Pathology of Pigmented Skin Lesions

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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

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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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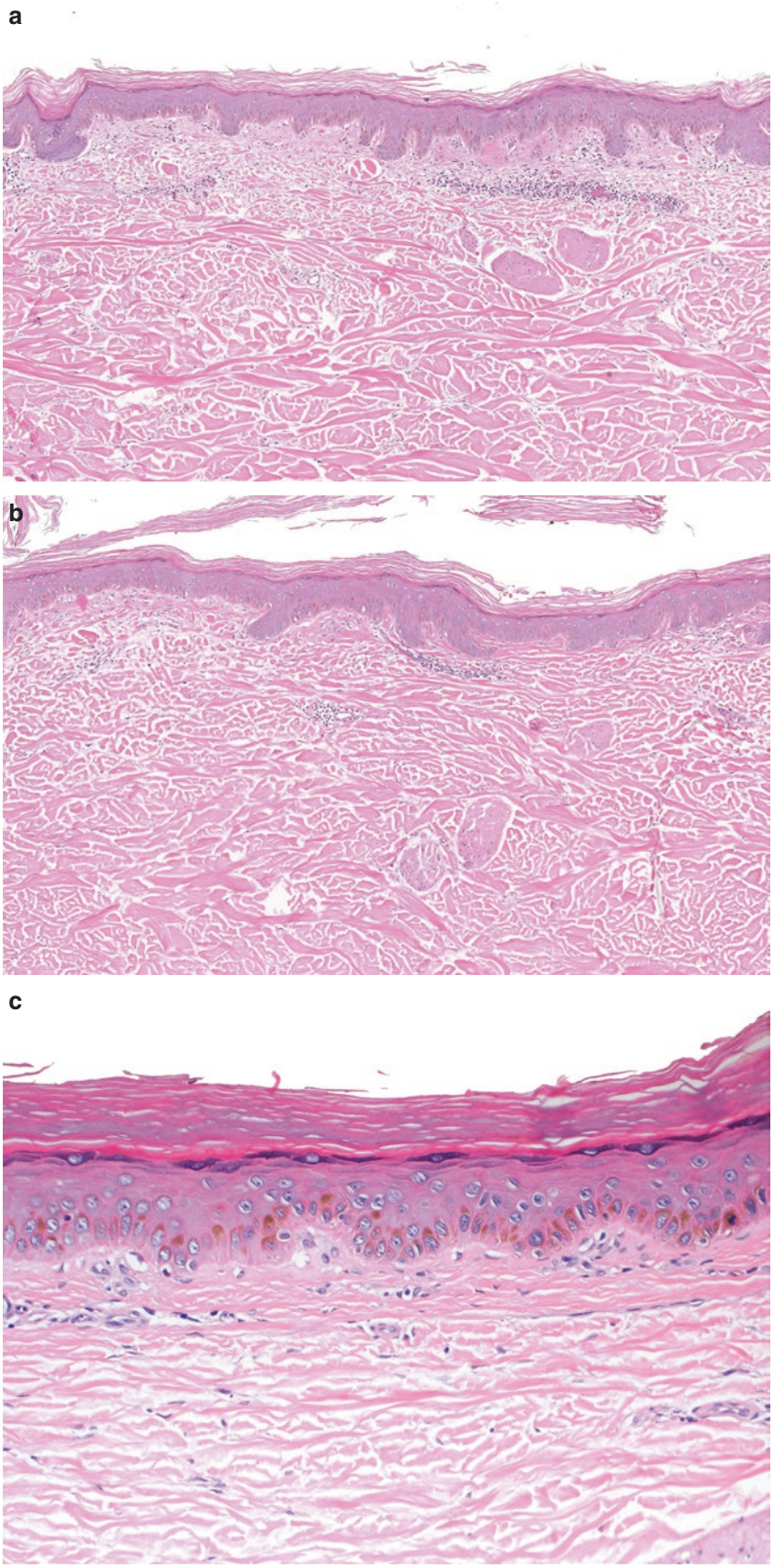

Fig. 1.1 Ephelides. Note the pigmented basal keratinocytes and the decreased number of melanocytes within epidermis (**a**). Higher magnification showing melanocytes with rare melanosomes (**b**). Observe the lack of melanocytes (**c**)

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

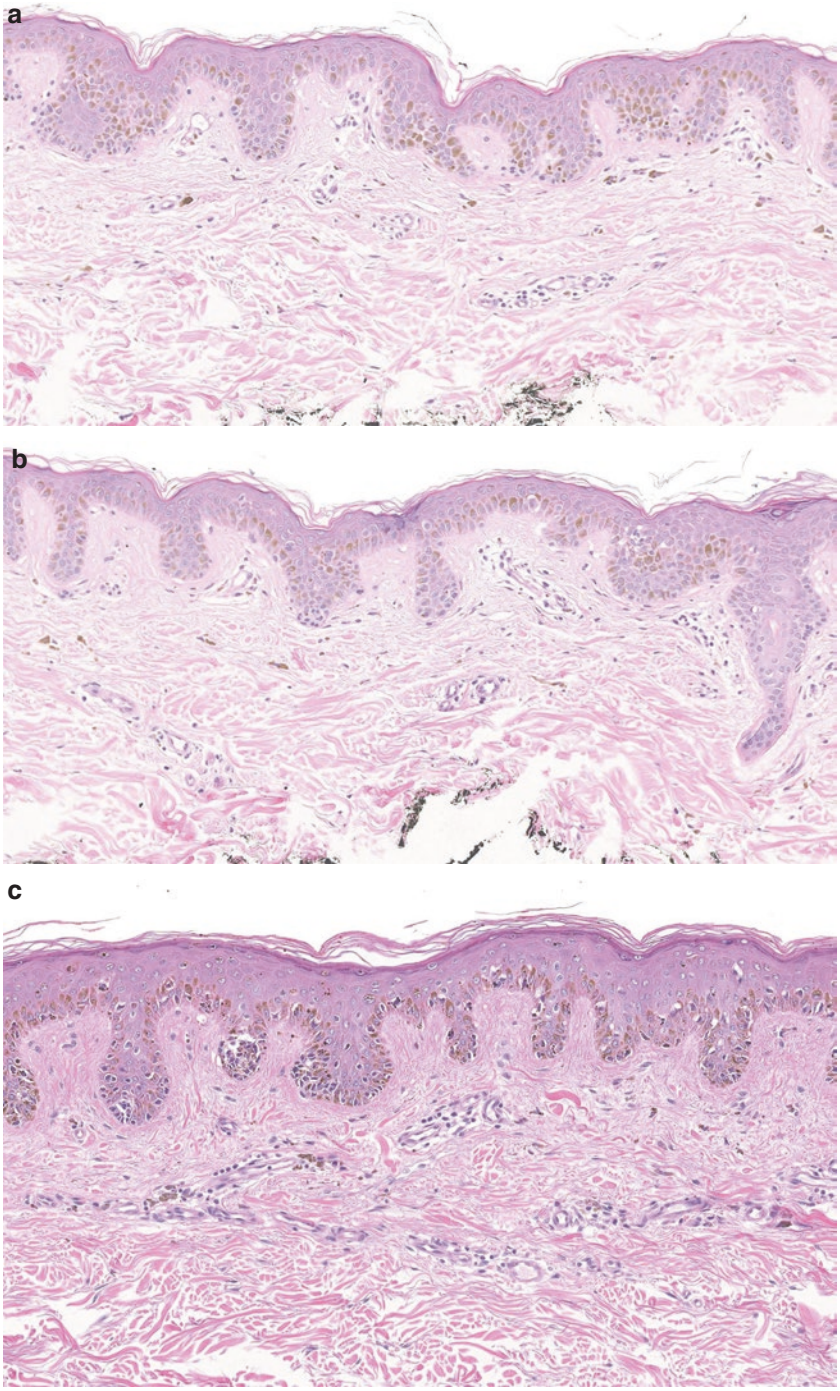

Fig. 1.2 Lentigo simplex. The lesion shows elongation of rete ridges and pigmented keratinocytes with absence of solar damage (**a**). The pigment varies within epidermis and can be prominent in some cases (**b**). An early transition into an early junctional nevus (jentigo) (**c**)

(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).

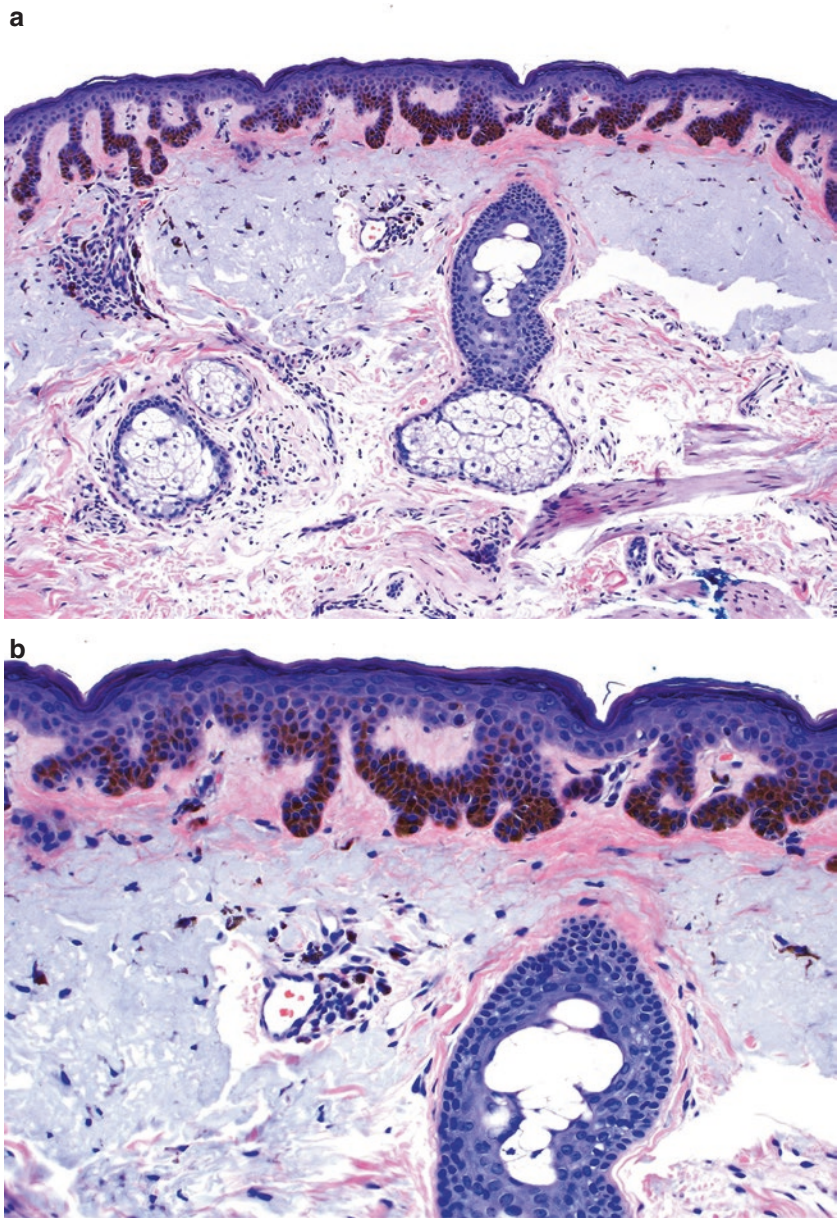

Fig 1.3 Solar lentigo. Elongated and pigmented rete ridges with prominent solar elastosis (**a**). High power showing pigmented retes and the lack of melanocytes (**b**)

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

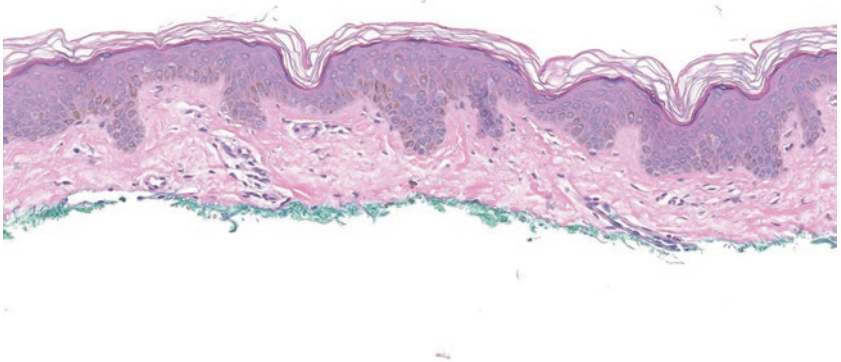

Fig 1.4 Solar lentigo with subtle intraepidermal melanocytic hyperplasia. Note the focal intraepidermal melanocytic hyperplasia most compatible with chronic sun damage

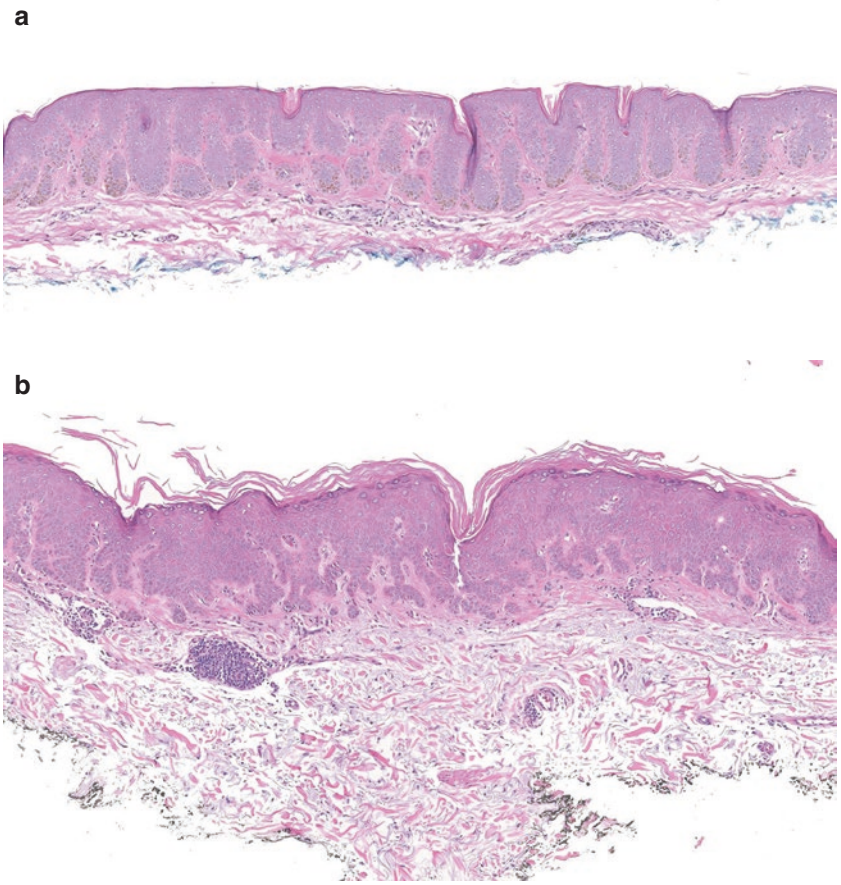

Fig 1.5 Solar lentigo with early progression to seborrheic keratosis. The lesion shows elongated rete with acanthosis in the background of solar damage (**a**). The retes are elongated and have pigmented keratinocytes in the basal layer. Prominent solar elastosis is present (**b**)

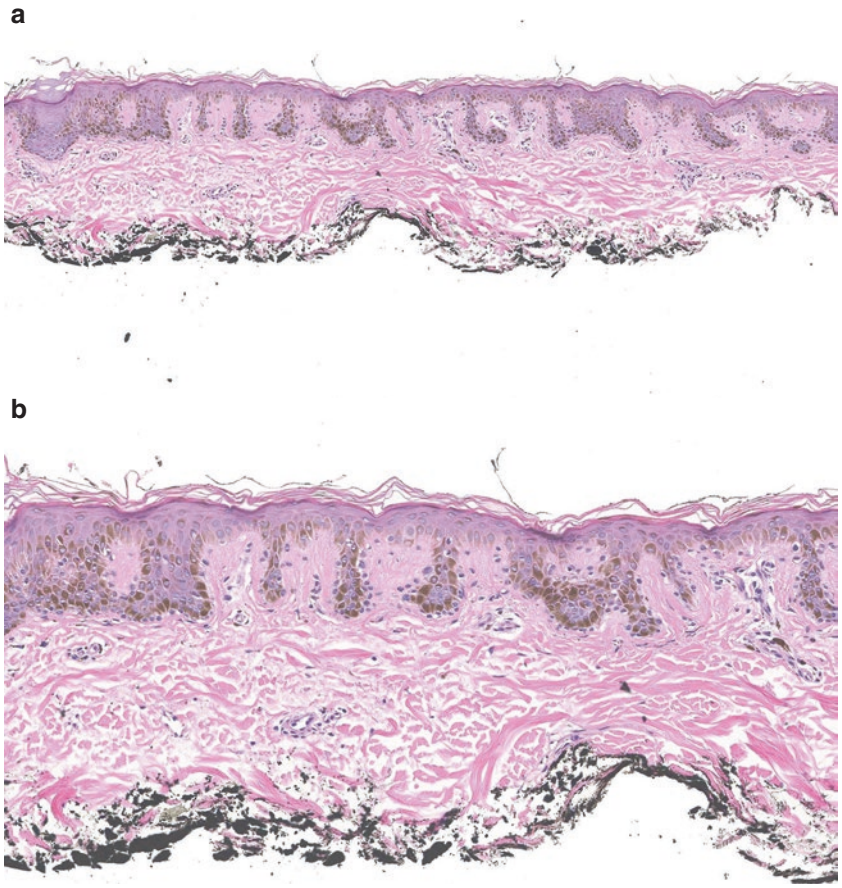

Fig 1.6 Solar lentigo with early junctional nevus ("jentigo"). This lesion shows classic features of a solar lentigo along with superimposed melanocytes forming small nests in the junction (**a**). High power showing fusion of the rete along with rare melanocytes within epidermis ("jentigo") (**b**).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

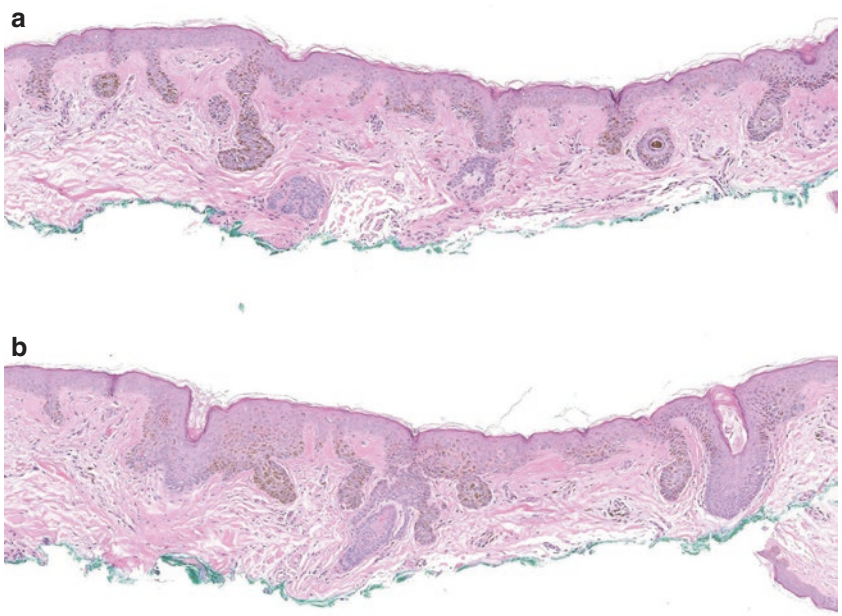

Fig 1.7 Solar lentigo with early junctional nevus. Another example with slight higher density of intraepidermal melanocytes and forming small nests (**a**). Higher magnification showing the rare and banal-appearing nests (**b**)

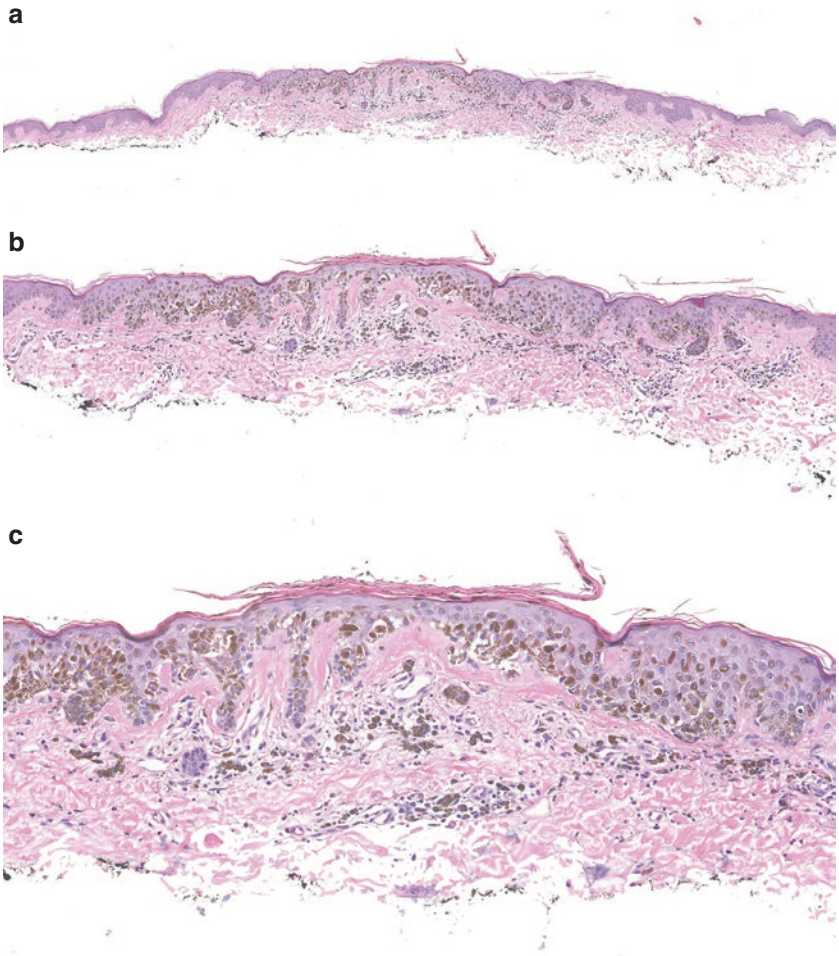

Fig 1.8 Ink-spot lentigo. Small lesion with pigmented epidermis and melanophages in dermis (**a**). Note the lentiginous hyperplasia of the epidermis and marked skipping hyperpigmentation of the basal layer (**b**). There is minimal increase in the number of melanocytes along with scattered melanophages 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.

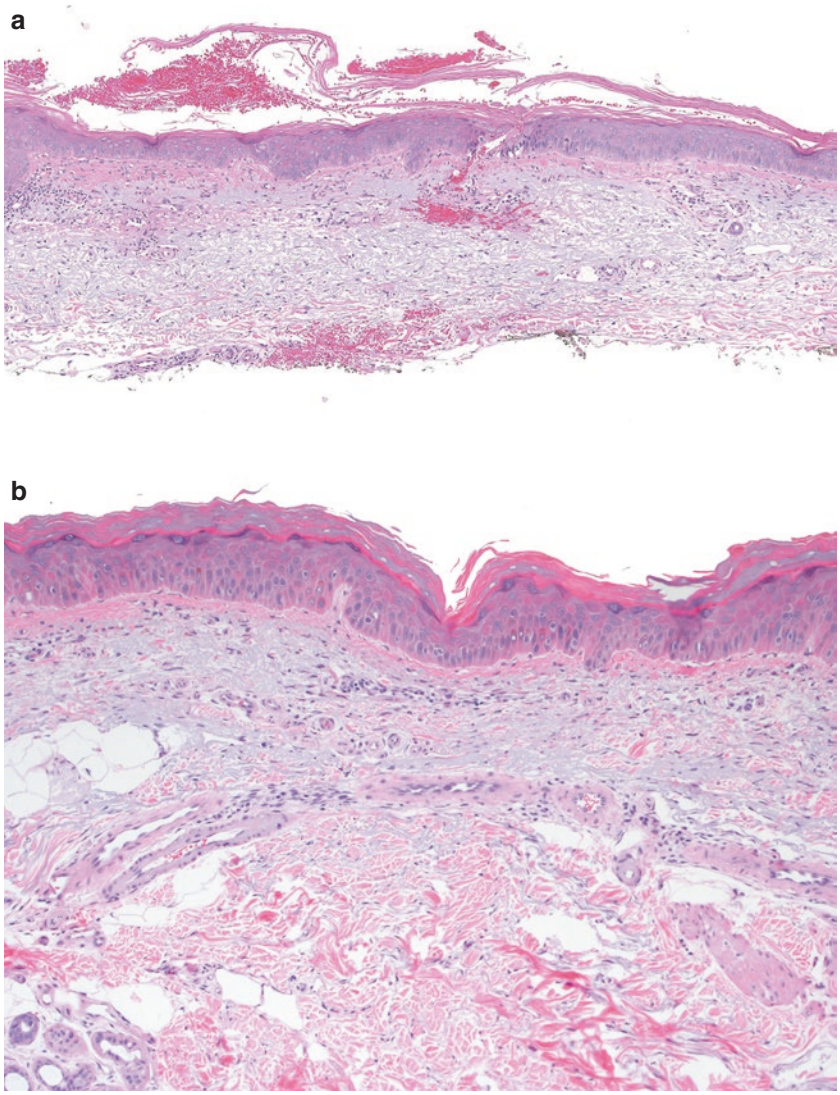

Fig. 1.9 Large cell acanthoma. The lesion is composed of large uniform pigmented keratinocytes (**a**). High power shows lack of elongated retes and the uniform pigmented keratinocytes (**b**).

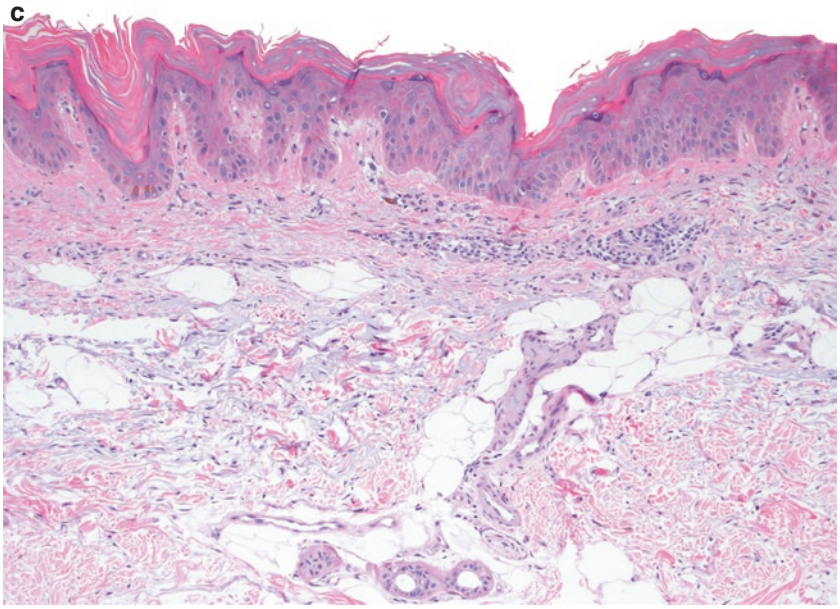

Fig. 1.9 (continued) Note the large keratinocytes (**c**)

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.

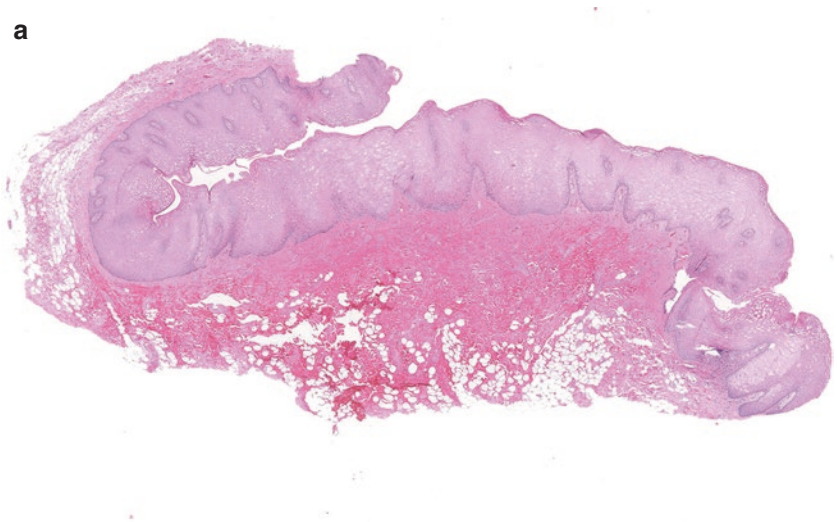

Fig. 1.10 Melanotic macule. This lesion is located in the lip of a 55-year-old female. Note the acanthotic epithelium with pigmented keratinocytes at the basal layer (**a**).

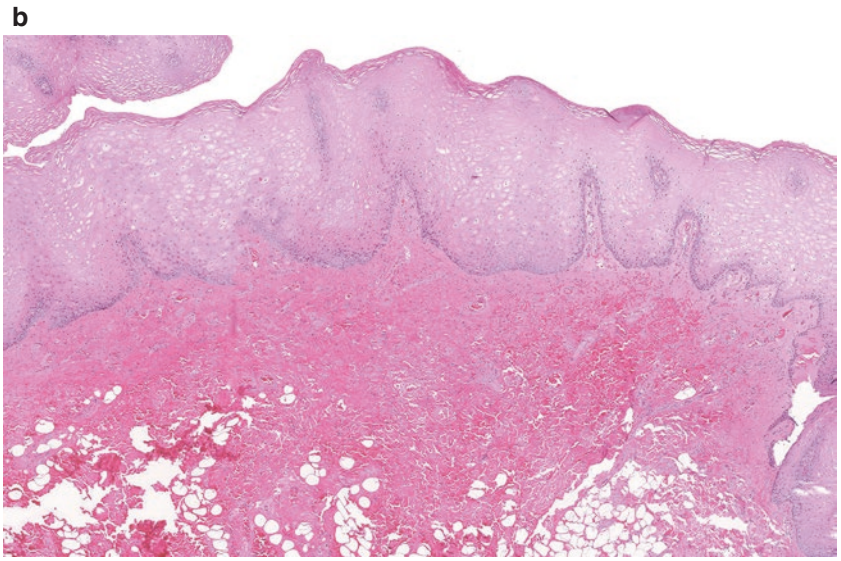

Fig. 1.10 (continued) High power showing the acanthotic epithelium with lack of cytologic atypia (**b**)

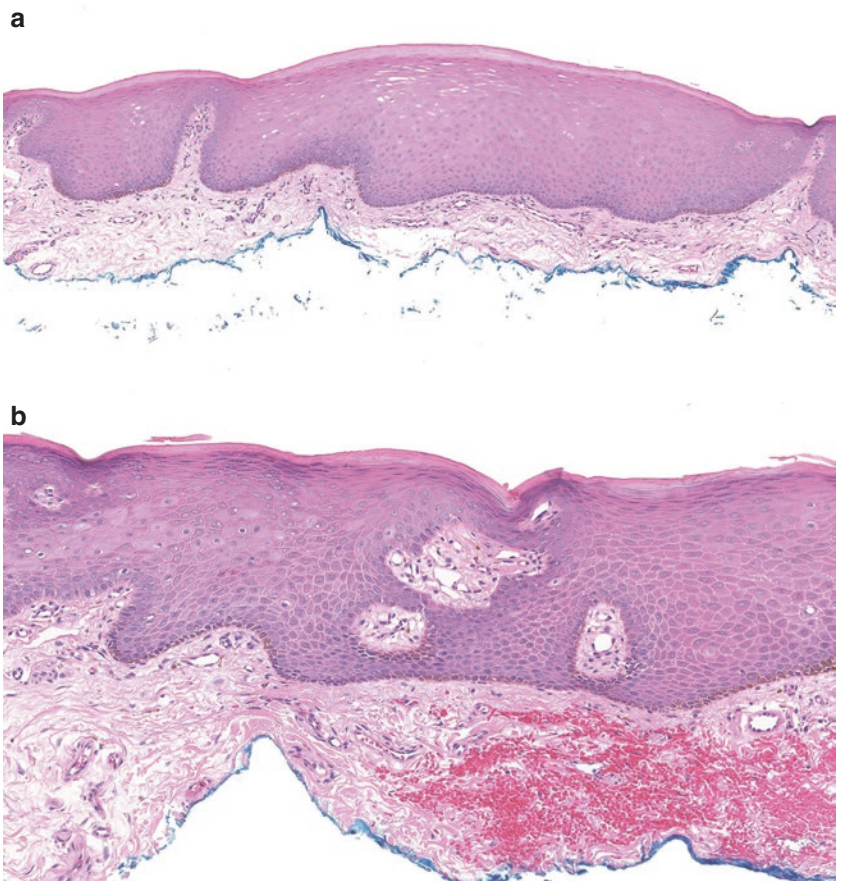

Fig. 1.11 Melanotic macule (lip). This case shows marked acanthosis with basal layer hyperpigmentation (**a**). At high magnification note the lack of melanocytes within the epidermis and rare pigmented melanophages in superficial dermis (**b**)

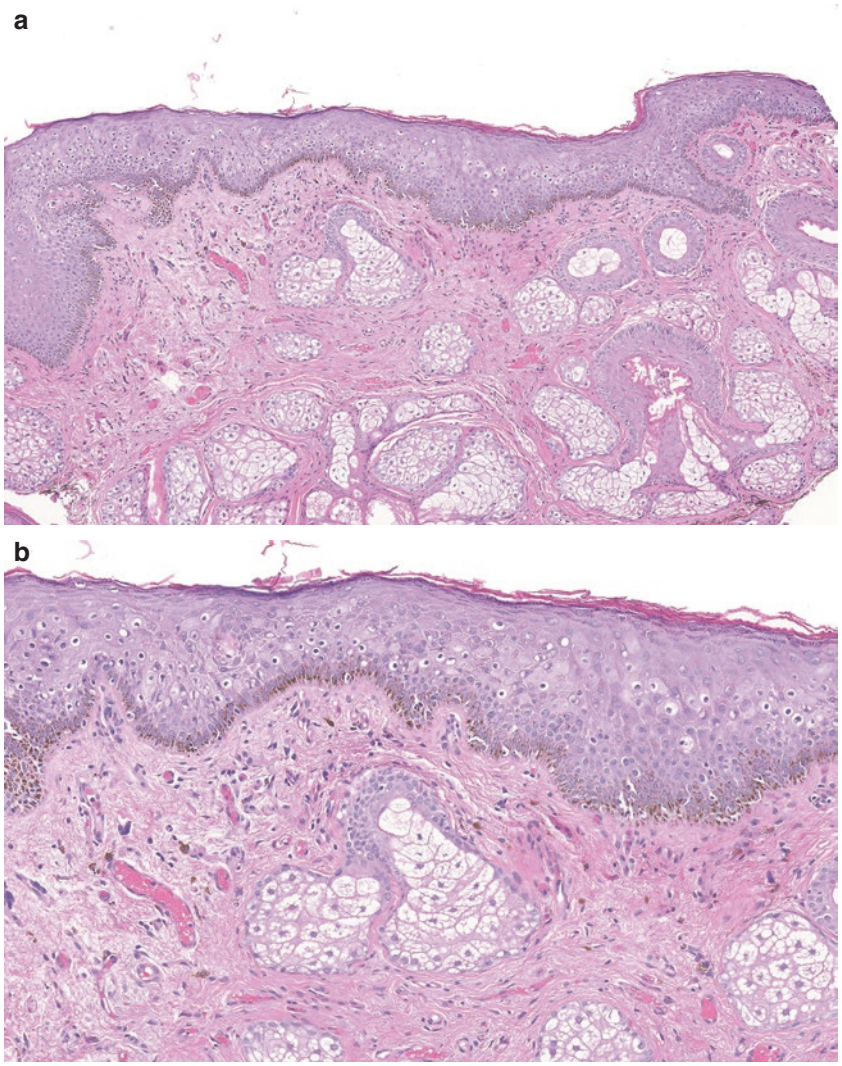

Fig. 1.12 Melanotic macule (vulva). This lesion is located in the vulva of a 28-year-old female. This example shows increase pigmentation in the basal layer, predominantly at the tips of the rete (**a**). Higher magnification showing the increase pigmentation in the basal layer (**b**)

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.

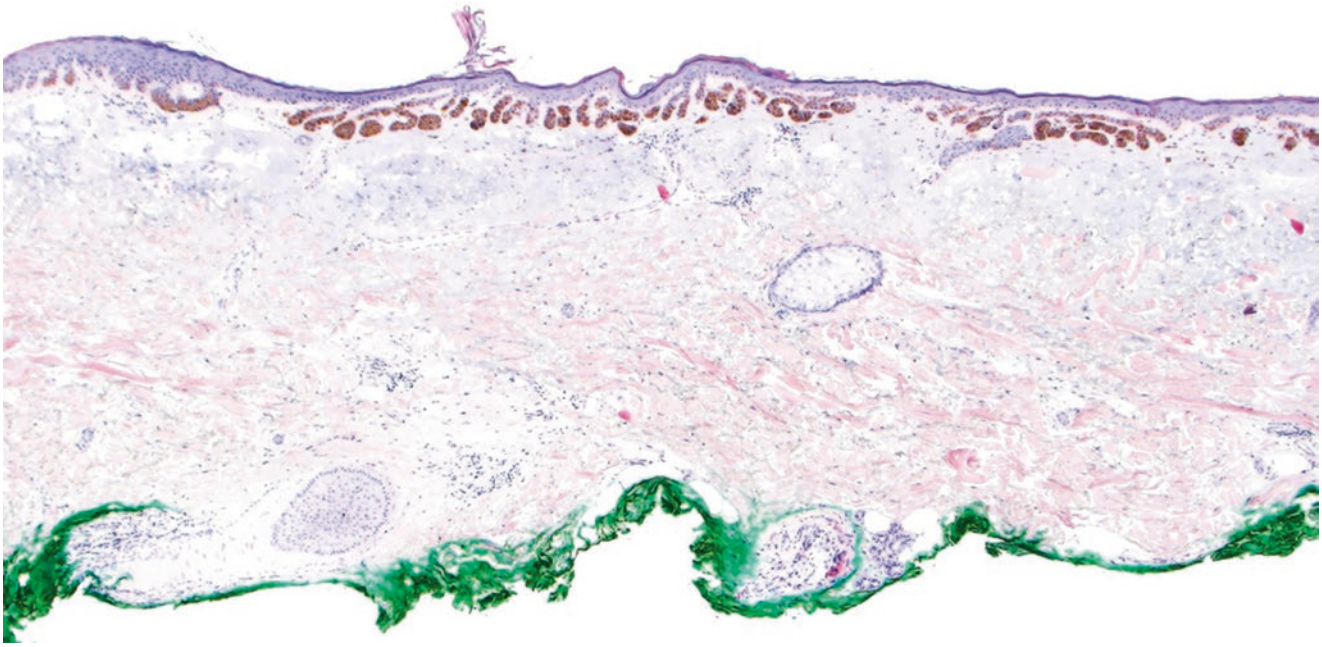

Fig. 1.13 PUVA Lentigo. Patients with history of psoriasis treated with PUVA can develop lentigines. Histology is identical to solar lentigo

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.

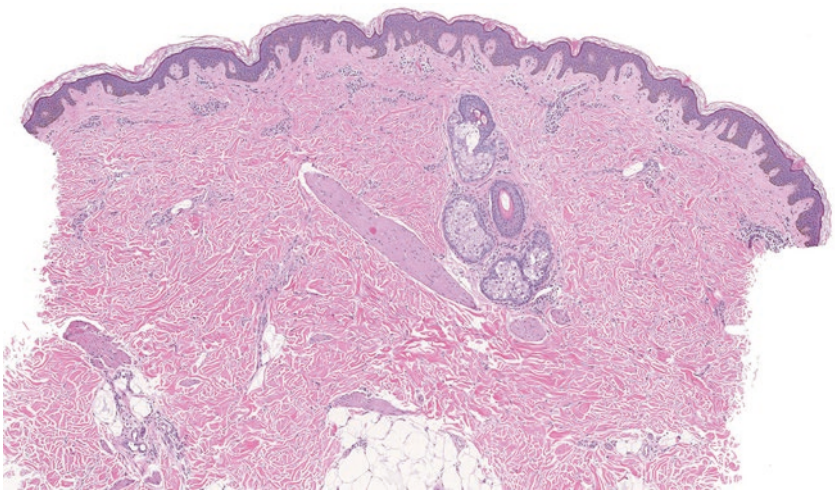

Fig. 1.14 Becker nevus. Low power showing epidermal hyperplasia and acanthosis

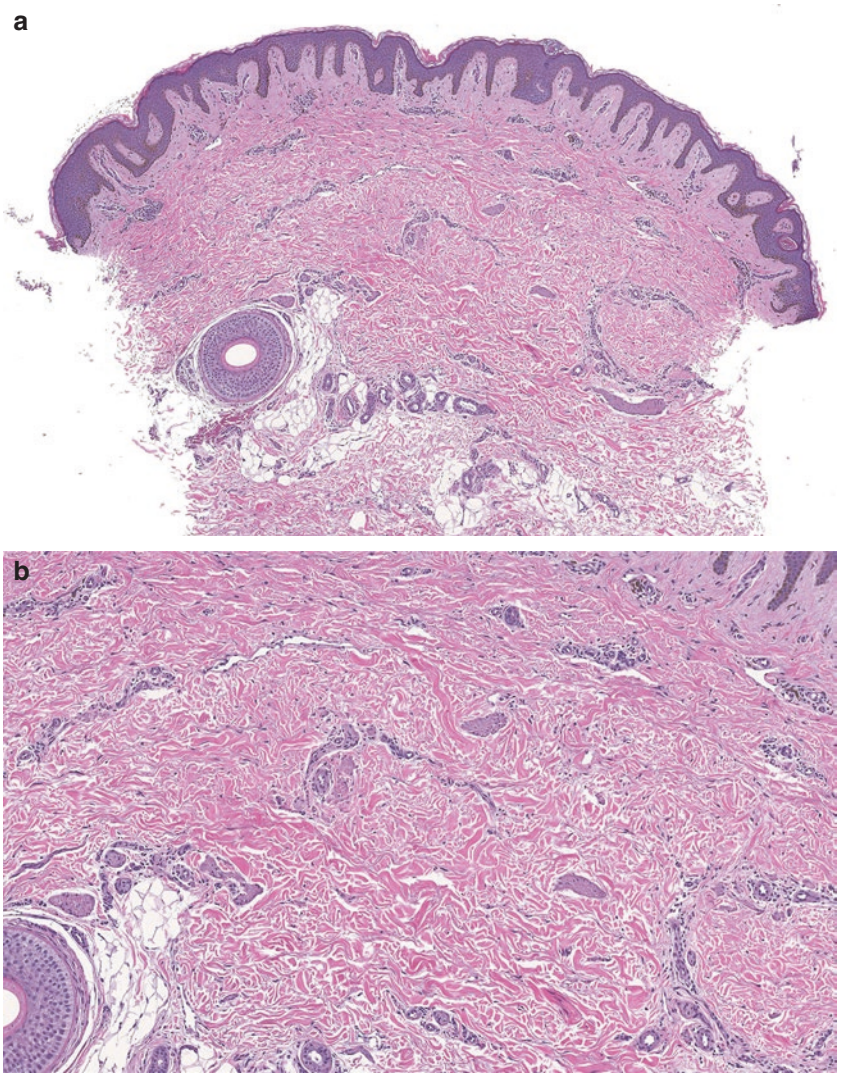

Fig. 1.15 Becker nevus. Another example showing regular epidermal hyperplasia with areas of hypermelanosis (**a**). Note the smooth muscle hyperplasia in dermis that is not associated with follicular units (**b**)

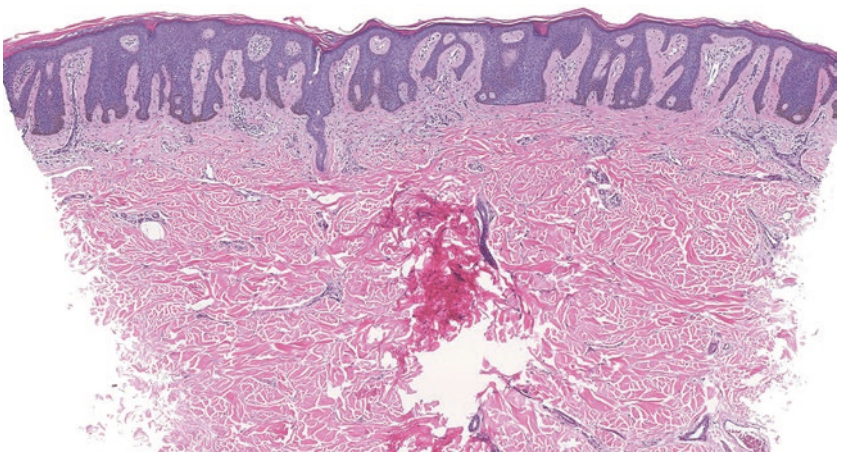

Fig. 1.16 Becker nevus. This example shows the characteristic irregular elongation of rete, increased basal layer pigmentation, mild acanthosis, and hyperkeratosis

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.