Benign Melanocytic Nevi
Spitz Nevus, Dysplastic Nevus, Mitoses in Benign Nevi

2014-02-13
Nevus Subtypes

**Nevus subtype**
- Common nevus
- Congenital nevus
- Blue nevus
- Spitz nevus
- Reed nevus
- Dysplastic nevus
- Combined nevus
- Acral nevus
- Nevi on special sites
- Nevi of the conjunctiva
- Nevi and inflammatory skin disease
- Halo nevus
- Recurrent or traumatized nevus

**Can look like melanoma**
- Cellular blue nevus, deep penetrating
- Spitz nevus
- Pigmented variant of Spitz nevus
- Dysplastic nevus with severe atypia
- Inverted type A nevus
- MANIAC
- Ear, milk line, nevi in pregnancy
- Nevi of the conjunctiva, PAM
- Lichen sclerosus, lichen ruber, psoriasis
- Regressing nevus
- Recurrent or traumatized nevus
Spitz Nevus : Melanoma = 60 : 1

Spitz Nevus : Melanoma = 1 : 60
At Age 27: Spitz : Melanoma = 1:1
Reed Nevus

Pigmented spindle cell variant
<table>
<thead>
<tr>
<th></th>
<th>Spitz nevus</th>
<th>atypical Spitz tumor</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>usually &lt; 1cm</td>
<td>often &gt; 1cm</td>
<td>usually &gt; 1cm</td>
</tr>
<tr>
<td><strong>Symmetry</strong></td>
<td>symmetric</td>
<td>often asymmetric</td>
<td>asymmetric</td>
</tr>
<tr>
<td><strong>Lateral borders</strong></td>
<td>sharp</td>
<td>poorly defined</td>
<td>poorly defined</td>
</tr>
<tr>
<td><strong>Lateral extension</strong></td>
<td>uncommon</td>
<td>common</td>
<td>common</td>
</tr>
<tr>
<td><strong>Lentiginous pattern</strong></td>
<td>uncommon</td>
<td>variable</td>
<td>common</td>
</tr>
<tr>
<td><strong>Irregular nesting</strong></td>
<td>uncommon</td>
<td>variable</td>
<td>common</td>
</tr>
<tr>
<td><strong>Upward migration</strong></td>
<td>common in children's nests&gt; single cells</td>
<td>variable, prominent</td>
<td>frequent, usually as single cells</td>
</tr>
<tr>
<td><strong>Ulceration</strong></td>
<td>uncommon</td>
<td>variable</td>
<td>common</td>
</tr>
<tr>
<td><strong>Kamino bodies</strong></td>
<td>common</td>
<td>less common</td>
<td>uncommon</td>
</tr>
<tr>
<td><strong>Cell type</strong></td>
<td>monomorphic</td>
<td>pleomorphic</td>
<td>pleomorphic</td>
</tr>
<tr>
<td><strong>Deep extension</strong></td>
<td>uncommon</td>
<td>common</td>
<td>variable</td>
</tr>
<tr>
<td><strong>Expansile nodules</strong></td>
<td>uncommon</td>
<td>common</td>
<td>frequent</td>
</tr>
<tr>
<td><strong>Maturation</strong></td>
<td>common</td>
<td>uncommon/absent</td>
<td>uncommon</td>
</tr>
<tr>
<td><strong>Deep border</strong></td>
<td>infiltrating</td>
<td>pushing</td>
<td>irregular</td>
</tr>
<tr>
<td><strong>Cellularity</strong></td>
<td>variable</td>
<td>prominent</td>
<td>prominent</td>
</tr>
<tr>
<td><strong>Cytologic atypia</strong></td>
<td>uncommon</td>
<td>common</td>
<td>prominent</td>
</tr>
<tr>
<td><strong>Deep mitoses</strong></td>
<td>uncommon</td>
<td>common</td>
<td>frequent</td>
</tr>
<tr>
<td><strong>Atypical mitoses</strong></td>
<td>uncommon</td>
<td>variable</td>
<td>common</td>
</tr>
<tr>
<td><strong>Mononuclear infiltrate</strong></td>
<td>perivascular</td>
<td>patchy</td>
<td>band-like, patchy</td>
</tr>
</tbody>
</table>
37 children (2-17 y) with spitzoid neoplasms with a positive multicolor FISH result
Correlation with extension beyond the sentinel lymph node (9/37):

Presence of homozygous 9p21 deletion (7/9) $p=0.046$
Positive sentinel lymph node (7/9) $p=0.01$
Atypical Spitz Tumor (0-17 y)

Total score and risk for metastasis
0-2: low risk
3-4: Intermediate risk
5-11: High risk

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>0-10</td>
<td>0</td>
</tr>
<tr>
<td>11-17</td>
<td>1</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td></td>
</tr>
<tr>
<td>0-10</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1</td>
</tr>
<tr>
<td>Involvement of subcutaneous fat</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>2</td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>2</td>
</tr>
<tr>
<td>Mitotic activity (mm²)</td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>0</td>
</tr>
<tr>
<td>6-8</td>
<td>2</td>
</tr>
<tr>
<td>&gt;9</td>
<td>5</td>
</tr>
</tbody>
</table>

Spitz Tumors in Children
A Grading System for Risk Stratification
Spatz A., Calonje E., Handfield-Jones S., Barnhill RL.
Dysplastic Nevus
Clinical Features

• Isolated lesion without increased risk
• Sporadic syndrome
  – >2-5 dysplastic nevi on sun exposed skin
  – Increased risk of melanoma (amount debated)
• Familial dysplastic nevus syndrome
  – Autosomal dominant
  – Hundreds of lesions sun exposed & protected skin
  – 2-28x risk of the general population
  – 148x risk in patients with family history of melanoma
• Problems:
  – Inappropriate term (no dysplasia in melanocytes)
  – Poor clinico-pathologic correlation (30%).
    DD: Lentigo simplex, naevus incipiens
  – Increased melanoma risk uncertain
Dysplastic Nevus

• Problems:
  – Imprecise histologic definition
  – Morphologic overlap of dysplastic nevi and melanoma (continuum)
  – Overdiagnosis as Mis/Melanoma > underdiagnosis
Common nevus

Dysplastic nevus

Severely dysplastic nevus

Thin melanoma
Cytologic Atypia

Discontinuous cellular atypia
- Enlarged nuclei
- Nuclear pleomorphism
- Hyperchromasia
- Prominent nucleoli
- Large melanin granules
Architectural Atypia

1. Often >5mm (clinically by definition >5mm)
2. Unsharp demarcation
3. Compound type with shoulder > 3 rete ridges
4. Long rete ridges with bridges
5. Lentiginous proliferation of single melanocytes
6. Variable nests (form, size, localisation)
7. Focal pagetoid spread (center of the lesion)
Stromal Changes

**Host reaction**
- Fibroplasia
- Small blood vessels ↑
- Spotty inflammation
- Melanophages

Concentric fibroplasia

Lamellar fibroplasia
### Grading: Architecture

<table>
<thead>
<tr>
<th>Architectural</th>
<th>Score 0</th>
<th>Score 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumscription</td>
<td>Junctional component nested at both edges of the lesion</td>
<td>Single-cell pattern of proliferation in at least one edge</td>
</tr>
<tr>
<td>Symmetry</td>
<td>Good overall symmetry regarding edges, size of junctional nests, and stromal response</td>
<td>Otherwise</td>
</tr>
<tr>
<td>Cohesiveness of nests</td>
<td>More than 50% of the junctional nests were compact and cohesive</td>
<td>Otherwise</td>
</tr>
<tr>
<td>Degree of pagetoid upward migration</td>
<td>Otherwise</td>
<td>Single or nested melanocytes present above the epidermal basal layer</td>
</tr>
<tr>
<td>Confluence of junctional nests</td>
<td>Otherwise</td>
<td>Confluence of junctional nests Otherwise Confluence of greater than 50% of the junctional melanocytic proliferation, either as bridging of melanocytic nests or as contiguous single cells</td>
</tr>
<tr>
<td>Degree of single-cell proliferation</td>
<td>Junctional melanocytes arranged as single cells in more than 20% of the lesion</td>
<td></td>
</tr>
</tbody>
</table>

Architectural atypia: mild (0-1) moderate (2-3) severe (4-6)

*Hum Pathol. 1999 May;30(5):500-5.*
Shea CR et al.
# Grading: Cytologic Atypia

Cytologic atypia: mild (0-1) moderate (2) severe (3-4)

<table>
<thead>
<tr>
<th>Cytologic</th>
<th>Score 0</th>
<th>Score 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear shape and chromasia</td>
<td>Nuclei round, oval, and euchromatic</td>
<td>Otherwise</td>
</tr>
<tr>
<td>Nuclear size</td>
<td>Otherwise</td>
<td>Diameter of the melanocyte nuclei greater than the basal keratinocyte nuclei</td>
</tr>
<tr>
<td>Nucleolar prominence</td>
<td>Otherwise</td>
<td>Prominent nucleoli</td>
</tr>
<tr>
<td>Cell size</td>
<td>Otherwise</td>
<td>Diameter of Melanocyte more than twice that of basal-layer keratinocyte nuclei</td>
</tr>
</tbody>
</table>
Diagnosis

• Formulation of diagnosis:
  – Junctional or compound nevus without cytologic
    atypia (gradual transition to common nevus)
  – Junctional or compound nevus with
    mild/moderate architectural disorder and
    mild/moderate cytologic atypia (dysplastic nevus)

Comment:
No increased risk compared to common nevus
Diagnosis

• Formulation of diagnosis:
  – Junctional or compound nevus with severe architectural disorder and severe cytologic atypia (dysplastic nevus)
    • Second opinion in house
    • (Re)excision with 5mm safety margin
    • Recommend clinical follow up
Diagnosis

• Formulation of diagnosis:
  – Atypical melanocytic lesion of unknown malignant potential (DD: dysplastic nevus with severe atypia, Mis, melanoma)
    • Second opinion
    • Communicate uncertainty
    • Do not call neither nevus nor melanoma
    • Complete excision like melanoma and clinical follow up
    • Describe depths of infiltration
### Reexcision of Dysplastic Nevi

<table>
<thead>
<tr>
<th>Degree of atypia</th>
<th>Reexcision if R1</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Low grade lesions</td>
<td></td>
</tr>
<tr>
<td>– Architectural disorder, no or mild cytologic atypia</td>
<td></td>
</tr>
<tr>
<td>• High grade</td>
<td></td>
</tr>
<tr>
<td>– Moderate atypia</td>
<td></td>
</tr>
<tr>
<td>– Severe atypia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– No</td>
</tr>
<tr>
<td></td>
<td>– Yes</td>
</tr>
<tr>
<td></td>
<td>– Yes, 5mm safety margin</td>
</tr>
</tbody>
</table>

*Pathology of Melanocytic Nevi and Malignant Melanoma*
Barnhill RL, Piepkorn M, Busam KJ. Springer. 2nd Ed. P. 86-88
Seek and you shall find: Mitoses in melanocytic nevi

Frequent mitotic activity in banal melanocytic nevi uncovered by immunohistochemical analysis.
Glatz K, Hartmann C, Antic M, Kutzner H.
353 unselected banal nevi

• Clinical parameters
  – Age
  – Sex
  – Localisation

• Morphologic parameters
  – Diameter and dermal surface area
  – Solar elastosis
  – Inflammation
  – Signs of trauma
  – Exophytic architecture
353 unselected banal nevi

- Stainings
  - H&E
  - PHH3
  - MPM2

- Mitotic counts
  - Junctional – upper dermal – lower dermal
  - Per dermal surface
  - Per mm2 hotspot
  - Mitoses in inflammatory cells
Immunohistochemistry

a-e: MPM2

f-j: PHH3
"Mitotic figures are rare in banal nevi although if sufficient sections and levels are examined they will almost always be identified".
Nevi with Mitotic Figures

<table>
<thead>
<tr>
<th>Method</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;E</td>
<td>19.5%</td>
</tr>
<tr>
<td>PHH3</td>
<td>31.3%</td>
</tr>
<tr>
<td>MPM2</td>
<td>42.8%</td>
</tr>
</tbody>
</table>
Mitoses/mm$^2$ Hotspot H&E

Common/dysplastic Nevi  

0.17 (0-3)  
3.20 (0-92)

Clusters of mitotic figures exclusively in malignant melanomas

← PHH3 Melanoma
Naevus Subtype

31 year old female
Compound
Spitz Nevus
Lower Extremity

Mitoses:
7 epidermal
6 upper dermis
3 lower dermis

MPM2
Dermal Mitoses

upper half : lower half = 3 : 1
Clinical Parameters

significant: age (<20J >50J)
not significant: sex
not assessed: time of the year
Morphologic Parameters

significant:  
↑ exophytic  
↑ signs of trauma

not significant:  
↑ inflammation  
↓ solar elastosis (age!)
Mitosereichster banaler Naevus

40 year old man, chest

1 epidermal
8 upper dermal
3 lower dermal
What is true? 😃
- Mitoses in banal nevi are rare
- Age dependence
- Increased in traumatized nevi
- Increased in inflamed nevi
- Frequent mitoses in inflammatory cells
- No clusters of mitoses
- Frequent mitoses in Spitz’s nevi

What is wrong? 😞
- No deep dermal mitoses in banal nevi
“The identification of a single mitosis in a banal nevus is not necessarily indicative of melanoma, but is a clear indicator to search for other features to support the diagnosis".