Dermatology Practical & Conceptual

Considerations on The Biologic Gray Zone of Melanocytic Tumors

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Dermatologists are well aware that there exist some melanocytic lesions which are morphologically very difficult to classify as benign or malignant and consequently of uncertain biological potential. This may be due partly on the biological complexity of such lesions and partly on the limitations of our diagnostic methods. We believe the introduction of new entities in the field of melanocytic lesions should be always accompanied with the formulation of specific, reliable and reproducible clinicopathologic criteria. Furthermore, a new entity makes sense when its recognition is of real practical use for patient management and care. In particular, the aim of the pathologist, despite the complexity of the subject, should be to render diagnoses that are as simple as possible, easy for clinicians to understand and above all that guide an appropriate therapeutic approach.

Actually, the World Health Organization (WHO) attempt to provide a new classification of melanocytic lesions on the basis of a model of tumor progression seems a bit forced to us (1). In fact, instead of proceeding from histological experience to create a model, WHO started from the theoretical model of tumor progression and within this, they tried to adapt the observations derived from histological experience. This unusual way of proceeding has led to the creation of a series of hypothetical "intermediate" entities, grouped under the term melanocytomas/MELTUMP (*BAP-1* inactivated melanocytoma, Deep penetrating melanocytoma, PEM, Atypical Spitz Tumor, STUMP and Atypical cellular blue nevus/melanocytoma) that together would constitute the so-called grey-zone of melanocytic lesions (1-5). In addition, within each of these entities it would be possible to recognize further subtypes on the basis of atypia grading (6). However, although WHO has established apparently specific clinical, histological and genetic criteria for identifying each of these entities, their applicability in daily clinicopathological practice has proven to be very difficult. In fact, both the clinical and especially the histological criteria are far from being specific and reliable; in particular, interobserver reproducibility among pathologists, even the most experienced ones, has turned out to be poor with diagnostic arbitrariness reigning supreme. Overall, this results in a terrible confusion of terminology that disorients clinicians and an absolute lack of consensus regarding the treatment of these lesions. To demonstrate this confusion, some authors recommend treating melanocytomas with re-excision followed by periodic ultrasonographic monitoring of the regional nodes and those with major atypical features (MELTUMP) with "…management as per melanoma of the same thickness". (7) In practice, they propose the same treatment for melanocytomas/

MELTUMP as for conventional melanomas. This is inexplicable because the same authors define melanocytomas as lesions that are "*...neither nevi nor melanomas...*" and that "... it is inaccurate to modulate the management of melanocytomas on the basis of their histological grade because the relationship between morphological atypia and biological risk has been unproven". (7)

This being the case, what could currently be a different and practical, albeit provisional, solution to the classification of melanocytic lesions of uncertain malignant potential?

I like to start from the following undeniable data: all so-called melanocytomas/MELTUMP have the potential to produce lymph node metastases and, albeit rarely, distant metastases (1-5). In particular, the percentage of lymph node metastases appears to be higher than that of conventional melanoma (7). There is no doubt that this biological behavior more or less overlaps with that we expect from thin melanomas (pT1a and/or pT1b).(8) Consequently, I wonder why melanocytomas/MELTUMP cannot be regarded as peculiar forms of less aggressive melanomas. According to some authors this would not be possible because The Cancer Genomic Atlas only recognizes four genetic types of melanomas (7). This does not seem to be a good reason, because, in our view, biological behavior is the most important feature that should guide the classification of melanocytic lesions instead of genetics. Consequently, we feel that the majority of lesions included in melanocytoma/MELTUMP group should be classified as "Low grade Melanomas (LgM)" precisely in consideration of their potential biological behavior. This terminology is widely used for other types of mesenchimal tumors characterized by intermediate histological features and low metastatic potential. (e.g. low grade fibromyxoid sarcoma, low-grade myofibroblastic sarcoma)(9) and there is no reason why it should not also be extended to melanocytic lesions. Thus, for practical purposes, in addition to the four classic types, we could imagine the existence of a fifth group of melanomas (LgM), including the majority of the so-called melanocytomas/MELTUMP, characterized by a different heterogeneous genetic profile and a low risk of metastases.

The introduction of the term "LgM" could have several practical advantages. First of all, the term is simple and easily understandable by both clinicians and pathologists. Secondly, it would greatly facilitate histological diagnosis with a consequent increase of interobserver reproducibility. Furthermore, the use of the single term (LgM) would relieve the pathologist of the difficult, at times impossible, task of recognizing a series of confusing, poorly reproducible and purely theoretical histological entities. Again, the term LgM clearly informs clinicians about both the nature of the lesion and the biological behaviour to be expected (low metastatic risk). Finally, It indicates to clinicians the appropriate treatment and management of the patient.

While waiting for new methods to allow more precise and perhaps personalized diagnoses, at the moment the one proposed seems to me the "less imperfect" solution to the problem of the gray-zone of melanocytic lesions.

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