Mimicry in Melanocytic Lesions

Mai P. Hoang, MD
Associate Professor of Pathology
Harvard Medical School
Medical Director, Immunohistochemistry Laboratory
Massachusetts General Hospital, Boston, MA

Outline

- Nevi that mimic melanoma
- Melanoma that mimic nevi

Nevi that mimic melanoma

- Inverted type A/ deep penetrating nevus
- Cellular blue nevi
- Proliferative nodule within congenital nevi
- Atypical genital nevi
- Nevus associated with lichen sclerosus
- Recurrent nevus
- Nevus in pregnancy
- Nevus in setting of BRAF inhibitor therapy

Inverted type A/ deep penetrating nevus

- Deep penetrating nevus – posterior back, upper back
- Inverted type-A nevus – variable

A 25 year-old woman presented with a pigmented lesion on her back.
Inverted type A/ deep penetrating nevus

- Deep penetrating nevus – posterior back, upper back
- Inverted type-A nevus – variable

- Pigmented type-A nevus cells distributed in an inverted triangle
- The lesion is well circumscribed
- Type-A nevus cell
  - Oval to round nuclei
  - Tiny nucleoli
  - Pal finly pigmented cytoplasm
- Scattered melanophages

- Recommend complete excision and follow-up for these lesions

Cellular blue nevus

- Biphasic appearance
- Areas of fibrosis with dendritic blue nevus cells admixed with melanophages
- Discrete large nodules of spindle cells within the deep dermis and subcutaneous fat
Cellular blue nevus

- Biphasic appearance
- Areas of fibrosis with dendritic blue nevus cells admixed with melanophages
- Discrete large nodules of spindle cells within the deep dermis and subcutaneous fat

- Atypical cellular blue nevus
  - Pigment free
  - Abundant atypical mitoses

- Malignant blue nevus
  - Highly invasive nodule into the subcutaneous fat
  - Necrosis
Inverted type-A, deep penetrating, and cellular blue nevi

Nevi with architecture of melanoma
- Asymmetry
- Deep pushing cellular nodule or finger-like projection into subcutaneous fat
- Occasional plexiform growth pattern in reticular dermis
- Foci of deep (as well as superficial) pigment production
- Lack of maturation at base (cells do not diminish in size)
- Few mitoses, apoptotic cells, or high-grade cytologic atypia

Atypical genital nevi

- First reported by Friedman and Ackerman
- Uncommon, accounts for 5-7% of benign vulvar nevi
- Commonly arise on the vulva of young women, and regarded as nevi of special sites (axillae, breasts, periumbilical region, groin, flexural and acral sites, ears)
- Predilection for the clitoris, labia majora, and labia minora
- Symmetric, circumscribed, with even pigmentation, and often less than 1 cm
• The junctional nests are large, irregular, coalescent, and with cellular dyscohesion and prominent retraction artifact.
• The melanocytes are enlarged and with angulated and hyperchromatic nuclei.
• Lentiginous growth and pagetoid upward migration are seen only in the center of the lesion.
• The dermal component is associated with coarse eosinophilic fibrosis of the papillary dermis arranged mainly in linear array parallel to the epidermis different from the lamellar fibrosis of the dysplastic nevus.
• Adnexal extension is often identified.

Grading of cytologic atypia of dysplastic nevus

<table>
<thead>
<tr>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>The size of the nuclei of melanocytes is slightly less than that or equal to that of spinous keratinocyte nuclei</td>
</tr>
<tr>
<td>Increase in size and hyperchromasia of nuclei</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear size is larger than that of spinous keratinocyte nuclei</td>
</tr>
<tr>
<td>Increase in nuclear size and often an increase in hyperchromasia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abundant and granular cytoplasm containing fine or dusty melanin pigment</td>
</tr>
<tr>
<td>Nuclei may be twice the size of those of spinous keratinocytes</td>
</tr>
<tr>
<td>Markedly hyperchromatic nuclei</td>
</tr>
<tr>
<td>Prominent nucleoli</td>
</tr>
</tbody>
</table>

Grading of cytologic atypia of dysplastic nevus

Mild: Cytologic atypia is minimal.
Moderate: Cytologic atypia is more pronounced, with increased nuclear size and hyperchromasia.
Severe: Cytologic atypia is extensive, with abundant cytoplasm and prominent nucleoli.

Malignant melanoma
Severe cytologic atypia
Consumption of epidermis
Sharply demarcated and well-formed nests
Absence of pagetoid spread

Severely atypical genital nevus
Severe cytologic atypia
Consumption of epidermis
Sharply demarcated and well-formed nests
Absence of pagetoid spread

Atypical genital nevi

- Histologic features of atypical genital nevi
- Large variably sized, pigmented junctional nests with cellular dyscohesion and retraction artifact
- The nests are fused and irregularly arranged at the dermal-epidermal junction

- Difference from dysplastic nevus
- The presence of coarse eosinophilic fibrosis in the papillary dermis rather than the dense and concentric fibrosis of the dysplastic nevus.

- Conservative re-excision is prudent to prevent recurrence, however a wide excision is not indicated.

- Histologic features of atypical genital nevi
- Large variably sized, pigmented junctional nests with cellular dyscohesion and retraction artifact
- The nests are fused and irregularly arranged at the dermal-epidermal junction

- Difference from dysplastic nevus
- The presence of coarse eosinophilic fibrosis in the papillary dermis rather than the dense and concentric fibrosis of the dysplastic nevus.

- Conservative re-excision is prudent to prevent recurrence, however a wide excision is not indicated.
### Table

<table>
<thead>
<tr>
<th>Atypical genital nevus</th>
<th>Vulvar melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Premenopausal, 20-30s</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Less than 1 cm</td>
</tr>
<tr>
<td>Circumscription</td>
<td>Yes</td>
</tr>
<tr>
<td>Symmetry</td>
<td>Yes</td>
</tr>
<tr>
<td>Lateral extension of junctional component</td>
<td>Focal</td>
</tr>
<tr>
<td>Lentigous junctional component</td>
<td>Focal</td>
</tr>
<tr>
<td>Junctional nests</td>
<td>Dyscohesion</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Absent</td>
</tr>
<tr>
<td>Pagetoid upward migration</td>
<td>Focal and central</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>Superficial</td>
</tr>
<tr>
<td>Dermal mitoses</td>
<td>Rare and superficial</td>
</tr>
<tr>
<td>Dermal maturation</td>
<td>Yes</td>
</tr>
<tr>
<td>Dermal fibrosis</td>
<td>Broad zone of superficial dermal fibrosis</td>
</tr>
</tbody>
</table>

### External trauma or internal factors

- Traumatized nevus
- Recurrent nevus
- Nevus in pregnancy
- Nevus in setting of BRAF inhibitor therapy

### Image

- A 16 year-old female with an irregular pigmented lesion on right vulva
- Concurrency of lichen sclerosus and pigmented lesions may be difficult to classify due to the concurrence of histologic features of nev of special sites and the changes produced by the interaction of melanocytes and stroma.

---

Trizonal pattern of recurrent nevus

- An atypical and pigmented lentiginous junctional melanocytic proliferation
- Underlying dermal fibrosis
- Residual dermal nevus component


- Junctional component limited to an area of dermal scar

- Nevus and lichen sclerosus
- Recurrent nevus

Heavily pigmented junctional melanocytes

- The nevus is confined to the area of lichen sclerosus.
- Symmetric, minimal upward migration and cytologic atypia of melanocytes

Concurrence of melanocytic nevus and lichen sclerosus

Dysplastic nevus on the back
- Area of lentiginous atypia confined to scar
- Telangiectasia
- Marked dermal inflammation

Malignant melanoma with regression
- Effacement of the rete ridges
- Prominent dermal melanophages
- Solar elastosis below scar

Dysplastic nevus on the back
- Residual nevus below area of fibrosis

Malignant melanoma with regression
A 35 year-old pregnant woman presents with a longstanding nevus on her neck that has increased in size.

**Cause of fibrosis**

<table>
<thead>
<tr>
<th>Cause of fibrosis</th>
<th>Vessels</th>
<th>Inflammation</th>
<th>Collagen orientation</th>
<th>Melanocytic proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>Vertically oriented vessels</td>
<td>Mixed infiltrate</td>
<td>Horizontal</td>
<td>Distorted architecture</td>
</tr>
<tr>
<td>Regression</td>
<td>Randomly oriented vessels</td>
<td>Lymphocytes, macrophages</td>
<td>Random, coarse</td>
<td>Focally replaced</td>
</tr>
</tbody>
</table>

**Dysplastic nevus on the back**

- Residual nevus below area of fibrosis
- Pagetoid spread lateral to regression
- Greater degree of cytologic atypia
- Prominent melanophages

**Malignant melanoma with regression**

- Greater degree of cytologic atypia
- Prominent melanophages
Melanocytic nevi in pregnancy: histologic features and Ki-67 proliferation index

A 49 year old woman with metastatic BRAFV600E mutant rectal carcinoma on BRAF inhibitor presented with new moles on her back and changing mole on her left leg

Courtesy of Dr. Mabet Alora-Palli, MGH Dermatology
Vemurafenib-treated patients can
- Develop new nevi
- Develop changes in existing melanocytic lesions (involution, increase in size, alteration of color)

Selective BRAF inhibitors have been studied for the treatment of metastatic melanoma and other malignancies with BRAV600E mutation.

The most frequent cutaneous toxicities include:

- New and evolving melanocytic lesions have also been reported in patients receiving BRAF inhibitors.


---

**Table 1.** Histologic and immunohistochemical features of melanocytic nevi excised during BRAF proto-oncogene (BRAF) inhibitor therapy: A study of 19 lesions from 10 patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>BRAF Inhibitors</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor thickness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>0/19 (0%)</td>
<td>0/16 (0%)</td>
</tr>
<tr>
<td>Multinucleation</td>
<td>1/19 (5%)</td>
<td>2/16 (13%)</td>
</tr>
<tr>
<td>Nests of atypical melanocytes</td>
<td>5/19 (26%)</td>
<td>2/16 (13%)</td>
</tr>
<tr>
<td>Atypical melanocytes</td>
<td>1/19 (5%)</td>
<td>0/16 (0%)</td>
</tr>
<tr>
<td>Atypical melanocytes</td>
<td>1/19 (5%)</td>
<td>0/16 (0%)</td>
</tr>
<tr>
<td>Inverted type nevus (nevus inverted</td>
<td>0/19 (0%)</td>
<td>0/16 (0%)</td>
</tr>
<tr>
<td>Progesterone-induced nevus</td>
<td>0/19 (0%)</td>
<td>0/16 (0%)</td>
</tr>
<tr>
<td>Progesterone-induced nevus</td>
<td>0/19 (0%)</td>
<td>0/16 (0%)</td>
</tr>
</tbody>
</table>

Sorafenib: 65 patients, JAAD 2009
BRAF Inhibitors: 18 patients, JAAD 2012

---

**Nevi that mimic melanoma**

- Inverted type A/ deep penetrating nevus
- Cellular blue nevi
- Proliferative nodule within congenital nevi
- Atypical genital nevi
- Nevus associated with lichen sclerosus
- Recurrent nevus
- Nevus in pregnancy
- Nevus in setting of BRAF inhibitor therapy
Melanomas that mimic nevi

- Nevoid melanoma
- Blue nevus-like metastases
Nevoid melanoma

- **Histologic features**
  - Solid pattern of growth
  - Gradual diminution in size of dermal nests simulating maturation
  - Dermal cords and strands of melanoma cells with cellular pleomorphism and atypia extending to the base
  - Mitoses at the bottom of the lesion

- **Immunohistochemistry**
  - HMB-45
  - Ki-67

Blue nevus-like metastases


- All 10 cases contained pigmented melanocytes and melanophages arranged in a blue nevus-like growth pattern.

Histologic clues of metastatic melanoma

- Presence of atypical epithelioid melanocytes
- Mitotic figures
- An associated inflammatory cell infiltrate at the periphery of the lesion
Another lesion on his right upper back.

Summary

- Nevi that mimic melanoma
  - Inverted type A/ deep penetrating nevus
  - Cellular blue nevi
  - Proliferative nodule within congenital nevi
  - Atypical genital nevi
  - Nevus associated with lichen sclerosus
  - Recurrent nevus
  - Nevus in pregnancy
  - Nevus in setting of BRAF inhibitor therapy
- Melanoma that mimic nevi
  - Nevoid melanoma
  - Blue nevus-like metastases