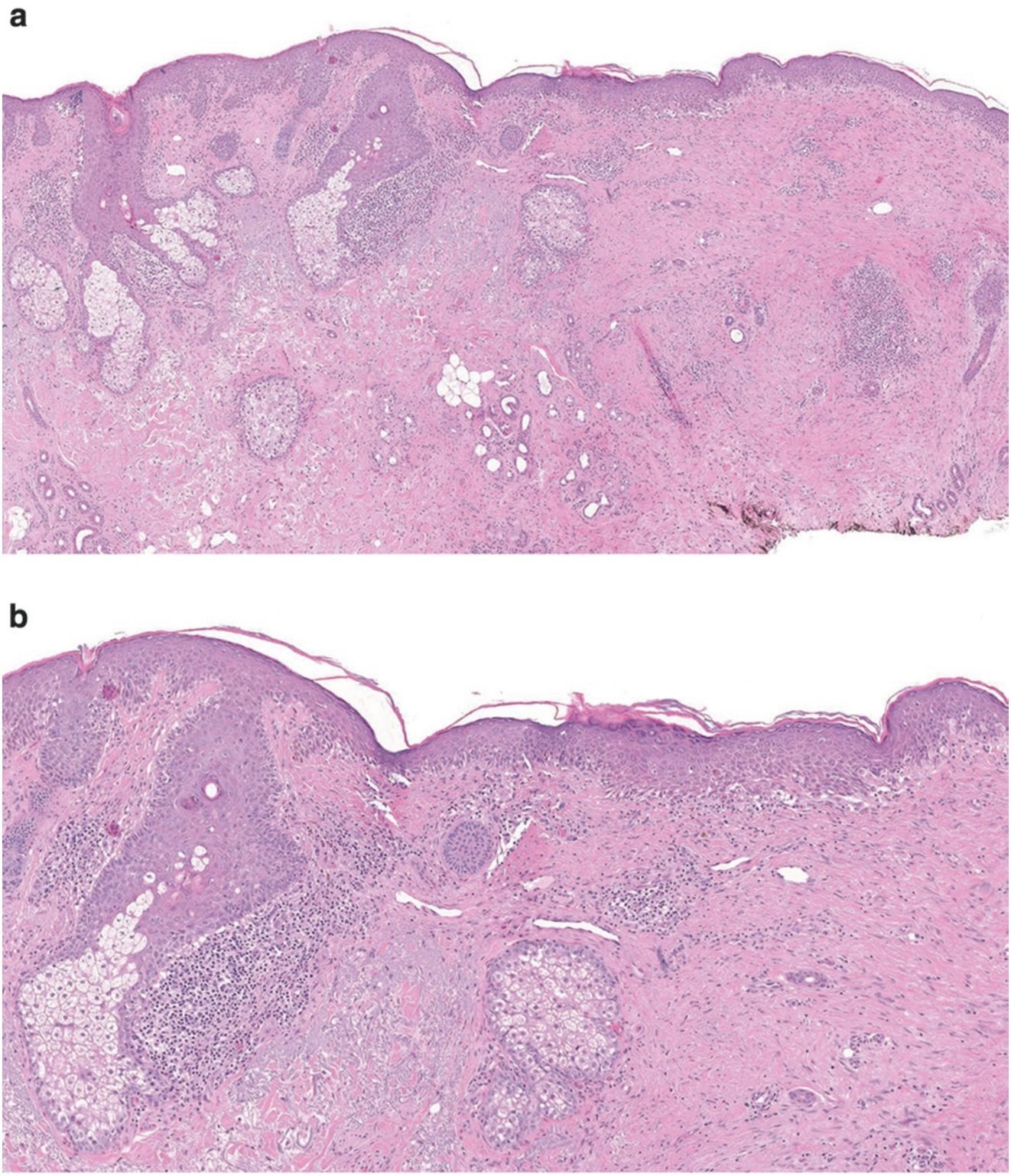


Fig. 7.28 Recurrent superficial spreading melanoma. This patient had a prior history of invasive melanoma s/p excision with clear margins and after 2 years develops this pigmented lesion in the same anatomic site. This case shows an old scar with a clear intraepidermal atypical population of melanocytes with a chronic lymphocytic infiltrate in the dermis (**a**). The epidermis overlying the scar shows loss of the rete ridge architecture (**b**).

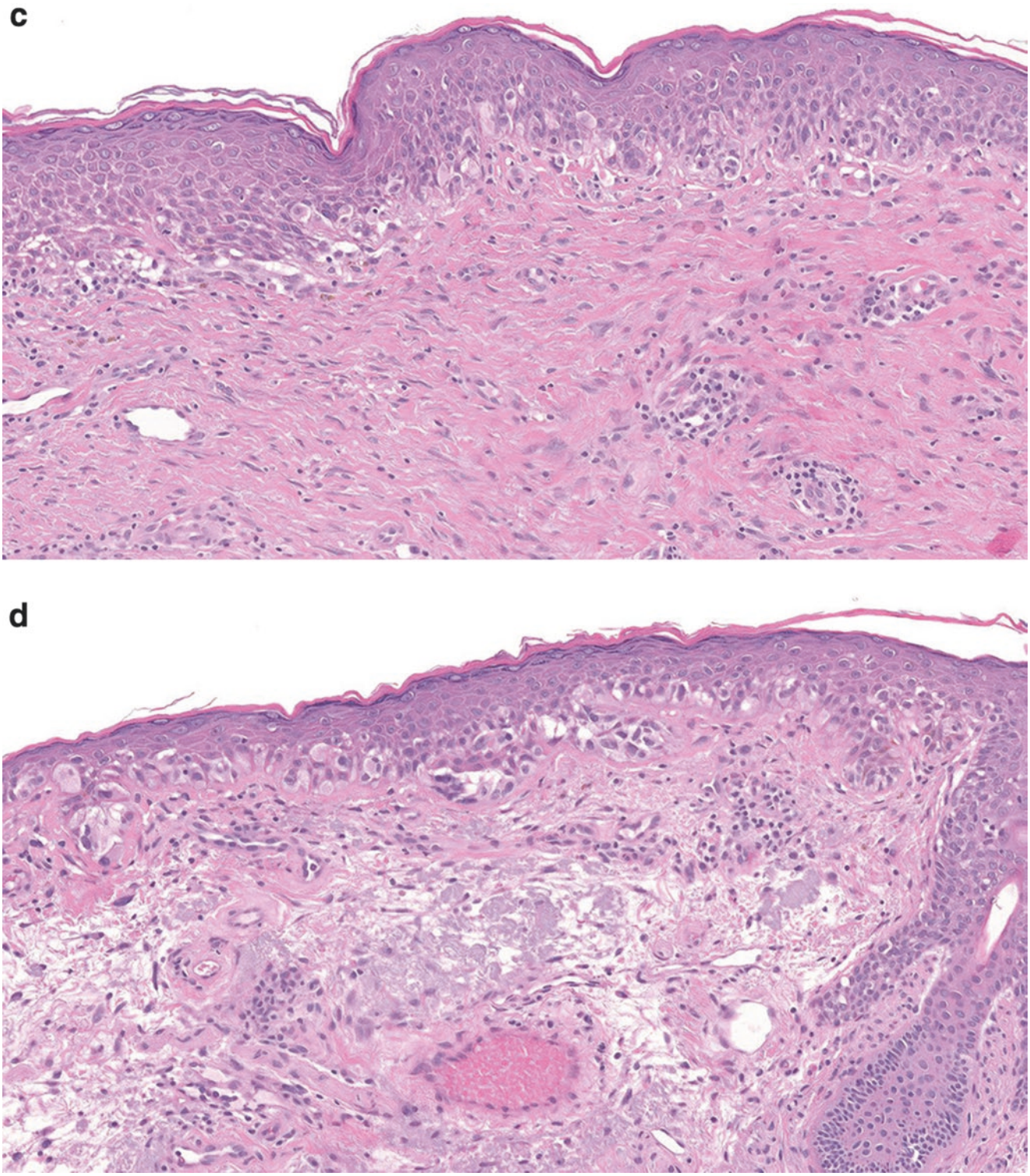


Fig. 7.28 (continued) One should keep in mind that a recurrent nevus might show similar features; however, this case shows changes that override a nevus including the predominant single-cell population of melanocytes and severe cytologic atypia (that is not seen in recurrent nevi) that is located next to the area of the scar in the dermis (**c**, **d**). Remember that recurrent nevi usually show pseudomelanoma changes in areas that overlie the scar; however, these changes are not seen beyond the scar

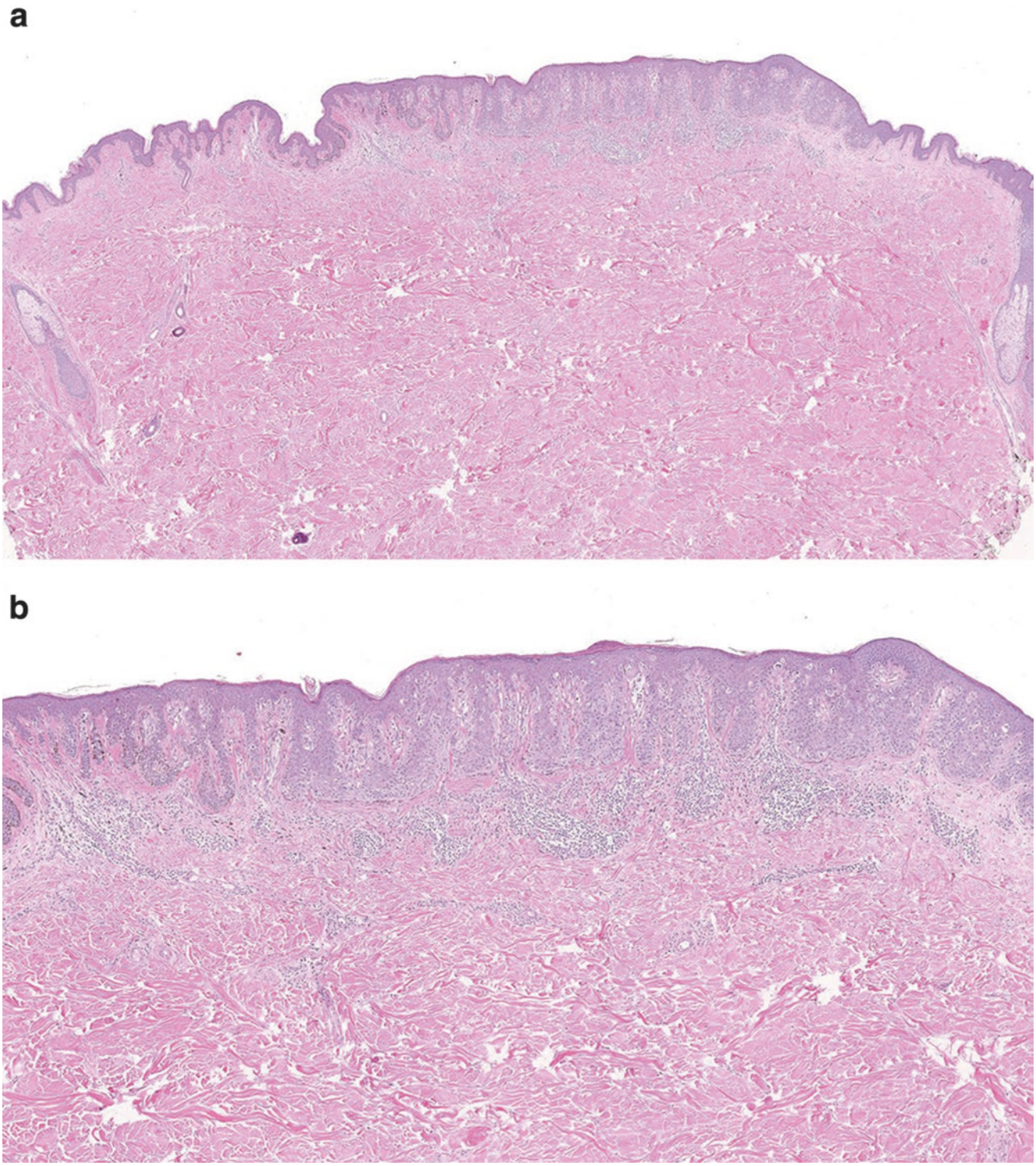


Fig. 7.29 Melanoma in situ associated with a dysplastic nevus. This lesion is located on the back of a 68-year-old male. The lesion is composed of elongated rete ridges with spindle and epithelioid melanocytes arranged in a horizontal pattern (**a**). Note that the nests connect the retes as observed in dysplastic nevi. However, the lesion shows a degree of cytologic that is not accepted for a nevus along with some pagetoid spread of melanocytes (**b**).

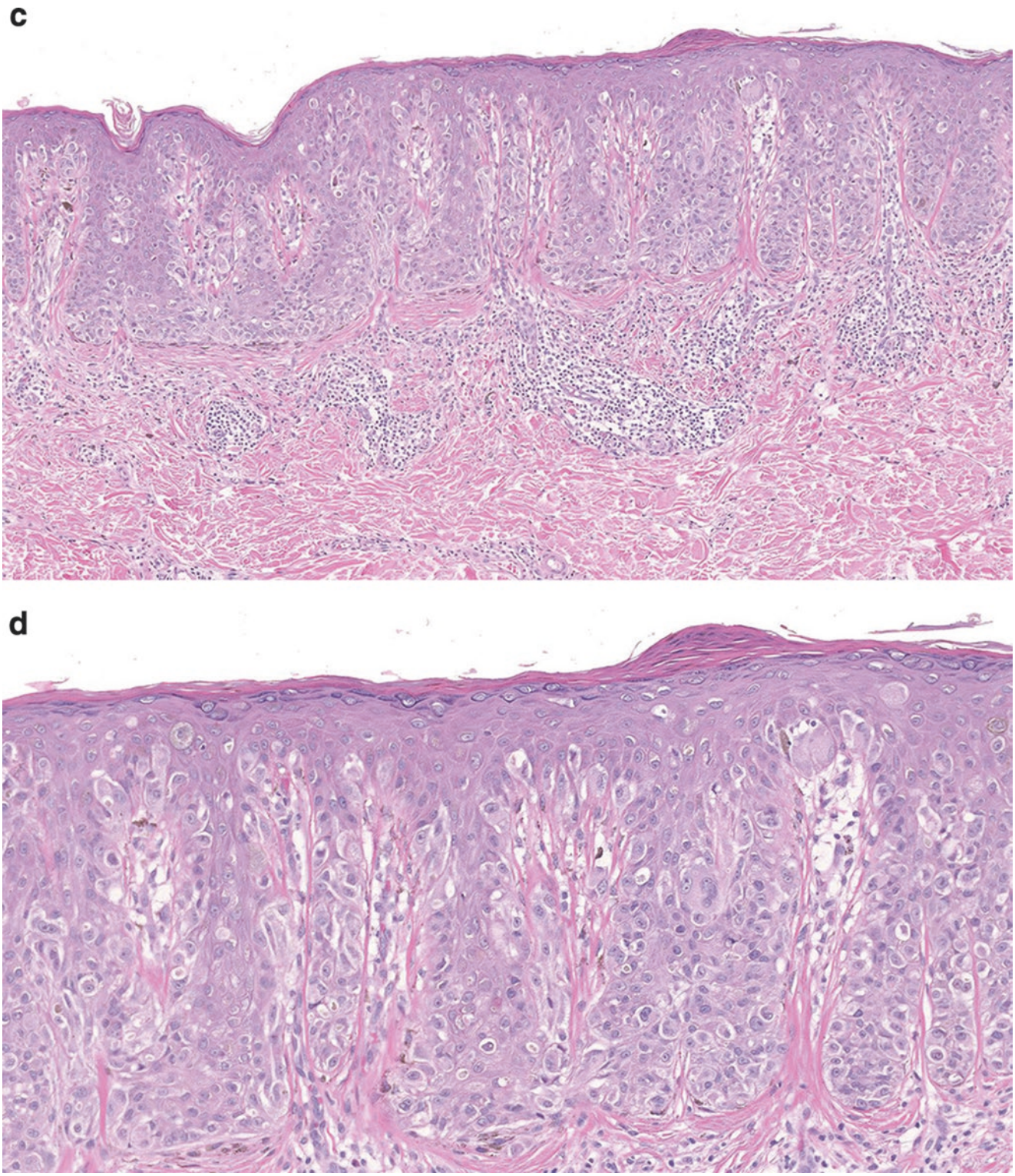


Fig. 7.29 (continued) The cytology of the melanocytes is quite striking and displays severe cytologic atypia with nuclear pleomorphism (**c**, **d**)

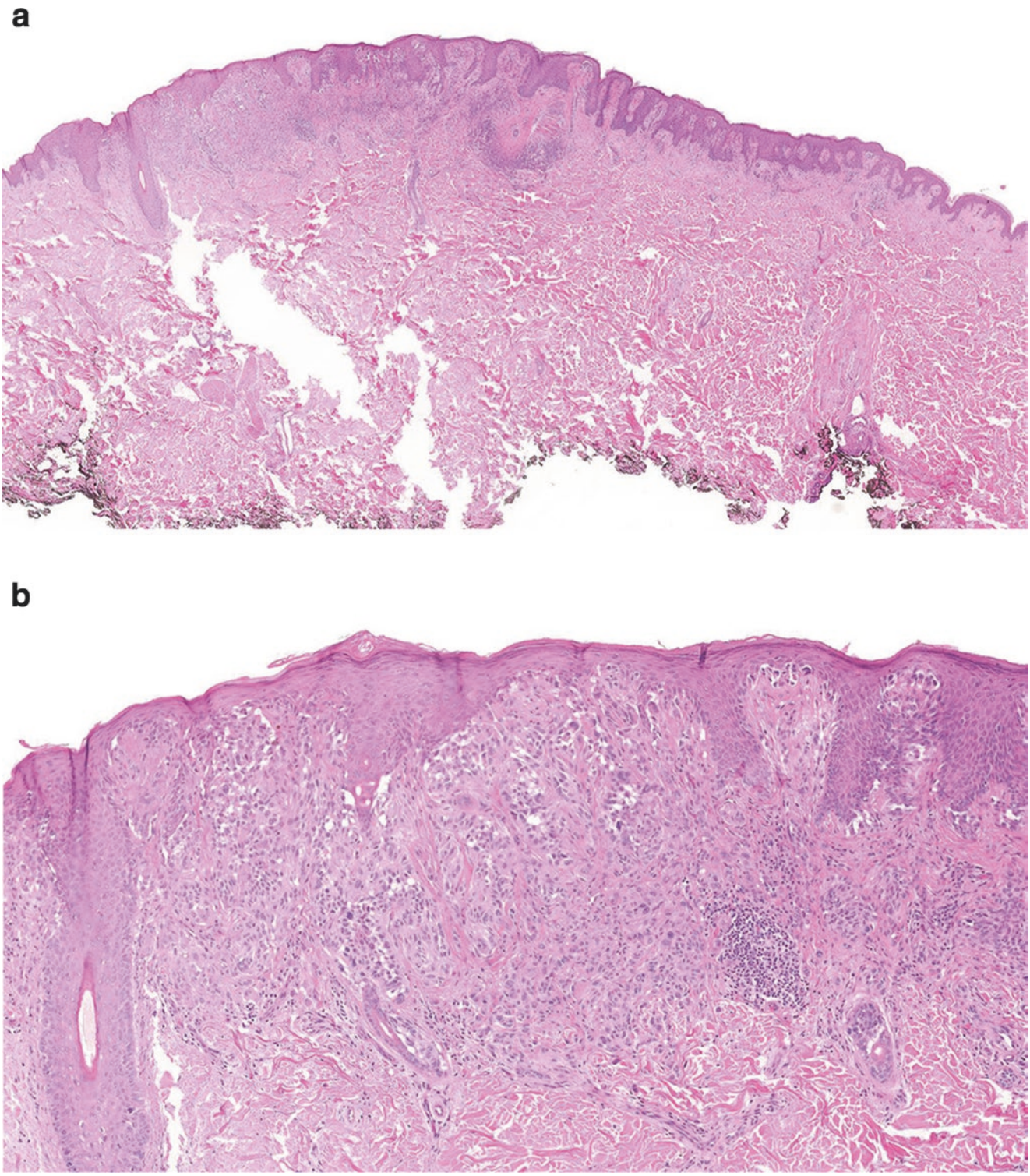


Fig. 7.30 Invasive melanoma associated with a dysplastic nevus. This lesion has two components: one is located at the far *left* of the image and shows a clear invasive melanoma and the second component is located in the center at the far *right* of the image and shows a dysplastic nevus (**a**). The melanoma displays characteristic changes and clearly blends with the adjacent dysplastic nevus (**b**, **c**).

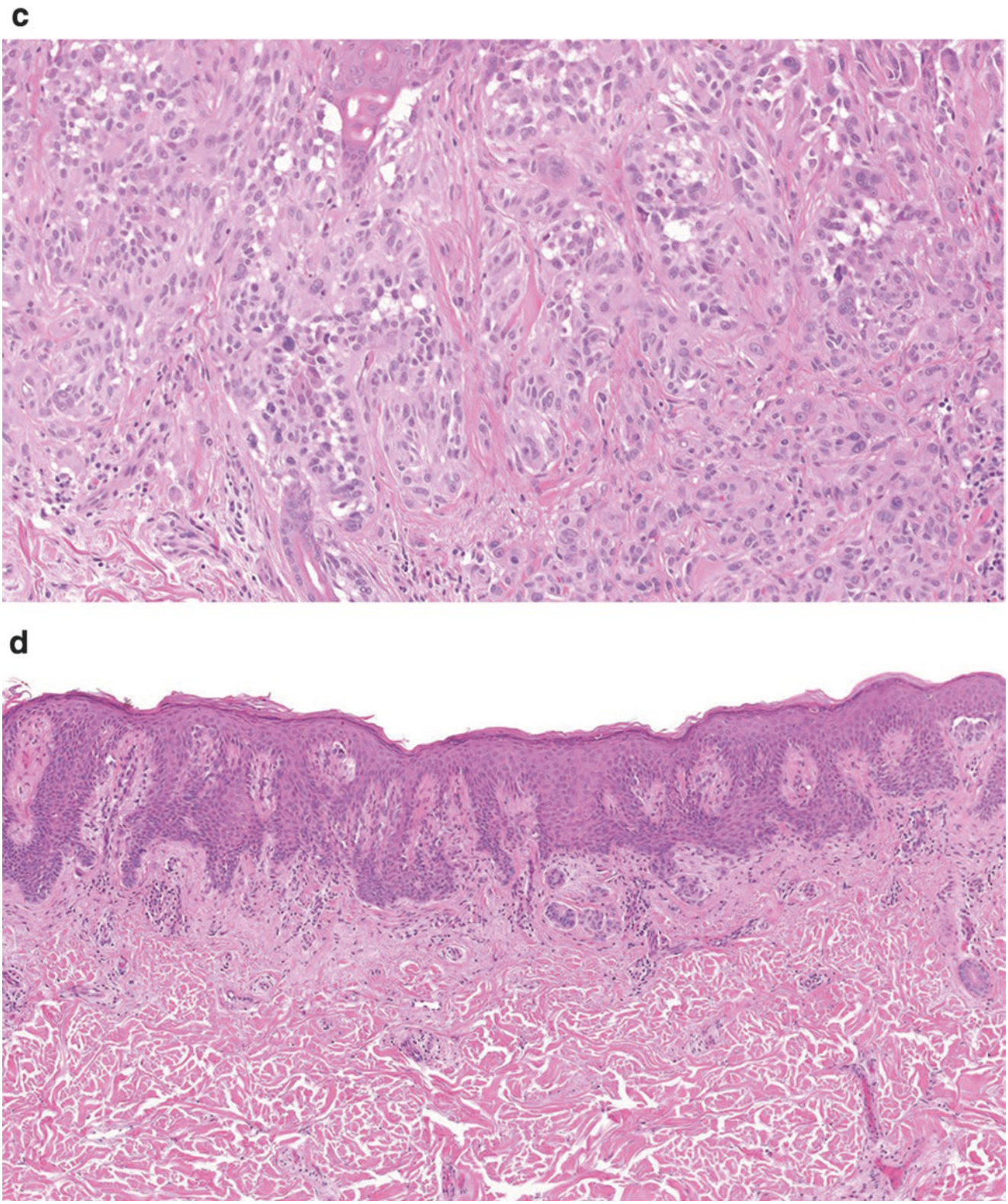


Fig. 7.30 (continued) We interpret this lesion as melanoma arising in a dysplastic nevus. The dysplastic nevus shows shouldering and bridging of melanocytes (**d**)

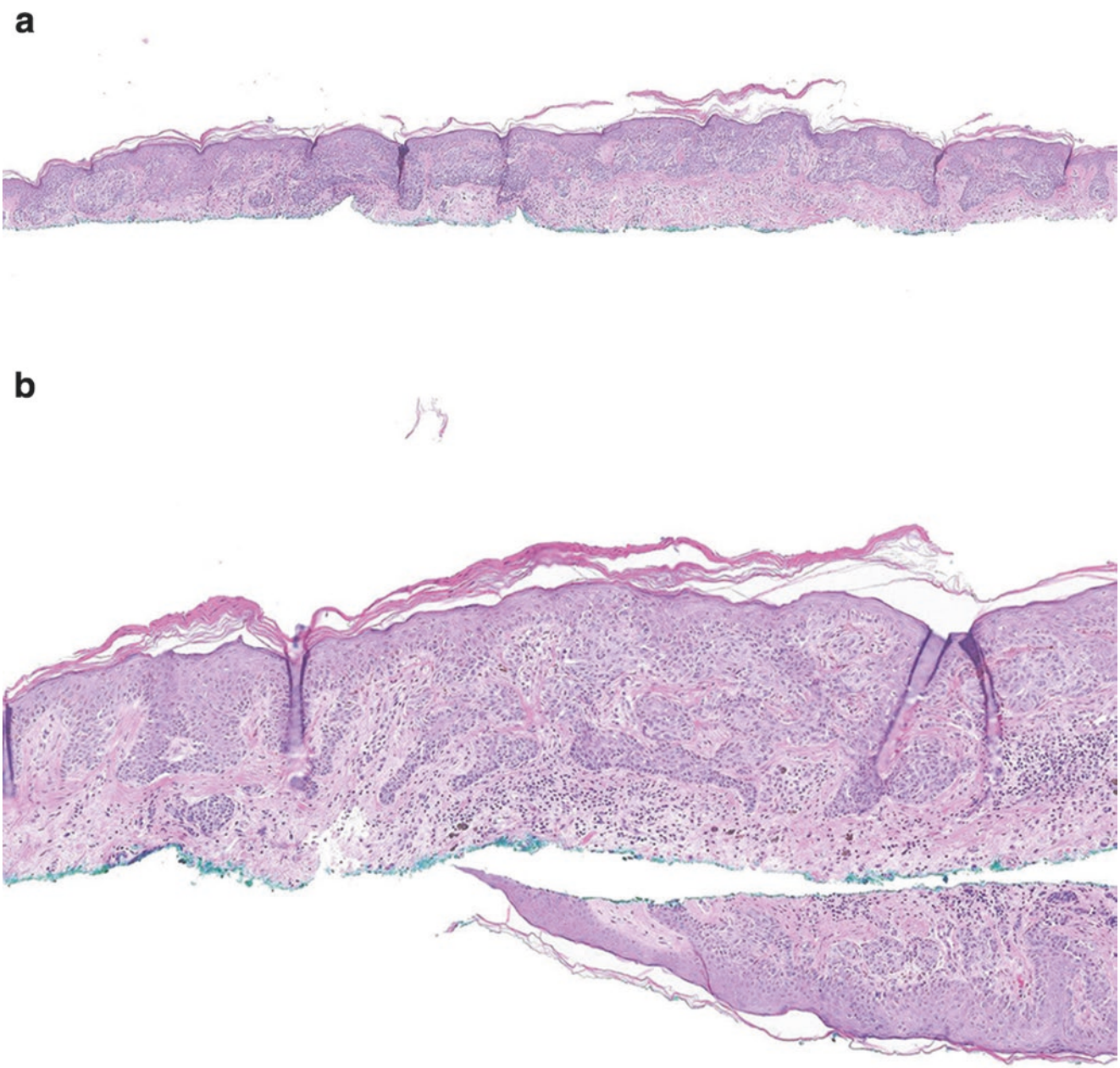


Fig. 7.31 Incipient melanoma in situ associated with dysplastic nevus. The low-power architecture of this lesion is that of a dysplastic nevus (**a**). However, in some areas the degree of single-cell proliferation is beyond to what we expect to see in a dysplastic nevus (**b**, **c**).

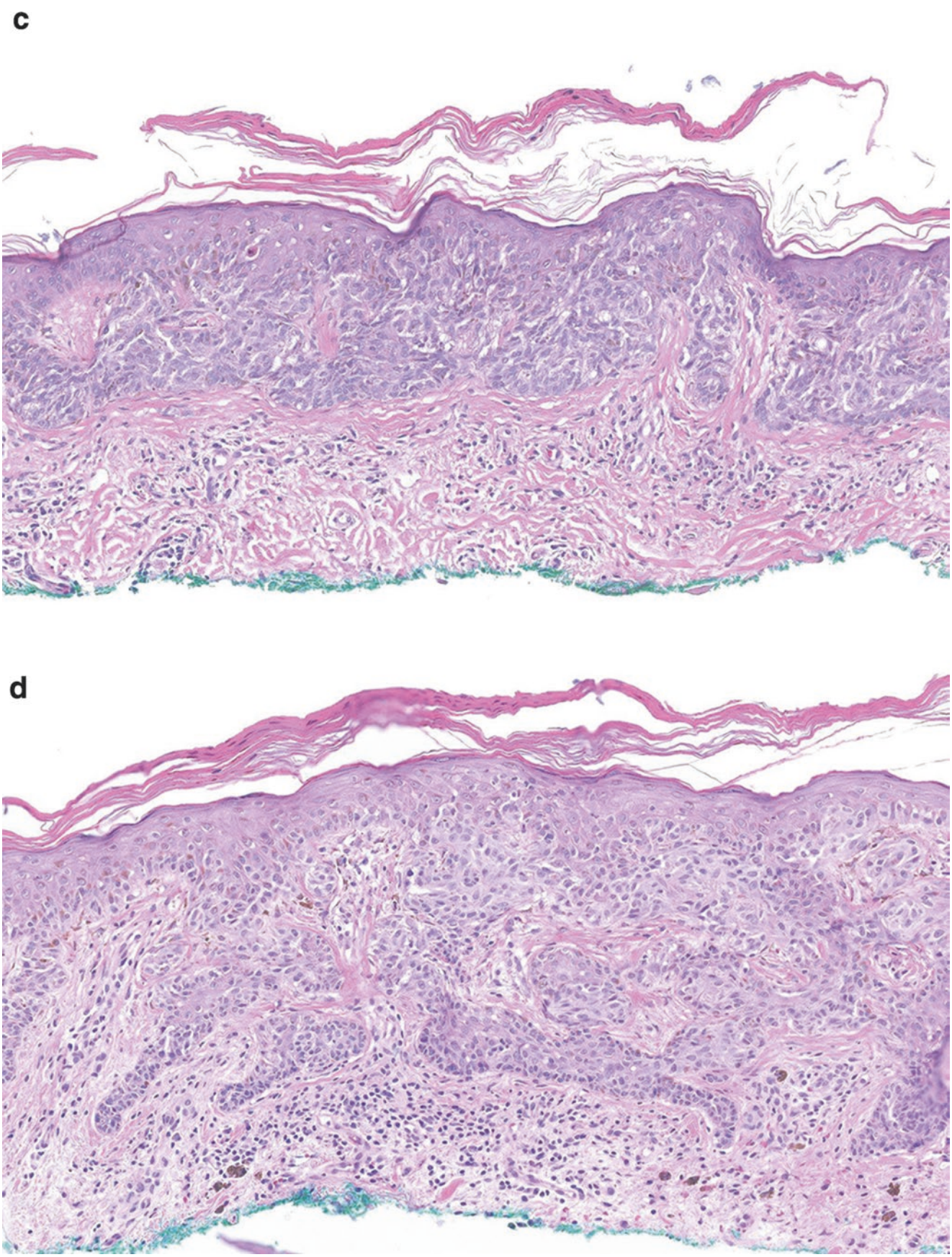


Fig. 7.31 (continued) Note the single-cell melanocytes that extend throughout all layer of the epidermis (**d**)

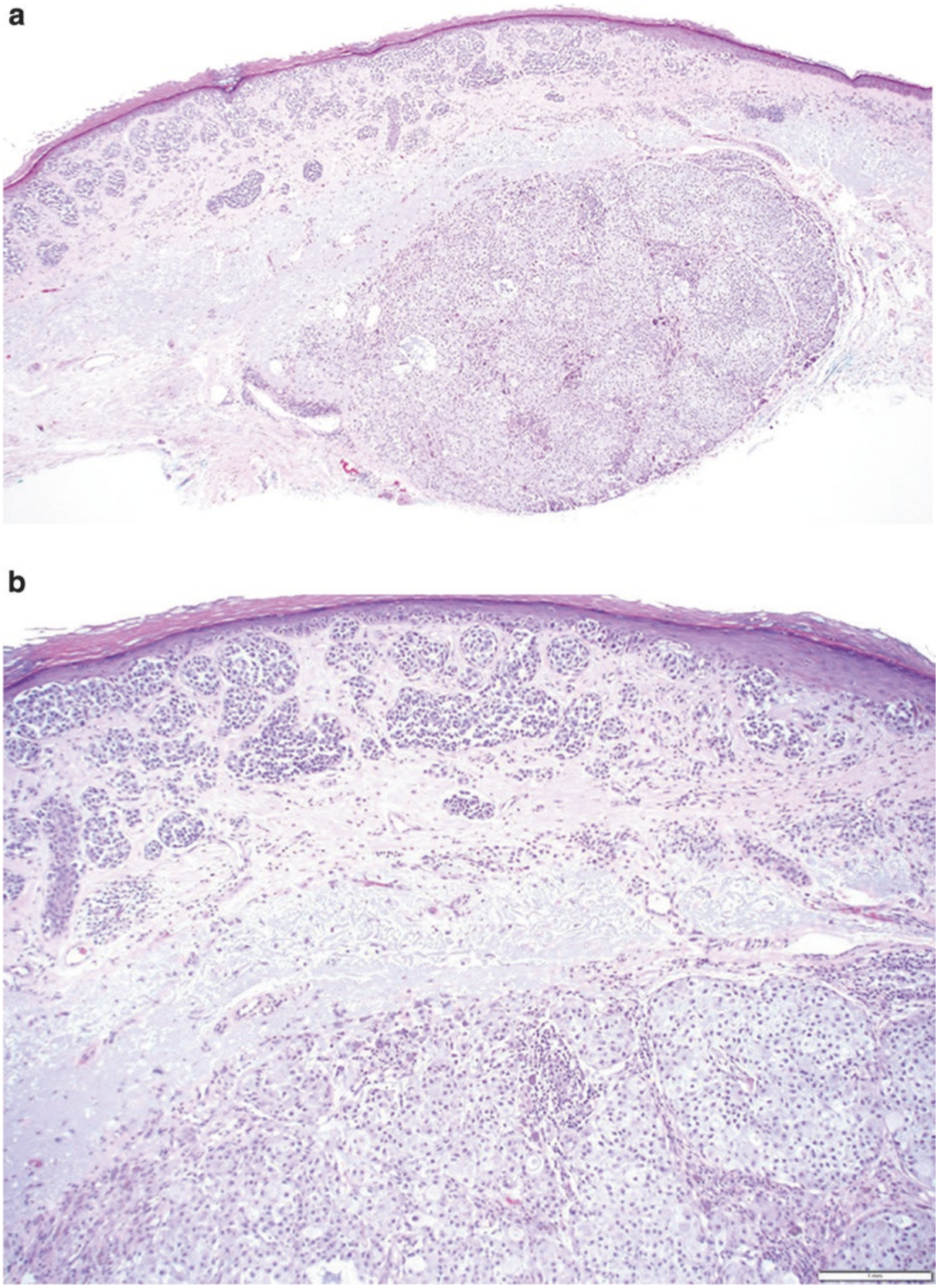


Fig. 7.32 Superficial spreading melanoma with microsatellite nodule. This is an example of invasive melanoma along with a microsatellite nodule in the dermis (**a**). The dermal nodule is separated from the invasive component by the normal dermis (**b**).

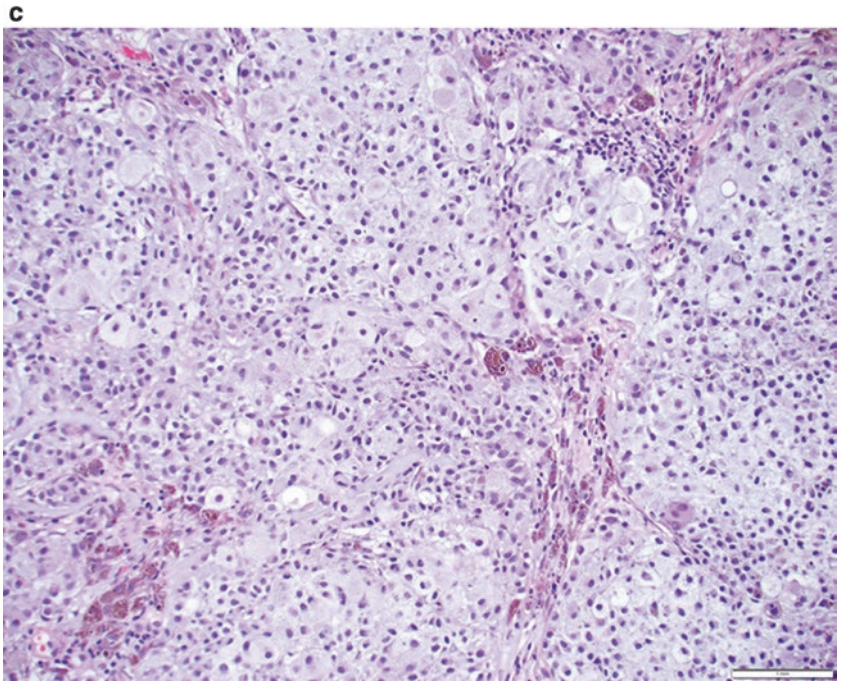


Fig. 7.32 (continued) Also, the cytology of the cells in the microsatellite nodule is different from the invasive component. It shows cells with higher degree of cytologic atypia (**c**)

Acral Lentiginous Melanoma

Clinical Features

Acral lentiginous melanoma (ALM) was first coined by Reed et al. in 1976. It occurs on acral sites, under the nail, and in mucosal surfaces. The overall incidence of melanoma in dark skin patients is low compared with whites; however, ALM makes up a much higher proportion of melanoma in dark skin patients such as in Asians, Hispanics, and African Americans. Hispanic populations seem to have the highest proportion of ALM, when compared with other types of melanoma. Although initially thought to be rare in whites, the difference is more a matter of relative frequency when compared with other types of melanoma occurring in areas continuously or intermittently exposed to sunlight. ALM is the least frequent of the four major histologic subtypes of melanoma overall and accounts for about 2–3 % of all melanomas [108]. The most common location of ALM is the palmar, plantar, and subungual skin. It usually presents as a pigmented macule or papule with irregular borders and variegated pigmentation on the palmar and plantar regions. ALM has a slight female predominance and presents most often in the elderly; however, in white patients ALM tends to have equal incidence in both sexes. Not all melanomas on volar and subungual skin are of acral lentiginous type, some being of superficial spreading, nodular, or unclassifiable type. It has been suggested that a diagnosis of ALM is generally associated with a relatively poor prognosis since tumors are generally thick by the time of diagnosis.

Mucosal melanomas of the oral cavity and other anatomic sites, such as the vagina or rectum, have been included in this histologic group as they share some clinical, histological, and molecular similarities with ALM. The predilection of ALM for plantar locations has led many authors to believe that trauma may play an important role in the etiology of ALM, since it does not appear that sun exposure plays a significant risk factor for ALM [109, 110].

Clinically, ALM is easier to identify clinically in advanced stages as it usually presents as irregular, asymmetric pigmented macules that can be several centimeters in diameter. As ALM progresses to vertical growth phase, it frequently ulcerates. All clinicians and pathologists should be aware of the importance of the diameter as a critical factor when diagnosing ALM. Many studies have clearly defined that acral

melanocytic lesions that are large (>7 mm in diameter), flat, and heavily pigmented are almost always ALM, even considering the subtle changes seen in some areas of such lesions [111]. Also, when ALM develops a vertical growth phase, it can mimic a nodular melanoma (see below). Clinically, nodular melanoma on acral sites is very rare, and when such a pattern is seen, it is most likely the vertical component of a flat lesion that went misdiagnosed for many years. Unfortunately, amelanotic forms of ALM can be exceedingly difficult to identify, and in such cases, the disease may go unsuspected even by experienced clinicians.

Histopathology

One of the major challenges in dermatopathology is to differentiate acral junctional nevus versus ALM in situ. Making a diagnosis of invasive melanoma on acral locations is not difficult; however, the diagnosis of acral lentiginous melanoma in situ can be quite difficult as it can mimic junctional nevi.

The early stage of ALM (in situ component) is composed of single melanocytes that are irregularly distributed along the dermal-epidermal junction. Intraepidermal nests are often absent at this stage and some lesions can even grow and reach a large size without forming nests. As the lesion evolves, nests can be observed, and when noted they are irregular in size and shape, are elongated, and are located parallel to the epidermis. Such nests show lateral confluence and spindle cell configuration. A characteristic feature when nests are present is that they alternate with single melanocytes forming skipping areas (in some cases one can notice areas that lack melanocytes altogether). Melanocytes tend to be elongated, plump, with darkly pigmented nucleus, and a surrounding halo. Dendrites are commonly visible, highlighting the presence of migrating melanocytes into mid- and higher levels of the epidermis. These dendrites are irregular in thickness, have different lengths, and have a tendency to form a web around the basal cells. Melanocytes with ample and dusky cytoplasm are rare but pagetoid spreading is not uncommonly observed. These pagetoid spread is not as noticeable as in other anatomic locations, mainly because of the small size of the nucleus in the melanocytes. Also, it is common to observe a cleft ("zipper" sign) at the dermal-epidermal junction in areas where basal melanocytes overwhelm the number of basal keratinocytes. Pigment is present irregularly along the stratum corneum (as opposed to being in columns characteristic of acral nevi). Early examples of ALM can be identified by the presence of individual melanocytes crowding around the crista profundae intermedia, especially if melanocytes are also detected along the junction between the cristae. This stage can be a diagnostic challenge as melanocytes display only minimal cytologic atypia. It is not unusual to identify melanocytes that extend irregularly into the eccrine ducts. This extension into the eccrine duct differs from that of nevi, as in nevi one can see melanocytes gathered in and around ducts forming well-defined nests as in ALM melanocytes are irregularly distributed and in a single-cell pattern. In some cases of ALM, this syringotropic spread of malignant melanocytes can reach the deep portion of the duct, and thus melanoma in situ may be present at the deep margin. The epidermis is usually acanthotic, hyperplastic, and hyperkeratotic. At this in situ stage, there may be a dermal lymphocytic infiltrate, a feature usually absent in acral nevi).

Experts in the topic have proposed that ALM in situ should be considered a clinicopathologic entity [112]. These authors have proposed that when a classic clinical picture of ALM is seen, e.g., irregularly shaped, darkly pigmented, flat lesion with a diameter >7 mm, pathologists should strongly suggest the diagnosis of ALM in situ if the histology shows a proliferation of single melanocytes along the dermal-epidermal junction.

Usually after years, the lesion, once limited to the epidermis, becomes infiltrative into the dermis. The overlying epidermis still shows the atypical lentiginous pattern and at this stage is more common to observe a nested component. The nests are irregular in size and shape and have a confluent pattern of growth and areas of epidermal "consumption." The dermal component can show either spindle or epithelioid melanocytes (more commonly spindle). The atypical features become more obvious, and a clear diagnosis of melanoma can be easily made. When ALM is already invading in the dermis, the overlying epidermal component can sometimes be limited to an inconspicuous lentiginous melanocytic proliferation as seen in the very early stage of ALM in situ (macular, in situ component of the invasive neoplasm).

Differential Diagnosis

Acral skin has peculiar anatomic aspects that are important to keep in mind when evaluating acral melanocytic lesions. Rather than flat surface, it is composed of ridges and furrows, as seen in fingerprints. Ridges are wider than furrows and at their center there is an opening of the eccrine ducts. This particular anatomic feature of the acral skin often causes nevi in these locations to adopt a striped arrangement; thus, this is very important to evaluate when inspecting acral nevi. It has been recommended to cut the microscopic sections of any melanocytic lesion on acral skin perpendicular to the furrow pattern, to allow a better appreciation of the symmetry and circumscription of the lesion. The pattern most commonly seen in acral nevi is that of individual melanocytes concentrating at the base of the furrows and sparing the areas at the base of the ridge around the acrosyringium.

The clinical history is important when evaluating acral melanocytic lesions; acral melanomas are almost always seen in older patients, whereas acral melanocytic lesions in younger patients are almost always benign nevi. The early phase of ALM in situ can be very difficult to distinguish from acral nevus, especially in small samples. When dealing with small, pigmented lesions on acral locations that are clinically suspicious for ALM, clinicians should consider an excisional biopsy with a narrow margin. ALM in situ tends to have a lentiginous growth pattern with rare nest formation (seen in more advanced stages) with melanocytes that are angulated and with hyperchromatic nuclei. When junctional nests are seen, they are irregular in shape and oriented parallel to the epidermis. In acral nevi, melanocytic nests appear at early stage, have well-defined borders, and are uniform in size and shape. As mentioned above, in general, large acral melanocytic lesions with a wide lentiginous intraepidermal component without nest formation is a diagnostic clue of ALM in situ. On the other hand, small acral melanocytic lesions with predominance of symmetrically distributed nests are overwhelmingly nevi. Dendritic morphology is also important in the evaluation of acral lesions. In ALM in situ, the dendrites are thick and numerous as opposed to acral nevus in which they are rarely seen. Another important clue to inspect is the distribution of pigment in the stratum corneum. In acral nevus, the pigment is commonly present in the stratum corneum arranged in columns rather that randomly through the entire width of the lesion (as it is commonly seen in melanoma).

A lesion that needs to be separated from ALM is "MANIAC" nevus (melanocytic acral nevus with intraepidermal ascent of cells). In these acral nevi, there is a tendency of melanocytes to be scattered throughout the entire thickness of the epidermis, giving the impression of pagetoid spreading, even at the periphery of the lesion. MANIAC nevi are usually seen in younger patients.

Genetics of Acral Lentiginous Melanoma

Recent studies have postulated that DNA repair mechanisms and cell growth pathways are involved in the development of ALM, particularly changes in the MAPK pathways. A recent study assessed the status of the MAP kinase pathways in the pathogenesis of ALM by analyzing the components of the RAS-RAF-MEK-ERK cascades by immunohistochemistry in tissue microarrays [113]. In that study the authors showed that more than half of cases were BRAF positive and most cases were also positive for MEK2, ERK1, and ERK2. RAS was not expressed in most cases and all cases were negative for MEK1. The combination of absence of RAS and expression of MEK2, ERK1, and ERK2 was most seen in invasive cases with high Breslow thickness.

Using comparative genomic hybridization (CGH), Bastian et al. compared acral melanomas and superficial spreading melanoma, demonstrating that all acral melanomas had at least one gene amplification, significantly more than superficial spreading melanoma [114]. The most frequently amplified regions in acral melanomas occurred at bands 11q13 (47 %) and 22q11–22q13 (40 %). These results suggested that ALM is a distinct type of melanoma characterized by focused gene amplifications occurring early in tumorigenesis. A different study analyzed the frequencies of regional changes in the number of copies of DNA and mutation frequencies in BRAF groups of different melanoma groups (melanomas from the skin with chronic sun-induced damage, melanomas from the skin without such damage, acral melanomas, and mucosal melanomas) [38]. In this study, melanomas arising on the skin with signs of chronic sun-induced damage and skin without sun damage could be correctly classified with 84 % accuracy, and acral melanoma could be distinguished from mucosal melanoma with almost 90 % accuracy. Most melanomas on the skin without chronic sun-induced damage had mutations in BRAF or NRAS, and the majority of melanomas in the other groups had mutations in neither gene. These results suggest that the genetic alterations identified in melanomas at different sites and with different levels of sun exposure indicate that there are distinct genetic pathways in the development of melanoma and implicate CDK4 and CCND1 as independent oncogenes in melanomas without mutations in BRAF or NRAS.

A different study analyzed mutations involving the gene encoding the c-Kit protein in melanomas [115]. Using quantitative PCR, C-Kit mutations were detected in 23 % of acral melanomas. These findings may explain some of the dramatic responses seen with imatinib mesylate in patients with lesions with very high c-Kit expression and/or c-Kit.

Immunohistochemistry may be helpful to predict mutations in KIT, since a number of acral lentiginous/mucosal melanomas, primary and metastatic, show KIT expression along with kit mutation [40, 116, 117]. The overall frequency of activating KIT gene mutations in acral lentiginous/mucosal melanomas was 15 % being the L576P mutation in exon 11 the most frequently detected. These results suggested that immunohistochemical expression of KIT in less than 10 % of the cells of the invasive component of acral lentiginous/mucosal melanomas appears to be a strong negative predictor of KIT mutation and therefore can potentially be used to triage cases for additional KIT genotyping.

In summary, although it is true that most of the described molecular changes follow the classic histologic subtypes of lentigo maligna, superficial spreading type, and acral lentiginous mucosal melanoma, it seems that genetic analysis will help in refining the classification of cutaneous and mucosal melanomas, particularly in relation to the discovery of effective targeted therapies.

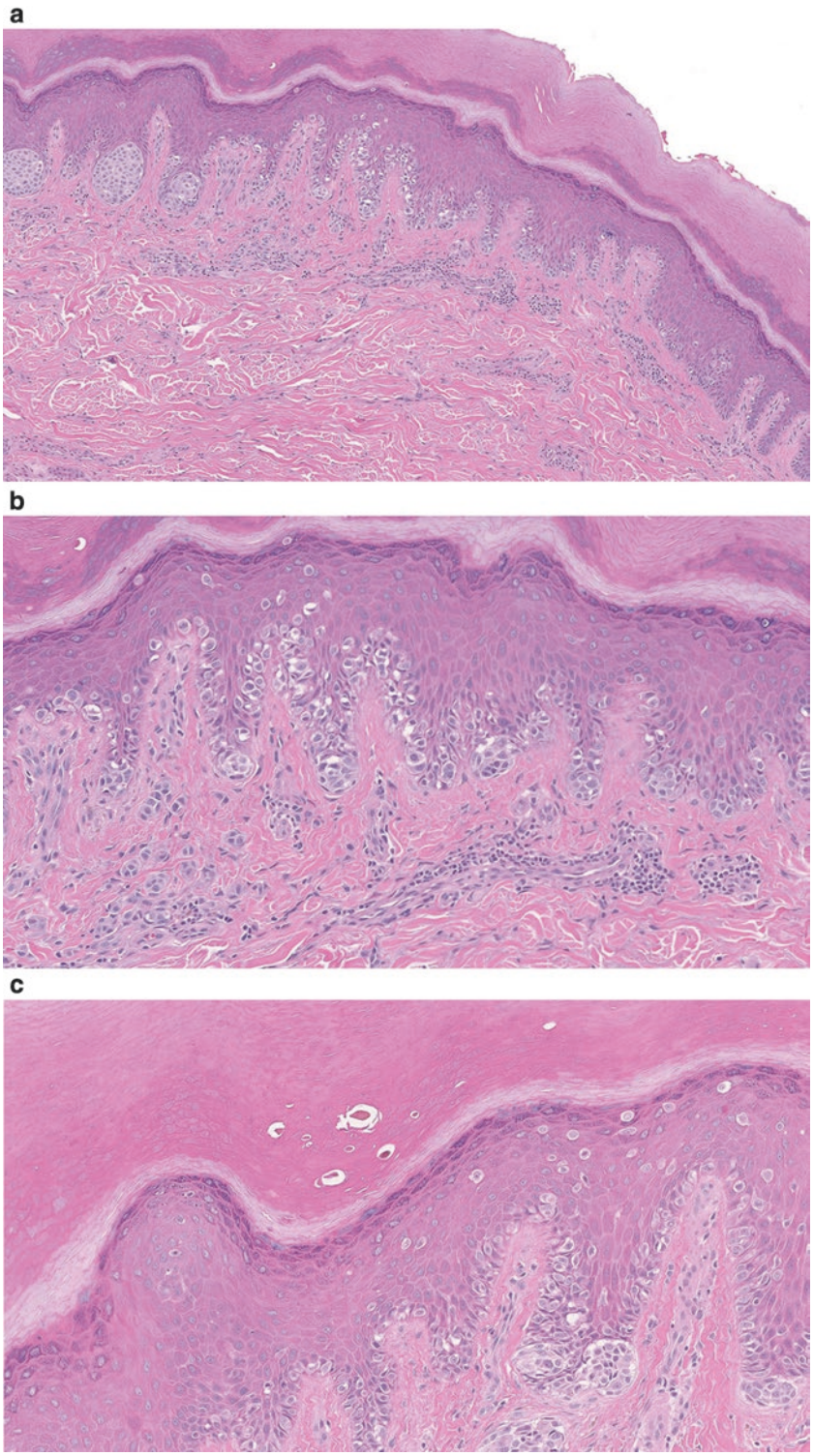


Fig. 7.33 Acral lentiginous melanoma. The lesion is broad and asymmetric and composed of discohesive nests and irregularly distributed single-cell melanocytes (**a**). The cells are large with an ample clear cytoplasm and hyperchromatic nuclei. In some areas the melanocytes are contiguous and have a lentiginous growth (**b**). Scattered dendritic cells are seen in the epidermis and it is common to see melanocytes surrounded by a clear halo (**c**)

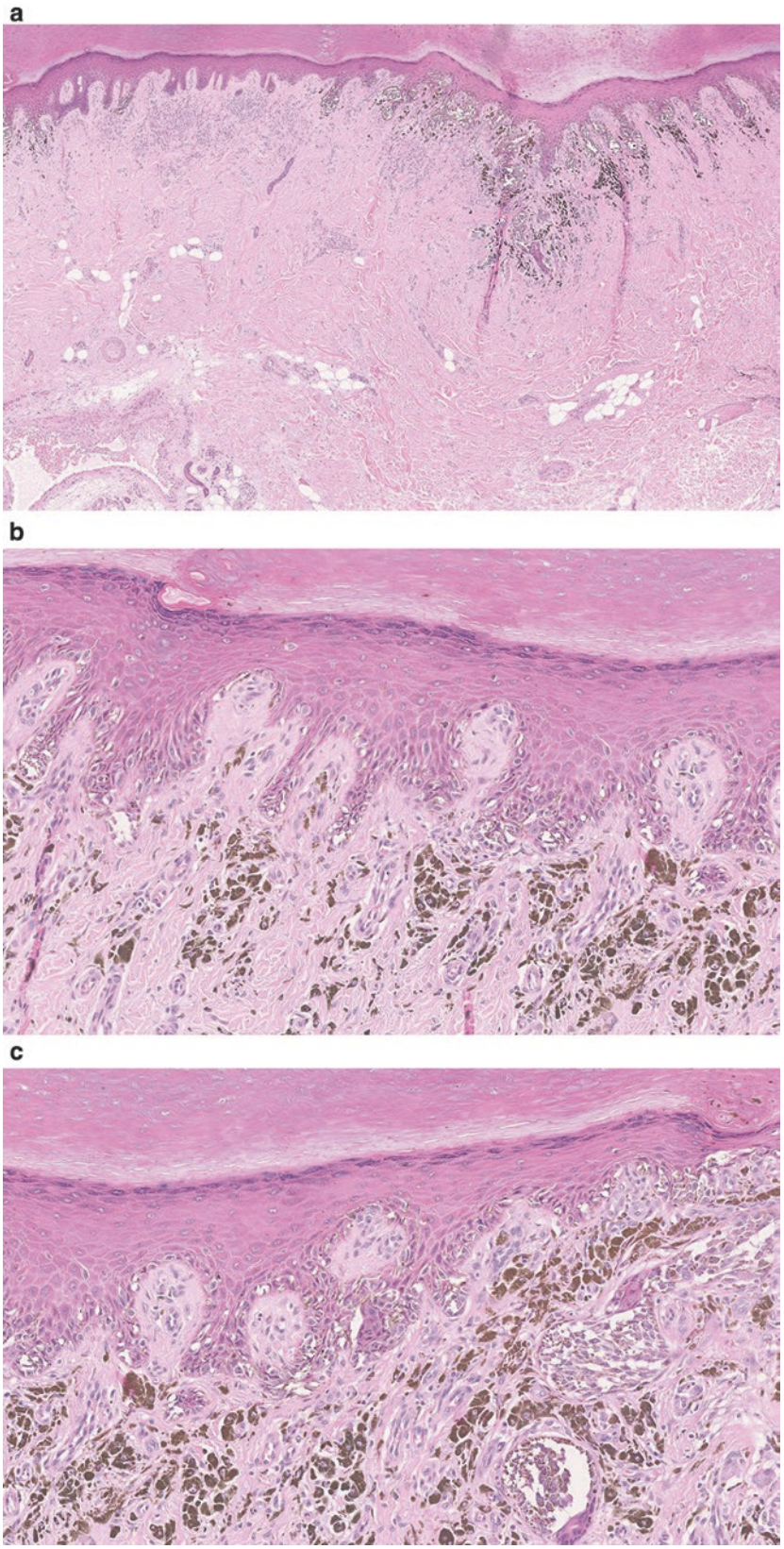


Fig. 7.34 Acral lentiginous melanoma. This example shows prominent asymmetric and irregular lentiginous junctional growth (**a**). The melanocytes are elongated with a hyperchromatic and vertically oriented nuclei. The cytoplasm of these cells is attenuated. The junctional nests are irregular in size and shape and mostly parallel to the epidermis. Note the characteristic skipping areas (single and nested melanocytes in the junction) (**b**, **c**)

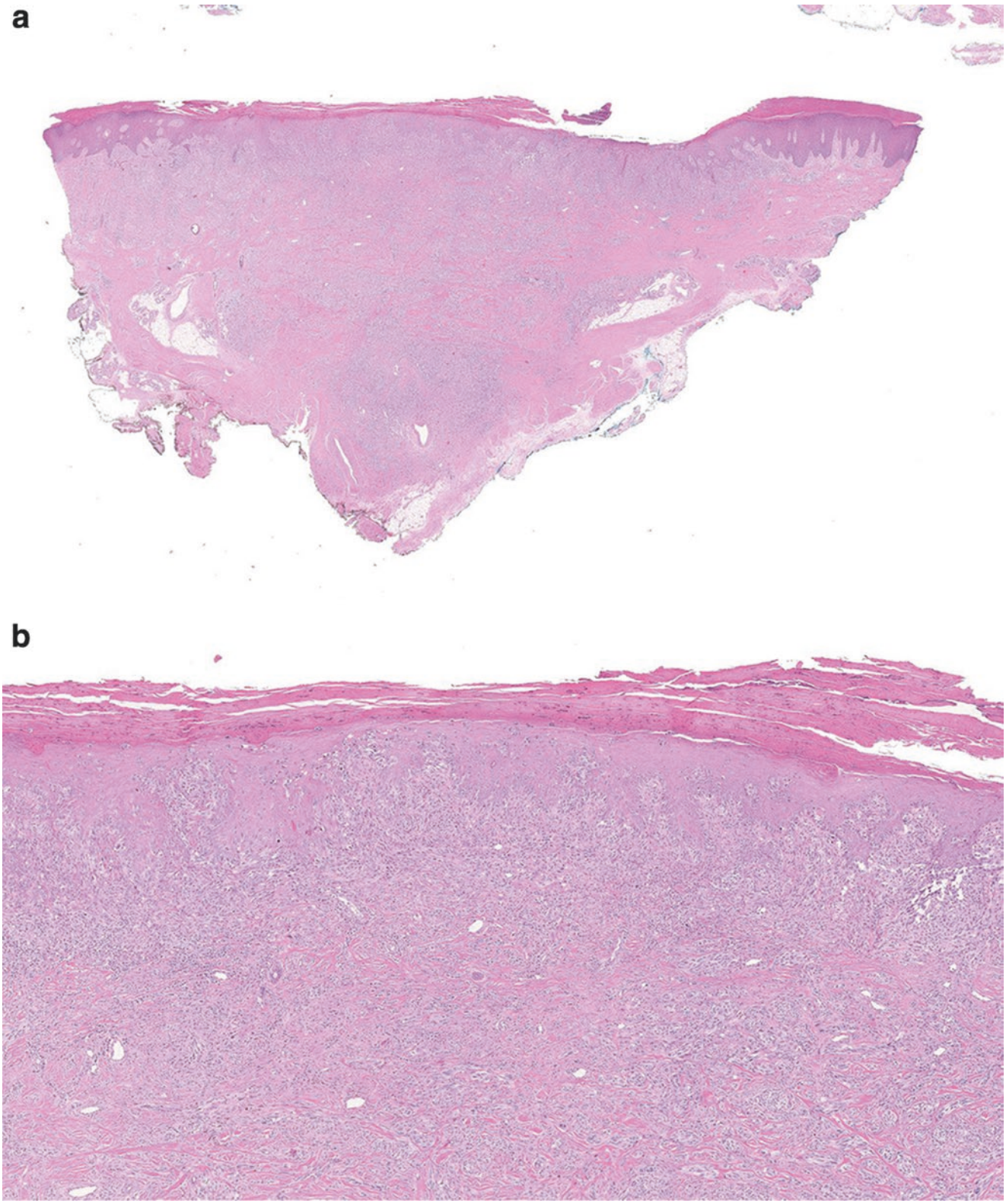


Fig. 7.35 Invasive acral lentiginous melanoma. This example shows a prominent junctional component with melanocytes distributed irregularly throughout the epidermis in single melanocytes and nests (**a**). The degree of pagetoid upward migration is high not only in single cells but also in nests (**b**, **c**).

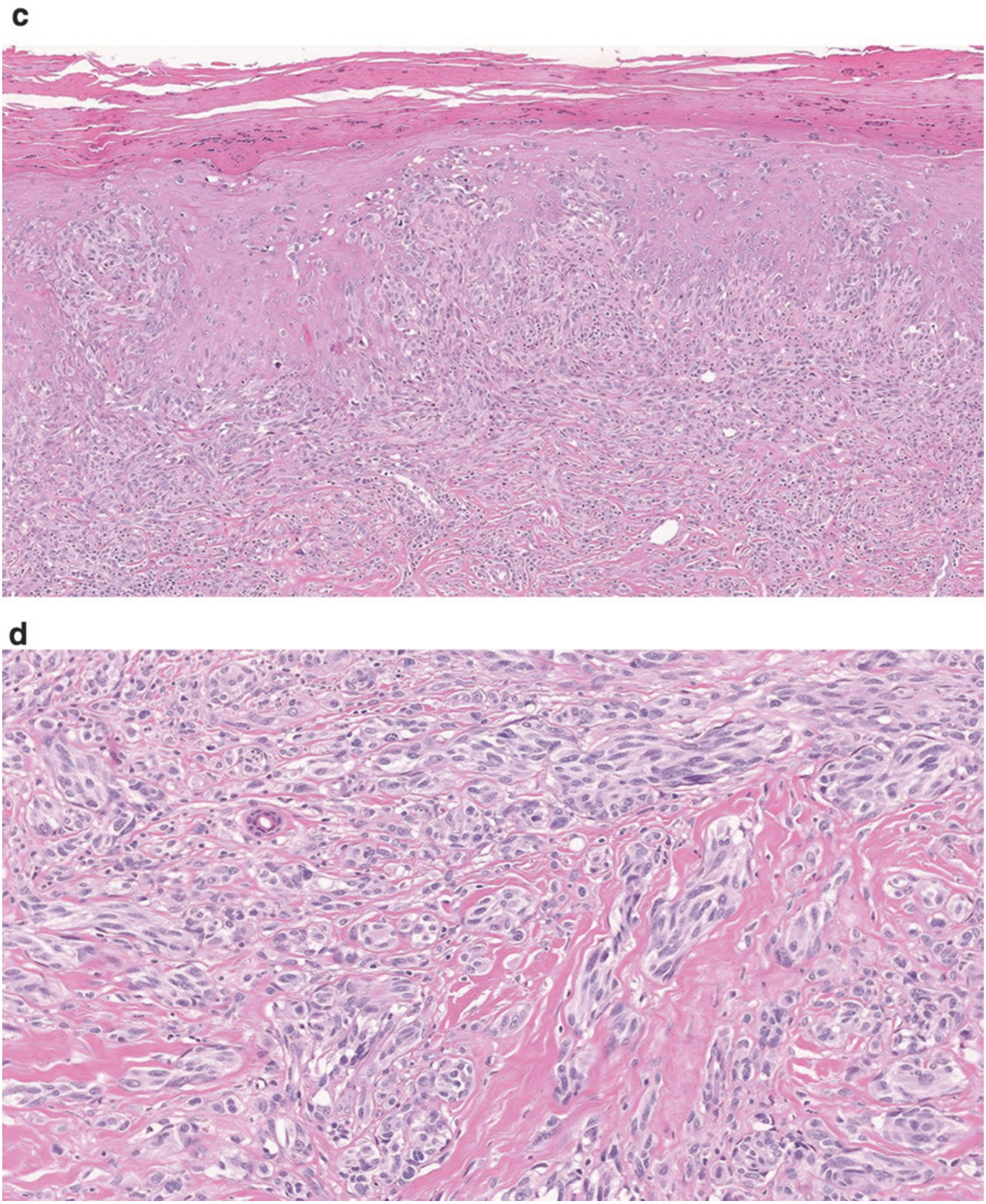


Fig. 7.35 (continued) An important feature is the presence of scattered atypical melanocytes within the stratum corneum. The melanoma in the dermis is composed of atypical spindle cells and arranged in a fascicular pattern. The cells in the dermis have scant cytoplasm, severe cytologic atypia, and hyperchromatic nuclei. Many atypical mitotic figures are seen in the dermal component (**d**)

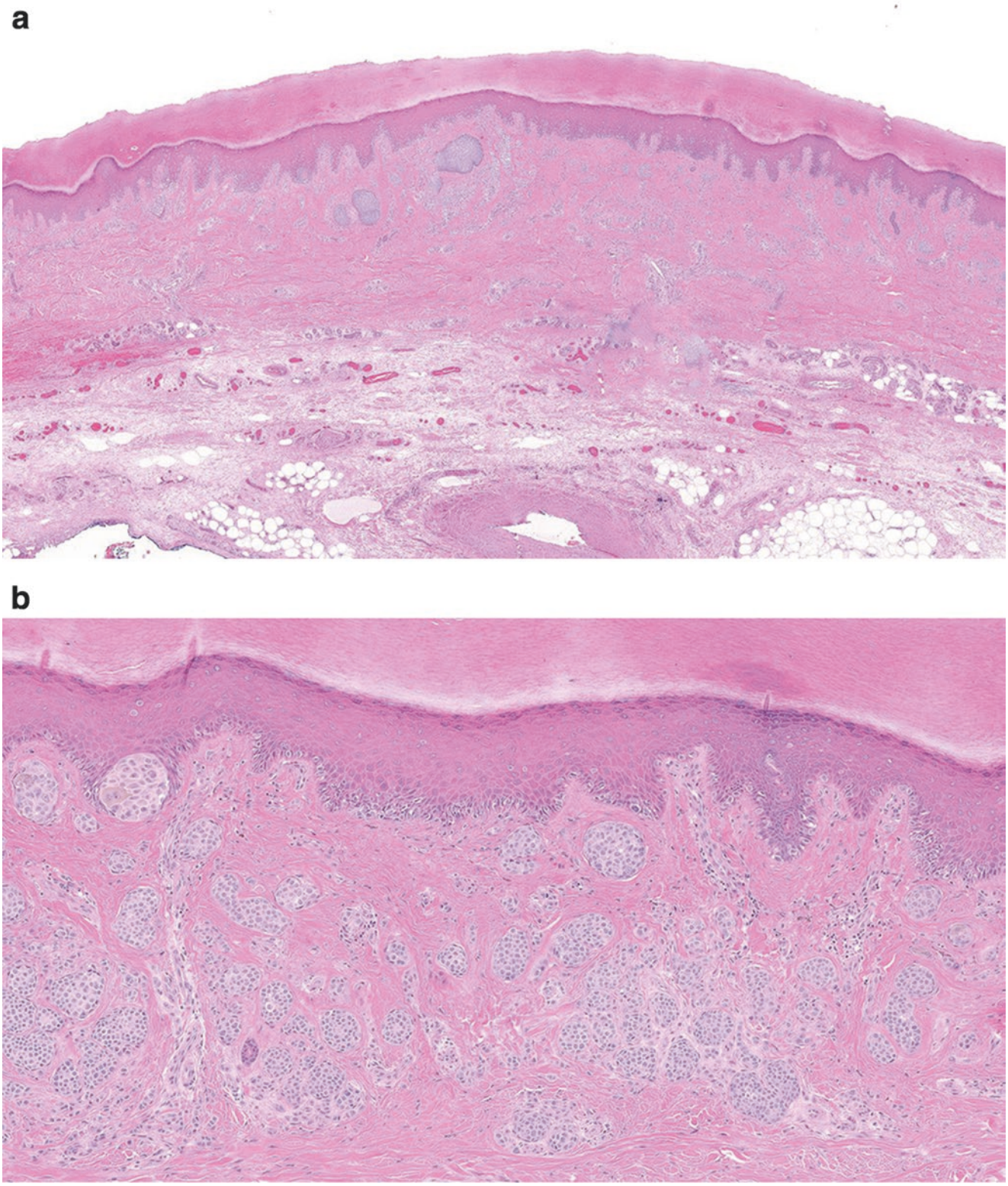


Fig. 7.36 Acral lentiginous melanoma. This is an example of invasive acral lentiginous melanoma with nevoid features. Depending on where the lesion is sampled, the diagnosis can be challenging to make as the lesion may simulate a nevus. On low magnification the lesion shows nevoid architecture (**a**); however, on closer look the nests in the junction are large and irregular in size and shape and with prominent discohesion and single cells (prominent pagetoid migration) (**b**).

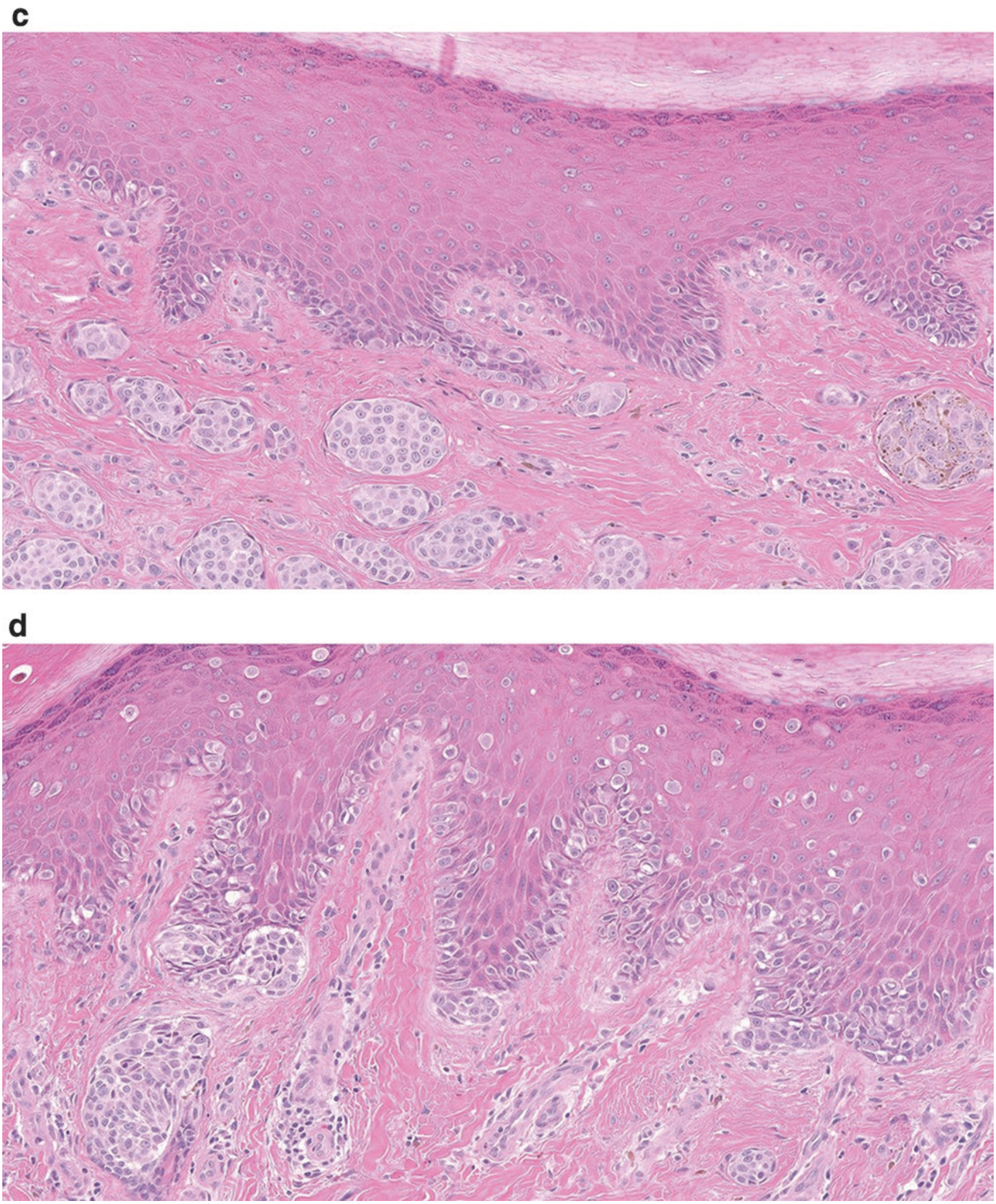


Fig. 7.36 (continued) Remember that pagetoid spread is characteristic in some acral nevi; however, the degree of pagetoid spread in this example is quite prominent and beyond to what is observed in some acral nevi. The melanocytes are atypical and pleomorphic with marked prominent nucleoli and have thickened nuclear membranes. Note the epithelioid aspect of the melanocytes in the dermis (**c**). These epithelioid melanocytes are arranged mostly in nests and are surrounded by mature collagen fibers (nevus-like); however, the epithelioid cells are atypical and pleomorphic and many atypical mitotic figures are noted (**d**)

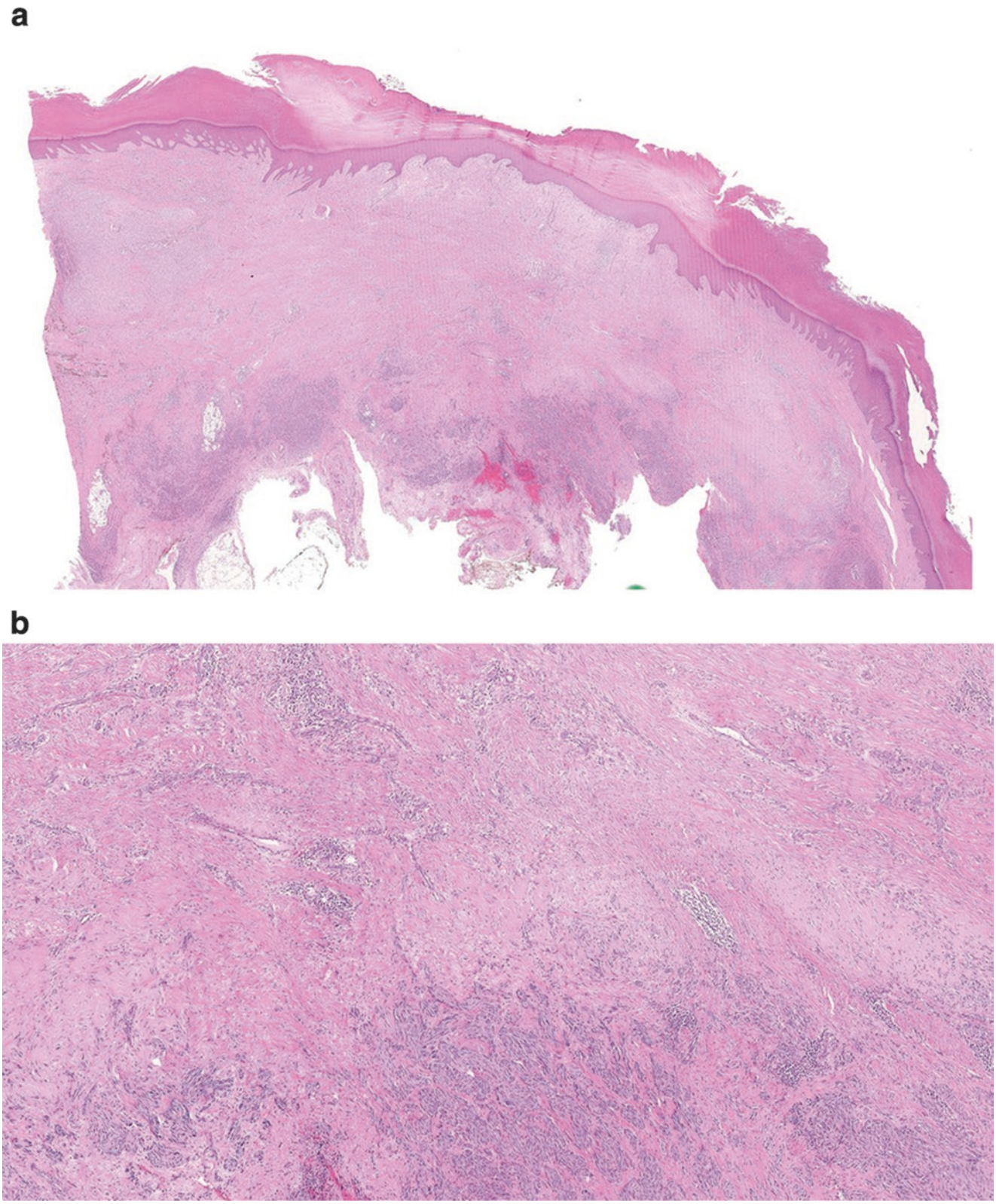


Fig. 7.37 Recurrent acral lentiginous melanoma. This patient had a history of acral melanoma that was excised with clear margin, and 10 months after surgery, the lesion recurred, requiring amputation of the toe. The lesion depicts a scar in the dermis with a diffuse growth of atypical melanocytes in the dermis (**a**). The melanocytes in the dermis have a spindle cell cytomorphology and are arranged in a fascicular growth pattern with many atypical mitotic figures (**b–d**)

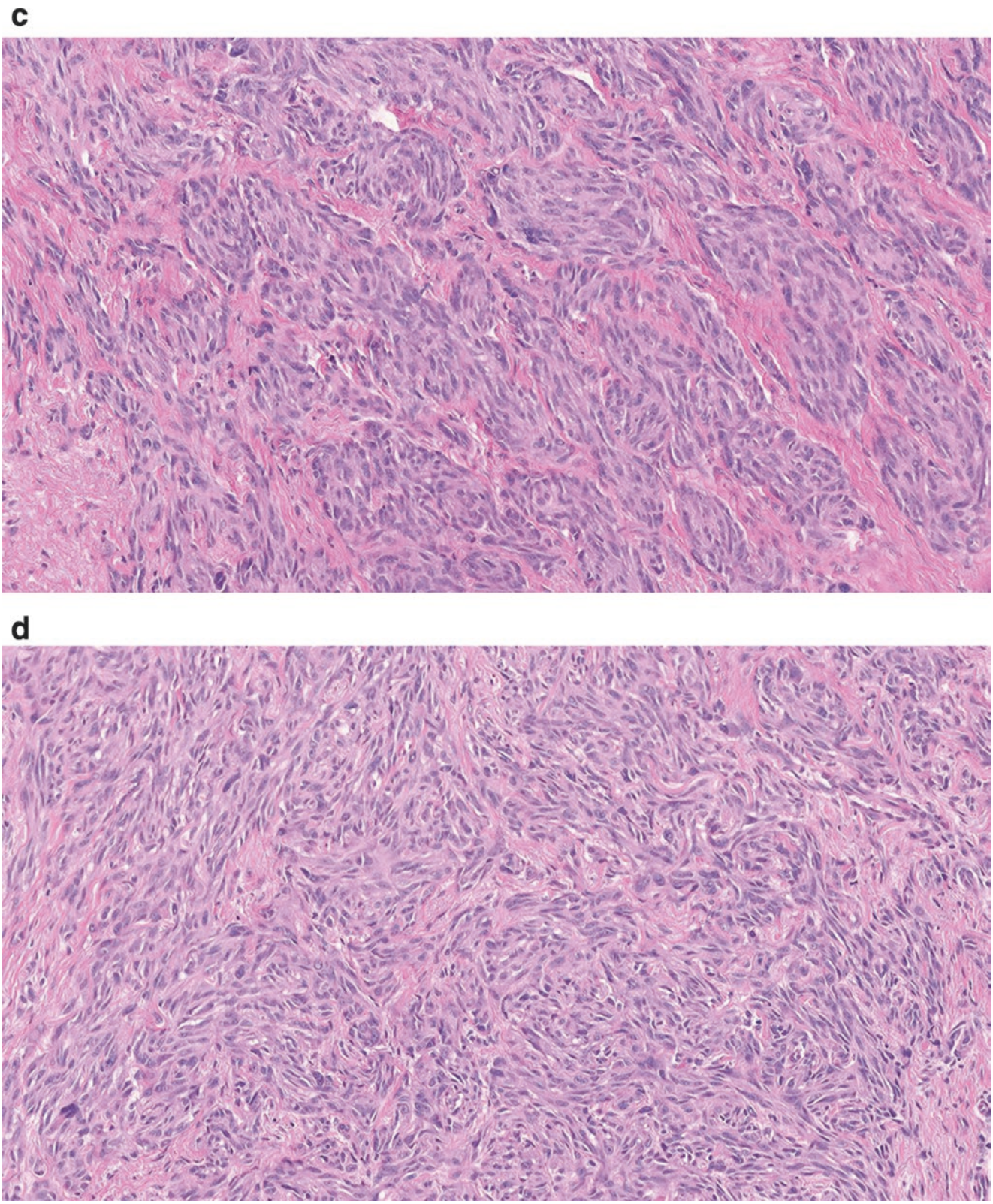


Fig. 7.37 (continued)

Nodular Melanoma

Clinical Features

The concept of nodular melanoma was coined by Dr. Clark as a diagnosis of exclusion, meaning that such diagnosis was established when the lesion did not fulfill the features of either superficial spreading, lentigo maligna, or acral lentiginous melanoma. The latter three lesions are characterized by a pattern of growth in the epidermis that extends beyond three rete ridges from the most lateral, invasive dermal component. When these histologic criteria are considered, nodular melanomas present as rapidly growing, commonly ulcerated lesions, in which the patient does not recall the presence of a preexisting pigmented lesion. Conceptually, nodular melanoma most likely reflects the rapid enlargement of areas of invasive melanoma that overrun the previously existing melanoma in situ.

In contrast with the other types of melanoma, nodular melanoma may present as a uniform, symmetrical, pigmented lesion, likely as a reflection of its rapid rate of growth. It has been suggested that nodular melanomas have a worse prognosis than the other subtypes. However, such a difference mostly disappears when the Breslow thickness is considered. Thus, it is likely that nodular melanomas behave in a more aggressive fashion because they are more difficult to detect (very short-lived radial growth phase) and thus achieve a relatively higher Breslow thickness (see also histologic features) [118].

Histopathology

As mentioned above, nodular melanoma lacks a distinct radial growth phase (i.e., it does not extend more than three rete ridges beyond the invasive dermal component). Therefore, most of the lesion occupies the dermis (or extends into the subcutaneous tissue) with only focal involvement of the overlying epidermis. The diagnosis of melanoma is relatively easy since, regardless of the presence or absence of a visible intraepidermal component, there is always a dermal, expansile pattern of growth of melanocytes, epithelioid or spindle, with irregular, hyperchromatic nuclei, visible nucleoli, and dermal mitotic figures. There is frequently vascular or perineural invasion.

Although there is no apparent difference in survival between nodular melanoma and the other subtypes when Breslow thickness is taken into consideration, it is reported that approximately 50 % of all melanomas thicker than 2 mm show a nodular pattern [119]. And even though we have encountered in our practice a number of melanomas originally reported as "nodular" that in reality corresponded to a superficial spreading or acral lentiginous melanoma with a large dermal component (i.e., a dermal "nodule"), in a recent series at our institution, out of 224 cases, the average of Breslow thickness was still clearly higher for nodular melanoma (2.6 vs. 1.4 mm; nodular vs. superficial spreading subtypes).

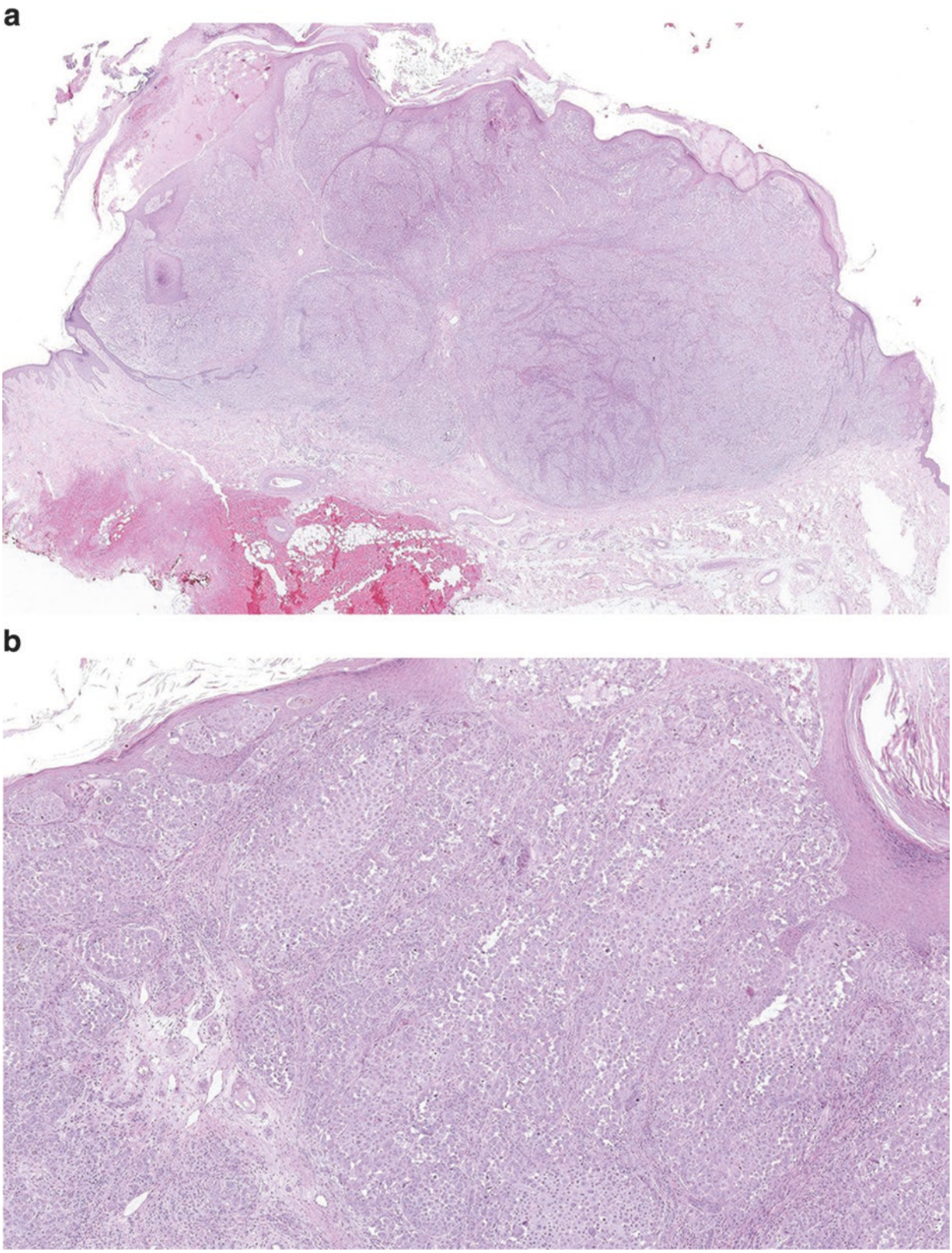


Fig. 7.38 Nodular melanoma. This case shows clear malignant features. The lesion is composed of sheets of large epithelioid cells that abut the epidermis (**a**). There is a junctional component overlying the dermal component, but it does not extend beyond the cells in the dermis. Note the collarette on low magnification (usually a sign of rapid growth). The cells in the dermis form solid, expansile sheets and large nests with little collagen or adnexal structures (**b**).

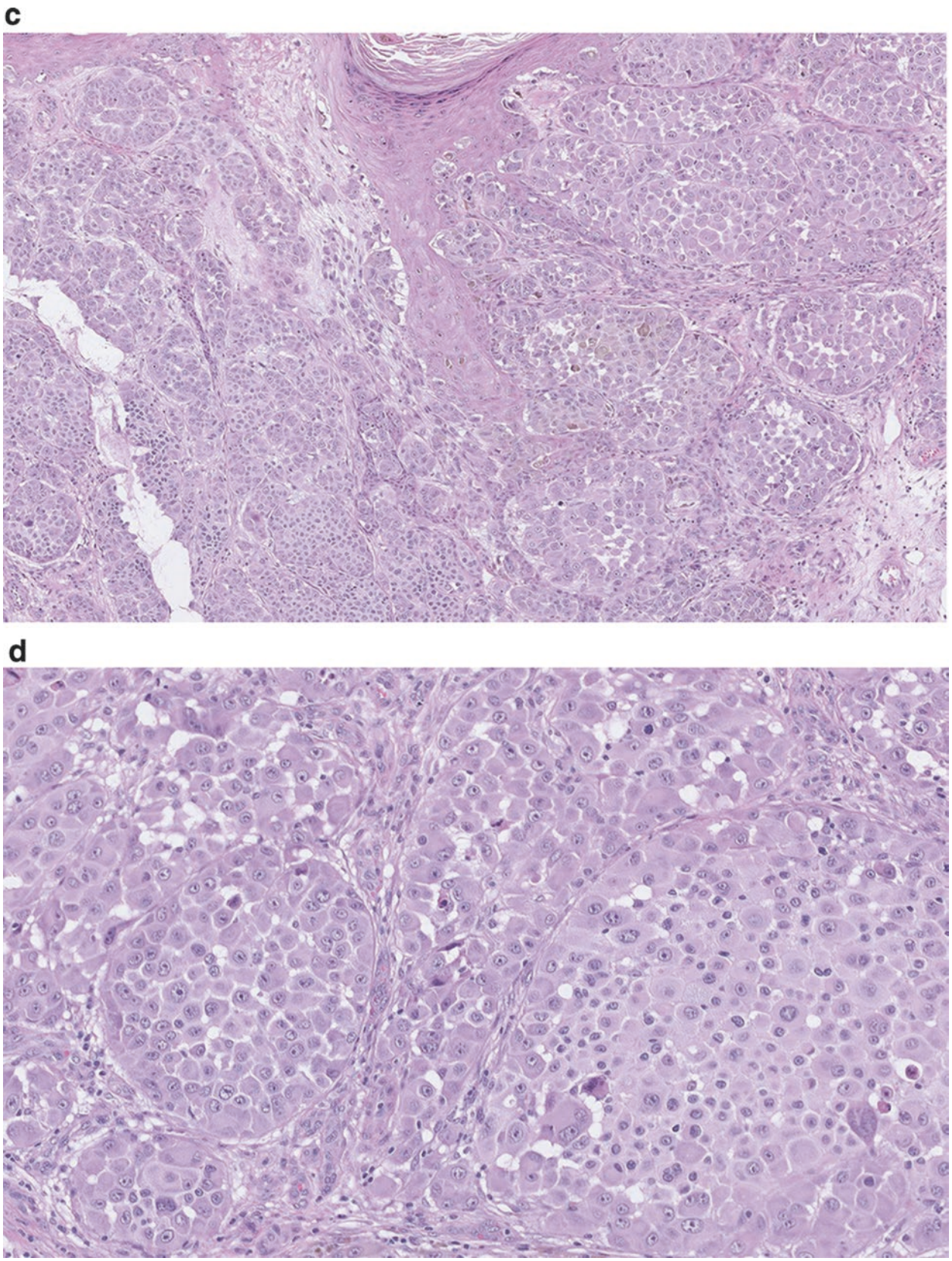


Fig. 7.38 (continued) Cells show prominent nucleoli, thick nuclear membranes, and prominent dusty melanin granules in the cytoplasm (**c**). Markedly atypical cells with prominent nucleoli and obvious mitotic figures (**d**)

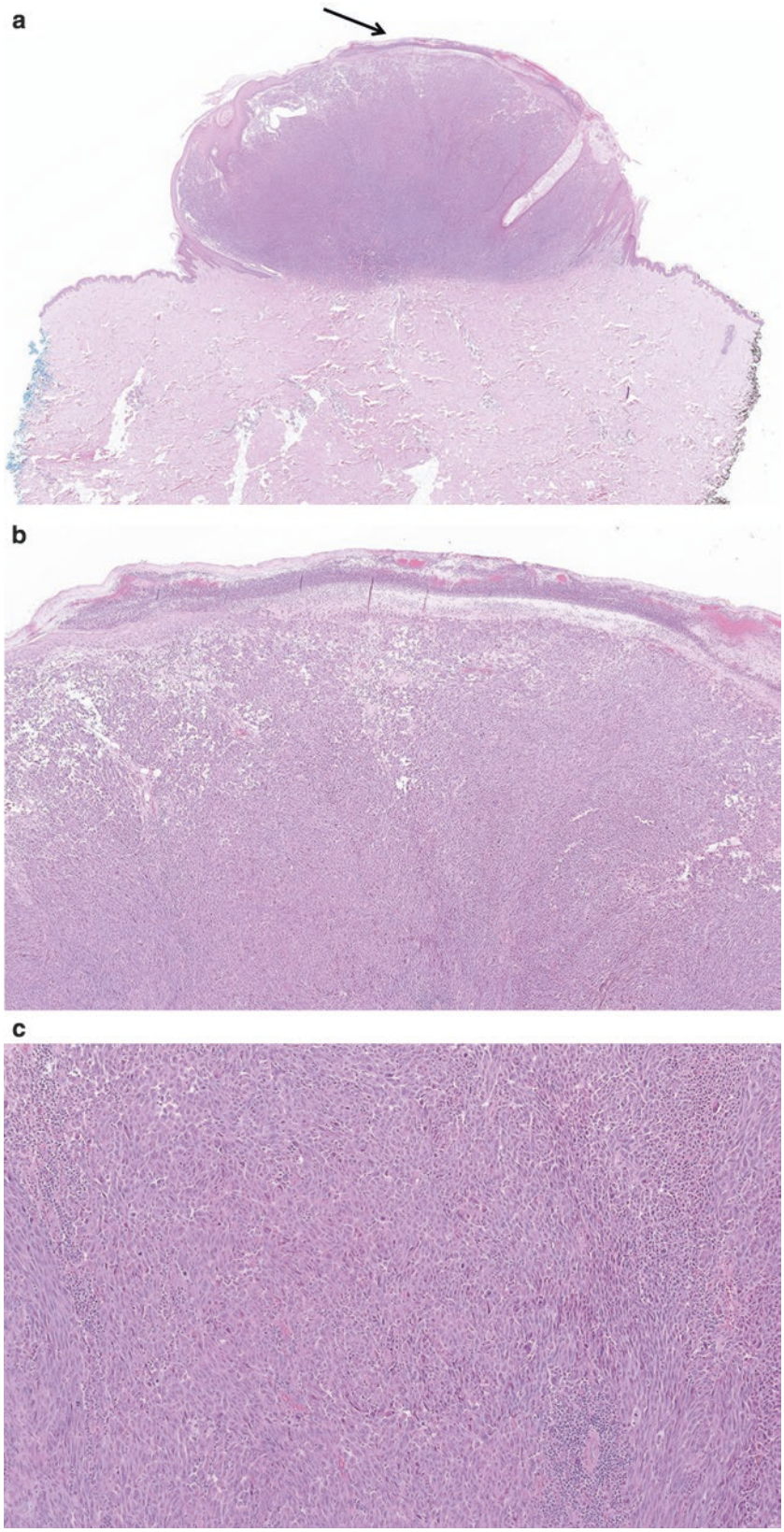


Fig. 7.39 Ulcerated nodular melanoma. Similar to Fig. 7.38, this lesion has an expansile growth of cells in the dermis. There is focal ulceration (*arrow*). By definition, there is no evidence of extension in the epidermis beyond the dermal component (**a**). The dermis is occupied by large sheets of epithelioid and spindle cells with very little intervening stroma (**b**). The deep dermis still contains densely packed fascicles and nests of melanocytes (absence of maturation) (**c**).

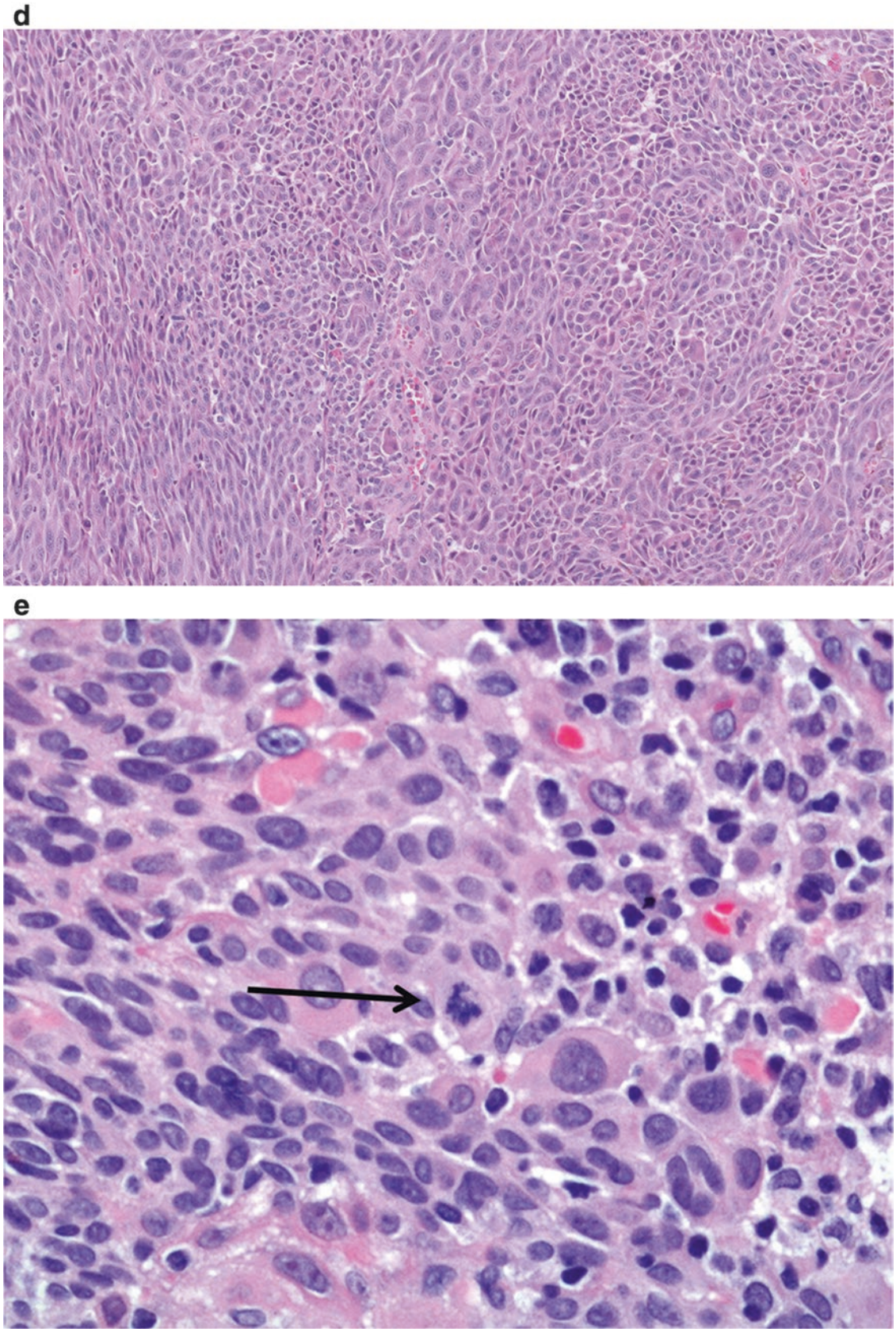


Fig. 7.39 (continued) Cells have severe cytologic atypia along with prominent nucleoli with numerous mitotic figures (**d**). High-power view with marked cytologic atypia (prominent pleomorphism, irregular chromatin, and atypical mitotic figures (*arrow*)) (**e**)

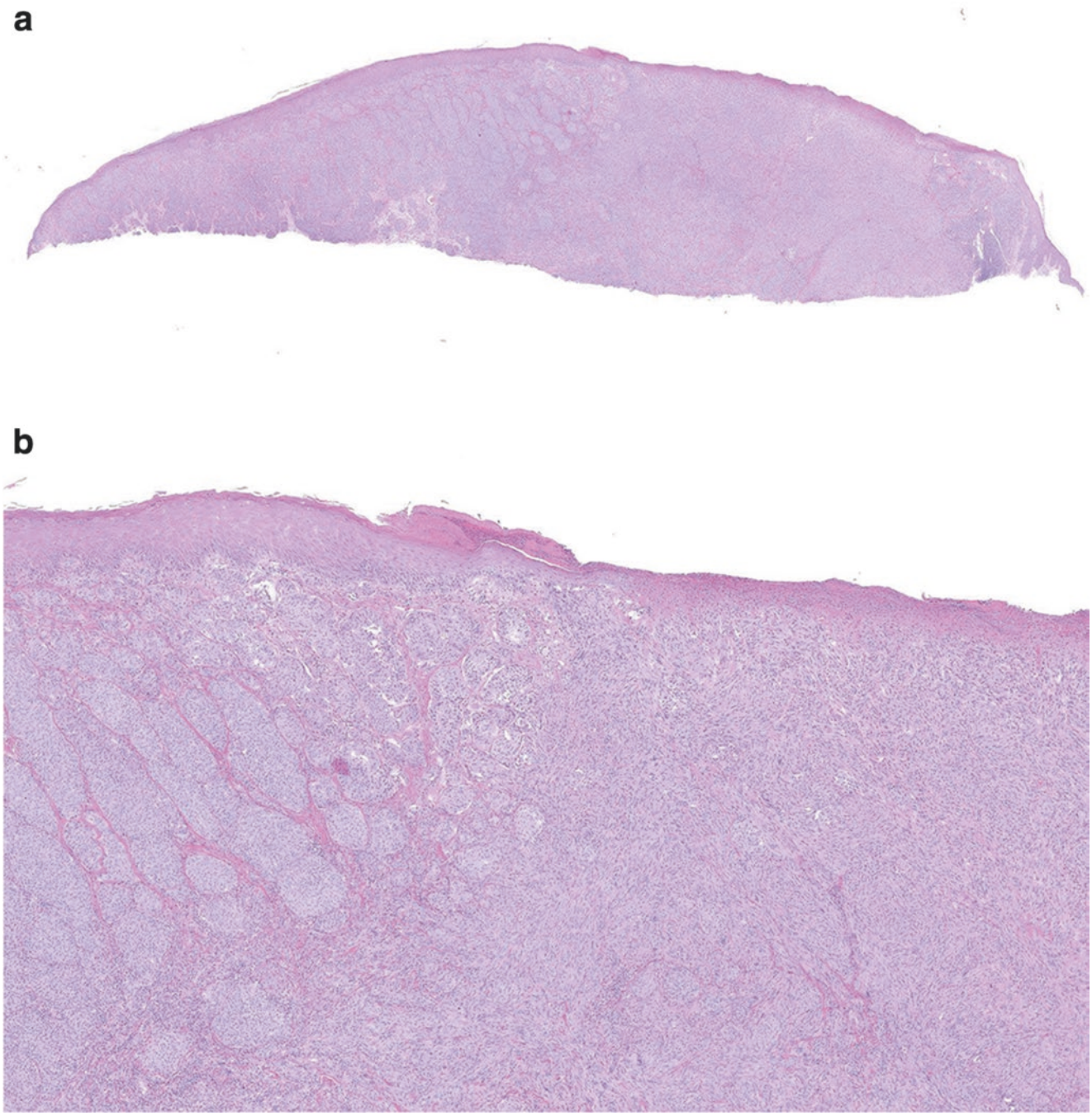


Fig. 7.40 Nodular melanoma with epithelioid and spindle cell melanocytes. This is another clear-cut example of melanoma that is composed of a dual population of atypical melanocytes. One side of the image shows malignant epithelioid cells and the other side is composed of malignant spindle cells (**a**, **b**).

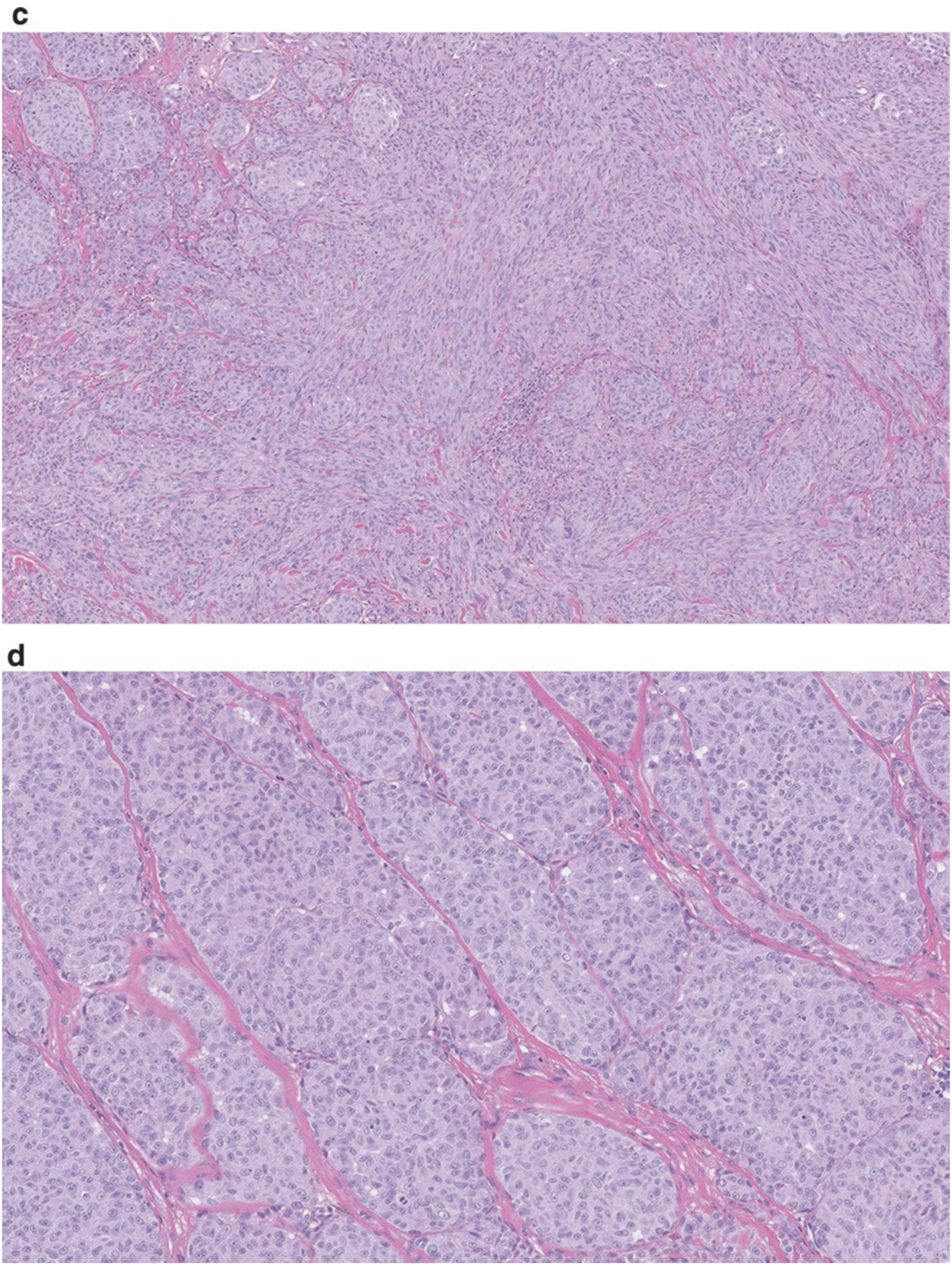


Fig. 7.40 (continued) Note that there is no mature collagen noted in the dermis and the adnexal structures are attenuated (**c**, **d**)

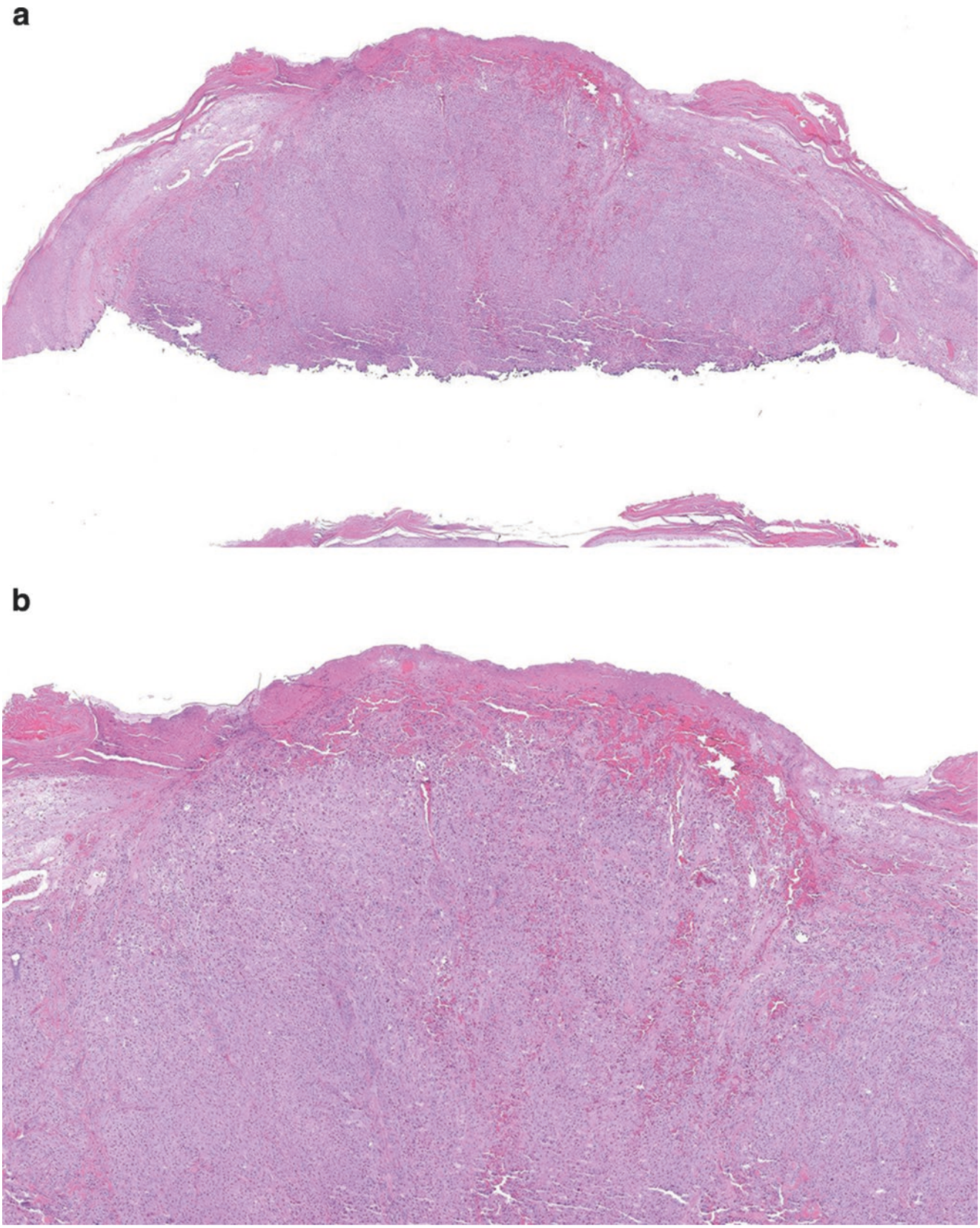


Fig. 7.41 Ulcerated nodular melanoma with pseudovascular spaces. This example of melanoma does not show a junctional component (the epidermis is ulcerated), and in the dermis there is hemorrhage and scattered pseudovascular spaces (**a**, **b**).

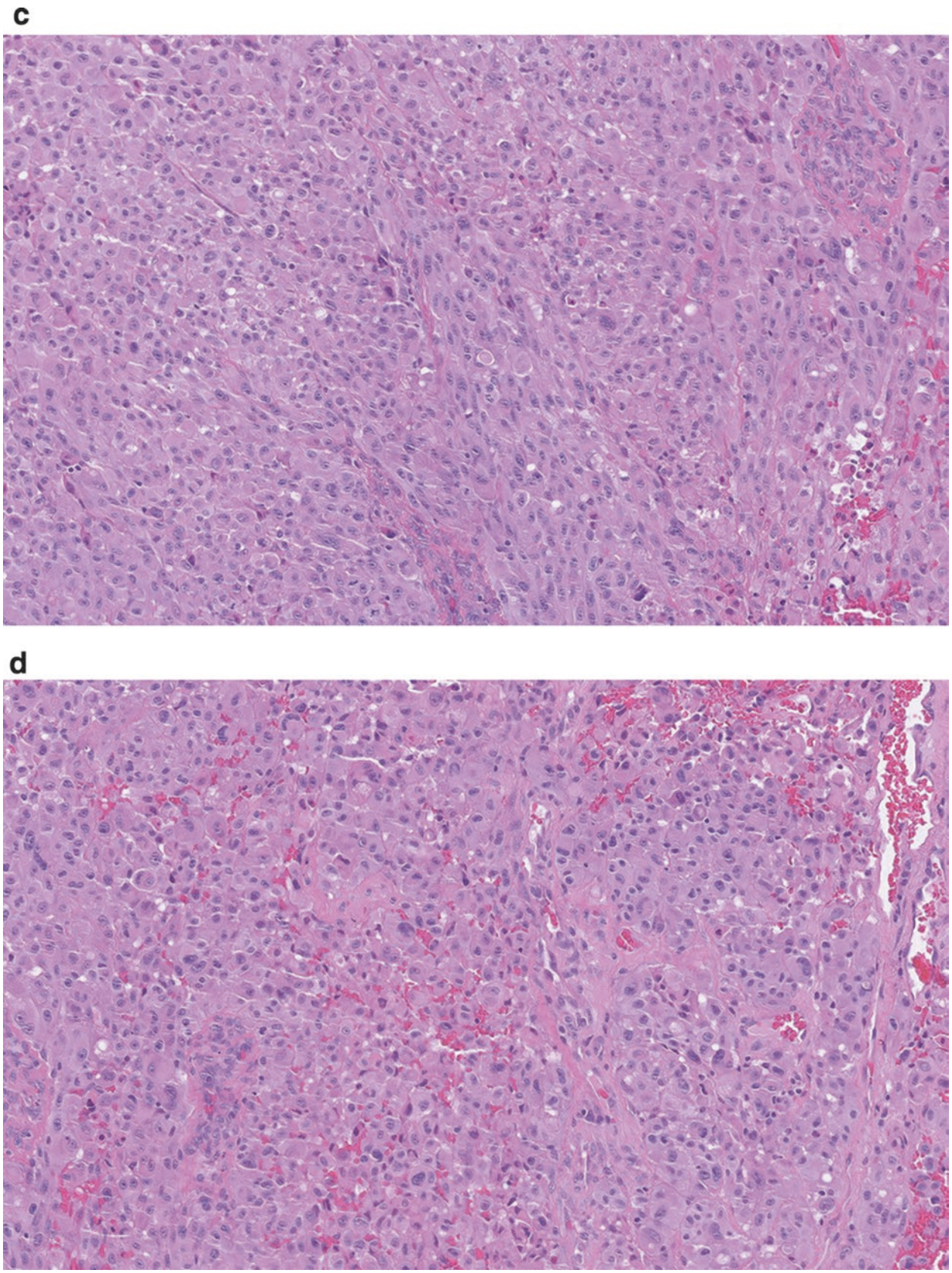


Fig. 7.41 (continued) In cases like this, it is always appropriate to perform immunostains to rule other malignancies, such as atypical fibroxanthoma (if the lesion is located on the head and neck) and epithelioid angiosarcoma which can show identical features to this tumor. The cells are epithelioid and display high-grade cytologic atypia, prominent nucleoli, and many atypical mitotic figures (**c**, **d**)

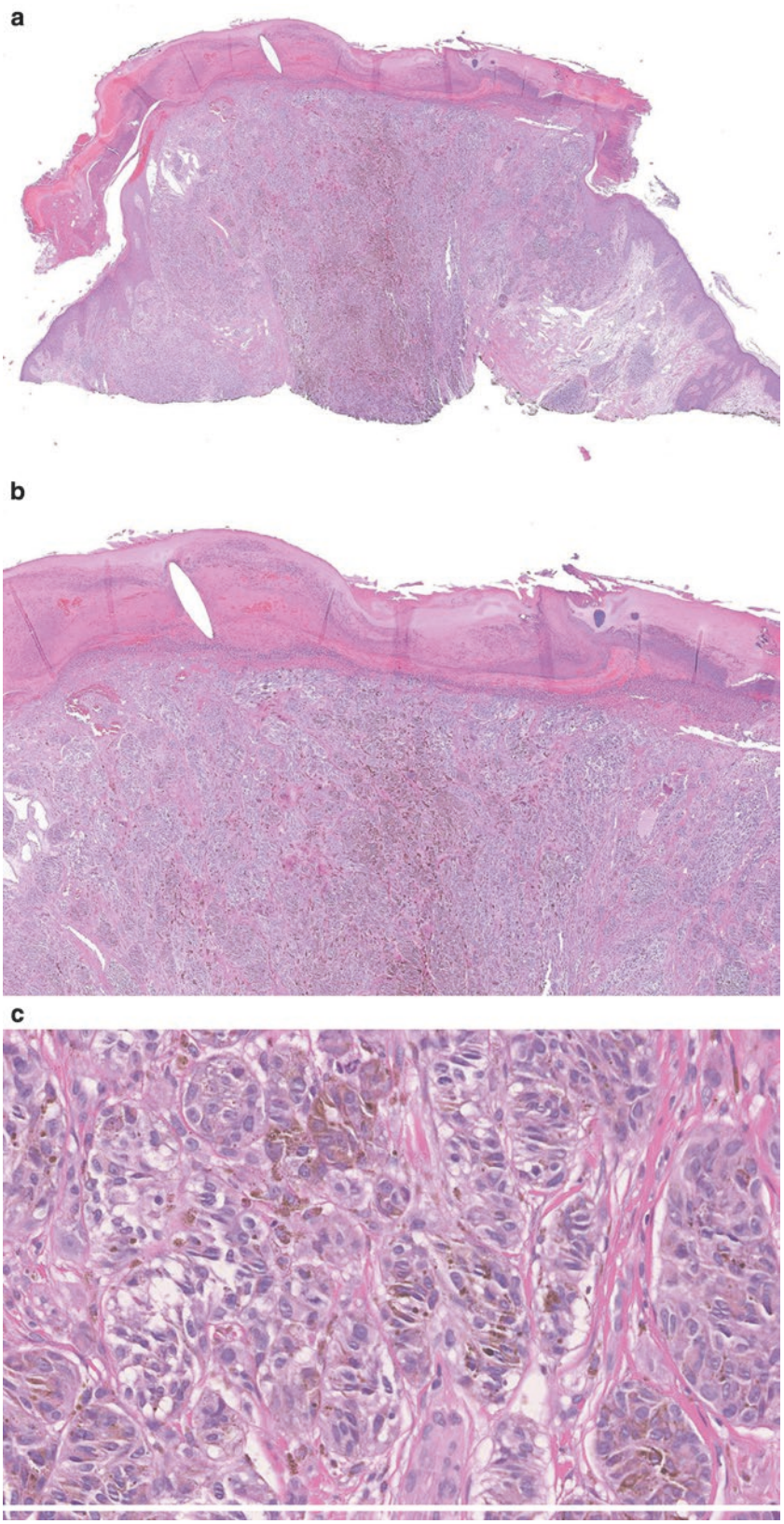


Fig. 7.42 Ulcerated pigmented nodular melanoma. This case of nodular melanoma is ulcerated and shows prominent pigmentation in the dermis (**a**). Note the overlying ulcer with a neutrophilic crust (**b**). Cells are large with irregular nuclei. There is abundant melanin pigment, mostly within macrophages (coarse granules) (**c**)

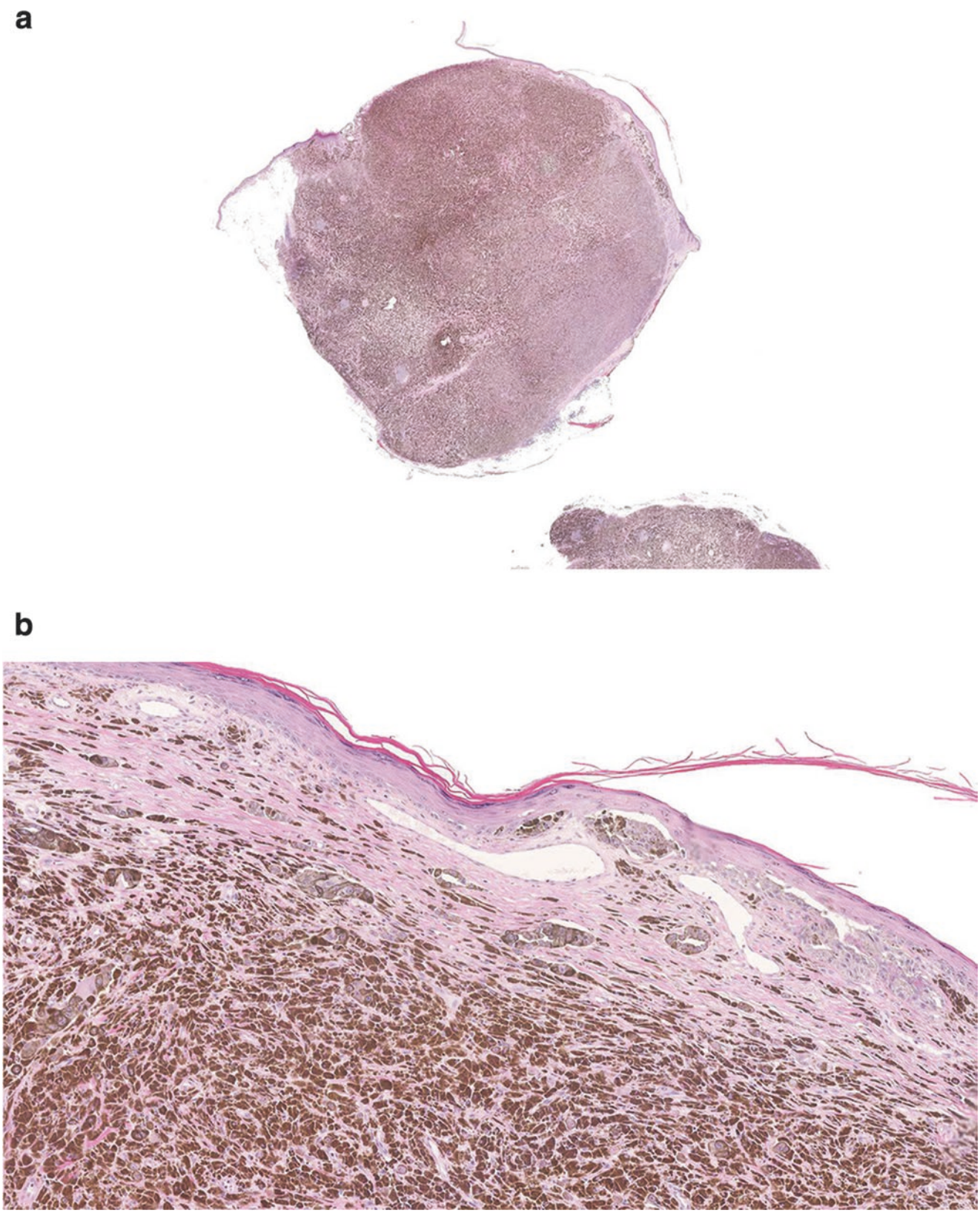


Fig. 7.43 Nodular melanoma with massive hyperpigmentation. The lesion shows a nodular neoplasm with compact growth pattern and uniform hyperpigmentation (**a**). There is focal in situ component with non-cohesive nests (**b**).

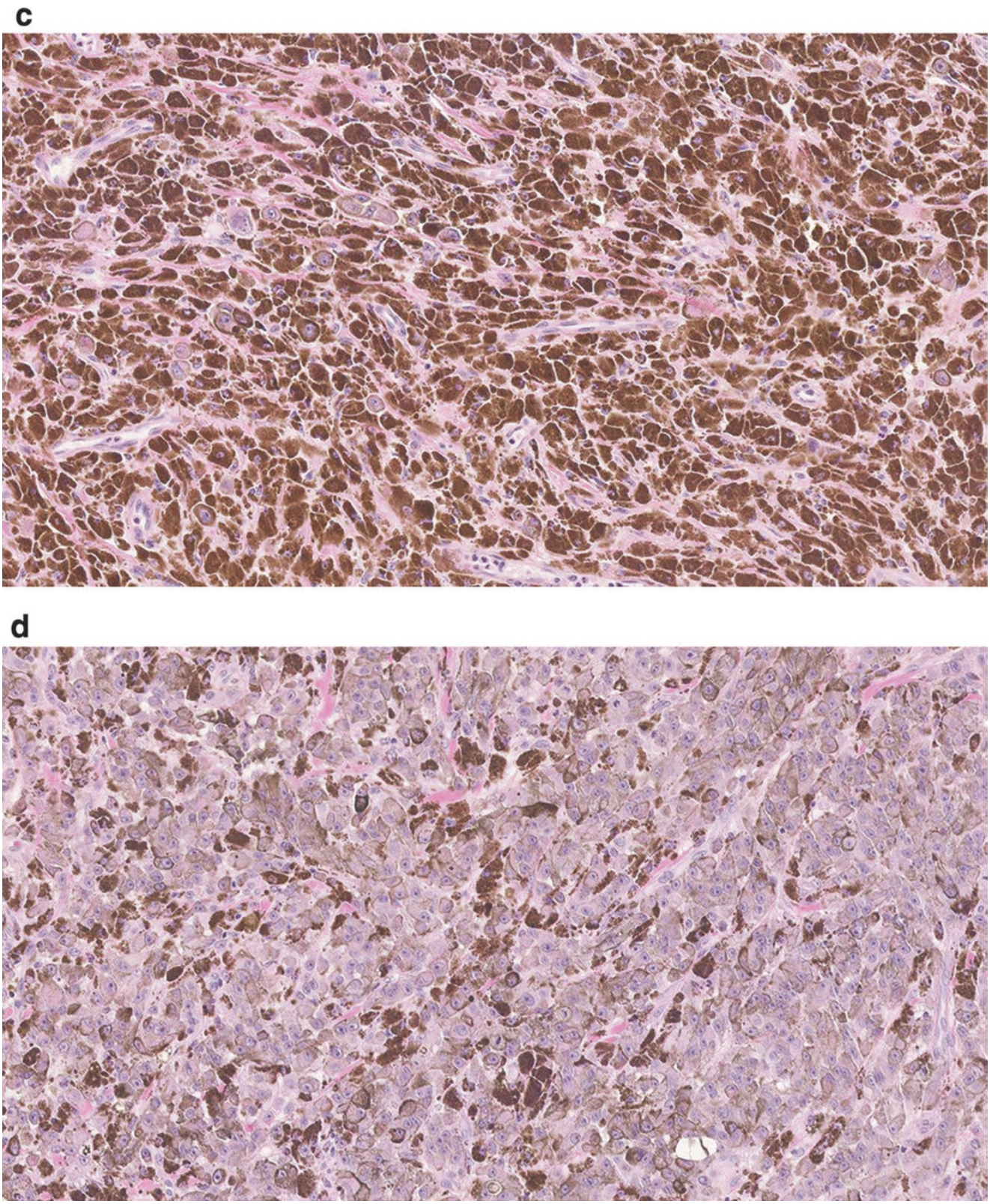


Fig. 7.43 (continued) Most of the pigment appears to be located within macrophages (coarse granules), thus consistent with extensive regression (**c**). Other areas have pigmentation of melanoma cells, similar to epithelioid pigmented melanocytomas (**d**)

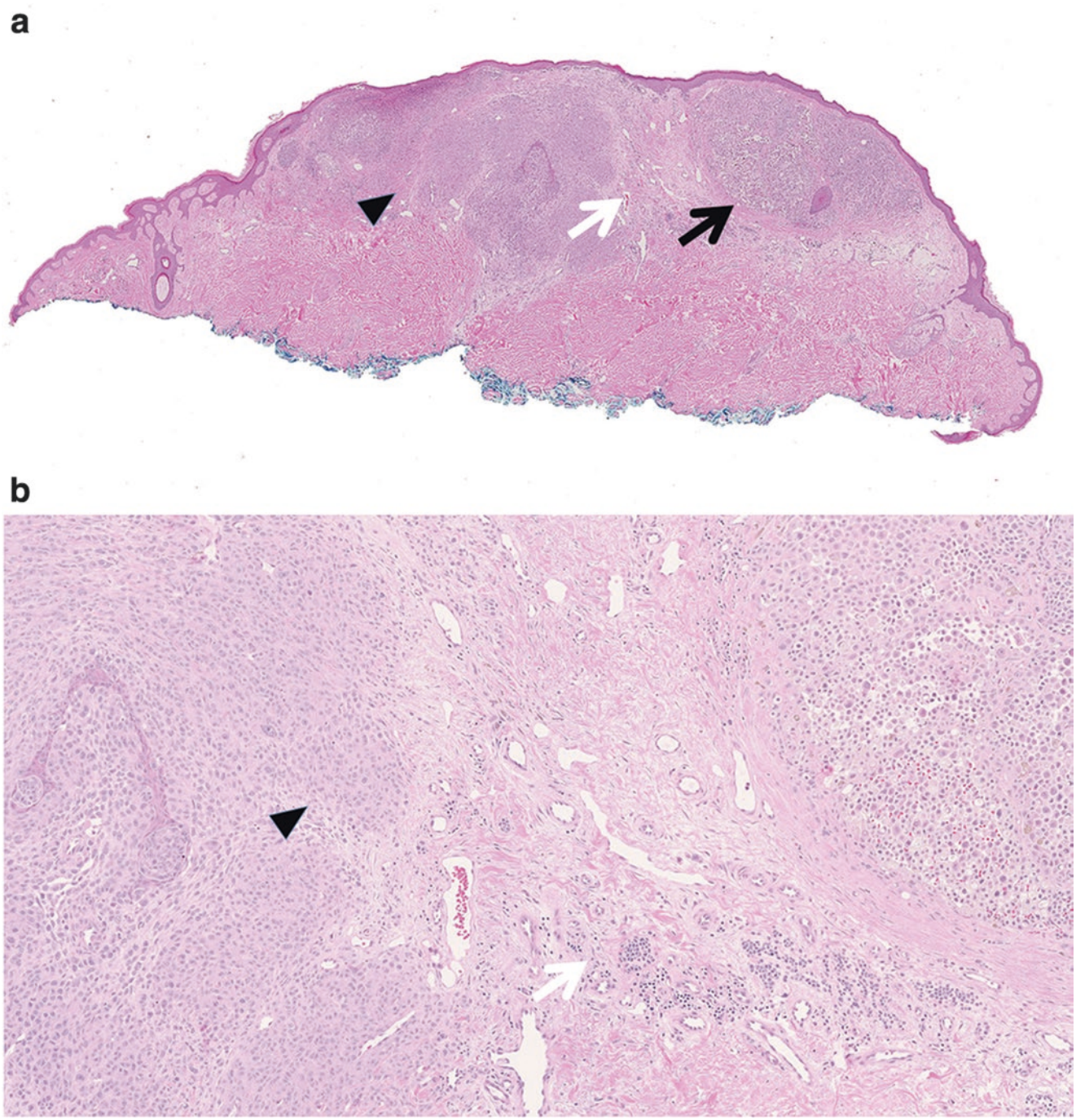


Fig. 7.44 Nodular melanoma associated with a dermal nevus. This example of melanoma has three components. The *right side* of the lesion shows an expansile area of large melanocytes with focal melanin pigment (epithelioid melanoma cells, *black arrow*), the center of the lesion shows an intradermal nevus (*white arrow*), and the *left side* shows melanoma in the dermis with nevoid features (*arrowhead*) (**a**). Intradermal nevus characterized by small melanocytes arranged in small, non-confluent nests (*arrowhead*). The nevoid component shows cells with mild degree of cytologic atypia but still displaying hyperchromatic nuclei and visible nucleoli and deep mitotic figures (**b**).

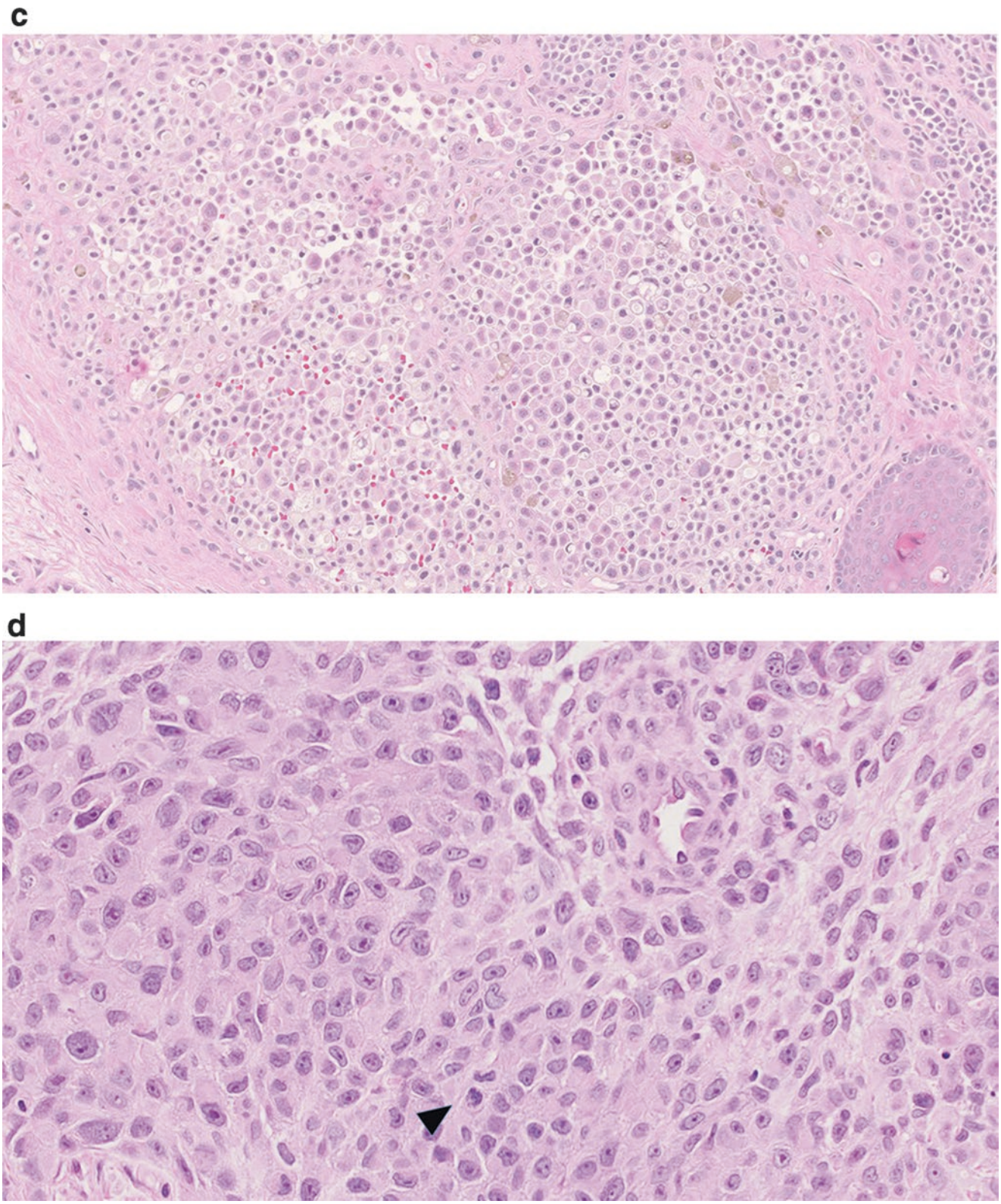


Fig. 7.44 (continued) The epithelioid component shows markedly pleomorphic cells with hyperchromatic nuclei and prominent nuclei along with dusty pigmented granules in the cytoplasm (**c**). Nevoid melanoma cells with large, irregular nuclei, visible nucleoli, and deep mitotic figures (*arrowhead*) (**d**)

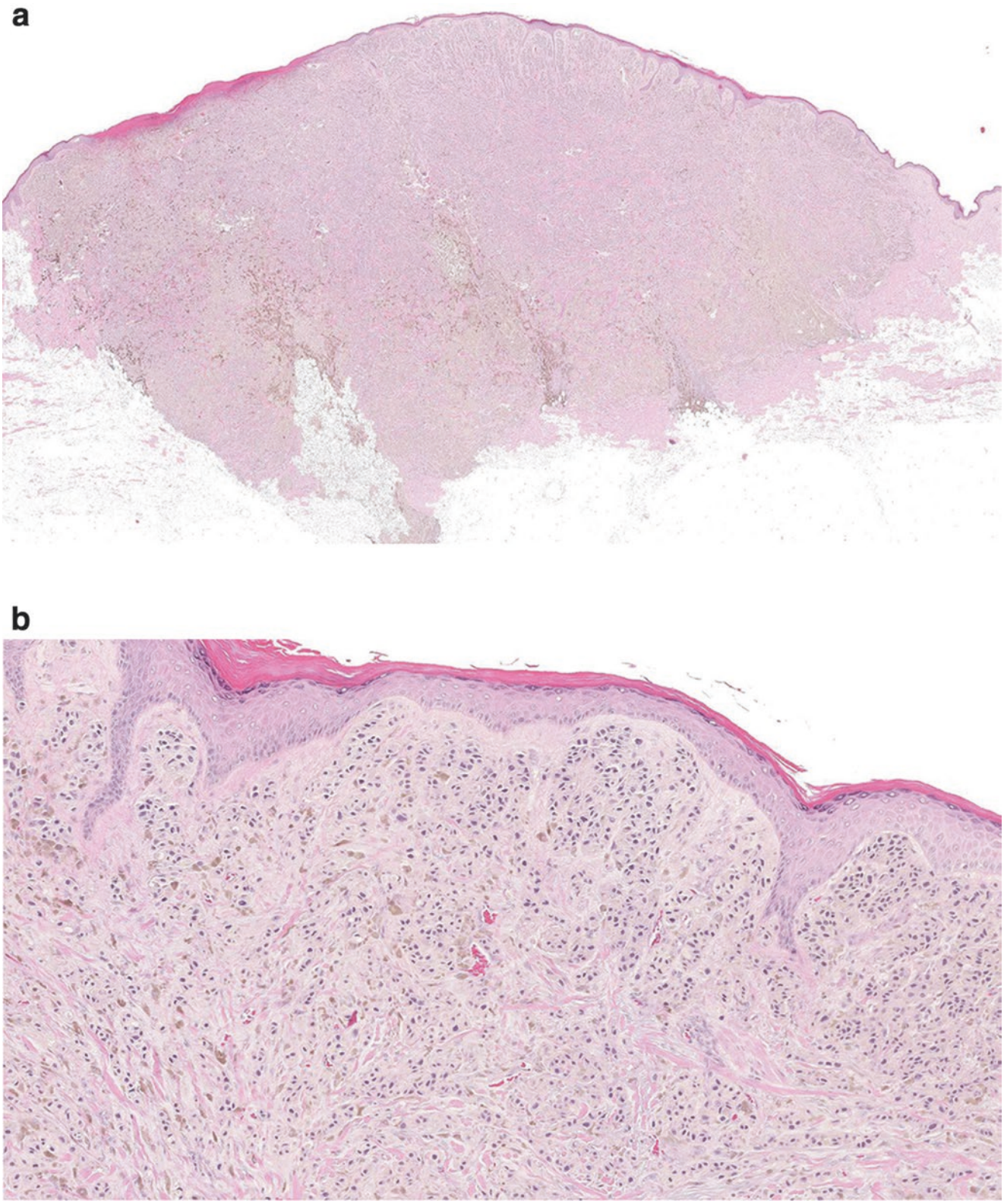


Fig. 7.45 Nodular melanoma composed of melanocytes with dusky cytoplasm. Large, expansile lesion with extensive involvement of the subcutaneous tissue (**a**). Note the deeply located melanin pigment. Melanocytes maintain the same size and amount of melanin pigment regardless the depth in the dermis (**b**, **c**).

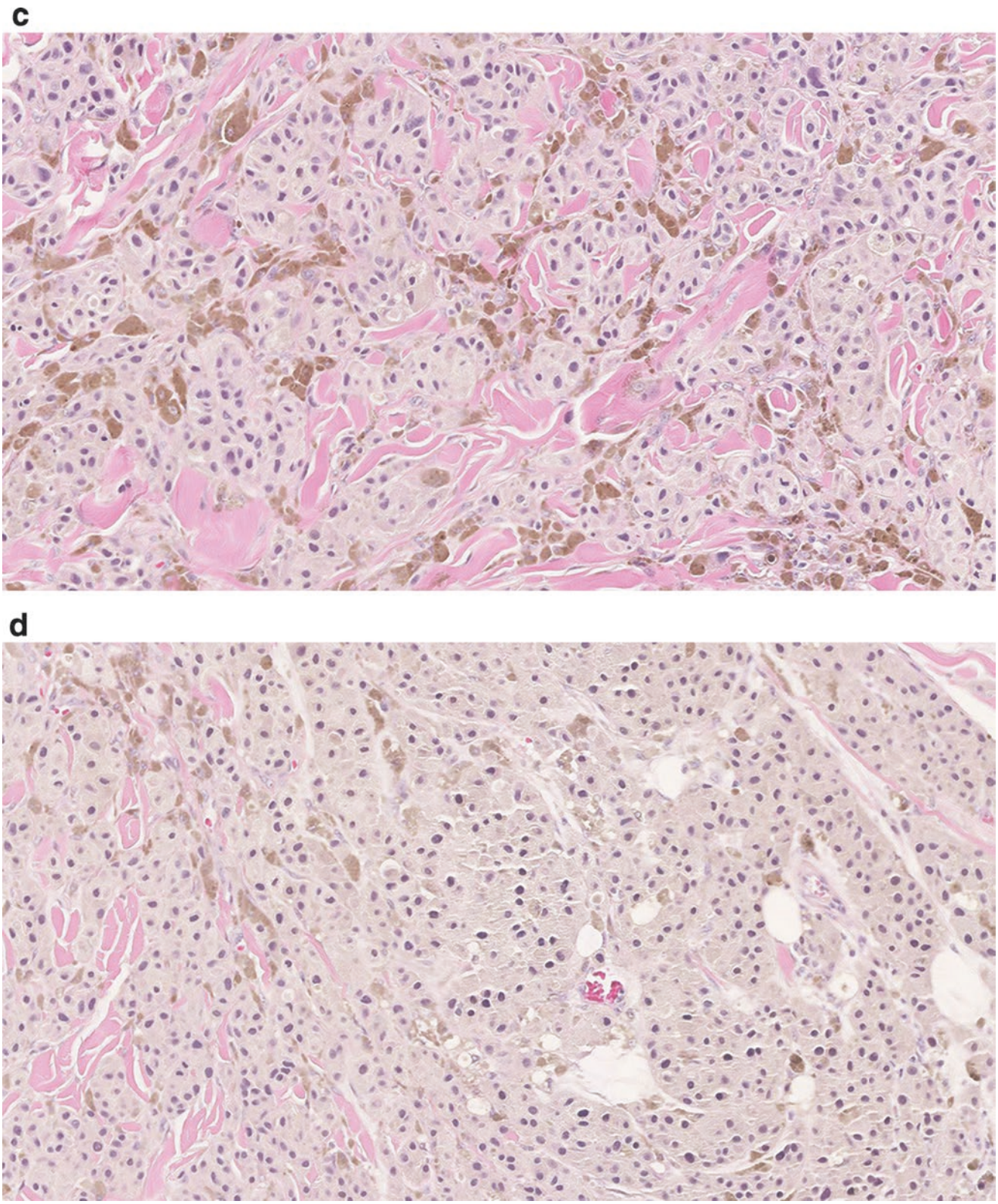


Fig. 7.45 (continued) High power, shows the atypical melanocytes with ample dusky cytoplasm. There is lack of maturation in deep dermis (**d**)

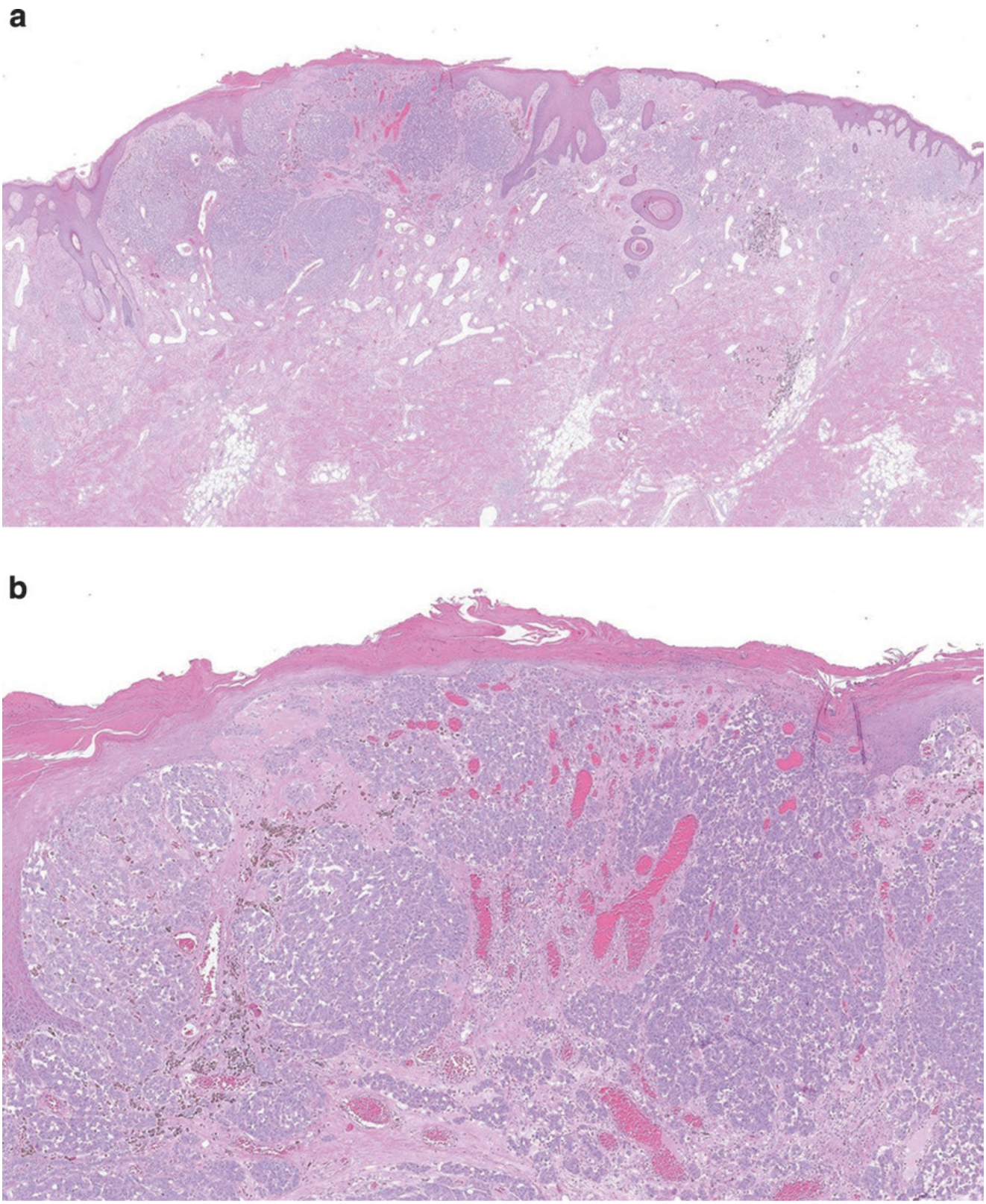


Fig. 7.46 Nodular melanoma with dermal regression. Large clusters of melanocytes in the upper dermis. Note the large, dilated vessels in the reticular dermis associated with focal areas of melanin pigment, consistent with focal regression (**a**). Large, hyperchromatic melanocytes in the dermis (**b**).

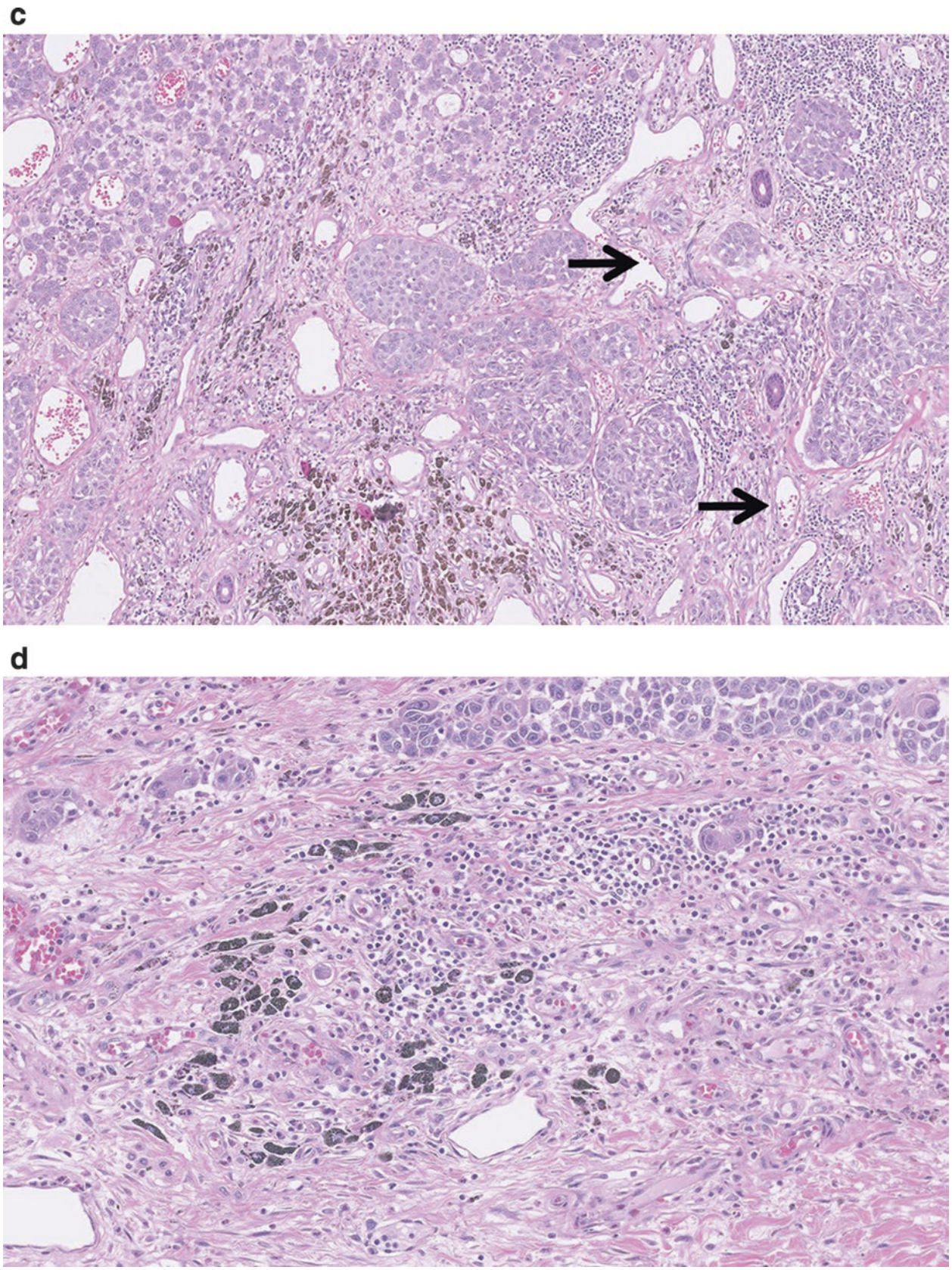


Fig. 7.46 (continued) In addition to the clusters of melanophages consistent with regression, there is vascular invasion (*arrows*) (**c**). High-power view of the areas of regression (fibrosis, dilated vessels, lymphocytic infiltrate, and melanophages) admixed with the neoplastic melanocytes (**d**)

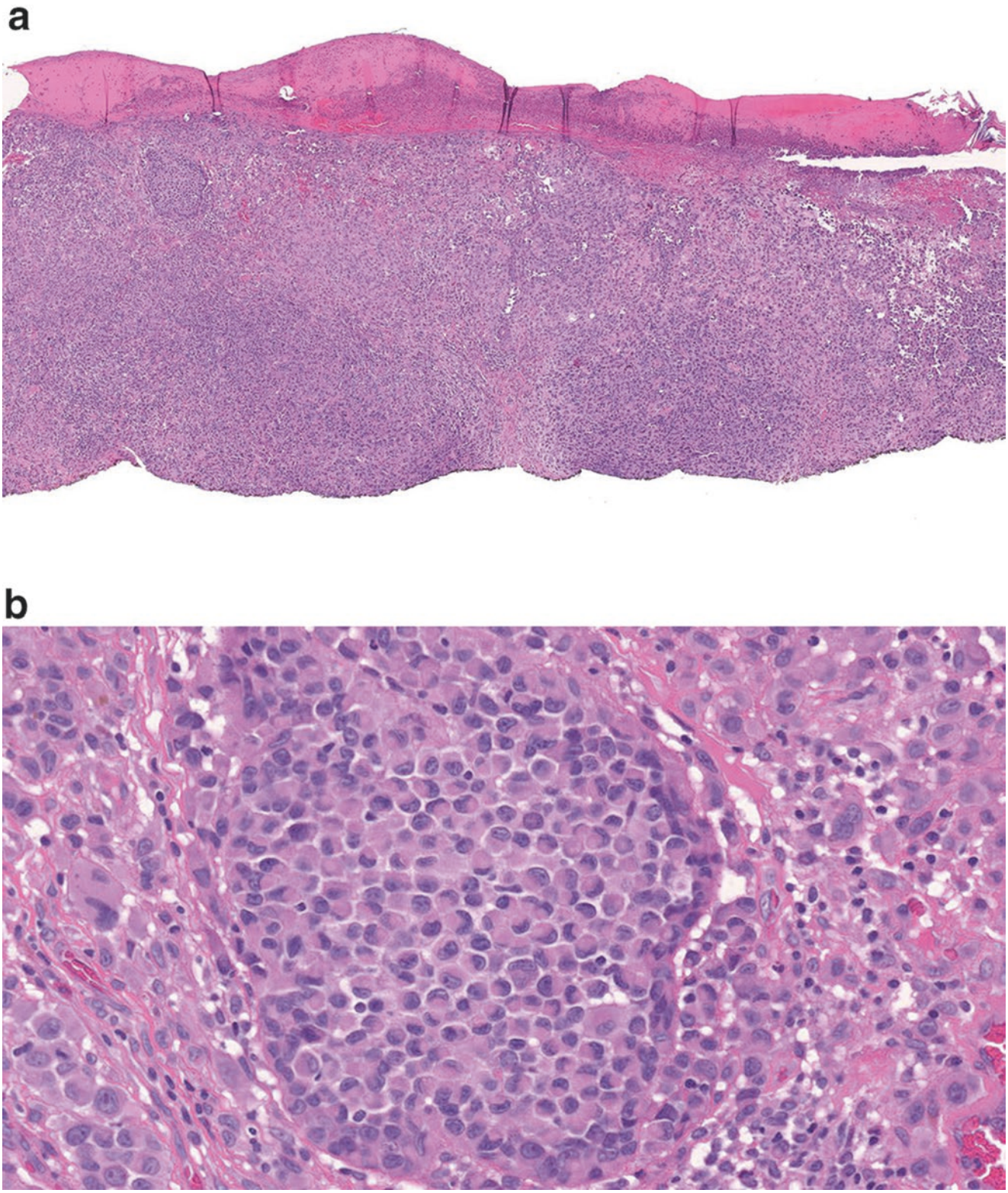


Fig. 7.47 Nodular melanoma with rhabdoid features. This lesion is located in the forehead of a 93-year-old male. The lesion is extensively ulcerated; thus, an intraepidermal component cannot be easily inspected (**a**). The cells in the dermis are clearly malignant and show plasmacytoid features with round to oval contour and large cytoplasm with inclusion-like material with hyaline appearance (**b**). In cases like this, immunohistochemistry will be helpful in determining the phenotype of the tumor cells (other malignant neoplasms may show similar features)

Desmoplastic Melanoma

The term desmoplastic melanoma (DM) was first used by Conley in 1971 to describe a variant of melanoma characterized by a dermal spindle cell population in a background of abundant collagen. Subsequently, Reed and Leonard used the term desmoplastic neurotropic melanoma to describe DM with nerve infiltration. DM is an uncommon variant of spindle cell melanoma (<3.8 % of primary melanomas). Although DM may arise de novo, it is most commonly associated with other types of melanoma (lentigo maligna in about 30 % of cases and less frequently acral lentiginous). DM is frequently encountered in patients with types of skin cancers associated with sun exposure (SCC and BCC). Like lentigo maligna, DM is more frequent in older individuals, most commonly in the sixth or seventh decade of life, and has a slight predilection for males. Lesions are mostly located on sun-exposed areas such as the head and neck but can also be located on the trunk (shoulder) or extremities (distal).

Clinical Features

DM is commonly misdiagnosed clinically due to its subtle presentation. DM presents with a nonspecific, innocuous clinical appearance as a raised, indurated skin-colored papule, plaque, or nodule or as a deep cutaneous neoplasm that is frequently associated with severe chronic sun damage. The main diagnostic challenge for DM is attributed to the fact that more than half of all cases are amelanotic (45–75 % of cases); thus, they are commonly mistaken for benign lesions, such as dermatofibromas or scars. And since the clinician does not consider likely the possibility of a malignant process, she/he may take a small, superficial biopsy, which may further compound the diagnosis. The presence of a new "scar" without a history of trauma may prompt the clinician to consider the possibility of DM among other differential diagnoses, especially if the scar is located on the head and neck region. Furthermore, due to the usually clinically benign appearance of DM, the diagnosis is often significantly delayed, and disease is usually advanced at the time of biopsy.

Histopathologic Features

DM can arise de novo or in association with other melanoma subtypes, most often of the lentigo maligna type. It can manifest significant variation with respect to the extent of intratumoral cellularity, fibrosis, and perineural invasion. There appears to be a morphologic continuum between DM and standard vertical growth phase spindle cell melanoma, the latter being the most frequent type of invasive melanoma seen in lentigo maligna melanoma.

Histologically, DM is characterized by a relatively homogeneous but poorly demarcated dermal-based neoplasm composed by a population of spindle cells amidst a fibrocollagenous or fibromyxoid background extending into the deep reticular dermis or subcutaneous adipose tissue. The average depth of invasion at time of first excision is 4 mm. There is often an accompanying atypical or frankly malignant melanocytic proliferation in the epidermis (most commonly lentigo maligna). Rarely is there a pagetoid pattern of epithelioid melanocytes consistent with superficial spreading melanoma.

The neoplastic melanocytic component in the dermis may adopt a single-cell dispersal pattern within the sclerotic dermis, be disposed in long fascicles, or sometimes assume a whorled or storiform pattern reminiscent of a fibrosarcoma. The fascicles may be surrounded by a mucinous matrix, imparting an appearance resembling a peripheral nerve sheath tumor such as neurofibroma, a known diagnostic pitfall. The spindle cells and collagenous process may lie in intimate apposition to the epidermis, which usually appears attenuated, or in some cases there may be a grenz zone. Also, not infrequently the most superficial aspect of the invasive dermal component may show a nested pattern of dermal infiltration in which the superficial nests are at varying angles to the long axis of the epidermis. In addition, an occasional nest of "standard" epithelioid melanoma cell may be seen amidst the dominant spindled, sclerotic component. The malignant dermal spindle cell population varies greatly in appearance as it may be hypocellular and bland appearing with minimal mitotic activity and thus mimicking a scar or fibromatosis. However, some cases can show dense hypercellularity and sufficient nuclear atypia and mitotic activity to mimic high-grade sarcoma.

DM usually involves the full thickness of the dermis and often extends into the subcutaneous tissue and skeletal muscle. The bulk of the neoplasm is composed of ill-defined fascicles of spindle cells that obliterate and destroy the preexisting structures of the dermis and invade the surrounding tissues. The spindle cells have an elongated, basophilic cytoplasm with hyperchromatic, coarse, irregularly distributed chromatin and conspicuous nucleoli. The attenuated cytoplasmic processes merge with the background stroma and there may be individual cell necrosis. Mitotic figures are identified throughout the tumor, although the mitotic index is usually low, averaging approximately 2/mm^2. The tumor cells are usually devoid of pigment, although there are often occasional melanophages scattered through the stroma. However, there are rare cases of heavily melanized neurotropic melanomas with perineural collections of pigment-containing cells. A characteristic finding is the presence of nodules of lymphocytes throughout the lesion. Furthermore,

the observation of a lymphocytic infiltrate in a desmoplastic melanocytic proliferation should be a red flag to prompt careful consideration of DM. DM usually infiltrates nerves, both surrounding and permeating cutaneous nerves, and giving the appearance of hypercellularity in the endoneurium. These infiltrated nerves may be found far away from the main tumor including within the subcutaneous fat. DM may manifest considerable pagetoid infiltration of the eccrine ducts.

Within the last 10 years, it has become clear that a strict definition of DM impacts clinical behavior and survival. Lesions that have more than 90 % of their invasive component showing a relatively hypocellular pattern, with spindle cells with hyperchromatic nuclei and within a fibromyxoid background, typically with lymphoid aggregates are described as "pure" DM and if equal or less than 90 % as "mixed" or "combined" DM. In one study with 92 patients with "pure" or "combined" DM from a single institution were studied [120]; pure DMs were associated with a longer disease-specific survival. The pure DM only rarely metastasizes to lymph nodes [41]. "Combined" DM has also higher rates of ulceration than pure DM. As expected, patients with combined DM have a higher risk to die of disease or to have metastatic disease than those with pure DM. Despite its tendency to recur locally at the primary site, DM is less likely to have nodal metastases compared to conventional cutaneous melanoma. In cases where sentinel node biopsies have been performed, only about 3–5 % of these patients are found to have involvement; thus, controversy exists regarding criteria for performing sentinel lymph node biopsy due to the rare occurrence of nodal invasion, and the incidence of lymph node involvement increases when there is nerve involvement.

The prognosis of DM is considered to be more favorable than that of other subtypes of conventional cutaneous melanoma. However, although DM is typically a slow-growing tumor, it commonly presents in an advanced stage due to its insidious nature. The mean Breslow thickness at diagnosis ranges from 2.0 to 6.5 mm (in comparison, in our series mentioned above with 224 cases of all subtypes, the average Breslow thickness was 1.86 mm). For stage I and II lesions, the 5-year survival rate is approximately 90 %, but only 30 % of cases are diagnosed in stage I for reasons explained above. DM has a high local recurrence rate that ranges from 7 to 56 %, and this is usually attributed to difficulties in defining surgical margin during resection of the tumor. Local recurrence is more common in desmoplastic neurotropic melanoma than in DM without nerve involvement. For DM without neural invasion, rates of metastatic disease were generally found to be as low as 7 %; however, desmoplastic neurotropic melanoma metastasizes at a higher rate of approximately 15 %.

Role of Immunohistochemistry in Desmoplastic Melanoma

Immunohistochemistry plays a crucial role in the histologic diagnosis of DM, particularly to separate DM from its histologic mimics. Several studies have delineated the immunohistochemical profile of DM but so far there are very few reliable markers available for the diagnosis of DM. Anti-S-100p is positive in most melanomas, including DM, while most other markers (MART-1, HMB-45 antigen, tyrosinase) are usually negative. However, S100p also has problems. Normal or abnormal dermis contains significant numbers of benign, S100p-positive dendritic cells. In addition, S100p is a labile protein, and in small biopsies, it is not unusual to see loss of expression of S100p in melanocytes, likely due to over- or underfixation. In our experience, there are other markers that have similar sensitivity to S100p and can, therefore, be of great value in the assessment of these tumors. We recently studied a large number of DM cases to characterize their immunohistochemical profile to obtain a more complete understanding of the potential use and the practical value of some of the newly described melanocytic antibodies [121]. Our study confirmed that in addition to S100 and SOX-10, a combination of WT-1, p16, nestin, and p75 offers pathologists a highly specific and sensitive panel for the diagnosis of DM.

Differential Diagnosis

As mentioned above, the diagnosis of DM can be difficult, not only clinically but histologically. Both benign and malignant lesions may be mistaken for DM, e.g., desmoplastic nevus, scar, dermatofibroma, neurofibroma, etc. A relatively common scenario is that of misdiagnosis at the initial biopsy; such delay may be an explanation for the relatively high Breslow thickness and local recurrence seen in this neoplasm. One of the most challenging differential diagnoses of DM is benign desmoplastic lesions, i.e., desmoplastic nevus/desmoplastic Spitz nevus. Desmoplastic nevus has a wedge-shaped pattern composed by an admixture of spindle cells with delicate elongate nuclei and occasional, bizarre, ganglion-like cells, within a dense, fibrous stroma with clusters of lymphocytes. These tumors tend to be symmetrical and circumscribed, with dermal melanocytic maturation and only exceptional dermal mitotic figures. The distinction with DM can be difficult, especially when dealing with superficial biopsies. In such cases, features that will favor DM include larger size, location in sun-exposed areas (particularly the head and neck), infiltrative growth, asymmetry, and increased number of atypical hyperchromatic spindle cells that deform the dermal architecture and invade the adventitial dermis of

hair follicles [122]. Although both desmoplastic nevi and melanoma may show neurotropism and foci of chronic inflammation, both are more common in DM. The nuclear/cytoplasmic ratio of DM is higher than in desmoplastic nevus, the cytoplasm is more sparse, and usually melanin pigment is absent in the tumor cells of DM. In limited tissue samples, it is important to evaluate the overlying epidermis as dishesive junctional nests, with variable size and shape, areas of single-cell growth, and pagetoid spread are significantly more frequent in DM. Desmoplastic nevi usually lack the areas of myxoid stroma that is often present in DM.

Some studies have used p16 as a possible immunohistochemical marker to distinguish between the two lesions. In one study, 81.8 % of DM were negative for p16 and 18.2 % were only weakly labeled. In contrast, all desmoplastic nevi were moderately to strongly positive for p16. However, in our experience many DM display strong p16 expression (this difference might be related to antibody dilution) [121]. HMB-45 is typically negative in DM while it labels the upper component of desmoplastic nevi (or rarely, diffusely the entire lesion, as in blue nevi). Ki-67 is expressed by relatively high numbers of cells in DM (more than 20/mm^2) as opposed to desmoplastic nevi [122]. Anti-Mart-1 can also be helpful; since this antibody is usually expressed in almost all melanocytic lesions, thus it is positive in desmoplastic nevus and uniformly negative in DM. A possible pitfall when evaluating Mart-1 in spindle cell melanocytic lesions is that neurotized nevi tend to show a decreased pattern of expression in the most spindled areas. An important study done by Gerami et al. highlighted the distinction of DM from desmoplastic nevi by using fluorescence in situ hybridization (FISH). In this study, the authors used a FISH assay targeting RREB1, MYB, Cep6, and CCND1. None of the desmoplastic nevi showed chromosomal aberrations that met FISH criteria for melanoma in contrast to 47 % of DM. Thus, a positive FISH test strongly supports the diagnosis of DM in this context.

It is well known that scars can mimic DM. Immunohistochemistry is also highly valuable in this distinction. Many cells in DM are positive for S100p and SOX-10, while scar shows only scattered S100p-positive dendritic cells and SOX10-positive Schwann cells. p75 is also strongly positive in DM, while only positive in the Schwann cells of scars. Neurofibroma can mimic DM in superficial biopsies. Neurofibroma and DM both contain numerous cells expressing S100p and SOX-10, but DM usually has a higher Ki-67 proliferation rate than neurofibroma. MPNST is also another tumor that can show overlapping features with DM. S100 is usually strongly and diffusely expressed in DM and usually patchy or negative in MPNST. SOX10 is not helpful as both tumors are diffusely positive. MITF may be helpful since MPNST are uniformly negative for MITF while DM usually shows at least a few cells [123]. A recent study showed that loss of H3K27me3 is highly specific in spindle cell MPNST and may be a useful diagnostic marker in such distinction [124].

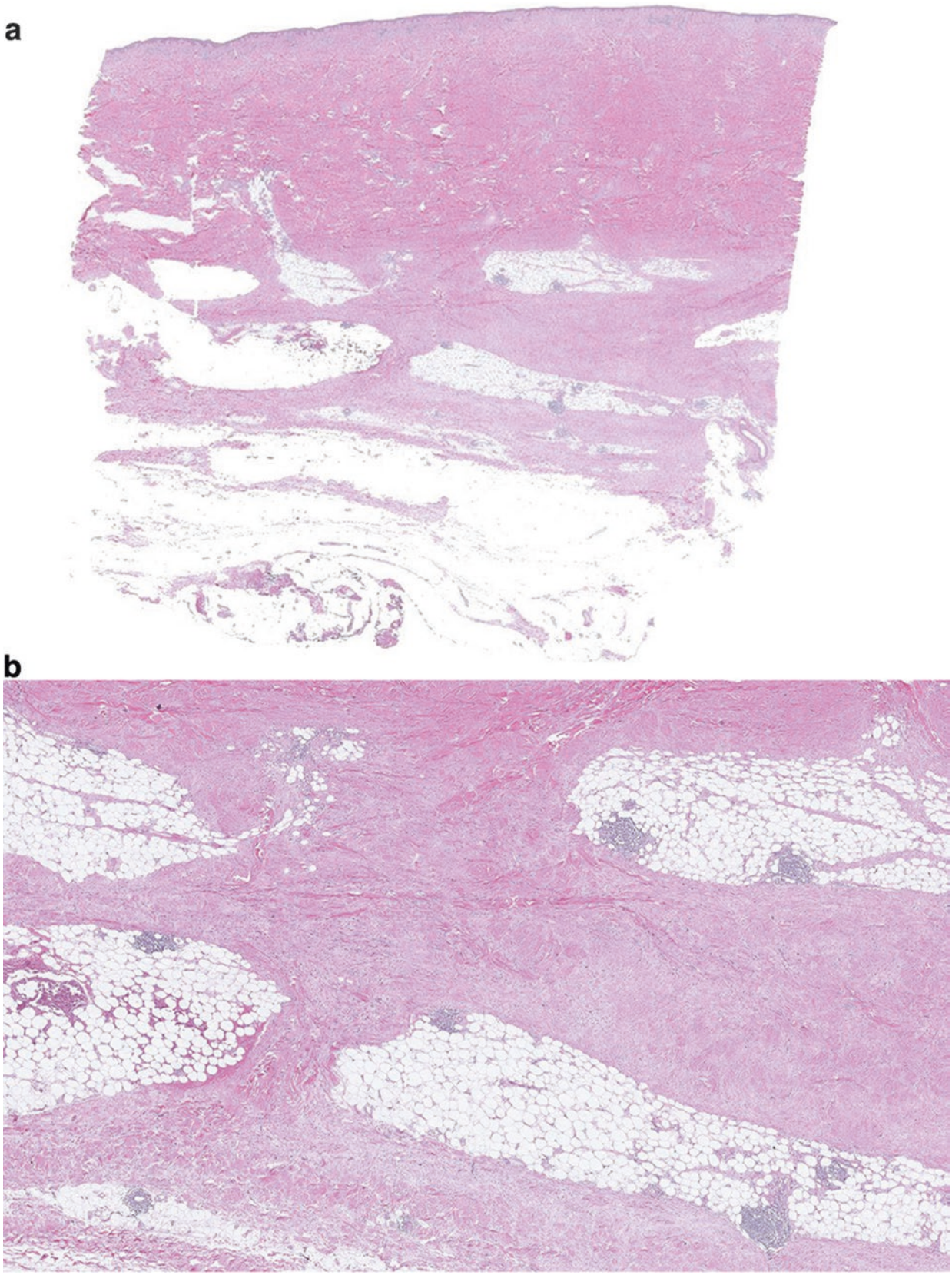


Fig. 7.48 Desmoplastic melanoma. This is a case located in the arm of a 65-year-old female. At low magnification the lesion is quite subtle and reminiscent of a scar (**a**). The cells are arranged in long fascicles throughout all levels of the dermis and extending into the subcutaneous fat. There is extensive collagen deposition both in the dermis and in the subcutaneous tissue (**b**).

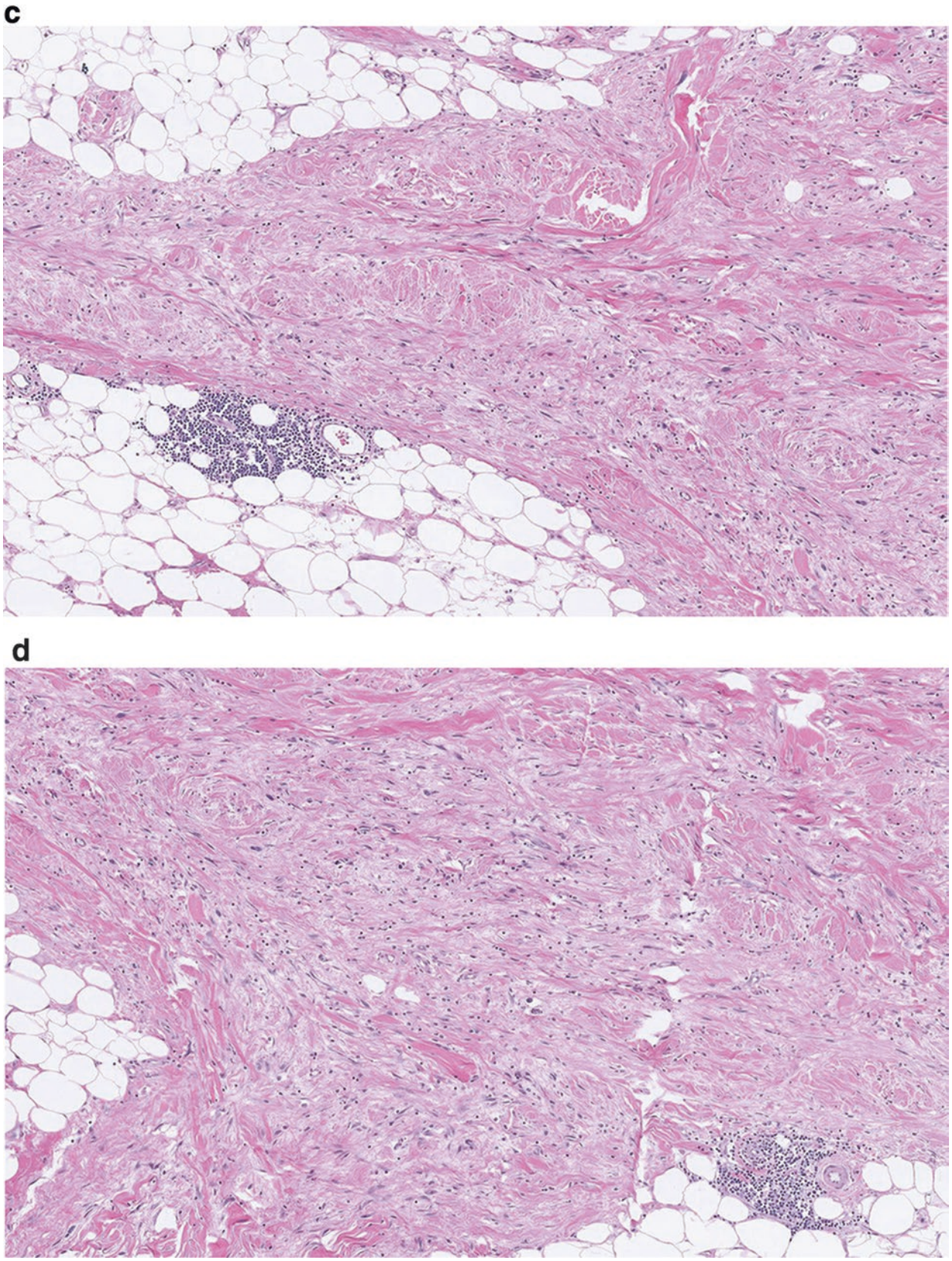


Fig. 7.48 (continued) Dense, large collagen fibers and small clusters of benign-appearing lymphocytes (characteristic finding in desmoplastic melanoma) (**c**). The spindle cells are large and show uniform hyperchromatic nuclei (diagnostic clue) (**d**).

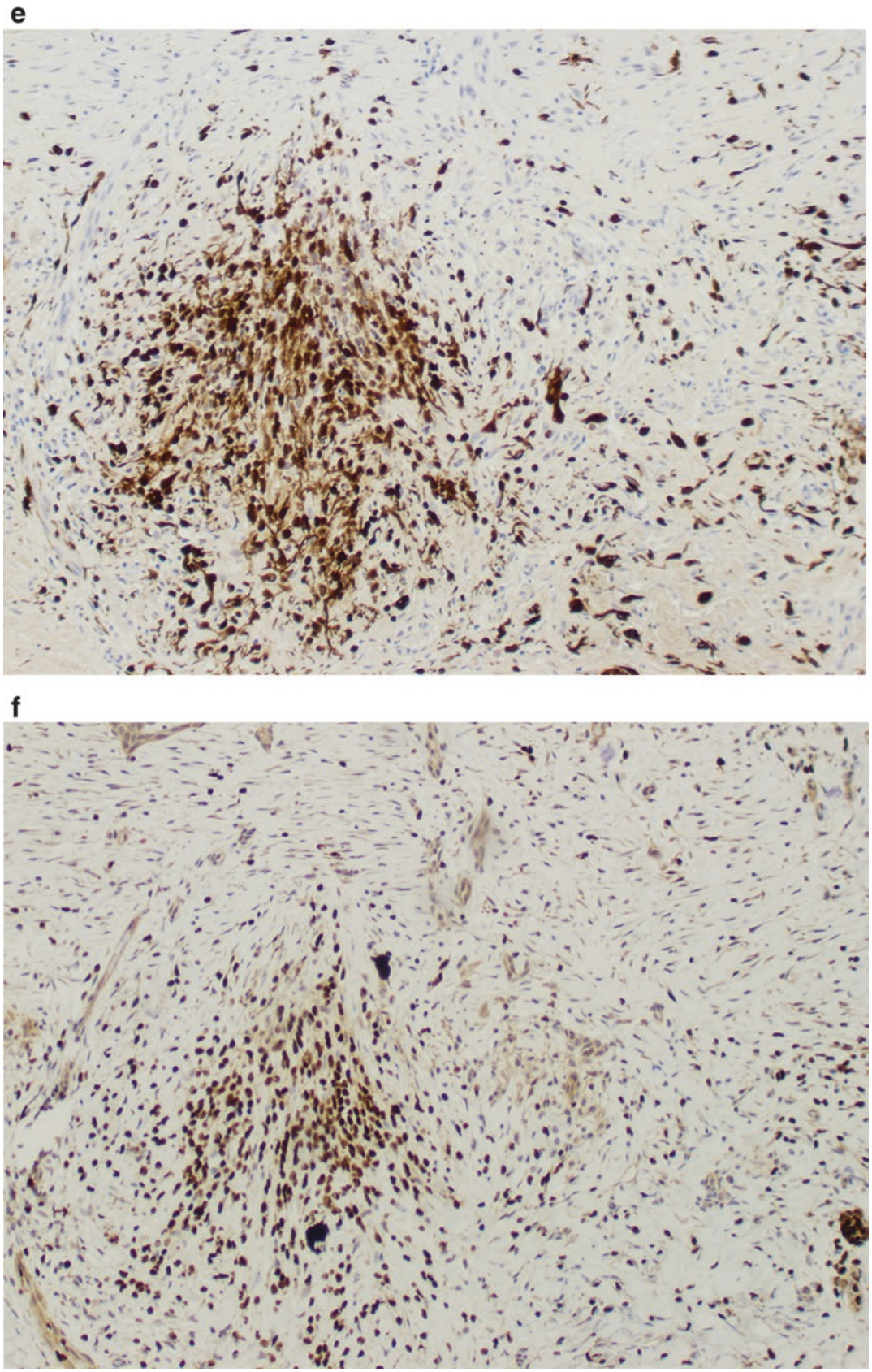


Fig. 7.48 (continued) The tumor cells express S100 protein, both in the nucleus and cytoplasm (**e**). The spindle cells express SOX10 (nuclear pattern), in a density similar to that seen with S100 (**f**)

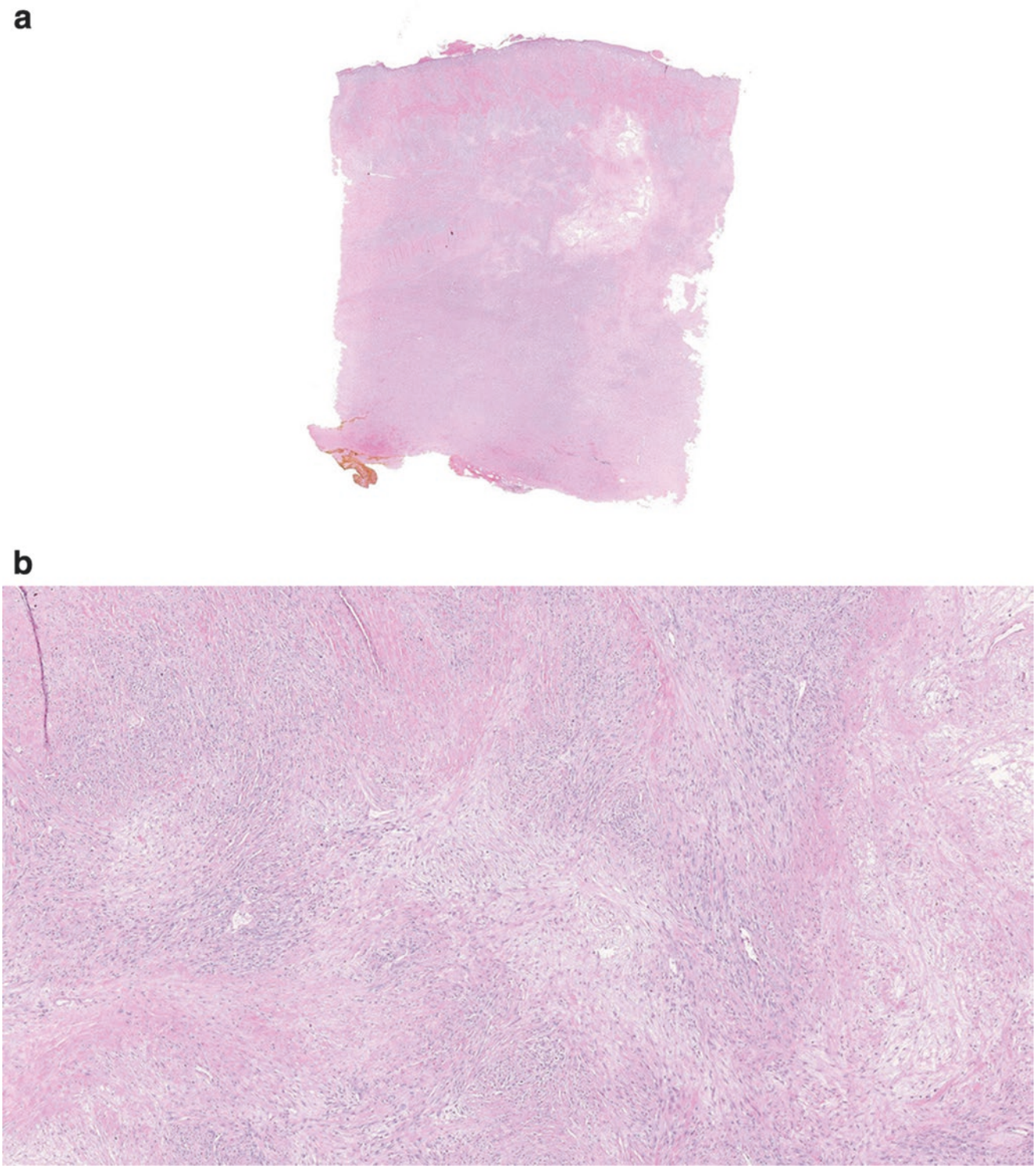


Fig. 7.49 Desmoplastic melanoma. This example shows an asymmetric dermal lesion composed of an infiltrate slightly more cellular than that seen in Fig. 7.48 (**a**). Spindle cells in the dermis arranged in a fascicular and vaguely storiform pattern (**b**).

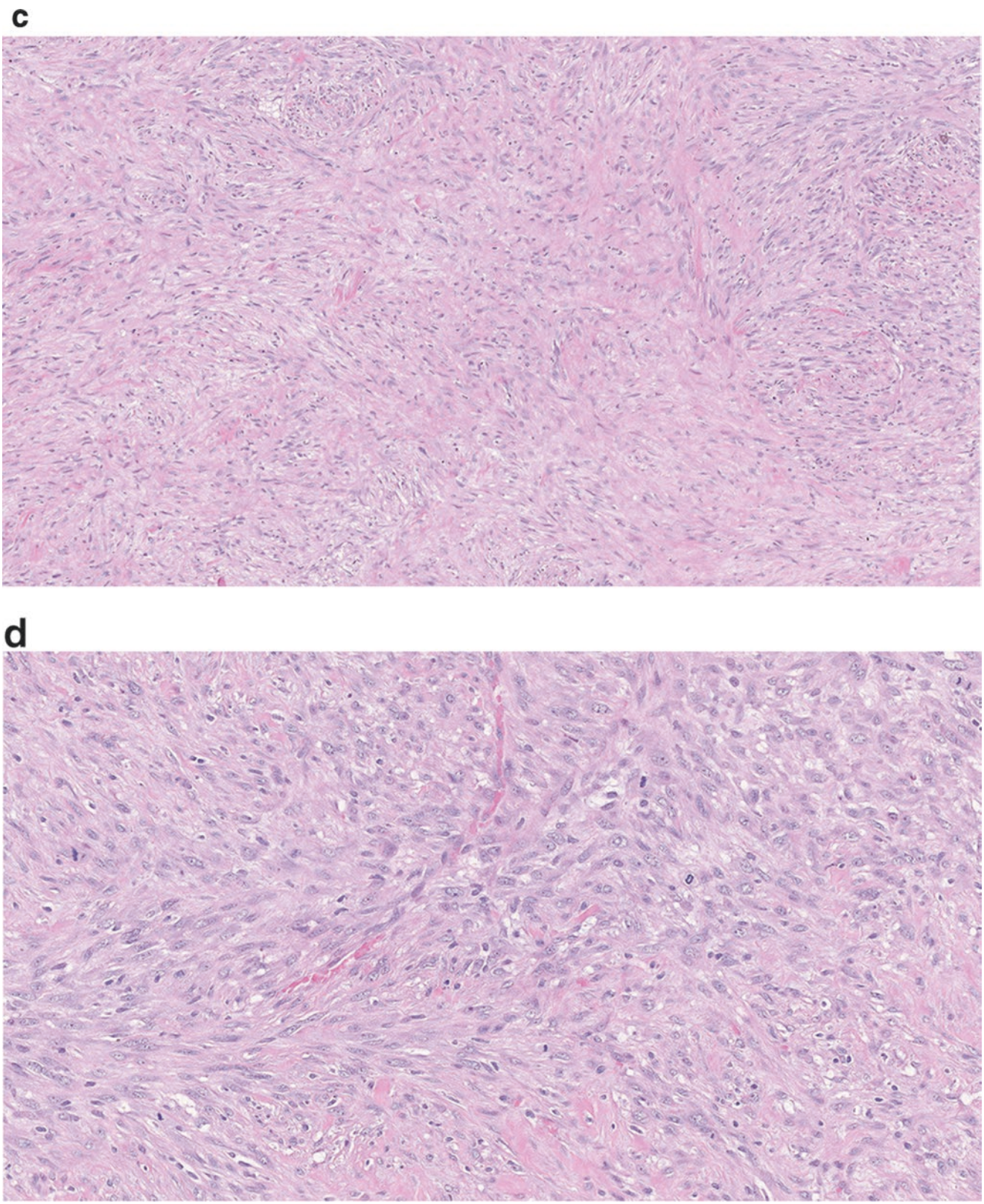


Fig. 7.49 (continued) Thick collagen bundles infiltrated by elongated, fibroblast-like melanocytes (**c**). The spindle cells are atypical and have a characteristic hyperchromatic and pleomorphic nuclei (**d**). If more than 10 % of the invasive component shows areas like this (**d**) it would be classified as *mixed spindle* cell melanoma.

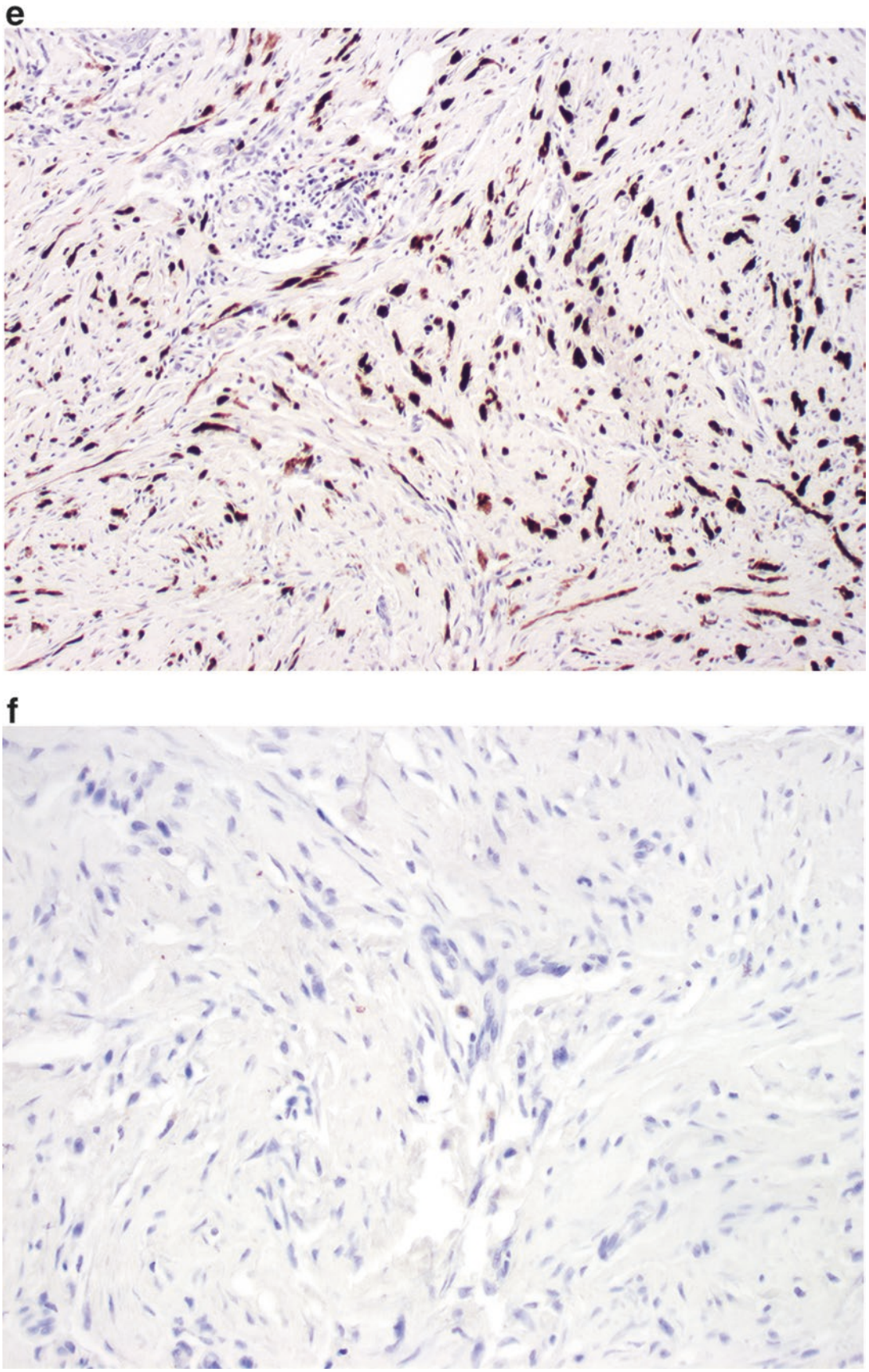


Fig. 7.49 (continued) Melanoma cells express S100 (**e**). As with most desmoplastic melanoma, the cells are negative for MART-1 (**f**)

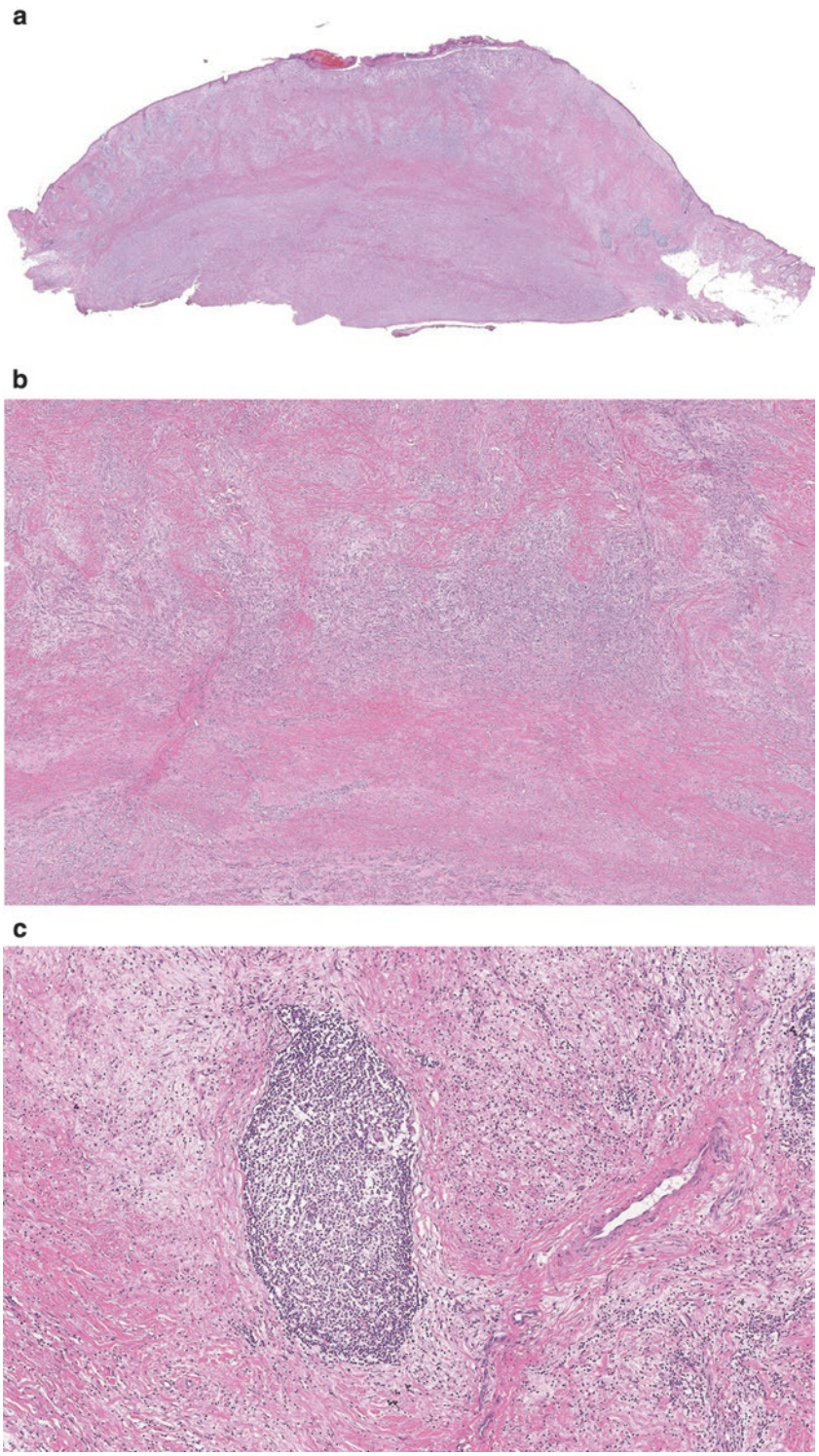


Fig. 7.50 Desmoplastic melanoma. This case shows a poorly circumscribed lesion with diffuse involvement of the dermis by an atypical population of spindle cells. Scattered lymphocytic aggregates are seen at the periphery of the lesion. There is prominent desmoplasia, especially at the base. The cellular density of the lesion varies in different areas (higher density at the base) (**a**). The spindle cells display hyperchromatic and pleomorphic nuclei admixed with the dense collagen fibers (**b**). Large cluster of lymphocytes (**c**).

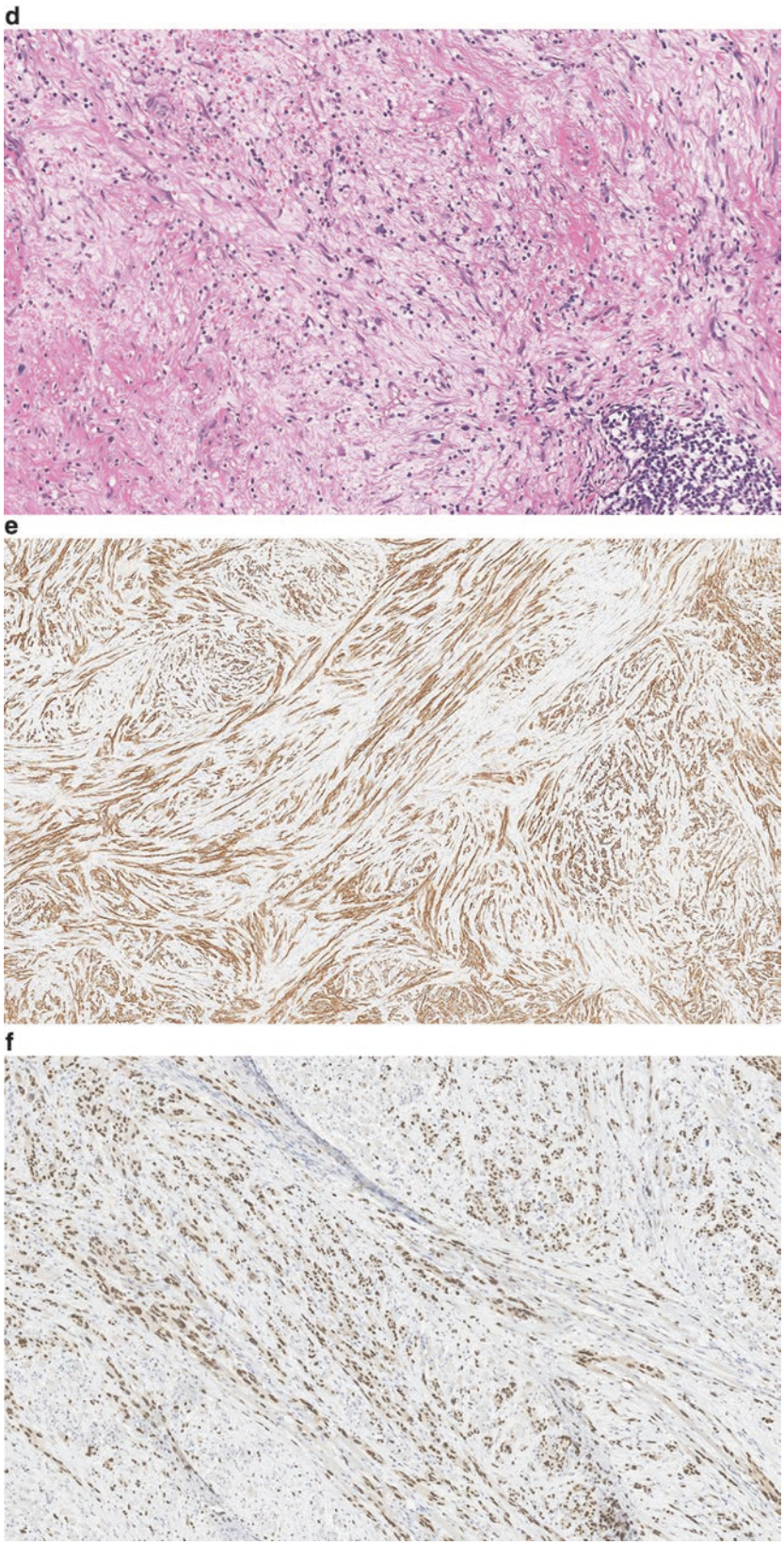


Fig. 7.50 (continued) Less cellular area along with a cluster of lymphocytes (**d**). Strong and diffuse expression of S100p (**e**). Characteristic diffuse, nuclear pattern of SOX10 (**f**)

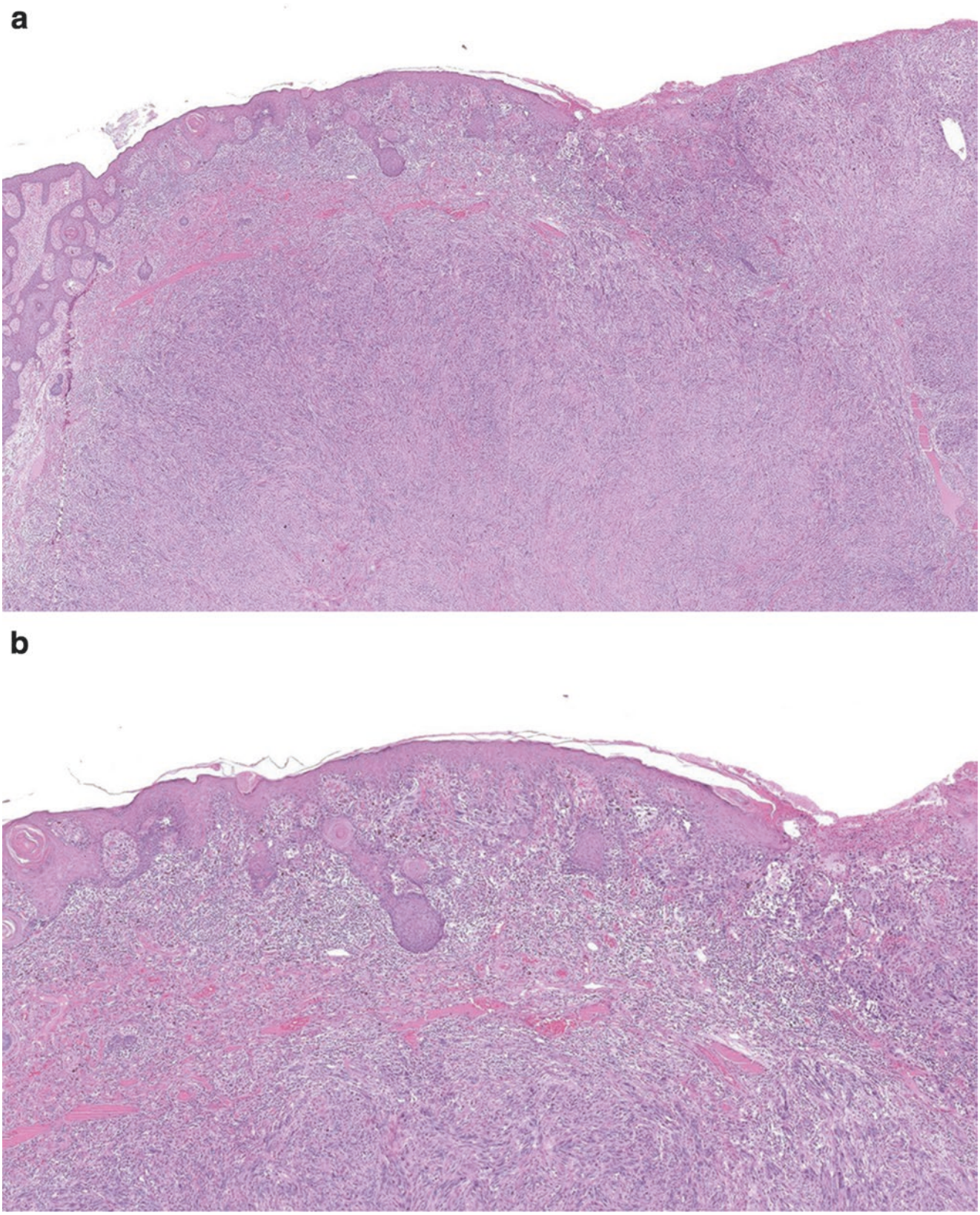


Fig. 7.51 Spindle cell melanoma with obvious intraepidermal component. Note the irregular elongation of the rete ridges and the obvious junctional component represented by irregularly shaped nests of melanocytes with only focal single-cell pattern of pagetoid upward migration. Ill-defined fascicles of spindle cells that obliterate the preexisting structures (**a**–**c**).

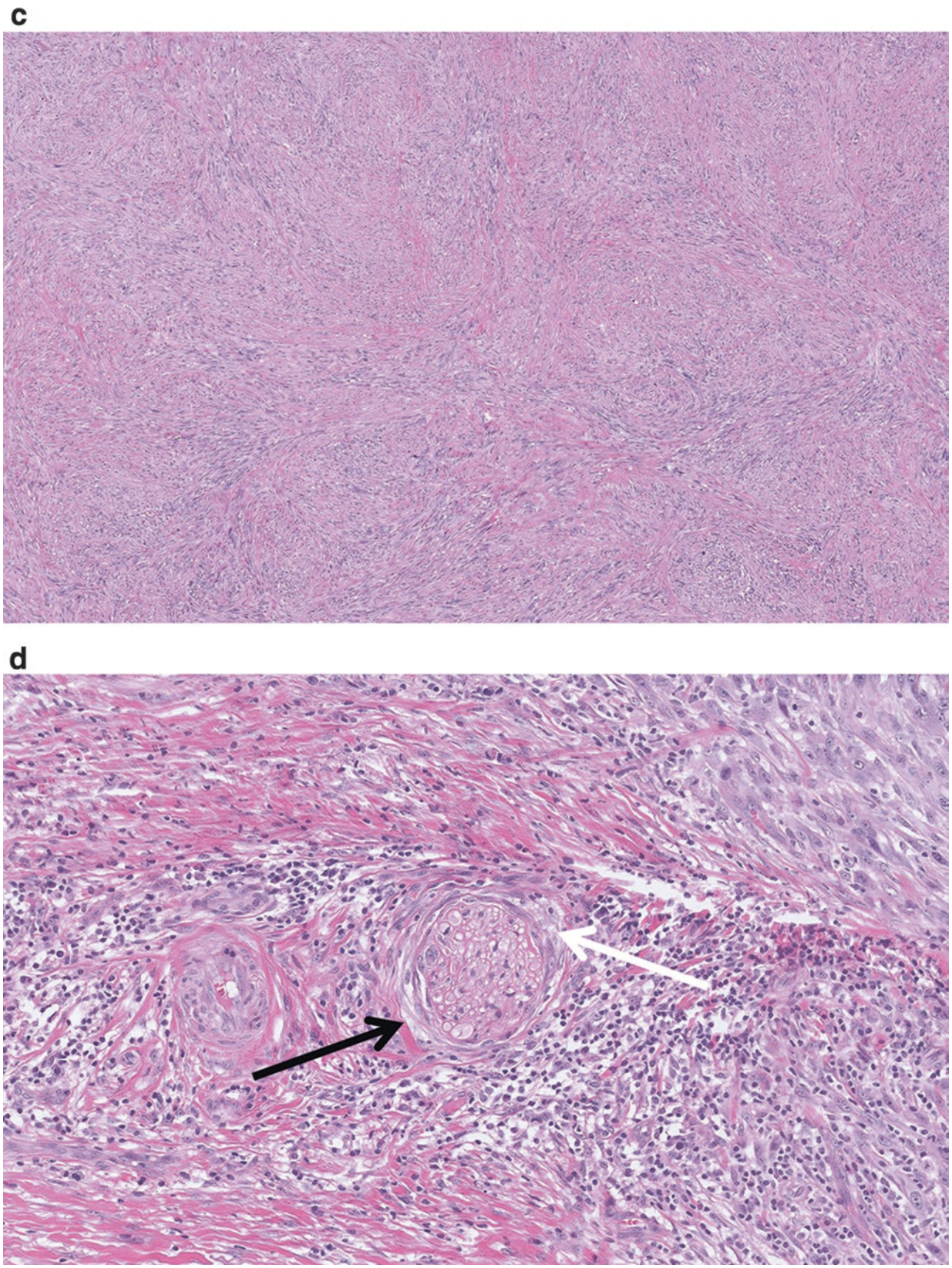


Fig. 7.51 (continued) Inflamed area with a nerve (*black arrow*) focally involved by melanoma cells (*white arrow*) (**d**)

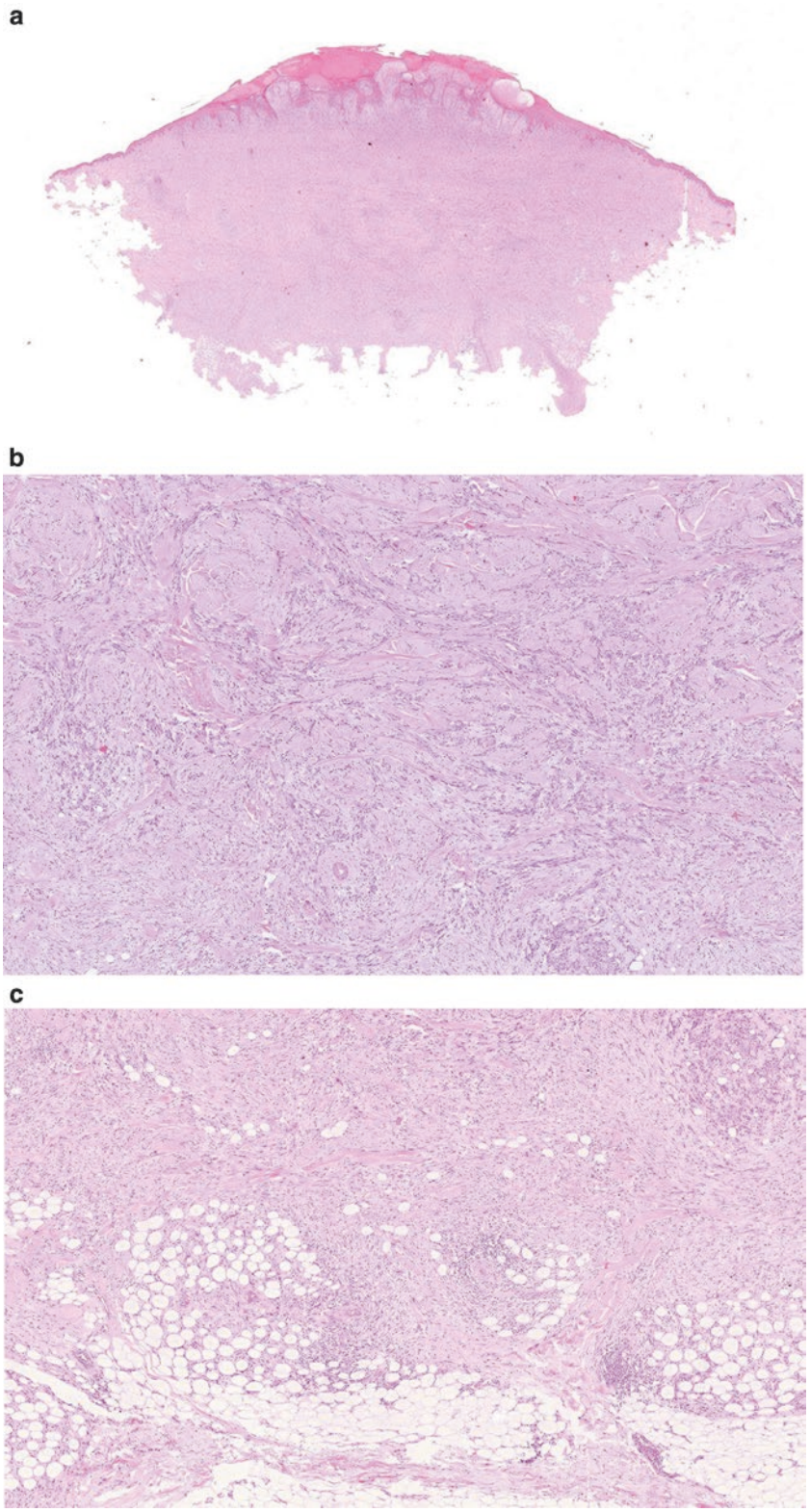


Fig. 7.52 Desmoplastic melanoma. This example shows a melanocytic component in the dermis with a single single-cell dispersal pattern within the sclerotic dermis disposed in short and long fascicles (**a**). Note the dermal fascicles of spindle cells with a whorled or storiform pattern reminiscent of a dermatofibrosarcoma protuberans (**b**). Infiltration of the subcutaneous tissue with a honeycomb pattern resembling dermatofibrosarcoma protuberans (**c**)

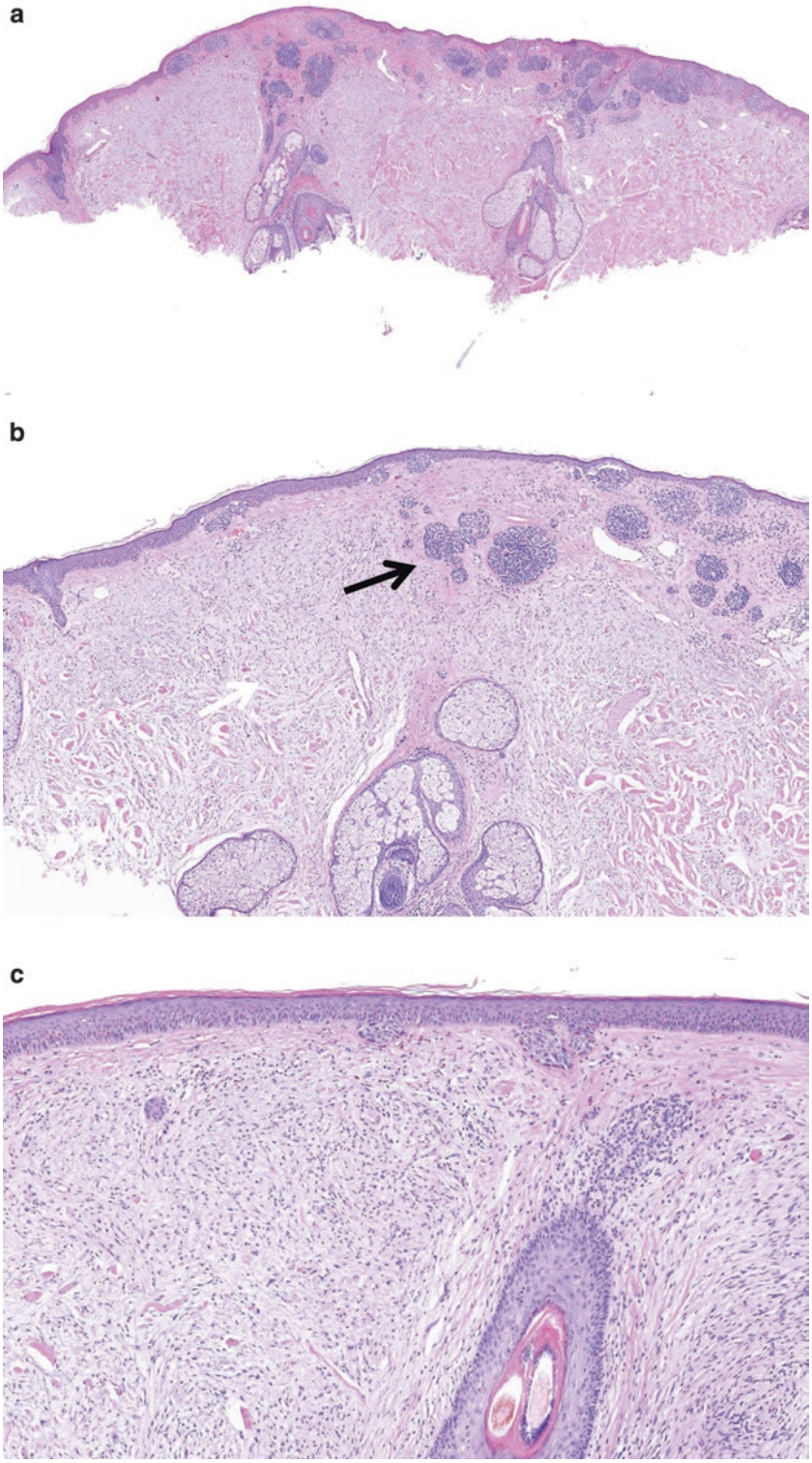


Fig. 7.53 Extraordinary case of a desmoplastic melanoma resembling neurofibroma and with a nevoid melanoma component. There are two different areas. One of clusters of eosinophilic intraepidermal and superficial dermal melanocytes; and one of deeper fascicles of spindle cells within a loosely myxoid stroma (**a**). Note the clusters of epithelioid melanocytes both in the epidermis and upper dermis resembling a compound nevus (*black arrow*). Also note the presence of short fascicles that are focally surrounded by a mucinous matrix, imparting an appearance resembling a peripheral nerve sheath tumor such as neurofibroma (**b**). The spindle cells have an elongated cytoplasm with hyperchromatic chromatin and conspicuous nucleoli. The attenuated cytoplasmic processes merge with the background stroma. This case showed rare mitotic figures (**c**).

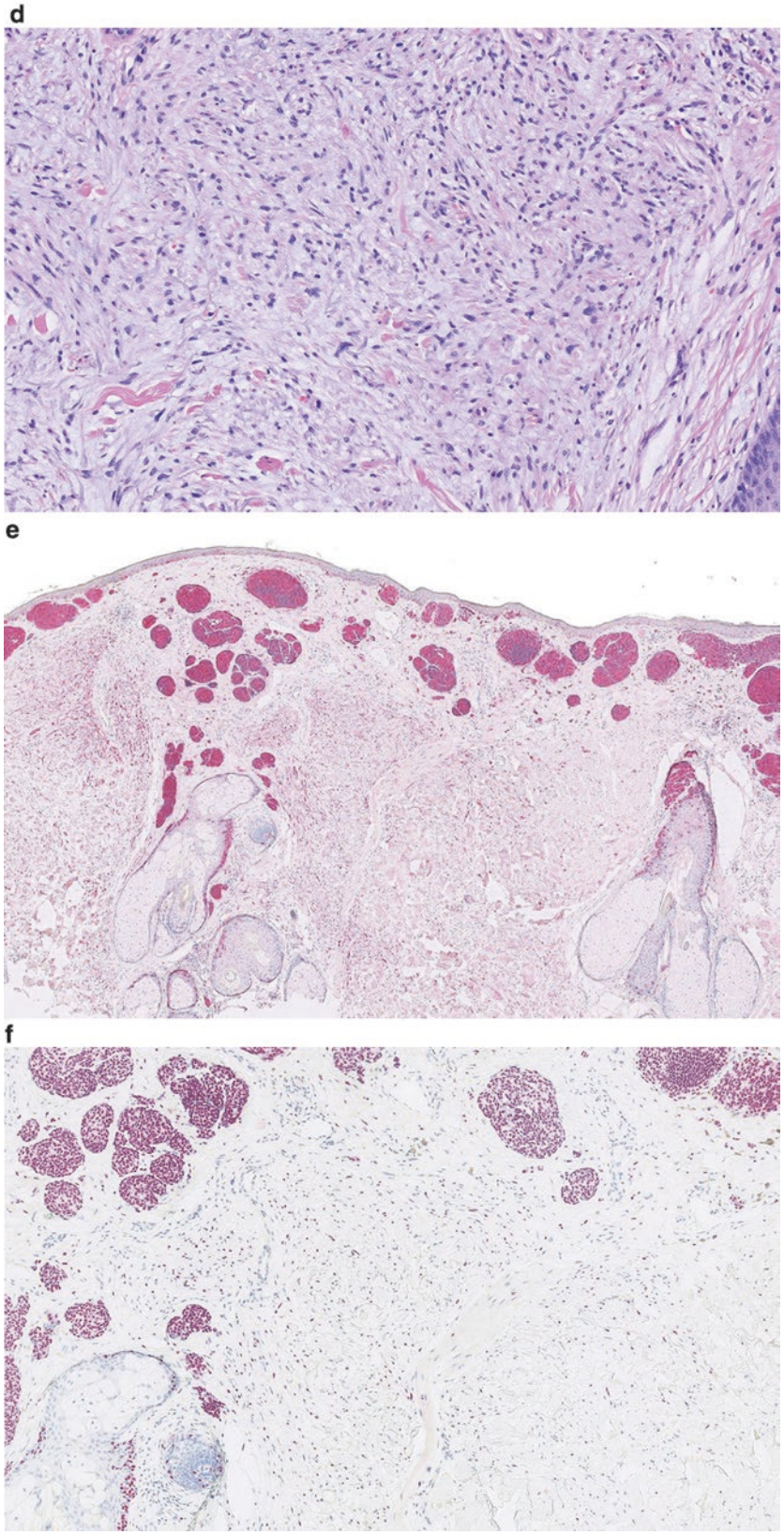


Fig. 7.53 (continued) Spindle cell area resembling neurofibroma with cellular atypia (**d**). There is diffuse expression of S100p in both epithelioid and spindle cell areas. Note the presence of focal single-cell growth in the epidermis (**e**). SOX10 is expressed in both areas (**f**).

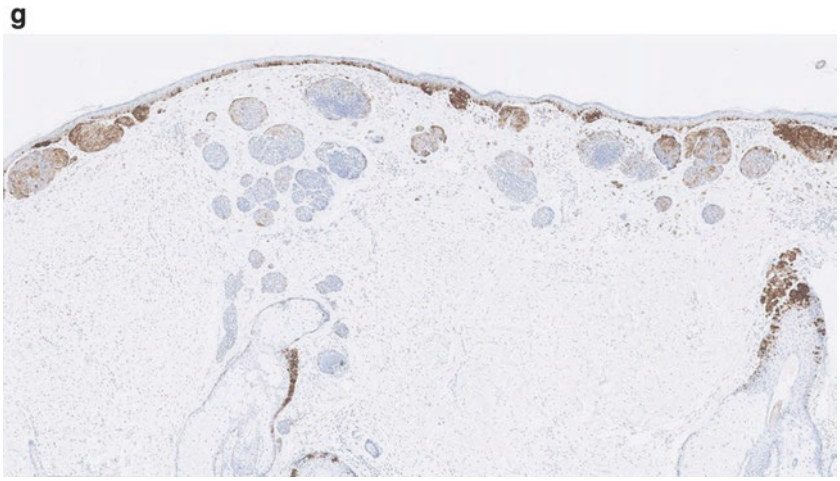


Fig. 7.53 (continued) In addition to highlighting the presence of a prominent junctional component, HMB45 shows a patchy pattern in the epithelioid cells, supporting the diagnosis of melanoma (**g**)

Nevoid Melanoma

Nevoid melanoma (NM) is one of the most challenging diagnoses in dermatopathology and one of the most common causes of litigation. These tumors, which mimic melanocytic nevi, were termed minimal deviation melanoma by Reed et al. and, later, nevoid melanomas by Schmoeckel et al. [125, 126]. This uncommon variant of melanoma, which represents approximately 1 % of all melanomas, resembles histologically melanocytic nevi. The fact that this lesion has a low rate of occurrence and shows many microscopic similarities with benign nevi makes this entity a challenging lesion to diagnose even for experienced dermatopathologists. Clinically, NM is more commonly seen in the fourth or fifth decade of life, equally seen in males and females. It presents as a slow-growing lesion most commonly seen in the proximal extremities and trunk and head, less commonly in the neck area. Some authors have suggested that this variant carries a better prognosis than the conventional variant of melanoma.

Because these lesions are rare, there are few studies that have analyzed long-term clinical follow-up. Given the lack of consensus on the biologic behavior of NM, the treatment options have remained the same as in conventional melanomas.

Histopathology

Histologically, NM resembles melanocytic nevus. The architectural pattern appears very similar to that of a compound or intradermal nevus with overall symmetry, well-circumscribed edges, and minimal or no intraepidermal pagetoid spread. Intradermal lesions tend to be well defined and are usually composed of nests and confluent sheets of melanocytes. The most significant morphologic feature that distinguishes NM from standard nevi is the presence of a diffuse, expansile, and monomorphous population of small, nevus-like melanocytes both in the superficial and deep dermis. When expansile growth is more prominent in one side of the lesion, it conveys to the lesion an appearance of asymmetry. Expansile nesting in the superficial dermis often results in expansion of the dermal papillae. In some cases the superficial nests may transition into smaller nests into the deeper dermis thus resembling dermal "maturation" (paradoxical maturation) resulting in a possible diagnostic pitfall.

There are certain histologic features that may help to render an accurate diagnosis; however, these features are better appreciated when analyzing these tumors at high magnification. The dermal nests in NM are hypercellular when compared with standard nevi. In NM there is cellular crowding and melanocytes tend to be "back to back" in many parts of the lesion. Also, this cellular crowding tends to be lost at the deeper portion of the lesion in cases in which there is paradoxical maturation. An important feature to be considered is the presence of diffuse nuclear pleomorphism and enlarged and hyperchromatic nuclei with irregular contours. Unfortunately, these features are mainly seen at higher magnification, and it is easily missed when one is evaluating the lesion at low magnification. NM tends to show increased numbers of both standard and atypical mitotic figures and they are easy to spot. However, we have observed lesions in which there are no mitotic figures and as such their presence is not required to make a diagnosis of NM. In our experience low-power scanning clues to the diagnosis of nevoid melanoma are the prominent asymmetry seen in some cases and

the expansion of the dermal papillae. One of our colleagues (Dr. Diwan, personal communication) applied the term "puffy shirt" to describe the crowded appearance of the expansile growth in the dermis.

Immunohistochemistry may aid in such diagnosis. HMB-45 shows abnormal maturation in cases of NM as either lack of labeling or labeling limited to a subpopulation of melanocytes in a patchy pattern. Ki-67 expression is often increased. Although the percentage of positive cells varies among cases, the distribution of expression is usually haphazard and not only limited to melanocytes located in superficial dermis. It is common to observe hot spots in cases of NM; thus, the distribution of expression appears more important than the actual number of cells expressing the marker [127]. A recent study analyzed FISH in nevoid melanoma and the test was positive in 74 % of the cases [128]. This is similar but slightly lower than the sensitivity reported for FISH in melanoma in general. It is possible that some cases of NM include "intermediate" grade melanomas, and as such they might not contain the standard chromosomal abnormalities.

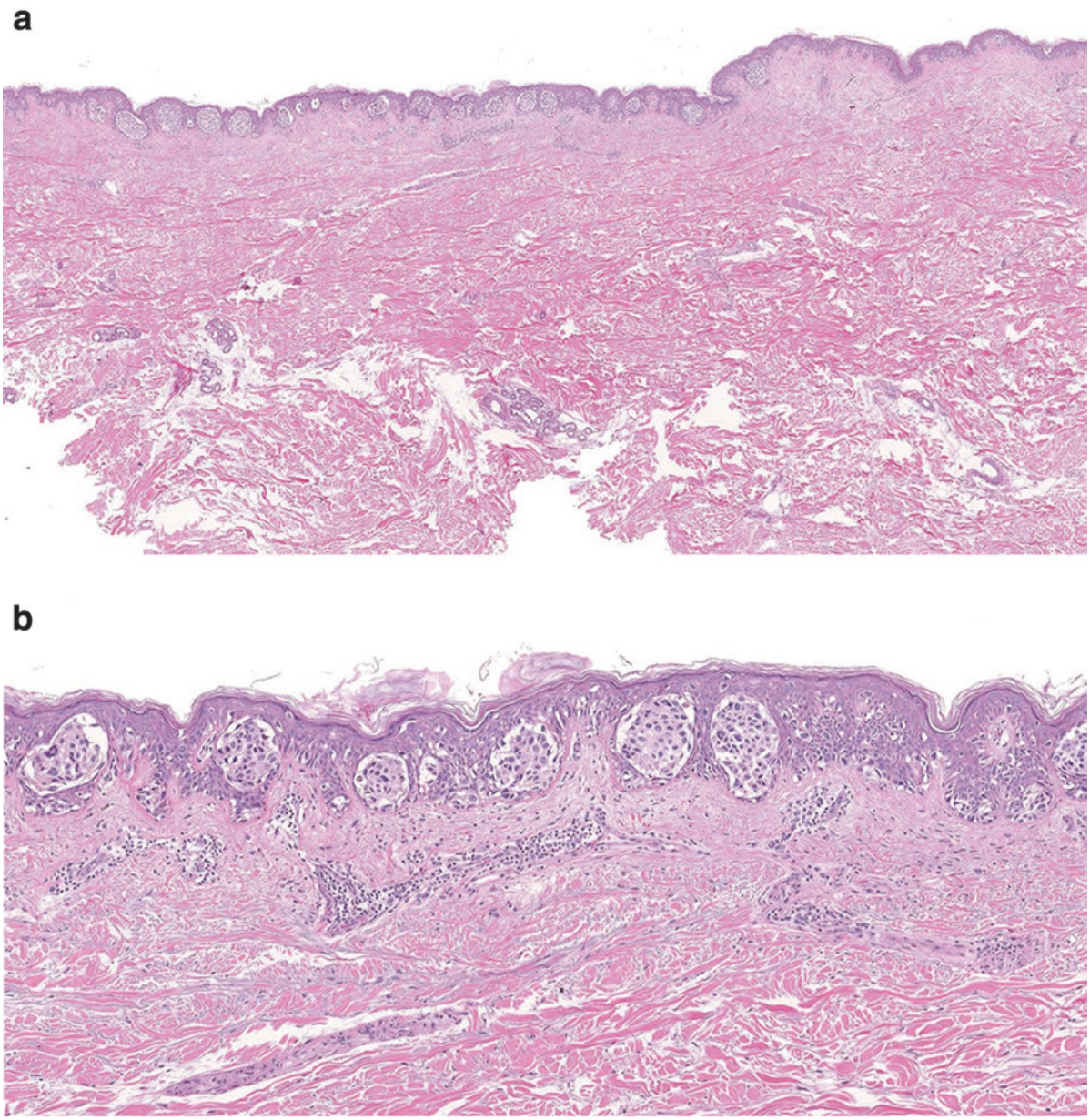


Fig. 7.54 Junctional nevoid melanoma. This lesion is located on the back of a 69-year-old male. This lesion is composed of large junctional nests that on low magnification show features reminiscent with a lentiginous junctional nevus (**a**). Despite the apparently nested pattern of growth, cells are markedly atypical and there is obvious pagetoid upward migration and focal single-cell growth (**b**).

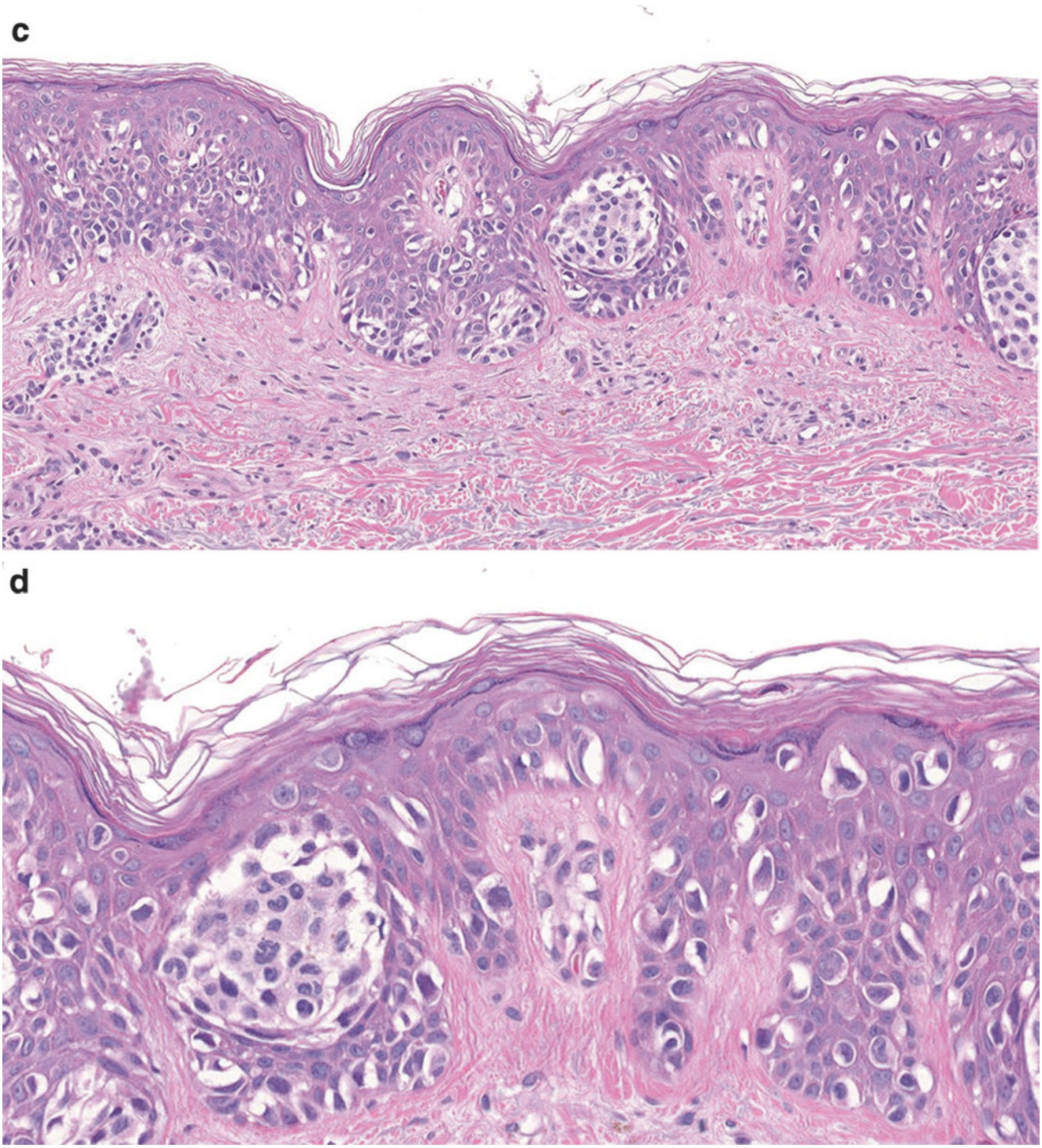


Fig. 7.54 (continued) Marked cytologic atypia and pagetoid upward migration (**c**). Focally prominent pagetoid upward migration. This image was taken from the periphery of the lesion (**d**)

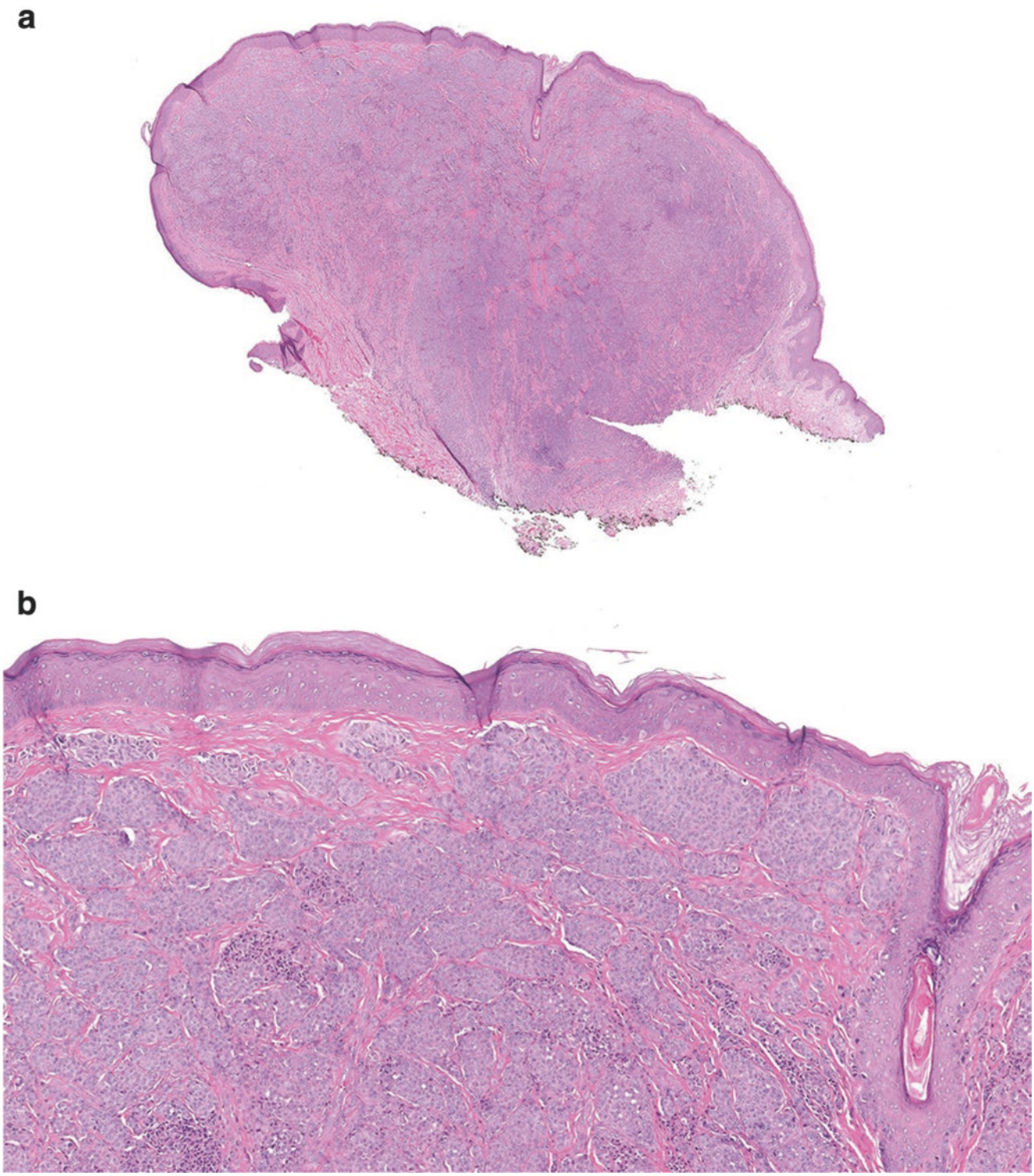


Fig. 7.55 Nevoid melanoma. The lesion is located on the trunk of a 55-year-old female. On low magnification, the lesion shows a polypoid architecture with features reminiscent of an intradermal nevus. At low power, points against a nevus include the high cellular density (cells arranged in large clusters and not in nests), without interposed mature collagen (**a**). Note the atypical cytologic features of melanocytes with nuclear pleomorphism and visible nucleoli (**b**).

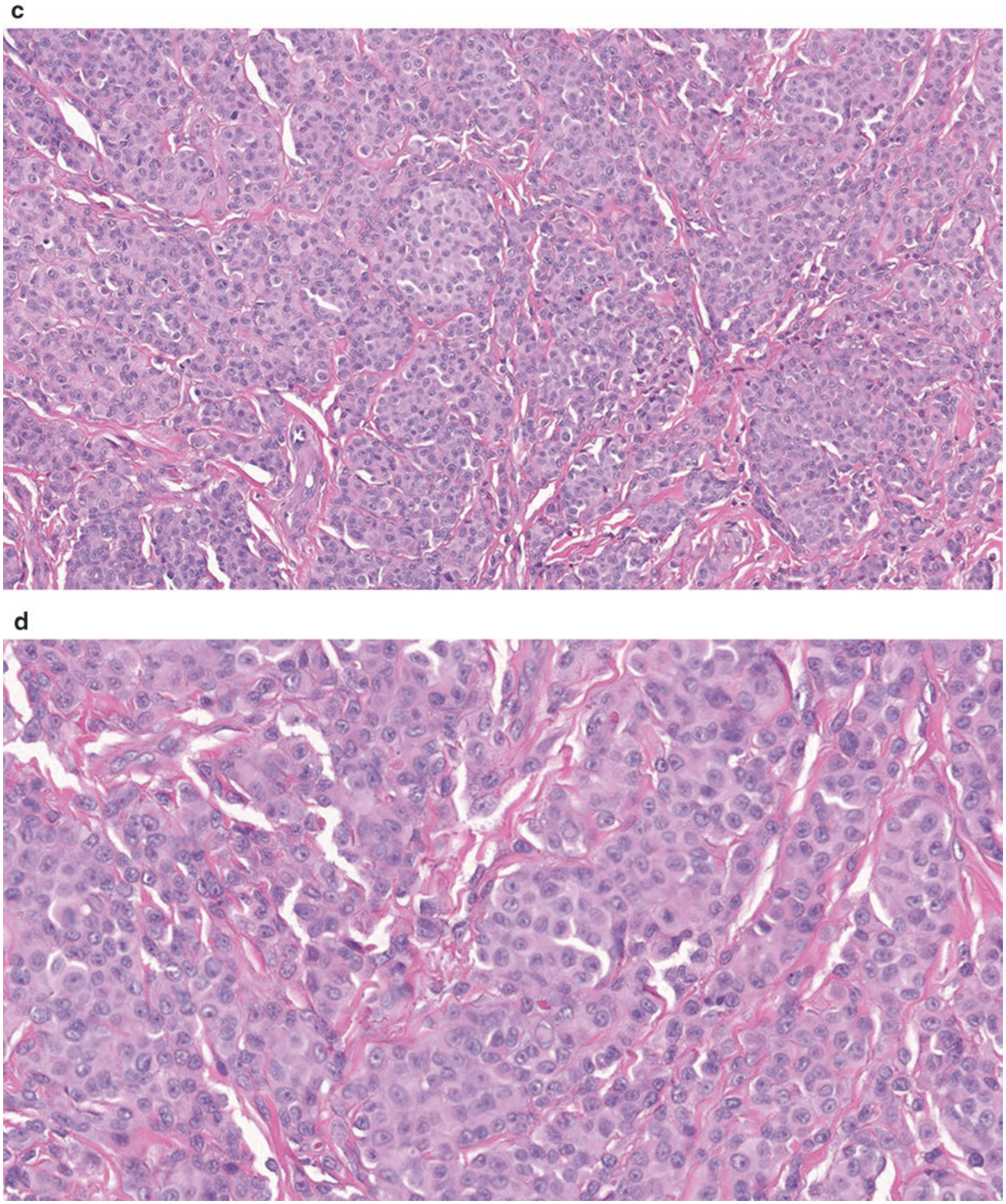


Fig. 7.55 (continued) Large epithelioid melanocytes without maturation in the deep dermis (**c**). Scattered mitotic figures (not only in the surface but also in the deep component of the lesion). This lesion was also studied with FISH, which showed an abnormal pattern (**d**)

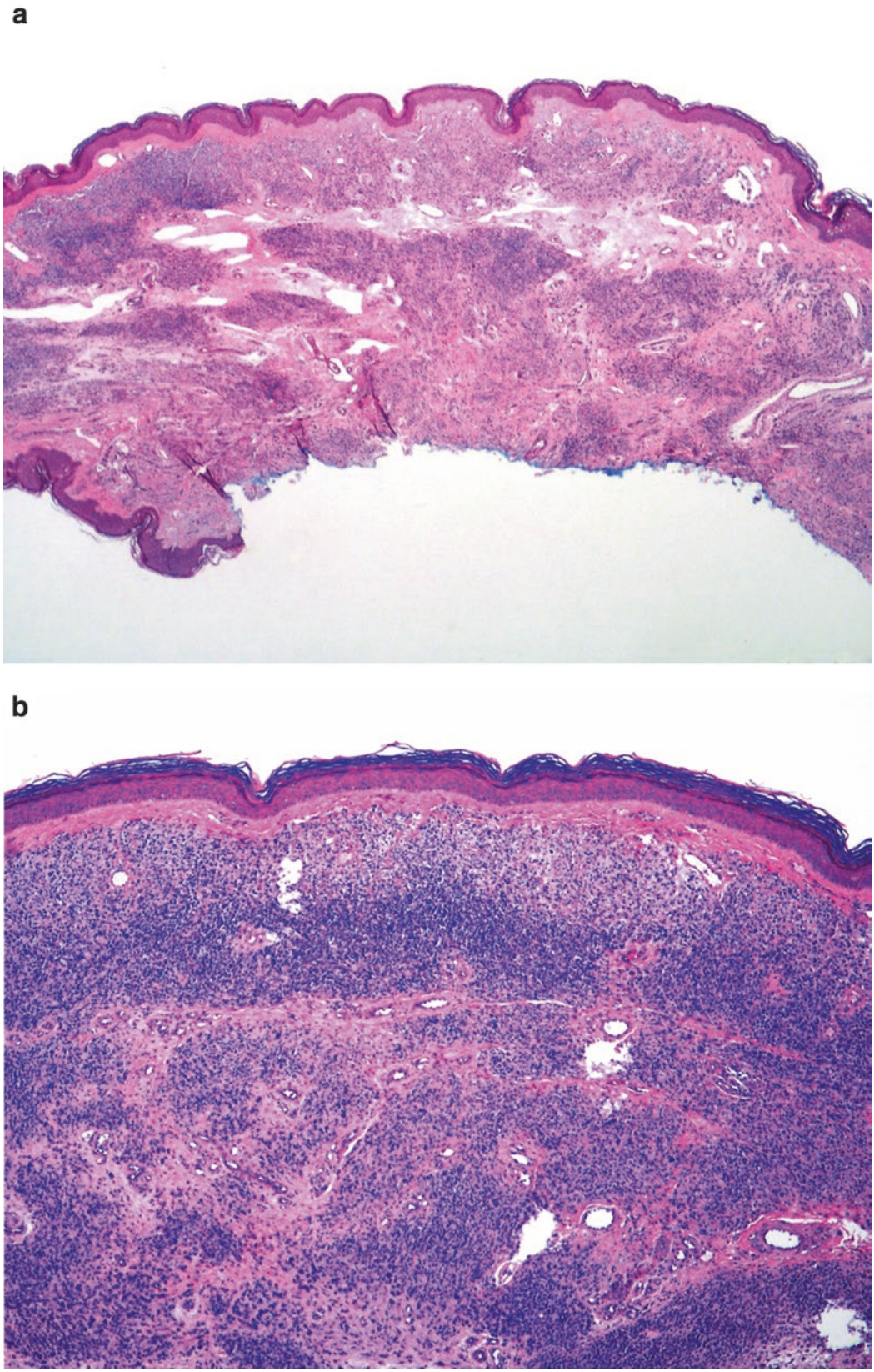


Fig. 7.56 Nevoid melanoma. This lesion is located on the trunk of a 60-year-old male. The lack of an obvious junctional component raises the possibility of an intradermal nevus with congenital pattern. At first glance there seems to be maturation in the dermis (**a**). Lack of junctional component (**b**).

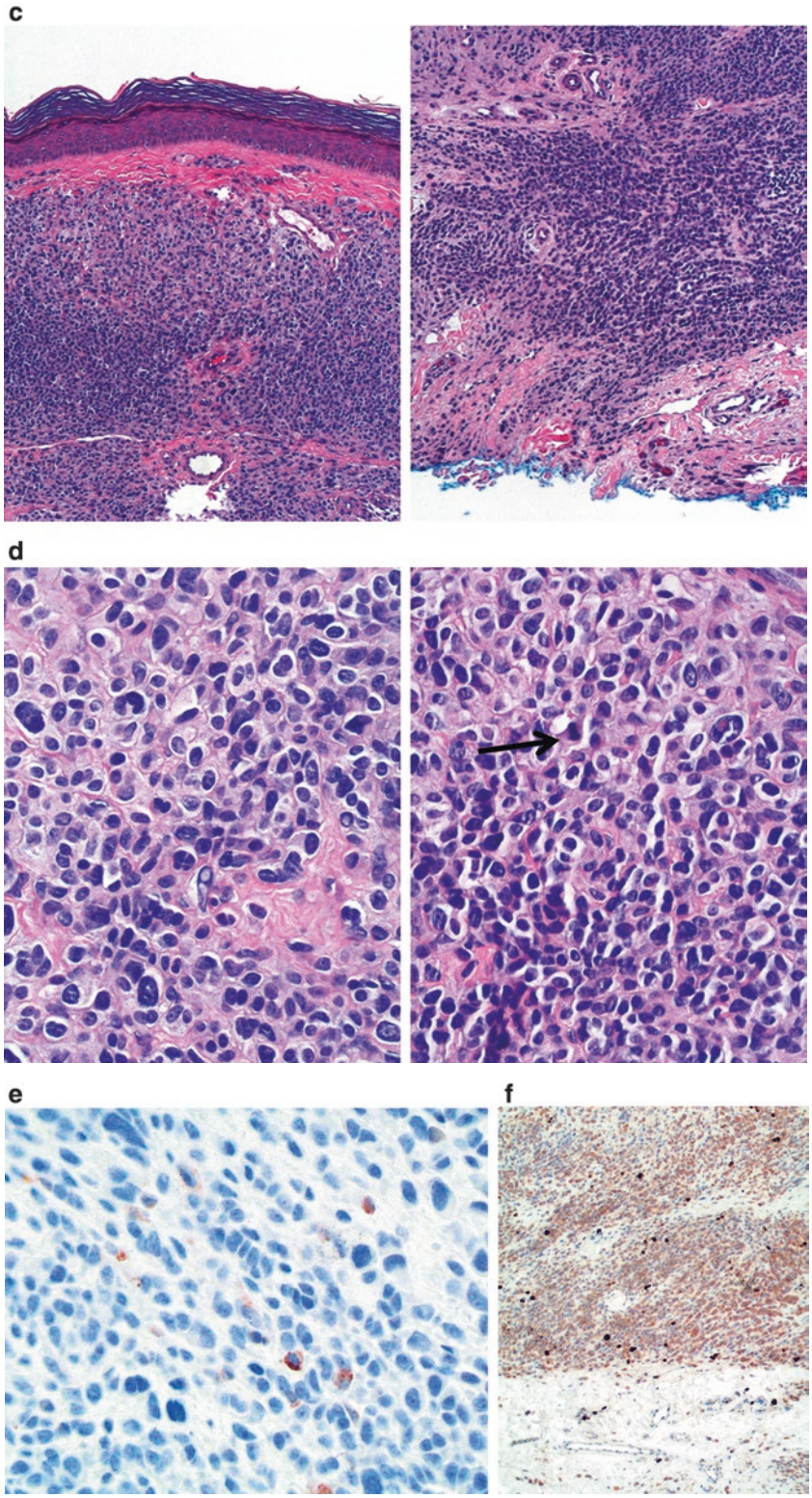


Fig. 7.56 (continued) Composite image to highlight the lack of maturation in the dermis (cells display the same size and degree of hyperchromatic nuclei throughout the lesion) (**c**). Similar morphology of the atypical melanocytes in the superficial (*left*) and deep regions (*right*) of the lesion. Note the presence of mitotic figures in the deep area (*arrow*) (**d**). HMB45 labels scattered cells throughout the lesion, thus supporting a diagnosis of melanoma (**e**). Note the scattered cells labeled for MART-1 (*red*) and Ki67 (nuclear, *brown*) in the deep areas of the lesion, supporting the diagnosis of melanoma (**f**)

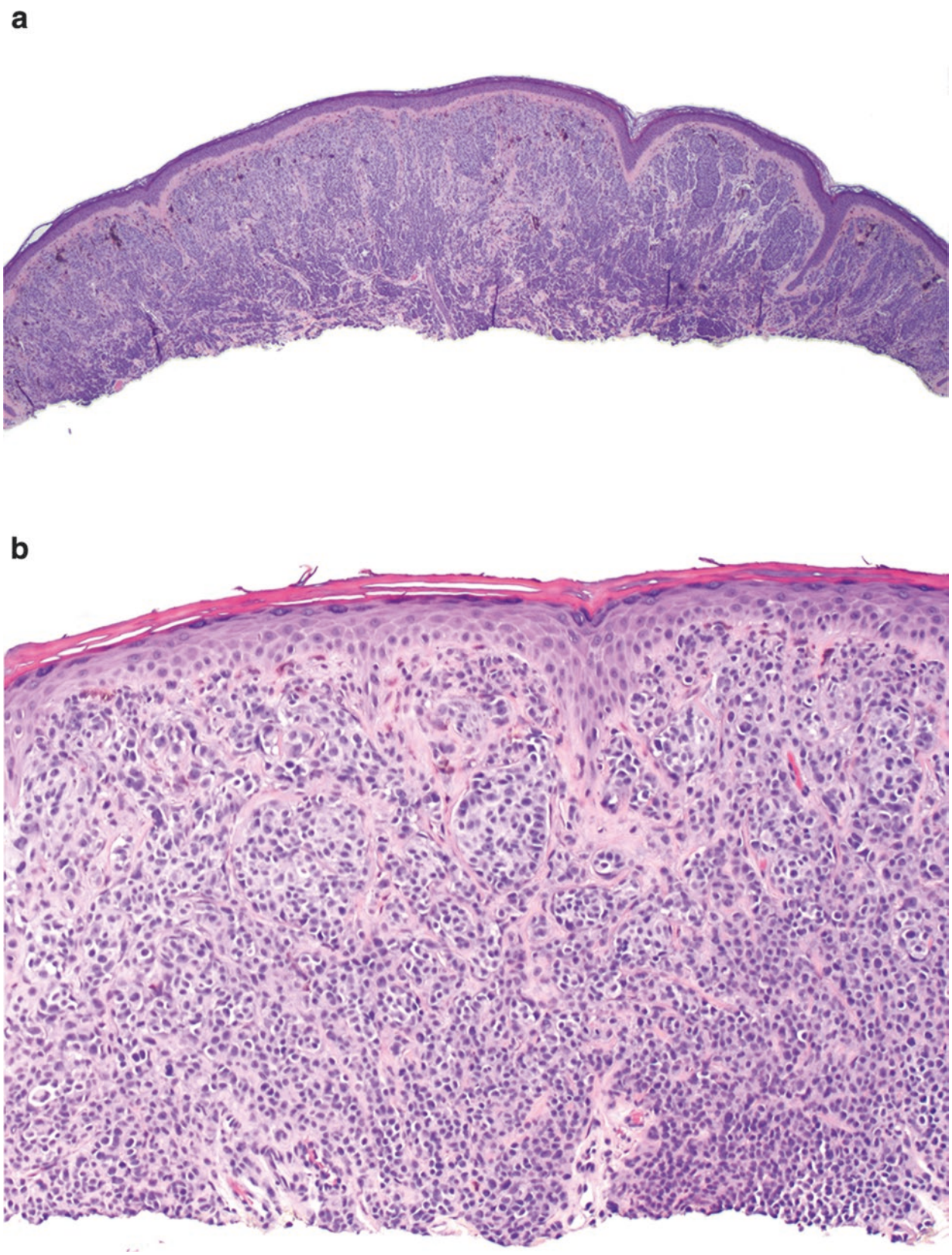


Fig. 7.57 Nevoid melanoma. The lesion is located on the upper arm of a 55-year-old female. On low magnification, the lesion is predominantly dermal. Although at first glance it mimics a nevus, there is no obvious maturation (cells appear to be of similar size both in the upper and lower dermis) (**a**). Higher-power view confirming the lack of an intraepidermal component (**b**).

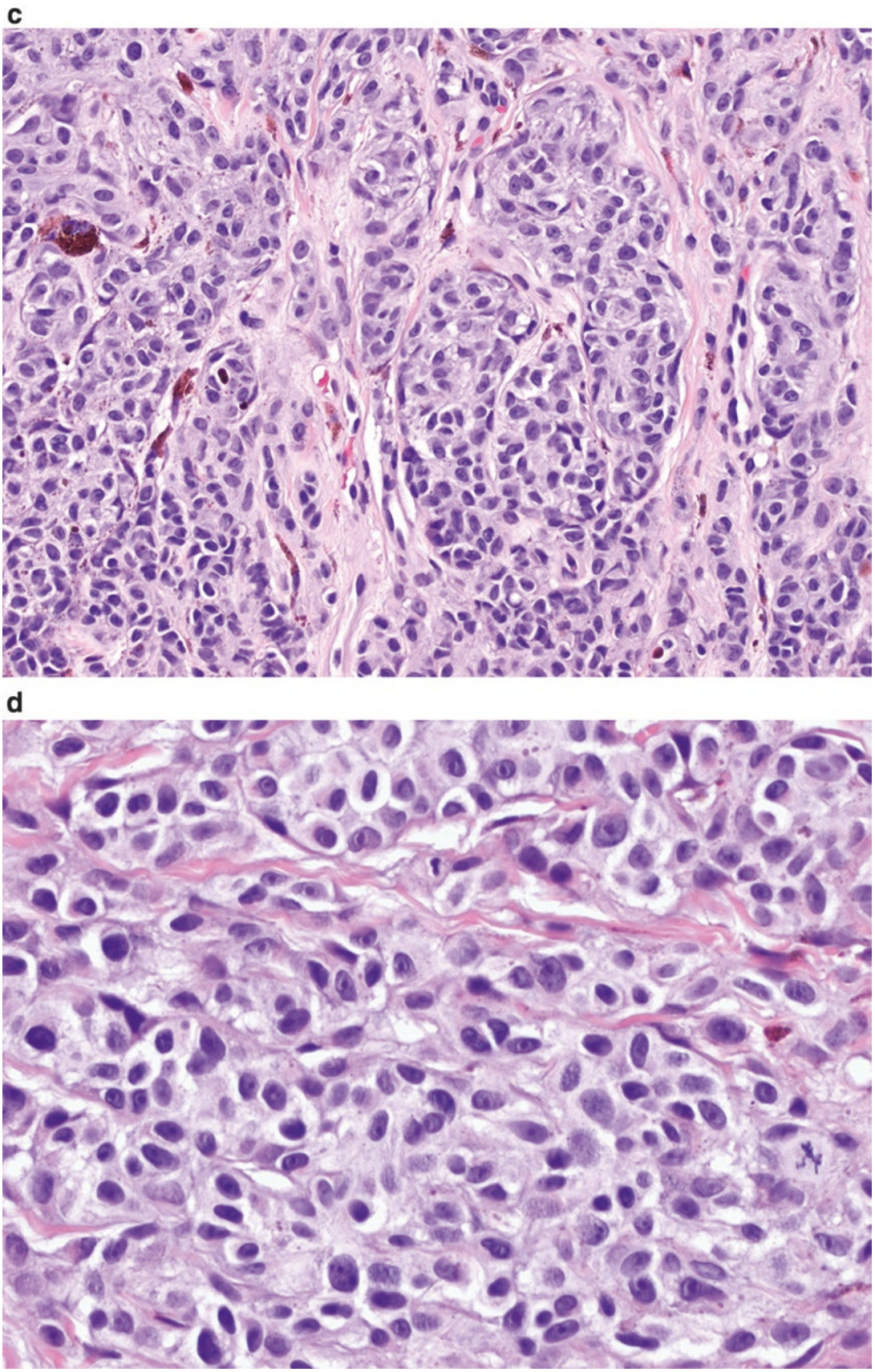


Fig. 7.57 (continued) Lack of maturation in the dermis (**c**). Marked cytologic atypia of melanocytes, including tetrapolar mitotic figures (**d**).

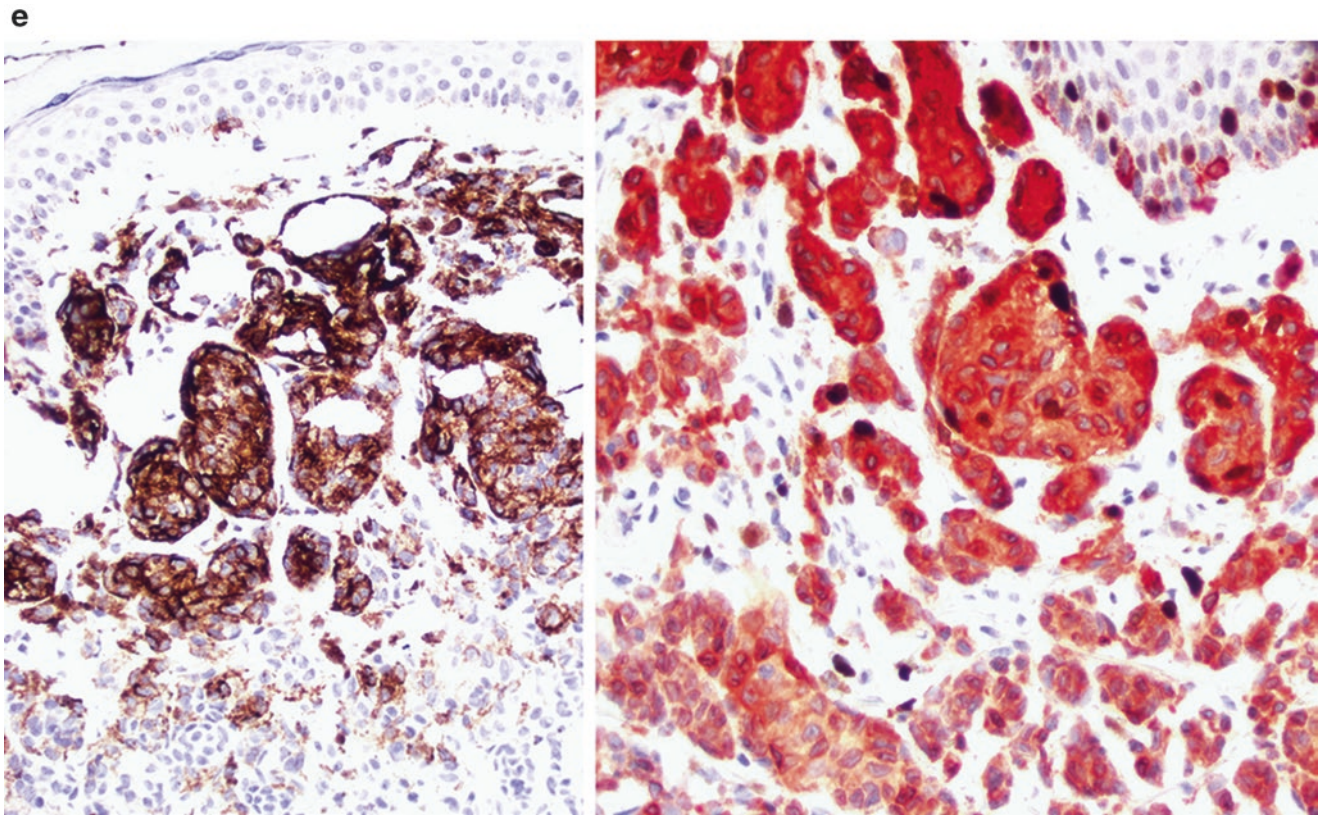


Fig. 7.57 (continued) Irregular labeling with HMB45 (*left*) and high proliferation rate in the dermal melanocytes (*red* MART-1, *brown* Ki67) (**e**)

Mucosal Melanoma (Oral Cavity, Vulva, and Penis)

Clinical Features

Almost any mucosal surface can develop primary melanoma (e.g., esophagus or gallbladder) [129, 130]. However, in this chapter we will concentrate in the most common ones, i.e., oral and nasal cavities, vulva, penis, and rectum. All these lesions have in common to present in most occasions as pigmented areas, with features similar to those seen in cutaneous melanoma (large size, asymmetry, irregular pigmentation, irregular borders, elevated areas, and color variegation, e.g., combinations of brown, black, blue, and red; areas of white color suggest regression).

In contrast with most cutaneous melanomas, which in general can be easily detected, lesions occurring in the mucosal surfaces are less likely to be detected early in their evolution, probably due to the lesser accessibility. Thus, they are likely to be detected at a higher size/stage [131]. Also common to these lesions is that they really occur in children or young adults. Most patients are beyond their fourth decade in life when a diagnosis of mucosal melanoma is established [132].

In the genital region, vulvar melanoma accounts for 8–10 % of all malignant tumors of the vulva [133]. It occurs on the clitoris, labia minora, and labia majora and may develop from a preexisting pigmented lesion. Vulvar bleeding is the most common symptom followed by "mass," ulcer, and "nevus" [134]. Indurated lesions are frequently associated with invasion. Up to 20 % of cases develop satellite

lesions. Melanomas can also develop in the conjunctiva as pigmented, irregularly shaped lesions [135].

Regarding etiology, the majority of mucosal melanomas are not associated with ultraviolet expression, also reflected in the type of mutations identified (unlikely NRAS or BRAF mutation, see also below) [136]. Interestingly, anorectal melanomas appear to be more prevalent in patients with red hair phenotype and poor tanning history [137].

Regarding prognosis, although in general mucosal melanomas are associated with poor prognosis, a recent large series comparing multiple anatomic sites reported that tumor thickness and geographic location were the most important factors, being vulvar melanomas among the ones with best prognosis [138, 139].

Histopathology

Acral lentiginous (mucosal lentiginous) melanoma is the most common type of mucosal melanomas. Melanoma in situ is composed of atypical melanocytes arranged both singly and in nests within the epithelium. In general, single cells often predominate over nests, typically with confluent growth in the epithelium, have relatively small but hyperchromatic melanocytes, and extend along the basal layer of the epidermis and into adnexal epithelium. Much less frequent is the pattern of superficial spreading melanoma, in which the tumor cells usually exhibit significant cytologic atypia (large, pleomorphic nuclei with prominent nucleoli) and prominent pagetoid spread through the epithelium. Some mucosal melanomas do not display an obvious radial growth phase (i.e., they correspond to the pattern of nodular melanoma).

Most mucosal melanomas have standard pattern of invasion, i.e., irregular nests and clusters of atypical melanocytes within variable degrees of fibrotic stroma. Some cases may display marked desmoplasia as seen in desmoplastic melanoma.

As mentioned above, tumor thickness appears to be the most important histology prognostic factor in mucosal melanoma, although there are slight differences among the different anatomic locations [140].

Differential Diagnosis

Mucosal melanoma must be distinguished from mucosal lentigo. Such lesions are more common than melanoma, particularly in patients younger than 50 years of age. Mucosal lentigo shows hyperpigmentation of basal keratinocytes, particularly in the tips of the rete ridges, with minimal increase of melanocytes. However, before rendering a diagnosis of mucosal lentigo, it is essential to know the clinical size of the lesion. We have encountered rare cases in which a patient has had one or more biopsies diagnosed as a "lentigo" only to discover by the second or third recurrence that the lesion was large (several cm in size). When the entire lesion was removed, it was clear that some areas showed evident proliferation of atypical melanocytes (i.e., melanoma in situ) while intervening areas mostly had hyperpigmentation of basal keratinocytes with only scattered intraepithelial melanocytes.

Other differential diagnoses are extrammamary Paget disease and carcinoma in situ [141]. In general, Paget cells are larger than those of melanoma and may form glandular structures. Squamous cell carcinomas usually involve the entire thickness of the epithelium. As with cutaneous melanomas, mucosal lesions are immunoreactive for S-100 protein, HMB-45 antigen, Melan-A, SOX10, and MITF. Paget disease usually shows mucin and expresses low-molecular-weight keratin and CEA.

A lesion that clinically can resemble melanoma is amalgam tattoo, due to the deposit of the metal in macrophages within the lamina propria. These lesions lack any intraepithelial melanocytic proliferation [142].

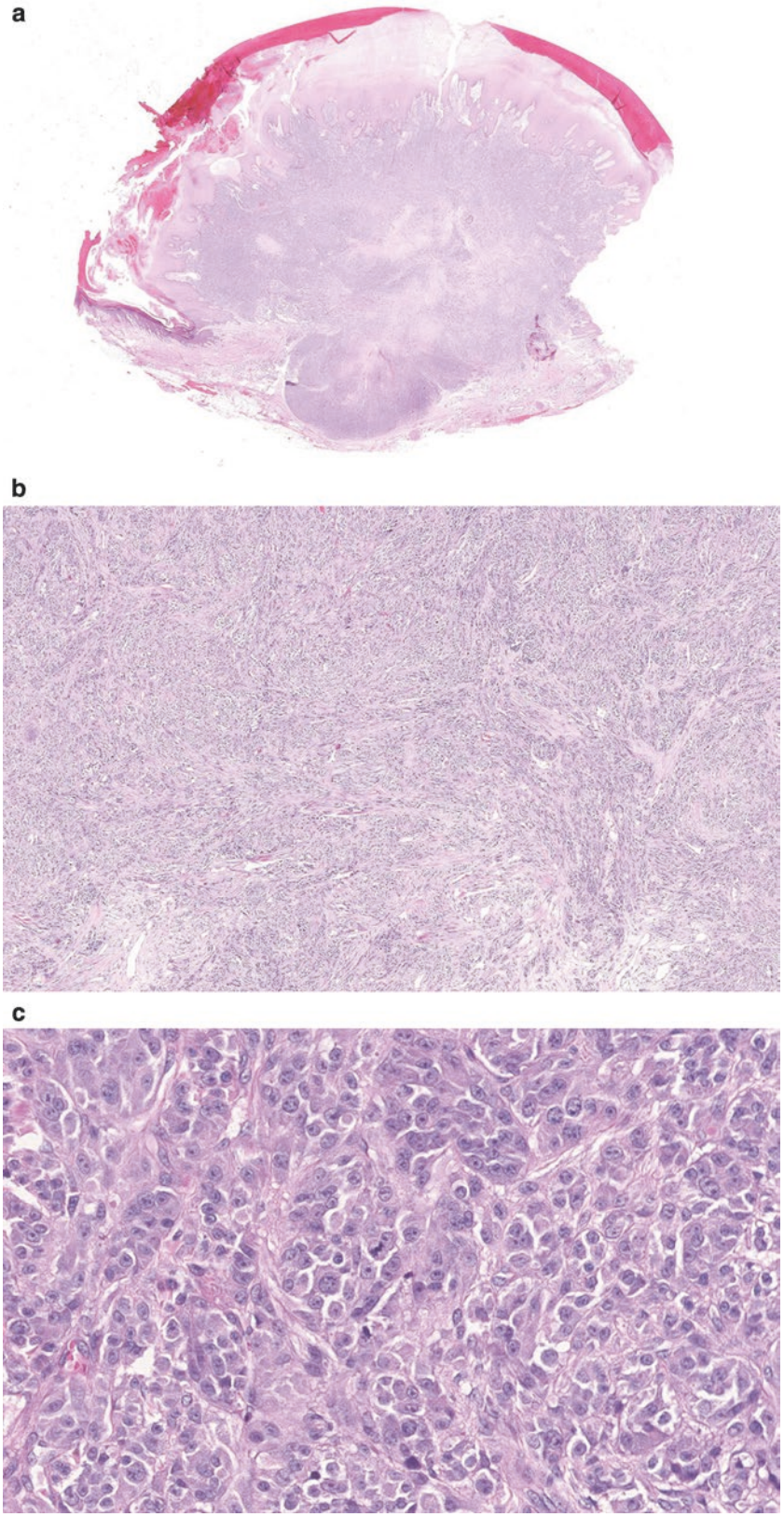


Fig. 7.58 Invasive melanoma of the oral mucosa. The tumor is composed of an expansile nodule with overlying ulcer (**a**). Cells have pleomorphic and hyperchromatic nuclei and thickened nuclear membranes and numerous atypical mitotic figures (**b**, **c**)

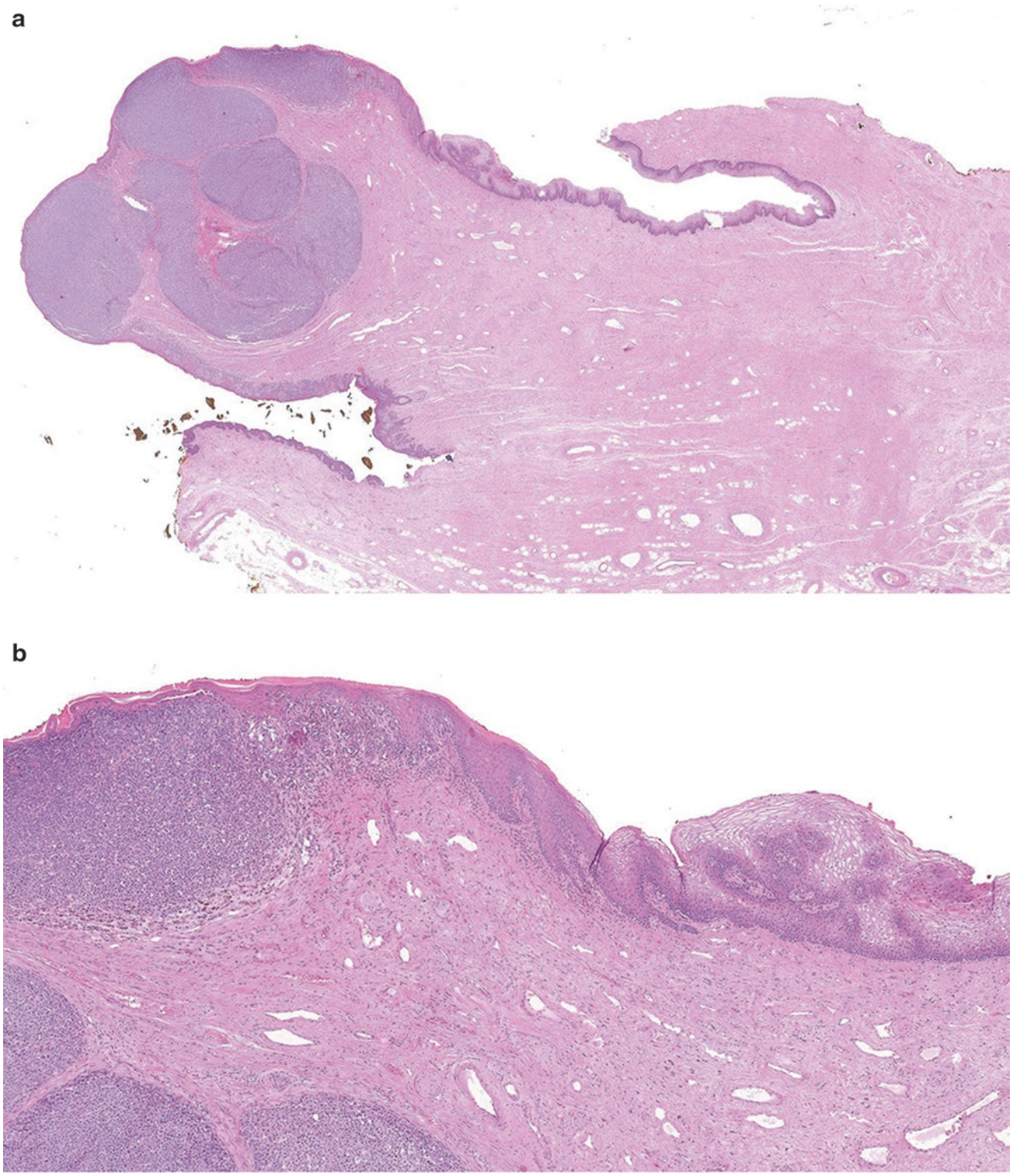


Fig. 7.59 Vulvar melanoma (acral lentiginous-mucosal type). This is an example of an invasive vulvar melanoma with an expansile pattern of growth in the mucosa (**a**). There is a prominent intraepithelial component of single melanocytes. Note the squamous epithelium with glycogenic change consistent with vulvar location (**b**).

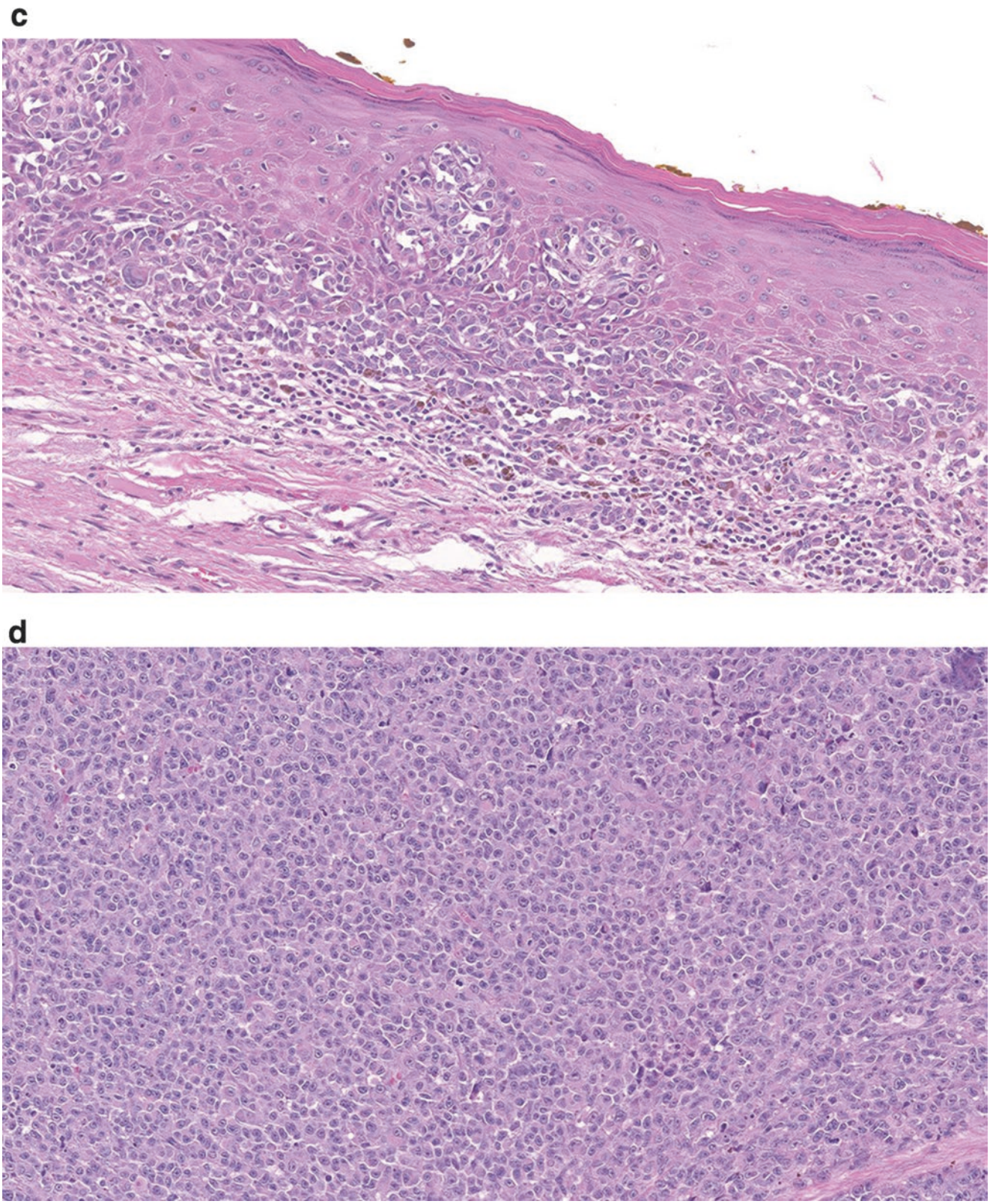


Fig. 7.59 (continued) Higher-power view of the in situ component with focal invasion (**c**). There is an expansile pattern of growth of the invasive component (**d**)

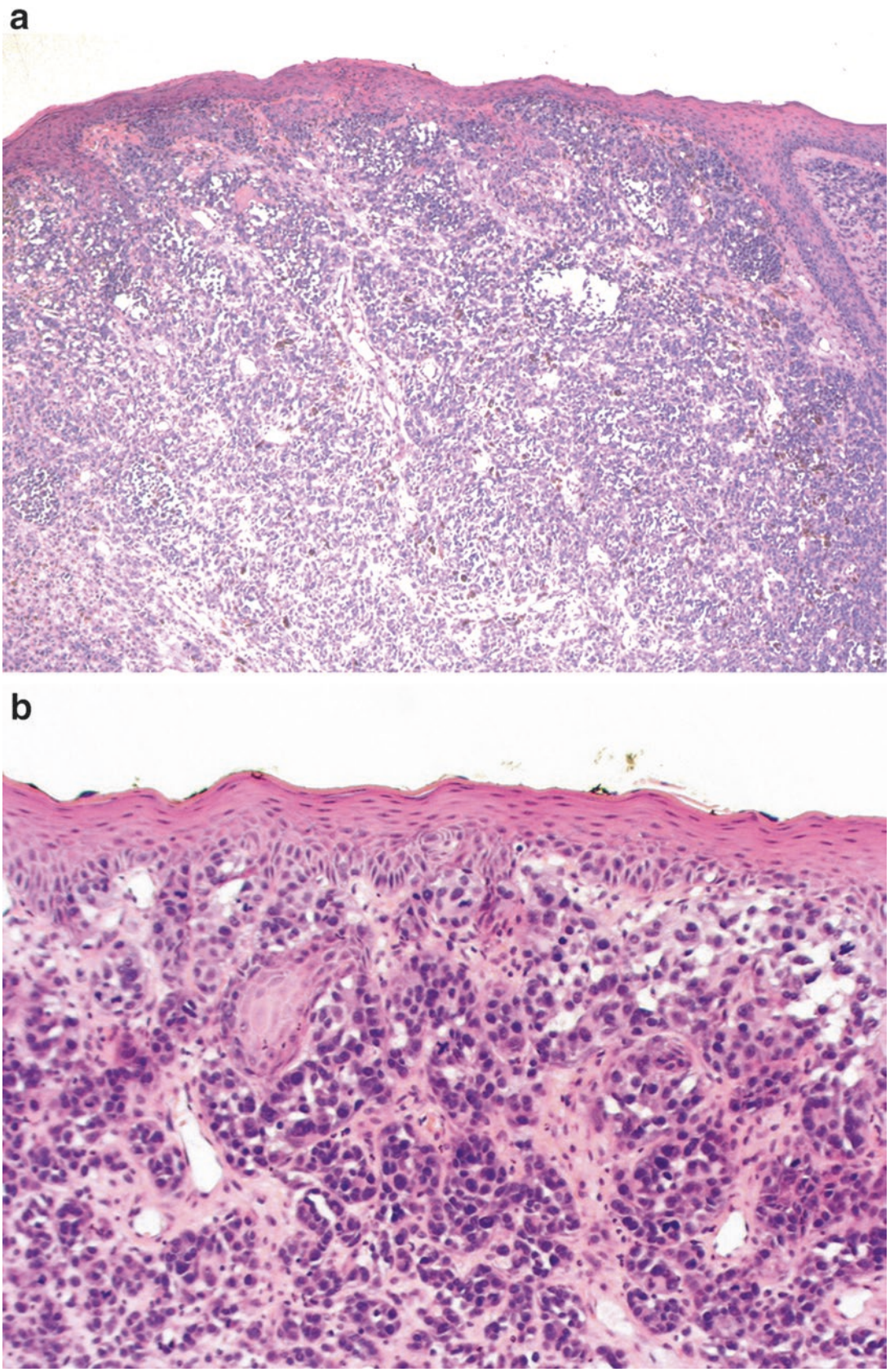


Fig. 7.60 Vulvar melanoma. Note the squamous mucosa with an atypical proliferation of melanocytes. Both in the epithelium and in the lamina propria (**a**). Higher-power view of the in situ component with focal invasion (**b**).

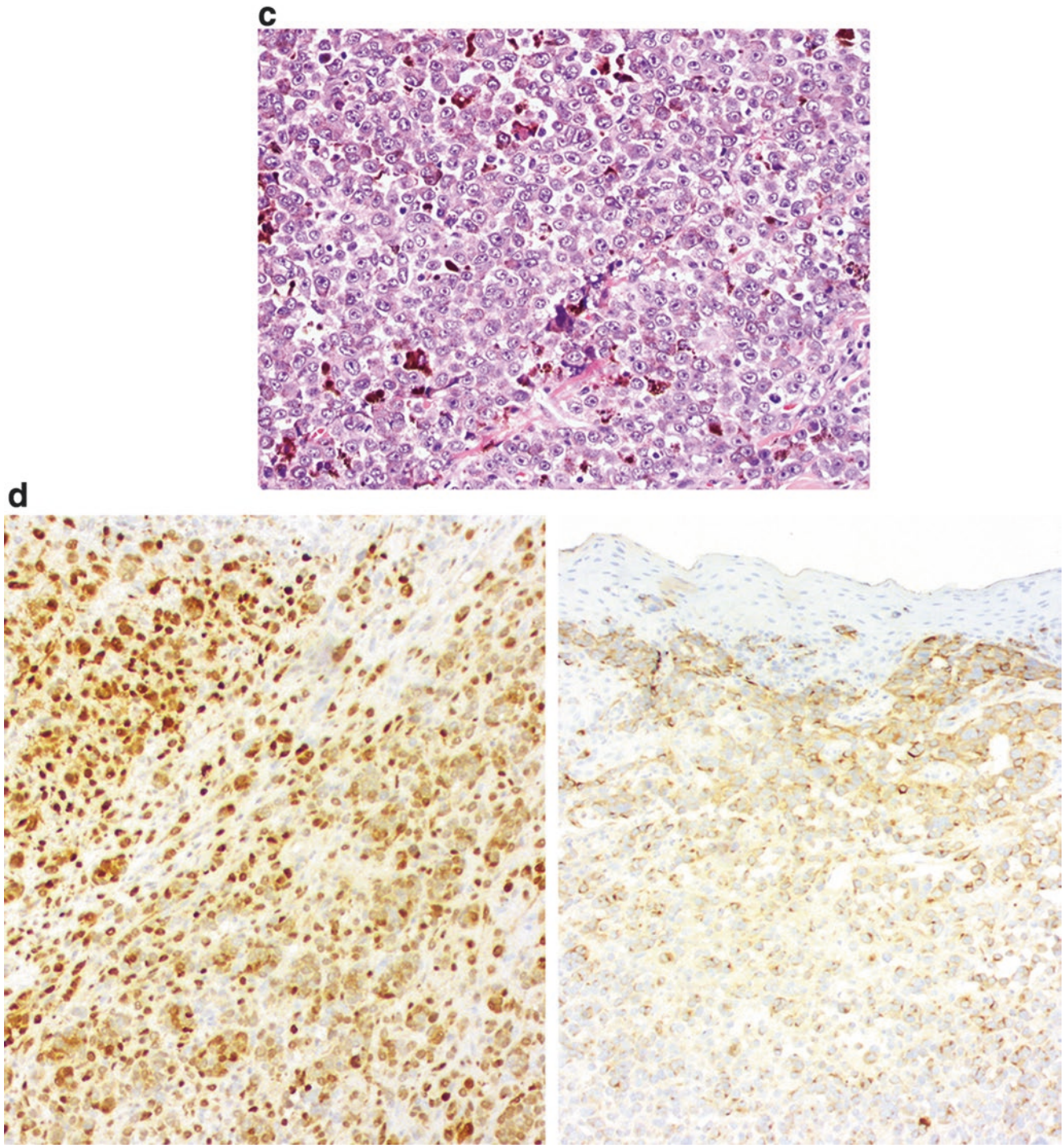


Fig. 7.60 (continued) High-power view showing the marked degree of cytologic atypia of the invasive component and the focal melanin pigment (**c**). Tumor cells express S100 protein and melanocytic markers (HMB45 antigen and MART-1) (**d**)

Lentiginous Melanoma

Several authors have recently proposed the term of lentiginous melanoma to describe a pattern of melanoma composed of a prominent, lentiginous, single-cell growth with focal, poorly cohesive nesting, focal suprabasilar migration of melanocytes, and preservation of the rete ridges [143, 144]. These cases typically occur in elderly patients, they commonly lack solar elastosis, and they have a prolonged in situ or radial growth phase. This concept has been proposed to encompass some lesions that in the past were classified as atypical lentiginous nevi, melanocytic hyperplasia, evolving melanoma in situ, or nevoid lentigo maligna [145–147]. However, the apparently unique clinical and histologic features of this distinct entity suggest that it represents a distinct clinicopathologic entity. These lesions occur most commonly on the trunk, head and neck, and proximal upper extremity, and it seems that when left untreated, they may progress to invasive melanoma. Clinically, these lesions resemble lentigo or junctional nevus but can grow and become asymmetric. These lesions tend to persist and grow and then adopt a large size (>1.0 cm). Recurrences of the lesion in the same anatomic area should be a red flag for the diagnosis of lentiginous melanoma.

Histopathology

Histologically, lentiginous melanoma is characterized by a lentiginous proliferation of melanocytes at the dermoepidermal junction, with areas of focal pagetoid spread and occasional melanocytic nest formation. The melanocytes are arranged as single melanocytes and as small nests with areas of confluent growth involving broad areas of the dermoepidermal junction. One clue to this diagnosis is that there is retention of the rete ridge pattern in the epidermis. In contrast with dysplastic nevus, lentiginous melanoma reportedly lacks papillary dermal fibrosis, either lamellar fibroplasia or concentric eosinophilic fibrosis. However, further studies are needed in order to fully distinguish this lesion from early dysplastic nevi [148].

As opposed to what is seen in lentigo maligna, there is only limited or no solar elastosis (another diagnostic clue) and minimal, if any, extension into skin adnexa. Also, there is at least subtle pagetoid spread of single melanocytes but it may be difficult to identify on H&E sections. Cytologically, the melanocytes demonstrate mild to moderate atypia with enlarged nuclei, thickened nuclear membranes, and prominent nucleoli. The melanocyte nucleus is close to the size of adjacent keratinocyte nuclei. Melanocytes may show ample gray cytoplasm with melanin pigment, and the dominant cell type is epithelioid, with only rare scattered spindled melanocytes. These latter cytologic features differentiate lentiginous melanoma from other variants of melanoma.

Accurate histologic identification of lentiginous melanomas in small tissue samples represents a diagnostic challenge in dermatopathology, and in such cases, it is very important to know the size of the pigmented lesion. The true nature of these melanocytic lesions is more readily apparent in completely excised specimens or large tissue samples, as the lesions exhibit a broad lentiginous melanocytic proliferation.

FISH has shown some diagnostic utility in the identification of lentiginous melanoma. One study showed that 84 % of the cases met one of the four FISH criteria for melanoma, and the abnormality in the majority of cases consisted of increased copy numbers of RREB1 (6p25) [149]. These findings support the classification of these lesions as melanoma at the molecular level.

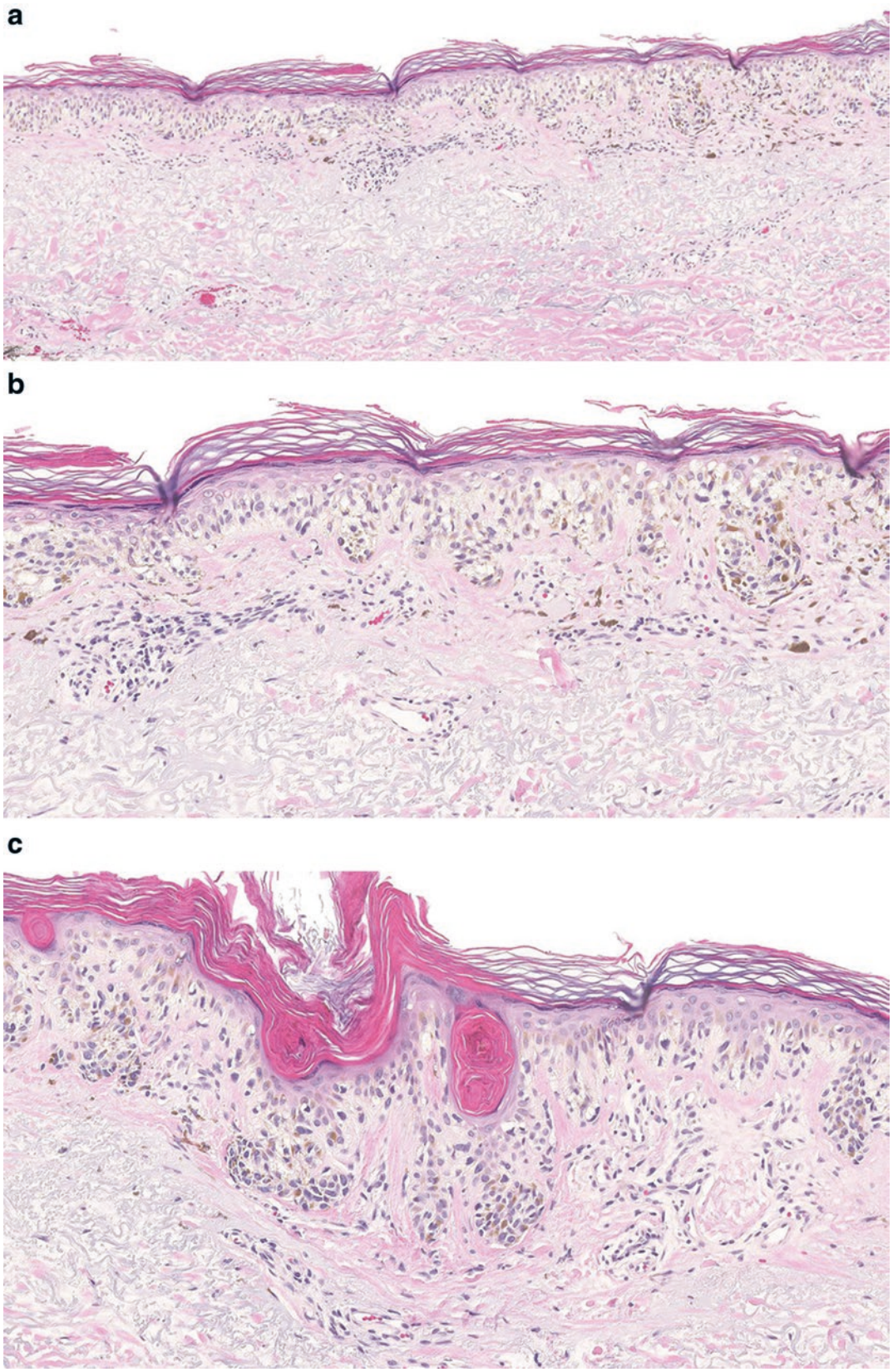


Fig. 7.61 Lentiginous melanoma. This lesion is located in the shoulder of an 83-year-old male. The lesion is composed of broad atypical lentiginous growth pattern without significant dermal fibroplasia or alteration of the rete ridges (**a**). Moderately atypical melanocytes showing focal nesting and pagetoid spread (**b**). The lack of significant dermal fibrosis or bridging is against a diagnosis of a severely dysplastic nevus (**c**)

Primary Dermal Melanoma

Primary dermal melanoma (PDM) is a rare variant of melanoma that has no connection to the overlying epidermis. There have been already a few studies describing the dermoscopic findings of these lesions [150].

Although there are relatively few cases, a few studies have shown that these lesions have an excellent 5-year survival approaching 90 % [151]. Histologically, these tumors are composed of a well-defined nodule of cytologically malignant melanocytes mostly located in the deep dermis and subcutaneous tissue [152]. The lack of significant intraepidermal involvement resembles the pattern of metastatic melanoma. Thus it is crucial to know the clinical history of the patient as both lesions have markedly different clinical behavior. The diagnosis of PDM needs to be made in patients with a solitary lesion with no known primary melanoma. But it has to be taken into account that up to 10 % of metastatic melanoma to the skin present without a known primary [123]. In such cases the primary tumor may have completely regressed or it may represent a non-cutaneous site.

At least one study has employed molecular analysis to try to distinguish PDM and metastatic melanoma [153]. Further studies are needed to determine the possible clinical application of this test.

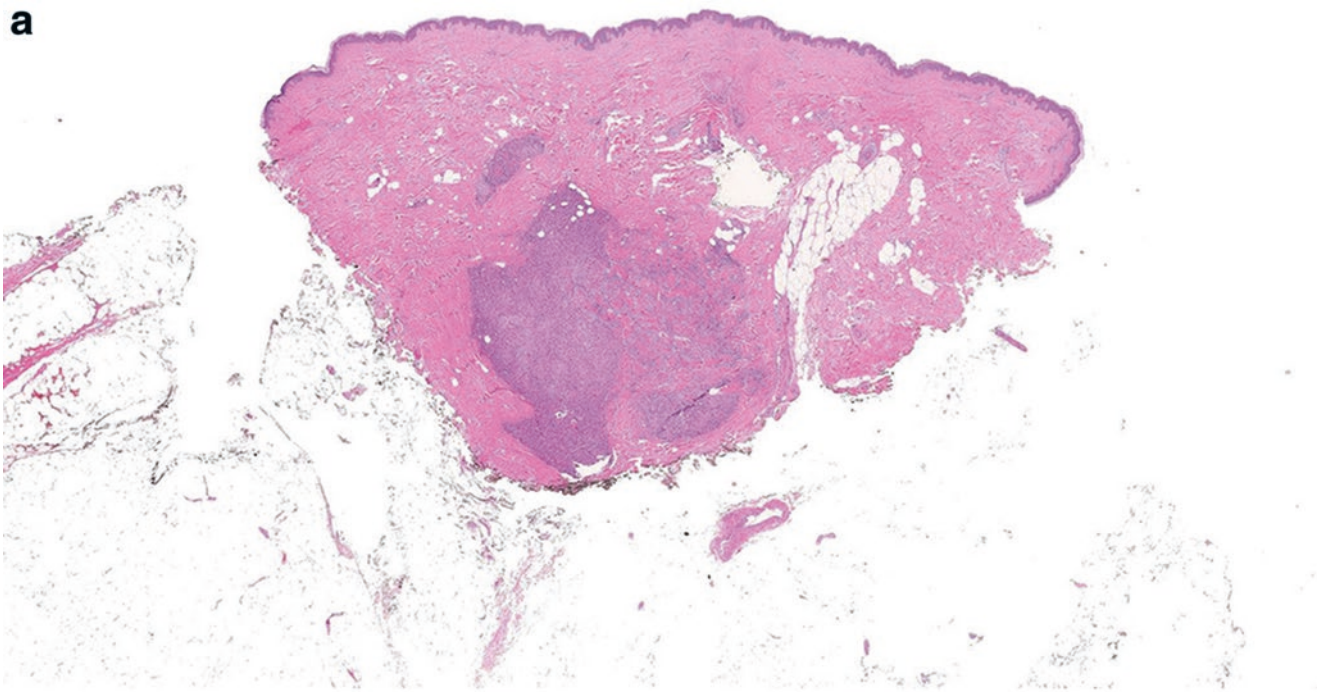


Fig. 7.62 Primary dermal melanoma. A 65-year-old male with a nodular lesion on the scalp that clinically was thought to be a cyst. The patient did not have a prior history of melanoma. The biopsy shows a dermal tumor without an intraepidermal component (**a**).

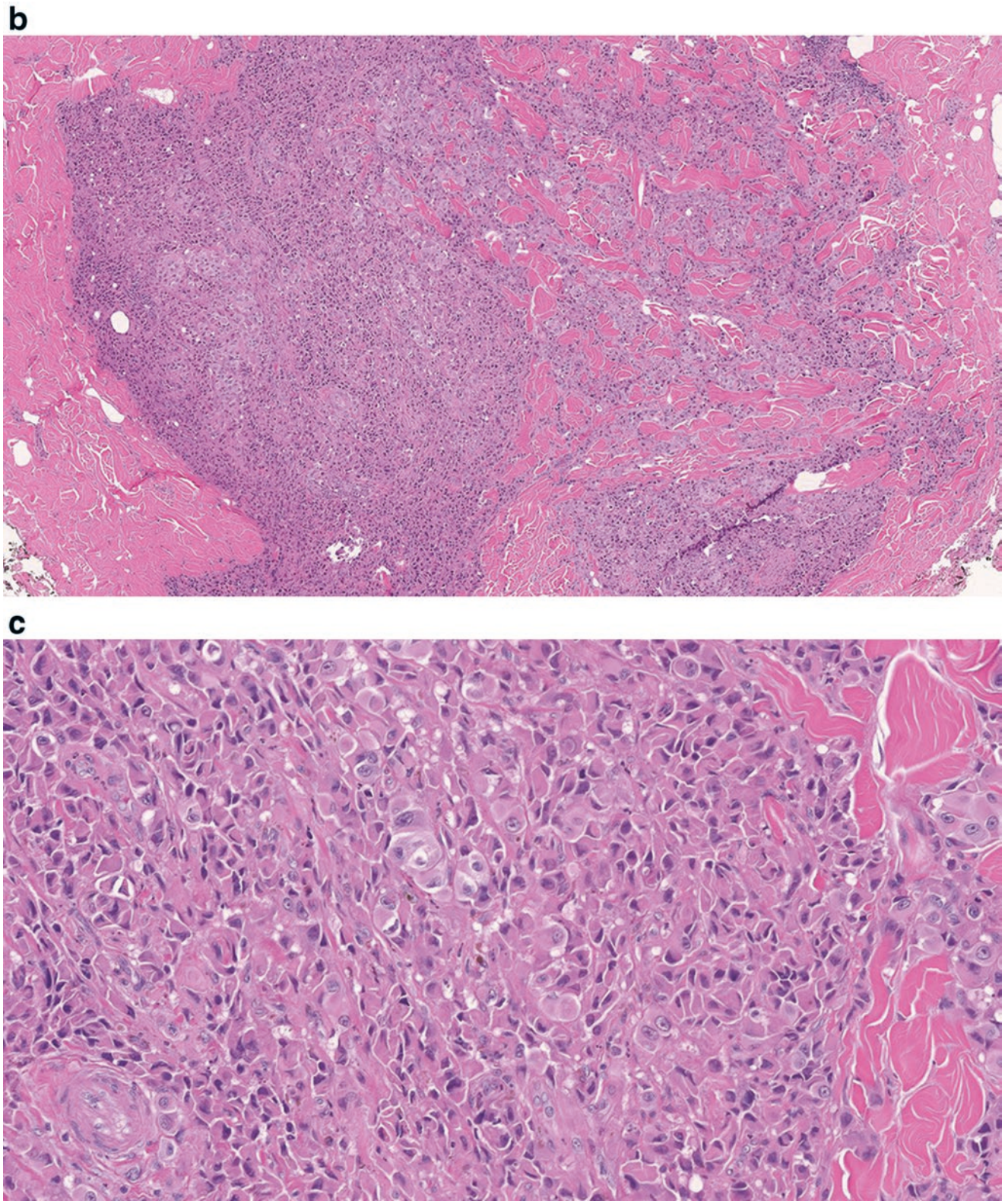


Fig.7.62 (continued) Large nodular lesion in the deep dermis (**b**). The cytology of the lesion is that of a malignant tumor composed of epithelioid cells arranged in a nested pattern. The cells have pleomorphic nuclei and visible mitotic figures (**c**)

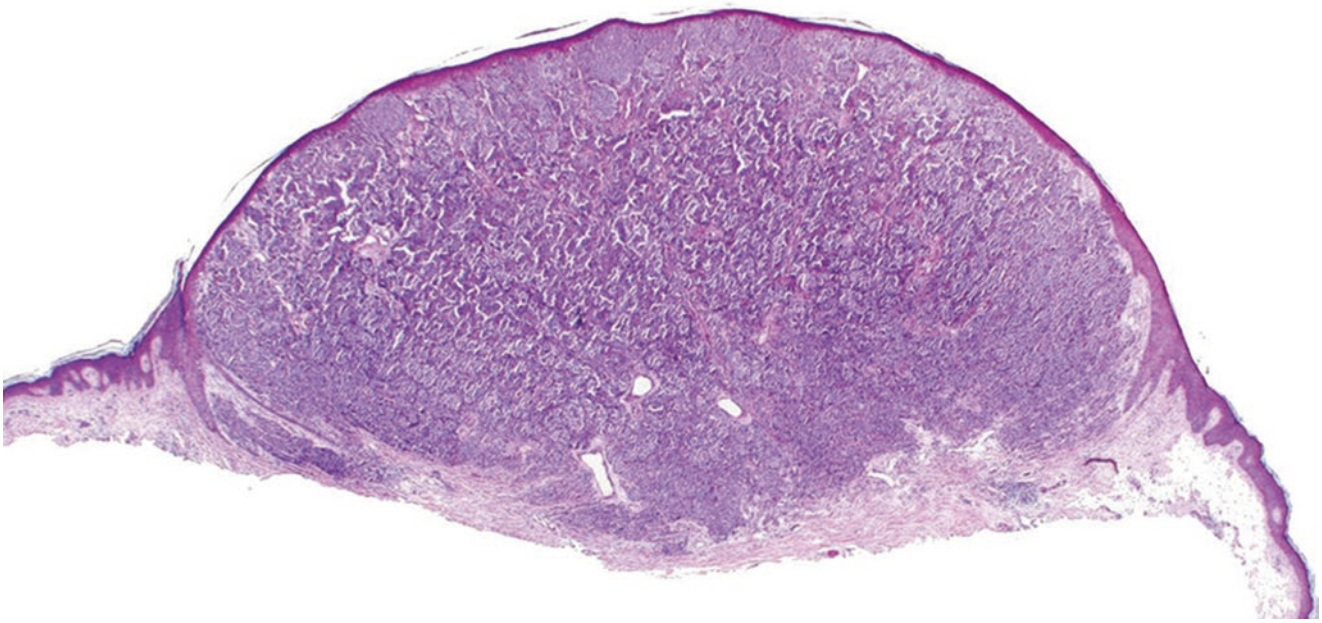


Fig. 7.63 Metastatic melanoma. The lesion shows a well-circumscribed nodule in the upper dermis with collarette formation with an epithelioid cytomorphology. Most metastatic melanomas do not show ulceration, regression, or an in situ component

Metastatic Cutaneous Melanoma

Metastatic melanoma is one of the most common sources of cutaneous metastasis, and in up to 5 % of patients, metastatic melanoma can be the first manifestation of the disease. Metastatic melanoma to the skin can many times simulate clinically and histologically primary melanoma or other malignant and benign neoplasms. The distinction between metastatic melanoma and primary benign or malignant melanocytic lesions is of great importance for clinical staging, treatment, and prognosis. In most of the cases, this distinction is clear-cut, but some lesions may resemble benign tumors, other malignant processes, or also primary melanoma. Primary melanomas in general can have the potential to adopt many histological architectural patterns, cytologic features, and stromal changes; hence they are sometimes called "the great mimickers." Metastatic melanomas to skin are no exception to this rule; therefore, they can also mimic epithelial, mesenchymal neoplasms, etc. The most common clinical presentation for cutaneous metastatic melanomas is that of a papule or nodule in a patient with a previously diagnosed primary melanoma. In our series, only 7.8 % presented without evidence of a primary melanoma.

Histopathology

Melanomas metastatic to the skin usually involve the deep dermis and subcutaneous fat; however, in some cases the lesions can be superficial. Many studies have analyzed the histopathologic features of melanomas metastatic to the skin and have described many histologic pitfalls including epidermotropic metastases, blue nevi-like metastases, etc., and have concluded that in some instances, it can be very difficult to differentiate metastatic melanoma from a primary lesion. We studied a large number of skin metastases from melanoma and analyzed their histomorphologic spectrum [154].

In our study we found that 5.2 % of cases had epidermotropism. The diagnosis of epidermotropic metastatic melanoma (EMM) can be extremely challenging for both clinicians and pathologists, as primary and metastatic melanomas display such dissimilar prognosis. Many histological criteria have been utilized for separating EMM from primary melanomas; however, it is unlikely that any criteria solely based on histology will consistently allow this distinction. Important features that may be of help include small tumor size, single-cell infiltration (pagetoid spread), fibrotic dermal stroma, and the fact that epidermotropic cells usually do not extend beyond the involved dermis in metastatic melanomas [155]. Also, it is very important to keep in mind that approximately 3–5 % of patients with primary melanoma can develop a second or third primary melanoma due to genetically determined predisposition, and in such instances, it may be impossible to ensure whether the lesion is a second primary melanoma or an EMM. Also, in our study we found that 4.6 % of metastatic melanoma had nevoid features.

One may argue that some of these cases may represent primary dermal melanomas (PDM). There is a relatively longer clinical history in PDM when compared to metastatic

melanoma. By IHC, PDM typically exhibits relatively low proliferation with MIB-1 when compared to metastatic melanoma. As in PDM, most metastatic melanomas show no ulceration, regression, or an in situ component and can create a diagnostic dilemma. However, metastatic melanomas to the skin more often form a well-circumscribed nodule in the upper dermis with collarette formation, stromal fibrosis, and usually with an epithelioid histology. For this reason, before entertaining the diagnosis of PDM, we recommend fully evaluating the clinical history of the patient.

Primary nevoid melanoma is a rare entity that can be extremely difficult to diagnose on histology (see above); attention to cytologic and architectural detail and high index of suspicion are essential to diagnose correctly these neoplasms. Histologically, both primary nevoid melanomas and nevoid cutaneous metastases of melanoma may often be indistinguishable; diagnostic pointers that will favor the diagnosis of nevoid cutaneous metastases include the presence of a nodular expansile nodule in the dermis and the presence of lymphovascular invasion [156]. Another potential pitfall in the diagnosis of metastatic melanomas to the skin is the adoption of an appearance that can simulate a blue nevus. Metastatic melanoma shows a predominance of atypical epithelioid cells, a dense perivascular lymphocytic infiltrate, and obvious mitotic figures. When in doubt, immunohistochemical studies can be of aid in such difficult cases by analyzing the proliferation rate, which is high in metastatic melanomas. As expected, knowledge of the patient's clinical history is crucial to avoid misinterpretation of such lesions.

Cases of metastatic melanoma to the skin can also mimic metastatic carcinoma, such as metastatic breast cancer. Immunohistochemical studies will be helpful in detecting an epithelial phenotype in such lesions.

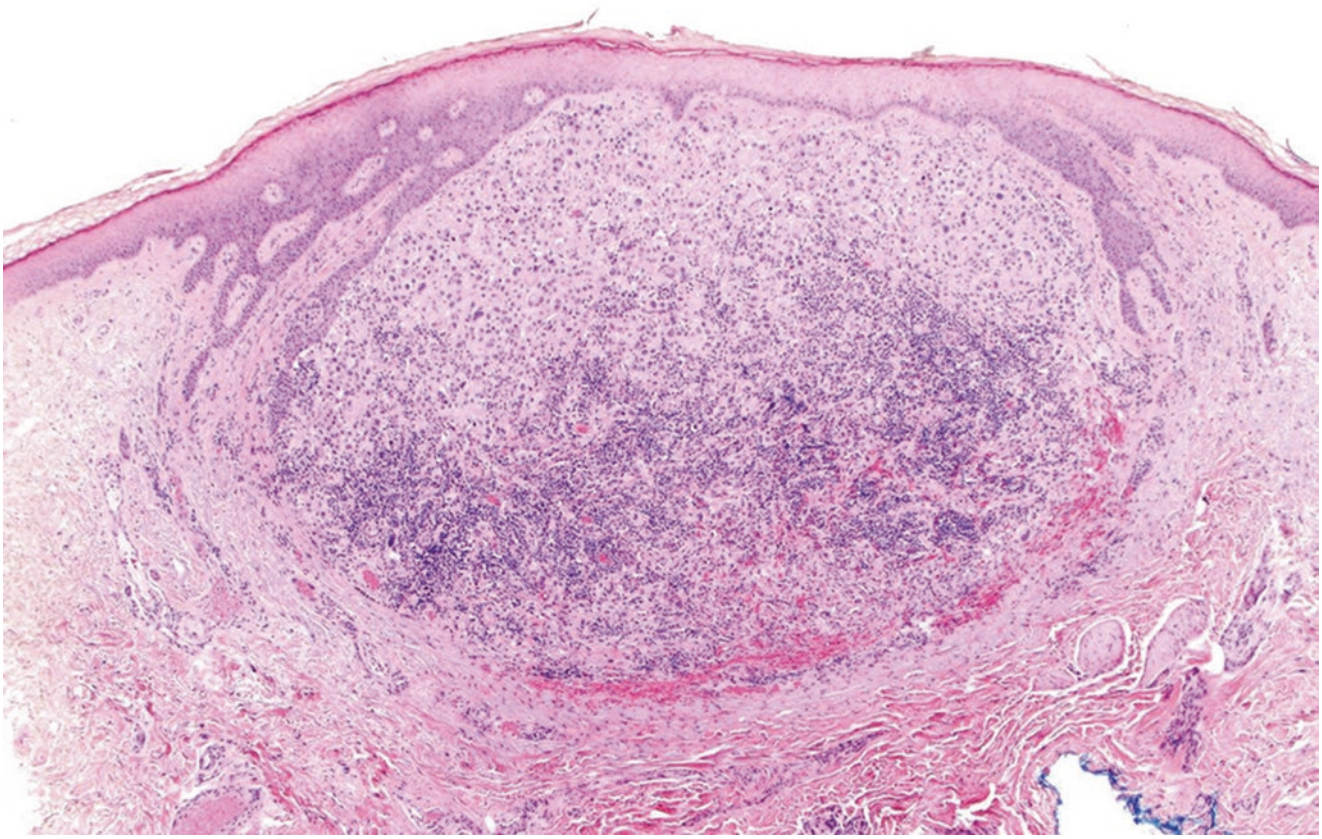


Fig. 7.64 Metastatic melanoma with spitzoid changes. This case shows spitzoid features, lacks an epidermal component, and shows epidermal collarette (which is very rare in Spitz nevi). Also, note the large sheets of cells intermixed with a prominent host response, a finding very unusual in Spitz nevi

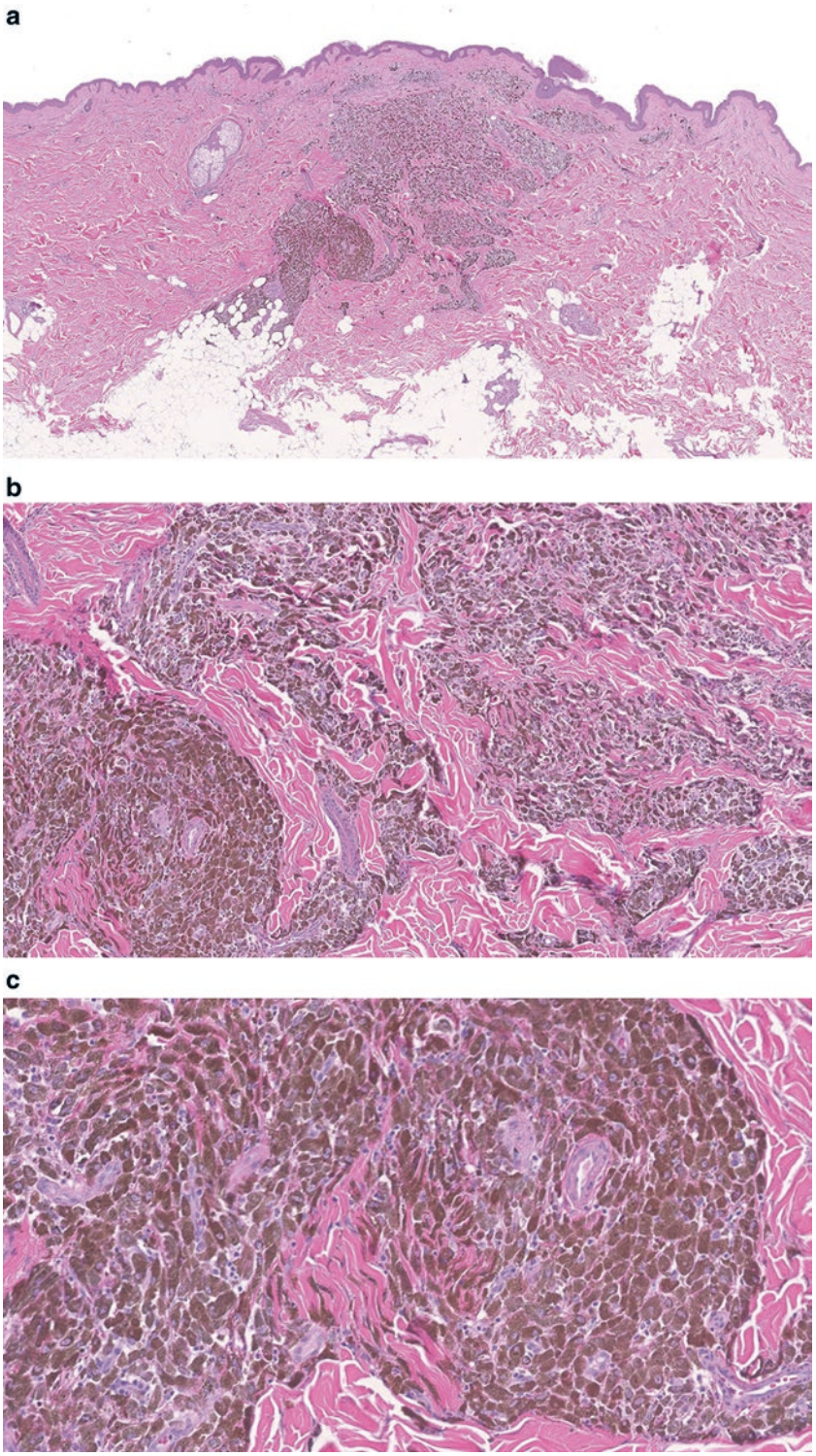


Fig. 7.65 Metastatic melanoma with blue nevus-like morphology. This patient had a melanoma close to where this lesion developed. On low magnification the lesion can be mistaken for a blue nevus (**a**). Cells are large and have prominent cytologic atypia. Diagnostic pointers useful for distinguishing metastatic melanoma from blue-nevi include the presence of atypical epithelioid cells and mitotic figures (**b**). High magnification of the large atypical epithelioid melanocytes (**c**)

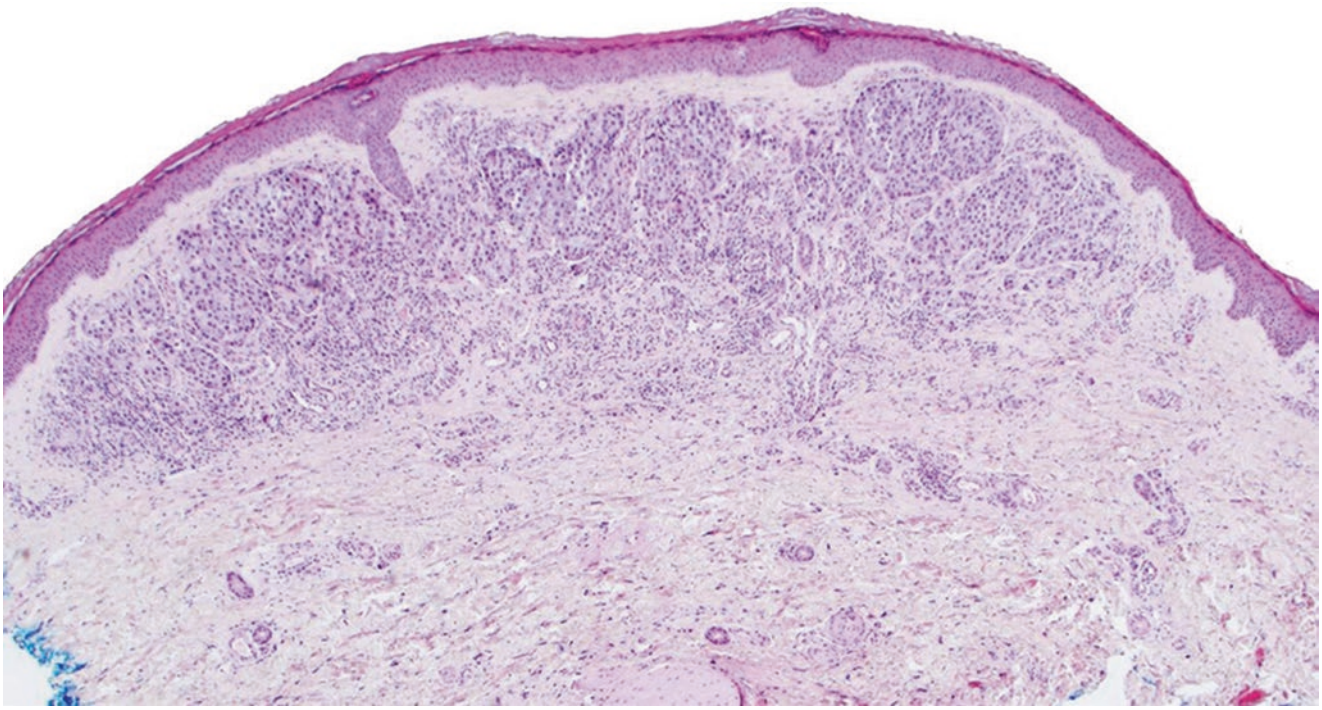


Fig. 7.66 Metastatic melanoma with nevoid features. A primary nevoid melanomas and nevoid cutaneous metastases of melanoma may be indistinguishable. The presence of lymphovascular invasion favors a metastatic origin, along with clinical correlation (prior history of melanoma). The lesion shows a tumor in the upper/mid-dermis composed of atypical epithelioid melanocytes with scattered atypical mitotic figures

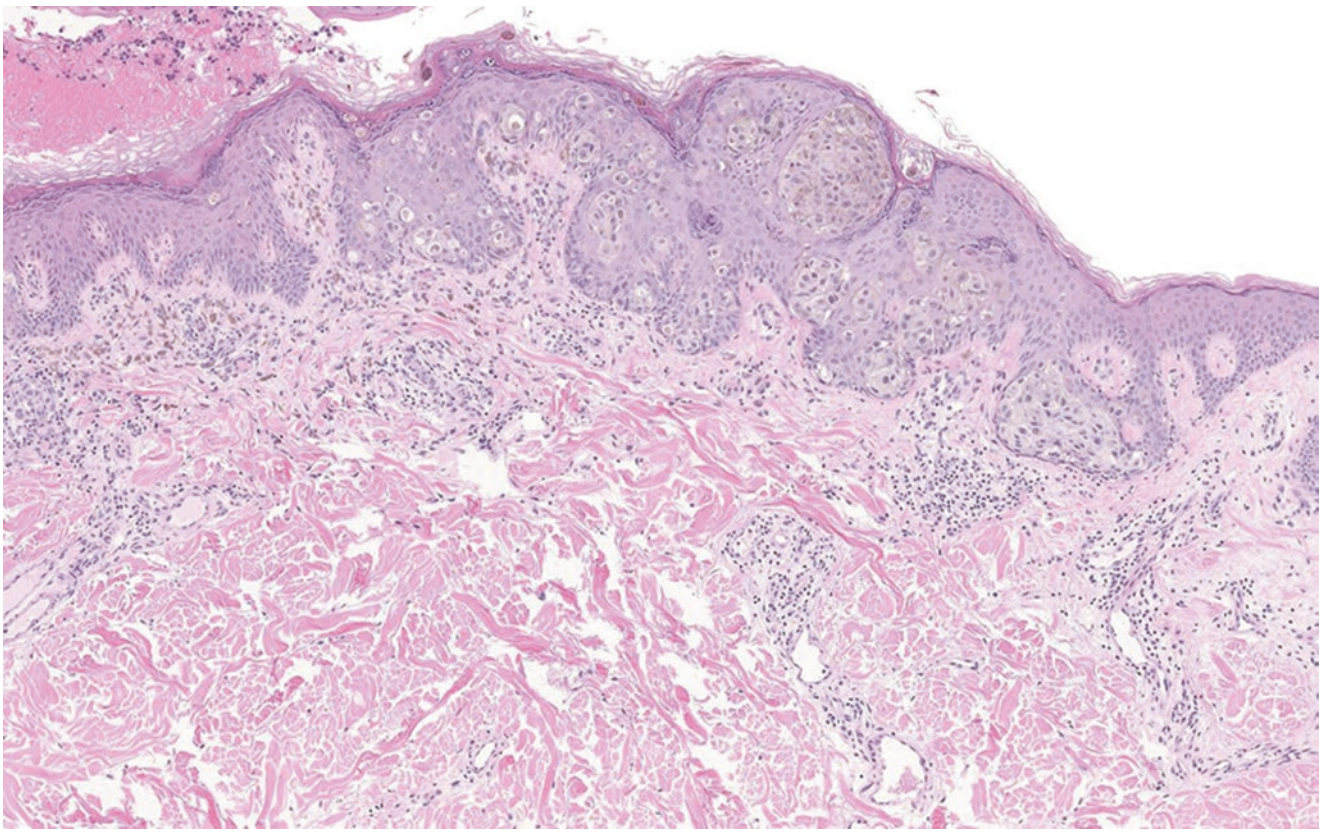


Fig. 7.67 Metastatic melanoma with epidermotropism. This patient is a 52-year-old male with a prior history of melanoma and metastasis, currently presenting with multiple, pigmented skin lesions. The lesion is small and it shows pagetoid upward migration with focal formation of nests

Melanoma of Childhood

Melanoma is a rare disease in pediatric patients; SEER data indicate an incidence of 0.7 per million, 2.2 per million, and 12.3 per million for ages <10, 10–14, and 15–19, respectively. It is not clear what, if any, role sun exposure plays in the development of melanoma in pediatric patients, with the exception of lesions in patients with xeroderma pigmentosum.

When a child presents with a pigmented skin lesion, it is frequently not considered to be melanoma due to the patient's age. However, as in adults, lesions that are irregularly colored, change color, rapidly increase in size, or have irregular borders should be considered for removal. The initial surgery is a conservative excision for pathologic evaluation, with possible subsequent definitive surgery based on pathologic findings. Notable findings in this population are the frequent presence of a precursor lesion and the occasional occurrence of metastases from relatively thin primary tumors.

Interestingly, a recent report has detected a decreased incidence of melanomas in children (<20 years of age) between 2004 and 2010 [157]. The authors propose as possible explanations about public health initiatives, decreased time spent outdoors, and increased sunscreen use. However, other epidemiological studies have not detected such a decreasing trend [158].

Histopathology

Many melanomas in children present unusual histologic findings. Out of 23 cases, a group of 5 small-cell melanomas was notable for localization to the scalp, significant thickness, and universally fatal outcome; 6 additional melanomas were histologically similar to conventional adult epithelioid cell melanomas. The other tumors were either "Spitz-like melanomas" eventuating in death or local metastasis (three cases) or so-called atypical Spitz tumors characterized by significant thickness and abnormal features including prominent cellularity and dermal mitotic figures (nine cases) [159]. This report underscored the frequent difficulty in predicting biologic behavior when confronted by atypical melanocytic neoplasms in children and in particular the difficulty of distinguishing melanoma from Spitz nevus.

In a review of 57 cases of melanoma in teenagers, the main features distinguishing them from Spitz nevus were large or irregular nuclei; greater Breslow thickness; fine, dusty melanin pigment; mitotic figures; pagetoid upward spread; and disproportionately large dermal nests [160]. Conversely, Spitz nevi in this population were characterized by the presence of Kamino bodies and dermal maturation. Less discriminatory features in favor of melanoma included cytologic atypia and dishesiveness of tumor nests deep in the lesion. Features favoring Spitz nevus included maturation, Kamino bodies, and edema and telangiectases of the stroma.

We have reviewed our experience on 137 melanomas arising in children (between 1992 and 2006) [161]. 39 children were younger than 10 years and 78 ≥ 10 years of age. There was almost equal sex distribution (50.4 vs. 49.6 %). The most frequent anatomic location was the trunk (35.1 %). A quarter of lesions (35 [26.1 %]) occurred on the head and neck area. Of the extremities, without counting the acral regions, the leg was more frequently involved than the arm (20 vs. 12.7 %). Only five lesions (3.7 %) were from hands and feet and 3 occurred in a mucosal site (2.2 %). Thirty-eight lesions had spitzoid features and those lesions, despite being thicker and having more frequent mitotic figures and positive sentinel lymph node, there were no differences regarding overall survival [162]. Interestingly, three patients were pregnant at the time of diagnosis [163].

Sixteen patients (15.5 %) had an associated nevus. The mean Breslow thickness was 2.23 mm with the majority of lesions (77 [73.3 %]) showing vertical growth phase. Twenty-four lesions (20.7 %) were ulcerated. A minority of lesions had vascular (9 [8.5 %]), perineural invasion (6 [5.8 %]), or regression (6 [5.8 %]). Superficial spreading melanoma was the commonest type. Spitzoid lesions, even though had thicker Breslow thickness and were more likely to have positive sentinel lymph node, showed slightly better survival rates than the non-spitzoid melanomas [164].

Univariate analysis showed significantly higher risk of metastases in patients with an unrelated malignancy and, regarding histologic features, in patients with lesions of nodular type, fusiform or spitzoid cytology, high Breslow thickness, vertical growth phase, high dermal mitotic activity and ulceration, and vascular invasion. Presence of an adjacent nevus or radial growth phase was associated with better prognosis. Twelve patients (10.3 %) died during follow-up. Decreased overall survival was significantly related to age ≥11 years, presence of an unrelated malignancy, high Breslow thickness, high Clark level, or presence of metastases at the time of the diagnosis. All patients who died were at least 11 years of age. Of those, 8 had shown metastases at the time of diagnosis. In multivariate analysis, higher Breslow thickness predicted increased risk of metastases while age ≥10 years and presence of metastases at the time of diagnosis were associated with decreased survival. Several studies have confirmed the significance of age at time of diagnosis, with a cutoff approximately of 11 years [165]. In another series, children with melanomas (not associated with congenital nevus) resulting in death had a mean age of 13.1 years at diagnosis [166].

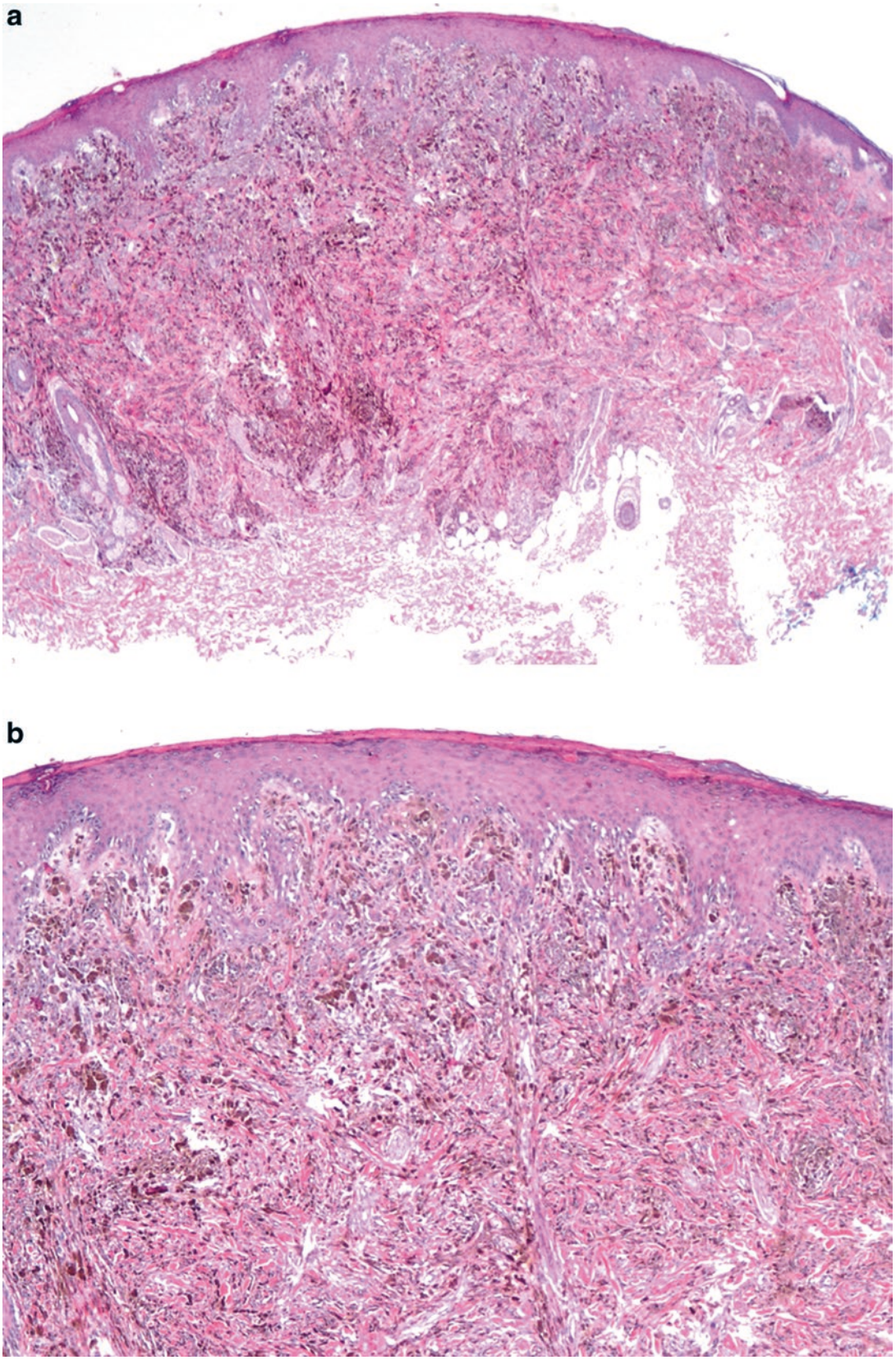


Fig. 7.68 Childhood melanoma. A 13-year-old male with a forearm lesion. The lesion appears wedge shaped but it is asymmetrical with irregular elongation of rete ridges. Diffuse pigmentation in the dermis with focal extension into the subcutaneous tissue (**a**). Focal single-cell intraepidermal proliferation (**b**).

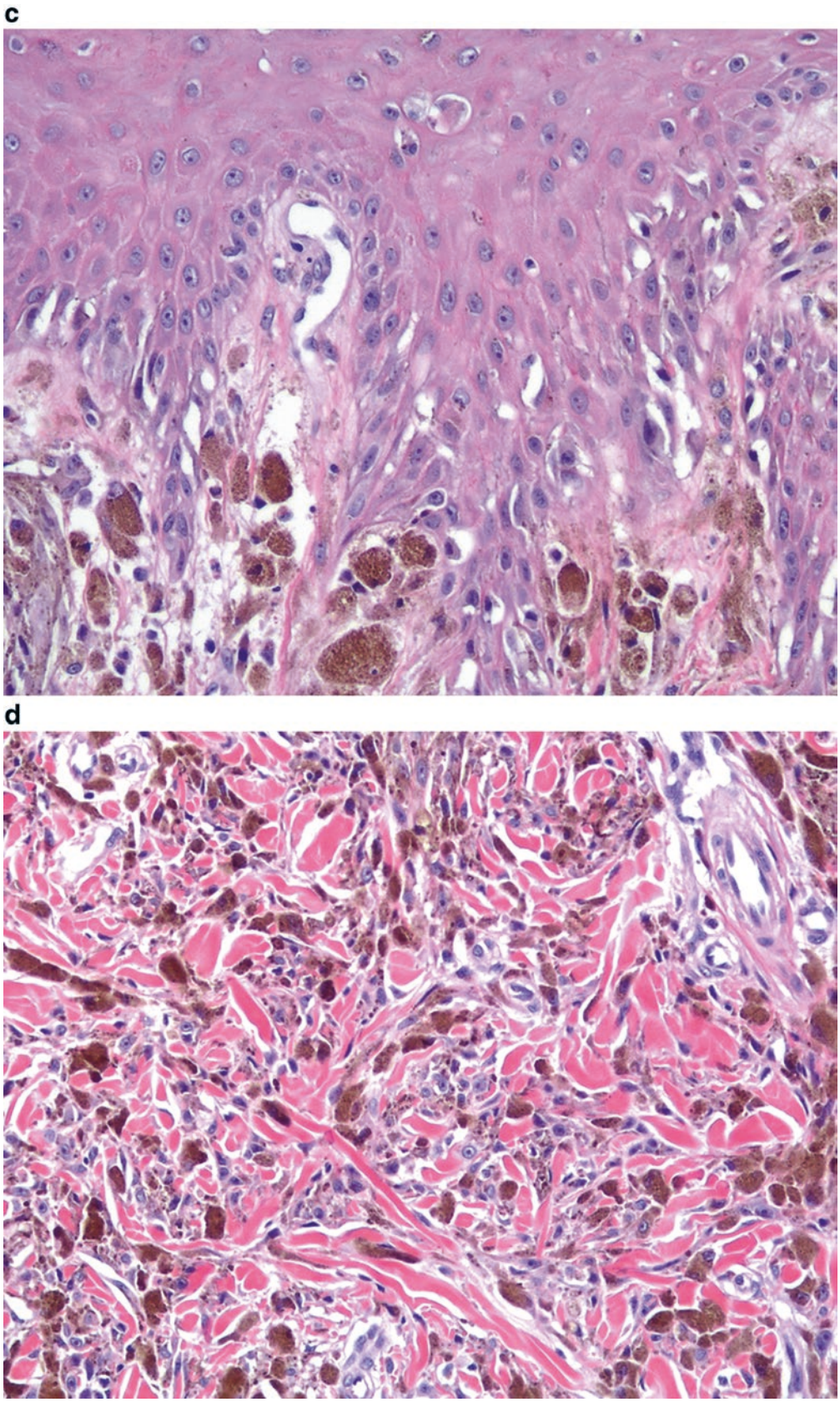


Fig. 7.68 (continued) Hyperchromatic, large cells, with focal pagetoid upward migration (**c**). Cytologic atypia of melanocytes among collagen fibers in the dermis (**d**).

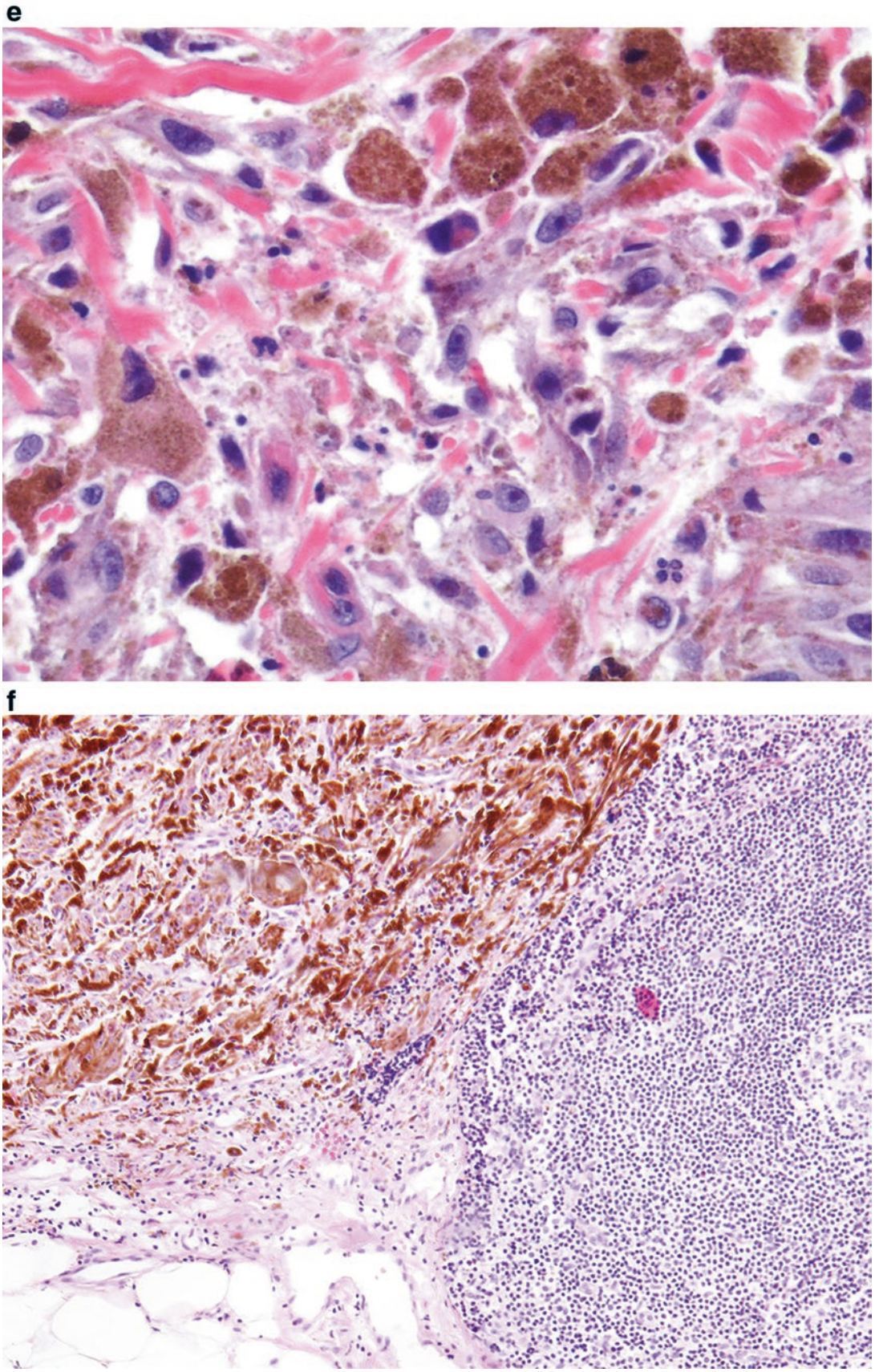


Fig. 7.68 (continued) Dermal mitotic figures (**e**). Metastatic melanoma to the axillary sentinel lymph node (**f**)

Spitzoid Melanoma

Spitz nevus is a benign lesion usually easily distinguished from melanoma. However, there is no single criterion to establish a definite distinction between Spitz nevus and melanoma [167, 168]. We support the hypothesis shared by other authors that these lesions span a broad histological continuum, extending from benign to malignant tumors, with a risk of malignancy proportional to how different the lesion is when compared to conventional Spitz nevi [169–171]. However, in contrast with some authors, we do not favor to extend the use of "spitzoid tumor" to include *all* lesions with spitzoid features. Rather, we recommend the use of the term "spitzoid tumor" or "spitzoid melanocytic proliferation" to those lesions in which we do not feel confident establishing a firm diagnosis of Spitz nevus or spitzoid melanoma.

Regarding clinical diagnosis, SM often have abnormal morphological features like size >5 mm, asymmetry, and irregular pigmentation. However, there are no uniformly reliable distinctive morphological attributes. Lesions in children/teenagers, located on the thighs, are more likely to behave in a benign fashion (i.e., to be Spitz nevi) than common melanomas do; however, such clinical features are not helpful in the majority of cases [172].

Histopathology

Histologically there is no universal agreement on the definition of "spitzoid." In our opinion, this term should be used in those lesions cytologically characterized by large epithelioid cells (round, large, occasionally multinucleated, with ground glassy, angulated, eosinophilic cytoplasm and intranuclear pseudoinclusions) or spindle cells (fusiform cells arranged in fascicles, with single, vesicular nucleus and eosinophilic nucleolus), usually arranged in nests or clusters, both in the epidermis and dermis [162]. We define spitzoid melanoma as a proliferation that retains some cytological attributes of Spitz nevus ("spitzoid" or "Spitz-like") with at least some features of melanoma (irregular junctional component with variably sized nests, dermal [deep] mitotic figures, possibly of atypical shape, pagetoid upward migration prominent or else at the periphery of the lesion, expansile pattern of growth in the dermis, and pushing border in the deep dermis). Supporting this definition of spitzoid melanoma is the fact that a number of such lesions were initially diagnosed as Spitz nevi and were only recognized as melanomas after recurrence or metastases.

In our series on 38 spitzoid melanomas in children (see also above), we have observed, as other authors have also reported, that the prognostic value of sentinel lymph node biopsy examination in spitzoid lesions in children is unclear [162, 173, 174]. In our series, 56 % of patients had positive SLND, but there were no cases of death in those patients [164]. Regarding the pattern of dissemination, among our 38 patients, there were 3 with metastases beyond the sentinel lymph nodes (to distant lymph nodes, lung, soft tissue, brain, liver, spleen, and humerus).

Immunohistochemistry may be helpful in this diagnosis [94]. As mentioned else in this book, there is a pattern of maturation in most Spitz nevi (change in expression of several markers from the top to the bottom of the lesion). HMB-45 antigen and Ki-67 are expressed in the intraepithelial and periepithelial components. A small subset of Spitz nevi may show diffuse labeling with HMB-45 throughout the lesion, similar to the pattern seen in blue nevi.

In contrast to any of these two patterns, spitzoid melanomas have patchy labeling with HMB-45 at multiple levels of the dermis, and there are areas in the deep dermis showing clusters of cells positive for Ki-67. Regardless of the absolute number of positive cells, nevi should have many fewer labeled cells at the base of the lesion than in the superficial areas (intraepithelial and periepithelial). It is important to remember that nevi from pregnant women may show dermal mitotic figures and slightly increased numbers of dermal cells positive for Ki-67 [175]. Another marker that has been suggested for the differential diagnosis between Spitz nevus and spitzoid melanoma is p16, since it is expressed in most benign melanocytes and only a fraction of melanoma cells [176, 177]. However, other studies have not supported its usefulness [178].

As explained extensively throughout this book, there are some settings in which FISH displays potential applicability. Among the various scenarios of challenging melanocytic lesions, spitzoid melanocytic proliferations are certainly the most controversial. However, when evaluating FISH results in spitzoid melanocytic tumors, it should be kept in mind that 5–10 % of Spitz nevi have a significant population of tetraploid cells (see below). Tetraploidy happens when melanocytes are stimulated to divide and hence replicate their DNA but do not divide as a result of a halting of the process by regulators of the cell cycle, and the cells undergo senescence. Tetraploidy can be seen in melanoma or Spitz nevi and is therefore nondiagnostic and it can give a false-positive FISH score. Thus, while this ancillary technique is useful, it is not a "magic bullet" for the diagnosis of melanocytic spitzoid neoplasms but represents an effective compromise between cost, technical complexity, and diagnostic accuracy. At present, molecular testing by FISH is not always clear-cut, and the lack of detection of any chromosomal or genetic abnormalities is not conclusive evidence that a lesion is benign. However, in morphologically ambiguous melanocytic lesions, the FISH assay adds further evaluation criteria that can assist the decision-making process about diagnosis and management.

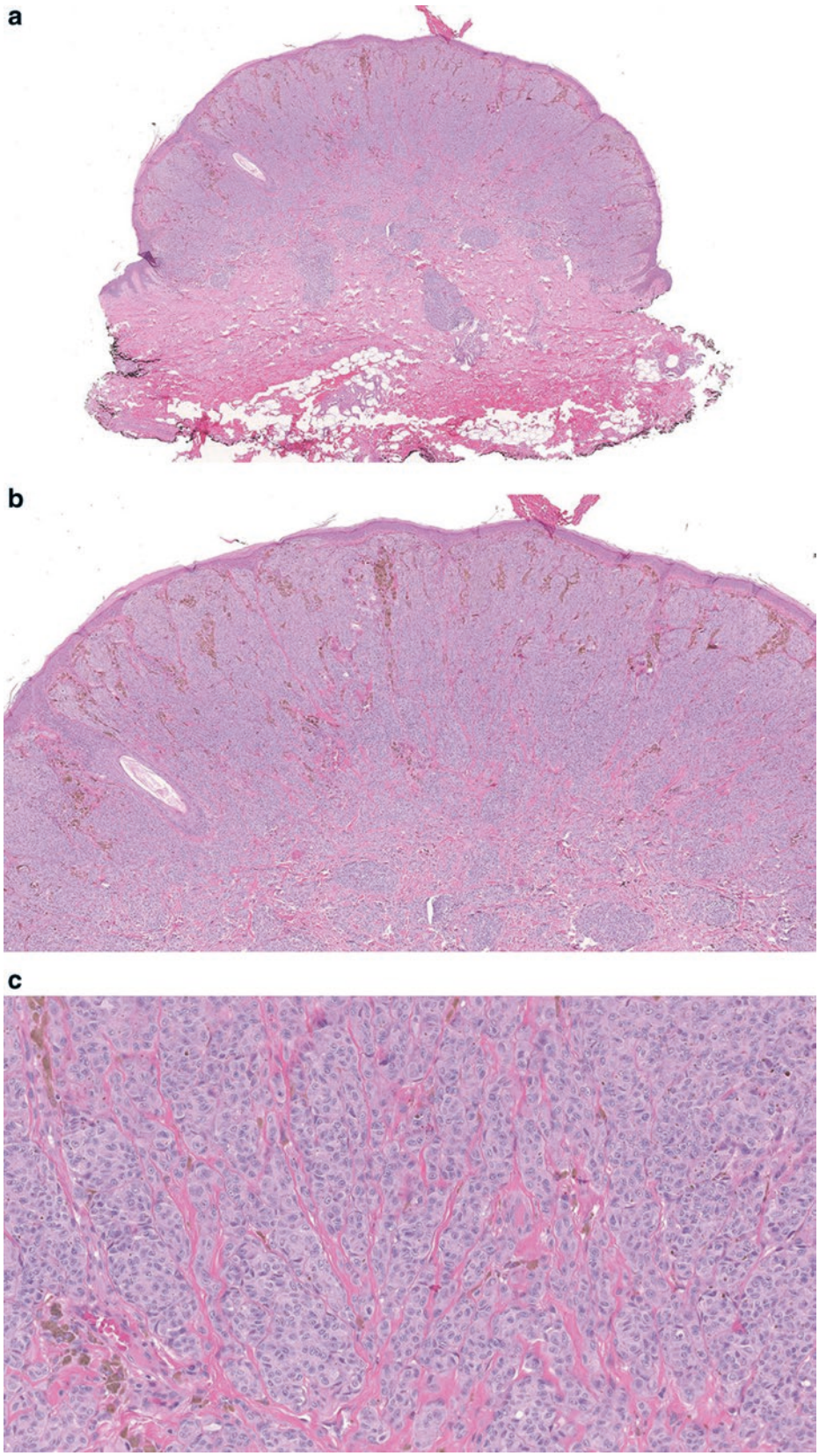


Fig. 7.69 Polypoid spitzoid melanoma. A 13-year-old male with a pigmented lesion on his trunk. The lesion is polypoid and well circumscribed reminiscent of a Spitz nevus (**a**). Expansile pattern of growth in the dermis with irregular elongation of rete ridges (**b**). Large epithelioid melanocytes in the dermis with very little collagen among melanocytes (**c**).

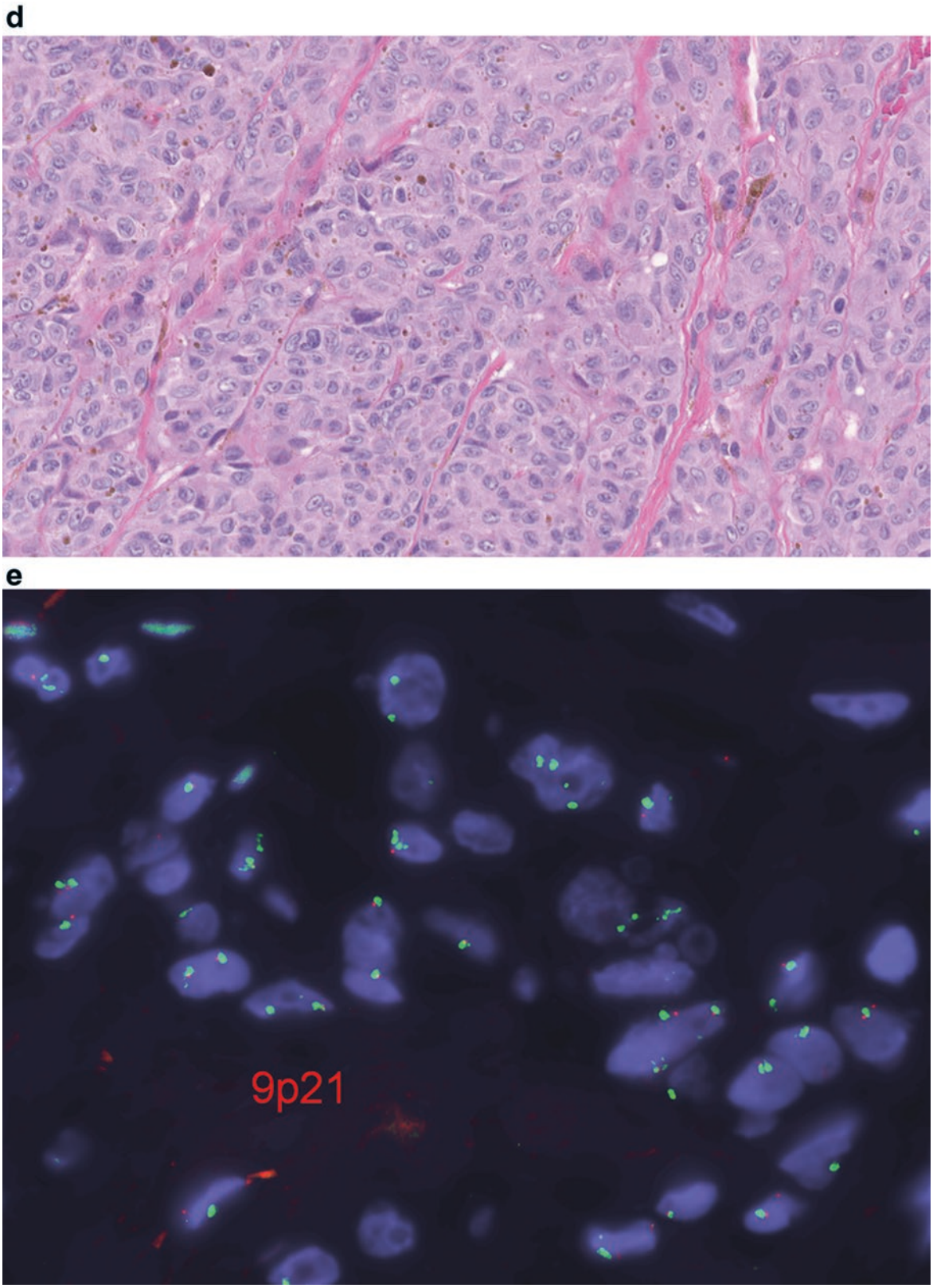


Fig. 7.69 (continued) The nests in the superficial dermis are confluent and irregular. The degree of cytologic atypia coupled with the mitotic figures in the deep dermis also supports the diagnosis of melanoma (**d**). FISH was positive on three of the four criteria, including homozygous loss of 9p21 (**e**). Courtesy of Dr. Julie Reimann (Miraca Life Sciences)

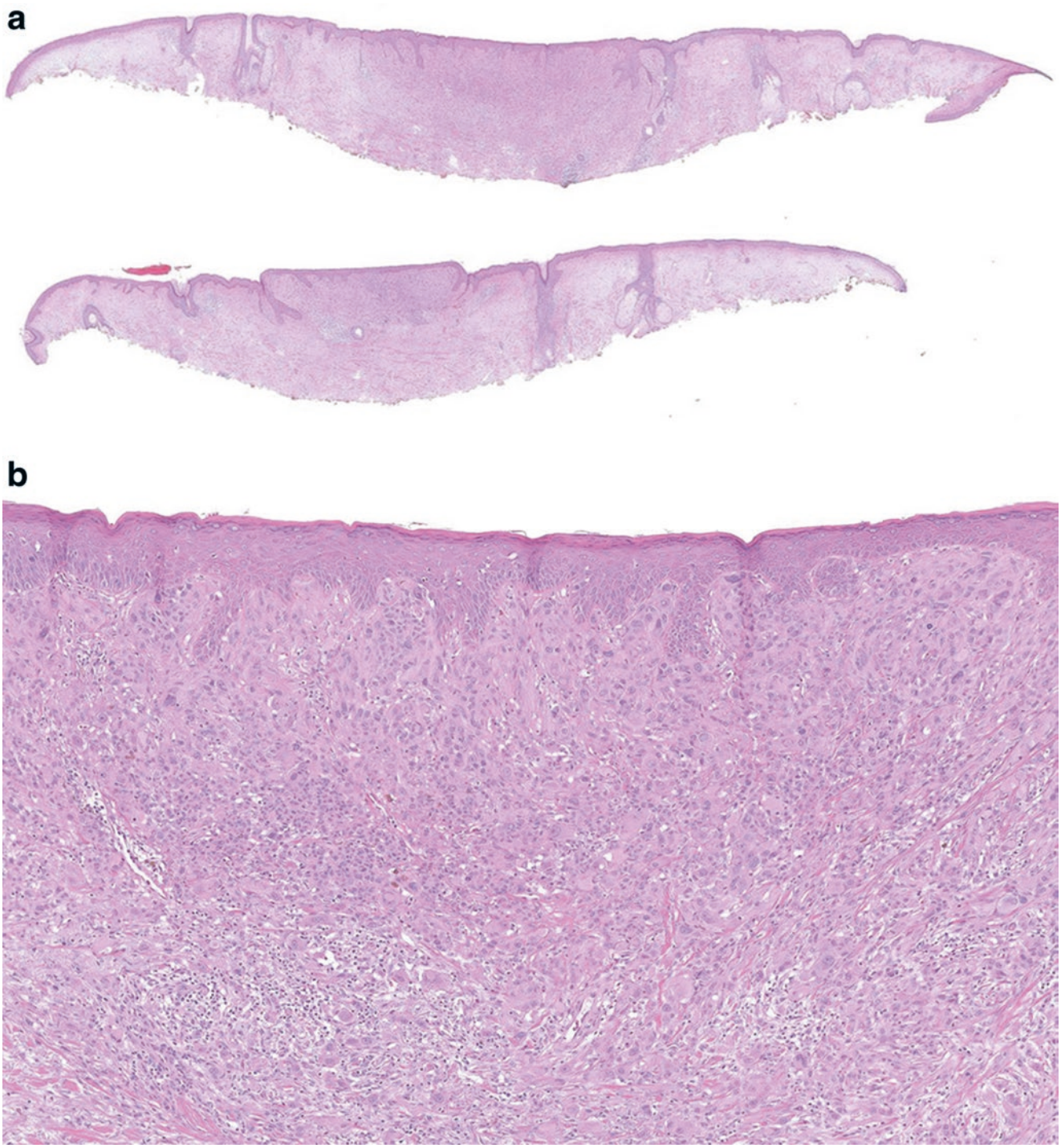


Fig. 7.70 Spitzoid melanoma. A 42-year-old female with a new lesion located on her arm. This melanocytic tumor is composed of an asymmetrical population of cells forming an ill-defined nodular area in the center (**a**). There is minimal pagetoid upward migration. The dermis has numerous epithelioid cells (**b**).

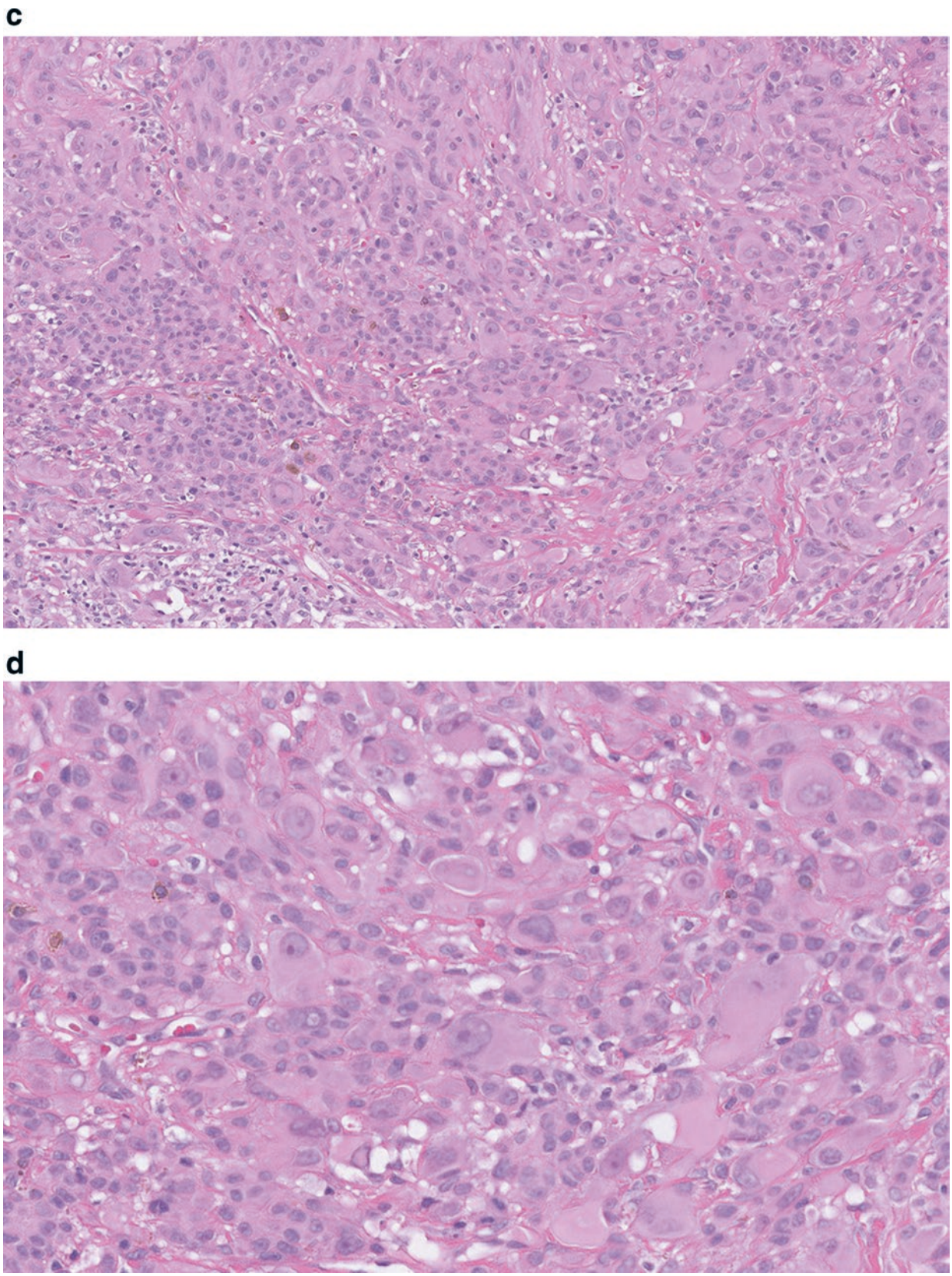


Fig. 7.70 (continued) Melanocytes are large and epithelioid without obvious dermal maturation, forming confluent nests and sheets of cells throughout the dermis. Higher magnification shows ample ground-glass eosinophilic cytoplasm (**c**). This case displayed five mitotic figures per mm2 (also located in the deep dermis) (**d**)

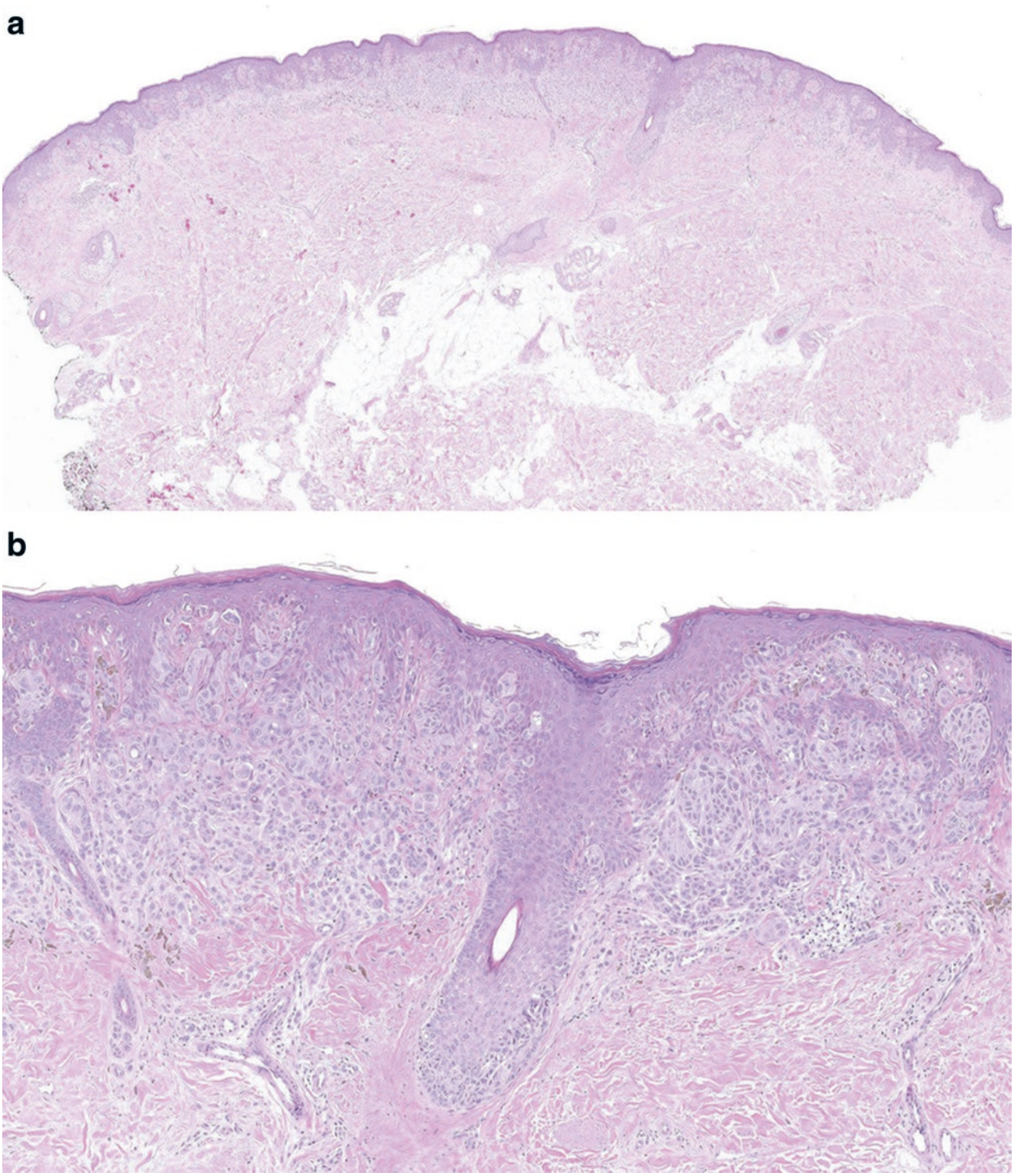


Fig. 7.71 Spitzoid melanoma. A 35-year-old male, with a lesion located on his back. There is elongation of rete ridges with focal bridging (**a**). Low magnification can mimic the features of a Spitz or dysplastic nevus (Spark nevus) (**b**).

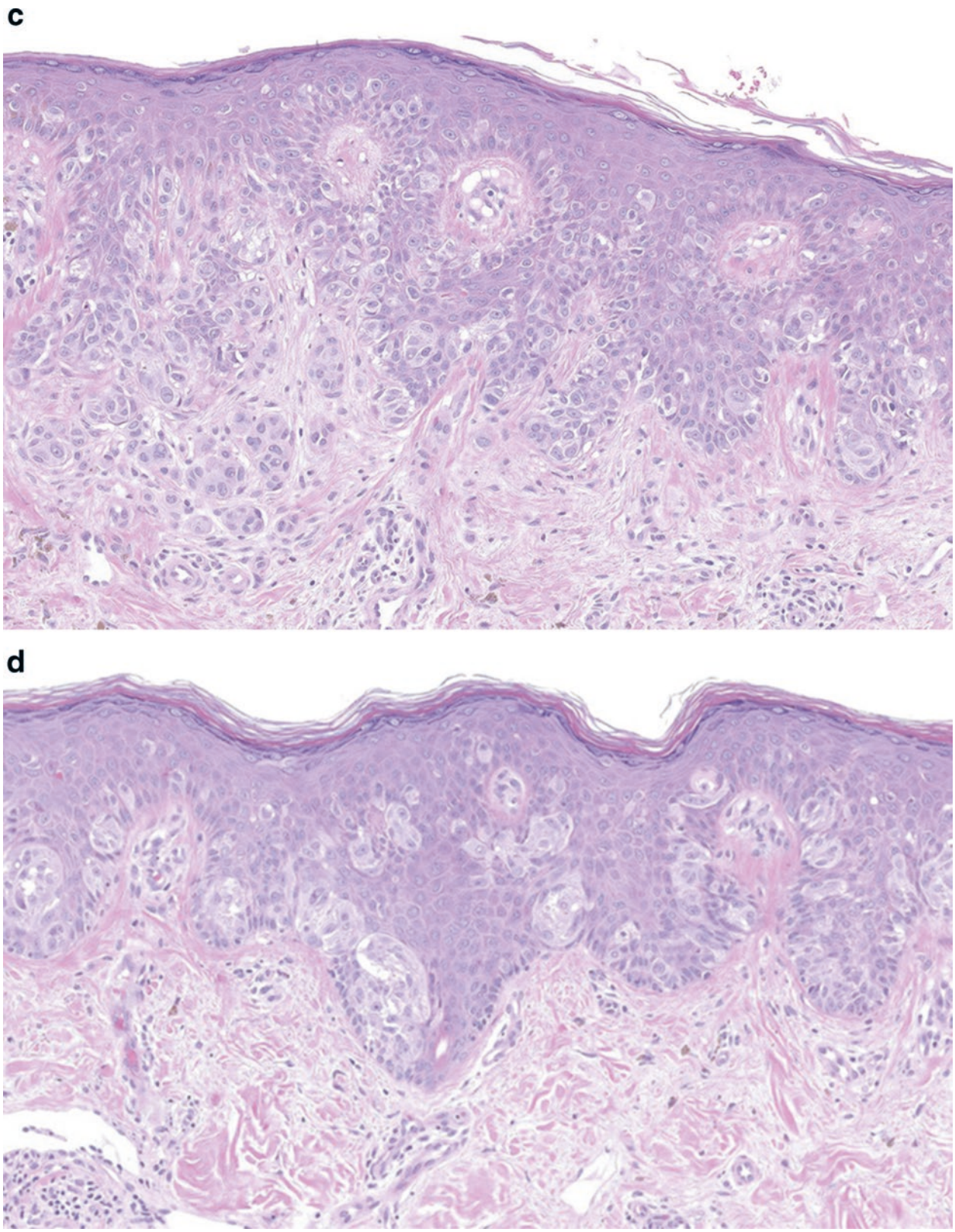


Fig. 7.71 (continued) Prominent nuclear pleomorphism with hyperchromasia along with scattered pagetoid upward migration, even at the periphery of the lesion, to a degree higher than one would expect in Spitz nevus. The same atypical cells are noted in the dermis (invasion) (**c**). The nests in the epidermis are both vertically and horizontally oriented along with many single melanocytes (**d**)

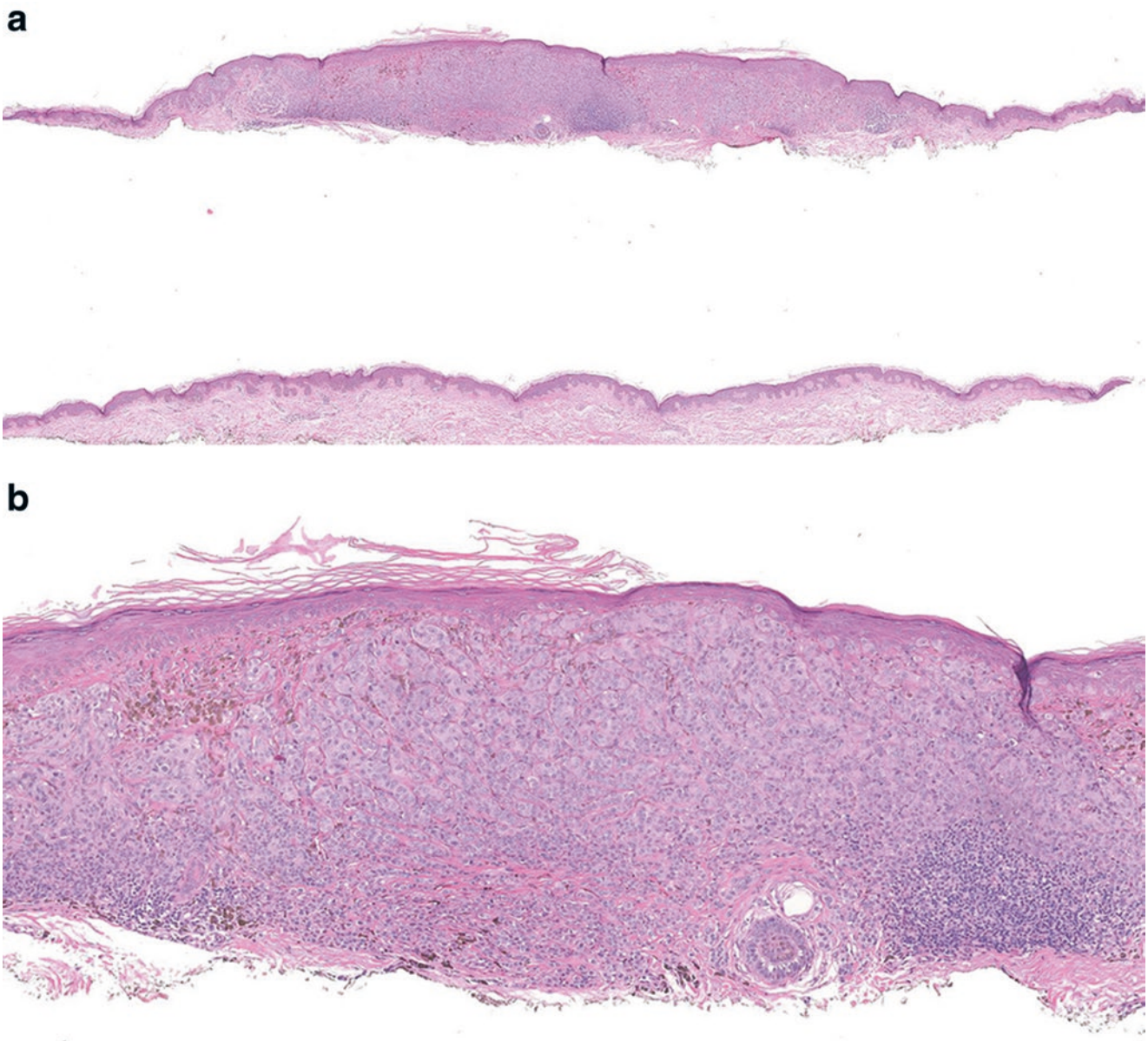


Fig. 7.72 Spitzoid melanoma. A 28-year-old female, with family history of melanoma presents with a pigmented lesion on her leg (**a**). The epidermis shows hyperplasia (the *left side* of the image), with irregular nests and epidermal consumption in the center of the lesion. The silhouette of the lesion is symmetrical and the cells appear to mature at the bottom at this power. Area of flattening of the epidermis. There are areas in the dermis with marked host response (**b**).

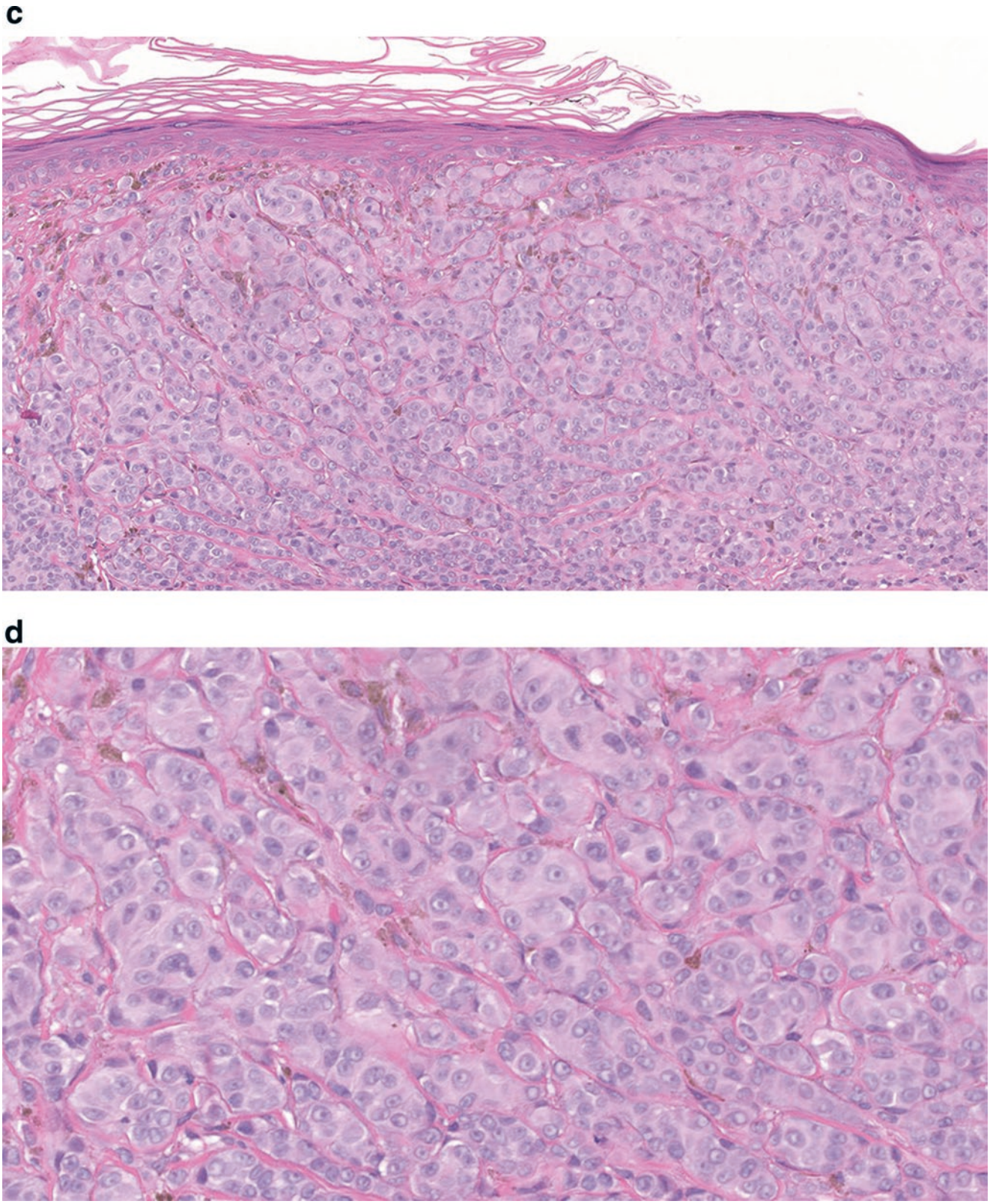


Fig. 7.72 (continued) Expansile pattern of growth in the dermis, with only rare cells in the epidermis (**c**). Higher magnification shows high degree of cytologic atypia that is beyond of what is accepted in a Spitz nevus. Mitotic figures were found throughout the lesion (7/mm2). FISH studies showed an abnormal pattern supporting the diagnosis of melanoma (**d**)

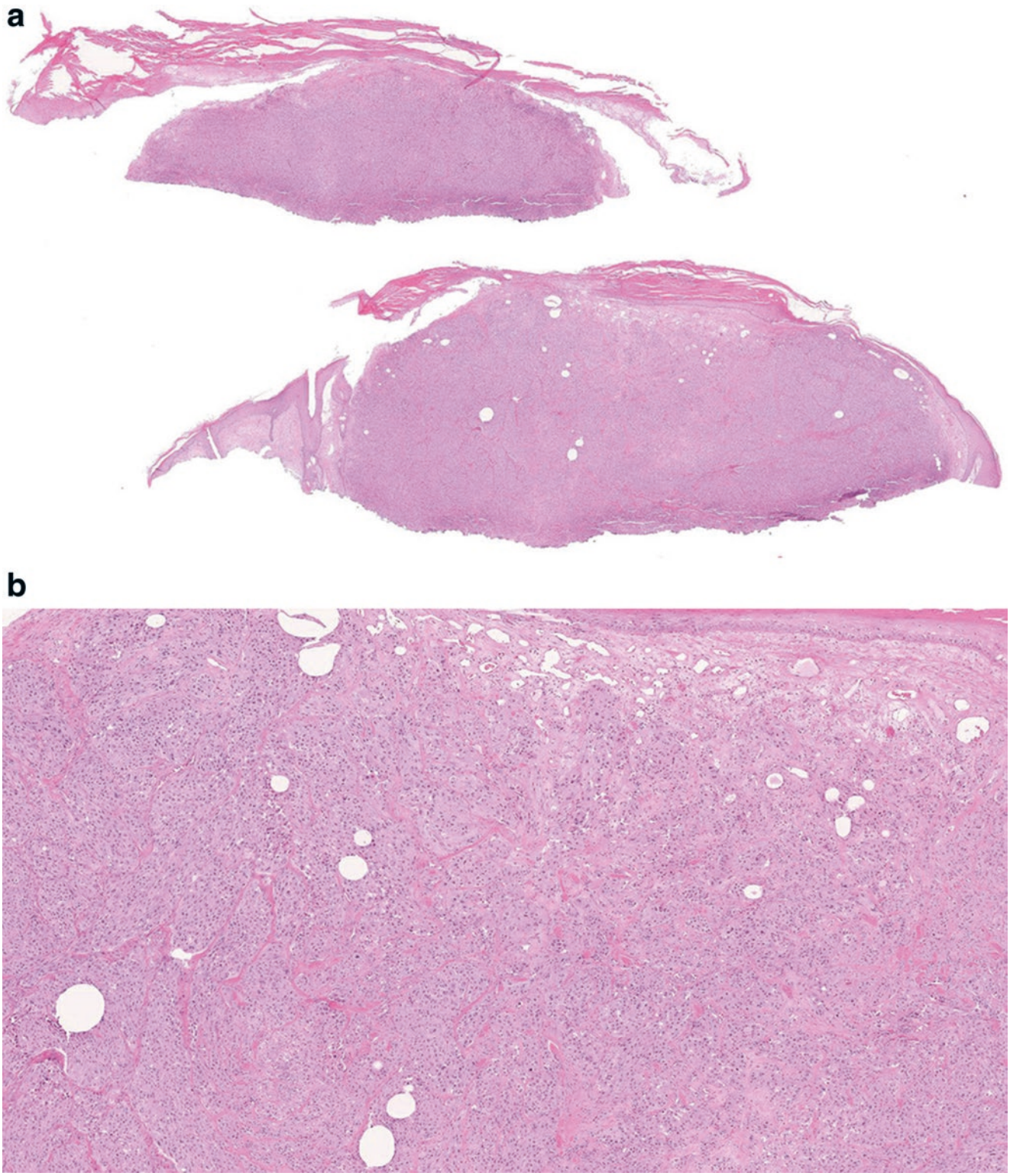


Fig. 7.73 Ulcerated spitzoid melanoma. A 45-year-old male, with a pigmented lesion on his shoulder. The lesion on low power shows a symmetrical architecture (albeit the bottom of the lesion is not available in this shaved biopsy), reminiscent of a Spitz nevus. The lesion is ulcerated and the adjacent viable epidermis is thinned and does not show a junctional component (**a**). The cells in the dermis form large confluent nests with very little collagen among them (**b**).

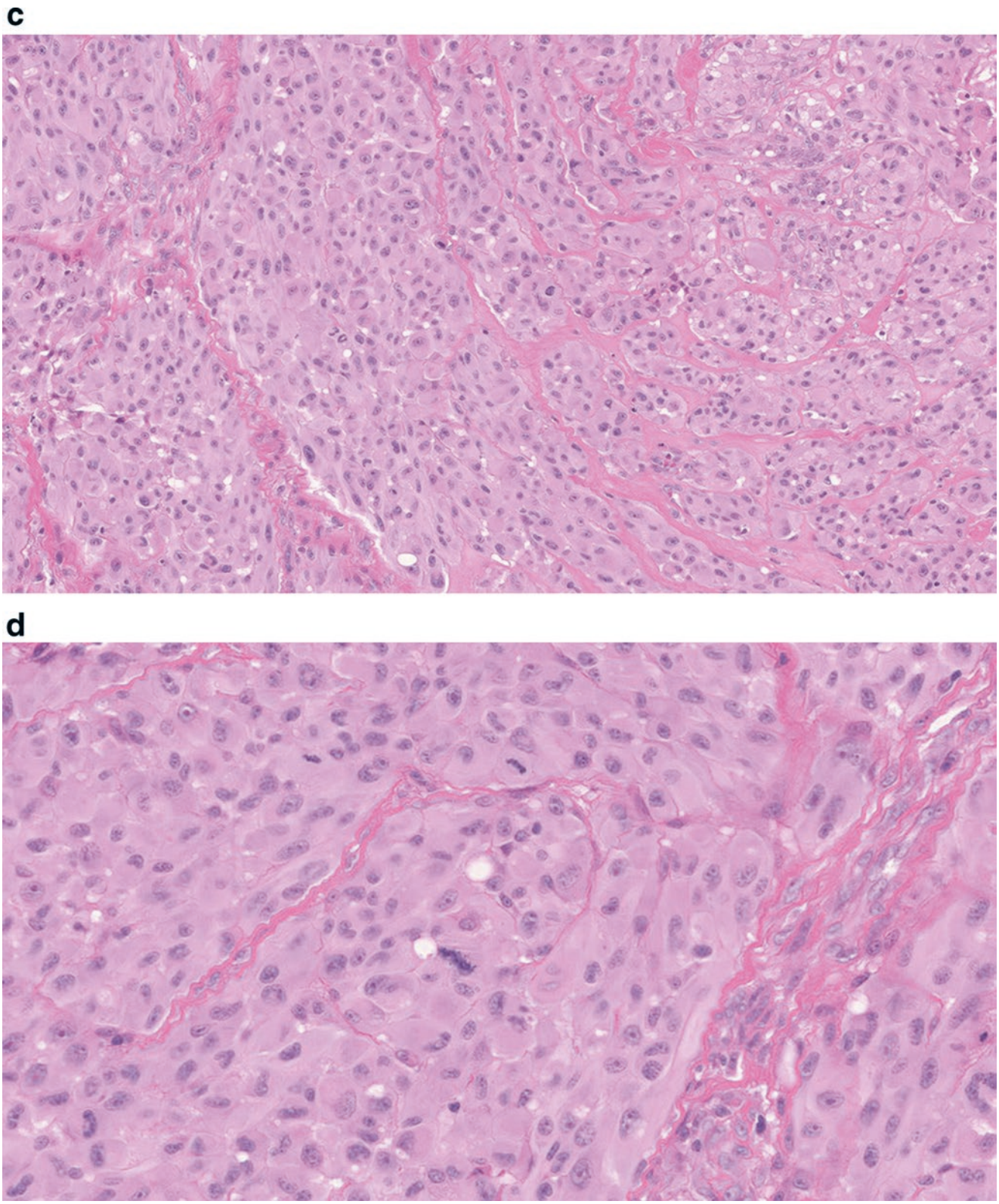


Fig. 7.73 (continued) Many of the epithelioid cells have ample, ground-glass eosinophilic cytoplasm (**c**). The lesion has easily identifiable mitotic figures, some of them with atypical shapes (**d**)

Melanocytoma (See Chap. 2)

Blue Nevus-Like Melanoma (See Chap. 2)

Comparative Genomic Hybridization and Fluorescence in Situ Hybridization in Melanoma

The diagnosis of melanocytic lesions is one of the most, if not the most, challenging areas in dermatopathology. As mentioned above, we believe that there is a spectrum of lesions going from obvious nevus to obvious melanomas, with some lesions in between that cannot be accurately classified as either benign or malignant by routine histology and immunohistochemistry studies. Recent molecular studies have shown that melanocytic proliferations display genetic differences between benign nevi and melanoma. It appears that most benign nevi are driven by point mutations and only exceptionally show gross chromosomal abnormalities. In contrast, tumor progression from a nevus to melanoma is associated with chromosomal instability resulting in gains, amplifications, and/or losses of specific chromosomal material, which can then be detected by genetic techniques.

Comparative Genomic Hybridization

Important studies have shown interesting data regarding the evaluation of melanomas and benign nevi with CGH [179]. CGH is based on the extraction of DNA from tumor cells to be amplified and labeled with a fluorescent probe and hybridized with a reference DNA. The advantage of CGH is its ability to simultaneously survey the entire genome of a tumor for relative DNA copy number changes (gains and losses) in a relatively high-throughput setting. Using this procedure CGH facilitates the identification of previously unknown tumor suppressors or oncogene in a single test. Authors have shown that the majority of melanomas had some type of chromosomal copy number aberration, only rarely seen in nevi. These findings showed not only that CGH may have utility as a diagnostic tool showing differences between these different types of melanocytic proliferations but also that the mechanism for genomic instability in these tumors may be different.

In one of the original studies, most (96 %) of melanomas carried chromosomal copy alterations, while only 13 % of the nevi studied showed chromosomal changes, primarily Spitz nevi with isolated gains in the entire short arm of 11p [180]. The utility of CGH as a diagnostic adjunct was explored in a series of subsequent studies. CGH has also been tested to define the genomic composition of large congenital melanocytic nevi and congenital melanocytic nevi containing different patterns of secondary melanocytic proliferations worrisome for melanoma [181]. This study showed that congenital nevi contained no abnormalities by CGH, whereas 100 % of the melanomas tested exhibited chromosomal abnormalities. In contrast, congenital nevi with expansile nodular proliferations with high cellularity showed whole chromosome copy number alterations rather than the partial chromosomal alterations seen in melanomas. Based upon these prior studies, CGH is now used in some centers as a diagnostic tool for histologically ambiguous melanocytic tumors.

While advances in CGH have provided understanding and ability to more thoroughly quantify the genomic composition of melanocytic lesions, there are important limitations in routine diagnosis. This technique is time consuming and requires relatively pure tumor population, possibly requiring microdissection. As a possible pitfall, CGH may yield a false-negative result in melanoma arising within a nevus in which the nevus component predominates. On the other hand, if an aberration is identified, then the findings are very specific, since the aberration must be highly representative of the examined cell population.

Fluorescence In Situ Hybridization

FISH is a molecular ancillary technique that can be used to detect chromosomal copy number aberrations. As mentioned above, CGH provides analysis of the entire genomic profile of a melanocytic proliferation. However, given its limitations, there was a critical need to develop a test with capacity to analyze smaller lesions and simple enough to be performed in laboratories. The process of formulating a FISH test for melanoma was initiated by examining CGH data for potential high-yield targets. Because of its relatively low cost, the possibility of performing the test on archival material, and its increasing availability in pathology laboratories, FISH has emerged as a preferred molecular technique to interrogate chromosomal abnormalities. In this test, short DNA fragments are hybridized, and overlapping wavelength spectrums of the currently available fluorochromes limit to a maximum of 4 the number of probes that can be concurrently hybridized in a single experiment. FISH offers the possibility of examining individual tumor cells in different areas of a lesion and of correlating the results with tumor morphology under conventional light microscopy. Each fluorescently labeled fragment of DNA that hybridizes to a tumor nucleus will appear as a distinct fluorescent dot. Each dot identifies a single copy of the chromosomal locus with a homologous DNA. The number of dots per nucleus with a specific fluorescent color can then be detected either manually or with software designed for automated analysis. Because of the variability of signals, a specific number of tumor cells must be examined in each experiment and strict quality control measures must be implemented. Gerami and colleagues

developed the initial conventional melanoma FISH assay [182–187]. These authors initiated the process of formulating a FISH test for melanoma by examining CGH data for potential high-yield targets. A combinatorial analysis of the CGH data set of Bastian and colleagues yielded regions on 8 different chromosomes, namely, chromosomes 1, 6, 7, 9, 10, 11, 17, and 20, which in combination, yielded the best discriminatory tool for distinguishing between melanomas and nevi. FISH probes targeting these regions were assembled, and if the chromosomal locus was commonly gained, then a well-described oncogene from the region was selected as the target of the FISH probe. Conversely, if a chromosomal region was commonly deleted, then a tumor suppressor gene was selected as the target of the FISH probe. The FISH probes were arranged in panels consisting of either 3 or 4 probes, with each probe within a panel labeled with a different distinct fluorophore. Each panel was hybridized to overlapping subsets of a group of melanomas and nevi, and from this study, a combination of four probes was identified as having the best combined discriminatory ability for distinguishing melanoma from benign nevi. This panel consisted of RREB1 (6p25), MYB (6q23), centromere 6, and CCND1 (11q13). The four-probe panel was applied to an additional cohort of melanomas and benign melanocytic nevi to determine the ideal parameters and signal cutoffs resulting in the best sensitivity and specificity (UCSF). From this analysis, the following four FISH criteria were identified [1]: if more than 38 % of enumerated cells contained more than two signals for CCND1 (11q13) or [2] if more than 55 % of nuclei contained more signals for 6p25 than for centromere 6 or [3] if more than 40 % of nuclei contained fewer signals for MYB (6q23) than for centromere 6 or [4] if more than 29 % of cells had more than 2 RREB1 (6p25) signals, then a case would be considered as positive for melanoma. Any one of these changes indicated a positive FISH result. In order to validate the UCSF cutoff parameters, they were then applied to a third cohort of melanomas and nevi at Northwestern University, and this resulted in the correct classification of melanomas and nevi for sensitivity of 86.7 % and a specificity of 95.4 %, respectively. This test has been patented by and is commercialized by Abbott Molecular. Also, it is important to remember that a critical point when interpreting FISH is the variability in the thresholds employed by different institutions in a positive FISH result. The cutoffs used by the centers at the UCSF and Northwestern University are slightly different than that of Neogenomics. The generally higher thresholds used by UCSF and Northwestern University compared to Neogenomics reflect an amalgamation of differing methodologies but result in a different sensitivity and specificity [184].

There are some important advantages offered by FISH over CGH. FISH only analyzes the composition of specific genomic loci, provides the investigation of the discrete tumor cells, and does not require a pure population of tumor cells for this. However, FISH relies on the ability of a counterstain to identify the neoplastic cells, and it creates problems when evaluating intraepidermal proliferations or dermal-based lesions with a nevoid morphology in the background of an associated lymphocytic infiltrate. Another common issue in the initial FISH study was the presence of polyploidy among the benign melanocytic nevi yielding a false-positive result. On the other hand, it is important to keep in mind that FISH is pretty much the only technique that can be used in superficial melanocytic neoplasms or lesions in which the malignant component may be composed of a proportion of the overall cell population, as well as large bulky tumors.

There have been a few studies to compare FISH and CGH. With FISH one can identify even small clones of chromosomally aberrant neoplastic cells within a larger tumor, while CGH can detect chromosomal abnormalities only if they involve a high percentage of cells.

The diagnostic application of FISH has been also studied in different settings, including subtypes such as blue nevus-like melanomas compared to blue nevi, and in this distinction FISH reportedly has a high sensitivity (90–100 %) and specificity (100 %) [188]. FISH has also been analyzed in differentiating lentiginous nevus of the elderly from melanoma in situ, with a high sensitivity (84–88 %) and specificity (100 %) [149]. In one study, FISH reliably distinguished nevoid melanoma from benign nevi with a reported 100 % sensitivity and specificity [128].

The use of FISH in the diagnosis of histologically borderline melanocytic lesions has been studied. An important study compared large number of ambiguous melanocytic tumors with and without evidence of disease recurrence at 5 years and found that FISH studies improved the sensitivity and specificity of the diagnosis [189]. In this study, authors used the same criteria developed in the multi-institutional study from UCSF and Northwestern University for determining a positive or negative FISH result. Authors concluded that the value of this FISH test is to add a reproducible demonstration of malignancy to the histopathological diagnosis, especially in ambiguous melanocytic tumors. A different study analyzed ambiguous melanocytic tumors using clinical outcome as the final end point measure and concluded that FISH assay did not reach a clinically useful sensitivity and specificity [190]. However, in this study authors used a different set of criteria developed earlier and perhaps that is why they reported a lower correlation between FISH results and histologic analysis of unambiguous nevi and melanomas than other validation studies. The outcome these studies has demonstrated that when performed as described in the original validation studies and using the same cutoffs, the Abbott FISH test has potential to be a useful adjunct test in evaluation of ambiguous melanocytic neoplasms. However, one

needs to remember that controversial melanocytic neoplasms are very difficult to diagnose and have a wide morphological spectrum, and there are no established and validated case sets of histologically ambiguous lesions that could serve as a reference; thus, to study these lesions with known long-term follow-up is important but have their limitations. In one of the most important studies that analyzed FISH testing on the assessment of morphologically ambiguous melanocytic lesions, authors studied a large number of ambiguous melanocytic lesions [191]. In this study, of the 630 cases that tested negative by FISH, the final diagnosis was benign in 78 % cases, ambiguous in 14 %, and malignant in 8 %. A positive FISH result was observed in 124 cases, with a final diagnosis of melanoma in 94 % of cases.

Other studies have analyzed a common encountered problem in dermatopathology that is the distinction between spitzoid melanomas from Spitz nevi. These studies have suggested a relatively high sensitivity and specificity for conventional FISH in differentiating spitzoid melanomas from Spitz nevi. One study assessed spitzoid melanomas and Spitz nevi by conventional FISH and showed a sensitivity of 87.5 % and a specificity of 100 % [192]. However, other studies have demonstrated that conventional FISH probes (6p25, 6q23, cen6, and 11q13) showed a sensitivity of only 70 % [193]. In this particular study, authors defined the homozygous deletion of 9p21 as a relatively frequent occurrence in spitzoid melanoma. However, other authors have indicated that 9p21 deletion may not be completely predictive of aggressive behavior (i.e., melanoma) [194]. Homozygous 9p21 loss was present in 41 % of cases tested. By combining the standard melanoma FISH assay with the 9p21 FISH assay, a combined sensitivity of 85 % was found in this study. Among these cases tested with 9p21, there were seven cases that were negative by the standard melanoma FISH assay but that were positive by 9p21, suggesting that the 9p21 assay may be highly complementary to the standard melanoma FISH assay. Hence, in this study, authors validated the efficacy of 9p21 as a diagnostic FISH assay in melanoma and demonstrated its complementary effect to the standard FISH assay [193].

One of the main limitations of the first-generation FISH assay is the presence of polyploidy/tetraploidy in a subset of Spitz nevi. Tetraploidy is the balanced gain in chromosomes that results after a melanocyte undergoes a cycle of DNA replication without subsequent cell division. In 5–10 % of lesions, they are present frequently enough to cause a false-positive result with the current FISH criteria if they are not identified as tetraploid cells by the interpreter of the assay. Tetraploid cells can be readily identified by the pattern of increased copy number changes affecting all four probes. From a genomic standpoint, melanomas are more typically aneuploid, typified by amplifications or deletions in discrete regions of chromosomes. The FISH assay does not discriminate between gains in all of the chromosomes from gains in discrete regions of chromosomes; it detects changes in copy numbers at specific loci. Thus, tetraploidy is the most common source of false positivity among histopathologically benign lesions, as tetraploidy would result in balanced gains in both 6p25 and 11q13 without altering the ratio between 6p25 or 6q23 and cen6. The presence of tetraploid cells is not diagnostic of Spitz nevus, as they can also be found in melanomas, including spitzoid melanoma, and other atypical nevi.

Recently, it has been proposed the use of a test with a 23-gene signature that promises to help in the differential diagnosis between nevus and melanoma [195].

In our group we have recently reported our experience with FISH and how to apply it to the diagnosis of melanocytic lesions [196]. We propose that FISH should be used in correlation with histologic and immunohistochemical findings and not as the only diagnostic criterion.

Mass spectrometry: The group of Yale University has recently reported that MALDI (matrix-assisted laser desorption/ionization) can detect differences between Spitz nevus and spitzoid melanoma [197]. Interestingly, the proposed differentiating algorithm includes five peptides, being two of them vimentin and actin (two proteins extensively distributed in most mammalian cells). Furthermore, the test was able to separate most nevi from melanoma just by analyzing the stroma immediately adjacent to the lesional cells. Additional studies are needed to confirm these findings.

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