Dermatology Practical & Conceptual

Biologic Gray Zone of Melanocytic Tumors in Reality: Defining 'Non-Conventional' Melanocytic Tumors

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Citation: Ferrara G, Gualandi A, Rizzo N. Biologic Gray Zone of Melanocytic Tumors in Reality: Defining 'Non-Conventional' Melanocytic Tumors. *Dermatol Pract Concept*. 2024;14(2):e2024149. DOI: https://doi.org/10.5826/dpc.1402a149

Accepted: March 12, 2024; **Published:** April 2024

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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The 'gray zone' and the 'borderline malignant' concepts are widely used in Surgical Pathology because of their considerable explanatory potential; however, they require a rigorous definition, since, as their very name suggests, they move within an ambiguous terrain (between white and black; 'borderline' between benign and malignant; and, specifically, 'borderline' between nevus and melanoma). Confusion exists between intermediate (borderline) morphology and intermediate (borderline) biology, both 'intermediates' being often approached with the same set of histopathological criteria, which, in our opinion, is a conceptual and practical mistake.

The concept of morphologically intermediate melanocytic neoplasms is implicit to the assumption that melanomas and nevi are "reciprocal morphological simulators"; the differential diagnosis between couples of simulators is based upon the simultaneous evaluation of a standard set of criteria which are subjectively implemented and evaluated, thereby bearing an inherent diagnostic uncertainty (and, parenthetically, a poor interobserver agreement) in some cases [1].

The concept of biologically intermediate melanocytic tumors is referred to neoplasms which are *sticto sensu* neither nevi or melanomas and are therefore not evaluable as couples of simulators. These tumors are identified as *melanocytomas* by the World Health Organization (WHO) [2]; we also define melanocytomas as "non-conventional melanocytic tumors", in order to underline their peculiar clinicopathological and biological properties [3].

The melanocytoma rubric encompasses:

i. tumors with a lymphotropic pattern of spread: pigmented epitelioid melanocytomas (PEM); atypical Spitz tumors (AST); WNT-activated/plexiform/deep penetrating tumors (DPN);
ii. other dermal-based tumorigenic neoplasms which, in spite of their histopathological atypia, are seldom associated with distant metastasis: BAP1 inactivated melanocytic tumors (BIMT); MITF pathway-activated (PEComa-like; clear cell sarcoma-like) melanocytic tumors (MAMT);
iii. in our opinion, also cellular blue nevus (CBN)-related dermal dendritic melanocytic neoplasms [4].

There is little doubt that many melanocytomas are so atypical that in a dichotomous (nevus vs melanoma) diagnostic approach they should be labelled as 'melanoma', and mostly as 'thick melanoma'. Nevertheless, all of them are associated with a very low incidence of distant metastases even

after spread to the regional nodes, the latter being found in a percentage (e.g.: up to 39% in AST [5]) even higher than in melanoma. The nodal melanocytoma deposits have a metastatic (subcapsular/intraparenchymal) morphological pattern (Figure 1), different from the capsular/settal pattern of nodal nevi. An abnormal spread to the nodes, if there were any, from common/dysplastic nevi should be a trivial incidental finding, given the frequency of common nevi and the high number of nodes which are daily examined from surgical specimens. We can thus conclude that some melanocytomas are 'lymphotropic neoplasms', whereas common/dysplastic nevi are not.

For the above, the nevus vs melanoma diagnostic approach might be retained only by labelling melanocytomas as 'low-grade melanoma'; the latter term, however, is incorrect because the genetic profile of these neoplasms is different from melanoma. Indeed, based on the presence of specific driver mutations, The Cancer Genome Atlas (TCGA) identifies four molecular melanoma subtypes: *BRAF*-mutated, *RAS*-mutated, *NF1*-mutated, and triple wild-type (a heterogeneous group characterized by one of the following: *KIT* mutations; early onset of *KIT*, *CCND1*, *CDK4*, *MITF*, and *TERT* amplification; gene deletion/loss-of-function of *TP53* and *CDKN2A*) [6]. With the exception of *BRAF* mutation of 'combined' (nevus-associated) subtypes, the genetic drivers of melanocytomas are completely different [2]:

- in PEM: *PRKAR1A* inactivation (in 'combined' tumors) or *PRKCA* fusion;
- in AST: *HRAS* activating mutations; activating fusions of receptor tyrosine kinases *ROS1*, *ALK*, *NTRK1/2/3*, *MET*, *MERTK*, *RET*; activating fusions of MAP kinases *BRAF*, *RAF1*, *MAP3K8*;

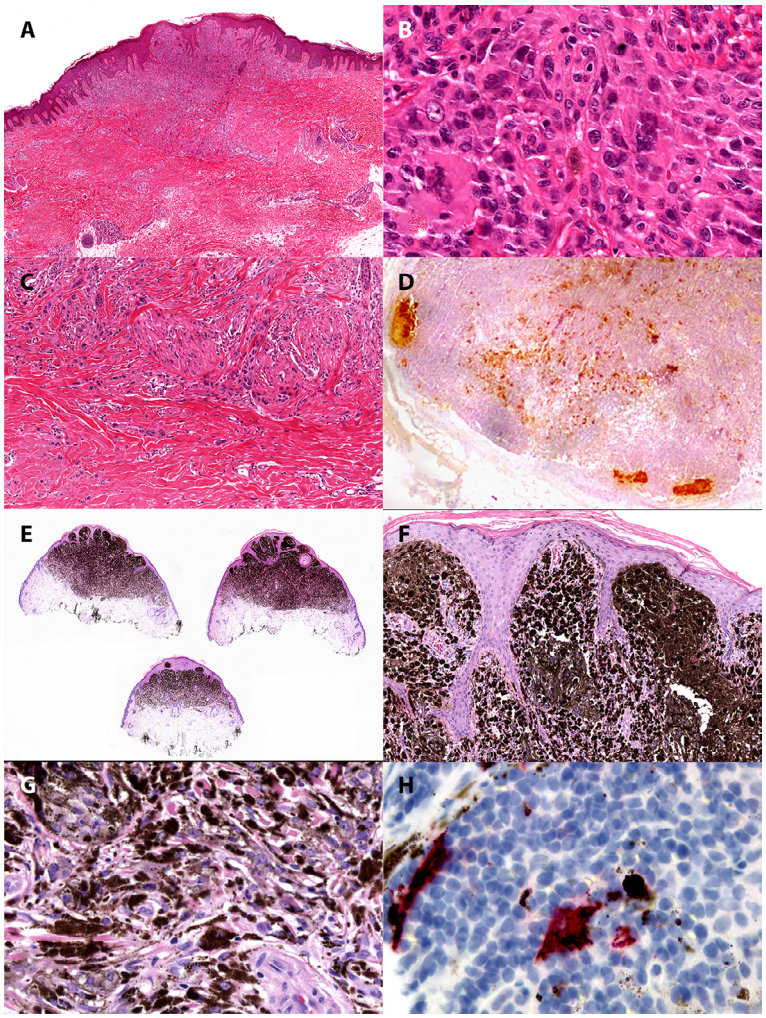

Figure 1. A-D) A 'Spitz-like' tumor of the thigh in a 7-year-old boy. The tumor is wedge-shaped but asymmetric (A) and with confluent (non-random) pleomorphism of epitheliod cells (B); there is a deep dermal desmoplasia. The sentinel node was positive with multiple small subcapsular aggregates of S100-positive cells (D). The patient is alive with no evidence of disease 17 years after surgery. Retrospective molecular examination has revealed *HRAS* G13R (p.Gly13Arg) mutation, which is typical of a subset of Spitz tumors morphologically typified by deep desmoplasia. E-H) A PEM removed from the ear in a 36-year-old woman. The tumor is heavily pigmented throughout (E), with epidermal hyperplasia and obliteration of the grenz zone (F); in less pigmented areas the nuclei show a typical 'fried egg' appearance (G); isolated HMB45-positive intraparenchymal tumor cells were found in the sentinel node (H; Courtesy of Dr. Antonio Perasole, Vicenza, I). No follow up data are available.

- in DPN: gain-of-function mutations in *CTNNB1* or, less commonly, loss-of-function mutations in *APC*;
- in BIMT: loss-of-function mutation in *BAP1*;
- in MAMT: *ACTIN::MITF* or *MITF::CREM* fusions.
- In CBN: activating mutations in *GNAQ*, *GNA11*, or *PLCB4* (or less frequently, in *CYSLTR2*).

Unfortunately, the full spectrum of initiating mutations in melanocytomas, remains to be characterized; in addition, a melanocytoma-like morphology may be associated with immunohistochemical and/or genetic findings of 'conventional' melanoma (Figure 2). Thus, a new problem is raising in dermatopathology, i.e.: the differential diagnosis between severely atypical melanocytoma and melanocytoma-like 'conventional' melanoma [3]. A flow-chart addressing this problem for neoplasms with 'Spitz-like' morphology is shown in Figure 3.

Upon recognition of a melanocytoma, it is suggested that low-grade and high-grade tumors must be differentiated on the basis of a list of general criteria, shared among the various melanocytoma subgroups [7]. In our routine histologic reports we do lists the atypical features of any melanocytoma, but with the following caveats:

1. A persistent conceptual contamination is evident between the melanocytoma grading and the risk of progression from melanocytoma to melanoma [2,7]; however, such a progression is even more exceptional than the nevus-melanoma progression [8];
2. A list of general criteria alone cannot work, since each melanocytoma subgroup has its own classical features and, therefore, its atypical features (e.g.: a 'brisk' lymphocytic infiltrate is typical for BIMT but atypical for other melanocytomas) [3,4];
3. Modulating the clinical management of melanocytomas on the basis of their histologic grade is inaccurate, because the relationship between morphological atypia and biological risk has been unproven (actually denied in the seminal paper on PEM [9]).

From a conceptual point, the definition of melanocytoma is not compatible with the terms 'nevus' and 'melanoma'; for practical purposes, however, we use the term 'nevus' for melanocytomas whose atypical features (as listed in [4]) are inconsistent. For all melanocytomas with atypical features, we recommend a narrow re-excision followed by periodic ultrasonographic monitoring of the regional nodes. Management as per melanoma of the same thickness should be recommended only for melanocytic tumors of uncertain malignant potential (MELTUMP), defined as severely atypical tumorigenic melanocytic neoplasms in which: i) morphology is in between a melanocytoma and a melanocytoma-like melanoma; and ii) a specific genetic driver is not identified [10]. Of course, each case should be evaluated in a multidisciplinary context by also considering the clinical data, namely: the patient's age; the location and the clinical features of the tumor.

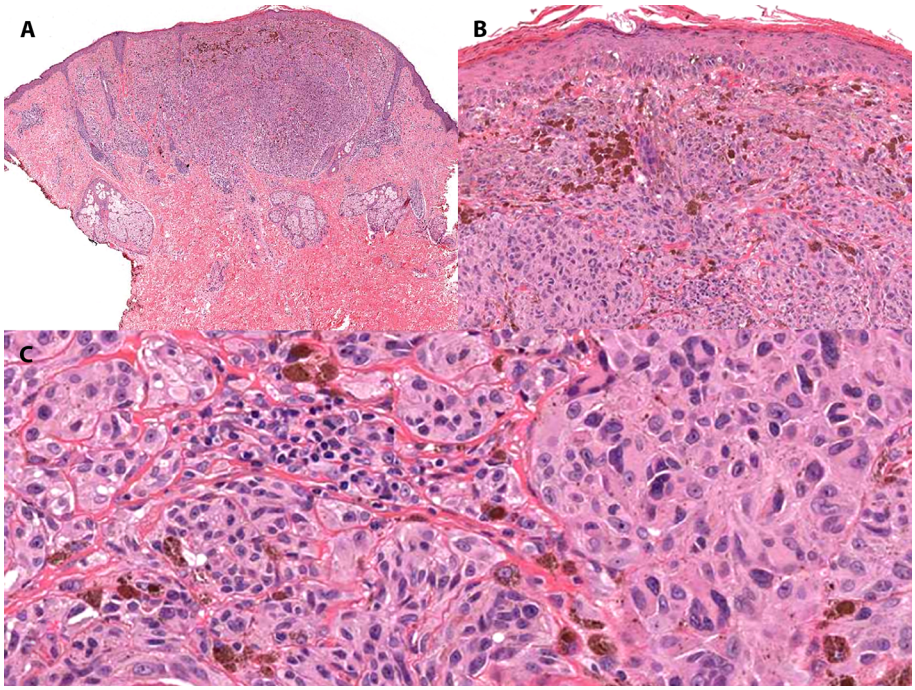

Figure 2. A-C) A melanocytic tumor removed from the cheek in a 19-year-old man. The tumor has a nodular silhouette with superficial melanin deposition (A); the epidermis is flattened but uninvolved (B); the dermal tumor shows spindle and epithelioid cells with confluent growth and confluent pleomorphism. In spite of the 'Spitz-like' cytological features, molecular examination revealed *KIT* p.Val569_Asp572del mutation and was thus diagnosed as melanoma.

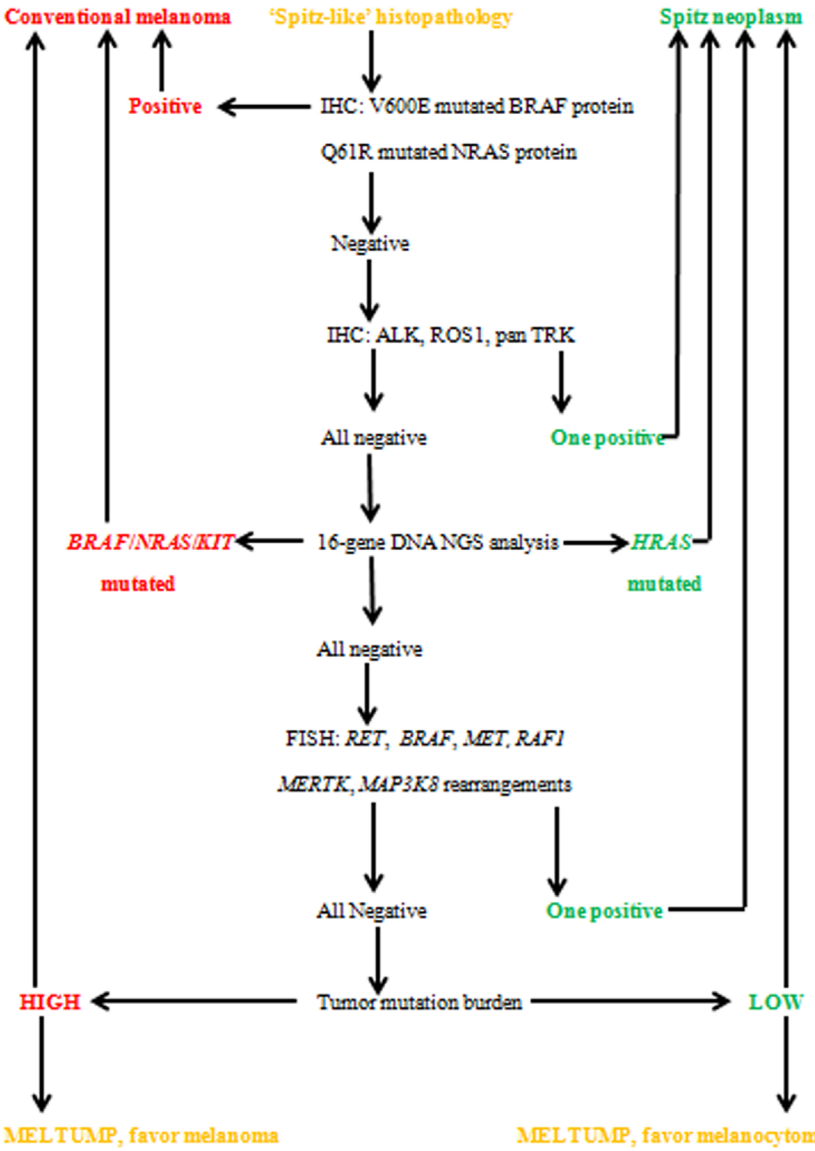

Figure 3. A flow-chart illustrating the sequential approach aimed at differentiating a Spitz neoplasm (melanocytoma) from a conventional (Spitz-like; Spitzoid) melanoma. Specific approaches are requested for the other neoplasms belonging to the melanocytoma rubric.

In conclusion, the biological gray zone of melanocytic tumors is currently identified in melanocytomas, whose peculiar genetic, histological, and biological features request a peculiar ('non-conventional') clinicopathological approach.

References

1. Ferrara G, Argenyi Z, Argenziano G, et al. The influence of clinical information in the histopathologic diagnosis of melanocytic skin neoplasms. PlosONE (2009) 4,e5375.
2. Elder DE, Barnhil R, Bastian BC, et al. "Melanocytic tumour classification and the pathway concept" in (2018) WHO Classification of Skin Tumours, 4th Edition, eds. Elder D.E., Massi D., Scolyer R.A., Willemze R. (Lyon, F: IARC), pp. 66–71.
3. Ferrara G, Argenziano G. The WHO 2018 classification of cutaneous melanocytic neoplasms. Suggestion from routine practice. Front Oncol 2021;11:675296,
4. Ferrara G, Bradamante M. Melanocytic Skin Tumors: Does the molecular progression model fit with the routine clinicopathological practice? Dermatol Pract Concept 2019;10:e2020001
5. Lallas A, Kyrgidis A, Ferrara G, et al. Atypical Spitz tumours and sentinel lymph node biopsy: a systematic review. Lancet Oncol 2014: e178-e183.
6. Cancer Genome Atlas N. Genomic Classification of Cutaneous Melanoma. Cell 2015;161,1681–1696.
7. de la Fouchardiere A, Blokx W, van Kempen LC, Luzar B, et al. ESP, EORTC, and EURACAN Expert Opinion: practical recommendations for the pathological diagnosis and clinical management of intermediate melanocytic tumors and rare melanoma variants. Virch Arch 2021;479:3–11.
8. Pampena R, Kyrgidis A, Lallas A, Moscarella E, Argenziano G, Longo C. A meta-analysis of nevus-associated melanoma: Prevalence and practical implications. J Am Acad Dermatol 2017; 77:938-945
9. Zembowicz A, Carney JA, Mihm MC. Pigmented epithelioid melanocytoma: a low-grade melanocytic tumor with metastatic potential indistinguishable from animal-type melanoma and epithelioid blue nevus. Am J Surg Pathol 2004;28:31–40.
10. Ferrara G, Rizzo N. Re: Molecular pathology as a diagnostic aid in difficult to classify melanocytic tumours with spitzoid morphology. Melanocytic tumors with Spitz-like morphology: toward a therapy-oriented diagnostic approach. Eur J Cancer 2021;157:511–513