Interstitial Granulomatous Drug Reaction to Adalimumab

To the Editor:

Interstitial granulomatous dermatitis (IGD) is a distinct inflammatory reaction pattern of the skin. Differential diagnosis for this histological pattern includes interstitial granuloma annulare, IGD of connective tissue diseases, leukemia cutis, necrobiosis lipoidica, granulomatous mycosis fungoides, deep fungal infections, paraneoplastic diseases, and interstitial granulomatous drug reaction (IGDR). The latter is an uncommon entity first described by Magro et al[1] as asymptomatic annular erythematous to violaceous plaques with a predilection for intertriginous areas, medial thighs, and inner aspects of the arms. The incidence of such reactions has been increasing with the use of biological agents. We report, to the best of our knowledge, the second such reaction to the tumor necrosis factor-α (TNF-α) inhibitor adalimumab (Humira).

A 45-year-old woman with psoriatic arthritis who had been treated with adalimumab (Humira) for 6 months presented with a 1-month history of painless violaceous dermal nodules located symmetrically on both thighs. Histological examination of a biopsy specimen showed an interstitial deep dermal infiltrate composed mostly of histiocytes and lymphocytes surrounding and entrapping degenerated collagen bundles, accompanied by a few interspersed neutrophils and eosinophils (Figs. 1A–C). Immunohistochemistry for CD68 highlighted numerous macrophages and a few neutrophilic cells present in the infiltrate (Fig. 1D). This lesion resolved after discontinuation of adalimumab.

IGDR has been reported as a cutaneous reaction induced by various medications, particularly calcium channel blockers, sennoside, angiotensin-converting enzyme inhibitors, lipid-lowering agents, antihistamines, diuretics, anticonvulsants, ganciclovir, antidepressants, and herbal medications.[2,3]

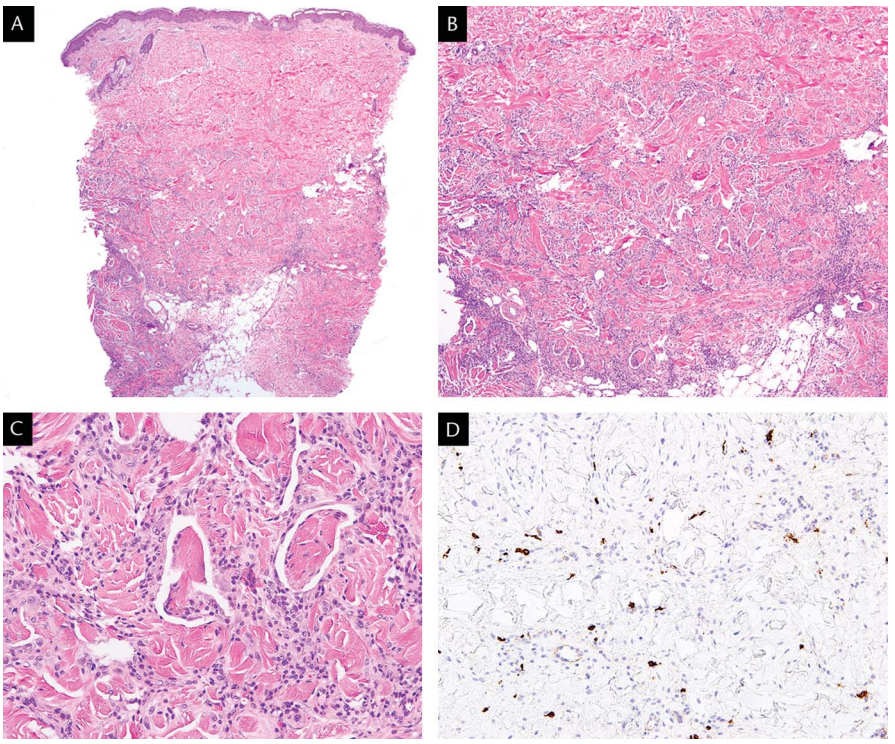

FIGURE 1. A, An interstitial granulomatous infiltrate affecting mid and deep reticular dermis (hematoxylin–eosin stain, original magnification ×10). B, C, The infiltrate was composed mainly of histiocytes and lymphocytes surrounding and entrapping degenerated collagen bundles, accompanied by few interspersed neutrophils and eosinophils (hematoxylin–eosin stain, original magnifications: B ×40; C ×200). D, CD68 stain showed substantial interspersed histiocytes (D ×200).

TNF-α is an inflammatory cytokine involved in normal and pathological human physiology. Biological treatments that inhibit this cytokine have been used with success in the treatment of autoimmune disorders such as psoriasis, inflammatory bowel disease, and rheumatoid arthritis. Although anti–TNF-α therapy is safe and well tolerated, various adverse cutaneous reactions have been documented. Adalimumab is a genetically engineered fully human IgG monoclonal antibody to TNF-α, with a high specificity and affinity, which is approved for use in rheumatoid arthritis, inflammatory bowel disease, psoriasis, and psoriatic arthritis. The most frequent adverse effects reported with this treatment include injection site pain local reaction, nausea, and upper respiratory tract infections. IGDR has been reported previously in an isolated case,[4] showing the same clinical and histopathological characteristics as our patient.

Clinical features include annular, erythematous, violaceous plaques on the arms, medial thighs, and intertriginous areas. The defining histopathological features include an interstitial lymphohistiocytic infiltrate, fragmentation of collagen and elastic fibers, a variable amount of mucin deposition, interface changes, lymphoid atypia, and the presence of eosinophils. Necrobiosis and vasculitis are characteristically absent.

It is likely that IGD represents a reactive phenomenon with a histopathological spectrum, which arises in conjunction with various disorders including autoimmune diseases, lymphoproliferative disorders, and drug reactions.

In summary, to our knowledge, we describe the second reported case of IGD in a patient with psoriasis receiving

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adalimumab. The increase in use of this agent in the management of autoimmune disorders emphasizes the importance of recognizing the secondary skin manifestations of this drug.

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Reparative Perineural Hyperplasia and Dermatofibroma

To the Editor:

In the February 2009 issue of this journal, Dr Beer published the original study titled "Reparative perineural hyperplasia: a series of 10 cases."[1] In that study, the author nicely described a series of 10 cutaneous reexcision specimens containing concentric proliferation of perineural cells around nerves in the mid or deep dermis. Such histological alteration occurred in intimate association to fibrosis and/or chronic inflammatory infiltrate. Immunohistochemistry confirmed the perineural differentiation and helped to exclude other processes such as neoplastic perineural invasion and reexcision perineural invasion. The author proposed the term "reparative perineural hyperplasia" (RPH) as a descriptor for this phenomenon.

Recently, we had the opportunity to observe similar findings in association to a dermatofibroma (DF) without history of previous local surgery. A 25-year-old woman sought medical attention for a lump on her right leg of 3-month duration. She denied previous local trauma and was otherwise in a perfect health condition. The attending dermatologist described the lesion as a 0.8-cm nodule over the anterior aspect of the right leg and performed a 4-mm punch biopsy. The microscopic low-power magnification revealed an unencapsulated and well-delimited deep dermal lesion, which spared the superficial dermis (Fig. 1A). Higher power examination showed classic features of DF, including spindle cells with inconspicuous nucleoli, homogeneous chromatin, and barely evident cytoplasm disposed in a slightly storiform collagenous stroma, as well as collagen entrapment in the outer portions of the lesion (Fig. 1B). No necrosis, mitosis, or nuclear atypia were observed. The deepest portion of the DF extended into the subcutaneous fat through the interlobular fibrous septa, toward the deepest margin of the specimen (Figs. 1A, C). At the dermohypodermic junction, close to an interlobular fibrous septum, one could observe a nerve entrapped by the main lesion (Fig. 1C). Interestingly, the perineurium of this nerve showed hyperplastic features including ring-like layers of spindle cells harboring plump and hyperchromatic nuclei and with immunoprofile confirmatory of perineurium (EMA^+, $AE1/AE3^-$, and $S100\ protein^-$) (Figs. 2A, B). A slight chronic inflammatory infiltrate composed of lymphocytes and plasmocytes was found in adjacent areas to this nerve.

Normal perineurium may present up to 12 concentric cell layers depending on the location and nerve size, and the cells are invariably flattened.[2] In nerves of the deep dermis or of the transition between the dermis and the subcutaneous tissue, the perineurium usually has 1–3 concentric layers of thin cells. Although

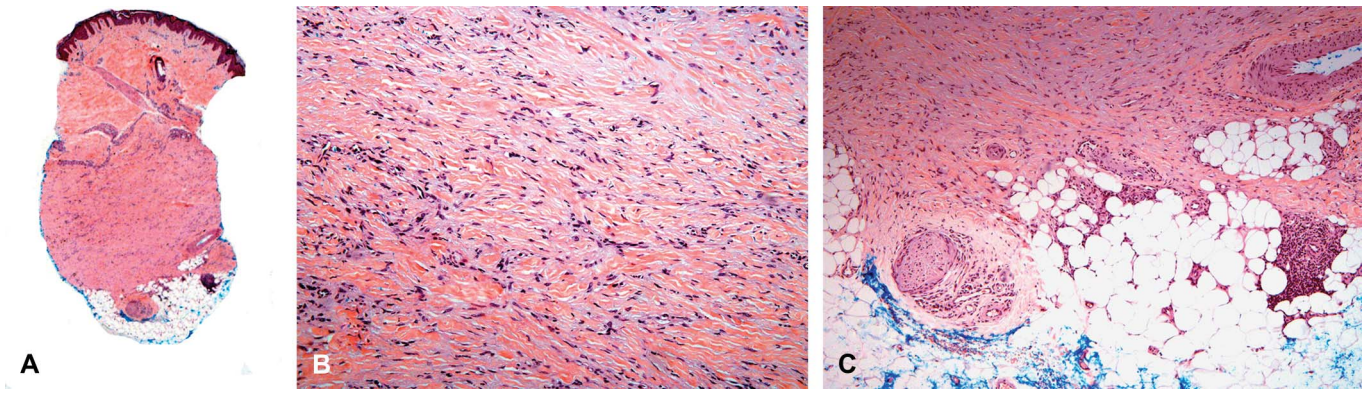

FIGURE 1. A, Low-power magnification revealed a deep dermal unencapsulated and well-delimited lesion. B, Classic features of DF: spindle cells with inconspicuous nucleoli, homogeneous chromatin, and barely evident cytoplasm disposed in a slightly storiform collagenous stroma and collagen entrapment. C, DF extension into the subcutaneous fat through the interlobular fibrous septa. Near to an interlobular fibrous septum, a nerve entrapped by the main lesion is seen.

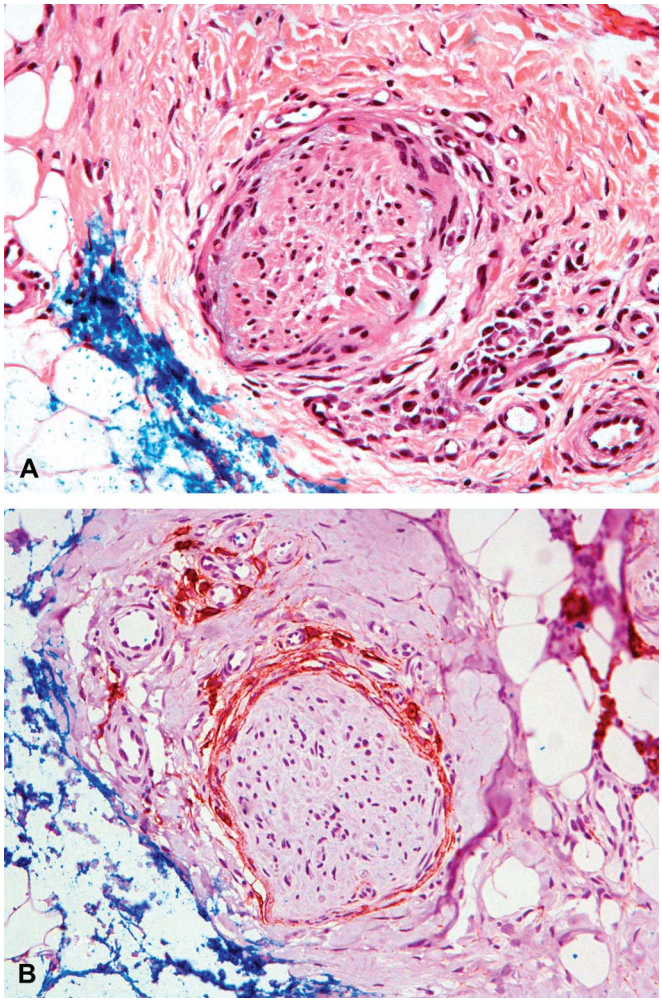

FIGURE 2. A, This nerve's perineurium showed hyperplastic features including 3–4 cell thick, ring-like layers of spindle cells harboring plump and hyperchromatic nuclei. B, Immunohistochemistry shows cytoplasmatic expression of EMA in the perineural cells.

in Dr. Beer's series, the illustrations depict 4–6 cells thick perineurium with slight hyperchromatic nuclei, the present case harbors a 3–4 cells thick perineurium with prominent nuclear enlargement and hyperchromasia. Except for this detail and for the association to DF, these nerve alterations were indistinguishable from the ones described by Dr. Beer in his article.

Despite the fact that the current patient denied previous local trauma, the role of trauma in the pathogenesis of perineural hyperplasia in this case cannot be ruled out for the following reasons: (1) unnoticed minor injuries are likely to occur in the lower leg of any healthy and active person; (2) it occurred in association to a DF, an entity that is widely known (at least a subset of cases) to be related to trauma; and (3) in Dr Beer's series (the only series so far on RPH), all patients had been submitted to cutaneous surgery.

This case illustrates that RPH is not restricted to the context of prior surgical procedure. Indeed, perineural hyperplasia such as the one described here may occur in other fibrosis-associated or trauma-elicited conditions, including cutaneous involvement by systemic sclerosis[3] and Morton's neuroma.[4] However, to our knowledge its association to a DF has not been noticed in the past.

The importance of recognizing RPH in the current case is to avoid potential misinterpretation of a DF as a peripheral nerve sheath tumor or desmoplastic melanoma. Perhaps, RPH is a phenomenon more common than one would expect, and we believe that from Dr. Beer's study on RPH will be observed more frequently, including in association to other cutaneous conditions related to local trauma or fibrosis.

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Spitz Nevus: An Evolving Clinicopathologic Concept

"Memory is treasure and guardian of every thing"
—M. T. Cicero (106 B.C.–43 B.C.)

To the Editor:

We read with great interest the article on 349 cases of Spitz nevi by Requena et al,[1] which was published in a recent issue of the *American Journal of Dermatopathology*, and we would like to

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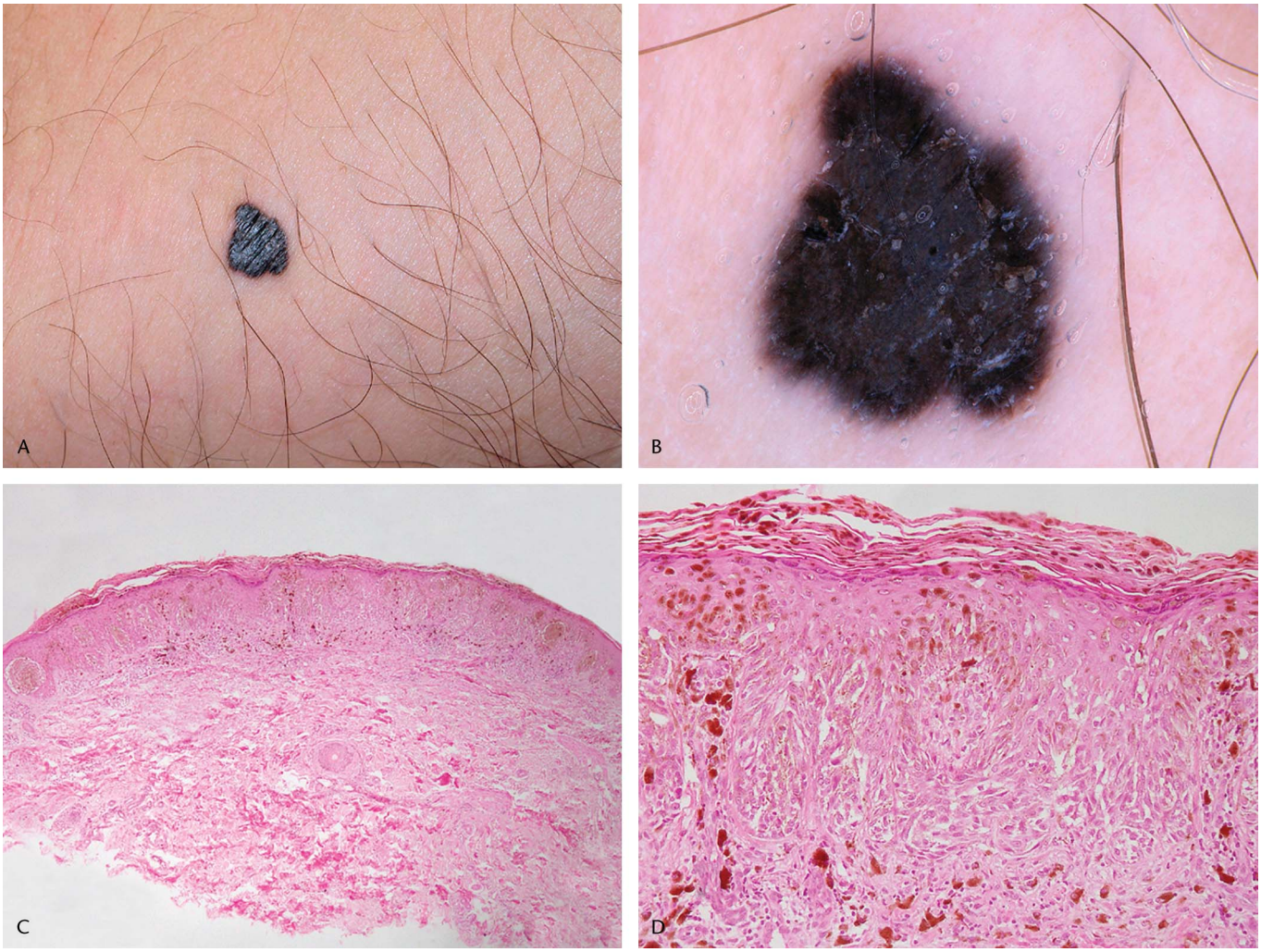

FIGURE 1. A, Clinical view of a heavily pigmented asymmetric plaque located on the left arm of a 33-year-old man. B, Dermoscopically, the lesion exhibits a starburst pattern typified by pigmented streaks distributed at the periphery in a regular fashion. Despite the shape, asymmetry, distribution of color, and structure are rather homogenous in dermoscopy. C, Histopathologically, the lesion is slightly raised and sharply circumscribed (hematoxylin–eosin ×40); D, there is a moderate epidermal hyperplasia with hypergranulosis and a prevailingly nested junctional proliferation of spindle and epithelioid melanocytes (hematoxylin–eosin ×250). The overall histopathologic features are quite in between a PSCSN and a RN.

underline and expand some of the findings by these authors.

As a preliminary observation, one can immediately realize that most of the histopathologic features and pictures of Spitz nevus described and shown by these authors[1] have little, if any, to share with the original description made by Spitz.[2] Over 60 years, the histopathologic spectrum of Spitz nevi has considerably expanded to such an extent that its clinical recognition has become challenging, just like Requena et al[1] overtly admit that, in fact, in their series, only 18.33% of cases were correctly diagnosed on clinical grounds. Clinicians can no longer identify Spitz nevus just as a pink–red dome-shaped lesion of the face and extremities of the childhood: Actually, such a "classical" Spitz nevus is highly uncommon in histopathologic series, probably also because it is rarely, if ever, excised.[3] In our opinion, this is the main reason why Requena et al[1]—not really surprisingly to us—found that only

TABLE 1. Histomorphologic Criteria for Metastasizing ASNT (Urso, 2006[32]) With Their Clinicodermoscopic Correlates

Histopathologic Features	Clinicodermoscopic 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

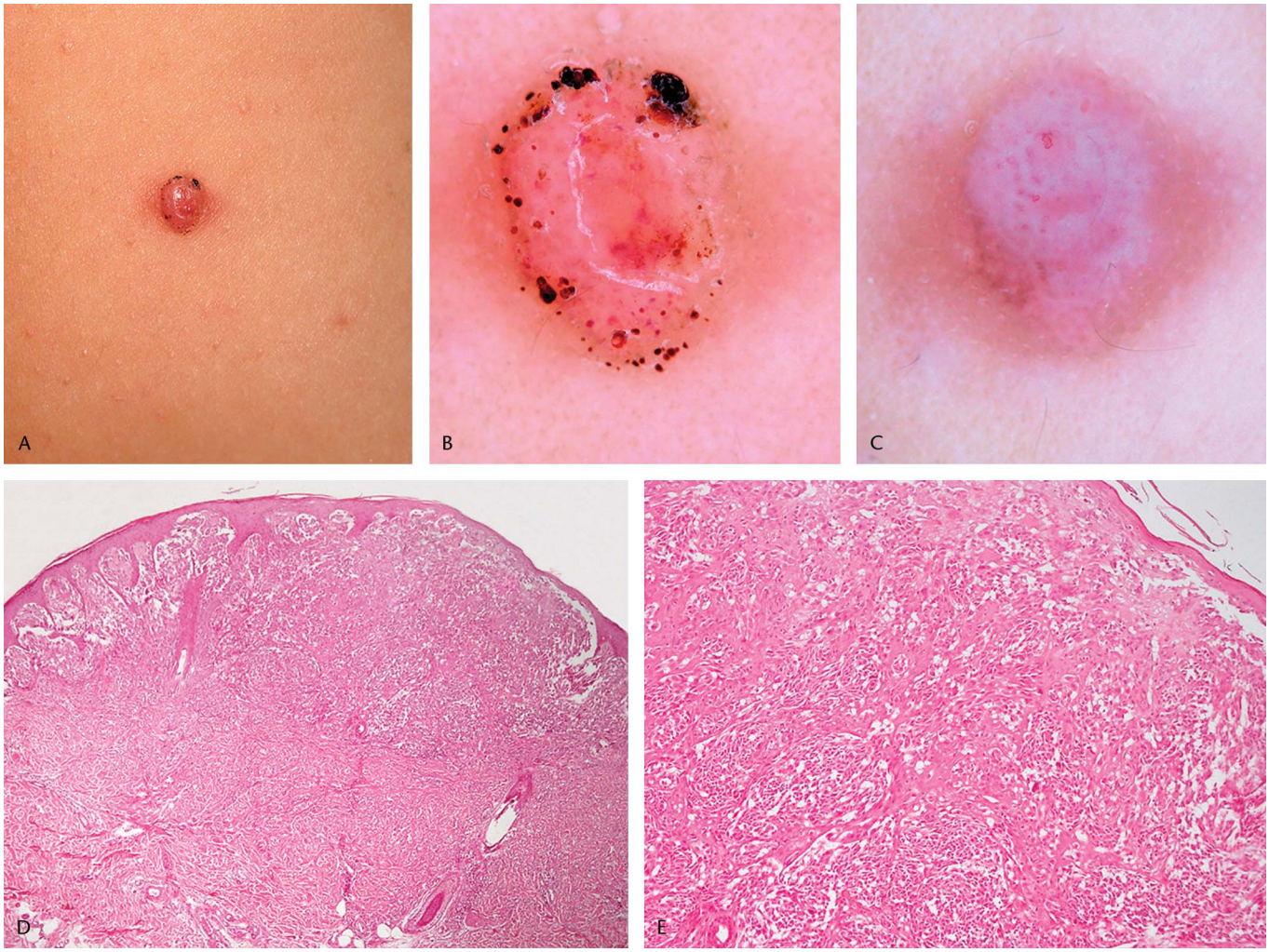

FIGURE 2. A, Clinical view of a pink nodule located on the right arm of an 11-year-old girl. B, At a first dermoscopic examination, the lesion exhibits a few red to black hemorrhagic globules over a pink background. C, The second dermoscopic view refers to the same lesion after 15 days when the planned excision was finally performed. The hemorrhagic globules are no more appreciated, and the lesion shows a tan pigmentation at the periphery with a few irregular vessels in the amelanotic central portion. D, Histopathologically, the lesion is nodular and asymmetric (hematoxylin–eosin ×40); E, despite the absence of any pagetoid spread, there is atrophy of the epidermis, together with some irregular architecture of the dermal nests, which are notably larger in the depth than close to the surface (hematoxylin–eosin ×100). The lesion was 4.48 mm in thickness: a sentinel node biopsy showed isolated tumor cells within the subcapsular sinus.

22.1% of their pediatric cases were located on the face.

The article by Requena et al[1] should prompt clinicians and histopathologists to identify a "new" prototype of Spitz nevus. And indeed, one major reason for this effort is the clinicopathologic definition and recognition of "atypical Spitz nevi/tumors" (ASNTs).[4–11] In fact, before defining what is "atypical," we should define what is "typical," and, should we be unable to define a "typical" Spitz nevus, we should reject at all these terms and classify spitzoid lesions into Spitz tumors without significant abnormality, atypical Spitz tumors, and spitzoid melanoma.[11] Such a cautious approach, however, is not easy to be accepted, nor is it in keeping with a "clinicopathologic terminology," because clinical dermatology defines "tumors" as cutaneous elevations exceeding the size of a cherry,[12] and this is seldom the case of spitzoid lesions.

In our opinion, the increasing use of dermoscopy (syn: dermatoscopy, skin surface microscopy) in the preoperative evaluation of cutaneous lesions is going to dramatically change our view on Spitz nevi.[3] Before dermoscopy (or without dermoscopy), Spitz nevus could be mainly identified by clinicians as a red nodule of the face and extremities of children; in addition, histopathologists previously stated that about one-fourth of Spitz nevi could be found in patients older than 14 years and that some cases could also present as tan or black macules or plaques.[13] However, such a "pigmented" variant of Spitz nevus, with only few exceptions[14] composed by spindle cells [pigmented spindle cell Spitz nevus (PSCSN)], was poorly characterized on clinical grounds; moreover, its histopathologic recognition

raised an "issue within the issue," namely, the nosologic autonomy, if any, of PSCSN[13,15] from Reed nevus (RN).[16] Such an "issue within the issue" is still unresolved. Requena et al[1] embrace the largely adopted theory, which considers RN, as belonging to the morphologic spectrum of Spitz nevus.[3,15,17] Actually, they state that RN is the most common variant of Spitz nevus (64 of 349 cases in their series).[1] Some authors, however, still maintain RN as a distinctive clinicopathologic entity.[18–23] Interestingly, Ackerman[15,17] first set forth a unifying concept but finally stated that "Spitz nevus is different morphologically from RN and both of these nevi are different morphologically and biologically from melanoma."[24] We already dealt with this "issue within the issue" and demonstrated that the histopathologic distinction between PSCSN and RN is not feasible.[3] But, even more important, such a distinction has no clinical relevance: clinically, both PSCSN and RN are commonly medium-sized (mean size in our series: 4.9 cm) black macules or plaques; dermoscopically, both PSCSN and RN are more or less heavily pigmented, with 3 main global patterns, namely, globular, starburst, and multicomponent (melanoma like).[3] In clinicodermoscopic–pathologic studies, tan–black macules and plaques account for the large majority of spitzoid lesions (79.5% in our previous study[3]); instead, pink–red papulonodular lesions with a dotted/polymorphous vascular pattern[25] are surprisingly rare (4.8% in our series[3]). Therefore, dermoscopy seems to allow clinicians to increasingly identify and excise PSCSN/RN, to such an extent that the previously poorly defined "tan or black" Spitz nevus is surprisingly becoming the most common Spitz nevus encountered in clinicodermoscopic–pathologic studies.[3,26,27] Of course, we cannot assess with absolute certainty whether such a predominance of tan–black macules and plaques over pink–red papulonodules is true or simply due to a selection bias in these studies. It must be emphasized, however, that lesions with a spitzoid dermoscopic pattern, regardless their amount of pigmentation and palpability, are basically managed according to the same rule, namely, because no absolute criterion allows a clinician to reliably differentiate Spitz nevus from melanoma,[3,28] all the lesions with spitzoid dermoscopic features need to be excised in patients older than 12 years.[29] The implementation of the same clinical management for both types of spitzoid lesion should minimize any selection bias and allow us to conclude that Spitz nevus is completely different from its classical description because it is most often a tan or black, flat or slightly raised lesion (Fig. 1). This lesion when detected in the childhood and followed over months or years can completely involute.[30,31]

Once defined, the most common clinicopathologic presentation of Spitz nevus, we should outline the clinicopathologic features of ASNT. In 2006, Urso[32] used a retrospective morphologic evaluation of metastasizing cases of ASNT reported in the literature (in all, 19 articles collecting 62 cases); thus, he found 9 criteria, which could be predictive of metastatic potential. Such criteria are not the very same as for conventional melanoma (provided that a conventional melanoma does exist[33,34]); but, most important, these criteria should be used in a completely different manner because even the presence of 1 criterion could be virtually incompatible with benignity. Urso's[32] criteria are listed in Table 1 along with their expected clinicodermoscopic counterpart. By accepting such a "pessimistic but realistic approach" by Urso,[32] ASNT could be outlined as medium to large, papulonodular, sometimes ulcerated, hypoamelanotic lesions (Fig. 2). In other words, pink–red papulonodular lesions, previously considered as the "classical" Spitz nevus, could be histopathologically atypical with a greater probability than tan–black macules and plaques of PSCSN/RN. And if we consider Urso's[32] approach in keeping with the hypothesis that ASNT are melanomas with a low or very low metastatic potential,[33] hence, we could conclude that maybe Spitz[2] was not completely wrong in her basic statements: after all, 1 of her 13 patients died of metastatic disease and this was surprisingly forgotten over decades.

In conclusion, dermoscopy is probably changing our diorama of spitzoid lesions, inasmuch as it is allowing a better recognition of flat or slightly raised tan to black PSCSN/RN. Should PSCSN/RN be the most common clinical picture of histopathologically benign spitzoid lesions, then ASNT would be clinically ascribed mainly to medium to large, mostly hypo-amelanotic (pink–red) nodules, to wit: those lesions, which classical clinical dermatology considered as stereotypical examples of Spitz nevi, could actually be the most common clinical presentation of ASNT.

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Squamous Cell Carcinoma With Osteoclast-Like Giant Cells: 2 Cases Misdiagnosed as Atypical Fibroxanthoma

To the Editor:

In this journal, Wooff et al[1] recently reported 2 cases of cutaneous squamous cell carcinoma with osteoclast-like giant cells. They discussed the differential diagnosis of this condition and concluded that the giant cells were an unusual reaction to the tumors, rather than representing neoplastic cells. Three similar cases were also reported in correspondence to this journal by Emanuel[2] earlier in 2009.

At *Cutaneous Pathology*, during a recent archival review of 183 cases diagnosed as atypical fibroxanthoma (AFX), 4 lesions were identified with osteoclast-like giant cells. Two cases were confirmed as AFX on the clinical and histological appearances allied with a panel of immunostains that included multiple melanocytic and epithelial markers. The clinical features of the other 2 cases are shown in the Table 1. Both lesions exhibited atypical spindle-shaped cells invading the dermis without pigmentation, junctional activity, or obvious keratinization. In case 1, there was also a small complement of epithelioid cells. Scattered diffusely throughout each neoplasm were multinucleated giant cells of osteoclast-like appearance, which were CD68 positive (Figs. 1, 2).

Occasional multinucleated neoplastic cells were also present in case 1. These were distinguishable from the osteoclast-like giant cells by nuclei that showed highly irregular contours with hyperchromasia, pleomorphism, and cytoplasmic cytokeratin positivity (Fig. 3).

TABLE 1. Selected Clinical and Histological Features of the Squamous Cell Carcinomas With Osteoclast-Like Giant Cells

Case	Sex	Age (yrs)	Site	Solar Elastosis	Ulceration	Cell Morphology
1	Male	95	Nose	Severe	Yes	Spindle and epithelioid cells
2	Male	75	Scalp	Severe	Yes	Spindle cells only

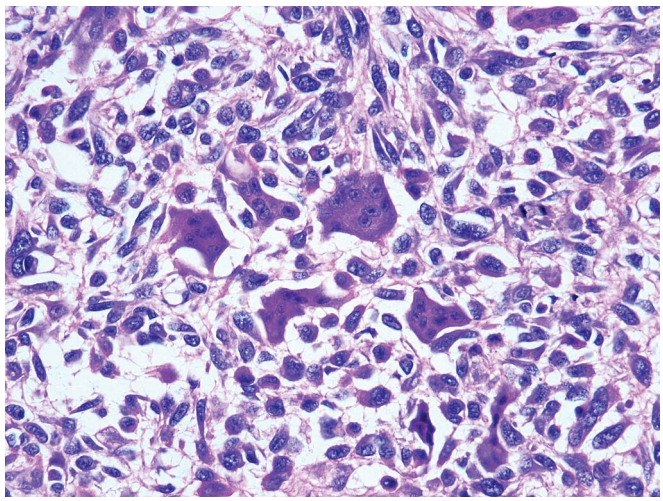

FIGURE 1. This poorly differentiated squamous cell carcinoma showed numerous osteoclast-like giant cells (case 1, hematoxylin and eosin stain).

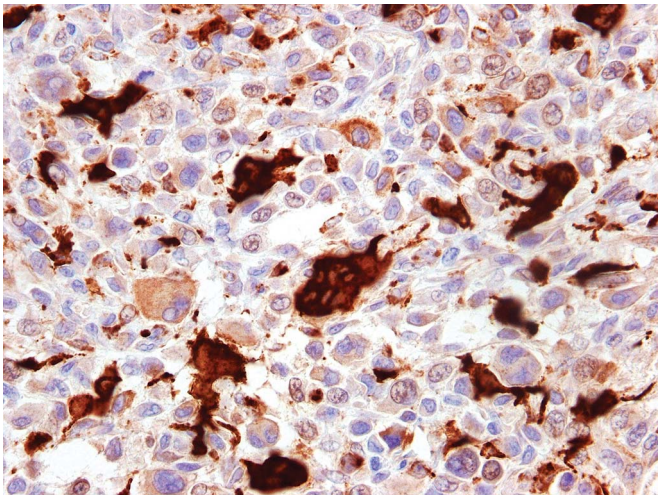

FIGURE 2. The osteoclast-like giant cells were strongly positive with CD68 and negative with multiple epithelial markers in each case (case 1, immunohistochemistry for CD68).

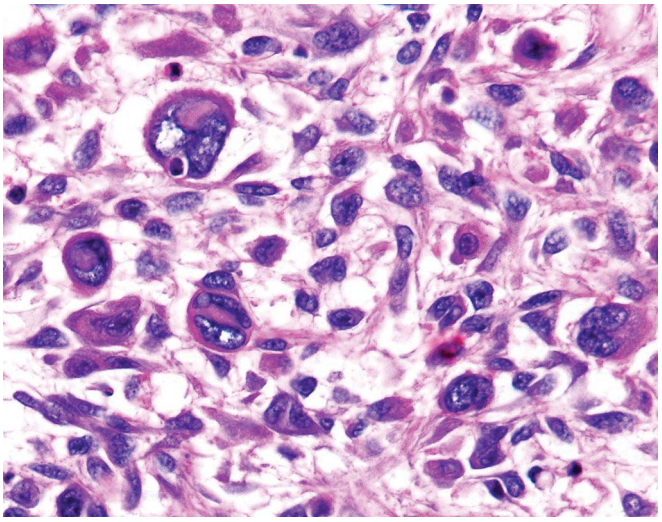

FIGURE 3. Multinucleated neoplastic cells were present in case 1, which were clearly distinguishable from the osteoclast-like giant cells by their marked nuclear atypia and lack of cytokeratin staining (hematoxylin and eosin stain).

Although both neoplasms had been previously categorized as AFX, reexamination of the immunostains revealed focal weak MNF116 and AE1/3 positivity in the atypical neoplastic cells in both cases. The osteoclast-like giant cells were negative. Case 2 was subsequently stained with 34betaE12, which showed more generalized and stronger neoplastic cell staining than had been seen on the previous epithelial stains, with negative staining of the osteoclast-like giant cells. The appearances in each case were reinterpreted as representing poorly differentiated (sarcomatoid) squamous cell carcinoma with osteoclast-like giant cells.

Osteoclast-like giant cells seem to be a rare feature of AFX, seen in only 2 of 183 cases in this series (1.0%). Because of the difficulty of excluding a poorly differentiated squamous cell carcinoma, it is possible that some of the cases previously reported in the literature as AFX with osteoclast-like giant cells may be erroneous.

In summary, I agree with Wooff et al[1] and Emanuel[2] that rare squamous cell carcinomas in the skin may demonstrate included osteoclast-like giant cells that are most likely to be macrophage derived. Their presence may invoke confusion with AFX, especially if cytokeratin stains are weak or patchy. Consequently, I recommend the use of a range of cytokeratin stains to distinguish poorly differentiated squamous cell carcinomas from AFX and suggest including 34betaE12 in this panel. The utility of 34betaE12 has been previously highlighted in the literature after a poorly differentiated recurrent squamous cell carcinoma was misdiagnosed as AFX until a high–molecular weight cytokeratin was applied.[3]

Finally, as to whether the osteoclast-like giant cells are neoplastic or reactive, I suspect that both forms may occur. In most instances, the cells are likely macrophage derived (they are CD68 positive, negative with epithelial markers, and not cytologically atypical), whereas in other cases, they are multinucleated neoplastic cells. This would account for the atypia and positive epithelial markers reported in some previous cases.

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Multinucleated Cells Angiohistiocytoma: A Reactive Lesion?

To the Editor:

First described in 1985 by Smith and Wilson-Jones,[1] multinucleate cells angiohistiocytoma (MCA) is a rare lesion

considered to represent a benign vascular or fibrohistiocytic tumor.[2] So far, around 55 cases have been reported in the literature. Most often occurring in middle-aged women, MCA is clinically characterized by multiple, red to violet papules usually located on the limbs, mainly on the legs or on the dorsum of the hands. Occasional cases were described on the face or chest, and one case in the oral mucosa has recently been reported.[3] Papules often tend to regroup in the same anatomic site, and can measure up to 1.5 cm. The lesions develop over several years and then cease growth; few cases have demonstrated spontaneous regression. Microscopic examination reveals proliferation of small vessels associated with spindle or round fibroblast-like cells and peculiar multinucleated cells in the superficial and upper mid-dermis. The latter are angulated, star shaped, and feature up to 10 hyperchromatic nuclei and a basophilic cytoplasm. Vessels are well differentiated and usually lined by CD34-positive endothelial cells with prominent nuclei. The surrounding

TABLE 1. Clinicopathologic Characteristics of Patients With MCA

Patient Number	Age (yrs)	Sex	Medical History	Associated Disease on Skin Biopsy	Location
1	56	F	Rheumatism	None	Leg
2	44	F	Unavailable	Basal-cell carcinoma	Inferior lip
3	64	M	Positive for the HIV	Squamous cell carcinoma	Face
4	50	M		Xanthelasma	Eyelid
5	21	F	Hidradenitis suppurativa	Dermal chronic inflammation and abcesses	Axilla
6	84	F	Breast cancer, Radiation therapy	Chronic radiation dermatitis	Breast
7	73	M	Knee prosthesis	Scar	Knee
8	29	F	Dermal lymphocytic capillaritis 15 months ago	None	Leg

F, female; M, male.

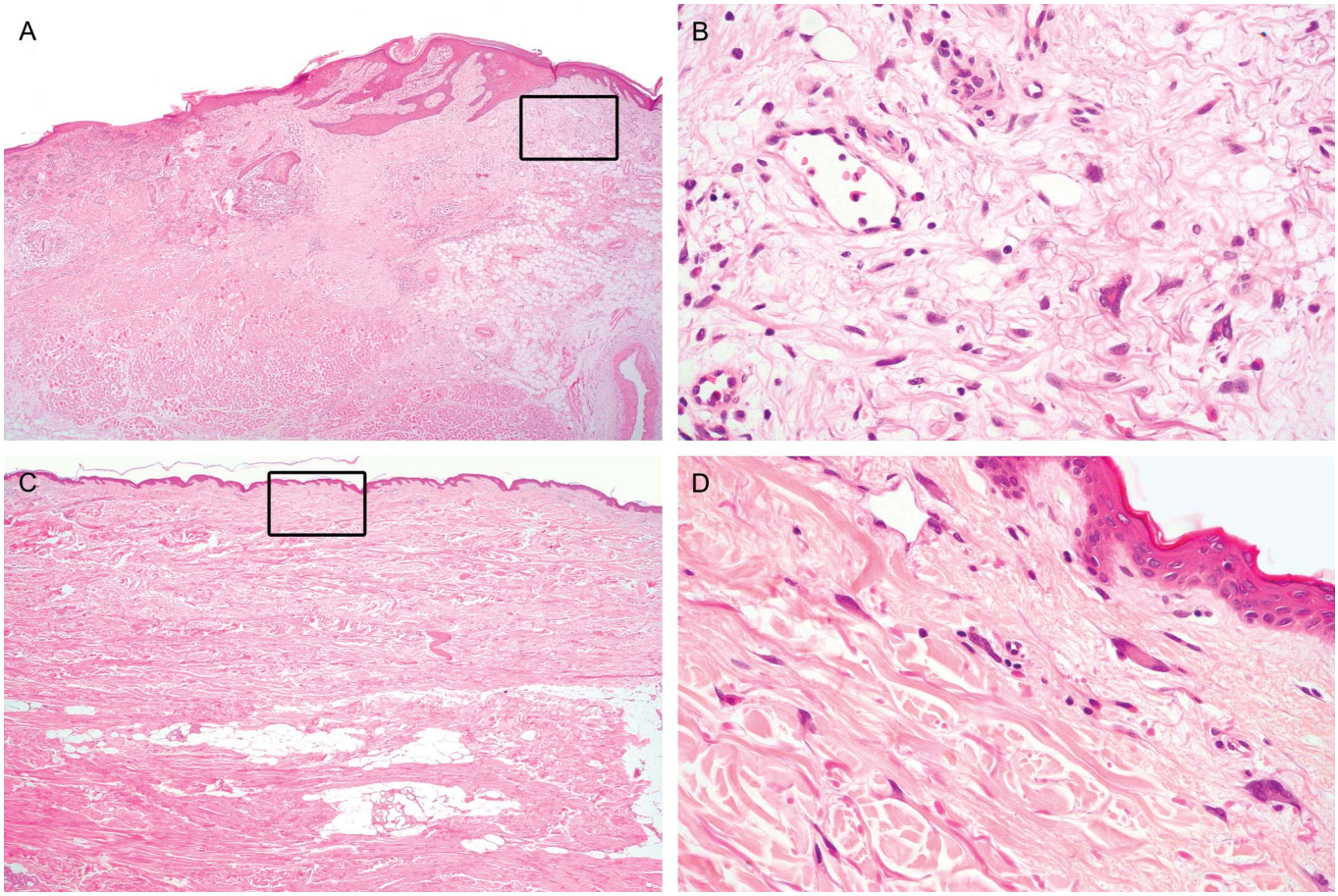

FIGURE 1. Tumor excision on the inferior lip of patient 2 shows on the left an ulcerated, infiltrating basal cell carcinoma, occupying the whole dermis with uninvolved orbicularis oris muscle. A, High-power field magnification (area framed in A) reveals the typical aspect of multinucleated cells angiohistiocytoma, with large angulated multinucleated cells, associated with numerous capillaries in a fibrous stroma with mast cells. B, Chronic radiation dermatitis lesions are seen in patient 6 skin sample, with dense dermal fibrosis associated with elastosis. C, Multinucleated cells are seen at high magnification in the upper part of the lesion, along with dilated capillaries (D, are framed in C).

dermis shows a variable degree of fibrosis, with mast cells and foci of inflammation. The positive staining of fibroblastic cells for CD68 and Factor XIIIa prompted some authors to consider this lesion as a member of the fibrohistiocytic skin tumor group,[4] although multinucleated cells, which are hallmark of the disease, are usually negative for both markers. However, histogenesis of these lesions remains largely unknown. Especially, whether it represents a neoplasm or a reactive process is a matter of debate. Due to its apparent rarity, literature about MCA is not yet well documented and we believe that MCA may actually be underdiagnosed by practicing pathologists.

Herein we report 8 patients in which we microscopically detected lesions with histological and immunohistochemical features reminiscent of MCA (CD34 and CD68 immunostainings were systematically performed). Interestingly, in most of these cases (n = 7), MCA developed within a cutaneous neoplastic or reactional process, whereas in the remaining case (patient 1, Table 1), it presented as erythematous papules on the leg, as classically described, allowing diagnosis of MCA.[2] As shown in Table 1, we identified MCA-like lesions at the periphery of nonmelanoma skin cancers (basal-cell carcinoma and squamous-cell carcinoma) in 2 cases (Fig. 1A–B), and surrounding a xanthelasma in another. In the 3 remaining cases, MCA arose in conjunction with various reactive conditions involving the skin. In one 21-year-old woman with hidradenitis suppurativa, it actually developed on the axilla, nearby chronic inflammatory lesions of the dermis, whereas in another 84-year-old woman, it was found within chronic radiation dermatitis (Fig. 1C–D), on a breast previously treated by tumor resection followed by chemotherapy and radiation therapy. In patient 7, MCA-like lesions were found on the knee, overlying a bone prosthesis placed because of degenerative joint disease. Although most of these cases do not fit within the classical clinical presentation of MCA, we believe they are closely related, if not similar lesions, because they all showed the prototypical morphologic and phenotypic features of this lesion. Our cases featured all histologic criteria of MCA, but whether they are "real" MCA or just reactive processes mimicking the microscopic aspects of MCA cannot be investigated, in the absence of a specific marker of MCA's cells. We may, however, speculate that the clinical spectrum of MCA could be broader than usually described in the literature and may encompass "idiopathic" and reactive variants. It is conceivable that in patients 2–8 from our series, MCA-like lesions rather represented a reactive process to chronic injury, that is, cancer with stroma inflammatory reaction, chronic inflammation (hidradenitis suppurativa), chronic radiation dermatitis, and scarring, than a neoplastic process per se. In agreement with our findings, a case of MCA associated with mycosis fungoides has been reported.[5] Interestingly, in the last patient reported here (patient 8), MCA was diagnosed on the leg and medical history revealed that she presented 15 months ago with an eruption, showing histologically a dermal lymphocytic capillaritis. We therefore may ask whether MCA may be caused, even partly or initially, by vascular injury. All this, however, remains speculative, all the more that classical MCA develop without prior history of skin tumor or reactive condition, as far as we know.

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Histopathologic Diagnosis of Leprosy in a Nonendemic Area

To the Editor:

Rongioletti et al,[1] in a recent case report, underlined the problem of leprosy diagnosis in nonendemic areas like Europe. We would like to report 3 additional cases that illustrate very well how in nonendemic countries both dermatologists and dermatopathologists often lack specific experience, with potentially harmful delay in patient's treatment. In this context, we would like to underline that in Italy (like in many other European Countries) the official resident immigrant population increased from 1,549,373 units in 2002 to 3,432,651 units in 2007 (data available at http://demo.istat.it/). Many other immigrants, however, do not appear in the official statistics, and the real number probably exceeds 4–5 millions units. In the years 2002–2008, the National Reference Center for Hansen's Disease (HD) in Genoa reported 64 new leprosy cases: 6 patients were Italians (5 infected during periods spent in endemic countries, 1 autoctonous) and 58 were immigrants from Africa (16 cases), South America (19 cases), and Asia (23 cases), respectively. In the first 6 months of 2009 alone, 9 new cases have been observed. These data clearly show that leprosy is not infrequent also in nonendemic countries, mainly due to immigration flows.

In the last few months, 3 immigrant patients from areas endemic for HD have been sent for consultation to the National Reference Center for HD in Genoa from different departments of Italy. All patients had been sent without a specific diagnosis and only because of the clinical history of immigration from endemic countries. Biopsy specimens had been taken, processed, and reported at the original departments, but leprosy had not been included in the differential diagnoses. After clinical reevaluation of the patients in the National Reference Center for HD in Genoa, the original biopsies were sent to Graz for second expert opinion. Patient 1 (28-year-old man, immigrant from Nigeria) was biopsied for the presence of "unclear

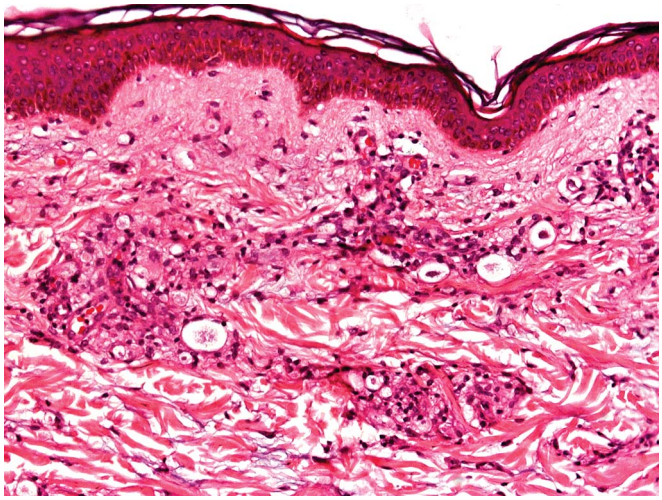

FIGURE 1. Patient 1. Dermal infiltrate constituted by Virchow cells and numerous giant vacuolated macrophages. A cleat-cut separation between the epidermis and the infiltrate is present. This case was misdiagnosed as "unusual xanthoma." Hematoxylin–eosin stain; original magnification ×100.

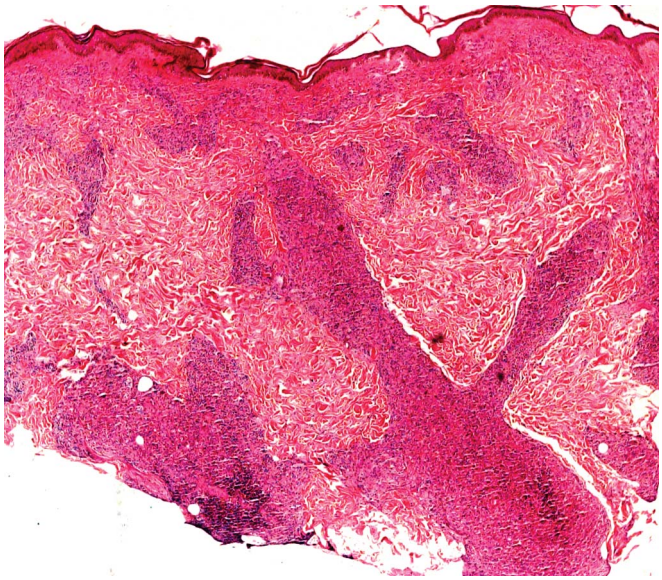

FIGURE 2. Patient 2. A grenz zone above a patchy nodular infiltrate in the dermis constituted by foamy macrophages and lymphocytes. Hematoxylin–eosin stain; original magnification ×20.

small nodules on the face." Histology showed a nodular dermal infiltrate without involvement of the epidermis. The infiltrate was composed by foamy macrophages, many of which showing giant, bizarre intracytoplasmic vacuoles (Fig. 1). The original histopathologic diagnosis was "unusual xanthoma." A Fite stain (previously not done) disclosed large numbers of solid bacilli forming typical "globi." Patient 2 (22-year-old man, immigrant from Colombia) presented with multiple nodules on the extremities and was biopsied without a specific clinical diagnosis. Histology showed a dermal, patchy-nodular infiltrate with a grenz zone; the infiltrate was composed of foamy macrophages and lymphocytes (Fig. 2). A Fite stain had disclosed numerous single solid bacilli and globi; however, a diagnosis of "unclear atypical mycobacterial infection" had been made (Fig. 3). Patient 3 (14-year-old boy, immigrant from Brazil) presented with multiple symmetric hypopigmented macules on the entire body, and was biopsied with the clinical differential diagnosis of pityriasis alba versus pityriasis versicolor (Fig. 4). In this case, too, the biopsy specimen showed a patchy-nodular infiltrate with vacuolated macrophages, many of which presenting giant vacuoles. Fite stain was clearly positive for solid bacilli and "globi," but the original histopathologic diagnosis was of "nontubercular mycobacterial infection." Interestingly, this child had been treated for 1 year for atopic dermatitis and pityriasis versicolor before being referred to the National Reference Center for HD in Genoa.

In patient 1, the correct histologic diagnosis of lepromatous leprosy probably had been simply overlooked, as a Fite stain had not been performed at all.[2–4] In patients 2 and 3, experience in histopathologic features of leprosy was lacking, and despite a positive Fite staining the correct diagnosis had not been made. Moreover, in all 3 patients the clinical diagnosis had been initially missed, too, thus underlying the difficulties for clinicians in making a diagnosis of "tropical" disorders in nonendemic countries.

Original histopathologic misdiagnosis in all of these patients resulted in the delay of appropriate treatment of highly infective patients, with potential harmful consequences both for the patients and the population. Moreover, these cases illustrate the difficulties of both clinical and histopathologic diagnosis of leprosy in nonendemic areas even in typical cases, and not only in patients with more challenging histopathologic features such as the one reported by Rongioletti et al. Concerning the patient presented by Rongioletti et al, we would also like to provide more detailed data, as she is followed in the National Reference Center for HD in Genoa. At first presentation in September 2006, the patient had multiple asymmetrical, oval-annular lesions on her legs, abdomen, and flank, with sensory anesthesia. The biopsy had been taken before referral to the National Reference Center for HD. At clinical investigation upon referral, the right ulnar nerve and the posterior tibial nerve were enlarged and

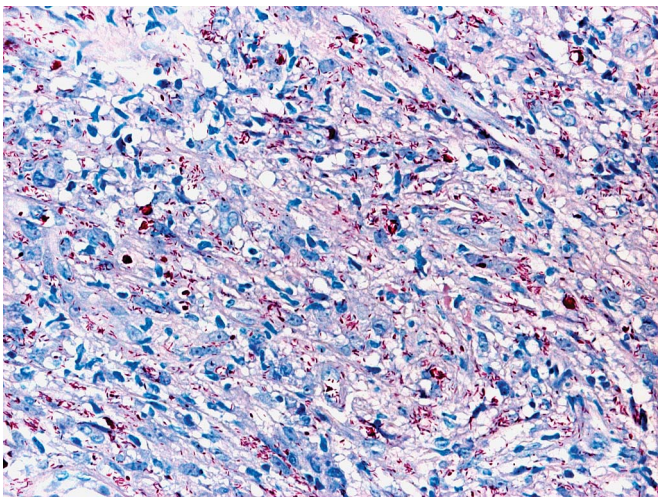

FIGURE 3. Patient 2. Fite stain disclosed numerous single solid bacilli and globi; LL had been misdiagnosed as "unclear atypical mycobacterial infection." Original magnification ×400.

painful. The original slides were reviewed and a skin smear was taken at the border of one lesion on the right leg, showing 2 solid bacilli. Based on these findings, a diagnosis of borderline tuberculoid leprosy was made, and treatment with World Health Organization multidrug therapy for multibacillary leprosy together with prednisolon 25 mg/d was started in October 2006. In February 2007, she developed a type 1 reaction with involvement of the right ulnar nerve and posterior tibial nerve. Prednisolon was increased to 60 mg/d with progressive tapering of the dose. At the last follow-up visit in June 2009, all skin lesions had completely regressed, and only a focal sensory deficit of the right planta was present.

Due to the increment of the immigration flows from endemic areas, leprosy cases might be more frequently observed also in nonendemic areas like Europe. Although HD remains a rare disease, histological confirmation is mandatory in all cases (in Italy it is requested by official guidelines of the Ministry of Health),[5] thus representing a potential pitfall for dermatopathologists without specific experience. Dermatologists and dermatopathologists should be aware of HD to properly and timely manage these patients.

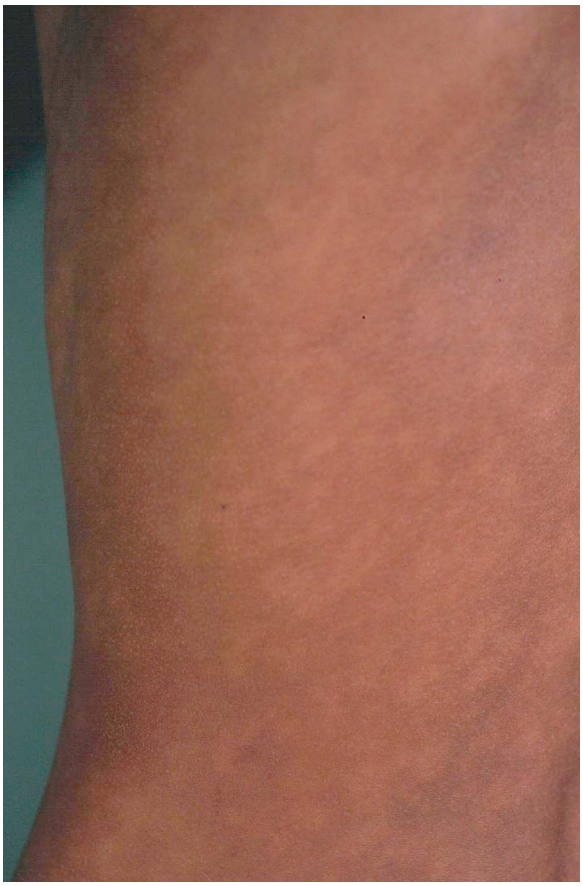

FIGURE 4. Patient 3. Multiple symmetric hypopigmented macule on flank and chest. This patient was clinically misdiagnosed as atopic dermatitits versus pytiriasis versicolor and histologically as "not-tubercular mycobacterial infection."

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Angiomatoid Intradermal Melanocytic Nevus or Chimeric Nevus?: A Potential Diagnostic Pitfall

To the Editor:

A prominent vascular component has been rarely described in melanocytic lesions. Diaz-Cascajo et al[1] were the first to report a particular variant of desmoplastic Spitz nevus with a striking fibrous stroma and many densely arranged small blood vessels. Due to its similarity to a vascular tumor, they proposed the term of "angiomatoid nevus" for this condition. Since then, few similar cases have been described, corresponding almost exclusively to Spitz nevi.[2,3] To the best of our knowledge, there is only one report of angiomatoid cellular blue nevus,[4] and we have not found any case of junctional, compound, or intradermal angiomatoid melanocytic nevus.

We recently observed a 53-year-old woman, with a progressively enlarging nodule, located on her right lumbar area, which was present for 7 years. The lesion measured 13 mm in diameter. It had a slightly pigmented and shiny surface. Telangiectasias could also be appreciated.

Dermoscopically, the lesion showed a background of light brownish pigment, with a prominent vascular pattern composed by arborizing vessels and hemorrhagic areas that were surrounded by a striking whitish veil, which was especially located in the central part of the lesion (Fig. 1).

We excised the lesion, and histologically, an intradermal melanocytic congenital type nevus was found. Several medium size vessels with thin fibrous wall, and red blood cell content were also found (Fig. 2). Significant subepidermal collagenous fibrosis was present above the vessels (Fig. 3). A cystic sudoriparous duct was present in association with the melanocytic proliferation in the lower part of the lesion.

A prominent vascular component is present histologically in a variety of

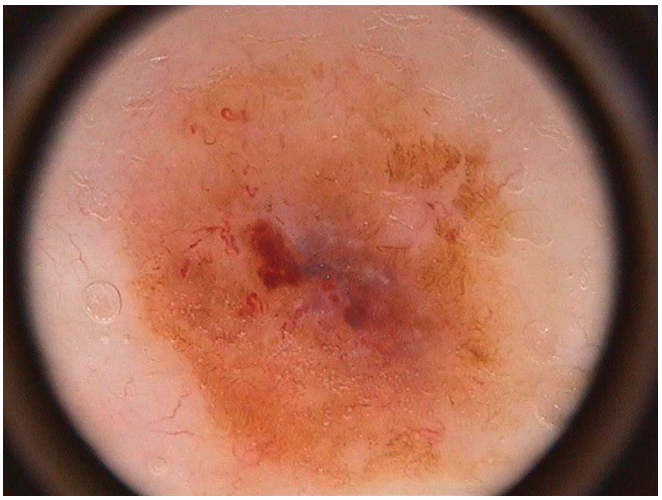

FIGURE 1. Dermoscopy shows a lesion with a multicomponent pattern, with multiple big-sized vessels and a prominent whitish veil especially located in the centre.

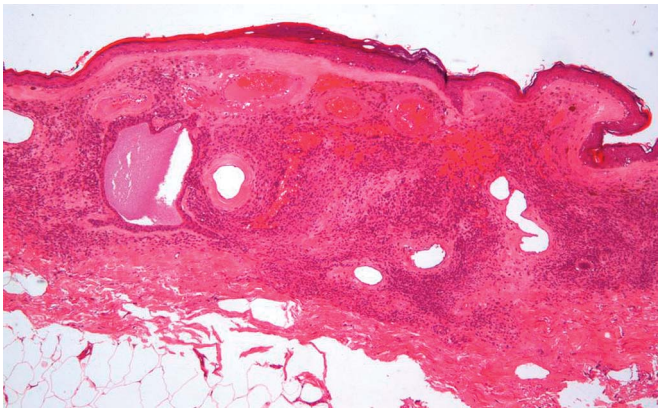

FIGURE 2. Low-power magnification showing medium sized blood vessels within a congenital intradermal melanocytic nevus, with superficial fibrosis and dilated sweat ducts (hematoxylin and eosin stain, ×40).

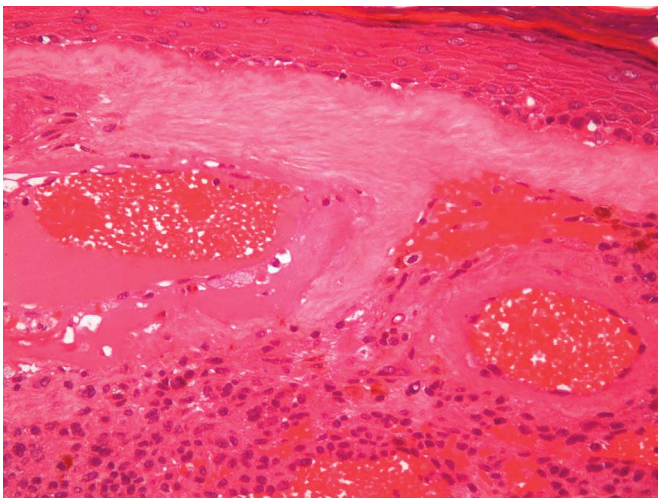

FIGURE 3. High-power view showing subepidermal fibrosis above medium sized vessels with no endothelial atypia (hematoxylin and eosin stain, ×400).

tumors. In spite of this, a vascular striking component is not frequent in melanocytic lesions, although they commonly display pseudovascular features.[4]

Angiomatoid nevus is characterized by its distinctive fibrovascular stroma. It was initially described in Spitz nevus. To date, 13 cases have been characterized in the literature (12 corresponding to Spitz nevus and 1 to cellular blue nevus).[1–4]

In angiomatoid Spitz nevus, there is a proliferation of numerous small blood vessels with plump endothelia, resembling a vascular tumor. Melanocytes are embedded in a fibrous stroma composed of thick collagen bundles distributed haphazardly. In all cases, the stroma showed large numbers of small thick-walled blood vessels with round to oval lumina lined by plump endothelial cells with monomorphous nuclei devoid of atypia. Mitotic figures were rare or absent. The vessels were distributed in clusters or as solitary units throughout the stroma, and they were preferentially located in the upper part of the lesions. A variably prominent, mostly perivascular, or diffusely distributed lymphoplasmacytic infiltrate, was noted in association with these prominent vessels. This lymphocytic infiltrate was composed predominantly of small, mature lymphocytes.[1,2]

The reported case of cellular blue nevus displayed a prominent angioma-like appearance due to the presence of numerous ectatic vessels throughout the neoplasm. Vessels were lined by flattened endothelium, incompletely filled with red blood cells and fibrinous material, and also showed fibrinous hyalinized walls of variable thickness. They were associated with irregular pseudovascular spaces, devoid of endothelial lining and directly delimited by neoplastic melanocytes. The size of these vessels was higher and they were less numerous compared with those appreciated in angiomatoid Spitz nevus.[4]

The ectatic vessels found in our case are similar to those reported by Urso and Tinacci,[4] and they were surrounded by a striking fibrous stroma that was also present in the subepidermal area. Clinically, the lesion was also a large nodule located in the lumbar area. Interestingly, dermoscopically, it showed a striking vascular pattern composed of large-sized vessels, which were embedded in a whitish veil that corresponded histologically with the significant fibrosis present in the papillary dermis and surrounding vessels.

Regarding its developmental origin one might consider the combination of what appears to be the equivalent of a vascular malformation or anomaly, for example, a superficial arteriovenous malformation, and a dermal melanocytic nevus. Perhaps the lesion could be a developmental anomaly with 2 components: vascular and melanocytic rather than 1 alone. Such a lesion might fall, therefore, under the rubric of a chimeric nevus. In this patient, the vascular pattern was only present in the raised lesion, and the adjacent back was devoid of any vascular structure suggestive of an extensive vascular malformation. Moreover, although histological features suggest a congenital origin, the patient reported that it appeared 7 years ago.

Nonetheless, many nevi exhibit relatively prominent vascular components and this simply may be an exaggerated version of a common nevus with prominent vascularity, although the combination of the prominent vascularity with the striking fibrosis is extremely rare.

The causes that would provoke this fibrosis and vascular proliferation remain unknown. In our case, the location of the raised lesion on the lumbar region, made it susceptible to repeated trauma. There are entities such as atypical decubital fibroplasia in which there is also a prominent myxoid stroma rimmed by ectatic, thin-walled vascular channels as the consequence of continued pressure of the skin against the subjacent bone.[5]

We do not have an explanation for the fact that angiomatoid nevi affect almost exclusively women (13/14 cases). Hormonal factors might be involved as benign vascular lesions such as acquired angiomas can be affected by hormonal alterations due to pregnancy or contraceptive treatments.[6]

Although sometimes angiomatoid nevi may enter the differential diagnosis of melanoma, clinically, dermoscopically, or histologically,[2,3] the absence of recurrences or metastases after complete excision in all cases reported supports the benign behavior of this lesion.

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