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WHO Pathology: Highlights of the 2020 Sarcoma Update

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INTRODUCTION

Soft tissue tumors comprise a wide range of entities, each with distinct diagnostic and biologic features with relevance for clinical management, which can make their diagnostic workup challenging. Recent advances in the molecular diagnostics workup of many benign and malignant mesenchymal neoplasms and the discovery of recurrent genetic aberrations have expanded the diagnostic spectrum and led to the discovery of new tumor types. The 5th edition of WHO Classification of Soft Tissue and Bone Tumors was published in early 2020[1], seven years after the 4th edition[2], and features a number of revisions to existing classification and risk stratification schemes. The update reflects a consensus among an international expert panel including pathologists, geneticists, a medical oncologist, surgeon, and radiologist.[3] We here highlight the most relevant changes to the soft tissue chapter in the 2020 World Health Organization Classification by diagnostic category and provide an update on modifications to diagnostic criteria and classification schemes. We further discuss challenging aspects in the diagnosis and/or prognostication of select well-established entities.

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CONFLICT OF INTEREST DISCLOSURE

The authors have nothing to disclose.

UPDATES TO THE 2020 WHO CLASSIFICATION:

ADIPOCYTIC TUMORS

Atypical Spindle Cell/Pleomorphic Lipomatous Tumor—Atypical spindle cell/pleomorphic lipomatous tumor (ASCLT/APLT) is a benign adipocytic neoplasm and mostly affects middle-aged adults with a slight male predominance with predilection for limbs and limb girdle.[4,5] ASCLT/APLT is characterized by ill-defined margins (Fig. 1) and nodular to multinodular growth, and can show a range of histologic appearances with varying proportions of atypical spindle cells, adipocytes, lipoblasts, and pleomorphic/multinucleated cells within collagenous and/or myxoid matrix (Fig. 2A, B). The tumors cells express CD34 (Fig. 2C), S100, and desmin to varying extent, but are generally negative for MDM2 (Fig. 2C, inset) and CDK4 given absence of *MDM2* or *CDK4* amplification.[4–6] ASCLT/APLT shows loss of RB1 expression in 50–70% of cases (Fig. 2D) resulting from deletions at 13q14 inactivating *RB1* and adjacent genes in a significant subset of cases (Table 1).[4,5,7] ASCLT/APLT has an excellent prognosis when completely excised and distant metastases have not been described.

Key Features: Atypical Spindle Cell/Pleomorphic Lipomatous Tumor

- Limbs and limb girdle
- Middle-aged adults, M≥F
- Mild to moderate atypia of spindle cells, adipocytes, lipoblasts, pleomorphic/multinucleated cells; myxoid to collagenous matrix
- Loss of RB1; variable expression of CD34, S100, and desmin
- Benign; local recurrence in 10–15% if incompletely excised

Myxoid Pleomorphic Liposarcoma—Myxoid pleomorphic liposarcoma (MPLPS) is exceptionally rare and extremely aggressive, mostly arising in the mediastinum of children and young adults with female predominance as a large, deep-seated mass with ill-defined margins.[8–11] MPLPS combines histologic features of conventional myxoid liposarcoma (Fig. 3A) and pleomorphic liposarcoma (Fig. 3B). MPLPS lacks both the *FUS-DDIT3* gene fusion characteristic of myxoid liposarcoma and *MDM2* and/or *CDK4* amplification found in dedifferentiated liposarcoma (Table 1) and instead, shows complex chromosomal alterations with occasional losses at 13q14 involving *RB1*.[12,13] MPLPS is extremely aggressive with frequent local recurrences and distant metastases associated with poor survival.[8,9]

Key Features: Myxoid Pleomorphic Liposarcoma

- Mediastinum
- Children and young adults, F>M
- Admixture of areas resembling conventional myxoid liposarcoma and high-grade pleomorphic liposarcoma-like

- RB1 loss in subset of cases
- Complex chromosomal alterations
- Extremely aggressive

FIBROBLASTIC AND MYOFIBROBLASTIC TUMORS

EWSR1-SMAD3*-Positive Fibroblastic Tumor—EWSR1-SMAD3*-positive fibroblastic tumor is a recently discovered benign neoplasm which has been included in the 2020 WHO classification as emerging entity under a provisional name.[1] These tumors show predilection for acral and superficial location, occur over a wide age range with female predominance, and are composed of a centrally located hypocellular hyalinized area (Fig. 4A) and more cellular areas at the periphery containing overlapping fibroblastic spindle cells without atypical features (Fig. 4B).[14–17] Diffuse nuclear expression of ERG is characteristic (Fig. 4C), whereas other markers such as CD34 and smooth-muscle actin (SMA), are negative. *EWSR1-SMAD3*-positive fibroblastic tumor is characterized by a fusion of *EWSR1* exon 7 and *SMAD3* exon 5 (Fig. 4D).[14,15] Their behavior is benign, but local recurrence has been observed if incompletely excised.[14,17]

Key Features: *EWSR1-SMAD3*-Positive Fibroblastic Tumor

- Acral location, superficial
- Wide age range, F>M
- Hypocellular center, hypercellular periphery
- Expression of ERG
- *EWSR1-SMAD3* gene fusion
- Benign behavior

Angiofibroma of Soft Tissue—Angiofibroma of soft tissue is a benign tumor composed of uniform bland spindle cells embedded in a network of prominent branching thin-walled blood vessels and fibromyxoid stroma with predilection for the lower extremities of middle-aged adults with slight female predominance.[18–20] Expression of CD34 and EMA is variable.[18,20] Angiofibroma of soft tissue is characterized by recurrent t(5;8)(p15;q13) resulting in *AHRR-NCOA2* gene fusion found in 60–80% of cases.[19–21] These tumors behave in a benign fashion with rare local recurrences and no risk of distant metastases.

Key Features: Angiofibroma of Soft Tissue

- Lower extremities
- Middle-aged adults, F≥M
- Bland spindle cells, network of branching blood vessels, fibromyxoid stroma
- Variable expression of CD34 and EMA

- *AHRR-NCOA2* gene fusion
- Benign behavior

Superficial CD34-Positive Fibroblastic Tumor—This distinctive low-grade neoplasm most frequently occurs in skin and subcutis of the lower extremities, especially the thigh, of middle-aged adults.[22,23] Superficial CD34-positive fibroblastic tumor is well circumscribed and composed of large spindle cells with abundant eosinophilic cytoplasm (Fig. 5A), marked nuclear pleomorphism (Fig. 5B), but a low mitotic rate.[20,23] They typically show strong, diffuse expression of CD34 (Fig. 5C) and focal cytokeratin in about two thirds of cases.[20,23] Morphologic overlap exists with tumors described at *PRDM10*-rearranged soft tissue tumors.[24] Superficial CD34-positive fibroblastic tumor has an excellent prognosis with no local recurrences reported and only one case with distant metastasis.[22]

Key Features: Superficial CD34-Positive Fibroblastic Tumor

- Lower extremities, superficial
- Middle-aged adults, M≥F
- Eosinophilic tumor cells with granular-to-glassy cytoplasm; marked pleomorphism, few mitoses
- Expression of CD34, focal cytokeratin
- Low-grade behavior, no local recurrences and very low risk of distant metastasis

SMOOTH MUSCLE TUMORS

Inflammatory Leiomyosarcoma—Inflammatory leiomyosarcoma is very rare and most frequently arises in the lower extremity of adults with male predominance.[1,25–27] Inflammatory leiomyosarcoma is characterized by eosinophilic spindle cells with blunt-ended elongated nuclei surrounded by a prominent inflammatory infiltrate, consisting mostly of small lymphocytes and occasionally admixed plasma cells or histiocytes with xanthomatous appearance (Fig. 6A, B). The tumor cells express SMA, desmin (Fig. 6C) and/or caldesmon. Inflammatory leiomyosarcoma shows a distinct near-haploid karyotype, with or without subsequent chromosome doubling.[26–28] The prognosis appears to be very good, with metastases being documented in only a subset of cases, although long-term follow up data are limited.[27,29]

Key Features: Inflammatory Leiomyosarcoma

- Lower extremity, trunk, retroperitoneum; deep-seated
- Mostly adults, M>F
- Eosinophilic spindle cells with blunt ended elongated nuclei; fascicular or storiform growth; mostly low grade

- Prominent inflammatory infiltrate
- Expression of SMA, desmin and/or caldesmon
- Near-haploid karyotype
- Good prognosis (data limited)

VASCULAR TUMORS

Anastomosing Hemangioma—Anastomosing hemangioma is most commonly found in the kidney and retroperitoneal adipose tissue, ovary, liver, and other anatomic locations affecting mostly adults and rarely children, without sex predilection.[30–33] Anastomosing hemangioma is characterized by a hemorrhagic mahogany spongy appearance, loosely lobulated architecture, and can be associated with a medium-caliber vessel.[32] Sinusoidal capillary-sized vessels (Fig. 7A) with scattered hobnail endothelial cells and a framework of nonendothelial supporting cells are characteristic.[32] While mild cytologic atypia can be found, mitoses are usually rare or absent and multilayering is not seen, helping in the distinction from angiosarcoma.[32,34] Vascular thrombi are frequent (Fig. 7B), extramedullary hematopoiesis and striking hyaline globules are found in a subset of cases.[32] The endothelial tumor cells express CD34, CD31, and ERG.[32] Recurrent *GNAQ*[34,35] or *GNA14*[34,36] activating mutations are characteristic of anastomosing hemangioma.

Key Features: Anastomosing Hemangioma

- Mostly kidney, retroperitoneum
- Adults, F=M
- Lobulated growth, anastomosing sinusoidal capillary-sized vessels with hobnailing endothelium; extramedullary hematopoiesis and hyaline globules in subset of cases
- No/rare mitoses, no endothelial multilayering; mild cytologic atypia in some cases
- Expression of vascular markers (CD34, CD31, ERG)
- Recurrent *GNAQ* or *GNA14* activating mutations
- Benign

TUMORS OF UNCERTAIN DIFFERENTIATION

NTRK*-Rearranged Spindle Cell Neoplasm (emerging)—NTRK*-rearranged spindle cell neoplasm is a molecularly defined category of tumors (outside of infantile fibrosarcoma) which includes the recently described lipofibromatosis-like neural tumor and tumors that closely mimic peripheral nerve sheath tumor.[37,38] Most cases harbor *NTRK1* gene fusions with various partners (eg., *LMNA*, *PTR*, *TPM3*), and rarely *NTRK2* or *NRTK3* gene rearrangements representing potential treatment targets for inhibitors of the TRK family of kinases.[39] *NTRK*-rearranged spindle cell neoplasm includes a wide range of morphologic

appearances, usually consisting of a population of haphazardly arranged monomorphic spindle cell, distinctive stromal and perivascular keloidal collagen, and infiltration into adipose tissue (Fig. 8A–D).[1] The tumor cells frequently express S100, CD34, and pan-TRK (Fig. 8C) but not SOX10.[40–42] The prognosis appears to depend on histologic grade. Benign lipofibromatosis-like neural tumor shows infiltrative growth and has a propensity for local recurrence if incompletely excised, but does not metastasize.[1,40] Distant metastases may be observed in tumors with high-grade morphologic features.[1]

Key Features: *NTRK*-Rearranged Spindle Cell Neoplasm

- Molecularly defined category of tumors
- Mostly children and young adults
- Extremities and trunk, superficial or deep location
- Wide morphologic range; monomorphic spindle cell, stromal/perivascular keloidal collagen, infiltrating fat
- Expression of S100, CD34, and pan-TRK; SOX10-negative
- *NTRK1, NTRK2* or *NTRK3* gene fusion
- Wide prognostic range depending on tumor grade

NEW CATEGORY: UNDIFFERENTIATED ROUND CELL SARCOMAS OF BONE AND SOFT TISSUE

A new category has been introduced for “undifferentiated small round cell sarcomas of bone and soft tissue” which includes Ewing sarcoma, sarcoma with *EWSR1*-non-ETS fusions, *CIC*rearranged sarcoma, and sarcoma with *BCOR* genetic alterations (Table 2).

Sarcoma with *EWSR1*-non-ETS Fusions—This group of round and spindle cell sarcomas includes those with fusions of *EWSR1* or *FUS* and fusion partners not belonging to the ETS gene family, specifically *EWSR1-NFATC2* and *EWSR1PATZ-1. EWSR1-NFATC2* and *FUS-NFATC2* sarcomas have a predilection for long bones, and rare cases of *EWSR1-NFATC2* sarcoma have also been reported in somatic soft tissue sites (Table 2).[43–45] *NFATC2*-rearranged sarcomas occur in children and adults with male predominance.[44,45] *EWSR1-PATZ1* sarcomas arise in deep somatic soft tissue, are most common in the chest wall and abdomen, and occur over a wide age range without sex predilection[1,46,47] In addition to the *EWSR1-PATZ1* gene fusion, frequent inactivation of *CDKN2A* has been observed.[47] *NFATC2*-rearranged sarcomas are composed of round cell and/or spindle cells with little cytoplasm in a fibrohyaline to myxohyaline background with expression of CD99 in about half of cases, PAX7, NKX2.2, and/or focal dot-like AE1/AE3 in a subset of cases.[1] *EWSR1-PATZ1* sarcomas consist of small round and/or spindled cells often with fibrous stroma (Fig. 9A, B), can express myogenic and neurogenic markers and CD34 to varying extent.[1] *NFATC2*rearranged sarcomas and *EWSR1-PATZ1* sarcomas show variable clinical behavior and may recur locally and/or develop distant

metastases[43,46–48], but long-term follow up data are limited. Both entities respond poorly to systemic chemotherapies.[1]

CIC*-Rearranged Sarcoma—CIC*-rearranged sarcoma mostly affects young male adults with predilection for the somatic soft tissue of trunk and extremities and behaves more aggressively than Ewing sarcoma (Table 2).[49] *CIC*-rearranged sarcomas contain moderately pleomorphic round to ovoid cells with frequent mitoses, apoptoses, and necrosis (Fig. 10A), and show expression of WT1 (Fig. 10B) and ETV4 in most cases, whereas CD99 staining is usually limited.[50,51] These tumors harbor characteristic

CIC-DUX4 fusion resulting from t(4;19)(q35;q13) or t(10;19)(q26;q13) and rarely alternate *CIC-FOXO4* fusion (Fig. 10C).[52,53] *CIC*-rearranged sarcomas are highly aggressive with frequent distant metastases and a poor prognosis.

Sarcoma with *BCOR* Genetic Alterations—This group of primitive round cell sarcomas includes *BCOR*-rearranged sarcoma and tumors with BCOR internal tandem duplication as described in infantile undifferentiated round cell sarcoma and primitive myxoid mesenchymal tumors of infancy. *BCOR*-rearranged sarcoma shows predilection for bone and soft tissue of male children[54,55] and is characterized by *BCOR-CCNB3* rearrangement resulting from inv(X)(p11) (Table 2) or rare, alternate rearrangement of *BCOR* with *MAML3* or *ZC3H7B*.[56] *BCOR*-rearranged sarcomas contain a uniform population of primitive small round to ovoid cells in solid sheets or nested, surrounded by a capillary network (Fig. 11A).[55] Expression of BCOR and/or CCNB3 (Fig. 11B, C) can be helpful in the differential diagnostic workup but is not entirely specific.[54,55,57] *BCOR*-rearranged sarcomas are less aggressive than *CIC*-rearranged sarcoma and have 5-year-overall survival rates of ~75%, comparable to Ewing sarcoma.[55,58]

REVISIONS TO NOMENCLATURE, GRADING, AND RISK STRATIFICATION

Select updates to concepts in nomenclature, grading, and risk stratification for malignant melanotic nerve sheath tumor, dedifferentiated liposarcoma, and solitary fibrous tumor (SFT) are summarized in Table 3. The 2020 WHO Classification discourages the terminology benign/malignant SFT and one of the (several) validated risk models is preferred. Please refer to chapter 9 for details on risk stratification for solitary fibrous tumor.

CHALLENGES IN THE CLASSIFICATION OF WELL-ESTABLISHED ENTITIES:

ATYPICAL LIPOMATOUS TUMOR/WELL-DIFFERENTIATED LIPOSARCOMA

Atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDPLPS) is a locally aggressive adipocytic neoplasm consisting either partly of entirely of an adipocytic component with at least focal nuclear atypia in both adipocytes and stromal cells.[1] ALT and WDLPS describe the same entity. However, by convention the term ALT is used when referring to tumors arising at anatomic sites amenable to complete surgical resection, such as the extremities or superficial locations. In contrast, WDLPS is used for lesions occurring at deep-seated, central body sites such as the retroperitoneum, for which radical multi-visceral

surgery is considered appropriate and where risk of disease progression either due to local spread or dedifferentiation causing systemic spread tends to be higher.[1,59] The overall risk of local recurrence for ALT/WDLPS ranges at 30–50%, but distant metastases virtually never occur (unless dedifferentiation develops). Anatomic location of ALT/WDLPS is the major prognostic factor: the 10-year to 20-year overall mortality rates vary by anatomic site and have been estimated as <2% for ALT arising in the extremities and >20% for WDLPS arising in the retroperitoneum.[1]

PROGNOSTIC IMPACT OF DIFFERENTIATION IN DEDIFFERENTIATED LIPOSARCOMA

Dedifferentiated liposarcoma (DDLPS) describes ALT/WDLPS that progressed to a non-lipogenic sarcoma.[60] The non-lipogenic component is generally high-grade and may exhibit a broad spectrum of histologic grades. Morphologically low-grade non-lipogenic components consisting of areas with relatively bland-appearing spindle cells with intermediate cellularity have been recognized and are described as “low-grade dedifferentiation” to emphasize the morphologic difference from conventional “high-grade” components.[1,61] Of note, “low grade” here represents a morphologic description (and not, for instance, to FNCLCC grading). The range of histologic appearances of high-grade non-lipogenic components in DDLPS is wide and occasionally, lipoblastic differentiation can be found in otherwise high-grade non-lipogenic areas which is termed “homologous” lipoblastic (pleomorphic liposarcoma-like) differentiation in analogy to the heterologous differentiation frequently observed in DDLPS.[62] In addition, it has been demonstrated that myogenic, in particular rhabdomyoblastic, differentiation in DDLPS is associated with worse outcome, as is higher FNCLCC grade .[63]

RISK STRATIFICATION IN MYXOID LIPOSARCOMA

Myxoid liposarcoma is a malignant adipocytic neoplasm composed of uniform, round to ovoid cells with admixed small lipoblasts, prominent branching capillary vessels surrounded by a myxoid stroma, and characteristic *FUS-DDIT3* (or rarely, *EWSR1-DDIT3*) gene fusion.[1] As defined by the WHO Classification of Soft Tissue and Bone Tumors, myxoid liposarcoma is considered high-grade if >5% of the tumor consists of areas of hypercellularity often displaying round cell morphology, with reduced myxoid matrix, less prominent capillary vasculature, increased nuclear grade, increased mitotic activity, frequently with a chorded or trabecular architecture and round cell morphology. While high-grade liposarcoma can histologically mimic other round cell neoplasms and was therefore in the past termed “round-cell liposarcoma”, “high-grade” myxoid liposarcoma is now the widely accepted terminology and significantly hypercellular tumors behave as aggressively as those with round cell morphology. However, a morphologic spectrum exists without easily defined or reproducible cut-offs. The presence of high-grade features is associated with significantly poorer prognosis[1] and presence and extent of hypercellularity should therefore be reported. As recently demonstrated, nuclear expression of DDIT3 can be observed in 96% of high-grade liposarcomas and may be helpful in the distinction from other round cell sarcoma.[64]

DIAGNOSTIC DISTINCTION OF MYXOFIBROSARCOMA AND UNDIFFERENTIATED PLEOMORPHIC SARCOMA

While myxofibrosarcoma and undifferentiated pleomorphic sarcoma may share certain overlapping features, their diagnostic distinction is generally made based on clinic-pathologic features (e.g., anatomic site and depth) and histomorphologic criteria summarized in Table 4

Myxofibrosarcoma is a malignant fibroblastic neoplasm characterized by multinodular growth, myxoid stroma, pleomorphism and distinctive curvilinear blood vessels occurring mostly in the lower extremity of adults with slight male predominance.[1,65] More than half of cases arise in dermal/subcutaneous soft tissue, whereas the remainder arise in fascia or deep skeletal muscle.[1,65] The histomorphologic spectrum is wide, but all cases share the features listed above and the diagnosis is generally based on histologic criteria since specific immunohistochemical markers or genetic markers are absent.[1] Myxofibrosarcoma demonstrates highly complex karyotypes with intratumor heterogeneity and triploid or triploid chromosome numbers.[1] Given their infiltrative growth, local recurrence occurs in 30–50% of cases, and distant metastases develop in 20–35% of cases.[1,65]

In contrast, undifferentiated pleomorphic sarcoma, belonging to the group of “undifferentiated sarcomas”, represents a diagnosis of exclusion given the absence of an identifiable line of differentiation as determined by histologic examination and available ancillary techniques.[1,66] Undifferentiated pleomorphic sarcoma usually affects adults, being most common between 50–70 years of age, and is usually deep-seated.[66] These sarcomas closely resemble other types of pleomorphic sarcomas and often show a patternless appearance with frequent bizarre multinucleated giant cells. Their karyotypes are complex without distinctive recurrent genetic aberrations. While long-term follow-up data are relatively limited, the 5-year metastasis-free survival for patients with undifferentiated sarcomas arising in limbs or trunk among the group of pleomorphic sarcomas in adults has been reported as 83%.[67]

SUMMARY

The 2020 WHO Classification of Soft Tissue and Bone Tumors includes several novel and emerging entities and features a number of revisions to existing classification and risk stratification schemes to incorporate recent advances in the diagnostic workup of these tumors. This update integrates a morphology-based approach combined with evaluation for characteristics cytogenetic/molecular genetic alterations and associated immunohistochemical markers to improve diagnostic precision, reproducibility, and prognostication for state-of-the-art clinical management.

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KEY POINTS

- The 2020 WHO Classification of Soft Tissue and Bone Tumors has incorporated a number of changes to reflect recent advances made in the histopathologic and molecular diagnostic workup of soft tissue tumors.
- New entities have been added to the categories of adipocytic tumors, fibroblastic and myofibroblastic tumors, smooth muscle tumors, vascular tumors, and tumors of uncertain differentiation.
- A new category has been introduced for "undifferentiated round cell sarcomas of bone and soft tissue" which includes Ewing sarcoma, round cell sarcoma with *EWSR1*-non-ETS gene fusion, *CIC*-rearranged sarcoma, and sarcoma with *BCOR* genetic alterations.
- *EWSR1-SMAD3*-positive fibroblastic tumor and *NTRK*-rearranged spindle cell sarcoma have been included as emerging entities.
- Revisions to nomenclature, grading, and risk stratification have been made for malignant melanotic nerve sheath tumor, dedifferentiated liposarcoma, and solitary fibrous tumor.

SYNOPSIS

The 2020 WHO Classification of Soft Tissue and Bone Tumors features revisions based on recent advances in the histopathologic and molecular diagnostic workup of soft tissue tumors. We herein highlight select new entities in the categories of adipocytic tumors, fibroblastic and myofibroblastic tumors, smooth muscle tumors, vascular tumors, and tumors of uncertain differentiation, a novel category for undifferentiated round cell sarcomas of bone and soft tissue, and revisions to nomenclature, grading, and risk stratification. This paper provides an overview on revised diagnostic criteria, state-of-the-art genetic and immunohistochemical markers, and prognostication with impact on clinical management. In addition, we discuss challenging aspects in the diagnosis and/or prognostication of select well-established entities that will be discussed in more detail in other chapters of this book.

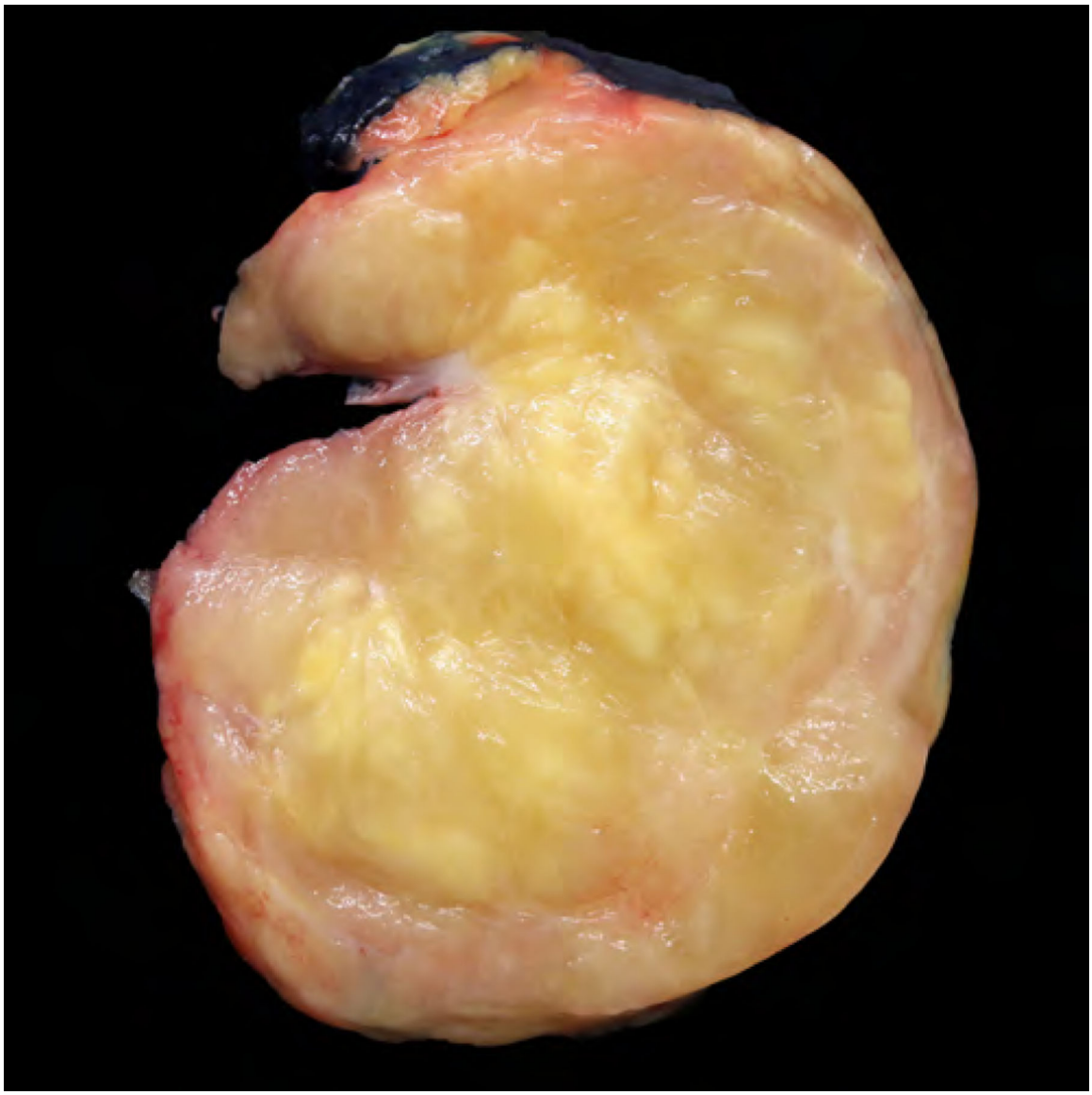

Figure 1.
Grossly, atypical pleomorphic lipomatous tumor is unencapsulated with ill-defined tumor margins and nodular growth displaying an admixture of fatty and myxoid to collagenous features.

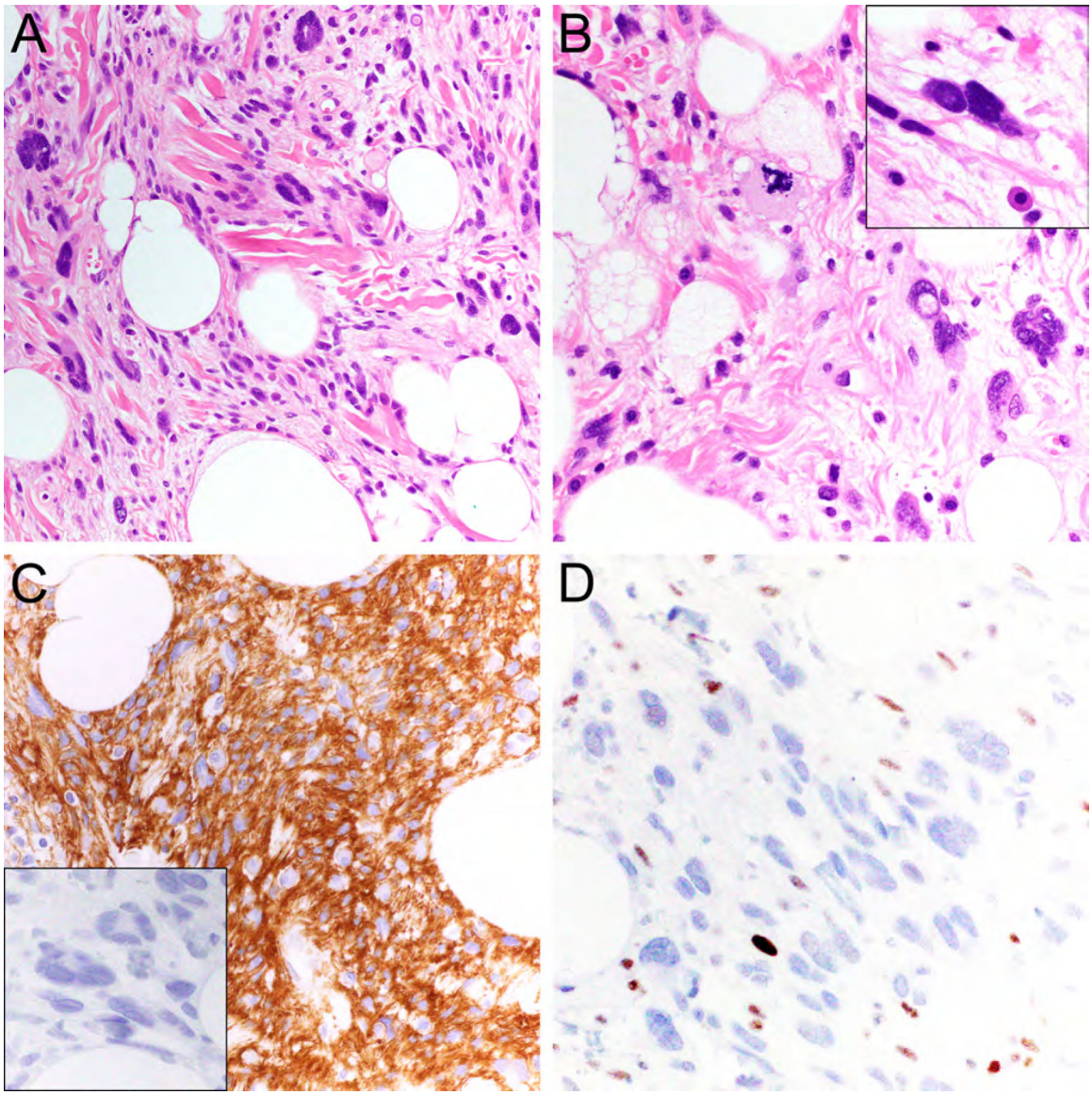

Figure 2.

Atypical pleomorphic lipomatous tumor comprised of spindle cells, adipocytic cells, pleomorphic giant cells, and scattered lipoblasts embedded in a myxoid and collagenous extracellular matrix (A, hematoxylin-eosin (HE), 200x; B, HE, x400) with occasional hyperchromatic nuclei (B, inset). The tumor cells express CD34 (C, x400), lack MDM2 expression (C, inset, x400), and show RB1 loss (D, x400).

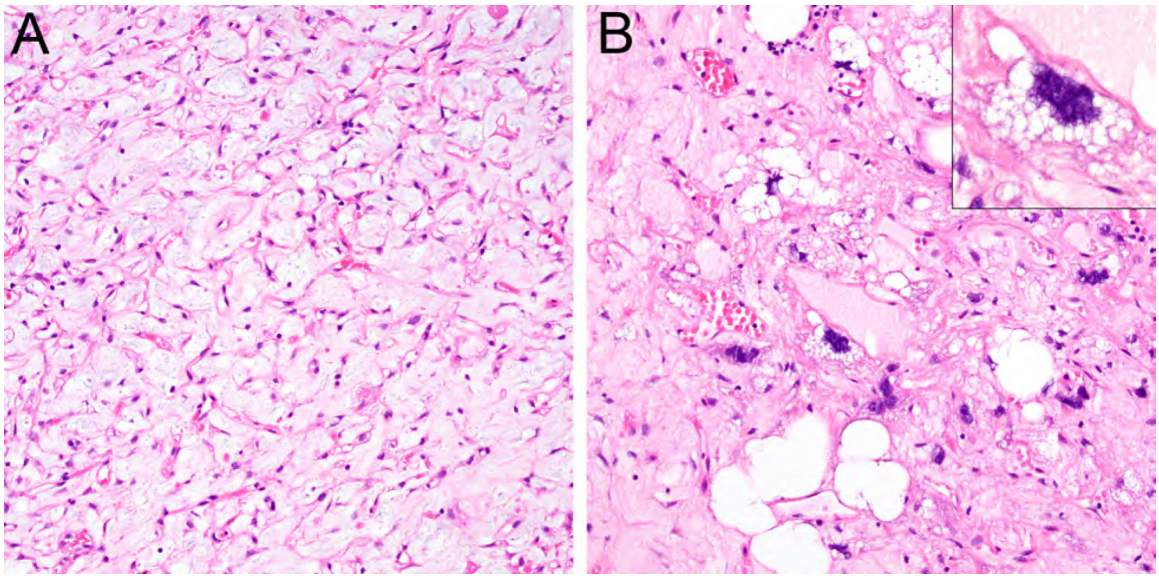

Figure 3.
Myxoid pleomorphic liposarcoma combining morphologic features of conventional myxoid liposarcoma (A, HE, x200) and pleomorphic liposarcoma (B, HE, x200; inset, HE, x400).

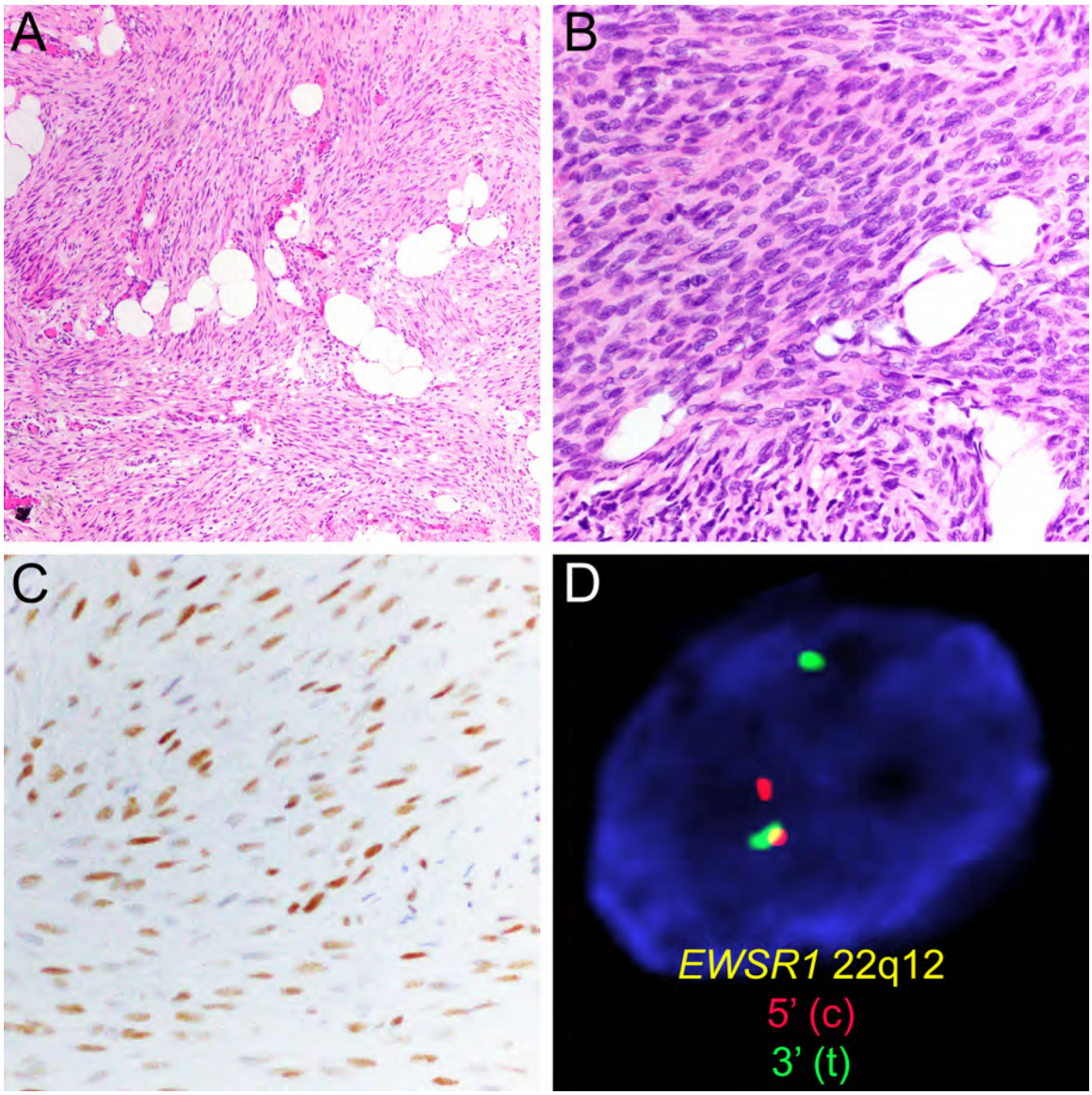

Figure 4.

EWSR1-SMAD3-positive fibroblastic tumor with hypocellular hyalinized area (A, HE, x200) and more cellular areas containing fibroblastic spindle cells (B, HE, x400) with expression of ERG (C, x200) and presence of *EWSR1* gene rearrangement detected by FISH (D).

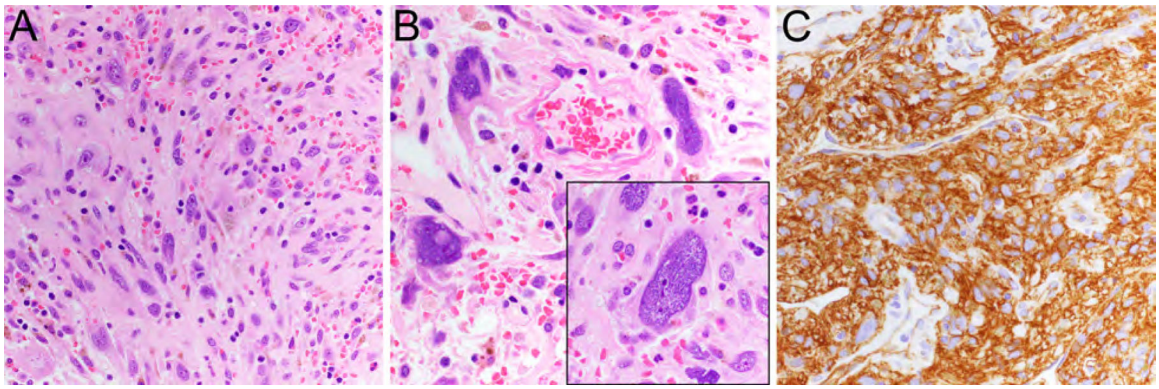

Figure 5.

Superficial CD34-positive fibroblastic tumor with sheet-like growth (A, HE, x200) of large eosinophilic tumor cells with marked nuclear pleomorphism (B, HE, x400; inset) and strong, diffuse expression of CD34 (C, x400).

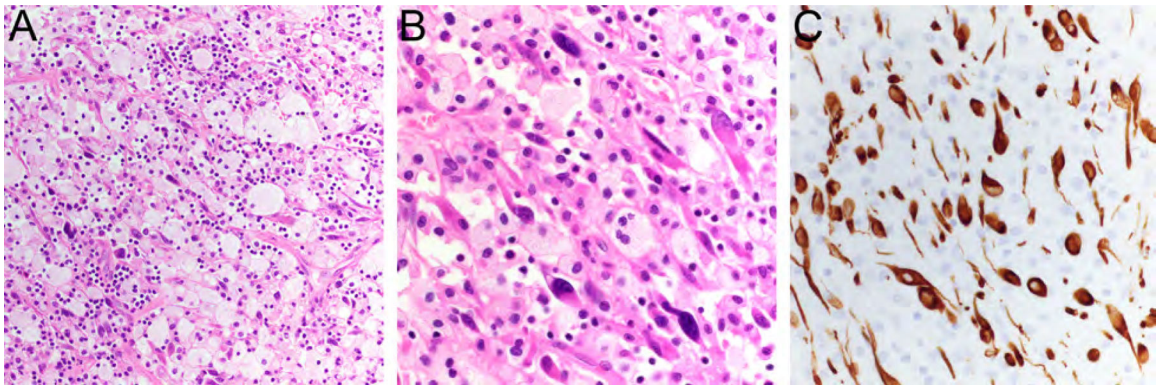

Figure 6.

Inflammatory leiomyosarcoma containing spindle cells with blunt-ended elongated nuclei surrounded by a prominent inflammatory infiltrate, consisting of histiocytes with xanthomatous appearance (A, HE, x200; B, HE, x400). The tumor cells are highlighted by strong expression of desmin (C, x400).

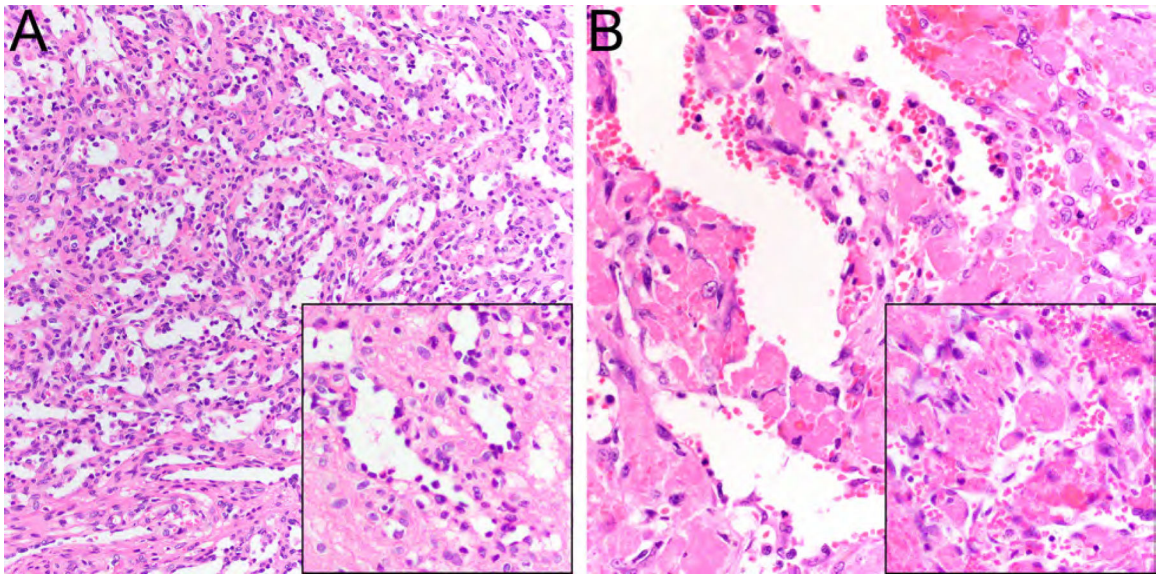

Figure 7.

Anastomosing hemangioma consisting of anastomosing sinusoidal capillary-sized vessels (A, HE, x200) with scattered hobnail endothelial cells (A, inset, HE, x400) and vascular thrombi (B, HE, x200; inset, HE, x400).

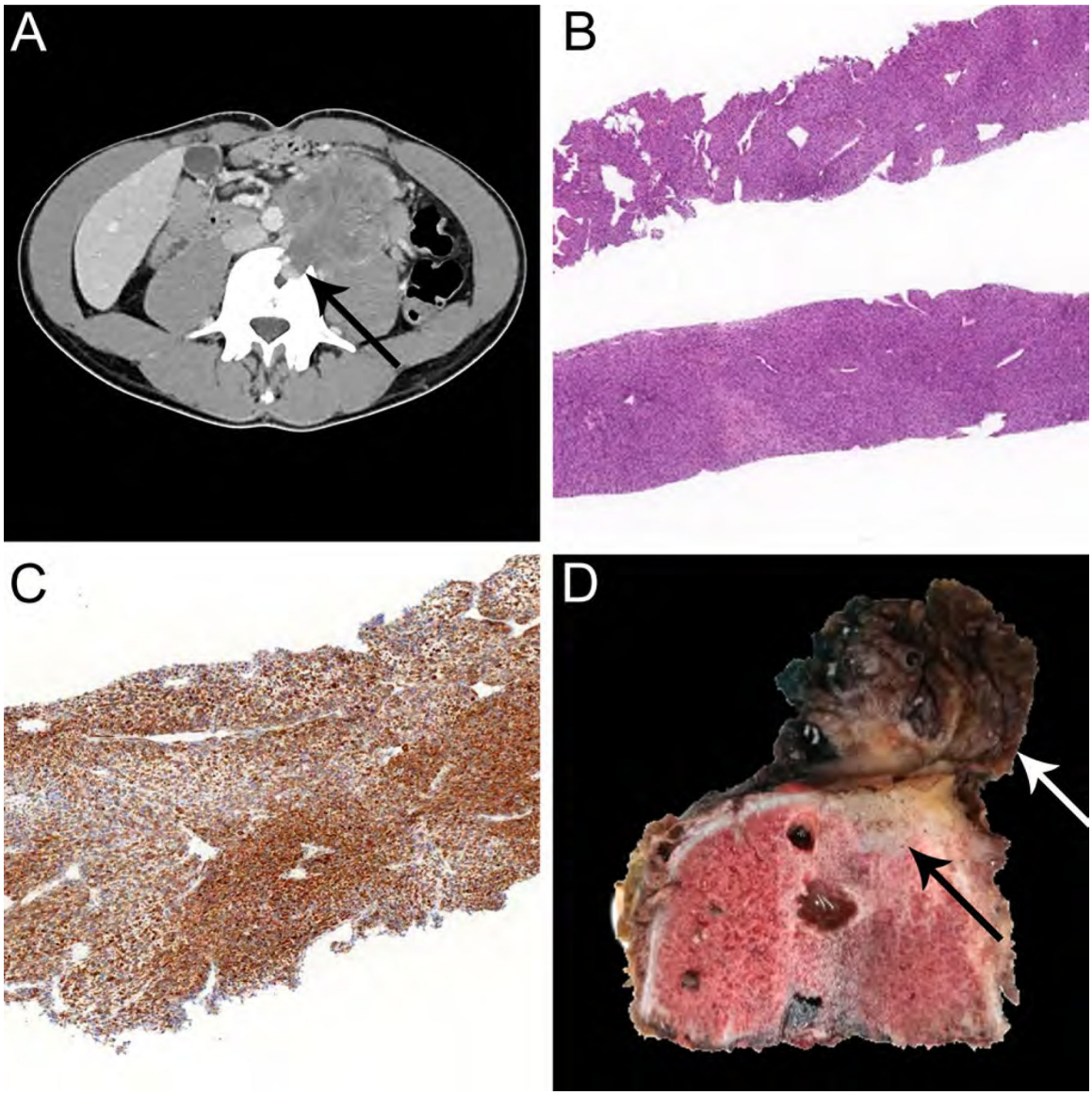

Figure 8.

NTRK-rearranged spindle cell neoplasm arising in the retroperitoneum on CT-imaging (A) showing infiltration into adjacent vertebral bone (A, arrow). This tumor consisted of a population of haphazardly arranged monomorphic spindle cells (A, HE, x40) with positive staining for pan-TRK in tumor cells (C, x40) on a pre-treatment biopsy. The patient received neoadjuvant NTRK-inhibitor therapy for 4 months resulting in partial response, before the tumor was surgically resected. The post-treatment specimen (D) reveals residual tumor (white arrow) invading vertebral bone (black arrow).

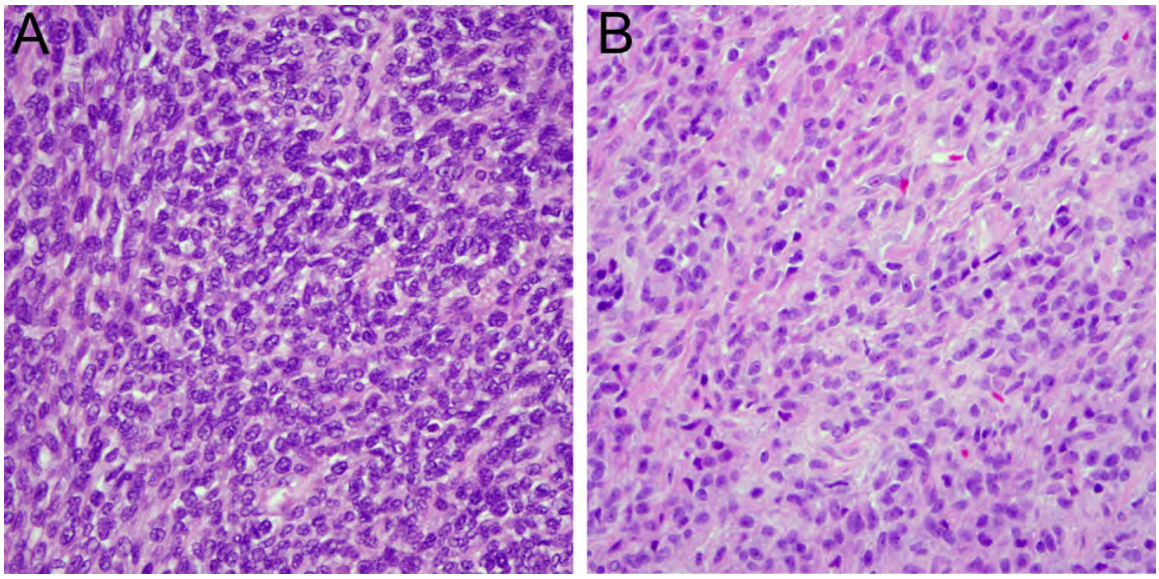

Figure 9.
Examples of *EWSR1-PATZ1* sarcoma (A and B, HE, x400) consisting of small round to spindled cells with varying extent of fibrous stroma.

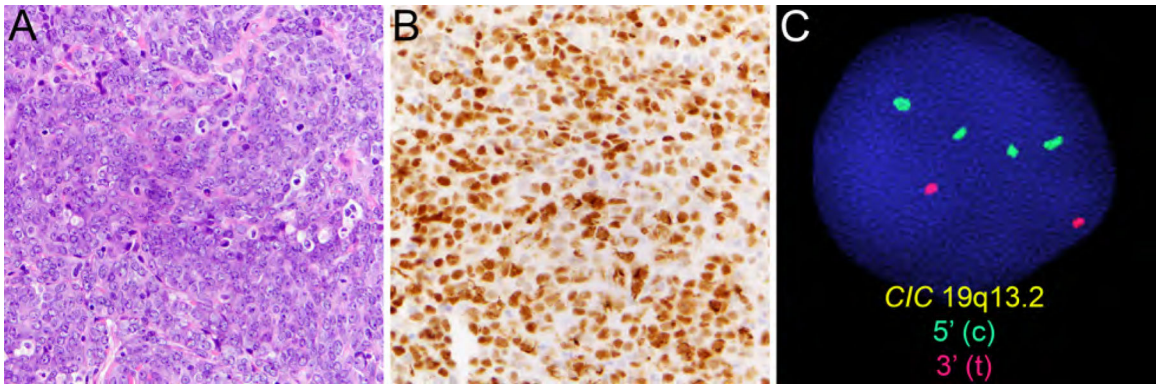

Figure 10.

CIC-rearranged sarcoma containing moderately pleomorphic round to ovoid cells with frequent mitoses, apoptoses, and necrosis (A, HE, x400) with expression of WT1 (B, x400) and detection of *CIC* rearrangement by FISH (C).

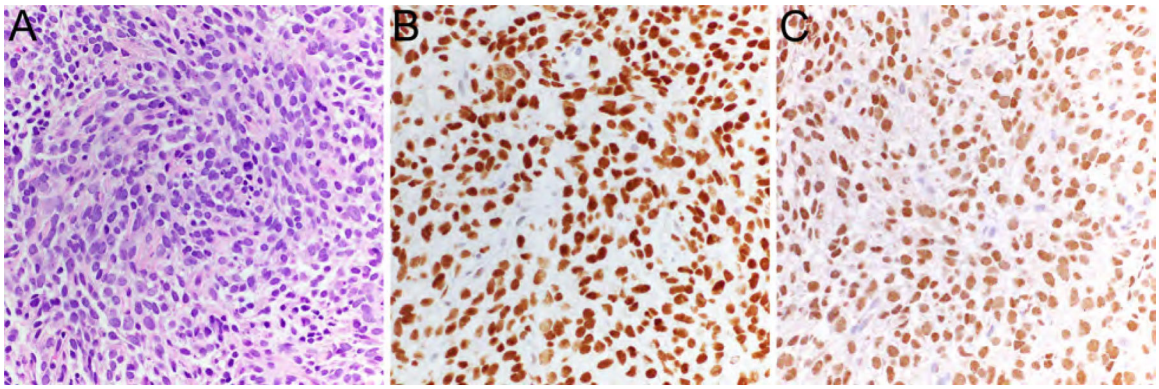

Figure 11.

BCOR-rearranged sarcoma consisting of a uniform population of primitive small round to ovoid cells (A, HE, x400) with expression of BCOR (B, x400) and CCNB3 (C, x400).

Table 1.

Summary of diagnostic and prognostic features of select adipocytic neoplasms.

Tumor Type	Useful Diagnostic IHC Markers	Characteristic Genomic Aberrations	Behavior
Spindle cell/pleomorphic lipoma	RB1 loss; variable expression of CD34, desmin, S100	13q14 deletion *(RB1)*	Benign
Atypical spindle cell/pleomorphic lipomatous tumor (ASCLT/APLT)	RB1 loss (50–70%); variable expression of CD34, desmin, S100	13q14 deletion *(RB1)*	Benign; local recurrence in 10–15% if incompletely excised
Atypical lipomatous tumor (ALT)/Well-differentiated liposarcoma (WDLPS)	Expression of MDM2 and/or CDK4	12q13–15 high-level amplification (*MDM2*, *CDK4)*	Locally aggressive; risk of dedifferentiation
Dedifferentiated liposarcoma	Expression of MDM2 and/or CDK4	12q13–15 high-level amplification (*MDM2*, *CDK4*)	Malignant
Myxoid liposarcoma	DDIT3 expression in high-grade cases	*FUS-DDIT3* gene fusion	Malignant
Pleomorphic liposarcoma	None	None	Malignant
Myxoid pleomorphic liposarcoma	RB1 loss (subset)	Complex chromosomal alterations	Highly malignant

Table 2.

Clinico-pathologic features of novel round cell sarcoma subtypes.

Differential Diagnosis		
***EWSR1-NFATC2* and *FUS-NFATC2* Sarcoma** • Mostly long bones • Children and adults, M>F • Round/spindle cells in hyaline background • Variable expression of CD99, PAX7, NKX2.2, AE1/AE3 • Local recurrence and distant metastasis ***EWSR1-PATZ1* Sarcoma** • Mostly chest wall • Wide age range, F=M • Small round/spindled cells, fibrous stroma • Variable expression of myogenic and neurogenic markers, CD34 • Local recurrence and distant metastasis	***C/C*-Rearranged Sarcoma** • Trunk and extremities • Young adults, M>F • Diffuse sheets of undifferentiated round to ovoid cells, intervening fibrous stroma; common necrosis, high mitotic rate • Expression of WT1 and ETV4; limited CD99 • T(4;19)(q35;q13) or t(10;19)(q26;q13) resulting in *CIC-DUX4* fusion • Very aggressive, poor prognosis	**BCOR-Rearranged Sarcoma** • Bone and soft tissue • Children, M>F • Primitive small round to ovoid cells solid sheets or nested; variable mitotic rate, rare necrosis • Expression of BCOR and/or CCNB3; variable CD99 • Inv(X)(p11) resulting in *BCOR-CCNB3* fusion • Aggressive, poor prognosis

Table 3.

Select updates to concepts in nomenclature, grading, and risk stratification (modified from: Kallen ME, Hornick JL. The 2020 WHO Classification: What's New in Soft Tissue Tumor Pathology? *Am J Surg Pathol.* 2021;45(1):e1-e23.).[3]

Key Revision to Nomenclature, Grading, and Risk Stratification
Malignant Melanotic Nerve Sheath Tumor (MMNST): • Formerly "melanotic schwannoma"; change in nomenclature to reflect aggressive clinical behavior
Dedifferentiated Liposarcoma (DDLPS): • Recognition of adverse prognostic impact of high FNCLCC grade and myogenic (specifically rhabdomyoblastic) differentiation
Solitary fibrous tumor (SFT): • New prognostic model predicting metastatic risk based on patient age, mitotic rate, tumor size, and necrosis

Table 4.

Clinico-pathologic features helpful in the distinction of myxofibrosarcoma and undifferentiated pleomorphic sarcoma.

Differential Diagnosis	
Myxofibrosarcoma	**Undifferentiated pleomorphic sarcoma**
• Mostly limbs and limb girdle (lower>upper extremities) • Adults (usually 50–70 years), M≥F • Multinodular architecture, infiltrative margins • Myxoid stroma, pleomorphism, characteristic curvilinear blood vessel, increased cellularity in higher-risk cases • Highly complex karyotypes • Local/repeated recurrences in 30–50% of cases; metastases in up to 35% of cases	• Wide anatomic distribution (extremities>trunk) • Mostly adults (50–70 years) • Diagnosis of exclusion, i.e., absence of specific morphologic, immunohistochemical or molecular genetic features • Pleomorphic morphology with frequent bizarre multinucleated giant cells, often patternless • Highly complex karyotypes • Local recurrence/distant metastases (limited data)