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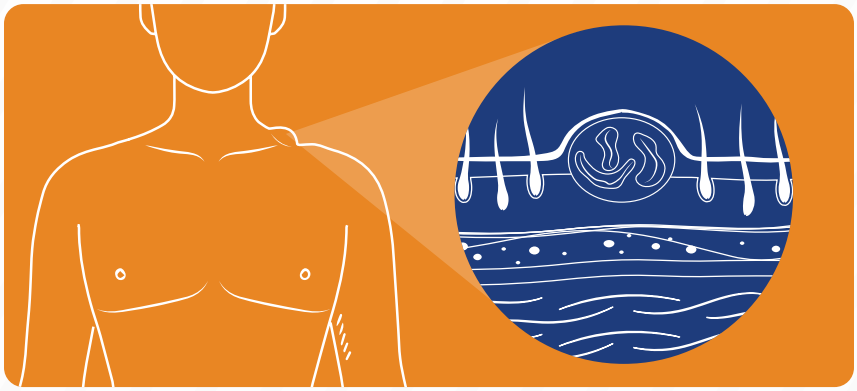
Pathology of Well-differentiated and Dedifferentiated Liposarcomas



Liposarcomas constitute a heterogenous group of soft tissue tumors that arise from fat cells and exhibit varying degrees of tissue differentiation[1]

They occur most commonly in the deep soft tissue of the proximal extremities and retroperitoneum[1,2]

They are classified into five major subtypes based on distinct histological and molecular characteristics[1,3]

50%–60%

Atypical lipomatous tumors (ALT)/well-differentiated liposarcoma (WDLPS)

of all liposarcomas, middle-aged to older adults, peaks at 4th and 5th decades

10%

Dedifferentiated liposarcoma (DDLPS)

of WDLPS, middle-aged and older adults, peaks from 6th to 7th decade

30%–35%

Myxoid liposarcoma (MLPS)

of all liposarcomas, age range 30–50 years, peaks at the 5th decade

10%

Pleomorphic liposarcoma (PLPS)

of all liposarcomas, rare, age range 50–80 years, peaks at the 7th decade

<1%

Myxoid pleomorphic liposarcoma (MPLPS)

of all liposarcomas. The most recent addition to the World Health Organization's (WHO) classification of soft tissue and bone tumors, predominantly affects young adults and children

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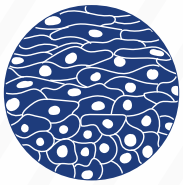
ALT/WDLPS[1–3]

Defined as locally aggressive mesenchymal neoplasm composed of adipocytic proliferation showing at least focal nuclear atypia in both adipocytes and stromal cells

Characteristic features of ALT/WDLPS



Histology

- Consists mainly of mature and variable-in-size adipocytes, atypical stromal cells, and a small number of scattered fat mother cells
- Similar to normal adipose tissue and mature benign lipoma tissues
- Fibrous bands and thick-walled vessels
- Atypical stromal cells within fibrous bands and perivascular
- Lipoblasts rare

Histological variants

Lipoma-like

Composed of variably-sized mature adipocytes

Fibrous bands and scattered atypical stromal cells

Rare lipoblasts

Sclerosing

Most common in the groin and retroperitoneum

Dense fibromyxoid to fibrous stroma with fewer adipocytes

Atypical stromal cells

Rare lipoblasts

Can be confused with DDLPS in both histology and radiology

Inflammatory

Dense lymphocytic inflammatory infiltrate associated with mature adipocytes

Atypical stromal cells

Rare lipoblasts

Rare variants

With smooth muscle components (lipoleiomyosarcoma)

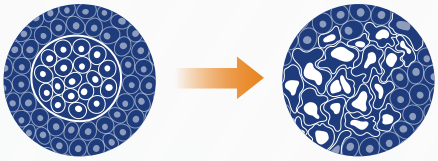
With low-grade osteosarcoma-like areas

Cytogenetic

- Supernumerary ring chromosome and/or giant marker chromosome composed of amplified products from the chromosome 12 q13–15 region
- Gene amplification of *MDM2, CDK4, HMGA2, CPM, SAS/TSPAN31, DYRK2, YEATS4*, and others. Amplification of *MDM2* and/or *CDK4* almost always present
- 10% of WDLPS transform into DDLPS accumulating complex genomic aberrations

Location – ALT and WDLPS can be differentiated based on their location

- Vast majority in the extremities (75%), less common in retroperitoneum, spermatic cord, and head and neck
- ALT – extremities, superficial trunk, and pelvis
- WDLPS – retroperitoneum, mediastinum, pelvis, and spermatic cord

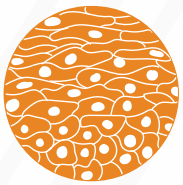


ALT/WDLPS are locally aggressive tumors that can transform into DDLPS with a higher invasive and metastatic potential

DDLPS[1–3]

About 10% of ALT/WDLPS, either in the primary or recurrent stage, exhibit non-lipogenic features of variable histological grade and are classified as DDLPS

Characteristic features of DDLPS



Histology

- A well-differentiated component may not be identifiable
- Significant intratumoral morphological variation

Histological variants

- **Fibrosarcoma-like**
  Cellular, spindle cell sarcoma arranged in fascicles or herringbone pattern
- **Pleomorphic**
  Anaplastic tumor cells
- **Myxofibrosarcoma-like**
  Myxoid stroma, curvilinear vasculature
- **Inflammatory**
  Subtype composed of pleomorphic tumor often obscured by prominent neutrophilic inflammation
- **"Low-grade" DDLPS**
  Bland–appearing spindle cell component with no/rare mitoses and no necrosis
  Appears similar to sclerosing WDLPS variant

Rare patterns of DDLPS with trans-differentiation

- Pleomorphic rhabdomyosarcoma
- Angiosarcoma
- Osteosarcoma
- Chondrosarcoma
- Pleomorphic liposarcoma
- DDLPS with meningothelial-like whorls and bone formation
- DDLPS with epithelioid morphology (resembling carcinoma/melanoma)

Cytogenetic

- Giant and ring chromosomes with amplifications in the chromosome 12 q13–15 region
- Larger and more complex gene amplifications compared to WDLPS
- ***MDM2* is overexpressed and amplification can be extended to other genes**
- Amplification event may extend to other genes – *CDK4, HMGA2, GLI1, STAT6, DDIT3*
- Result in overexpression of *MDM2, CDK4, HMGA2, GLI1, STAT6,* and *DDIT3*

Location

- 75% Retroperitoneum
- 10%–20% Extremities
- 10% Head and neck
- 10% Groin or spermatic cord

Immunohistochemistry combined with molecular techniques, such as fluorescent *in situ* hybridization and next-generation sequencing analysis, can help in the differential diagnosis of DDLPS

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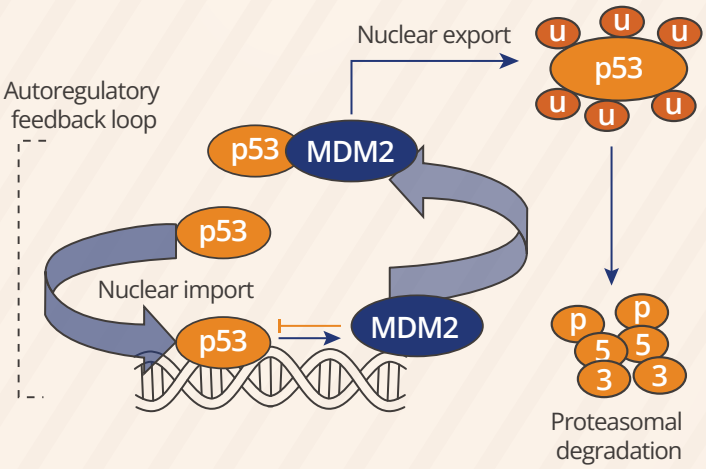
Role of *MDM2* in the pathogenesis and diagnosis of WDLPS and DDLPS[1,4]



- p53 is a crucial tumor suppressor protein that regulates cell proliferation, DNA repair, and apoptosis
- The functions of p53 are defensive against cancer onset and progression
- MDM2-p53 interaction is known to negatively regulate p53 function and drive tumorigenesis
- MDM2 recruits p53 for ubiquitination and subsequent proteasomal degradation
- MDM2 amplification and overexpression promote the accumulation of DNA damage and uncontrolled cell proliferation

The subset of ALT/WDLPS with or without DDLPS does not harbor *MDM2* amplification

- Only *CDK4* amplification
- Only *MDM4* amplification (*MDM4* is structural homologue of *MDM2*)
- Other complex and unknown genetic aberrations

Identifying a well-differentiated adipocytic component can aid their diagnosis

MDM2 amplification and overexpression have been associated with other tumor types[5]

- Parosteal osteosarcoma
- Low-grade central osteosarcoma
- Intimal-type sarcoma

Rare

- Myxofibrosarcoma and undifferentiated pleomorphic sarcoma
- Leiomyosarcoma
- Malignant peripheral nerve sheath tumors

MDM2 amplification/overexpression alone, therefore, cannot be used to conclusively diagnose liposarcoma

Key messages

- Liposarcomas encompass a group of rare malignancies among which DDLPS stands out as an aggressive subtype
- DDLPS is a rare malignancy that transitions from an ALT to a sarcoma with a variable morphologic appearance
- DDLPS presents diagnostic challenges due to its diverse histological variants and cytogenetic features, including *MDM2* amplification
- DDLPS carries a higher risk of progression and metastasis compared to WDLPS
- Early detection and precise classification of DDLPS variants are crucial for determining appropriate treatment strategies and predicting patient outcomes

References

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