Dermatology Practical & Conceptual

Rethinking Melanocytic Tumors: A Critical Appraisal of the WHO Classification and the Myth of Nevus-to-Melanoma Progression

Giuseppe Argenziano[1], Giulia Briatico[1], Eugenia Veronica Di Brizzi[1], Camila Scharf[1], Gabriella Brancaccio[1], Elvira Moscarella[1], Maria Maddalena Nicoletti[1], Pasquale Verolino[1], Aimilios Lallas[2], Harald Kittler[3]

1 Dermatology Unit, University of Campania, Naples, Italy

2 First Department of Dermatology, School of Medicine, Faculty of Health Sciences, Aristotle University, Thessaloniki, Greece

3 Department of Dermatology, Medical University of Vienna, Vienna

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Corresponding Author: Giulia Briatico, MD PhD, Dermatology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania Luigi Vanvitelli, Via Sergio Pansini, 5, 80131 Naples, Italy. E-mail: giuliabriatico@gmail.com

ABSTRACT

Introduction: The recent WHO classification of melanocytic tumors introduces a refined molecular and histopathological framework suggesting distinct pathways and precursor lesions for all melanoma subtypes. While conceptually appealing, its clinical applicability is increasingly questioned.

Objectives: This review critically examines the transformation theory from benign nevi to melanoma, highlighting inconsistencies between the proposed models and real-life practice.

Methods: Through illustrative cases and key epidemiological evidence, we evaluated the validity of current models proposing intermediate lesions in melanoma development.

Results: We argue that most melanomas arise de novo and that the so-called intermediate lesions, such as dysplastic nevi and atypical Spitz tumors, may mimic melanoma but are not true biological precursors.

Conclusions: We propose a simplified, clinically oriented reclassification of melanocytic lesions based on morphologic ambiguity and actual behavior, aiming to guide therapeutic decisions and reduce diagnostic overinterpretation.

Introduction

The classification and management of melanocytic tumors remain among the most debated areas in dermatology. Advances in molecular diagnostics and the recognition of a diagnostic gray zone [1] have blurred the boundaries between nevi, atypical lesions, and melanoma. This gray zone comprises lesions that resist clear categorization, resulting in considerable variability in diagnosis, terminology, and management.

The latest World Health Organization (WHO) classification [2] seeks to impose order by introducing molecularly defined pathways and attributing biological significance to many lesions traditionally regarded as intermediate. According to this model, virtually all melanomas arise from precursor lesions that evolve from benign to intermediate, then finally, to malignant, following specific molecular trajectories (Table 1).

While theoretically elegant, this concept has raised concerns among clinicians who rarely observe these progression models in everyday practice. This review critically examines the WHO model, particularly its concept of biologically intermediate melanocytic tumors. We argue that the transformation theory, in which nevi evolve into melanocytomas and ultimately into melanoma, is overemphasized and sometimes misleading. Instead, we advocate for a pragmatic, observation-based classification focused on morphologic ambiguity and risk of recurrence or invasion.

The Diagnostic Gray Zone: Clinical and Pathological Perspectives

Most melanocytic lesions encountered in dermatology can be safely diagnosed as clearly benign or clearly malignant. Yet a small but important subset falls into a diagnostic gray zone, displaying architectural disorder, cytologic atypia, or unusual dermoscopic patterns without fulfilling the criteria for melanoma [1].

For dermatologists, this gray zone consists of lesions that raise suspicion but lack definitive malignant features. For pathologists, the dilemma is greater; they are expected to provide definitive diagnoses, yet many such lesions can only be described with umbrella terms such as dysplastic nevus, atypical Spitz tumor, or melanocytoma that convey uncertainty more than precision.

These ambiguous lesions are often graded biologically (low or high grade) to imply malignant potential. However, such assessments rely on variably interpreted histopathological criteria and lack robust prospective validation.

The result may be over- or underdiagnosis, over- or undertreatment [3], and patient anxiety. A biopsy showing architectural disorder and cytologic atypia may be labeled high-grade dysplastic nevus, prompting re-excision despite no clinical evidence of aggressiveness. Conversely, a melanoma with blunt morphologic features might be under-classified and undertreated. These paradoxes highlight the limits of current diagnostic frameworks and the need for a case based clinical approach.

The WHO Classification: A New Paradigm or Theoretical Overreach?

The 2018 WHO Classification of Skin Tumours marked a conceptual shift. Moving beyond the traditional clinical and histopathological categories of superficial spreading, nodular, lentigo maligna, and acral lentiginous melanoma, it proposes nine molecularly-defined pathways, each linked to a specific melanoma subtype and its putative precursor.

Table 1. WHO Melanoma Pathways: The 9 Progression Routes.

Pathway No.	WHO Designation	Cumulative Sun Damage (CSD)	Proposed Precursor
1	Low-CSD melanoma including superficial spreading melanoma	Low	Common and dysplastic nevus
2	High-CSD Lentigo Maligna Melanoma	High (chronic)	Intraepidermal melanocytic proliferation
3	Desmoplastic Melanoma	High (chronic)	Intraepidermal melanocytic proliferation
4	Spitz Melanoma	None	Spitz nevus
5	Acral Melanoma	None	Acral nevus*
6	Mucosal Melanoma	None	Mucosal melanosis*
7	Melanoma in Congenital Nevus	Variable	Congenital nevus
8	Melanoma in Blue Nevus	None	Blue nevus
9	Uveal Melanoma	None	Uveal melanocytic proliferation

*Note: In some pathways (e.g., mucosal, acral), the precursor lesion is hypothetical or histologically undefined.

According to this model, most melanomas emerge through stepwise transformation from a benign nevus to an intermediate lesion and ultimately to melanoma. Each pathway is presented as a predictable, lineage-specific progression, similar to the multistep evolution of certain epithelial cancers.

While intellectually appealing and valuable for research, the clinical utility of this stratified model is doubtful. The assumption that every melanoma derives from a known precursor contradicts decades of clinical observation [4]. Several proposed sequences remain biologically speculative and lack corroboration in daily practice.

For example, the Spitz pathway posits a linear evolution from Spitz nevus to Spitz melanocytoma to melanoma, a sequence rarely, if ever, documented [5]. Likewise, the idea that all superficial spreading melanomas arise from a common acquired nevus progressing through dysplastic stages to melanoma in situ and then invasive disease is seldom reflected in clinical case series or histopathological slides [6].

The most striking logical flaw involves congenital nevi. The WHO classification suggests that transformation proceeds through proliferative nodules to an in situ melanoma. Yet by definition, an in situ melanoma confined to the epidermis cannot logically arise as the next step after an already invasive dermal proliferative nodule.

Thus, while the WHO framework enriches molecular taxonomy, applying it rigidly in clinical dermatology risks overinterpreting histopathological atypia as biological aggressiveness, leading to unnecessary surgeries and psychological burden.

Class I and II Melanocytic Tumors: What Do They Really Mean Clinically?

A central feature of the new WHO classification is the division of melanocytic tumors into four broad classes according to biological behavior and presumed risk of progression. While Classes III and IV refer to clearly malignant melanomas (thin and thick invasive lesions, respectively), Classes I and II encompass the so-called precursor melanocytic tumors.

Class I lesions are described as low-grade melanocytic tumors with an estimated risk of malignant transformation of about 1 in 10,000 [7]. The WHO advises no treatment beyond conservative excision. This group includes:

- Common acquired nevi (no atypia)
- Congenital nevi (no atypia)
- Dysplastic nevi (low grade)
- Common blue nevi

For clinicians this categorization seems acceptable. These lesions have indolent behavior and are rarely problematic. Yet calling them precursor lesions creates confusion, because they appear entirely banal clinically and dermoscopically.

Class II lesions, in contrast, are labeled as high-grade melanocytic tumors, with a low but not negligible risk of progression (approximately 1 in 100) [7]. The WHO recommends complete excision and often re-excision. This group includes:

- Dysplastic nevi (high grade)
- Spitz nevi
- Cellular blue nevi
- Deep penetrating nevi (plexiform)
- Lentigo maligna
- Melanoma in situ

This classification leads to striking therapeutic inconsistencies. Conventional Spitz nevi and melanoma in situ, which are biologically and clinically distinct, are placed in the same category. Likewise, the inclusion of cellular blue nevi, lesions that very rarely progress to melanoma, alongside lentigo maligna is not supported by clinical experience.

A particularly problematic example is the high-grade dysplastic nevus. Despite its ominous label and histopathological atypia, it is very common, especially in young individuals, and usually benign. Many dermatologists therefore find themselves re-excising lesions that are biologically indolent simply because of a category assignment rather than any real clinical risk. By contrast, dysplastic nevi are very rare in the elderly, a diagnosis in this age group likely representing an under-classification of a featureless melanoma. These contradictions expose the gap between histopathological theory and patient care. The WHO framework assigns a theoretical progression risk based on morphology, whereas clinical decision-making must also consider age, body site, dermoscopic pattern, patient history, and lesion dynamics. Without this context, strict application of the WHO classification system risks unnecessary treatment and loss of personalized care.

The Spitz Conundrum

Among the most debated elements of the WHO classification is the idea that Spitz tumors represent a biological continuum culminating in melanoma. The proposed Spitz pathway describes a linear evolution from Spitz nevus to Spitz melanocytoma (previously termed atypical Spitz tumor), then to melanocytic tumor of uncertain malignant potential or spitzoid tumor of uncertain malignant potential, and finally to Spitz melanoma.

This sequence finds little support in clinical reality. Dermatologists and dermatopathologists seldom observe a conventional Spitz nevus evolving into melanoma. In fact, Spitz nevi, especially in children and adolescents, usually regress or stabilize and often develop a more conventional appearance over time [8]. Even when they grow asymmetrically or exhibit worrisome features, excision typically confirms a benign Spitz nevus without evidence of progression.

Moreover, the diagnosis of Spitz melanoma is exceptionally rare and often based solely on histopathological features without documented clinical evolution from a precursor. This raises the possibility that some lesions classified as Spitz melanoma are actually melanomas with spitzoid morphology rather than descendants of a benign Spitz lineage.

Confusion is amplified by the bidirectional overlap of morphology: some melanomas can mimic Spitz nevi and vice versa. As a practical safeguard, any spitzoid-looking lesion that appears after puberty is usually excised [9].

The overall picture is not one of linear progression but of morphological overlap between two distinct entities. Conflating overlap with true progression risks diagnostic inflation and unnecessary re-excisions, increasing both patient anxiety and healthcare costs. The Spitz example illustrates the danger of applying rigid theoretical models to lesions whose behavior is better understood through clinical observation and dermoscopic follow-up.

Three Clinical Cases that Challenge the Progression Theory

While the transformation model from benign nevus to melanoma is conceptually appealing, clinical evidence often tells a different story. The following cases highlight how real-world dermatology practice contradicts the notion of stepwise nevus to melanoma transformation.

Case 1: The Supposed Precursor that Became a 7.5 mm Melanoma

A 45-year-old male presented with a pigmented lesion on the face that was excised and diagnosed as a junctional melanocytic proliferation consistent with a dysplastic nevus, a WHO Class I low-grade lesion (Figure 1). Two and a half years later, a nodular lesion appeared in the same location and proved to be a 7.5 mm thick melanoma with 12 mitoses per square millimeter (Figure 2).

Either the first lesion transformed in record time, or it was already a melanoma misdiagnosed as a nevus. Given the short interval and aggressive behavior, misclassification is the more likely explanation.

Case 2: A High-Grade Dysplastic Nevus that was Clearly Benign

A 27-year-old female had two pigmented lesions excised. One was called a low-grade dysplastic nevus, and the other one was diagnosed as a high-grade dysplastic nevus. This latter lesion, located on the leg, showed no clinical or dermoscopic sign of malignancy (Figure 3). The WHO guidelines called for re-excision, yet clinical judgment favored simple observation.

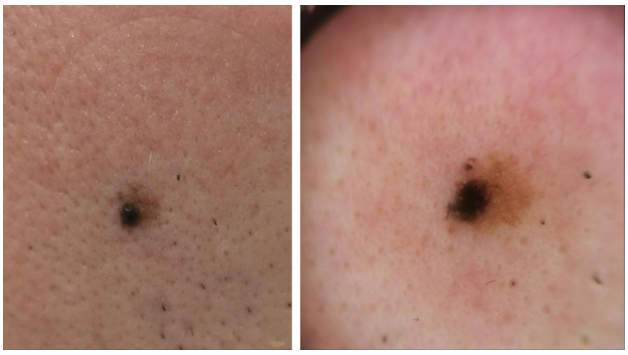

Figure 1. A pigmented lesion on the cheek of a middle-aged male. Dermoscopically, no prevalent benign criterion is seen. Furthermore, a black blotch could be suggestive of an invasive melanoma, a diagnosis that was not supported by the histopathologists, who concluded it was a dysplastic nevus.

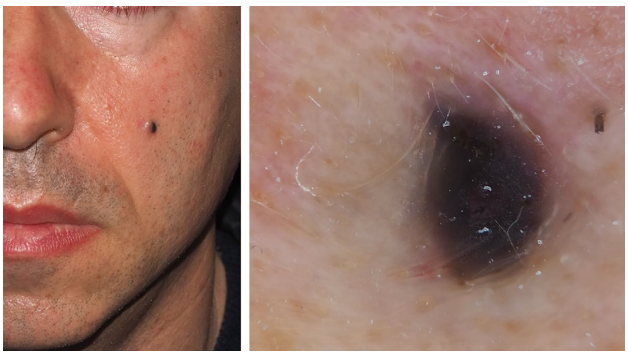

Figure 2. Same patient as Figure 1. A relapse of the previous lesion was observed and diagnosed histopathologically as a melanoma, 7.5 mm Breslow thickness.

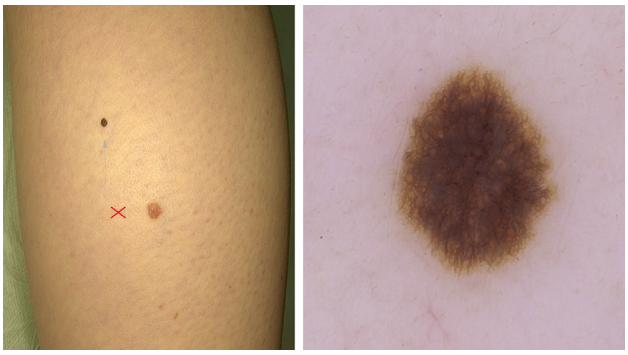

Figure 3. The patient's young age and the regular pigment network suggest the diagnosis of a benign nevus. However, histopathologically, this lesion was diagnosed as high-grade dysplastic nevus.

Case 3: A High-Grade Dysplastic Nevus that was a Melanoma

A 58-year-old female presented with a solitary pigmented lesion on the leg (Figure 4). Histopathology labeled it a compound nevus with severe dysplasia. However, the asymmetry and dermoscopic pattern strongly suggested melanoma in situ.

Together, these cases show that so-called intermediate diagnoses can obscure the true nature of a lesion, either by exaggerating or underestimating risk, and they demonstrate

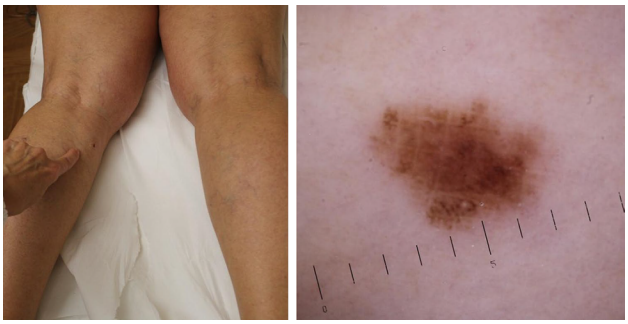

Figure 4. Solitary lesion on the leg of a middle-aged female. Dermoscopically, atypical network, atypical globules, and prominent skin markings are visible, suggesting the diagnosis of melanoma in situ. Again, the histopathological diagnosis was high-grade dysplastic nevus.

the need to integrate clinical and dermoscopic information with histopathology.

Three Facts That Undermine the Precursor Theory

Fact 1: Over 70% of Melanomas Arise De Novo

Multiple studies have shown that more than 70% of melanomas are not associated histopathologically with a pre-existing nevus [10]. In other words, in the majority of cases, no nevus remnant is found within or adjacent to the melanoma. Proponents of the progression theory argue that the original nevus may have been obliterated early in the malignant process, thus becoming undetectable. However, this explanation is neither parsimonious nor consistent with clinical experience. It implies that nevus remnants should vanish while the lesion is still very small, given that even in a series of very small melanoma, excised when they were less than 5 mm, nevus remnants are usually not found (Figures 5 and 6). The absence of nevus remnants in the vast majority of melanomas weakens the concept of obligatory precursor lesions and instead supports the idea that most melanomas arise de novo, from a single melanocyte of the normal skin acquiring tumorigenic mutations.

Fact 2: The Progression Sequence Is Never Seen in Full

If the stepwise model were valid, we would expect to see histopathological specimens showing coexisting zones of common nevus, dysplastic nevus, and melanoma within the same lesion. In practice, such histopathological continuity is extremely rare-to-nonexistent. Moreover, among the minority (about 30%) of melanomas that do appear associated with a nevus, more than half arise from banal dermal nevi, not dysplastic ones [11] (Figure 7). This observation challenges the logic of the progression model, which would require dysplastic nevi as obligatory intermediates. Rather than true

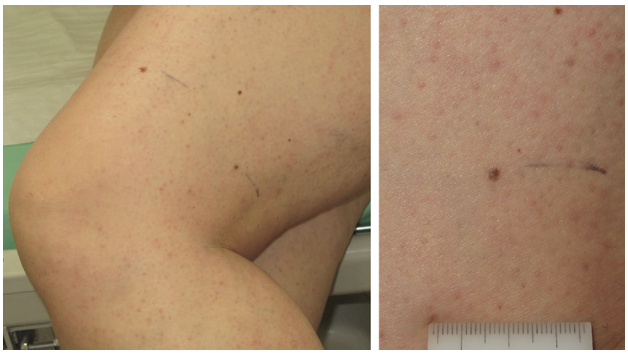

Figure 5. This is a melanoma in situ with a diameter of about 2 mm.

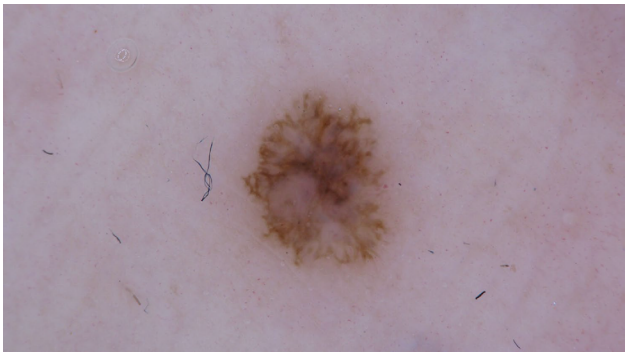

Figure 6. Dermoscopic image of the lesion shown in Figure 5 showing clear-cut melanoma-specific features such as irregular streaks at the periphery and regression structures in the center. This is a melanoma in situ with no clinical, dermoscopic, or histopathological sign of an associated nevus.

progression, these may represent collision tumors, i.e., the coexistence of an evolving melanoma adjacent to or superimposed on a pre-existing nevus, without biological lineage continuity.

Fact 3: The Statistical Probability Is Exceedingly Low

Large-scale epidemiological studies have estimated that the risk of malignant transformation of a single nevus is approximately 1 in 200,000 [7]. This extremely low figure is incompatible with the idea that nevi are common steppingstones toward melanoma.

Even in high-risk patients with hundreds of nevi, most melanomas still arise de novo (Figures 8 and 9). This further invalidates the rationale for treating dysplastic or atypical nevi as biologically dangerous entities requiring special attention. Certainly, individuals with many nevi need long-term monitoring with total body photography and sequential digital dermoscopy imaging [12], but the main aim of sequential surveillance is to facilitate the detection of a melanoma developing among the numerous clinically similar nevi rather than monitoring nevi that may progress to melanoma, which is much less likely to happen.

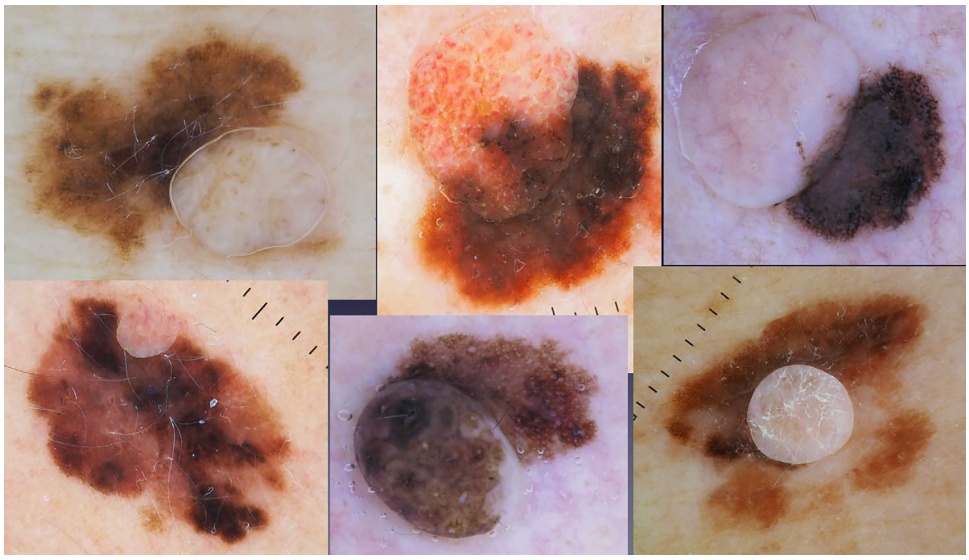

Figure 7. Six dermoscopic images of nevus-associated melanomas. The nevus component is represented by a classical dermal nevus.

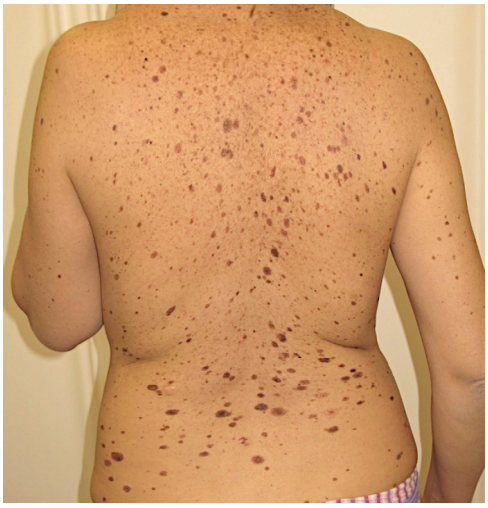

Figure 8. Clinical image of a patient with multiple nevi.

Taken together, these three facts provide compelling evidence that the nevus-to-melanoma transformation model is an exception, not the rule. As such, it should not drive routine clinical decision-making, particularly in the absence of a good clinical-histopathological correlation.

A Proposal for a More Useful Classification

The current WHO classification, while theoretically sophisticated and grounded in molecular pathology, attempts to impose a linear logic on the process of melanoma genesis. However, clinical observations suggest that, like most complex biological phenomena, melanoma genesis is nonlinear, chaotic, and unpredictable. As discussed, the insistence on assigning to every melanoma a defined precursor lesion is not supported by clinical experience or epidemiological data.

In light of these discrepancies, we propose a simplified and pragmatic classification of melanocytic tumors that better reflects the reality of clinical dermatology. Rather than relying on assumed biological progression or histopathological terminology with variable interpretation, we suggest categorizing lesions based on the degree of morphological ambiguity and actual clinical behavior.

This framework would consist of three primary categories:

1. Clearly Benign Melanocytic Nevi
   - Diagnostically straightforward in most cases
   - Rarely if ever recur or evolve
2. Clearly Malignant Melanomas
   - In situ or invasive melanomas with well-established clinical, dermoscopic, and histopathological criteria
   - Require prompt excision and staging
3. Ambiguous Melanocytic Tumors (The "Gray Zone")
   - Lesions that defy easy classification, either clinically, dermoscopically, or histopathologically
   - Management should be individualized based on clinical scenario, dermoscopic features, histopathological criteria, and multidisciplinary discussion
   - Re-excision should be decided case-by-case, not mandated by label alone

Such a framework would better align with daily practice, minimize over- and underdiagnosis and over- and undertreatment, and still integrate pathology and molecular insights where they add genuine value.

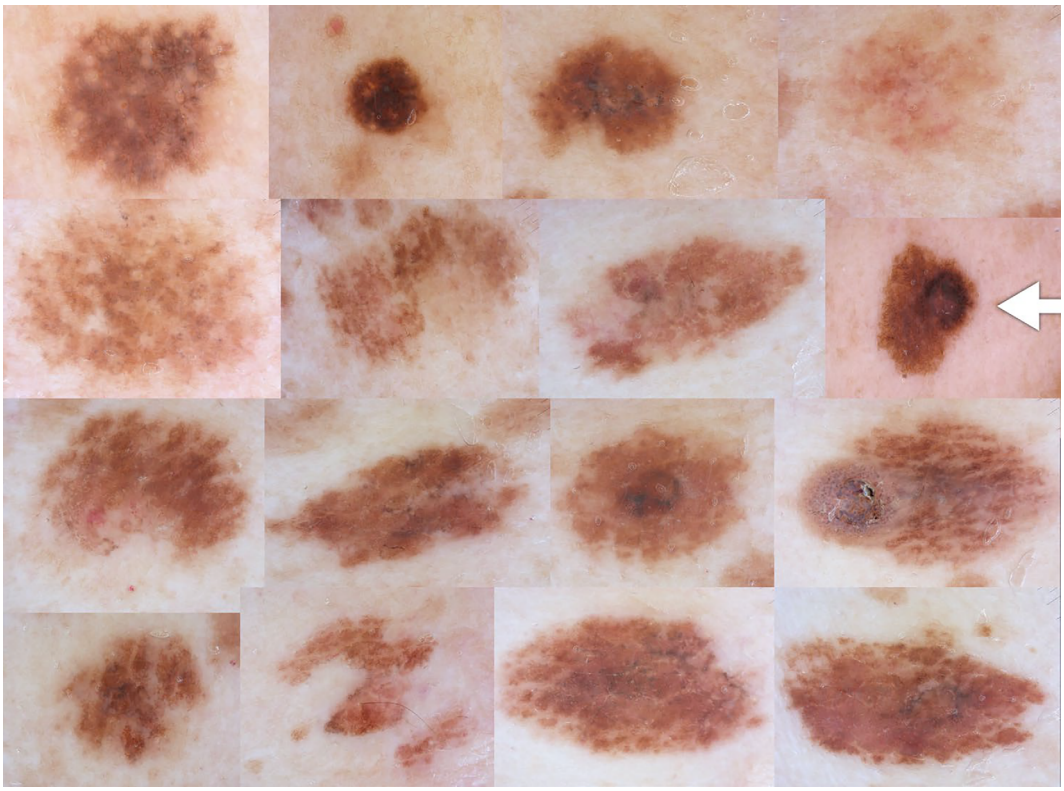

Figure 9. Dermoscopic images of some of the lesions of the patient in Figure 8. Many of these lesions are dermoscopically atypical. However, only the lesion indicated by the arrow was diagnosed histopathologically as a de novo melanoma in situ.

Conclusions and Practical Recommendations

The management of melanocytic tumors, particularly those falling into the so-called "intermediate" or "gray zone," remains one of the most challenging aspects of dermatology practice. While the latest WHO classification offers a refined framework rooted in molecular pathology, its clinical transposition is far from straightforward.

This review highlights how many of the assumptions underlying the nevus-to-melanoma transformation model are not corroborated by real-world evidence. Most melanomas arise de novo, not from pre-existing nevi, many so-called "high-grade dysplastic nevi" are biologically indolent, and some melanomas with bland histopathological features are misclassified as borderline lesions, delaying appropriate management.

Instead of rigidly adhering to histopathological labels or theoretical pathways, clinicians must embrace a case-by-case approach that prioritizes clinical scenario, dermoscopic morphology, lesion dynamics, and patient history. Only through this integrative method can we avoid both over- and undertreatment.

The ultimate goal should not be to fit every lesion into a predefined category but to provide patients with the most appropriate precision care based on the best available clinical, dermoscopic, and histopathological evidence, used in harmony, not in isolation.

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