

# Melanocytic nevi and non-neoplastic hyperpigmentations

C. CLEMENTE

Servizio di Anatomia Patologica e Citodiagnostica, I.R.C.C.S. Policlinico San Donato, Milano

## Preface

This is the first of three chapters that will be progressively published on Pathologica as updating activity of the Italian Study Group of Dermatopathology (GISD), Italian Society of Pathology and Cytology (SIAPeC IAP). The first chapter concerns non-neoplastic hyperpigmented skin lesions and nevi, the second will address the topics of dysplastic nevus, borderline and low malignant potential melanocytic proliferations and the third melanoma in its variants and differential diagnoses with a supplement on the immunohistochemistry and molecular support to diagnostic and prognostic definition of nevi and melanomas. Although we believe that great advances were made in the application of ancillary genetic, immunohistochemical and molecular techniques, for the diagnosis and biological characterization of melanocytic tumors the morphology still remains the gold standard. These chapters are not intended as substitutes or even claim to be compared to the numerous and valuable texts that are also recently published, but they want to present, concisely and quickly available, all of those traits that we believe essential to the histopathological evaluation of a melanocytic lesion. No morphological parameter is exclusive and individually sufficient to make the correct diagnosis of nevus or melanoma but to reach a final conclusive and appropriate interpretation a set of morphological characters must be evaluated and compared. I was lucky enough to be able to examine several thousand cases and to draw lessons from each of these increasing my diagnostic experience. I had a great lesson by my teacher and good friend Prof. Martin C. Mihm Jr of Boston, dermato-pathologist with undisputed international reputation, who, with great passion, patience and friendship, transferred me much of his experience and knowledge and for which I always thank him. Special thanks I would like to address Dr. Agostino Crupi, dermatologist, skin-oncologist and brilliant dermatoscopist who taught me how the diagnosis of melanocytic lesions starts from the clinic examination and the mutual comparison between dermatologist and pathologist is a great richness of knowledge for both. Finally thank to my collaborators Barbara Rubino, Barbara Bruni and Antonella Festa for the large number of material collected in these years at the Pathology Service of the IRCCS Policlinico San Donato and a particular thank to Marco Turina who collaborated in the drafting of this text.

Milan, March 2017

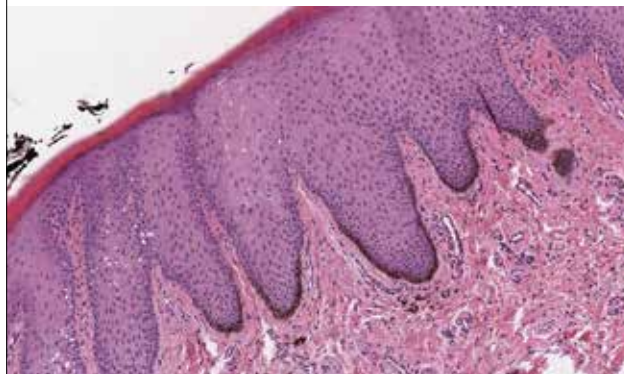
Claudio Clemente

## 01 Non-neoplastic hyperpigmented lesions

### 01A EPHELIDES (FRECKLES)

Ephelides are light tan, uniform skin lesions with irregular and poorly defined borders, frequently less than 2 mm in diameter, on light-exposed skin (particularly the face, dorsa of the hands, forearms and perioral skin), shoulders and upper limbs. Ephelides are more evident after sun exposure and they are inconspicuous in winter. They are numerous in people with fair skin, red hair and clear blue eyes. Ephelides are characterized by hyperpigmentation of the epidermal basal keratinocytes without melanocytic proliferation and elongation of rete ridges. The skin appendages are usually not involved. Pigmented melanophages may be dispersed in the superficial dermis.

Fig. 1. Ephelides: hyperpigmentation of the basal keratinocytes without melanocytes junctional nests.



The differential diagnoses include the **lentigo simplex**, characterized by slight or variable increased melanocytic

### Correspondence

Claudio Clemente, Servizio di Anatomia Patologica e Citodiagnostica, I.R.C.C.S. Policlinico San Donato, via Morandi 20, 20097 San Donato Milanese (MI) - E-mail: cclemente.ap@iol.it

proliferation with lentiginous elongation of the rete ridges, the **café au lait spot** that shows a moderate or slight increase of melanin pigment with giant melanosomes and normal epidermal architecture. **Melanotic macules** are benign, oral pigmented lesion more frequently in females, adulthood, usually in the lower lip (**labial melanotic macule**) and gingiva. Unlike an ephelides, the melanotic macules do not become darker with sun exposure. Other differential diagnoses are **amalgam tattoo** and focal **traumatic ecchymosis**, the last to correlate to anamnestic data.

**Ephelides: key histopathological diagnostic features**

- Increased content of melanin in keratinocytes without evidence of melanocytes proliferation
- No rete ridges elongation and junctional nests
- Normal epidermal architecture

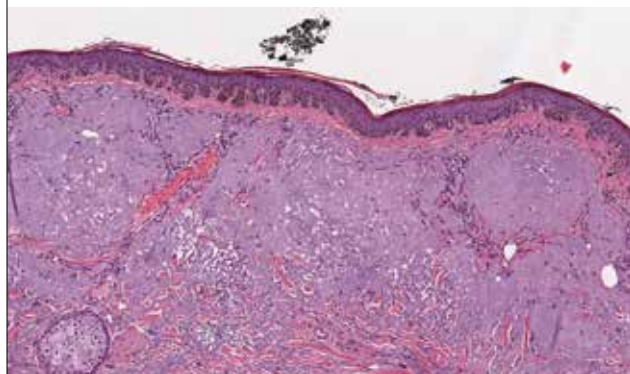
### 01B ACTINIC (SOLAR) LENTIGO

Actinic (solar) lentigo are irregular and focal areas of hyperpigmentation of the skin more large (about 4 to 10 mm in diameter) than the ephelides, with a slight increase of the basal melanocytes number. Frequently the lesions are present in middle age, in individual with fair skin (photo-type I). Actinic (solar) lentigo represents a heterogeneous group of lesions characterized by different patterns that depends on the state of its evolution. In the early stage, there is uniform slight basilar hypermelanosis and mild squamous atypia. In evolved stages, epidermis shows irregular lentiginous elongation of rete ridges with hyperpigmentation and increase of melanocytes. In the superficial papillary dermis may be present heavily pigmented melanophages, few sparse lymphocytes and variable elastosis frequently also severe.

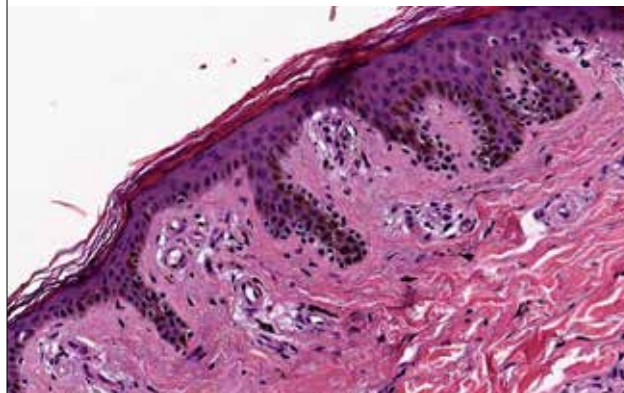
The single intraepidermal melanocytes are sometimes enlarged and immature but not organized in nests.

The differential diagnoses include the **hyperpigmented variant of actinic (solar) lentigo (reticulated lentigo, ink spot lentigo)** that clinically may suggest a **melanoma** but atypia is light and focal, the basal proliferation of the melanocytes is not continuous and lack of aggressive epidermal infiltration with apoptosis and necrosis of the keratinocytes. In **lentigo maligna** a well evident

**Fig. 2.** Actinic (solar) lentigo: increase of the basal melanocytes and dermal elastosis.



**Fig. 3.** Actinic lentigo with reactive melanocytic hyperplasia along the basal layer and focal irregular enlarged melanocytes with epithelioid appearance that should not be confused with dysplastic nevus.



a continuous basal proliferation of atypical melanocytes with extension to hair follicles is usually well evident with irregular junctional nesting and focal atypical cells migration into the spinous layer of the epidermis. Hyperplastic retia is present in actinic lentigo whereas lentigo maligna shows flattening of the rete ridges with atrophy and dermal elastosis. In the **pigmented actinic keratosis** the skin shows variable keratinocytic atypia extended to the whole thickness of the epidermis. The **pigmented seborrheic keratosis** is characterized by acanthosis and increased proliferation of the supra-basal keratinocytes. In the **large cell acanthoma** the basal keratinocytes are uniformly enlarged with increase of the nuclear cytoplasmic ratio; the immunostaining with HMB45 (melanocytes positive and keratinocytes negative) may be useful in the **differential diagnosis**. **Becker's nevus** (pigmented hairy epidermal nevus) is a rare hamartomatous lesion with acanthosis, hyperkeratosis and elongation of the rete ridges and marked hyperpigmentation of basal keratinocytes. Increased number of smooth muscle hamartomatous bundles are present.

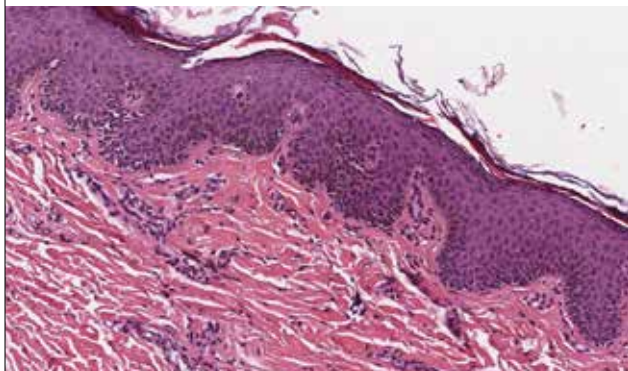
**Actinic (solar) lentigo: key histopathological diagnostic features**

- Irregular elongation of rete ridges and increase of melanocytes
- Hyperpigmentation of basal keratinocytes
- No junctional nests or confluent proliferation of the melanocytes
- Variable dermal elastosis

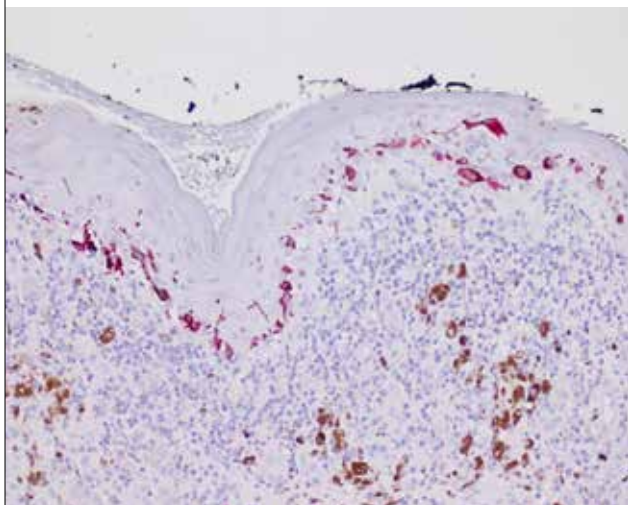
### 01C MUCOSAL MELANOSIS

Mucosal melanoses include different pigmented lesions: **genital lentiginos** (vulvar, vaginal and penile melanosis), **labial melanotic macule** frequently on the lower lip or rarely localized in other areas of the oropharynx and conjunctive. Alternating irregular areas of pigmented and normal mucosa may simulate a melanoma with regression. The mucosal melanosis may be variable in color, diffusely dark brown and to measure up to 15 mm of diameter and sometimes, in genital areas, several centimeters. Histologically a diffuse basal layer hyperpig-

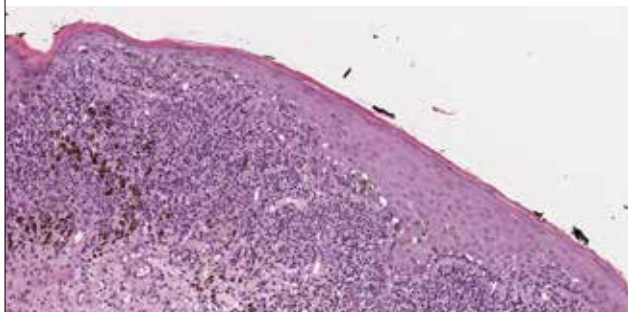
**Fig. 4a.** Mucosal melanosis with increase of the basal melanocytes and light hyperpigmentation.



**Fig. 4b.** HMB45 positivity of basal melanocytes and intraepidermal dendrites.



**Fig. 5.** Vaginal melanosis: increase of junctional melanin and melanocytes associated to dermal.



mentation with increased numbers of basal melanocytes is usually present with long and prominent dendritic processes extended into the epidermis up to the superficial layers.

The most important **differential diagnosis** is the **mucosal lentiginous melanoma** that is characterized by nested junctional proliferation of atypical melanocytes

with lentiginous growth pattern and spread to the adnexa.

**Mucosal melanosis: key histopathological diagnostic features**

- Hyperpigmentation of basal keratinocytes
- Increased number of melanocytes with long dendrites through the inter-keratinocytes space to the superficial layers of the epidermis
- Absence of nested proliferation and cytologic atypia

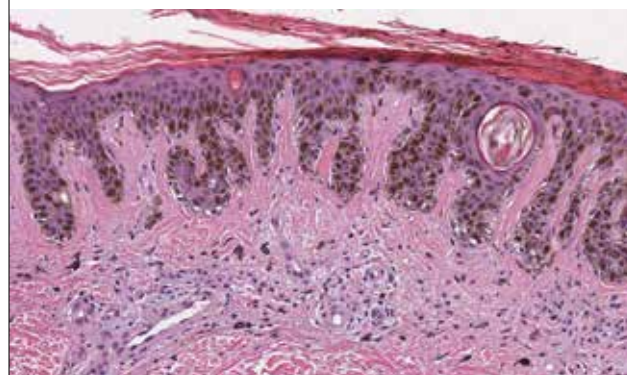
**02 Acquired melanocytic nevi**

**02A LENTIGO SIMPLEX**

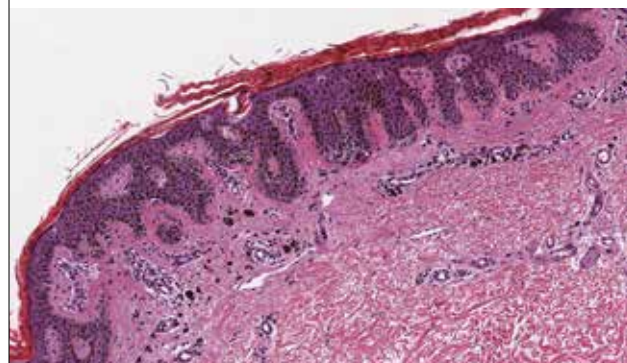
Lentigo simplex is a common melanocytic lesion localized anywhere in the tegument, not related to sun exposure. Clinically it is a well-circumscribed, uniformly pigmented, tan brown to black, 0.1-0.5 cm in maximum dimension. They are very common in childhood and adolescence. Histologically lentigo simplex shows an increased number of melanocytic cells in the dermo-epidermal junction with a slight elongation of the rete ridges. This lesion is not associated with nests of the nevus cells. There is an increased pigmentation both in the epidermal and in the papillary dermis within melanophages and sparse dermal chronic inflammatory infiltrate.

When present in a large number they may be a feature of a syndrome (LEOPARD, LAMB, Carney’s complex, Peutz-Jeghers, Laugier-Hunziker). Occasionally small

**Fig. 6.** Lentigo simplex: lentiginous elongation of rete ridges and increase of basal melanocytes.



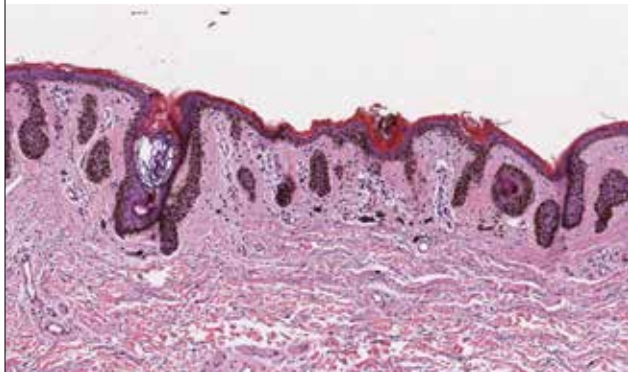
**Fig. 7.** Jentigo: a nevus that combines features of junctional nevus and lentigo simplex.



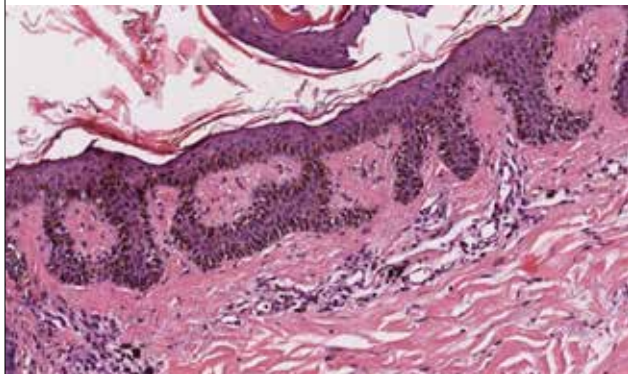
nest of melanocytes are present at the tip of the rete ridges and the term “**lentigo**” has been used (Ber Rahman and Bhawan 1969).

A variant of the lentigo simplex is the **nevus spilus** which clinically presents small hyperpigmented macules and papules and histologically may be indistinguishable from lentigo simplex. The differential diagnoses include **psoralen** and **ultraviolet A (PUVA) lentigo**, a lesions with an irregular hyperplasia of the epidermis with scattered atypical junctional melanocytes, pigmentation of the basal keratinocytes extending to the granular and spinous layer with a like pagetoid spread. Others differential diagnoses include freckle, junctional nevus, or dysplastic nevus. The **freckle** is a not proliferative lesion of melanocytes associated to hyperpigmentation of the basal skin layer. If junctional nests are present in lentigo it is impossible to exclude that the lesion represents a true early junctional nevus. The **dysplastic nevus** presents a proliferation of nevus cells along the dermal/epidermal junction with lentiginous pattern and evident cytologic atypia; furthermore there are stromal changes including increased vascularity, prominent inflammation associated with striking lamellations of collagen. **Senile lentigo** shows irregular rete ridges hyperplasia with dense hyperpigmentation without melanocytic hyperplasia and frequently focal irregular melanocytic atypia. **Acral lentigo** is a pigmented macula on the palm or soles and beneath the nails.

**Fig. 8a.** Senile (solar or actinic) lentigo: characterized by hyperpigmentation of basal keratinocytes and elongation of rete ridges.



**Fig. 8b.** Senile (solar or actinic) lentigo: prominence of isolated junctional melanocytes.



In **malignant lentigo** the prominent single cell proliferation along the epidermis may appear benign in early lesions and simulate a lentigo simplex. Malignant lentigo presents a strikingly atrophic epidermis, sun damaged dermis, and often a bandlike or lichenoid inflammatory infiltrate admixed with melanophages; furthermore the proliferation of melanocytes extends along the external root sheath of the hair follicles, even to the base of the hair follicle.

**Mucosal lentiginos** (labial and genital), vulvar, penile and acral lentiginos may closely resemble lentigo simplex with increased number of intraepidermal basal pigmented melanocytes with well evident dendritic morphology.

**Lentigo simplex: key histopathological diagnostic features**

Hyperpigmentation of the basal layer of the epidermis

- Lentiginous elongation of the rete ridges
- Irregular increase of the number of junctional melanocytes

**02B JUNCTIONAL, COMPOUND AND DERMAL NEVI**

Melanocytic nevus is a benign tumor, most often found during childhood or adolescence, which may develop on hair bearing skin or also on other sites including glabrous skin, nails or mucosae. The most frequent sites in males are head, neck and trunk; in females lower limbs. The majority of nevi change and regress in the elderly. They are more common in individuals with pale skin (phototype 1). Three nevi types can be recognized: junctional, compound and dermal nevi. Clinically junctional nevi are macular, flat, small, up to 0.5 cm in greatest dimension, uniformly pigmented and well circumscribed. Color vary from light to dark brown. Compound nevus usually is usually raised, it can be dome-shaped, warty, and often darkly pigmented. Intradermal nevi often have scarce or no pigmentation, they can be pedunculated or papillomatous/dome-shaped.

The histological features of nevi depend upon the stage of maturation. **Junctional nevi** exhibit nests of nevomelanocytes in the basal and lower part of the epidermis, usually at the tips of the slightly hyperplastic rete ridges but they can present also in a lentiginous pattern. A nest is considered if five or more cells in a single cluster are present. The melanocytic cells are polygonal, epithelioid or spindle, with well-defined cell boundaries; the cytoplasm is clear or pale, eosinophilic to amphophilic, with sparse, usually coarse, melanin pigment. The junctional and superficial dermal melanocytes present nuclei round to oval and have prominent nucleoli (type A cells). The aggregates of the melanocytes are cohesive and a clear space separates the nest from the adjacent epidermis. To note the regular and repetitive nesting architecture.

Occasionally the nevi of the childhood, nevi in pregnancy and in special sites as the scalp and genitalia, a junctional nevus may simulate an in situ or superficially invasive melanoma. Despite the architectural disorder the junctional melanocytic proliferation is usually monomorphic and discontinuous without pagetoid spread at the shoulder of the nevus. A variant of the junctional nevus, frequently observed in elderly patients, shows elongation of the rete ridges in lentiginous pattern.

Fig. 9a. Verrucous (Misher) nevus.

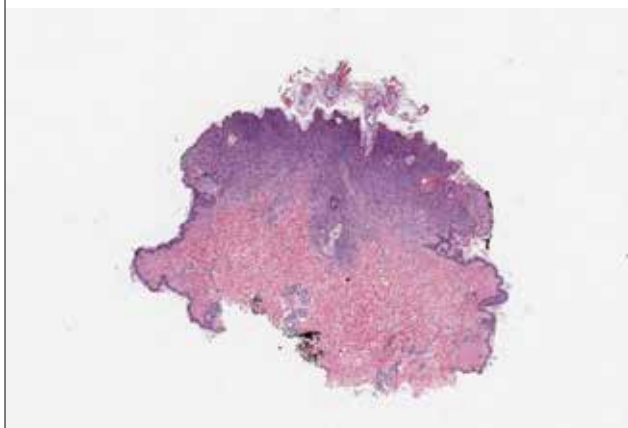


Fig. 9b. Dome shaped (Unna) nevus.

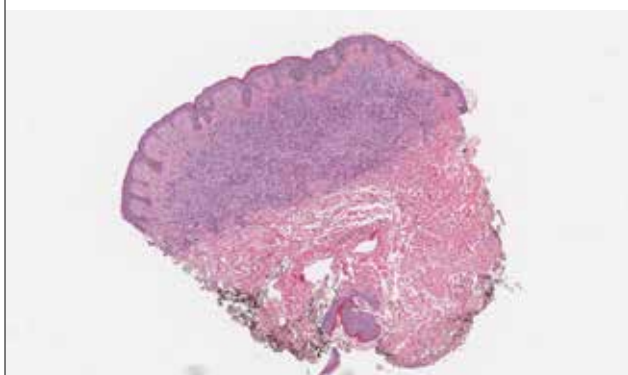
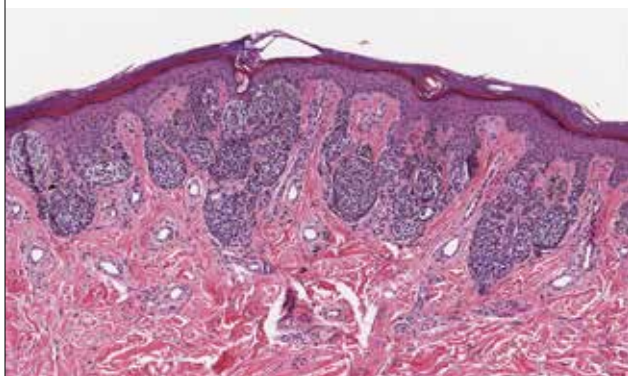


Fig. 10. Junctional nevus; nests of melanocytes at the tip of the rete ridges.



The differential diagnoses include the **pigmented junctional spindle cell nevus** composed of a uniform population of characteristic spindle cells in nests well defined and oriented perpendicular or parallel to skin surface. The **lentiginous junctional dysplastic nevus** that shows variation in morphology of the single cells and in the size of the nests. The dysplastic nevi are characteristically discohesive with proliferation along the lateral portion of the rete ridges not at the tip. **Superficial spreading melanoma** may show a prominent nesting pattern but the cells are large, have prominent eosinophilic nucleoli, large cytoplasm filled with fine, dust like, melanin

granules, there is less retraction from keratinocytes of the nests and it is evident an “aggressive” proliferation with keratinocytes apoptosis.

**Compound nevi** show junctional and dermal nests of nevus cell, extended to the papillary dermis in acquired nevi and to reticular dermis in congenital nevi. They are well-circumscribed and symmetrical lesions and usually do not have the “shoulder phenomenon”. In dermal component the cells are smaller, resemble lymphoid cell, have less cytoplasm and dark nuclei (type B cells) and in deep component the nevus cell are spindle, fibroblastic-like (type C cells). Mitotic activity is very low and atypical mitoses are absent.

A lentiginous proliferation, simulating a dysplastic nevus may be variably present in the compound congenital nevus, localized in the central area of the lesion. 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 epithelioid cells. These cells are large round nevus cells with coarse melanin granules within them. In

Fig. 11. Lentiginous proliferation in junctional nevus in elderly patients to differentiate from a lentiginous junctional dysplastic nevus.

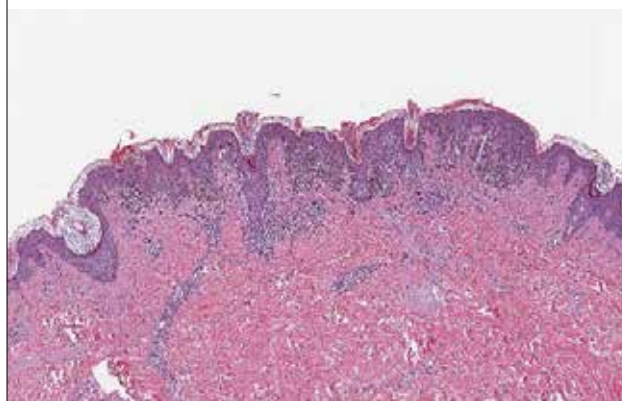
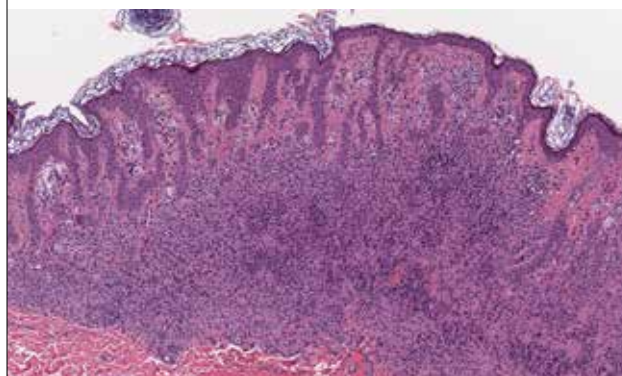


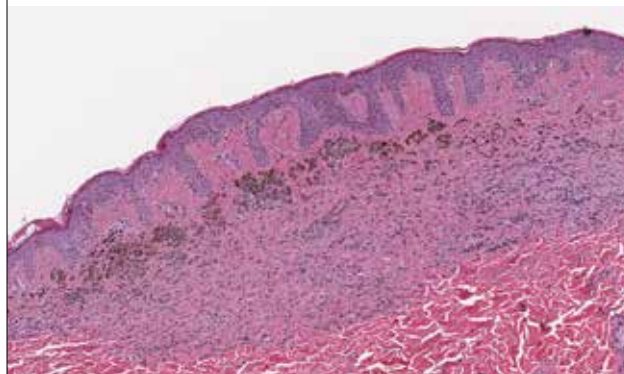
Fig. 12. Compound nevus: superficially plump type A nevus cells and lymphoid-like type B cells at the middle and deep component are present. To note the different color of the dermal nevus due to crowding of nuclei and reduction of nuclear cytoplasmic ratio.



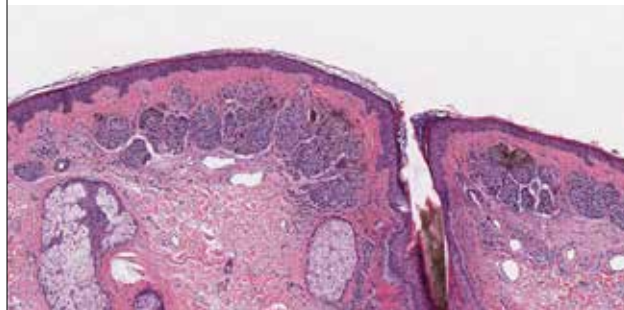
the dermal component of the lesion the picture is quite variable. In early lesion there are small nests of cells, many similar to type A cells, with large round nuclei present in the papillary dermis. These cells as they increase in number with lesion aging become smaller and round without pigment, type B cells. They exhibit tiny nucleoli and are associated with a 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. The type C cells are associated with increase of the reticulum fibers separating the C cells from one another. The type C cells can become arranged in complex patterns resembling neuroid structures. Type A cells express S100 protein and HMB45. Type B cells may express either S100 or the Schwann cell associated antigen but they are mostly HMB45 negative. This variation in morphology and immunohistochemical findings is considered as a maturation phenomenon of the nevus cells in their dermal component. Junctional and dermal nevus cells are usually p16 positive; the small B nevus cells may lost the p16 positivity. A variant of the compound nevus is considered the **nevus spilus**, characterized by a junctional melanocytic hyperplasia of single cells or nest associated with a variable pigmentation of adjacent keratinocytes, elongation of rete ridges and thickening of papillary dermal collagen. In **differential diagnosis** the compound **dysplastic nevus** exhibit 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. In **melanoma** in addition to irregular nesting intraepidermal pagetoid aggressive spread of malignant melanocytes is present at the shoulder of the lesion furthermore the characteristic maturation of type A to B to C cells is absent. In the vertical growth of a monomorphic, expansive, centrifugal proliferation is characteristic. The melanoma cells frequently exhibit finely granulated melanin pigment in their cytoplasm while it is an atypical and rare finding in compound nevi. Mitotic activity in the dermal component is extremely rare in compound and dermal nevi whereas it is common and variable in melanomas. The mitotic activity must be evaluated along all the proliferative margin of the lesion. Finally, compound nevi very rarely have a striking inflammatory response, whereas melanoma is commonly, especially below the intraepidermal component, associated with a lymphocytic host brisk response.

**Intradermal nevus** represents the late stage of maturation; it shows usually less pigmentation with progressive accumulation of fibrous stroma. The cells are frequently spindled with fibroblast or schwannian-like appearance (wavy nuclei, pale cytoplasm, fibrillar appearance, type C cells). The nevus cells are confined to the dermal component with no intraepidermal involvement. The epidermis may be flattened because of effacement of the rete ridges. The presence in the deep reticular dermis and around the adnexal structure suggests a congenital nevus. There is no evidence of

**Fig. 13a.** Intradermal nevus: there is not intraepidermal nevus. The dermal component shows a superficial deposition of melanin pigment and a proliferation of small nevomelanocytes between the dermal stroma.



**Fig. 13b.** Nevus with dermal nests.



prevalent expansile growth 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. The type C cells proliferate as S-shaped fibroblast like cells with increasing ground substance resembling neurofibromas. Lesions containing prominent type C cell proliferation with extensive ground substance are dubbed "**neuro nevi**" by Masson (see pag.75).

**Junctional nevus: key histopathological diagnostic features**

- Flat or slight raised pigmented lesion
- Junctional nest of cohesive melanocytes
- Nests at the tip of the rete ridges
- Epithelioid or less often spindled morphology
- Uniform melanocytes in regular and repetitive nests

**Compound nevus: key histopathological diagnostic features**

- Dome shape (Unna) or verrucous (Miescher)
- Circumscribed and symmetrical
- Junctional component usually not beyond the dermal component
- Maturation in depth
- Melanocytes type A (epithelioid), B (lymphocyte-like) and C (neural/fibroblastic like)
- Dermal mitoses rare or absent

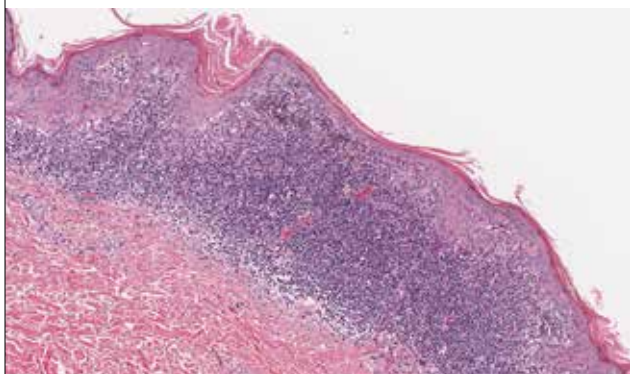
**Dermal nevus: key histopathological diagnostic features**

- Dome shape (Unna) or verrucous (Miescher)
- Maturation with depth
- Type B and C cells
- Neurotization, multinucleate cells, pseudovascular and pseudoglandular change
- Stromal mucin deposits, fatty infiltration, sclerosis
- Pseudovascular invasion
- Dermal mitoses rare or absent

**02C HALO NEVUS**

Halo nevi, also termed *leukoderma acquisitum centrifugum*, are benign melanocytic nevi surrounded clinically by a hypopigmented zone. They usually occur in childhood or adolescence. The prevalence is about 1% of the population; its incidence in men and women is equal and the most frequent site is the trunk. In about half of the cases, multiple lesions can be observed. Vitiligo and halo nevi are strongly associated. It has been estimated to occur in up to 26% of patients which have vitiligo. The epidermis is often acanthotic and frequently hyperkeratotic, the nevus is usually compound and infiltrated by lymphocytes and histiocytes with occasional mast and plasma cells. The inflammatory infiltrate exhibits a band like extension throughout all the nevus, virtually obscuring the dermal component. The melanocytic junctional cells are organized in nests and clusters with rare or without pagetoid intraepithelial spread. The melanocytes have relatively large nuclei with small nucleoli and abundant eosinophilic cytoplasm, with focal signs of cellular atypia. The dermal melanocytic cells obscured by the inflammatory infiltrate may be highlighted using S-100 protein and thyrosinase. About 80% of the lymphoid cells are T-lymphocytes with a relatively high percentage of suppressor/cytotoxic T-cells. Epithelioid granulomata can occasionally be found within the inflammatory cell infiltrate. Frequently, pigment containing macrophages are found in the inflammatory cell infiltrate. There is no fibrosis, in contrast to melanoma. The halo nevus must be distinguished from regressing melanoma. An important feature to differentiate is the diffuse distribution of the inflammatory infiltrate throughout all the nevus while in melanoma usually the

**Fig. 14.** Halo nevus: a band-like lymphoid infiltrate and pigmented melanocytes type A in junctional nests and isolated not to be confused with an atypical junctional proliferation.



infiltrate is partial, multifocal and irregularly distributed. Mitotic activity and nuclear and cytoplasmic pleomorphism of the dermal component are not features coherent with halo nevus while are present in melanoma.

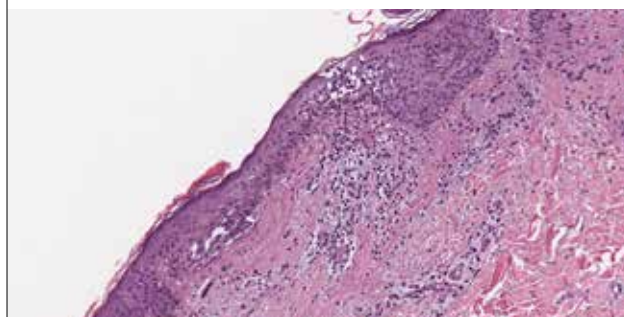
**Halo nevus: key histopathological diagnostic features**

- Presence of numerous lymphocytes in dermal and junctional component of the nevus
- Band like extension of the inflammatory infiltrate throughout all the nevus
- Junctional nevus cell with eosinophilic cytoplasm and focal atypia

**02D MEYERSON'S (INFLAMED) NEVUS**

The Meyerson's (inflamed) nevus is an eczematous process associated to a nevus. The eczematous lesion consists of psoriasiform and spongiotic epidermal changes with superficial perivascular dermal infiltrate. The nevus retains its characteristic features despite the inflammatory reaction. The Meyerson's nevus must be differentiated from the **halo nevus** that represents an active lymphocyte-nevus cell response and that usually it is not associated with an eczematous process.

**Fig. 15.** Meyerson's (inflamed) nevus with associated spongiotic epidermal and dermal inflammatory infiltrate.

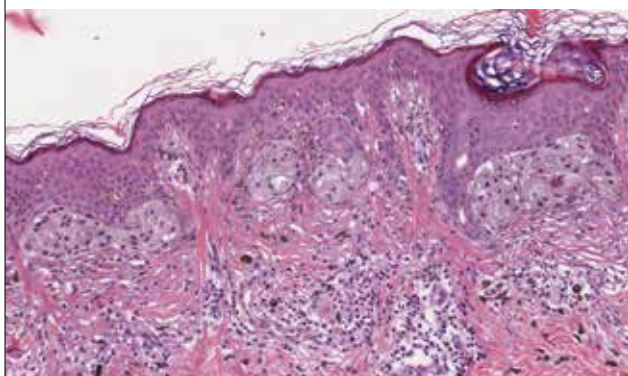
**Meyerson's (inflamed) nevus: key histopathological diagnostic features**

- Psoriasiform and spongiotic epidermal picture
- Superficial perivascular dermal infiltrate
- Occasional dermal eosinophils
- The eczematous process is intra-epidermal and spares the nevus
- Frequently a congenital nevus

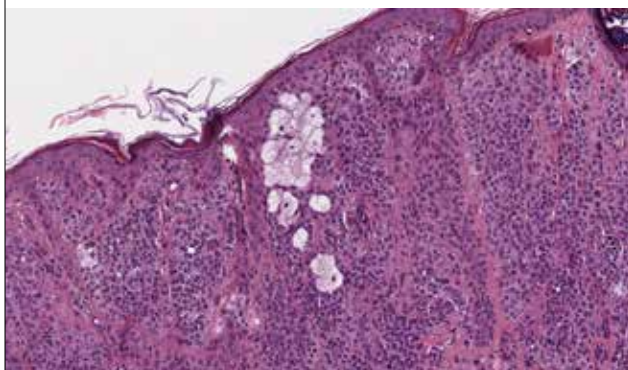
**02E BALLOON CELL NEVUS**

Balloon cell nevus is a benign melanocytic lesion most often diagnosed in the first three decades of life and with predilection for the head, neck and trunk. It can be found also in other sites including iris, conjunctiva, caruncle, soft palate, pharynx. Clinically it presents as a red or brown papule or nodule, with no special features. Balloon cell nevus is composed of round to oval sized melanocytic cells with abundant foamy pale-staining or clear cytoplasm; it can be compound or entirely intradermal. The cell nucleus is hyperchromatic or vesicular, the nucleolus is conspicuous. Mitoses are rare or absent.

**Fig. 16a.** Balloon cells junctional nevus; junctional nests of clear cells with variably sized vacuoles.



**Fig. 16b.** Focus of balloon cells in dermal nevus.



Foci of balloon cells can be found in 2% of different nevi and in melanoma. To identify this lesion as balloon nevus this cytoplasmic change must be present in over 50% of the cells. Balloon cells are positive for melanocytic markers but interestingly, a misleading CD68 positive balloon cell nevus on the penis in a child has been described. The most important **differential diagnosis** is with **balloon cell melanoma**. Important features to consider include age of the patient, cytological features like striking pleomorphism and large nuclei typical of malignancy, presence of mitoses and of an inflammatory infiltrate between the melanocytic cells. Other lesions may be similar to balloon cell nevus, including **clear cell dermatofibroma, granular cell tumor, xantoma, sebaceous tumors, clear cell sarcoma, clear cell renal carcinoma metastatic to the skin**.

**Balloon cell nevus: key histopathological diagnostic features**

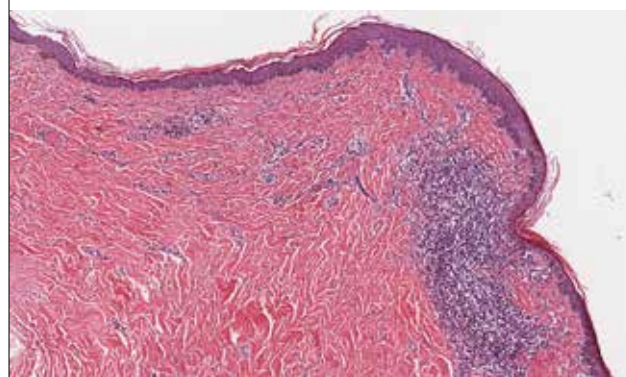
- Presence of large cells with abundant vacuolated cytoplasm in number greater than 50%
- No mitoses
- Nuclear cytoplasmic ratio quite small

**02F RECURRENT (PERSISTENT) NEVUS**

Recurrent (persistent) nevus is the development of a melanocytic lesion at the site of removal of a previous benign nevus. Its recognition is very important because it can resemble a regressing melanoma. There have a female predominance; mostly found on the back and

abdomen. The interval of time between the excision of the primary lesion and the recurrence is mostly about 3-6 months. The majority of cases occur in the first four decades of life. Clinically, recurrent nevi are usually flat and variously pigmented; most often stippled, but some are uniformly black, or irregularly pigmented. They may have different patterns including hypopigmentation, linear, halo, diffuse. They are usually less than 1.5 cm in diameter, with a variable degree of scarring, sometimes hypertrophic. They most frequently follow after shave biopsies, traumas, laser treatment, local application of topical agents. Recurrent nevi histologically show sharp circumscription, atypical melanocytes frequently confined to the epidermis, increased number of melanocytes, isolated or in nests within and above the basal cell layer. A great variation in the size and shape of melanocytic nests frequently confluent. Few atypical melanocytes with large hyperchromatic and pleomorphic nuclei and cytoplasmic coarse pigmented granules are present. The papillary dermis shows fibrosis and a perivascular sparse lympho-histiocytic infiltrate. Epidermal hyperplasia in a retiform pattern confined to the area of the scar can be seen. Some pagetoid spread sometimes is observed above the dermal scar and usually rete ridges is effaced above the fibrosis. Dermal melanophages are frequently conspicuous. Mitotic figures are rare or absent and apoptosis is not an evident feature. The main differential diagnosis is with superficial spreading melanoma and the clinical informations are mandatory. Histological points of distinction include: the restriction of the junctional component to the area overlying the fibrosis, sharp circumscription of the intraepidermal melanocytic component, atypical melanocytes confined to the epidermis, few, if any, mitosis, fibrosis in the papillary dermis.

**Fig. 17a.** Recurrent nevus: junctional proliferation of pigmented melanocytes over a scar and inflammatory dermal infiltrate.

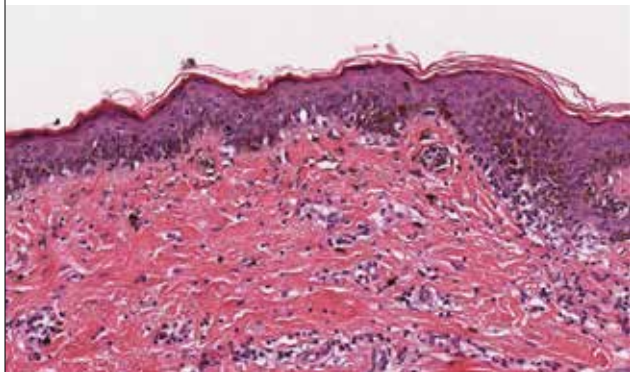


**Recurrent nevus: key histopathological diagnostic features**

- Intraepidermal and junctional proliferation limited above the dermal scar
- Pagetoid and lentiginous hyperplasia in the center of the scar
- Marked pigmentation
- Mild inflammation
- Focally moderate atypia
- Residual nevus in deep dermis



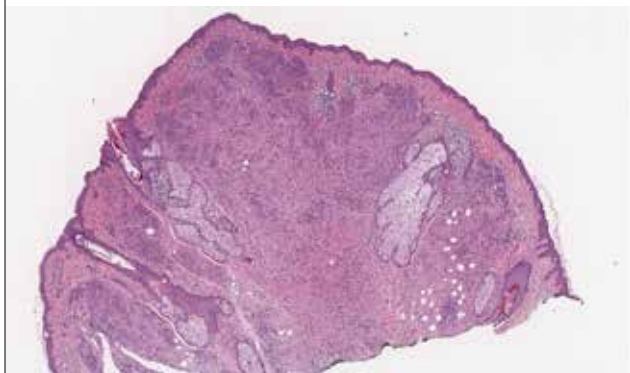
**Fig. 17b.** Recurrent nevus: basal irregular proliferation of melanocytes with mild atypia overlying the sclerotic dermis.



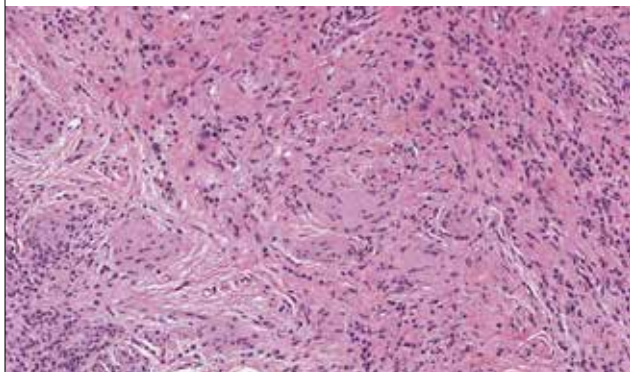
**02G NEVUS WITH NEUROTIZATION**

Melanocytes can mature into cells similar to Schwann cells characterized by spindled or S shape and surrounded by mature collagen fibers. The cells of the neurotized nevus can be organized in tactoid bodies or corpuscles similar to Meissner bodies or in a palisaded pattern. To differentiate neurotized nevi 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 while neuro nevi respect the adventitial dermis. Melan

**Fig. 18a.** Nevus with neurotization; dermal proliferation of melanocytes superficially type A and B and in the middle and deep component melanocytes with prevalent eosinophilic cytoplasm.



**Fig. 18b.** Focal dermal area with neurotization; spindle and epithelioid melanocytes with fibrillar eosinophilic cytoplasm reminiscent of cell of neurofibroma or schwannoma.



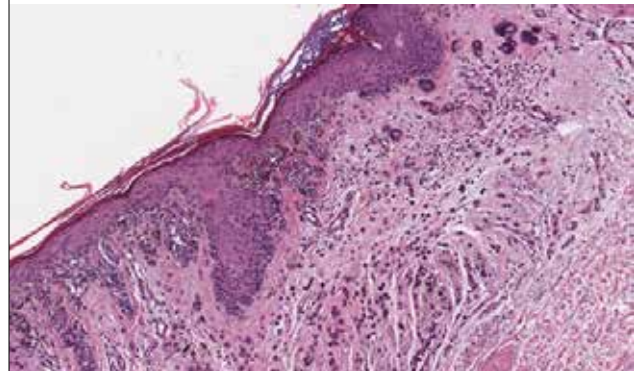
A immunohistochemical staining is also helpful to differentiate neurotized melanocytic nevi (positive) from neurofibroma (negative).

- Neuro nevus: key histopathological diagnostic features**
- Spindle cells similar to Schwann cells
  - Mature collagen fibers
  - Frequent presence of residual foci of common nevus
  - No infiltration of adventitial dermis

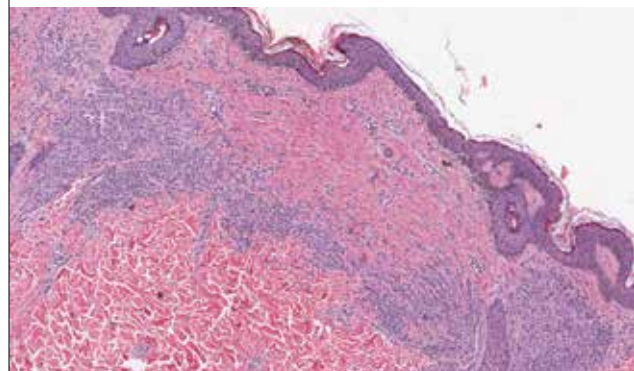
**02H AGING (ANCIENT) NEVUS**

Aging of dermal nevi has been associated with senescent changes as balloon cell changes, sclerosis, giant cells, mucinous degeneration, neurotization, and infiltration by fat cells. Ancient nevus, described by Kerl (1998), is a nevus generally localized on the face that presents a mixture of pleomorphic epithelioid melanocytes and small, uniform nevus cells, fibrosis, mucinosis, hemorrhage and vascular thrombosis.

**Fig. 19a.** Ancient nevus: dermal fibrosis and degenerative nuclear changes of melanocytes; presence of multinucleated cell and diffuse reactive inflammatory infiltrate.



**Fig. 19b.** Involutive sclerosis in compound ancient nevus.

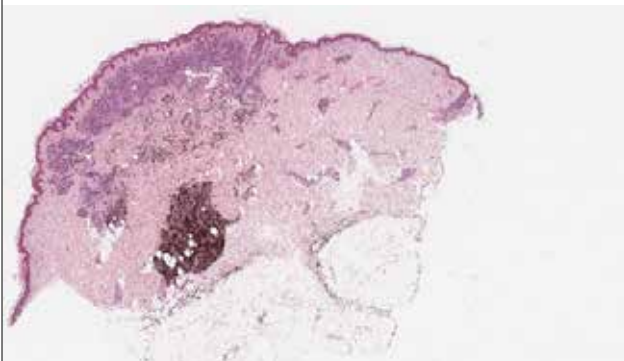


- Ancient nevus: key histopathological diagnostic features**
- Balloon cell changes, sclerosis, giant cells, mucinous degeneration, neurotization, and infiltration by fat cells
  - A mixture of pleomorphic epithelioid melanocytes and small, uniform nevus cells, fibrosis, mucinosis, hemorrhage and vascular thrombosis

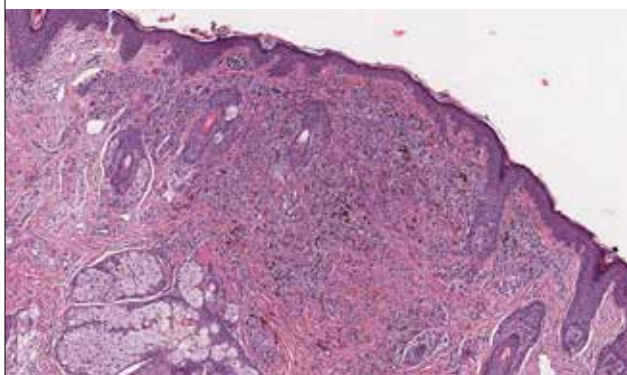
## 02I COMBINED NEVUS

A combined nevus is the presence of two or more types of different nevi in the same lesion. The main component is usually an intradermal or compound nevus. The most frequent combinations are a common nevus with a blue nevus and a Spitz nevus, deep penetrating nevus combined with a blue nevus. The presence of foci of A/B melanocytic cells in deep dermis may simulate absence of maturation.

**Fig. 20a.** Combined nevus: compound and deep penetrating nevus.



**Fig. 20b.** Combined nevus: dermal and blue epithelioid nevus.



### Combined nevus: key histopathological diagnostic features

- Well identified different common nevi
- No cytological atypia, mitoses and aggressive infiltrative growth
- Simulation of deep maturation

## 02K OTHER RARE VARIANTS OF NEVI

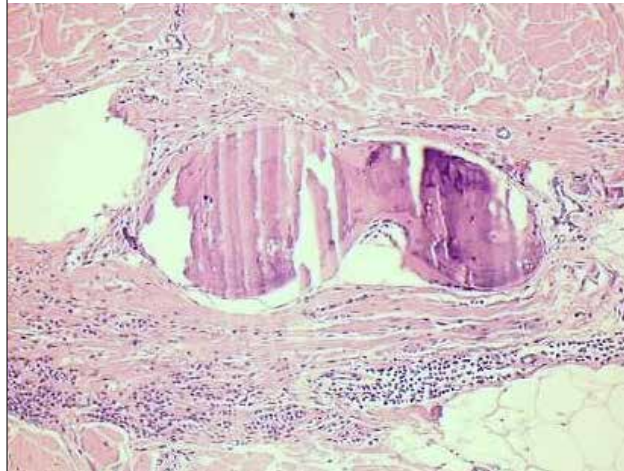
### *Nevus of Nanta (dermal nevus with ossification)*

Foci of ossification are present in the dermal component of a nevus, usually on the face of a woman, as the result of a folliculitis (Colin 2002) or result of a metaplastic process. Around the foci of ossification a rim of osteoblasts is usually present. Ossification may be observed also in Spitz nevus and in melanoma.

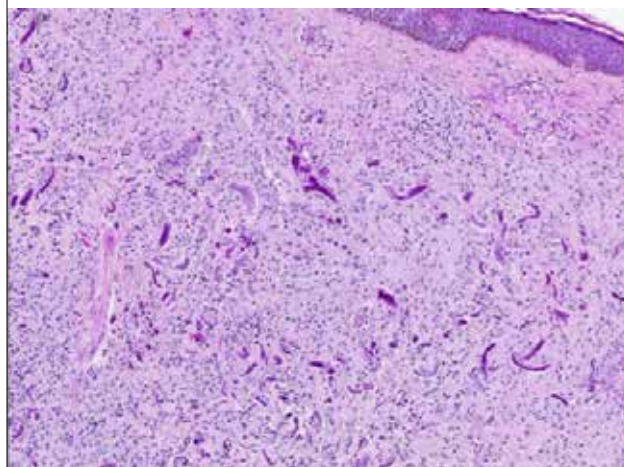
### *Elastic fibers in nevi*

Frequently some increase of dermal elastin is present in intradermal, compound and blue nevi, especially at the periphery. In 0.5% of nevi there is an evident increase

**Fig. 21.** Focus of metaplastic ossification in dermal nevus.



**Fig. 22.** Dermal elastin fibers, coarse and irregularly distributed between the dermal melanocytes.

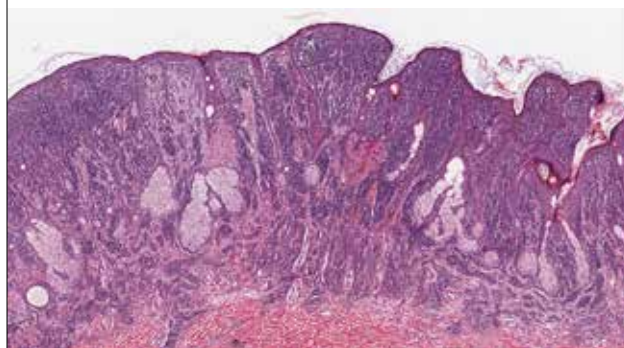


of coarse elastin fibers. This increase is most prominent in congenital nevi. These fibers are notably absent in melanoma and its presence may be useful to support the benign nature of a lesion.

### *Nevus with trichostasis spinulosa*

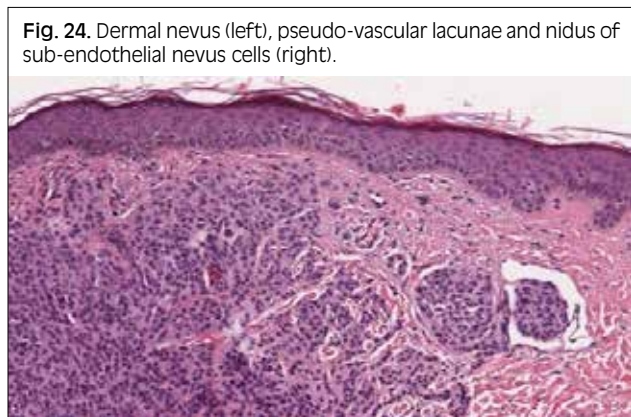
This is a nevus, usually on the face, with associated dilated large hair follicles like comedones and numerous vellus hairs.

**Fig. 23.** Dermal nevus associated to numerous vellus hairs.



***Nevus with pseudo-vascular lacunae***

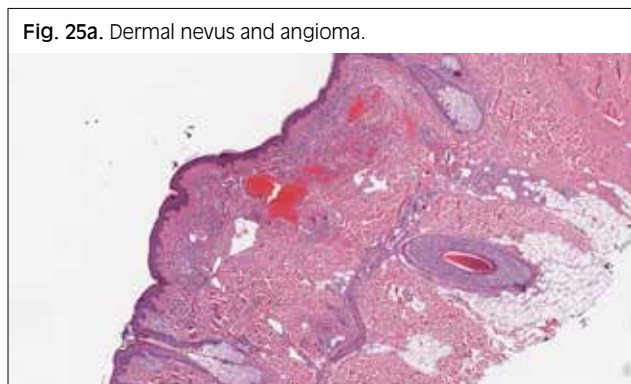
Occasionally a compound or intradermal nevi contain irregular interconnected spaces empty or containing mucina, slit-like clefts with pseudo-vascular sinusoidal appearance. Pseudo-vascular spaces within the nevus cells give an angiomatous-like appearance and protrusion of sub-endothelial nevus cells in vascular lumen may simulate vascular invasion. Staining with S100 protein, p16 and CD31 is useful to identify the nevus cells under the endothelial layer.



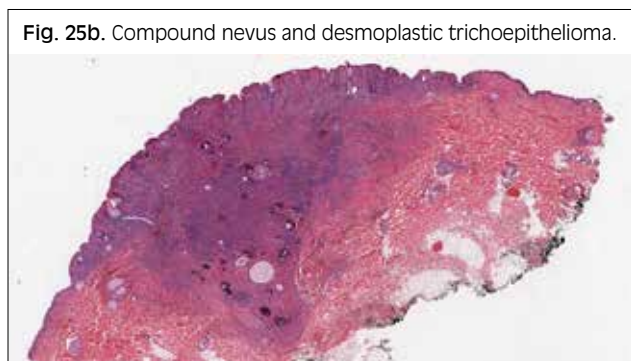
**Fig. 24.** Dermal nevus (left), pseudo-vascular lacunae and nidus of sub-endothelial nevus cells (right).

***Nevus in combination with other not melanocytic neoplasms***

Desmoplastic trichoepithelioma, basal and squamous cell carcinoma, syringoma, dermatofibroma, atypical fibroxantoma, angioma, inclusion cysts may be associated with nevi. This combination is the result of coincidence not etiologically related.



**Fig. 25a.** Dermal nevus and angioma.



**Fig. 25b.** Compound nevus and desmoplastic trichoepithelioma.

***Traumatized nevus***

Nevi can be ulcerated, abraded and present irregular scar. Traumatized nevi have special features like parakeratosis, dermal telangiectasias, inflammation and fibrosis. These patterns may simulate a regressing melanoma.



**Fig. 26.** Traumatized nevus; skin ulcer and cap of fibrinoid inflammatory exudate.

***Nevus with myxoid change***

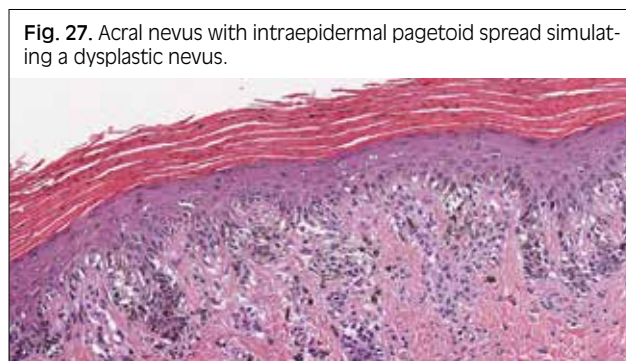
Mucin is occasionally present in nevi, preferably in the superficial portion of the dermal component. The mucin is often visible with hematoxylin and eosin stain or enhanced with alcian blue. Mucin deposits can be also present in Spitz nevus and in cellular blue nevus (myxoid blue nevus).

***Nevus with amyloid***

Amyloid deposits were identified within the tumour mass of three melanocytic naevi. Amyloid in this situation is likely to be derived from degenerating naevus cells.

***Nevus with pagetoid cells***

The presence of solitary and small groups of pagetoid melanocytes in the superficial layers of the epidermis it is generally considered to be a diagnostic hallmark of melanoma but it may also be seen in certain melanocytic naevi (nevi in special site, acral nevus, nevi of the scalp, Spitz nevi, nevi in childhood, Reed nevus, congenital nevi, nails nevi, genitalia nevi, flexures nevi, milk line nevi). In naevi, pagetoid intraepidermal spread tends to be limited laterally not beyond the underlying junctional component and there is no marked cytological atypia.



**Fig. 27.** Acral nevus with intraepidermal pagetoid spread simulating a dysplastic nevus.

### ***Lobulated intradermal nevus***

Lobulated intradermal nevus is described as an unusual sign of aging or regressing melanocytic nevus. The nevus clinically shows lobulation and histologically exhibits fat cell within nests of nevus cells, fibrosis and neurotization. In nevi, pagetoid spread tends to be limited and there is no marked cytological atypia and laterally beyond the underlying junctional component.

### ***Inverted type A nevus***

Nevus with multiple small nests of large pigmented A cell in the dermal component associated to a prevalent proliferation of lymphocyte like B cells and shwannian like C melanocytes. Some authors consider this variant a combined nevus (common nevus associated with deep penetrating nevus or epithelioid blue nevi).

Fig. 28a. Inverted type A nevus.

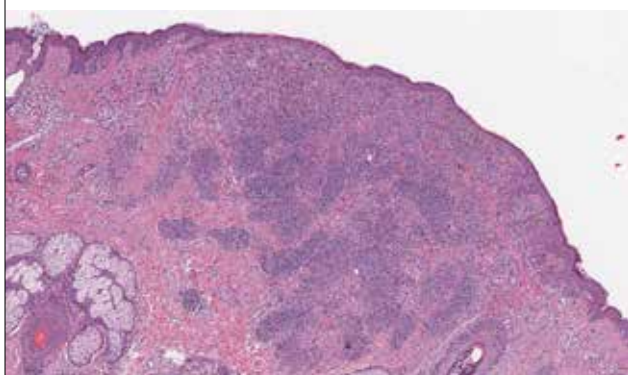
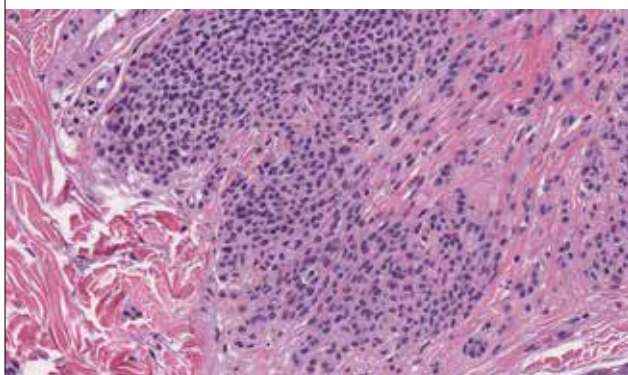


Fig. 28b. in deep component lack of mitoses and necrosis/apoptosis.



### ***Incidental nevus***

Small nevi or aggregates of nevus cells are present in the dermis of skin excised for unrelated reasons. Frequently, in the face, these nevi have a peri-appendageal localization.

### ***Fat cells in intradermal nevus***

Aggregates of adipocytes within a dermal nevus mixed to type C spindle cell nevus cells. This is a pathway of regression and disappearance of the nevus; the other manners in which nevus cells disappear spontaneously are: halo reaction, neurotization and fibrosis.

Fig. 29a. Fat cells in intradermal nevus.

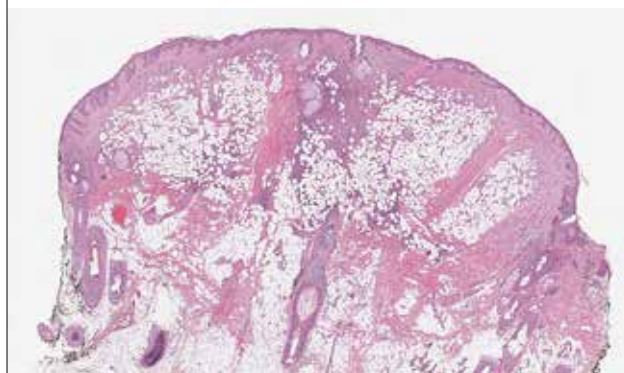
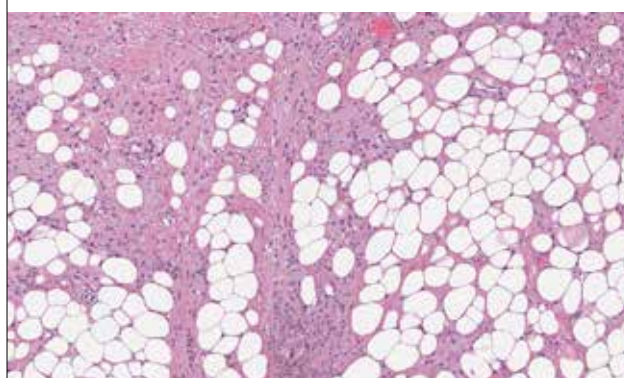


Fig. 29b. Fat cells scattered between the melanocytes of an intradermal nevus.



### ***Nevi in pregnancy or hormonal therapy***

Uniform darkening and enlargement of nevi is common in pregnancy. Possible changes are mild degree of cytological atypia, active junctional proliferation and rare mitoses.

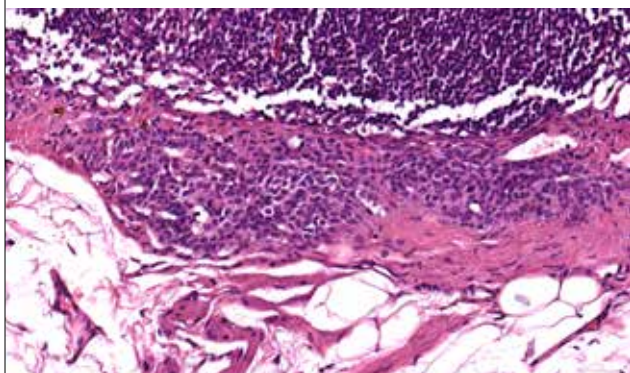
### ***Nevus in childhood***

Nevi in childhood are more proliferating and cellular compared with the nevi of adults. The nevus cells are larger in children than in adults and the deep maturation less evident. Mitoses may be seen, but atypical mitoses are absent. The trans-epidermal elimination of single or nests of melanocytes are not infrequent observation simulating an intraepidermal pagetoid spread.

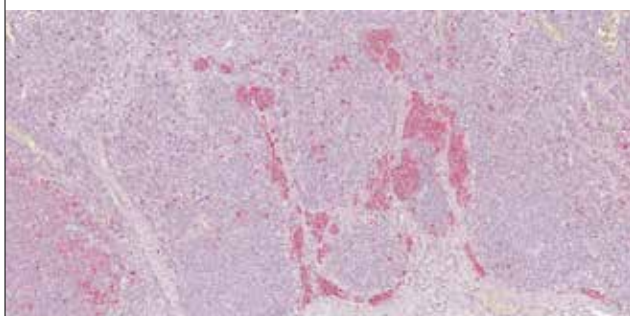
### ***Nevus cells in lymph nodes (nodal nevus)***

Aggregates of nevus cells are occasionally observed within lymph nodes, usually small foci or isolated cells but rarely they may occupy most of the lymph node. The prevalence of nevus cells in the lymph nodes varies from 1% in patients undergoing surgery for breast cancer to 3.9% in patients with melanoma submitted to sentinel lymph node biopsy. Nodal nevus cells are often located in the fibrous capsule and trabeculae of the lymph node arranged in nests and strands. The nevus cells are small, cytologically benign with round or oval nuclei with delicate chromatin. Nodal nevus cells are negative with HMB-45 and positive with p16, S-100 and tyrosinase. Presence of capsular nevus cells are significantly associated with an increasing nevi count on the skin of the patients.

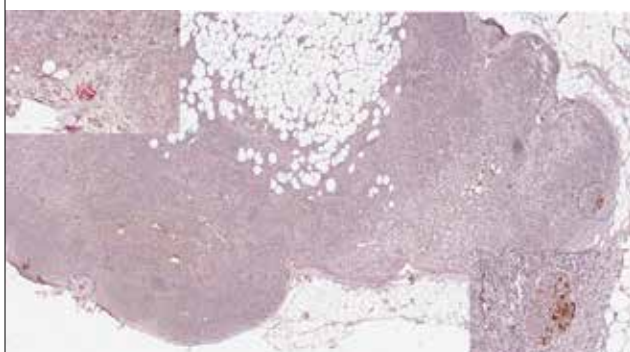
**Fig. 30a.** Nests of nevus cells into the nodal fibrous capsule.



**Fig. 30b.** S 100 immunohistochemical stain highlights the nevus cells into the nodal fibrous septa and the dendritic cells into nodal parenchyma.



**Fig. 30c.** p16 immunohistochemical stain shows positivity of a small nest of nevus cells (left) and negativity of a pigmented micrometastatic focus of melanoma (right) in the same lymph node.



### 03 Nevi of special sites

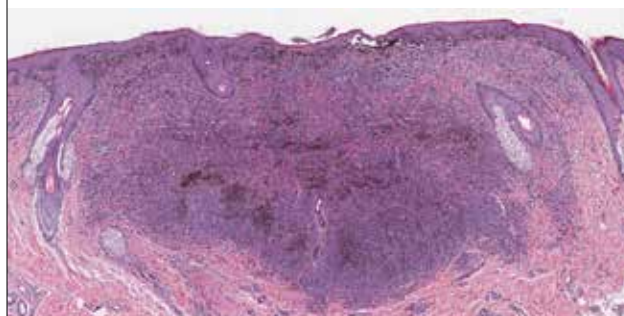
Genitalia, acral skin, milk line, umbilicus, ear, scalp and body folds are considered special sites. The majority of nevi in special site are compound nevi and are characterized by large and confluent junctional nests sometimes with bizarre shape and variable cytologic atypia. The melanocytic lesions in flexural sites may have identical worrisome histological features.

#### 03A GENITAL NEVI

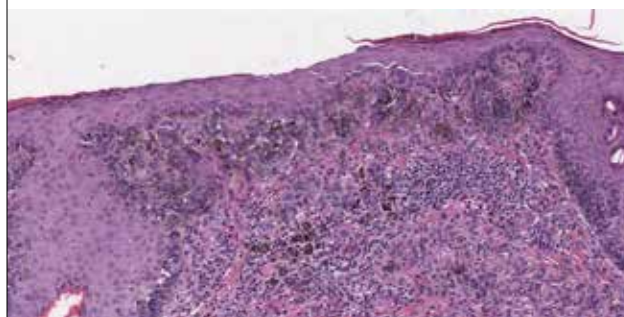
Melanocytic lesions of the genital area are rare. Anatomic sites include the labium major, mons pubis, labium minus, clitoris and perineum. The genital nevi can

be junctional, compound or dermal. The main feature is characterized by a florid junctional melanocytic proliferation of large and variable sized nests often with retraction artifacts and/or cellular discohesion. Cytologic atypia, frequently present, vary from mild, to moderate and severe. The atypical melanocytes are frequently epithelioid, type A, with abundant eosinophilic cytoplasm and variably prominent nucleoli or polygonal with angulated cells with hyperchromatic nuclei and scant cytoplasm. Rare dermal mitoses and focal pagetoid intraepidermal spread, centrally located and usually confined to the stratum sub-corneum, can be seen. A subset of genital nevi show distinct features which may have some similarities with melanoma. This variant is defined **atypical genital nevus** that are found generally in young/adult female patients, with a mean size of 0.6 cm in diameter. Some “dysplastic features” can be seen in atypical genital nevi: focal bridging of rete ridges, a lentiginous single cell proliferation, dusty cytoplasmic melanin, mild superficial chronic inflammatory infiltrate and dermal fibrosis.

**Fig. 31a.** Atypical genital compound nevus.



**Fig. 31b.** Atypical genital nevus; irregular junctional proliferation of focally atypical pigmented melanocytes.



Despite occasionally striking cytologic and architectural atypia the atypical genital nevi have a benign clinical course. The recognition of these melanocytic lesions is important to avoid over diagnosis of melanoma. The main differential diagnoses are with dysplastic nevus in which the lentiginous proliferation is disorganized, rete ridges are elongated and cytological atypia is focal and random whereas in genital nevus and in atypical genital nevus it is relatively uniform. Melanoma shows a predominance of single pagetoid melanocytes compared

to nests, greater cytological atypia and dermal mitoses, lack of deep maturation and generally it occurs in post-menopausal women.

**Genital nevi: key histopathological diagnostic features**

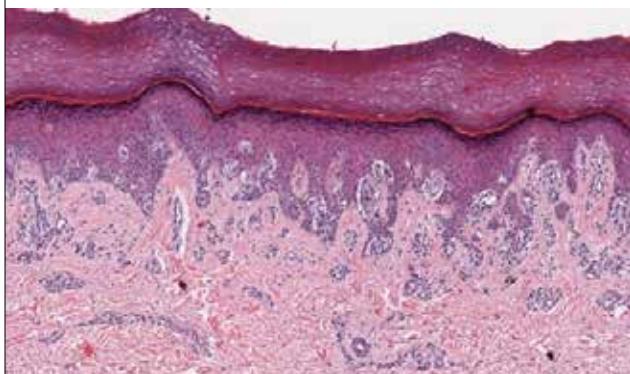
- Single cells and irregular confluent nests at the dermal epidermal junction
- Uniform cytological atypia
- Lentiginous proliferation with fusion of the nests
- Dyscohesive nests with retraction artifact
- Fibrosis in papillary dermis

### 03B ACRAL NEVUS

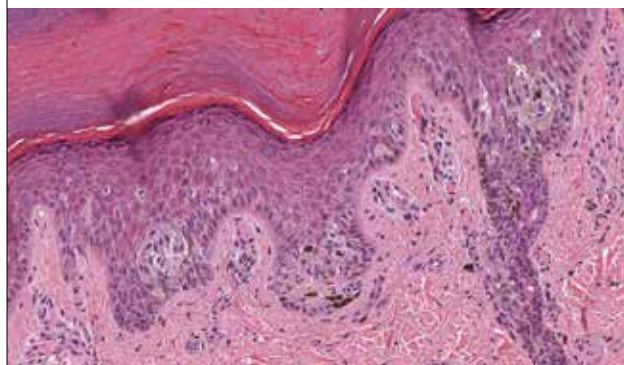
Acral nevus is a benign melanocytic lesion which is found on the palms and soles of hands and feet. They are found in approximately 25% of the entire population, with no difference of prevalence between men/women and whites/negroes. Peak of incidence is between second and third decades, and rarely acral nevi are found in infants. The clinical diameter ranges from 0.5 mm to 12 mm, with a median of 2 mm. They are usually symmetrical and well circumscribed, uniformly pigmented, as dark brown to black macule/papule. The main features of acral nevi are circumscription, symmetry, and some degree of fibroplasia. The melanocytic nests are variable in size, frequently vertically oriented, and they are found along the dermo-epidermal junction as a lentiginous and quite continuous proliferation.

Mild to moderate pagetoid spread is commonly found, and if it is very marked, the name MANIAC (melanocytic acral nevus with ascent of cells) have been used to classify the lesion with this feature. Other typical features of acral nevi are: trans-epidermal elimination of nests, maturation of the dermal component, and no mitotic activity. The main differential diagnosis is with dysplastic nevus, which shows the shoulder phenomenon, dusty pigmentation, and bridging, in addition to lamellar and eosinophilic fibrosis. To differentiate acral nevus from dysplastic nevus and melanoma Clemente et al. described a special variant named acral lentiginous nevus. This variant is characterized by lentiginous melanocytic proliferation

**Fig. 32a.** Acral compound nevus; junctional nests with elongation of rete ridges in lentiginous arrangement. Isolated cells or small aggregates of melanocytes ascending into the epidermis are evident simulating a pagetoid proliferation.



**Fig. 32b.** Acral nevus; to note the sharp demarcation between melanocytes nest and the epidermal keratinocytes without evidence of aggressive infiltration.



with confluent nests at the dermal epidermal junction, dermal fibrosis and cytological atypia. Acral lentiginous melanoma usually shows irregular epidermal acanthosis, severe cytological atypia, mitotic activity, no maturation of the dermal component and often a dermal irregular lymphocytic infiltrate and destructive intra-epidermal growth.

**Acral nevus: key histopathological diagnostic features**

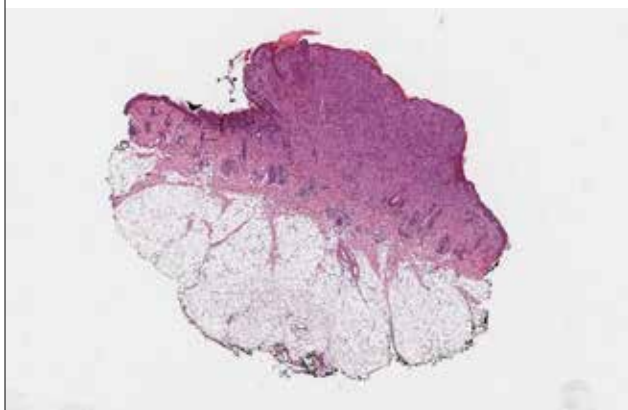
- Nests at the dermal epidermal junction
- Lentiginous proliferation
- Cytological uniform atypia
- Dermal fibrosis
- Trans-epidermal migration of single cells or nests
- Absence of pagetoid intra-epidermal spread at the shoulder of the nevus

### 04 Spindle and epithelioid cell nevi

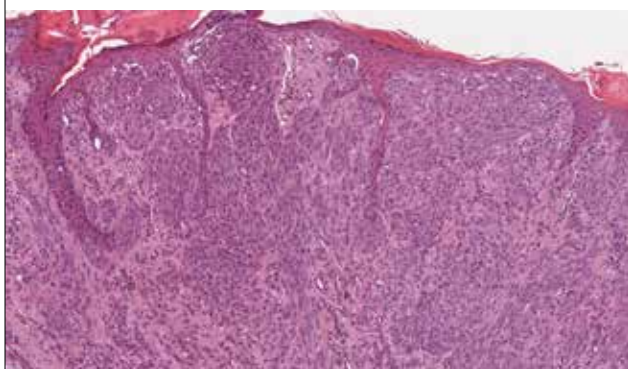
#### 04A SPINDLE AND EPITHELIOD CELL NEVUS (SPITZ NEVUS)

Spitz nevus is a benign, infrequent, melanocytic tumor with a wide range of distribution but it occurs mainly in childhood and in adolescence. The most frequent locations are head and neck, especially the cheek, extremities, in a female, and trunk. Its male to female ratio changes according to the age of presentation: 1/1 between 0-15 years and beyond 45; 3.5/1 and 1.9/1 in patients respectively between 16-30 years and 31-45 years. The mean age of presentation is 21 years old (range: 2 to 69). It is very rare to encounter in black patients and oriental. Clinically it usually appears as asymptomatic, dome-shaped, round to oval, firm papule or nodule. The Spitz nevi are pink, red or tan, sometimes described as nonpigmented or purple, brown/black in **differential diagnosis** with dermatofibroma and hemangioma. Spitz nevi can range in size from 1 mm to 3 cm; most are less than 1 cm in diameter. Ulceration is usually absent or either rarely seen. Spitz nevus may be compound, junctional or entirely intradermal. The classical compound tumor is dome-shaped, with lateral circumscription and symmetry. Spitz nevus has two types of cell components: spindle, epithelioid or mixed.

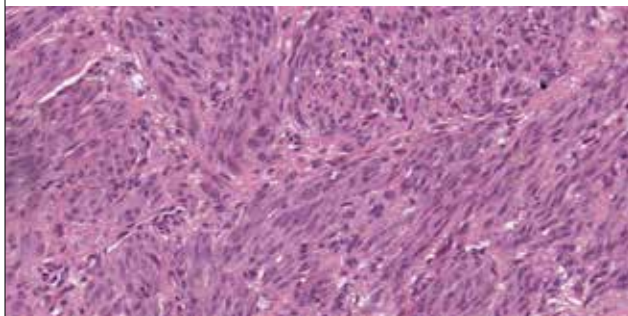
**Fig. 33a.** Spitz nevus; dermal monomorphic proliferation with a similar architecture and cell type from side to side at any given level (junction, upper dermis and lower dermis).



**Fig. 33b.** Spitz nevus; spindle and epithelioid cells in nests and bundles preferentially vertically oriented; epidermal hyperplasia and hyperkeratosis.



**Fig. 33c.** Spitz nevus; spindle and epithelioid cells with dense eosinophilic cytoplasm, elongated, ovoid or round nuclei with a well demarcated nuclear membrane and prominent central nucleolus.



The epidermis frequently shows hyperkeratosis, patchy parakeratosis, acanthosis, sometimes marked pseudo-epitheliomatous hyperplasia. Kamino bodies are found more often in junctional/compound Spitz nevus rather than in intradermal nevi: often in aggregates, they are situated at the dermo-epidermal junction. The classical epithelioid Spitz cells shown a dense eosinophilic cytoplasm, rounded or oval nuclei with well demarcate nuclear membrane and a prominent eosinophilic nucleolus. Maturation is seen towards the dermal component of the lesion and it is characterized by cells with scanty

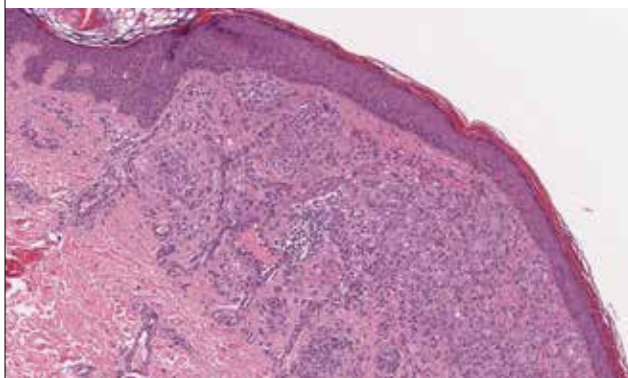
cytoplasm that have a single-cell infiltrating pattern at the base of the tumor. Sometimes, in children, the maturation is limited to small number of cells to demonstrate with immunohistochemical stains. Mitoses can be found in the nests located in the epidermis or superficial dermis and they may even be quite common in lesions in infants or young children. Very rarely or never the mitoses are atypical. A perivascular, diffuse or band-like inflammatory infiltrate can be found in up to 70% of cases, ranging from light, to moderate/severe. Telangiectasias are found in about half of the cases, more commonly in compound and intradermal Spitz nevi in the upper part of the papillary dermis. Melanin is found in about 50% of cases, more often in junctional/compound nevi than in intradermal nevi; it ranges from scarce, to abundant and rarely heavy. Spitz nevus shows strong and diffuse S100 protein expression, both in junctional and in dermal components. HMB45 usually shows an irregular patchy positivity; p16 is often diffusely positive both in

**Tab. I.** Variants of Spitz nevus.

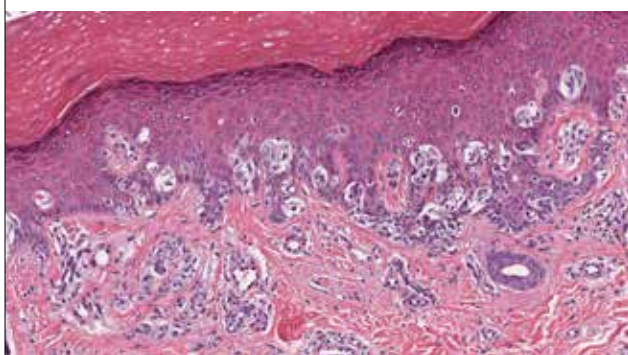
<b>Acral</b> (Jang YH Ann Dermatol 2011; Banba K J Dermatol 2000;27:333-6)
<b>Angiomatoid</b> (Diaz-Cascajo C Am J Dermatopath 2000; Kwon O Ann Dermatol (Seoul) 2008; Rawson R Pathology 2016;48:739-42)
<b>Agminated</b> (Gupta R Indian J Dermatol 2015)
<b>Balloon cells</b> (Borsa S Hautarzt 1991, Valdivielso-Ramos M J Eur Acad Dermatol Venereol. 2016)
<b>Combined</b> (Jin ZH J Dermatol 2000)
<b>Conjunctival</b> (Vervaeet N Bull Soc Belge Ophtalmol 2007;303:63-7; Kantelip B Ann Ophthalmol 1989;21:176-9)
<b>Desmoplastic</b> (Barr R Cancer 1980; Dhoubil RS 2008; Nojavan 2009)
<b>Epithelioid cell of eyelid</b> (Hiscott P Am J Ophthalmol 1998;126:735-7)
<b>Halo</b> (Fernandez-Flores A Am J Dermatopathol 2017;39:130-3)
<b>Homer-Wright rosette-like structures</b> (Miller K Am J Dermatopathol 2012;34:457-9; Kantrow S J Cutan Pathol 2008;35:510-2)
<b>Hyalinizing</b> (Suster S Am J Dermatopath 1994; Liu J South Med J 2004; Cho SB Int J Dermatol 2009; Lee MW J Dermatol 2000;27:273-5)
<b>Intradermal</b> (Plaza J Am J Dermatopathol 2014;36:283-94)
<b>Intraoral</b> (Li CC Oral Surg Oral Med Oral Pathol Oral radiol 2014;117:e320-4)
<b>Junctional/superficial</b> (Magro CM J Am Acad Dermatol, 2009; Piperi EP Head Neck Pathol 2014;8:354-8)
<b>Lichenoid</b> (Harvell JD J Cutan Pathol, 1997)
<b>Lipoblastoid/signet-ring cell-rich</b> (Salviato T J Cutan Pathol 2014;41:762-4)
<b>Myxoid</b> (Hoang MP J Cutan Pathol 2003)
<b>Multiple</b> (Zayour M J Am Acad Dermatol 2012;67:451-8)
<b>Oral cavity</b> (Pediatr Dermatol 2016; 33:e154-5)
<b>Pagetoid</b> (Busam KJ Am J Surg Pathol 1995; Fernandez AP J Cutan Pathol 2016;43:932-9; Han MH Int J Dermatol 2000;39:555-7; Harris K Arch Dermatol 2012;148:370-4)
<b>Persistent (recurrent)</b> (Omura EF, Am J Dermatopathol 1984; Harvell JD Am J Surg Pathol 2002)
<b>Pigmented epithelioid cell nevus</b> (Choi JH J Am Acad Dermatol 1993;28:497-8)
<b>Plexiform</b> (Spatz A Am J Dermatopath 1999; Clarke B Int J Surg Pathol 2002; Barnhill RL Histopathology 1991)
<b>Polypoid</b> (Fabrizi G Br J Dermatol 2000;142:128-32)
<b>Pseudogranulomatous Spitz nevus</b> (Marco VS J Cutaneous Pathology 2012)
<b>Rich in melanophages</b> (Celleno L Acta Derm Venereol 2002)
<b>Tubular</b> (Burg GJ J Cutan Pathol 1998; Zimmer MJ 2000; Soyer HP J Cut Pathol 1999)
<b>Verrucous</b> (Moscarella E Br J Dermatol 2015;172:1045-51; Honda R Case Rep Dermatol 2013;5:304-8)

superficial and deep component of the nevus. The different variants of Spitz nevus are reported in Table I.

**Fig. 34.** Angiomatoid Spitz nevus.



**Fig. 35.** Acral Spitz nevus.



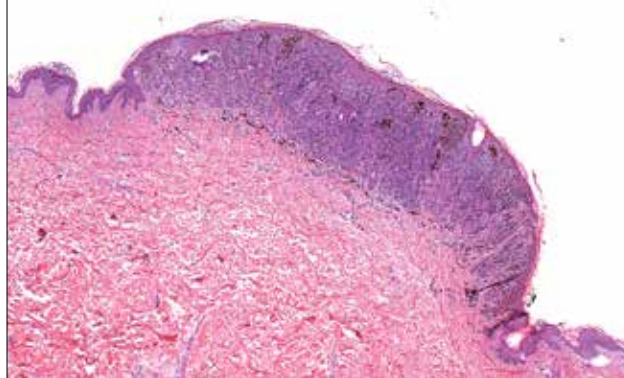
**Spitz nevus: key histopathological diagnostic features**

- Symmetric papule or nodule that involve papillary and reticular dermis
- Hyperkeratosis and epidermal hyperplasia
- Uniform cytology from side to side
- Maturation in deep component of the lesion
- Sharp demarcation of the lateral borders

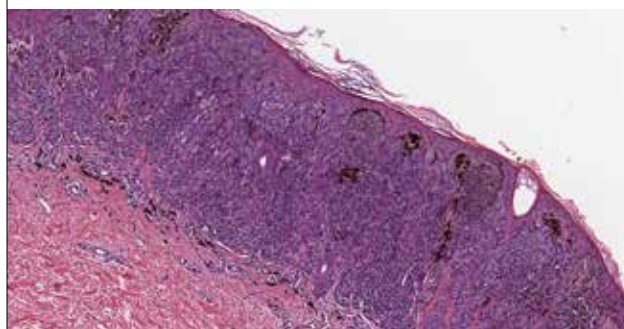
**04B PIGMENTED SPINDLE CELL NEVUS (REED NEVUS)**

Reed nevus is benign melanocytic lesion which it can sometimes be misdiagnosed, clinically and histologically, as melanoma. Clinically it presents as a usually recent and rapid onset heavily pigmented papule. Usually it is less than 10 mm in diameter, with a mean size of a 4.5 mm. It occurs frequently on the lower limbs or trunk of a female patient in the second/third decade of life (median age 25). Histologically Reed nevus has a fairly well marked lateral symmetry, sharp demarcation, usually with defined theques of junctional spindle cells. The overlying epidermis often shows some degree of hyperplasia, and in a minority of cases single melanocytes at the lateral epidermo-dermal junction. The tumor is composed by large and orderly arranged fascicles of spindle cells confined to the epidermis and papillary dermis differently oriented, parallel or perpendicular to the epidermis surface.

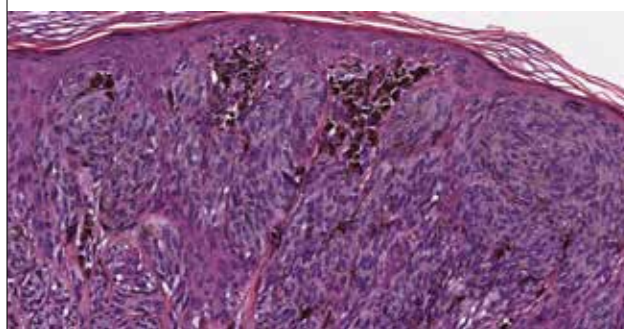
**Fig. 36a.** Reed nevus; superficial, densely cellular and symmetrical proliferation of spindle melanocytes in nests with different orientation perpendicular or parallel to epidermis; sharp delimitation of the lateral shoulders.



**Fig. 36b.** Reed nevus; compact junctional proliferation of pigmented spindle melanocytes.



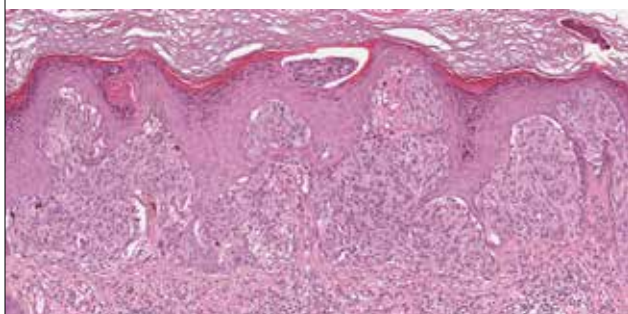
**Fig. 36c.** Reed nevus; spindle shaped pigmented melanocytes with large nuclei and plump nucleoli. Pigment is coarsely granular rather than dustlike.



Epithelioid and multinucleated cells are sometimes found. The spindle cells have slightly eosinophilic or amphophilic cytoplasm with abundant melanin pigment. At the dermal-epidermal junction the proliferation of the tumor cells is discontinuous. The dermal component is usually inconspicuous and consist of small fascicles of spindle cells and single cells, exhibiting maturation with smaller nuclei and cell masses. The cytoplasmic melanin is present to a varying degree, from moderate to heavy in the majority of cases and nucleoli are prominent. Mitoses may be present, usually rare. The trans-epidermal migration of single cells or nest is frequent and it should not be misinterpreted as aggressive pagetoid invasion of the epidermis.



**Fig. 37.** Reed nevus; trans epidermal migration of single cells and nests.



Eosinophilic globules (Kamino's bodies) are present in up to 80% of cases. A frequently perivascular host inflammatory cell response, made by lymphocytes and melanophages, are seen at the deep lower margin of the lesion. Rare variants of Reed nevus are **hypopigmented Reed nevus** which shows all the typical features of conventional pigmented spindle cell nevus, but it does not contain abundant melanin and the mainly **epithelioid Reed nevus**. HMB45 immunohistochemical stain is positive in the intraepidermal and junctional component of Reed nevus and spindle cell melanoma, whereas dermal component is negative in pigmented spindle cell nevus while it is irregularly positive in spindle cell melanoma. The main **differential diagnosis** is with melanoma.

**Reed nevus: key histopathological diagnostic features**

- Circumscribed and symmetrical
- Junctional or compound
- Oval expansile junctional nests parallel or perpendicular to skin surface oriented
- Spindle uniform nevus cell with small nucleoli
- Junctional mitoses not uncommon
- Heavy pigmentation common
- Single cells or small intraepidermal nests (trans-epidermal migration)
- No pagetoid spread at the shoulders

## 05 Dermal melanocytosis

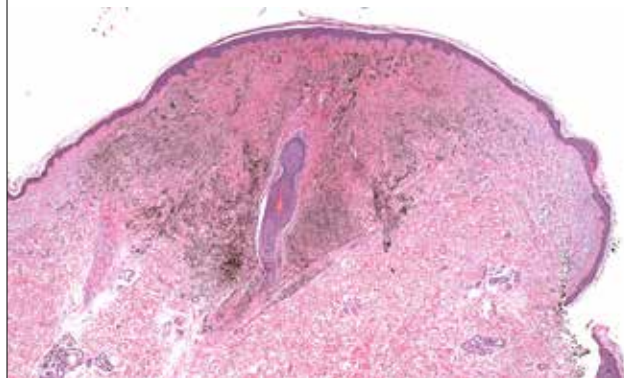
Dermal melanocytosis is a group of melanocytic lesions with dendritic fine pigmented melanocytes, oval or round nuclei and tiny nucleoli. A common immune-histochemical feature is the diffuse and intense immunohistochemical HMB-45 positivity. The group of dermal melanocytosis includes: blue nevus, cellular blue nevus, desmoplastic nevus, deep penetrating nevus, Mongolian spot, nevus of Ota and Ito and neurocristic hamartoma.

### 05A BLUE NEVUS

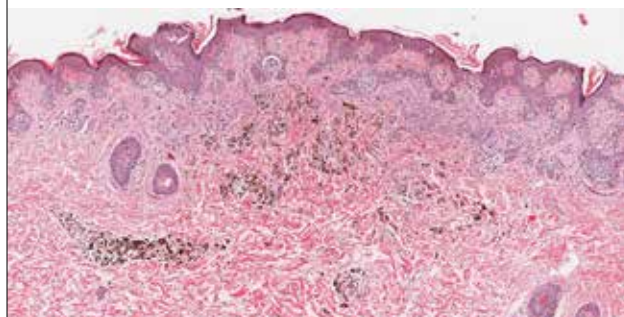
Blue nevus is a common heavily pigmented lesion of bipolar and dendritic dermal melanocytes. The female to male ratio is 2.5 to 1; range of presentation is 1 to 79 years, with an average of 38.6 years, and a peak of incidence between 30 and 39 years. It can be found both in Caucasian and in Negroes. The topographic distribu-

tion in a decreasing order of frequency is: scalp and face, hand, arm and forearm, foot, buttock and sacro-coccygeal area, chest and breast. Blue nevus usually occurs in skin, but it has been reported in oral mucosa, sclera, uterine cervix, vagina, prostate, spermatic cord, pulmonary hilus, orbit, conjunctiva, maxillary sinus, lymph nodes. Clinically, blue nevus presents as a flat or discretely raised, dome-shaped, lesion. Its largest diameter is between 0.3 to 0.9 cm and the color varies from blue, to blue-black and dark brown. Blue nevus is predominantly situated into the dermis and sometimes can extend to the subcutaneous fat. Usually junctional activity is not seen, unless there is a not infrequent combined blue nevus. It presents two components: melanocytes and melanophages with stromal reaction. Melanocytes are spindle-shaped, bipolar, with dendritic processes and cytoplasm stippled with fine melanin granules, frequently grouped in multiple irregular bundles in the dermis usually parallel to the epidermis.

**Fig. 38a.** Blue nevus; an ill defined dermal proliferation of spindle elongated pigmented melanocytes around an hair follicle.



**Fig. 38b.** Multifocal blue nevus and compound nevus.



The dermal component can show a marked desmoplastic reaction and numerous melanophages. Blue nevus usually follows skin appendages, blood vessels and nerves. Mitotic figures are rarely found. Some cases with satellitosis mimicking melanoma have been reported. Variants of classical blue nevus have been described: the most frequently encountered are **epithelioid**, **desmoplastic**, **plaque** types and **blue nevus with ipercellularity**. An intermediate entity is the **blue nevus with ipercellularity** in which the cellular proliferation is marked but it

Fig. 39. Desmoplastic blue nevus.

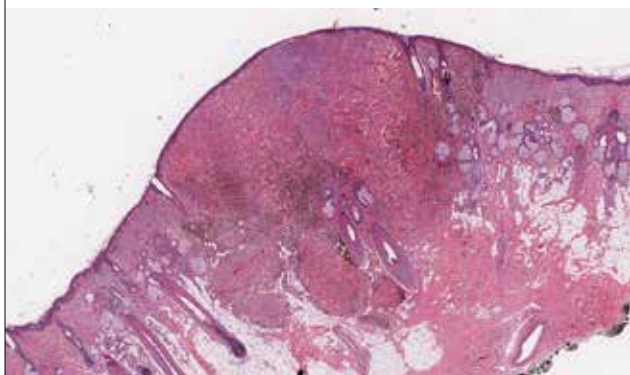


Fig. 40. Blue nevus plaque type.

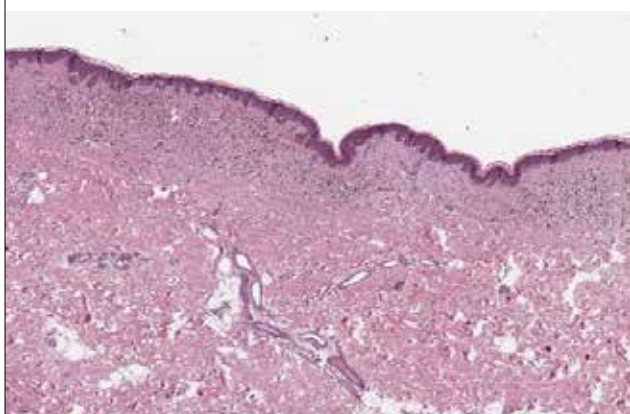


Fig. 41. Epithelioid blue nevus.

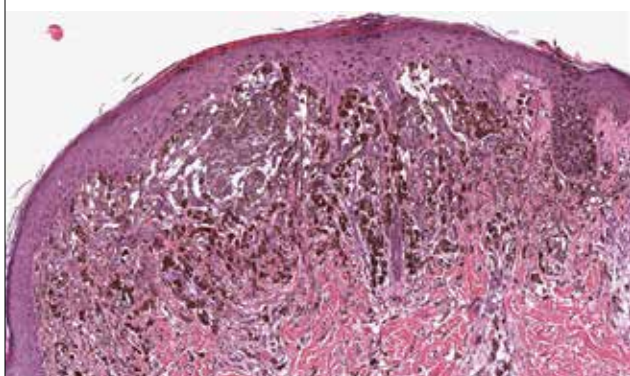
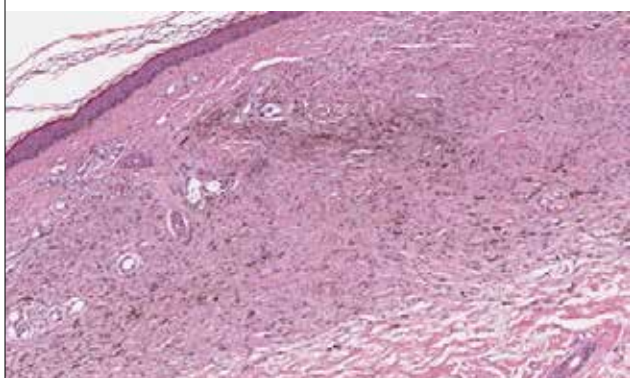


Fig. 42. Blue nevus with hypercellularity.



is absent the biphasic pattern characteristic of the cellular blue nevus. The epithelioid blue nevus may be sporadic and it is mostly associated with the Carney complex (autosomal dominant condition characterized by cutaneous lentiginos, mammary, cutaneous and cardiac myxomas, Cushing's syndrome, acromegaly, and sexual precocity). The epithelioid blue nevus is often part of a combined nevus. The blue nevus tumor cells are positive for melanin stains, S-100 protein and all other melanocytic markers and particularly it presents a diffuse and marked HMB-45 positivity. Blue nevus must be differentiated from desmoplastic melanoma which shows an atypical lentiginous melanocytic proliferation, mitoses also atypical mitoses, microscopic perineural or endoneural involvement, expression of S-100 protein but negative p16 stain.

Tab. II. Variants of blue nevus.

<b>Bizarre</b> (Youngberg GA J Am Acad Dermatol 1986;15:336-41)
<b>Colorectal mucosa</b> (Schreiber ZJ Ann Diagn Pathol 2011;15:128-30)
<b>Combined</b> (Baderca F Rom J Morphol Embryol 2013;54:413-7)
<b>Compound</b> (Ferrara G J Am Acad Dermatol 2002;46:85-9)
<b>Congenital pauci-melanotic</b> (Busam KJ J Cutan Pathol 2004;31:312-7)
<b>Epithelioid</b> (Pouryazdanparast P Am J Surg Pathol 2009;33:1396-400; Izquierdo MJ Br J Dermatol 2001;145:496-501; Moreno C J Cutan Pathol 2000;27:218-23)
<b>Hypopigmented</b> (Carr S J Cutan Pathol 1997;24:494-8)
<b>Multiple</b> (deGiorgi J Cutan Pathol 2004;1:185-8; Knoell KA J Am Acad Dermatol 1998;39:322-5)
<b>Nodal</b> (Epstein JI Am J Surg Pathol 1984;8:907-15)
<b>Oral mucosa</b> (Pinto A Oral Surg Oral Med Oral Path Oral Radiol Endod 2003;96:429-36)
<b>Plaque type</b> (Busam KJ Am J Surg Pathol 2000;24:92-9)
<b>Prostate</b> (Kovi J Urology 1977;9:576-8)
<b>Sclerosing mucinous</b> (Rongioletti F Br J Dermatol 2003;148:1250-2)
<b>Sinonasal mucosa</b> (Chuang WY Laryngoscope 2007;117:371-2)
<b>Uterine cervix</b> (Zevallos-Giampietri EA Appl Immunohistochem Mol Morphol 2004;12:79-82; Donofrio V Pathologica 1992;84:539-45)

#### Blue nevus: key histopathological diagnostic features

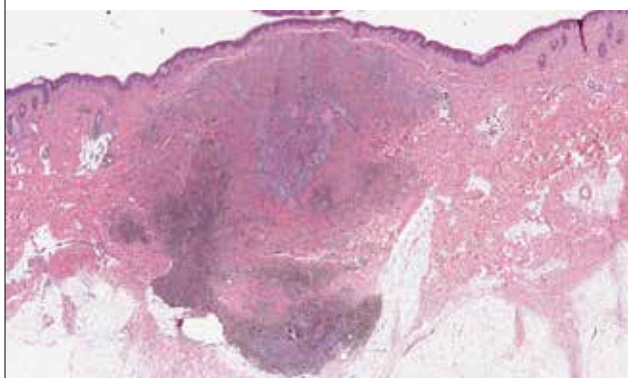
- Heavily pigmented dendritic and bipolar melanocytes
- Dense fibrous stroma
- Numerous melanophages
- No pleomorphism
- Present frequently multiple foci at any level of the dermis
- Appendageal extension
- Often combined with other melanocytic lesions

### 05B CELLULAR BLUE NEVUS

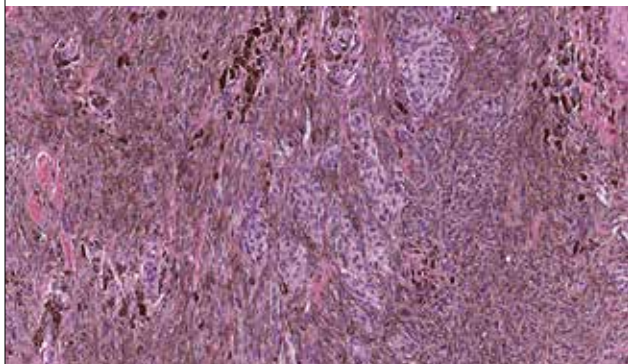
Cellular blue nevus is an uncommon benign melanocytic lesion which occur more often in females. The female/male ratio is 2.2/1. It can present at all ages, but, coarsely, the peak of incidence at presentation is between 10-40 years old (Rodriguez et al reported a range of 7-60) and a mean age of 32.6 years. Occasionally it occurs at birth. It is more frequent in Caucasians than in Negroes. About 50% of cellular blue are located over the skin of buttocks and sacro-coccygeal region, then on the scalp and face. It can also occur on other different sites which include foot, hand, arm and forearm, knee, chest and breast. Cellular blue nevi have been also described in other locations including spermatic cord, female genital

tract, breast, subungual, intraocular and conjunctival. Clinically, it is a dome-shaped nodule with a range of color that varies from blue, blue-black or black, to dark brown, pigmented or not pigmented; the consistency of the lesions vary from firm to soft and rubbery. Average largest diameter of cellular blue is 1.76 cm, and about 50% measure 1 to 1.9 cm. Larger lesions, including giant tumors measuring more than 10 cm, were documented. Cellular blue nevus is a nodular or multilobulated, well-circumscribed tumor, usually localized in the dermis; when it reaches a certain diameter, it either grows outwards, penetrate into the subcutaneous tissue or both. The borders are often sharp. The cellular component has different growth patterns. The prevalent pattern is mixed biphasic: areas histologically indistinguishable from blue nevus alternating with nodular lands which contain numerous spindle cells.

**Fig. 43a.** Cellular blue nevus; dermal proliferation extending to subcutis.



**Fig. 43b.** Biphasic pattern with compact sheets and nodules of pale cells are surrounded by more darkly pigmented group of melanocytes.



The nuclei of the spindled cells are oval to spindle-shaped and the chromatin is scanty; nucleoli are single and inconspicuous, the cytoplasm pale, eosinophilic or clear; occasionally multinucleated cells are seen. The stroma is sclerotic and it varies depending on the anatomical location of the lesion. The alveolar pattern is made by well-defined nests of mainly amelanotic cells surrounded by collagen and variable numbers of den-

dritic melanocytes and melanophages. Cellular atypia is infrequent; occasionally, multinucleated cells are seen. Cellular blue nevus is devoid of any type of inflammatory response within the dermal component and/or at the periphery; necrosis is absent unless associated with hemorrhage. Mitotic activity is almost absent or less than 1 per mm<sup>2</sup>. Melanogenesis is variable: in some cellular blue nevi the tumor cells are heavily pigmented, in others a silver stain is required to demonstrate melanin. A fascicular or neuronevoid variant is rarely seen: it consists of fascicles and nests of spindled amelanotic melanocytes with clear cytoplasm, surrounded by fibrous tissue with numerous melanophages and dendritic melanocytes. Other variants of cellular blue nevus have been described: a sclerosing one simulating melanoma, balloon cell, amelanotic, angiomatoid, ancient and desmoplastic. Cellular blue tumor cells show uniform and strong positivity for HMB-45 antibody. A small subset of are CD34 positive, appearing to fit within the spectrum of neurocristic cutaneous hamartomas and to arise from more primitive neurocristically derived cells. Gerami et al. showed 100% sensibility and specificity in distinguishing cellular blue nevi from blue nevus-like melanoma, using an assay targeting 6p25 (RREB1), 6q23 (MYB), 11q13 (CCND1) and the centromere of chromosome 6 (Cep6) of fluorescence in situ hybridization technique (FISH). The main differential diagnosis is with malignant blue nevus/blue-nevus-like melanoma: the features which favor malignancy include: tumor size greater than 1-2 cm, infiltrative borders, necrosis, pleomorphism, high mitotic rate and atypical mitoses.

#### Cellular blue nevus: key histopathological diagnostic features

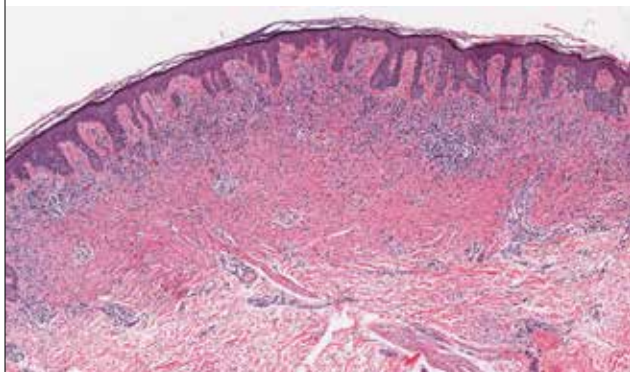
- Well circumscribed dermal nodule
- Extension to subcutaneous fat with a dumbbell pattern
- Nested and biphasic growth
- Clear and bipolar dendritic cells
- Mitoses rare or absent
- Vascular ectasia, hemorrhagic foci, myxoid change, cyst formations
- Necrosis absent
- Neural infiltration

#### 05C DESMOPLASTIC NEVUS

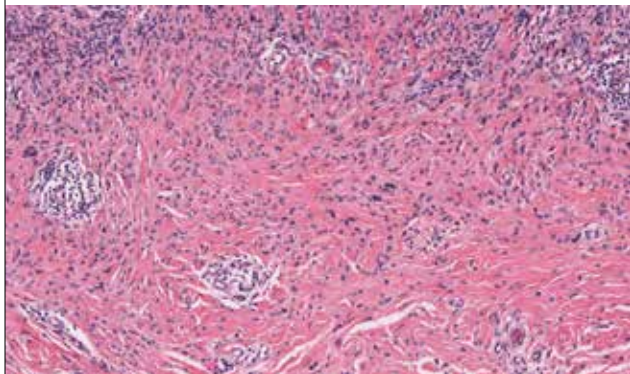
Desmoplastic nevus is a rare, benign melanocytic lesion with a female predominance. The age of presentation is wide, but most patients are in third decade. It predominantly affects the trunk, extremities, and the face. Desmoplastic nevus usually presents as an erythematous or red-brown papule or nodule, which can resemble intradermal nevus, atypical nevus, melanoma, and/or pigmented basal cell carcinoma. It is generally small, with an average of 3.5 mm in diameter, symmetric and well-circumscribed. At scanning magnification, the lesion has a symmetric microscopic growth pattern, it can be compound or entirely situated into the papillary and often extended to reticular dermis. Desmoplastic nevus mainly presents two components: melanocytic spindle or Spitzoid cells and a very dense stroma. It is unclear

whether desmoplastic nevus is a variant of Spitz nevus, sclerosing blue nevus, deep penetrating nevus with spindle type C cells or a distinct entity. It can show junctional activity characterized by the presence of both nested and lentiginous melanocytic proliferation or it may be unaffected. In the dermis, tumor cells are pleomorphic, and rarely have Spitzoid features especially in the superficial dermis; they have abundant eosinophilic cytoplasm, dark or vesicular nuclei and vesicular nucleoli. Intranuclear cytoplasmic pseudoinclusions (cytoplasmic invaginations) are often prominent.

**Fig. 44a.** Desmoplastic nevus; dermal proliferation of predominantly spindle cells associate to sclerotic reaction.



**Fig. 44b.** Deep component similar to desmoplastic melanoma; focal lymphoid cells in dermal melanocytic proliferation with diffuse sclerosis; to note the absence of marked cytologica atypia and mitoses.



Other types of cells which can be found are type A/B nevus cells, ovoid or dendritic melanocytes. Tumor cells typically mature with depth. Melanin pigment may be present focally/diffusely simulating a blue nevus, or absent at all. In about half of the cases, some melanophages can be found which are variable in amount and distribution. Mitotic activity is virtually always absent. The stroma is dense and sclerotic dermatofibroma-like, made by eosinophilic collagen bundles, or fibrillar and neurofibroma-like. The tumor cells are S-100 and HMB-45 positive and have moderately to strong nuclear positivity for p16. In **differential diagnosis**, **epithelioid benign fibrous histiocytoma** presents usually with an epidermal collarette and the tumor cells are round, with

abundant eosinophilic cytoplasm and a vesicular nucleus with small eosinophilic nucleoli. By immunohistochemistry, fibrous histiocytoma shows positivity for CD34 and factor XIIIa and negativity for S-100 and Melan-A. **Desmoplastic melanoma** is the main **differential diagnosis**: morphologically melanoma has an *in situ* component and a dermal component made by spindled cells with nuclear basophilia and hyperchromatism, deeper invasive growth pattern, frequent perineural invasion and patchy lymphoid aggregates. Desmoplastic nevus shows low proliferative index assessed by mitotic count and/or ki67 expression while in desmoplastic melanoma mitoses, also atypical, are present. By immunohistochemistry, virtually all desmoplastic nevi are HMB-45, Melan A and p16 positive and desmoplastic melanomas are almost totally negative for HMB-45, positive in only 3% of cases for Melan-A and in 18% they present a focally and weakly p16 positivity.

**Desmoplastic nevus: Key histopathological diagnostic features**

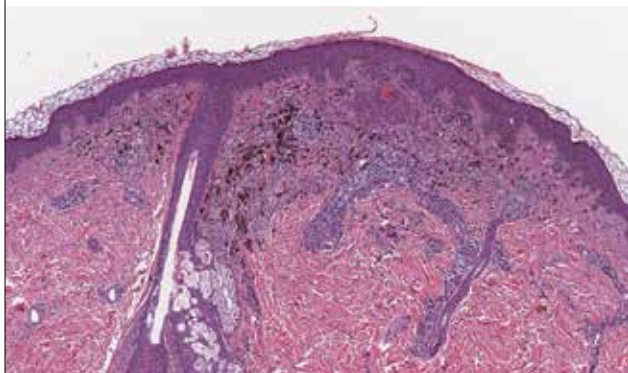
- Spindle cell proliferation
- Extension to deep reticular dermis and subcutaneous fat
- Small spindle cells with scant cytoplasm
- The cells are intermingled with dermal collagen fibers
- Extension along the neurovascular bundles

### 05D DEEP PENETRATING NEVUS

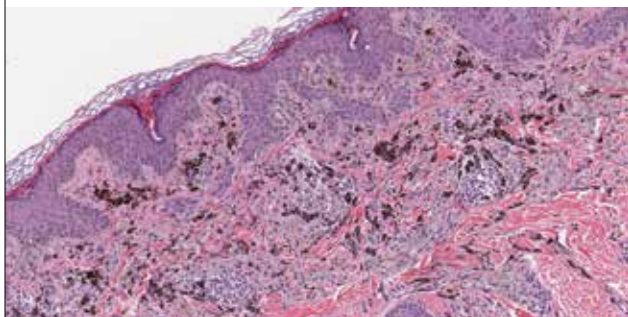
Deep penetrating nevus is a benign melanocytic lesion which has an age of presentation quite large: 3-64 years, very rare after sixth decade, with the peak between second and third decades of life. It usually presents as a solitary nodule or papule of less than 1 cm in diameter. A slight female predominance (female to male ratio of 1.3:1) is reported. Most lesions are darkly pigmented but pigmentation can be variegated, from light brown to black, especially if part of a combined melanocytic nevus. The lesion may appear asymmetrical and unevenly pigmented, thus raising a clinician suspicion of melanoma. The most frequent site is the skin of the head and neck, followed by the extremities and trunk; Robson et al. describe only a deep penetrating nevus on the toe of a 10 yo male, demonstrating the rarity of this tumor in acral sites. At scanning magnification, deep penetrating nevus has a sharply demarcated, circumscribed, often symmetrical and usually wedge-shaped configuration. The base is toward the epidermis and the tip toward the reticular dermis/subcutis with a narrow portion and frequent extensions along the skin adnexa or neurovascular bundles. The epidermis may show junctional melanocytic hyperplasia or it may present a limited junctional melanocytic component in from 60% to 85% of cases. Focal upward epidermal migration is rarely found and it should be seen carefully to exclude melanoma. The papillary dermis is frequently not involved. The dermal component is usually located in the reticular dermis and consist of loose and vertically oriented fascicles or nests of epithelioid and less frequently, short spindle-shaped melanocytes. The epithelioid morphology is normally found in upper parts of the lesion,

and usually predominates while the spindle-cell morphology may be found in the deeper parts. In the deep portion, individual melanocytes appear to lie singularly between the connective tissue bundles, with frequent evidence of cytological atypia, suggesting an erroneous consideration of malignant lesion.

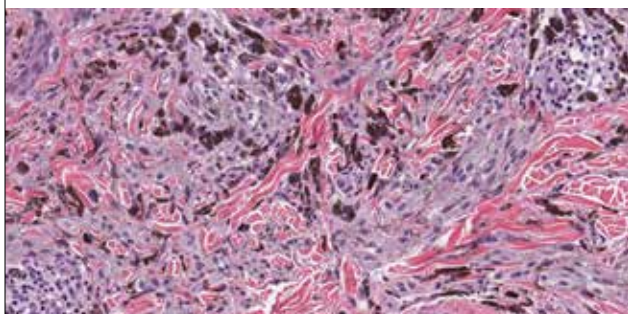
**Fig. 45a.** Deep penetrating nevus; extension of the nevus proliferation along an hair follicle into the dermis without evidence of progressive maturation of the nevus cells.



**Fig. 45b.** Deep penetrating nevus; spread of the pigmented cell between the collagen fibres as small nodules.



**Fig. 45c.** Deep penetrating nevus; the cells are rather large oval or spindle shape with amphophilic cytoplasm containing dusty pigment. The nest of melanocytes are surrounded by pigmented melanophages.



The melanocytic tumor cells have moderate to abundant cytoplasm, lightly to moderately pigmented, with often areas of clear changes. Nuclei are hyperchromatic, with variation of their size and shape from round to oval, mild to moderate nuclear pleomorphism, and no

obvious maturation of melanocytes. Cytoplasmic nuclear inclusions can be usually found. Nucleoli are small to medium sized and eosinophilic. Mitoses can be present even in the deeper parts of the lesion. The proliferative index measured with Ki-67 antibody, is either absent or low. Pigment is present in melanophages that surround individual nests and bundles of melanocytes. Background presents usually focal mature lymphocytes and rarely plasma cells. Moderate cytological atypia and mitoses may be identified in some tumors; this and the lack of deep maturation could lead the pathologist to think about a melanoma. In summary the histological atypical features found in up to 40% of deep penetrating nevus include: asymmetry of the lesion, expansive melanocytic nests in the dermis, conspicuous eosinophilic nucleolus, absence of maturation, and inflammation. Deep penetrating nevi are may be present associated to common acquired melanocytic nevi, blue nevi and also Spitz nevus. The main **differential diagnosis** is with **melanoma**. The features that favor a diagnosis of deep penetrating nevus include: the clinical presentation on the head and neck area of young individuals (< 50yo), circumscription, wedge-shaped architecture, lack of clonal expansive growth, significant cytological atypia and nuclear pleomorphism, numerous mitoses (including abnormal forms). Immune-histochemical stains for S-100 protein and HMB-45 are positive deep penetrating nevus.

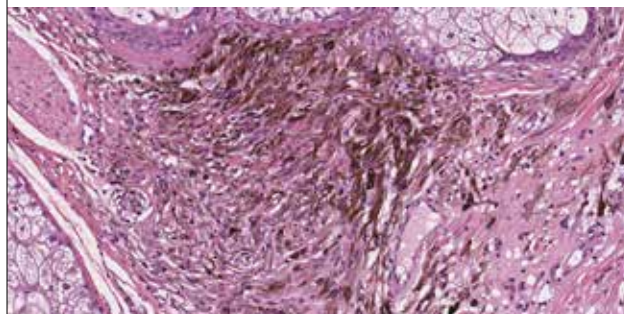
**Deep penetrating nevus: key histopathological diagnostic features**

- Well circumscribed, symmetric, reverse triangle architecture
- Epithelioid pale cells in nests surrounded by melanophages
- Fascicles of variably pigmented spindle cell admixed with melanophages
- Smaller nests in deep than those superficially
- Mitoses rare, always typical
- Focal slight maturation present

**05E MONGOLIAN SPOT AND NEVUS OF OTA AND ITO**

The **Mongolian spot** is a slate gray macular pigmentation present in the lumbosacral area in 90% of Asian population and in 20% Caucasians. Usually disappear with the age. Histologically the Mongolian spot consists of dendritic pigmented melanocytes scattered in reticu-

**Fig. 46.** Mongolian spot: dermal spindle and dendritic melanocytes with pigmented cytoplasm.



lar dermis or subcutaneous fat. The histology of **Ito and Ota nevus** is similar and it is characterized by a band-like disposition of melanophages mixed with dendritic melanocytes similar to that found in blue nevus in the upper dermis. Dermal fibrosis and melanophages may be present. Mongolian spot unlike the nevus of Ito and Ota is of lower cellular density, no fibrous reaction and few melanophages.

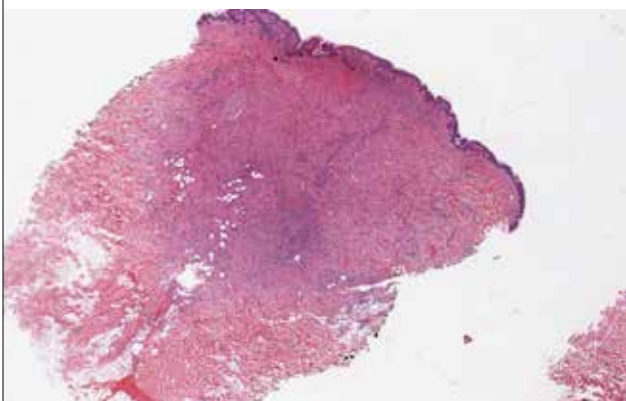
**Mongolian spot and nevus of Ota and Ito: key histopathological diagnostic features**

- Dendritic pigmented melanocytes in dermis and subcutaneous fat
- Pigmented melanophages
- Fibrous response

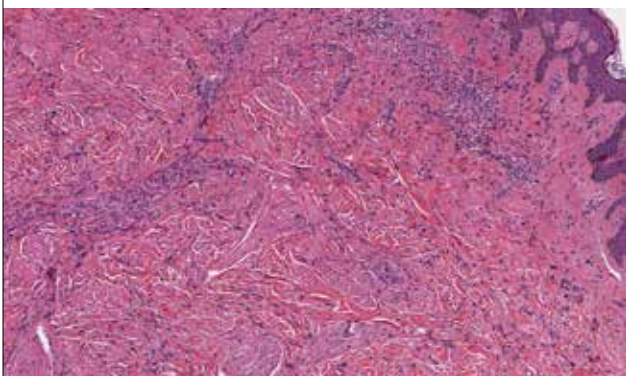
**05F NEUROCRISTIC HAMARTOMA**

Rare lesion that occur on the scalp but has been described elsewhere in the skin. It is a pigmented lesion that tends to aggregate along hair follicles characterized by spindle cell melanocytes admixed with dendritic blue nevus cells, schwann cells, melanophages within a dense collagenous stroma perifollicular and along the subcutaneous fascia.

**Fig. 47a.** Neurocristic hamartoma: proliferation of spindle cells along adnexa extending to deep dermis.



**Fig. 47b.** Neurocristic hamartoma: spindle cells in a dense collagenous background.



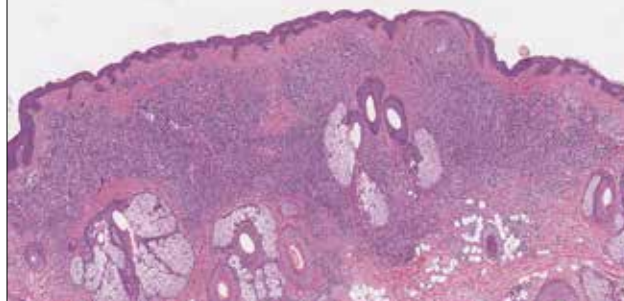
**Neurocristic hamartoma: key histopathological diagnostic features**

- Proliferation of pigmented spindle melanocytes along the hair follicles extending to subcutaneous
- Fascial involvement
- Perineural and perivascular invasion but no intralymphatic invasion

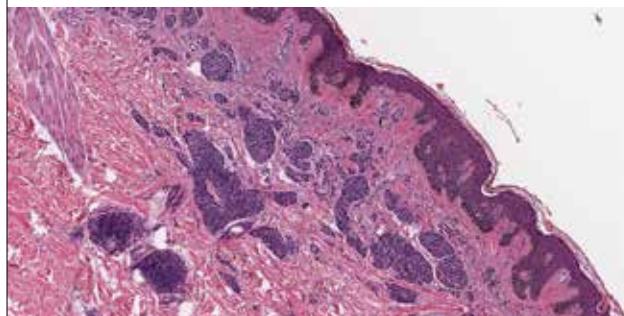
**06 Congenital nevus**

Congenital nevi are defined as nevi present at birth and they are identified in 1-2% of newborn infants. The size of congenital nevi varies from few mm to many cm sometimes occupying large part of the body. Some congenital nevi extend to subcutaneous fat and they may involve muscle and bone. Histologically the congenital nevus present the same types of cells of acquired nevi. Neuroid differentiation is quite frequent. Some histological features are characteristic of congenital nevi: presence of nevus cells in the wall of veins and lymphatics or in endoneurium but also in sebaceous glands, eccrine coil and duct, the external root sheath and subcutaneous septa. Presence of single nevus cells in mid and deep reticular dermis and around the adnexa in characteristic. Not infrequently other benign mature neuroid proliferations may coexist with congenital nevi such as neurofibromatous and ganglioneuromatous patterns. About 10% of congenital nevi show an intraepidermal proliferation with dysplastic like features but true dysplasia is usually absent. Nodules of confluent melanocytes with

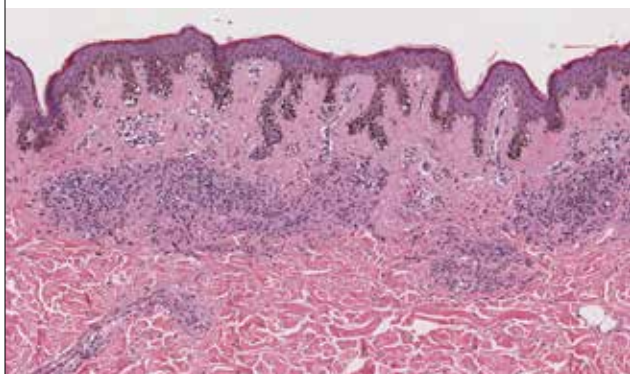
**Fig. 48a.** Dermal congenital nevus; the nevus cells extend irregularly and deeply to the reticular dermis surrounding the adnexa. Frequently the pigmentation is restricted to superficial parts.



**Fig. 48b.** Dermal congenital nevus: multiple dermal nevus cells nodules.



**Fig. 48c.** Compound congenital nevus; frequently the junctional proliferation of the nevus cells simulate a dysplastic nevus but this pattern is usually absent at the shoulder of the nevus.



different dimensions may be observed in the superficial dermis, so-called proliferative centers or nodules (see forward). Halo phenomenon may be also present.

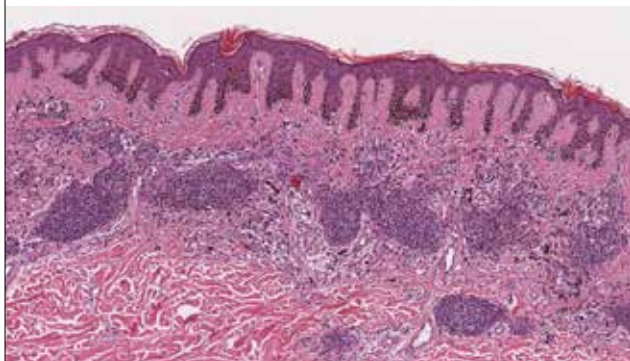
**Congenital nevus: key histopathological diagnostic features**

- Different sizes from 1-5 cm to covering large skin areas (garment distribution)
- Lentiginous junctional proliferation of melanocytes with focal slight atypia and nests
- Dermal appendageal and subcutaneous involvement by B nevus cells
- Multiple nests and single nevus cell diffusely arranged
- Perivascular and perineural extension

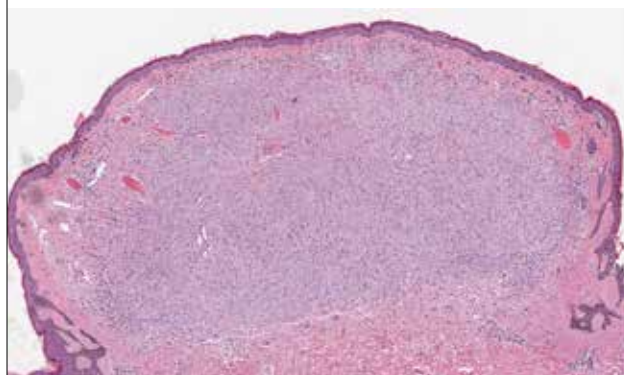
**06A BENIGN PROLIFERATIVE NODULES IN CONGENITAL NEVUS**

The development of focal nodular proliferations within large congenital melanocytic nevi can simulate melanoma. Clinically they are described as black, brown, or pink papules or macules within the melanocytic congenital nevi, most often measuring less than 1.0 cm and only sometimes they become ulcerated. Proliferative nodules have increased cellularity, usually expansive growth pattern with pushing borders, and larger melanocytes than in the background melanocytic component. The cells are epithelioid or spindled with abundant cytoplasm. They have small nucleoli, frequent intranuclear pseudo-inclusions. Mitoses are rare, there is no necrosis. Sometimes

**Fig. 49a.** Congenital compound nevus with dermal nodules.

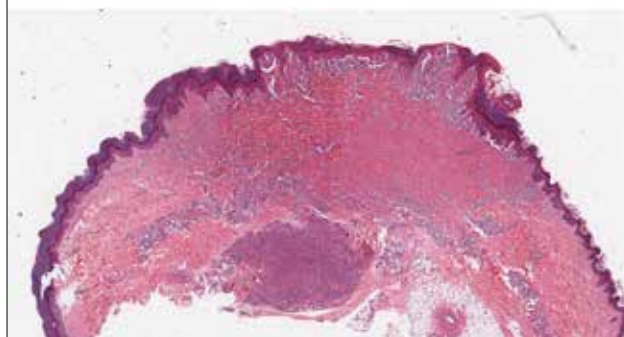


**Fig. 49b.** Proliferative nodule in compound nevus.

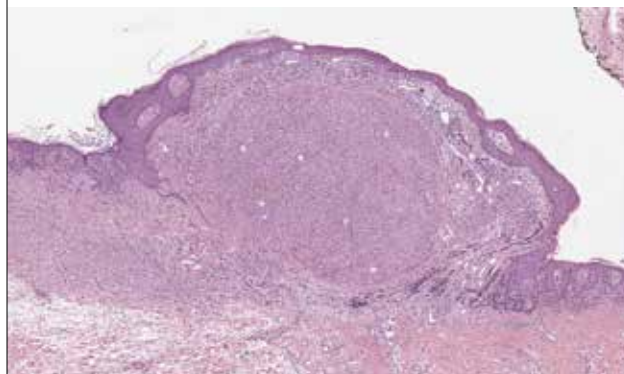


nuclear pleomorphism can be observed, but it is not associated with increased mitotic activity. No pagetoid spread is seen. Some inflammatory cell infiltrate composed of lymphocytes can be present in the background. Both congenital melanocytic nevi and proliferative nodules express S-100 protein, HMB-45, and Melan-A. Interestingly, p16 and CD95 are positive in all proliferative nodules in one study; CD117 is intensely positive in almost all proliferative nodules despite its absence in nearly all adjacent congenital melanocytic nevi. Proliferative index (Ki-67) is usually low in proliferative nodules. The nodule may be also present in Spitz nevus. The main **differential diagnosis** is with **neonatal melanoma in nevus**. The most important features to consider include: marked pleomorphism, high mitotic activity, abnormal mitoses and presence of necrosis.

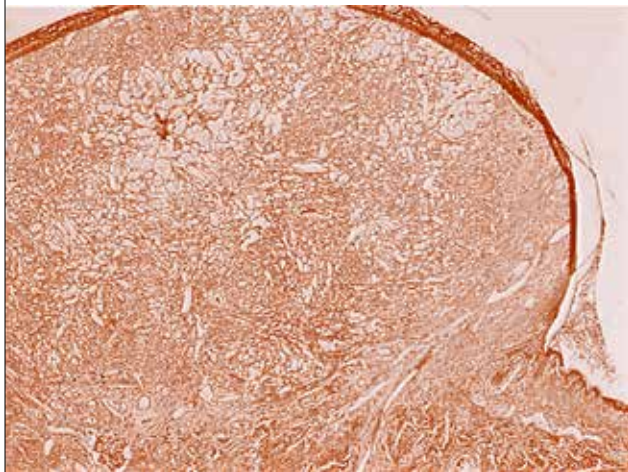
**Fig. 50a.** Proliferative nodule in Spitz nevus.



**Fig. 50b.** Proliferative nodule in congenital nevus.



**Fig. 50c.** Reticulum positive stain positive around single nevus cells of a proliferative nodule in dermal nevus.



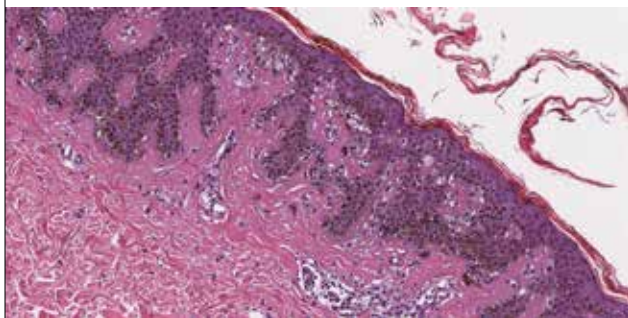
**Benign proliferative nodules in congenital nevus: key histopathological diagnostic features**

- Nodules cytologically homogeneous, rounded, well defined but not sharply demarcated
- Symmetry, no necrosis, no inflammation
- Rare and always typical mitoses
- Reticulum fibers stain positive around the single nevus cell

**06B SUPERFICIAL ATYPICAL MELANOCYTTIC PROLIFERATION IN CONGENITAL NEVI**

The observation of striking epithelioid cells in the epidermis and superficial dermis of congenital nevi, especially in young children and neonates may simulate a superficial spreading melanoma. The trans-epidermal elimination of single cells or nests is more common in juvenile nevi than in adult nevi. These lesions may be present in particular body sites (genital skin, breast area, acral skin, flexural and head and neck skin) and in physiologic states such as old or young age or pregnancy. Frequently the nevi are junctional or compound with large junctional nests and pagetoid intraepidermal spread. Mitoses in both junctional and dermal components may be present. Maturation in deep part is irregular or absent and the appendageal involvement may be frequent. The nevus cells may show prominent nuclei with evident nucleoli and finely granular melanin in their cytoplasm.

**Fig. 51.** Junctional nevus with "atypical" epithelioid cells in a child 14 yrs old, periareolar skin (special site).



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 absence of pagetoid spread at the nevus shoulder. The dermal component show a propensity to mature and blend with the underlying dermal nevus cells. In differential diagnosis it is to considerer the melanomas in children are very rare and most frequently they arise in the deep component of a large congenital nevus.

**Superficial atypical melanocytic proliferation in congenital nevi: key histopathological diagnostic features**

- Lack of aggressive proliferation of the junctional and intraepithelial component
- Occasionally large abnormally located junctional nests
- Pagetoid spread limited to epidermis over the dermal component
- Cytological atypia and mitoses
- Irregular maturation
- Clinicopathological correlation and second opinion are important

**07 Conjunctival melanocytic proliferations**

Melanocytic lesions are not uncommon in the conjunctiva but they may present clinical and histopathologic problems. In a large series of 1643 conjunctival different lesions by Shiels et al. 53% were nevi and melanomas. Conjunctival melanocytic proliferations are classified as freckle, acquired or congenital nevi, stromal and episcleral melanocytoses, primary acquired melanosis without and with atypia, primary acquired melanosis associated to nevi and conjunctival melanoma.

**07A FRECKLES AND EPHELIDES** of the conjunctiva are similar to those of the skin with increased pigment within basal conjunctival epithelium.

**Conjunctival freckles or ephelides: key histopathological diagnostic features**

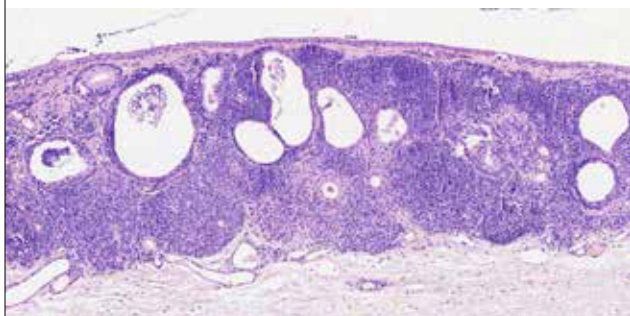
- Hyperpigmentation of basal keratinocytes
- Normal epithelial architecture
- Melanocytes present in normal number or diminished

**07B CONJUNCTIVAL NEVI**

Conjunctival nevi are present frequently in young individuals and situated near to the junction between sclera and cornea. Acquired conjunctival nevi arise on the bulbar conjunctiva and congenital conjunctival nevi may occur on both the upper and the lower eyelids. Histologically the conjunctival nevi may exhibit an intraepidermal junctional or a sub epithelial component or both. Frequently the nevomelanocytic component is densely pigmented and hyperchromatic. A variant of **conjunctival nevus is associated with multiple apocrine cysts**. Cyst like spaces with goblet cell are present in 70%



Fig. 52. Compound conjunctival nevus.

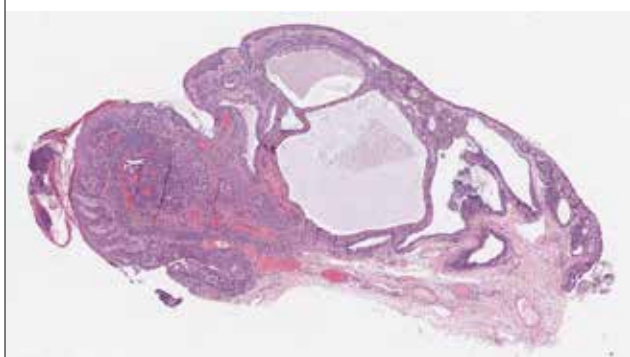


#### Conjunctival nevus: key histopathological diagnostic features

- Junctional nevi
  - Intact surface epithelium of normal thickness
  - Epithelial down-growths with or without cyst formation
  - Rare mitoses
  - Nest or linear arrangement of junctional melanocytes
- Compound nevi
  - Prominent epithelial down-growths with or without cyst formation
  - Superficial nests heavily pigmented
  - Maturation of dermal component
  - Stromal inflammatory infiltrate
- Sub epithelial-stromal nevi
  - No junctional component
  - Maturation
  - Cyst formation

compound, 58% stromal (sub-epithelial) and 40% junctional nevi. Less than 1% of acquired conjunctival nevi progress to melanoma.

Fig. 53. Multiple apocrine cysts in compound conjunctival nevus.



### 07C PRIMARY CONJUNCTIVAL MELANOSIS

Melanosis can be primary, secondary, congenital or acquired. The most common is the primary acquired melanosis (PAM) with or without atypia. Conjunctival melanosis may present three histologic patterns: hyperpigmentation of the basilar epithelial keratinocytes without melanocytic hyperplasia, or benign melanocytic hyperplasia with hyperpigmentation or atypical melanocytic hyperplasia with hyperpigmentation (PAM). The last may be considered a precancerous melanosis. PAM

without atypia presents as flat non-cystic patches of the conjunctival pigmentation usually in patients over the age of 40 years.

#### Primary conjunctival melanosis without atypia: key histopathological diagnostic features

- Hyperpigmentation of basal keratinocytes
- Basilar melanocytic hyperplasia without atypia in lentiginous pattern.
- Rare nests may be present

### 07D STROMAL AND EPISCLERAL MELANOCYTOSES

The stromal and episcleral melanocytoses are: **nevus of OTA** (oculo-dermal melanocytosis) with bipolar spindled or multipolar melanocytes that involve all or part of the uveal tract (iris, ciliary body and choroid) as well as the episclera; the **blue nevus** and the **cellular blue nevus** characterized by spindled-shaped melanocytes in conjunctival stroma with schwannian appearance and multiple **combined nevi** (acquired or congenital and blue nevi).

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