



The spectrum of melanocytic nevi and their clinical implications

Nina Frischhut¹, Bernhard Zelger¹, Fiona Andre¹, Bettina Gudrun Zelger²

(1) Department of Dermatology, Venereology, and Allergology, Medical University Hospital Innsbruck, Austria

(2) Institute of Pathology, Medical University Hospital Innsbruck, Austria

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Prof. Dr. Trautinger, St. Pölten

Summary

The magnitude of the topic of melanocytic nevi (MN) is directly related to its relevance in everyday clinical work. The different MN have different prognostic significance in regard to comorbidity and possible risk of transformation. In addition to the criteria of the ABCDE rule, relevant criteria in the assessment of an MN are the time of occurrence, the growth tendency, the distribution and the comparison with other MN of the respective individual.

The present CME article provides an overview of the knowledge that has been gained with regard to the development and genetic background of MN and any risk of degeneration that may exist. In addition, certain clinical and/or dermatoscopic features may provide the clinician with a decision-making aid in the management of different MNs.

Introduction

Melanocytic nevi (MN) are defined as benign, well-circumscribed melanocyte proliferations in the skin. As opposed to the commonly dendritic shape of solitary melanocytes in the epidermis, melanocytes in MN appear round to oval or spindle-shaped. These melanocytes are aggregated in 'nests' and represent a special form of melanocyte differentiation, called nevus cells [1].

Such melanocytic proliferations are mostly located in the basal epidermis (junction zone – junctional MN) or the dermis (dermal MN), but they may also extend into the deeper layers beyond the subcutis into the muscles (deep penetrating nevi).

Melanotic macules (freckles/sun spots, café-au-lait macules, lentiginos senilis/flat seborrheic keratoses) are by definition not categorized as melanocytic nevi. These lesions show a circumscribed increase of pigment but the number of epidermal melanocytes is basically normal or only slightly increased. These hyperpigmentations and their sometimes complex associated syndromes will not be covered in detail here even if mentioned in passing.

Fundamentals and melanocyte function

Human melanocytes are found in all areas of the skin, the mucous membranes, hair follicles, hair matrix and other organ systems, including the heart, the uvea in the eyes, the inner ear, and the leptomeninges [2, 3].

During embryonic development, precursor melanocytes (melanoblasts) migrate to the skin from the neural crest within the first 40 days of pregnancy. The sequence of melanoblast migration into the skin follows a clearly defined time schedule: intradermal (6th to 8th week), intraepithelial (12th to 13th week), and intrafollicular (15th to 17th week), as well as cephalocaudal and dorsoventral progression [4].

After injuries to the epidermis, re-population of melanocytes occurs from the stem cell reserve in the hair follicles.

It is assumed that melanin may provide an SPF (sun protection factor) of up to four.

MN in “special locations” are not essentially a risk marker for malignancy.

Further proliferation and differentiation from melanoblasts to melanocytes are regulated by the surrounding tissue. After injuries to the epidermis, re-population of melanocytes occurs from the stem cell reserve in the hair follicles. The outer sheath of the hair root contains multipotent stem cells that can differentiate into various cell lines [5, 6]. Both intrinsic factors (such as signals from fibroblasts, keratinocytes, endocrine, inflammatory, and neuronal cells) and extrinsic factors (such as medication and UV rays) impact the recruitment of melanocytes, the number of dendrites, and the transfer of melanosomes to the keratinocytes (pigment transfer) [7]. Individual melanocytes are situated at the junctional zone and via their dendrites provide a varying number of keratinocytes with melanosomes – this number is greatly dependent on body region (with variations in pigmentation) and UV exposure [7]. The entirety of keratinocytes per providing melanocyte is defined as an epidermal unit. Pigment transfer within this epidermal unit occurs right up to the stratum spinosum. Keratinocytes deposit the incorporated melanin (a polymerization product from tyrosine) above the nucleus (supranuclear) to protect the genetic material from UV rays. It is assumed that melanin may provide an SPF (sun protection factor) of up to four [8].

MN are categorized according to various aspects: clinical (such as anatomical location) and histological criteria, but also genetic characteristics. Melanocytic nevi in special locations are acral, umbilical, subungual (melanonychia striata), or genital MN as well as MN on the breast/areola. Due to distinctive tissue characteristics in the various locations, these MN show special histological features. MN in “special locations” are not essentially a risk marker for malignancy [9].

The question of when these lesions develop, and if MN are genetically determined malformations, hamartomas, or benign neoplasias of the melanocytes, is the topic of controversial discussions and cannot be answered uniformly for all MN. A large congenital MN shows a genetic pattern that differs from an MN caused by UV exposure, manifesting during puberty or even later. These differences between acquired and congenital MN are reflected in the various mutations in the MAPK pathway.

Melanocytic nevi developing *in utero* show genetic differences from those that appear later. The two groups cannot be differentiated via histopathological criteria alone. Melanocytic nevi that develop on skin exposed to UV radiation during childhood to young adulthood frequently display BRAF mutations and more rarely NRAS mutations. These results correlate with the observation that BRAF mutations in melanomas are rare in anatomical regions not exposed to UV (such as the mucous membranes) [10, 11].

Melanocytic nevi

Many different forms of MN have been described in the literature, which cannot be included here in their entirety and are only mentioned by name: Halo nevus (with a hypopigmented margin) [12], Mark nevus (hairy melanocytic nevus extending into the deep connective tissue of the dermis), Kopf nevus (Spitz MN with a halo phenomenon), Meyerson MN (eczematous MN), Kerl MN (ancient features) [13].

Dermal melanocytoses

Dermal melanocytoses include Ota’s nevus, Ito’s nevus, and congenital dermal melanocytosis (Mongolian spot). Histological characteristics reveal pigmented

The location of the pigmented melanocytes in the deep layers of the dermis causes the clinically characteristic color of the melanocytoses.

spindle-shaped to dendritic melanocytes extending into the deep layers of the dermis. The location of the pigmented melanocytes in the deep layers of the dermis causes the clinically characteristic color of the melanocytoses. Dermal melanin reflects blue light (Tyndall effect), resulting in a blue-gray hue.

Extrasacral spots, sizes of > 10 cm, very dark and multiple spots are markers for persistence of congenital dermal melanocytosis above one year.

Congenital dermal melanocytosis (Mongolian spot)

More than 90 % of cases of congenital melanocytosis occur in neonates in Asia. This is characterized by a smudged, bluish-gray skin discoloration in the lumbal and sacro-gluteal region, with extrasacral spots occurring in some cases. Congenital dermal melanocytosis will usually disappear completely within the first two years of life, but may persist in about 10 % of cases [14]. Extrasacral spots, sizes of extension >10 cm multiple, very dark spots are markers for persistence of congenital dermal melanocytosis above one year [15].

Extensive, dark, and progressive congenital dermal melanocytoses may indicate neurocristopathies and congenital metabolic disorders such as Hurler disease (mucopolysaccharides) and monosialotetrahexosyl ganglioside (GM1) gangliosidosis and should thus prompt the attending physician to initiate further genetic and neurological investigations [16].

Ito's nevus and Ota's nevus

Ito's nevus and Ota's nevus (Figure 1) do not differ histologically and are distinguished clinically by their location. Ito's nevus occurs in the shoulder/arm region, Ota's nevus on the face.

People of Asian descent are affected more frequently by these melanocytoses (0.014 % to 0.034 % of the population), and women are affected much more frequently (gynecotropism; f : m = 5 : 1) [14, 17]. These nevi are usually present at birth but may also appear during puberty or during pregnancy due to hormonal changes. Individual case reports have described malignant transformation of Ota's nevus, and even more rarely of Ito's nevus [18, 19].

The exact etiology of these melanocytoses is unknown; they may occur within the context of syndromes [20] (Table 1).



Figure 1 MN Ota with pigmentation of the conjunctiva and periocular.

Table 1 Syndromes with frequent MN and/or hyperpigmentation (lentiginos).

Syndrome	Gene	Dermatological presentations	Other presentations
BAP1 tumor predisposition syndrome	<i>BAP1</i>	Skin-colored to reddish brown, dome-shaped to stalked, well-circumscribed papules	Melanomas and uveal melanoma; in bi-allelic loss of <i>BAP1</i> : breast cancer, thyroid cancer, urothelial cancer, and neuroendocrinological cancers
Carney syndrome (LAMB/NAME)	<i>PRKAR1A</i>	Lentiginos and blue MN sun exposed areas	Cutaneous and cardiac myxomas, mammary myxoid fibroadenomas, testicular tumors, pituitary adenomas
Dermatopathia pigmentosa reticularis	<i>KRT14</i>	Generalized reticular hyperpigmentation, onychodystrophy	Alopecia
Familial atypical multiple mole melanoma (FAMMM)	<i>CDKN2A/CDK4</i>	Multiple melanocytic nevi, usually > 50, melanomas in the family history	Malignomas in other organ systems such as pancreas, brain (melanoma-astrocytoma syndrome), esophagus, stomach, bladder, lungs
LEOPARD syndrome	<i>PTPN11</i>	Lentiginos	ECG alterations Ocular Hypertelorism, Pulmonary stenosis, Anomalies of the genitals, Retardation, Deafness
McCune-Albright syndrome	<i>GNAS1</i>	Café-au-lait macules (sometimes segmental and following the Blaschko lines) usually generally fewer and with irregular borders as compared with NF1	Precocious puberty, fibrous dysplasia with premature closing of the epiphyses and resulting stunted growth, acromegaly, endocrinological disorders
Mulvihill-Smith syndrome	unknown	Multiple MN, lack of axillary hair, sparse hair on the scalp	Pointed face, premature ageing, stunted growth, microcephaly with or without low IQ, hypodontia, deafness, chronic infections
Naegeli-Franceschetti-Jadassohn syndrome	<i>KRT14</i>	Reticular hyperpigmentation, onychodystrophy and lack of digital ridges with palmoplantar hyperkeratoses	Hypohidrosis
Neurofibromatosis (Recklinghausen disease)	<i>NF1</i>	Café-au-lait macules and axillary freckling, Lisch nodules (iridal hamartomas), neurofibromas, hemangiomas, lymphangiomas, anemic nevus, juvenile xanthogranulomas	Skeletal deformities (pseudarthrosis, sphenoid wing dysplasia, long bone dysplasia, scoliosis), pheochromocytoma, spinal neurofibromas, malignant nerve sheath tumors, plexiform neurofibromas, optic nerve gliomas
Noonan syndrome	<i>PTPN11, SOS1, BRAF, KRAS, RAF1</i>	Café-au-lait macules, diffuse hair loss, rarefied eyebrows, keratosis pilaris, photosensitivity, circumscribed lymphangioma	Dysplasia of the heart, kidneys, and bones, webbed neck, tooth position anomalies, cryptorchidism or testicular aplasia
Peutz-Jeghers syndrome	<i>STK11</i>	Mucosal lentiginosis of the lips, nose, and cheeks	Intestinal polyps or adenocarcinomas in the small intestine, associated with other neoplasms of internal organs
Phakomatosis pigmentokeratotica	<i>HRAS</i>	Segmental nevus spilus, nevus sebaceus	Segmental hyperhidrosis and dysesthesia, ptosis, deafness, epilepsy, muscle weakness
Tuberous sclerosis	<i>TSC1/TSC2</i>	Café-au-lait macules, ash-leaf spots, cutaneous angiobromas/sebaceous adenoma	<i>Kidney</i> : Angiomyolipomas and cysts <i>Heart</i> : Rhabdomyomas
Turner syndrome	Xo Monosomy	Multiple MN, Café-au-lait macules	Stunted growth, gonadal dysgenesis, facial dysmorphism, webbed neck, coarctation of the aorta, renal dysplasia, lymph vessel dysplasia, skeletal deformities

In the context of tumor syndromes (such as Li-Fraumeni syndrome, Lynch syndrome [HNPCC – hereditary non-polyposis colorectal cancer] and Cowden syndrome) the risk of melanoma is also increased.

Various factors have been investigated: It has been shown that GNAQ is mutated in about 6 % of Ota's nevus cases. The additional monosomy of chromosome 3 and increase of the long arm of chromosome 8q is a risk factor for uveal melanoma [17, 21, 22]. If melanomas develop within an Ota's nevus, they frequently show locally destructive growth. Out of eleven cases reported in the literature, five (45 %), developed metastases, mostly in the liver followed by the lungs [23].

Ota's nevus is most frequently found in the supply areas of the first two branches of the trigeminal nerve, the ophthalmic nerve, and the maxillary nerve (nevus fusco-coeruleus ophthalmico-maxillaris, also called oculodermal melanocytosis). This causes the mostly unilateral distribution of the slate-blue/blue-gray macule; bilateral occurrence has also been reported in rare cases [17, 24–26].

If hyperpigmentation of the eye (conjunctiva, sclera, cornea, or uvea) is present in a patient with Ota's nevus, a thorough ophthalmological investigation is indicated to exclude glaucoma.

Apart from the face, pigmentation can also affect the eye, the oral cavity, and the nasal mucous membranes. If hyperpigmentation of the eye (conjunctiva, sclera, cornea, or uvea) is present in a patient with Ota's nevus, a thorough ophthalmological investigation is indicated to exclude glaucoma.

Tanino classifies Ota's nevus into four types [27]:

- *Type I (mild)*: Type A in the periocular region, type B in the cheek bone region, type C on the forehead, type D on the nose.
- *Type II (moderate)*: similar to type I, but more pronounced.
- *Type III (intense)*: periocular, affection of the nose and scalp.
- *Type IV*: Bilateral affection.

Ito's nevus (nevus fusco-coeruleus acromio-deltoides or deltoideo-acromial melanocytosis) presents as a slate-blue/gray-blue macula in the shoulder/breast and lateral arm region in the supply area of the brachial nerve, in infants or until puberty [28]. Very rare cases of malignant transformation within existing Ito's nevi have been reported [19, 29]. The clinical sign of melanoma within the existing Ito's nevus was a newly developed nodule [29].

There have been numerous reports of successful treatment of cosmetically bothersome dermal melanocytoses with a 755-nm picosecond laser. According to the authors, in the six patients treated, the lesions almost completely disappeared after only one or two treatment sessions [30]. There has been an ongoing discussion about the risks of laser treatment regarding follow-up monitoring for MN. We are of the opinion that cosmetic laser treatment should be limited to selected cases only.

Blue MN and variants

Blue nevus, nevus coeruleus (Jadassohn-Tièche) (Figure 2a)

Clinically, it is sometimes difficult to differentiate blue MN from melanoma or cutaneous melanoma metastases, or even basal cell carcinoma or Morbus Kaposi.

Blue MN were first described by Tièche in 1903 [31]. They are mostly acquired in early childhood but may also develop in adults, preferentially in females. Blue MN typically presents as a solitary bluish macule or papule to nodule with a smooth surface and a diameter of 0.5 to 1 cm, mostly on the limbs (Figure 2b), the buttocks, and the head, but also in extracutaneous locations such as the genital, oral or nasal mucous membranes and lymph nodes [32–34]. Clinically, it is sometimes difficult to differentiate blue MN from melanoma or cutaneous melanoma metastases, or even basal cell carcinoma or Morbus Kaposi.

The typical dermatoscopic characteristic of blue nevi is homogeneous blue, blue-gray, blue-brown or blue-black pigmentation. There is a broad spectrum of dermatoscopic features (Talbe 2), such as whitish scar-like depigmentation, dots,



Figure 2 MN blue, type deep penetrating MN (blue arrow: strongly pigmented melanocytes reaching into the subcutaneous fat tissue) (a). Blue MN: Acral (heel) solitary bluish papule, 1 cm in diameter, dermoscopic: structureless blue-gray brown pattern, furrowed through the acral ridges, lighter in the furrows, darker on the ridges (b).

peripheral stripes, or vessels. Differentiation from melanoma or non-melanocytic neoplasias can thus be clinically quite difficult and may necessitate surgical excision [35].

Blue MN frequently show histological overlaps between the simple and the cellular variant [36]. Based on the cellular feature and the abundance of pigment, they have repeatedly been diagnosed as “melanosarcoma”.

A “malignant blue nevus” according to current definition is a melanoma with dendritic melanocytes, with or without high cell density, partially deeply situated and frequently intensely pigmented melanocytes with mitoses and necroses, but it is not in itself a new or distinct entity. Clear differentiation between atypical cellular blue nevi (ACBN), cellular blue MN, and melanomas that are combined with cellular blue nevi remains a histopathological challenge. To highlight the weak diagnostic criteria, Barnhill et al. reported on the diagnosis of 26 different cellular blue melanocytic neoplasias (6 melanomas that had developed within or with cellular blue MN features; 11 “atypical cellular blue nevi [ACBN] with indeterminate biological potential”; 8 conventional cellular blue MN; 1 combined blue MN) by 14 dermatohistopathologists who routinely investigate melanocytic neoplasias. Diagnostic sensitivity among the 14 pathologists was 68.6 % for melanoma, 33.1 % for ACBN, and 44.6 % for cellular blue MN.

The results of this study clearly show that even among experienced histopathologists, there are significant discrepancies about the definition and biological properties of cellular blue melanocytic neoplasia, especially those presumed to display atypical features (ACBN) [37].

Lentigo simplex, junctional nevus, compound nevus, dermal nevus

Clinically, lentigo simplex presents as a flat pigmented macule, a possible early manifestation of MN; it is characterized by a subtle increase in basal melanocytes. This may or may not develop into an MN with melanocyte nests. The next step in nevogenesis is focal proliferation of junctional melanocytes with the formation of nests. At first, these appear as spheric structures in the junctional zone (junctional nevi). Some of these later “drop” into the dermis (compound nevi) and form cord-shaped or clustered aggregates. Finally, the cell nests disappear from the epidermis and can be found only in the dermis (dermal MN).

Various factors play a role in the development of melanocytic nevi. Genetic factors: A large number of MN, including clinically atypical MN, run in families. Hormonal factors: New development and changes of melanocytic nevi during puberty and pregnancy are known.

UV radiation: Intermittent UV exposure with erythema-inducing doses especially during childhood is an important factor (solar nevocgenesis) [38, 39].

Immunosuppression: Both iatrogenic immunosuppression after organ transplants and chemotherapy during childhood, and immunodeficiency in the context of HIV infection may lead to an increase or changes of MN [1].

The most frequently described and clinically observed purely junctional, compound (extending from the junctional zone into the dermis), or purely dermal MN are called Miescher, Unna, and Clark nevi. However, these names are not used uniformly, and depending on the laboratory and investigator, names such as “Zitelli” may also be used.

Miescher nevus

Miescher nevus is a common, dome-shaped and mostly skin-colored nevus located primarily on the face. Hairs may grow on top, and colloquially it is sometimes called “witch’s wart”. Histologically, it shows endophytic and exophytic growth and usually an extensive wedge-shaped dermal component, incorporating the adnexal structures down into the deeper layers.

Zitelli nevus (Figure 3)

Zitelli nevus is located mainly on the torso as a pigmented papule.

As in Miescher nevus, histology shows a wedge-shaped to sawtooth-like dermal component with integration of the adnexal structures.

Unna nevus (Figure 4)

Unna nevus is a papillomatous MN located mostly on the neck, the axillae, and the inguinal area.

Clinical differentiation from seborrheic keratosis or fibroma pendulans (“skin tags”) is sometimes difficult. Pigmentation varies from virtually skin-colored to deeply pigmented. This MN, as well, has an extensive dermal component, affecting the papillary dermis with integration of the adnexal structures.

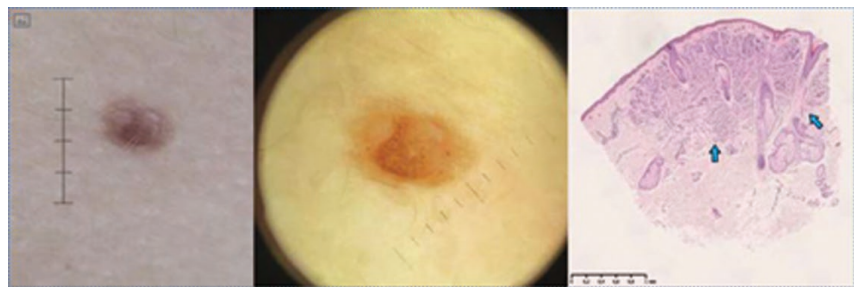


Figure 3 Pictures described from left to right: MN Zitelli, clinical exposure: pigmented papule (0,5 cm), dermatoscopically: central structureless pattern, reticular in the edge, histologically: papillomatotic MN with dermal deep endophytic growth (left blue arrow), involving adnexe (right blue arrow).

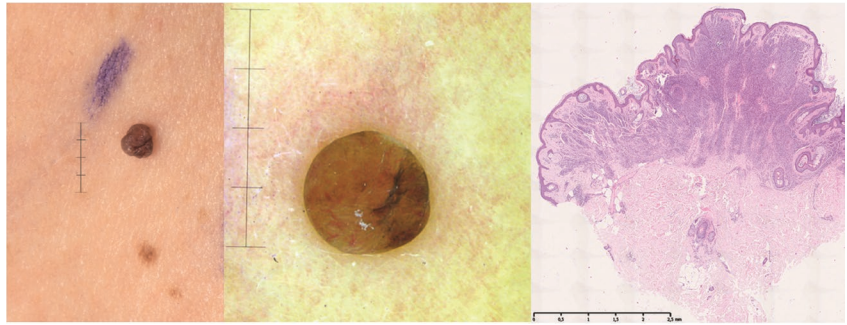


Figure 4 Pictures described from left to right: MN Unna, clinical exposure: exophytic pigmented papule (0,5 cm), dermatoscopically: brown, structureless pattern, histologically: papillomatotic MN with deep endophytic growth (border of papillary and reticular dermis).

Clark nevus (Figure 5)

This usually presents as a flat and clearly circumscribed plaque frequently located on the torso. Histology is characterized by an increase of melanocytes, frequently limited to the junctional zone (and thus clinically flat and dermatoscopically reticular) with sometimes pronounced pigmentation (Figure 6). Although Ackerman and Magana-Garcia had originally proposed to call flat MN “Clark nevi”, these are frequently confused with the poorly defined term “dysplastic nevus” or are labeled thus [40]. The term “Spark nevus”, found time and again in the more recent literature, describes an MN with histological characteristics of both Spitz and Clark nevus [41]. Clinically, this presents as an asymmetric, irregular, multi-colored, pigmented lesion which may be difficult to differentiate from melanoma or Clark nevus.

Distribution of MN in the Caucasian population

A prospective study in 400 patients investigated the frequency, location, age distribution and sex ratio of flat MN/Clark nevi, Miescher nevi, and Unna nevi in the Caucasian population. MN were counted in 400 patients of whom 47 had had a melanoma in their past medical history. The average age was 52.4 years in the non-melanoma group and 58.6 years in the melanoma group. Mean age when the

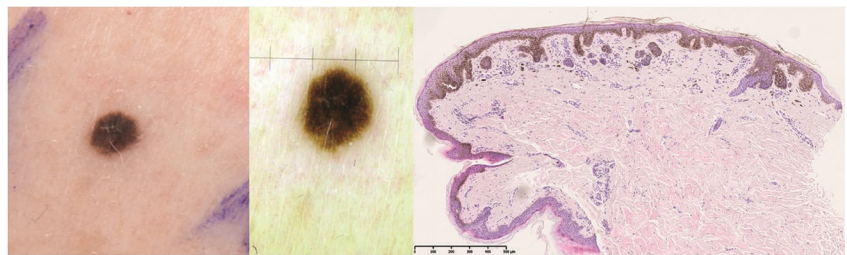


Figure 5 Pictures described from left to right: MN Clark, clinical exposure: flat, well-circumscribed and homogeneously pigmented plaque, dermatoscopically: reticular pattern, histologically: increased melanocyte nests in the junction zone, pigment incontinence superficial dermal.

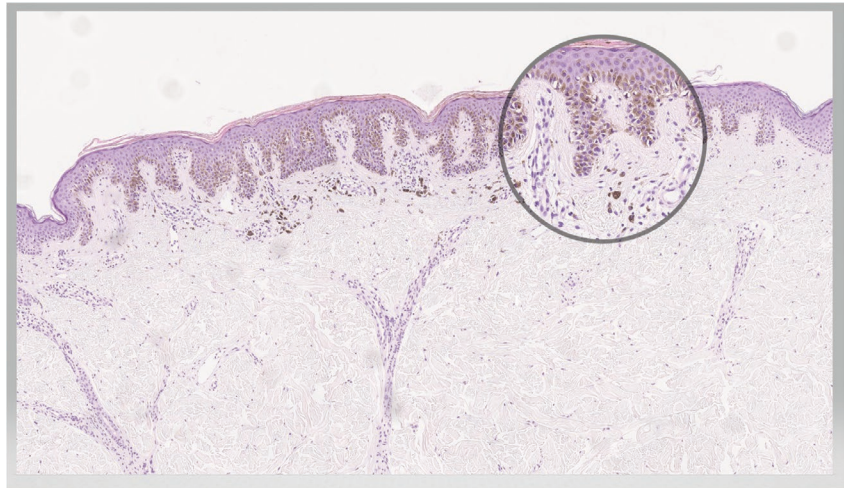


Figure 6 MN Clark with increased single melanocytes in the dermoepithelial junction zone (zoom), pigment incontinence (melanophages) located superficially dermal.

Distribution according to age groups showed a significant peak in the total number of MN in the third decade of life (age 21 to 30), followed by a gradual decrease.

melanoma was diagnosed was 52.5 years, and average melanoma thickness was 2.7 mm. The mean number of MN in all patients was 64.

Distribution according to age groups showed a significant peak in the total number of MN in the third decade of life (age 21 to 30), followed by a gradual decrease. Differences between the non-melanoma group and the melanoma group were significant for all decades between 21 and 80 years of age. Melanocytic nevi identified in the clinical examination as flat MN/Clark nevi constituted the most common MN subtype (91.6% of all nevi – 92.5% in the melanoma group and 91.3% in the non-melanoma group). Miescher nevi, found mostly in the head and neck area (45.5%), amounted to 5.8 % of all MN (5 % in the melanoma group, 6 % in the non-melanoma group). Unna nevi, found mostly on the torso (65.5 %), were the least common nevus subtype in both groups (2.4% in the melanoma group, 2.6 % in the non-melanoma group). The total number of MN was higher in the melanoma group [42].

Nevus spilus (spilus: “speckled”)

Nevus spilus is an MN characterized by a brown macule. The café-au-lait component (of very varying size) is usually present at birth while speckles develop during the first years of life and can represent various different types of MN.

These include Clark or combined MN, Spitz nevi, and rarely also blue nevi. Nevus spilus is therefore a combined MN. Its risk of malignant transformation is not clearly defined but is reported to be between 0.13 % and 0.2 %. There is one case report in the literature of a patient with multifocal melanomas within a nevus spilus occurring in late adult life [43].

A segmental nevus spilus may indicate the presence of RASopathy (a heterogeneous group of genetic diseases with the common denominator of a mutation in the RAS/mitogen activated protein kinase signaling pathway) [44]. Symptoms of RASopathy frequently involve the skin, cardiovascular system, skeleton, muscles, gastrointestinal tract, CNS, and eyes. Some syndromes present with typical craniofacial characteristics, others are associated with an increased

tumor risk. There are extensive clinical overlaps between the various disorders, such as phacomatosis pigmentokeratolica (Table 1) and Schimmelpenning-Feuerstein-Mims-Syndrom (therefore it's not mentioned separately in the table). These combine nevus spilus and nevus sebaceous [45, 46].

The underlying mutation in phacomatosis pigmentokeratolica (Table 1) is located in the *HRAS* gene. Sometimes this condition is associated with additional neurological symptoms such as epilepsy and deafness [47].

Congenital melanocytic nevi (CMN)

Congenital melanocytic nevi are medium brown to intensely dark brown MN, sometimes with proliferating nodules or increased hair (hairy nevus) and may affect entire body regions (bathing trunk nevus). Satellite nevi are solitary MN found in the vicinity of a CMN (Figure 7).

CMN are categorized according to their projected size (prognosis of their size in adulthood):

- small CMN: < 1.5 cm,
- medium-sized CMN: 1.5–10 cm,
- large CMN: 11–20 cm,
- melanocytic giant nevi: > 20 cm.

To calculate its adult size, the current size of the CMN is multiplied by a factor depending on its anatomical location. Congenital melanocytic nevi on the head will grow by about factor 1.7, on the lower limbs by factor 3.3, and on the torso by factor 2.8 [48].

Melanocytic giant nevi are further categorized into G1 (21–30 cm), G2 (31–40 cm), and G3 (> 40 cm). If a CMN has more than 50 satellite nevi, it is allocated to the next higher category [49].

If a CMN has more than 50 satellite nevi, it is allocated to the next higher category.



Figure 7 Congenital giant nevus (G3) in a 7-year-old girl: Dorsally, with distinct hairiness and satellite nevi on the lower extremity (a). Ventrally, with proliferating nodules suprapubic (b).

The earlier the somatic mutation occurs in embryonic development, the more intense the clinical presentation of the CMN is, and possibly leading to involvement of other organ systems.

In about one in 20 000 births, the infant is born with a CMN of more than 20 cm in diameter [50], usually associated with other, smaller CMN (satellite nevi). They are characterized by *NRAS* mutations.

CMN are permanent: they grow in proportion with the child, and they can frequently develop proliferation nodules which clinically may be difficult to differentiate from melanoma [51]. Histologically, melanocytes in CMN are located both in the dermis and the subcutaneous tissue, and sometimes in even deeper tissues. In many cases, they infiltrate the adnexal epithelia (hairs, sweat glands) as well as vessel and nerve structures. CMN are the result of post-zygotic mutation. Depending on when the mutation occurs, it may affect a multipotent precursor cell. The earlier the somatic mutation occurs in embryonic development, the more intense the clinical presentation of the CMN is, and possibly leading to involvement of other organ systems. Apart from CMN, patients may be affected by subtle endocrine dysfunctions and characteristic facial features [52, 53]. In 2012, Kinsler et al. proposed the term “CMN syndrome” for patients with extracutaneous symptoms. This appears more appropriate than “neurocutaneous melanosis”, since melanosis is only one aspect of the congenital neurological anomalies that may affect patients with CMN and have a significant impact on their prognosis [53]. Melanomas and extracutaneous symptoms are most likely to occur in patients whose CMN localize to the torso, have a final size of > 40 cm, and are associated with numerous satellite nevi [54]. Cerebral involvement is diagnosed via magnetic resonance imaging (MRI).

Congenital melanocytic nevi frequently present a challenge for affected children and their parents. The situation has two separate aspects which must be clearly differentiated when attending and counseling patients:

1. The health aspect: How high is the risk of melanoma as well as the risk of other, mainly neurological complications (epilepsy, cerebrospinal fluid congestions, developmental disorder)?
2. The cosmetic aspect, and the associated psychological burden. At this usually very early stage (infancy), the parents decide on the therapeutic approach for their child.

Counseling of patients with CMN and their families as to which surgical treatment goal can be realistically achieved at what point in time should be offered as early as possible in a specialized center.

Above a certain size of the CMN, or for special locations (such as the face), multidisciplinary cooperation is required to achieve optimum surgical treatment results [55].

Both superficial treatment approaches (such as dermabrasion and ablative laser) and deep interventions (serial excision with ‘power stretching’, flap reconstruction, or split-skin grafts) are available [56–58]. Several aspects must be considered and compared when choosing the most promising approach: Necessity of histological evaluation, pain and risk of infection, duration of hospital stay, cosmetic result, recurrence risk, and prevention of melanoma [56].

The risk of melanoma in CMN patients has been investigated and qualified several times in recent years. A systematic overview in 2006 analyzed a total of 14 studies on the epidemiology of malignant transformation in CMN [59]. The risk of malignant transformation stated in these studies varied from 0.05 % to 10.7 %, and significantly decreased with increasing study size. In about three-quarters of melanoma cases, the CMN had a diameter of > 40 cm. This literature search confirmed that patients whose CMN is > 40 cm in diameter are at increased risk of melanoma and that the melanoma can occur at a much younger age than is usual for this malignancy. It is assumed that even in giant nevi, the risk of malignant transformation is not more than about 3–5 % [59].

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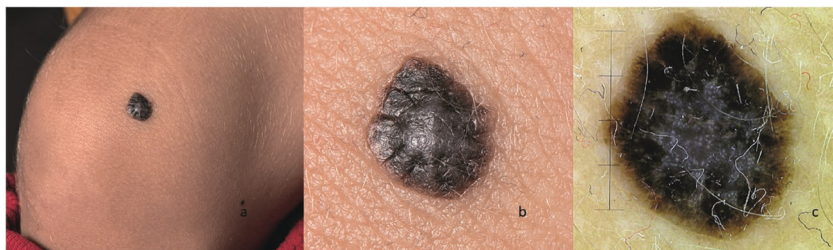


Figure 8 MN Reed, clinically highly pigmented raised papules (a); slightly papillomatous and with sharp edges (b); radial lines, dark brown or almost black, without structure in the center, starburst pattern – approximately 1.3 cm diameter (c).

Spitz nevi are mainly found in children, particularly on the face and limbs. They show a tendency towards rapid growth and may regress over time.

Spitz nevus and atypical spitzoid neoplasia (ASN)

Spitz nevi are named after Sophie Spitz, a pathologist born in 1910 in Nashville, Tennessee, who lived and worked in New York. In “*Melanoma of the childhood*”, published in 1948, she described a case series of children with characteristic MN. Based on histological criteria, these MN had been classified as melanomas, but the clinical course was completely benign in twelve out of thirteen cases [60]. We can therefore deduct that this series represented twelve cases of Spitz nevus and one case of spitzoid melanoma.

MN with “Spitz nevus-like characteristics” are described as ‘spitzoid’. The MN frequently present as skin-colored to orange-red papules to nodules of 0.5–2 cm in size. Spitz nevi are mainly found in children, particularly on the face and limbs. They show a tendency towards rapid growth and may regress over time.

There are various histological variants of Spitz nevus. One deeply pigmented and clinically distinctive variant is Reed nevus, which is comparatively common (Figure 8). Various authors actually consider this to be a separate entity of MN due to its distinct clinical and dermatoscopic presentation [61].

Histologically, Spitz nevi show a dominance of large epithelioid and/or spindle-shaped melanocytes; the melanocyte nests show a clear tendency towards confluence and sometimes also mitotic figures in the upper portions of the lesion. Kamino bodies, while rare, are a specific histological characteristic of Spitz nevi, representing the residue of apoptotic melanocytes along the dermo-epidermal junction zone.

The most frequently observed gene mutated in Spitz nevi is the *HRAS* gene. Cumulative data from several studies showed that 48 out of 293 Spitz nevi (16.4 %) contained *HRAS* mutations. *HRAS* is a member of the *RAS* gene family, which has two other members called *KRAS* and *NRAS* [62]. A *HRAS* mutation in MN appears to occur almost exclusively in Spitz nevi [63]. Cases presenting clear characteristics of melanoma are termed “spitzoid melanoma”.

According to some authors, atypical spitzoid neoplasia (ASN), also called “Spitz tumor of uncertain malignant potential” or STUMP, represent an intermediary lesion and thus a type of melanocytic lesion with histological characteristics that are difficult to differentiate from melanoma [64]. In some cases, sentinel lymph node biopsy was adopted as an additional diagnostic procedure for better reassurance patient management [65].

Although sentinel lymph nodes of patients with atypical Spitz tumors frequently contain melanocyte nests, the prognosis for these patients is markedly better than for patients with melanoma and positive sentinel lymph node biopsies [66].

No prognostic benefit of sentinel lymph node biopsy was shown for patients with atypical Spitz tumors

Wiesner nevus

Wiesner nevus is a spitzoid MN characterized by *BRAF* mutation combined with biallelic *BAP1* loss.

Wiesner et al. described MN with autosomal-dominant heredity in two unrelated families that are clinically, histopathologically, and genetically different from other acquired MN [67] and thus are indicator for the “tumor predisposition syndrome”.

Wiesner nevus is a spitzoid MN characterized by *BRAF* mutation combined with biallelic *BAP1* loss [68].

Germ line mutations in the BRCA1-associated protein 1 (*BAP1*) are associated with various neoplasms (breast cancer, thyroid cancer, urothelial carcinoma, neuroendocrine carcinoma, and others) including *BAP1*-inactivated melanocytic tumors (BIMT) [69]. *BAP1*-inactivated melanocytic tumors are classically described as melanocytic proliferations with *BAP1*-deficient large epithelioid melanocytes that exhibit various degrees of cytological anomalies.

In families with germ line mutations in the BRCA1-associated protein 1 (*BAP1*), an increased incidence of melanomas, including uveal melanomas, was observed.

This heterogeneous group of MN shows histological characteristics that may occur in both Spitz nevi and melanomas [63]. From the second decade of life onwards, affected family members will gradually develop skin-colored to reddish-brown, dome-shaped to pedunculated, clearly circumscribed papules with an average size of 5 mm. The number of MN per patient varies greatly from five to more than 50. The cytological characteristics of some cells are similar to Spitz nevi, however characteristic features seen frequently in Spitz nevi are lacking (such as epidermal hyperplasia, hypergranulosis, Kamino bodies, fissures around melanocytic nests, and spindle-shaped melanocytes). In addition, 37 out of 42 tumors (88 %) in the families carried *BRAF* mutations which are not usually seen in Spitz nevi [68, 70]. In families with germ line mutations in the BRCA1-associated protein 1 (*BAP1*), an increased incidence of melanomas, including uveal melanomas, was observed. *BAP1*-inactivated melanocytic tumors may serve as early markers for the inherited “tumor predisposition syndrome” [71, 72]. If a patient shows a papule that presents as pink to tan, with structureless areas and peripheral irregular dots/clods or networks in dermatoscopy, BIMT should be suspected [72].

Recurrent MN (persisting MN, pseudomelanoma)

In the dermatoscopic investigation of recurrent MN, pigmentation extending beyond the scar constitutes the strongest indication of melanoma.

Without sufficient information about previous surgery, incomplete excision of a pigmented lesion always constitutes a pitfall for the pathologist. Scar contractures with newly developed melanocyte nests show an altered structure and configuration, they tend to coalesce and may be scattered irregularly into deeper layers. In 2014, a retrospective analysis was published in *JAMA Dermatology*, analyzing features of 98 recurrent MN and 62 recurrent melanomas and developing criteria for more accurate evaluation of dermatoscopic patterns and colors in correlation with the histopathological findings [73].

For a final interpretation, several factors must be considered: patient’s age, anatomical location, time until recurrence, growth pattern, and if available the histopathological findings of the previous excision. Other dermatoscopic criteria such as radial lines, symmetry, and a centrifugal growth pattern are significantly more common in recurrent MN.

In contrast, circles and off-center peripheral hyperpigmentation were significantly more common in recurrent melanoma. Patients with recurrent melanoma were also significantly older than patients with recurrent MN (mean age 63.1 years as opposed to 30.2 years) [73]. These criteria offer valuable assistance in the clinical evaluation of recurrent MN and melanoma, respectively.

Dysplastic MN (DMN)

The histological diagnosis “dysplastic nevus” is the subject of great controversy and is not used in a uniform manner. Thus, the percentage of DMN varies significantly depending on who analyzed the sample, and some pathologists will not use the term at all. Basically, the dilemma is the same as with blue nevi with atypical features (atypical cellular blue nevi, ACBN) or Spitz tumors of uncertain malignant potential (STUMP).

Unfortunately, there is hardly any correlation between clinically atypical nevi and those with histological characteristics of dysplasia.

Some authors prefer to use “atypical nevus” in the clinical description and use “dysplastic nevus” only for the histological diagnosis. Unfortunately, there is hardly any correlation between clinically atypical nevi and those with histological characteristics of dysplasia [73].

Clinically, DMN are melanocytic lesions that show features of malignancy according to the ABCDE rule (A: asymmetry, B: border irregularity, C: color variation, D: diameter, E: elevation).

Melanocytic nevus and melanoma

Melanocytic nevi and melanomas share common driver mutations.

Melanocytic nevi are benign clonal proliferations of melanocytes possessing generally heterogeneous clinical and molecular properties. Melanocytic nevi and melanomas share common driver mutations. It is assumed that after the initial driver mutation, a senescence program stops the growth of MN. Malignant progression only occurs in the presence of additional oncogenic changes (“second hit”), such as mutations in the *TP53* gene. This gene encodes p53 which induces dysfunction of DNA repair mechanisms and is responsible for cell arrest and apoptosis [63]. The frequency and dominance of *BRAF* mutations also depends on the histopathological subtype and the stage of development of an MN [74]. MN frequently regress with increasing age. Due to age-related involution and apoptosis of melanocytes, the *BRAF* mutation in MN is lost. This also concurs with the observation that *BRAF* mutations are more frequently found in melanomas from younger patients [75].

Due to age-related involution and apoptosis of melanocytes, the *BRAF* mutation in MN is lost.

The presence of multiple MN in the context of genetic syndromes (Table 1) illustrates the multigenetic conditions in the development of MN and melanomas [63].

The presence of multiple MN in the context of genetic syndromes illustrates the multigenetic conditions in the development of MN and melanomas.

Individual syndromes and genetic characteristics associated with an increased incidence of melanoma are well-known. In about 25–50 % of cases, familial atypical multiple mole melanoma syndrome (FAMMM, also called BK mole syndrome) is caused by mutations in the *CDKN2A* gene, which encodes protein p16, one of the control proteins in the cell cycle. Thus the risk of malignomas developing in other organs is also increased (pancreas, brain [melanoma-astrocytoma syndrome], esophagus, stomach, or bladder) [76]. Apart from *CDKN2A* and *CDK4*, germ line variants in *MC1R*, *TERT*, *ACD*, *POT1*, *TERF2IP*, *MITE*, and *BAP1* were included in the list of genes that carry mutations predisposing for melanoma [77]. These may be direct oncogenic mutations, or proteins responsible for DNA repair (such as in Xeroderma pigmentosum) and telomere stability as well as processing (*POT1*, *ACD*, and *TERF2IP*), or a G-protein-bound receptor regulating pigmentation of skin and hairs, as in *MC1R* (melanocortin receptor 1). In cases of early occurrence and/or familial clusters of malignomas, a tumor syndrome should be considered. Patients with invasive melanoma should be offered genetic analysis in case of 3 or more and/or a positive family history (two relatives in the direct line) of melanoma and/or pancreatic carcinoma [77, 78].

In cases of early occurrence and/or familial clusters of malignomas, a tumor syndrome should be considered. Patients with invasive melanoma should be offered genetic analysis in case of 3 or more and/or a positive family history (two relatives in the direct line) of melanoma and/or pancreatic carcinoma.

For patients from such a “high-risk population”, total body photography with sequential digital dermatoscopy is a useful tool for early diagnosis of melanoma [79].

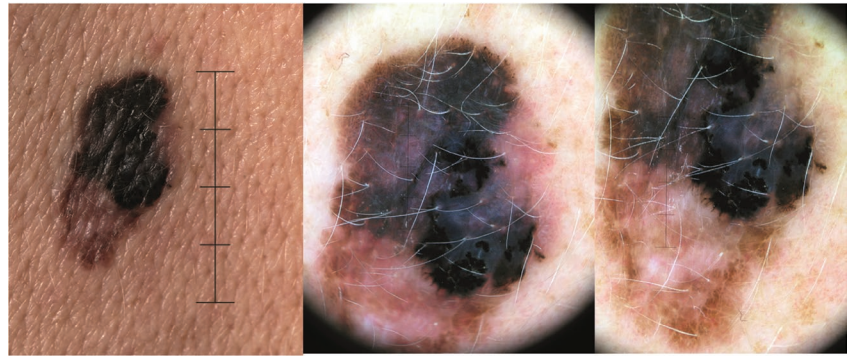


Figure 9 Pictures described from left to right: Melanoma (invasive, tumor thickness 0.3 mm, Clark Level III, size 3,5 × 2 cm), developed on a pre-existing MN (in the lower third) clinically asymmetrical and inhomogeneous plaque with several colors (from skin-colored to black) and blurred borders. Dermatoscopically: several patterns, asymmetrically arranged, several colors, white and gray veils, pseudopodia and marginal dots.

If medical history, clinical presentation, and dermatoscopy do not offer any clear indication of malignancy so it is impossible to confirm that the tumor is benign at the time of examination, follow-up observation over a period of two to three months can be performed as an alternative to immediate excision of the lesion.

Comparing the lesion with other MN in the same patient is necessary to detect deviations from the patient's basic patterns and increases the success rate in the early detection of melanomas (comparative approach).

About 30 % of melanomas develop directly from MN [80] (Figure 9). However, the overwhelming majority of MN caused by *BRAF*-V600E-activating mutations never progress to melanoma.

If medical history, clinical presentation, and dermatoscopy do not offer any clear indication of malignancy so it is impossible to confirm that the tumor is benign at the time of examination, follow-up observation over a period of two to three months can be performed as an alternative to immediate excision of the lesion [81, 82].

Mackie et al. have succinctly presented the positive association of melanoma incidences in a Scottish population, with the total number of clinically benign pigmented nevi of more than 2 mm in diameter, tendency to freckle, number of clinically atypical nevi, and a history of severe sunburns [83, 84].

Dermatoscopy

Dermatoscopy is an effective standard procedure for the diagnostics and early detection of melanoma. Choosing the most eye catching pigmented lesion is essential for the diagnostic accuracy of the dermatoscopic investigation (“ugly duckling”). Comparing the lesion with other MN in the same patient is necessary to detect deviations from the patient's basic patterns and increases the success rate in the early detection of melanomas (comparative approach) [83].

Dermatoscopic diagnosis involves a description of the visible findings (size, color, pattern, composition). In collision of pigmented skin lesions, these different aspects should be studied within the lesion (single component analysis), and if necessary, a division into quadrants should be made [85]. From a collection of five basic elements in the descriptive terminology (lines, circles, pseudopods, clods, and dots), a pattern emerges. A pattern have to include at least 25 % of the lesion [86]. There are also line patterns (network/reticular, branched, angulated, parallel, and curved) and vascular patterns. In the metaphoric, more pictorial terminology, the choice of terms is larger but not necessarily more specific. The terms from the two different terminologies are frequently not strictly separated and may complement each other [86].

Structures such as milia-like pseudocysts, comedo-like openings, blue-gray homogeneous areas, peppering white-blue regression structures, and light-colored

Table 2 Dermatoscopic criteria of different MN, melanoma and lentigo senilis/solaris.

Pigmented lesion	Dermatoscopic criteria typical for this lesion
Blue nevus	Structureless, blue, blue-white veil
CMN	Central dots and clods between reticular lines, tan to dark brown
Lentigo senilis/solaris*	Interruption of parallel, homogeneously brown pigmentation by hair follicles, structureless and/or dots, lack of gray or dark brown structures
Melanocytic nevus	Skin-colored to dark brown pigmentation, different dermatoscopic criteria depending on the type: <ul style="list-style-type: none"> – <i>junctional MN</i>: reticular lines, dots, and clods in the marginal area – <i>compound MN</i>: reticular lines, structureless pattern – <i>dermal MN</i>: polygonal clods, structureless pattern
Melanocytoses	Blue-gray/slate blue and structureless
Recurrent MN	Radial lines, symmetry, and centrifugal growth pattern
Reed nevus	Peripheral pseudopodia or radial lines, dark brown or almost black, structureless in the center, starburst pattern
Spitz nevus	Brown or skin-colored clods, reticular white/hypopigmented lines
Wiesner nevus	Structureless pink to tan with irregular dots and clods and eccentric pattern, peripheral vessels
Melanoma	Several patterns, asymmetric pattern, several colors, white or gray veils, thick reticular lines, pseudopodia
Melanoma in situ/Lentigo maligna	Non-homogeneous pigmentation, slate gray-bluish color, rhomboidal pattern, asymmetrical follicle ostia, lack of pseudo-horn cysts
Recurrent melanoma	Pigmentation beyond the scar, circles and eccentric hyperpigmentation in the periphery

Variants exist in each case and a complete list cannot be given here (see further literature on dermatoscopy of pigmented lesions). Vascular patterns are not as specific as pigment patterns and not discussed here. Note that the differentiation criteria lose clarity due to frequent collisions of different MN as well as lentigo senilis with melanoma in situ, type lentigo maligna. The ABCD rule (asymmetry, border, color, dermatoscopic structure) is an additional helpful algorithm for differentiating MN and melanoma.

*The criteria of lentigo senilis/solaris is mentioned here due to the important differential diagnostic aspect.

areas are all easier to detect by using polarized dermatoscopes. To combine the advantages of both types of dermatoscopes, it is advisable to use a dermatoscope with dual light sources (non-polarized and polarized [87]).

A summary of the most important dermatoscopic criteria for MN, melanoma, and their differential diagnoses is provided in Table 2.

Summary

Clinical differentiation of MN is a daily challenge to health care providers. The standardized diagnosis is dermatoscopy, whole-body photography and histopathological analysis. This article aims to shed light on a complex topic of different MN and offer a comprehensive guide to a heterogenic field. Various clinical aspects can provide indications of possible underlying diseases and, if necessary, lead the patient to targeted diagnostics and therapy. Knowledge about the development and genetic background of MN has multiplied in recent years. The article aims to provide an overview of the most common and clinically relevant types of MN and their characteristics.

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Correspondence to

Dr. med. Nina Frischhut
Abteilung für Dermatologie,
Venerologie und Allergologie
Medizinische Universitätsklinik
Innsbruck

Anichstraße 35
6020 Innsbruck, Österreich

E-mail: nina.frischhut@tirol-
kliniken.at

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CME Questions/Lernerfolgskontrolle

1. Welche Aussage ist richtig?

- a) Melanozyten kommen in allen Geweben des menschlichen Organismus vor.
- b) Melanozyten kommen nur in Haut und Haarfollikeln vor.
- c) Melanozyten kommen in der Uvea des Auges, im Innenohr und in den Leptomeningen des Gehirns vor.
- d) Melanozyten kommen ebenso in ossären Strukturen vor.
- e) Melanozyten wandern innerhalb des ersten Lebensjahres in die Haut ein.

2. Welche Aussage ist richtig?

- a) Durch die natürliche Melaninpigmentierung wird ein Eigenschutz erreicht, der einem Sonnenschutzfaktor von ungefähr 8 entspricht.
- b) Der Pigmenttransfer in der Epidermis erfolgt bis in das Stratum basale.
- c) Es entscheidet die Anzahl der Melanozyten über die Intensität des Hautkolorits.
- d) Die Aktivität der Pigmentzellen entscheidet über die Intensität des Hautkolorits.
- e) Die Dichte der Melanozyten an der Junktionszone ist überall an der Haut dieselbe.

3. Welche Aussage ist richtig?

- a) Grundsätzlich sind MN an „speziellen“ Lokalisationen ein Risikomarker für Malignität.
- b) Erworbene und klassisch kongenitale MN tragen dieselben genetischen Mutationen.
- c) Die Unterschiede zwischen erworbenen und kongenitalen MN können in den unterschiedlichen Mutationen im MAPK-Signalweg nachvollzogen werden.
- d) Mittels histopathologischer Kriterien kann man erworbene und kongenitale MN zuverlässig voneinander unterscheiden.

- e) *BRAF*-Mutationen sind häufig in kongenitalen MN nachweisbar.

4. Welche Aussage ist richtig?

- a) Kongenitale dermale Melanozytosen (Mongolenflecke) werden zumeist bei Neugeborenen aus dem europäischen Raum beobachtet.
- b) Die schieferblaue Farbgebung der Melanozytosen kommt durch die sehr oberflächlich gelegenen Melanozyten zustande.
- c) Kongenitale dermale Melanozytosen (Mongolenflecke) bleiben klinisch praktisch immer persistierend.
- d) Beim Nävus Ota ist am häufigsten das Versorgungsgebiet des Nervus brachialis beteiligt.
- e) Die schieferblaue Farbe der Melanozytosen entsteht durch ein physikalisches Phänomen, welches als Tyndall-Effekt bezeichnet wird.

5. Welche Aussage ist richtig?

- a) Angeborene MN und blaue MN beherbergen häufig *BRAF*-Mutationen.
- b) Spitz- und atypische Spitz-Tumoren weisen häufig *BRAF*-Mutationen auf.
- c) *GNAQ*-Mutationen in MN sind zusammen mit p53 in der Entstehung des Melanoms ein wesentlicher Faktor.
- d) In Melanomen junger Patienten werden seltener *BRAF*-Mutation nachgewiesen als bei Patienten im hohen Alter.
- e) Ungefähr 30 % der Melanome stammen von MN.

6. Welche Aussage ist richtig?

- a) Das familiäre atypische multiple Muttermal- und Melanomsyndrom (FAMMM) ist in circa 25–50 % der Fälle auf Mutationen im *CDK-N2A*-Gen zurückzuführen.

- b) Das familiäre atypische multiple Muttermal- und Melanomsyndrom (FAMMM) prädisponiert ausschließlich für Melanome.
- c) Patienten mit einer Mutation im *CDKN2A*-Gen entwickeln auch häufig Lymphome.
- d) Die Anzahl schwerer Sonnenbrände ist kein Risikofaktor für Melanome.
- e) Die überwiegende Mehrheit der MN, die sich als Folge von *BRAF*-V600E-aktivierenden Mutationen bilden, schreiten zum Melanom fort.

7. Welche Aussage ist richtig?

- a) Kongenitale MN haben für sich genommen ein erhöhtes Entartungsrisiko.
- b) Kongenitale MN entwickeln sich zumeist innerhalb der ersten Lebensmonate.
- c) Kongenitale MN werden abhängig von ihrer Größe in zwei Kategorien eingeteilt.
- d) Das Vorliegen von über 50 Satelliten Nävi bei KMN (G3) ist von prognostischer Bedeutung in Bezug auf das Vorliegen von Melanomen sowie neurologischen Komplikationen.
- e) Kongenitale MN weisen zumeist Mutationen in *BRAF* auf.

8. Welche Aussage ist richtig?

- a) Häufig präsentieren sich die Spitz Nävi als bläulich schimmernde Papel.
- b) Kamino-Körperchen sind ein häufiges histologisches Merkmal für Spitz Nävi.
- c) Sophie Spitz beschrieb den Spitz Nävus als „melanoma of the childhood“
- d) Eine Sentinel-Lymphknoten Biopsie ist von prognostischer Bedeutung für Patienten mit atypischen Spitz-Tumoren.

e) Sophie Spitz beschrieb diese rasch wachsenden MN als *Spitz tumor of uncertain malignant potential*.

9. Welche Aussage ist richtig?

- a) In der dermatoskopischen Analyse eines Rezidivs nach Entfernung einer pigmentierten Läsion ist eine Pigmentierung jenseits der Narbe der stärkste Hinweis auf ein Melanom.
- b) Wiesner beschrieb eine Gruppe von melanocytic Nävi, welche sich allein auf Grund der klinischen Präsentation eindeutig von anderen MN unterscheiden lassen.
- c) Bei Patienten, die einer „Risikopopulation“ angehören, sollten MN so rasch wie möglich exzidiert werden.

d) Die Ganzkörperfotografie und sequenzielle digitale Dermatoskopie sind ein unzureichendes Werkzeug, um Melanome früh zu erkennen.

e) Das Konzept des dysplastischen Nävus ist ein wohl etabliertes und klar definiertes.

10. Welche Aussage ist richtig?

- a) In der Dermatoskopie ist die metaphorische/bildliche Sprache der deskriptiven Terminologie deutlich überlegen.
- b) Unpolarisierte Dermatoskope sind die besten in der Diagnostik pigmentierter Läsionen.
- c) Die Musteranalyse ist in pigmentierten Läsionen spezifischer als die Gefäßanalyse.

d) Periphere Pseudopodien oder radiale Linien sind ein spezifisches dermatoskopisches Merkmal für den blauen MN.

e) Die Grundelemente in der deskriptiven Terminologie sind auf zwölf beschränkt.

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 30. Juni 2022. Die richtige Lösung zum Thema „Alopecia areata – Current understanding and management“ in Heft 1 (Januar 2022) ist: 1c, 2d, 3c, 4e, 5e, 6a, 7d, 8c, 9a, 10c

Bitte verwenden Sie für Ihre Einsendung das aktuelle Formblatt auf der folgenden Seite oder aber geben Sie Ihre Lösung online unter <http://jddg.akademie-dda.de> ein.
