Case 2

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Case 2

26 year-old female
Presented during pregnancy with obstructive urinary symptoms
Pelvic/retroperitoneal mass
Serum germ cell markers in normal range

En bloc resection of retroperitoneal/pelvic mass
Hysterectomy, BSO and total cystectomy
15 x 12.5 x 10 cm lobulated mass
Case 2

**Diagnosis**

Dedifferentiated liposarcoma (DDL)

**FISH**

- **MDM2** gene at 12q15
- Chromosome 12 centromere (CEP12)

- High-level **MDM2 amplification**
Case 2

**Diagnosis**

- Dedifferentiated liposarcoma (DDL)
- Homologous lipoblastic differentiation
- ‘Pleomorphic liposarcoma-like DDL’

**Follow-up**

- Aggressive behavior
- Pulmonary metastases 2 months after surgery
- Death from progressive disease 20 months after presentation

**Unusual features**

- Young patient
- Aggressive behavior
- Homologous lipoblastic differentiation

**Dedifferentiation**

- Subset of neoplasms
- High grade tumor, without evidence of line of differentiation of original neoplasm
Dedifferentiation

Mesenchymal tumors
- Chondrosarcoma
- Chordoma
- Liposarcoma
- Solitary fibrous tumor
- MPNST
- Dermatofibrosarcoma
- GIST

Chondrosarcoma

Dedifferentiation

Arises de novo or as complication of recurrent, previously well differentiated tumor

Abrupt transition

Confers more aggressive behavior

Solitary fibrous tumor

Dedifferentiated liposarcoma

Non-lipogenic sarcoma without evidence of original adipocytic line of differentiation

- in conjunction with ALT/WDL
- recurrence of WDL
- de novo

Middle-aged to older adults

Retroperitoneum
Extremities
Trunk
Paratesticular region

WDL ➔ DDL

Biologic and morphologic spectrum

Biologically aggressive end of the WDL/DDL spectrum

Genetics

Ring/giant chromosomes with amplified 12q13-15

CDK4 and MDM2 oncogenes
Case 2

Dedifferentiated liposarcoma

Genetics
DDL has additional genetic events
e.g. ASK1 6q23 (MAP3 kinase)
JUN 1p32

Behavior
Typically less aggressive than other pleomorphic sarcomas

Morphology
Heterogeneous
Undifferentiated pleomorphic sarcoma (UPS)
(formerly malignant fibrous histiocytoma; MFH)

Most retroperitoneal MFH (UPS) are dedifferentiated liposarcomas
Coindre et al. 2003

Morphology
Myxofibrosarcoma-like

Morphology
Inflammatory MFH-like
**Dedifferentiated liposarcoma**

**Morphology**

- Giant cell-rich
  
  **Lucas et al. 2010**

- Can resemble other soft tissue neoplasms
  e.g. inflammatory myofibroblastic tumor-like

**Low-grade dedifferentiation**

- e.g. low grade fibromyxoid sarcoma-like
  
  **Evans et al. 1994**

  **Henricks et al. 1997**

  **Nascimento et al. 1998**

- Fibromatosis-like
  
  **Fanburg-Smith & Miettinen 1998**

**Heterologous differentiation**

- Towards other mesenchymal lineages
  e.g. myoid, chondroid, osteoid
  
  **Henricks et al. 1997**

- Meningothelial-like whorls
  
  **Evans et al. 1994**

  **Henricks et al. 1997**

  **Nascimento et al. 1998**

  **Fanburg-Smith & Wettinen 1998**
Dedifferentiated liposarcoma

Heterologous differentiation

Meningothelial-like whorls

Evans et al. 1994
Henricks et al. 1997
Nascimento et al. 1998
Fanburg-Smith & Miettinen 1998

Adipocytic differentiation in DDL

Homologous differentiation

Adipocytic differentiation is very rare

Adipocytic differentiation in DDL

WDL with pleomorphic liposarcoma-like areas

Hasegawa et al. 2000
Evans 2007
Suster & Morrison 2008

Adipocytic differentiation in DDL

Debate
DDL defined as non-lipogenic sarcoma
‘Mixed liposarcoma’
‘WDL with pleomorphic liposarcoma’
‘Sclerosing poorly differentiated liposarcoma’

Adipocytic differentiation in DDL

Boland et al. 2010
Mariko-Enriquez et al. 2010
Rekhi et al. 2012
Liu et al. 2013

Adipocytic differentiation in DDL

Liposarcoma With Mixed Well-differentiated and Pleomorphic Features: A Clinicopathologic Study of 11 Cases

Adipocytic differentiation in DDL

Dedifferentiated Liposarcoma With “Homologous” Lipoblastic (Pleomorphic Liposarcoma-like) Differentiation: Clinicopathologic and Molecular Analysis of a Series Suggesting Revised Diagnostic Criteria
Case 2
Homologous lipoblastic differentiation in DDL

Retroperitoneum
Small numbers: abdomen, groin, scrotum, thigh, buttoc, mediastinum, chest wall

Primary or recurrent
Distant (lung) metastasis of previous classical DDL

Clinical course variable
No prognostic differences with classical DDL

Composition varies
Variable numbers of lipoblasts
Spectrum of morphologic atypia

Composition varies
Spectrum of atypia
Homologous lipoblastic differentiation in DDL

Composition varies
Individually
Small clusters
Sheets

Variants
Epithelioid lipoblasts resembling epithelioid variant of pleomorphic liposarcoma
May coexist with other lines of heterologous differentiation

Genetics
Similar to classical DDL
Amplifications at 12q14-15 >90% (MDM2, HMGA2 and CPM)

CDK4 p16
Homologous lipoblastic differentiation in DDL

**Diagnosis**

- More difficult in Tumors without discernible WDL component
- Patients without previous history of WDL

Why is correct diagnosis important?

**Prognostication**

DDL typically more indolent than other pleomorphic sarcomas

McCormick et al. 1994

**Management: targeted therapies**

- MDM2 antagonists- nutlins
- CDK4 inhibitor- flavoperidol
- ASK1 antagonist- thioridazin
- JNK activator (apoptosis)- aplidin
- C/EBPa- restoration - demethylating agents

Differential diagnosis

**Adipocytic neoplasms**

- Tumors with lipoblasts or lipoblast-like cells

**Differential diagnosis**

**Pleomorphic liposarcoma**

- Older population
- Extremity and trunk
- Rare in retroperitoneum/pelvis

**Pleomorphic myxoid liposarcoma**

- Mediastinum
- Pediatric population

Alaggio et al. 2009
Boland et al. 2010
**Case 2**

**Differential diagnosis**

**Pleomorphic myxoid liposarcoma**

- Mediastinum
- Pediatric population
  - Alaggio et al. 2009
  - Boland et al. 2010

**Spindle cell liposarcoma/Atypical spindle cell lipomatous tumor**

- Limbs/limb girdles; rare in retroperitoneum
  - Dei Tos et al. 1994
  - Mentzel et al. 2010
  - Deyrup et al. 2013
  - Creytens et al. 2014

**Spindle cell liposarcoma/Atypical spindle cell lipomatous tumor**

- Limbs/limb girdles; rare in retroperitoneum
  - CD34 (64%), S100 (40%), desmin (22%)
  - Rb loss in 57%

**MMMT/Carcinosarcoma with heterologous lipoblastic differentiation**

- Older (>65 years)
- Uterine corpus
  - Other gynecologic sites
  - Biphasic tumors - epithelial and mesenchymal elements
  - Focal keratin expression

**Pseudolipoblasts in other sarcomas**

- Myxoinflammatory fibroblastic sarcoma
- Vacuolated fibroblasts
  - t(1;10)(p22;q24) with TGFBR3 and MGEA5 rearrangements
  - Marker/ring chromosome 3 with 3p amplicons
**Differential diagnosis**

**Pseudolipoblasts in other sarcomas**

Chemotherapy

Rhabdomyosarcoma with pseudolipoblasts

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**Differential diagnosis**

**Pseudolipoblasts in other sarcomas**

Chemotherapy

Desmin

Rhabdomyosarcoma with pseudolipoblasts

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**Differential diagnosis**

Other neoplasms in the differential diagnosis of DDL

Negative CDK4, MDM2 and p16 immunohistochemistry

No MDM2 amplification with FISH

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**Homologous lipoblastic differentiation in DDL**

Rare but increasingly recognized

12q13-14 + additional

Principal differential diagnosis: pleomorphic LPS

Can behave aggressively

Specific targeted treatments

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THANK YOU