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The many faces of blue nevus: A clinicopathologic study

Background: In recent years, several histopathologic variants of blue nevus have been identified, whose clinical and dermoscopic correlates need further clarification.
Methods: A comparative evaluation of histopathologic and dermoscopic features was carried out on 52 melanocytic proliferations belonging to the morphologic spectrum of blue nevus.
Results: On dermoscopy, all lesions showed a homogeneous, structureless pigment pattern, with a curious variety of colors (blue, white–blue, black, brown, and polychromatic). Histopathologically, the majority of blue lesions were common blue nevi (11/19); the majority of white–blue lesions were 'hypochromic' (sclerotic, hypomelanotic, and amelanotic) blue nevi (17/22); all the black lesions were 'compound' blue nevi (2/2); the majority of brown lesions were combined blue nevi (3/4); the unusual polychromatic dermoscopic appearance was often associated with a histopathologic diagnosis of deep penetrating nevus (2/5).
Conclusion: A dermoscopic–pathologic approach now allows us to identify 'blue' (common) blue nevi, 'white' (hypochromic) blue nevi, 'black' (compound) blue nevi, 'brown' (combined) blue nevi, and 'polychromatic' (deep penetrating) blue nevi. A better recognition of the many dermoscopic faces of blue nevi is expected to give a morphologic guideline for the clinical management of these lesions.

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Dermal dendritic melanocytic proliferations (DDMP) can be defined as a spectrum of congenital and/or acquired melanocytic lesions whose histopathologic hallmark is the presence of variable proportions of oval/spindle and bipolar dendritic cells, the latter being usually heavily pigmented.[1]

Three categories of DDMP were identified in the classical dermatopathology literature: hamartomatous dermal melanocytoses (Mongolian spot, nevi of Ota and Ito), classic and cellular blue nevi, and melanoma arising in blue nevus.[1] In addition 'combined' lesions made up of DDMP admixed with any other benign melanocytic proliferation (congenital non-blue, common acquired, dysplastic/Clark, and Spitz nevi) were considered as well.[2–4]

In recent years, a number of additional histopathologic variants of DDMP have been described.[1–22] Table 1 shows a comprehensive histopathologic classification of these entities, many of which are still poorly defined from a clinical and dermoscopic point of view.

In the present study, we evaluate the clinical and dermoscopic correlates in a series of melanocytic lesions belonging to the histopathologic spectrum of blue nevus.

Materials and methods

Lesions were collected from the pathology files of the University Dermatology Departments in Graz, Austria, L'Aquila and Naples, Italy, and Barcelona and Madrid, Spain. They had been consecutively excised with a clinical and dermoscopic diagnosis of 'blue nevus with atypical features', namely a lesion

Table 1. A classification of dermal dendritic melanocytic proliferations

Benign
Hamartomatous
Mongolian spot
Nevus of Ota
Nevus of Ito
Non-hamartomatous
Common blue nevus
Cellular blue nevus
classical
angiomatoid
with schwannian differentiation (Masson neuronevus)
'Hypochromic' blue nevus/cellular blue nevus
myxoid (cystic)
desmoplastic/sclerotic
hypomelanotic
amelanotic
Deep penetrating nevus
Compound blue (Kamino) nevus
Combined blue nevus
Atypical blue nevus*
Borderline
Large infiltrative cellular blue nevus
of the scalp
of other sites
Cellular blue nevus with prominent vascular network (paraganglioma-like dermal melanocytic tumor)
Cutaneous neurocristic hamartoma/ malignant neurocristic tumor
Pigmented epithelioid melanocytoma**
Malignant
Melanoma arising in blue nevus
Blue nevus-like (dendritic cell) primary melanoma
Blue nevus-like metastatic melanoma

*If strict morphologic criteria are used, atypical blue nevus has a completely favorable clinical outcome.[1,5]

**Cases of epithelioid blue nevus in Carney complex did not metastasize to date. However, they cannot be morphologically distinguished from cases of metastasizing epithelioid blue nevus and from animal-type melanoma, thereby justifying their inclusion into a unique category designated 'pigmented epithelioid melanocytoma'.[1]

with overall clinical and dermoscopic features of blue nevus but with some atypical findings. Atypical findings included large size, history of recent growth or change, inflammatory perilesional halo or dermoscopic features deviating from the stereotypical steel blue pigmentation.[23–26] The previously reported cases of 'compound' blue nevus[16] were also included in the study. Cases with incomplete clinical data and/or no preoperative dermoscopic documentation were excluded. The study was conceived as a comparative evaluation of specific histopathologic diagnoses and dermoscopic features. Therefore, both histopathologic specimens and dermoscopic images needed to be first reviewed blindly by the respective experts and then re-evaluated in order to produce a combined set of dermoscopic and histopathologic data.

Dermoscopic evaluation, performed by one of us (G. A.), was based on JPEG files either obtained from 35-mm color slides (acquired by Dermaphot lens, Heine Optotechnik, Herrsching, Germany, mounted on a standard reflex camera) or by using a digital imaging dermoscopy system (Dermlite Foto, 3-Gen llc, Salvador Bay, Dana Point, CA, USA; Videocap system, DS Medica, Milan, Italy; or Molemax system, Derma Medical Systems, Vienna, Austria). Since blue nevi are dermoscopically characterized by a diffuse, structureless pigmentation,[23–26] attention was mainly given to the different colors that typify the pigmentation seen by dermoscopy. Each lesion was thus recorded as blue, white–blue, black, brown, or polychromatic. Lesions were evaluated as white–blue in the presence of white areas clearly discernible from areas of blue color. In these lesions, the percentage of white areas was recorded as well. Polychromatic lesions were defined as having at least three easily discernible colors.

In each case, the detailed histopathologic categorization was made by one of us (G. F.) on a single hematoxylin–eosin-stained specimen, which had been considered as representative of the lesion by the referring histopathologists. Paraffin blocks were not available for further studies. The histopathologic evaluation was made based on the classification given in Table 1. Each entity was defined according to the criteria listed in Table 2. These criteria were

Table 2. Histopathologic features of benign, non-hamartomatous dermal dendritic melanocytic proliferations

Dendritic cell proliferation	Hallmark features
Common blue nevus	A heavily and uniformly pigmented proliferation of dendritic melanocytes with a subepidermal grenz zone
Cellular blue nevus, classical	A proliferation of heavily pigmented dendritic melanocytes with island of pale and plump cells
Cellular blue nevus, angiomatoid	A cellular blue nevus with wide congested vascular spaces
Cellular blue nevus, with schwannian differentiation (Masson neuronevus)	A cellular blue nevus with 'neuroid' fascicles of spindle cells with a wavy silhouette
'Hypochromic' blue nevus, myxoid (cystic)	A common/cellular blue nevus with either intercellular mucin deposition or a central empty mucinous-like or myxohyaline core
'Hypochromic' blue nevus, desmoplastic/sclerotic	A common/cellular blue nevus with a central area of dense sclerosis harboring only a few interspersed pigmented cells
'Hypochromic' blue nevus, hypomelanotic	A common blue nevus with loss of melanin within the 10–95% of the area of the lesion
'Hypochromic' blue nevus, amelanotic	A common/cellular blue nevus with loss of melanin in more than 95% of the area of the lesion
Deep penetrating nevus	A wedge-shaped lesion composed by fascicles of spindle cells and dendritic cells with some interspersed 'sebocyte-like' epithelioid cells
Compound blue (Kamino) nevus	A blue nevus with no appreciable subepidermal grenz zone and prominent intraepidermal dendritic melanocytes arranged in single units
Combined blue nevus	A common/cellular blue nevus mixed and regularly merged with a nevus of different kind
Atypical blue nevus	A common/cellular blue nevus with one or several atypical features (typical mitoses up to 3–4/mm^2, ulceration, size $>$50 mm, deep extension, nuclear pleomorphism)

derived from reference dermatopathology textbooks,[2–4] with only one minor change, namely: a '*hypochromic' blue nevus* was defined as a benign DDMP in which on histologic specimens pigmentation is not heavily distributed throughout the lesion, either because of the deposition of an abundant extracellular matrix (*myxoid* and *sclerotic* variants) or because of the loss of melanin within a substantial area (more than 95% in the *amelanotic* variant;[10] 10 through 95% in the *hypomelanotic* variant). In each case, the presence of dendritic, oval/spindle, and epithelioid cells was semiquantitatively scored as absent, present, or prevailing . The presence of melanophages was also recorded if abundant (i.e. readily discernible throughout the lesion).

In cases of hypomelanotic and sclerotic blue nevi the pigment decrease as well as the amount of sclerosis was quantified in percentage throughout the entire area of the lesion. The depth of pigmentation was also histopathologically measured by means of a micrometer as the distance from the granular layer to the deepest dermal pigment. For each lesion the measurement was carried out in the area with the most deeply located pigmentation. Cases of 'compound' blue nevus were not submitted to any of these measurements because of their definitional feature of pigmented dendritic melanocytes just within the epidermis.[16]

Results

Table 3 summarizes the clinicopathologic features of the 52 cases classified according to the histopathologic diagnosis and the dermoscopic features. The 52 lesions were removed from 19 men and 33 women ranging in age from 7 to 87 years (mean 44.7 years, median 43 years). Their size ranged from 1.3 to 8 mm (mean 3.3 mm, median 2.9). The limbs were the most common location (27 cases), followed by the head (16 cases).

On dermoscopic examination, the common denominator of all lesions was a homogeneous, structureless pigment pattern of different colors or combination of colors (Table 3). No cases with a dotted–globular pattern were found. Most lesions were either white–blue (22/52) or blue (19/52). A minority of lesions were found to be either brown and structureless (4/52) or polychromatic (5/52). The size was not related to any dermoscopic feature. Likewise, the location of the lesions did not influence the dermoscopic features, with the relevant exception of white–blue lesions, most of which were from the limbs (18/22); in these lesions the percentage of white areas seen at dermoscopy ranged from 30 to 80% (mean 59.5%, median 60%).

Histopathologically, most of the lesions diagnosed as 'common' blue nevus were removed from the head–neck region (8/15), while the majority of hypomelanotic–amelanotic nevi were from the limbs (16/21). Hypomelanotic and amelanotic blue nevi often showed some degree of sclerosis and the final diagnosis in some cases was often decided based on the prevailing histopathologic features. Thus, these 'hypochromic' (hypomelanotic, amelanotic, and sclerotic) blue nevi could represent a unique morphologic spectrum of lesions. As a whole, in the present series, the number of 'hypochromic' blue nevi (24/52) was higher than common blue nevi (15/52): and even more surprisingly, patients with these 'hypochromic' blue nevi had a mean age (44.3 years) and a median age (45 years), which was consistently lower than patients with common blue

Table 3. Clinicopathologic features of 52 cases of benign dermal dendritic melanocytic proliferations belonging to the histopathologic spectrum of the blue nevus

	Common blue nevus (n = 15)	Hypomelanotic blue nevus (n = 13)	Amelanotic blue nevus (n = 8)	Sclerotic blue nevus (n = 3)	'Compound' blue nevus (n = 4)	Blue nevus with myxoid changes (n = 1)	Deep penetrating nevus (n = 2)	Combined blue nevus (n = 6)	Total
Age range (years)	22–87	24–67	20–66	41–67	7–25	67	20–32	25–54	7–87
Mean	53.3	43.3	42.8	58.3	14.5	67	26	41	44.7
Median	60.5	41	45	52	12	67	26	43	43
M:F	3:12	5:8	4:4	2:1	2:2	0:1	0:2	3:3	19:33
Size range (mm)	1.5–4.0	1.5–4.5	1.6–8.0	2.4–3.2	3.0-6.0	4.0	2.2–8.0	1.3–3.3	1.3–8.0
Mean	2.4	3.0	3.0	2.7	4.5	4.0	5.1	3.2	3.3
Median	2.5	2.5	2.5	2.6	4.5	4.0	5.1	2.5	3.5
Location									
Head/neck	8	1	1	1	1	1	1	2	16
Trunk	1	1	1	-	3	-	1	-	7
Limbs	5	11	5	2		-	-	4	27
Acral	1	-	1	-		-	-	-	2
Dermoscopy color									
Blue	11	4	-	-	2	-	-	2	19
White–blue	4	8	6	3		1	-	-	22
Black	-	-	-	-	2	-	-	-	2
Brown	-		1	-			-	3	4
Polychromatic	-	1	1	-			2	1	5

- is for 0 (no case)

nevi (mean age 53.3 years, median age 60.5 years). The percentage of pigment decrease on histologic sections from hypo-amelanotic lesions ranged from 15 to 80% (mean 36%, median 30%); the percentage of fibrotic areas in sclerotic blue nevi ranged from 60 to 90% (mean 76.6%, median 80%).

Histopathologic evaluation also included six combined blue nevi: common blue nevus with Spitz nevus ('blitz nevus';[27] two cases), common blue nevus with dysplastic (Clark) nevus (one case), common blue nevus with congenital nevus (one case), 'compound' blue nevus with dysplastic (Clark) nevus (one case[16]), and deep penetrating nevus with dermal nevus, Miescher type.

The dermoscopic–pathologic correlation data are shown in Table 3. Most blue lesions were common blue nevi (11/19) (Fig. 1); the majority of white–blue lesions were 'hypochromic' blue nevi (17/22) (Figs 2 and 3); all the black lesions were 'compound' blue nevi (2/2); the majority of brown lesions were combined blue nevi (3/4) (Fig. 4); the unusual polychromatic dermoscopic appearance (i.e. presence of three different colors) showed some association with a histopathologic diagnosis of deep penetrating nevus (2/5) (Fig. 5).

As expected, the dermoscopic color was also related to the cell population, as the prevailing components of blue lesions were dendritic melanocytes (9/12), while most white–blue lesions mainly showed oval/spindle cells (12/21). Melanophages were scored as abundant in black lesions (2/2), in brown lesions (4/5), and in polychromatic lesions (3/5). Instead, melanophages were found to be abundant only in a minority of white–blue lesions (7/22) and blue lesions (5/19); in the latter group, the melanophage component was probably overshadowed by the dendritic cell component.

Quite surprisingly, the percentage of dermoscopic loss of pigmentation (white areas) was not strictly related with the loss of pigmentation seen histopathologically. In fact, 'hypomelanotic' blue nevi with a white–blue color dermoscopically showed a percentage of white areas (range 30–70%, mean 55.5%, median 60%), which was similar to the percentage of white areas found in white–blue amelanotic nevi (range 40–70%, mean 58.3%, median 60%). Even the percentage of sclerosis failed to show any clear relationship with the extent of dermoscopic white areas (data not shown).

Likewise, the measurement of the depth of pigmentation by means of an ocular micrometer (Table 4) failed to show any significant data, except for the range of measures, which was slightly wider in white–blue lesions than in blue lesions.

In the context of an 'overall' (see Discussion) dermoscopic–pathologic correlation, we found some peculiar cases. Four common blue nevi showed a white–blue dermoscopic color due to the deeper location of the lesions within the dermis and the presence of a thicker subepidermal grenz zone. Likewise, four hypomelanotic blue nevi showed a homogeneous blue dermoscopic color because of the deep dermal location of the area of depigmentation. Finally, two 'hypochromic' blue nevi showed a polychromatic appearance due to a focal residual pigmentation under an attenuated subepidermal grenz zone. As stated above, the percentage of pigment loss had no influence on the dermoscopic color within the hypomelanotic group of lesions. However, no 'amelanotic' blue nevus was blue in color by dermoscopy. This finding confirms that the previously identified threshold of 95% of pigment loss for the definition of 'amelanotic' blue nevus is of clinical value.

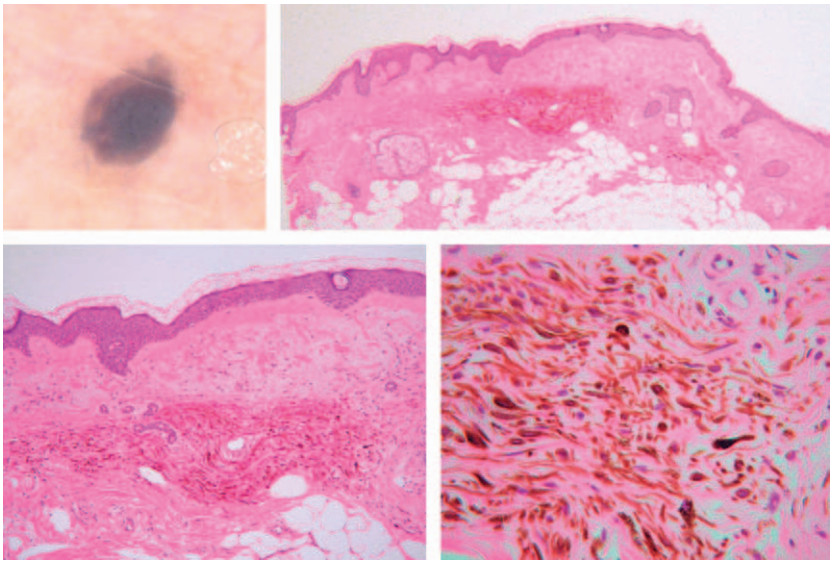

Fig. 1. A lesion removed from the forehead of a 62-year-old woman. On dermoscopy there is a typical homogeneous, steel blue color. Histopathologically, pigmentation is heavy throughout the lesion with a subepidermal grenz zone ('common'blue nevus).

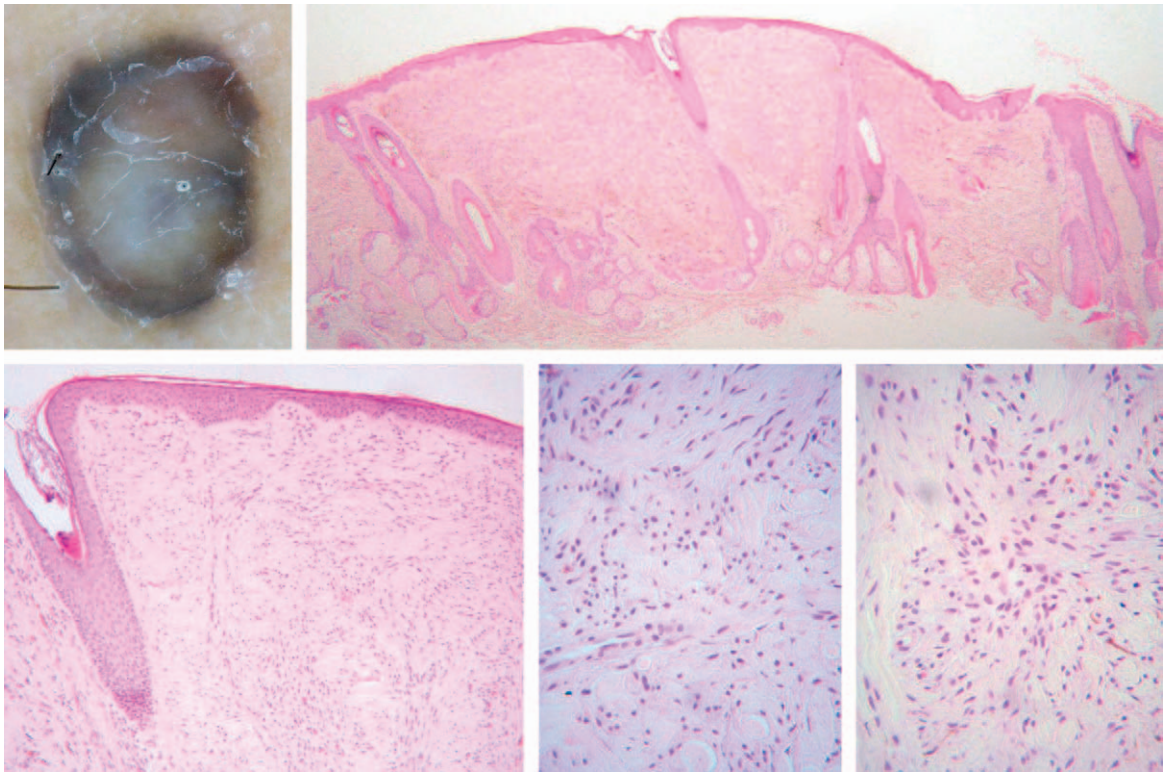

Fig. 2. A lesion from the face of a 37-year-old man. Dermoscopy shows blue–white color. In the center, the color is much paler than at the periphery. Histopathologically, the lesion is mainly composed of oval/spindle cells with some interspersed residual pigmentation within dendritic melanocytes ('hypochromic'blue nevus, amelanotic).

Discussion

DDMP are congenital or acquired melanocytic lesions composed by variable proportions of oval/spindle and bipolar, usually pigmented dendritic cells.[1] These cells resemble melanocytes migrating from the neural crest into the epidermis. Immunohistochemically, they usually express HMB45, together with S100 protein and Melan A/MART1.[1] The histopathologic classification proposed in Table 1 encompasses several histopathologic variants of blue nevus, which probably merge with each other along a spectrum of morphologic changes. This conceptual approach is in keeping with the well-documented occurrence of 'mixed' types of nevi e.g.

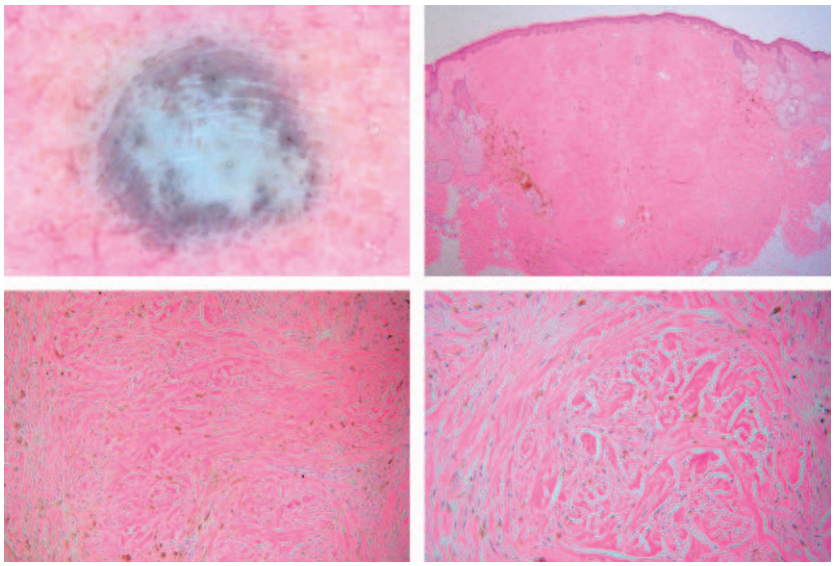

Fig. 3. A lesion from the face of a 41-year-old man. On dermoscopy, a white–blue color is evident. Histopathologically, the lesion is hypocellular with large areas of sclerosis ('hypochromic'blue nevus, sclerotic).

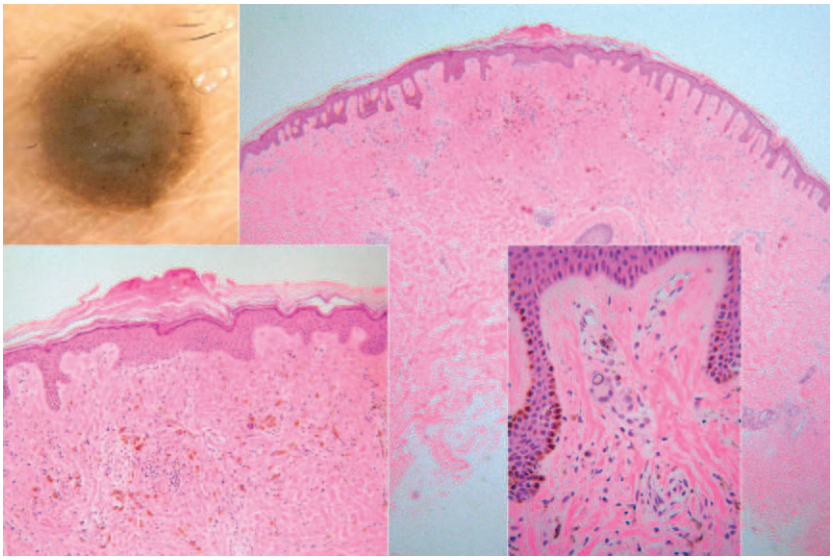

Fig. 4. A nevus from the leg of a 43-year-old man. Dermoscopy shows a prevailing brown color. Histopathologically the lesion is hypopigmented because of a mixture of dendritic melanocytes with large epithelioid melanocytes featuring 'spitzoid'cells ['combined'blue and Spitz ('blitz') nevus].

common and cellular;[4] sclerosing and mucinous,[18] as well as with our own observations about the presence of some degree of sclerosis in hypomelanotic and amelanotic blue nevi.

In recent years dermoscopy (dermatoscopy, skin surface microscopy, and epiluminescence microscopy) has been used with a greater and greater frequency in the preoperative diagnosis of pigmented skin lesions.[23–26,28–31] It has been underlined that new hand-held dermatoscopes using polarized light now allow physicians to rapidly visualize every cutaneous lesion, thereby expanding the use of dermoscopy in clinical practice.[31] Therefore, dermoscopy is increasingly representing

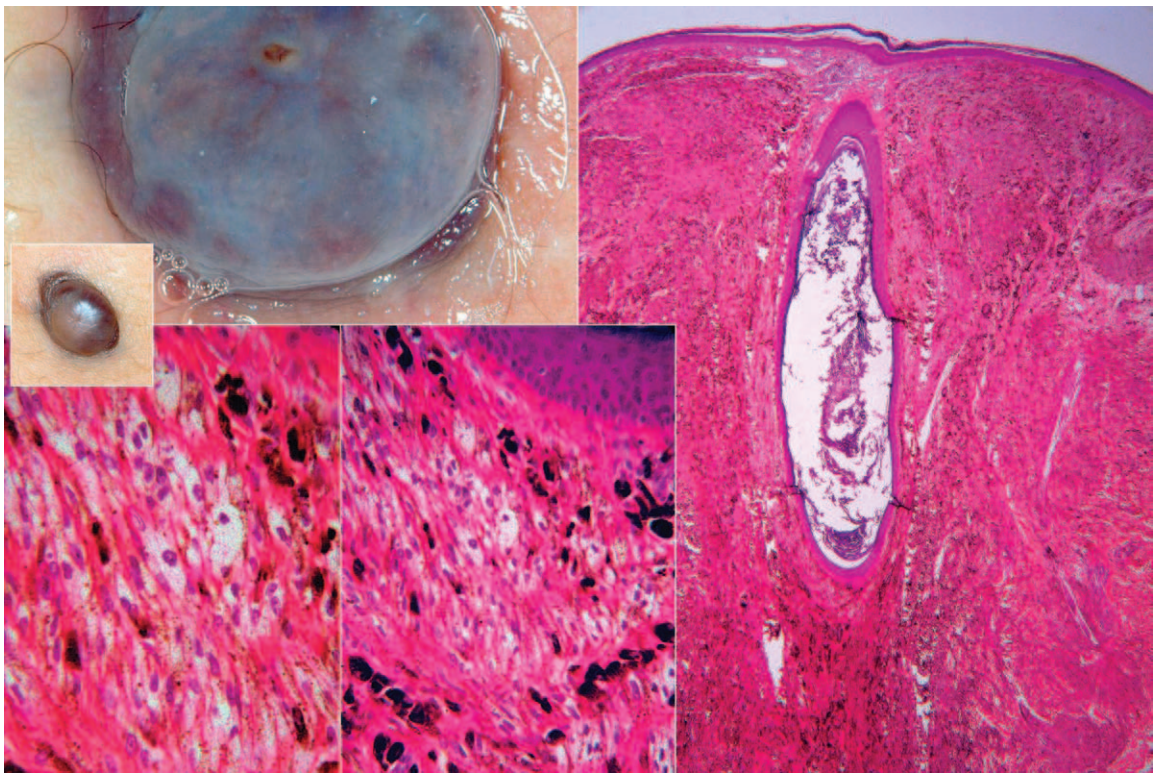

Fig. 5. A huge lesion removed from the back of a 32-year-old woman. Dermoscopy shows a polychromatic (blue, brown, and white) nodular lesion. Histopathologically, the neoplasm is mainly made up of dendritic and spindle melanocytes with sparse 'sebocyte-like'(finely vacuolated) cells (deep penetrating nevus).

Table 4. The depth of the pigmentation and the dermoscopic color of the lesions

	Dermoscopic color			
Depth of pigmentation (mm)	Blue (n = 17)*	White–blue (n = 22)	Brown (n = 4)	Polychromatic (n = 4)*
Range	0.20–1.00	0.20–1.40	0.20–1.10	0.15–1.00
Mean	0.66	0.66	0.61	0.37
Median	0.60	0.60	0.65	0.17

*Cases of black (n = 2), blue (n = 2), and polychromatic (n = 1) 'compound' blue nevus were not submitted to this measurement.

the *conceptual* and *practical* link between clinical dermatology and histopathology, allowing the clinician to visualize structures that are not discernible by the naked eye. The dermoscopic features of common blue nevi are considered to be specific enough in order to recognize them with certainty. In fact, they are described as showing a characteristic steel blue pigmentation – either in a diffuse 'structureless',[24,25] or, rarely, in a 'dotted–globular' pattern.[26] We also know that 'compound' blue (Kamino) nevi are often '*black–blue' nevi;* in fact, they are recognizable on dermoscopy by the presence of a homogeneous bluish pigmentation with a central black lamella, the latter being histopathologically made up of pigmented parakeratosis overlying intraepidermal dendritic melanocytes.[16]

Little is known about the dermoscopic–pathologic correlations in the many 'variations on the theme' of blue nevi shown in Table 1. In 1999, Bhawan and Cao[14] retrieved 38 amelanotic blue nevi over a series of 1358 blue nevi (2.8%) and they found that only three out of these 38 cases had been clinically recognized as blue nevi. As clearly shown in our study, dermoscopy draws the attention of clinicians to this kind of lesions. In fact, all the presented cases had been clinically and dermoscopically recognized as blue nevi [albeit 'atypical' (see Materials and methods section) and therefore worthy of surgical excision]. Histopathologically, we found a sizable decrease of melanin pigment in 24 out of 52 cases. Since any decrease of pigmentation can influence the clinical features of the lesions, we propose the term 'hypochromic' blue nevus to encompass the hypomelanotic, amelanotic, desmoplastic/sclerotic, and myxoid variants. The large majority of these lesions are '*white–blue*' *nevi* by dermoscopy, because they show a white–blue, rather than a steel blue dermoscopic color. In particular, in our experience, the amelanotic variant is invariably white–blue on dermoscopy, thus confirming that the previously identified threshold of 95% of pigment loss for the definition of this kind of 'hypochromic' blue nevus is of clinical value. The age of onset of the lesions included in the present study was unknown. However, the young age of most of the patients (mean age in the present study: 44.3 years) suggests that 'hypochromic' nevi do not simply represent an 'ageing' or 'degenerative' pattern of common blue nevi. Based on the HMB45-positivity of dermal melanocytes, Carr, et al.[10] speculated that the tumor cells contain abundant immature melanosomes, which for unknown reasons are not fully melanized. The Mel-5-positivity of the cases collected by Bhawan and Cao[14] also might be in keeping with this hypothesis.

Interestingly, most 'hypochromic' blue nevi of the present series (18/22) were removed from the limbs, as also reported by Carr, et al.[10] Thus, pigment decrease in blue nevi could be a 'site-related' rather than an 'age-related' phenomenon.

A detailed correlation of single dermoscopic features with their histopathologic counterpart (i.e. the percentage of 'white' dermoscopic areas with the percentage of histopathologic pigment loss or sclerosis; the dermoscopic color with the depth of dermal melanin deposition) failed to show any correlative data. This can be probably explained by an 'intrinsic' limitation of the dermoscopic–pathologic correlation. Dermoscopy and histopathology reflect different planes that are perpendicular to each other and thus a 'semiquantitative' or 'quantitative' dermoscopic evaluation has to be related to histopathology by means of a complete (or almost complete) step sectioning through the paraffin blocks combined with a three-dimensional analysis. We therefore conclude that in the present study an 'overall' rather than a 'detailed' (feature by feature) correlation between dermoscopy and histopathology has been carried out.

Two other interesting, albeit unusual dermoscopic–pathologic subsets of lesions were observed in the present study, namely, combined blue nevi and deep penetrating nevi.

Combined blue nevi are prone to be clinically diagnosed as melanoma just because of the presence of two or more different types of melanocytic nevi in a single lesion. Scolyer, et al.[32] recently underscored that a correct clinical diagnosis of combined nevus was given only in 2.4% of their cases. On the other hand, De Giorgi, et al.[33] stated that dermoscopy can provide useful information for a conservative management of combined nevi, at least when a clear-cut blue nevus component is present. In the present study, combined blue nevi were often '*brown–blue*' *nevi*, which were all retrospectively identifiable as benign lesions by dermoscopy.

Deep penetrating (plexiform spindle cell) nevus,[34,35] although not included in a recent review on DDMP,[1] is considered by some authors as either belonging to[32] or morphologically overlapping with the spectrum of blue nevus.[36] Deep penetrating nevus is recognized with a certain frequency as

a component of combined nevi.[32,35] Dermoscopy of deep penetrating nevus has been recently described as a single case report in which rapid morphologic changes had been documented.[37] A similar case with a history of rapid changes was also found in the present case series (not shown). Undoubtedly, a much larger number of cases must be collected in order to have more reliable clinical and dermoscopic information about deep penetrating nevi. At this juncture, we define them as '*polychromatic' blue nevi.*

In conclusion, we presented the dermoscopic–pathologic features of the many faces of blue nevi. This melanocytic proliferation shows a variety of dermoscopic colors with the common denominator of a homogeneous blue coloration, which prompted us to identify

- a 'blue' blue nevus, corresponding to the histopathology of a 'common' blue nevus;
- a 'white' blue nevus, with the histopathologic features of a 'hypochromic' (hypomelanotic, amelanotic, desmoplastic/sclerotic, myxoid) blue nevus;
- a 'black' blue nevus, histopathologically typified as a 'compound' blue (Kamino) nevus;
- a 'brown' blue nevus, consistently associated with a histopathologic diagnosis of 'combined' blue nevus;
- a 'polychromatic' blue nevi, often histopathologically diagnosed as 'deep penetrating' nevus.

A better recognition of the many dermoscopic faces of blue nevi is expected to provide a morphologic guideline for the clinical management of these lesions.

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