Common Challenging Diagnoses in Soft Tissue Pathology

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Topics
1. Pseudosarcomas
2. Borderline soft tissue tumors
3. Dedifferentiation
4. “New” sarcomas and relationships (audience choice!)

Pseudosarcomas
- 25 year old man with 3 cm forearm mass, present for 3-4 weeks, recently painful (821)
Nodular fasciitis

- **Clinical**
  - Age: Peak 20-40
  - Growth: Rapid (weeks/months)
  - Antecedent trauma: ~50%
  - Spontaneous resolution >98%
  - Recurrence <1% (re-evaluate those!)
- **Gross**
  - Size: Usually < 5 cm
  - Circumscribed or infiltrative depending on location
- **Low power**
  - Zonation
  - No characteristic vascular pattern
  - Tissue culture growth
- **High power**
  - "Reactive myofibroblast" + lymphocytes
  - Brisk mitotic activity
  - Microcysts, extravasated RBC
- **Absent**
  - Nuclear hyperchromasia, atypical mitoses, neutrophils, necrosis

Tissue culture growth pattern

Fasciitis. Not always nodular
Immunohistochemistry summary

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>SMA</th>
<th>MEC</th>
<th>CD10</th>
<th>Her2</th>
<th>AE1/3</th>
<th>CK5/6</th>
<th>ALK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular fascitis</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>DF/BFN</td>
<td>a/-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myofibrosarcoma</td>
<td>+</td>
<td>a/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myoma</td>
<td>+</td>
<td>a/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dermoid</td>
<td>a/-</td>
<td>a/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>IMT</td>
<td>+</td>
<td>a/+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>+</td>
<td>+</td>
<td>a/+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Myofibroblastic sarcoma</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Pseudosarcomas

- Slide 416, 1312
- 36 year old woman with 2 cm thigh soft tissue mass
  - Present for a year or more, recently painful
  - Does not recall trauma
Myositis ossificans

- Clinical
  - Young adults, wide age range
  - Rapid onset
  - Trauma <50%

- Gross
  - Small, < 5 cm
  - Calcifications or dense bone depending on chronicity

- Low power
  - Zonation
    - Bone peripheral with osteoblastic activity
    - Nodular fasciitis centrally

- High power
  - Nodular fasciitis-like myofibroblasts
  - Woven to lamellar bone with benign osteoblasts
  - Hyaline cartilage with endochondral ossification (fracture callus)

- Synonyms: Florid reactive periostitis, fibro-osseous pseudotumor of the digits

Case 3

- Slide 120
- 73 year old man with hard 12 cm mass on lateral thigh, present for many years

Myositis ossificans or osteosarcoma?

<table>
<thead>
<tr>
<th></th>
<th>Myositis ossificans</th>
<th>Extraskeletal Osteosarcoma</th>
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</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Young adults, trauma</td>
<td>Older adults, radiation</td>
</tr>
<tr>
<td>Size</td>
<td>&lt;6 cm</td>
<td>&gt;10 cm</td>
</tr>
<tr>
<td>Bone</td>
<td>Periphery</td>
<td>Central</td>
</tr>
<tr>
<td>Atypia</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Mitotic activity</td>
<td>+</td>
<td>+ (Atypical)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Genetics</td>
<td>USP6 fusions</td>
<td>Variable</td>
</tr>
</tbody>
</table>
Soft tissue osteosarcoma: is this osteoid?

Borderline soft tissue tumors

- Slide 400
  - 35 year old man, 9 cm pelvic mass attached to prostate

- Slide 650
  - 23 year old man 5 cm forearm mass
Solitary fibrous tumor (SFT)

- Clinical
  - Middle age
  - Deep soft tissue
  - Hypoglycemia ~5%

- Histopathology
  - Variable cellularity
  - Branching vessels
  - Round (HPC) to spindled (SFT) cells
  - Minimal pleomorphism
  - Low mitotic activity (<4 mf / 10 hpf)
  - Patternless pattern

Solitary fibrous tumor

Solitary fibrous tumor: spindled, vaguely fascicular

Solitary fibrous tumor: hyalinized stroma
Immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>Hemangiopericytoma</th>
<th>Solitary fibrous tumor</th>
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</thead>
<tbody>
<tr>
<td>CD34</td>
<td>50%, patchy</td>
<td>100%, diffuse</td>
</tr>
<tr>
<td>BCL2, CD99, CD10</td>
<td>Variable positive</td>
<td>Variable positive</td>
</tr>
<tr>
<td>Keratin</td>
<td>Negative</td>
<td>Rare, malignant SFT</td>
</tr>
<tr>
<td>STAT6</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

STAT6

![STAT6](image)

Genetics

Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing

Robinson DR et al. Nature Genetics 2012, 44: 180-185

Comprehensive Genetic Analysis Identifies a Pathognomonic NAB2/STAT6 Fusion Gene, Nonrandom Secondary Genomic Imbalances, and a Characteristic Gene Expression Profile in Solitary Fibrous Tumor

Mohajri A et al. Genes, Chrom, Cancer 2013, 52:873-886
Why does this antibody work so well?

STAT6

Solitary fibrous tumor: Risk stratification

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>= 30</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>1</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>0</td>
</tr>
<tr>
<td>10-15</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 15</td>
<td>2</td>
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<td>Mitotic figures (10 high power fields)</td>
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<tr>
<td>0-4</td>
<td>0</td>
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<tr>
<td>&gt; 4</td>
<td>1</td>
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<tr>
<td>Risk</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0-2</td>
</tr>
<tr>
<td>Moderate</td>
<td>3-4</td>
</tr>
<tr>
<td>High</td>
<td>5-9+</td>
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</tbody>
</table>

Demicco EG et al. Modern Pathol 2012 25:1298-1306
Borderline lesions: risk stratification

Differential diagnosis

- Branching vessels and spindle cells
  - Synovial sarcoma
  - Mesenchymal chondrosarcoma
- Alternating cellular and hyalinized zones
  - Schwannoma
- Pleural based spindle cell tumor
  - Sarcomatoid mesothelioma
  - Synovial sarcoma

SFT Differential diagnosis: IHC

<table>
<thead>
<tr>
<th></th>
<th>CD34</th>
<th>SSTR1</th>
<th>Keratin</th>
<th>S100</th>
<th>Other</th>
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<tbody>
<tr>
<td>Solitary fibrous tumor</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>S100 FISH</td>
</tr>
<tr>
<td>Mesenchymal chondrosarcoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>S100 FISH</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>S100-30</td>
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<tr>
<td>Sarcomatoid mesothelioma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>WT1, DO-40</td>
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<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>FO94- FISH</td>
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Borderline lesions

• Slide 672
  – 44 year old woman with wrist mass
• Slide 30
  – 35 year old man with knee swelling

Tenosynovial giant cell tumor
Clinical

<table>
<thead>
<tr>
<th></th>
<th>Localized</th>
<th>Diffuse (PVNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>F:M 2:1</td>
<td></td>
</tr>
<tr>
<td>Course</td>
<td>Years</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Pain, decreased ROM</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>30-50</td>
<td>&lt;40</td>
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<tr>
<td>Size</td>
<td>1-2 cm</td>
<td>&gt;5 cm</td>
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<tr>
<td>Location</td>
<td>Wrist, digits</td>
<td>Knee, hip</td>
</tr>
<tr>
<td>Recurrence</td>
<td>4-30%</td>
<td>18-50%</td>
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</tbody>
</table>

Tenosynovial giant cell tumor
Histopathology

<table>
<thead>
<tr>
<th></th>
<th>Localized</th>
<th>Diffuse (PVNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borders</td>
<td>Circumscribed</td>
<td>Infiltrative, diffuse</td>
</tr>
<tr>
<td>Pigment</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Giant cells</td>
<td>Present in nearly all</td>
<td>May be rare or absent</td>
</tr>
<tr>
<td>Mononuclear cells</td>
<td>Small histiocyte like cells (synoviocytes)</td>
<td>Larger, epithelioid and dendritic cells</td>
</tr>
<tr>
<td>Foam cells</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Cholesterol clefts</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Mitoses</td>
<td>5-10 / 10 hpf common</td>
<td>common</td>
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Tenosynovial giant cell tumor: IHC

<table>
<thead>
<tr>
<th></th>
<th>Clusterin</th>
<th>CD68</th>
<th>S100</th>
<th>Desmin</th>
<th>Other</th>
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<tbody>
<tr>
<td>Tenosynovial giant cell tumor</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>CD64X-CD75 fusion</td>
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<tr>
<td>Granulomatous inflammation</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>AFB, fungus, history of collagen vascular disease</td>
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<tr>
<td>Epithelioid sarcoma</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Keratin INI1</td>
</tr>
<tr>
<td>Achromic or tendon sheath</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>May be related, more hyalinized</td>
</tr>
</tbody>
</table>

Dedifferentiation

- Slide 60
  - 64 year old man with retroperitoneal fatty mass
- Slide 1225
  - 70 year old man with scrotal mass

Dedifferentiated liposarcoma

- Clinical
  - Retroperitoneum > deep soft tissue
  - 70-90% synchronous
- Gross
  - Macroscopic (>1 cm), fleshy area separate from fatty area
- Micro
  - Well differentiated liposarcoma + non-lipogenic sarcoma
  - Heterologous differentiation: bone, muscle, cartilage
  - May be low grade
- Ancillary studies
  - 12q amplification
  - MDM2 CDK4
Is grade of dedifferentiation significant?


Low-grade dedifferentiation

Approach to dedifferentiation
Dedifferentiation

- 33 year old man with abdominal wall mass (547)

Fibrosarcomatous DFSP

- Clinical
  - Same as DFSP: mid-age, trunk
  - Behavior possibly more aggressive than DFSP (margin status important)
- Gross
  - Multinodular, fleshy, >5 cm (larger than DFSP), necrosis
- Micro
  - Conventional or myxoid DFSP: storiform, fat trapping (swiss cheese)
  - >5% = Herringbone fascicles, hypercellular; > 7 mf / 10 hpf
- Ancillary studies
  - CD34 strong in DFSP, weaker and marbled in fibrosarcoma
  - COL1A1:PDGFβ fusion

Fibrosarcomatous DFSP differential diagnosis: IHC

<table>
<thead>
<tr>
<th></th>
<th>CD34</th>
<th>Keratin</th>
<th>S100</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosarcomatous DFSP</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>PDGFβ FISH</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>SSL1 FISH</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>
“New” sarcomas

1. The tongue twister group:
   a) Hemosiderotic fibrohistiocytic lipomatous tumor (HFLT)
   b) Pleomorphic hyalinizing angiectatic tumor (PHAT)
   c) Myxoinflammatory fibroblastic sarcoma (MIFS)

2. The CREB group:
   a) Low-grade fibromyxosarcoma
   b) Hyalinizing spindle cell tumor with giant rosettes
   c) Sclerosing epithelioid fibrosarcoma

3. The neurothekeoma group
   a) Neurothekeoma
   b) Nerve sheath myxoma

4. Pseudomyogenic hemangiendothelioma (PMHE)

5. Soft tissue angiofibroma

The tongue twister group

- 80 year old woman, mass on dorsum of foot (775)
- 40 year old man, lower leg mass (1467)
- 39 year old man, left elbow mass (1093)
Pseudomyogenic hemangioendothelioma

- 31 year old man with abdominal wall mass (1413)

Pseudomyogenic Hemangioendothelioma: A Distinctive, Often Multicentric Tumor With Indolent Behavior

Jason L. Hornick, MD, PhD and Christopher D.M. Fletcher, MD, FRCPath

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Pseudomyogenic hemangioendothelioma

- Clinical
  - Peak 3rd decade
  - Multicentric in same limb, soft tissue or bone
  - ~60% local, nondestructive recurrence, very rare met

- Histo:
  - Myoid spindle cells, tightly packed fascicles
  - Occasional intracytoplasmic lumens
  - IHC: AE1/AE3+ (CAM5.2 usually -), FLI1+, CD31+, INI1 intact

- Genetics: t(7;19)(q22;q13) SERPINE1-FOSB
The CREB group

- 48 year old man, deep thigh mass (1118)
- 67 year old man, posterior thigh (865)
- 53 year old woman, pelvic mass (716)

Fibrosing fibrosarcoma family (MUC4+)

LGFMS HSPCGR
Mixed LGFMS SEF
PURE SEF

EWSR1-CREBL32 (most) FUS-CREBL32 (most) EWSR1-CREBL32 (most) -CREBL32 (rare)

The CREB group

Neurothekeoma vs. Nerve Myxoma

- 47 year old woman, groin mass (1187)
- 16 year old, cheek mass (1252)
Neurothekeoma vs nerve sheath myxoma

<table>
<thead>
<tr>
<th></th>
<th>Neurothekeoma</th>
<th>Nerve sheath myxoma</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>Children, young adults</td>
<td>Young to mid adult</td>
</tr>
<tr>
<td></td>
<td>Rare recurrence</td>
<td>~50% recurrence</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Face, proximal upper extremity</td>
<td>Distal extremity</td>
</tr>
<tr>
<td><strong>Growth pattern</strong></td>
<td>Multinodular, plexiform</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Myxoid</strong></td>
<td>None to focal</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td>Plump, epithelioid, stellate</td>
<td>Bipolar, long processes</td>
</tr>
<tr>
<td><strong>Mitoses</strong></td>
<td>&gt;5 / 10 hpf possible</td>
<td>&lt;1 / 10 hpf</td>
</tr>
</tbody>
</table>

**Classification**

![Diagram showing classification]

**Soft tissue angiofibroma**

*Original Article*

Angiofibroma of Soft Tissue: Clinicopathologic Characterization of a Distinctive Benign Fibrovascular Neoplasm in a Series of 37 Cases

Adrián Martín-Enríquez, MD and Christopher B. M. Finnucan, MD, FRCPath

Soft tissue angiofibroma

- **Clinical**
  - Wide age range, female predominant
  - Circumscribed
  - Most lower extremity, near joints
  - ~20% local, nondestructive recurrence

- **Histo:**
  - Fibroblastic cells + rich capillary network
  - IHC: EMA (44%), rare CD34, actin desmin

- **Genetics:** t(5;8)(p15;q13) AHRR-NOCA2