The Spitz question: notes for an alternative view

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Melanocytic lesions described by Sophie Spitz in 1948 were first considered as representing a juvenile variant of malignant melanoma, because they showed an atypical histological appearance and occurred in children and in young individuals. Subsequently, such lesions were regarded as constituting an atypical variant of nevus, because they appeared to show a clinically benign behaviour. Also, they were considered as insidious simulators of malignancy, because histologically they strongly resembled melanoma. Later, some lesions displaying the histological characteristics of such tumors were considered to be malignant, because patients showed lymph node metastases. Consequently, hypothesized was a histological spectrum of lesions; including benign, atypical and malignant forms, whose relative borders were ill defined. However, the existence of such a spectrum was denied, considering Spitz lesions as nevi, only pseudomalignant lesions, biologically unrelated to malignancy and to malignant melanoma. Moreover, the diagnosis of such lesions may be extremely difficult, even among experts.

Probably, only new future techniques will solve these problems. However, an analysis of facts may suggest that Spitz lesions have been and still are regarded in an incorrect perspective. Certainly, Spitz lesions are enigmatic, but, perhaps, they may have also been misunderstood.

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FROM JUVENILE MELANOMA TO SPITZ NEVUS

At the end of 1940s, attention was drawn to melanocytic lesions occurring in childhood. In 1948, G. T. Pack noted that some cutaneous melanocytic lesions in infancy and childhood, labeled as malignant melanomas (prepubertal melanomas), resembled malignant melanomas of adults, but did not behave as such. He believed that melanocytic lesions were closely related to the endocrine system and that prepubertal melanomas did not behave as malignant only because they were not influenced by the endocrine activity of the pubertal age; consequently, he advised that all deeply pigmented nevi in childhood be surgically removed before

puberty[1]. The history of Spitz nevus began, however, in the same year, when Sophie Spitz published her famous article concerning childhood melanoma, segregating it from melanoma of adults. She reported 13 young patients with lesions labeled as malignant melanomas, describing 12 cases that showed a benign clinical outcome, without recurrence or metastasis, and one, a 12-year-old girl, who had a malignant and fatal course. Consequently, she considered such lesions to represent a variant of malignant melanoma, occurring in childhood, with a relatively favorable prognosis (juvenile melanomas). In that paper, Spitz also proposed some histological criteria (presence of giant cells, less pigmentation, less mitoses) to differentiate such lesions from adult melanomas[2]. Just one year later, however, opinions on juvenile melanomas began to change radically. In 1949, Allen stated that juvenile melanomas did not behave as malignant lesions and classified them among benign nevi[3]. In 1953, Allen & Spitz described juvenile melanomas as benign lesions and published a list of histological features that to distinguished them from melanoma of adults. The list included features of compound nevus, presence of subepidermal edema and teleangiectasia, absence of confluent nests or single cells, occurrence of large cells with abundant, myogenous-appearing cytoplasm, superficial giant cells with a single large nucleus or with many nuclei, abrupt transition between loose junctional cells and the still intact adjacent epidermis, relative sparsity of pigmentation, relative superficiality of the major landmarks of the lesions[4]. Moreover, the authors noted that juvenile melanomas occasionally persisted into adult life and possibly developed after puberty[4,5]. In 1954, Helwig renamed juvenile melanomas as spindle cell nevi, as a more appropriate term for a group of melanocytic lesions that were benign and characterized by the presence of spindle cells[6]. In 1960, Kernen and Ackerman confirmed that juvenile melanoma was a distinct clinico-pathological entity with a benign clinical course to be diagnosed by its histological appearance. The authors also provided a clinical description of such lesions, as being small and slightly elevated cutaneous tumors, red, brown or black in color, often found about the face. Histologically, they were described as showing a slight degree of pleomorphism, rarity of large nucleoli, relatively low mitotic activity and virtual absence of atypical mitoses[6]. Some years later, it was definitively established that spindle and epithelioid cell nevi occurred in adults and distinct criteria to differentiate them from malignant melanoma were provided[7]. In 1967, the term of Spitz nevus was proposed, giving the credit to the late Sophie Spitz who had first recognized and outlined such lesions[8]. There after lesions described by Spitz were considered to be nevi, that is, fully benign lesions representing a particular variant of nevus that displayed atypical histological features, evoking malignancy, and, therefore, to be distinguished from malignant melanoma[8,9]. Having several histological in common with melanoma, Spitz nevus was considered a histological pseudomalignancy, i.e., a benign lesion which mimicked a malignant tumor, and regarded as an insidious simulator of melanoma[4,6]. Cases with the histological features of Spitz nevi, which had given metastases, were considered as malignant melanomas erroneously diagnosed as Spitz nevi[6].

THE ATYPICAL SPITZ NEVUS AND ORIGIN OF THE SPITZ QUESTION

In 1989, Smith et al. reported 32 lesions with the histological features of Spitz nevi, 6 of which presented with lymph node metastases[10]. Spindle and epithelioid cell lesions with metastases did not constitute a surprising observation, because other similar cases had been previously reported[11,12]. The new concern of that paper, however, was that the authors did not consider their cases as malignant melanomas, although metastases occurred. Smith et al. termed their cases as malignant Spitz nevi, because they found that such lesions displayed the histological characteristics of Spitz nevi and, although showing some atypical features, were not outside the range of Spitz nevi. Moreover, such tumors did not appear to display histological features sufficient to support a diagnosis of melanoma and did not seem to show "the potential of widespread metastasis"[10]. Lesions described by Smith et al. were mostly larger than 1 cm, had a well circumscribed junctional component, exhibited sharp lateral margins, and extended deep into the subcutaneous fat, forming a rounded border that appeared to be pushing, rather than infiltrating the surrounding tissues. They also showed marked edema in the papillary dermis, prominent desmoplasia and increased vascularity, associated with high mitotic rate, mitoses deep within the lesion, lack of maturation of melanocytes, increased cellularity, increased cellular pleomorphism, loss of cellular cohesion and ulceration[10]. As patients did not show a fatal clinical course, the authors believed that such lesions metastasized to regional lymph nodes, but were not capable of widespread metastases[10].

The term "malignant Spitz nevi", chosen by Smith et al., was certainly improper, because the words malignant and nevus are conflicting. However, if the problem is considered in its essence, rather than in mere terms of words, in that paper, Smith et al. described a pathological entity different from both classical benign Spitz nevus and conventional malignant melanoma, recognizing a malignant counterpart of Spitz nevus. They proposed that some lesions belonging to the group of Spitz lesions could be capable of metastasis and could be malignant, in contrast to the then current rule that melanocytic lesions with metastases were to be automatically labeled as melanomas[12]. Smith et al. considered their lesions as tumors with a low malignant potential, because metastases were limited to lymph nodes and patients had a benign course[12]. In 1995, Barnhill et al. reported 12 cases of melanocytic tumors with the histological characteristics of Spitz nevus and the atypical features previously described by Smith et al., classifying them on the basis of clinical outcome. One case with a fatal course was labeled as Spitz-like melanoma, 2 cases with lymph node metastases as metastatizing Spitz tumors and 9 non-metastatizing cases as atypical Spitz tumors[13]. A subsequent study established that Spitz tumors with atypical features (atypical Spitz nevi/tumors) posed substantial diagnostic difficulties, even among experts, and that objective criteria for their distinction from melanoma and for gauging their malignant potential were lacking[14]. The authors considered such lesions as having an uncertain prognosis and a low metastatic potential[14]. The existence of a malignant counterpart of Spitz nevus or of Spitz tumors with a malignant potential was not universally accepted. Some

authors, rejecting the conclusions of Smith and Barnhill, entrenched themselves behind the old statement of Kernen and Ackerman that all Spitz lesions were nevi and, therefore, benign and that malignant cases were only undiagnosed melanomas[15]. The proposed terminology was also easily criticized. "Malignant Spitz nevus" and "metastatizing Spitz nevus" violated the fundamental principles of classic pathology, because a Spitz nevus was a nevus and a nevus, like all kinds of melanocytic nevi, is incapable of metastasis[16]. "Atypical Spitz nevus" was a misnomer because all Spitz nevi are atypical histologically by definition[16]. They confirmed the opinion that Spitz nevi displaying stereotypical histological features could be unequivocally diagnosed[17] and that such lesions could be differentiated from malignant melanomas by a set of histological criteria which worked and were reliable[15]. Others contended that cases displaying classic histopathologic features were rare, because the majority of Spitz nevi deviated from the ideal[18]. They viewed Spitz nevi as existing along a histologic continuum from classic Spitz nevi at one end of the spectrum to atypical Spitz nevi and malignant Spitz nevi at the opposite end[18,19]. They agreed that histological criteria to correctly diagnose classical Spitz nevi and classical malignant melanomas were available, but reliable histological criteria to diagnose intermediate forms seemed to be lacking[14,18]. A grading system for risk stratification of atypical Spitz tumors was proposed[20], but it does not seem to work[21].

THE DOGMA OF BENIGN SPITZ LESIONS

The observation that patients with juvenile melanomas generally had a benign course led to reinterpret these lesions as nevi[3,4]. However, juvenile melanoma, renamed Spitz nevus, was a very particular type of nevus that displayed several histological features such as irregular nests and cytological atypia. Therefore, inasmuch as Spitz nevus resembled melanoma, it was regarded as simulating of it[3-4,6,9,22-24]. The concept of simulator, i.e. a lesion that mimicks another, implied that a melanocytic lesion composed of spindle and epithelioid cells with atypical histological features was no longer automatically interpreted as a malignant melanoma, because it could be a Spitz nevus[6]. However, in 1975, Reed et al. described a type of lesion composed of spindle cells and with malignant behaviour they considered a type of melanoma representing "an evolving malignant variant of the Spitz tumor"[25]. Moreover, in 1979, Okun reported 3 cases of melanocytic lesions composed of spindle and epithelioid cells showing a clearly malignant course[11]; these cases were interpreted as malignant melanomas resembling spindle and epithelioid cell (Spitz) nevi[11], i.e. malignant melanomas that mimicked Spitz nevi. At this point, the context had become extremely difficult because there were Spitz nevi that mimicked melanomas and, at the same time, malignant melanomas that mimicked Spitz nevi[23-24,26-27]. Considering Spitz nevi as simulators of malignant melanoma and malignant melanomas resembling Spitz nevi as simulators that in turn simulated their simulators, it is not surprising that the diagnosis of such lesions had become extremely difficult or impossible. In fact, pathologists, who had just learned to avoid a pitfall, recognizing Spitz nevus as a pseudomalignancy, had to avert an even more dangerous trap: a pseudo-pseudomalignancy. The diagnosis of such lesions became an

authentic hazard, because pathologists, while trying to unmask a supposed impostor, risked making a fatal error of under-diagnosing another slier impostor. In time, this complex context became a source of a great number of problems, causing numerous diagnostic errors and producing a wide discordance in the diagnosis of melanocytic lesions, even among expert pathologists, as has emerged from several studies[14,28-29].

Analyzing carefully the facts, the described state of things curiously appears to be produced essentially by a simple but undemonstrated conceptual syllogism: 1. lesions originally described by Spitz are nevi; 2. all nevi are benign; 3. lesions originally described by Spitz are benign. Unfortunately, however, the first sentence was incorrect and therefore the conclusion was wrong. In fact, it was not true that all lesions originally described by Spitz were nevi and were benign because among the 12 benign lesions, 1 was malignant. The 13 lesions had a samilar histological appearance and Spitz considered them all as melanomas. When juvenile melanomas were reclassified as nevi, the 13th case with a malignant course described by Spitz was forgotten. In time, other cases of spindle and epithelioid cell tumors with fatal outcome were reported[11,12,22,30], but according to Kernen and Ackerman, they were simply considered as melanomas erroneously diagnosed as Spitz nevi[6]. Moreover, the philosophic dogma of benign Spitz nevus has forced us to consider as benign spindle cell and epithelioid cell lesions displaying behaviours or features that in pathology are generally associated with malignancy, such as local or regional recurrence, satellite lesions, lymphatic invasion and lymph node metastases[31-36]. Every diagnosis of a spindle and epithelioid cell lesion was evaluated only a posteriori, i.e. on the basis of the clinical course: if the patient had died, the diagnosis of Spitz nevus was erroneous and the lesion was reclassified as melanoma; if the patient had survived, the diagnosis of Spitz nevus was correct. If the same criterion were applied to other lesions, most level II melanomas and all thin squamous cell carcinomas would be classified as benign lesions because patients have not died.

PROBLEMS IN THE DIAGNOSIS OF SPITZ LESIONS

The differential diagnosis between Spitz nevus and melanoma is considered the most difficult or one of the most difficult differential diagnoses in pathology[16]. In some cases the differential diagnosis between Spitz nevi and melanoma may be impossible on histologic grounds[37,38] and definite diagnosis often rests on the occurrence of widespread metastasis. In Spitz lesions, diagnostic concordance may be surprisingly poor, even among expert pathologists[28]. In a recent study, a group of experts concluded that objective and reliable criteria distinguishing some Spitz nevi from some melanomas were lacking[14]. Several special techniques have been tested and proposed to distinguish Spitz nevi from melanomas, including immunohistochemical staining with Ki-67[39,40], with bcl-2 and Ki67[41] and with proliferating cell nuclear antigen[42-44], analysis of AgNOR staining pattern[45], detection of cyclin-D1 protein[46], p53 protein[47], c-myc protein[48] and c-fos protein[49], *in situ* hybridization to detect melastatin[50,51], DNA *in situ* hybridization with a chromosome-1 centromere probe[52], comparative genomic hybridi-

zation[53,54], loss of heterozygosity (LOH) and microsatellite instability (MSI) analysis[55], Bayes rule associated with MIB-1 proliferation index[56], human telomerase RNA component expression[57]. Unfortunately, results from these studies have shown that none of these special techniques has appeared capable to unequivocally make such a distinction[21,58-59]. The exceedingly difficult differential diagnosis between some cases of Spitz nevus and some of melanoma may have one or more causes that may reside in Spitz nevi, in the human observers or in the adopted diagnostic criteria. It is possible that the diagnosis of some Spitz nevi is difficult or impossible because such lesions have morphologic, immunohistochemical, molecular and genetic profiles too similar to malignant melanoma, so that clear-cut differences do not exist. In this case, the problem cannot be solved, until new and more specific techniques become available in the future. Ackerman stated that the problem in the differential diagnosis between Spitz nevus and melanoma is only due to the human brain that fails to correctly apply the current histological criteria that are valid and reliable[16,23]. All certainly can agree that the human brain may fail; it is, however, extremely difficult to explain why the human brain fails so frequently when it applies the histological criteria to differentiate Spitz nevi from melanoma but does not fail with the same frequency when it applies histological criteria to diagnose other lesions, such as basal cell carcinoma, seborrheic keratosis or dermatofibroma. Moreover, a failure of the human brain does not explain why expert pathologists achieve a poor diagnostic concordance of only 35%[28] regarding melanocytic lesions. If currently there is a relatively high rate of errors in diagnosing Spitz nevi and a much lower one in diagnosing other lesions, it is more probable that the true cause of the disappointing results in the diagnosis of Spitz nevi does not reside in the human brain, but rather simply in the criteria used for diagnosis. Criteria used to distinguish Spitz nevi from melanoma may not work because they are insufficient or inappropriate. The list of proposed criteria is long enough to make it improbable that by adding one or two new features the problem can be solved. It is more probable that the proposed criteria are inappropriate. The histological features used in Spitz lesions are the same as those used in the distinction between common nevus and melanoma, in which they generally work. The fact that they do not work with the same efficacy in the differentiation of Spitz nevi from melanoma suggests that other more specific criteria may be required.

NOTES FOR AN ALTERNATIVE VIEW ON SPITZ TUMORS

The lesions Spitz originally described were composed of large cells with abundant myogenous-appearing cytoplasm[4]. As noted just a few years later, such a specific type of cell was what properly characterized and set those tumors apart from the other melanocytic lesions that did not show it[60]. Such a large epithelioid and/or spindle melanocyte appeared to be so characteristic of Spitz lesions that Paniago-Pereira et al. proposed as appropriate the term large spindle and epithelioid cell nevi[9] for defining them. Thus, at least morphologically, the lesions described by Spitz appear to constitute a distinct class of lesions characterized by a peculiar and exclusive type of melanocyte. Spitz believed they

were low grade melanomas[2], Allen, Allen & Spitz, Helwig, Kernen & Ackerman, Paniago-Pereira et al. considered them as benign nevi[3-4,6,9]. However, the lesions Spitz described were not a group of lesions with a homogeneous clinical behaviour but rather a mixed group encompassing benign and malignant tumors. In fact, one of the 13 patients reported by Spitz died of widespread metastases[2], and other cases of large epithelioid and/or spindle cell lesions with a malignant behavior have also been described[10-11,13]. Piepkorn proposed that such tumors formed a wide spectrum, including benign lesions (Spitz nevi), which he considered uncommon lesions with a uncertain malignant potential globally estimated as low (atypical Spitz nevus), and malignant metastatizing lesions which may have less competence for generalized metastasis than true melanomas (malignant Spitz nevi)[18]. To avoid an improper terminology, such an entire group of lesions has been termed "spitzoid tumors"[61], but they can be better termed Spitz tumors because they do not resemble but properly are the tumors originally described by Spitz in 1948. It is evident that, in this specific case, the word "tumor" is not used to evade a definite diagnosis[62], but because it is the best and simplest word to indicate a composite group of benign and malignant neoplasms. It is also evident that, in this specific case, no one attributes mystical qualities to the word "tumor"[62], since it is used in conjunction with precise qualifying adjectives, such as "benign" or "malignant", configuring a precise diagnosis (benign Spitz tumors or malignant Spitz tumors). In any case, it appears too simplistic to reduce this complex problem, which is a problem of concrete things, to a sophistic problem of words. Indeed, this is not a problem of words: if the standard terminology appears preferable, Spitz tumors can also be said to comprise benign Spitz nevi and malignant Spitz(oid) melanomas, on condition that the terms "nevus" and "melanoma" do not obscure the fact that such tumors form a separate group of lesions.

In such a view, benign Spitz tumors currently included among nevi (Spitz nevi)[63-66] are not variants of nevi, just as malignant Spitz tumors currently included among melanomas (Spitzoid melanomas)[67] are not variants of melanomas. Results from recent studies showed important differences between Spitz tumors and conventional melanocytic lesions at various levels and seem to support such a view. At the molecular level, Spitz nevi have been found to exhibit stronger Fas (CD95) expression than conventional nevi and malignant melanoma[68]; S100A6 protein expression was demonstrated to be significantly higher in Spitz nevi than in melanocytic nevi and malignant melanoma[69]; typical and atypical Spitz nevi seemed to show significantly greater expression of p21 than conventional nevi[59]. Genetic profile analysis has shown that Spitz nevi differ from conventional nevi. Sequence alterations in B-RAF (V599 codon substitution), found in 73-82% of conventional nevi (including junctional, compound, intradermal, congenital and dysplastic nevi)[70,71], are absent in Spitz nevi[72-76]. At the same time, it has emerged that conventional nevi and conventional melanomas show common genetic characteristics. Mutations in B-RAF have been identified in 59-80% of conventional melanomas[77-79] and in 73-82% of common melanocytic nevi, including compound, junctional, intradermal and dysplastic nevi[70,71]. Moreover, an analysis of

the genetic profile of spitzoid melanomas have shown that such tumors are more similar to Spitz nevi than to conventional (adult-type) malignant melanomas. Mutations in B-RAF, which are very common in conventional melanomas and in conventional nevi[70,71,77-79], and mutations in N-RAS, which are rather frequent in conventional melanomas[80], have not been found in Spitz nevi or in spitzoid melanomas[81]. A subsequent study obtained discordant results, showing that B-RAF and N-RAS mutations are present in spitzoid melanomas and absent in Spitz nevi and in atypical Spitz nevi[82]. It should be noted, however, that the results from the two studies are not properly comparable, because the cases of Spitz nevi and spitzoid melanomas studied by Gill et al. were selected by clinical criteria, i.e. occurrence of metastases[80], whereas the cases of Spitz nevi, atypical Spitz nevi and spitzoid melanomas studied by van Dijk et al. were assessed histopathologically by a single pathologist[81]. Apart from some discordant data, the morphology and the results from several immunohistochemical, molecular and genetic studies would suggest that Spitz tumors are an autonomous group of benign and malignant lesions with peculiar clinical and histological characteristics. They are melanocytic lesions, so it is not surprising that some of their histological characteristics are seen in other melanocytic lesions, as in conventional nevi or in conventional melanomas. Benign Spitz tumors (Spitz nevi) are not and have never been simulators of melanoma; they are not and have never been simulators at all. Conversely, malignant large spindle and epithelioid cell lesions are not Spitzoid melanomas (i.e. melanomas that resemble Spitz nevi), but properly are malignant counterparts of Spitz nevi (malignant Spitz tumors or Spitz melanomas). They are not and have never simulated a supposed simulator; they are not and have never been a pseudo-pseudomalignancy, but only malignant tumors with their own specific features. Spitz tumors do not exist along any type of histological spectrum. They form a spectrum of lesions, just as every class of lesions does. They should be diagnosed as benign and malignant tumors in the same way as conventional nevi and conventional melanomas are currently diagnosed as benign (nevi) or malignant (melanomas) forms. Of course, such a differential diagnosis can be made only by appropriate histological criteria.

POSSIBLE EFFECTS ON DIAGNOSIS OF SPITZ TUMORS

Such an alternative view may have some relevant effects on the problems related to the diagnosis of Spitz tumors. First of all, it can explain why the diagnosis of Spitz tumors has been – and still is – so problematic. In fact, if Spitz tumors constitute a distinct class of lesions composed of large spindle and epithelioid cells, they should not be properly evaluated in differential diagnosis with conventional melanomas, because conventional melanomas, composed of different types of cells, belong to a different class of lesions. Benign Spitz tumors (Spitz nevi) are to be differentiated from malignant Spitz tumors (Spitz melanomas) in the same way as conventional melanomas are to be differentiated from conventional nevi. In other words, it is inappropriate to pose the problem of the diagnosis of Spitz tumors in terms of differential diagnosis between Spitz nevi and conventional melanoma. In fact, the histological features use-

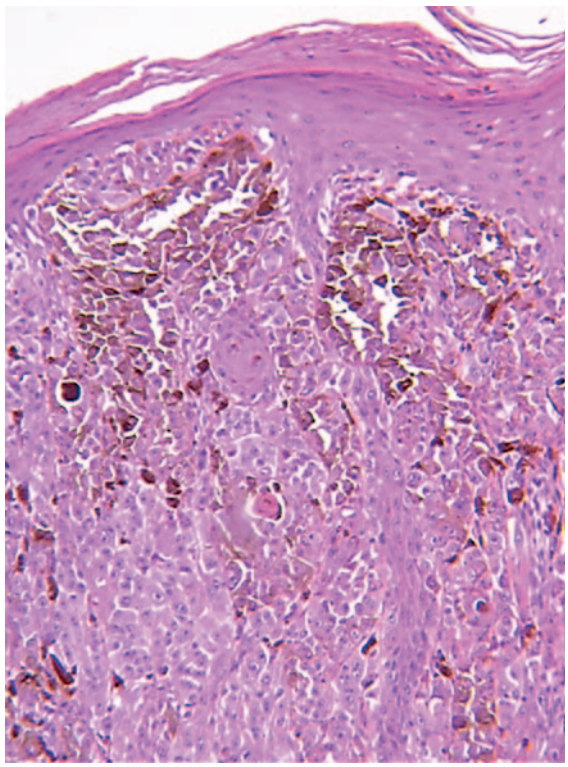

Figure 1. Malignant Spitz tumor in a 30-month-old boy; the 8 mm lesion was located on the right thigh; sentinel node biopsy showed two small deposits of atypical melanocytes. The melanocytic proliferation did not involve the epidermis (H&E, original magnification x100).

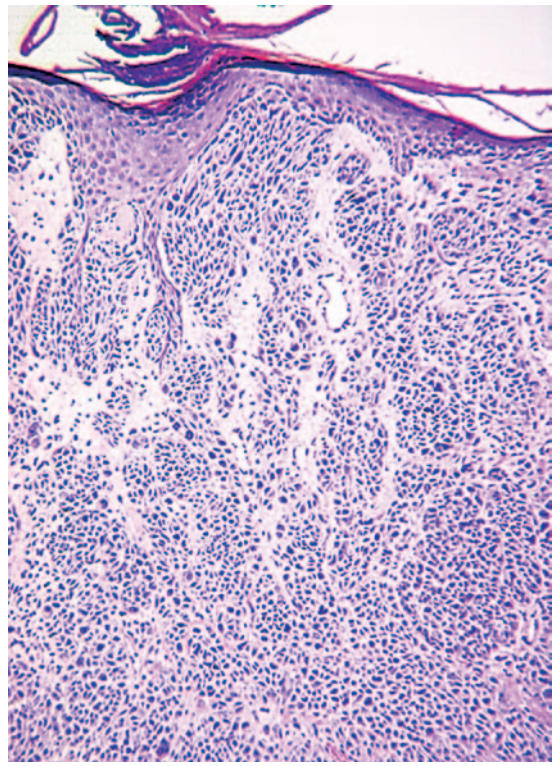

Figure 2. Malignant Spitz tumor in a 30-year-old woman; the lesion measured 6 mm and was located on the trunk; sentinel node biopsy showed multiple metastatic nodal deposits; after lymphadenectomy, an additional nonsentinel lymph node was found to contain neoplastic cells. In the epidermis, the melanocytes were arranged in well delimited nests; single cell proliferation and pagetoid infiltration were absent (H&E, original magnification x80).

ful to differentiate benign from malignant Spitz tumors might not be the same as those commonly used to distinguish conventional nevus from conventional melanoma. The same criteria that may work in one group of lesions and may not work another. Conventional melanoma frequently shows asymmetry, poor circumscription of the epidermal melanocytic proliferation, pagetoid infiltration of epidermis, single cell predominating over nests and cellular necrosis. Malignant Spitz tumors often show none of these (Fig. 1, 2). In other words, the histological features useful to distinguish malignant from benign Spitz tumors cannot be simply recruited from the list of features used to distinguish conventional melanomas from conventional nevi, because they may be inappropriate. Appropriate features for the diagnosis of Spitz tumors can be identified by only studying the structure of malignant versus benign cases. Malignant Spitz tumors are neoplasms which kill patients by widespread metastases. However, metastasizing lesions, which do not kill patients, are also malignant, because metastases are a commonly accepted expression of malignancy in pathology. Squamous cell carcinoma of the skin, an undisputable malignant neoplasm, can give metastases, without killing patients. Reviewing

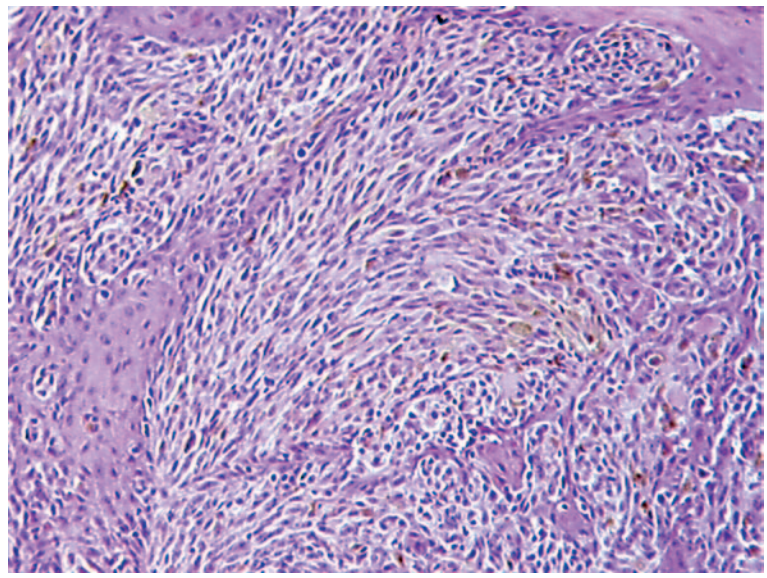

Figure 3. Malignant Spitz tumor in a 17-year-old girl; the 6 mm lesion was located on the thigh; 28 months after the diagnosis, an inguinal lymph node appeared to be metastatic; after lymphadenectomy, 4 additional lymph nodes resulted to be involved. In the dermis, the melanocytic proliferation showed a nodular growth, forming large cellular sheets with no collagen fibers interposed (H&E, original magnification x125).

the pertinent literature, almost 100 cases of metastasizing Spitz tumors can be found[2,10-15,21,27,30,32, 58,83-94]. Such cases, reported over a long period of time (1948-2003), are difficult to interpret, because histological data are not always homogeneously recorded. However, a careful examination shows that they invariably presented a certain number of the following histological features: 1. nodular growth in the dermis and/or large confluent, solid, cellular sheets with no collagen fibers interposed between cells (Fig. 3); 2. extension of the neoplastic proliferation to the mid-deep dermis (Fig. 4) or to subcutaneous fat, especially if associated with absent or impaired maturation; 3. dermal mitoses, especially in the deep aspects of the tumor; 4. marked nucleolar and/or nuclear pleomorphism (Fig. 5); 5. heavy melanization in the deep part of the tumor (Fig. 4); 6. asymmetry; 7. cellular necrosis; 8. epidermal ulceration (Fig. 6); 9. numerous suprabasal epithelioid melanocytes associated with parakeratosis (Fig. 7); 10. neoplastic cells in lymphatic vessels[10-15,21,27,30,58,85-89,91-92]. In all the cited studies, such features have been reputed to have a high value in the diagnosis of malignant Spitz tumors in respect to benign ones. They can be considered as "malignant features", that is, signs that connote malignancy. Therefore, a Spitz tumor that shows a certain number of such features should be regarded as malignant, even if metastases have not occurred, because a tumor that shows the same histological features of a malignant lesion cannot be considered as benign only because it has not (yet) metastasized. Many squamous cell carcinomas of the skin are malignant, even if they have not given metastases. Moreover, it should be noted that malignant Spitz tumors not infrequently show only few malignant features, appear-

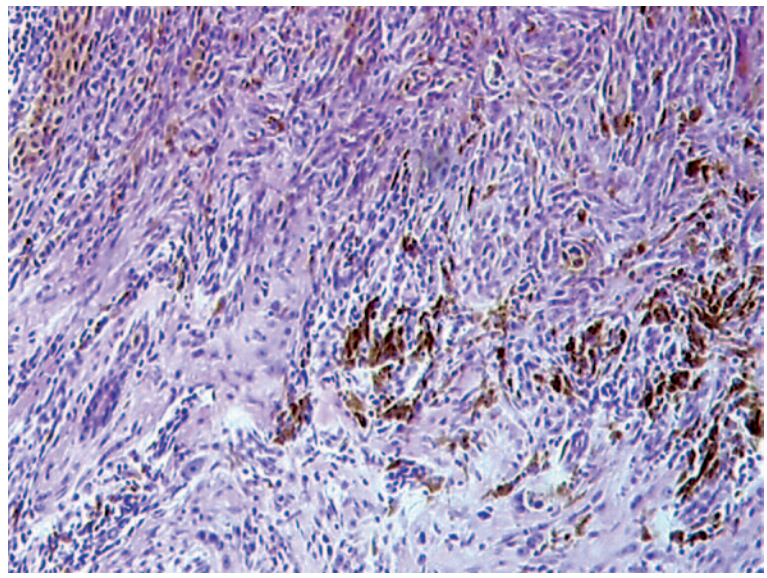

Figure 4. Same lesion as in Fig. 3. The melanocytic proliferation extended into the deep dermis, partially showing signs of maturation and deep melanization (H&E, original magnification x100).

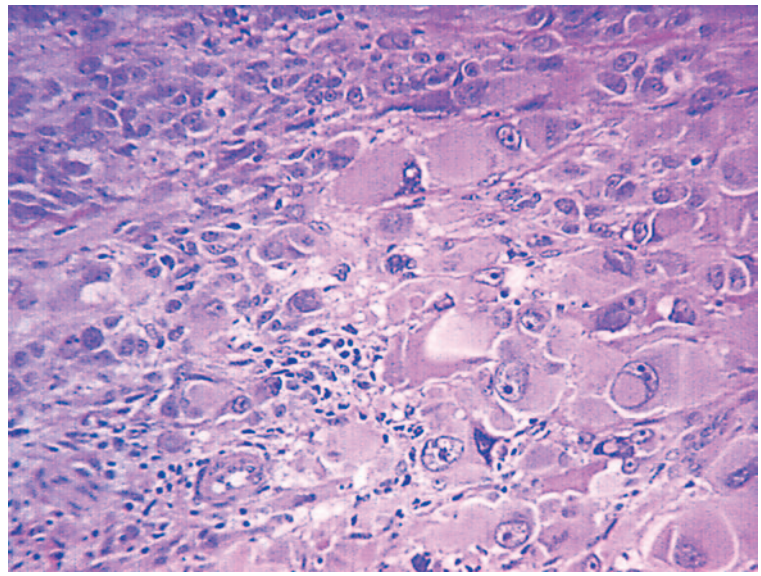

Figure 5. Malignant Spitz tumor in a 24-month-old boy; the lesion measured 5 mm and was located on the right leg; sentinel node biopsy showed several small deposits of atypical melanocytes in 3 sentinel nodes. The melanocytic proliferation was composed of large pleomorphic cells, with large atypical nuclei (H&E, original magnification x300).

ing very difficult to be diagnosed[92]. In some reported cases, metastasizing Spitz tumors displayed only a few or just one of the above listed 10 histological features, as Cases 5 e 6 reported by Mehregan & Mehregan[86], Cases 19, 21 and 22 reported by Walsh et al.[27], Case 7 reported by Su

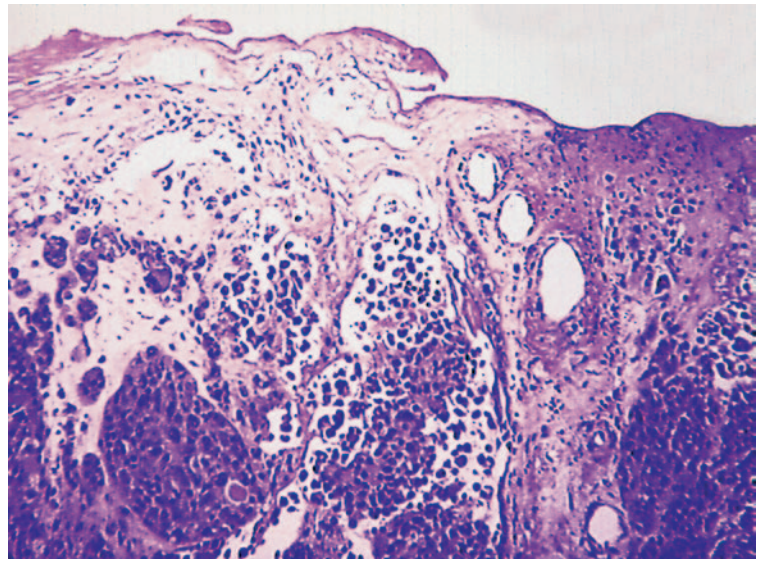

Figure 6. Same lesion as in Fig. 5. The melanocytic proliferation ulcerated the epidermis. Subepidermal edema and teleangiectasia were evident (H&E, original magnification x125).

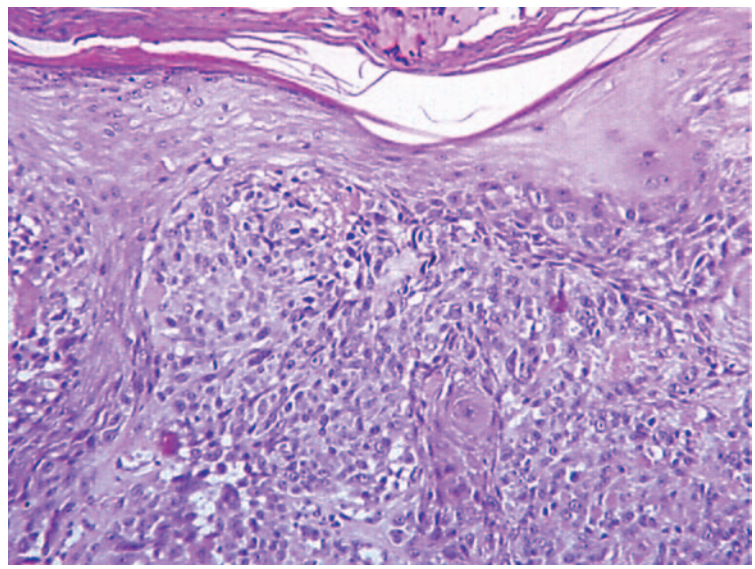

Figure 6. Malignant Spitz tumor in a 27-year-old woman; the 6 mm lesion was located on the left forearm; sentinel node biopsy showed a small parenchymal deposit of atypical melanocytes. The epidermis was not involved and showed focal parakeratosis (H&E, original magnification x125).

et al.[58]. Spitz tumors showing only a few or just one of the above mentioned features will probably go underdiagnosed as "atypical Spitz nevi/tumors" or also simply as "Spitz nevi". A review of the literature, however, shows that 30/55 cases, variously labeled as "atypical Spitz nevi/tumors", "diagnos-

tically controversial Spitzoid melanocytic tumors", or "problematic Spitzoid melanocytic lesions" have given metastases in 54% of cases[14,21,58,93,95-96]. Neoplasms indisputably accepted as malignant often show a lower metastatic rate. This high rate of metastasis suggests that cases currently diagnosed as "atypical Spitz nevi/tumors" are not biologically intermediate or indeterminate[14,18,66,97] but rather behave as malignant tumors. Consequently, Spitz tumors can be more realistically classified into 2 category of lesions: benign Spitz tumors (Spitz nevi) and malignant Spitz tumors (Spitz melanomas)[98] rather than in 3 categories (benign Spitz tumors/atypical Spitz tumors/malignant Spitz tumors[97]). In conclusion, until new reliable techniques become available, to avoid underdiagnoses and risks for patients, the presence at least of one of the 10 above listed "malignant features" in a Spitz tumor should be seriously considered and prudently regarded as a sign of suspect malignancy[98]. In such cases, a wide excision of the lesion, sentinel lymph node biopsy and a long-term follow-up are strongly recommended.

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