Pathogenesis and Comparison of Atypical Spitz Nevi vs Benign Spitz, and Childhood Melanoma

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Conflict of Interest

- Chairman Scientific Advisory Board – Caliber I.D. Inc.
- Member Scientific Advisory Board – MELA Sciences Inc.
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: Histomorphology

- Architecture:
  - Sharply circumscribed dermoeidermal 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 fascicles
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

Pagets spread phenomenon

Melanoma

Carcinoma

- Paget's disease
- Bowen's disease
- Sebaceous carcinoma
- Merkel cell carcinoma

Kohler S, Roux RV, Smoller BR, Mod Pathol 11 (1), 1998
Leboit PE, Crighton WA, Shapiro PE, AM J Surg Pathol 16 (6), 1992
### Frequency of Pagetoid Melanocytosis

<table>
<thead>
<tr>
<th></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>Nevus of palms and soles</td>
<td>61</td>
<td>18</td>
</tr>
<tr>
<td>Pigmented spindle cell nevus</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


### Spindle cell nevus

(Reed et al., 1975)

- **Clinical features:**
  - black or dark plaque, sometimes 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)

- **Histological features:** architecture
  - Superficial plaque-like growth involving epidermis+/−dermis (2/3 compound)
  - Vertically oriented spindled cells in rete; horizontal disposition when fused
  - Fine papillary dermal collagen present; lamellar fibroplasia usually absent
  - Pagetoid spread common; whole nests classic
  - Inflammation frequent but regression rare
Atypical Spitz tumor
(Spatz et al, Arch Dermatol 1999)

- Histomorphologically 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 tumor
(Busam and Barnhill, 1995)

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

- **Atyp. Spitz Tumor**
  - Size: >1 cm
  - asymmetrical
  - poor demarcation
  - irregular nesting
  - deep extension
  - expansile nodule present

Spitzoid Melanoma

- 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

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.
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HMB45

Ki67

12
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 for high risk lesions.
- **Spitzoid melanoma**: conventional melanoma therapy with sentinel node biopsy for lesions greater than 1 mm

**Spitz nevi 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 ↑

**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
- More recent studies emphasized extremities and trunk
Childhood Melanoma.

General considerations.
• Melanoma in patients less than 20 years of age account for 1.2 to 2% of all cutaneous melanomas.
• Melanomas in prepuberal children comprise 0.3 to 0.4% of cutaneous melanomas.
• Thirty three per cent of prepuberal melanomas arise in giant congenital nevi, with 50% reported in the first decade of life.
• A study of SEER Database reveals 44 to 65% in tumors in young melanoma patients, diagnosed as histologically as tumor of uncertain prognosis or borderline lesions.

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. 1986.
• Survival of congenital melanoma poor, > 40% dead within 18 months.

Childhood Melanoma

Risk Factors.
• Dysplastic nevus syndrome.
• Xeroderma pigmentosum.
• Giant congenital nevus. (Bathing trunk nevus)
**Figure 1.** History of melanoma in one family.

Saenz et al. 1999, Cancer.

**Figure 2.** Survival distribution of patients according to tumor thickness is shown.

Saenz et al. 1999, Cancer.
Childhood Melanoma.

Case #1
- 13 years-old, female.
- Primary tumor was 2.2 mm thick (Clark level IV, ulcerated, with a mitotic rate of 3 mit./mm^2) and located on the foot. Her lymph node was positive at the time of excision.
- Died of metastatic melanoma 2 years later.
Childhood Melanoma.

- Case #2:
  - Eleven year old boy.
  - Followed for two years as benign lesion.
  - 23 mitoses in 10 HPF.
  - Level 5, >7mm.
  - 12 of 23 lymph nodes positive.
  - Died within 16 months.
Childhood Melanoma.

- **Case #3:**
  - Seven year old girl.
  - Lesion on lower leg, diagnosed as Spitz nevus.
  - Level V, marginal mitoses.
  - First metastasized at age of 11 to inguinal lymph nodes.
  - Died of systemic metastasis at age 16.
Childhood Melanoma.

- **Case #4:**
  - Thirteen year old boy.
  - Large nodular mass on scalp.
  - Massive posterior cervical lymph node involvement.
  - Died 6 months after.
Childhood Melanoma.

Features associated with death:
- Large bulky lesions usually deeply invasive.
- Ulceration.
- Necrosis.
- Severe pleomorphism.
- Numerous dermal and marginal mitoses.
- Intravascular invasion.
- Multiple positive lymph nodes in draining basin.
- Deeply invasive small cell melanomas of scalp (Barnhill et al., Cancer, 1995.)
Acknowledgments

• Klaus Busam MD
• Kerry Crotty MD
• Harry Kozakewich MD
• Adriano Piris MD
• Nicolas Prieto MD
• Victor Prieto MD
• Cecilia Lezcano MD
• Richard Scolyer MD

THANK YOU