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The Morphologic Universe of Melanocytic Nevi

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Different types of nevi do exist in relation to their epidemiology, morphology, evolution, and associated melanoma risk. The introduction of dermoscopy opened a new dimension of the morphologic universe of nevi and allowed clinicians to observe colors and structures within nevi that are otherwise not visible to the unaided eye. Because most of these colors and structures correspond to well-defined histopathologic correlates, dermoscopy enables clinicians to date to more precisely predict the histopathology diagnosis and thereby improve on their clinical diagnostic accuracy. Besides the diagnostic impact, the *in vivo* observation of thousands of nevi using dermoscopy and digital dermoscopic follow-up has opened new understanding about the evolution of nevi and factors influencing the nevus pattern. In consequence, a new nevus classification has been proposed, subdividing nevi into 7 categories, which are as follows: (1) globular/cobblestone nevi, (2) reticular nevi, (3) starburst nevi, (4) homogeneous blue nevi, (5) nevi on special body sites, (6) nevi with special features, and (7) and unclassifiable melanocytic proliferations. This article provides an overview on the morphologic classification of nevi and the factors influencing the nevus pattern.

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The term “nevus family” indicates a heterogeneous group of benign melanocytic proliferations that differ in epidemiology, morphology, evolution, and associated melanoma risk. Based on the latter, currently 2 main categories, namely congenital and acquired nevi, are distinguished. The former are considered to have a certain risk for malignant transformation, which seems to increase linearly with the clinical size and is definite only for large congenital nevi (>20 cm).¹ In contrast, acquired nevi, particularly when multiple or clinically atypical, are indicators for an increased risk for *de novo* development of melanoma.² Because in the past, with the exception of large (>20 cm) and intermediate (>15 mm) congenital nevi, the clinical criteria were insufficient to distinguish between various types of nevi; our current classification, diagnosis, and understanding of evolution of nevi are largely based on histopathology.

This mixture of few clinical and mostly histopathologic criteria, particularly for diagnosing the spectrum of small nevi (<15 mm in size), has been proven to be problematic in

the daily routine. This is because clinicians are confronted with histopathologic diagnosis that allows only limited conclusions about the clinical appearance of the nevus. Equally, pathologists sometimes face difficulties in differentiating small congenital nevi from acquired nevi of the compound or dermal type if a reliable history is missing.³ As a consequence, there is considerable confusion in terminology and classification of nevi, leading to the introduction of “congenital-like” nevi or nevi with “congenital-like” features.⁴ The problem of this classification is perhaps best demonstrated by a practical example: It is virtually impossible for a clinician to understand the clinical aspect of a nevus defined as “a small congenital-like nevus of the compound type,” which at the same time expresses the pathologist’s uncertainty to classify the nevus accurately into the spectrum of congenital or acquired nevi. Although histopathology at the current stage remains the “gold” standard in the diagnosis of melanocytic proliferations, it must be further acknowledged that histopathologic studies commonly rely on a significant selection bias, despite allowing the view just on a moment in the life of nevi. Thus, histopathology does not permit conclusions about the epidemiology or dynamics in the evolution of nevi. The introduction of dermoscopy opened a new morphologic dimension and allowed clinicians to observe colors and structures within nevi that are otherwise not visible to the unaided eye. Because most of these colors and structures correspond to well-defined histopathologic correlates, it does not come as a

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surprise that dermoscopy enables clinicians to more precisely predict the histopathology diagnosis and thereby improve on their clinical diagnostic accuracy.^{5,6} Besides the diagnostic impact, the *in vivo* observation of thousands of nevi using dermoscopy and digital dermoscopic follow-up has allowed a new understanding about the epidemiology, morphology, and evolution of nevi and led recently to a new proposal of nevus classification.⁷

Dermoscopic Classification of Nevi

The most significant difference between the new and traditional classification of nevi is that the new classification no longer classifies small nevi into “congenital” or “acquired.” Instead, nevi are summarized into 4 main categories based on common epidemiologic and morphologic features, irrespective of their history. These 4 main features are the globular, reticular, starburst, and homogeneous blue pattern, of which each corresponds to specific histopathologic substrates⁵ (Table 1).

More importantly, in this simplified classification, small “congenital” nevi, “congenital-like” nevi, and “acquired” nevi of the compound and dermal type are considered together 1 category of “globular” nevi based on their common dermoscopic-histopathologic features, namely, variably large globules corresponding to predominantly dermal nests of melanocytes (Fig. 1). In light of the remarkable clinical and histopathologic difficulties to reliably differentiate small “true congenital” nevi from “congenital-like” or “acquired” nevi of the compound and dermal type, the advantage of this new classification is obvious.

Reticular pattern correspond either to small junctional nests of melanocytes or to single melanocytes at the basal layer (ie, junctional or lentiginous nevi) (Fig. 2), whereas the group of “starburst” nevi summarizes pigmented Spitz/Reed nevi (SN/RN) in 1 group based on their striking dermoscopic features of starburst pattern (ie, regular peripheral streaks)⁸ (Fig. 3). The fourth category includes blue nevi typified dermoscopically by homogenous structureless blue pigmentation in the absence of any additional dermoscopic structures⁹ (Fig. 4). The previously introduced homogeneous brown

Table 1 Dermoscopic Structures, Colors, and Their Pathologic Correlates Associated with Melanocytic Skin Lesions

Pattern	Description	Pathologic Correlate	Diagnostic Significance
Reticular network	Network of brownish interconnected lines over a background of tan diffuse pigmentation	Regularly elongated, notably pigmented rete ridges with increased melanocytes in the basal layer and nests of melanocytes at the tips of the rete ridges	Junctional nevus Lentiginous nevus
Globular cobblestone	Numerous, variously sized, round to oval structures with various shades of brown and gray-black × large, closely aggregated, somehow angulated globule-like structures resembling a cobblestone	Variable large nests of melanocytes at the dermo-epidermal junction or in the papillary dermis	Congenital nevus Compound nevus Dermal nevus
Starburst	Bulbous and often kinked or fingerlike projections seen at the edge of a lesion. They may arise from network structures but more commonly do not. They range in color from tan to black.	Well-demarcated junctional nests of melanocytes The longitudinal shape of the streaks leads one to assume that the junctional melanocytic nests form strand-like structures parallel to the skin surface	Pigmented Spitz nevus Reed nevus
Homogeneous blue	Structureless blue pigmentation in the absence of pigment network or other distinctive local features	Diffuse infiltrate of dendritic melanocytes and melanophages in the papillary and/or reticular dermis	Blue nevus
Color	Pathologic Correlate	Anatomic Level in the Skin	Diagnostic Significance
Black	Melanin in keratinocytes or melanocytes	Stratum corneum	Nevus with epidermal involvement
Brown	Melanin in keratinocytes or melanocytes	Basal layer or upper dermis	Nevus with epidermal involvement
Gray	Melanin in either keratinocytes, melanocytes, or melanophages	Upper dermis	Nevus with epidermal and dermal involvement
Blue	Melanin either free or within melanocytes or within melanophages	Upper to deep dermis	Nevus with dermal involvement

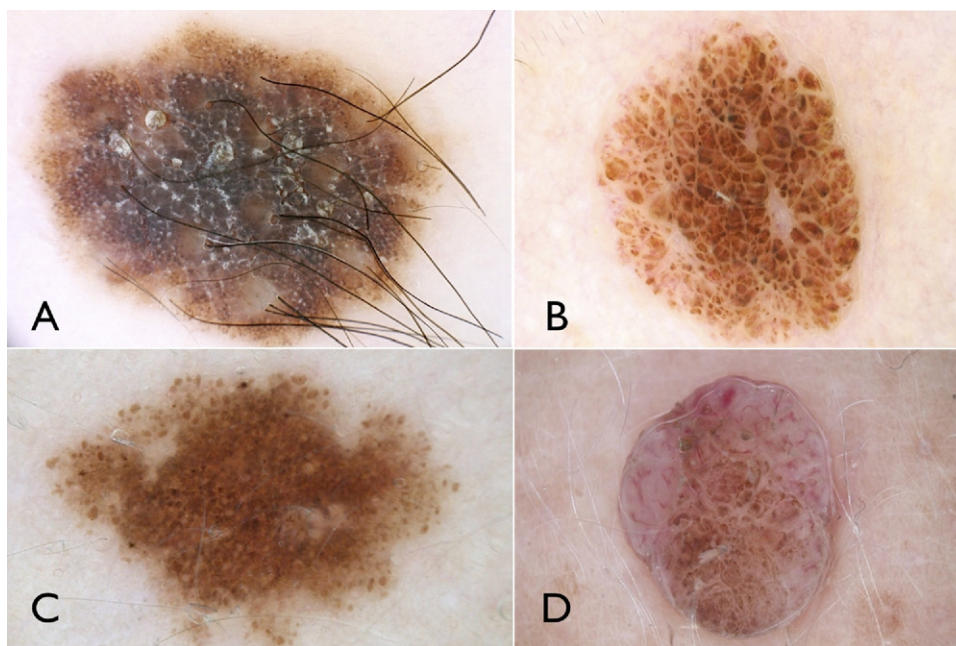


Figure 1 Dermoscopy images of (A) small congenital nevus with a documented history of being present since birth, (B) congenital-like nevus with a history of development when the patient was 6 years old, (C) compound nevus in a 30-year-old patient, and (D) dermal nevus in a 50-year-old patient. All types are dermoscopically characterized by a globular/cobblestone pattern underlining a common histogenetic background (original magnification, $\times 10$).

pattern is not considered an own category because recent studies demonstrated that it reveals overlapping histopathologic correlations with the globular and reticular pattern.¹⁰ Furthermore, it has yet to be determined whether nevi with a mixed pattern (reticular and globular or reticular and homogeneous) represent a specific entity or belong to the group of globular or reticular nevi.

Besides these 4 main morphologic categories, the dermoscopic classification further distinguishes between 3 subgroups, which are nevi of special body sites (including facial, acral, subungual, and mucosal nevi), nevi with special features (halo nevus, Meyerson nevus, traumatized targetoid hemosiderotic nevus, cockade nevus, combined nevus, and recurrent nevus), and unclassifiable melanocytic proliferations.

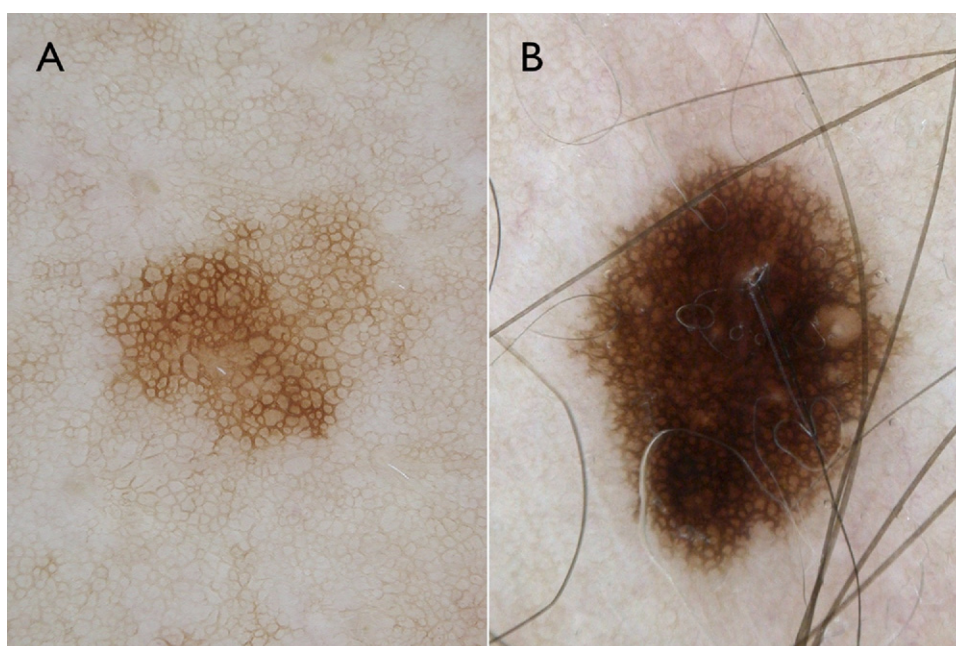


Figure 2 Lentiginous (A) and junctional nevi (B) are dermoscopically characterized by a reticular pattern (original magnification, $\times 10$).



Figure 3 Dermoscopy of starburst nevus showing regular streaks at the periphery (original magnification, $\times 10$).

Nevi located on the face, palms and soles, subungual, or mucosal sites exhibit peculiar dermoscopic features that are related to the specific anatomic structure of the skin of these locations. Such nevi are therefore also referred to as nevi of special body sites and show a pseudonetwork pattern, parallel-furrow pattern, regular band-like pattern, and often mixed-globular pattern, respectively^{6,7} (Table 2).

Notably, the nevi with special features and unclassifiable melanocytic proliferations are not considered as separate entities as melanocytic lesions from all previous categories may fall into these categories.

Nevi with special features differ from the 4 main categories inasmuch as they exhibit peculiar clinical features (white, red-eczematous, or purple halo and/or targetoid appearance) or a special clinical history (biopsy or trauma)^{11,12} (Table 2).

Importantly, lesions from all previous categories may show conflicting diagnostic criteria from a clinico-dermoscopic and/or a histopathologic point of view, which are encountered in the group of unclassifiable melanocytic proliferations (synonyms: atypical melanocytic proliferations or gray zone lesions). Examples for such gray zone lesions are atypical Spitz tumors, melanocytic tumors with extensive regression,

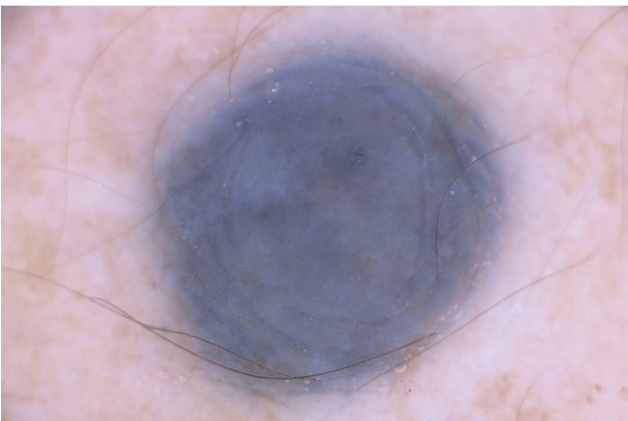


Figure 4 Dermoscopy of blue nevus shows homogeneous blue pattern in the absence of any discernible morphologic patterns (original magnification, $\times 10$).

Table 2 Dermoscopic Pattern of Nevi Located on Special Body Sites and Nevi with Special Features

Nevi at Special Body Sites	Dermoscopy
Acral	Parallel pigmented lines within the furrows or perpendicular to the furrows
Nail	Small pigmented band composed by parallel lines of uniform color and width
Genital	Mixed pattern composed of prominent network structures and/or gray-blue globules and/or homogeneous blue-gray pigmentation
Face	Pseudo-network pattern intermingled by hairs
Nevi with Special Features	Dermoscopy
Halo nevus	The central nevus often exhibits a globular or homogeneous pattern, which is surrounded by a variable rim of a white scar-like depigmentation. In fully regressed halo nevi, the central nevus component lacking entirely and a reddish papule eventually revealing visible vessels from the dermal vascular plexus may be seen
Meyerson nevus	The central nevus component appears often blurred and as an unspecific pattern due to overlying superficial serocrusts
Irritated, hemosiderotic targetoid nevus	The central nevus component shows typical features of globular nevus with vascular-hemorrhagic (red to purple or black) changes superimposed on the nevus. Typically the purple ecchymotic rim surrounds the nevus
Cockade nevus	This nevus shows a central pigmented papular component of gray-brown color surrounded by a depigmented inner rim and outer rim composed of globules or network
Combined nevus	Its stereotypical appearance is that of a central homogeneous blue structureless area surrounded by a globular or reticular pattern
Recurrent nevus	Round scar exhibiting a central irregular pattern composed of atypical network, streaks, and globules

severely dysplastic nevi, melanocytic tumors of uncertain malignant potential, or superficial atypical melanocytic proliferation of uncertain significance.

Last, the new dermoscopic classification is designed for the management and diagnosis of the most common types of

nevi, which are small nevi (<15 mm in size), but does not include large- to intermediate-sized (ie, nevi larger than 15 mm or more) congenital melanocytic nevi. The latter are considered to represent “true congenital nevi” as also confirmed in most cases by the patient’s history. For these lesions, dermoscopy is only of limited diagnostic value and clinical size or history of changes remain the most important criteria for their diagnosis and management.

The Concept of the Predominant Nevus Pattern

It has been shown that most individuals with multiple or clinically atypical nevi harbor a predominant nevus pattern among all their nevi (defined as the pattern seen in more than 30% of all nevi).^{10,13} The diagnosis of the predominant nevus pattern relies not only on the prevailing structural morphology of the nevi, but additionally considers colors and pigment distribution. Colors in dermoscopy are quite important because they allow estimations about the localization of pigmented cells in the different compartments of the skin.⁵ Black and brown represent pigmentation in the epidermis or at the dermo-epidermal junction. Accordingly, they are mostly seen in nevi with significant epidermal components. Gray or blue represents pigmentation in the upper or mid dermis and are therefore observable in nevi with dermal involvement (Table 2). With regard to the pigment distribution, the following 6 types can be distinguished: uniform, multifocal, central (central area of hyper- or hypopigmentation), or eccentric (eccentric foci of hyper- or hypopigmentation) pigment distribution.^{10,14}

The importance of identifying the predominant nevus type in the management of persons with multiple nevi has been repeatedly addressed in the literature as it aids the identification of “atypical” lesions with deviant patterns, which may require closer examination.¹⁰ There is mounting evidence that both the prevalent nevus pattern and the patterns of single nevi are influenced by age, skin type, history of melanoma, ultraviolet (UV) exposure, and pregnancy as well as reveal time-related dynamic changes.¹⁵

Factors Influencing the Nevus Pattern

Age

The prevalent nevus pattern is significantly influenced by the age of a person. In prepubertal children most nevi exhibit a globular pattern, while nevi developing during puberty (until the second decade of life) often reveal a central reticular-homogeneous pattern surrounded by rim of small brown globules (sign of nevus growth).¹⁶⁻¹⁸ In contrast, nevi with reticular or mixed patterns are the most frequent types in adults, although a few globular nevi (typically located on the chest or head/neck areas) can be seen throughout all ages. Besides the age-related morphologic pattern, epidemiologic studies suggest that the number of nevi steadily increase from puberty until midlife (fourth to fifth decade of life), while later a decline in number of nevi can be observed.^{19,20}

Age also plays a critical role in the dermoscopic or histopathologic diagnosis of SN/RN and nevi on special body sites. It is well known that the former are rare after the third decade of life.²¹ Similarly, subungual lesions or mucosal nevi are much more common in children or young adults but rarely observed after the fifth decade of life.²²⁻²⁴ The new development of a pigmented melanocytic lesion after this age should therefore always raise the suspect for melanoma. Similarly, a facial nevus with a pseudo network pattern and a histopathologic diagnosis of junctional nevus after the fifth decade of life should be carefully reviewed to rule out lentigo maligna melanoma in its early phase.²⁵

Skin Type

The prevalent nevus pattern in an individual is also influenced by the individuals’ skin photo type (ST).²⁶ Individuals with ST I typically harbor nevi with a light-brown color, reticular pattern (which is however sometimes less evident or visible) and a central hypopigmentation, while individuals with a ST IV mostly exhibit nevi with a dark-brown color reticular pattern and a central hyperpigmentation (so-called black or hypermelanotic nevi) (Fig. 5). The latter corresponds to pigmented parakeratosis and appears as central

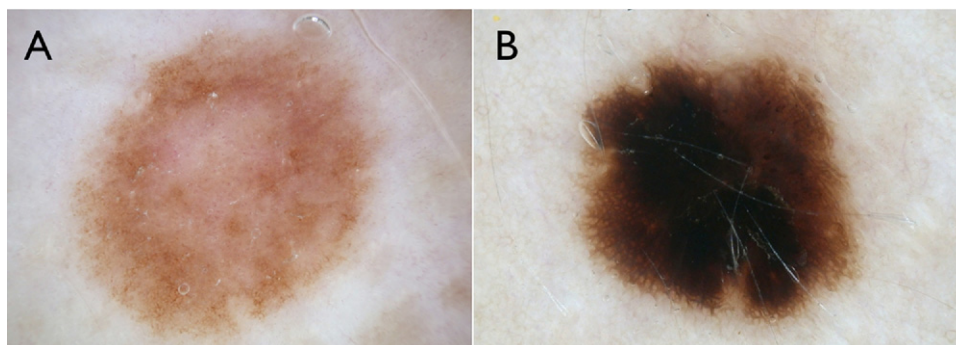


Figure 5 (A) Nevi in individuals with a fair skin type reveal typically a light brown color and a central hypopigmentation, while in dark skin types, nevi exhibit a dark brown color and a central hyperpigmentation (B) (original magnification, $\times 10$).

black lamella covering the underlying network. This may sometimes cause diagnostic difficulties. However, the central black lamella can be easily removed by a tape or plaster, allowing the visualization of the typical network (reticular pattern) and the diagnosis of black nevus with increased confidence. Although globular nevi are the most common types of nevi in children, a recent study found a higher prevalence of small reticular nevi in children with a dark ST.¹¹ Nevi in ST II and III are often characterized by a reticular pattern and a multifocal hyper-hypo-pigmentation. It should be noted that a fair ST does not necessarily rule out the additional presence of nevi with different pigmentation types and vice versa, but a single lesion revealing deviating patterns from the others (ugly duckling sign) may require closer observation.¹³

Melanoma-associated Pattern and Melanoma Risk

Various studies report consistently on a higher frequency of nevus-associated melanomas on axial body sites with respect to the lower extremities. Notably, the associated nevus component often shows significant dermal involvement by histopathology (ie, congenital-like pattern). Based on the dermoscopic-pathologic correlation of globular nevi and the more frequent location of this type on the upper axial body sites than on extremities, it is legitimate to conclude that a certain proportion of melanoma arises in nevi dermoscopically characterized by variations of a globular pattern (Fig. 6). Because the risk of malignant transformation is considerably low, particularly for small congenital or congenital-like nevi, systematic excision of these common nevi is certainly not indicated.^{11,15}

By contrast, a high number of nevi have been shown to be a risk factor mostly for the *de novo* development of melanoma. In light of this, a recent study is of particular interest in which the authors identified significant differences in dermo-

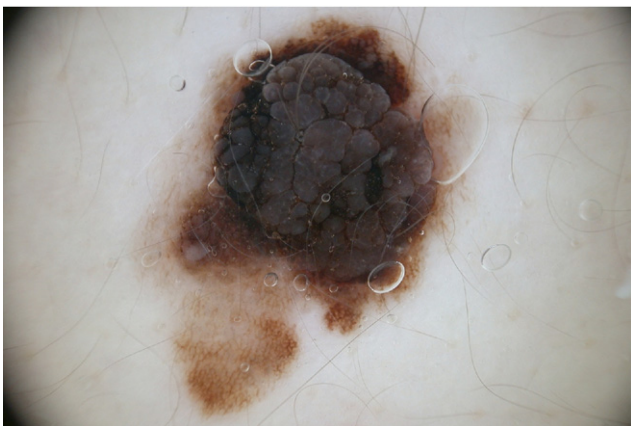


Figure 6 Dermoscopic image of a nevus-associated melanoma. The flat component shows an atypical network pattern and corresponds to the melanoma, while the central elevated area showing globular pattern corresponds to the nevus component (superficial spreading melanoma arising in a globular nevus-dermal type, tumor thickness according Breslow <1 mm) (original magnification, $\times 10$).

scopic patterns of nevi between individuals with a personal history of melanoma and a healthy control group.²⁷ According to this study, patients with melanoma more frequently exhibited nevi dermoscopically characterized by a mixed pattern with a prevailing globular component (reticular-globular pattern or homogeneous-globular pattern) compared to a more uniform pattern often showing superficial black dots in healthy individuals. Consequently, individuals harboring nevi with complex patterns may be considered at higher risk of melanoma development and subsequently may require a closer surveillance than individuals with nevi revealing a uniform pattern. Based on personal observations, patients with clinically so-called “dysplastic nevus syndrome” often reveal nevi of larger size (>5 mm) that dermoscopically exhibit a central globular or structureless pattern associated with an often atypical-appearing network, but further studies are needed to confirm these preliminary observations (Fig. 7).

Per definition, starburst nevi are benign nevi that do not require further treatment. However, because melanoma may mimic such nevi clinically, dermoscopically, and also histopathologically, excision of lesions with Spitzoid features is generally recommended.^{8,11}

Blue nevi are rarely a precursor of melanoma, although cases of malignant transformation of cellular blue nevus, which is a peculiar histopathologic variant of blue nevus, have been reported. The latter is clinically characterized by a large size (often >10 mm) and a certain predilection for the scalp. Therefore, excision of large blue nevi or blue nevi located on difficult-to-examine body sites, such as the scalp, is generally recommended.^{9,11}

UV Exposure

UV exposure may cause significant but reversible changes of dermoscopic features of nevi, including significant darkening of pigmentation, fading of the pigment network, increase in size, erythema, and new development of irregular dots, globules, or blotches.^{28,29} Such changes may be associated with a higher (more suspicious) dermoscopy score using dermoscopic algorithms.⁶ Because they are reversible after 1-3 months after discontinuation of UV exposure, examination of nevi recently exposed to UV should be generally avoided or scheduled between 1 and 3 months after discontinuation of UV exposure.

Pregnancy

Similar to UV-induced changes, pregnancy causes transient changes of dermoscopic patterns of nevi, such as progressive lightening or darkening, progressive reduction of thickness and prominence of reticular pattern, new appearance of dots or globules, increase in size (irrespectively of location but most prominent at the abdomen), and increased vascularization.^{30,31} The latter is particularly visible in raised globular nevi. These changes linearly increase with time of pregnancy and are most evident at third trimester and time of delivery but are reversible approximately 3-6 months after delivery. Because changes at the end of pregnancy may be also corre-

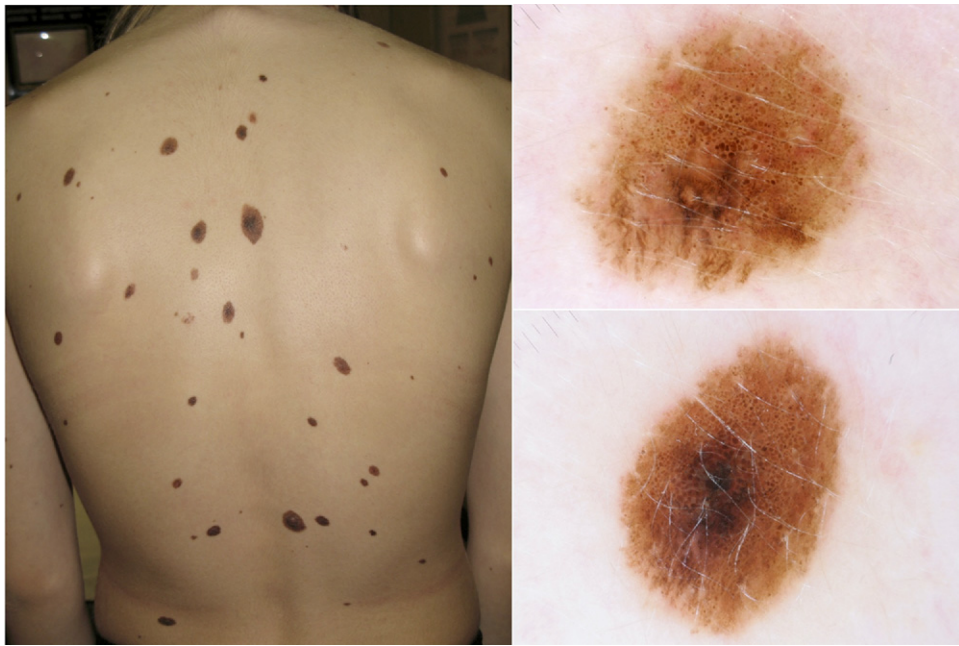


Figure 7 Clinical and dermoscopic image of a patient with numerous clinically atypical nevi. These nevi are clinically often larger than common nevi and reveal by dermoscopy a mixed pattern composed by central globules or homogeneous areas and peripheral often atypical network pattern (original magnification, $\times 10$).

lated with a higher dermoscopy score, re-examination of nevi 3-6 months after delivery is generally recommended.

Time-related Dynamic Changes

The age-related difference of nevus pattern between children (globular nevi) and adults (reticular nevi) and the presence of usually few nevi with globular pattern throughout all ages has led to the concept that globular nevi represent dermal proliferations that develop during early childhood and persist throughout lifetime showing only little changes and acquire the stereotypical appearance of dermal nevi in elderly persons.³²

In contrast, reticular nevi develop as epidermal proliferations in response to UV exposure or hormonal growth factors. These nevi reveal a dynamic life (increasing and decreasing nevus number). In line with this is the presence of evolving nevi dermoscopically characterized by a reticular-homogeneous pattern surrounded by a peripheral rim of brown globules in young adolescence³³ (Fig. 8). The peripheral rim of brown globules is a well-recognized sign of nevus growth. Such nevi show a symmetric enlargement during digital dermoscopic follow up until the disappearance of peripheral globules indicate stabilization of growth. At this stage, the nevus reveals a reticular pattern as the only dermoscopic feature. As a consequence, the most common pattern of nevi in adults is the reticular pattern. The decline in number of acquired melanocytic nevi after the fifth decade of life can be explained by a progressive involution, regression, or apoptosis of reticular nevi until their final disappearance.

Of peculiar interest are the typically rapid time-related changes of starburst nevi.³⁴⁻³⁶ Notably, the starburst pattern represents only an intermediate pattern in the evolution of

Spitz nevi that at initial growth commonly exhibit a globular pattern. In contrast to the uniform appearance of globular nevi, the globules of SN/RN are much more irregular in size and color and less densely distributed. After a variable time of months, the globular pattern develops into the classic starburst pattern and subsequently into a homogeneous-reticular pattern. The latter indicates a stabilization of growth. In this phase, the Spitz/Reed nevus may be indistinguishable from common reticular nevi. However, there is upcoming evidence that SN/RN seem also to involute, which explains the epidemiologic data that SN/RN are rare after the third decade of life.²¹

Finally, blue nevi, once developed, are highly stable lesions that persist throughout lifetime. This stability of blue



Figure 8 Typical example of evolving reticular nevus showing at the periphery small brown globules (original magnification, $\times 10$).

nevi is an important criterion in their diagnosis because blue color alone is a highly unspecific feature that may occur also in nodular melanoma, melanoma metastases, or pigmented basal cell carcinoma.^{6,9} Therefore, the diagnosis of blue nevi should be based on the combination of the dermoscopic pattern and a “convincing subjective” lacking history of changes. The combination of blue color with a history of changes should always lead to rule out nodular melanoma, basal cell carcinoma, or melanoma metastases. In situations in which a reliable history is difficult to obtain, excision must be always weighted over watch and wait.

Conclusion

Different types of nevi do exist in relation to their epidemiology, morphology, evolution, and melanoma risk. The knowledge of the dermoscopic patterns of nevi and the factors influencing the nevus pattern improves the diagnosis, classification, and management of the heterogeneous spectrum of benign melanocytic proliferations.

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