Soft Tissue Pathology: Common Diagnostic Dilemmas

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Disclosures

Relevant financial relationships:
None

Off-label usage:
None
Two common histologic patterns

Case 1

53-year-old man presenting with a 15 cm intraabdominal mass, adherent to ileum and large bowel
Diagnosis?

**CD117**

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**Case 2**

49-year-old woman presenting with a 4.7 cm retroperitoneal mass, surgically excised
Learning Objectives

Pleomorphic sarcomatoid neoplasms:
1. Review diagnostic approach
2. Understand importance of sub-classification

Well-differentiated lipomatous neoplasms:
1. Review diagnostic approach
2. Understand utility and indications for MDM2 FISH
Pleomorphic Sarcomatoid Neoplasms

Where do I start?
Main Diagnostic Issues

1. Exclude non-sarcomatous tumors

Cancer statistics

<table>
<thead>
<tr>
<th></th>
<th>New cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>1,660,290</td>
<td>580,350</td>
</tr>
<tr>
<td>GI tract</td>
<td>290,200</td>
<td>144,570</td>
</tr>
<tr>
<td>Lung</td>
<td>246,210</td>
<td>163,890</td>
</tr>
<tr>
<td>Breast</td>
<td>234,580</td>
<td>40,030</td>
</tr>
<tr>
<td>Melanoma</td>
<td>76,690</td>
<td>9,480</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>79,030</td>
<td>20,200</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>11,410</td>
<td>4,390</td>
</tr>
</tbody>
</table>

American Cancer Society, 2013
**Step 1:**
Exclude carcinoma, melanoma, lymphoma

- Clinical history
- Histologic clues
- Immunohistochemistry
  - Keratins (AE1/AE3, CAM5.2, CK5/6)
  - S-100 +/- HMB45, melanA, tyrosinase
  - Hematolymphoid markers

80 y.o. man with thigh mass
CAM5.2

Sarcomatoid carcinoma

TTF-1
55 y.o. woman with foot mass
Malignant melanoma

HMB45

64 y.o. man with retroperitoneal mass
Large B-cell lymphoma

CD20

Pitfalls

• Epithelioid sarcoma
• Aberrant keratin expression in sarcoma
• S-100 positive dendritic cells
• Clear cell sarcoma
Epithelioid sarcoma

AE1/AE3

INI-1

Clear cell sarcoma

HMB45
Main Diagnostic Issues

1. Exclude non-sarcomatous tumors
2. Consider benign mimics

67 y.o. man with 2.5 cm wrist mass
Step 2: Exclude benign mimics

- Atypical fibroxanthoma (AFX)
- Pleomorphic lipoma
- Pleomorphic fibroma of skin
- “Ancient” schwannoma
- “Symplastic” leiomyoma of uterus
- Pleomorphic hyalinizing angiectatic tumor (PHAT)
Main Diagnostic Issues

1. Exclude non-sarcomatous tumors
2. Consider benign mimics
3. Maximize efforts to subclassify, and avoid using “UPS” whenever possible

Why subclassify pleomorphic sarcomas?
Not all pleomorphic sarcomas are created equal


Not all pleomorphic sarcomas are created equal

FIGURE 4. Follow-up. A, OS of the 19 patients with peripheral UPS with MDM2 amplification (in blue), the 62 with peripheral conventional DDLPS (in red), and the 153 with peripheral UPS without MDM2 expression (in black). B, MFS of the 19 patients with peripheral UPS with MDM2 amplification (in blue), the 62 with peripheral conventional DDLPS (in red), and the 153 with peripheral UPS without MDM2 expression (in black). C, LRFS of the 19 patients with peripheral UPS with MDM2 amplification (in blue), the 62 with peripheral conventional DDLPS (in red), and the 153 with peripheral UPS without MDM2 expression (in black).


Subtype-Specific Treatments

- GIST – imatinib
- Rhabdomyosarcoma – VAC
- DFSP, desmoids, TGCT – imatinib
- Myxoid/round cell liposarcoma -- trabectedin
- PEComas – sirolimus
- ASPS, malignant SFT, clear cell sarcoma -- sunitinib, pazopanib
- Liposarcoma – MDM2 inhibitors (trials)
- Leiomyosarcoma, liposarcoma – eribulin (trials)
Step 3: 
Subclassifying Pleomorphic Sarcomas

- Myogenic differentiation?
  - Pleomorphic leiomyosarcoma
  - Pleomorphic rhabdomyosarcoma

- Features of myxofibrosarcoma?
  - Myxofibrosarcoma (high grade)

- Atypical fat next to it?
  - Dedifferentiated liposarcoma

- Lipoblasts within it?
  - Pleomorphic liposarcoma

- Malignant osteoid?
  - Extraskeletal osteosarcoma

- No identifiable line(s) of differentiation?
  - Undifferentiated pleomorphic sarcoma

Pleomorphic Leiomyosarcoma

- Older adults
- M:F ratio – 1:2
- Retroperitoneum > abdominal cavity >> extremities
- 5-year metastasis: >60%
- 5-year survival: 50%
• Areas of recognizable intersecting fascicles

• Myxoid change
• Densely eosinophilic cytoplasm
• Cigar-shaped nuclei

h-caldesmon
Pleomorphic Rhabdomyosarcoma

- Almost exclusively in older adults
- More common in men
- Deep soft tissues of extremities (especially thigh)
- 5-year metastasis: >80%
- 5-year survival: 10-15%

- Sheets of pleomorphic cells
- Loose and haphazardly arranged
• Deeply eosinophilic cytoplasm
• Rhabdoid inclusions

[Image of tissue section with staining for desmin]
Myxofibrosarcoma

- Old term: “Myxoid MFH”
- Elderly (6th-8th decades)
- Limbs (lower ext > upper ext)
- ~2/3 arise in subcutaneous location
- Atypia and myxoid stroma vary
- 5-year metastasis: 30-35%
- 5-year survival: 50-70%
• Subcutaneous
• Lobulated

• Strikingly infiltrative margins
• Myxoid zones
• Delicate curvilinear vessels

Dedifferentiated Liposarcoma

• Definition: Development of (usually) high grade, non-lipogenic sarcoma in setting of pre-existing well-diff. LPS
• Older adults (M:F ratio -- 3:1)
• Retroperitoneum > groin >>>>> extremities
• 5-year metastasis: 15-20%
• 5-year survival: 70%
• >90% amplification of 12q13-15 (MDM2)
• Pleomorphic sarcoma in retroperitoneum = DDLPS until proven otherwise
High grade DDLPS
Pleomorphic Liposarcoma

- Older adults (> 50 years)
- Deep soft tissues of extremities
- 5-year metastasis: 30-50%
- 5-year survival: 20%
• Unequivocal lipoblasts within pleomorphic tumor
Well-Differentiated Lipomatous Neoplasms

Diagnostic Challenges

• Morphologic overlap
• IHC usually unhelpful
• Rarity of some entities
• Inconsistent application of terminology
• Recent advances in cytogenetics and molecular diagnostics
Rules of fatty tumors

1. Location:
   • Lipomas occur in superficial soft tissue
   • Liposarcomas occur in deep soft tissue

2. Do not look for lipoblasts

3. Cytogenetics can be helpful
Important (and not important) cells in fatty lesions

Lipoblasts
Lipoblasts in well-differentiated fatty tumors?

1. They may be seen in benign lesions (e.g. lipoblastoma, spindle cell/pleomorphic lipoma, chondroid lipoma)

2. Most liposarcomas do not have them

I never look for them.

Atypical hyperchromatic stromal cells
Atypical hyperchromatic stromal cells

Lipoma

- Age: 40-60
- Mobile, painless
- No fibrous or solid areas; <10 cm
- No atypical hyperchromatic stromal cells
- 2/3 have 12q13-15 aberrations
Atypical Lipomatous Tumor / Well-Differentiated Liposarcoma

- Terminology is confusing!!!
- ALT and WDLPS are the same entity
Atypical Lipomatous Tumor / Well-Differentiated Liposarcoma

- 6th and 7th decades of life
- M=F
- Deep soft tissue sites
- Non-metastasizing
- Local recurrence (rate related to site)
- May dedifferentiate (rate related to site)
- Characteristic cytogenetic abnormalities in almost all cases

Why “Atypical Lipomatous Tumor”? 

<table>
<thead>
<tr>
<th>Site</th>
<th>Recurrence (%)</th>
<th>Died of disease (%)</th>
<th>Dedifferentiation (%)</th>
<th>Years of follow-up range and median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremity</td>
<td>43</td>
<td>0</td>
<td>6</td>
<td>2–25 (9)</td>
</tr>
<tr>
<td>Retropertioneum</td>
<td>91</td>
<td>33</td>
<td>17</td>
<td>1–35 (10)</td>
</tr>
<tr>
<td>Groin</td>
<td>79</td>
<td>14</td>
<td>28</td>
<td>2–25 (8)</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>


Why “Atypical Lipomatous Tumor”?  

- “ALT” was introduced to avoid labeling pts with tumor in extremity with “sarcoma”  
- In the retroperitoneum / groin, only use “WDPLS”  

• Intersecting fibrous bands
• Atypical hyperchromatic stromal cells

Potential mimics of atypical hyperchromatic stromal cells
Atrophic skeletal muscle
Lochkern cells

Cytogenetics of fatty tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Chromosomal aberration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoma (ordinary)</td>
<td>Translocations involving 12q33–15</td>
</tr>
<tr>
<td></td>
<td>Interruption deletions of 13q</td>
</tr>
<tr>
<td></td>
<td>Rearrangements involving 6q21–23</td>
</tr>
<tr>
<td>Angiolipoma</td>
<td>None</td>
</tr>
<tr>
<td>Spindle cell liposarcoma</td>
<td>Loss of 16q13</td>
</tr>
<tr>
<td>Lipoma</td>
<td>Unbalanced 13q alterations</td>
</tr>
<tr>
<td>Lipoepitheliomatous lipoma</td>
<td>Translocations involving 9q11–13</td>
</tr>
<tr>
<td>Hibernoma</td>
<td>Translocations involving 11q13</td>
</tr>
<tr>
<td></td>
<td>Translocations involving 10q22</td>
</tr>
</tbody>
</table>

Advances in Brief

Translocation t(2;16)(q13;p11) in Myxoid Liposarcoma and Round Cell Liposarcoma: Molecular and Cytogenetic Analysis

Jennifer C. Knight, Pamela J. Stoeck, Paula Dai Cun, Herman van den Berghe, and Christopher D. M. Fletcher
Genetics of ALT / WDLPS

- Giant ring and marker chromosomes
- Amplification of 12q14-15, including MDM2, CDK4, SAS, and HMGIC
- Amplification and overexpression of MDM2 and CDK4
- IHC, FISH, CISH testing
Case examples

45 y.o. man with 4 cm subcutaneous thigh mass
• Is this an atypical lipomatous tumor?
  • Location: Superficial
  • Atypical hyperchromatic stromal cells? No

Lipoma with fat necrosis

52 y.o. man with 14 cm intramuscular thigh mass
• Is this an atypical lipomatous tumor?
  • Location: Deep, in extremity
  • Atypical hyperchromatic stromal cells: YES

Atypical lipomatous tumor
(with fat necrosis)
47 y.o. man with 18 cm intramuscular thigh mass
• Is this an atypical lipomatous tumor?
  • Location: Deep
  • Large (18 cm)
  • Atypical hyperchromatic stromal cells: No
  • What next?
**MDM2 FISH**

- Our case
- Control with *MDM2* amplified

- Is this an atypical lipomatous tumor?
  - Deep
  - Large (18 cm)
  - No atypical hyperchromatic stromal cells
  - *MDM2* is not amplified

**Intramuscular lipoma**
When do I do FISH studies for MDM2 amplification?
Other well-differentiated fatty tumors

• Spindle cell / pleomorphic lipoma
• Lipomatous SFT
• Fat-predominant AML
• Silicone reaction
• Massive localized lymphedema
Case 1

53-year-old man presenting with a 15 cm intraabdominal mass, adherent to the ileum and a segment of large bowel
Case 2

49-year-old woman presenting with a 4.7 cm retroperitoneal mass, surgically excised
Angiomyolipoma, fat-predominant variant, mimicking well-differentiated liposarcoma

Melan A

Take-Home Points

- Consider carcinoma / melanoma / lymphoma first
- Don’t forget benign mimics
- Subclassify pleomorphic sarcomas if possible
- Avoid “UPS” diagnosis if possible
- Any pleomorphic sarcoma in retroperitoneum = DDLPS (until proven otherwise)
Take-Home Points

• For ALT / WDLPS:
  • Use “WDLPS” – retroperitoneum, groin, mediastinum
  • Use “ALT” – deep soft tissue of extremities

• Consider *MDM2* FISH if:
  1. Cytologic atypia equivocal
  2. Recurrent “lipoma”
  3. Large, deep extremity tumors without atypia
  4. Retroperitoneal, intraabdominal, groin tumors without atypia

QUESTIONS?