Evolving Concepts of Cutaneous Neural Tumors with Mixed Differentiation

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Cutaneous Neural Tumors

- New variants → More confusion
- Recognition vs. Reinvention vs. Splitting?
- Semantic issues vs. Relevance
- Morphologic entities without established clinical features

Nostalgic slide from 10 years ago
Where do we see the changes?

1) Well-established entities with new information
   e.g.: atypical neurofibroma, cellular Schwannoma

2) Recently established entities with new developments, e.g.: cellular neurothekeoma, soft tissue perineurioma

3) New observations on evolving entities
   e.g.: epithelial sheath neuroma, dendritic neurofibroma

Nostalgic slide from 10 years ago
Classification of CUTANEOUS NEURAL TUMORS

Tumors of the peripheral nerves

Hamartomatous neural tumors

Neuromas
  - Traumatic
  - Encapsulated

Neurofibroma

True nerve sheath tumors

1) Schwannoma
2) Nerve sheath myxoma
3) Granular cell tumor
4) Malignant nerve sheath neoplasms

Tumors of ectopic or heterotopic neural tissue

1) Nasal glioma
2) Extracranial meningioma
3) Neuroectodermal tumors
   a) undifferentiated:
      - peripheral neuroepithelioma
   b) differentiated:
      - neuroganglioma
Peripheral Nerve Sheath Tumors (and Mimics) outside of the conventional classification (A)

1) Disputed Histogenesis
   • Granular cell tumor
   • Cellular neurothekeoma
   • Morton’s neuroma (interdigital neuritis)
   • Epithelial sheath neuroma
   • Lipoblastic nerve sheath tumor
   • Ganglion cell choristoma
Peripheral Nerve Sheath Tumors outside of the conventional classification (B)

2) Tumors with composite cell types or mixed growth patterns

A. Distinct separate components
   a) Neurofibroma and perineurioma
   b) Schwannoma and perineurioma
   c) Schwannoma and granular cell tumor
   d) Schwannomma and neurofibroma

B. Hybrid components
   a) Neurofibroma and perineurioma
   b) Schwannoma and perineurioma
   c) Granular cell tumor and perineurioma
   d) Granular cell tumor and neurothekeoma
Historical Background

1) Traditional classification of peripheral neural tumors (Virchow).
2) Description and further classification with subtypes (P. Masson).
3) Ultrastructural and immunohistochemical characteristics of classical types.
4) Expanding spectrum of peripheral nerve sheath tumor beyond the classical types.
Historical Observations and Studies

1) Pierre Masson
2) Richard Reed
3) Jurecka
4) Fletcher/Feany
5) Michal
6) Kazakov
7) Others…
Neural tumors with composite or “biphasic” growth patterns


Summary

• 9 cases
• Adults, males, trunk, extremities
• Only 2 in the dermis, 7 in subcutis
• Neurofibroma with focal schwannomatous areas (Antoni A type)
• 5 cases had plexiform pattern
• S100 protein & neurofilaments
• EMA positive in capsule
Neural tumors with composite or “biphasic” growth patterns


**Summary**

- 8 cases out of 99 neurofibromas
- Adults, females > males, trunk and extremities
- 5/8 cutaneous
- 1/8 plexiform
- Lamellar, fascicular, whorls
- Bipolar cells
- EMA, CD34 +
- Admixed with S100 protein positive cells
Schwannoma and Perineurioma


Summary

• 6 cases, adults, women > men
• All tumors on fingers and hands
• No history of neurofibromatosis
• Non-encapsulated
• Multilobular with myxoid and pseudocystic changes
• Distinct separation
• Schwannomatous: S100 +, CD34 -, EMA –
• Perineuriomatous: S100 -, CD34 +, EMA +
• Benign
From “A benign neoplasm with histopathological features of both schwannoma and retiform perineurioma (benign schwannoma-perineurioma)” by Michal Michal, Dimitry V. Kazakov, et al., ADP (2005).
Composite Neural tumors with mixed pattern (true hybrid tumors)


Summary

- 3 cases, adults, women
- Trunk, extremities
- No neurofibromatosis
- Schwannoma and perineurioma
- Neurofibroma and perineurioma
- Intimate mixture of various elements
- One case had point mutation for NF2 gene
- Recognizable mainly by immunohistochemistry
Mixed differentiation in “Atypical neurofibroma”


Summary

• 11 cases with atypical neurofibromas, female
• Extremities, trunk
• Fibrillar and lamellar patterns
• Lamellar pattern had distinct EMA expression
• Hypercellular, pleomorphic cells
• Rare mitosis
• No recurrence
Hybrid Schwannoma and Perineurioma


**Summary**

- 42 cases, adult, male: female = 1:1
- Extremities, trunk
- Subcutis > Dermis
- Well-circumscribed, but non encapsulated
- Storiform, lamellar, whorled patterns
- Spindled and bipolar cells
- Degenerative atypia
- Low mitotic rate
- S-100, EMA, CD34, GFAP, claudin +
- 60% Schwann cells 30% perineurial cells
- Short follow-up, no recurrence
Other rare cutaneous Neural Hybrid Tumors

Other rare cutaneous putative Neural Hybrid Tumors

Cellular Schwannomma with Neuromatous features
S100 protein
# Differential Diagnosis of Hybrid and Composite Neural Tumors


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<th>SC/NF</th>
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<td>CD21/CD 35</td>
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<td>Cytogenetic abnormalities</td>
<td>22q11-q13.1; loss of Cr 13; 10q24 (SP)</td>
<td>22q12 (SC); 17q11.2 (NF)</td>
<td>17q24-17; 7p22; Xq26; 13p; 11q22; 9p22, others</td>
<td>t(6;8), t(8;22), +7 (p15)</td>
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Morphologic and Biologic ground of Hybrid and Composite Peripheral Nerve Sheath Tumors

Morphologic and Biologic ground of Hybrid and Composite Peripheral Nerve Sheath Tumors

1) Peripheral nerve sheath components represent an embryonically determined histologic unit of cells.

2) These cells capable of facultative differentiation to each other.

3) The combination of facultative differentiation and clonal proliferation of specific cells can create hybrid tumors.
Peripheral Nerve Sheath Tumors outside of the conventional classification (B)

2) Tumors with composite cell types or mixed growth patterns

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   d) Granular cell tumor and neurothekeoma
Things to consider

- The combination of new variants are endless.
- Represents a classification problem when using the traditional system.
- The more ancillary studies is used, the more complicated is the classification.
- Are these subtypes are true entities or just variation of the same themes?
- Does this make a real difference in patient management or just fancy terms?
Conclusions

1) Rare tumors, which are difficult to recognize on routine histopathology.

2) Although they can occur in the skin, they are mainly subcutaneous or in the deeper soft tissues.

3) Their recognition requires familiarity about their features and appropriate use of immunohistochemistry.

4) Currently they are considered benign tumors, but atypical variants are described.

5) Their classification present a conceptual challenge and likely will modify our current nomenclature.

6) Molecular biologic studies needed to better understand their complex histories.
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