Dedifferentiated liposarcoma with myxoid liposarcoma-like features and amplification of DNA damage-inducible transcript 3 (DDIT3) - an important diagnostic pitfall

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I have no conflict of interest to declare.
## Liposarcoma

### ALT/WDLPS

### DDLPS
- 10%
- Retroperitoneum
- 60-70 years old
- M>F
- 12q13-15 amplification [MDM2 amplification is found in 100%]

### Myxoid LPS
- 30-35%
- Extremities (thigh)
- 30-50 years old
- M=F
- t(12;16)(q13:p11)
- t(12;22)(q13;q12)

### Pleomorphic LPS

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Practical Soft Tissue Pathology: A Diagnostic Approach, 12, 311-340
Histopathology features of DDLPS and myxoid LPS

**DDLPS**

- presence of highly differentiated fat component (ALT/WDLPS) and additionally sarcoma fields mostly non-adipocytic, cellular, high-grade with significant pleomorphism;
- most often the morphology of undifferentiated pleomorphic sarcoma and myxofibrosarcoma or with heterologous differentiation towards rhabdomyosarcoma, leiomyosarcoma, osteosarcoma, angiosarcoma;
- the dedifferentiated component should occupy a diameter of at least 1 cm and exhibit mitotic activity of at least 5/10 HPF (0.2 mm).

**Myxoid LPS**

- prominent myxoid stroma with branching vasculature (so-called chicken wire vasculature);
- relatively low cellularity, low cytological atypia, without significant mitotic activity;
- numerous, scattered signet ring lipoblasts;
- high-grade myxoid LPS cases (formerly round cell liposarcoma) are characterized by the presence of fields with increased cellularity/round cell (> 5%).

DDIT3
- DDIT3 is a member of the C/EBP transcription factor family that plays an important role in adipocyte differentiation;
- Fusion proteins (DDIT3-FUS or DDIT3-EWSR1) responsible for dysregulation of adipocyte differentiation

MDM2
- MDM2 is an ubiquitin-protein ligase that promotes p53 protein degradation.
- Increased MDM2 protein is a key factor in blocking p53 signal transduction → tumor formation.
- [CDK4 – a key regulator of cell cycle – coamplified in over 90%]
MDM2 probes for FISH:
DDIT3 break apart probes for FISH:
AIM:

to present a case series of DDLSP with myxoid LPS-like features harboring both, *MDM2* and *DDIT3* amplification.
Inclusion criterion: DDLPS with myxoid LPS-like morphology

6 patients

Methods:

- **Pathologic features:** the presence of myxoid LPS-like morphology, homologous lipoblastic differentiation and round-cell component

- **Immunohistochemistry:** status of MDM2 by mouse monoclonal antibody MDM2 (clone SMP14), Zeta Corporation, USA

- **Molecular genenetics:** status of MDM2 and DDIT3 genes by fluorescence *in situ* hybridization (FISH)
Myxoid LPS-like morphology:

- prominent myxoid stroma with branching capillary network and associated with uniform, oval neoplastic cells lacking pleomorphism.

Homologous lipoblastic differentiation:

- features resembling pleomorphic liposarcoma including pleomorphic lipoblasts with multivacuolated cytoplasm.


Methods (FISH):

**DDIT3 positive:**
100 tumor cells
> 25% of tumor nuclei demonstrating rearrangement
[split signal → space between the two signals should be larger than that of one signal]

**MDM2 positive:**
60 tumor cells
MDM2/CEP 12 ratio ≥ 2

FISH probe: **CytoTest, Inc. (USA)**
## Results:

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Size [cm]</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>53</td>
<td>30</td>
<td>Retroperitoneum</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>44</td>
<td>20</td>
<td>Suprapubic area</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>75</td>
<td>14</td>
<td>Retroperitoneum</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>85</td>
<td>22</td>
<td>Thigh</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>56</td>
<td>23.5</td>
<td>Retroperitoneum</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>68</td>
<td>10</td>
<td>Suprapubic area</td>
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</table>
### Results:

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Morphology</th>
<th>Recurrence</th>
<th>CHTH</th>
<th>Follow up</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Myxoid LPS-like</td>
<td>Pleomorphic LPS-like</td>
<td>Round cell LPS-like</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>-</td>
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<tr>
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<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Case no. 1

Myxoid LPS-like morphology, H&E

MDM2 IHC
Case no. 2

Myxoid LPS-like morphology, H&E

MDM2 IHC
Case no. 3

Myxoid LPS-like morphology, H&E

MDM2 IHC
Case no. 4

Myxoid LPS-like morphology, H&E

MDM IHC
Case no. 5

Myxoid LPS-like morphology, H&E

Pleomorphic LPS-like morphology, H&E
Case no. 5

Myxoid LPS-like + pleomorphic LPS-like morphology, H&E

MDM2 IHC
Case no. 6

Myxoid LPS-like morphology, H&E

Pleomorphic LPS-like morphology, H&E
Case no. 6

Myxoid LPS-like + pleomorphic LPS-like morphology, H&E

MDM2 IHC
Results (FISH): ALL cases $DDIT3$ amplification
Results (FISH): ALL cases *MDM2* amplification
DDLPS with *DDIT3* amplification:

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cases</th>
<th>Age [years]</th>
<th>Sex [M:F]</th>
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<th>Morphology</th>
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<td>Retroperitoneum</td>
<td>Extremities</td>
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<td>Presented</td>
<td>6</td>
<td>63.5</td>
<td>2:1</td>
<td>3</td>
<td>1</td>
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<td>Mantilla et al.</td>
<td>16</td>
<td>54.3</td>
<td>1:1</td>
<td>12</td>
<td>1</td>
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<tr>
<td>Rao et al.</td>
<td>5</td>
<td>65.8</td>
<td>3:2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Ma et al.</td>
<td>1</td>
<td>70</td>
<td>1F</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>


Conclusions:

- **DDIT3** amplification correlates with myxoid LPS-like features;
- **DIDT3**-amplified DDLSP with areas resembling myxoid and pleomorphic liposarcoma may be misclassified as myxoid or pleomorphic liposarcoma [new proposal WHO 2020 myxoid pleomorphic liposarcoma! without any gene alteration (?!)].
- The morphology is no longer enough – both MDM2&DDIT3 should be evaluated [small biopsies!!!]
- **DDIT3** & **MDM2** coamplified dedifferentiated liposarcoma with myxoid-like morphology? New / the same entity?

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Thank you for your attention!

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