Deceptive Soft Tissue Tumors

Steven D. Billings
Cleveland Clinic
billins@ccf.org
The Good, the Bad and the Ugly of Cutaneous Soft Tissue Tumors
A 25-year-old man presented with a non-pigmented, small nodule on the posterior neck.
Diagnosis?
Cellular Fibrous Histiocytoma

Variant of Dermatofibroma
The Good

Things that look bad but aren’t
Cellular Fibrous Histiocytoma

• Variant of benign fibrous histiocytoma (dermatofibroma family)

• Clinical features
  – Most frequently presents on proximal extremities and head and neck area
  – Clinical differential diagnosis: basal cell carcinoma, epidermoid cyst, pyogenic granuloma, dermatofibroma
Cellular Fibrous Histiocytoma

- Composed of lightly eosinophilic to amphophilic spindled cells with fascicular to storiform pattern
- Monomorphous, without siderophages and foam cells seen in ordinary BFH
- Few admixed inflammatory cells
- Necrosis in 10%
Cellular Fibrous Histiocytoma

- Mitotic figures frequent
- May show limited involvement of subcutaneous fat
- Recognition of features of ordinary BFH essential
  - Overall low-power circumscription
  - Variable epidermal hyperplasia
  - Peripheral “collagen trapping”
Differential Diagnosis

- Dermatofibrosarcoma protuberans
- Nodular fasciitis
- Spindled variant of epitheliod sarcoma
- Leiomyosarcoma
CFH vs. DFSP
<table>
<thead>
<tr>
<th></th>
<th>CFH</th>
<th>DFSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumscription</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Epidermal hyperplasia</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Collagen trapping</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Secondary elements</td>
<td>Focal</td>
<td>-</td>
</tr>
<tr>
<td>Pattern of fat infiltration</td>
<td>Limited, lace-like</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Immunostains</td>
<td>Factor XIIIa -/+; CD34 -</td>
<td>Factor XIIIa-; CD34+</td>
</tr>
</tbody>
</table>
12-year-old boy with lesion on hand
Diagnosis?

Negative for cytokeratin, S100, and INI-1 expression retained
NKI-C3 and CD10
Cellular Neurothekeoma

- Benign tumor (rare local recurrence)
- Head and neck and proximal upper extremity of young adults
- Present as painless flesh colored papules or nodules
- Originally considered a nerve sheath tumor; now considered a fibrohistiocytic tumor
Histopathology

- Distinctly nested to fascicular growth pattern
- Subtle whorling arrangement of tumor cells in tumor nests
- Hyalinized stroma
- Myxoid stroma less prominent
- Neoplastic cells have abundant eosinophilic cytoplasm and round to oval nuclei
- Focal nuclear atypia common
- Mitotic figures may be present (<5/10 HPF)
Mitotic Rate

- Counted using the hot-spot method per mm$^2$
- Cases varied from 0-10 mitoses/mm$^2$ Mean (2.35)
Atypical Cellular Neurothekeoma

- Increased atypia
- Mitotic activity
- Perineural invasion
- Vascular invasion
- Does not impact behavior
  - Very rare local recurrence
  - No metastasis
Cellular Neurothekeoma

- Immunophenotype variable
  - Useful positives: NKIC3 and CD10, S100A6, MiTF
  - Sometimes positive: SMA
  - Positive but not all that helpful: vimentin, PGP9.5
  - Negative: cytokeratin, S100
Cellular Neurothekeoma

• Differential Diagnosis
  – Myxoid neurothekeoma/dermal nerve sheath myxoma
  – Plexiform fibrohistiocytic tumor
  – Epithelioid sarcoma
Dermal Nerve Sheath Myxoma

- True nerve sheath tumor
- Distinct nodules of spindled cells in myxoid stroma
- Nodules separated by fibrous septae
- S100+
Plexiform Fibrohistiocytic Tumor

- Children or young adults
- Extremities
- Cutaneous or subcutaneous
- Distinctly plexiform growth pattern
- Minute nodules of round cells and interspersed osteoclasts surrounded by fascicles of myofibroblasts
- May be primarily rounded or spindled
- Immunophenotype: Overlap with CNT but MiTF negative
Behavior

- Tumor of intermediate malignancy
- Local recurrences in 12-40% of cases
- Recommend wide excision
- Metastatic disease very uncommon
  - Several reported lymph node metastases
  - Three reported pulmonary metastases
- Single report of t (4;15) (q21; q15)
54-year-old diabetic woman presented with depressed plaque with focal ulceration. Patient reports burning sensation in arm.
Diagnosis

• Granuloma annulare?
• Necrobiosis lipoidica?
• Rheumatoid nodule?
• Dermatofibroma?
• Scar?
• Something else?
Epithelioid Sarcoma

Cytokeratin AE1/3
The Bad

Things that are bad even though they don’t look bad
Epithelioid Sarcoma

- **Clinical Features**
  - Children and young adults (wide age range)
  - Most common on distal extremities
  - Subcutaneous nodule, often ulcerated

- **Microscopic features**
  - Nodules of relatively bland epithelioid cells, often with central necrosis
  - May be predominantly spindled

- **Immunophenotype**
  - Positive for cytokeratin, EMA, and CD34 (50%)
  - Negative for INI-1
  - May be Factor XIIIa-positive
Behavior

- Frequent local recurrence and metastasis
- 5 year survival 50-85%
- 10 year survival 42-55%
- Treatment
  - Wide local excision
  - Amputation
  - Lymph node dissection
Differential Diagnosis

- Granulomatous processes
  - Infection, sarcoidosis, granuloma annulare, necrobiosis lipoidica, rheumatoid nodule
- Cellular fibrous histiocytoma
  - Rule of thumb: Consider ES when contemplating CFH of distal extremity
- Cellular neurothekeoma
- Plexiform fibrohistiocytic tumor
- Epithelioid hemangioendothelioma
- Epithelioid sarcoma-like hemangioendothelioma
Epithelioid Hemangioendothelioma

- Clinical Features
  - Usually adults
  - Usually nondescript appearance
  - Usually not violaceous

- Microscopic features
  - 50% associated with vessel (less commonly seen in cutaneous tumors)
  - Cords to nests of epithelioid cells
  - Bland nuclei with intracytoplasmic lumens
  - 25% significant atypia
  - Myxohyaline stroma
  - CD31 and CD34+; 25% Keratin+
Epithelioid Hemangioendothelioma: New insights into pathogenesis

• Cytogenetics
  – >90% Epithelioid hemangioendotheliomas have t(1;3)(p36;q25)
  – Fusion of WWTR1 and CAMTA1
  – WWTR1: transcriptional coactivator highly expressed in endothelial cells
  – CAMTA1: DNA binding transcriptional regulatory protein usually expressed in brain
  – Possible therapeutic target

Epithelioid Hemangioendothelioma

• Behavior
  – Considered tumor of intermediate malignancy
  – Frequent recurrence (10-15%)
  – Lymph node and pulmonary metastasis (up to 30%)
  – Overall mortality: 10-20%
Epithelioid Sarcoma-like Hemangioendothelioma

- Rare entity originally described in 2003
- Equally involves superficial or deep soft tissue
- Can present as ulcerated lesion

Epithelioid Sarcoma-like Hemangioendothelioma

- Ill-defined nodules, sheets or fascicles
- Epithelioid to spindled tumor cells
- Abundant eosinophilic cytoplasm
- No overt vascular channels
- Subtle evidence of vascular differentiation consisting of focal intracytoplasmic lumen
- Unique immunophenotype
  - AE1/3+, CD31+, Fli-1+
  - CD34-
“Pseudomyogenic Hemangioendothelioma”

Epithelioid Sarcoma-like/Pseudomyogenic Hemangioendothelioma

- Behavior
  - Relatively indolent
  - Risk of local recurrence
  - Multifocal disease ~2/3 of patients
  - Rare lymph node and distant metastasis
Case

A 4-year-old girl presented with a flank mass
Diagnosis?
Immunostains

- S100 protein negative
- CD34 negative
- EMA negative
- Cytokeratin negative
FSH for FUS

FUS (16p11) translocated

FUS (16p11) intact
Low Grade Fibromyxoid Sarcoma

- 1986: First described by Evans
  - 2 cases of deceptively bland sarcomas with paradoxically aggressive behavior
- 1993: 12 additional cases
  - Similarly bland features
  - Aggressive behavior:
    - Metastasis in 7/12
    - 4 DOD
    - 3 AWD
Hyalinizing Spindle Cell Tumor with Giant Collagen Rosettes (HSTGR)

• Described in 1997 (Lane et al, AJSP 1997)
• Clinical and histologic similarities to LGFMS
• Possibly a variant of LGFMS
• Relationship with LGFMS supported by presence of focal rosettes and small collagen rosettes in cases of LGFMS (Folpe et al, AJSP 2000)
Cytogenetics

• Both HSTGR and LGFMS share common cytogenetic abnormality
  – t(7;16)(q34;p11)
  – Fusion of FUS/CREB3L2
  – FUS: RNA-binding protein
  – CREB3L2: member of OASIS B-ZIP family of transcription factors
Clinical Features

- Primarily affects young to middle-aged adults
  - 10-20% of cases present in children
- Predominantly present as deep soft tissue mass
  - 20% present as superficial tumors of dermis or subcutis (Billings, et al AJSP 2005)
  - Superficial tumors relatively common in children (~40% of superficial tumors)
Histologic features
Immunohistochemistry

Previously a tool of exclusion

- Vimentin +
- Actins +/-
- EMA -/+ (30%)
- S100 -/+ 
- CD34 – (rare focal positivity)
- Desmin –

- Exception: MUC-4 positive >90%
FISH

- Dual color break apart probes for FUS
- Positive in 70-90%

LGFMS clinically behaves as low-grade sarcoma if accurately diagnosed and treated like a sarcoma.
Low-Grade Fibromyxoid Sarcoma: A Clinicopathologic Study of 33 Cases With Long-Term Follow-Up

Harry L. Evans, MD

• 21 patients recurrences after intervals up to 15 years (median 3.5 yrs)
• 15 with metastasis after periods up to 45 years (median 5 yrs)
• Still aggressive
• Patients need lifelong follow-up
Differential Diagnosis
Soft tissue perineurioma
Fibrous Hamartoma of Infancy

• **Clinical features**
  – First two years of life, ~20% at birth
  – Dermal or subcutaneous mass
  – Present on upper half of body, especially around axilla
Fibrous hamartoma of infancy

- Triphasic tumor
  - Fibromatosis like fascicles
  - Myxoid nodules with bland spindled to stellate cells
  - Mature fat
LGFMS vs. Fibrous hamartoma

LGFMS
• Older patients
• Biphasic (lacks fat)
• Myxoid areas with prominent vasculature
• More atypia
• t(7;16)

Fibrous hamartoma
• Infants
• Triphasic with fat
• Myxoid areas without prominent vasculature
• No atypia
• No characteristic genetic findings
Myxoid DFSP
<table>
<thead>
<tr>
<th></th>
<th>LGFMS</th>
<th>Myxoid DFSP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whorled to fascicular</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Pushing border</td>
<td>Infiltrative</td>
</tr>
<tr>
<td></td>
<td>Myxoid/collagenous</td>
<td>Purely myxoid</td>
</tr>
<tr>
<td></td>
<td>Rosettes (sometimes)</td>
<td>No rosettes</td>
</tr>
<tr>
<td></td>
<td>CD34 -</td>
<td>CD34+</td>
</tr>
<tr>
<td></td>
<td>t(7;16)</td>
<td>t(17;22)</td>
</tr>
</tbody>
</table>
Myxofibrosarcoma (myxoid MFH)

• Clinical features
  – Older patients
  – Extremities (esp. thigh) rarely involves head and neck
  – Often a subcutaneous mass
  – Larger tumor
Myxofibrosarcoma (myxoid MFH)

- **Microscopic features**
  - Infiltrative tumors extending along subcutaneous septae
  - Spectrum from low to high-grade tumors
  - Low-grade tumors are purely myxoid with low cellularity and often subtle atypia
  - Intermediate and high-grade tumors have increasing solid areas, greater nuclear pleomorphism, mitoses and necrosis
  - Neoplastic cells proliferate off arborizing thick-walled vessels
LGFMS vs. Myxofibrosarcoma

**LGFMS**
- Less atypia
- Pushing border (superficial)
- Myxoid/collagenous
- Rosettes (sometimes)
- MUC4 positive
- t(7;16)

**Myxofibrosarcoma**
- More atypia
- Infiltrative
- Purely myxoid (low grade)
- No rosettes
- MUC4 negative
- No characteristic genetic findings
35-year-old woman presented with nodule on the leg. Rule-out dermatofibroma.
How worried are you?

- Dermatofibroma?
- Undifferentiated pleomorphic sarcoma (MFH)?
- Atypical fibroxanthoma?
Atypical Fibrous Histiocytoma (DF with Monster Cells)
The Ugly

Things that are not as bad as they look…
Atypical Fibrous Histiocytoma

Clinical features
- Similar to conventional dermatofibroma
- Extremities of young patients
- Non-sun damaged skin

Microscopic features
- Low power resemblance to ordinary DF
  - Epidermal hyperplasia
  - Circumscribed
  - Peripheral collagen trapping
- High power:
  - Markedly atypical, sometimes multinucleated cells admixed with bland spindled cells
  - Mitotic figures (including atypical forms)
Behavior

- Fundamentally benign
- Frequent local recurrence (~20%)
- Rare metastasis (one patient DOD)
- Conservative but complete excision and follow-up
DDx: Atypical Fibrous Histiocytoma

- Atypical fibroxanthoma
  - Usually much older patients
  - Sun damaged skin
  - Absence of areas of typical dermatofibroma

- Pleomorphic sarcoma (MFH)
  - Infiltrative, deep soft tissue
43-year-old man with mass on upper extremity

43-year-old man with mass on upper extremity
Diagnosis?
Angiomatoid Fibrous Histiocytoma (AFH)

• Occurs in children and young adults
• Nodular dermal or subcutaneous mass
• May have systemic symptoms
  – Anemia
  – Pyrexia
  – Weight loss
• Frequently recur (20-40%)
• Low risk of metastasis (<5%)
  – Regional lymph nodes or lungs
AFH

Histologic Features

- Circumscribed
- Fibrous pseudocapsule
- Chronic inflammation with lymphoid aggregates
- Solid proliferation of histiocyte-like cells
- Hemorrhage
- Pseudovascular spaces
- May have significant pleomorphism (no impact on behavior)
Life is a long lesson in humility. (James M. Barrie, 1860-1937)
77-year-old woman with scalp lesion
Dx: Malignant spindle cell neoplasm, see comment

- Comment: Sections demonstrate pleomorphic, hyperchromatic spindled cells arranged in irregular fascicles. By immunohistochemistry, the tumor cells are negative for cytokeratin 5/6, p63 and S100 protein. The histologic features and immunophenotype are consistent with atypical fibroxanthoma (AFX). If this is a larger lesion, it could represent a superficial pleomorphic sarcoma (MFH). A re-excision and clinical correlation is recommended.
Two weeks later.....

- My colleague comes into my office and says the words that no pathologist wants to hear:
- “Remember that case I showed you? I have the slides from the resection specimen....”
What did I miss?
Tumor is infiltrating around adnexal structures
Intratumoral hemorrhage
90-year-old man with lesion on face; rule out basal cell carcinoma
90 year-old man; rule out BCC

- Malignant spindle cell neoplasm
- Negative for CK5/6, p63, S100 protein
Negative for CK5/6, p63, and S100 protein.
Angiosarcoma

- Can have solid spindle cell areas
- Keep a high index of suspicion for this diagnosis in tumors from the head and neck of older patients
- Infiltrative growth and hemorrhage are clues to the diagnosis
- Look at periphery of tumor: vasoformative areas often present at periphery
- Immunostains for ERG and CD34 are best stains to confirm diagnosis
ERG

- ETS family of transcription factors factor
- Sensitive and specific marker for vascular tumors
- Nuclear stain
  - Positive in all hemangiomas and lymphangiomas
  - 96/100 angiosarcomas
  - 42/43 epithelioid hemangioendotheliomas
  - 26/26 Kaposi sarcoma

Spindle cell angiosarcomas may be negative or only weakly positive for CD31.
The Good, The Bad, and The Ugly
The Good,
The Bad,
and The Ugly