Spitz nevus

- Until the late 1940s, Spitz nevus was commonly diagnosed as melanoma
- The original term used by S. Spitz was „juvenile melanoma”
- A variety of other names have been proposed (spindled and epitheloid cell nevus)
- Spitz nevus came into use in the late 1960

Mainly in caucasian
- Most Spitz nevi are diagnosed in childhood and adolescence
- No marked sex preponderance (female > male?)

<table>
<thead>
<tr>
<th>Site</th>
<th>All skin and some mucous membranes; preferred site are face, ear in childhood; extremities and trunk in adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Generally under 1 cm, but exceptional reported cases up to several centimeters</td>
</tr>
<tr>
<td>Shape</td>
<td>Symmetrical, papillomatous or smooth dome shaped</td>
</tr>
<tr>
<td>Color</td>
<td>Skin colored, reddish or light brown; rarely dark brown</td>
</tr>
<tr>
<td>Variants</td>
<td>Multiple, pruritic, combined with congenital nevus</td>
</tr>
</tbody>
</table>

Pathology of Melanocytic disorders. WJ Mooi and T Krausz 2nd edition
Histological features

- Symmetrical
- Proliferation of large epitheloid or spindle shaped melanocytes
- Spindel cells tend to be vertically oriented
- Shrinkage artifacts with clefs between the cells and around the cells
- Infiltrative growth at the base
- Kamino bodies
- Associated epidermal hyperplasia

Spitz Nevus/Tumor and variants

- Spitz nevus: junctional, compound, dermal
- Desmoplastic Spitz nevus
- Pigmented spindle cell nevus
- Plexiform pigmented spindle cell nevus
- Spitz nevus, halo variant
- Recurrent Spitz nevus
- Spitz tumor with atypical features
  - Pagetoid Spitz nevus/tumor
  - Spitz nevus/tumor with architectural disorder and cytologic atypia
- Spitz nevus/tumor with atypical features and indeterminate biological potential (STUMP „Spitzoid tumor of uncertain malignant potential“)
- „Spitzoid melanoma“
  
Adv Anat Pathol 2010, 17:73

Special techniques

- Immunohistochemistry
  - HMB-45
  - Ki67 (MIB1)
  - P53
  - p16
  - E-Cadherin
  - Cyclin D1

- Molecular biology
  - BRAF
  - H-RAS
  - N-RAS

- DNA gain/loss
  - Aneuploidy
  - CGH
  - FISH

RESULTS

- Cyclin D1: no statistical significant differences
- E-Cadherin: subtle and focal qualitative differences
- p16: dermal p16 was the best discriminator

Immunohistochemical Evaluation of p16INK4A, E-Cadherin, and Cyclin D1 Expression in Melanoma and Spitz Tumors

Evan George, MD, Noyok L. Peltzer, PhD, and Mark Wood, MD

Am J Clin Pathol 2010, 133:370-379
E-Cadherin

Spitz

Melanoma

p16

Spitz

Melanoma

Molecular biology

Cell survival

Cell proliferation

N-Ras

H-Ras

Blokx WAM. Histopathology 2010, 56:121-132

Copy number increase of 11p in 20% Spitz nevi

Bastian BC. J Invest dermatol 1999, 113:1065

Bastian BC. Am J pathol 2000, 157:967-972

Frequencies of mutations

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>BRAF</th>
<th>NRAS</th>
<th>HRAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common acquired nevus</td>
<td>Up to 87%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Dysplastic or atypical nevus</td>
<td>52-62%</td>
<td>Up to 71%</td>
<td>0%</td>
</tr>
<tr>
<td>Blue nevus</td>
<td>0-12%</td>
<td>0%</td>
<td>ND</td>
</tr>
<tr>
<td>Spitz nevus</td>
<td>0%</td>
<td>0%</td>
<td>Up to 29%</td>
</tr>
<tr>
<td>Congenital nevus</td>
<td>30-88%</td>
<td>64%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Chromosomal gains or losses

Bastian BC. J Invest dermatol 1999, 113:1065
Bastian BC. Am J pathol 2000, 157:967-972
Chromosomal gains or losses

<table>
<thead>
<tr>
<th>Melanoma subtype</th>
<th>BRAF mutation</th>
<th>NRAS mutation</th>
<th>Chromosomal aberrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin MC6</td>
<td>99%</td>
<td>22%</td>
<td>Increased copy no: 6p, 7q, 17q, 20q</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduced copy no: 9p, 10q, 21q</td>
</tr>
<tr>
<td>Skin CSD</td>
<td>11%</td>
<td>15%</td>
<td>Increased copy no: 6p, 7q, 17q, 20q</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduced copy no: 9p, 10q, 21q</td>
</tr>
<tr>
<td>Mucosal</td>
<td>11%</td>
<td>5%</td>
<td>Increased copy no: 1q, 6q, 7q, 11q, 17q, 20q</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduced copy no: 4q, 6q, 8q, 9p, 10, 11p, 17q, 21q</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amplification: 1q13, 4p12, 12q14</td>
</tr>
<tr>
<td>Acral</td>
<td>23%</td>
<td>10%</td>
<td>Increased copy no: 6p, 7q, 17q, 20q</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduced copy no: 6q, 9p, 10, 11q, 21q</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amplification: 5p15, 5p13, 11q, 12q14</td>
</tr>
</tbody>
</table>

Melanoma FISH assay

FISH and SPITZ

- In a series of ambiguous cases with long-term clinical follow-up (about five years), Gaiser and colleagues were able to investigate three cases with FISH. One Spitz nevus with a FISH+ status and one Spitz nevus with a FISH- status had a benign follow-up, whereas one FISH- Spitz nevus was found in a patient with malignant evolution.

- In a second study, on a large series of 41 definitely diagnosed Spitz nevi with a median follow up of two years, Isaac and colleagues identified a FISH+ profile in four cases (10%), three of which were from the same patient. The authors hypothesised that the FISH+ profile in Spitz nevi reflected a polyploid state rather than true clonal aberrations, as is the case in malignant tumours, and they confirmed and supported this thought by the detection of chromosome X polysomy in all cases.

Conclusions

- The presence of gene copy number changes in Spitz nevi as detected by FISH analysis with probes targeting 6p25, 6q23, CEP 6, and 11q13 is higher than expected.
- The presence of cytogenetic abnormalities in Spitz nevi may not be solely explained by a polyploid state.
- FISH- or FISH+/POLY+ Spitz nevi are most likely "true" benign lesions, whereas additional studies are warranted to clarify the biological significance of Spitz nevi bearing gene amplifications or a FISH+/POLY- profile.

Proposal for diagnostic algorithm

- Clinical findings (features worrisome for melanoma?)
- Histological findings (Consult with experienced colleagues)
- Uncertainty persists
- Poly- Complex abnormalities
- Manage as melanoma? HRAS, BRAF, NRAS?
- Poly +
- FISH pos
- FISH neg
- Spitz nevus
- Spitz nevus, most likely

Patient 1

- 12 years old boy, scalp, diameter 1 cm
- Ulceration
- > 6 mitoses
- FISH neg.

Spitz nevus
Patient 2

- 29 years old man, right knee, diameter 0.8 cm

FISH pos.
Favor Melanoma
Cohesive, mitosis