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Hypopigmented atypical Spitzoid neoplasms (atypical Spitz nevi, atypical Spitz tumors, Spitzoid melanoma): a clinicopathological update

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Introduction

The clinicopathologic classification, diagnosis, and management of Spitzoid melanocytic lesions is one of the most problematic topics in dermato-oncology and dermatopathology. After earlier anecdotal reports [1,2], the controversial history of these controversial lesions began in 1948 when Sophie Spitz described 13 cases of what she called "juvenile melanoma," underlining its presumably good prognosis because only one case of her series had proven fatal [3]. During the following forty years, however, the entity described by Sophie Spitz was thought to be completely benign, with metastasizing cases being intuitively considered as cases of melanomas simulating Spitz nevus (Spitzoid melanoma) [4]. In 1989, Smith and co-worker described the so-called "Spitz nevus with atypia and metastasis" or "malignant Spitz nevus," i.e., a kind of lesion showing histopathologic features not enough for a diagnosis of malignancy, yet capable of nodal metastasis, usually with no further dissemination [5]. This apparently contradictory concept was then set forth by Barnhill with the diagnostic category of "metastasizing Spitz tumor" [6], or "atypical Spitz nevus/tumor" [7]. To date, while some opinion leaders maintain that there are only two diagnostic categories (nevus and melanoma) and that every "abnormal" behavior is simply a diagnostic mistake [8], some others suggest that Spitzoid lesions are indeed a "morpho-biologic spectrum" of lesions ranging from benignity to full-blown malignancy [9], and sharing a peculiar genetic profile, with chromosome rearrangements involving kinase fusions [10]. Intermediate lesions within such a spectrum eventually show:

i) an **equivocal histomorphology**, featuring a diagnostic agreement among experts which is consistently lower than for "conventional" (non-Spitzoid) melanocytic neoplasms [7,11];
ii) **peculiar clinical features and behavior** with a relatively high incidence in prepubescent patients [12] and a higher incidence of regional (sentinel) node involvement [13] but a better prognosis than "conventional" (non-Spitzoid) melanoma of the same thickness/stage [14] (possible low-grade malignancies [11]).

We have already pointed out that dermoscopy seems to allow clinicians to increasingly identify and excise pigmented spindle cell Spitz nevus and Reed nevus (which are basically the same clinicopathological entity), to such an extent that the brown-black plaque-like "variant" is surprisingly becoming the most common (and therefore "typical") Spitz nevus encountered in clinico-dermoscopic-pathologic studies [15-17]. The present paper will focus on the clinicopathological features of papulonodular hypopigmented Spitzoid lesions, which are "atypical" with a much greater frequency than their plaque-like heavily pigmented counterpart [16,17].

The proposed classification systems for Spitzoid neoplasms

The dermatopathologist's mission is to provide an accurate, specific, and comprehensive diagnosis, thereby enabling the clinician to estimate the prognosis and develop the optimal plan of treatment and follow up for any single patient. There is little doubt that the simple designation "benign" vs "malignant" provides the clinician with all of the necessary information for the patients' care. A. Bernard Ackerman taught us that each pigmented lesion may have only three diagnoses: "melanoma," "nevus" or "I don't know," with the "I don't know" cases to be referred to an expert who will be finally able to place them into either of the first two entities. According to this view, the adjective "atypical" is redundant and useless, because any Spitz nevus is "atypical" by definition; nevertheless, it can be differentiated from its malignant simulator (i.e., Spitzoid melanoma) according to a well defined set of histologic criteria; every Spitzoid (and non-Spitzoid) melanocytic proliferation behaves as either a benign or a malignant neoplasm which we can be unable to correctly categorize simply because our brain can fail to correctly apply the diagnostic criteria [8].

A.B. Ackerman's approach delivers a clear-cut message to the clinicians; nevertheless, it carries at least two major problems, which are still waiting to be overcome. The first problem is purely morphologic: by assuming that Spitz nevus is a simulator of melanoma (Spitz nevus as a pseudomalignancy) and that melanoma resembling Spitz nevus is a simulator of its simulator (Spitzoid melanoma as a pseudo-pseudomalignancy), it is not surprising that the diagnosis of such lesions is a quandary even among experts who may be indeed unable to place an "I don't know" lesion into a either "nevus" or "melanoma" category [7,11,18].

The second problem with A.B. Ackerman's approach is biological. A tutorial held in Graz, Austria, in 2008 evaluated 57 melanocytic tumors of uncertain malignant potential, 35 of which being thick Spitzoid neoplasms: a panel of expert was unable to differentiate cases with favourable and unfavourable behaviour on morphologic grounds; therefore, it was concluded that the cases were all malignant, albeit clearly different from "conventional" melanoma because of a great thickness associated with a relatively low metastatic rate [18].

Because of all these uncertainties and under medicolegal pressure, a dichotomic "benign vs malignant" approach unavoidably leads to a frequent overdiagnosis of melanoma or, else, to the cautious suggestion of a management as per melanoma for lesions that, even if malignant, are biologically different from "conventional" melanoma.

These reasons led Barnhill to set forth a three-tiered classification system by assuming an "intermediate" category ("atypical Spitz nevus/tumor") between Spitz nevus and melanoma [6,7]. Within Barnhill's "intermediate" category, the risk of malignancy of each lesion was considered as allegedly proportional to its "deviance" from the conventional stereotype of the Spitz nevus.

As an extreme consequence of this view, in 2006 Barnhill proposed that every Spitzoid lesion could be actually classified "intermediate" and thereby designated as "tumor" (without or with atypical features) [19]: more explicitly, all Spitzoid lesions could be virtually "non-benign," with the new dichotomic approach thus being "tumor vs melanoma." The message to the clinician, which stems from Barnhill's approach is that basically all Spitzoid lesions represent a harmful occurrence, and in our opinion, this is too much.

In keeping with the concept of Spitzoid neoplasms as a morpho-biological spectrum, we have adopted a four-tiered classification system proposed by Da Forno [20] and encompassing: i) Spitz nevus; ii) atypical Spitz nevus; iii) (atypical) Spitz tumor; iv) Spitzoid melanoma [17]. The histopathologic criteria for the differential diagnosis between the two "intermediate" categories of the spectrum—atypical Spitz nevus and Spitz tumor—are provided in Table 1. Briefly, a Spitz tumor is—by definition—"tumorigenic," i.e., it is characterized by a nodular silhouette made by confluent sheets of cells in the dermis without intervening collagen, and/or (non-traumatic) ulceration, and/or relevant mitotic activity [17]. The decision-making process following a diagnosis based on our classification system is itemized in the "Guidelines for management" section.

An algorithm for the clinical diagnosis of Spitzoid neoplasms

It is commonly said that Spitz nevus can show all the "local" dermoscopic features of melanoma, but in a more or less tidy fashion [15,17]. The occurrence of an atypical (melanoma-like) dermoscopic pattern in Spitz nevus is also possible. However, the relationship between dermoscopic and histopathologic atypia is not absolute, inasmuch as dermoscopically atypical lesions are not necessarily histopathologically atypical as well; conversely, it is well known that amelanotic

TABLE 1. Proposed histopathologic criteria for the differential diagnosis between atypical Spitz nevus and Spitz tumor (Copyright: ©2015 Ferrara et al.)

Microscopic features	Atypical Spitz nevus	Atypical Spitz tumor
Size	7-10 mm	>10 mm
Tumorigenicity (nodule)	-	+
Asymmetry	Superficial	Deep +/- superficial
Sharp circumscription, intraepidermal	+/-	+/-
Sharp circumscription, lateral dermal	-	-/+
Sharp circumscription, deep dermal	-	+/++
Epidermal atrophy	-/+	+/++
Ulceration	-	-/+
Large dermal nests	Superficial	Deep +/- superficial
Dermal sheets of cells	-	+/++
Deep extension	-	+
Melanin in the depth	-	-/+
Cytologic atypia	Focal ('random')	Widespread
Maturation	+	-
Mitotic figures	Few	Numerous and/or close to the base

melanoma can show a tidy ("Spitz nevus-like") dermoscopic appearance [21].

Since a fully reliable clinico-dermoscopic distinction between Spitz nevus and melanoma is not possible, surgical excision is warranted for all lesions with Spitzoid features. There is, however, a remarkable exception to this rule: since in pre-puberty Spitz nevus is relatively common [12] whereas melanoma is exceedingly rare [22], a Spitzoid lesion in patients younger than 12 years can be managed conservatively unless it stands as atypical on clinical and/or on dermoscopic grounds, either at the baseline or during follow up [12]. For the above, the clinical evaluation of such lesions can be accomplished according to the following algorithm:

1. Recognition of a Spitzoid melanocytic lesion on dermoscopy: this is enough to warrant surgical excision after puberty.
2. Recognition of atypical clinicodermoscopic features in a Spitzoid melanocytic lesion: this is the threshold for surgical excision in prepubescent patients.
3. Recognition of atypical clinicodermoscopic features during follow up of a Spitzoid melanocytic lesion in prepubescent patients.

The following sections will focus on hypopigmented Spitzoid lesions; nevertheless, the above-specified algorithm must be implemented for all Spitzoid lesions, irrespective of the amount of their pigmentation.

Recognition of a hypopigmented Spitzoid lesion

A hypopigmented Spitzoid melanocytic neoplasm can be typified by at least one of the following:

1. Homogeneous pink color: sometimes associated with a brownish hue or remnant(s) of brown pigmentation.
2. Dotted vascular pattern: short capillary loops visible as pinpoint dots, best appreciated with non-contact dermoscopy.
3. "Starburst" vascular pattern: long centrifugal capillary loops visible as regular lines radiating toward the periphery of the lesion, easier to be observed with non-contact dermoscopy.
4. Reticular depigmentation: a grid of whitish areas delineating pink (homogeneous or "dotted") areas representing the holes of the net.
5. Chrystalline (chrysalis-like) structures (with polarized dermoscopy only): a variation on the theme of reticular depigmentation, featuring white shiny parallel or orthogonal or disordered linear streaks or short lines which can be seen only with polarized light dermoscopy.

These features can consistently help the clinical differential diagnosis with hypopigmented Clark nevus, pyogenic granuloma, juvenile xanthogranuloma, molluscum contagiosum, and viral wart.

Any single above-listed feature can be seen also in melanoma. Symmetric and plaque-like or slightly raised (dome-

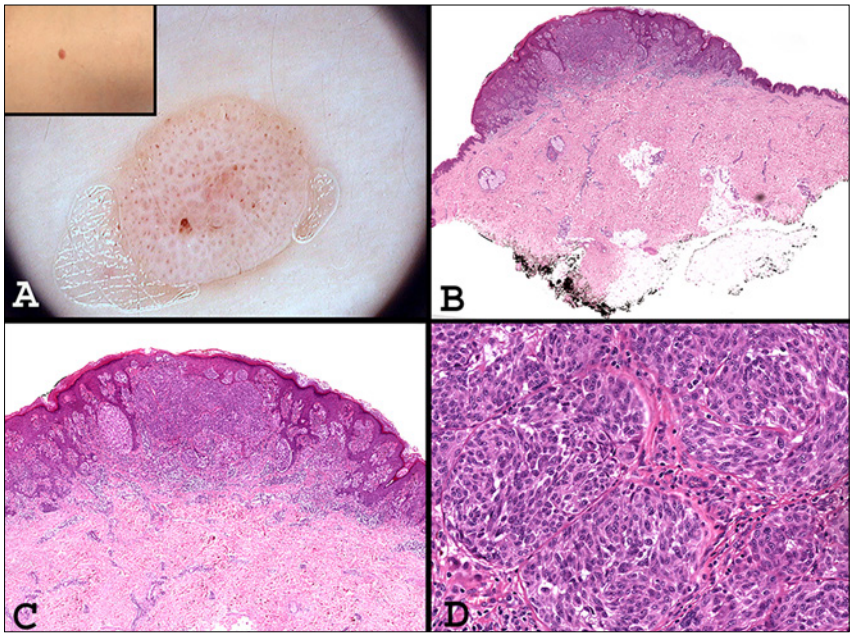

Figure 1. A lesion of the right thigh in a 22-year-old woman. The lesion is clinically (A, inset) reddish and sharply circumscribed; on dermoscopy (A) its main feature is reticular depigmentation, which is associated with regularly distributed light brown dots/globules. Overall, the lesion is very symmetric. Nevertheless, it is slightly atypical histopathologically. The silhouette is dome-shaped, with a sharp lateral circumscription (B) but also with a central exaggerated confluence of nests within the superficial dermis (C) at this level, cytomorphology is very bland and monomorphic, with no mitotic figure (D). Histopathological diagnosis: Spitz nevus according to Ackerman's classification [8]; Spitz tumor with atypical features according to Barnhill's classification, 2006 [19]. Our histopathological diagnosis was atypical compound Spitz nevus and a narrow re-excision was advised. (Copyright: ©2015 Ferrara et al.)

shaped) cutaneous lesions showing these dermoscopic features in a tidy fashion are most commonly Spitz nevi; nevertheless, a histopathologically atypical Spitzoid proliferation can be dermoscopically quite tidy and symmetric (Figure 1), thereby underlining once again the need to excise all lesions with Spitzoid features after puberty.

Recognition of atypical clinicodermoscopic features in a Spitzoid melanocytic lesion

This topic is of paramount importance in prepubescent patients. In 2005, Urso [23] performed a review of 19 papers reporting 62 Spitzoid neoplasms showing an aggressive biological behavior in spite of histopathologic features not enough for a diagnosis of clear-cut malignancy. Nine criteria were thus found to be predictive of metastatic potential: notably, such criteria were not the very same as for "conventional" melanoma and, most important, they had to be used in a completely different manner, because even the presence of one criterion could be virtually incompatible with benignity. Urso's [23] criteria are listed in Table 2, along with their expected clinico-dermoscopic counterpart. By accepting Urso's approach [23], atypical (possibly malignant) Spitzoid neoplasms are most often:

A. Large, commonly >7 mm in diameter;
B. Nodular: more or less irregularly raised, palpable, firm, sometimes polypoid and/or ulcerated;
C. Hypo-amelanotic: pink-reddish in color, with a nondescript or, else, with a prominent and/or polymorphous vascular pattern.

The above listed features have been summarized in the clinicopathologic definition "red Spitz tumors," as opposite to the "blue Spitz tumors" [12], the latter histopathologically corresponding to epithelioid (Spitzoid) proliferations intermingled with heavily pigmented dendritic melanocytes (so-called "pigmented epithelioid melanocytomas" [24]). The two cases of red Spitz tumors shown in Figure 2 demonstrate that such lesions sometimes disclose unspecific dermoscopic features with a clinical picture which is, however, definitely worrisome.

The unique banal cutaneous lesion, which cannot be differentiated from a red Spitz tumor on the basis of dermoscopy, is pyogenic granuloma: this is the reason why always submit to histopathologic examination the curetted material of any pyogenic granuloma look-alike lesion. The quality of the vascular pattern is of paramount importance for the differential diagnosis of "red Spitz tumors" from more common and banal lesions, such as viral warts (Figure 3) and molluscum contagiosum (Figure 4). In our experience, a diagno-

TABLE 2. Histomorphologic criteria for metastasizing atypical Spitz nevi/tumors (Urso, 2005 [23]) with their clinico-dermoscopic correlates (Copyright: ©2015 Ferrara et al.)

Histopathologic Features	Clinico-Dermoscopic Correlates
Expansile dermal nodule	(Large) nodule
Deep extension	(Large) nodule
Deep mitoses	Nodule
Abundant melanin in depth	Gray-blue or pink color
Great nuclear pleomorphism	No correlate
Asymmetry	Asymmetry (when superficial)
Necrosis	No correlate
Epidermal atrophy	Prominent vascular pattern, ulceration
Cells within the lymph vessels	No correlate

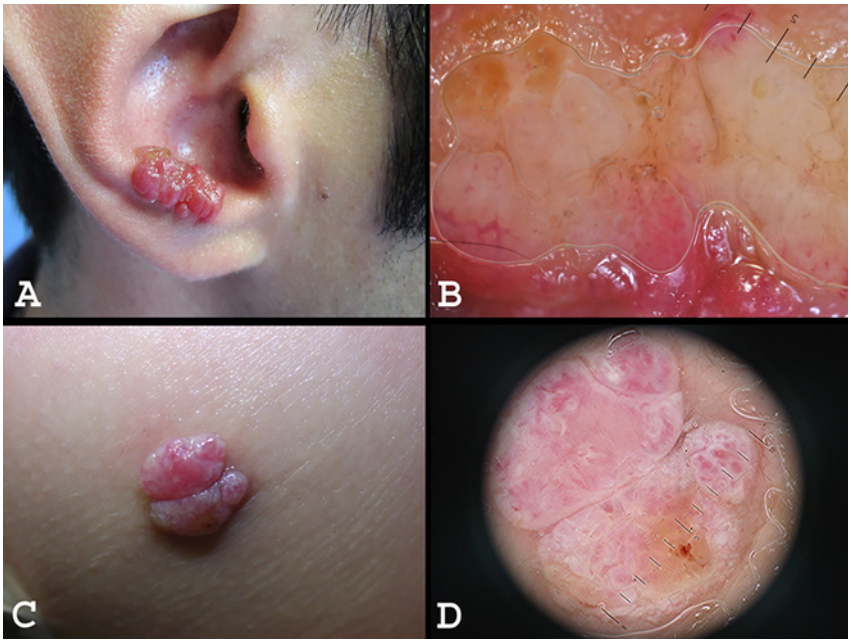

Figure 2. Two examples of "red tumors" which are not easily recognizable as "Spitzoid" on clinicodermoscopic grounds. On the top, a multinodular polypoid neoplasm of the external ear (A) in a 9-year-old boy. The neoplasm is dermoscopically typified by a prominent ad atypical vascular pattern (diffuse reddish areas, dotted vessels, peripheral thick linear irregular vessels); a few light brown areas are also visible and can dermoscopically suggest that this highly atypical lesion is melanocytic (B). On the bottom, a raised multinodular pink-reddish lesion of the buttock (C) in an 11-year-old boy; dermoscopy (D) shows whitish-pink lobules with a polymorphous vascular pattern (diffuse pink-red areas, thin and elongated linear-irregular vessels, hairpin vessels), peripheral white globules, and light brown structureless areas. Also in this case dermoscopy discloses remnants of pigmentation, which are not clinically evident and, again, can suggest that the lesion is melanocytic. In both cases our histopathological diagnosis was (atypical) Spitz tumor. (Copyright: ©2015 Ferrara et al.)

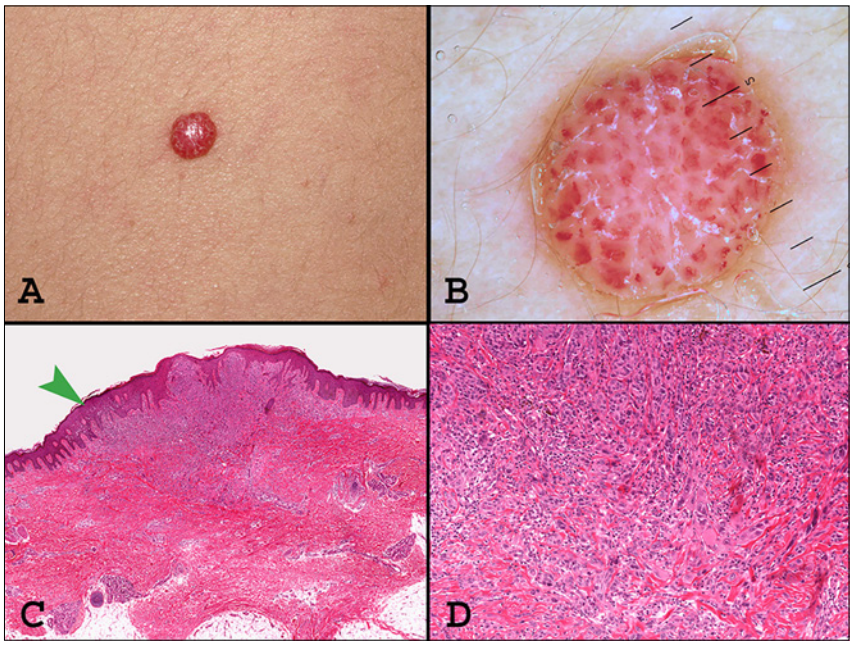

Figure 3. A dome-shaped red lesion with a light verrucous surface (A) located on the back in a 7-year-old girl. Dermoscopy (B) suggests that the lesion is probably not a viral wart, because of the presence of a thick reticular depigmentation surrounding linear irregular vessels; some small white scales and a peripheral light brown symmetric pigmentation are visible as well. Histopathologically, the lesion is very atypical, with an asymmetric involvement of the epidermis (C, arrow) and a deep dermal component made by epitheloid (spitzoid) cells with a confluent pleomorphomism and a larger size than the overlying melanocytes (D). Histopathological diagnosis: Spitzoid melanoma, according to Ackerman's classification [8]; Spitz tumor with atypical features, according to Banhill's classification, 2006 [19]. Our histopathological diagnosis was (atypical) Spitz tumor. In this case, a sentinel node biopsy disclosed few parenchymal aggregates of pleomorphic melanocytes; no completion lymph node dissection was performed. The patient is alive with no evidence of disease after six years. (Copyright: ©2015 Ferrara et al.)

sis of Spitz nevus in the presence of a polymorphous vascular pattern must be made only under a compelling histopathological evidence of benignity; we have also suggested that when a given Spitzoid lesion is histopathologically atypical but its "grading" is uncertain, the presence of a highly atypical vascular pattern could point toward its management as a "tumor" instead of an "atypical nevus" [17].

Recognition of atypical clinicodermoscopic features during follow-up of a Spitzoid melanocytic lesion in prepubescent patients.

Dermoscopic monitoring of Spitzoid proliferations can be recommended only for plaque-like or dome-shaped dermoscopically symmetric lesions before puberty [12]: the suggested protocol is based on clinico-dermoscopic controls every three to six months [25]. A completely benign hypopigmented lesion is expected to enlarge, even very rapidly but always very symmetrically, and then to slowly involute, either completely [26] or up to a "dermal nevus-like" homogeneous light brown pattern [27,28]. Abnormal dermo-

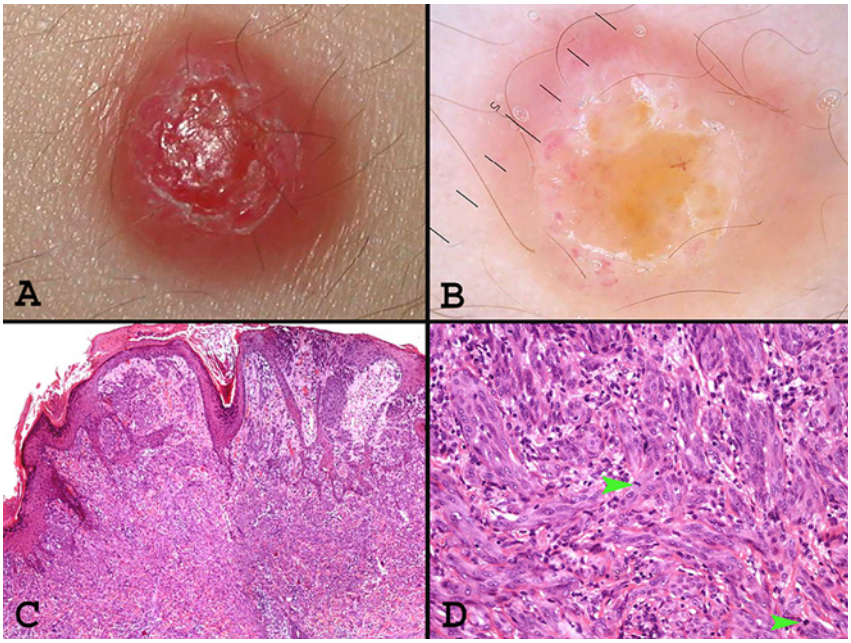

Figure 4. A melanocytic neoplasm removed from the forearm of a 10-yr-old girl. Clinically (A) the lesion is firm red nodule with a central depression. Dermoscopically (B), a central yellow crust could resemble the umbilication of a molluscum contagiosum; however, vessels around the crust are atypical; in addition there is a peripheral reddish area with dotted vessels which suggest that the lesion is melanocytic. Histopathologically the neoplasm is strikingly cellular and focally eroded with large dermal sheets of cells (C); several mitotic figures (D; arrows) are detected in the mid-dermal component. Histopathological diagnosis: melanoma according to Ackerman's classification [8]; Spitz tumor with atypical features according to Barnhill's classification, 2006 [19]. Our histopathological diagnosis was (atypical) Spitz tumor. Histologic images kindly provided by Prof. Raffaele Gianotti, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy. (Copyright: ©2015 Ferrara et al.)

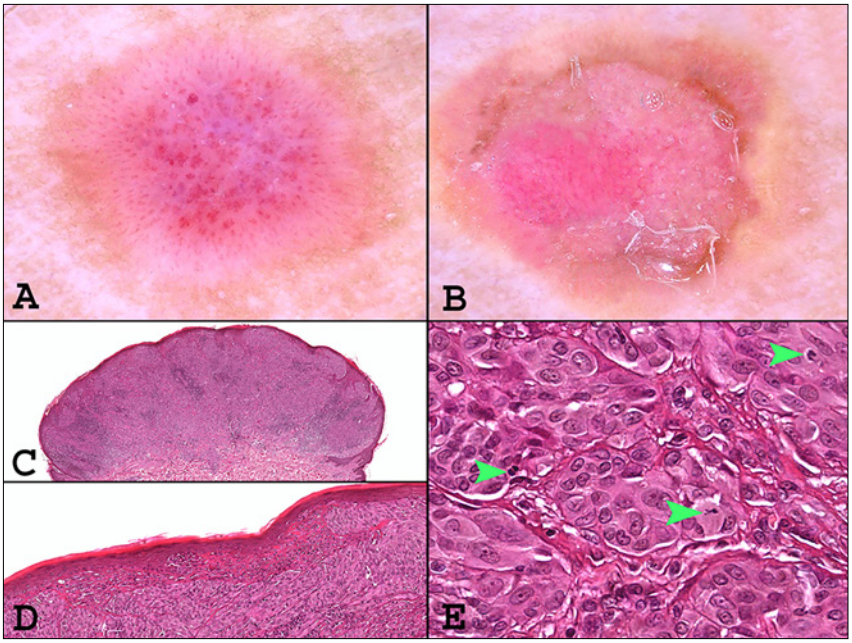

Figure 5. Dermoscopic digital monitoring of a red lesion of the arm in a melanocytic lesion of the leg in a 5-year-old girl. At the baseline (A), the lesion is typified by a quite symmetrical 'starburst' vascular pattern associated with a reticula depigmentation; rare coiled vessels are also present. After 17 months (B), there is evidence of early nodular growth in the central area, which appears homogeneous pinkish-red with some dotted vessels and thin linear vessels. A brownish peripheral hue is also evident. Histopathologically, the silhouette is nodular (C), with wide areas of epidermal atrophy (D) and crops of dermal mitotic figures (E; arrows). Histopathological diagnosis: melanoma according to Ackerman's classification [8]; Spitz tumor with atypical features according to Barnhill's classification, 2006 [19]. Our histopathologic diagnosis was (atypical) Spitz tumor. (Copyright: ©2015 Ferrara et al.)

scopic digital follow up findings (an example is given in Figure 5) include:

A. Asymmetric growth
B. Nodular/polypoid growth
C. Ulceration
D. Increased atypia in the vascular pattern.

Any of the above features warrant immediate surgical excision.

Spitzoid melanoma: a clinicopathological reassessment

While adult Spitzoid melanoma is often clinically and dermoscopically indistingiuishable from "conventional" melanoma, pediatric Spitzoid melanoma shows very peculiar clinicopathologic features. Histopathologically, it differs from atypical Spitz nevus or Spitz tumor by showing a non-Spitzoid cytomorphologic clone arising in the context of a Spitzoid lesion. Such a highly unusual occurrence can be detected even clinically and dermoscopically. In Figure 6 the "clone" is the red nodule with a nondescript vascular pattern; the nodule was initially treated as per pyogenic granuloma, but histopathologically disclosed a highly atypical proliferation of pleomorphic epithelioid cells. On the excision specimen, the "shoulder" of the neoplasm disclosed a bland morphology, featuring monomorphic spindle cells, probably representing a benign background (Spitz nevus) in which Spitzoid melanoma had been developing. Based on the very few exceptional cases we have seen, pediatric Spitzoid melanoma is a malignancy

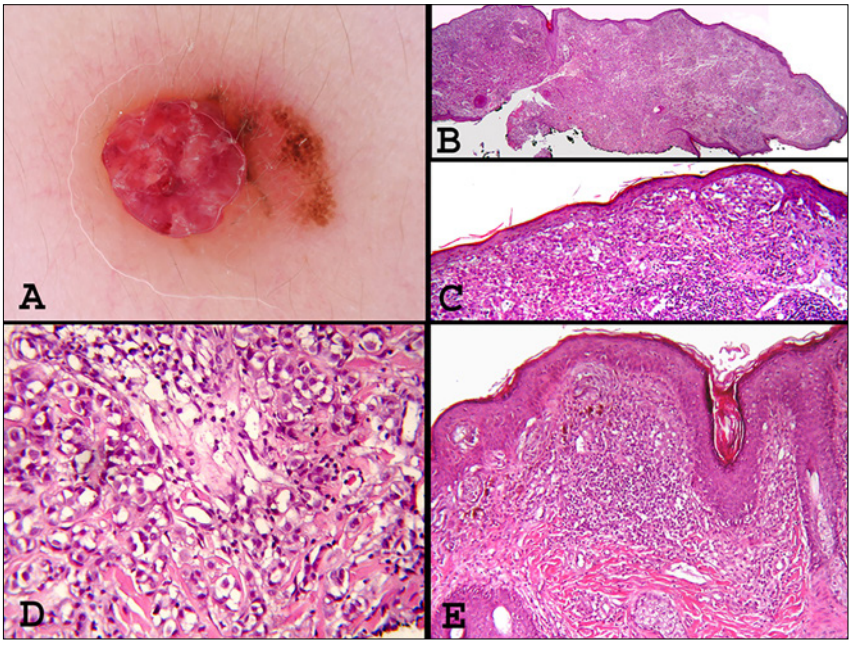

Figure 6. An atypical neoplasm of the face in an 11-year-old girl. Dermoscopically (A) the lesion is biphasic: a flat portion shows reticular depigmentation along with structureless and globular brown areas; a nodular area discloses a non-descript vascular pattern, featuring a diffuse reddish area. The lesion was clinically diagnosed as a pyogenic granuloma associated with a Spitz nevus. For aesthetic reasons, the nodular portion was thus curetted. Histopathologically, the nodule showed a widespread derma atrophy (B) with large sheets of epithelioid cells at the junction (C); cytomorphologically, dermal melanocytes were epithelioid but devoid of true 'Spitzoid' features (D). The excision specimen showed a bland junctional proliferation of spindle cells (E), which were clearly different from epithelioid melanocytes of the previously curetted nodule (F). Histopathological diagnosis: melanoma according to Ackerman's classification [8]; Spitzoid melanoma according to Barnhill's classification, 2006 [19]. Our histopathological diagnosis was pediatric Spitzoid melanoma (melanoma over a Spitz nevus). The dermoscopic differential diagnosis between pyogenic granuloma and nodular melanoma is virtually impossible; nevertheless, histopathologically we have never seen a pyogenic granuloma associated with a melanocytic nevus.

arising in the background of a Spitz nevus [17], just like already suggested for melanoma arising in Spitz tumor [29].

Guidelines for management

Surgical excision is recommended for all lesions with Spitzoid dermoscopic features detected after puberty. Before puberty, plaque-like or dome-shaped dermoscopically symmetric lesions with Spitzoid features can undergo dermoscopic digital monitoring [12]. Large (>1cm), nodular, ulcerated, rapidly growing/changing, or otherwise atypical Spitz nevi of the childhood must be excised.

The management of patients with a histopathologic diagnosis of atypical Spitz nevus and Spitz tumor should be decided with a multidisciplinary approach and on an informed consent basis. A narrow re-excision can be considered for atypical Spitz nevi and must be recommended for all incompletely excised lesions, as well as for Spitz tumors. The opportunity of a sentinel node biopsy for Spitz tumors should be evaluated case by case. The decision must be made by preliminarily considering that in Spitz tumors the presence of isolated tumor cells in the sentinel node is not an unequivocal sign of malignancy [30,31] and is not an indication to completion lymphadenectomy, based on the ambiguity of the primary. It must be also underlined that, in a recent meta-analysis, 98-99% of young patients with Spitz tumors had no evidence of disease after a median follow-up of 59 months, regardless the sentinel node positivity [14]; therefore, the diagnostic and prognostic information given by a positive sentinel node in young patients seems to be negligible.

If this is true, an echotomographic monitoring of the regional nodes (and an echotomography-guided fine needle aspiration biopsy cytology) can even replace sentinel node biopsy, because it allows to efficiently detect massive replacement of the node(s) by neoplastic cells, thereby addressing selected patients to election lymphadenectomy [31]. Such a follow up protocol is probably the best choice in patients younger than 10 years, especially for lesions located in the head/neck area, a region in which surgical procedures are aesthetically relevant and are hampered by a sizable failure rate [32].

The prognosis of Spitz tumors is age-dependent [33]. Adult patients, who are expected to be at greater risk, could be managed more aggressively. The risk stratification for atypical Spitzoid melanocytic proliferations has been recently addressed with the use of a new four-probe fluorescence in-situ hybridization (FISH) assay for 6p25 (RREB1), 11q13 (CCND1), 9p21 (CDKN2a), and 8q24 (MYC) [34]. The following categories have been individuated: i) Spitzoid melanoma with homozygous 9p21 deletion (high risk); ii) Spitzoid melanoma with 6p25 and/or11q13 gain (intermediate to high risk); iii) atypical Spitz tumor with isolated 6q23 deletion (low risk); iv) atypical Spitz tumor with no FISH abnormality (low to very low risk). So far, the number of investigated cases is too low to validate the above-detailed risk stratification system. However, the use of FISH techniques for prognostic—rather than for diagnostic—purposes seems to be a very promising tool. In adult patients, cases of Spitz tumor with homozygous deletion of 9p21, best evaluated using a dual color FISH test targeting CDKN2a (SpectrumOrange) and Cep9 (SpectrumGreen), might be managed as per melanoma.

The suggested management for both pediatric-type and adult-type Spitzoid melanoma is obviously the same as for "conventional" melanoma.

Conclusions

The introduction of dermoscopy has significantly changed the clinical diorama of Spitzoid lesions. Since there are still many controversial points in the histopathologic categorization of these lesions, clinicopathologic correlation must be the mainstay for their diagnosis and proper management.

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