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Diagnostic Challenges in Dysplastic Nevi: A Retrospective Case Series With Histopathological Reassessment and Immunohistochemistry

Natália N. Freitas [1], Guilherme Henrique N. Freitas [1], Débora Salles [1], Leonardo Sementilli [2], Angelo Sementilli [1]

1. Pathology, Universidade Metropolitana de Santos, Santos, BRA 2. Pathology, Santa Casa Hospital, São Paulo, BRA

Corresponding author: Débora Salles, debsalles@gmail.com

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Abstract

Background: Dysplastic nevi remain diagnostically challenging because of their histopathological overlap with early melanoma.

Objective: This study aimed to evaluate the challenges in differentiating dysplastic nevi from melanoma, emphasizing histopathological reassessment and the complementary role of immunohistochemistry.

Methods: This retrospective case series included 31 melanocytic lesions initially diagnosed as atypical melanocytic proliferations between 2022 and 2023. Clinical, histological, and immunohistochemical data were reviewed, and cases were reassessed by an experienced dermatopathologist.

Results: Diagnostic discrepancies were identified, particularly among lesions with high-grade atypia. Ki-67 and other available immunohistochemical findings provided complementary information in diagnostically challenging lesions. Overall, 16 of 31 lesions (51.6%) were reclassified as melanoma; among the 26 lesions initially diagnosed as dysplastic nevi, 16 (61.5%) were reclassified as melanoma.

Conclusion: These findings highlight the diagnostic complexity of dysplastic nevi and support expert dermatopathological review, careful clinicopathological correlation, and the integration of immunohistochemistry in borderline melanocytic lesions. This integrated approach may help reduce diagnostic misclassification and support appropriate clinical management.

Categories: Pathology, Dermatology
Keywords: dermatopathology, differential diagnosis, dysplastic nevi, histopathology, immunohistochemistry, melanoma

Introduction

Dysplastic nevi, also referred to as atypical nevi, are melanocytic lesions that present clinical and histopathological features overlapping with melanoma [1,2]. Despite decades of study, their biological significance remains controversial, particularly regarding their role as true precursor lesions or merely markers of increased melanoma risk [3,4].

From a histopathological perspective, dysplastic nevi exhibit architectural disorder and cytological atypia, including lentiginous melanocytic proliferation, nuclear irregularities, and stromal changes such as fibrosis and inflammatory infiltrate [5,6]. However, these features may also be observed in early melanoma, leading to significant diagnostic challenges.

The 2018 World Health Organization (WHO) Classification of Skin Tumours and subsequent updates published in 2024 emphasize the importance of integrating histopathological and molecular features into the classification of melanocytic lesions [3,4]. This framework recognizes the heterogeneity of melanocytic tumors and highlights the diagnostic challenges associated with lesions exhibiting overlapping features. Within this spectrum, distinguishing high-grade dysplastic nevi from melanoma in situ remains particularly difficult.

Terminology for dysplastic nevi has evolved with updates to the WHO classification of melanocytic lesions. The WHO-based approach uses a two-tier grading system, distinguishing lesions with low-grade from those with high-grade cytological atypia. Lesions previously classified as mildly dysplastic nevi may instead be described as melanocytic nevi with architectural disorder and minimal to mild cytological atypia, without the designation of dysplasia [3,4]. Because this is a retrospective study, the terminology used in the original pathology reports has been retained when describing the initial diagnoses.

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Histopathological assessment remains central to the diagnosis of dysplastic nevi, although variability in diagnostic criteria and the biological heterogeneity of melanocytic lesions continue to pose challenges in distinguishing these lesions from melanoma [6,7]. Given these diagnostic uncertainties, ancillary techniques such as immunohistochemistry have gained importance. Markers such as HMB-45 and Ki-67 can contribute to the assessment of melanocytic differentiation and proliferative activity, respectively, but their findings must be interpreted in conjunction with histopathological features [8,9].

Therefore, this study aims to evaluate the diagnostic challenges in differentiating dysplastic nevi from melanoma, with emphasis on the role of histopathological reassessment and immunohistochemical analysis.

Materials And Methods

Study design

This retrospective case series included melanocytic lesions diagnosed between January 1, 2022, and December 31, 2023. The cases were identified from the archives of the pathology service where the original diagnoses had been established, and the corresponding histopathological material was retrieved for reassessment. This study was approved by the Research Ethics Committee of the Universidade Metropolitana de Santos (UNIMES) (approval number: 01000126.0.0000.5509; protocol number: 8.779.650). The study was conducted in accordance with applicable ethical principles for research involving human participants. Written informed consent was obtained in accordance with the protocol approved by the Research Ethics Committee.

Sample selection and data collection

A total of 31 melanocytic lesions were included in the study, comprising 26 cases initially diagnosed as dysplastic nevi and five cases initially diagnosed as melanoma. All cases had adequate tissue preservation and available histological slides and paraffin blocks for reassessment. Cases with insufficient material or diagnoses outside the scope of the study were excluded. Clinical data included age, sex, and lesion location. Initial diagnoses and the results of histopathological reassessment were recorded for comparison.

Histopathological and immunohistochemical analysis

Histopathological evaluation followed standardized criteria based on established pathology guidelines [10,11]. All cases were independently reassessed by an experienced dermatopathologist blinded to the initial histopathological diagnoses. The reassessment focused on the morphological features of the lesions, following established histopathological criteria.

Immunohistochemical findings were reviewed, when available, as complementary evidence to the histopathological assessment. HMB-45 and Ki-67 staining were documented in representative melanocytic lesions. Immunohistochemical findings were interpreted in conjunction with histopathological features and were not considered independently diagnostic.

Immunohistochemical staining for Ki-67 and HMB-45 was performed using monoclonal antibodies. For Ki-67, the MIB-1 clone was used at a 1:200 dilution, according to the laboratory's protocol. For HMB-45, the corresponding monoclonal antibody was used at a 1:100 dilution. Antigen retrieval, detection systems, chromogens, and counterstaining were performed according to the laboratory's validated procedures. Appropriate positive and negative controls were used in accordance with laboratory protocols.

Ki-67 immunohistochemical results were available for a subset of 17 cases from the original study population, based on the prior availability of the corresponding immunohistochemical examination. As Ki-67 staining was not performed systematically in all cases, quantitative analysis was restricted to lesions with documented Ki-67 percentages. Values were grouped according to the final diagnosis, and no values were imputed for cases without quantitative results. Ki-67 labeling was interpreted based on nuclear immunoreactivity, with percentages representing the proportion of positive tumor-cell nuclei as documented in the available records. HMB-45 expression was interpreted according to the presence and distribution of immunoreactivity in melanocytic cells.

Data analysis

Data were summarized using descriptive statistics. Categorical variables were expressed as absolute frequencies (n) and percentages (%). Continuous variables were summarized descriptively when applicable. Diagnostic concordance was assessed by comparing the initial diagnosis recorded in the pathology service with the diagnosis established after specialized histopathological reassessment. Data organization was performed using Microsoft Excel (Microsoft Corporation, Redmond, Washington, United States), and descriptive analyses and graphical representations were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Diagnostic agreement between the initial and revised diagnoses was assessed using Cohen's kappa

coefficient (κ), with a 95% confidence interval (CI). The analysis was based on the cross-tabulation of initial and revised diagnostic categories and evaluated agreement beyond that expected by chance.

Results

The sample consisted of 31 patients, including 19 females (61.3%) and 12 males (38.7%). The trunk was the most frequently affected anatomical site. Of the 31 cases, 15 (48.4%) had concordant initial and revised diagnoses, whereas 16 (51.6%) had a change in diagnosis after reassessment. Among the 26 lesions initially diagnosed as dysplastic nevi, 16 (61.5%) were reclassified as melanoma, while 10 (38.5%) retained the diagnosis of dysplastic nevus. These findings highlight the substantial diagnostic discrepancy among lesions initially classified as dysplastic nevi. Demographic and clinical characteristics, as well as the initial and revised diagnoses and diagnostic concordance, are summarized in Table *1*.

Variable	n (%)
Sex	
Female	19 (61.3)
Male	12 (38.7)
Most frequent anatomical location	
Trunk	11 (35.5)
Initial diagnosis (N=31)	
Dysplastic nevus (moderate/high grade)	26 (83.9)
Melanoma	5 (16.1)
Revised diagnosis (N=31)	
Dysplastic nevus	10 (32.3)
Melanoma	21 (67.7)
Diagnostic reassessment: overall sample (N=31)	
Concordant initial and revised diagnoses	15 (48.4)
Diagnosis changed after reassessment	16 (51.6)
Outcomes among cases initially diagnosed as dysplastic nevi (n=26)	
Retained diagnosis of dysplastic nevus	10 (38.5)
Reclassified as melanoma	16 (61.5)

TABLE 1: Demographic and clinical characteristics of the study population and diagnostic reassessment

Percentages for the overall sample are calculated using the total number of cases (N=31). Percentages for outcomes among lesions initially diagnosed as dysplastic nevi are calculated using that subgroup (n=26). Diagnostic reclassification refers to a change from the initial diagnosis to the diagnosis established after histopathological reassessment.

Overall diagnostic concordance between the initial and revised diagnoses was 48.4% (15/31 cases). Cohen's kappa coefficient was 0.168 (95% CI: 0.011-0.325), indicating limited agreement beyond chance between the initial and revised diagnostic classifications.

Among the 26 lesions initially diagnosed as dysplastic nevi, 16 (61.5%) were reclassified as melanoma after histopathological reassessment. Representative histopathological features of a junctional dysplastic nevus are shown in Figure *1*, while Figure *2* illustrates HMB-45 immunohistochemical expression in a junctional dysplastic nevus.

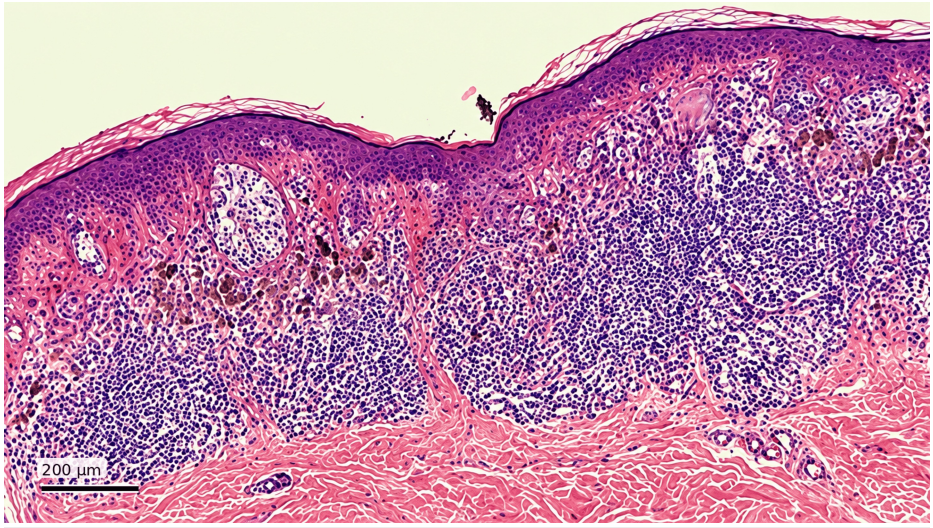


FIGURE 1: Junctional dysplastic nevus showing proliferation of melanocytes arranged in nests along the basal layer of the epidermis (hematoxylin and eosin, 100×)

Scale bar: 200 µm.

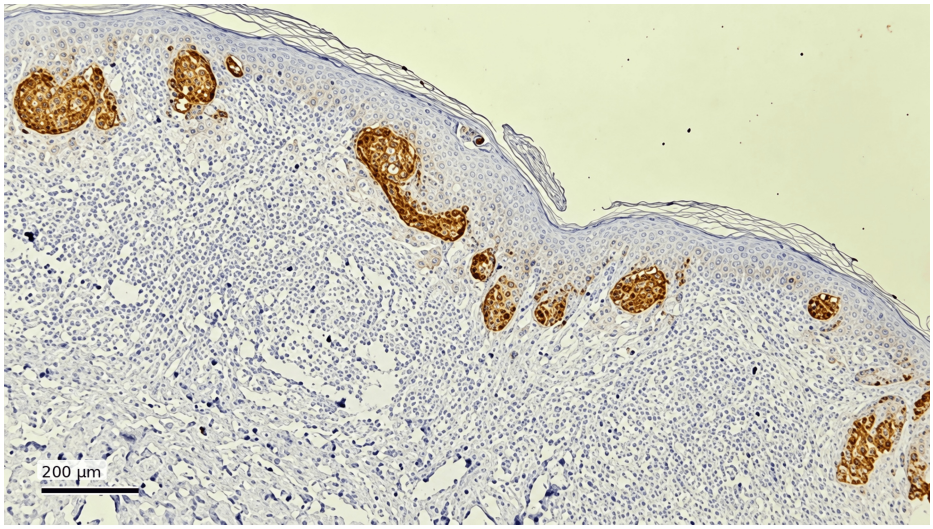


FIGURE 2: Junctional dysplastic nevus with immunohistochemical expression of HMB-45 highlighting melanocytic proliferation at the dermoepidermal junction (100×)

Scale bar: 200 µm.

In several cases, histopathological reassessment combined with immunohistochemical findings led to reclassification as melanoma, including melanoma in situ and microinvasive melanoma. Figure *3* shows the histopathological features of melanoma in situ, characterized by atypical melanocytic proliferation with pagetoid spread and irregular nesting within the epidermis. Figure *4* illustrates diffuse HMB-45 immunohistochemical expression in melanoma in situ.

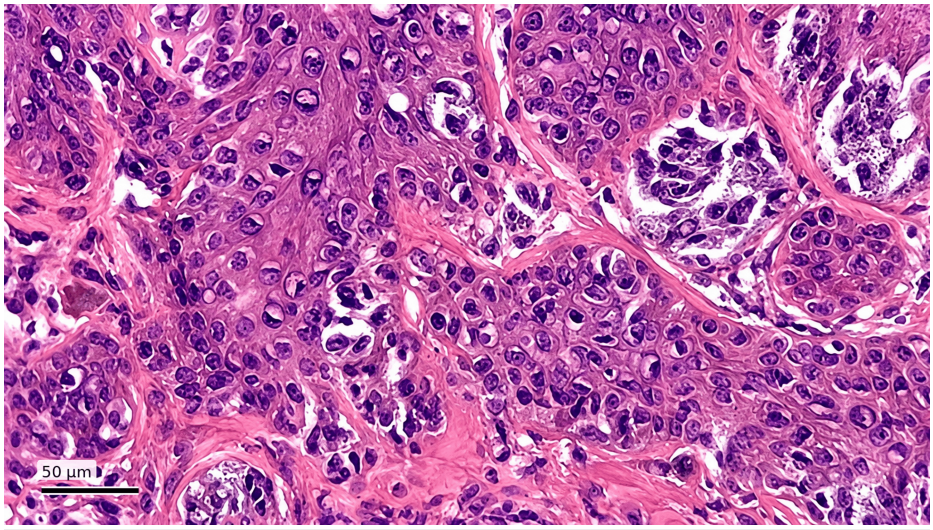


FIGURE 3: Melanoma in situ demonstrating atypical melanocytic proliferation with pagetoid spread and irregular nesting within the epidermis (hematoxylin and eosin, 400×)

Scale bar: 50 µm.

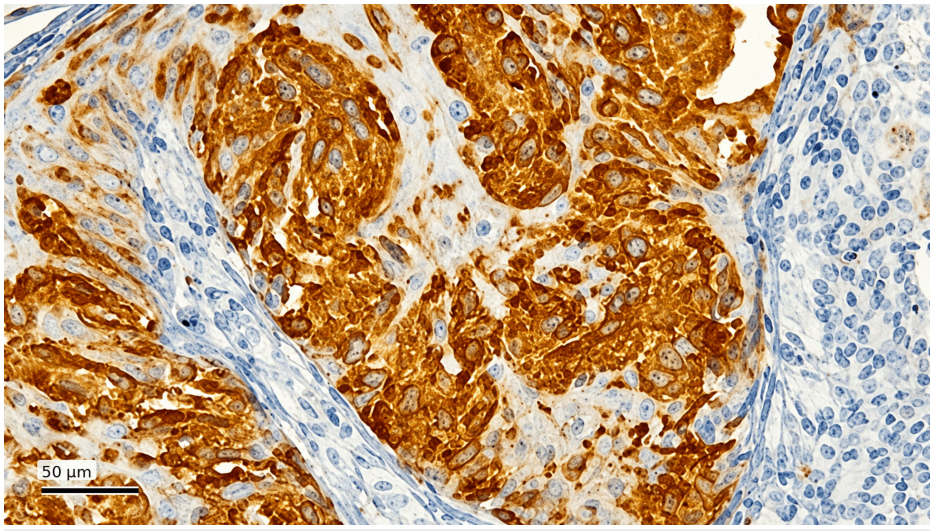


FIGURE 4: Melanoma in situ with diffuse HMB-45 expression throughout the full thickness of the epidermis supporting the diagnosis (400×)

Scale bar: 50 µm.

In addition to melanoma in situ, histopathological reassessment identified lesions with invasive features. Figure *5* illustrates microinvasive melanoma, characterized by atypical melanocytic proliferation, architectural disorder, and early invasion into the dermis.

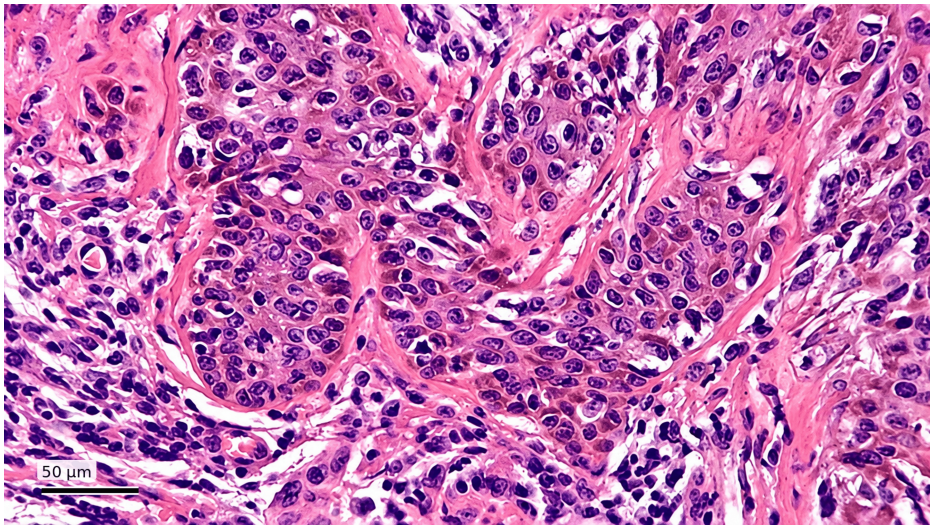


FIGURE 5: Microinvasive melanoma showing atypical melanocytic proliferation with architectural disorder and early dermal invasion (hematoxylin and eosin, 400×)

Scale bar: 50 µm.

Ki-67 immunohistochemical staining was evaluated as a marker of proliferative activity in melanocytic lesions. Quantitative Ki-67 data were available for a subset of 17 cases in which the corresponding immunohistochemical examination had previously been performed. Of these, 12 were classified as melanoma and five as dysplastic nevi. The median Ki-67 index was 20% (interquartile range (IQR): 17.5-30%; range: 10-60%) in melanomas and 10% (IQR: 0.5-30%; range: 0.5-30%) in dysplastic nevi. The difference between groups was not statistically significant (exact two-sided Mann-Whitney U test; p=0.279). These results should be interpreted cautiously because quantitative data were available for only a subset of the study population. Figure *6* illustrates Ki-67 immunoreactivity in a representative lesion. The mean Ki-67 proliferative index across the five diagnostic categories is summarized in Table *2*.

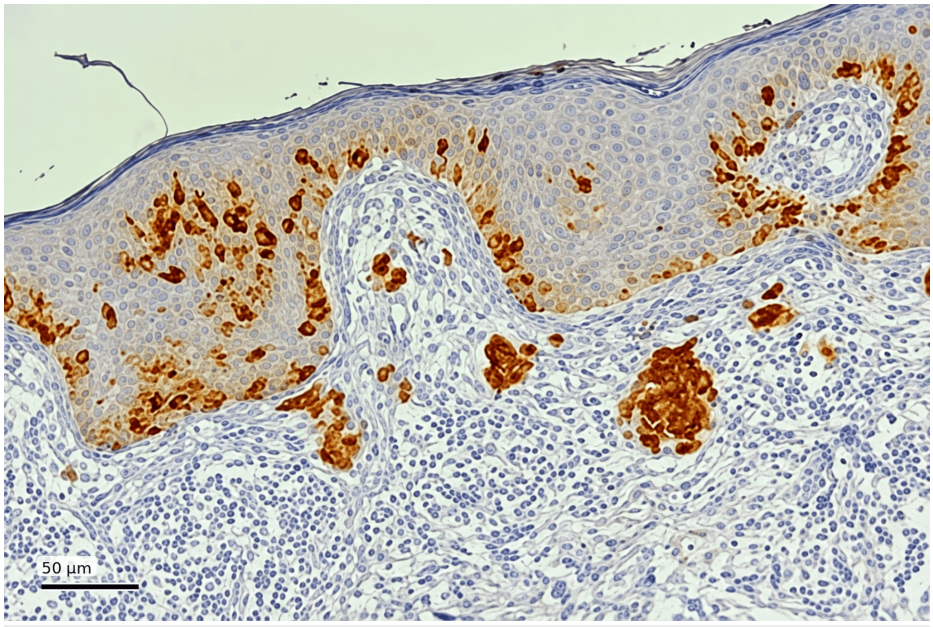


FIGURE 6: Ki-67 immunohistochemical staining showing proliferative activity in a melanocytic lesion (400×)

Scale bar: 50 µm.

Final diagnostic category	Mean Ki-67 index (%)
Compound dysplastic nevus	0.5
Junctional dysplastic nevus	5
Melanoma in situ	20
High-grade dysplastic nevus	30
Invasive melanoma	35

TABLE 2: Mean Ki-67 proliferative index according to diagnostic category

These findings highlight the diagnostic complexity of melanocytic lesions with atypical features and the potential for initial misclassification in routine practice.

Discussion

The differentiation between dysplastic nevi and melanoma remains one of the most challenging areas in dermatopathology [2,11]. The findings of this study reinforce the concept that lesions with high-grade atypia exist within a diagnostic gray zone, where morphological criteria alone may be insufficient for definitive classification.

Diagnostic variability in dysplastic nevi has been consistently described in the literature. Histopathological features, including nuclear characteristics, may provide useful information in distinguishing dysplastic nevi from melanoma, although substantial morphological overlap remains [12]. Hastrup et al. evaluated the reproducibility of histological criteria among pathologists and found limited agreement for several nuclear features, whereas architectural features showed better reproducibility, highlighting the difficulty of establishing consistent diagnostic thresholds [13]. Similarly, Duncan et al. reported substantial overall concordance in the recognition of dysplastic melanocytic nevi, but considerably lower agreement when lesions were graded according to the degree of atypia, particularly at the more extreme ends of the diagnostic spectrum [14]. These observations are consistent with the diagnostic discrepancies identified in the present study, particularly among lesions initially interpreted as showing high-grade atypia.

The reproducibility of histological criteria has also been explored in studies emphasizing the importance of cellular morphology. Rhodes et al. proposed a reproducible histologic definition of dysplastic melanocytic nevi based on specific cellular features, reflecting the continuing effort to reduce subjectivity in the diagnosis of these lesions [15]. More recently, Aydin Ulgen et al. evaluated the application of the 2018 WHO grading criteria and demonstrated only fair overall interobserver agreement, despite better reproducibility for some architectural parameters [16]. Taken together, these studies support the interpretation that diagnostic disagreement in atypical melanocytic lesions is not necessarily attributable to inadequate assessment by individual pathologists, but may reflect the intrinsic overlap of morphological features between dysplastic nevi and melanoma.

Rather than indicating true biological progression, the observed diagnostic shifts in this study likely reflect the inherent difficulty in distinguishing borderline lesions. This is consistent with previous literature, which emphasizes interobserver variability and the lack of universally accepted criteria [2,12]. In this context, the reclassification of some lesions as melanoma should be interpreted primarily as a diagnostic reassessment rather than evidence that a dysplastic nevus has undergone malignant transformation. The biological relationship between melanocytic nevi and melanoma is complex, and not all dysplastic nevi should be regarded as direct melanoma precursors [3,7].

Recent WHO classifications further emphasize a spectrum-based approach to melanocytic lesions, recognizing increasing degrees of architectural and cytological atypia and the importance of integrating morphology with the overall clinicopathological context [3,4]. This approach is particularly relevant to high-grade lesions in which the distinction between a severely atypical nevus and melanoma in situ may remain challenging.

Immunohistochemistry may provide complementary information in the evaluation of diagnostically challenging melanocytic lesions. In the present study, quantitative Ki-67 data were available for only 17 cases because immunohistochemical testing had not been performed systematically across the entire study population. Although the median Ki-67 index was numerically higher in melanomas than in dysplastic nevi, the difference was not statistically significant. The small, selectively available subset limits the generalizability of this comparison and does not establish the diagnostic performance of Ki-67 in the full cohort. Nevertheless, Ki-67 may contribute to the assessment of proliferative activity when interpreted

alongside histomorphological findings. Similarly, HMB-45 should be interpreted as an ancillary marker rather than an independent diagnostic test. Although benign melanocytic nevi may also exhibit HMB-45 positivity, diffuse staining throughout the full thickness of an epidermal melanocytic proliferation may support a diagnosis of melanoma when considered in the appropriate morphological context [9].

Molecular techniques have been investigated in the literature as potential complementary tools for the differential diagnosis of melanocytic lesions. However, no molecular testing was performed in the present study, and no molecular data were collected or analyzed. The following discussion is therefore based exclusively on previously published literature. Xavier-Junior and Ocanha-Xavier emphasized the molecular heterogeneity of dysplastic melanocytic nevi and the absence of a single molecular alteration that reliably distinguishes all dysplastic nevi from melanoma [17]. Accordingly, molecular approaches may be considered in selected diagnostically challenging cases, although histopathological assessment remains central to the classification of these lesions.

The relatively small sample size and retrospective design represent important limitations. Additionally, the absence of longitudinal clinical follow-up precludes conclusions regarding the biological progression of the lesions. Reclassification reflects diagnostic reassessment, not documented malignant transformation. The study also reflects the diagnostic experience of a single pathology service, which may limit the generalizability of the findings. Furthermore, quantitative Ki-67 data were available for only a subset of 17 cases, limiting the statistical comparison of proliferative activity between diagnostic categories and the generalizability of the findings. Nevertheless, the histopathological reassessment by an experienced dermatopathologist provides a clinically relevant perspective on the diagnostic challenges encountered in routine practice.

Despite these limitations, this study contributes to the understanding of diagnostic pitfalls in melanocytic lesions and underscores the importance of cautious interpretation, particularly in lesions with severe atypia. The findings support the need for careful clinicopathological correlation and recognition of the limitations of individual histological or immunohistochemical parameters. In diagnostically borderline lesions, an integrated approach remains essential to minimize both underdiagnosis of melanoma and overdiagnosis of lesions with benign or uncertain biological behavior.

Conclusions

Differentiating dysplastic nevi from melanoma can be challenging, particularly in lesions with high-grade atypia, underscoring the importance of expert dermatopathological review. Accurate classification requires the integration of histomorphological findings with clinicopathological correlation, while ancillary immunohistochemical markers such as HMB-45 and Ki-67 should be interpreted as complementary rather than independently diagnostic tools. In this context, careful integrated assessment may help reduce diagnostic misclassification and support appropriate clinical management.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Débora Salles, Natália N. Freitas, Guilherme Henrique N. Freitas, Leonardo Sementilli, Angelo Sementilli

Acquisition, analysis, or interpretation of data: Débora Salles, Natália N. Freitas, Guilherme Henrique N. Freitas, Leonardo Sementilli, Angelo Sementilli

Critical review of the manuscript for important intellectual content: Débora Salles, Leonardo Sementilli, Angelo Sementilli

Supervision: Débora Salles, Leonardo Sementilli, Angelo Sementilli

Drafting of the manuscript: Natália N. Freitas, Guilherme Henrique N. Freitas

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Research Ethics Committee of the Universidade Metropolitana de Santos (UNIMES) issued approval 01000126.0.0000.5509 under protocol number 8.779.650. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial

relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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