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Time to reconsider Spitzoid neoplasms?

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SUMMARY

Background: Spitzoid neoplasms may pose significant diagnostic problems because in a fraction of them it is quite difficult or impossible to establish if they are benign or malignant lesions. An extraordinarily large number of studies have been made in attempts to solve this problem; regrettably, the histological criteria proposed and the various special sophisticated techniques employed have proven to be ineffective in making this distinction with confidence.

Objectives: To explore the possible causes for this diagnostic failure and an attempt to identify the source of this problem.

Method: A historical and technical analysis of the specialized literature is performed, critically evaluating the main points of this controversial topic.

Results: The reasons for the diagnostic failure in Spitzoid neoplasms are not clear but could be the result of inappropriate conceptual representation. The analysis of available data and a rational review of old and new assumptions and concepts may suggest a different representation for Spitzoid neoplasms: Spitz nevus, atypical Spitz tumor and Spitzoid melanoma, rather than being three different tumors that are difficult or impossible to distinguish with assurance, could be viewed as one unique entity, *Spitz tumor* (ST). This tumor is a low-grade malignant neoplasm, in which the amount of intrinsic risk is variable, ranging from very low to high (ST1, ST2, ST3), and malignant potential could be estimated.

Conclusions: The proposed alternative representation of Spitzoid neoplasms as a unique tumor may help in overcoming the difficulty in diagnosis of these tumors.

"The difficulty lies, not in the new ideas, but escaping from the old ones, which ramify . . . into every corner of our minds."
JM Keynes
***The General Theory of Employment, Interest and Money* (1936; Palgrave Macmillan)**

Problems in the diagnosis of Spitzoid neoplasms and possible causes

Spitzoid neoplasms may pose significant diagnostic problems, because in a fraction of them it is quite difficult or impossible to establish if they are benign or malignant lesions. An

extraordinarily large number of studies have been made in attempts to solve the problem of the differential diagnosis of Spitzoid neoplasms, i.e., distinguishing Spitz nevus (SN) from Spitzoid melanoma (SM) [1–2]. Regrettably, the proposed histological criteria have often proven to be ineffective in making this distinction with confidence, and the concordance of dermatopathologists is excessively low [1,3]. Moreover, immunohistochemistry and other special techniques, including polymerase chain reaction (PCR) and *in situ* hybridization (ISH), have proven to be either totally ineffective for the diagnosis or useful just as ancillary tools [4]. Finally, molecular genetic studies, including analysis of gene mutations, fluorescence in situ hybridization (FISH) analysis and comparative genomic hybridization (CGH) [5-10], have also failed to achieve a consistent distinction between malignant from benign forms [11-12].

In this disappointing context, the vexing question remains as to *why* the diagnosis of Spitzoid neoplasms appears to be so exceedingly difficult and, therefore, so dramatically exposed to error. Many possible causes may be at the source of this problem. Years ago, Ackerman wrote that this problem was due to the failure of the human brain [13]; however, this opinion does not appear fully convincing, because it is very difficult to explain why it does not generally fail in the diagnosis of basal cell carcinoma, actinic keratosis, or dermatofibroma, and so frequently fails in Spitzoid neoplasms. A second possibility may be that, despite the numerous studies, a special technique capable of producing a reliable distinction between SN and melanoma has not been yet found. It is possible that such a technique will be available in the future; however, after more than 60 years, the large number and the great variety of very sophisticated special techniques employed with relatively disappointing results [4] may suggest that the achievement of this technique is not probable. A third possibility may lie in the fact that the histological criteria currently used to segregate benign from malignant forms do not work properly because they are inadequately studied or poorly reproducible. Actually, an examination of the pertinent literature shows that histological differential criteria between SN and melanoma have been very accurately studied and globally have a good reproducibility [2]. In sum, not one of analyzed causes seems be convincingly identifiable as the source of the problematic histologic diagnosis of Spitzoid neoplasms.

Looking for a new perspective

In 2004, Cerroni hypothesized that the perspective from which Spitzoid neoplasms were regarded might be wrong [14] and, therefore, a possible cause of diagnostic failure might be an inadequate conceptual *representation* of these tumors. In the current representation, SN and SM are considered mere morphologic variants, respectively, of melanocytic nevus and of malignant melanoma. Between these two diagnostic categories, it is admitted to exist an ill-defined gray area encompassing lesions variously termed "tumors of difficult or uncertain diagnosis or potential," "MelTUMPs," or "I don't know" [13,15–19]. This representation appears to be essentially based on two old postulates, frequently repeated, but never properly demonstrated: 1) malignant melanoma is a unique neoplasm and 2) SN is a nevus. The first postulate was enunciated by Ackerman in the 1980s [20]; however, increasing data coming from mutational and genetic studies show that what is currently called "melanoma" is an assemblage of different tumors [21]. The second dates back to 1949, when Allen established the "juvenile melanoma" to be a nevus [22].

In subsequent years, the *a priori* assumption that juvenile melanoma, renamed as SN, was a nevus and therefore fully benign, was largely accepted. Although not scientifically demonstrated, this statement significantly influenced the evaluation of Spitzoid neoplasms. In fact, although local recurrences, cutaneous satellitosis, cells in lymphatics and nodal metastases/deposits—features traditionally associated with a malignant behavior—were occasionally observed, SN was considered benign because the outcome was favorable or more favorable than expected [23–26].

On the other hand, cases with the same clinical and histological features but with visceral metastases and unfavorable outcome were regarded as melanomas, erroneously diagnosed as SN [27]. The following syllogism seems to be the basis for the current representation: 1) SN is a nevus; 2) a nevus is invariably benign; 3) SN is invariably benign. This syllogism is formally correct, but the first premise ("SN is a nevus") is not demonstrated; it is an *a priori* enunciation that might be not true.

In subsequent years, in an attempt to explore a possibly different perspective, it was proposed to set Spitzoid neoplasms apart from the other melanocytic lesions. They were defined as *an autonomous class of benign and malignant* tumors with a peculiar features. The immediate consequence of this representation was that, if Spitzoid neoplasms were a separate group of lesions, diagnostic histological criteria to differentiate benign form malignant forms might not be the same used to differentiate conventional nevi from conventional melanoma; so, new criteria, or a new use of existing criteria, appeared to be opportune [28]. This class of lesions included poorly understood cases labeled as atypical Spitz tumor (AST). There is more than one reason to think that understanding AST may be the key to the problem.

Understanding atypical Spitz tumors

In a recent review, the clinicopathological characteristics of 541 ASTs were tabulated [29]. In this study, it was reported that AST has a relevant rate of positive sentinel nodes (39%),

a relatively high rate of non-sentinel node involvement (19%), a very low incidence of local recurrences (<1%), a small but definite rate of regional metastases (3%), a very small rate of distant metastases (1%), and a very low mortality (1%). Discussing their results, the authors posed the question of the nature of ASTs, recalling two hypotheses: 1) ASTs are a confused assemblage of morphologically ambiguous benign nevi with associated benign cells in lymph nodes and of morphologically ambiguous malignant melanomas; and 2) ASTs are a group of biologically intermediate tumors, i.e., melanomas with a relatively good prognosis. Unfortunately, in their paper, the authors did not discuss the problem any further.

Actually, these two hypotheses deserve to be deeply analyzed. The first implies that ASTs—belonging to the same cellular lineage, with the same clinicopathologic characteristics, not distinguishable on clinical and/or histological grounds, nor with the available special techniques—may be different tumors with totally different biology, some ASTs being benign and some malignant. This is to say that these tumors cannot be appropriately diagnosed on the basis of their morphology or structure but only *a posteriori* on the basis of follow-up data and of the final outcome. If a principle like this were extensively applied, a lesion presently diagnosed as "superficial spreading melanoma" should be *a posteriori* classified as a "melanoma" only if the patient developed metastases or died, but regarded as "nevus" or as "atypical nevus" if the patients survived. This is illogical. This hypothesis produces an insurmountable diagnostic impasse, due to the fact that the same histologic appearance may not imply the same diagnosis.

The second hypothesis implies that ASTs—belonging to the same cellular lineage, with the same clinicopathologic characteristics, not distinguishable on clinical and/or histological grounds, nor with the available special techniques—cannot be biologically different tumors, but are to be regarded as a unique group of neoplasms. The existence of a reliable correspondence between the histologic appearance and the diagnosis permits these tumors to be diagnosed on the basis of their morphology and overcomes the diagnostic impasse.

At least pragmatically, the first hypothesis should be rejected because it inhibits the diagnosis; the second should be accepted because it makes the diagnosis possible and could solve many problems. In fact, if ASTs are a unique group of tumors that are diagnosable clinically and histopathologically and that represent a unique clinicopathologic entity, the nature of such tumors ceases to be nebulous. They are not nevi and are not benign, because they are capable of metastases and, albeit rarely, of killing patients [29]. However, the low rates of distant metastases and of deaths (in part due to the fact that the tumors with the characteristics of AST and unfavorable outcome are currently separated *a posteriori* under the label of SMs [30]) demonstrate that they properly are *malignant tumors*, albeit with a relatively favorable prognosis. They possess a low malignant potential.

It has been underscored that considering the malignant potential of tumors as an *all-or-none* phenomenon is an oversimplification. The paradigm "benign-versus-malignant," based on the clinical course of the disease, seems to be a rather rough approach to a biologic property (the malignant potential) of tumors, which in reality could have a different expressivity [31]. It is not possible to precisely estimate the malignant potential of a given lesion, but that is certainly not the same in all tumors and can be approximately defined as low, moderate or high. Available data show that ASTs are malignant but seem to have a relatively low malignant potential [29]. A tumor with low malignant potential is not necessarily a tumor having an invariably limited metastatic capability (for example, a tumor capable of regional but not distant metastases) [32]. It can be a tumor with a metastatic rate *statistically* lower than expected. In effect, ASTs have metastatic and mortality rates statistically lower than "conventional melanomas" [29]; they could be properly considered low-grade melanomas, as Sophie Spitz did in 1948 [33]. The notion that ASTs constitute a unique clinicopathologic entity and therefore are melanomas, albeit of low-grade, may explain many, if not all, issues, including why they are so similar to SM, why AST and SM may be histologically indistinguishable, why they are not separable by any special technique, why more than occasionally the attempts to differentiate them fail, and finally why the diagnostic concordance among pathologists is so low [1,3,4].

Spitzoid neoplasms as a unique entity: the Spitz tumor

Moreover, as we extend our analysis from ASTs to the entire category of Spitzoid neoplasms, it is interesting to examine the tables concerning the differential features between SN, AST and SM, for example, that published by Barnhill in 2004 [34]. In this table, and in similar ones, no one single criterion or groups of criteria appear to be really distinctive of AST in respect to SM. All parameters listed are shared by both the lesions. There is no substantial difference in their histologic appearance or in their structure but only a *modulation* of the histological features, being less pronounced in AST and more prominent in SM [34]. AST and SM seem to have the same histological characteristics and no special technique is capable to distinguish them confidently. Morphologically and structurally, they appear as a unique tumor. In addition, in the same table, the same circumstances can be noted comparing AST to SN. Again, no one single criterion or groups of criteria appear to be distinctive of AST in respect to SN. All parameters listed are shared by both the lesions. There is no substantial difference in their histologic appearance or

in their structure but only a modulation of the histological features, being less pronounced in SN and more prominent in AST [34]. AST and SN seem to have the same histological characteristics, and no special technique is capable to distinguish them confidently. Morphologically and structurally, they appear as a unique tumor.

In sum, all Spitzoid neoplasms, including forms currently labeled as SN, AST and SM, share the same histological characteristics, and no special technique is capable to distinguish them confidently; morphologically and structurally, they appear as being a unique tumor. Spitzoid neoplasms, rather an autonomous class of tumors, including benign, borderline and malignant forms [28], more properly seem to be a unique entity, showing a modulation of the histologic features, of the risk and, consequently, of the prognosis [18]. This unique entity, which may be termed as *Spitz Tumor* (ST), appears to be characterized histologically by the presence of atypical large spindle and/or epithelioid cells, as noted in early papers [35], and genetically by chromosome rearrangements involving kinase fusion [36]. ST is malignant, but seems to possess a low malignant potential. The malignant potential of ST is globally lower that expected in conventional melanoma of the same thickness, but variable, as it does not seem to be the same in all cases. It is impossible to obtain a precise quantitative estimation of the malignant potential of a single ST, but it is possible to have an approximate estimation of it, evaluating the amount of risk. In ST, this risk may range *from very low to high* and may be expressible as statistical probability that an adverse event (nodal or visceral metastasis, death) occurs *or is detected*; in each single case, however, the prognosis is unpredictable. The representation of Spitzoid neoplasms as a unique tumor (ST) makes the diagnosis possible and relatively easy, relying only on the recognition of the peculiar cell type.

Proposal for risk assessment in Spitz tumor

The challenging subsequent steps concern the assessment of risk in ST. In previous studies, some features associated with a potential risk have been pointed out. In 2005, in a review of 100 cases reported in 24 studies published between 1948 and 2003, a list of histologic features associated with metastases and/or a potentially adverse prognosis was compiled [28]. The following revised list includes 10 histologic parameters:

1) Solid sheets and nodular growth
2) Deep dermis and/or subcutaneous fat extension
3) Dermal mitoses (>2 per section)
4) Marked nuclear pleomorphism
5) Abundant melanin in deep cells
6) Marked asymmetry
7) Cellular necrosis
8) High number of suprabasal melanocytes
9) Epidermal ulceration
10) Cells in lymphatic vessels

This 10-feature list is different from the lists commonly employed in the differential diagnosis between SN and SM, and it is used in a different way. In fact, these latter lists generally contain a higher number of parameters to assess any given lesion; the diagnosis emerges from a quantitative and qualitative evaluation of the considered parameters. Unfortunately, however, it is not specified how many parameters are requested for the diagnosis, and if it is requested the presence of the majority of them, if all parameters have the same weight, if there exist major and minor parameters and, in this case, how many major and how many minor parameters are necessary. Moreover, there are no indications for a qualitative evaluation of any single parameter. This is certainly at the source or, at least, substantially contributes to producing the disappointingly low diagnostic concordance [3].

The proposed use of the 10-feature list is different and suggested by the analysis of previously published cases [28]. In 2001, Fabrizi and Massi stated that a combination of just three features (nuclear/nucleolar pleomorphism, mitoses and growth in solid sheets) should suggest the diagnosis of malignancy (melanoma) "without hesitation" [37]. Similarly, in 2014, Massi and LeBoit recently wrote that "even a single mitotic figure favors melanoma" in an appropriate context (cellular atypia and growth in solid sheets) [38]. Moreover, Case 21 published by Walsh et al in 1998, a woman aged 24, who died 73 months after excision, presented a small 3 mm papular lesion "simulating Spitz nevus" without evident mitotic figures; from the microphotograph the lesion seemed to show just an extension to the reticular dermis and an incomplete maturation [2]. In addition, Case 19 published in the same study, a woman aged 32 with regional lymph node metastasis 11 months after excision, presented a small 5 mm, clinically symmetrical, papular dome-shaped lesion with "spindled melanocytes resembling those of a Spitz nevus" and just an asymmetric shoulder in half of the lesion [2]. Therefore, the study of previously published cases demonstrates that Spitzoid neoplasms with metastases and/or fatal outcome might present only a few or *just one* parameter that would indicate malignancy. Consequently, to avoid under-diagnosing Spitzoid neoplasms [39], it was suggested that the very presence of at least one of the features of the 10-feature list be considered as sufficient for a diagnosis of potential malignancy [28]. Therefore, in a Spitzoid neoplasm, if even a single feature included in the list, evaluated as present/absent, is identified, the diagnosis should not be SN, but at least AST [28].

On the other hand, data collected showed that ASTs are tumors with a low malignant potential and with a risk of an adverse event estimable as low or moderate [29]. Consequently, an ST showing at least one of the features of

the 10-feature list (although often, more than one feature is detected) should be considered "Spitz tumor with low-moderate risk" (ST2). Moreover, in 2010, three features were found to be statistically associated with a high risk and an unfavorable outcome: dermal mitoses (>4 per section), deep or marginal mitoses, and heavy inflammatory infiltrate [18]. Therefore, the presence of one or more of these three features in an ST that also shows a variable number of the 10 abovementioned features, evaluated as present/absent, may confer a high risk of an adverse event, and these cases should be diagnosed as "Spitz tumor with high risk" (ST3). Conversely, lesions showing none of the 10 features, nor one of the three features and that are small, symmetric, with a horizontal silhouette, with uniform cells and evident maturation can be assumed to have a very low malignant potential and diagnosed as "Spitz tumor with very low risk" (ST1). The re-definition of lesions currently labeled SN that are considered fully benign as ST1, and considered as very low risk, takes into account *the objective impossibility* of excluding the minimal risk implicit in the diagnosis of SN, as sagaciously noted by Piepkorn [40].

Results of genetic analyses may be used for a further evaluation of risk. Provisionally, FISH analysis, if positive, should prevent the diagnosis of ST1; if negative it should not impede the diagnoses of ST2 and ST3. Chromosomal alterations, as homozygous 9p21 deletion and 6p25 and/or 11q13 gains, indicating a high risk, prevent the diagnoses of ST1 and ST2 [41]. In comparing this diagnostic approach to the current system of diagnosis, part of SN could probably be diagnosed as ST2 and part of AST as ST3. On the basis of the class of risk (ST1, ST2, ST3) an appropriate gradable management of patients with ST can be established [19].

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