Mimicry in Melanocytic Lesions

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Outline

- Nevi that mimic melanoma
- Melanoma that mimic nevi
- Non-melanocytic tumors that mimic melanoma

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
  - Pale finely 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

**Proliferative Nodules Arising Within Congenital Melanocytic Nevi: A Histologic, Immunohistochemical, and Molecular Analyses of 43 Cases**

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**Abstract**

The histopathologic interpretation of proliferative nodules (PNs) in congenital melanocytic nevi can present diagnostic challenges. In some PNs, they might arise in congenital nevi that contain melanocytic naevi (MCNs) of malphigian type. We investigated whether MCN/PNs express the same dermal markers, and we used a common immunohistochemical panel (Ki-67, p53, PTEN, and MMPI) in 26 congenital nevi, 25 congenital naevi, and 5 cutaneous melanomas. Although numerous mutations are detected in the variable, the diagnostic use of molecular markers in this context is limited.

**Key Words:** proliferative nodule, congenital nevus, immunohistochemistry, molecular analysis

**Table 1**

<table>
<thead>
<tr>
<th>Relationship to adjacent congenital nevus</th>
<th>Benign proliferative nodule</th>
<th>Atypical proliferative nodule</th>
<th>Malignant melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blends with adjacent nevus</td>
<td>Discrete nodule</td>
<td>Sharply demarcated nodule</td>
<td></td>
</tr>
<tr>
<td>Expandable growth</td>
<td>No</td>
<td>Can have infiltrative growth</td>
<td>Destructive expandable growth</td>
</tr>
<tr>
<td>Effacement of epidermis and/or pagetoid spread</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Necrosis</td>
<td>No</td>
<td>Rare single cell necrosis, mucinosis may be seen</td>
<td>Extensive single cell and/or zonal necrosis</td>
</tr>
<tr>
<td>Pleomorphism</td>
<td>No</td>
<td>Variable</td>
<td>Present</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Rare</td>
<td>Variable, atypical mitoses</td>
<td></td>
</tr>
</tbody>
</table>
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

Bridging of junctional nests
Coarse superficial dermal fibrosis
Retraction artifact
Coalescent junctional nests


- The junctional nests are large, irregular, coalescent, and with cellular dyshesion 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>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>The size of the nuclei of melanocytes is slightly less than that or equal to that of spinous keratinocyte nuclei. Increase in size and hyperchromasia of nucleus.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Nuclear size is larger than that of spinous keratinocyte nucleus. Increase in nuclear size and often an increase in hyperchromasia.</td>
</tr>
<tr>
<td>Severe</td>
<td>Abundant and granular cytoplasm containing fine or dusty melanin pigment. Nuclei may be twice the size of those of spinous keratinocytes. Markedly hyperchromatic nuclei. Prominent nucleoli.</td>
</tr>
</tbody>
</table>
Moderate cytologic atypia
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 nevi
  - 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.
Atypical genital nevus Vulvar melanoma

<table>
<thead>
<tr>
<th>Atypical genital nevus</th>
<th>Vulvar melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Pre-menopausal, 20-30s</td>
</tr>
<tr>
<td>Size</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>Lentiginous junctional component</td>
<td>Focal</td>
</tr>
<tr>
<td>Junctional nests</td>
<td>Dycohesion</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>

Age Pre-menopausal, 20-30s Post-menopausal
Size Less than 1 cm Greater than 1 cm
Circumscription Yes No
Symmetry Yes No
Lateral extension of junctional component Focal Present
Lentiginous junctional component Focal Yes
Junctional nests Dyscohesion Coalescence
Ulceration Absent Often present
Pagetoid upward migration Focal and central Prominent
Cytologic atypia Superficial Confluent and deep
Dermal mitoses Rare and superficial Many and deep
Dermal maturation Yes No
Dermal fibrosis Broad zone of superficial dermal fibrosis Regression type
External trauma or internal factors

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

A 16 year-old female with an irregular pigmented lesion on right vulva

Concurrence of lichen sclerosus and pigmented lesions may be difficult to classify due to the concurrence of histologic features of nevi of special sites and the changes produced by the interaction of melanocytes and stroma

A 32-year-old woman presented with a recurrent lesion at prior biopsy site of a compound nevus.

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 sclerosus
Junctional component limited to an area of dermal scar

Nevus and lichen sclerosus
Recurrent nevus
Concurrence of melanocytic nevus and lichen sclerosus

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

<table>
<thead>
<tr>
<th>Cause of fibrosis</th>
<th>Vessels</th>
<th>Inflammation</th>
<th>Collagen orientation</th>
<th>Lesional cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>Prominent, vertical orientation</td>
<td>Mixed cell types if present</td>
<td>Horizontal</td>
<td>Distorted architecture</td>
</tr>
<tr>
<td>Regression</td>
<td>Prominent, random orientation</td>
<td>Lymphocytes, macrophages</td>
<td>Random, coarse</td>
<td>Focally replaced</td>
</tr>
</tbody>
</table>
Melanocytic nevi in pregnancy: histologic features and Ki-67 proliferation index

Background: Changes in the clinical appearance of benign skin nevi during pregnancy may be concerning for malignant transformation. Because the hormonal milieu of pregnancy has not proven to alter dermal melanocytes, biopsies in pregnancy may be deferred unless clinically suspicious.

Methods: Biopsied skin from pregnant women (n = 30) were compared with skin from the non-pregnant age-matched control group (n = 15). Histologic features and Ki-67 proliferation index were recorded.

Results: No significant differences were noted except for increased Ki-67 staining (p = 0.002) and higher risk of nevi (1.88 vs. 1.01 in non-pregnant vs. pregnant). Ki-67 staining was significantly increased in the pregnant group (21.7% vs. 17.4%, p = 0.04) and showed a trend in increased risk for melanoma.

Conclusion: Dermatologists should be aware of the increased Ki-67 staining in pregnancy. "Pregnancy may allow differentiation between benign and malignant melanocytic lesions."

A 49-year-old woman with metastatic BRAF V600E 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-Pali, MGH Dermatology
Biopsy of lesion on her left leg
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.


Frequency of Lesions Observed in Patients on Kinase Inhibitors

<table>
<thead>
<tr>
<th>Sorafenib</th>
<th>BRAF inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 patients, JAAD 2009</td>
<td>18 patients, JAAD 2012</td>
</tr>
<tr>
<td>hand-foot-skin reaction (63-78%)</td>
<td>Verrucous keratosis (86%)</td>
</tr>
<tr>
<td>facial/scalp erythema (63-68%)</td>
<td>SCC (57%)</td>
</tr>
<tr>
<td>nail changes, alopecia (32-33%)</td>
<td>SCC, KA type (29%)</td>
</tr>
<tr>
<td>cysts (5-27%)</td>
<td>acantholytic dyskeratosis (57%)</td>
</tr>
<tr>
<td>eruptive keratoacanthomas (4-7%)</td>
<td>eruptive nevi (7%)</td>
</tr>
<tr>
<td>eruptive nevi (0-2%)</td>
<td>atypical melanocytic nevi</td>
</tr>
</tbody>
</table>

Melanocytic nevi excised during B-Raf proto-oncogene (BRAF) inhibitor therapy: A study of 19 lesions from 10 patients

Mark C. Hochel, MD; Marc E. Hammoud; Ummawi E. Badreldin; Mark K. Abraham, MD; Antonio Pino, MD; Mark D. Rozen, MD; and Xia P. Huang, MD; Boston, Massachusetts

Table 1. Histologic and immunohistochemical features of melanocytic nevi excised during B-Raf proto-oncogene inhibitor therapy compared with control nevi

<table>
<thead>
<tr>
<th>Staining Factors</th>
<th>BRAF Inhibition</th>
<th>Control N.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>nuclear membrane</td>
<td>11 of 19 (61%)</td>
<td>5 of 19 (26%)</td>
<td>.005*</td>
</tr>
<tr>
<td>increased keratinocytes</td>
<td>16 of 19 (84%)</td>
<td>1 of 19 (5%)</td>
<td>.001*</td>
</tr>
<tr>
<td>normal keratinocytes</td>
<td>8 of 19 (42%)</td>
<td>19 of 19 (100%)</td>
<td>.0001*</td>
</tr>
<tr>
<td>basal, epidermal</td>
<td>12 of 19 (63%)</td>
<td>1 of 19 (5%)</td>
<td>.0001*</td>
</tr>
<tr>
<td>suprabasal, intermediate</td>
<td>5 of 19 (26%)</td>
<td>1 of 19 (5%)</td>
<td>.047</td>
</tr>
<tr>
<td>sarcoma-like</td>
<td>3 of 19 (16%)</td>
<td>1 of 19 (5%)</td>
<td>.0025*</td>
</tr>
<tr>
<td>hyperkeratosis</td>
<td>17 of 19 (95%)</td>
<td>1 of 19 (5%)</td>
<td>.0001*</td>
</tr>
<tr>
<td>acantholytic dyskeratosis</td>
<td>9 of 19 (47%)</td>
<td>1 of 19 (5%)</td>
<td>.0001*</td>
</tr>
<tr>
<td>melanocytic nevus</td>
<td>1 of 19 (5%)</td>
<td>19 of 19 (100%)</td>
<td>1</td>
</tr>
</tbody>
</table>

BRAF, B-Raf proto-oncogene; LCA, lymphocytic capillaritis; B-E, dysplastic lentigo; pMLT, phosphorylated protein kinase B; pMK, phosphorylated signal-regulated kinase; pERK, phosphorylated extracellular signal-regulated kinase.

*Statistically significant, P < .05.
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

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**Fig. 2.** In contrast to compound nests (Fig. 1), nevi (not seen in the nevoid type) A and B, usually show patchy labeling with HMB-45 at back (D), and variant (E) areas of the lesion, whereas Ki-67 is expressed in smaller proportions of cells both top (F) and bottom (G) areas. [A and B], hematoxylin and eosin (H and E), HMB-45, and Ki-67, with high-magnification (H and E), and Ki-67, ABC with light hematoxylin.

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

Non-melanocytic mimics
- Cellular neurothekeoma
- Sarcomatoid carcinoma
- Atypical fibroxanthoma
- Merkel cell carcinoma
- Lymphoma

**Summary**

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