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Melanocytic Skin Tumors: Does the Molecular Progression Model Fit With the Routine Clinicopathological Practice?

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The definition of a spectrum of melanocytic tumors, with superficial atypical proliferations (*high-grade dysplastic nevus* and *melanoma in situ*) and mass-forming (*tumorigenic*) neoplasms (*melanocytomas*) considered as an intermediate molecular progression stage in melanomagenesis, has been recently set forth by the WHO Working Group [1]. The existence of a molecular spectrum involves progressive accumulation of genetic abnormalities which, in turn, implies an increasing risk of unfavorable biological behavior. It is thus supposed that:

1. Benign nevi harbor a single driver mutation (involving *NRAS* in congenital nevi, *BRAF* in acquired nevi, *HRAS* in a few Spitz nevi, *GNAQ* or *GNA11* in blue nevi) or translocation (kinase fusion of *ALK*, *BRAF*, *ROS1*, *NTRK1*, *NTRK3*, *MET*, *RET*, *MAP3K3*, or *MAP3K8* in several Spitz nevi) [2].
2. Intermediate melanocytic tumors may develop from benign nevi by acquiring an additional pathogenic mutation (*BAP1* mutation in *BAP1*-inactivated nevus [3], *CTNNB1* or *APC* in deep penetrating nevus [DPN] [4], *PRKAR1A* or *PRKCA* in pigmented epithelioid melanocytoma [PEM] [5]).
3. Malignant melanoma develops after additional promoting mutations involving *MAPK* pathway genes (eg, *NF1*, *KIT*, *CCND1*), G1/S checkpoint regulation genes (eg, *CDKN2A*, *CDK4*, *p53*), chromatin modifier genes (*SWI/SNF*, *BAP1*), and/or telomere regulation genes (*TERT*, *SF3B1*, *EIF1AX*) [6].

According to the WHO Working Group, intermediate melanocytic tumors are histopathologically defined as having increased cellularity and/or atypia if compared with a common nevus [1]. Thus, the molecular intermediate progression stage corresponds to a morphological intermediate and both are also mirrored by the intermediate biological behavior of melanocytomas, with their characteristically high incidence of nodal metastases coupled with a very low incidence of distant metastases [7].

In the progression model described above, nevi can be melanoma precursors because they are composed by partially transformed melanocytes. If so, common nevi do not

exist at all because all of them harbor 1 potentially dangerous mutation; thus, a dichotomic histopathological approach (nevus vs melanoma) can no longer be applied as being too simplistic a view. However, the paradox according to which completely innocent nevi do not exist at all (because all of them harbor a potentially dangerous mutation) is obviously misleading because the estimated risk of malignant transformation of a nevus is roughly 1:33,000 [8]. Thus, the progression model from nevus to melanoma applies to a percentage of melanocytic tumors that is indeed minimal (even negligible, if one does not consider the potentially dramatic clinical consequences of such an unlikely event). Likewise, with distant metastases as the surrogate gold standard for malignancy, a progression of melanocytoma to conventional melanoma is highly unlikely.

In addition, the correlation between molecular and histopathological features is clearly imperfect to date, because melanocytomas themselves can show various degrees of histopathological atypia, and this "morphological spectrum within the spectrum" is incompletely mirrored by the molecular data available so far [9]. The consequence is that the mutations listed above for both benign and intermediate melanocytic tumors have no diagnostic or prognostic significance; they simply allow one to ascribe a given melanocytic tumor to a given subgroup (conventional, spitzoid, BAP1-deficient, dendritic cell [cellular blue nevus-like], DPN-like, PEM) [10].

Even the correlation between morphology and biological behavior of melanocytoma can be questioned, because several studies carried out on melanocytomas (all based on a low number of cases because of the relative rarity of such tumors and the need for long-term follow up [11]) have disclosed no clear-cut relationship between the qualitative and quantitative histopathological features of atypia and the clinical outcome. Notably, these studies were conceived with the goal of differentiating benign from malignant tumors with the use of different kinds of surrogate gold standard (interobserver agreement, nodal metastases, distant metastases, disease-related death [11,12]). However, the attempt at differentiating benign and malignant tumors within the intermediate category might be wrong: melanocytomas might represent a unique broad category (with some morphomolecular subgroups) of tumors completely different from conventional melanocytic tumors, because they might not be morphobiologically intermediate, but morphobiologically peculiar. In fact, their rate of nodal metastases is much higher than that of conventional melanoma and their

Table 1. Proposed List of Histopathological Criteria of Atypia for Prognostic Assessment of Melanocytomas

Entity	Proposed Criteria of Histopathological Atypia
Melanocyoma (applicable to all entities listed below)	• Large diameter (>4 mm) • Asymmetry/asymmetric involvement of the epidermis • Necrosis (single cell or en masse) • Ulceration • Mitoses >2/mm^2 • Cells within the lymph vessels
Atypical Spitz tumor	• Deep or marginal mitoses • Solid sheets/nodular growth • Brisk or heavy inflammatory infiltrate • Deep extension (>2 mm in thickness) • (Abundant) melanin in deep cells • Confluent (nonrandom) nuclear pleomorphism
BAP1-inactivated nevus/ melanocytoma (*BAP1*-inactivated melanocytic atypical intradermal tumor)	• Deep or marginal mitoses • Confluent (not loose) sheets of cells • Expansile growth • Melanocytes with increased nucleo-cytoplasmic ratio
Atypical cellular blue nevus/ melanocytoma (atypical dendritic cell tumor)	• Irregularly oriented fascicles • Areas of predominance of melanophages over melanocytes • Brisk or heavy inflammatory infiltrate • Cytological atypia (prominent nucleoli; dendritic cells with thick and irregular processes)
Atypical deep penetrating nevus/melanocytoma (atypical deep penetrating nevus-like tumor)	• Quadrangular/nodular silhouette • Lack of the context of a combined nevus • Brisk or heavy inflammatory infiltrate
Pigmented epithelioid melanocytoma	• Deep or marginal mitoses • Quadrangular/nodular silhouette • Deep extension (>2 mm in thickness) • Confluent (nonrandom) nuclear pleomorphism of the epithelioid cell component • Brisk or heavy inflammatory infiltrate • Dendritic cells with thick and irregular processes

rate of distant metastases is extremely low (and not simply lower than that of melanoma of the same thickness); thus, they are peculiar because they probably stand as strongly lymphotropic (low-grade) melanocytic malignancies [13].

If we consider melanocytomas as a unique broad category (with its subgroups), then it is not surprising that morphology alone cannot be predictive of the clinical outcome, because even in a cohort of conventional thick melanomas morphology alone cannot allow one to discriminate cases that will metastasize from cases that will not. In conventional melanoma, after making the diagnosis, there are some prognostic parameters (the most important being Breslow thickness and ulceration) that can help assess the risk of a melanoma to give metastasis; likewise, after making a diagnosis of melanocytoma, the histopathological assessment might be aimed at a prognostic evaluation. Thus, the best strategy might be listing the morphological features of atypia observed in any melanocytoma, thereby considering these features as prognostic factors and not as histopathological differential features between benign and malignant tumors. A list of these putative histopathological prognostic criteria for any category of melanocytoma is given in Table 1; and not secondary to these histopathological criteria, the clinical features of any melanocytoma—the patient's age; the location and the clinical features of the tumor—should be fully considered in order to assess the best management strategy.

Conclusions

The correlation between molecular and histopathological features of melanocytic tumors is still largely incomplete. From a practical point of view, however, only a very limited number of cases seen in clinical practice run the entire spectrum of molecular and biological progression of melanomagenesis; thus, the molecular progression model has a very limited clinical impact. Rather than intermediate stages in an unlikely path toward melanoma, melanocytomas are probably best regarded as morphobiologically peculiar melanocytic tumors, namely, strongly lymphotropic (low-grade) melanocytic malignancies; their clinical management should be thus discussed case by case in a multidisciplinary setting by integrating the histopathological findings with the clinical data.

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