Dysplastic Nevus and Differential Diagnoses

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There are many controversial topics in melanocytic pathology, but perhaps the most commonly encountered in routine practice is the dysplastic nevus.

The lesion currently known as a dysplastic nevus was delineated by Clark and colleagues as a type of large, atypical nevus that they encountered in patients who had an inherited tendency to develop melanoma.
A subset of melanocytic nevi that are **atypical clinically**

It is important, however, to note that not all clinically atypical nevi are dysplastic

Thus **flexural** and **acral** nevi, for example, may be clinically and histologically atypical and of concern to both the dermatologist and the pathologist but, as defined below, they are not dysplastic
Histologic features of dysplasia may be occasionally found in clinically ‘typical’ banal nevi and the reverse is also sometimes true, although to some extent this may be a reflection of clinical inexperience and lack of clinicopathological correlation.
Clinical, microscopic morphology and genomic aspects:

Intermediate between common acquired nevi and radial growth phase melanoma
Synonyms

- Atypical nevus  
- Large atypical nevus
- B-K mole
- Atypical mole
- Melanocytic dysplasia
- Nevus with architectural disorder and melanocytic atypia
Epidemiology

• First: Hereditary melanoma kindreds
• Later: Patients with non-familial melanoma, and in people unaffected by melanoma
• Typically develop in adolescence, declines in older age groups
Etiology

- Genetic
- Environmental
- Phenotypic

☑ Stimuli from chronic UV radiation exposure and the resulting CSD acting on a nevus
Genetic Profile

- Activating mutation of an oncogene: **BRAF or NRAS**
- Mutation of **TERT promoter**: An early event in the progression towards melanoma in situ
- Occasionally hemizygous loss of **CDKN2A**
Localization

- Paralleling the distribution of melanoma in skin with a **low degree of CSD** (low CSD melanoma)
- Tend to arise in skin that is **intermittently** sun-exposed
- The most common site is the **back**
• **The importance** of the dysplastic nevus syndrome is that it identifies an **at-risk population group** for the subsequent development of melanoma
Clinical Features

• Definition published by IARC in 1990 and then modified:

• There **must** be a flat *(macular)* component in at least one area  **Plus**

• The presence of **at least three** of the following features:
  i. Not well defined **border,**
  ii. **Size** greater than or equal to 5 mm,
  iii. **Variegated color**, a **mixture of pale and dark brown**, and **pink**
  iv. Uneven **contour,**
  v. Surrounded by an **erythematous macule** *(the shoulder phenomenon).*
• Resemblance to a **fried egg** or a **target**:
• Almost **always** have a **flat component** and a **central raised portion**
• Partially **overlap** with those for melanoma

Lesions with **markedly atypical** attributes

- **New**
- **Changing** lesions

Should be submitted for evaluation
• Careful and frequent clinical follow-up examinations with photographic records are mandatory (have an increased risk of developing melanoma)

• Features suggestive of malignant transformation include:
  • The acquisition of contour asymmetry,
  • Excessive pigment variegation, and
  • Development of black foci or
  • Presence of a gray coloration suggestive of regression
Histopathology

• Whether familial or sporadic, show identical histologic features

• Architectural disorder

• Cytologic atypia (Melanocytic dysplasia) not amounting to melanoma in situ

  Always involving their junctional component

✓ Host responses

May be junctional or compound
Architectural Disorder

- **Deviation** from a **stereotypical** junctional nevus pattern
- Within the epidermis
- The junctional component often extends beyond any intradermal component ("junctional shouldering"),
- The nevus cells are distributed both **singly along the basal layer** of the epidermis (lentiginous hyperplasia) and also as **nests**
- **Nests** are irregular in both shape and distribution, **not confined** to the tips of the epidermal ridges
- They therefore may be present **along the sides of the rete ridges** or at the **tips of the dermal papillae**
- **Bridging** between adjacent nests is commonly seen
Architectural Disorder

- Areas with lentiginous single-cell growth predominates, particularly at the sides of the rete ridges.
- Epidermis: usually of normal thickness, sometimes slightly acanthotic typically shows marked elongation of the rete ridges.
- Effacement of the rete ridges and attenuation of the epidermis overlying melanocytic proliferation, e.g., consumption of the epidermis, are features generally not seen in dysplastic nevus and suggest melanoma.
- Subtle suprabasal scatter of melanocytes confined to the lower epidermal levels.
Host responses

Within the papillary dermis:

- Often a patchy lymphocytic infiltrate
- Characteristic stromal reaction comprising either:
  * Lamellar fibroplasia, characterized by horizontal collagen with clefts parallel to the epidermis, or
  * Concentric fibrosis, where the collagen bundles orient around the bases of the rete ridges
Cytological Atypia

- Increased nuclear size,
- Nuclear membrane irregularity,
- Prominent nucleoli,
- Nuclear and cytoplasmic pleomorphism, and variable hyperchromatism (Chromatin clumping)
- Dusty pigmentation giving rise to an olive green coloration
- The atypical melanocytes may be present singly or in small clusters and characteristically appear to sit within a lacuna due to a marked fixation retraction artifact
- Typically, in any one nevus there is an admixture of normal and atypical nevus cells, i.e., the cytological atypia is random
• **Confluent (diffuse) cytological atypia** should raise concern for in situ melanoma

• Mitosis of intraepidermal lesional melanocytes are uncommon
  *If present: Constitute a severe cytological feature*

• Although **one or two cells** may be seen in the suprabasal epidermis, any **significant degree of pagetoid spread** should be taken as evidence of **evolving in situ melanoma**

• The dermal component, if present, often appears **cytologically banal** although in some nevi it shows superficial cytological atypia comparable to the junctional component.
Consensus meeting Working Group recommends against the continued use of the term “mildly dysplastic nevus” and recommends only two grades of dysplasia:

- Low-grade dysplasia
- High-grade dysplasia
<table>
<thead>
<tr>
<th>WHO classification (2018)</th>
<th>Former grade</th>
<th>Nuclear size vs resting basal cells</th>
<th>Chromatism</th>
<th>Variation in nuclear size and shape</th>
<th>Nucleoli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not a dysplastic naevus</td>
<td>0 (mild dysplasia)</td>
<td>1×</td>
<td>May be hyperchromatic</td>
<td>Minimal</td>
<td>Small or absent</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>1 (moderate dysplasia*)</td>
<td>1-1.5×</td>
<td>Hyperchromatic, or dispersed chromatin</td>
<td>Prominent in a small minority of cells</td>
<td>Small or absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(random atypia)</td>
<td></td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>2 (severe dysplasia*)</td>
<td>≥1.5×</td>
<td>Hyperchromatic, coarse granular chromatin, or peripheral condensation</td>
<td>Prominent in a larger minority of cells</td>
<td>Prominent, often lavender</td>
</tr>
<tr>
<td>Parameter</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
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<tr>
<td>--------------------------</td>
<td>----------------------------------------------------------------------</td>
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<td>---------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear size</td>
<td>Approximate size of keratinocyte nucleus</td>
<td>1–2 × keratinocyte nucleus</td>
<td>2 × or greater keratinocyte nucleus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromatin</td>
<td>Hyperchromatic</td>
<td>Hyperchromatic or vesicular</td>
<td>Vesicular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleolus</td>
<td>Absent or small</td>
<td>Absent or small</td>
<td>Prominent and enlarged</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Usually little but sometimes abundant with dusty pigmentation</td>
<td>Usually little but sometimes abundant with dusty pigmentation</td>
<td>Often abundant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Previously Mild Dysplasia
Previous Moderate Dysplasia
New: Low-Grade
Previous: Severe dysplasia
New: High-Grade Dysplasia
• Architectural features are **required** for the diagnosis

• Also **contribute to grade**, indicate a diagnosis of **high-grade (severe)** dysplasia even when cytologic atypia is low-grade:

  ✓ **Pagetoid scatter** above the basal layer, **not above the middle third**, focal, contained within an area < 0.5 mm²

  ✓ Focal **continuous** basal proliferation

  ✓ **Intraepidermal mitoses** (any dermal mitosis or anything more than a rare mitosis should raise concern for **melanoma**)
**IHC**

- **Melanocytic markers:**
  - S100 protein
  - melan-A
  - MITF
  - Tyrosinase
  - SOX10
  - \textit{HMB}45 \textbf{Stratification}
  - Ki67 < 5% (in the dermal hot spot)
• **Ki67** in junctional component **in dysplastic nevus:**

• **Most** cells are **unlabeled**

• **In melanoma in situ:** ki67 can be > 30%

• **Tumor suppressor p16:** useful for ruling out homozygous loss of CDKN2A
  
  * Positive p16 staining does not rule out melanoma
Diagnostic Criteria for Dysplastic Nevi
(by IMPSG)

Dysplastic naevus
- Width > 4 mm in fixed sections (> 5 mm clinically)
- Presence of architectural disorder, which requires both of the following:
  - Irregular (i.e. horizontally oriented, bridging adjacent rete, and/or varying in shape and size) and/or
dyscohesive nests of intraepidermal melanocytes
  - Increased density of non-nested junctional melanocytes (e.g. more melanocytes than keratinocytes
  in an area ≥ 1 mm²)
- Presence of cytological atypia, which is graded on the basis of the highest degree of cytological atypia
present in more than a few melanocytes (see Table 2.13)
Differential Diagnosis

- Other nevus variants
- Melanoma in situ
- Invasive melanoma
Other Nevus Variants

• Simple lentigo
  * Solar lentigo: A primary keratinocyte neoplasm
• Lentiginous junctional nevus/lentigo
• Lentiginous compound nevus
• Nevus with architectural disorder and minimal or mild cytologic atypia
cytological atypia is absent
• Benign junctional and compound nevi
Simple Lentigo

- **Single cell** melanocytic proliferation at the **basal aspect of the epidermis**
- Small round or oval **monomorphous** nuclei
- Spaced equally
- Variably **elongated and hyperpigmented** rete ridges
- **No junctional nests** are evident
- Simple lentigo (lentigo simplex)
- Pigmented **macules**
- **Localization:** Anywhere in the skin or mucous membranes
- May represents **early stages** in the development of so-called ordinary melanocytic nevus
Diagnostic Criteria for Simple Lentigo

Simple lentigo
- Width usually < 4 mm in fixed sections
- Increased density of junctional melanocytes, mainly around the tips and sides of (often elongated) rete
- No nests (by definition)
- No to mild cytological atypia

Exclusions: Moderate or severe atypia of more than a few melanocytes suggests atypical lentigo or lentigo maligna, but not dysplastic naevus (use descriptive diagnosis, e.g. atypical lentiginous melanocytic proliferation).
Lentigo Simplex
• **Lentiginous junctional or compound nevus** (formerly known mildly dysplastic nevus):
  • **Not** associated with melanoma risk
  • Are **very common** in the general population
  • Have a **very low** probability of progression to melanoma
  • Have **poor diagnostic reproducibility**
• Lentiginous **junctional** melanocytic nevus:
  ✓ Small melanocytic **nests** at the epidermal **base** as well as **lentiginous single cell** melanocytic proliferation

• Lentiginous **compound** melanocytic nevus:
  ✓ Additionally contain small groups of lesional melanocytes in the papillary dermis
Diagnostic Criteria for Lentiginous Junctional Nevus / Lentigo

**Lentiginous junctional naevus / lentigo**
- Width usually < 4 mm in fixed sections
- Increased density of non-nested junctional melanocytes around the tips and sides of (usually elongated) rete
- Nested junctional melanocytes range from collections of a few melanocytes to well-formed nests
- Usually symmetrical, but with poorly defined borders
- No to mild cytological atypia
- Minor / variable features (also seen in dysplastic and shoulder naevi): elongated rete, epidermal hyperpigmentation, pigment incontinence, papillary dermal fibrosis, patchy lymphocytic inflammation, adnexal involvement, lichenification, and upward spread of bland melanocytes to the mid-spinous layer
Exclusions

• Moderate or severe atypia of more than a few melanocytes plus high solar elastosis (CSD): 
  ✓ Suggests: *Atypical lentiginous nevus or lentigo maligna*, but not dysplastic nevus (use descriptive diagnosis)

• Moderate or severe atypia of more than a few melanocytes plus irregularity and high cellularity with pagetoid scatter in the setting of a low degree of CSD:
  ✓ Suggests early melanoma.
Lentiginous Junctional Nevus
Lentiginous Junctional Nevus
Diagnostic Criteria for Lentiginous Compound Nevus

Lentiginous compound naevus
- Any width
- Increased density of non-nested melanocytes between junctional nests, often extending out along the shoulders of the nested junctional and/or intradermal components
- Junctional nests are prominent, well formed, and usually round
- Nested melanocytes are often larger than non-nested melanocytes, with larger nuclei and more-abundant cytoplasm
- Nuclei of nested melanocytes are uniform and not greatly enlarged or hypochromatic
Exclusions

• Moderate or severe atypia of more than a few melanocytes plus irregular and dyscohesive nesting **without** CSD:
  ✓ Suggests: Dysplastic nevus or early melanoma
  ✓ Specially if there is also **pagetoid scatter**, 
• Moderate or severe atypia of more than a few melanocytes **plus** CSD
  ✓ Suggests: Atypical lentiginous nevus or lentigo maligna, **but not** dysplastic nevus (use descriptive diagnosis)
The diagnosis of dysplastic nevus should be made with caution if there is a background of solar elastosis, particularly on the face.

And in our view

- All dysplastic nevi on sun-damaged skin should be completely excised with a margin of normal tissue.
Diagnostic Criteria for Nevus with Architectural Disorder and Minimal or Mild Cytologic Atypia

Naevus with architectural disorder and minimal or mild cytological atypia
- Width often < 4 mm in fixed sections
- Architectural features of dysplastic naevus
- Grade of cytological atypia and/or density of atypical melanocytes below the threshold for dysplastic naevus (see Table 2.13)
Melanoma In Situ and Superficially Invasive Melanoma

- Superficial spreading melanoma
- Lentigo maligna melanoma
Modified IMPSG Diagnostic Criteria for Melanoma

Superficial spreading melanoma in situ

- Contiguous proliferation of uniformly (e.g. > 50%) moderately to severely atypical melanocytes in an area $\geq 0.5 \text{ mm}^2$
  
  and/or

- Upward intraepidermal spread of moderately to severely atypical melanocytes involving the superficial spinous and granular layers in an area $\geq 0.5 \text{ mm}^2$
  
  and/or

- Large irregular junctional nests of different sizes, with focal confluence and variable nuclear atypia together with lesion asymmetry (so-called nested melanoma) \{1472\}
Superficial Spreading Melanoma In Situ
Note

• **Minimal/equivocal involvement** may be reported as for example:

  “Severely dysplastic nevus with focal superficial atypical melanocytic proliferation of uncertain significance (SAMPUS)- cannot rule out evolving or early established melanoma in situ, superficial spreading melanoma type”
• Difference, is **subjective** and usually **one of degree**.
• Severely dysplastic nevi show a **continuum** with early melanoma.
• Although **most cases** are readily classified, it must be acknowledged that they form a **histologic (if not biological) spectrum**.
• **Reliable** morphological criteria for their distinction **do not exist**.
• *Since a diagnosis of either in situ melanoma or severely dysplastic nevus generally leads to the same therapy, such distinction is of little practical importance*
Exclusions

- Recurrent nevus
- Traumatized nevus
- Recent UV radiation exposure
- Other reactive processes
Lentigo Maligna

- Prominent solar elastosis
- Epidermal atrophy and flattened rete, at least focally
- Increased number of basal naevoid to epithelioid melanocytes, usually with contiguous proliferation in an area $\geq 0.5 \text{ mm}^2$
- Usually some pagetoid scatter
- Irregularly distributed junctional nests
- Uniform cytological atypia of nested and non-nested junctional melanocytes
- Often involves adnexa, especially hair follicles
- Sometimes atypical multinucleated melanocytes (starburst cells)
Note

- **Minimal/equivocal involvement** may be reported as:

  “Lentiginous nevus with focal superficial proliferation of uncertain significance—cannot rule out evolving or early established melanoma in situ, lentigo maligna type.”
• Acral nevi and melanoma:

• A melanocytic proliferation in acral skin is much more likely to be an acral nevus (or melanoma) than a dysplastic nevus
• There is **potential overlap** with features of **melanoma**:
• The presence of **significant pagetoid spread** of melanocytes (particularly at the **edges** of the lesion),
• **Asymmetry**, both of the **junctional component** and of any associated lymphocytic infiltrate;
• **Diffuse** cytologic atypia, and
• **Mitotic figures** in the **intradermal** component are
• **Important clues to evolving melanoma**
It should also be noted that dysplastic nevi can show superimposed features of:

- Regression and/or
- Traumatization,

Further adding to the difficulty of the distinction from melanoma
• **Finally**, melanoma (particularly melanoma in situ) can be seen in association with dysplastic nevi;
• indeed,
• There is increasing evidence that the morphologic borderline is characterized by cumulative acquisition of the molecular attributes of frank melanoma.
• There is very **significant interobserver variability** in interpreting lesions in this group

• **Complete excision** is prudent in **all lesions** where there is **doubt**, and it is important for the **pathologist, the clinician, and the patient** to recognize that the outcome is always **excellent** in completely excised lesions with borderline or equivocal changes of melanoma in situ,  **and**

• **Almost always excellent** in lesions where the differential diagnosis **lies between** a severely dysplastic nevus and a thin invasive melanoma.