Cellular Neurothekeoma

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Clinical

- Predilection for the upper limbs and head and neck
- Young female pts (mean 25 years)
- Present as solitary, superficial, slow-growing painless nodules or masses
- Mean tumor size: 1.1 cm (range 0.3-2.0 cm)
- Behave in a benign fashion and rarely recur, if incompletely excised (3.3%)
Typical histological appearance

Non-encapsulated, lobulated or micronodular architecture
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Nests and bundles of epithelioid to spindled cells with palely eosinophilic cytoplasm

Background of dense hyaline collagen

Mitotic rate: 3/10 HPF

Sometimes have atypical features: scattered pleomorphic cells, infiltrative growth into fat or skeletal muscle, vascular invasion, perineural invasion, and high mitotic rate (>10/HPF)

Mild cytologic atypia with nuclear variability and small nucleoli

Background of dense hyaline collagen

Immunohistochemical Profile

- Positive NKI/C3 (100%)
- NSE (66-89%)
- CD10 (97-100%)
- MITF (81-100%)

Immunohistochemical Profile

- S100A6 (95-100%)
- PGP9.5 (60%)
- Focal SMA (20-57%)

CD68 (50-59%)

**All negative for S-100 (100%)**
Molecular studies

- Of probable fibrohistiocytic origin based on microarray-based gene expression profile studies done in our institution (2010)

Principal component analysis using 452 differentially expressed genes between neurothekeomas and nerve sheath myxomas demonstrates one major group composed of schwannomas and nerve sheath myxomas and another major group composed of neurothekeomas and cellular fibrous histiocytomas (>threefold change; P-value <0.005).

Histologic overview of variants

myofibroma-like variant  xanthomatous variant  chondroid-like variant

diffuse variant with abundant inflammation  epithelioid variant  granular cell variant
Myofibroma-like variant

- Nests of cells
- Fibrotic dermis
- Dome-shaped proliferation

Hyalinized fibroblastic tissue separates nests

Tumor cells are cytologically bland with round to oval nuclei

Cells that demonstrate an unusual "blue tinged" cytoplasmic hue
Xanthomatous Variant

- Fibrotic dermis
- Dome-shaped proliferation
- Hyalinized fibroblastic tissue separates nests
- Clear cells with foamy cytoplasm
- Tumor cells are cytologically bland with round to oval nuclei
Tumor cells are bland

low mitotic index

xanthomatous-like cells

Diffuse Variant with Inflammation

Case 1

Case 2
Diffuse with Inflammation #1

Fibrotic dermis

Diffuse proliferation

Tumor cells are cytologically bland with a fibrohistiocytic appearance

Hyalinized stroma

Eosinophils and lymphocytes
Diffuse with Inflammation #2

- Lymphocytic infiltrate
- Proliferation of spindle and epithelioid cells
- Lymphoid infiltrate
- Pale histiocytoid and spindle cells
Granular cell variant

- Granular cell NK
- Non-neural Granular Cell Tumor

Granular cell variant

- Hyalinized collagen bundles
- Dome-shaped proliferation
No nuclear pleomorphism

Hyalinized background stroma

Low mitotic index

Bland epithelioid cells with granular cytoplasm
NNGCT (Non-neural granular cell tumor)

- Low mitotic index
- No nuclear pleomorphism
Bland epithelioid cells with granular cytoplasm

Table 1. Characteristics and immunohistochemical profile of cellular neurothekeomas and variants

<table>
<thead>
<tr>
<th>Case</th>
<th>Location</th>
<th>Age (years)</th>
<th>S100</th>
<th>NK1/C3</th>
<th>PGF9.5</th>
<th>MIF</th>
<th>NSE</th>
<th>Factor 13a</th>
<th>CD68</th>
<th>CD163</th>
<th>CD10</th>
<th>SMA</th>
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</thead>
<tbody>
<tr>
<td>Typical NK* neurothekeoma-like variant</td>
<td>Upper arm</td>
<td>39</td>
<td>+</td>
<td>+</td>
<td>n/a</td>
<td>+</td>
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<td>n/a</td>
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<tr>
<td>Xanthomatous variant</td>
<td>Face</td>
<td>29</td>
<td>n/a</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>n/a</td>
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<td>Chronic/scar-like variant</td>
<td>Back</td>
<td>32</td>
<td>-</td>
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<tr>
<td>Diffuse with inflammation variant (2 cases)</td>
<td>Ear</td>
<td>23</td>
<td>-</td>
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<tr>
<td>Epithelioid variant (2 cases)</td>
<td>Verrucous-like</td>
<td>37</td>
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<td>Granular variant</td>
<td>Head &amp; neck</td>
<td>21</td>
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<td>Non-neural granular cell tumor</td>
<td>Forehead</td>
<td>46</td>
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</table>

* NK= Neurothekeoma
Molecular Findings

- 54 genes in common between NK and variants.
- Most of these genes are expressed by fibroblasts or macrophages, pointing to their similar fibrohistiocytic origin.
  - fibroblast growth factor 5, platelet-derived growth factor receptor-like, platelet-derived growth factor receptor, alpha polypeptide, platelet-derived growth factor D, chemokine (C-C motif) ligand 13, beta 5 integrin, lysyl oxidase, collagen type X alpha 1

Conclusions

- Variants of cellular NK with bland cytologic features exist (we note 6 different variants)
  - myofibroma-like variant
  - xanthomatous variant
  - chondroid-like variant
  - diffuse variant with abundant inflammation
  - epithelioid variant
  - granular cell variant
Conclusions

- These variants of cellular NK are closer to a fibrohistiocytic origin than a neural one
- Immunohistochemical stains are important in diagnosing these variants as they are morphologically different from the typical cellular NK, although their IHC pattern is the same (always S100 negative; NKI/C3 positive, and usually at least focally positive for NSE and MITF)
- NNGCT is molecularly different from the granular variant of cellular NK
- This study is limited by the small sample size of each of the variants.
- More samples of each of the variants is required in order to accurately investigate their molecular characteristics

References