Liposarcomas and Their Distractors

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Classification

1. Atypical lipomatous tumor/Well-differentiated liposarcoma
2. Dedifferentiated liposarcoma
3. Myxoid liposarcoma
4. Pleomorphic liposarcoma

<table>
<thead>
<tr>
<th>Type</th>
<th>Estimated frequency (%)</th>
<th>Age at presentation</th>
<th>Typical sites</th>
<th>Behavior</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL/ALCLS</td>
<td>&lt;10-40</td>
<td>Middle-aged to old</td>
<td>Retroperitoneum, extremity, trunk, wall</td>
<td>Local recurrence and risk of dedifferentiation</td>
<td>12p13-15 deletion, 16q22 amplification</td>
</tr>
<tr>
<td>Dedifferentiated liposarcoma</td>
<td>15-30</td>
<td>Middle-aged to old</td>
<td>Retroperitoneum, extremity, trunk, wall</td>
<td>Risk for recurrence, especially with high-grade dedifferentiation</td>
<td>12p13-15 deletion, 16q22 amplification</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>20-25</td>
<td>Adult, often &gt;40 years, rare in childhood</td>
<td>Thigh, other extremity sites, retroperitoneum</td>
<td>Recurrence common, metastatic rate 30-40%, in long-term follow-up</td>
<td>ETV6-RUNX1 gene fusion</td>
</tr>
<tr>
<td>Pleomorphic liposarcoma</td>
<td>&lt;5</td>
<td>Old adults</td>
<td>Extremity, trunk, wall</td>
<td>High risk for recurrence and metastasis</td>
<td>Complex, poorly understood</td>
</tr>
</tbody>
</table>
Lipoblasts

Atypical Lipomatous Tumor/Well-differentiated Liposarcoma
- Non-metastasizing, locally aggressive
- Middle-age-elderly adults
  - Very rare under 30 yo
- Retroperitoneum & thigh (50%)
- Retroperitoneal tumors do worse
  - Wide excision not possible
  - Recur multiple times
- May dedifferentiate into a fully malignant sarcoma

- Often form very large masses
- Histologic (overlapping) variants
  - Lipoma-like
  - Sclerosing
  - Inflammatory
Sclerosing Liposarcoma

Typically seen in the scrotal/inguinal region as a dominant component.
Inflammatory Liposarcoma
ALT/WDL with Myxoid Stroma

Ring and Giant Marker Chromosomes

MDM2 Amplification by FISH
Uncommon Locations for ALT/WDL

- Mediastinum
  - Most common liposarcoma of mediastinum
  - Thymoliposarcoma
- Larynx, hypopharynx
- GI tract, esophagus (giant polyp)

Spindle Cell ALT/WDL

Poorly-defined entity, Good prognosis, MDM2 not amplified

Lipoma with Fat Necrosis
Nuclear Vacuoles (Lochkerns)

Lipoma-like Hibernoma
Localized Massive Lymphedema
Prognosis in ALT/WDL

- No metastatic potential
- Local recurrences
  - Retroperitoneum: Very high
  - Extremities: Half of cases
- Progression to dedifferentiated liposarcoma at recurrence

Dedifferentiated Liposarcoma

- Described and defined by Evans in 1979
  - Distinct areas of WDL and non-lipogenic (high-grade) spindle cell or pleomorphic sarcoma
- Definition has been expanded to include:
  - Low-grade tumors
  - Distinctive patterns
  - Heterologous and homologous (lipogenic) differentiation
  - Tumors diagnosed by molecular biology without seeing ALT/WDL component
Dedifferentiated Liposarcoma

- Derives from ALT/WDL
  - Supernumerary ring & giant marker chromosomes
  - Amplification of 12q13-15
    - MDM2, HMGA2, CDK4
    - Cell cycle regulation
  - Additional genomic alterations and genomic instability

Dedifferentiated Liposarcoma

- 10-20% of Liposarcomas
- Retroperitoneum, most common
- 90% arise de novo
- 10% in recurrent ALT/WDL
- Better prognosis than other pleomorphic sarcomas
  - Less apt to metastasize (6% MSKCC)
  - Very high rate of local recurrence

Amount of dedifferentiation is highly variable and not proven to be prognostic
Wide Histologic Variation

- Undifferentiated pleomorphic sarcoma
- Inflammatory MFH
- Undifferentiated spindle cell sarcoma
- Rhabdomyosarcoma
- Well-differentiated fibrosarcoma
- Rhabdomyosarcoma
- Fibromatosis
- OFSP
- Malignant solitary fibrous tumor / HPC
- Epithelial with prominent nucleoli
- Myxofibrosarcoma
- Low-grade myxofibrosarcoma
- Malignant fibrous histiocytoma +/- osteoclast
- Capsular / saffron
- Embryonal rhabdomyosarcoma

- Small cell sarcoma
- Parangangioma-like
- Myofibroblastic sarcoma
- Myofibroblastic with prominent cellular fibroblast
- Lymphangiosarcoma
- Leiomyosarcoma
- Osteochondrosarcoma
- Angiosarcoma
- Hemangioendothelioma
- Pleomorphic liposarcoma
- Pleomorphic liposarcoma, epithelioid variant
- Low-grade pleomorphic liposarcoma
- Spindle cell liposarcoma
Low-Grade Dedifferentiated Liposarcoma

- Often resembles desmoid-type fibromatosis
- Precursor to high-grade DL
- Metastatic potential
- Not associated with improved survival

(Henricks 1997)
Most Retroperitoneal UPS are DL

Most Inflammatory MFH are DL
Most Retroperitoneal Sarcomas with Myxoid Stroma are DL

Meningotheelial-Like Whorls
Heterologous Differentiation

Rhabdo.  Leio.  Osteo.

Myogenin

DL with Myosarcomatous Differentiation

- Virtually all pleomorphic rhabdomyosarcomas in the retroperitoneum are DL

- DL with leiomyosarcomatous differentiation
  - Less apt to metastasize than pure LMS
  - More apt to recur locally


DL with Pleomorphic Liposarcoma-like Areas (Homologous DL)
Homologous (Lipogenic) Differentiation

• DL with pleomorphic LPS-like areas (Evans 2007, Boland & Morice-Lencastre 2010)
  – Molecular features in common with ALT/WDL
  – Less aggressive than pleomorphic LPS
• Low-grade homologous DL (Liau, 2013)
• Lipogenic differentiation in “comingling” areas of ALT/WDL and DL (Iwasa, 2013)
Myofibroblastic Differentiation in DL

- Henricks (1997)
  - Low grade DL resembling fibromatosis & Palisaded myofibroblastoma with amianthoid fibers
- Hasegawa (2000)
  - 44% actin, 44% desmin
  - 3/32 myofibroblastic
  - 2 ultrastructural features of myofibroblasts
- Lucas (2010)
  - 6 cases IMT-like
- Rekhi (2012)
  - 1/25 myofibroblastic
  - 1/25 IMT-like

DL with Myofibroblastic Features
Smooth Muscle Actin

Desmin

DL with Inflammatory Myofibroblastic Tumor-like Features
Dedifferentiated Liposarcoma

- Tremendous histologic variation
- Original definition has been expanded to include low-grade tumors and ones with lipogenic differentiation
- Most poorly-differentiated sarcomas, myxoid sarcomas, and rhabdomyosarcomas in the retroperitoneum are DL

Dedifferentiated Liposarcoma

- ALT/WDL/DL represents a spectrum within a single disease entity
  - Multi-step genomic progression
- Evidence suggest certain histologic patterns are associated with specific genetic alterations and clinical behaviors
  - (Crago AM, Clin Cancer Res 2012)
- Greater understanding of pathways may help identify specific therapeutic targets

Myxoid Liposarcoma

- Translocation-associated sarcoma
- Spectrum from low- to high-grade
- t12:16 (FUS-DDIT3) fusion forming a transcription factor in 90-95%
- t12:22 (EWSR1-DDIT3) in a minority
Myxoid Liposarcoma

- Common sites in extremities
- Only very rarely seen as primary retroperitoneal tumor
- Propensity for metastasis to other soft tissue sites and bone
Myxoid Liposarcoma
Myxoid LPS with Spindle Cell and Pleomorphic Features
DDIT3 Rearrangement

Histologic Spectrum

- Myxoid
- Myxoid / Round Cell 5%
- Round Cell
Round Cell Liposarcoma
Prognosis in Myxoid Liposarcoma

- 20% to 40% develop metastases
  - Peculiar tendency to metastasize to peripheral soft tissue and bone
- Tumors with a round cell component have higher risk for metastasis
  - Worse prognosis with increasing proportion of round cell areas
  - 5-25% round cells portends worse prognosis
  - Spontaneous tumor necrosis unfavorable

Important Differential Diagnoses in Myxoid Liposarcoma

- Lipoblastoma
- Intramuscular myxoma
- Myxoid DFSP
- Myxofibrosarcoma
- ALT/WDL with myxoid stroma
MFS with Pleomorphic Nuclei

MFS with Curvilinear Vessels and Perivascular Condensation

ALT/WDL with Myxoid Stroma
Pleomorphic Liposarcoma

- Pleomorphic, necrotizing, high-grade
- Often resemble UPS with only scattered lipoblasts
- Other tumors are loaded with lipoblasts
- Giant cells are common
- "Epithelioid" variant
- Complex cytogenetic profiles
Epithelioid Variant of PL

Pleomorphic Liposarcoma with Myxoid Stroma

Prognosis in Pleomorphic Liposarcoma

- Metastatic and mortality rates range from 32% to 45% and 30% to 50%, respectively
- Cutaneous examples are indolent if completely excised, but local recurrence is possible
Liposarcoma of Bone

- Very rare
- Usually in long bones
- Most are high grade pleomorphic liposarcomas
- Aggressive behavior
- Must exclude metastasis from a soft tissue tumor

Thank you