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Grading Melanocytic Dysplasia: Updated Histopathologic Criteria

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ABSTRACT

Dr. Martin C. Mihm, Jr.'s innovative work on the dysplastic nevus achieved a milestone in his chapter in the *World Health Organisation Classification of Skin Tumours* (WHO-C). WHO-C presents a dichotomous classification (high-grade versus low-grade dysplastic nevi) and a quantitative metric to assess melanocytic nuclear enlargement. The Duke classification is a related approach that provides mostly quantitative histopathologic criteria for dysplastic nevi and gives due weight to architectural features as well as cytology. This paper proposes and illustrates updated criteria for scoring and grading melanocytic dysplasia, incorporating some of the definitions and categories of WHO-C, while refining the quantitative and architectural elements of the Duke grading system to facilitate more detailed and precise assessment of dysplastic nevi.

1 | Dr. Martin C. Mihm, Jr. And the Dysplastic Nevus

Among Dr. Martin C. Mihm, Jr.'s many seminal publications, his work to advance scientific understanding of the dysplastic nevus is particularly noteworthy. Dr. Mihm's contributions in this field include: Demonstration of the histopathologic association of dysplastic nevi with melanoma [1] and the role of dysplastic nevi as a formal precursor of melanoma [2]; studies of intraepidermal melanocytes in dysplastic nevi and melanoma [3]; trends in the incidence of dysplastic nevi submitted to pathology [4]; molecular correlates including relative expression of phosphatase and tensin (PTEN) [5], galectin-1 [6], and 5-hydroxymethylcytosine [7]; application of quantitative image analysis [8]; and description of novel entities such as *de novo* intraepidermal epithelioid melanocytic dysplasia [9, 10]. Among Dr. Mihm's most important work in this area was the formulation of standard nomenclature and reproducible criteria for dysplastic nevi [11–17]. As a result of these dedicated efforts, the dermatopathology community now shares a general understanding of the architectural, cytologic, and host-response criteria to be applied in the pathologic diagnosis and grading of dysplastic nevi.

2 | Dysplastic Nevus and the World Health Organisation (WHO)

In 1991 Dr. Mihm was a key member of a WHO consensus workshop that met to arrive at major and minor criteria for the diagnosis of dysplastic nevi; these criteria included a requirement for melanocytic atypia as well as several architectural features, as set forth in the resulting publication [12]. Since then, many variations on the use of these criteria have been reported, all including architectural features and cytological atypia. For the most part, grading of dysplastic nevi has historically been based solely on cytological atypia, except for suprabasal (pagetoid) scatter, which in the 1990s was interpreted as severe atypia but is now often deemed a criterion for melanoma in situ.

Dr. Mihm's innovative work on the dysplastic nevus achieved a milestone in one of his last completed works on the topic, a chapter in the fourth edition of the *World Health Organisation Classification of Skin Tumours* (WHO-C) [18]. Dr. Mihm's work in WHO-C is being carried forward in a fifth edition, to which he also contributed in its early stages [19]. WHO-C is an authoritative reference providing criteria for diagnosing and grading dysplastic nevi. The architectural features assessed include lateral junctional extension (shoulder phenomenon), bridging of nests between adjacent elongated rete ridges, and suprabasal melanocytosis (pagetoid spread). Other aspects of the architectural disorder in dysplastic nevi include a relatively large lesional size compared to common acquired nevi and lentiginous spread of single melanocytes between junctional nests. WHO-C groups under architectural criteria certain features reflecting host response to neoplastic cells, such as dermal fibrosis and patchy lymphocytic infiltrates. Architectural disorder is necessary but not sufficient to render a diagnosis of dysplastic nevus, and the degree of disarray does not affect the assigned grade of dysplasia. Instead, WHO-C grades dysplastic nevi solely by nuclear atypia, characterized by variable enlargement and irregularity (pleomorphism) of nuclei, chromatin alterations including clumping and hyperchromasia, and prominence of nucleoli. WHO-C also states that the presence of mitotic figures in epidermal melanocytes indicates severe atypia.

WHO-C provides for two grades of dysplastic nevi, namely, **low-grade dysplasia** (formerly termed moderate dysplasia) and **high-grade dysplasia** (formerly severe dysplasia). Of note, WHO-C no longer classifies as dysplastic nevi those lesions formerly designated as nevi with mild dysplasia, because their subtle histopathologic abnormalities are poorly reproducible; moreover, these nevi are very common, have a very low rate of progression to melanoma, and do not indicate increased risk of melanoma. Instead, WHO-C designates lesions formerly labeled as mildly atypical dysplastic nevi simply as **nevi with architectural disorder and minimal to mild cytologic atypia**, or alternatively as **lentiginous nevi**, without attaching the terms "dysplastic" or "dysplasia."

WHO-C is a major step forward in the classification of dysplastic nevi. Its promotion of a two-grade system brings welcome clarity and simplification to a sometimes-fraught topic. Another strong point is WHO-C's use of a quantitative metric for melanocytic nuclear enlargement, using keratinocyte nuclei as a reference point; however, most of the other criteria in the schema remain qualitative. Histopathologic grading constitutes only part of a brief discussion of dysplastic nevi in WHO-C, in the context of a general reference covering all cutaneous neoplasia. WHO-C does not provide detailed instructions or an algorithm to apply the criteria, and the text is ambiguous in places. In low-grade dysplastic nevi, the nuclear size of the depicted melanocytes is $\leq 1.5\times$ that of keratinocytes, constituting moderate random cytologic atypia; for high-grade dysplastic nevi, "some" of the lesional cells have a nuclear size $> 1.5\times$ that of keratinocytes, constituting severe random cytologic atypia [18, 19]. WHO-C equates random atypia with "a small minority of cells" but does not clarify this phrase. Dysplastic nevi are to be graded based on the highest degree of cytologic atypia present "in more than a few" melanocytes [18, 19]. This imprecise language may impede uniform application of the criterion.

Furthermore, although WHO-C expunges mildly atypical dysplastic nevi as a named entity, the criteria defining that eliminated grade overlap with those of low-grade (formerly moderate) dysplasia1 [18, 19]. So-called mildly atypical dysplastic nevi are stated to have a nuclear size value of 1× compared with resting basal-layer keratinocytes. However, the new category of low-grade dysplasia has an overlapping range of 1–1.5×; hence, at the lower limit, nevi composed of melanocytes with nuclear size equivalent to keratinocytes could be assigned to either group. Similarly, mildly atypical dysplastic nevi "may be hyperchromatic," while low-grade dysplasia is assigned the overlapping criterion "hyperchromatic or dispersed chromatin." Variation in nuclear size and shape is called "minimal" in mildly atypical dysplastic nevi, compared with "prominent in a small minority of cells" in low-grade dysplasia. Finally, mildly atypical dysplastic nevi and low-grade dysplasia share the exact description of having "small or absent" nucleoli. The WHO-C schema could be strengthened by eliminating equivocal or overlapping vocabulary and replacing it with sharper, quantitative definitions.

WHO-C offers no clear rules for applying detailed architectural criteria. While architectural disorder is a threshold requirement for inclusion in the category of dysplastic nevus, nuclear cytologic atypia alone determines the formal grade of dysplasia assigned. However, in practice most dermatopathologists give architectural as well as cytologic features considerable importance when diagnosing and grading dysplastic nevi.

3 | Duke Grading System for Dysplastic Nevi

The Duke system provides mostly quantitative histopathologic criteria for dysplastic nevi and gives considerable weight to architectural features in diagnosis and grading [20]. This system assigns a sub-score of either 0 or 1 to six architectural features: circumscription, symmetry, cohesion of nests, suprabasal melanocytosis, confluence of epidermal melanocytes, and single-cell pattern of melanocytic proliferation. Similarly, four cytologic features are sub-scored as either 0 or 1: nuclear shape and chromatism, nuclear size, nucleolar prominence, and cell size. A final score is obtained separately for architecture and cytology by calculating the sum for each class of criteria. Based on these operations, dysplastic nevi are graded as having mild, moderate, or severe architectural disorder and, independently, mild, moderate, or severe cytologic atypia.

In a prospective study of 166 consecutive dysplastic nevi using the Duke system, summed scores for cytology and architecture tended to fall mainly in the low to medium range, and the two classes of criteria had a statistically significant association with each other, supporting the nosologic integrity of dysplastic nevi as an entity. The explicit incorporation of architecture into grading permits better clinical-pathologic correlation and gives a more complete picture of dysplastic nevi.

Although the degrees of architectural disorder and cytologic atypia in dysplastic nevi are generally significantly correlated [20], instances do occur in which the two categories are

somewhat dissociated, such that one or the other class of criteria predominates. However, in our experience, it would be unheard of for a dysplastic nevus to have a marked degree of cytologic atypia while completely lacking architectural disorder. We recommend that any such lesion be simply described as having severe cytologic atypia, without the specific designation of dysplastic nevus. Conversely, a lesion that has considerable architectural disorder while completely lacking cytologic atypia would not qualify as a dysplastic nevus but might represent some other kind of atypical nevus (recurrent nevus, special-site nevus, etc.). Dysplastic nevi, by definition, must achieve at least some non-zero score regarding both classes of criteria. Note that in the original Duke schema, and in this update, several threshold entry criteria are required for a lesion to qualify as a dysplastic nevus at all, namely: "shoulder" phenomenon (lateral extension of junctional component beyond any dermal component) and host response in the form of characteristic patterns of papillary dermal fibrosis and lymphocytic infiltrates. Lesions lacking these entry criteria should not be classified as dysplastic nevi regardless of their degrees of architectural disorder or cytologic atypia.

4 | Updated Histopathologic Criteria for Melanocytic Dysplasia

We herein propose updated criteria for scoring and grading melanocytic dysplasia, incorporating some of the definitions and categories of WHO-C, while refining the quantitative and architectural elements of the Duke grading system. In the update, each architectural and cytologic criterion is scored on a four-point scale, to facilitate more detailed and precise assessment.

A. **ARCHITECTURAL CRITERIA**

1. ***Asymmetry of melanocytic proliferation***

Scored as: low; minimal; moderate; high.

Assessed globally for entire lesion.

Definition: **Bilateral (mirror-image) asymmetry is assessed as a Gestalt impression at low magnification, using the full range of all architectural features**. These may include extent and location of the junctional component with respect to any intradermal component, size of nests, extent and location of any inflammatory infiltrate, and so on.

Note: A lesion with minimal asymmetry is equivalent to a highly symmetrical lesion. Unlike most other criteria in this system, asymmetry is a qualitative metric. It is to be assessed independently of all other criteria. One should not assess asymmetry together with any cytopathologic features. Asymmetry is assessed by considering all architectural features, without giving special weight to any criterion, partially those to be scored separately (border imprecision, dyshesion, etc.; see below). In congenital-pattern nevi, the intradermal component arranged around vessels and adnexa is not considered when assessing asymmetry.

2. ***Border imprecision (poor circumscription) of melanocytic proliferation***

Scored as: 0 border; 1 border; 2–3 borders; ≥4 borders.

Assessed globally for entire lesion.

Definition: Precision (circumscription) denotes the presence of discrete borders to the junctional component: that is, nested at both edges and/or with a clear lateral demarcation of melanin pigment. A precise or well-circumscribed lesion is one where the lateral junctional borders can be identified with confidence, ending with a discrete nest (≥2 cells together) and not as single cells; or else with clearly demarcated melanin. A lesion with imprecise borders lacks these features.

Note: A lesion with low border imprecision is equivalent to one with highly precise (well-circumscribed) borders. "Borders" refers to the edges of the lesion itself, not the surgical resection margins of the specimen. The number of borders available for analysis depends on the nature of the specimen; for example, a bisected punch specimen will have up to four borders available for analysis (two for each of the two halves of the specimen). A shave biopsy, ellipse, and so on, may have more borders, depending on the size of the specimen and the method by which it was grossly prosected.

- 0 border: no border appears imprecise (i.e., lesion is very well-circumscribed).
- 1 border: only one border appears imprecise, while all other borders appear precise.
- 2–3 borders: two or three borders appear imprecise.
- ≥4 borders: at least four borders appear imprecise (i.e., lesion is very poorly circumscribed).

3. ***Dyshesion of melanocytic nests***

Scored as: 0%–25%; >25%–50%; >50%–75%; >75%.

Assessed globally for entire lesion.

Definition: Melanocytic nests tend to be composed of loose collections of cells rather than tightly aggregated cells.

Note: The stated ranges refer to the **percentage** of **junctional nests** in which **at least half** of the **melanocytes** are **loosely aggregated**.

4. ***Confluence of melanocytes***

Scored as: 0%–25%; >25%–50%; >50%–75%; >75%.

Assessed globally for entire lesion.

Definition: Junctional melanocytes tend to run together.

Note: The stated ranges refer to the **percentage** of the **epidermal basal layer** length in which the **melanocytes appear to run together or touch** one another. This criterion is not applicable to the dermal component (if any). Confluence is applicable to both single-cell and nested patterns at the

dermal-epidermal junction (DEJ) and includes "bridging" whereby adjacent rete ridges appear to fuse together by the joining of junctional nests.

5. ***Suprabasal melanocytosis***

Scored as: absent; present in center only; present in 1–2 peripheries; present in ≥ 3 peripheries.

Assessed globally for entire lesion.

Definition: Melanocytes are present above the epidermal basal layer either as isolated cells or in nests.

Note: Suprabasal (pagetoid) melanocytosis is assessed in at least two high-power fields in the central one-third of the lesion and in the remaining peripheral one-thirds (arbitrarily, the "left" and "right" portions of the section). "**Periphery" is not the same as "border**;" the latter refers strictly to the actual edges of the lesion, not its lateral one-third portions.

6. ***Single-cell pattern of melanocytic proliferation***

Scored as: 0%–25%; > 25%–50%; > 50%–75%; > 75%.

Assessed globally for entire lesion.

Definition: M**elanocytes tend to be arranged at the epidermal basal layer as individual cells**. The stated ranges refer to the **percentage** of the epidermal **basal layer** length in which melanocytes are arranged mainly as single cells **rather than aggregated in nests.**

Note: The single-cell (lentiginous) pattern of spread is considered atypical in the context of nevi and melanomas; however, it is characteristic and defining for lentigo simplex and solar lentigo.

Figure 1 illustrates examples of low and high scores for each of these six architectural criteria.

B. **Cytologic criteria.**

1. ***Nuclear size***

Scored as: 1× or less; > 1.0–1.5×; > 1.5–2.0×; > 2.0×.

Assessed in region exhibiting the greatest degree of atypia ("hot spot").

Definition: Size of nuclei of neoplastic melanocytes compared with basal keratinocytes.

Note: The final assigned score represents the **highest value seen in > 50% of melanocytes in two 40×-objective fields.**

2. ***Cell size***

Scored as: 1× or less; > 1.0–1.5×; > 1.5–2.0×; > 2.0×.

Assessed in region exhibiting the greatest degree of atypia ("hot spot").

Definition: Overall size of neoplastic melanocytes compared with basal keratinocytes.

Note: The final assigned score represents the **highest value seen in > 50% of melanocytes in two 40×-objective fields.**

3. ***Nuclear pleomorphism***

Scored as: 0%–5%; 5%–20%; > 20%–50%; > 50%.

Assessed in region exhibiting greatest degree of atypia ("hot spot").

Definition: Variation in nuclear size and/or shape in neoplastic melanocytes.

Note: The final assigned score represents the **highest percentage of pleomorphic melanocytes in two 40×-objective fields.**

4. ***Nuclear chromatism***

Scored as: normal; dispersed; coarsely granular or with peripheral condensation; hyperchromatic or irregularly chromatic.

Assessed in region exhibiting greatest degree of atypia ("hot spot").

Definition: Chromatism of nuclei of neoplastic melanocytes compared with normal melanocytes.

Note: The final assigned score represents the **highest percentage of melanocytes with abnormal chromatism in two 40×-objective fields.**

5. ***Nucleolar prominence***

Scored as: 0%–5%; > 5%–20%; > 20%–50%; > 50%.

Assessed in region exhibiting greatest degree of atypia ("hot spot").

Definition: Prominence of nucleoli of neoplastic melanocytes compared with normal melanocytes.

Note: The final assigned score represents the **highest percentage of melanocytes with prominent nucleoli in two 40×-objective fields.**

Figure 2 illustrates examples of low and high scores for each of these five cytologic criteria.

5 | Application of Updated Criteria to Grade Dysplastic Nevi

In the Duke grading schema, each criterion is assigned a score of either 0 or 1; simple summation yields an overall score for architecture (0–6) and cytology (0–4). These summed scores are then grouped into three architectural ranges (mild: summed score 0–1; moderate: summed score: 2–3; and severe: summed

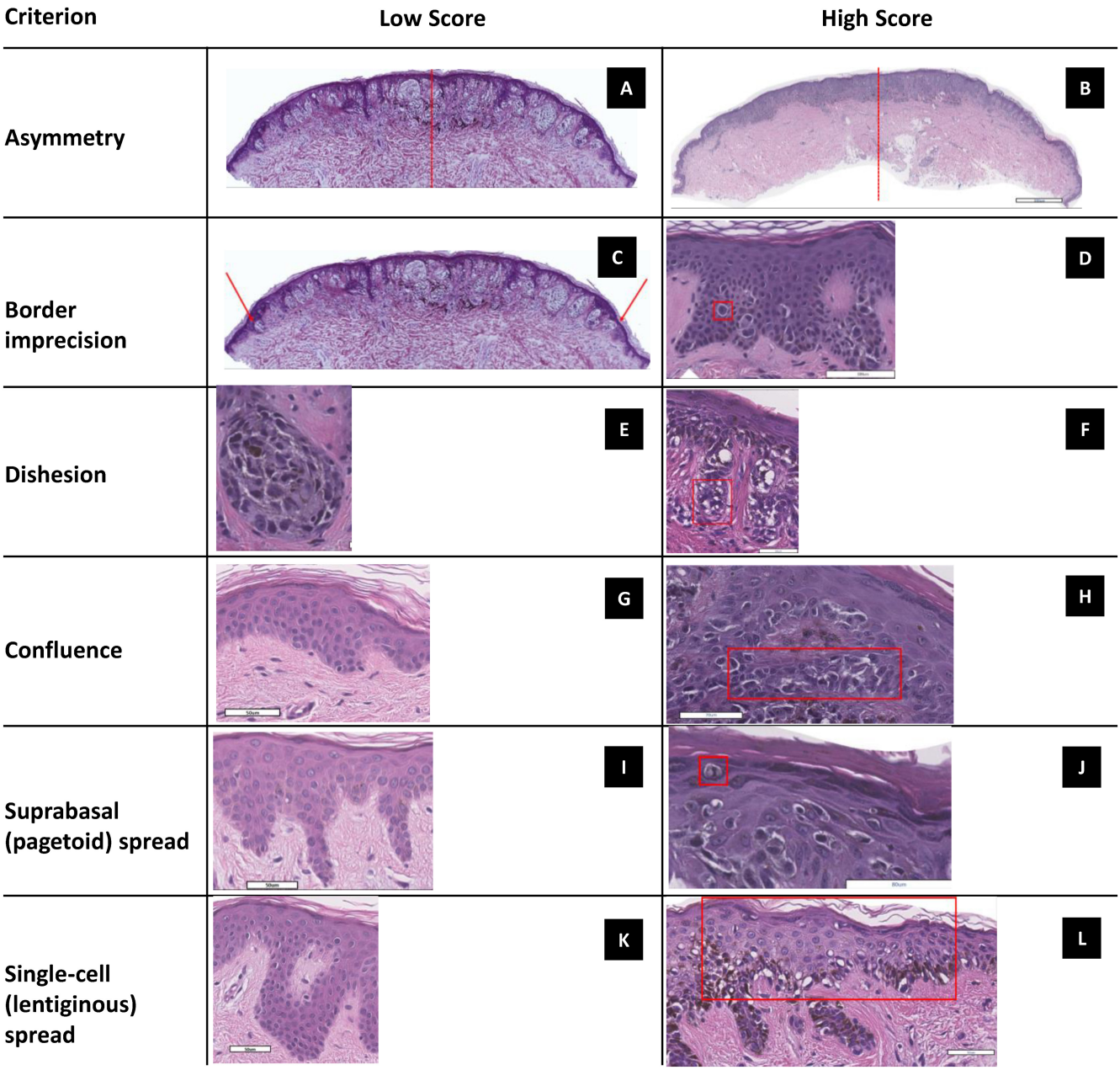

FIGURE 1 | Architectural disorder. A. Asymmetry Score 0 (minimal). Dashed red line represents axis by which asymmetry is evaluated. Note that a lesion with minimal asymmetry is equivalent to a highly symmetrical lesion. B. Asymmetry Score 3 (high). Dashed red line represents axis by which asymmetry is evaluated. C. Border imprecision Score 0 (low, 0 borders imprecise), with discrete melanocytic nests at each peripheral border. The red arrows indicate sharply circumscribed peripheral junctional nests. Note that a lesion with low border imprecision is equivalent to highly precise or well-circumscribed borders. D. Border imprecision Score 3 (high, ≥4 borders imprecise). The border of the lesion is imprecise because it is not formed of well-defined nests; single melanocytes (red box) extend to the periphery as shown at left of panel D. E. Dyshesion Score 0 (low, 0%–25%) The great majority of melanocytic nests are tightly aggregated. Note that a lesion with low dyshesion is equivalent to a highly cohesive lesion. F. Dyshesion Score 3 (high, >75%). The melanocytic nests are only loosely aggregated, with many clear spaces between melanocytes (red box). G. Confluence Score 0 (low, 0%–25%). Melanocytic nests are discrete and do not exhibit significant confluence. H. Confluence Score 3 (high, >75%). There is a marked tendency for melanocytes to run together (red box). I. Suprabasal (pagetoid) spread Score 0 (absent). The melanocytes are confined to junctional nests and the epidermal basal layer. J. Suprabasal (pagetoid) spread Score 3 (high, present in ≥4 peripheries). The red box highlights a suprabasal melanocyte in the granular layer. K. Single-cell (lentiginous) spread Score 0 (low, 0%–25%). The melanocytic proliferation is predominantly arranged in nests rather than as single cells. L. Single-cell (lentiginous) spread Score 3 (high, >75%). Melanocytes at the basal layer are mainly arranged as individual cells rather than aggregated in nests.

score: 4–6), and three cytologic ranges (mild: summed score 0–1; moderate: summed score 2; and severe: summed score 3–4). Because the present update uses a quartile scoring method for each criterion, simple summation is not directly applicable as in the original Duke system. However, collapsing the two lowest sub-scores and the two highest sub-scores for each criterion

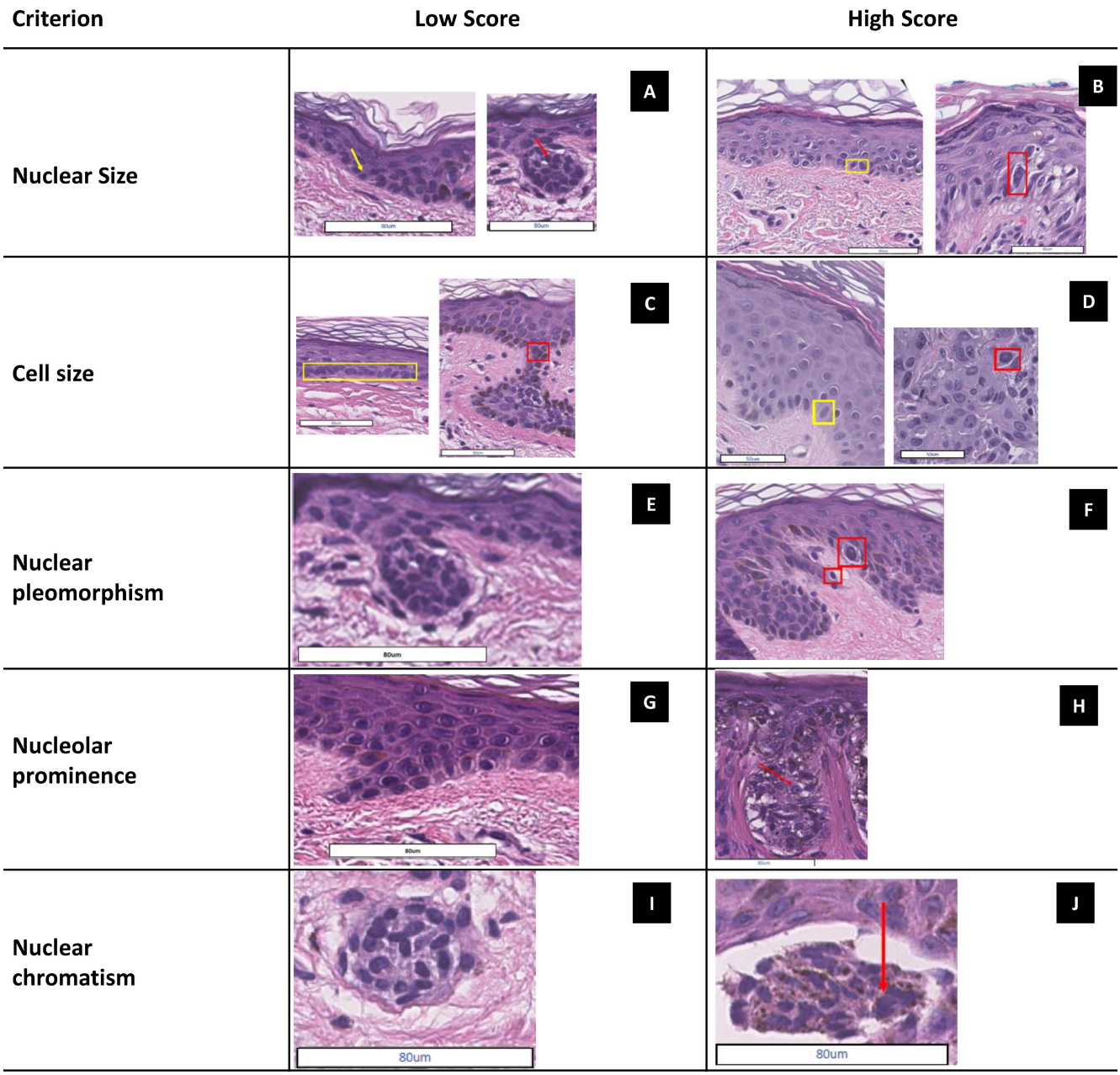

FIGURE 2 | Cytological atypia. A. Nuclear size Score 0 (low, melanocyte: Keratinocyte ratio ≤ 1). Yellow arrow indicates control basal-layer keratinocyte. Red arrow indicates melanocyte similar in size to keratinocytes. B. Nuclear size Score 3 (high, melanocyte: Keratinocyte ratio > 2.0). Yellow box on left indicates control basal-layer keratinocytes. Red box on right indicates melanocyte with greatly enlarged nucleus. C. Cell size Score 0 (low, melanocyte: Keratinocyte ratio ≤ 1). Yellow box on left indicates control basal-layer keratinocytes. Red box on right indicates melanocytes similar in size to keratinocytes. D. Cell size Score 3 (high, melanocyte: Keratinocyte ratio > 2.0×). Yellow box on left indicates control basal-layer keratinocytes. Red box indicates enlarged melanocytes. E. Nuclear pleomorphism Score 0 (low, 0%–5%). Melanocytic nuclei are relatively uniform in size and shape. F. Nuclear pleomorphism Score 3 (high, > 50%). Red boxes highlight marked variation in nuclear size of melanocytes. G. Nucleolar prominence Score 0 (low, 0%–5%). Melanocytes have inconspicuous nucleoli. H. Nucleolar prominence Score 3 (high, > 50%). Red arrow indicates melanocyte with prominent nucleolus. I. Nuclear chromatism Score 0 (low, normal). Melanocytic nest with normal chromatism. J. Nuclear chromatism Score 3 (high). Melanocytic nest with hyperchromatic and irregularly-chromatic nuclei.

into summed scores of 0 or 1 permits simplified, binary scoring of architecture and cytology for dysplastic nevus in this update (Tables 1 and 2) while preserving a more detailed tally of sub-scores for potential use in further analysis.

In this update, dysplastic nevi are ultimately diagnosed as either low- or high-grade, considering both the extent of architectural disorder and the degree of cytologic atypia. This dichotomy aligns with WHO-C's recommendation to eliminate so-called mildly atypical dysplastic nevi, which should instead be designated "nevus with architectural disorder and mild/minimal cytologic atypia" or some equivalent, non-dysplastic nomenclature. Designation of minimally irregular lesions as dysplastic may risk triggering undue anxiety among patients and prompting

TABLE 1 | Architectural disorder, scored globally in entire lesion.

Criterion	Sub-score = 0	Sub-score = 1
Asymmetry	Low to minimal	Moderate to high
Border imprecision	≤ 1 border	≥ 2 borders
Dyshesion of nests	≤ 50%	> 50%
Confluence of melanocytes	≤ 50%	> 50%
Single-cell proliferation	≤ 50%	> 50%
Suprabasal melanocytosis	Absent or present at center only	Present at ≥ 1 periphery

Note: Sum of architectural sub-scores: interpretation. 0–1: Not a dysplastic nevus; 2–3: Dysplastic nevus with low architectural disorder; 4–6: Dysplastic nevus with high architectural disorder. The final diagnosis of either low-grade DN or high-grade DN reflects the combined architectural and cytologic scores (Table 3).

TABLE 2 | Cytological atypia: highest score present in > 50% of melanocytes in two 40× objective fields.

Criterion	Sub-score = 0	Sub-score = 1
Nuclear size	≤ 1.5× keratinocyte	> 1.5× keratinocyte
Cell size	≤ 1.5× keratinocyte	> 1.5× keratinocyte
Nuclear pleomorphism	≤ 20% of melanocytes	> 20% of melanocytes
Nucleolar prominence	≤ 20% of melanocytes	> 20% of melanocytes
Nuclear chromatism	Normal or dispersed	Coarsely granular, peripheral condensation, hyperchromatic, and/or irregularly chromatic

Note: Sum of cytology sub-scores: Interpretation. 0–1: Not a dysplastic nevus; 2–3: Dysplastic nevus with low cytologic atypia; 4–6: Dysplastic nevus with high cytologic atypia. The final diagnosis of either low-grade DN or high-grade DN reflects the combined architectural and cytologic scores (see Table 3).

TABLE 3 | Diagnostic algorithm based on combined scores for architecture and cytology.

	Low cytologic score	High cytologic score
Low architectural score	Diagnosis: Low-grade dysplastic nevus	Diagnosis: High-grade dysplastic nevus
High architectural score	Diagnosis: High-grade dysplastic nevus	Diagnosis: High-grade dysplastic nevus

unnecessary excisions. In contrast, use of a low-grade/high-grade dysplastic nevi dichotomy is easy to grasp and has immediate relevance as an actionable guide to clinicians.

Diagnosis of a dysplastic nevus as low-grade will usually prompt less intense clinical management (regarding surgical intervention, follow-up appointment schedule, screening of family members, etc.) than for high-grade dysplastic nevus. Specifically, in the revised Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx) schema, low-grade dysplastic nevus with positive surgical margins falls into MPATH-Dx class I and as such usually will not require any further treatment. On the other hand, high-grade dysplastic nevus, like melanoma in situ, falls into MPATH-Dx class II, for which re-excision is usually indicated if the margins are positive [21].

When architectural and cytologic scores agree (i.e., dysplastic nevi with the combinations of either low architecture/low cytology or high architecture/high cytology) the lesion is diagnosed as either low-grade dysplastic nevus or high-grade dysplastic nevus respectively. In cases where the two categories conflict, the final grade is assigned in accordance with whichever category (architecture or cytology) has the higher score. In other words, a dysplastic nevus is considered low-grade only if both its architectural score and its cytologic score are low (Table 3).

6 | Host Response in Dysplastic Nevi

Several aspects of host response were considered but ultimately not included as criteria for grading in this update. In general, host response provides useful clues for distinguishing dysplastic from non-dysplastic nevi but is not used to assign the histopathologic grades of dysplasia. For example, most common nevi do not induce a significant amount of **fibrosis** (increased dermal collagen), so its absence can suggest benignity. On the other hand, dysplastic nevi classically exhibit superficial **lamellar fibroplasia** (relatively straight layers of collagen in the papillary dermis, immediately underlying the junctional component) and **concentric fibrosis** (rounded pattern of collagen layers surrounding the junctional component at the rete pegs). Both patterns of fibrosis in dysplastic nevi are commonly associated with mild to moderate, superficial **infiltrates of dermal lymphocytes** but the density and distribution of such infiltrates are not generally used for grading the degree of dysplasia. Apart from the characteristic

fibrotic changes of dysplastic nevi, desmoplasia (dense and deep fibrosis) occurs uncommonly in nevi and melanomas and is not used to grade dysplasia. Fibrosis also characterizes the late stage of regression, a complex, immune-mediated phenomenon that sometimes occurs in dysplastic nevi but usually points to vertical-growth-phase melanoma.

Angiogenesis or neovascularization is another host response not included in the present update. Angiogenesis is crucial in the pathogenesis of many types of cancer; however, it is difficult to assess the degree of vascularity of a neoplasm by the sole use of routine histopathologic methods. Quantitative study in a research setting is possible, with adjunctive use of vascular-specific immunohistochemical markers combined with computerized image analysis. Melanocytic neoplasms may show subtle changes in vascularity as part of the dysplastic phenotype; however, overt neovascularization is usually associated only with frankly malignant melanoma. Accordingly, it is not practical to use vascularity as a criterion for grading degrees of dysplasia short of outright malignancy. Vascularity also characterizes the active stage of regression, where it usually points to vertical-growth-phase melanoma.

7 | Discussion

This proposal does not represent a truly novel method for diagnosing and grading dysplastic nevi. Rather, we have attempted to refine further the system first promulgated by Dr. Mihm and colleagues in 1991 [12] and currently represented in WHO-C [18, 19], by substituting quantitative or semiquantitative criteria whenever possible, along the lines of the Duke system published in 1999 [20]. We also provide detailed instructions and an algorithm to apply the updated criteria.

We have been motivated by the observation that criteria dependent on "soft" terms (e.g., "few, mild, minimal") are notoriously subject to various interpretations by different pathologists and are therefore more likely to be associated with poor agreement. While we hope that our updated criteria will prove more reliable, we acknowledge that rigorous, prospective research studies will be needed to test the utility of our proposal and to improve on it further. Studies are currently underway in our group to test the concordance of groups of pathologists in applying the updated criteria. We present our proposal now to encourage other colleagues to test these ideas in their own practice and research.

These updated criteria aim to provide a relatively straightforward metric to grade dysplastic nevi in routine diagnostic practice, and for simplicity this initial attempt employs an unweighted method permitting assessment of dysplasia by summation of simplified criteria to assign a final grade (Tables 1–3). This approach retains the relative simplicity of the original Duke system; in our experience, most learners internalize that method after brief, formal training and soon can apply it comfortably in practice. However, simplification risks loss of valuable information; for example, experienced pathologists may not (and perhaps should not) give equal weight to suprabasal melanocytosis and symmetry when assessing architectural disorder, and the same is probably true of other criteria as well. The condensed summation approach described here is merely a first step; we are currently performing more sophisticated studies using mathematical modeling techniques on the full range of scores, rather than binary combinations of sub-scores, to assess the detailed contributions of individual criteria to the ultimate grade of dysplasia. Further research will be necessary to test the performance of these criteria in other categories of melanocytic lesions besides dysplastic nevi, including Spitz nevi, combined nevi, recurrent nevi, melanoma arising in nevi, and so on. We especially recommend that these updated criteria be applied with due regard to clinical data, including but not limited to patient age, size and anatomic site of the lesion, and any history of trauma. For example, future research should study the performance of these updated criteria in so-called special-site nevi. It will also be of interest to perform correlative studies analyzing the association of grade of dysplasia with immunohistochemical and molecular markers and outcome data. In this regard, quantitative image analysis (e.g., assessment of symmetry and suprabasal melanocytosis using immunohistochemical markers of melanocytes) should be feasible. It also seems likely that machine learning and other artificial intelligence technology could soon be fruitfully applied to the histopathologic characterization of dysplastic nevi.

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Conflicts of Interest

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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