What’s new in adipocytic neoplasia?

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Since the publication of the 2013 WHO classification, the most notable change in the category of adipocytic tumors has been made in the group of ‘atypical low-grade adipocytic neoplasms with spindle cell features’

These tumors, first described by Dei Tos et al as ‘spindle cell liposarcoma’ are characterized by atypical spindle cells and a variably prominent adipocytic component, associated with a risk of local recurrence, but lack of dedifferentiation or distant metastasis

‘spindle cell liposarcoma’ has been a confusing and evolving entity over the past few decades

In the WHO 2013 classification, ‘spindle cell liposarcoma’ was still considered as an uncommon morphologic variant of atypical lipomatous tumor/well-differentiated liposarcoma (but lacks the pathognomonic MDM2 gene amplification!)

It has become clear that these subset of adipocytic tumors (in the past also variably referred to as ‘well-differentiated spindle cell liposarcoma’, ‘fibrosarcoma-like lipomatous neoplasm’ and ‘atypical spindle cell lipoma’) does not seem to fit into any of the existing diagnostic categories of adipocytic tumors

Since the publication of the 2013 WHO classification, however, there have been substantial steps forward in the clinicopathologic and molecular (cyto)genetic characterization of this family of adipocytic tumors, for which the term atypical spindle cell/pleomorphic lipomatous tumor has been proposed
What’s new in adipocytic neoplasia? (2)

- Another substantive change in the group of adipocytic tumors is the introduction of pleomorphic myxoid liposarcoma (myxoid pleomorphic liposarcoma) as an apparently novel subtype of aggressive liposarcoma, especially occurring in children and young adults with a predilection for the mediastinum
Atypical spindle cell/pleomorphic lipomatous tumor
Atypical spindle cell/pleomorphic lipomatous tumor is a benign adipocytic neoplasm, characterized by ill-defined tumor margins and the presence of variable proportions of mild to moderately atypical spindle cells, adipocytes, lipoblasts, pleomorphic multinucleated giant cells and a myxoid or collagenous extracellular matrix.

It has a low tendency for local recurrence if incompletely excised.

Unlike conventional atypical lipomatous tumours, there is no risk for dedifferentiation.
Clinical features

- Persisting or enlarging soft tissue mass, nodule, or swelling, arising in the subcutis slightly more frequently than in deep (subfascial) somatic soft tissues (occasionally intracavitary or visceral locations)
- **Wide anatomic distribution**, predominating in the limb and limb girdles
- The most common locations: hands and feet, and the thigh, followed by the shoulder, upper arm, forearm, knee, lower leg, and buttock
- Less common locations: head and neck, trunk, back, and genital area
- Rare sites of involvement include retroperitoneum, mediastinum, larynx, trachea and appendix
- **Predominantly in middle aged adults** with a peak incidence in the sixth decade of life (but can affect patients of any age); slight male predominance
Pathologic features

• Grossly, these tumors are **unencapsulated**, show a nodular or multinodular growth pattern, and demonstrate **ill-defined tumor margins**

• Tumor size is variable (range 0.5 to 28 cm, median 5 to 8.5 cm)

• Histologically, a **wide range of microscopic appearances can be observed**, even regionally within the same lesion, depending on the relative proportions of atypical spindle cells, adipocytes, lipoblasts, pleomorphic (multinucleated) cells, and the variable amount of collagenous and/or myxoid extracellular matrix
Pathologic features

- The adipocytic component has a predominantly mature morphology with variation in adipocytic size and shape
- The morphology of the lipoblasts can vary from small univacuolated, or bivacuolated to larger multivacuolated (‘pleomorphic’) lipoblasts
- Bizarre, hyperchromatic, and sometimes pleomorphic multinucleated cells are often scattered within the spindle cell or adipocytic components
- Mitotic figures are often present, but mostly scarce
- Tumor necrosis is absent
- A rare finding is heterologous (metaplastic) differentiation, including presence of smooth muscle, cartilaginous, and/or osseous elements
Pathologic features

• The morphology of these tumors can best be described as a broad spectrum defined by 2 dissimilar extremes: ‘low-cellularity end’ and ‘high-cellularity end’ of the morphological spectrum

• Other peculiar growth patterns:
  - presence of staghorn-like vessels in a collagenous-rich background (solitary fibrous tumor-like growth pattern)
  - the presence of a prominent branching capillary network (soft tissue angiofibroma-like growth pattern)
  - presence of abundant myxoid matrix and prominent capillary chickenwire-like vascular network (myxoid liposarcoma-like growth pattern)
  - striking perivascular location of the atypical spindle cell/pleomorphic cells (pericytic mimicry)
‘Fat-rich’ (spindle cell-poor) variant of atypical spindle cell/pleomorphic lipomatous tumor
FIGURE 1. Microscopic appearance of fibrosarcoma-like lipomatous tumor. Tumors were composed of slender bipolar spindled cells resembling fibroblasts and arranged parallel to one another with a spectrum of lipoblastic differentiation (A and B) and loosely separated by a variably myxoid stroma with arborizing capillaries (C). D, Rarely, myxoid change was prominent. E, The least differentiated cells resemble preadipocytes with a symmetrically tapered shape and an elongated nucleus with finely stippled chromatin and no atypia. F, The more-differentiated cells showed a dominant vacuole that indented the nucleus (ice cream cone lipoblast) or 2 vacuoles resembling an hourglass.
‘Pericytic mimicry’ in atypical spindle cell/pleomorphic lipomatous tumor

Immunohistochemistry and genetic/molecular studies

• The tumor cells show **variable expression for CD34, S100, and desmin**

• Weak and/or focal expression for MDM2 or CDK4 can be rarely seen; however the combination of MDM2 and CDK4 expression is not encountered

• **Loss of nuclear Rb expression** is observed in around 50-70% of cases

• **Deletions/losses of 13q14** (including *RB1* and its flanking genes *RCBTB2, DLEU1, ITM2B*) in a significant subset of cases

• **Consistent absence of MDM2/CDK4 amplification**
Prognosis and prediction

• Mostly indolent behavior with local recurrence occurring in 10-15% of patients

• No reported distant metastasis or death of disease

• No documented risk for dedifferentiation

• Most patients will have an excellent prognosis if the lesion is completely excised
Differential diagnosis

- spindle cell/pleomorphic lipoma
- ‘classical’ atypical lipomatous tumor/well-differentiated liposarcoma
- diffuse neurofibroma
- mammary-type myofibroblastoma
- solitary fibrous tumor
- dermatofibrosarcoma protuberans (DFSP)
- low-grade malignant peripheral nerve sheath tumor (MPNST)
- ‘low-grade’ dedifferentiated liposarcoma
- pleomorphic liposarcoma


Mentzel T, Palmego D, Kuhnhen C. Well-differentiated spindle cell liposarcoma ('atypical spindle cell lipomatous tumor') does not belong to the spectrum of atypical lipomatous tumor but has a close relationship to spindle cell lipoma: clinicopathologic, immunohistochemical, and molecular analysis of six cases. Mod Pathol. 2010 May;23(5):729-36.


Agaimy A. Anisometric cell lipoma: Insight from a case series and review of the literature on adipocytic neoplasms in survivors of retinoblastoma suggest a role for RB1 loss and possible relationship to fat-predominant ('"fat-only") spindle cell lipoma. Ann Diagn Pathol. 2017 Aug;29():52-56.


Pleomorphic myxoid liposarcoma (myxoid pleomorphic liposarcoma)
Definition WHO 5th edition (2020)

Pleomorphic myxoid liposarcoma is an exceptionally rare, aggressive adipocytic neoplasm, typically occurring in children and adolescents.

Pleomorphic myxoid liposarcoma shows mixed histological features of conventional myxoid liposarcoma and pleomorphic liposarcoma.

Pleomorphic myxoid liposarcoma lacks the gene fusions and amplifications of myxoid liposarcoma, atypical lipomatous tumour and dedifferentiated liposarcoma.
Clinical features

• Tumor generally manifests as a large, deep-seated soft tissue mass
• Predilection for the mediastinum
• Other reported locations include the thigh, head and neck, back, abdomen, and perineum
• Tumors occur **predominantly in children and adolescents**; patient age in the large majority of published cases is under 30 years old with a female predominance
• Association with Li-Fraumeni syndrome has been described
Pathologic features

- Grossly, these tumors are **non-encapsulated with ill-defined margins**
- Histologically, these tumors show **variable proportions of conventional myxoid liposarcoma-like areas** (abundant myxoid matrix; relatively bland primitive round to oval cells; scattered lipoblasts; delicate curvilinear to plexiform capillary network; “lymphangioma-like” myxoid pools)
- Pleomorphic spindled to ovoid cells with hyperchromatic nuclei may be scattered within the myxoid component, with a **progressive transition into more cellular, solid, sheet-like, high-grade pleomorphic liposarcoma-like areas** (severe cytological atypia; pleomorphic lipoblasts; increased mitotic activity; atypical mitoses; and occasional necrosis)
Immunohistochemistry and genetic/molecular studies

- **Nonspecific immunophenotype**
- **Negativity for MDM2 and CDK4**; and variable expression for S100 are reported
- **Genetic data are scarce** and the molecular characteristics have so far only been explored in small series and case reports
- **PML lacks the FUS/EWSR1-DDIT3 gene fusions** seen in conventional myxoid liposarcoma, and **MDM2/CDK4 amplifications** present in well-differentiated/dedifferentiated liposarcoma
- Additional aCGH studies have revealed a **complex pattern of chromosomal gains and losses**; **inactivation of RB1 tumor suppressor gene** is pathogenetically important in this tumor type
- PML lacks the complexity of conventional pleomorphic liposarcoma alterations, which typically involve focal copy number changes, rather than **whole gains and losses**
Prognosis and prediction

- Extremely aggressive tumor type

- High recurrence rate; metastasis to lung, bone, and soft tissue; and poor survival rates
Pleomorphic myxoid liposarcoma (myxoid pleomorphic liposarcoma)

• Based on the **particular clinical presentation** (usually occurring in young patients), the **distinctive histological features** and the **molecular features** (no FUS/EWSR1-DDIT3 gene fusions; differences in aCGH findings), PML must be differentiated from conventional myxoid liposarcoma and pleomorphic liposarcoma and may represent a new and separate subtype of liposarcoma.
Differential diagnosis

• Myxoid liposarcoma

• Pleomorphic liposarcoma

• Dedifferentiated liposarcoma


conclusion

• The classification of adipocytic tumors has evolved considerably in the past three decades, largely due to **advances in understanding the pathogenetic basis** of many of these tumors.

• The **identification of characteristic molecular alterations for many tumor types** has led to **reproducible and uniform diagnostic criteria**, as well as the **development of useful ancillary diagnostic tests** (e.g. MDM2 overexpression/amplification in well-differentiated/dedifferentiated liposarcoma).

• Since the 2013 WHO classification the principal changes in the group of adipocytic tumors have been the introduction of **atypical spindle cell/pleomorphic lipomatous tumor** and **pleomorphic myxoid liposarcoma (myxoid pleomorphic liposarcoma)** as novel emerging entities, which will be incorporated in the upcoming new edition of the WHO classification of soft tissue and bone tumors.
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<tr>
<th>Classification</th>
<th>Examples</th>
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<tr>
<td><strong>Benign</strong></td>
<td>Lipoma, Lipomatosis, Lipomatosis of nerve, Lipoblastoma/lipoblastomatosis, Angiolipoma, Myolipoma, Chondroid lipoma, Extra-renal angiomyolipoma, Extra-renal myelolipoma, Spindle cell/pleomorphic lipoma, Hibemona, Atypical spindle cell/pleomorphic lipomatous tumor**</td>
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<td><strong>Intermediate (locally aggressive)</strong></td>
<td>Atypical lipomatous tumor/well-differentiated liposarcoma</td>
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<td><strong>Malignant</strong></td>
<td>Dedifferentiated liposarcoma, Myxoid liposarcoma, Pleomorphic liposarcoma, Pleomorphic myxoid liposarcoma (myxoid pleomorphic liposarcoma)**</td>
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**Novel emerging entities**