The Relevance of Cytologic Atypia in Cutaneous Neural Tumors

Recent Findings - New Developments – New Problems

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Biologic Spectrum of Cutaneous Neural Tumors

- **Benign**
  - De novo MPNST
  - Ex-plexiform neurofibromas
  - Diffuse neurofibromas
  - Schwannomas
  - Granular cell tumors

- **Atypical**
- **Malignant**
Cardinal Features of Malignant Peripheral Nerve Sheath Tumors

- Size
- Necrosis
- Mitotic rate
- Cellularity
- Atypia
Growing Number of Cases With Atypia Alone

What is the relevance of cytologic atypia in these tumors?

- reactive changes?
- borderline tumors?
- low grade malignancy?

Very limited studies to determine outcomes
Growing Spectrum of Atypical Cutaneous Neural Tumors

“What constitutes atypia” in these tumors?

1. Cytologic deviation from normal cell types
   - epithelioid
   - pleomorphic
   - multinucleated cells
2. Nuclear atypia
3. Mitotic atypia
4. Cellularity
5. Growth pattern
The Most Common Cutaneous Neural Tumors With Atypia

1. Neurofibromas
2. Schwannomas
3. Neurothekeomas
Atypia in Neurofibromas
Atypical Neurofibroma
Differential Diagnosis

- Malignant peripheral nerve sheath tumor
- Pleomorphic liposarcoma
- Pleomorphic lipoma
- Myxoid MFH
- Cellular Schwannoma
- Cellular dermatofibroma
Relevance of Atypia Cutaneous Neurofibromatosis

• Important distinctions:
  – Plexiform type → high association with NF-1
  – Solitary, sporadic type; benign subtype or malignant?

• Prior studies:
  – predominantly superficial soft tissues
Neurofibroma and Cellular Neurofibroma With Atypia

- 14 cases of 6 patients, mean age 40, F:M = 2:1
- Head (5), trunk (5) and extremities (4)
- 3 patients with type I neurofibromatosis
- Benign behavior (limited F/U)
Neurofibroma and Cellular Neurofibroma with Atypia

Histopathologic features

- Usual growth pattern of neurofibromas
- Mild to severe cytologic atypia, nuclear enlargement, hyperchromasia, bizarre giant cells
- Mitotic activity $1 < 10$ HPF (3 cases) or absent
- Degenerative changes
- Focal hypercellularity (3 cases)
- Lack of necrosis
- Low p53, Ki-67, and S-phase values as compared to MPNST
Atypical Neurofibromoma of the Skin

Clinical Data

• 11 cases, 80% females, 20% males
  – Age range 8-70, mean
• Predominantly trunk
• 1 patient with NF
• No history of PMNST
Atypical Neurofibromas of the Skin

**Pathology**

- Dermis/superficial subcutis
- Growth type: fibrillary and lamellar
- Cellularity: mild to moderate
- Cytologic atypia (5-50% of cellularity)
- Pleomorphic cells
- Mitotic figures:
  - Absent 9/11
  - Present 2/11
- No necrosis
# Atypical Neurofibromas of the Skin

## Immunohistochemistry

<table>
<thead>
<tr>
<th>Case number</th>
<th>S-100 protein</th>
<th>p16</th>
<th>p53</th>
<th>MIB-1</th>
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<th>EMA</th>
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<td>+(P)</td>
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<tr>
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<td>+++</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>
Cutaneous Atypical Neurofibroma

Clinical Outcome

- No tumor recurrence
- No new malignancy
- Follow-up range 6 – 63 months
  (mean: 33 months)
Atypical Neurofibroma

Conclusions

• Distinct subset of neurofibromas.
• The designation should be better accepted.
• Atypia could be analogous to lesions in:
  – Ancient Schwannomas with degenerative changes
  – Cellular Schwannomas with limited mitotic activity
• Cytologic atypia alone in NF does not appear to be associated with Neurofibromatosis type-1
• There is no apparent short term risk for recurrence or malignancy.
• Awareness of atypia helps better patient management
• These lesions can be treated conservatively.
Problematic Aspects of Atypical, “Cellular Schwannomas”

1. The diagnostic criteria are still disputed → difficult to apply for cutaneous lesions.
2. Confusing terminology for cutaneous lesions → unclear biologic potential.
3. Expanded differential diagnosis in the skin → malignant melanoma.
Cellular Schwannoma

The term was coined by Woodruff in 1981

Synonyms: atypical Schwannoma (Reed)
cellular Schwannoma (Woodruff)
transformed Schwannoma (Reed)
low-grade malignant Schwannoma (Ducatman)
Cellular Schwannoma

General features

1. Affect mainly females.
2. Tumors of the deep soft tissue (mediastinum, pelvis).
3. Association with NF-1 less than 5%.
4. Evolving histologic criteria.
5. Considered benign.
6. Cutaneous involvement is rare.
Cutaneous Cellular Schwannomas

The Spectrum of Cutaneous Schwannomas

- Common Type
- Ancient
- Malignant
- Cellular
- Epitheloid
Cellular Schwannoma (deep soft tissue type)

Key Histopathologic Features

- Well circumscribed
- Nodular
- Hypercellular (Antoni A-Type)
- Fascicles and whorls
- Hyperchromasia
- Spindled atypical nuclei
- Mitotic rate < 4/10 HPF (depending on authors)
- Thick-walled vessels
- Lymphoid aggregates in the wall of the capsule
- Diffuse, strong S-100 protein expression
Histopathologic Spectrum of “Cellular Schwannomas” in the cutaneous literature

<table>
<thead>
<tr>
<th>Feature</th>
<th>“Atypical”</th>
<th>“Cellular”</th>
<th>“Transformed”</th>
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</thead>
<tbody>
<tr>
<td>Hypercellularity</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Interlacing fascicles</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Storiform pattern</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Hyperchromatism</td>
<td>+/-</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>&lt;2/10 HPF</td>
<td>2-10/10 HPF</td>
<td>&gt;10/10 HPF</td>
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<tr>
<td>Stellate necrosis</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Nuclear palisading</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Verocay bodies</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lymphoid follicles</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Epithelioid cells</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Lipid laden histiocytes</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Cutaneous Cellular Schwannoma

Differential Diagnosis

- Malignant peripheral nerve sheath tumor (MPNST)
- Malignant melanoma (primary or metastatic) (broad panel of immunohistochemistry, electron microscopy, clinico-pathologic correlation)
- Leiomyosarcoma (growth pattern + immunohistochemistry)
- “Benign imitators” ; ancient, epitheloid schwannomas, angiomyomas, neuromas
Cutaneous Cellular Schwannoma

“Benign Imitators”

- Ancient Schwannoma
- Epitheloid Schwannoma
- Palisaded Encapsulated Neuroma
- Epitheloid Angiomyoma
# Differential Diagnosis of Schwannomas with Atypia

<table>
<thead>
<tr>
<th></th>
<th>Epithelioid</th>
<th>Cellular</th>
<th>MPNST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth Pattern</strong></td>
<td>nodular, oblong</td>
<td>nodular, oblong</td>
<td>variable</td>
</tr>
<tr>
<td><strong>Encapsulation</strong></td>
<td>usually present</td>
<td>well-preserved</td>
<td>partial → infiltrative</td>
</tr>
<tr>
<td><strong>Cellularity</strong></td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Architecture</strong></td>
<td>trabecular, nodular, syncytial, myxoid</td>
<td>fascicular</td>
<td>fascicular “herring bone”</td>
</tr>
<tr>
<td><strong>Cell Type</strong></td>
<td><em>epitheloid</em> with or without spindled cells</td>
<td><em>spindled</em> cells</td>
<td>spindled or pleomorphic</td>
</tr>
<tr>
<td><strong>Atypia</strong></td>
<td>mild</td>
<td>moderate</td>
<td>moderate to severe</td>
</tr>
<tr>
<td><strong>Mitotic Rate</strong></td>
<td>&lt; 1/10 HPF</td>
<td>&lt; 4/10 HPF</td>
<td>&gt; 4/10 HPF</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td>none</td>
<td>none or very focal</td>
<td>geographic</td>
</tr>
<tr>
<td><strong>Vascularity</strong></td>
<td>focal mild</td>
<td>focal, prominent</td>
<td>not characteristic</td>
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<tr>
<td><strong>Lymphoid Infiltrate</strong></td>
<td>variable</td>
<td>patchy aggregates</td>
<td>not characteristic</td>
</tr>
</tbody>
</table>
Conclusions

1. No comprehensive studies on cutaneous cellular schwannoma and MPNST
2. Application of diagnostic criteria is often “arbitrary”
3. Important differential diagnostic challenge (melanoma vs. MPNST)
Cellular Neurothekeoma

- Entity described in 1986 by Rosati et al.
- Well-established clinico-pathologic features.
- Controversial histogenesis; neural vs. other
- Synonyms: cellular nerve sheath myxoma
  - immature nerve sheath myxoma
  - “epithelioid” nerve sheath myxoma
- and a plethora of others....
- Recently recognized atypical variants
Cellular Neurothekeoma

Histologic Features

1. Dermal/subcutaneous tumor
2. Multi-lobular or fascicular growth
3. Not encapsulated
4. Scant mucin
5. Epithelioid or spindle cells
6. Characteristic nuclei
7. Rare mitotic figures
8. Heterogeneity of cell components can occur
Cellular Neurothekeoma
Atypical (♀ malignant variants)

- **Atypical variants** (Busam et al. 1998)
  - **Clinical**
    - 10 patients
    - Median age 20.5 years
    - Head and neck
  - **Pathological**
    - Large size
    - Deep penetration
    - Diffusely infiltrative borders
    - Vascular invasion
    - “Marked” cytologic atypia
    - Mitotic rate > 5/10 HPF
  - **Follow up**
    - (1-5 years) - no recurrence

- **Additional Cases:**
  - Bhatia et al. 2003
  - Benbenisty et al. 2006 (advocating Mohs surgery)
Atypical Neurothekeoma
Additional observations; Hornick and Fletcher, 2007

- Clinical follow-up on 69 cases with the mean F/U of 44 mo. showed recurrence of 10 cases.

- Atypical morphologic features of 133 cases;
  - size>2cm (10%), mitosis >5/10HPF (21%), pleomorphism (25%), infiltration of fat (25%) were too common to represent increased risk for local recurrence.

**Conclusions:**
Only head and neck location and incomplete surgical excision correlated with recurrence.
Cellular Neurothekeoma
Practical Conclusions

• CNT has distinct enough clinical and pathological features to accept as a distinct entity, with the notion that the histogenesis is still uncertain.
• Atypical variants are reported more often than original studies indicated.
• Currently there are somewhat contradicting data regarding the significance of atypia in Cellular Neurothekeomas.
• Considering the uncertain biologic potential a cautious clinical approach with adequate excision seems prudent.
The Relevance of Atypia in Cutaneous Neural Tumors

Conclusions

- Recognition of several new morphologic subtypes.
- Biologic potential has not been fully established yet.
- Most of the atypical variants without other morphologic features of malignancy follows a benign or indolent behavior.
- Familiarity with these new variants remains important for better patient management.