DENDRITIC CELL NEOPLASMS: HISTOLOGY, IMMUNOHISTOCHEMISTRY, AND MOLECULAR GENETICS

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Dr. Jason Hornick declares he has no conflicts of interest

Origin of histiocytic and dendritic cell tumors

BONE MARROW
- MYELOID PRECURSOR
  - monocyte
- FOLLICULAR PRECURSOR

STROMA
- MESENCHYMAL PRECURSOR
  - fibroblastic reticular cell

Histioytes
- histiocyte
- Langerhans cell
- interdigitating dendritic cell
- follicular dendritic cell
- fibroblastic reticular cell
- indeterminate cell

Immunophenotypic markers

- histiocyte: CD68, CD163, CD4, Lysozyme, +/- S100
- Langerhans cell: CD1a, Langerin, CD4, +/- CD68
- interdigitating dendritic cell: S100, CD1a, CD4, CD6, +/- lysozyme
- follicular dendritic cell: CD21, CD23, CD35, podoplanin, clusterin, CXCL13
- fibroblastic reticular cell: +/- SMA, +/- desmin, +/- keratin

Dendritic Cell Tumors
- Myeloid/monocyte lineage
  - Langerhans cell sarcoma
  - Interdigitating dendritic cell sarcoma
- Mesenchymal (stromal) origin
  - Follicular dendritic cell sarcoma
  - Fibroblastic reticular cell sarcoma
Langerhans Cell Sarcoma

- Exceptionally rare
- High grade neoplasm with overtly malignant cytologic features and a phenotype of Langerhans cells
- Cytology usually not similar to LCH
- Nuclear grooves clue to lineage
- BRAF V600E reported
- Skin most common site
- Advanced, disseminated disease in 50%
- High mortality rate

Interdigitating Dendritic Cell Sarcoma

- Exceedingly rare
- Easily mistaken for other tumor types (especially metastatic melanoma)
- Lymph nodes >> GI tract, soft tissue, skin, spleen
- May present as transdifferentiation of lymphoblastic leukemia/lymphoma or low-grade B-cell lymphomas (similar to histiocytic sarcoma)
Interdigitating Dendritic Cell Sarcoma: Histology

- Paracortical distribution, sparing follicles
- Fascicular or sheet-like architecture
- Ovoid or spindled cells with vesicular chromatin, small nucleoli, abundant eosinophilic cytoplasm with ill-defined cell borders
- Most tumors relatively uniform
- Focally epithelioid cytomorphology may be seen (mimicking histiocytic sarcoma)

Interdigitating Dendritic Cell Sarcoma: Immunophenotype and Genetics

- Strong and diffuse expression of S100 protein
- Usually positive for CD45RO
- Variable staining for CD45, CD68, CD163, lysozyme
- Negative for CD1a, langerin, CD21, CD35

- Limited data re: molecular genetics
CASE:
57-year-old woman with a history of Burkitt lymphoma in remission; 3 years later presents with multiple lesions in the liver, lungs, and bones

<table>
<thead>
<tr>
<th>Immunohistochemistry</th>
<th>Positive</th>
<th>Negative</th>
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<tr>
<td>C68</td>
<td>CD20</td>
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<tr>
<td>MYC</td>
<td>CD1a</td>
<td></td>
</tr>
<tr>
<td>CD45RO</td>
<td>langerin</td>
<td></td>
</tr>
<tr>
<td>S100 (weak)</td>
<td>SOX10</td>
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<tr>
<td>PU.1 (SPI1)</td>
<td>keratins</td>
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Diagnosis:
HISTIOCYTIC SARCOMA
(transdifferentiation from Burkitt lymphoma)

Follicular Dendritic Cell Sarcoma
- Adults over wide age range
- No gender predilection
- ~10% arise in background of hyaline-vascular Castleman disease
  - Associated FDC hyperplasia/dysplasia
- 60% arise in lymph nodes (cervical most common, then axilla)
- 40% arise at extranodal sites (GI tract/abdominal cavity, mediastinum, tonsil, liver/spleen – distinctive variant)

Hyaline Vascular Castleman Disease

FDC sarcoma arising in hyaline vascular Castleman disease

podoplanin

podoplanin

podoplanin
Follicular Dendritic Cell Sarcoma: Immunophenotype

- Usually positive for CD21, CD23, and/or CD35
- CXCL13 diffusely positive; highly sensitive and specific
- Clusterin and podoplanin sensitive but not specific
- EMA focally positive 50%
- S100 protein 10%
- FDCSP and SRGN highly specific FDC markers identified by whole transcriptome sequencing

Lorenzi et al. Oncotarget. 2017 Jan 27. [Epub ahead of print]

Inflammatory Pseudotumor-like Follicular Dendritic Cell Sarcoma

- Very rare
- Female predominance
- Occurs almost exclusively in liver or spleen
- Sheet-like and fascicular growth pattern
- Lacks storiform and whorled architecture of conventional variant
- More variable cytomorphology
- Epstein-Barr virus positive (EBER)
Conventional FDC Sarcoma of Spleen


Targeted genomic sequencing of follicular dendritic cell sarcoma reveals recurrent alterations in NF-κB regulatory genes

Gabriel K. Griffin1,2, Lynette M. Sholl1,2,3, Neal I. Lindeman1,2,5, Christopher D. Fletcher1,2 and Jason L. Horning1,2

In revision

Genomic Analysis of Follicular Dendritic Cell Sarcoma by Molecular Inversion Probe Array Reveals Tumor Suppressor-Driven Biology

Authors:
Erica F. Anderson1,2, Christian N. Paxton3, Dennis P. O'Malley1,2, Agner Louisaint, Jr.1, Jason L. Horning1,2, Gabriel K. Griffin2, Yuki Fedorov4, Young S. Kim3, Lawrence M. Weiss1, Shane L. Perkins5, Sarah T. South1,2,3
Frequent Alterations in NF-κB Regulatory Genes

PD-L1 / PD-L2 Copy Number Gains

Andersen et al. 2017

Fibroblastic Reticular Cells

- Lymphoid tissue-associated dendritic cells
- Mesenchymal in origin
- Found in lymph nodes, spleen, tonsil, among other sites
- Keratin-positive dendritic cells found in lymph nodes: fibroblastic reticulum cells ("cytokeratin-positive interstitial reticulum cells")

Fibroblastic Reticular Cell Sarcoma

- Exceedingly rare – very few cases reported
- Formal diagnostic criteria not well established
- Usually affect adults
- Described in lymph nodes, spleen, soft tissue
- Variable clinical course, ranging from indolent to highly aggressive

Reticulum Cell Neoplasms of Lymph Nodes: A Clinicopathologic Study of 11 Cases With Recognition of a New Subtype Derived From Fibroblastic Reticular Cells

Jo-Ann W. Andriko, M.D., Eric P. Kaldjian, M.D., Maria Tsokos, M.D., Susan L. Abbondanzo, M.D., Elaine S. Jaffe, M.D.


Fibroblastic Reticular Cell Sarcoma: Histology

- Overlap with other dendritic cell tumors (esp. FDC sarcoma, IDC sarcoma)
- Sheets of spindled to polygonal cells
- Irregular nuclei, pale eosinophilic cytoplasm
- Admixed with small lymphocytes (helpful clue)
- Variable expression of desmin, keratin, SMA (dendritic processes)
- Difficult to distinguish from metastatic sarcomatoid carcinoma, soft tissue sarcomas
Fibroblastic Reticular Cell Sarcoma

- keratin
- desmin
- keratin

Fibroblastic Reticular Cell Sarcoma

- desmin
- keratin

Fibroblastic Reticular Cell Sarcoma

- keratin
Summary

- Histiocytic and (myeloid lineage) dendritic cell sarcomas may arise through transdifferentiation of B-cell lymphomas
- Some histiocytic and dendritic cell sarcomas harbor \textit{BRAF} mutations
- FDC sarcomas show multiple chromosomal losses suggesting tumor suppressor-driven biology
- FDC sarcomas harbor recurrent mutations in NF-\textit{kB} regulatory genes
- Frequent high-level PD-L1 expression implications for immunotherapy