Dermatology Practical & Conceptual

The Gray Zone of Melanocytic Tumors - A Clinical Point of View

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Citation: Scharf C, Briatico G, Brancaccio G, Moscarella E, Ronchi A, Argenziano G. The Gray Zone of Melanocytic Tumors - A Clinical Point of View. *Dermatol Pract Concept.* 2024;14(2):e2024153. DOI: https://doi.org/10.5826/dpc.1402a153

Accepted: April 22, 2024; **Published:** April 2024

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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As discussed by Kittler and Ferrara, melanocytic lesions, particularly those exhibiting challenging histopathologic features, pose a significant diagnostic and therapeutic dilemma for clinicians. While Kittler navigates the nuanced territory of diagnosing melanocytic proliferations, critically examining the notion of the gray zone, debating its reality versus its conceptual fiction, the author also assumes that a melanocytic lesion cannot simultaneously be benign and malignant, highlighting the dichotomy between biological and diagnostic uncertainties.

The World Health Organization's latest classification of melanocytic tumors attempts to navigate these complexities by delineating distinct pathways of progression from benign to malignant lesions. [1] Yet, the classification acknowledges the persistent ambiguity in defining clear precursor lesions for some pathways, highlighting the ongoing debate between biological versus diagnostic gray zones, as implicated by Ferrara.

From the 1970', when first described, dysplastic nevus (DN) has always been a source of confusion. The key is whether, and to what level, DN represents a premalignant lesion that will progress to melanoma. [2] This assumption has been propagated over the years, considering that grading nevus cytologic atypia as mild, moderate, or severe by the pathologists could imply this continuous progression of DN towards melanoma, as it happens in actinic keratosis. [3]

It is true that numerous studies have documented the relationship between DN and familial melanoma, and in fact, they were originally described in melanoma-prone families, with the implication that such lesions had a higher risk of transformation to melanoma than the patients' regular nevi. However, in patients with familial melanoma and those with a high number of DN, still melanoma is most frequently developing de novo and not in association to a pre-existing DN. [4]

The basic concept included in the last WHO classification is that all melanomas develop from a benign precursor. The latter progresses first to a biologically intermediate lesion (DN, melanocytoma, atypical Spitz tumor, etc.) that finally transforms into a melanoma. The point is that clinically this concept if very difficult to belive, mainly for the following evidence:

1. More than 70% of melanomas are not found histopathologically in association to a pre-existing nevus. [5] How can it be possible that no nevus remnants are

found in such a high number of melanomas if it were true that all of them should be the result of a nevus transformation?

2. Of the minority of melanomas (less than 30%) found in association to a pre-existing nevus, more than half are associated to a common dermal nevus and not to a DN. [6] How can it be possible that the biologically intermediate lesion is so frequently missing if the stepwise transformation were true?
3. The probability of a single nevus to transform into melanoma is exceedingly low, being calculated in the order of 1 out 200.000 nevi and even in patients with multiple nevi still melanoma develops most frequently de novo. [7]

Although we believe the presence of multiple nevi in an individual is associated with increased melanoma risk, nevi are not melanoma precursors, and DN, melanocytomas and atypical Spitz tumors are not nevi evolving into melanoma but benign lesions with challenging histopathological features.

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