Spindle Cell Melanocytic Tumors

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Conflicts of Interest

• Chairman Scientific Advisory Board – Caliber I.D. Inc.
• Member Scientific Advisory Board – MELA Sciences Inc.
• Consultant – Novartis
• Consultant – Alnylam
**Maturation:**
Reduction in nest size and cell size as base is approached
Classical Spitz nevus: clinical morphology
- characteristically on the face of a child
- recent onset and rapid growth
- dome-shaped papule or nodule
- pink-tan or reddish color
  - becomes brown with diascopy
- epiluminescence microscopy:
  - large globules in light tan background
  - radial streaming in a starburst array

Spitz nevus
- Darier and Civatte (1910): noted that some pigmented childhood lesions were indolent
- Spitz (1948): defined giant cells as predictive of benign outcome in “juvenile melanoma”
- McGovern (1967): coined the term “Spitz nevus”
- other appellations:
  - spindle cell nevus: (Helwig, 1954)
  - epithelioid cell nevus: (Kernan and Ackerman, 1960)
  - spindle and/or epithelioid cell nevus (Paniago-Periera and Maize, 1978)

Spitz nevus: histology
- compound Spitz nevi: 65%
- junctional Spitz nevi: 10%
- dermal Spitz nevi: 25%
  - mainly seen in adults

Spitz nevus: histomorphology
- Architecture:
  - sharply circumscribed dermoepidermal melanocytic proliferation
  - an inverted cone with base parallel to epidermis and apex in reticular dermis
  - large junctional theques separated by cleft-like spaces from hyperplastic epidermis
  - “raining-down” vertical spindled fasicles

Spitz Nevus: Histology
- More common childhood features (especially in first 2 years of life):
  - edema
  - telangiectasia
  - epithelioid cell predominance
  - papillomatosis
  - abrupt maturation – ie – one or two layers at base – common in infancy
CLASSIC SPITZ'S NEVUS: Nest-epidermal dyshesion with cell to cell cohesion

Spitz nevus: cytomorphology

3 cell types:
- ganglion cell
- epithelioid melanocytes:
  - large smooth-contoured nuclei with prominent nucleoli, evenly-distributed chromatin, chromatinic rims of uniform thickness; low N/C ratio
  - abundant eosinophilic cytoplasm; spherical shape
- spindled melanocytes:
  - similar nuclei but fusiform clear to variably pigmented cytoplasms
THE CHARACTERISTIC CYTOMORPHOLOGY OF THE SPITZ’S NEVUS

Spitz nevus: histomorphology

- **Epithelioid**: Nest and cell sizes diminish towards depth of biopsy, where nests break up into single cells with an infiltrative pattern
  - Morphometry confirms diminishing nuclear sizes (Steiner et al., 1994; Bergman et al., 1996)
  - Careful 40X magnification to assess for even scattered small nuclei at base is warranted
  - 500 cubic microns vs 775 in melanoma
- **Spindled**: Mitotic figures
  - Present in 20% of cases
  - Superficial and junctional areas
  - Marginal mitoses (ie within 0.25 mm of lesional edge) prompt concern (McCarthy 1994)
    - >5 per mm² should prompt concern
- **Bizarre ganglion-like cells**: Intravascular proliferations
  - Seen in 14% of childhood Spitz nevi (Howatt and Variend, 1985)

Spitz nevus: Pagetoid spread

- Present to some degree in most cases
  - Prominence in children > adults and in acral > other sites
  - Most prominent centrally near maximal nested junctional component
  - Does not extend at lateral edges past nested component
  - Single cell and nested pattern
  - May involve eccrine/follicular adnexae

Prominent Pagetoid infiltration with epithelioid cytology:
Confined mainly to center of lesion

Practice point:
The epithelioid cytology is more common in childhood but is unusual in adults and may point to a melanoma when present

Classic Spitz Nevus: Maintaining a uniform and benign cytology, cells diminish in size as the base is approached.

Epithelioid

Spindled

Bizarre ganglion-like cells

Practice point:
The epithelioid cytology is more common in childhood but is unusual in adults and may point to a melanoma when present.
Pagetoid spread in this Spitzoid lesion in a 43 year old was a clue to melanoma

Spitz nevus: histomorphology

- Kamino bodies: (Kamino et al., 1979)
  - seen in 60% of all types of Spitz nevi
  - eosinophilic hyalin bodies 30-40 microns
  - PAS-D-positive/trichrome-positive
  - bundles of filaments and basement membrane components derive from either keratinocyte or melanocyte cytosolic shell
  - coalescence/smaller size variably held to suggest melanoma (Weedon, 1984) or benignancy (McCarthy et al., 1994)
Variants of The Spitz’s Nevus

**Plaque-like Spitz nevus**

- Most commonly on thighs of women from 20 to 40 years of age.
- Clinically a plaque up to 1.0 cm in size.
- Color variable, pink, brown to black, or flesh colored.
- Clinical diagnosis usually nevus, ? Atypia; if pink or flesh colored, lichenoid dermatitis or flat wart, respectively.

**Plaque-like Spitz nevus**

- Normal to slightly hyperplastic epidermis
- Prominent intraepidermal nests with sometimes often pagetoid spread.
- Single and small nested melanocytes in dermis of same morphology as in epidermis- mitoses rare.
- Dermal fibrosis common with prominent vessels.
- Minimal melanophages.
Pagetoid Spitz nevus

Busam and Barnhill (1995)

- **clinical features**:
  - pigmented macule < 0.4 cm in young adult

- **histopathology**:
  - single cell-nested Pagetoid array of epithelioid cells showing sharp circumscription
  - cells lack angular nuclei
  - abundant cytoplasm with uniform melanization
  - no dominant dermal nodule

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**Pagets spread phenomenon**

- Melanoma
- Carcinoma
  - Paget’s disease
  - Bowen’s disease
  - Sebaceous carcinoma
  - Merkel cell carcinoma

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**Frequency of Pagetoid Melanocytosis**

<table>
<thead>
<tr>
<th>Type</th>
<th>Percent</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>96</td>
<td>25</td>
</tr>
<tr>
<td>Spitz Nevus</td>
<td>38</td>
<td>47</td>
</tr>
<tr>
<td>Nerves of palms and soles</td>
<td>63</td>
<td>18</td>
</tr>
<tr>
<td>Pigmented spindle cell nerves</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Recurrent nevus</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Vulvar nevus</td>
<td>80</td>
<td>5</td>
</tr>
<tr>
<td>Nevus of infancy and childhood</td>
<td>100*</td>
<td>3</td>
</tr>
<tr>
<td>Ordinarily acquired nevus</td>
<td>none</td>
<td>3</td>
</tr>
</tbody>
</table>

*cases predicted for pagetoid melanocytosis


Kohler S, Rouse RV, Smoller BR, Mod Pathol 11 (1), 1998
Leboit PE, Cratcher WA, Shapiro PE, Am J Surg Pathol 16 (6), 1992
Desmoplastic Spitz nevus

- Clinical features (Reed et al; 1975):
  - presents in adult life as tan or flesh colored nodule <1.0cm
  - extremities, trunk; duration >3 years
  - spares palms and soles
  - differential diagnosis:
    - scar, dermatofibroma, appendage tumor, or desmoplastic melanoma

Desmoplastic Spitz nevus

- Differential diagnosis:
  - other forms of sclerosing nevus, ie:
    - desmoplastic type A nevus
    - desmoplastic combined nevus
    - sclerosing fibrohistiocytic lesion
    - desmoplastic melanoma

Spindle cell nevus

(Reed et al., 1975)

- Clinical features:
  - black or dark dome shaped lesion
  - 2-6 mm in diameter
  - located on proximal extremities or trunk
  - classically young woman (second decade)
  - preferentially on knees + elbows in children
  - 50% on thigh or arm in 1 series (Sagebiel, 1984)
Spindle cell nevus
(Reed et al., 1975)

- Histological features: architecture
  - a superficial plaque-like growth involving epidermis +/- dermis (2/3 compound)
  - vertically oriented spindled cells in retia; horizontal disposition when fused
  - fine papillary dermal collagen present; lamellar fibroplasia usually absent
  - Pagetoid spread common; whole nests classic
  - Inflammation frequent but regression rare

Practice point: spindle cells are uniform in size and shape with uniform nucleolation; spindle cell melanomas show nuclear overlay with higher N/C ratios + pleomorphism
Dysplastic variant of a Spitz’s nevus

- There are atypical nevomelanocytic proliferations which manifest overlap features between a Spitz’s nevus and a dysplastic nevus.
- The cardinal features are a cytomorphology defining that encountered in the Spitz’s nevus in concert with an architecture typical for a dysplastic nevus.
- **The designation:** Dysplastic nevus with overlap cytomorphologic features with a Spitz’s nevus/dysplastic Spitz’s nevus

Spindle / Epithelioid Cell Nevus

Typical

Atypical
Atypical Spitz Nevus

• Superficial expansile nodules
• Asymmetry
• Impaired maturation
• Rare dermal mitosis, especially deep in adults

- These are changes that, as single features, would prompt the diagnosis of “Atypical Spitz Nevus”
Atypical Spitz’s tumor
(Barnhill et al., 1999)
• Subset of Spitzoid melanocytic proliferations with a worrisome histology but indeterminate biologic behaviour
  • architecture resembles VGP melanoma
  • cytology resembles conventional Spitz
  • metastases, when present, tend to confine to regional lymph nodes
• often larger than usual Spitz nevus: >2cm
• clinical appearances otherwise similar to common Spitz’s nevi

Atypical Spitz’s tumor
(Spatz et al, Arch Dermatol 1999)
• Histomorphology divided by a scoring system into low/intermediate and high risk
• Conclusion of study: the only independent prognostic variables were:
  • age > 10 years
  • ulceration
  • involvement of subcutis
  • mitotic rate >6 per square mm
Atypical Spitz’s tumor
(Busam and Barnhill, 1995)

- **Classical Spitz**
  - Size: <1 cm
  - symmetrical
  - sharp demarcation
  - regular nesting
  - absent deep extent
  - absent expansile nodule

- **Atypical Spitz**
  - Size: >1 cm
  - asymmetrical
  - sharp demarcation-ve
  - irregular nesting
  - deep extension
  - expansile nodule present
Criteria to Distinguish Spitz Nevus From Malignant Melanoma

Table derived from:

Spitz Nevus versus Spitzoid Malignant Melanoma: An Evaluation Of the Current Distinguishing Histopathologic Criteria

Walsh N, Crotty K Palmer A, McCarthy S. Human Pathol 29: 1105-1112

Malignant

• Breslow thickness (thicker than 2.0 mm)
• Diameter greater than 1.0 cm
• Asymmetrical
• Marked pagetoid spread, especially in teenagers, of epithelioid cells
• Ulceration (childhood)
• Dermal nests larger than intraepidermal nests
• Marked nuclear hyperchromasia
• Dermal mitosis > 5 mm² (childhood)

Malignant (cont)

• Mitosis in papillary dermis ≥ 4 mm²
• Atypical mitosis
• Marginal mitosis
• Large pigment granules especially in deep nests
• Large distinctly more pleomorphic deep dermal nests

Benign

• Symmetry
• < 1.0cm in diameter
• Sharp circumscription of epidermal components
• Epidermal hyperplasia
• Nests relatively uniform in size and shape
• Small uniform nests toward base
Benign (con’t)

• Single cells at base
• Cells uniform from side to side
• Predominance of spindle cells
• Rare or no mitosis in lower third
• No mitosis at base
• Maturation (diffuse)
• No regression

Spitzoid Melanoma

• Architecture: Dominantly dermal based expansile nodule with variable permeation of the subcutis
• Numerous bizarre appearing giant cells similar to those described in the Spitz nevus but with greater pleomorphism and striking nuclear atypia; the cells assume a confluent sheet like disposition.

• The classic Spitzoid melanoma is seen mainly in the pediatric population most commonly in the head and neck
• The differential diagnosis is primarily the high risk atypical Spitz tumor
• The consensus is that biological behavior is unpredictable
• Longer term follow up may reveal a clinical course no different from other types of melanoma
**Treatment**

- **Spitz nevi and variants**: complete excision with minimal morbidity
- **Atypical Spitz’s tumors**: excision with current melanoma margins. Narrow margins would be inadequate; sentinel node biopsy with high risk lesions greater than 1 mm.
- **Spitzoid melanoma**: conventional melanoma therapy with sentinel node biopsy for lesions greater than 1 mm.

**Childhood Melanoma**

Sites of involvement: Head and neck. Especially scalp when arising in congenital nevi

Dorsal surface favored for lesions arising in congenital nevi

For all types: Head and neck > extremities > trunk > generalized skin
Case:

- 13 year old boy with a “bump” on the scalp for some time that suddenly grew rapidly and ulcerated.
- Clinical Diagnosis: Atypical nevus Vs. Melanoma Vs. Other
- Died within 2 years
Case:
- 13 years-old, female.
- Primary tumor was 2.2 mm thick (Clark level IV, ulcerated, with a mitotic rate of 3 mit./mm²) and located on the foot. Her lymph node was positive at the time of excision.
- Died of metastatic melanoma 2 years later.
Atypical Spindle/Epithelioid Cell Nevus Resembling Childhood Melanoma

Clues for the diagnosis of Melanoma

- Pleomorphism from one area to another at some level
- Deep expansile nodule with monomorphous cells
- Multiple deep and marginal atypical mitosis
- Lack of maturation with individual cell necrosis
- Fine pigment in deep cells

Childhood Melanoma Survival

All patients with metastatic melanoma arising in giant nevi dead within 5 years in study of Trozak et al in 1974

Patients with melanoma arising de novo or in other lesions, including small congenital nevi had 34% survival at 5 years according to Melnick et al

Survival of congenital melanoma poor, >40% dead within 18 months

Spitz nevus versus melanoma

- 102 Spitz nevi studied for 11p copy number increases by FISH; 11p is site of hRAS gene
- 11.8% had at least 3X copy number
- Tumors with 11p copy number larger, more often dermal with desmoplasia, characteristic cytology and an invasive growth pattern
- Sequence analysis of hRAS showed oncogenic mutations in 67% of cases with 11p copy number vs only 5% of tumors with no copy number

Spitz nevus vs melanoma

- Comparative genomic hybridization of 17 Spitz nevi versus melanoma
- 13 Spitz nevi had no chromosomal anomalies
- 3 Spitz nevi had gains of 11p
- 1 Spitz nevus had a gain of 7q21
- Melanomas had deletions of 9p (92%), 10q (63%), 6q (28%), +8p (22%); gains of chromosomes 7 (50%), 8 (34%), 6p (28%), 1q (25%)
Molecular Diagnosis in Nevi and Melanoma

- Fluorescent In Situ Hybridization (FISH)
- Comparative Genomic Hybridization (CGH)

Fluorescence in Situ Hybridization

- Identifies chromosomal copy number aberrations
- Fish probes (short DNA fragments)
- Slide containing 5µm thick paraffin embedded section of tumor (test sample)

Fish probes

- **RREB1, 6p25**: Ras responsive element binding protein 1
- **CEN6**: Centromere 6
- **MYB, 6q23**: v-myb myeloblastosis viral oncogene homologue
- **CCND1, 11q13**: cyclin D1

4 Fish Criteria for Melanoma diagnosis

1. More than 38% of enumerated cells contain >2 signals for CCND1, or
2. More than 55% of nuclei contain more signals for 6p25 than for centromere 6, or
3. More than 40% of nuclei contain fewer signals for MYB than for centromere 6, or
4. More than 29% of cells have >2 RREB1 signals
FISH

• These probes and the diagnostic criteria were developed based on the CGH data of Bastian et al at UCSF
• Validation studies were performed at Northwestern
• Analysis of 86 nevi and 83 melanomas rendered a sensitivity of 86.7% and a specificity of 95.4%

FISH in ambiguous melanocytic lesions

Gaiser et al, Modern Pathol; 2010

• FISH/Clinical Behavior ► 60% sensitivity
  50% specificity

Improved FISH

• 322 tumors, including 152 melanomas and 170 nevi
• A more discriminatory probe set: 9p21, 6p25, 11q13, and 8q24
• Sensitivity of 94%
• Specificity of 98%

Risk Assessment for Atypical Melanocytic Neoplasm

• 75 Atypical Spitz tumors (US & Aus.)
• 64: benign behavior (5 year f/u)
• 11 with metastasis and/or death (3)
• Greater risk: homozygous 9p21 deletion
• High risk: 6p25 or 11q13 gains

*6 cases with isolated 6q23 loss showed no evidence of met or death (96 month f/u)
• 64 cases with benign behavior: 23.4% has a positive FISH result

Comparative Genomic Hybridization (CGH)

- Chromosomal CGH: when the test and normal DNA is hybridized to metaphase chromosomes
- Array CGH: hybridization to DNA microarrays
- CGH represents the first efficient approach to scanning the entire genome for variations in DNA copy numbers


- 96% of 132 melanomas had chromosomal copy number aberrations
  - Gains in 6p, 1q, 7p, 7q, 8q, 17q, 11q, and 20q
  - Losses in 9p, 9q, 10p, 10q, and 6q
- 13% of all nevi evaluated (54) showed the same gain in 11p ▶ Spitz nevi

Gaiser et al, Modern Pathol;2010

- Fish results compared with CGH and long-term clinical follow up in 22 melanocytic proliferations, 12 of which were ambiguous lesions.
- FISH/Clinical Behavior ▶ 60% sensitivity
  - 50% specificity
- CGH/Clinical Behavior ▶ Lesions that metastasized showed significantly more chromosomal aberrations

Molecular tests in Pigmented Lesions: Conclusion

"Correlation between precise molecular attributes and exacting histomorphology is in its infancy"

Tim McCalmont et al
J Cutan Pathol, 2011

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