Time to reconsider Spitzoid neoplasms?

Carmelo Urso

Department of Anatomic Pathology, Dermatopathology Section, SM Annunziata Hospital, AUSL Toscana Centro, Florence, Italy

Key words: Spitz tumors, Spitz nevus, atypical Spitz tumor, Spitzoid melanoma, melanoma

Citation: Urso C. Time to reconsider Spitzoid neoplasms? Dermatol Pract Concept 2016; 6(2):8. doi: 10.5826/dpc.0602a08

Received: December 6, 2015; Accepted: March 12, 2016; Published: April 30, 2016

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Funding: None.

Competing interests: The authors have no conflicts of interest to disclose.

All authors have contributed significantly to this publication.

Corresponding author: Carmelo Urso, MD, Department of Anatomic Pathology, Dermatopathology Section, SM Annunziata Hospital, AUSL Toscana Centro, Antella, Florence, I-50012 Italy. Tel. +39 055 6936416; Fax. +39 055 6936294. Email: cylaur@libero.it

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; regretfully, 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.

SUMMARY

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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 melanomas, 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 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.

**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.

**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 con-
fused assemblage of morphologically ambiguous benign nevi
with associated benign cells in lymph nodes and of morpho-
logically 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 ana-
yzed. The first implies that ASTs—belonging to the same cel-
lar 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 “super-
ficial 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 histo-
logical 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 histopathologi-
cally 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 metas-
tases 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 prog-
nosis. 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 “con-
ventional melanomas” [29]; they could be properly consid-
ered 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 differ-
entiate 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 com-
paring 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 [33], 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 than 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 disappointing 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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