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Dermoscopic-Pathologic Correlation: Apropos of Six Equivocal Cases

Gerardo Ferrara, MD,* Giuseppe Argenziano, MD,† Caterina M. Giorgio, MD,† Iris Zalaudek, MD,‡ and Harald Kittler, MD§

The increasing use of dermoscopy in preoperative diagnosis of melanocytic skin neoplasms is impacting on routine histopathology to a relevant extent. We herein present the dermoscopic-pathologic features of 6 cases of histopathologically controversial melanocytic skin neoplasms. By illustrating these cases, we emphasize at least 3 different fields of interest for a combined (clinico-)dermoscopic-pathologic diagnostic approach, namely, information about the evolution of lesions; detection of gross sampling errors; definition of peculiar clinicopathologic entities. The theoretic and practical aspects of a close interaction among dermoscopists and histopathologists are itemized in detail.
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Dermatopathologists, like pathologists in general, are often asked by clinicians whether, on the basis of the histologic findings, a particular neoplasm is benign or malignant. The question seems simple enough, but an answer as simple is often too simple.

A.B. Ackerman (1936-2008)

The histopathologic diagnosis of melanocytic skin neoplasms (MSN) is often matter of considerable debate even among experienced histopathologists[1-7] and therefore is not a true "golden standard" but rather an "assessment of probability." A recent study based on a stepwise histopathologic examination of clinically equivocal MSN has shown that the increasing amount of clinical information can raise the histopathologists' level of confidence in their own diagnosis.[8] Among the relevant clinical information about any given MSN, dermoscopy can be viewed as the conceptual and practical link of histopathology (micro cosmos) with clinical dermatology (macro cosmos).[9-15] Like clinical dermatology, dermoscopy works parallel to the skin surface (and perpendicular to the histologic plane); like histopathology, it allows the viewing of structures not discernible by the naked eye.

Dermoscopy is increasingly impacting routine histopathology: case series of MSN selected by the dermoscopic examination show an unexpectedly high frequency of some peculiar lesions (nevi with regression-like fibrosis,[16] pigmented Spitz nevi,[17] hypopigmented blue nevi,[18] lentiginous melanomas[19,20]), which were previously poorly characterized and/or considered highly unusual. Currently, the gross sampling techniques on skin biopsy specimens are probably an underestimated source of diagnostic errors: a thorough dermoscopic-pathologic correlation could draw the attention of histopathologists to the suspicious areas of MSN,[13,15] thus orienting the macroscopic sampling and/or suggesting the need of step-sectioning the paraffin block(s). In a teleconsultation setting, dermoscopy allows for the detection of cases with inadequate image sampling.[17]

We know that progress in medicine is based on evidence and not on anecdotal observations. Sometimes, however, some straightforward and simple observation tells the story well, and in this context, we exhibit the dermoscopic and histopathologic features of 6 equivocal cases of MSN, to outline the diagnostic relevance of an integrated (clinico-)dermoscopic-pathologic diagnostic approach.

*Department of Pathology, Gaetano Rummo General Hospital, Benevento, Italy.
†Department of Dermatology, Second University of Naples, Naples, Italy.
‡Department of Dermatology, Medical University of Graz, Graz, Austria.
§Department of Dermatology, Division of General Dermatology, Medical University of Vienna, Vienna, Austria.
Address reprint requests to Gerardo Ferrara, MD, Pathologic Anatomy Unit, Gaetano Rummo General Hospital, Via dell'Angelo 1, I-82100 Benevento, Italy. E-mail: gerardo.ferrara@libero.it

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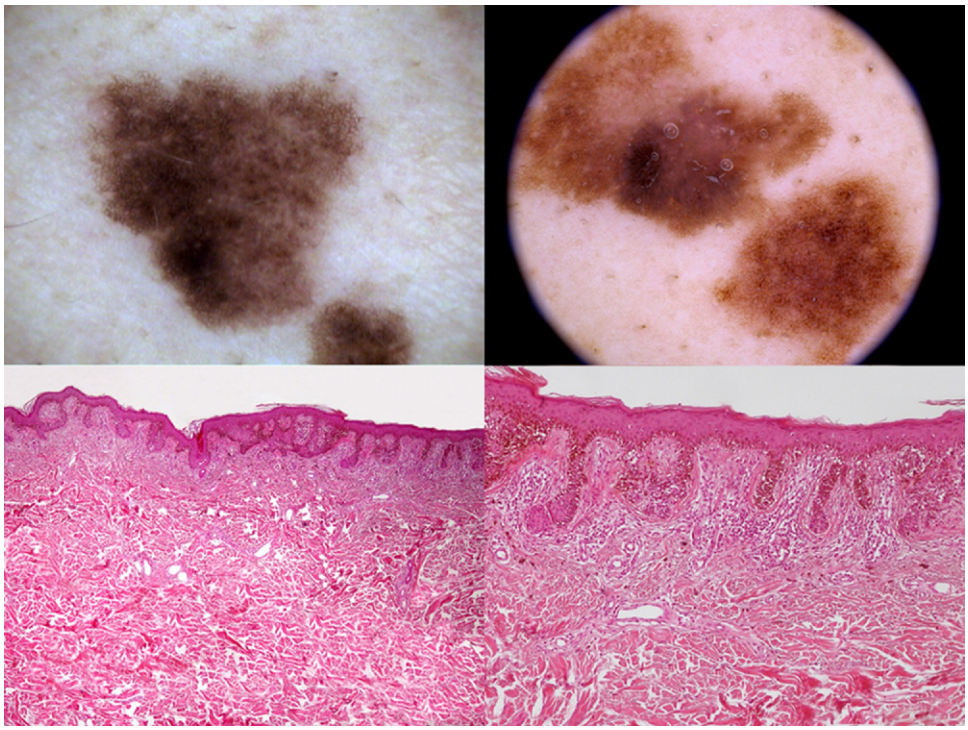

Figure 1 Case 1—Low-resolution digital dermoscopic image (top left) shows an irregularly distributed network, structureless areas, and an eccentric located black blotch. At the right lower corner of the image, a neighboring nevus can be partially seen. High-resolution digital dermoscopic image of the same lesion 8 years later (top right) shows that the previously separately located nevus seems now part of the lesion, indicating an enlargement of the lesion. In addition, the lesion reveals in the follow-up a pronounced asymmetry due to a centrally located grayish structureless area, which was not present in the baseline image. Histopathology features a large intraepidermal lesion with slightly irregular retiform epidermal hyperplasia (bottom left; H&E, ×40). There is a striking packing of melanocytes mainly arranged in single units at the junction (bottom right; H&E, ×100). Final diagnosis: lentiginous melanoma in situ.

Case Studies

Case 1

In 2002, a 53-year-old Caucasian man was seen for the first time for a screening examination of his cutaneous lesions. A 5-mm-sized pigmented lesion was noticed on his back and examined on dermoscopy (Fig. 1; top left): it was typified by an asymmetric and irregular pigment network with an eccentric black lamella. A neighboring MSN showing a regular pigment network was seen as well. Because the patient disclosed other lesions showing similar clinico-dermoscopic features, a short-term follow-up was recommended. The patient, however, returned after 7 years: at this stage, the lesion measured 8 mm, had joined with the neighboring MSN, showed a greater asymmetry, and presented the black lamella surrounded by a bluish hue (Fig. 1; top right). The lesion was excised and histopathologically typified as lentiginous melanoma in situ associated with a Clark (dysplastic) nevus. The histopathologic hallmark of the malignant proliferation was a regular (retiform) epidermal hyperplasia (Fig. 1; bottom left) with a striking predominance of single melanocytes tightly packed at the junction, little nest formation, and little pagetoid spreading (Fig. 1; bottom right). The morphologic changes detected on dermoscopic follow-up over 7 years were significant enough as to exclude a histologic diagnosis of dysplastic lentiginous nevus.

Case 2

A 31-year-old white male was under dermoscopic digital follow-up for multiple atypical MSN, mainly located on the back. One of these lesions was characterized by a fragmented pigment network with a diffuse erythematous hue and areas of reticular depigmentation (Fig. 2; top left); over 7 months, no relevant structural changes were detected (Fig. 2; top right), but the lesion was excised as being the patient's most atypical one. Histopathologic examination showed a large asymmetric melanocytic proliferation with a "trizonal" pattern (Fig. 2; bottom left): an irregular junctional component with irregular epidermal hyperplasia and areas of prevailing single cell proliferation; a significant area of dermal sclerosis with architecturally atypical melanocytic nests; and residual, bland-appearing nevus tissue around and deep into the cicatricial tissue (Fig. 2; bottom right). Based on these histopathologic features, a diagnosis of sclerosing nevus with pseudomelanomatous features (compound nevus with regressionlike fibrosis) was made. The lack of dermoscopic changes over 7 months suggested that the lesion was no longer as "active" as expected in a melanoma with regression.

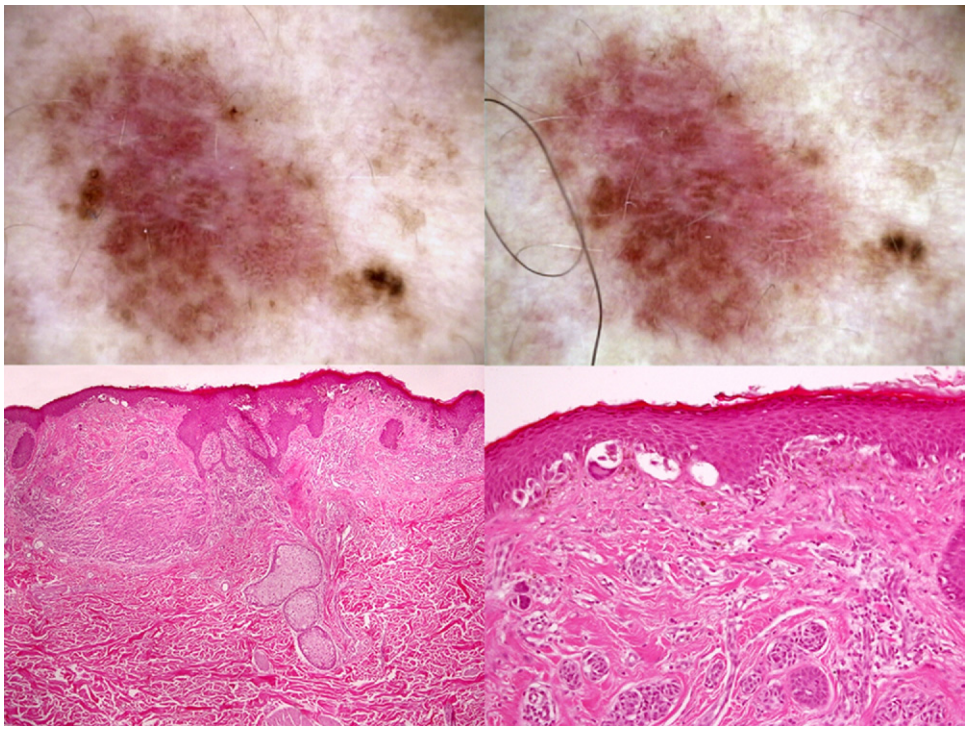

Figure 2 Case 2—Dermoscopically, this hypopigmented melanocytic lesion is characterized by large areas of erythema intermingled with a negative pigment network (whitish lines resembling a network) and residual pigmented network. Side-by-side comparison of the digital dermoscopic images at baseline (top left) and after 7 months follow-up (top right) fails to show any significant structural or size changes, thereby suggesting a "biologically stable" lesion. Histopathologically, the lesion is strikingly asymmetric, with irregularly sized, shaped, and spaced junctional nests, and fibrous thickening of the upper two-thirds of the dermis (bottom left; H&E, ×40). A closer examination discloses areas of prevailing single cell proliferation at the junction with little pagetoid extension and a bland cytomorphology of the dermal component (bottom right; H&E, ×100). Final diagnosis: sclerosing nevus with pseudomelanomatous features (nevus with regression-like fibrosis).

Case 3

A 51-year-old white male with a history of melanoma underwent excision of a large, asymmetric lesion of his scapular region (Fig. 3; top left). Dermoscopically, the lesion was typified by a large area of regression together with focal reticular depigmentation (Fig. 3; top right). Histopathologic examination showed a sharply circumscribed lesion, mainly growing as nests at the junction and within the papillary dermis (Fig. 3; bottom left). The nests had a somewhat irregular confluence but were not associated with any relevant pagetoid spreading; a fibrous thickening of the superficial and middle dermis was appreciable as well (Fig. 3; bottom right). Overall, the above-described histopathologic features were somewhat conflicting; however, a careful (clinico-)dermoscopic-pathologic correlation disclosed a striking discrepancy between the size of the lesion as clinically evident (about 8 mm) and its size as measured on the histologic slides (about 4 mm; Fig. 3; bottom left, demonstrates a single ×40 microscopic field encompassing the lesion as a whole). Histologic serial sections failed to show any further microscopic feature of atypia, probably because the lesion had undergone a macroscopic sampling along its minor axis. A final diagnosis of regressing melanoma was established by coupling the histopathologic features of the lesion with its dermoscopic features, the latter being not consistent with a nevus with regressionlike fibrosis (see dermoscopic features of case 2 for comparison).

Case 4

A 30-year-old female patient consulted a dermatologist because of a changing pigmented skin lesion on her back. Clinically the lesion was multicolored and asymmetric but also papillomatous at 1 edge (Fig. 4; top left). The differential diagnoses included a congenital nevus or a melanoma. On dermoscopy (Fig. 4; top right), the lesion consisted of 2 parts: a lightly pigmented part with polygonal, skin-colored and light brown clods that corresponded to the papillomatous zone (line A); and a more heavily pigmented part, with black and gray dots, thick reticular lines, and a structureless black zone (line B). Sections through the line B (Fig. 4; bottom left) disclosed a mainly intradermal melanocytic neoplasm that consisted of nests and cords of small and monomorphic melanocytes arranged in an periadnexal fashion and showing signs of maturation with progressive descent into the dermis consistent with a "superficial and deep" congenital nevus. A melanoma was not visible in this section of tissue. However, sections through line A (Fig. 4; bottom right) showed a clear-cut melanoma in situ.

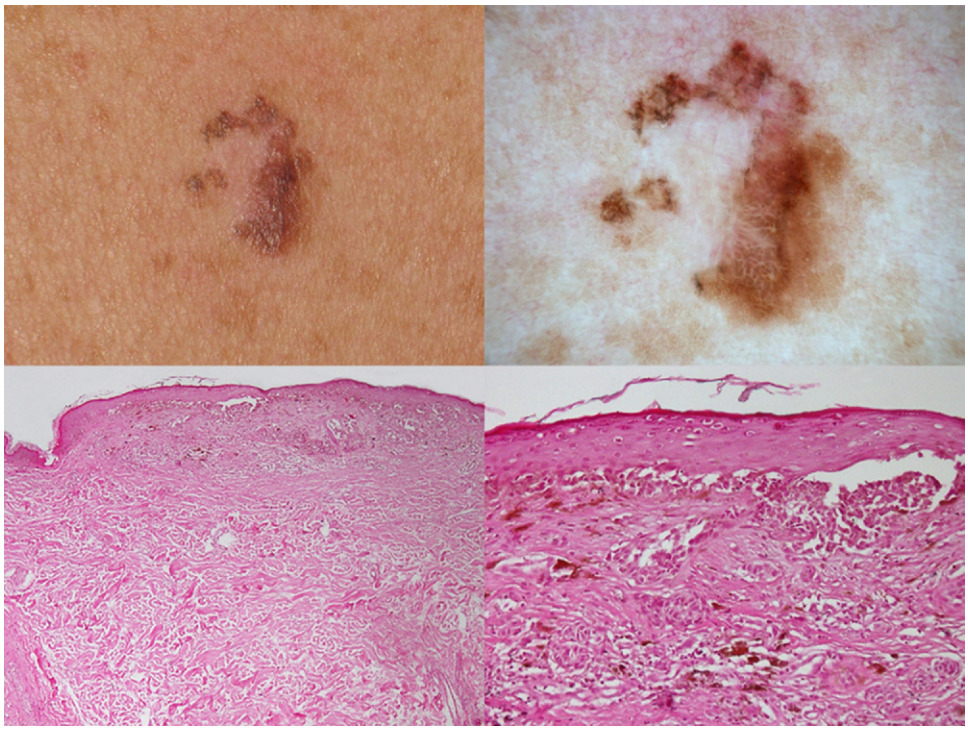

Figure 3 Case 3—Clinical features (top left) of a large MSN with extensive regression. Dermoscopy (top right) shows white structureless areas and gray pepper-like granules, which are particularly well seen close to residual brown pigmentation. In addition, a negative pigment network can be seen; dermoscopically, regression spans over >50% of the surface of the lesion. Histopathologically, the lesion is unexpectedly small (about 4 mm) and sharply circumscribed (bottom left; H&E, ×40X). There is a strikingly irregular confluence of nests (bottom right; H&E, ×100). Final diagnosis: melanoma with regression. The small size seen histopathologically (bottom left) was probably due to a macroscopic section performed along the minor axis of the lesion.

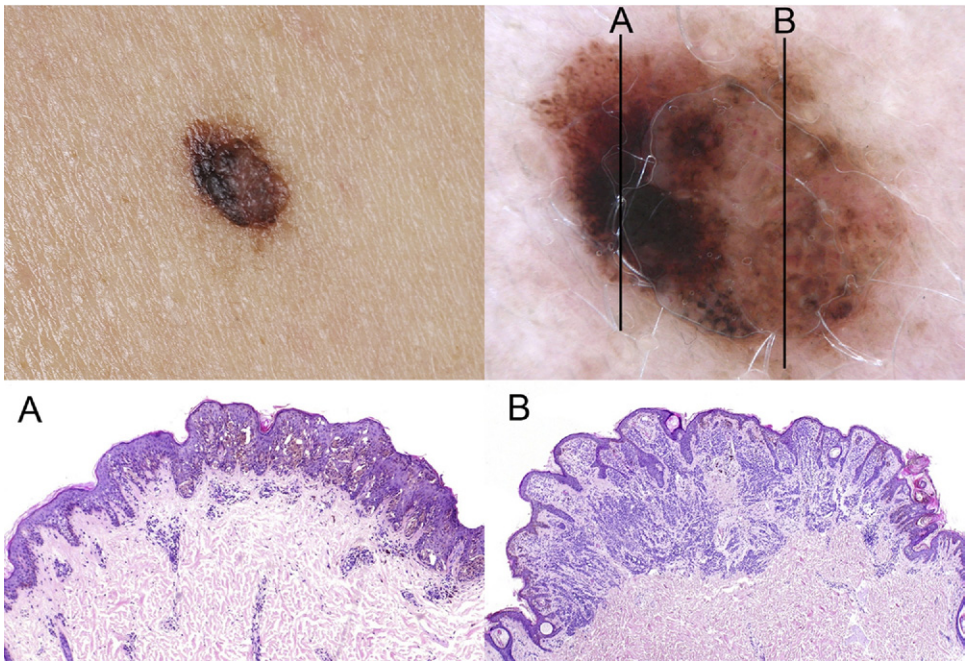

Figure 4 Case 4—Clinically (top left) the lesion is asymmetric, multicolored, and papillomatous. Dermoscopically (top right) the asymmetry is even more striking. There is a skin-colored light brown part on the right side consistent with a "dermal nevus" (line B) and a suspicious part with black and gray dots, thick reticular lines, and a black structureless zone (line A). Because of inappropriate cross-sectioning the asymmetry visible by dermoscopy is not preserved in the histopathologic slides. Sections along line A show a melanoma in situ (bottom left; H&E, ×100) and sections along line B show a "superficial and deep" congenital nevus (bottom right; H&E, ×40). As documented in this example, there is a certain risk of missing the diagnosis of a melanoma due to inappropriate orientation of the sample. Final diagnosis: melanoma arising in a "superficial and deep" congenital nevus.

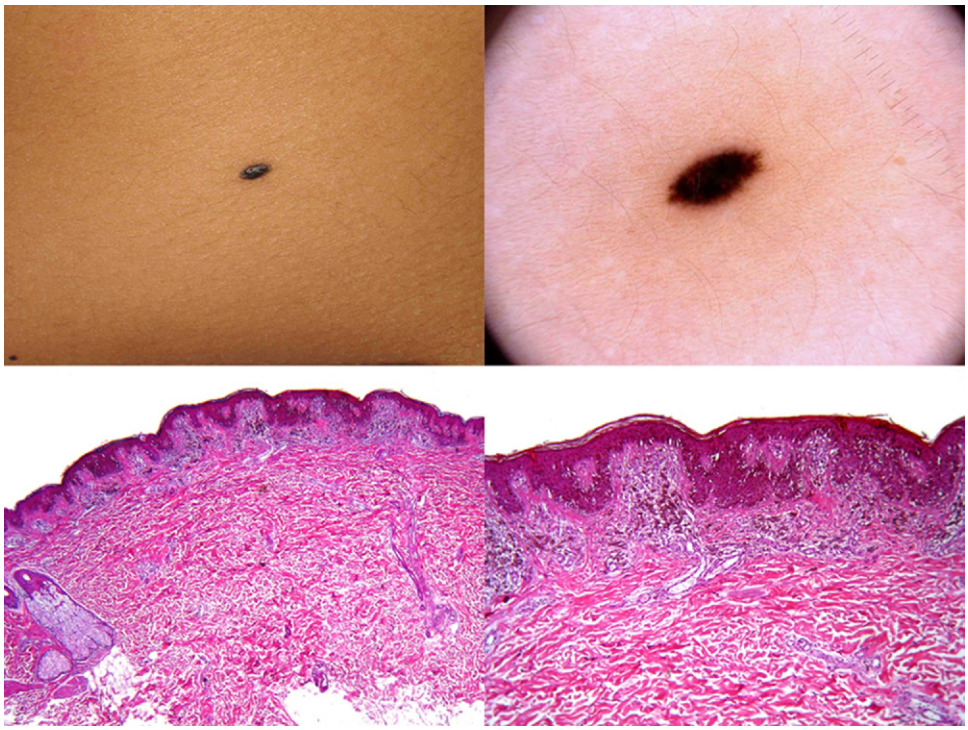

Figure 5 Case 5—The lesion is clinically evident as a small dark plaque (top left). It is dermoscopically typified by a regular star burst pattern as frequently seen in pigmented Spitz or Reed nevus: this pattern is composed by radial lines arising from a hyperpigmented dark brown to black homogeneous center (top right). Histopathologically, there is a regular epidermal hyperplasia with somewhat broad rete pegs (bottom left; H&E, ×25) and an intraepidermal proliferation of spindle melanocytes mainly arranged in single units within the lower layers of the epidermis. The nest formation is "inconsistent," and there is a vaguely band-like dermal infiltrate of melanophages (bottom right; H&E, ×100). Final diagnosis: early ("baby") Reed nevus.

This example demonstrates the importance of orienting the macroscopic samples according to clinical and dermoscopic findings.

Case 5

A 16-year-old white woman underwent excision of a MSN of the back (Fig. 5; top left). On dermoscopy, the lesion was characterized by radial streaks regularly arranged at its periphery (Fig. 5; top right), as commonly observed in Reed nevus. The lesion was excised because the patient was older than 14 years.[10] Histopathologically, the lesion was mainly composed of a single-cell proliferation within the lower layers of the epidermis; a vaguely band-like infiltrate of lymphocytes and melanophages filled the superficial dermis (Fig. 5; bottom left). The epidermis showed a regular hyperplasia with rather broad rete ridges; the melanocytes were spindle-shaped and monomorphic, and the junctional nests were inconsistent (Fig. 5; bottom right). These unusual microscopic features, evaluated together with the clinical picture, were considered consistent with a Reed nevus in an early growth phase ("baby" Reed nevus), rather than with a melanoma in situ.

Case 6

A 47-year-old woman requested clinical consultation because of a recently detected pigmented lesion of her inner right thigh. Dermoscopically, the lesion showed a homogeneous pattern with a few colors and structures, and a focal vaguely "starburst" appearance (Fig. 6; top left). These highly unusual dermoscopic features were not easily ascribed to any known type of nevus; therefore, the lesion was excised. Histopathologically, there was a prevailing single-cell proliferation within a slightly papillated epidermal hyperplasia (Fig. 6; top right). Most melanocytes were confined within the lower layers of the epidermis (Fig. 6; bottom left); they showed an epithelioid cytomorphology with a "monotonous atypia" and a drop-like shape (Fig. 6; bottom right). Overall, the lesion resembled an early ("baby") Spitz nevus, but dermoscopy did not fit with this hypothesis. Therefore, based on the dermoscopic-pathologic correlation, the lesion could be ascribed to a peculiar kind of nevus, different from the Spitz nevus (see Discussion).

Discussion

The cases we illustrated above highlight at least 3 fields of interest for a combined (clinico-)dermoscopic-pathologic approach for the diagnosis of MSN. They include information about the evolution of lesions, detection of gross sampling errors, and definitions of peculiar clinicopathologic entities.

The histopathologic picture is basically a snapshot within a dynamic biological process. The dermoscopic digital fol-

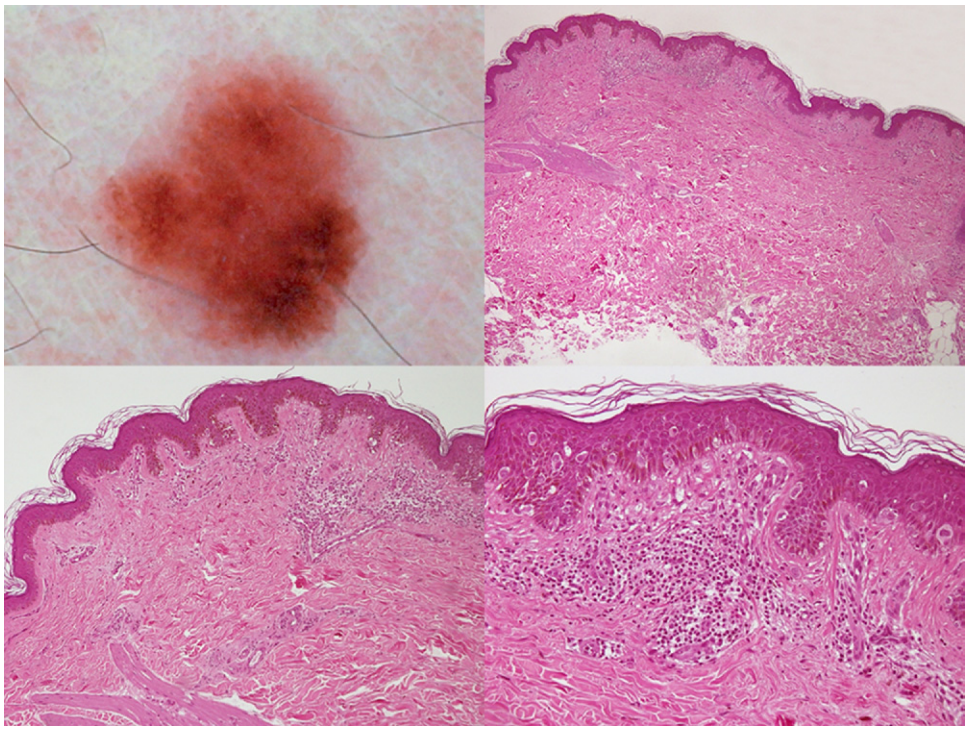

Figure 6 Case 6—Dermoscopically (top left), the lesion shows structureless brownish areas and irregular streaks on the right border resulting in a significant asymmetry of the lesion. Histopathologically, the lesion is small, with some papillated epidermal hyperplasia (top right; H&E, ×40); there is a poor circumscription, as well as a poor nest formation (bottom left; H&E, ×100). Melanocytes are epithelioid, often "drop-shaped," with a "monotonous atypia"; they lie mainly in single units within the lower layers of the epidermis (bottom right; H&E, ×200). Final diagnosis: benign MSN with spitzoid features, consistent with epithelioid cell nevus of the thigh of women.

low-up of the lesions can give information about the evolution of the lesions, a parameter which histopathology alone would be never able to give. Lentiginous melanoma can be described as a peculiar melanocytic proliferation of the non-sun-exposed skin in elderly people, characterized by a large-size predominant single-cell proliferation at the dermoepidermal junction, little pagetoid spreading, and regular ("retiform") epidermal hyperplasia.[21,22] The concept of lentiginous melanoma has been strongly criticized[23]; it is even possible that cases of lentiginous melanoma were previously reported as "atypical lentiginous junctional nevus,"[24] or "severely dysplastic nevus."[25] However, the present case 1, along with our previously reported cases dealing with this topic,[19,20] is characterized by dermoscopic follow-up findings, which are consistent with a slow-growing melanoma and not with a nevus. Conversely, the lack of relevant changes on dermoscopic follow-up can help the histopathologic recognition of the so-called "sclerosing nevus with pseudomelanomatous features"[26] or else nevus with regression-like fibrosis. Chronic, unnoticed trauma(s) could play a major role in the histogenesis of such a benign MSN by inducing fibrosis together with an atypical regenerative hyperplasia of the junctional melanocytes. In other words, a MSN like the present case 2 could be defined as a "chronically recurrent nevus." It can be differentiated from thick regressing melanoma because it lacks cytologic atypia, dermal mitoses, cell necrosis, tumoral melanosis, and expansible dermal nodule(s) of atypical melanocytes. However, the "atypical junctional proliferation" described in nevus with regression-like fibrosis (Fig. 2; bottom right) is sometimes present to such an extent as to raise the suspect of an early regressing melanoma. In this context, the lack of dermoscopic changes on digital follow-up can be viewed as an additional criterion pointing toward benignity.

Table 1 shows the differential features between nevus with regression-like fibrosis, recurrent/persistent melanoma, and regressing primary melanoma. Among the criteria listed in Table 1, case 3 showed only 2 histopathologic criteria for malignancy, namely, asymmetry and irregular confluence of nests. The lesion, however, was most probably a regressing melanoma in which the diagnostic difficulties were due to a poor gross sampling technique. As already emphasized,[17,18] by applying dermoscopy and a standardized gross pathology protocol to the diagnosis of MSN, a more precise clinicopathologic correlation can be achieved between relevant dermoscopic features and histopathologic findings. Along with this concept, case 4 shows that dermoscopy, by focusing the histopathologists' attention to a suspect area, no matter how small, can reverse the initial histopathologic evaluation. To guide the gross sampling technique of MSN, Braun et al[26] suggested performing a 1-mm micropunch biopsy in dermoscopically determined relevant parts of any given MSN. We think that the orientation of the surgical specimen and its gross section along a line identified by the dermoscopic im-

Table 1 Histopathologic Features of Nevus with Regression-Like Fibrosis, Recurrent/Persistent Melanoma, and Regressing Primary Melanoma

	NRLF	RPM	RM
Asymmetry	+	++	++
Poor lateral circumscription	−/+	++	++
Prevailing single-cell junctional proliferation	+/++	++	++
Irregular architecture of nests	+	++	++
Pagetoid spreading	−/+	++	++
Epidermal atrophy/consumption	−/+	+/++	+/++
Maturation	++	−	−
Cytologic atypia	−/+	+/+	+/++
Deep dermal mitoses	−	+/++	+/++
Fibrosis	++ (Tidy, in parallel bundles)	++ (More or less cellular)	++ (Pale, irregular, with "wiry" bundles)
Melanophages	−/+	+/++	+/++
Lymphocytic infiltrate	−/+ (Patchy)	+/+ (Patchy or lichenoid)	+/++ (Lichenoid)
Vertically oriented vessels	+/++	−/+	++
Fibrosis/inflammation beyond the lateral borders of the lesion	−	++	+/++

Abbreviations: NRLF, nevus with regression-like fibrosis (sclerosing nevus with pseudomelanomatous features); RPM, recurrent/persistent melanoma; RM, regressing primary melanoma.
+, Usually mild.
++, Usually moderate to marked.
−, Usually absent.

age will probably suffice. Therefore, 3 orienting sutures can be placed at the edges of the excision biopsy sample: 2 sutures are laid down at the margin close to the dermoscopic structure(s) that must be evaluated with histopathology; the third suture is placed at the opposite side. Dots drawn ex vivo on the skin surface with white liquid eraser can be used instead of the suture stitches. The lesion will be finally sectioned with parallel 2-mm sections, with the first of these sections taken to join the previously marked opposite edges.

The recognition of specific clinicopathologic entities is another crucial issue in dermoscopic-pathologic correlation studies. Spitzoid lesions are well-recognized sources of diagnostic disagreement among histopathologists, and even if most histopathologic studies focus on "thick" lesions (the so-called "atypical Spitz tumors"),[3-6] there is little doubt that a precise histopathologic evaluation of intraepidermal thin lesions would help refine their clinical recognition and management. Histopathologic examination of cases 5 and 6 showed medium-sized MSN predominantly composed by spindle (case 5) or epithelioid (case 6) cells mostly arranged in single units within the lower layers of the epidermis. These microscopic features, albeit not clear-cut, could recall a "pagetoid" Spitz nevus,[27] or an early ("baby") Spitz nevus,[28] which are probably overlapping entities.[29] In case 5, dermoscopy was characterized by regularly arranged radial streaks, in keeping with the histopathologic evaluation of the lesion as belonging to the "benign" end of the clinicopathologic spectrum of Spitz and Reed nevi.[18] In case 6, dermoscopy showed some structureless areas not completely fitting with the histopathologic diagnosis of Spitz nevus. A clear-cut explanation for such a discrepancy cannot be currently given. On the basis of a dermoscopic-pathologic correlation, a diagnosis of early melanoma in situ cannot be excluded with absolute certainty. However, case 6 recalls a study by Donati (submitted for publication) who recently collected 27 peculiar cases of Spitzoid MSN of the thigh, 25 from females. None of the lesions from their series showed Spitzoid features on dermoscopy, with a homogeneous pattern being by far the most common global feature. These data suggest that a subgroup of (Spitzoid) MSN from the thigh of women ("epithelioid cell nevus of the thigh") probably exists and that a close dermoscopic-pathologic correlation is required for its recognition.

In conclusion, we have shown a small series of MSN in which the histopathologic criteria, albeit still capable of work as such,[8] can take advantage of the dermoscopic findings. Today, we, on the edge of a new biology in histopathology, can foresee that our beloved classic morphology will soon be replaced by new technologies. In the meantime, a combined morphologic approach linking dermoscopy and histopathology might be helpful for pathologists to come to more reliable diagnostic conclusions for patients and their physicians.

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