Pathology of Melanocytic Skin Tumors

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Claudio Clemente and Martin C. Mihm Jr.

The histological classification of melanocytic tumors is poorly correlated to the prognosis. The diagnostic criteria are not unequivocally accepted and often are poorly reproducible even among experts. The emphasis of the chapter is to present as clearly as possible the histological diagnostic features of each lesion along with the most important differential diagnostic considerations. A review of prognostication with emphasis on the latest recommendations of the American Joint Committee on Cancer, Melanoma subcommittee is presented.

Several areas of the pathology of the skin melanocytic tumors are, as yet, subject to doubts and disputes, and not all authors agree on the definition, the terminology, and the natural history of some histotypes. Also the diagnostic criteria are not unequivocally accepted and often are poorly reproducible even among experts [1]. In recent years a great help to the clinical diagnosis of nevi and melanomas has come by dermatoscopy and image analysis, which is placed in an intermediate position between the clinical/macroscopic and the histopathological diagnoses. The diagnostic procedure for the definition of a melanocytic lesion begins from the clinical macroscopic and the dermoscopy images. It is important that the dermatologist/dermatoscopist sends to the pathologist, together with the biopsy, the clinical "in vivo" image in addition to the clinical diagnosis and the medical history, which are essential information for the final histopathological diagnosis. The pathologist samples the lesion according to the clinical and dermatoscopic informations received, and only with this procedure the pathologist may discuss with the dermatologist the different patterns of the lesion with a reciprocal exchange of important diagnostic informations [2].

The histological classification of melanocytic tumors is poorly correlated to the prognosis; however, it is important to identify every entity with a reproducible and well-identifiable name. More recently a new subset of melanocytic tumors, with unpredictable biologic behavior, was described. These tumors, difficult to insert into the specific histotypes, are reported as *melanocytic tumor of uncertain malignant potential*, *severely atypical melanocytic proliferations*, *borderline melanocytic tumor*, *nevomelanocytic tumor of undetermined risk*, *etc*. [3], but they might be included under the general term of *atypical melanocytic tumors*. A proposed

C. Clemente (✉)
Department of Pathology and Cytopathology,
San Pio X Hospital, Milan, Italy

Department of Pathology and Cytopathology,
IRCCS Policlinico San Donato, San Donato Group,
San Donato Milanese, Milan, Italy
e-mail: cclemente.ap@iol.it

M.C. Mihm Jr.
Pathology and Dermatology Department,
Harvard Medical School, Boston, MA, USA

Melanoma Program, Department of Dermatology,
Brigham and Women's Hospital, Boston, MA, USA

Melanoma Program,
Dana Farber and Brigham and Women's Cancer Center,
Boston, MA, USA

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Table 7.1 Proposed morphological classification of melanocytic tumors

A. Melanocytic nevi
1. Lentigo simplex
2. Junctional, compound, and dermal nevus
3. Congenital nevi
(i) Proliferative nodules in congenital nevus
(ii) Superficial atypical melanocytic proliferation
4. Nevi, rare variants
(i) Halo nevus
(ii) Balloon cell nevus
(iii) Recurrent melanocytic nevus
5. Nevi of special sites
(i) Genital nevi
(ii) Acral nevus

B. Spindle and epithelioid cell nevi
1. Pigmented spindle cell nevus (Reed nevus)
2. Epithelioid and spindle cell nevus (Spitz nevus)

C. Dermal melanocytosis
1. Blue nevus
2. Cellular blue nevus
3. Desmoplastic nevus
4. Deep penetrating nevus

D. Dysplastic nevus

E. Atypical melanocytic tumors
1. Atypical Spitz/Reed tumors

F. Atypical dermal melanocytosis
1. Pigmented epithelioid melanocytoma
2. Dermal melanocytic tumors of uncertain malignant potential (MELTUMP)

G. Melanoma
1. Precancerous melanosis (in situ melanoma)
(i) Lentigo maligna
2. Superficial spreading melanoma
3. Lentigo maligna melanoma
4. Acral lentiginous melanoma
5. Mucosal lentiginous melanoma
6. Nodular melanoma
7. Melanoma, rare variants
(i) Melanoma in congenital nevus
(ii) Desmoplastic melanoma
(iii) Neurotropic melanoma
(iv) Nevoid melanoma and minimal deviation melanoma
(v) Malignant blue nevus
(vi) Others

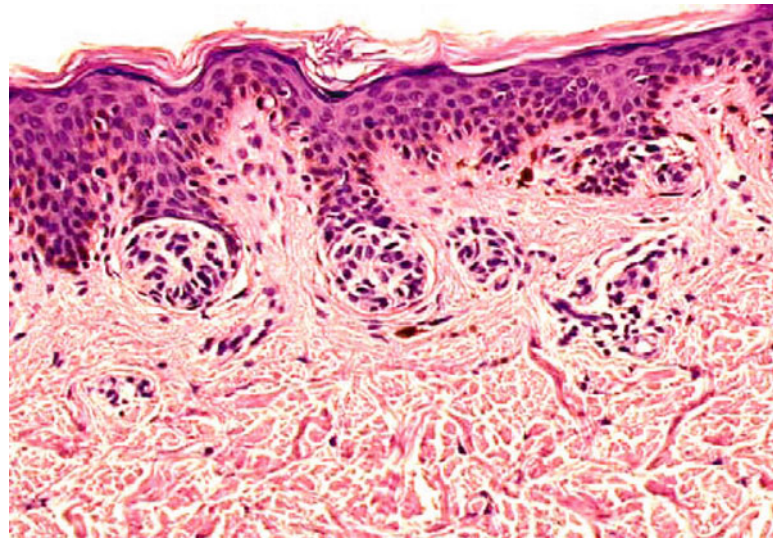
classification of the melanocytic tumors is reported in Table 7.1.

Melanocytic Nevi

Lentigo Simplex

Lentigo simplex is a small well-defined localized area of hyperpigmentation that is associated with proliferation of melanocytes along the dermoepidermal junction in contiguity (Fig. 7.1). This lesion characteristically is not associated with the nesting phenomenon of the nevus cells, and there are elongated retia, melanophages, and sparse dermal chronic inflammatory infiltrate. The main variants of lentigo simplex include *nevus spilus* which histologically may be indistinguishable from lentigo simplex or may show the features of lentigo simplex with occasional junctional nesting (*jentigo*). The principal differential diagnosis of lentigo simplex includes freckle, junctional nevus, or dysplastic nevus. The *freckle* is a nonproliferative lesion of melanocytes which is associated with hyperpigmentation of the basal skin layer. It usually is not associated with hyperplasia of the rete ridges. If junctional nests are present in a lentigo, it is impossible to exclude that the lesion represents an early *junctional nevus*. According to Hafner [4] the absence of BRAF, FGFR3, and PIK3CA mutations differentiates lentigo simplex from melanocytic nevus and solar lentigo. The *dysplastic nevus* characteristically is associated with a proliferation of nevocytes along the dermoepidermal junction but with cytologic atypia. The nests in lentigo simplex when present are small and lie at the tips of the rete ridges; the nests in dysplastic nevi vary in size, are associated with discohesion of nevocytes, and lie variously along the lateral side of the rete ridges and even between them in the superpapillary epidermis. Furthermore, there are stromal changes including increased vascularity and prominent inflammation associated with striking lamellations of collagen and often concentric eosinophilic fibrosis around

Fig. 7.1 Junctional nevus



the rete ridges. *Senile lentigo* shows irregular rete hyperplasia with often irregular shapes at the base of the rete ridges. The most common shape is a "footlike" array with dense hyperpigmentation without melanocytic hyperplasia. *Lentigo maligna* is more strikingly different than lentigo simplex/senile but must be included because of the prominent single cell proliferation along the epidermis which may appear benign in early lesions. Lentigo maligna differs with a strikingly atrophic epidermis and sun-damaged dermis and often with a band-like or lichenoid inflammatory infiltrate admixed with melanophages. Furthermore in lentigo maligna the proliferation of melanocytes extends along the external root sheath of the hair follicles, even to the base of the hair follicle. *Mucosal lentigines* (labial, vulvar, penile) and acral lentigines may closely resemble lentigo simplex with increased number of intraepidermal basal pigmented melanocytes with dendritic morphology. Lentigines may be associated with systemic syndrome (LAMB, LEOPARD, Carney complex) [5].

Junctional, Compound, and Dermal Nevus

Junctional melanocytic nevi are focal pigmented lesions that by definition are flat to slight raised and exhibit intraepidermal nesting of nevomelanocytes usually localized to the tip of slightly hyperplastic rete ridges (Fig. 7.2). A nest of nevomelanocytes is considered to be five or more cells in a single cluster. Characteristically, the cells in the nests of junctional nevi are round to oval and lie contiguously together with scattered, usually coarse, melanin granules in their cytoplasm. The nucleus of the junctional nevus cells is larger than the normal nevomelanocyte and is round to oval, and usually a delicate nucleolus is evident. While the melanocytes in a nest are clumped together, because of separation artifact they usually are clearly separate from the adjacent keratinocytes with a space separating the nests from the keratinocytes. Often the nevus nests compress the adjacent keratinocytes that become elongated and fusiform with oval nuclei. No necrosis or apoptosis of the epidermal cells is present. At low-power magnification, one appreciates a well-circumscribed lesion that usually has hyperplasia of rete ridges with lentiginous proliferation of nevomelanocytes along the dermoepidermal junction but with nesting. The nevocytes have round to fusiform nuclei with tiny dot-like blue nucleoli. Their cytoplasm is clear and contains rather coarse melanin granules. Dendritic processes are not obvious although stubby small dendrites may be observed by high-power examination or with immunohistochemical stains

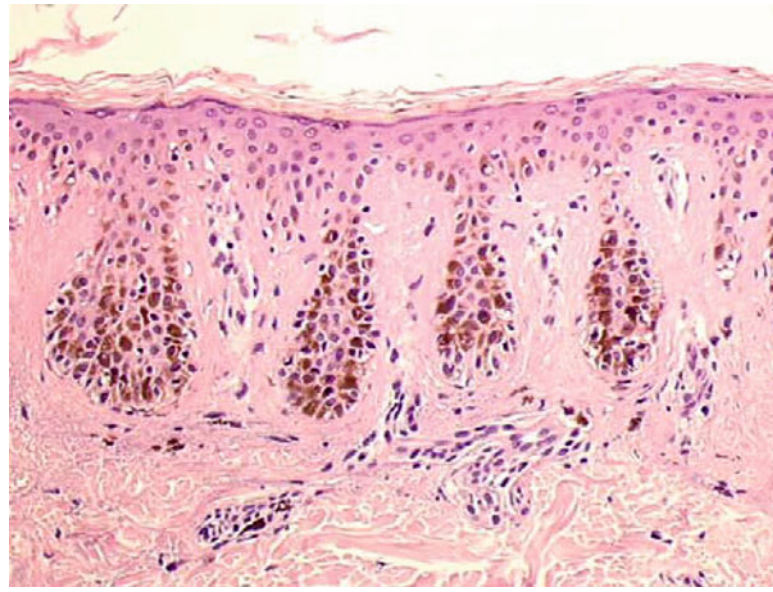


Fig. 7.2 Lentigo simplex

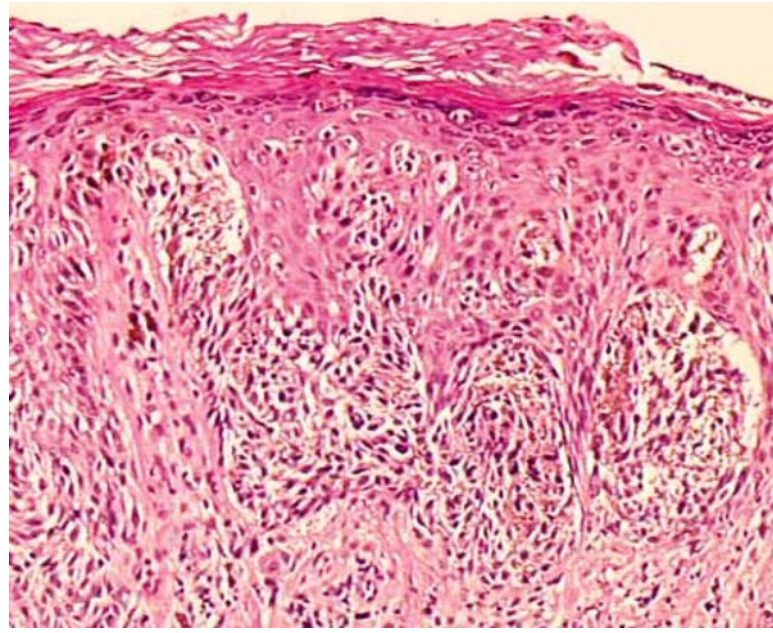


Fig. 7.3 Childhood junctional nevus

(HMB45). Occasionally the lesions, especially in acral sites, may not be associated with a lentiginous proliferation of melanocytes but with junctional nests. In such instances there may be trans-epidermal elimination of nests with their presence being noted even in the stratum corneum. The variants in junctional nevi include the *nevi of childhood* in which there may be prominence of single cells in the epidermis even to the level of the granular cell layer (pagetoid pattern), confined to the central part of the nevus (Fig. 7.3). Such intraepidermal proliferation, however, retains the benign characteristics of the cells in lentiginous array and in nests. *Congenital junctional* nevi are histologically indistinguishable from *acquired nevi* in small biopsies except that

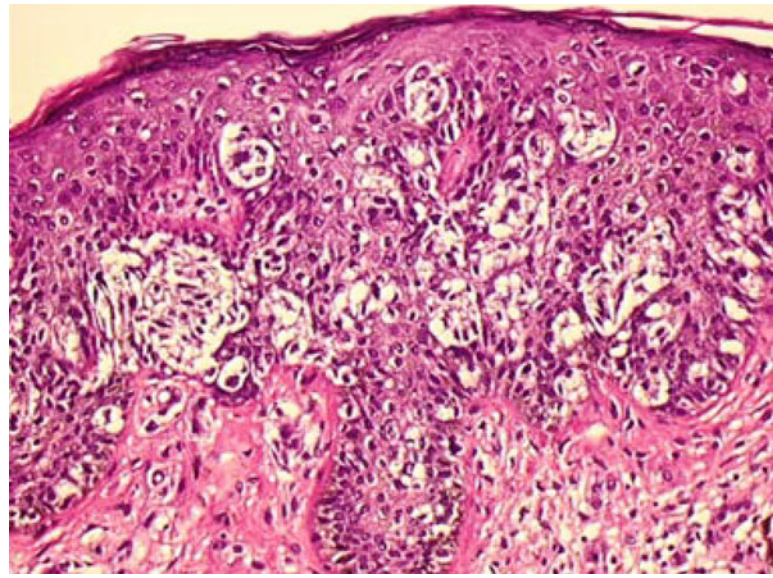


Fig. 7.4 Melanoma, pagetoid spread

the predominance of deep dermal or periadnexal nests is more common in the congenital nevus than in the acquired nevus. *Acral junctional nevi* are often associated with a proliferation of single cells in the *stratum spinosum* characteristically overlying the junctional nests. The *lentiginous junctional dysplastic nevus* shows variation in morphology of the single cells and also in the size of the nests. Likewise, rather than showing a cohesive aggregate of nevus cells in the nests, the dysplastic nevocytes are characteristically discohesive in nests and show irregularities in nuclear size and shape in individual nests. *Superficial spreading melanoma* may show a prominent nesting pattern, but the cells are large and have prominent eosinophilic nucleoli and large cytoplasm filled with fine, dustlike, melanin granules; there is less retraction from keratinocytes of the nests; and it presents an "aggressive" proliferation with keratinocytes apoptosis (Fig. 7.4). Finally, the *pigmented junctional spindle cell nevus* is composed of a uniform population of spindle cells in well-defined and oriented nests, perpendicular or parallel to the skin surface. A *compound melanocytic nevus* refers to a lesion in which there is a proliferation of nevus cells in nests both in the epidermis and in the dermis. Low-power examination reveals a well-circumscribed symmetrical lesion. The intraepidermal component usually is associated with well-developed nests present at the tips of the rete ridges with a regular and repetitive pattern. A lentiginous proliferation, similar to dysplastic nevus, is variably present in the compound nevus and in particular in the central area of congenital compound nevi (Fig. 7.5). Usually the intraepidermal component does not extend beyond the dermal component but if present, the extent beyond the dermal component is symmetrical on both sides of the lesion. The junctional nests are identical to those described under the junctional nevus. Intraepidermal junctional nevus cells have been described by the designation type A cells. These A cells are large round nevus cells with coarse melanin granules within them. In the dermal component of the lesion the picture is quite variable. In early lesions there are small nests of cells, many similar to type A cells, with large round nuclei present in the papillary dermis. These cells as they increase in number with lesion aging become smaller and round without pigment. They exhibit tiny nucleoli and are associated with fine fibroblast-like cells surrounding the nest. As the lesion ages, these cells are associated with a spindle-shaped cell that has been designated a type C cell at the base of the lesion. The type C cells are associated with increase in stroma with eosinophilic ground substance, an increased reticulum fibers present separating the type C cells

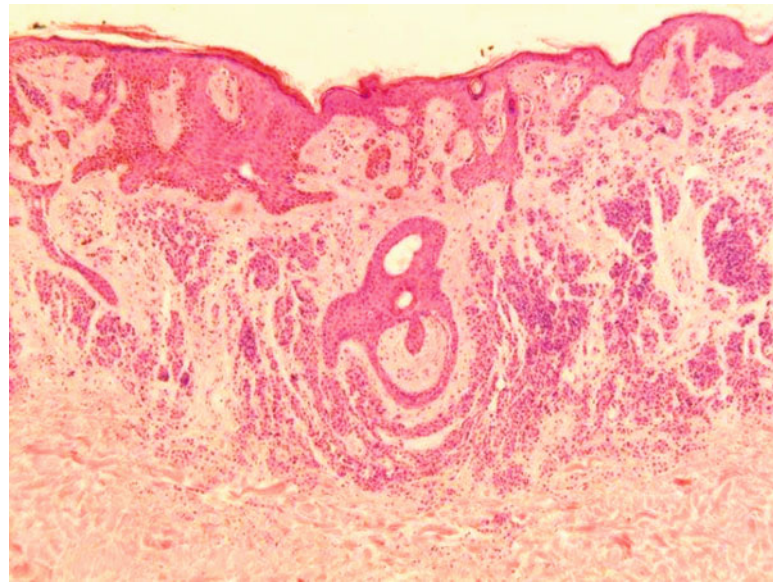


Fig. 7.5 Congenital compound nevus, lentiginous proliferation-like dysplastic nevus

from one another. The type C cells can become arranged in highly complex patterns resembling neuroid structures or neurofibromas. Type A cells express S100 protein and HMB45. Type B cells may express either S100 or the Schwann cell-associated antigen but they are HMB45 negative. This variation in morphology and immunochemical findings is considered to be a maturation phenomenon of the nevus cells in their dermal component (Fig. 7.6). If the dermal component extends deeply into the dermis, in particular along adnexal structure, one must consider a *congenital nevus*. The differential diagnosis of the compound nevus includes *nevus spilus*. Some variants of nevus spilus have dermal nests and therefore represent variants of compound nevus. The *dysplastic nevus* usually is a type of compound nevus but with an irregular proliferation of atypical nevomelanocytes in the epidermis overlying the dermal component. There is no symmetry in this lesion so that the dermal component lies eccentrically in relationship to the epidermal component. Also in the compound nevus there is no atypia. *Nodular melanoma* can be differentiated from the compound nevus by the fact that there is, in addition to intraepidermal nesting, usually pagetoid aggressive spread of malignant melanocytes at the shoulder. Furthermore the characteristic maturation of type A to B to C cells is absent. In melanoma the deeper cells frequently exhibit finely granulated pigment in their cytoplasm, an atypical and rare finding in compound nevi. Also, the deeper component is not associated with a pushing border or expansive dermal nodule formation in nevi; this change is characteristic of melanoma. Mitotic activity in the dermal component is extremely rare in compound and dermal nevi, whereas it is common in melanomas [6]. Finally, compound nevi very rarely have a striking inflammatory response, whereas melanoma is commonly, especially below the intraepidermal component, associated with a lymphocytic host response. The term *dermal melanocytic nevus* refers to a lesion in which the nevus cells are completely confined to the dermal component with no intraepidermal involvement. The epidermis may be normal or flatted because of effacement of the rete ridges. There is no melanocytic proliferation or nesting in the typical dermal nevus. Occasionally, scattered single large nevomelanocytes are present overlying a dermal nevus but they are not considered significant unless there is a striking contiguous proliferation of them. The papillary dermis is unremarkable although occasionally there is some fibrosis of the papillary dermis. The nevic component of the dermal nevus exhibits nests of cells and sheets of cells that extend into the deep widened papillary dermis.

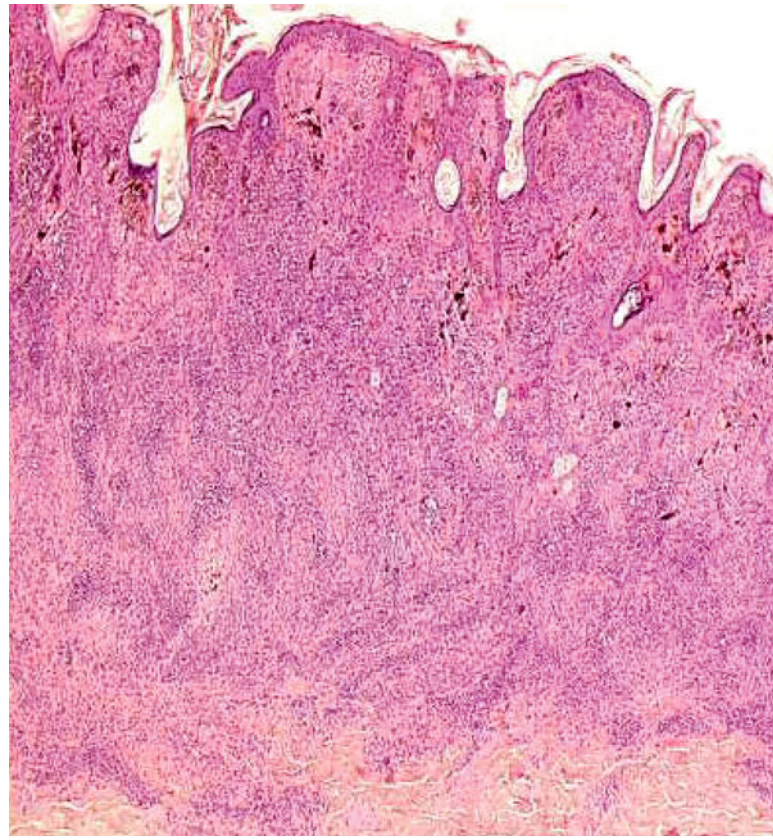


Fig. 7.6 Compound nevus: maturation

As the cells reach the papillary-reticular dermal junction, they frequently are noted to infiltrate as single cells into the superficial reticular dermis. The presence of nests of cells in the reticular dermis in an otherwise banal appearing dermal nevus is considered an abnormality of maturation (see section "Proliferative Nodules in Congenital Nevi", pag. 119). The characteristic lesion shows single cells that often have a fibroblast-like appearance. These cells are confined to the upper reticular dermis but presence in the deep reticular dermis suggests a congenital nevus. There is no evidence of preferential expansile growth in the form of expansile nodules in the deep component of a dermal nevus. The dermal nevus cells are usually type B and type C in nature. The superficial portions may be associated with nests of type B cells, while the deeper portions show the fibroblast-like changes associated with type C cells. Occasionally in the very superficial portions of the dermal component, type A cells as large round pigmented cells may be present within the upper papillary dermis. As the type C cells proliferate as S-shaped fibroblast-like cells with increasing ground substance, they resemble neurofibromas. Extensive organized stromal aggregates may resemble Wagner-Meissner corpuscles. Lesions containing prominent type C cell proliferation with extensive ground substance are dubbed "neuronevi" by Masson. In most such lesions one can still observe evidence of melanocytic proliferation, specifically nests of nevic cells. However, in some lesions there is no evidence of melanocytic activity. To differentiate such lesions from neurofibromas, one must observe the adventitial dermis of hair follicles and vessels. Neurofibromas infiltrate the adventitial dermis up the basement membrane of the external root sheath. Neuronevi on the whole respect the adventitial dermis. Mitoses do not occur in benign dermal nevi nor is the reevidence of expansile nodule formation deep in the nevus. "Aging" of

dermal nevi has been associated with senescent changes which have been likened to the "ancient change" of schwannomas. Balloon cell changes also represent a possible senescent phenomenon due to degeneration of melanosomes. Sclerosis and infiltration by fat cells is related to involuting phase of the nevus. In such lesions there are hyperchromasia of nuclei, multinucleate giant cell formation, and large blue nucleoli; however, mitoses are absent. More than three mitoses in one section suggest to perform multiple levels to exclude a nevoid melanoma. In dermal nevus there is no evidence of necrosis and expansile clonal nodule formation and the nuclei do not contain the bright eosinophilic nucleoli of melanoma cells. One interesting change that occurs in dermal nevi is the presence of multiple large spaces lined by nevus cells. These spaces resemble vascular structures. The most important differential diagnostic consideration of the dermal nevus is melanoma. In melanoma there is no evidence of maturation of type B to type C cells. Rather, the lesion is composed of a uniform clonal population (single or multiple) of pleomorphic cells. In the depth of the lesion, often cells are larger rather than smaller in melanoma in contrast to the maturation of nevi. Mitoses are present throughout the lesion, in particular in the proliferative marginal areas, whereas in dermal nevi no mitotic activity is observed. A useful method in differentiating compound and dermal nevi from melanoma is to use the immunocytochemical stain with HMB45 and p16 antibodies. HMB45 usually does not stain the dermal deep component of ordinary acquired nevi. However, up to 30–40 % of the dermal component of dysplastic nevi can stain with HMB45 and all the dermal melanocytosis are positive. In such cases the histology of the lesion allows for the correct diagnosis. p16 is strong positive both in the nuclei and the cytoplasm of the nevi and negative in the vertical phase of the melanoma.

Congenital Nevi

Congenital nevi, by definition, are pigmented skin lesions present at birth. These lesions are divided in small (up to 1.5 cm in size), intermediate, and giant congenital nevi. Intermediate lesions are greater than 1.5 cm but can be removed by simple excision. Giant lesions, on the other hand, require often multiple staged excisions for removal. The histopathologic picture of a congenital nevus may be indistinguishable from an acquired nevus. According to Mark and Mihm [7], the following patterns are diagnostic of congenital origin: (*1*) *intramural or subendothelial nesting of nevus cells in small- to medium-size arteries*, *veins*, *and lymphatic vessels*; (*2*) *nevus cell nests in the papilla of the hair follicle*; (*3*) *nevus cells scattered in single cell array throughout the lower reticular dermis and subcutaneous fat*; (*4*) *nevus cells in arrector pili muscles*; *and* (*5*) *nevus cell in tight perivascular array mimicking an inflammatory infiltrate throughout the reticular dermis*. Thus, a congenital nevus may show areas of lentigo, areas of junctional nevus, areas of compound nevus, or areas of dermal nevus with limitation to the papillary-reticular dermal junction of the nevus cells. However, in many congenital nevi in striking contrast to acquired nevi, the nevocytes extend into the lower third of the dermis and may even involve the subcutaneous fat. The presence of this change is often also associated with involvement of skin appendages, vessels, and nerves. The dermal involvement in the lower reticular dermis and fat is predominantly composed of single cell array resembling the so-called Indian file. Involvement of the hair follicle includes nests in the lower two-third of the external root sheath, nests in sebaceous glands, or even nests of nevic cells in the papillae. Similarly, nests may occur in eccrine ducts or in eccrine glands. Subendothelial deposits of nevocytes may be observed in both the walls of arteries and veins. Finally, protrusion of nevus cells, delimitated by endothelial cells, into the lymphatics in the superficial and deep dermis may also be noted and distinguished by true lymphatic invasion by a melanoma (Fig. 7.7). Less specific is a pattern of nevic cells surrounding the appendages in the adventitial dermis and extending out into the collagen of the reticular dermis. At times the reticular dermal collagen may be strikingly abnormal in the congenital nevus.

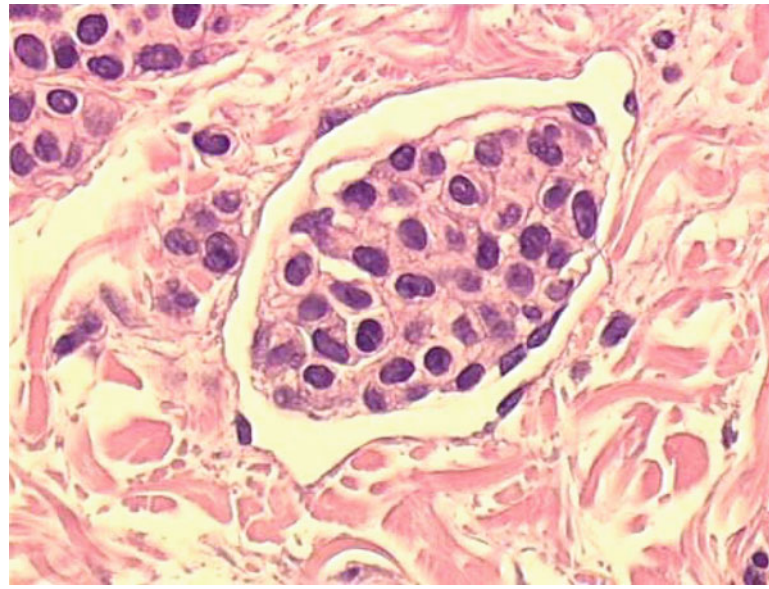


Fig. 7.7 Congenital compound nevus: subendothelial deposits of nevus cells (pseudo-vascular invasion)

Thus, the collagen is infiltrated by the nevic cells, but the fibers of collagen are small in diameter, do not show striking interlacing as normal reticular dermal collagen fibers, and often lie parallel to the long axis of the epidermis. This type of reticular dermal change is more common in adult nevi in our experience than in the children's congenital nevi. High magnification reveals the cells to be of the type B cell in the superficial dermis but more of a type C cell appearance in the deeper dermis having a more fusiform aspect. Thus, the cells infiltrate singly amidst collagen fibers in the subcutaneous fat, have a rather fusiform appearance. However, at times throughout the entire dermis and into the subcutaneous fat, type B nevus cells may be noted. The giant congenital nevus [8], on the other hand, more commonly has extensive proliferation of nevus cells that are present throughout the entire dermis and into subcutaneous fat and may even be present in fascia and muscle beneath the cutaneous lesion. The histological alterations in these lesions, while composed of type B and type C cells or fusiform cells, are much more extensive and the changes involving appendages much more easily observed in the giant congenital nevus than in the small congenital nevi. Likewise in the large congenital nevi there are often quite prominent complex neuroid structures, areas of neurofibroma-like differentiation associated with chondroid and cartilage. Areas of cellular blue nevi and blue nevi may be observed in the giant congenital nevus as well as areas of spindle and epithelioid cell nevi. Frequently, when one is dealing with a congenital nevus that is extensive and deep, it is necessary to perform S100 stain to identify the depth margin of the lesion. If a congenital nevus is removed regardless of reason, the fascia and muscle below the skin must always be observed for the possibility of residual nevi nests.

Proliferative Nodules in Congenital Nevi

Congenital nevi can exhibit expansile nodular proliferations of nevus cells which are a cause for concern and present difficulties in the histopathologic diagnosis [9]. The more common nodule is composed of nevocytes that are type B in character; it is benign and shows no mitotic activity (Fig. 7.8). Any expansile aggregate of melanocytic origin must be carefully evaluated for features of malignancy which include severe nuclear atypia, the presence of necrosis of nevocytes with or without ulceration, the presence of an expansile destructive behavior of the nodule with deformity and obliteration of adjacent structures, and the presence of mitoses. Very importantly, there is usually a striking and abrupt border between the benign nevus cells and the atypical

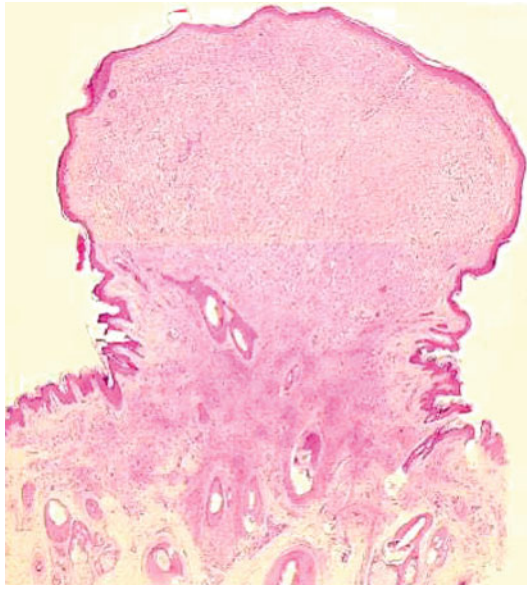


Fig. 7.8 Proliferative nodule in congenital nevus

melanocytic cells in the malignant lesions. Benign lesions show cells that tend to blend with the nevus cells in the adjacent congenital nevus. Thus, there appears to be a maturation from those cells in the midst of the lesion to the surrounding nevic cells. Malignant nodules are usually greater than 5.0 mm. in size. Lesions that show some mitotic activity (less than 7/mm^2), without necrosis, without ulceration, and without destructive deforming architectural features are considered as atypical and diagnosed the lesion as an *atypical nevomelanocytic proliferation* in a congenital nevus (see section "Atypical Melanocytic Tumors", pag. 139). The cellular components of these nodules may include populations of type B nevus cells or population of spindle and epithelioid cells. The histochemical stain for reticular fibers (silver impregnation method) can be useful in the differential diagnosis with melanoma; the positive fibers surround with a dense network every individual cell in the proliferative nodule; on the contrary, they are pushed to the periphery in the nodule of melanoma vertical growth. The congenital nevus of the scalp in the occipital region has been associated with intracranial nevocytic proliferations. Meningeal proliferations occur as well as proliferations of nevus cells along penetrating arteries of the brain substance. Rarely, proliferations in the cisterna have led to internal hydrocephalus. The combination of an occipital congenital nevus and internal hydrocephalus is known as Touraine's syndrome. The principle differential diagnostic considerations include tumors of neural and fibroblastic origin. The common presence of neuro-differentiation resembling neurofibromas and schwannomas in giant congenital nevi may lead to an erroneous diagnosis if the entire clinical picture is not evident. We have found that in cases of peripheral nerve sheath tumors occurring in the setting of giant congenital nevi, one may find striking involvement of nerves by nevus cells in such cases. This change may help to identify the origin of the peripheral neural proliferation in a congenital nevus. However, taken along the peripheral nerve sheath, tumors can be indistinguishable from spontaneous neurofibromas or schwannomas and the clinical history may be necessary to identify the correct pathogenesis of the lesions. The dermatofibrosarcoma protuberans, especially the Bednar tumor or pigmented variant, can sometimes be confused with a fibroblastic variant of the congenital nevus. In congenital nevi, however, one does not find a storiform pattern. Also, the dermatofibrosarcoma protuberans is a large deforming nodule which displaces appendages. The fibroblastic variant of the congenital nevus is associated with a linear deposition of collagen fibers parallel to the long axis of the epidermis frequently, does not act as a deforming nodule, and hence leaves appendages unaltered.

Superficial Atypical Melanocytic Proliferation in Congenital Nevi

Another difficult histologic interpretation is the observation of striking epithelioid cells in the epidermis and superficial dermis of congenital nevi, especially in young patients that may simulate a superficial spreading melanoma. The nevus cells may show prominent nuclei with evident nucleoli and finely granular melanin in their cytoplasm. A careful evaluation of these proliferations reveals that the nuclei show very delicate and regular chromatin and that nuclear cytoplasmic ratios are small. Another important pattern is the

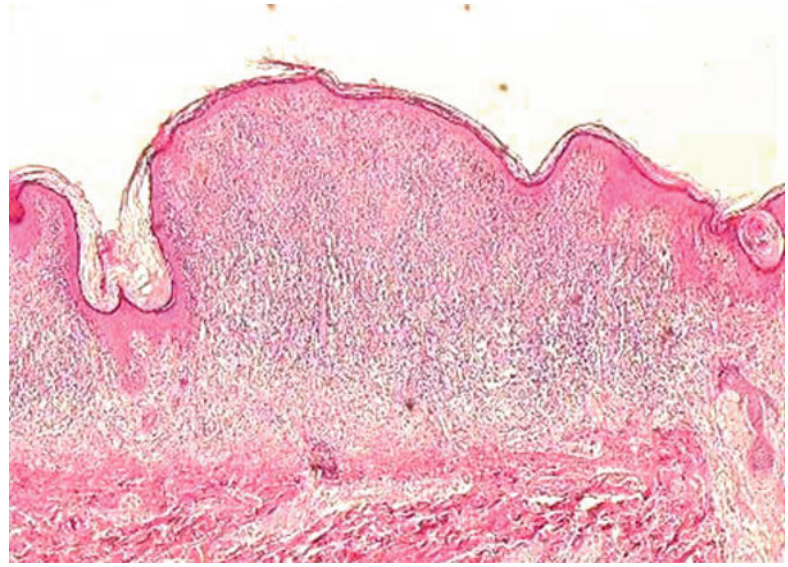


Fig. 7.9 Halo nevus

absence of pagetoid spread at the nevus shoulder. Also the dermal component shows a propensity to mature and blend with the underlying dermal nevus cells.

Nevi, Rare Variants

Halo Nevus

The *halo nevus* is defined as a pigmented lesion with usually benign clinical characteristics surrounded by a zone of depigmentation that is symmetrically disposed [10]. This rim of depigmentation gives rise to the name halo. Histologically there is a compound nevus usually associated to a very striking, band-like, infiltrative lymphocyte response that is present among the dermal component of the nevus (Fig. 7.9). In addition there is loss of melanin with tagging of lymphocytes along the dermoepidermal junction in the depigmented area. The halo nevus has also been known as *Sutton's nevus* or *leukoderma acquisitum centrifugum*. The halo is usually round or oval and the pigmented lesion is symmetrically disposed in the center of the lesion. The type of pigmented lesion that may give rise to a halo nevus includes ordinary acquired compound, junctional compound and dermal nevi, compound nevi of Spitz, dysplastic nevi, and rarely congenital nevi. Halo blue nevi rarely occur. Characteristically the cells that infiltrate the nevus are T cell in type. Halo nevi are most commonly associated with compound nevus that is symmetrical, well circumscribed, and composed of intraepidermal nesting with type B cells and C cells in the dermis. At times one may see lymphocytes migrating into the junctional nests with lymphocyte nevus cell satellitosis. Lymphocyte nevus cell satellitosis is commonly observed in the dermal component. Altered nevus cells have an eosinophilic appearance to their cytoplasm and many binucleate with prominent nuclei forms are noted. On the whole most of the dermal nevus cells are larger than normal nevus cells. Mitotic figures are only rarely found in halo nevi and should alert suspicion of possibly an atypical proliferative lesion leading to examination of multiple sections. As far as pigmentation is concerned, the nevus cells may show residual melanin pigment. Occasionally scattered melanophages are noted around the inflamed dermal component as well as below the adjacent epidermis. Halo nevi must be distinguished from halo dysplastic nevi or from melanoma with vertical growth phase. In halo dysplastic nevi in addition to the brisk infiltrate, one observes a proliferation of atypical nevomelanocytes in the epidermis well away from the dermal component. These cells

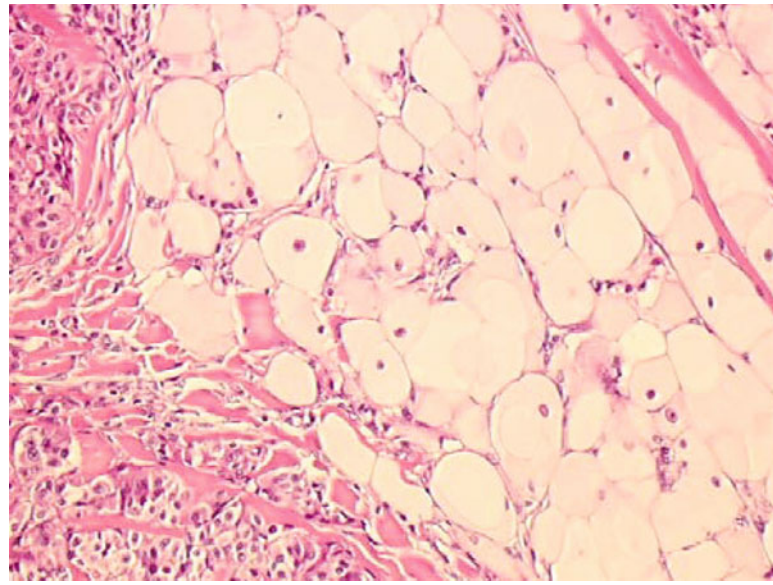


Fig. 7.10 Balloon cell nevus

are present in lentiginous array and show irregular nesting. One must be aware, however, that most dysplastic nevi have some host response associated with them. The host response is usually not associated with lymphocyte nevus cell satellitosis of either the intraepidermal or the dermal component of the nevus or with the presence of lymphocytes along the dermoepidermal junction with lymphocyte nevus cell satellitosis. Melanoma can be differentiated histologically on the basis of the atypia of the cells, the presence of an expansile nodule growth in the dermal component and aggressive infiltration of the epidermis with pagetoid spread, and the presence of scattered mitoses with or without ulceration and necrosis. As far as the cytology of the individual cells is concerned, the halo nevus cells may be larger than normal nevus cells but show benign nuclear characteristics, whereas the melanoma cells show very pleomorphic nuclei with irregular chromatin patterns and with very prominent eosinophilic nucleoli. Likewise in the halo nevus, pagetoid spread is usually absent or minimal. Furthermore the intraepidermal component is a well-defined nested pattern as opposed to the melanoma which shows both irregular-sized nests and pagetoid spread. Nevus cells may be very difficult to discern in the midst of the inflammatory infiltrate. The S100 and particularly p16 stain may be helpful in finding the nevus cells in a suspect lesion.

Balloon Cell Nevus

In *balloon cell nevus* more than 50 % of dermal nevomelanocytes manifest abundant clear, finely vacuolated cytoplasm and small hyperchromatic nuclei with a scalloped contour (Fig. 7.10) [11]. Multinucleation may be observed. The main differential diagnosis is that of balloon cell melanoma, based on the recognition of a malignant neoplastic cytology; in balloon cell melanoma, the majority of cells manifest pleomorphism, the nuclei appearing large with irregularly distributed chromatin, mitoses, and necrosis.

Recurrent Melanocytic Nevus

Usually the *recurrent nevus* is a compound nevus but in 32 % of cases it is a dermal nevus and a junctional nevus in 5 % of cases. Less than 10 % of recurrent nevi are dysplastic nevi. The recurrent nevus describes the appearance of pigmentation at the site of a previously removed benign (Fig. 7.11) lesion usually incompletely affected by shave biopsy [12]. The histological problem is frequently an intraepidermal melanocytic growth of atypical melanocytes in lentiginous array over the previous scar that suggests pagetoid melanoma [13]. Clinically, the recurrence occurs very

Fig. 7.11 Recurrent nevus and scar

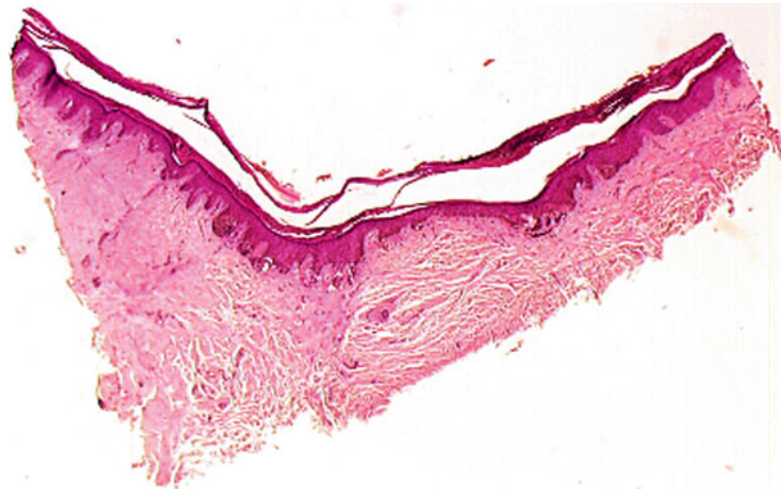


Fig. 7.12 Recurrent nevus

rapidly, usually in 1–2 months. This speed of recurrence is helpful in distinguishing a recurrent nevus from a recurrent melanoma which usually takes a much more protracted period of time even up to years for the recurrence to appear. The recurrent nevus presents a broad intraepidermal proliferation of melanocytes, sometimes greater than 6.0 mm in width with a combination of intraepidermal nests and single cells. The pagetoid spread of both nests and single cells is frequently observed. However, involvement in the stratum corneum does not commonly occur. Mitoses are characteristically absent in the intraepidermal component and in the superficial dermal component where single cells sometimes infiltrate the scar (Fig. 7.12). Nests predominate over single cells in this proliferation. The intraepidermal cells often have an epithelioid or round appearance with scattered melanin in their cytoplasm. This change resembles superficial spreading melanoma cells but the nuclear picture is that of a benign process with finely dispersed nuclear chromatin and small blue nucleoli. In the dermis beneath the proliferated lesion, there may be single round cells of a melanocytic nature but there are often numerous melanophages with scattered inflammation. Admixed with the depth of the scar or beneath it, one will find at the base of the scar

nests of type B or type C nevus cells evidence of the residual dermal component of the lesion. Recurrent spindle and epithelioid cell nevi are one variant which may cause difficulty because of the propensity of the nevic cells to infiltrate the collagen of the scar. However, the spindle and epithelioid cell recurrences do not form expansile nodules but rather wedge-shaped proliferations with a mimicry of the inverted triangle of the benign spindle and epithelioid cell nevus. The recurrent dysplastic nevus is associated with epidermal atypia of a more marked degree. We have rarely seen epidermal hyperplasia with elongate rete in recurrent dysplastic nevi overlying the scar. The recurrent blue nevus shows characteristic dendritic cells that lie adjacent to the dermal fibrotic zone of the scar. Recurrent melanoma is the most significant differential diagnostic consideration in which one finds pagetoid spread of severely atypical epithelioid cells in the area adjacent to the scar in addition to the area overlying the scar. Likewise, if there be a dermal component, it is composed of an expansile nodule or vertical growth phase equivalent. One must always remember that recurrent nevi may be associated with single cell infiltration of the scar; this change should not be interpreted as melanoma. Review of prior material is essential when available.

Nevi of Special Site

The nevi of particular body sites (skin of genital, breast, acral, and belt area) and in physiologic states such as old or young age or pregnancy may show junctional or dermal proliferation that simulates dysplastic nevi and melanoma. This relatively frequent, recently recognized, and growing group of nevi has been termed, generically, *nevi of special sites*.

Nevi of Genital Skin

These nevi commonly affect the vulva of young women but occasionally occur on the male genitalia as well. Low-power examination reveals usually a well-circumscribed lesion with nevus cells in nests both intraepidermally and dermally. There is often easily visible a single cell basal

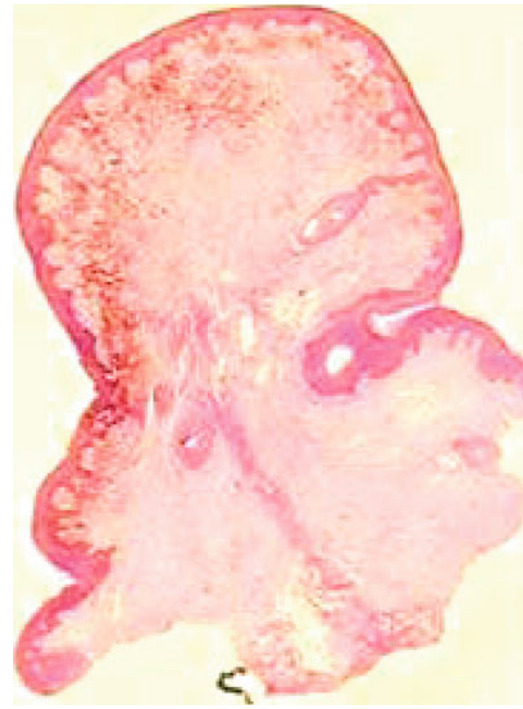


Fig. 7.13 Vulvar nevus: superficial dermal component

proliferation which may extend on both sides of the dermal component of the lesion when present; pagetoid spread, but of benign melanocytes, is found in approximately two-thirds of the patients. Keratinocytic hyperplasia is variable and does not show the regular rete ridge elongation of the dysplastic nevus [14]. Beneath the epidermis there is a coarse fibrosis without pattern that is distinctly different than the lamellar fibroplasia of the dysplastic nevus. The dermal component is usually confined to the upper half of the reticular dermis (Fig. 7.13) and consists of nests of nevus cells. High-power magnification usually shows a lentiginous and nested proliferation of nevomelanocytes but often spindle or epithelioid forms. These cells form oval discohesive theques that are present at both sides of the tips of the rete ridges and sometimes span the supra-papillary epidermis. Fusion of adjacent rete at their tips and even confluence of junctional nests in a plaque-like configuration may be noted. Extension along the basal layer of appendageal structures, especially the outer root sheath of the hair follicles, may be a striking feature. The high-power examination

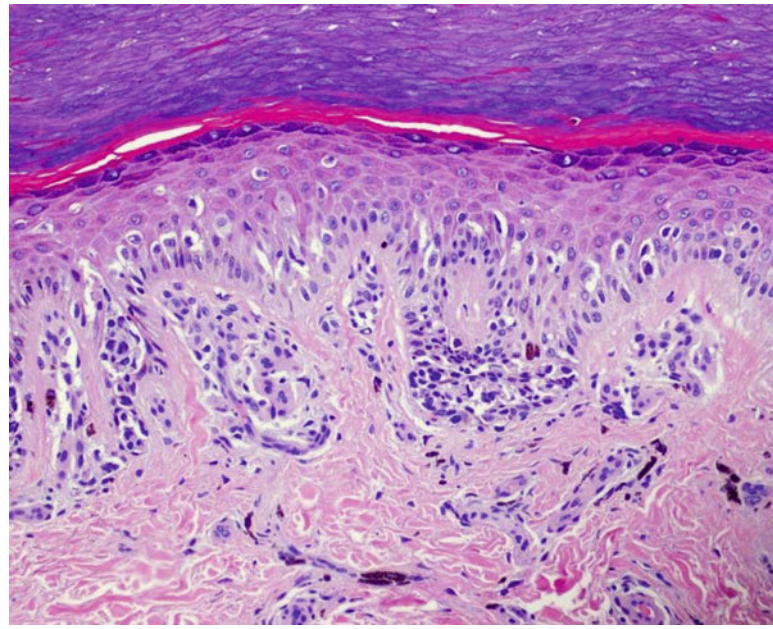


Fig. 7.14 Acral nevus

reveals that the spindle cells resemble some constituents of the compound nevus of Spitz, but these are smaller than the Spitz nevus cells and have less evident nuclear membrane and less prominent nucleoli. Chromatin however is evenly dispersed through the nucleus and there is a thin chromatin rim. Multinucleate giant cells in the intraepidermal component are a frequent finding. Often there are nests of pigmented epithelioid cells in the epidermis that are variably pigmented. These cells have small nuclei but often prominent nucleoli. As stated above, pagetoid spread may be observed but the pagetoid cells are not malignant in appearance and have a nuclear morphology similar to those in the intraepithelial and intradermal nests. The lesions tend to be symmetrical; if they have lateral extent, it appears symmetrically on both sides of the dermal component. Cells in the dermal component are disposed in nests which become smaller both in the size of the nests and in the size of the cells as they infiltrate into the papillary-reticular dermal junction and deeper into the reticular dermis. However, in some lesions one observes small nests of pigmented epithelioid cells entrapped in the collagen. The deeper cells mature into ordinary type B nevus cells. The lesion most commonly mistaken for the vulvar nevus is superficial spreading melanoma. One confidently can exclude superficial spreading melanoma by appreciating the characteristic spindle and epithelioid morphology of the intraepidermal component, the lack of cytologic features of malignancy including pleomorphism and prominent eosinophilic nucleoli, as well as an absence of mitotic activity. The second lesion to be considered is the *dysplastic nevus*. Dysplastic nevi may occur on vulvar skin as well as on male genital skin but they are very rare. The genital nevi are usually isolated lesions and are not associated with evidence of dysplastic nevi elsewhere.

Acral Nevus

The main morphological features distinguishing the *acral lentiginous nevi* from other acral non-lentiginous nevi are: elongation of rete ridges; continuous proliferation of melanocytes at the dermoepidermal junction; presence of single scattered melanocytes, or less commonly small clusters, within the upper epidermis; poor or absent lateral circumscription; melanocytes with abundant pale cytoplasm and round to oval, sometimes hyperchromatic, nuclei; and prominent nucleoli present at the dermoepidermal junction (Fig. 7.14). Some histological features of acral

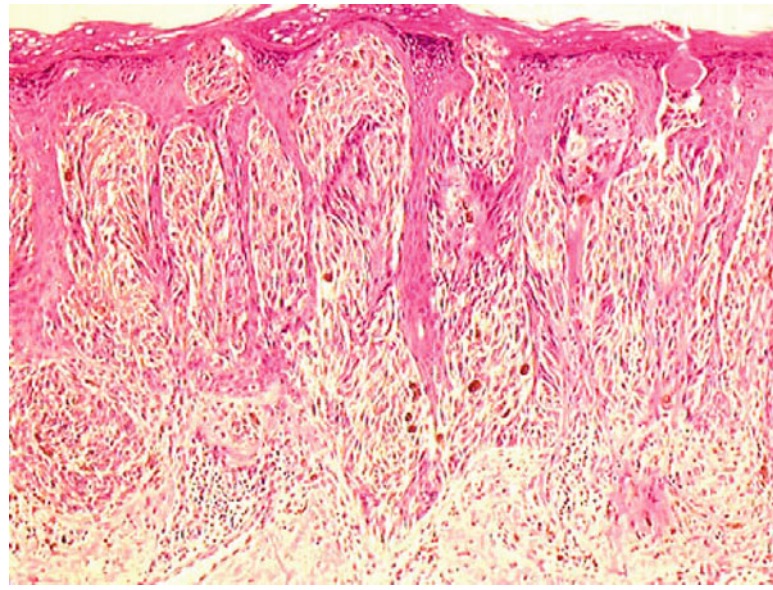


Fig. 7.15 Pigmented spindle cell nevus

lentiginous nevi are similar to those of dysplastic nevi; however, anastomosing rete ridges, cytological atypia, and well-formed lamellar fibroplasia are usually absent. The histopathological criteria to distinguish these nevi from melanoma are the lack of pagetoid lateral spread, the absence of mitotic activity in the deep dermal component, and the evidence of dermal nevocytic differentiation. The identification of this benign acral nevus, which we have identified as the benign counterpart of acral lentiginous melanoma, is important in order to avoid misdiagnoses and consequent under- or over-treatment of doubtful pigmented lesions of acral skin [15].

Spindle and Epithelioid Cell Nevi

Pigmented Spindle Cell Nevus (Reed Nevus)

It is a benign tumor characterized by proliferation of spindle nevus cells intensely pigmented that are confined at the dermoepidermal surface or the top portion of the papillary dermis. Described by Reed in 1975 as pigmented spindle cell nevus, "non-Spitz" is also considered a variant of the epithelioid and spindle cell nevus. Its identification has clinical significance. The lesion is usually a patch or plaque or a plaque with a small papule in contrast to the compound nevus of Spitz that is a papule or nodule. The spindle cell nevus is a symmetrical lesion, with sharp margins, characterized by a proliferation of spindle nevus cells, intensely pigmented, with typical superficial location limited to the dermoepidermal junction and sometimes extended to the superficial portion of the papillary dermis (Fig. 7.15). In the typical form the melanocytes are arranged in bundles or nests fairly regular in shape, size, and distribution and oriented in a vertical or horizontal pattern to occupy the junction and supra-basal portion of the epidermis and the superficial papillary dermis [16]. The extension to the dermis is often absent and, when present, is usually in bundles or small sharply demarcated nest and rarely to individual cells or in small groups irregularly shaped that may mimic melanoma in its spindle cell variant. In spindle cell nevus, however, the haphazard growth and pagetoid intraepidermal spread of melanocytes, especially at the lateral shoulder of the lesion, are absent. Pagetoid spread in the central nested area of the lesion is observed. The cell population often occurs uniformly in fusiform shape, with elongated nucleus and dispersed chromatin, small inconspicuous nucleoli, and little cytoplasm, with abundant melanin pigment, often in coarse

granules. Epithelioid cells are rarely observed and even rarer is the presence of multinucleated giant cells. Mitosis may be present, even in large number, but at the junction the presence of a high mitotic index with evidence of atypical mitoses and depth should suggest the possibility of melanoma. The epidermal changes are characterized by elongation of the rete ridges and moderate hyperkeratosis. Frequently in the dermis, a lymphocytic infiltrate and numerous melanophages are present. Ulceration and foci of necrosis are usually absent. In addition to the previously described typical pattern, variants of the spindle cell nevus are reported: pigmented spindle cell nevus with prevalent epithelioid cells, atypical pigmented spindle cell nevus, plexiform pigmented spindle cell nevus, and combined spindle cell nevus. Plexiform pigmented spindle cell nevus is characterized by the extension of the melanocytic proliferation in the reticular dermis in the form of bundles of spindle cells intensively pigmented often in intimate association with adnexal structures, nerve or vascular, and interspersed by melanophages, isolated and in aggregates. This variant simulates the deep penetrating nevus, from which it differs, in particular, for the presence of an evident junctional proliferation of spindle cells in nests. The combined pigmented spindle cell nevus variant is characterized by the combination of a spindle cell nevus with another different nevus, more frequently dermal nevus or blue nevus. Although the spindle cell nevus shows cytoarchitectural aspects similar to epithelioid cell nevus (Spitz nevus) can be easily distinguished from this, especially for the presence of abundant melanin pigment and the presence of a junctional proliferation with little or minimal dermal extension. Differential diagnostic problems may arise with melanoma and dysplastic nevus, especially for the atypical variant of spindle cell nevus. The distinction from *dysplastic nevus* can be difficult when the spindle cell nevus presents cytoarchitectural focal atypia, in which case the marked tendency to arrange themselves in bundles of melanocytes and the general uniformity of the cell population are the main morphological aspects for a correct diagnosis of spindle cell nevus. The absence of a high degree of architectural disorganization and severe cytological atypia; the intraepidermal spread of melanocytes confined mostly to the lower half of the epidermis, with rare isolated melanocytes in the superficial portions, but limited to the central portion of the tumor; and the presence of uniform cell population within the entire lesion represent the essential criteria for distinguishing spindle cell nevus from *melanoma*. The trans-epidermal migration of isolated cell or small nests is frequently present in pigmented spindle cell nevus and can simulate a pagetoid intraepidermal infiltration; however, the lack of malignant cytologic character, the absence of spread beyond the nests into the normal epidermis, and the absence of destruction of the epidermis are the most important characters in differential diagnosis with melanoma.

Epithelioid and Spindle Cell Nevus (Compound Nevus of Spitz Nevus)

This lesion is a benign tumor composed of spindle-shaped epithelioid melanocytes that occurs predominantly on the skin of the face or limbs in young individuals. It was described for the first time by Sophie Spitz [18] who designated the lesion as juvenile melanoma [17, 18] and, subsequently, as benign juvenile melanoma by Kopf and Andrade [19] or as pseudomelanoma. Today, these terms are to be avoided. In 1960, Kernen and Ackerman introduced the term epithelioid and spindle cell nevus [19], which is now universally accepted. This terminology, highly descriptive, on the one hand underlines the salient histopathological appearance, represented by a benign proliferation of fusiform and epithelioid melanocytes. The spindle and epithelioid cell nevus shows typically a symmetrical appearance often with a triangular pattern with the base in the upper dermis parallel to the long axis of the epidermis and the apex toward the depth (Fig. 7.16). The melanocytes are frequently large with spindle and/or epithelioid appearance (Fig. 7.17), arranged mainly in bundles or nests or alveolar structures. The cytoplasm is often abundant, dense, and large; is finely vacuolated

and even wispy, eosinophilic, or amphophilic; and, in some cases diffusely pigmented with sparse and small melanin granules. The nucleus of melanocytes presents a dispersed chromatin and a well-demarcated nuclear membrane. The nucleolus is often centrally located, prominent, basophilic, or eosinophilic. There are sometimes multiple (two or three) nucleoli, sometimes with cytoplasmic invaginations (intranuclear pseudoinclusion). The spindle and epithelioid cell nevus can be junctional, compound, or dermal. The spindle and epithelioid cell compound variant is the most common. Each type of the cell population may consist primarily of fusiform melanocytes, epithelioid cells, or both cell types. However, the pure epithelioid variant is most common in infancy. The presence of numerous epithelioid cells in an adult should prompt careful review and even levels if necessary to rule out a melanoma. It is not uncommon to find plurinucleate giant cells, also with four to five large nuclei. A useful rule of thumb is that the multiple nuclei are similar in a benign lesion. The malignant giant cell is associated with pleomorphic nuclei and nucleoli. The junctional component shows aggregate and nests of variable-size melanocytes unevenly distributed along the dermoepidermal junction (Fig. 7.18), often with major axis perpendicular to the skin surface. A halo, optically empty due to a fixation artifact phenomenon, separates the nests of the melanocytes from the epidermis. The junctional proliferation stops abruptly on the side margins and, if the nevus is compound, its lateral extension does not exceed the dermal component. The absence of lateral extension and dissemination supra-basal intra-epidermal-type "pagetoid" cells represents an important criterion for differentiating epithelioid and spindle cell nevus from melanoma, especially in adults. In the child, in fact, you can also see frequently involved even up to the stratum corneum of the epidermis with trans-epidermal elimination of individual melanocytes or nests. In the superficial dermal layer, typical mitoses can be observed but also very rare atypical

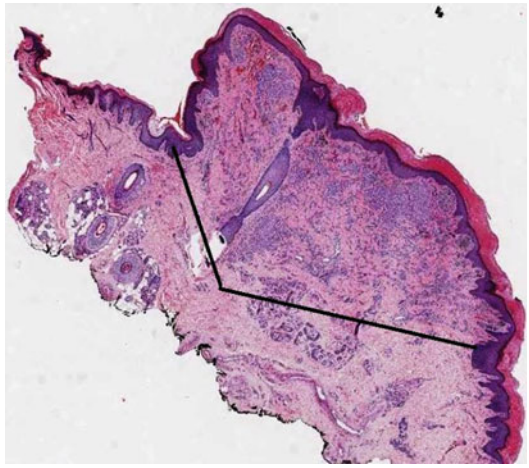


Fig. 7.16 Spitz nevus: reverse triangle

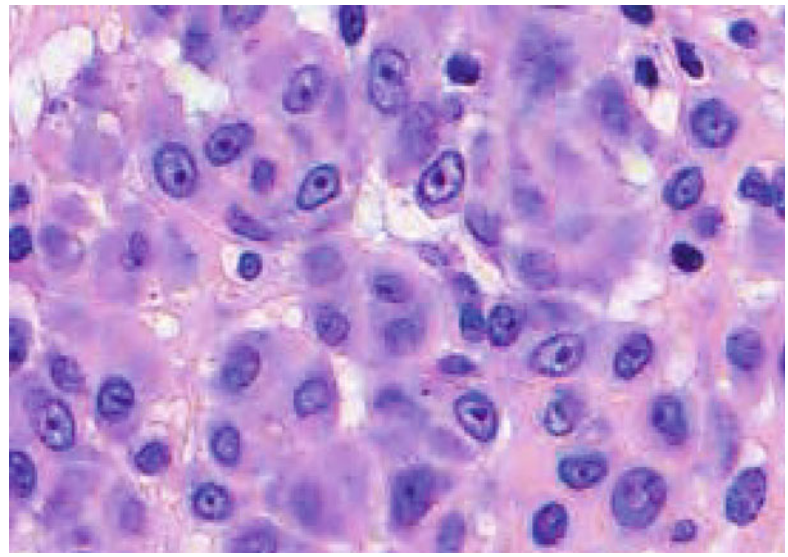


Fig. 7.17 Spitz nevus, epithelioid cells

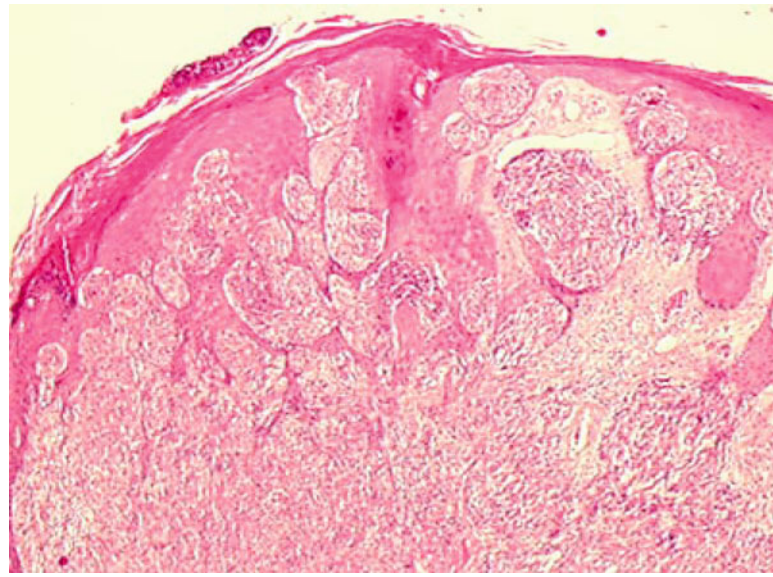


Fig. 7.18 Spitz nevus, junctional and dermal proliferation

mitoses can sometimes be present even in the deep dermal portion; however, this character must be evaluated with caution because in the deep dermal portion, and along the proliferation margin, mitoses are more frequently present in melanoma. Marginal mitoses, namely, those within 250 μm of the peripheral border of the lesion, are of most concern and usually are associated with a metastatic potential of the lesion. In the dermal component, the melanocytes are arranged mainly in nests, bundles, or cords. The nests become smaller as they extend deeply and break up into single cells. These cells do not cause disruption of the dermal architecture so that the fibers appear to be falling apart. Rather, the cells appear as fibroblasts without destroying the architecture. Dr. Elston Helwig used to teach that the cells of the Spitz nevus look "at home in the dermis", much like the space between the collagen fibers of the reticular dermis separated without destroying a feature often available in single file. The size of the cells decreases in the reticular dermis, becoming more rounded with little cytoplasm (maturation). This kind of transformation is a morphological appearance characteristic and important for the diagnosis of epithelioid and spindle cell nevus. Two other histological features are important for the histological diagnosis: the uniformity of the cell population morphology from side to side of the lesion and the presence of isolated single cells in a pseudoinfiltrative pattern at the base of the nevus, which reaches sometimes into the subcutaneous fat. The melanin pigment, when present, is in small quantities, most often in the superficial lesions, especially just below the epidermis. The spindle and epithelioid cell nevus is frequently accompanied by epidermal and stromal changes. Acanthosis, hyperkeratosis, pseudoepitheliomatous hyperplasia, and, less frequently, parakeratosis are frequently observed, especially in the epithelioid and spindle cell nevi of junctional or compound type, more rarely in the epithelioid and spindle cell dermal variant. The stromal alterations include frequently the presence of telangiectasia and edema of the papillary dermis, sometimes so marked as to create a clear zone of separation ("grenz zone") between the epidermis and the dermal component of nevus. Near the dermoepidermal junction, the "bodies of Kamino" can be found; these are rounded eosinophilic bodies present singly or in small clusters; they were interpreted as "apoptotic bodies," but they are now known to be portions of epithelial cell as well as nevus cell membranes admixed with cytosol. Lymphohistiocytic infiltrates are occasionally present and are scattered usually in the depth of the lesion. Dense infiltrates raise the

question of a halo nevus or possibly an atypical lesion. Evidence of focal regression superficially with inflammation and fibrosis is usually a sign of a melanoma. *Halo Spitz nevi*, as any other halo nevus, have a prominent infiltrate that affects the entire lesion, not a focal portion. Numerous histopathological variants of the spindle and epithelioid cell nevus can be recognized. A *desmoplastic variant* [20] in which there is a striking pericellular fibrosis that encompasses the entire lesion. The brightly eosinophilic fibers highlight the often quite densely stained nevus cells. Clear epithelioid cell forms help to differentiate the lesion from a desmoplastic melanoma or sclerosing blue nevus. According to Hilliard [21], the staining pattern for p16 in desmoplastic melanomas and Spitz nevi in conjunction with the histopathologic features, S100 staining, Ki67proliferation index, and clinical scenario may aid in the difficult differential diagnosis between these two entities. There is also a *balloon cell variant* [22], a *lichenoid variant*, and as noted a *halo variant* [23]. Rarely a granulomatous response has been described. The *myxoid variant* [24], often with the presence of mast cells, is reported. The spindle and epithelioid cell nevus often poses problems of differential diagnosis with melanoma. In fact, some important characters for the histopathological diagnosis of malignancy, such as cellular atypia, intraepidermal spread, and the presence of mitosis, are not as conclusive if detected in epithelioid and spindle cell nevi. Knowledge of clinical features (age, location, mode of onset, duration, macroscopic and dermatoscopic appearance) is very important and sometimes essential for a correct interpretation of the lesion. One of the most important patterns is the cytology monomorphism present in Spitz nevus and absent in polyclonal proliferation of the melanoma. The junctional/superficial spindle and epithelioid cell nevus must be distinguished from dysplastic nevus and melanoma in situ. In favor of the dysplastic nevus are the proliferation of basal melanocytes with freckled "atypical" and polymorphic pattern and the presence of fused nests with major axis parallel to the skin surface, the elongation of the rete ridges, and the fibrosis of the superficial dermis. The presence of a continuous proliferation of atypical melanocytes with a tendency to invade aggressively the more superficial layers of the epidermis, atypical mitoses, and marked dermal inflammatory infiltrate, referring to the diagnosis of melanoma in situ or invasive horizontal growth phase melanoma. The compound spindle and epithelioid cell nevus can pose problems of differential diagnosis with invasive superficial spreading melanoma. In particular the epithelioid and spindle cell nevi that have marked trans-epidermal migration in nests or single cells epidermal infiltration can simulate a "pagetoid" spread and those with numerous mitoses especially in the deepest portion of the lesion. The dermal epithelioid cell and dermal spindle nevus can be misinterpreted as nodular melanoma; in these cases the clonal proliferation without evidence of deep dermal maturation, the presence of atypical mitoses, and the cellular necrosis and apoptosis can be important characters to distinguish Spitz nevus from melanoma. The use of additional diagnostic methods such as immunohistochemical stains with monoclonal antibodies and/or polyclonal (anti-S100, NSE, HMB45), the determination of DNA content (ploidy) by means of flow cytometry or image analyzer, and the evaluation of cell proliferation (PCNA) still do not allow to differentiate with certainty nevus epithelioid and spindle cell melanoma. In our experience and in recent report [25], p16 expression in nodular spitzoid melanomas and Spitz nevi, in conjunction with clinical and histopathological evaluation, may be a useful tool in differentiating between these two entities. Melanoma cases are associated with loss of p16 immunoreactivity without any correlation with their Breslow thickness, whereas the Spitz nevi have a strong positive nuclear and cytoplasmic expression of p16 staining (Fig. 7.19). More recently, techniques of in situ hybridization of DNA in paraffin slides have demonstrated some chromosomal abnormalities suggestive of melanoma [26]. Furthermore, the technique of comparative genomic hybridization (CGH) has revealed that in Spitz one can find an increased copy of the short arm of chromosome 11 [27]. Less often changes in chromosome 6 have been

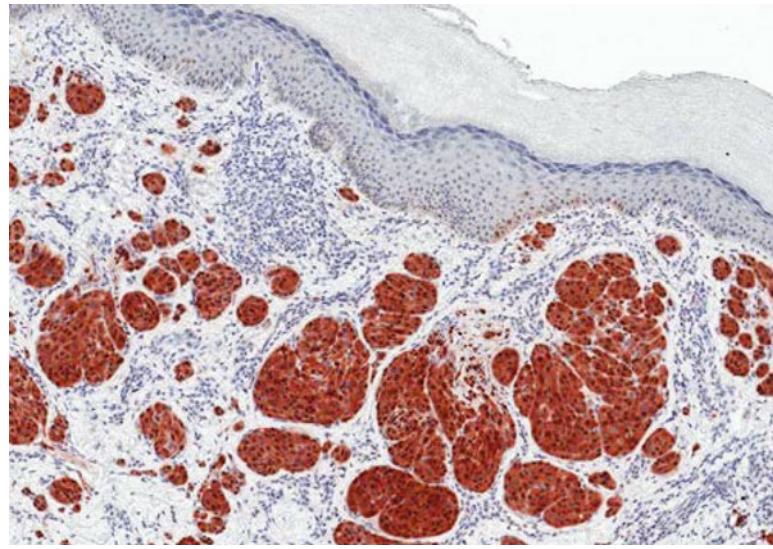


Fig. 7.19 Spitz nevus: nuclear and cytoplasm p16-positive stain

described [28]. These very limited changes are strikingly different than the myriad changes found in malignant melanoma.

Dermal Melanocytosis

The blue nevus and its variants (cellular, atypical, and combined) belong together with desmoplastic blue nevus, deep-penetrating nevus, Mongolian spot, and the Ota and Ito nevi, are a group of lesions defined as the "dermal melanocytoses" [29]. These lesions are characterized by the proliferation of pigmented dendritic or epithelioid melanocytes located in the papillary and reticular dermis and by a prevalent immunohistochemical positivity with HMB45 antibody stain.

The Common Blue Nevus

The blue nevus is a benign melanocytic tumor in which the depth of melanin pigment present in nevus cells in the deep dermis is responsible for the characteristic color of the lesion which takes its name (Fig. 7.20). The blue nevus occurs predominantly in young people, with equal frequency in both sexes. The sites most affected are the skin on the backs of hands and feet and buttocks. Lesions also may be found on the trunk and on the scalp. Cases have been reported in extra-cutaneous site: oral cavity [30], uterus [31, 32], vagina [33], spermatic cord [34], and prostate (Fig. 7.21) [35, 36]; one case was described in a teratoma involving a mature cystic ovary [37] and in the bronchial tree [38]. Clinically, the lesions exhibit a blue, deep blue, blue-gray, or royal blue color. The blue nevus is characterized by three fundamental morphological aspects: (1) proliferation of dendritic melanocytes in the reticular dermis, (2) numerous melanophages, and (3) fibrogenetic stromal reaction. The dendritic melanocytes show typical elongate fusiform shape, with thin cytoplasmic extensions and prominent melanin pigment granules that sometimes obscure the nucleus. However, the pigment is always a brown finely granular one that differentiates the blue nevus cell from a melanophage in which the pigment is dense and coarse and often obscures the nucleus. In the blue nevus, the latter is oval to egg-shaped and displays finely dispersed chromatin, thin nuclear membrane, and inconspicuous nucleolus. Only rarely pleomorphism is present. The mode of cellular growth, individually or in small bundles, creeping between the collagen fibers of the dermis in a sometimes serpiginous pattern, without collagen fragmentation, is responsible for the apparent lack of cellularity of the lesion, which in low magnification can simulate the benign fibrous

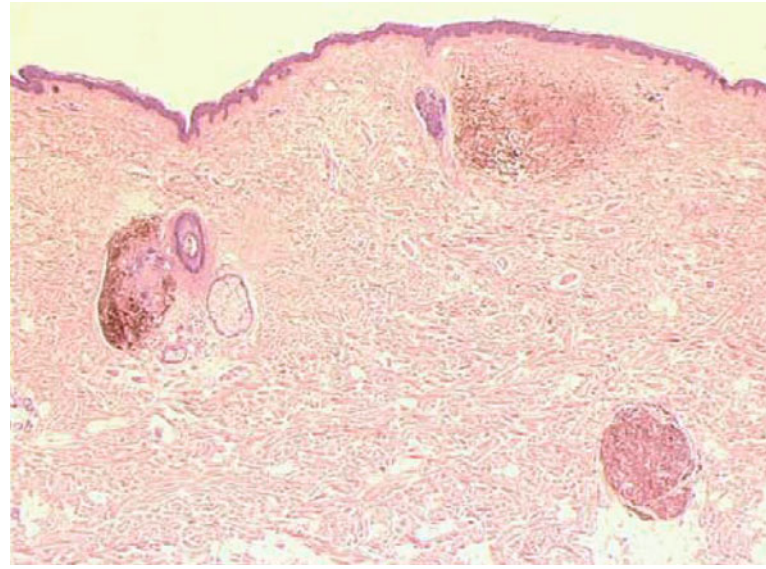


Fig. 7.20 Blue nevus

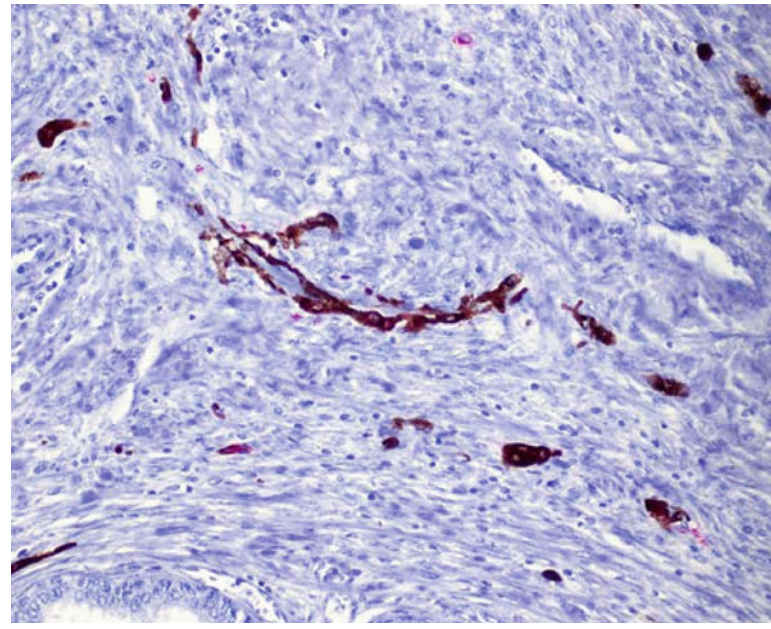


Fig. 7.21 Blue nevus prostate, HMB45 immunostain

histiocytoma. Often one can observe a tendency of the nevus cells to arrange themselves around the skin appendages or along vessels or nerves. The fibrogenesis shows varying degrees, from mild to intense, until the formation of dense bundles that give the appearance of a desmoplastic or sometimes neuroid lesion. Commingled with the melanocytes melanophages with cytoplasm packed with large granules of melanin pigment are still present. In the typical form mitoses are usually not observed. The presence of a melanocytic proliferation-free zone immediately below the epidermis (grenz zone) is a characteristic feature. The epidermis may occasionally exhibit hyperplasia and hyperpigmentation of basal melanocytes very similar to the findings of a benign dermal fibrous histiocytoma. Frequently it is possible to observe multifocal areas of proliferation

of the blue nevus. Among the variants of the blue nevus, one of the most common is the *combined blue nevus* where the lesion is presented in association with usually an acquired nevus. The ordinary nevus component may be a junctional, compound, or dermal nevus type. Less commonly, it may be a spindle and epithelioid cell Spitz nevus. Certainly one may find a combined congenital/blue nevus. The change may be present at birth. When it is acquired in the congenital setting, it appears as a change in the lesion. Because pigmented melanomas can occur in the deep portion of a congenital nevus and have a blue discoloration, we recommend always a biopsy of any acquired blue discolored area in one of these congenital lesions. The differential diagnosis of blue nevus is usually not a problem especially for the typical form. The differential diagnosis with other forms of dermal melanocytic proliferation must be considered. The nevus of Ota and Ito that, however, present a typical clinical pattern and location. The ectopic Mongolian spot is usually a congenital lesion that has similar coloration to the Mongolian spot in the lower posterior trunk. It is also a flat lesion with no consistency compared to blue nevi that are usually at least firm and slightly raised. The benign dermal fibrous histiocytoma, especially when there are marked hemosiderin deposits, and the tattoo should be also considered in differential diagnosis [39].

Cellular Blue Nevus

Cellular blue nevus is a characteristic melanocytic tumor frequently localized in sacral coccygeal and gluteal area with a marked cellularity involving not only the reticular layer but also the hypodermis often with a characteristic dumbbell-shaped pattern" (Fig. 7.22). The tumor frequently exhibits a multinodular growth, and three different patterns can be identified: (1) mixed biphasic, (2) alveolar, and (3) neuro-nevoid. The *mixed biphasic* is the most frequent and is composed of large nodules of spindle cells intermingled with nests of epithelioid cells resulting from cross section of spindle cell fascicles. These nodules are separated from one another by zones of fibrosis. These fibrous zones contain melanophages but also exhibit characteristic blue nevus cells. Rare mitoses can be observed in these nodules as can some pleomorphism. The *alveolar* type presents rounded nests, with sharp edges; polyhedral and spindle cells, often pigmented with vesicular nuclei; inconspicuous nucleoli; and typical clear cytoplasm. The nests are surrounded by pigmented dendritic melanocytes and melanophages commingled with little stromal collagen which can occasionally occur edematous. In the *neuro-nevoid* type, the cells present schwannian differentiation and tend to aggregate in bundles that simulate the appearance of peripheral nerves; collagen and macrophages can be abundant. At times the cellular blue nevi can be so strikingly proliferative with ulceration that they raise the question with a nodular melanoma. However, the presence of dendritic cells with melanophages in fibrous stroma between the nodular islands of cellular blue nevi helps to

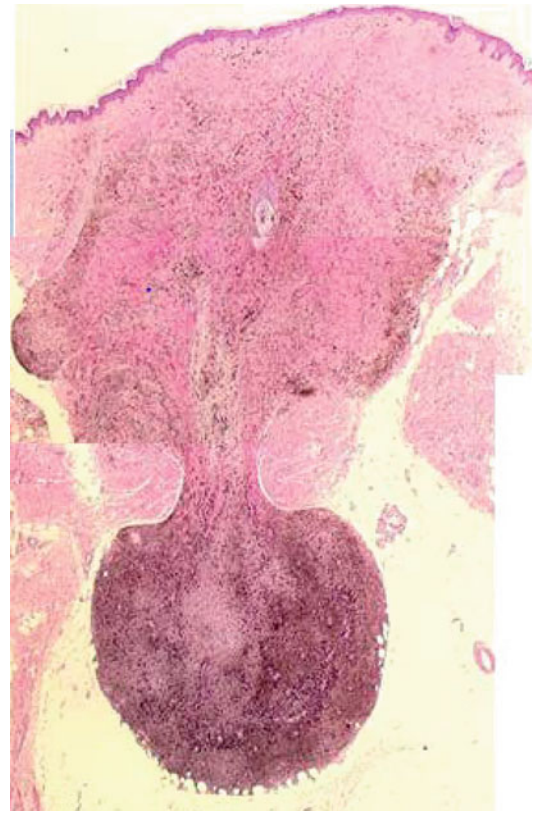


Fig. 7.22 Cellular blue nevus

differentiate this tumor from nodular melanoma. Likewise, the islands of cells are filled with cells containing clear cytoplasm with coarse melanin granules scattered amidst the clear cytoplasm. Overall the nuclei are repetitively similar and mitotic figures may be observed but the mitoses are not atypical and are not frequent in number. In nodular melanoma which resembles cellular blue nevi, there is very high grade nuclear atypia associated with mitotic activity and necrosis.

Desmoplastic Nevus

Some nevi present or may become fibrous nodules for the presence of desmoplasia. The recognition of the desmoplastic nevus is important to distinguish from other benign skin lesions such as fibrous histiocytoma and dermal neurofibroma but also from desmoplastic melanoma [40]. The presence of desmoplasia in nevus may be related to regressive or reactive phenomena. The proliferation is usually centered in the papillary dermis but can also be extended to the reticular dermis and junctional activity often is minimal or absent. The epidermis overlying the tumor may present pseudoepitheliomatous hyperplasia, irregular acanthosis, and hyperkeratosis. The nevus cells are arranged singly or in small clusters, nests, or cords, and spindle cells predominating type C cells and epithelioid types A and B are less frequent or rare but always readily apparent. Sometimes there are bizarre giant cells with or ganglion-like aspects. Not uncommon is the finding of intranuclear inclusions caused by invaginations of the cytoplasm to the nucleus. Mitoses are rare and atypical mitoses are absent. The melanin pigment is irregularly distributed granules of different sizes and quantitatively variable. Rare are the melanophages. The stroma consists of eosinophilic collagen bundles usually much thicker than those normally recognized in the papillary dermis. The stroma often surrounds and isolates individual cells. Characteristic is a convex lens patter with sharp margins (Fig. 7.23). In Table 7.2 the main characteristics between desmoplastic nevus and desmoplastic melanoma are compared.

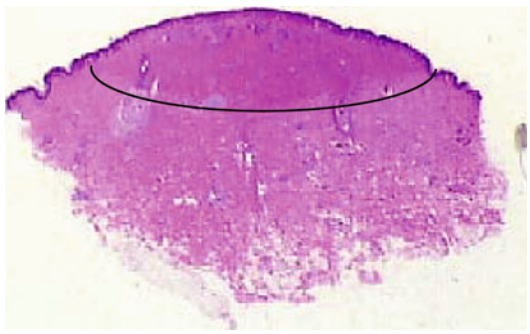


Fig. 7.23 Desmoplastic nevus, convex lens pattern

Deep-Penetrating Nevus

The deep-penetrating nevus is a benign acquired melanocytic proliferation that often has a brown to blue/black coloration with histological features that resemble the combined nevus, a blue nevus and a spindle and epithelioid cell nevus [41].

Table 7.2 Differential diagnosis between desmoplastic nevus and desmoplastic melanoma

	Desmoplastic nevus	Desmoplastic melanoma
Junctional activity	Poor or absent	Nests of melanocytes with acral or lentiginous pattern
Epidermis	Hyperkeratosis or irregular acanthosis	Atrophy and thinning
Margins	Well demarcated	Irregular (neurotropism)
Type of cells	Predominance of spindle cells rare epithelioid and giant cells	Epithelioid cells on the surface and spindle cells in depth
	Some bizarre ganglion-like cells	Rare polymorphism
Mitoses	Rare, superficial; no atypical mitoses	Present at all levels and atypical
Necrosis	Absent	Variable
Melanin pigmentation	Moderate	Usually scarce or absent

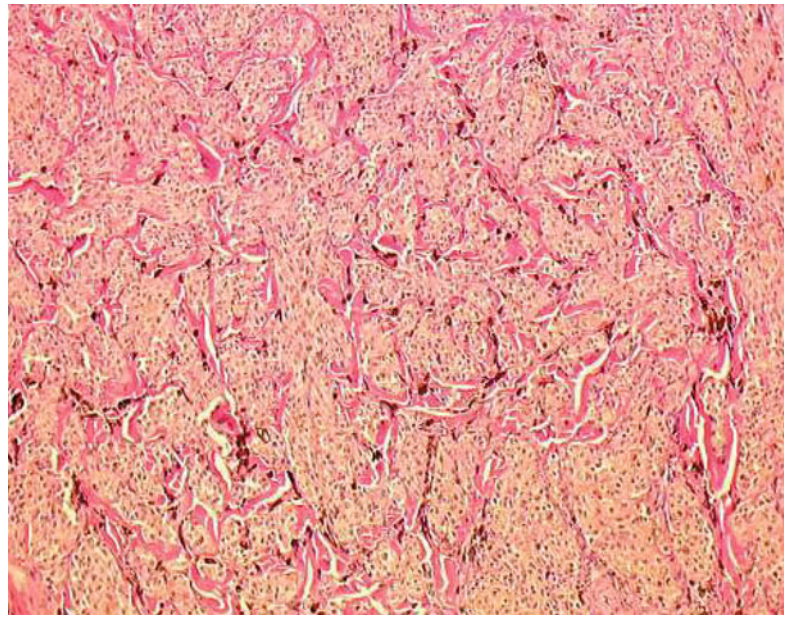


Fig. 7.24 Deep penetrating nevus

Necrosis, ulceration, and/or significant mitotic activity is usually absent. Low-power examination reveals a strikingly circumscribed but deeply penetrating lesion that is usually wedged shape. The base of the lesion lies along the long axis of the epidermis and the apex or apexes are present in the deep dermis and in the subcutaneous fat. The intraepidermal component consists of nests of nevus cells that are usually similar to the deep dermal proliferation. The dermal component of the lesion shows numerous fascicles and nests or cords of nevus cells surrounded by melanin-laden macrophages (Fig. 7.24). Most lesions have a focal scattered lymphoid infiltrate. The presence of a compound nevus with extensive deep infiltration with scattered melanophages and with an irregular border with theques of cells following neurovascular bundles is quite characteristic. There is some diminution in cell size from superficial to deep, but overall the cells remain about similar in size throughout, without evidence of maturation from the superficial to deep component of the nevus. The cells of the deep-penetrating nevus are S100 andHMB45 antigen positive; p16 may be variable with isolated positive nevus cell. They are negative for keratin and lysozyme except in the areas of the macrophages. The deep penetrating nevus poses a striking problem frequently in differential diagnosis from nodular melanoma [42]. Nodular melanoma usually presents large intraepidermal clonal nests of severely atypical cells. Melanomas are usually lesions with broad bases and with a narrower origin site, the converse of the deep penetrating nevus which has a broad base superficially and a tapered apex. Also melanomas tend to expand more laterally with expansile nodule formation in the dermis, whereas the deep penetrating nevus extends outward into the dermis along neurovascular bundles. Furthermore, melanoma shows much more pleomorphism and polyclonal nest. In the compound nevus of Spitz the fascicles become much smaller as they reach the mid to deep reticular dermis and there is often an insinuation of single cells in the lower reticular dermis.

Dysplastic Nevus

Dysplastic nevi are a type of acquired nevus usually greater than 6.0 mm in diameter, with irregular borders and irregular coloration, present in sun-exposed areas on the arms and trunk but importantly can also affect the scalp and covered areas of the body, namely, the female

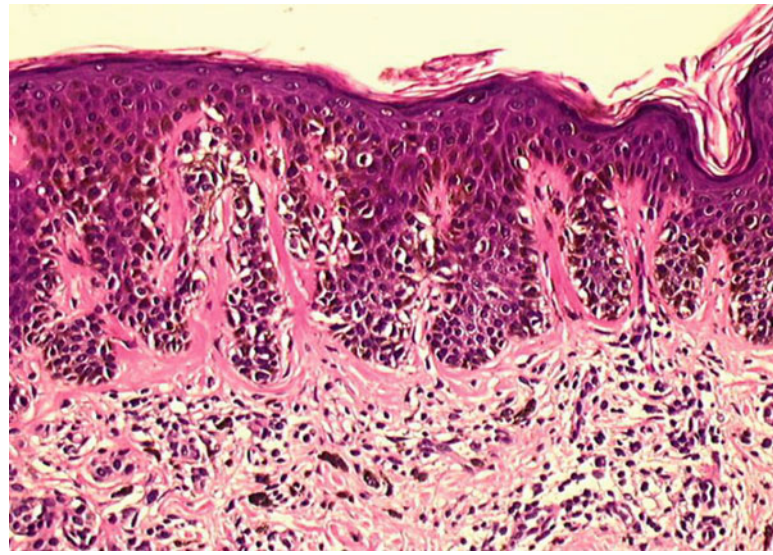


Fig. 7.25 Dysplastic nevus

breasts and the bathing trunk areas. These lesions represent risk markers and potential melanoma precursors. They occur both sporadically or are inherited as an autosomal dominant. They rarely can be noted at birth. When sporadic, they can be single or only a few in number; when present in the familial setting, they can be numerous with some patients presenting with hundreds of lesions. The presence of a single dysplastic nevus is associated with a slight increase in incidence of melanoma. Multiple dysplastic nevi, especially in the familial setting have a substantial risk of increased incidence often as much as 125-fold compared to a person without the family involvement [43]. Genomic analysis of dysplastic nevi are associated with nonrandom mutations often involving chromosome 6. Dysplastic nevi exhibit an atypical proliferation of nevocytes with specific epidermal and dermal architectural features. In the heritable setting they are associated with the family history of atypical moles and/or melanoma and are referred to as the *dysplastic nevus syndrome*. The histopathological diagnosis of a dysplastic nevus requires an appreciation of both cytologic and architectural features [44]. The cytologic patterns have been described as lentiginous and epithelioid. The architectural features combine both epidermal and stromal changes and they are divided into major and minor criteria. The presence of both major criteria and at least two of the minor criteria is requested for the diagnosis (Fig. 7.25). Dysplastic nevi may be junctional or compound. The important epidermal criterion is a hyperplasia and elongation of the rete ridges similar to the hyperplasia observed in lentigo simplex. The principal cytologic features are an atypical nevocytic proliferation with either a lentiginous pattern with small cells with irregular-shaped nuclei confined to the dermoepidermal junction or an epithelioid cell pattern with large round cells with fine melanin granules in their cytoplasm. These cells have also round nuclei with oval shape and small nucleolus. When the lesions are compound, they frequently show an irregular extent of the atypical proliferation beyond the dermal component. The stromal changes include patterns of collagen deposition around the rete ridges, increased vascularity, and inflammation. The histopathologic criteria have been formulated as follows:

Major criterion: A basilar proliferation of atypical nevocytes extending at least three rete ridges beyond any dermal nevocytic component. An organization of this proliferation in a lentiginous or epithelioid cell pattern

Minor criterion: The presence of lamellar fibroplasias or concentric eosinophilic fibrosis, neovascularization, inflammatory host response, and fusion of rete ridges

The major feature exhibits basilar proliferation of atypical nevocytes consists of a proliferation of nevocytes along the dermoepidermal junction in characteristically hyperplastic rete resembling lentigo simplex but with cytologic atypia. The atypia consists in pleomorphism of the melanocytic population with increase of the nuclear dimension, irregular chromatin pattern and presence of some cells with prominent nucleoli. In the junctional dysplastic nevus it is this change solely that is present and fulfills the requirement of the first major criterion. If there is a preexisting dermal component, then it is necessary to identify the extent at least three rete ridges beyond the dermal component. This change has also been referred to as the "shoulder" effect as described by Clark [45]. Similar pattern is present frequently in congenital and some acquired compound nevi but the intraepidermal proliferation beyond the dermal component in these nevi is absent. If present, the intraepidermal component is symmetrical on both sides of the lesion, whereas in the dysplastic nevus, it is asymmetrical. Occasionally pagetoid spread may be noted but consists of small nevocytes with hyperchromatic nuclei. The pagetoid spread is usually confined to the lower half of the epidermis. It is quite characteristic for an occasional single cell to be found in the papillary dermis beneath the atypical lentiginous proliferation. In epithelioid cell dysplasia the nevocytes have a characteristic appearance of ample cytoplasm surrounding usually round small nuclei. The cytoplasm contains fine melanin granules. The nuclei may have visible nucleoli which are small and blue or amphophilic, or the nuclei may be quite densely hyperchromatic. However, importantly the nuclear to cytoplasmic ratios are small. Often in epithelioid dysplasia the epidermis is slightly hyperplastic without the striking elongation of the rete ridges as seen in the lentiginous dysplasia. The epithelioid cells are present singly along the dermoepidermal junction, form nests of various sizes, and may be associated with pagetoid spread confined to the lower half of the epidermis without aggressive epidermis infiltration. Likewise, single cells may be noted in the papillary dermis with similar cytologic character to those in the epidermis. This change is especially important in scalp dysplastic nevi in children and adolescents where there is marked atypia of the intraepidermal nevomelanocytes with always scattered single cells in the dermis. Misinterpretation of this finding can lead to misdiagnosis and often quite radical unnecessary treatment. In both the lentiginous and epithelioid cell patterns, single cells or nests are present along the lateral side of the rete ridges with an irregular growth of nests toward the outside of the rete ridges; bridges between the elongated and filiform rete ridges are common. The minor criteria include the collagenous changes in the dysplastic nevus that may be divided into two types. The first is lamellar fibroplasias which describes a repetitive laying down of fine collagen fibers or lamellations of collagen at the tips of the rete ridges lying parallel to the long axis of the epidermis. These fibers are interspersed with what appear to be fibroblasts. However, these cells are S100 positive and probably represent transformed nevomelanocytes that have the capacity to lay down these fibers. The second type of collagenous change describes concentric eosinophilic fibrosis which is a dense application of bright eosinophilic tissue around the rete ridges with minimal cellularity. The second minor criterion for diagnosis of the dysplastic nevi is the frequent association with an increase in vascularity of capillary and venules in the papillary dermis. The third criterion is the presence of an inflammatory reaction consisting of a lymphocytic infiltrate scattered in the papillary dermis both in perivenular and intervenular arrays. The intensity of the reaction is related to the degree of atypia. More severe atypia is frequently associated to more striking inflammatory infiltrate. The importance of the infiltrate as a marker also of transformation of the dysplastic nevocytes has been described as occurring with the expression HLA-A,B,C (HLA) and beta-2 microglobulin (beta 2 m) [46]. The final aspect that serves as a minor criterion is the apparent fusion of the rete ridges at their tips by nests of nevic cells. While this change is most common in the lentiginous proliferation of nevomelanocytes, it can clearly also be observed in association with the epithelioid cell pattern. Frequently the bridging cells have a spindle configuration with the orientation of their nuclei parallel to the long axis of

the epidermis. It is custom to grade melanocytic atypia in the dysplastic nevus as to slight, moderate, and severe. To define the nuclear atypia, we used to compare the dimension of the melanocytic cells to the keratinocytic nucleus of the stratum spinosum. Slight atypia refers to melanocytic nuclei that are approximately one and a quarter to one half the size of the spinous layer keratinocytic nucleus. Moderate atypia refers to nuclei that are one half to equal to the size of the spinous layer keratinocytic nucleus and severe atypia, the size of or up to 1 ½ to 2 times the size of the keratinocytic nucleus. In contrast the melanoma cells are very variable in their nuclear size. A characteristic of melanoma, pleomorphism, is demonstrated by sizes ranging from that of a slightly atypical nevocytic nucleus to several times the size of a spinous layer keratinocytic nucleus. Another approach to atypia is more descriptive. In this approach mild atypia shows a pleomorphism of small densely hyperchromatic cells confined to the dermoepidermal junction. The pleomorphism mainly has to do with irregularities and shape of the nuclei. Cytoplasmic retraction is marked. Moderate atypia refers to nuclei with more angular configurations even rectangular or triangular with a dense eosinophilic cytoplasm visible minimally around the nucleus. In severe atypia, the nuclei are larger, more hyperchromatic, but with nucleoli and with more ample cytoplasm. However, the cells do not show the type of open chromatin patterns of melanoma cells nor does the cytoplasm qualify for that of the finely granular pigment of melanoma cells. The epithelioid cells under this descriptive system of classification have small nuclei with very small nucleoli or markedly hyperchromatic small nuclei approximately ½ the size to 2/3 the size of squamous cell layer keratinocytic nuclei but are surrounded by ample cytoplasm and finely granular melanin within it. In both systems of classification of atypia, multinucleate giant cells may be observed. Mitosis is extremely rare. Another approach to grading is to use a two-grade system, namely, low grade and high grade. In this approach, high-grade atypia is equivalent to severe atypia. Low grade is identified as slight to moderate atypia using the above descriptions [47]. Finally, an antibody that reacts with adenylyl cyclase has been found to be useful in grading. It stains the Golgi apparatus in benign nevi. In atypical lesions there is focal increase in Golgi staining but also variable staining of the nuclei and cytoplasm. In severe there are admixed nuclei that are diffusely and strongly positive [48]. With regard to therapy, the first rule is regardless of the degree of atypia, even if slight, any residual lesion should be re-excised. The reason for this strong recommendation is that there is an approximately 20 % error in the choice of the most atypical area by the clinician. In dysplastic nevi, there are cases in which the melanoma appears as the benign portion or as an area of regression. If a lesion has slight or moderate atypia even with positive margins and there is no residual, we recommend follow-up of the site with the question of re-excision left to the clinician. For any lesion that is severely atypical, we recommend a 5 mm margin. The atypia of the dysplastic nevus is in striking contrast to that of melanoma in situ. In dysplastic nevi the atypia is variable from cell to cell so that there is a discontiguous atypia present. Also the junctional proliferation is discontiguous in dysplastic nevus in contrast to horizontal growth of melanoma where the atypical cells are disposed side by side along the dermoepidermal junction replacing the basilar layer and are associated with aggressive pagetoid spread up to the level of the granular cell layer. It is this discontiguous uniform atypia that allows for the diagnosis of melanoma and differentiates this lesion from the dysplastic nevus in which there is no contiguous uniform atypia but random discontiguous atypia. One of the problems that is confronted in the dysplastic nevus is to separate severe atypia from melanoma in situ. We believe that this can best be effected by clearly appreciating the extent of atypia and the extent of pagetoid spread so that severely atypical dysplastic nevi with minimal pagetoid spread can clearly be classified as dysplastic nevi in our opinion. When the pagetoid spread extends beyond the upper half of the squamous cell layer, especially up the granular cell layer, then we believe that the diagnosis appropriately is focal melanoma in situ arising in association with the dysplastic nevus. A word of emphasis should be said concerning single cell infiltration of the papillary dermis. Dysplastic nevi characteristically may be associated as has been stated above with single cell

infiltration of the papillary dermis more commonly in moderate to severe atypical proliferations and in the epithelioid cell proliferation. In such instances the cells are of the same character of the intraepidermal component and do not require a diagnosis of invasive melanoma. An appreciation of this type of infiltration in dysplastic nevi is extremely important to prevent over diagnosis of melanoma. Dysplastic nevi arising in association with a preexisting dermal component usually exhibit typical type B and type C nevus cell proliferation of the dermal component. However, in our experience, especially in persons with the dysplastic nevus syndrome, the dermal component may be quite hyperchromatic and fail to show type C nevus cell formation. These hyperchromatic nests of nevic cells frequently abut the papillary-reticular dermal junction and interestingly enough are often HMB45 positive. This type of atypia, so long as the nuclei show a rather banal chromatin pattern, there are no mitoses, and diminution in cell size with maturation is present, is not indicative of melanoma. At times these dermal nests may be associated with a linear fibrosis of eosinophilic collagen surrounding them and separating them from the overlying epidermis. This type of change should not be mistaken for melanoma with regression in which there are linear fine bands of collagen with increased vascularity that entrap and separate the nests of hyperchromatic cells. Nests of hyperchromatic melanoma cells entrapped in fibrous tissue usually are quite compact, have quite strikingly hyperchromatic nuclei, are highlighted by epithelioid cells with fine melanin in their cytoplasm, and show mitotic figures. If they are nested, the peripheral cells will be plump and hyperchromatic rather than those surrounding nevus nests that are thin and delicate fibroblast-like type C cells.

Atypical Melanocytic Tumors

Atypical Spitz/Reed Tumors

The problem of atypical Spitz nevomelanocytic/tumors is one of the most difficult that pathologists and dermatopathologists encounter. There are several very important issues. First, one must distinguish an atypical nevus from a malignant tumor. Secondly, if a tumor, an attempt must be made to predict if the lesion has a metastatic potential. Third, even if the lesion metastasizes, it may not spread systemically. Finally, can one identify conclusively a lesion that can kill the, especially in childhood and adolescence where most of the lesions occur. At times, one may be forced to write a descriptive diagnosis in a difficult case. There are several significant studies that discuss these difficulties. In a study in which nine cases selected for their diagnostic difficulty were circulated among "expert" pathologists, the reproducibility of the diagnosis of Spitz tumor was very poor [49]. In a subsequent study of 17 spitzoid lesions, there was no consensus as to diagnosis; some of these cases metastasize [50]. Of great significance, several lesions were diagnosed by most of the pathologists as Spitz nevus or Spitz tumor and proved fatal. Another study of mainly 72 cases of Spitz tumors and so-called "spitzoid" melanomas resulted in a 35–40 % overall disagreement rate among six reference pathologists [51]. Elder [52] reports the following criteria (Table 7.3) to distinguish Spitz tumor from nodular melanoma and pigmented spindle cell nevus from superficial spreading melanoma (Table 7.4).

Hybrid lesions, however, have characteristics that fall between those of classic Spitz tumor and vertical growth phase melanoma. These diagnostically challenging lesions have been termed *atypical Spitz tumors*, as has been proposed by Barnhill [50] and Spatz [53]. For such lesions, it has been proposed that points be assigned if certain features are present (designated by asterisks in Table 7.3). A patient over 10 years of age or a tumor diameter over 10 mm is assigned 1 point; fat involvement, ulceration, or a mitotic rate of 6–8 mitoses/mm^2 is assigned 2 points; and a mitotic rate of over 8 is assigned 5 points. On this scale, 0–2 points indicate low risk, 3–4 indicate intermediate risk, and 5–11 indicate high risk. Among the 30 children with Spitz tumor, 19 of whom had long disease-free follow-up, and 11 had a history of metastasis. The statement that "difficult" lesions are usually benign in terms of long-term follow-up [54], metastases and mortality do occur in some cases. In our opinion, equivocal lesions exhibiting the features listed

Table 7.3 Features for the differential diagnosis between Spitz nevus and nodular melanoma

	Spitz tumor	Nodular melanoma
Architecture		
*Diameter	Usually < 10 mm	Often > 10 mm
*Symmetry	Often present	Often absent
*Lateral borders	Sharply demarcated	Often poorly demarcated
*Irregular nesting	Uncommon	Common
*Ulceration	Absent	Sometimes present
*Deep extension (into fat)	Uncommon	In thick tumors
*Expansile nodule	Uncommon	Common (vertical growth phase)
*Cellularity	Variable, nested	Sheet-like, cohesive, polyclonal
Epidermal hyperplasia	Present	Absent, rarely present
Junctional proliferation	Discontinuous	Often continuous
Junctional nest orientation	Perpendicular to epidermis	Random
Pagetoid spread	Inconspicuous or absent	Often apparent
Pigment distribution	Little or no pigment	Patchy, asymmetric
Nesting pattern at base	Small, uniform	Larger, variable
Nuclear pleomorphism	Mild to moderate	May be severe
Maturation	Present	Absent
Regression	Usually absent	May be present
Cytology		
*Mitoses in lower third	Absent	Often present
*Maturation/zonation	Present	Generally absent
*Deep border	Infiltrating	Rounded, pushing, fascicular
Kamino bodies	Single and confluent	Inconspicuous or absent
Chromatin pattern	Delicate, evenly dispersed	Coarse, clumped
Necrosis	Absent	Often present

Modified from Elder [52]
The features marked with an * are reported by Barnhill [50] and Spatz [53] for the atypical Spitz tumor grading system

Table 7.4 Features for the differential diagnosis between pigmented spindle cell nevus from superficial spreading melanoma

	Pigmented spindle cell nevus	Superficial spreading melanoma
Architecture		
Diameter	Usually < 6 mm	Usually > 6 mm
Symmetry	Present	Usually absent
Lateral borders	Sharply demarcated	Pagetoid spread (shoulder)
Junctional nest shape	Ovoid, uniform	Variable in size and shape
Junctional nest orientation	Perpendicular to epidermis	Random
Pagetoid spread	Inconspicuous or absent	Present and conspicuous
Pigment distribution	Abundant, coarse	Less conspicuous, dusty
Cytology		
Cell size	Dermal cell < junctional cells	Dermal cell = junctional cells
Cell shape	Elongated spindle cells	Large epithelioid cells
Intraepidermal mitoses	Common	Common
Intradermal mitoses	Absent	Present only with vertical growth
Necrosis	Absent	Often present
Maturation	Present	Absent

Modified from Elder [52]

Table 7.5 Atypical Spitz tumor: features associated to death

Features associated with death:
Large bulky lesions usually deeply invasive
Ulceration
Necrosis
Severe pleomorphism
Numerous dermal and marginal mitoses
Intravascular invasion
Multiple positive lymph nodes in draining basin
Deeply invasive small cell melanomas of scalp [61]

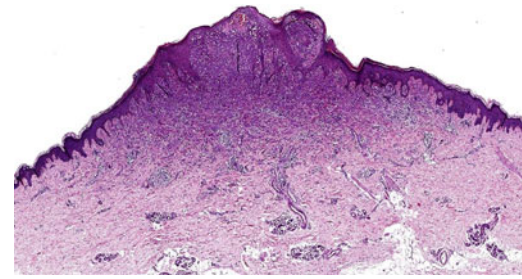


Fig. 7.26 Atypical Spitz tumor, asymmetry

in Table 7.3 as well as lesions that have any of the following characteristics (Table 7.5), if considered to fall short of an unequivocal diagnosis of melanoma, should be specially classified. The Penn group has chosen to call such lesions as a *MELTUMP* (*melanocytic tumors of unknown metastatic potential*) [3] followed by a differential diagnosis of melanoma with therapeutic discussion. In our approach we will diagnose such lesions as borderline tumors and then suggest based on our criteria whether the lesion should be excised and whether a sentinel lymph node biopsy should be considered. The possibility of more aggressive management of these lesions must be considered. Urso [55] found about 100 cases of metastasizing Spitz tumors. Although histologic data were not uniformly recorded, this review indicated that any number of the following histologic features could be found in a metastasizing lesion: (1) nodular growth in the dermis and/or large confluent, solid, cellular sheets with no collagen fibers interposed between cells; (2) extension of the neoplastic proliferation to the mid-deep dermis or to subcutaneous fat, especially if associated with absent or impaired maturation; (3) dermal mitoses, especially in the deeper part of the tumor; (4) asymmetry (Fig. 7.26); (5) heavy melanization in the deeper part of the tumor; (6) marked nucleolar and/or nuclear pleomorphism (Fig. 7.27); (7) necrosis; (8) epithelioid epidermal melanocytes below parakeratosis and/or epidermal ulceration; and (9) neoplastic cells in lymphatic vessels. Management of problematical spitzoid lesions should usually include a re-excision procedure and follow-up of the patient. A sentinel lymph node sampling procedure may also be considered and in several reported studies was occasionally positive [55–59]. Interestingly, among 25 reported patients with atypical spitzoid lesions and positive sentinel nodes, not a single death occurred, although follow-up intervals have generally been short. In another series from the University of Michigan [60], in 69 patients with atypical Spitz tumors, 27 of whom had positive sentinel lymph nodes; there was no mortality in an average follow-up of 43.8 months. The only mortality occurred in a patient who refused a sentinel node biopsy. This study is supportive of the possibility of these lesions metastasizing as nevi. The other possibility is that the lesions are actually well-developed melanomas that will only demonstrate their potential later in life. John Kirkwood has stated: "We will only understand melanoma biology when we have 35 or more years of follow up." We agree with this wise statement. Nevertheless, it seems likely that atypical spitzoid lesions may be associated with excellent survival rates after positive sentinel node metastasis, especially in children. Many of these tumors, in our opinion, are best regarded as borderline lesions with a risk of metastasis estimated as determined above. During one of the annual meetings of the International Society of Dermatopathology in Graz, Austria (2008), a group of cases that were selected, because they were "bulky" tumors, were assembled by Cerroni and reviewed by a group of experts [3]. Most of the cases had some Spitz-like characteristics, but there were other cases that were included such as pigmented epithelioid melanocytomas, cellular blue nevi, and deep penetrating nevi. About one-third of these lesions had metastases, most

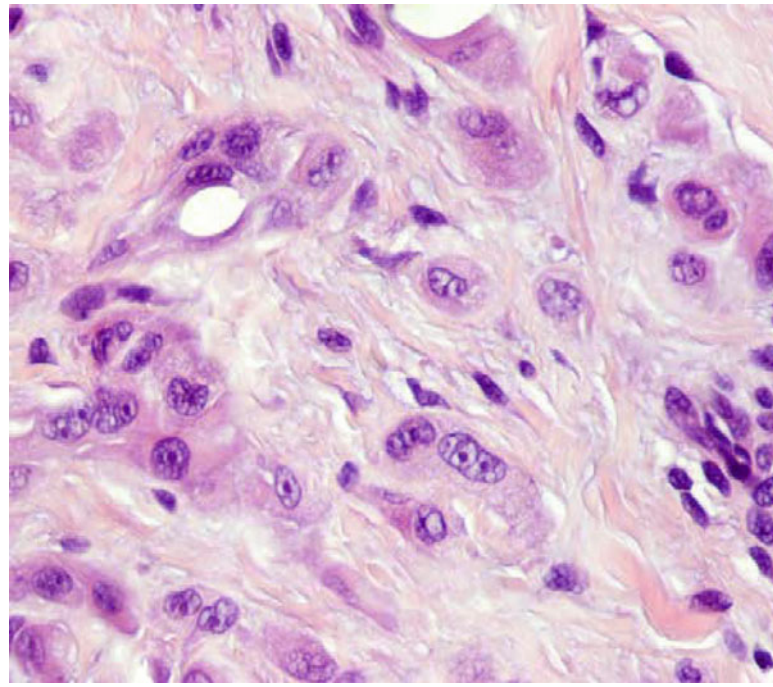


Fig. 7.27 Atypical Spitz tumor, cytologic pleomorphism

often to regional nodes, and in 20 % of the cases, the patients died, usually after a rather long disease-free interval. The use of the term *melanocytoma* was offered for these lesions. The definition of risk for aggressive behavior in these melanocytomas included the presence of mitoses, mitoses in the lower third of the lesion, and the presence of inflammation. It was suggested to tentatively classify these lesions into three risk groups: low risk, no inflammation, no mitoses; medium risk, presence of inflammation and/or mitoses not located at the base of the lesion; and high risk, presence of inflammation and/or mitoses near the base. Finally, in order to attempt to better understand fatal lesions, we studied 11 cases of children who died of melanoma originating in a tumor diagnosed before 13 years of age. We found the factors that were critical as listed in Table 7.5.

With regard to genomic studies, Bastian and his group reported that in 11 % of Spitz nevi there is an increase in the copy number of 11p, the site of the RAS gene, as determined by FISH [62]. In another study they found, in some Spitz nevi, a gain in 6p [27].

Atypical Dermal Melanocytosis

Pigmented Epithelioid Melanocytoma

Among the dermal melanocytoses, there are a group of tumors that are composed of epithelioid and dendritic melanocytes. These cells have very densely crowded cytoplasm filled with coarse melanin granules (Fig. 7.28) when compared to the delicate melanin granules of the blue nevus. These tumors were originally designated *animal-type melanoma* by Darier [63]; a series of six cases was reported by Crowson [64]. In this series one patient died; the others were still alive at last follow-up. This term was used because of the similarity of these lesions to the melanoma found in horses and other animals. Several years before this publication, Carney described his syndrome (myxomas [especially cardiac], spotty skin pigmentation, endocrine overactivity, and schwannomas) [65–67] that included the presence of what he termed "epithelioid blue nevi." In 1993 Carney, Zembowicz, and Mihm reviewed 41 cases of so-called animal-type melanoma and all the cases of Carney's epithelioid blue nevus.

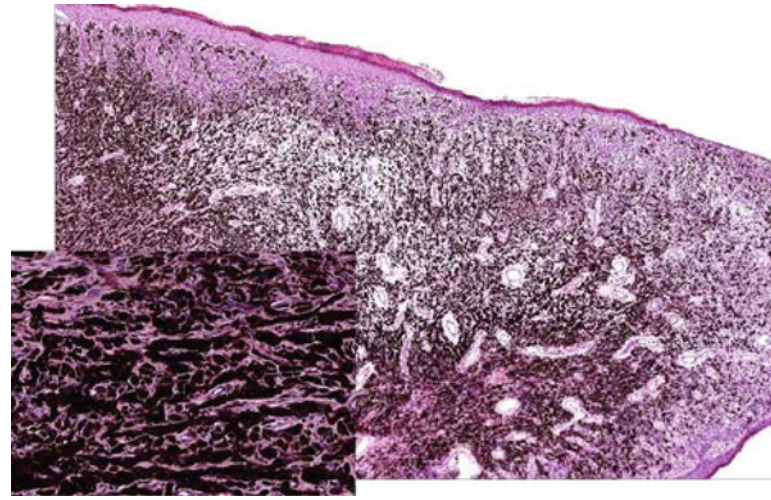


Fig. 7.28 Pigmented epithelioid melanocytoma

All concurred that there was no difference histologically between the two groups of cases. These authors then suggested a new nomenclature for these lesions, namely, the *Pigmented Epithelioid Melanocytoma (PEM)* [65]. Subsequently a genetic analysis found mutations of the protein kinase A regulatory subunit type, 1alpha (R1alpha), coded by the *PRKAR1A* gene, which is found in more than half of Carney complex patients, is also found in most PEMs but not in equine melanomas, nevi including deep penetrating and cellular blue nevi, or human melanomas [67]. The expression of R1alpha offers a useful test that could help to distinguish PEM from lesions that may mimic it histologically. Clinically these lesions present as blue-black nodules. They vary in size from a centimeter to several centimeters. They are usually asymptomatic. They affect both sexes equally and can be found anywhere on the body surface but are more common on the extremities. The lesions have a gradual growth course. They may occur at any time in life; a congenital example has been reported. They differ clinically from the Carney lesion by their occasional ulceration. In the follow-up about 40 % metastasize to regional lymph nodes without spread beyond the draining lymph node basin. It is noteworthy that no case of metastasis has been observed in Carney's syndrome. In all the reports of the PEM and animal-type melanoma, there has been only one death. The metastatic behavior appears to be related to thickness. Lesions less than 2.0 mm in thickness virtually never spread. Even in these cases there is virtually no spread beyond the lymph node basin. The previously reported congenital nevus occurred in the scalp and involved the cranium and the dura. It was surgically excised. This little girl also had a tumor in the lung and the liver. These were not excised and she is alive and well when last checked at 11 years with no progression of tumor at any site. Morphologically the lesions resemble nodular melanoma but with very heavy pigmented melanocytes comprising the greatest portion of the lesion. The diagnostic cell is a large pigmented epithelioid melanocyte. The central mass of the lesion is composed of numerous melanocytes of both dendritic and epithelioid shapes. The dendritic processes are very thick and often have a thick spindled appearance. The cytoplasm is filled with numerous coarse melanin granules. Toward the periphery there are more prominent thick dendritic cells. The nuclei of the characteristic lesion are round to oval with a prominent rim of chromatin. There is a large blue nucleolus that stands amidst the dense melanin granularity. This feature clearly aids in differentiating the cells from the melanophages that have very vesicular nuclei with small gray nucleoli or the much larger red nucleoli of the melanoma cell. Usually the cells have bland morphology and mitoses are infrequent. Inflammatory infiltrates

are usually quite limited. One very important feature that often causes confusion is the presence of dendritic melanocytes in the epidermis along the basal layer with prominent dendrites, a picture that is quite often present when the cells are in the papillary dermis. In some lesions there is also pagetoid spread. They have no relationship to aggressive behavior. When there is a doubt about the type of lesion, special stains such as Mart 1 or Melan-A compared to CD163 will allow identification of the melanocytes and exclude histiocytic cells. As far as atypia is concerned in the great majority of these lesions, the usual lesion is quite bland in spite of its cellularity. Mitoses are infrequent but can be observed. When there is significant atypia with frequent mitoses, then the differential diagnosis must include animal-type melanoma or a malignant blue nevus or melanoma arising in a neurocristic hamartoma. Although none of the patients died of the disease, clinical follow-up was short (mean, 32 months; range, up to 67 months) [68]. In subsequent follow-up of 5 years, there was no recurrence in the patients. What is problematic is that there were no histologic criteria separating PEMs with nodal involvement from those without nodal involvement, and the only feature more common in PEM in patients without the Carney complex than in epithelioid blue nevi of Carney complex was ulceration. These lesions should also be distinguished from unusually heavily pigmented examples of blue nevi. In our studies of these very difficult lesions, we have attempted to offer a novel approach to a lesion, the biologic potential of which is unknown until much longer follow-up is available. Its great resemblance to the melanoma of gray horses and Sinclair swine suggests that it may live symbiotically with the patient as in the case of man of the child with the congenital scalp PEM and the lung and liver nodules.

Dermal Melanocytic Tumors of Uncertain Malignant Potential

A variety of melanocytic tumors have been described that are usually bulky and exhibit nuclear atypia, mitotic activity, and other features suggestive of malignancy but do not fully qualify for an unequivocal diagnosis of malignancy. The Penn group has suggested that these lesions be designated as dermal melanocytic tumors of unknown malignant potential (MELTUMP) [3]. While this designation is very useful, it does not reflect any difference between tumors that notoriously do not metastasize, such as PEM, and tumors that more frequently metastasize such as the atypical Spitz tumor or the atypical plexiform deep penetrating nevus. Furthermore, in our consultative experience we find the term very liberally used for lesions with small vertical growth phase, even for lesions with radial growth phase and regression and sometimes for unusual radial growth phase lesions. The Penn group has also proposed the term SAMPUS for these lesions that designates a superficial atypical melanocytic proliferation of unknown biologic significance [69]. In our approach we will designate a lesion as borderline in nature and then give an estimation as to the risk of metastasis based on the various features including depth, presence of ulceration, mitoses per millimeter square, pleomorphism, and lymphatic invasion. We consider this to be more useful to the clinician and helpful in deciding whether further diagnostic therapy is necessary.

Melanoma

Since the original descriptions of subtypes of melanoma [70, 71], many advances have been made in the field of oncology since the advent of genetic studies. The classification has come under criticism as not being biologically base, but, interestingly enough, the most recent studies support the original classification. To wit, melanomas in sites of chronic sun exposure, such as lentigo maligna, do not exhibit the most common mutation in melanoma, the BRAF mutation, but rather do exhibit in many cases a c-kit mutation. Melanomas of the intermittently sun-exposed areas frequently express the BRAF mutation. Melanomas of non-sun-exposed skin, such as acral lentiginous or mucosal melanoma, also

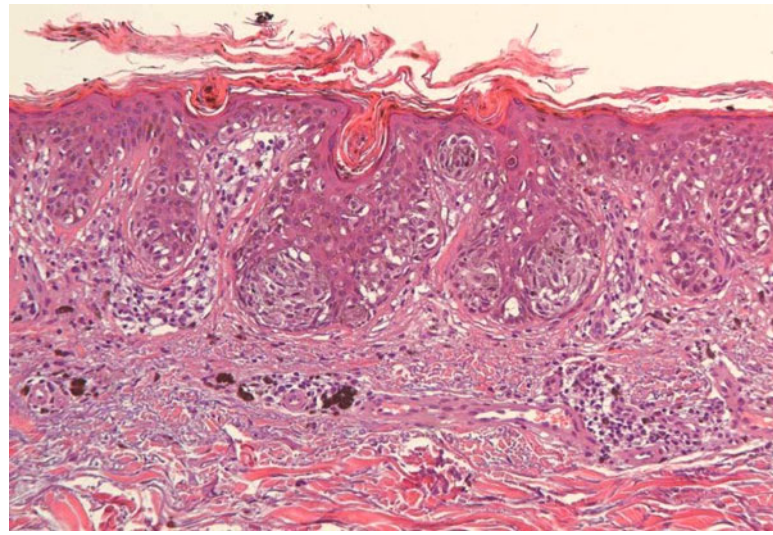


Fig. 7.29 Melanoma in situ, pagetoid intraepidermal spread

show, among other mutations, a c-kit mutation. As these aspects have also therapeutic importance, they imbue the basic classification with further significance [72].

Melanoma In Situ

Noninvasive melanoma or melanoma in situ refers to the in situ intraepidermal proliferation of malignant melanocytes usually 1.0–1.5 cm in size. The histopathologic changes of noninvasive superficial spreading-type melanoma are associated with two patterns. The first is one of epidermal hyperplasia without prominent rete ridges hyperplasia and a proliferation of pagetoid cells from the basilar region to the granular cell layer (intraepidermal aggressive pagetoid invasion) (Fig. 7.29). These so-called pagetoid cells have large ample cytoplasm filled with fine melanin granules. The nuclei are very variable in size but have marked irregular chromatin distribution and very prominent large eosinophilic nucleoli. Some of the nuclei are darkly hyperchromatic without visible chromatin patterns. The second pattern observed in superficial spreading melanoma is one that resembles the dysplastic nevus with elongation of the rete and with a confinement of the epithelioid cells to the dermoepidermal junction where they are disposed in a uniform contiguous array (Fig. 7.30). The cells usually replace the lower two or three layers of keratinocytes. Characteristically in dysplastic nevus the basilar proliferation is discontinuous. Some pagetoid spread is noted in this pattern but it usually is confined to the lower half of the epidermis and in the central area of the lesion. As far as *acral lentiginous melanoma in situ* is concerned, there is a uniform proliferation of cells with large nuclei and large cytoplasm. The large nuclei have prominent nucleoli that are either amphophilic or brightly eosinophilic. The cytoplasm is noted to extend by long dendrites even to the granular cell layer and filled with melanin granules emphasize the dendritic character of the cell. These cells are often contiguously arrayed along the dermoepidermal junction. Mitotic figures may be observed. Pagetoid spread is minimally present in the acral lentiginous melanoma in situ. A variant of acral lentiginous melanoma in situ is associated with a prominent proliferation of epithelioid cells without the prominent dendritic masses but with finely granular melanoma cells present throughout the epithelioid cells. This variant resembles superficial spreading melanoma in situ but is associated with marked epidermal hyperplasia, and the great majority of the cells are confined in the lower epidermis (Fig. 7.31). The greatest difficultly in interpretation of acral lentiginous melanoma in situ occurs when the cells are small without prominent cytoplasm and with small nuclei. Such lesions can best be

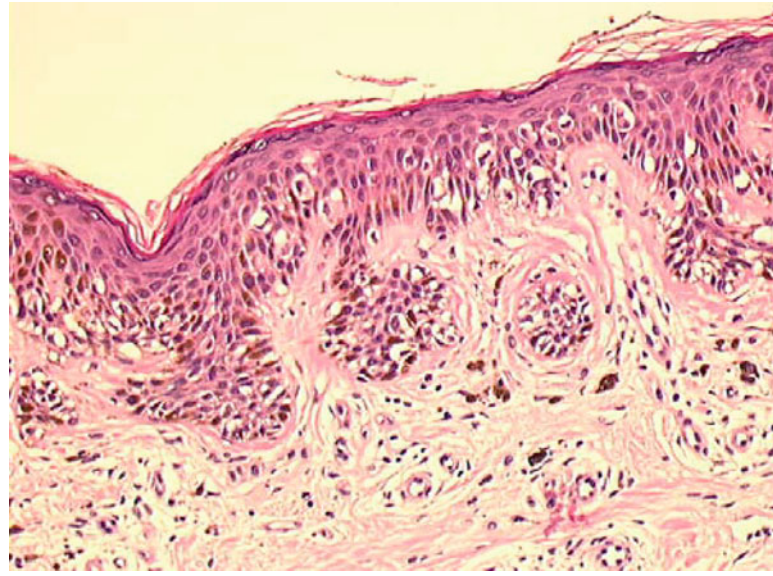


Fig. 7.30 Melanoma in situ, dysplastic nevus-like spread

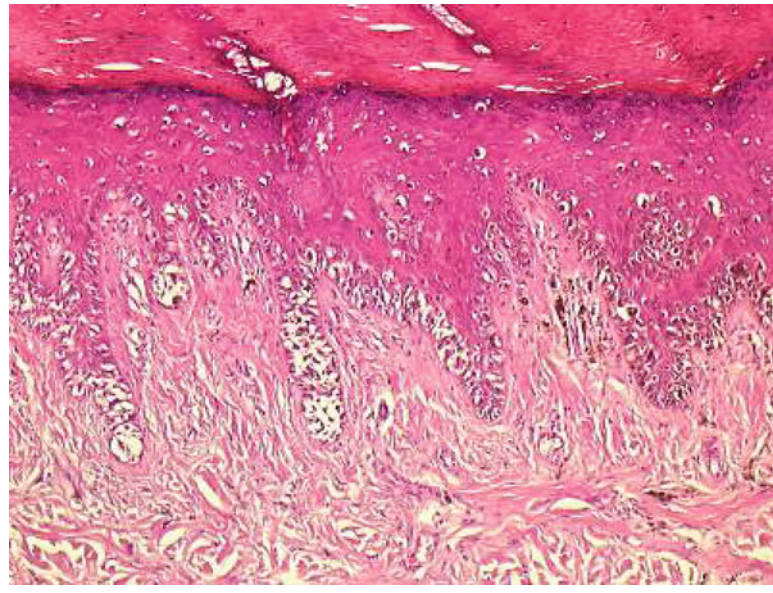


Fig. 7.31 Acral melanoma in situ

appreciated when one realizes that the cells uniformly replace the dermoepidermal junction and that the nuclei of the cells are similar one to another. Especially helpful in this type of proliferative process is the observation of mitoses. The epidermis is almost always markedly hyperplastic in acral lentiginous melanoma in situ and there may be an inflammatory infiltrate present in the dermis beneath. In instances where the melanocytic proliferation is difficult to detect and is associated with a markedly lymphoid infiltrate, one must be cautious not to mistake the lesion for an inflammatory process. The differential diagnosis of intraepidermal superficial spreading melanoma includes squamous cell carcinoma in situ with pagetoid appearing cells or Paget's disease. Squamous cell carcinoma in situ can be differentiated on the basis of

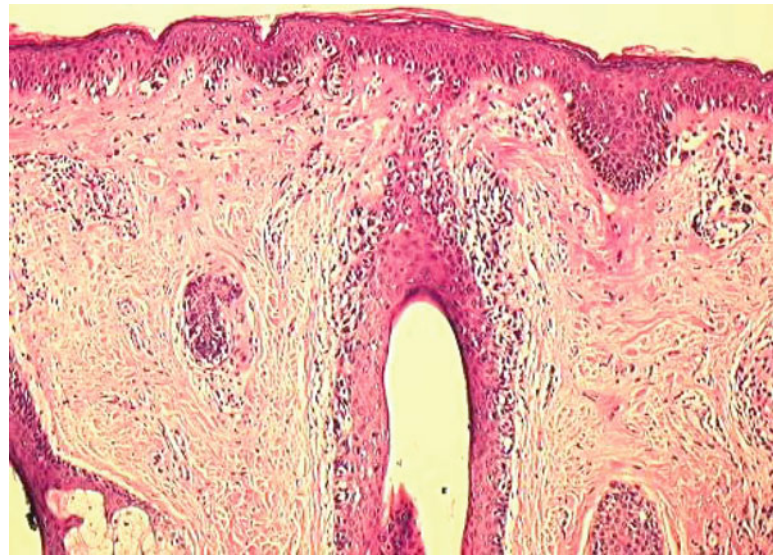


Fig. 7.32 Lentigo maligna

dyskeratosis of cells and the presence of intracellular bridges between the malignant anti-cytokeratin-positive cells. Likewise multinucleate giant cells often with dyskeratosis are common in squamous cell carcinoma in situ and are more uncommon in intraepidermal melanoma. Paget's disease is associated with cells that do not lie along the basilar region of the epidermis but rather above the basal cell layer. Careful histologic examination of lesions of Paget's disease reveals that there are small basal cells beneath the Paget cells. Likewise even if the cells of Paget's disease are pigmented, a rare finding, they have nuclei that have usually an open vesicular quality with prominent nucleoli. The cytoplasm of these cells is usually vacuolated. Striking pleomorphism of the cell is not noted. The use of mucicarmine or alcian blue stains will show mucin present in the Paget cells. Examination with immunoperoxidase stains for keratin and carcinoembryonic antigen will stain positively the Paget cells and negatively the melanoma cells.

Lentigo Maligna

We recognize an evolutionary concept of lentigo maligna (Fig. 7.32) melanoma that begins with a premalignant precursor, lentigo maligna, that goes on to an in situ phase and then invasive melanoma. Lentigo maligna describes a gradually spreading freckle-like lesion of the sun-exposed skin of the elderly which begins as a small flat tan macular pigmentation and may extend to several centimeters in size before invasive melanoma supervenes. This lesion, which has highly irregular coloration and irregular borders, is associated with a proliferation of irregular melanocytes confined to the epidermis in an atrophic epidermis. These cells are discontiguously arrayed and can extend down the hair follicle. This lesion has been variously defined by Jonathan Hutchinson lentigo melanosis or precancerous melanosis by Dubreuilh, but today it is commonly called Hutchinson's melanotic freckle or commonly termed *lentigo maligna*. Low-power examination reveals a proliferation of melanocytes along the dermoepidermal junction in a strikingly atrophic epidermis. In the early lesion there is a discontiguous proliferation of atypical cells randomly scattered above the markedly sun-damaged dermis. Frequently the cells may be noted to extend in scattered fashion down the superficial aspect down the hair follicle. These cells have pleomorphic nuclei. Some are round, others are rectangular, and others crescent shaped. As the lesion increases in size, there is continued proliferation but no confluence of cells, nesting, or pagetoid spread.

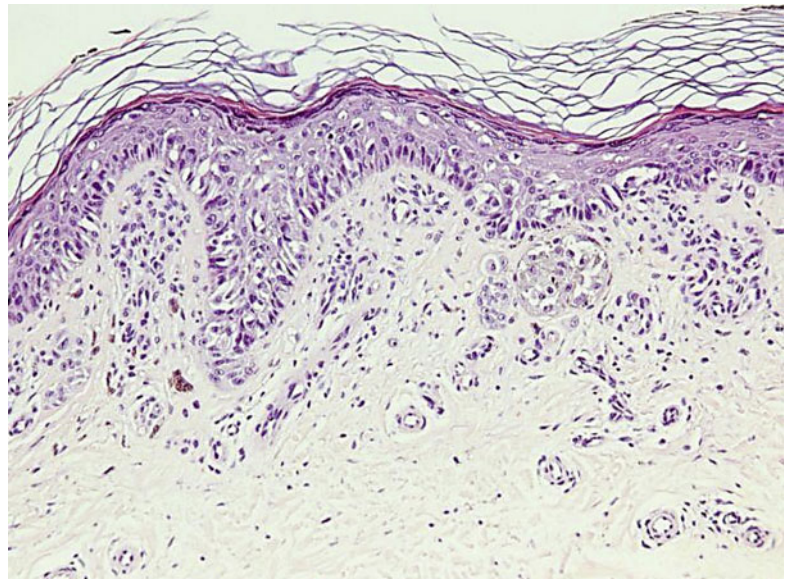


Fig. 7.33 Melanoma HGP

Superficial Spreading Melanoma

Superficial spreading melanoma represents the most common type of melanoma found in Caucasian persons. It is described histologically as showing large epithelioid cells in pagetoid array. In addition to the intraepidermal proliferative process with patterns of extensive pagetoid spread and the epithelioid cell proliferation in lesions with epidermal hyperplasia frequently resembling the dysplastic nevus, there supervenes infiltration of the papillary dermis by single cells or nests of cells. With this invasion a marked inflammatory response of lymphocytes is noted. Macrophages may also be scattered amidst the inflammatory infiltrate. The intradermal cells in the *horizontal* (*radial*) *growth phase* have the same histological characteristics as those in the epidermis, and the nests of cells are of similar size to those present in the epidermis (Fig. 7.33). The *vertical growth phase* can be detected by the appearance of cells in nests larger than the intraepidermal nests (Fig. 7.34). These clonal nests usually have a countable number of cells [25–50], which have a different cytologic appearance than those of the intraepidermal component. For example, if the intraepidermal component is characteristic with pagetoid cells with fine melanin pigment, the early vertical growth phase cells may be small nevus-like melanoma cells or spindle cells or epithelioid cells without pigment. From this nest of cells which also show frequently quite prominent mitotic activity, the vertical growth phase continues to expand so that it either fills the papillary dermis (level III according to Clark classification) and widens it with subsequent invasion into the reticular dermis (level IV) or even into the subcutaneous fat (level V). Vertical growth phase melanoma cells are usually epithelioid or spindle in character but in most cases show a mixture of cells. In the invasive melanoma various prognostic parameters can be applied including thickness, tumor-infiltrating lymphocytes, mitotic rate, and presence or absence of regression to define the prognosis.

Differentiation from Melanoma with Regression and Recurrent Melanoma

Regressive fibrosis in melanoma is different from a scar, with a delicate pattern of thin collagen fibers in an edematous matrix containing scattered mononuclear cells with prominent ectatic venules oriented perpendicularly to the epidermis (Fig. 7.35). A scar is often hypovascular with laminated thick bundles of collagen in a parallel disposition to the epidermis. When vessels are present, they are small and may be closely aggregated. In regressed melanoma, there is usually

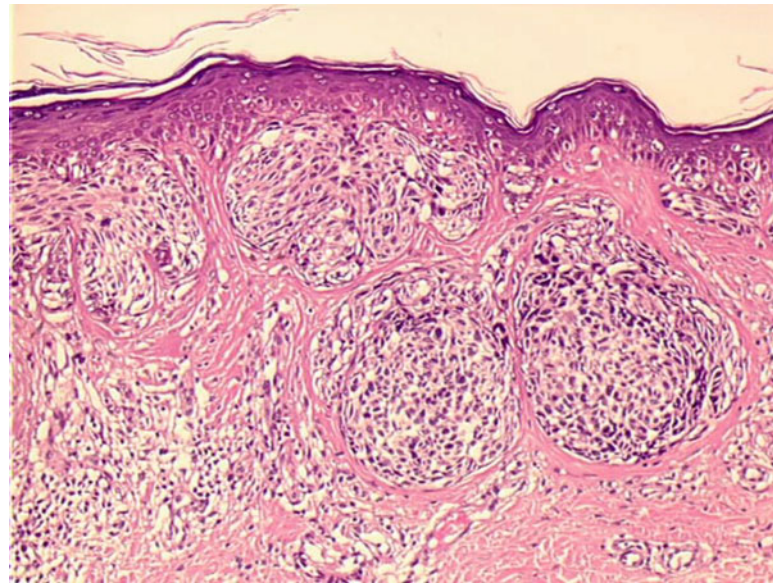


Fig. 7.34 Melanoma VGP

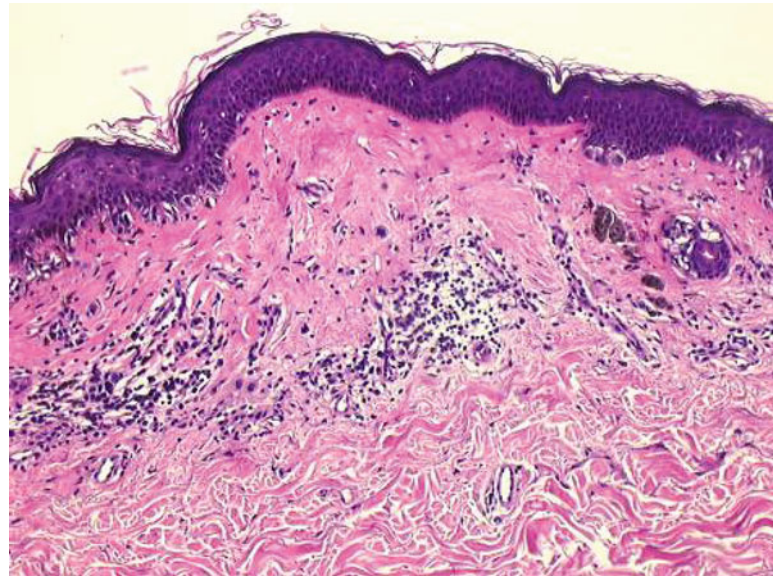


Fig. 7.35 Regressed melanoma

prominent inflammation that may be lichenoid with conspicuous melanophages accumulation (i.e., tumoral melanosis). In regressed melanoma, there may be no discernible melanocytes. In recurrent nevi, the epidermis shows melanocytic hyperplasia and hypermelanosis. In regressed melanoma, a severely atypical intraepidermal or dermoepidermal melanocytic proliferation is found outside the areas of regressive stromal fibrosis, in contrast to recurrent nevi where the pattern and cytology of melanocytic growth are typically banal outside the scar. The residual dermal lesion in melanoma is usually severely atypical, while the residual dermal lesion in a recurrent nevus is not.

Lentigo Maligna Melanoma

Lentigo melanoma is characteristically a lesion of sun-exposed areas of the elderly and classically

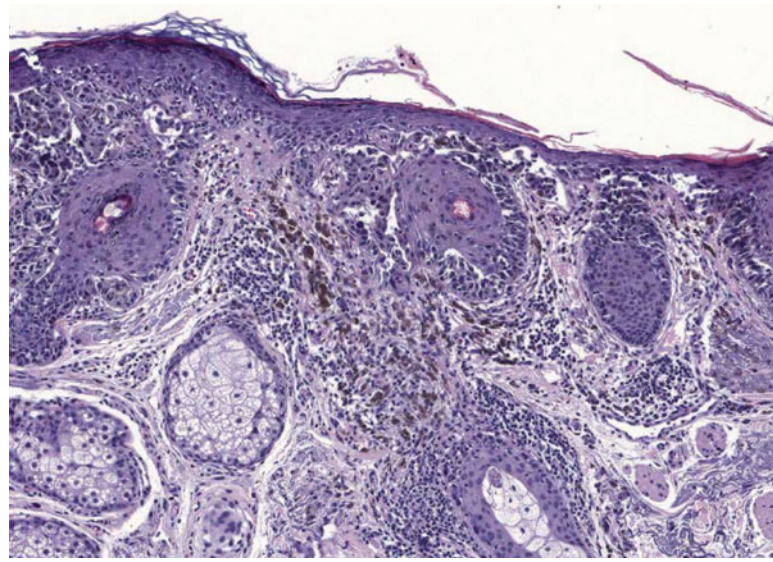


Fig. 7.36 Lentigo maligna melanoma

presents as a large freckle-like lesion on the face, surmounted by nodules. Histologically the nodules are often spindle cell in character. In a background of the severely atrophic epidermis with the lentiginous proliferation of atypical melanocytes, there supervenes single cell infiltration of the papillary dermis. We require the presence of an epithelioid cell usually with ruddy brown or dusky brown cytoplasm with large nucleus with prominent nucleolus to identify single cell infiltration. The presence of fibroblasts altered by chronic sun exposure with atypical forms, melanophages with dense pigment accumulation, and lymphocytes admixed with these melanophages often renders single cell infiltration difficult. Thus, the presence of an easily visible epithelioid cell allows for easy identification of single cell invasion. Nests of malignant cells invading the papillary dermis are usually fusiform in nature and are easily identified as distinct from the intraepidermal population. These single cells have more hyperchromatic nuclei, more prominent nucleoli, and usually a pigmented cytoplasm compared to the delicate cells that characterize the intraepidermal nests of lentigo maligna. The single cell infiltration and the infiltration of small nests of spindle cells are associated with a quite dense lymphocytic infiltrate with melanophages (Fig. 7.36). The vertical growth phase with the equivalent of level III, IV, and V invasion in lentigo melanoma is commonly spindle cell in character. Although frequently there are admixed epithelioid cells with the spindle cell population and occasionally pure epithelioid populations may be also noted. There is one variant of vertical growth phase in lentigo maligna that is associated with numerous melanophages admixed with the spindle cells. The presence of this variant requires bleaching with potassium permanganate or other melanin bleach reagents in order to visualize the densely pigmented cells and to identify mitotic activity. Occasionally all the cells of the vertical growth phase of lentigo maligna melanoma are densely pigmented and must be bleached in order to separate them from aggregates of melanophages. The spindle cell population of lentigo maligna can be associated with a desmoplastic response. One of the problems with regard to lentigo maligna melanoma is the determination of margins, because of the variable activation of melanocytes in sun-exposed skin. We usually will declare a margin free if there is no significant contiguity of the atypical cells for at least 2 mm from the edge of the tumor. A recent study by Magro et al. has shown the usefulness of the s adenyl cyclase stain in helping to determine the margins [48]. This technique results in strong complete staining of the nuclei

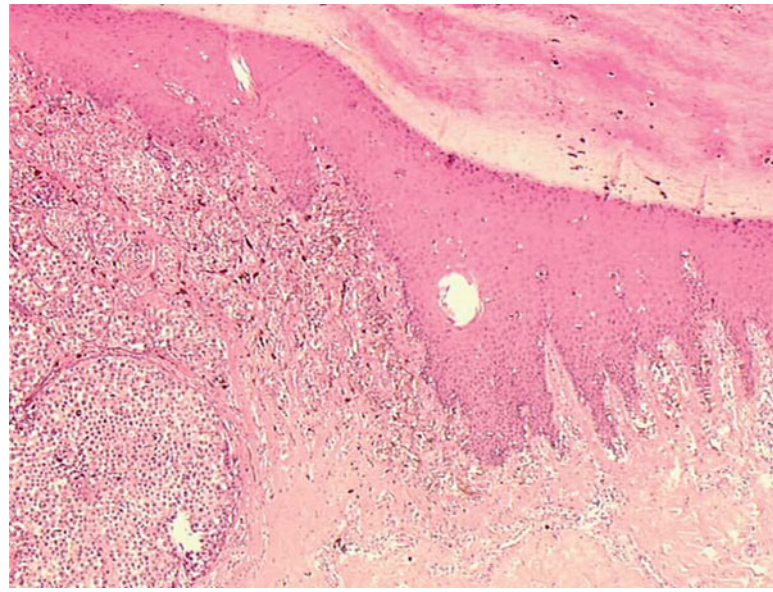


Fig. 7.37 Acral lentiginous melanoma

in malignant melanoma cells and is particularly helpful in detecting lentigo maligna melanoma in situ in the margin [73]

Acral Lentiginous Melanoma

Acral lentiginous melanoma presents as a flat, usually dark brown lesion with irregular areas of brown/black scattered over the surface and with an irregular border all surmounted by a nodule often with a hyperkeratotic surface. Histologically, the macular portion of the lesion shows a characteristic in situ proliferation of malignant melanoma cells contiguously arrayed along the dermoepidermal junction with long dendritic cytoplasmic extensions into the superficial epidermis (Fig. 7.37). The vertical growth phase can be composed of spindle cells, epithelioid cells, or a mixture of the two. Also, nevoid vertical growth phase can be occasionally seen as well as desmoplastic melanoma. A very important aspect of the vertical growth phase is that the cells can track along the eccrine adventitia into the reticular dermis and even into subcutaneous fat. Thus, this melanoma can rarely present as a flat lesion in which the entire tumor is spread along the eccrine apparatus into level V with poor prognosis.

Mucosal Melanoma Including Vulvar Melanoma

One of the most difficult types of melanoma involves the mucosa and has been termed *lentiginous mucosal melanoma*. This tumor usually demonstrates a striking pattern of atypical cells along the dermoepidermal junction in contiguous array. The nuclei of these cells are small and hyperchromatic and it is often difficult to visualize nucleoli in these hyperchromatic nuclei (Fig. 7.38). However, the aspect that allows for diagnosis is the presence of a contiguous proliferation of repetitively similar cells containing very dark nuclei with variable cytoplasm. Occasionally prominent dendritic processes filled with melanin can be noted and are very helpful in diagnosis. These dendritic processes extend up into the keratinizing layer of the mucosa. A brisk inflammatory infiltrate is often noted in the submucosa with scattered melanophages. Once again the presence of small cells without pigment associated with an inflammatory infiltrate may lead to the misdiagnosis of an inflammatory lesion. However, careful examination shows that the cells have uniformly dark nuclei, larger than lymphocytes and are associated with ample space around them to indicate cytoplasm of the malignant melanocyte. Mucosal lentiginous melanoma

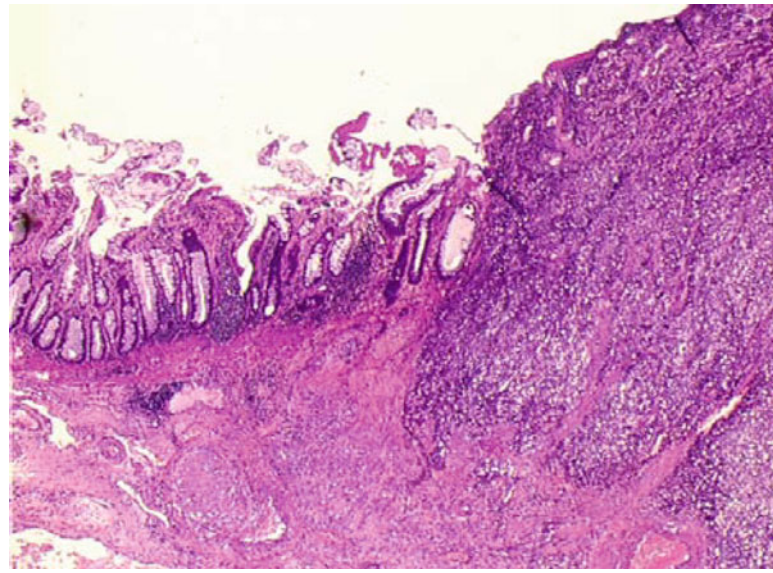


Fig. 7.38 Lentiginous mucosal melanoma of rectum

with radial growth phase presents as a large irregular pigmented macule of the mucosa surmounted often with a nodule or plaque as the vertical growth phase supervenes. In addition to the proliferation of uniformly atypical melanocytes contiguously placed along the dermoepidermal junction, sometimes with prominent dendritic forms it is present invasion of the submucosa by single cells in the radial growth phase. These single cells are often fusiform and are mistaken for fibroblasts, especially in the mouth and in the vagina. A brisk inflammatory infiltrate associated in both regions may be confused for inflammatory lesion especially if melanophages are admixed. Certainly, there is a pattern of mucosal melanoma that can resemble superficial spreading melanoma. It is much more easily diagnosed. Many mucosal and paramucosal melanomas can exhibit a mixed pattern. For example, in a series of 54 vulvar melanomas (personal observation), 15 % had a lentiginous pattern, 45 % had a pattern similar to superficial spreading melanoma, 20 % were mixed, 12 % were nodular, and the rest were unclassifiable. As the vertical growth phase appears, nests of cells are noted usually with often different histological appearance than the intraepidermal component. Thus the large epithelioid cells may be present or spindle cells at times a desmoplastic vertical growth phase is likewise found. Neurotropism may be present with or without the desmoplastic response. These lesions almost never arise in association with a preexisting nevus.

Nodular Melanoma

Nodular melanoma is a rapidly growing raised pigmented lesion with no preexisting pigmented flat or radial growth phase. Low-power examination reveals a striking papulonodular excrescence that is frequently well defined, usually by a hyperplastic epidermis at each side but without any intraepidermal proliferation extending beyond the dermal component. There is no surrounding cell infiltration other than for an occasional cell adjacent to the nodule in the intraepidermal portion of the lesion. It is immediately appreciated that the tumor is composed of an expansile aggregate of melanocytes that variably infiltrate the reticular dermis and may even infiltrate the subcutaneous fat (vertical proliferation). Interestingly there is a certain symmetry to the nodular centrifugal proliferation because of its sharp demarcation. The dermal component of the lesion is associated with a highly pleomorphic population of cells that are usually epithelioid or more frequently mixed

spindle and epithelioid but other cytotypes (balloon, nevoid, giant, etc.) may be present as clonal foci of proliferation. Well-differentiated pure spindle cell or nevoid populations are rare in nodular melanoma and should raise the possibility of minimal deviation or nevoid melanoma. The individual cells in nodular melanoma usually show striking pleomorphism and mitotic figures are often easily visible. This lesion may arise in association with a preexisting dysplastic nevus in which case there is an intraepidermal component of dysplasia. It may likewise arise in association with a preexisting dermal nevus in which remnants of the dermal nevus may be found scattered adjacent to the nodular proliferation. Many poorly differentiated skin tumors may simulate a nodular melanoma. The spindle cell squamous non-keratinizing carcinoma may be difficult to differentiate from a nodular melanoma but careful inspection of the epidermis will show the malignant cells to take origin there from and to have zonal processes extending between them. The presence of keratin by immunoperoxidase stains in the absence of S100 staining allows for conclusive diagnosis. Atypical fibroxanthoma can be difficult to distinguish from nodular melanoma but often shows more severe marked pleomorphism of the infiltrating cells with many bizarre atypical mitoses than in the usual nodular melanoma. However, one usually must rely on immunoperoxidase stains with the cells staining for macrophagic and lysosomal enzymes rather than for S100 and HMB45, the commonly positive stains in nodular melanoma. The reticulin stain may be helpful in that mesenchymal cells are all each surrounded by reticulum, whereas melanoma cells show nests surrounded by reticulum fibers. Leiomyosarcoma at times can pose a problem in differential diagnosis. If careful inspection of multiple levels fails to reveal pigment if one suspects melanoma, then appropriate immunoperoxidase stains with actin and desmin will allow for the correct diagnosis. The mixture between nevus and melanoma cell in particular in the deep part of a nodular melanoma may be important to identify to evaluate a correct thickness of the tumor; in these cases the immunohistochemical stain with p16 may be useful to differentiate nevus from melanoma cells and to define a correct thickness.

Melanoma, Rare Variants

Melanoma in Congenital Nevus

Melanoma in congenital nevi may occur anytime in life and in nevi of any size. However, most melanomas in giant nevi occur in early childhood in the first 5 years or in adulthood. Melanomas in small nevi or nevi of intermediate size occur almost exclusively in adult life. The most common melanoma presentation in the congenital nevus is a dermal nodule that is distinctly sharply demarcated from the surrounding nevi component. Low-power examination reveals this strikingly distinctive population of cells that almost invariably is more markedly hyperchromatic from the nevus cells and stands out in sharp contrast to them. p16 immunostain may be useful to distinguish the two different components (Fig. 7.39). Closer examination reveals that they are most commonly composed of spindle cells with admixed epithelioid cells with mitoses easily visible within them. Single cell necrosis is likewise present and there may be a host inflammatory response. The second commonest presentation is that of a pagetoid pattern of melanoma proliferation focally appearing in a congenital nevus. One must be very careful in the interpretation of this type of change and distinguish it from an epithelioid cell proliferation common especially in the first 2 years of life. The epithelioid cells that are benign have very delicate characteristics and are usually amelanotic. The epithelioid cells of melanoma have strikingly atypical nuclei with large eosinophilic nuclei and with finely granular melanin in their cytoplasm. As these cells infiltrate into the dermis, they do not blend or mature into the nevus cells of the congenital nevus but form an advancing sharply demarcated plaque or nodule contiguous with the epidermal component and easily distinguishable from the dermal component. Pleomorphism of this nodule is easily noted as are numerous mitotic figures with variable host response. Individual

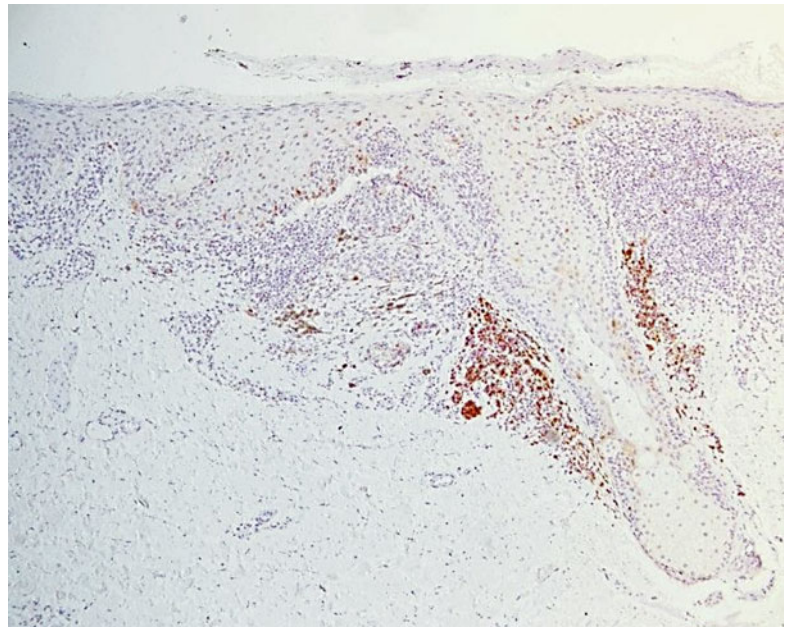


Fig. 7.39 Melanoma (left, negative p16 immunostain) and dermal nevus (periadnexal positive p16 immunostain)

cell necrosis can also be observed. Any evidence of maturation of the cells into small nevus cells should dissuade one from diagnosing the lesion as malignant.

Desmoplastic Melanoma

Desmoplastic melanoma is a particular variant of melanoma characterized by a proliferation of predominantly spindle cells, collagen production, and spread of differentiation, or neurofibromatosis-type schwannian and brisk lymphoid cell dermal aggregates. Desmoplastic melanoma is considered as a separate entity because this cancer as well as raise some problems of diagnostic, clinical, histopathological, and therapeutic, shows a natural history that differs from that of a common melanoma. In desmoplastic melanoma we recognize two components: a junctional and intraepidermal lentiginous or pagetoid proliferation and a dermal component of spindle cells arranged in irregularly distributed bundles that extend from the papillary dermis to the reticular dermis, associated to a variable degree of proliferation of collagen, with irregular and ill-defined margins. The cells insinuate themselves between the collagen fibers as they are often not recognizable above the edge of the lesion. These characteristics are responsible for underdiagnosis of desmoplastic melanoma and, above all, frequent errors in the evaluation of macroscopic and histologic margins of resection with inadequate surgical therapy that leads to frequent relapses. Collagen, which determines the characteristic appearance described as desmoplasia, is produced under the influence of TGF beta. The actual mechanism is unclear. Sometimes the production of collagen can be so marked as to simulate a fibromatosis. Other histological features described in desmoplastic melanoma include the presence of cells plurinucleate, or myxoid and storiform areas. The desmoplastic melanoma cells are in spindle-shaped arrangement in corrugated beams that simulate a neurofibroma or a schwannoma. The spindle cells are prevalent. Nuclear polymorphism is present and the nuclei are elongated and often S shaped. Sometimes it can be demonstrated fusiform and dendritic extensions of the cytoplasm of malignant melanocytes. Mitoses are rare and are often found only in areas of epithelioid cells present in the superficial papillary dermis. The neurotropism is a character that is considered important by many authors for the diagnosis but not always present. The neurotropism is a characteristic of desmoplastic melanoma, which seems associated with a high rate of recurrence but does not seem related in the same

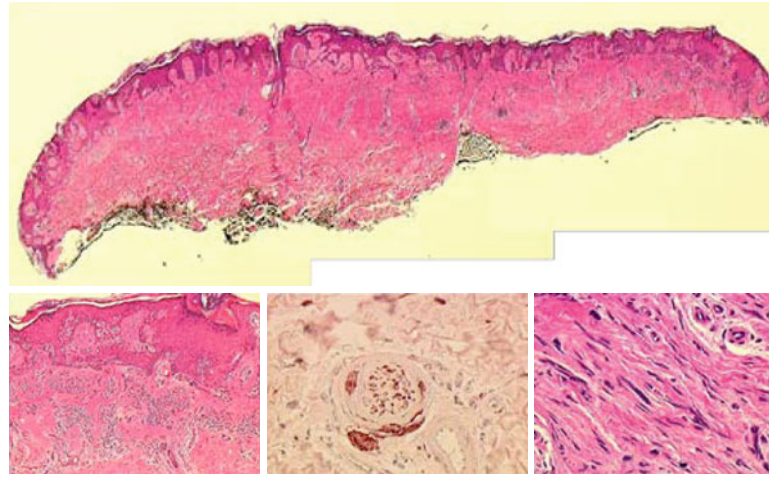


Fig. 7.40 Desmoplastic melanoma, S100 immunostain of perineural invasion

way the appearance of metastases. Frequently focal lymphocytes infiltrative aggregates are present (Fig. 7.40). Desmoplastic melanoma must be differentiated from a number of pigmented and unpigmented tumors characterized by proliferation of spindle cells in the dermis. If the pigment is present, must be taken into account the desmoplastic nevus and desmoplastic Spitz nevus, cellular blue nevus, malignant blue nevus, spindle cell melanoma, and metastatic malignant schwannoma; among non-pigmented as some sarcomas: the dermatofibrosarcoma protuberans, fibrosarcoma, leiomyosarcoma skin surface, the malignant schwannoma, and atypical fibroxanthoma; more rarely can be considered in the differential diagnosis of fibromatosis and hyperplastic scars with marked cellularity. Desmoplastic melanoma shows an intense and diffuse positivity for serum anti-S100 protein, but it is negative (except in rare superficial epithelioid cells) to HMB45, Leu 7, and NK1-beteb. p16 is very useful to differentiate desmoplastic nevus (p16 positive) from desmoplastic melanoma (p16 negative). The use of antibody anti-S100 protein is particularly important to highlight the perineural invasion and resection margin; otherwise, with the traditional histological examination alone, this could be underestimated. Also the skin of the re-resection for enlarging the margins must be examined by immunocytochemical S100 stain to exclude residual neoplastic foci and neural invasion.

Neurotropic Melanoma

Neurotropic melanoma is characterized by invasion and perineural extension. Unlike the desmoplastic melanoma, which may have perineural invasion, the neurotropic melanoma desmoplasia is poor or absent, while the tumor is characterized by a marked proliferation of spindle cells. The perineural invasion should be carefully sought, especially in peripheral portions of the tumor even at a distance from the margins, and must be differentiated from satellite and from lymphatic vascular neoplastic invasion. The perineural invasion may have very different quantitative aspects of a massive proliferation with expansive infiltration of the surrounding soft tissues or of individual cells; this pattern is often difficult to identify without the support of immunocytochemical staining with antiserum protein S100.

Nevoid Melanoma and Minimal Deviation Melanoma

Minimal deviation or nevoid melanoma describes a tumor proliferation of nevomelanocytes that resemble nevus cells but with mild atypia of the cells (Fig. 7.41). This lesion usually occurs in association with a preexisting nevus and is considered a histologic variant of melanoma which may have a more favorable prognosis than a fully evolved melanoma with the same measured depth. Lower-power magnification reveals an expansile nodule with or without reticular dermal

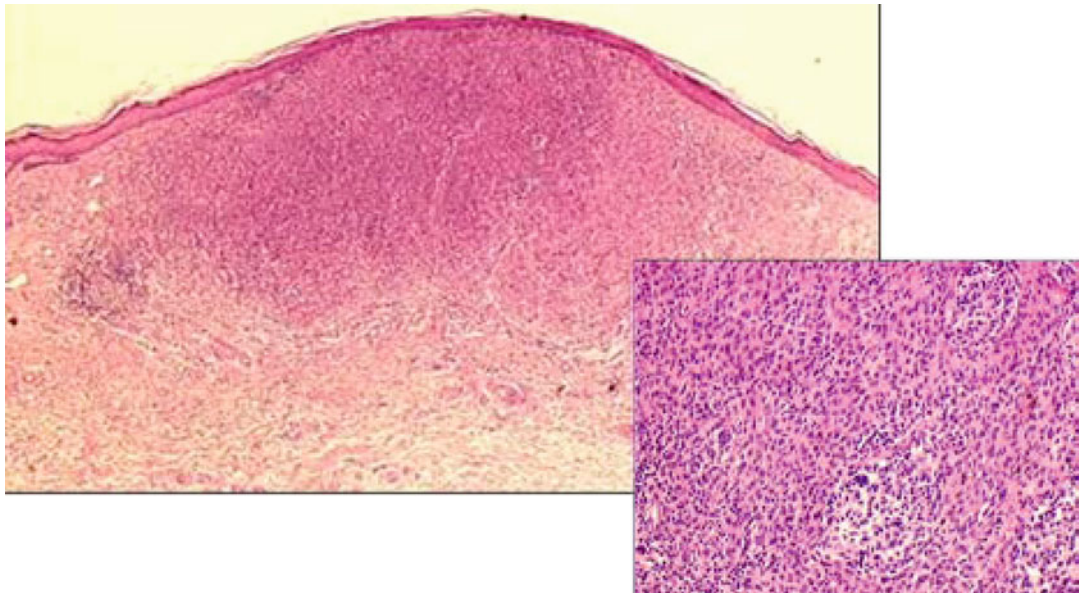


Fig. 7.41 Nevoid melanoma

involvement of usually quite pale cells unless there is a prominent pigment component. The pallor of the cells of the minimal deviation melanoma appreciated at low magnification is due to the banal nuclear characteristics without evidence of, or with low, hyperchromasia of the nuclei. The lesion is usually quite symmetrical usually oval in shape but with fascicles of cells extending into the reticular dermis. High-power evaluation of the cells resemble nevus, most commonly similar to the spindle and epithelioid cells of the Spitz nevus and often type B nevus cells. Some variants of minimal deviation melanoma consist of a proliferation of type A or type C cells. The most significant feature, at high-power examination, is the uniformity of the cells throughout the entire lesion, all resembling one type of nevus cell but with mild to moderate atypia. Thus, the cells are larger than normal nevus cells with more prominent nuclei and slightly increased in the nuclear to cytoplasmic ratio. If the cells are of the spindle and epithelioid cell type, they usually present nucleoli that are blue to amphophilic and are surrounded by a delicate chromatin rim. The cytoplasm of the spindle and epithelioid cells is a fine wispy cytoplasm, whereas the cytoplasm of the type B cells is more of a finely vacuolated and hyalinized type. The cells from top to bottom and side to side are similar. Some diminution in cell size may be noted as the cells approach the reticular dermis, evidence of maturation (also called aberrant maturation). Mitotic figures are usually very rare. The presence of numerous mitoses excludes the diagnosis of minimal deviation melanoma. If reticular dermal involvement is present, fascicles of cells extend into the reticular dermis separating collagen and fibers but without destructive and deforming infiltration. Thus, the fascicles much more resemble the fascicles of the Spitz nevus in the reticular dermis than of fully evolved melanoma. There is no necrosis noted among the cells in the superficial or the deep component of the lesion and usually a host response is absent to minimally present with the exception of the rare presentation of a halo minimal deviation melanoma in which there is a brisk dense lymphocytic response with permeation throughout the lesion. Extension into the subcutaneous fat is unusual and speaks against the diagnosis of minimal deviation melanoma. While perineural infiltration may be observed, reactive fibrosis to the tumor is likewise absent. Occasionally in minimal deviation melanoma there is an intraepidermal component which

consists of discrete nests of cells identical to those in the dermal nodule. If the intraepidermal component qualifies for radial growth phase melanoma of any type, superficial spreading, lentigo maligna, or other lentiginous types of melanoma, the diagnosis of minimal deviation melanoma is precluded. The variance of minimal deviation melanoma includes a halo minimal deviation melanoma in which there is brisk lymphocytic response throughout the entire tumor. This rare variant must be very carefully differentiated from melanoma with regression. Another variant is the desmoplastic minimal deviation melanoma which probably is a variant of type C cell proliferation with benign fibroblast-like cells forming an expansile nodule with fibrous response. The pigmented variant composed of pigmented spindle cells and associated with melanophages occurs; this lesion must be carefully distinguished from a spindle cell melanoma and can be done by appreciating that the melanoma cells usually have large nuclear to cytoplasmic ratios, are closely applied to one another, and have prominent nuclei and nucleoli with irregular heterochromatin. These spindle cells of the pigmented variant of minimal deviation melanoma have large amphophilic cytoplasm and large nuclei with small nucleoli and show very banal chromatin patterns. Of course the principal differential diagnosis with minimal deviation melanoma is fully evolved melanoma which can be distinguished on the basis of the pleomorphism of the cells, the high mitotic activity, the high nuclear atypia, the presence of single cell necrosis, and the presence of host lymphoid response. Minimal deviation melanoma of the spindle and epithelioid cell type can be differentiated from the compound Spitz nevus by the absence of maturation in minimal deviation melanoma, the presence of fascicles of cells rather than individual cells or small nests in the reticular dermis. Likewise the presence of an expansile nodule filling and widening the papillary dermis precludes the diagnosis of an ordinary compound nevus of Spitz. The deep penetrating nevus is differentiated from minimal deviation melanoma by the presence of a large epithelioid cells with finely granular melanin in their cytoplasm that fall on appendages and neurovascular bundles associated with a prominent melanophages aggregation. Careful examination of the deep penetrating nevus reveals that it does not form an expansile nodule but rather is composed of a network of cells among the neurovascular bundles. Minimal deviation melanoma is composed of an expansile nodule of spindle cells that resemble cells of the compound nevus of Spitz but that show slight atypia. Thus, the cells are somewhat larger than spindle cells but are uniformly so. The nuclei have elongate fusiform shapes but rather delicate nuclear chromatin. Fascicles of spindle cells infiltrate the reticular dermis but do not usually infiltrate subcutaneous fat. There is no mitotic activity is observed. If there is an intraepidermal component it is composed of cells identical to those in the dermis.

Malignant Blue Nevus

The malignant blue nevus is a very rare entity. In agreement with Maize and Ackerman (1987), the primary criterion for diagnosis of malignant blue nevus is the finding of a proliferation of fusiform melanocytes and intense pigmentation, with cytological characteristics of malignancy: marked cytologic atypia, nuclear polymorphism, and dense aggregates of malignant cells that expand and destroy the fibers of the reticular dermis extending to the hypodermis, without invasion of the epidermis. The typical "biphasic aspect" of the cellular blue nevus, due to the presence of nests of clear cells alternating with bands of pigmented spindle cell, fails in malignant blue nevus. Occasional is the finding of epithelioid cells and multinucleated giant. Foci of necrosis and atypical mitoses characterize the lesion, although the mitotic index is often low. The blue nevus must be distinguished from malignant cellular blue nevus. An asymmetric multinodular tumor bigger than 3 cm with frank cytological aspects of malignancy, atypical mitosis, and necrosis militates in favor of a malignant blue nevus. More complex is the distinction between malignant blue nevus and "atypical" cellular blue nevus because the differential diagnosis is placed on the degree of cytologic atypia, on these fairly subjective criteria, as well as on the presence of atypical mitoses. Precisely because of the lack of clear

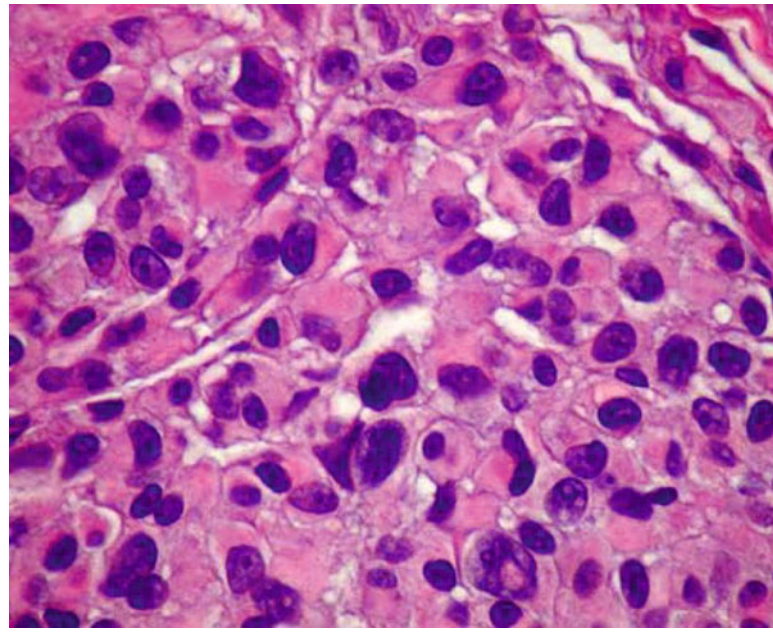


Fig. 7.42 Rhabdoid melanoma

characteristics of malignancy, an atypical blue nevus can be regarded as "dermal melanocytic lesions of uncertain potential" and requires a radical surgical treatment and appropriate follow-up long term. Since there are no pathognomonic histopathological aspects of malignant blue nevus, the differential diagnosis of nodular melanoma or against metastatic requires copresence of residues or the onset of blue nevus at the site of a preexisting blue nevus. The use of immunocytochemical methods has not shown any interest, because the reactivity with S100 and HMB45 form has been demonstrated in both benign and malignant blue nevus [74]; p16 is negative. The presence of lymph node metastases with malignant cytologic features confirms the diagnosis.

Other Rare Melanomas

Small Cell Melanoma

Small cell melanoma is rare, but it is particularly important because it may easily be confused histologically with other small cell tumors, including lymphoma, Merkel cell carcinoma, undifferentiated carcinoma, Ewing's sarcoma, and peripheral neuro-ectodermal tumor. Cytologically small cell melanoma may also simulate benign nevus. Poorly differentiated small cell foci are frequently encountered in a melanoma that has arisen in a giant congenital nevus. The ulcerated small cell melanomas have frequently an aggressive course with an increased probability of positive sentinel lymph nodes (35 %). Small cell melanoma is also reported in the rectal/anorectal site.

Rhabdoid Melanoma

Rhabdoid features have been described primarily in metastatic melanoma, and rare cases of primary totally rhabdoid melanoma have been reported. Rhabdoid melanoma are characterized by large sheets of polygonal cells with abundant cytoplasm containing hyaline filamentous and eosinophilic inclusions (Fig. 7.42), an eccentric displaced vesicular nucleus, and large nucleoli. Ultrastructural analysis showed cytoplasmic whorls of intermediate filaments with entrapped rough endoplasmic reticulum, mitochondria, and lipid. The tumor cells are strongly immunoreactive with S100 protein, vimentin, and CD56 and are focally reactive with Mart-1 and, in some cases, keratins and desmin. Tumor cells were negative for Melan-A, tyrosinase, and HMB45. The differential diagnosis of the rhabdoid melanoma is wide and must be supported by a broad panel of immunohistochemical stains. In general non-melanocytic rhabdoid tumors are positive for vimentin, glial fibrillary acidic protein, desmin, actin, and AE1/AE3. Moreover,

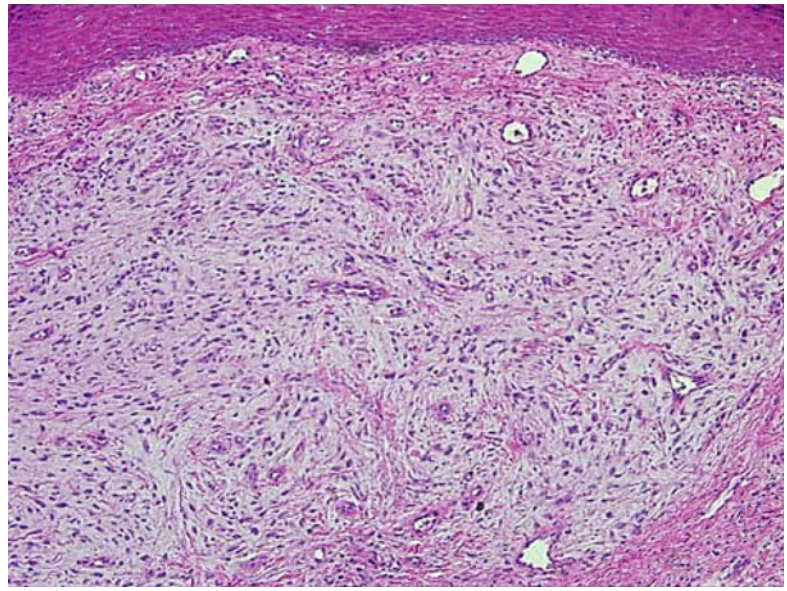


Fig. 7.43 Myxoid melanoma

S100 protein expression has not been observed in renal rhabdoid tumors. Malignant peripheral nerve sheath tumor, especially the epithelioid variant, is positive for epithelial membrane antigen and synaptophysin and is only focally positive for S100 protein. Plasmacytoma or plasmablastic lymphoma and anaplastic large cell lymphoma would be positive for CD138 and CD30, respectively. Rhabdoid morphology has been described in carcinoma; however, the lack of expression of both high- and low-molecular-weight cytokeratins excludes an epithelial neoplasm as well as epithelioid mesothelioma. Rhabdomyosarcoma would express muscle markers, such as desmin and myoglobin, and it is quite easy to differentiate from rhabdoid melanoma.

Myxoid Melanoma (Fig. 7.43)
Myxoid melanoma is a rare variant with large malignant cells amidst a basophilic mucinous matrix. The myxoid stroma comprises mesenchymal acidic mucopolysaccharides, as opposed to neutral epithelial mucins and the epithelial mucin preparations (mucicarmine and PAS-diastase) are negative, whereas stains for acidic mucosubstances (i.e., Alcian blue at low pH) are positive. Myxoid melanomas are frequently amelanotic. Most often these tumors are metastatic deposits and a differential diagnosis with a primary lesion may be difficult without the evidence of intraepidermal melanocyte proliferation. S100 decoration is frequently present but HMB45 and Melan-A positivity is less uniform, with both positive and negative results reported. The differential diagnosis of myxoid melanoma is broad, encompassing as it does other benign and malignant myxoid neoplasms that include soft tissue malignancies (myxoid liposarcoma, myxoid malignant fibrous histiocytoma, low-grade fibromyxoid sarcoma, low-grade myofibroblastic sarcoma, myxoid chondrosarcoma, myxoid peripheral nerve sheath tumors, myxoid rhabdomyosarcoma, malignant myoepithelioma, myxoid synovial sarcoma, myxoid follicular dendritic cell sarcoma, myxoid dermatofibrosarcoma protuberans, metastatic chordoma and its benign mimic parachordoma) as well as epithelial cancers (metastatic adenocarcinomas and malignant sweat duct tumors including malignant mixed skin tumor) and also sarcomatoid variant of anaplastic large cell Ki-1 lymphoma that can produce areas strikingly similar to myxoid melanoma.

Plasmacytoid Melanoma (Fig. 7.44)
The plasmacytoid cytological pattern is very rare in melanoma but sporadic cases are described; a case of primary melanoma of the oral cavity and a case of liver metastasis.

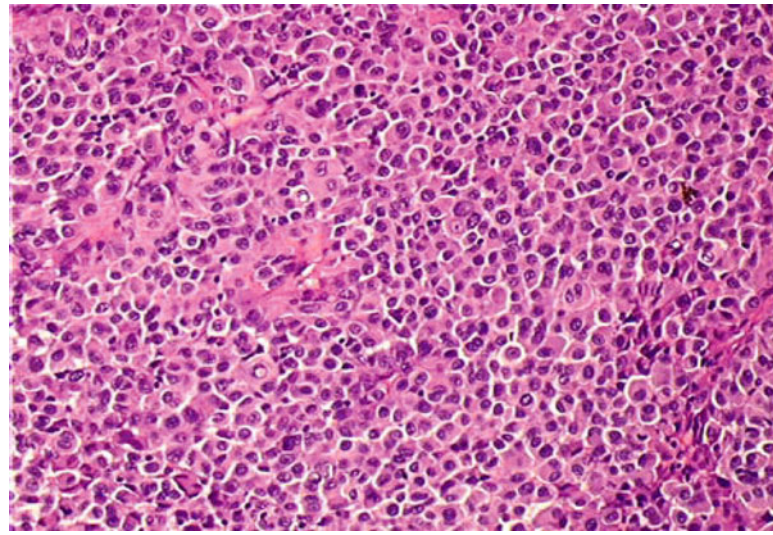


Fig. 7.44 Plasmacytoid melanoma

Follicular Melanoma

Follicular melanoma is a rare variant of melanoma with aggressive behavior. The melanoma involves the hair follicle with pagetoid spread into the follicular epithelium and invasion of papillary dermis. Only few cases are reported in literature.

Metaplastic Change in Melanoma

Divergent differentiation or metaplastic change is a rare phenomenon in melanoma and, when it occurs, can be misinterpreted and lead to diagnostic uncertainty. These events in melanomas are defined as the development of morphologically, immunohistochemically, and/or ultrastructurally recognizable non-melanocytic cell or tissue components. Different types of divergent differentiation are reported and include fibroblastic/myofibroblastic, schwannian and perineurial, smooth muscle, rhabdomyosarcomatous, osteocartilaginous, ganglionic and ganglioneuroblastic, neuroendocrine, and probably epithelial. A carefully chosen immunohistochemical panel and the input of electron microscopy can help to clarify the nature of the cellular differentiation of these tumors and lead to a correct final diagnosis. The clinical significance of such aberrations is uncertain, nor are the underlying mechanisms as yet well defined. Metaplastic foci mimicking osteogenic sarcoma and cartilaginous metaplasia have been described in one case of a nasal mucosal primary and its metastasis and in cases of subungual melanoma. Mesenchymal elements with rhabdomyoblastic, lipoblastic, and neurogenous features have been also described in those melanomas that arise in giant congenital nevus.

Chondroid, Osteogenic Melanoma (Fig. 7.45)

This variant of metaplastic melanoma is quite important as it most commonly, as a primary tumor, affects the great toe or the thumb. There is almost always a history of a trauma that is given as the source of the swollen digit. Biopsy usually will demonstrate an atypical chondroid or osteoid with associated ossification and is usually misinterpreted as osteogenic sarcoma. Careful evaluation of the intervening stroma will usually raise the suspicion of a spindle cell or epithelioid cell tumor. Often there will be pigmentation. The final clue is the observation of a radial growth phase. Confirmation by S100 and Melan-A is necessary to identify the malignant melanocytes and differentiate them from S100 chondrocytes.

Signet Ring Melanoma (Fig. 7.46)

A signet ring primary melanoma is a very rare event, being seen in some 0.5 % of melanomas. This variant must be considered with particular attention to differentiate a metastatic non-melanocytic tumor, particularly in pleural or peritoneal effusion, from a signet ring melanoma. Cytologically the signet ring

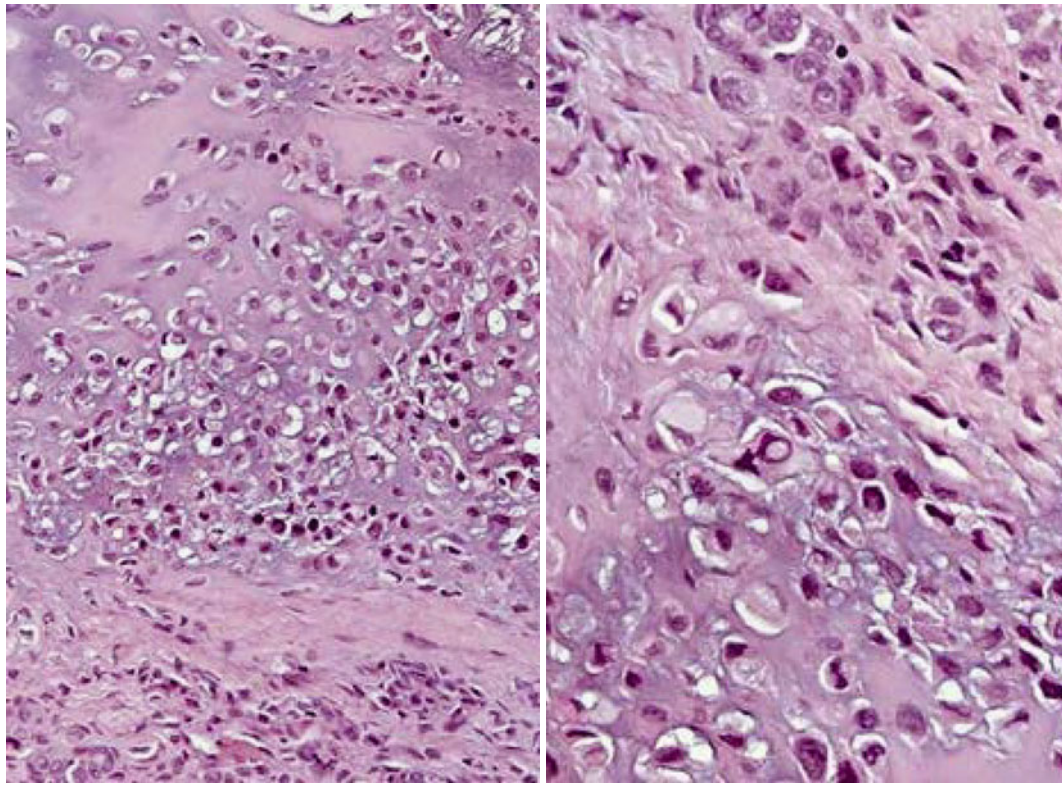


Fig. 7.45 Chondroid melanoma

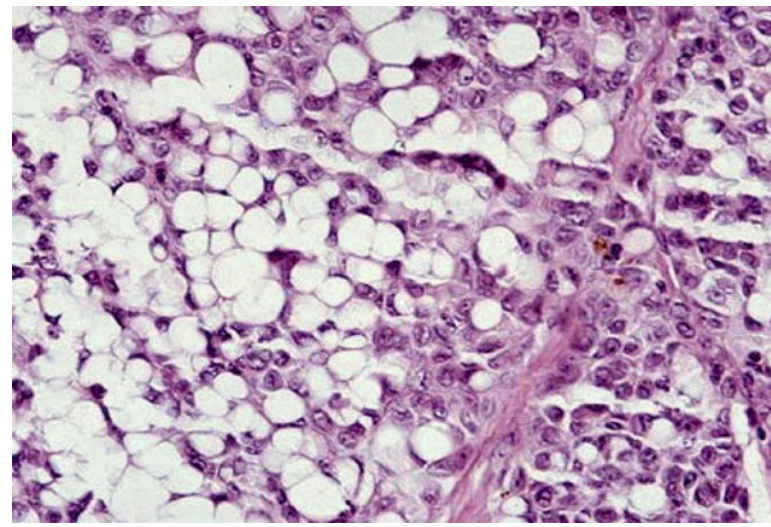


Fig. 7.46 Signet ring melanoma

melanoma cell may present different morphology as small, large, or giant cells. An unusual histological variant with a combination of the signet ring cell melanoma with desmoplastic, pseudoglandular, and oncocytoid features is described. Ultrastructurally in the cytoplasm it is possible to demonstrate an accumulation of intermediate filaments, specifically vimentin. The signet ring cells are S100 protein and HMB45 positive; however, exceptions to this immunohistochemical profile are reported. Cases

of S100-positive, HMB45-negative signet ring melanoma are described as are cases of HMB45-positive, S100-negative signet ring melanoma. In rare examples, intracytoplasmic neutral mucin may be observed. The histological differential diagnoses include all the tumors with prominent cytoplasmic vacuolation; tumors of vascular endothelium or adipose tissue, signet ring lymphoma, and epithelioid smooth muscle lesions as well as the more frequent signet ring adenocarcinoma are thus considered.

Spindle Cell Melanoma

Spindle cell melanoma is a rare variant that may present diagnostic difficulties particularly when staining with S100 is negative, weak, focal, or a combination of these and the other conventional melanocytic markers are negative. p75 NGF-R exhibits superior staining characteristics and greater sensitivity in identifying spindle cell melanoma than S100. p75 NGF-R may be a useful diagnostic and ancillary stain in addition to S100. Spindle cell melanoma has been described in urinary bladder, in primary melanoma associated to myxoid and cribriform pattern, in liver metastasis, and in melanoma on old burn scar. The c-kit expression, reported in literature, in the spindle cell melanoma could represent a major diagnostic pitfall.

Balloon Cell Melanoma

The balloon cell melanoma is a rare histological type of melanoma composed of nests and sheets of large polyhedrical and foamy cells with an abundant, clear, or finely vacuolated cytoplasm. Frequently its benign cytologic appearance presents a challenge for a correct histopathological diagnosis. In fact the tumor may simulate a balloon cell nevus but cytologic atypia, mitotic activity, and necrosis may be useful characters for the differential diagnosis. The presence of multinucleated giant balloon cells and deep maturation are features that suggest the diagnosis of balloon nevus. No intervening stroma is present between the malignant cells; the nuclei are irregular and large with prominent nucleoli. The cytoplasm is clear and in some case a PAS positivity and diastase sensitivity may be demonstrated due to the intracytoplasic accumulation of glycogen. In most cases ultrastructural reports have demonstrated the presence of intracytoplasmic degenerating melanosomes or lipid similar to the balloon cell change of benign nevi. No case is described of balloon cell melanoma in situ. Immunohistochemical stains reveal reactivity with antibodies to S100 protein, Melan-A, HMB45, vimentin, and negative stain with p16. Numerous differential diagnoses must be considered including common acquired nevi, with which balloon cell melanoma may coexist, as well as other malignant non-melanocytic clear cell neoplasms as clear cell sarcoma of soft parts, atypical fibroxanthoma, granular cell carcinoma with clear cell change, metastatic renal cell carcinoma, clear cell basal cell carcinoma, malignant clear cell acrospiroma, sebaceous carcinoma, and clear cell squamous cell carcinoma.

Melanocarcinoma (Melanoma with Intermixed Epithelial Component or Divergent Differentiation)

A very rare variant with two distinct but intimately admixed components: melanocytic and epithelial described by Wen [75]. The immunohistochemical stains demonstrate the epithelial differentiation on the basis of cytokeratin (CAM5.2 and AE1/AE3) expression and melanocytic differentiation (HMB45, PNL2, MITF, and S100) of melanoma component. MITF is expressed in both components, raising the possibility of dual differentiation in a single tumor, rather than the alternative considerations of a collision tumor or a reactive pseudoepitheliomatous hyperplasia with eccrine duct lumen formation within a melanoma (Fig. 7.47). This unusual tumor with both melanocytic and epithelial components may represent a true melanocarcinoma, which becomes a plausible consideration, in view of melanoma plasticity and recent experimental evidence and speculation about the role of stem cells in melanoma.

Melanoma Prognostication

Great advances have been made in understanding the prognosis in melanoma. The first breakthrough was the classification of melanoma into subtypes and the definition of levels of invasion [70, 71].

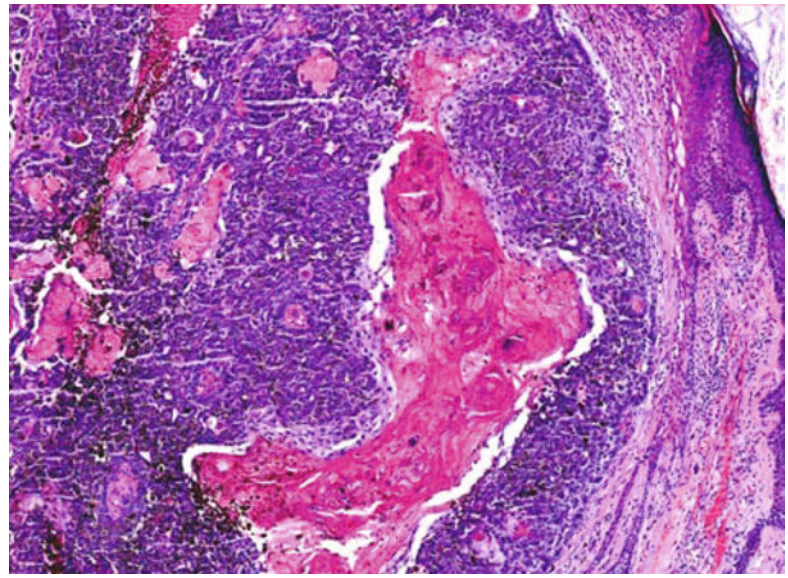


Fig. 7.47 Melanocarcinoma: melanocytic and epidermoid differentiation

The measured thickness as introduced by Breslow is determined by measuring with a micrometer from the granular cell layer to the deepest tumor cell and expressing the result in millimeters [76]. This measurement and its relationship to prognosis are linear. It has been included in the 9th edition of the American Joint Committee on Cancer, Melanoma Committee Recommendations [77]. The other parameters that were included are ulceration and mitoses. The presence of mitoses would now replace the level of invasion. Hence, the designation "a" would indicate no ulceration or mitoses, and the designation "b" would indicate the presence of either mitoses or ulceration or both. Thus, the designation would be T1a or T1b, T2a, and following. Microscopic satellites also are to be included in the report. The number of mitoses is found by searching the field at 20× for the area of most mitoses. When that is found, it is considered the "hot spot" and it is counted in square millimeter. In most mitoses this area corresponds to 4 to 4 ½ 40× fields, counted consecutively in the manner to reflect as close to a square as possible. Then the amount is expressed in mitoses per mm squared. Less than one mitosis is not acceptable. The designation must be zero or the amount reached by counting in the above method. If there is only one mitosis, that area becomes the "hot spot" and is reported as 1 mitosis per mm. square. Microscopic satellites are reported as islands of tumor cells >0.05 mm in width that are separated by a significant distance from the vertical growth phase. The islands may be present below the vertical growth phase of around it. This finding is now reported as N2c. The other criteria that can be entered include tumor-infiltrating lymphocytes, regression, and vascular or neural invasion. Also, margins are reported and the presence of a preexisting lesion as appropriate. Another important feature relates to the sentinel lymph node positivity. It was determined immunohistochemical detection of nodal metastases is acceptable. With the much greater understanding of the morphology of melanoma cells by the community of pathologists, it was determined that one no longer must prove the presence of deposits by confirmation with hematoxylin and eosin-stained sections. Furthermore, the committee determined that, until more information is available, there should be no lower limit to the size of the deposit required to determine that a sentinel lymph node is positive. Even a single clearly malignant cell in the parenchyma should be so designated. Finally, it was decided that microscopic and macroscopic deposits in lymph nodes should only refer to the gross inspection of the tumor deposit. A macroscopic deposit is one that is clearly visible to the

naked eye as observed in sectioning the lymph node. Other features that were considered but about which there was insufficient information to be cited in the mandatory report include the presence of tumor-infiltrating lymphocytes, regression, and neural and/or vascular invasion. For further details the reader is referred to a review of prognostic variable. For further details on these parameters, the reader is referred to the review by Piris and Mihm [78].

Conclusion

In this chapter we have attempted to review the various parameters of pigmented lesions in progression from the benign to the atypical to the malignant. There are many suggestions in the chapter about clues to diagnosis. We hope the reader will profit from this exercise and will also liberally use the references to further strengthen their understanding.

Glossary

Atypical melanocytic tumors a subset of melanocytic tumors, with unpredictable biologic behavior.

Dermal melanocytosis benign, flat, congenital birthmark with wavy borders and irregular shape

Dysplastic nevus a junctional or compound nevus with cellular and architectural dysplasia

Melanocytic nevi a pigmented lesion of the skin caused by a disorder involving melanocytes

Melanoma malignant tumor of melanocytes.

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