Bone and Soft Tissue Pathology

Diagnostic and Prognostic Implications

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KEYWORDS

• Soft tissue • Bone • Sarcoma • Diagnosis • Prognosis • Pathology • Molecular

KEY POINTS

- A multidisciplinary team approach is necessary for optimal treatment of sarcomas, and the role of pathology is important for each member to be familiar with.
- Recent advances in immunohistochemical markers, cytogenetics, and molecular pathology techniques have lead to more accurate diagnoses and have improved the management of sarcomas.
- The current pathological definitions, classification and grading systems, and ancillary techniques are summarized here for some of the more common soft tissue and bone tumors.

INTRODUCTION

Most soft tissue and bone tumors are benign, requiring only conservative management. Soft tissue and bone sarcomas, on the other hand, require a multidisciplinary team approach for optimal diagnosis and management.[1–3] They are rare malignant neoplasms, accounting for less than 1% of all adult and up to 20% of all pediatric malignancies, and may be classified according to the type of tissue that they most closely histologically resemble.[3,4] The large majority are soft tissue sarcomas, most of which originate within the soft tissue of extremities, while the remaining approximately 10% are bone sarcomas.[3,5,6] Numerous advances in immunohistochemical markers, cytogenetics, and molecular pathology techniques have led to more accurate diagnoses and have improved the management of sarcomas over the past decade.[7–10] However, sarcomas are rare and diverse, often with overlapping histologic and

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immunophenotypical features, making them a challenging group of tumors to accurately diagnose. Numerous online references and algorithmic clinical guidelines (Table 1), such as those created by the National Comprehensive Cancer Network (NCCN), are also readily available to help guide the diagnosis and management of soft tissue and bone tumors.[11–18]

All members of a multidisciplinary team should have an understanding of the role of pathology, including the availability of ancillary studies, in order to optimize patient care. Clinical and radiologic information plays a key role in the initial workup and is often followed by tissue sampling, such as fine-needle aspiration (FNA), image-guided biopsy, or open biopsy, for definitive pathologic diagnosis before therapy or surgical resection. Although core biopsy with image guidance is the most accepted method for initial sampling of suspected sarcomas, FNA is especially useful in the evaluation of possible recurrent or metastatic disease. The appropriate selection of a sampling technique improves the accuracy and timeliness of the definitive pathologic diagnosis.[1,11] Ancillary techniques, including immunohistochemical studies and molecular studies, then facilitate in the definitive diagnosis of most sarcomas.[7,10]

This article begins with a brief summary of the changes included in recently updated World Health Organization (WHO) classification series of soft tissue and bone tumors. Although a comprehensive discussion of every currently recognized bone and soft tissue tumor and variant is not possible to cover in this article, the authors aim to discuss the key pathologic findings, grading and staging systems, and prognostic implications of some of the more common malignant, intermediate, and benign soft tissue and bone tumors.

WORLD HEALTH ORGANIZATION 2013 UPDATE

The most recently updated WHO classification series of soft tissue and bone tumors includes several newly recognized entities and reflects changes that have resulted from improved understanding of tumor characteristics.[19–22] In summary, compared with the previous 2002 edition, this updated version better defines diagnostic criteria, allowing for more reproducible diagnoses, with some additional changes in the classification of various tumors. It incorporates updated molecular and genetic characteristics of tumors, shedding more light on possible factors influencing the pathogenesis of some previously obscure entities.[20]

The update includes discussions that explain why some of the definitions of certain entities have changed. For example, the term atypical lipomatous tumor is preferred over well-differentiated liposarcoma, because they have no metastatic potential. The later term is now reserved, according to clinical judgment, for tumors that are impossible to completely surgically excise with adequate margins, because they are

Table 1
Selected examples of online references for pathology and clinical guidelines or information

Pathology	College of American Pathologists	http://www.cap.org/web/home/resources/cancer-reporting-tools/
	Tampa Path	http://tampapath.com
	BoneTumor.org	http://www.bonetumor.org/
	Pathology Outlines	http://www.pathologyoutlines.com/softtissue.html
Clinical oncology	NCCN	https://www.nccn.org/
	European Society for Medical Oncology	http://www.esmo.org/
	American Cancer Society	http://www.cancer.org

locally aggressive and likely to eventually have uncontrollable recurrent disease. In the fibroblastic/myofibroblastic section, solitary fibrous tumors (SFT) and hemangiopericytomas (HPC), previously considered separate entities, have been combined into one entity, now diagnosed as SFT. Similarly, the term Ewing sarcoma/primitive neuroectodermal tumor is no longer used and is now diagnosed, more simply, as Ewing sarcoma, since molecular analysis has supported the current understanding that they are the same entity with varying degrees of neuroectodermal differentiation, accounting for the histologic differences.[20,23]

Undifferentiated sarcomas, historically also known as malignant fibrous histiocytomas (MFHs), were moved out of the fibrohistiocytic section, forming a new section of undifferentiated/unclassified sarcomas.[19] These undifferentiated sarcomas are a diagnosis of exclusion and should be reported as undifferentiated spindle cell sarcoma, undifferentiated pleomorphic sarcoma, undifferentiated round cell sarcoma, undifferentiated epithelioid sarcoma (ES), or undifferentiated sarcoma, not otherwise specified (NOS). Myofibroma and angiomyolipoma were both moved into the perivascular section, from the fibroblastic and smooth muscle sections, respectively. In addition, the mixed-type liposarcoma subtype has been removed, whereas extraskeletal myxoid chondrosarcoma and angiomatoid fibrous histiocytoma have been reclassified as tumors of uncertain differentiation, because of their unclear line of differentiation when analyzed by presently available technology.[20]

Newly recognized entities or variants have also been added, such as the new spindle cell/sclerosing variant of rhabdomyosarcoma and the pseudomyogenic hemangioendothelioma. Entirely new sections have been added to include tumors such as gastrointestinal stromal tumors (GIST) and nerve sheath tumors. A few bone tumors and variants were also added, including the benign notochordal cell tumor and primary non-Hodgkin lymphoma of bone, whereas other entities, such as schwannoma and leiomyoma of bone, were removed. In addition, the controversial issue regarding the coexistence of several grading systems of soft tissue tumors is discussed, focusing on the 2 most common grading systems in regards to their main advantages and limitations.[20,22,24]

PATHOLOGIC GRADING OF SOFT TISSUE SARCOMAS

Soft tissue sarcomas are a heterogeneous and diverse group of tumors proven very difficult to uniformly grade. However, in 1984, Costa and colleagues[25] introduced a grading system known as the National Cancer Institute system. However, the grading system proposed by French Federation of Cancer Centers (Federation Nationale des Centres de Lutte Contre le Cancer, FNCLCC) popular in Europe is the most widely used system.[26] In addition, it has been validated by the largest number of patients studied, and its reproducibility has been tested with a large number of pathologists.[27,28] The FNCLCC grading system of soft tissue sarcomas is based on the total score obtained from the summation of points for 3 factors: differentiation, mitotic rate, and tumor necrosis (**Box 1**).[29] For each soft tissue sarcoma type, points are assigned (1–3) for level of differentiation (**Box 2**), mitotic count, and tumor necrosis. The sum of the points is then categorized as either grade 1 (2–3 points), grade 2 (4–5 points), or grade 3 (6–8 points). The mitotic count refers to the number of mitotic figures counted in 10 high-power fields (HPF; field size of 0.174 mm^2). It is not practical to grade soft tissue sarcomas status after chemotherapy or radiation because treatment tends to affect the mitotic counts, increase necrosis, and sometimes seemingly induce differentiation or cause selection for more differentiated components.[29] Other histopathologic features not used in the grading system that are prognostically important include

Box 1
The French Federation of Cancer Centers grading system

Tumor differentiation (see Box 2)

Score 1: Sarcomas resembling normal tissue

Score 2: Sarcomas with defined histologic differentiation

Score 3: Undifferentiated sarcomas or sarcomas of uncertain histologic differentiation

Mitotic count

Score 1: 0–9/10 HPF

Score 2: 10–19/10 HPF

Score 3: ≥20/10 HPF

Tumor necrosis

Score 1: Absent

Score 2: <50%

Score 3: ≥50%

Histologic grade

Tumor differentiation + Mitotic count + Tumor necrosis (sum of scores)

Grade 1: 2–3

Grade 2: 4–5

Grade 3: 6–8

Adapted from Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol 1997;15(1):350–62; and Coindre JM. Grading of soft tissue sarcomas: review and update. Arch Pathol Lab Med 2006;130(10):1449.

surgical margin status and presence of vascular invasion.[30] For some histologic types of sarcoma, grade is of no prognostic value, such as in malignant peripheral nerve sheath tumor (MPNST), and its use is not recommended for angiosarcoma, extraskeletal myxoid chondrosarcoma, alveolar soft part sarcoma (ASPS), clear cell sarcoma, and ES.[31–35] Separate from grading, a classification based on biological behavior of soft tissue tumors is provided within the WHO classification series of soft tissue and bone tumors.[22] The soft tissue tumor types are divided into benign, intermediate (locally aggressive or rarely metastasizing), and malignant.

PATHOLOGICAL STAGING OF SOFT TISSUE SARCOMAS

The current American Joint Committee for Cancer (AJCC) Staging System for Soft Tissue Sarcomas manual incorporates the tumor stage, extent of tumor, and tumor grade.[36] This TNM system evaluates tumor size (whether greater than 5 cm or not), depth (whether suprafascial or infrafascial), and localized or disseminated (presence or absence of lymph node or distant metastases) (**Table 2**).

PATHOLOGIC GRADING OF BONE TUMORS

Bone tumors comprise a diverse group of neoplasms that are either cartilaginous, osteogenic, fibrogenic, fibrohistiocytic, hematopoietic, or of other mesenchymal tissue differentiation. The grading of bone neoplasms is largely driven by the histologic diagnosis, and

Box 2
Tumor differentiation score (according to histologic type in updated version of the FNCLCC system)

Score 1

Well-differentiated (liposarcoma, fibrosarcoma, MPNST, leiomyosarcoma, chondrosarcoma)

Score 2

Myxoid (liposarcoma, MFH, and chondrosarcoma), conventional (fibrosarcoma, MPNST, leiomyosarcoma, and angiosarcoma), well-differentiated malignant HPC, typical storiform/pleomorphic MFH

Score 3

Round cell liposarcoma, pleomorphic liposarcoma, dedifferentiated liposarcoma, poorly differentiated fibrosarcoma, poorly differentiated MPNST, epithelioid MPNST, malignant Triton tumor, conventional malignant HPC, giant-cell and inflammatory MFH, poorly differentiated/pleomorphic/epithelioid leiomyosarcoma, synovial sarcoma, embryonal/alveolar/pleomorphic rhabdomyosarcoma, mesenchymal chondrosarcoma, poorly differentiated/epithelioid angiosarcoma, extraskeletal osteosarcoma, Ewing sarcoma, ASPS, ES, malignant rhabdoid tumor, clear cell sarcoma, undifferentiated sarcoma

Adapted from Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol 1997;15(1):352.

based on the system advocated by Broders, which assesses cellularity and nuclear features.[37] Generally, the more cellular the tumor is, the higher the grade. Nuclear membrane irregularities, nuclear enlargement, and nuclear hyperchromasia correlate with grade.[22] Mitotic figures and necrosis are other histologic features helpful in grading. According

Table 2
American Joint Committee on Cancer version 7 staging for soft tissue sarcomas

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T1a	Superficial tumor
T1b	Deep tumor
T2	Tumor more than 5 cm in greatest dimension
T2a	Superficial tumor
T2b	Deep tumor
Regional lymph nodes (N)	
NX	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

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to the AJCC Cancer Staging manual, a 4-grade system is recommended; however, G1, G2 are regarded as low grade, whereas G3, G4 are regarded as high grade (**Box 3**).[36]

Chondrosarcomas are graded based on cellularity, cytologic atypia, and mitotic activity. Grade 1 chondrosarcoma is histologically similar to enchondroma, but shows radiographic or histologic evidence of aggressive growth. Grade 2 chondrosarcomas are more cellular than grade 1 chondrosarcomas; have more cytologic atypia, greater hyperchromasia, and nuclear size; or have prominent myxoid change. Grade 3 chondrosarcomas are hypercellular with significant nuclear pleomorphism and prominent mitotic activity.[38]

Chordomas are locally aggressive with a propensity for metastasis and are not graded. Adamantinomas are considered low grade. Sarcomas of types that occur in both bone and soft tissue (eg, mesenchymal chondrosarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma) are graded according to the FNCLCC system.

PATHOLOGIC STAGING OF BONE TUMORS

As with soft tissue sarcomas, the AJCC Cancer Staging manual staging of bone tumors incorporates grade of the tumor and the extent of disease. It includes a 4-grade

Box 3
Bone tumor grading

Grade 1

Low-grade central osteosarcoma

Clear cell chondrosarcoma

Grade 1 chondrosarcoma

Parosteal osteosarcoma

Adamantinoma

Grade 2

Periosteal osteosarcoma

Grade 2 chondrosarcoma

Grade 3

Conventional osteosarcoma

Telangiectactic osteosarcoma

Small cell osteosarcoma

Secondary osteosarcoma

High-grade surface osteosarcoma

Malignant giant cell tumor

Ewing sarcoma

Grade 3 chondrosarcoma

Mesenchymal chondrosarcoma

Dedifferentiated chondrosarcoma

From Randall LR. Approach to the diagnosis of bone and soft tissue tumors – clinical, radiologic, and classification aspects. In: Folpe AL, Inwards CY, eds. Bone and soft tissue pathology. Philadelphia: Saunders/Elsevier; 2010; with permission.

system based on differentiation that can be converted into high grade and low grade. In other words, grade 1 tumors = low grade and grade 2 to 3 tumors = high grade.[36,39] The TNM system evaluates tumor size (whether greater than 8 cm or not) with or without discontinuous tumors in the primary bone site, and localized or disseminated (presence or absence of lymph node or distant metastases) (Table 3).

OVERVIEW OF THE PATHOLOGIC ASPECT OF DIAGNOSIS, PROGNOSIS, AND THERANOSTICS

Although soft tissue and bone tumors are classified by the histologic differentiation in the medical textbooks, the tumors encountered by pathologists present with various histologic findings, such as spindled cells, round cells, epithelioid cells, pleomorphic cells, giant cells, myxoid, fibrous, choroid, osteoid, and so forth. The pathologist then formulates a list of pertinent differential diagnoses, using the histologic information, in conjunction with clinical and radiological information, followed by ancillary techniques, such as immunohistologic, flow cytometry, cytogenetic, and molecular techniques, to define the histologic lineage and determine an accurate diagnosis. Biomarker studies of the tumor may also provide insight into response to therapy or prognosis.

The survival of patients with any high-grade or metastatic sarcoma is usually poor and with limited therapeutic options. The urgent need for improved targeted therapies for these rare aggressive tumors has led to chemotherapy-predictive (theranostic) molecular profiling services, particularly for patients with aggressive cancers and advanced stage of disease. Molecular profiling to uncover potential theranostic biomarkers are being evaluated with the use of various methods, such as immunohistochemistry, fluorescence in situ hybridization (FISH), polymer chain reaction

Table 3
American Joint Committee on Cancer staging version 7 for bone tumors

Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor $\leq$8 cm in greatest dimension
T2	Tumor >8 cm in greatest dimension
T3	Discontinuous tumors in primary bone site
Regional lymph nodes	
NX	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Other distant sites

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(PCR)-based panels, comparative genome hybridization, whole-genome transcriptome analysis, and next-generation exome sequencing, among others.[40,41] Analysis of the molecular profile findings has the potential to provide therapeutic targets, such those involved in cell cycle regulation, DNA replication, the receptor tyrosine kinase pathway, among others, predicting susceptibilities to certain chemotherapeutic agents, and ultimately individualizing therapy.[40–42]

MALIGNANT SOFT TISSUE AND BONE TUMORS

Liposarcoma

Malignant liposarcomas include dedifferentiated liposarcoma, myxoid liposarcoma, and pleomorphic liposarcoma.[6,22] Atypical lipomatous tumors (ALT) may undergo dedifferentiation resulting in a nonlipogenic sarcomatous component, consistent with dedifferentiated liposarcoma (**Fig. 1**). Typically the nonlipogenic sarcomatous component, of variable grade, is at least several millimeters in diameter and is either associated with a primary ALT/well-differentiated liposarcoma or in a recurrence.[43,44] Myxoid liposarcomas, formerly also known as round cell liposarcomas, account for up to 20% of all liposarcomas and are composed of primitive mesenchymal cells, with a variable number of signet-ring cell lipoblasts, within an abundant myxoid stroma, characteristically with a delicate arborizing vascular pattern.[22,45] Pleomorphic liposarcoma is the most rare subtype and contains a variable amount of pleomorphic lipoblasts, with no associated well-differentiated component.

Dedifferentiation occurs in up to 10% of well-differentiated liposarcomas, with 90% observed at the time of initial diagnosis, and 10% presenting as a recurrence.[2,46] The concept of low-grade dedifferentiation has been increasingly recognized, which can present as an area resembling low-grade myxofibrosarcoma, well-differentiated fibrosarcoma, dermatofibrosarcoma, or even desmoid-type fibromatosis,[47] Myxoid liposarcomas (**Fig. 2**) are the second most common subtype of liposarcoma, comprising one-third of all liposarcomas, whereas pleomorphic liposarcomas account for only about 5% of all liposarcomas.[2,3,17] Dedifferentiated liposarcomas occur most often in the retroperitoneum, whereas myxoid and pleomorphic liposarcomas most frequently affect the deep tissues of the extremities.

Ancillary studies

Dedifferentiated liposarcoma is characterized by the presence of a supernumerary ring or giant rod chromosome containing amplified 12q13 to 15 region segments,

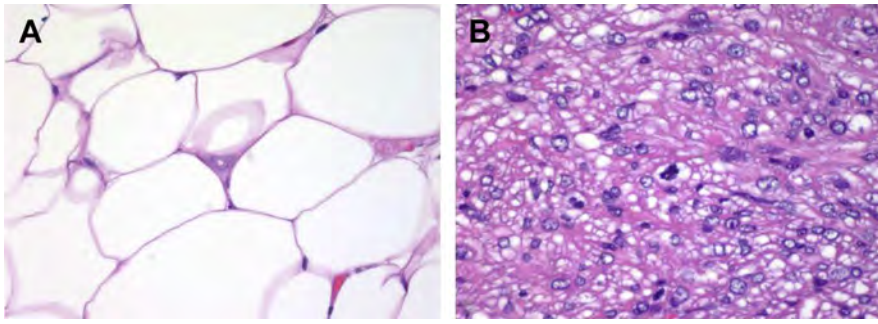

Fig. 1. Well-differentiated component, high power (*A*) (hematoxylin-eosin, original magnification ×40), of a dedifferentiated liposarcoma (*B*), high power (hematoxylin-eosin, original magnification ×20).

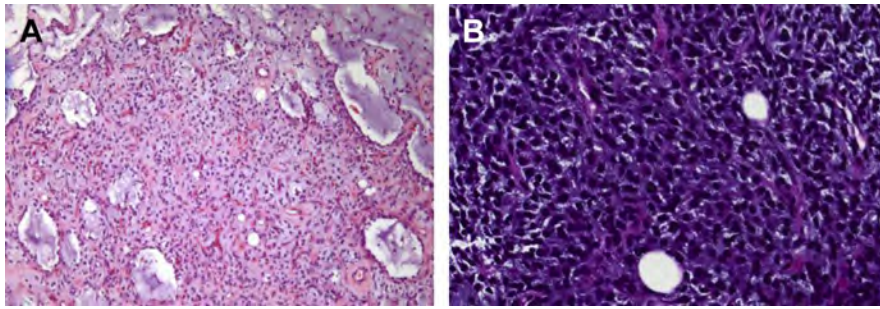

Fig. 2. A myxoid liposarcoma, low power (*A*) (hematoxylin-eosin, original magnification ×4) and high power (*B*), the latter showing a round cell histologic appearance (hematoxylin-eosin, original magnification ×20).

with several oncogenes identified within this region, including MDM2, CDK4, HMGA2, CHOP (DDIT3), and GLI1, among others.[47,48] MDM2 and CDK4 testing is very useful in the diagnosis of dedifferentiated liposarcomas or atypical lipomatous tumor, and they are usually negative in myxoid and pleomorphic liposarcomas. Poorly differentiated sarcomas with no identifiable atypical lipogenic component can be diagnosed as dedifferentiated liposarcoma on the basis of MDM2.[47] Gene amplification or protein overexpression of these markers can be detected by molecular studies, including FISH and immunohistochemistry. Greater than 90% of myxoid liposarcomas harbor the t(12;16)(q13;p11) karyotypic hallmark, which leads to the fusion of the FUS (TLS) and DDIT3 (CHOP) genes, generating a FUS/DDIT3 hybrid protein.[22,49–51]

Prognostic implications

Anatomic location is the most important known prognostic factor in dedifferentiated liposarcomas, with retroperitoneum tumors having the worst clinical behavior. The retroperitoneum is the most common primary location, and the lungs are the most common metastatic site.[44] Histologic grade, presence of necrosis, and TP53 overexpression are also associated with a less favorable prognosis.[49,52] Complex karyotypic aberrations and TP53 mutations are relatively uncommon in dedifferentiated liposarcomas, when compared with other high-grade sarcomas, which may contribute to the greater overall survival.[2,23,53,54] TP53 mutations are much more common in pleomorphic liposarcomas.[47] Myxoid liposarcoma is usually the least aggressive subtype, with less than 10% of low-grade tumors progressing to metastatic disease. In addition to histologic grade, TP53 and CDKN2A mutations are unfavorable prognostic markers for myxoid liposarcoma.[10,22,53,55] Likely oncogenic roles have been demonstrated for MDM2, CDK4, HMGA2, and TSPAN31 in dedifferentiated liposarcoma (and atypical lipomatous tumor/well-differentiated liposarcoma). Amplification of the fibroblast growth factor receptor substrate 2 gene in dedifferentiated (and well-differentiated) liposarcomas has also been recently described.[56]

Fibrosarcoma

Malignant fibrosarcomas include adult fibrosarcoma, myxofibrosarcoma, low-grade fibromyxoid sarcoma, and sclerosing epithelioid fibrosarcoma. Adult fibrosarcoma is a malignant fibroblastic tumor with variable collagen production, classically demonstrating herringbone architecture. They are thought to account for 1% to 3% of all adult sarcomas,[5,22] typically involving deep soft tissue of the extremities, trunk, or head and neck regions.[3,5] Myxofibrosarcomas (**Fig. 3**) have a variable amount of myxoid stroma, pleomorphic nuclei, characteristically with a curvilinear vascular pattern. They are more

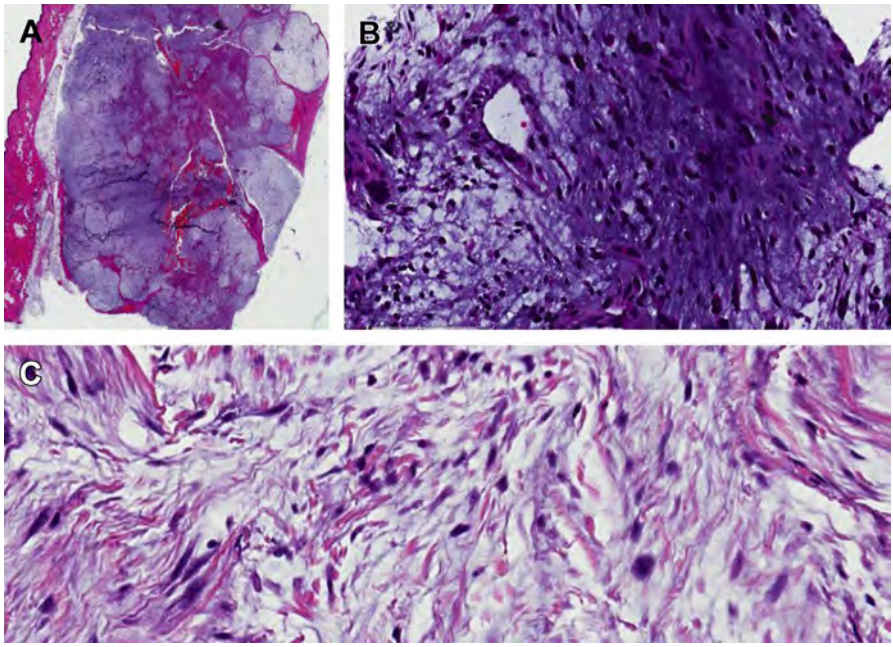

Fig. 3. Myxofibrosarcoma, low power (*A*, *B*) (hematoxylin-eosin, original magnifications ×2, ×10) and high power (*C*) (hematoxylin-eosin, original magnification ×40).

common in elderly patients and most commonly arise in the extremities.[3,17] Low-grade fibromyxoid sarcomas are composed of blander-appearing spindled cells with admixed myxoid and collagenous stromal areas, a whorled pattern of growth, and a curvilinear vascular pattern. Sclerosing epithelioid fibrosarcomas have a densely sclerotic stroma with cords and nests of epithelioid fibroblasts.

Histopathology and ancillary studies

The spindled cells in adult fibrosarcoma are characteristically angled in a herringbone or chevronlike pattern with hyperchromatic nuclei, variably prominent nucleoli, and scant cytoplasm. The neoplastic cells may phenotypically show myofibroblastic differentiation with SMA positivity. To date, there are no characteristic molecular studies to help definitively diagnose difficult cases of adult fibrosarcomas; however, disruption of one or more genes in the 2q14 to 22 region have been described as possibly contributing to the pathogenesis of at least some cases.[17,51,57,58] Infantile fibrosarcomas are histologically identical to adult fibrosarcomas, but they carry a distinctive translocation, t(12;15)(p13;q26), resulting in the ETV6-NTRK3 fusion, which can be detected by FISH or PCR.[51] Low-grade fibromyxoid sarcoma consistently has either a t(7;16) or t(11;16) translocation, resulting in an FUS-CREB3L2 or FUS-CREB3L1 gene fusion, respectively.[51] A few low-grade fibromyxoid sarcomas have been shown to have the EWSR1-CRE-B3L1 gene fusion; however, EWSR1 gene rearrangements are much more frequent in sclerosing ES. Low-grade fibromyxoid sarcomas and sclerosing ES also share mucin 4 immunoreactivity.[51]

Prognostic implications

The reported recurrence rates for adult fibrosarcomas and myxoinflammatory fibromyxoid sarcomas after complete excision range anywhere from 12% to 80%. Lung

and bone are most common sites of metastasis for adult fibrosarcoma, and local bone and lymph node involvement is more common in myxoinflammatory fibroblastic sarcoma.[3,53] High histologic grade, mitotic rates of greater than 20 per 10 HPF, and minimal amount of collagen are associated with a worse prognosis in adult fibrosarcomas.[22] Infantile fibrosarcomas have an overall much more favorable prognosis, only rarely metastasizing, and even with cases of spontaneous regression reported,[22,59,60] although retroperitoneal location may be associated with a worse prognosis.[60]

Undifferentiated Sarcomas

The undifferentiated/unclassified sarcoma category was created as category of differentiation for any undifferentiated soft tissue sarcoma (USTS) and can be divided into subtypes based on morphologic findings as either undifferentiated spindle cell sarcoma, undifferentiated pleomorphic sarcoma, undifferentiated round cell sarcoma, undifferentiated ES, or undifferentiated sarcoma, NOS (**Fig. 4**). These USTS were previously included in the fibrohistiocytic section as "undifferentiated pleomorphic sarcoma," historically also known as "malignant fibrous histiocytoma", as they were previously thought to likely be of fibrohistiocytic differentiation. They lack a defined line of differentiation with the use of currently available technology and should be a diagnosis of exclusion. USTS usually occur in adults over the age of 40, accounting for up to 20% of all sarcomas and one-fourth of radiation-related sarcomas.[22] Most USTS arise within deep soft tissue of extremities, with some occurring in the trunk region, and less than 10% occurring superficially within subcutaneous tissue.[22]

Ancillary studies

Tumors should be sampled generously, and ancillary techniques must be used in order to rule out a defined line of differentiation. USTS may show a small number of cells expressing keratins, smooth muscle markers, epithelial membrane antigen (EMA), CD99, or CD34, insufficient for definitive differentiation.[22] Molecular studies have shown several genomic imbalances and alterations of TP53, CDKN2, and RB1, which may play a role in the development of USTS, but further studies are required to more clearly understand this relationship.[22,51]

Prognostic implications

USTS are aggressive tumors with a 50% to 60% overall 5-year survival.[61] Genetic analysis could be particularly beneficial for the possible identification of a

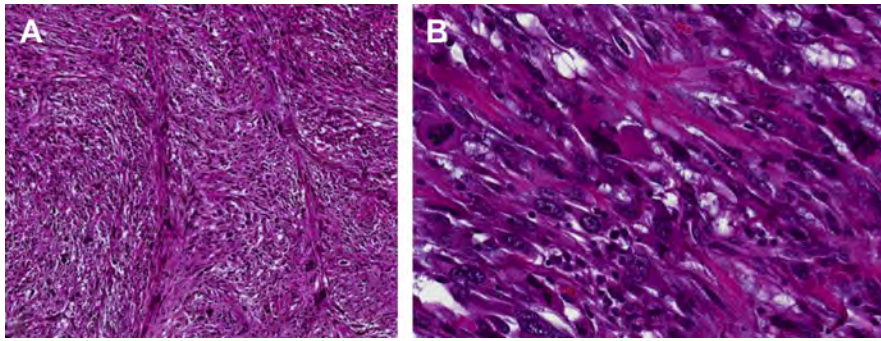

Fig. 4. USTS, low power (*A*) (hematoxylin-eosin, original magnification ×2) and high power (*B*) (hematoxylin-eosin, original magnification ×40).

dedifferentiated liposarcoma, which carries a more favorable prognosis. Undifferentiated round cell sarcomas occasionally have gene rearrangements involving the fusion of the EWSR1 gene with a non-Ewing sarcoma tumor gene, sometimes showing a possible close molecular link with Ewing sarcoma, and are usually even treated the same as Ewing sarcoma clinically.[22,62,63]

Angiosarcoma

Angiosarcoma of soft tissue is a rare malignant vascular tumor, which variably resembles normal endothelial cells. Most angiosarcomas present as a primary cutaneous tumor, and they less often present as a deep soft tissue mass.[3,5,17] Several mechanisms of pathogenesis have been suggested because they are known to be associated with radiation therapy; tumor syndromes, such as neurofibromatosis (NF); and foreign material, including grafts. They typically have areas of spindled cells and areas of epithelioid cells, with high nuclear grade, arranged in sheets or chords, and irregularly intercommunicating vascular channels. Epithelioid angiosarcoma is a variant composed predominantly of epithelioid cells with vesicular nuclei and abundant eosinophilic cytoplasm.

Ancillary studies

Immunohistochemical studies for CD34, CD31, and von Willebrand factor (vWF) support the diagnosis of angiosarcoma. vWF is the most specific, but least sensitive marker, whereas CD34 is the least specific and most sensitive marker. CD31 has both excellent sensitivity and specificity. New vascular markers that are useful in diagnosing angioarcoma include FLI1 and ERG. High levels of MYC (8q24) amplification and occasional FLT gene abnormalities have been reported in radiation-induced angiosarcomas, whereas neither have been associated with primary angiosarcomas or even radiation-associated vascular lesions.[7,22,51]

Prognostic implications

Angiosarcomas are highly aggressive with frequent local recurrences. The most common site of metastatic disease is the lung, but may often also involve lymph nodes, bone, and soft tissue. Large tumor size, retroperitoneal location, older age, and high Ki-67 proliferative index are associated with a worse prognosis.[22]

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is a malignant vascular tumor that is most commonly seen in adolescents and adults, usually presenting as a mildly painful soft tissue mass within the upper extremities. Histologic evaluation reveals angiocentric cords of epithelioid endothelial cells with eosinophilic cytoplasm containing frequent vacuoles (**Fig. 5**), within a myxo-hyalinized stroma, usually with complete obliteration of the associated vascular lumens.[22]

Ancillary studies

EHE should be immunoreactive with vascular markers such as CD34, CD31, FLI1, and ERG transcription factor. They may also show epithelial marker expression, often with keratin 7, 8, 18, or EMA.[22] Approximately 90% of EHE cases harbor the characteristic WWTR1-CAMTA1 fusion,[22,64] which leads to overexpression of both genes. The WWTR1 protein is known to be expressed by many cell types, but the CAMTA1 protein expression is usually limited to the brain. A recent study used a new polyclonal antibody, different than a previously studied one, directed against the C-terminus of CAMTA1, with findings suggesting that it may be a useful diagnostic marker for EHE.[64]

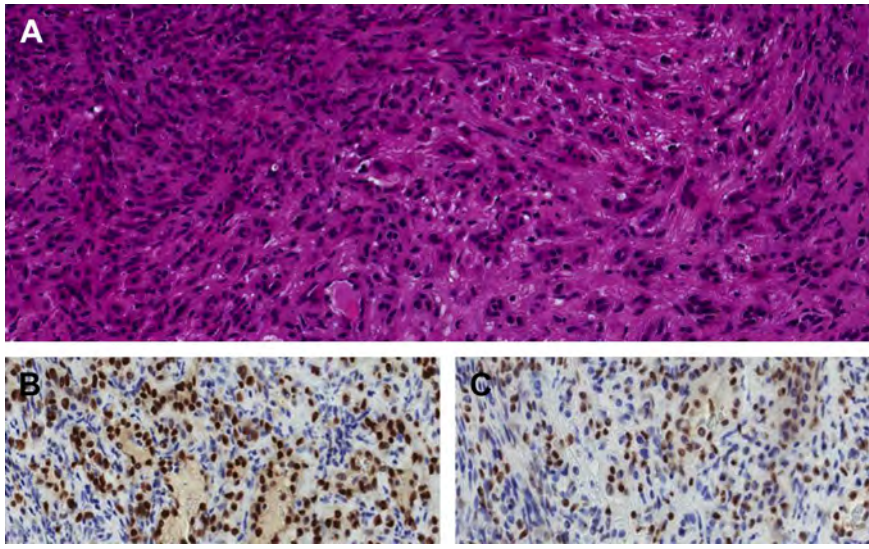

Fig. 5. EHE (*A*), low power (hematoxylin-eosin, original magnification ×10), showing nuclear immunoreactivity for ERG (*B*) and FLI1 (*C*) (original magnification ×10).

Prognostic implications

Risk stratification may be useful for categorizing these tumors into low-risk or high-risk groups, with high-risk features including tumor diameter greater than 3 cm and greater than 3 mitoses per 50 HPF. One study showed the disease-free survival at 5 years for patients with these high-risk features as nearly 60%, whereas the lack of these features showed a 100% survival at 5 years.[22,65]

Leiomyosarcoma

Leiomyosarcomas are malignant tumors that have distinct smooth muscle features. They account for a large portion of retroperitoneal sarcomas and less commonly arise within the extremities.[6,22] They are also the most common sarcoma that can arise from large blood vessel walls. They are more commonly seen in women, usually presenting as a large, variably painful, retroperitoneal or pelvic tumor.[61] If associated with a large vessel, the most common sites are the inferior vena cava and the large vessels of the lower extremities.[3,17] If the upper portion of the inferior vena cava is involved, an obstruction may result in Budd-Chiari syndrome.[66,67] Involvement of the middle portion may lead to renal vein obstruction and renal dysfunction, while involvement of the lower portions of the vessel may cause lower extremity edema.[22]

Classically, leiomyosarcomas exhibit a fascicular growth pattern, with cellular bundles of spindled cells, which are well delineated from and intersect with other bundles of spindled cells (**Fig. 6**). The cells typically have hyperchromatic and elongated nuclei with blunted ends, commonly with indentations and often with notable pleomorphism. Brisk mitoses and areas of tumor necrosis are commonly present, especially in larger tumors.[22]

Ancillary studies

Immunohistochemical studies for smooth muscle markers, such as smooth muscle actin (SMA), desmin, and caldesmin should be positive. Most reported karyotypes performed on leiomyosarcomas have shown complex karyotypes with no consistent

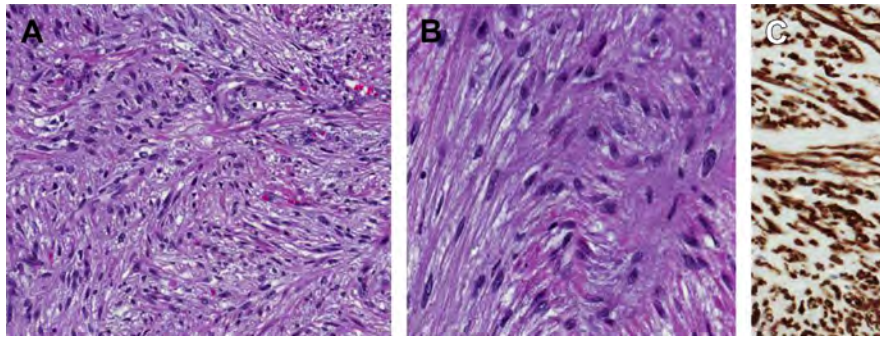

Fig. 6. Leiomyosarcoma, low power (*A*) (hematoxylin-eosin, original magnification ×10) and high power (*B*) (hematoxylin-eosin, original magnifications ×20), showing strong diffuse immunoreactivity to desmin (*C*) (Original magnification ×10).

aberrations. The RB1 gene has been frequently implicated in the pathogenesis of leiomyosarcomas with frequent abnormalities observed during analysis of the Rb-cyclinD pathway. TP53 and MDM2 are less frequently seen, but may have prognostic value, correlating with a worse prognosis.[8,51]

Prognostic implications

Retroperitoneal leiomyosarcomas are often larger than 10 cm at the time of diagnosis and may be extremely difficult to excise, commonly resulting in both local and distant metastases.[3,22,68] On the other hand, nonretroperitoneal leiomyosarcomas are generally smaller at presentation and more amenable to surgical resection with more favorable overall outcomes.[17,69] Greater histologic grade, osseous invasion, and vascular involvement are poor prognostic factors.[61] Potential therapeutic targets, such as FOXM1, are under investigation, which may have the ability to decrease the cell proliferation and increase chemosensitivity for LMS.[70]

Rhabdomyosarcoma

Rhabdomyosarcomas are malignant mesenchymal tumors that exhibit skeletal muscle differentiation. Currently, the 4 recognized subtypes include the embryonal, alveolar, pleomorphic, and spindle-cell/sclerosing rhabdomyosarcomas.[20] Embryonal rhabdomyosarcoma phenotypically and biologically resembles embryonic skeletal muscle and includes the botryoid and anaplastic variants. A spindle cell variant was previously included, but is now considered a separate subtype of rhabdomyosarcoma.[71,72] Alveolar rhabdomyosarcoma is another primitive soft tissue sarcoma, with partial skeletal muscle differentiation, which cytologically more closely resembles lymphoma.[73–76] Pleomorphic rhabdomyosarcomas should have no embryonal or alveolar components and consist of bizarre polygonal, spindled, or round cells, which have evidence of skeletal muscle differentiation.[22]

Rhabdomyosarcomas account for the largest number of sarcoma cases among children and adolescents, affecting 4 to 5 per every million US children under the age of 15.[3,53,77,78] Embryonal rhabdomyosarcoma is the most common subtype with nearly 50% occurring in children less than 5 years of age, and with a slight male predominance.[3,77,78] Alveolar rhabdomyosarcoma most often occurs in adolescents and young adults, whereas pleomorphic rhabdomyosarcoma occurs almost exclusively in adults.[3,22,78] Clinical symptoms are usually related to local mass affect and obstruction of nearby structures. The botyroid variant typically presents within

hollow viscera (eg, gallbladder or urinary bladder) and has a unique appearance consisting of a cluster of variably sized tumor nodules.[22]

The most primitive histologic appearance of rhabdomyosarcoma consists of stellate rhabdomyoblasts with central oval nuclei and slightly amphophilic to eosinophilic cytoplasm. As the cells acquire greater differentiation toward mature skeletal muscle, their cytoplasm becomes eosinophilic and they become more elongated. Terminal differentiation is indicated by cross-striation and multinucleation.[22] Of note, cross-striations are a helpful diagnostic histologic feature, but are exceedingly rare in pleomorphic rhabdomyosarcomas. Alveolar rhabdomyosarcomas may present with typical morphologic features, with nested tumor cells separated by fibrovascular septa, a solid pattern, or with mixed alveolar and embryonal features.[22,75,78]

Ancillary studies

Desmin and actin immunoreactivity is acquired early on by rhabdomyoblasts. Markers for skeletal muscle differentiation, such as Myo-D or myogenin, typically show a diffusely strong nuclear staining pattern, but primitive tumors may show only focal or negative immunoreactivity. Most embryonal rhabdomyosarcomas have a loss in the chromosomal region 11p15, a region also affected by the inherited Beckwith-Wiedemann syndrome. Cytogenetic analysis of alveolar rhabdomyosarcomas revealed a specifically associated translocation, t(2;13)(q35;q14), in greater than 75%, and a t(1;13)(p36;q14) in a smaller subset, involving the PAX3 gene (chromosome 2) or the PAX7 gene (chromosome 1) and the FKHR gene on chromosome 13, forming chimeric genes, resulting in chimeric fusion proteins.[51,79–81] Chromosome analyses of pleomorphic rhabdomyosarcoma cases have shown complex karyotypes, but they lack a known recurrent genetic alteration.[23,80]

Prognostic implications

Pathologic stage, histologic classification, patient age, and site of origin help determine the prognosis of embryonal and alveolar rhabdomyosarcomas. The botyroid variant of embryonal rhabdomyosarcoma and the spindle-cell/sclerosing rhabdomyosarcoma subtype typically have more favorable outcomes, whereas alveolar and pleomorphic rhabdomyosarcomas are more aggressive subtypes. Some evidence has suggested an improved outcome with PAX7/FKHR-positive tumors when compared with PAX3/FKHR tumors.[8–10,46,54,58,79,80,82–86] In addition, a recent meta-analysis showed indications suggestive of PAX3-FOXO1 being an unfavorable prognostic factor; however, no statistically significant difference in overall survival was found.[81,87]

Synovial Sarcoma

Synovial sarcoma is currently a tumor of uncertain differentiation that shows variable epithelioid differentiation, with no identified epithelial origin to date. Despite the name, it has no association with synovial tissue. Synovial sarcoma has distinct morphologic and genetic findings, including spindled cells, often with an epithelioid component, and the chromosomal translocation t(X;18)(p11;q11). They account for up to 10% of soft tissue sarcomas and may occur at any age, most often between the ages of 15 and 40.[3,7,18,22] They can present at any site, usually as a slowly growing mass, the large majority of which develop within the deep soft tissue of the extremities, primarily near the knee region, and less than 5% occurring within a joint or bursa.[17,22] The patient may report a history of a slow-growing mass, often first noted greater than 2 years before presentation. Synovial sarcomas may be monophasic (**Fig. 7**), appearing as uniform sheets of spindled cells with ovoid pale-staining nuclei and inconspicuous nucleoli, or can be biphasic, which also includes an epithelial component. The

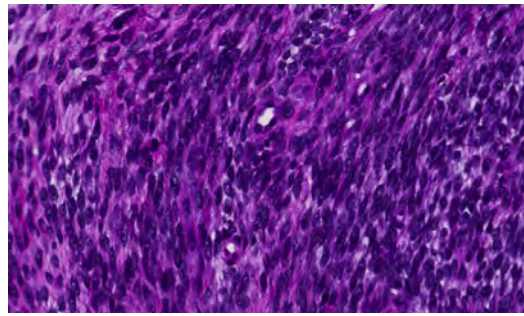

Fig. 7. Synovial sarcoma, high power, showing monophasic spindle cell component (hematoxylin-eosin, original magnification ×20).

epithelial component may even predominate over the spindle cell component and can be glandular, chordlike, or nested.[22]

The epithelial components of synovial sarcomas typically express cytokeratins (CKs) and EMA immunoreactivity. Immunohistochemical staining for Bcl2, CD99, and calponin is typically also positive, whereas S100 may be positive in as many as 30% of synovial sarcomas. The TLE1 (transducer-like enhancer of split 1) has a moderate-to-strong nuclear staining pattern in the majority (80%–90%) of synovial sarcomas, although it is not entirely specific, showing immunoreactivity in other soft tissue tumors, such as nerve sheath tumors and in SFT.[88,89] The cytogenetic hallmark for a synovial sarcoma is the recurrent reciprocal t(X;18)(p11;q11), which is present in greater than 90% of reported cases, involving the fusion of the SYT (18q11) gene with either the SSX1, SSX2, or SSX4 gene,[51] resulting in the respective fusion protein. FISH studies and real-time (RT) -PCR are widely used to detect these molecular findings and can provide a relatively rapid and definitive diagnosis for synovial sarcomas.[51,58] A relatively new immunohistochemical marker for SYT, when strongly and diffusely positive, may be useful in the rapid diagnosis of synovial sarcoma, especially when material is insufficient for PCR or FISH analysis.[90]

Prognostic implications

Tumor size greater than 5 cm, greater than 10 mitoses per HPF, the presence of extensive (>50%) necrosis, the presence of rhabdoid cells, and poorly differentiated variants are all poor prognostic factors. On the other hand, tumors less than 5 cm, young patient age, and the SS18/SSX2 are associated more favorable outcomes. The reported 10-year survival rates vary widely, ranging from about 20% to 75%.[17,22,51,72,91]

Alveolar Soft Part Sarcoma

ASPS accounts for less than 1% of all soft tissue sarcomas, affecting mostly adolescents and young adults. Morphologically, it is composed of fairly monotonous, large, round, or polygonal epithelioid cells containing abundant eosinophilic, granular cytoplasm, arranged in an organoid or nested pattern, usually separated by thin sinusoidal vessels.

Central necrosis of the nested cells may give the appearance of an alveolar pattern, hence the name. Nearly half of ASPS originate within the deep soft tissue of the thigh or buttock, and they typically present as a slowly growing painless mass.

Ancillary studies

The immunohistochemical marker TFE3 shows at least moderate nuclear reactivity in most cells, but is not entirely specific. Periodic acid–Schiff (PAS) with diastase is a

useful special stain, which can highlight intracytoplasmic crystal formations that are also immunoreactive for MCT1 and CD147. Molecular evaluation for the detection of the ASPL/TFE3 fusion protein is highly sensitive and specific for ASPS and results from the classic t(X;17)(p11;q25) translocation, although it has also been identified in a small subset of renal cell carcinomas.[51]

Prognostic implications

ASPS is a slow-growing tumor, with an infrequent local recurrence rate; however, early and late metastatic disease is common. Patients often already have distant metastatic disease on initial presentation, usually involving lung, bone, or brain.[2,22,84] The most influential poor prognostic factors include increased patient age, larger tumor size, and the presence of metastasis at presentation.[22]

Clear Cell Sarcoma of Soft Tissue

Clear cell sarcoma of soft tissue, also known as melanoma of soft parts, is a soft tissue sarcoma with melanocytic differentiation that usually involves aponeurosis and tendons. Greater than 90% present as slow-growing, deep-seated extremity tumors, most often affecting young adults. They are composed of polygonal or spindled cells with abundant clear to eosinophilic cytoplasm, arranged in a nested or fascicular pattern, separated by fibrous septa. Mitotic activity and nuclear polymorphism are usually relatively low, but marked pleomorphism and brisk mitotic activity may be seen.[22]

Ancillary studies

Almost all cases of clear cell sarcoma are positive for melanocytic markers, such as S100, HMB45, and Melan-A. Melanosomes are almost always present, varying in their degree of maturation. The hallmark cytogenetic finding is the reciprocal translocation t(12;22)(q13;q12), which results in the EWS/ATF1 fusion.[10,51,83]

Prognostic implications

Overall prognosis is poor, especially with larger tumor size and the presence of necrosis. The 5-year survival is less than 70%, but the 10-year disease-free survival is only about 33%, because the development of late recurrences or metastatic disease is common.[22,51,83,92]

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a tumor of uncertain differentiation that is composed usually of small round cells with prominent stromal desmoplasia, harboring the consistent presence of the t(11:22)(p13;q12) translocation.[7,23,51,83,93] DSRCT primarily affects children and young adults, with a male predominance, and very often presents with widespread abdominal serosal involvement.[20,83] Morphologic evaluation of the tumor cells typically shows small, uniform cells with hyperchromatic nuclei, dispersed chromatin, and inconspicuous nucleoli, with a high nuclear-to-cytoplasmic ratio, indistinct cell borders, and frequent mitoses.

Ancillary studies

Immunohistochemical studies are usually helpful, with the majority of DSRCT, which show positive immunoreactivity for CKs, EMA, desmin, and WT1. SMA is typically positive in the stromal component. The characteristic t(11:22)(p13;q12) translocation results in the EWS/WT1 fusion, and the resulting chimeric fusion transcript may also be detected with excellent sensitivity and specificity for diagnosis.[7,8,51,58,83,93]

Prognostic implications

Unfortunately, the overall clinical outcomes for this rare entity remain poor, even with aggressive therapy.[94,95] Surgical excision with combination of chemotherapy and possibly the utilization of whole abdominopelvic radiation therapy may significantly improve survival outcomes for abdominal and pelvic DSRCT.[94–96]

Ewing Sarcoma

Ewing sarcoma is considered to be of neuroectodermal origin. The term primitive neuroectodermal tumor is no longer used, because molecular analysis helped show it was a histologic variation of Ewing sarcoma, differing only in the degree of neuroectodermal differentiation. The Ewing sarcoma family of tumors (EFT) also includes extraskeletal Ewing sarcomas, and Askin tumors, all of which are characterized by the recurrent t(11;22)(q22;q12) chromosomal translocation. Ewing sarcoma is the second most common primary sarcoma in children, involving either bone or soft tissue, with almost 80% of affected patients younger than 20 years of age. Ewing sarcoma commonly presents as a painful mass arising in the diaphyseal or metaphyseal-diaphyseal portion of a long bone, pelvis, or ribs. Radiographically, they appear as osteolytic lesions with a characteristic multilayered periosteal reaction. Macroscopically, during a biopsy procedure, this tumor may actually be mistaken as pus, due to its often necrotic and tan-yellow, semifluid appearance. Morphologically, most EFT are composed of small round cells with round nuclei and a fine chromatin pattern, with scant clear-to-eosinophilic cytoplasm, usually containing PAS positive glycogen.

Ancillary studies

Ewing sarcoma is usually CD99 positive, with a membranous staining pattern. Markers for vimentin and nonspecific enolase are also often positive. However, the above markers are nonspecific, and newer, more specific markers, including FLI1, ERG, and EWSR1, have become available, improving the accuracy of the initial diagnosis while definitive molecular studies are pending or unavailable. The characteristic recurrent translocation t(11;22)(q22;q12) most commonly involves the EWS gene (22q12) and FLI1 genes (85% of cases), producing a chimeric protein.[8,20,51,58] The second most common combination (10%–15%) includes the fusion of EWS with the ERG gene. Other genes, such as ETS, ETV1, E1AF, FEV, and ZSG, have also been involved in the rearrangement with the EWS gene, but these are seen in less than 1% of all EFT.[22]

Prognostic implications

Molecular markers, such as TP53, telomerase expression, or CDKN2A loss, have shown prognostic significance, while the EWSR1-ETS fusion status is no longer thought to have prognostic value.[3,7,8,10,51,58,82,83] Therapeutic advances have greatly improved clinical outcomes, with most patients presenting with localized tumors being cured of disease. The presence of metastatic disease continues to be the most important prognostic factor.[10,22]

Chondrosarcoma

Chondrosarcomas are a heterogeneous group of malignant tumors, which includes the primary central, secondary central, periosteal, dedifferentiated, mesenchymal, and clear cell variants, all of which exhibit some amount of hyaline cartilage differentiation. They are the third most common primary tumor of the bone, most often arising within the pelvic bones, femur, or humerus, typically with localized pain and swelling.[3,17] Primary central chondrosarcomas are by far the most common, arise centrally within a bone, and account for 20% of all malignant bone tumors.[3,22,83]

Secondary central chondrosarcomas arise within a benign precursor, such as an enchondroma. Periosteal chondrosarcomas arise from the surface of bones, most commonly involving the long bones.[22] These chondrosarcomas have an irregular pattern of cartilage lobules that vary in size and shape that may be separated by bands of fibrosis. Myxoid changes or ossification may also be seen. Mesenchymal chondrosarcomas have a bimorphic pattern with islands of well-differentiated hyaline cartilage and areas of small round undifferentiated cells. Clear cell chondrosarcoma is a rare low-grade subtype of chondrosarcoma, composed of hyaline cartilage and bland clear cells (**Fig. 8**). Dedifferentiated chondrosarcoma accounts for approximately 10% of chondrosarcomas and contains a well-differentiated cartilaginous tumor component with an abrupt transition to a high-grade sarcoma lacking cartilaginous differentiation.[22]

Ancillary studies

Bcl-2 may be a helpful immunohistochemical marker for distinction between an osteochondroma and low-grade secondary peripheral chondrosarcoma. Isocitrate dehydrogenase genes 1 and 2 (IDH1 and IDH2) somatic mutations are seen in most chondrosarcomas.[22,97,98] In addition, RB1 pathway mutations are seen in most high-grade central chondrosarcomas.[22,97,98]

Prognostic implications

Histologic grade is the most important prognostic indicator, with low-grade tumors having the least chance of recurrence or metastasis, and a nearly 90% overall 5-year survival.[22,99] Clear cell chondrosarcomas have excellent outcomes after complete resection with clear margins, whereas dedifferentiated chondrosarcomas have the worst prognosis, with as many as 90% of patients presenting with metastatic disease within 2 years of initial diagnosis.[3,17,97–102]

Osteosarcoma

Conventional osteosarcomas are high-grade intramedullary tumors that produce any amount of osteoid (**Fig. 9**) and include the osteoblastic (80% of cases), chondroblastic, fibroblastic, and secondary variants.[22] Osteoblastic osteosarcomas have a sclerotic appearance with a predominantly osteoid matrix, which can be thick or thin and branching. Chondroblastic osteosarcomas, on the other hand, have a predominant chondroid matrix. Fibroblastic osteosarcomas produce only minimal amounts of osteoid and have high-grade spindled cell architecture. Osteosarcoma is the most common nonhematopoietic primary malignant tumor of the bone, most commonly arising within the appendicular skeleton, and affecting about 5 in every

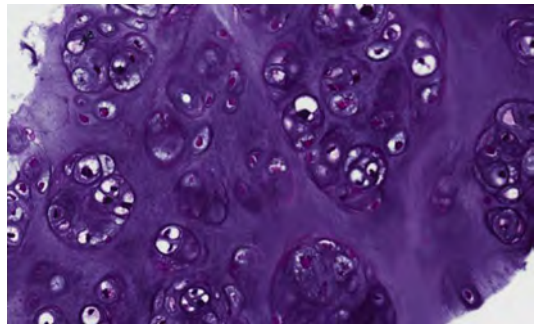

Fig. 8. Chondrosarcoma, low grade, high power (hematoxylin-eosin, original magnification ×40).

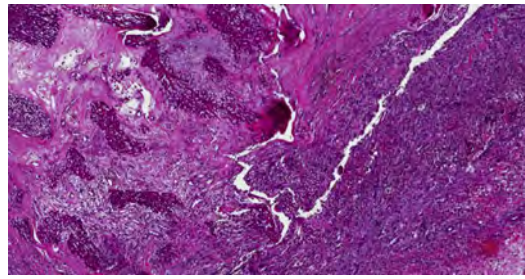

Fig. 9. Osteosarcoma, low power (hematoxylin-eosin, original magnification ×2).

million people.[22] Most cases occur in patients under the age of 25. The neoplastic cells can have one or more of many histologic appearances, including epithelioid, plasmacytoid, ovoid, multinucleated, or spindled cell morphology.[22]

Other subtypes of osteosarcoma include the telangiectatic, small cell, parosteal, periosteal, and high-grade surface osteosarcoma. Telangiectatic osteosarcoma, also previously known as malignant bone aneurysm or hemorrhagic osteosarcoma, is characterized by having large blood-filled spaces, which are usually separated by thin septa.[11,22,82] Although prognosis is thought to be similar to conventional osteosarcomas, they are much more sensitive to chemotherapy. Small cell osteosarcoma produces variable amounts of osteoid and morphologically resembles Ewing sarcoma, but lacks the t(11;22) translocation.[61] Parosteal osteosarcomas are low grade and arise on the surface of bones, most frequently involving the femur. Periosteal osteosarcomas are intermediate-grade chondroblastic osteosarcomas that also arise in the surface of bone, most commonly arising within or near the diphyseal areas of the long bones.[22]

Ancillary studies

Osteosarcomas are typically CD99 positive, and osteocalcin might be useful for highlighting osteoid, but in general immunohistochemical stains are primarily used to rule out other entities. Recurrent amplifications at 1q21 to 23 and 17p are commonly seen, and comparative genomic hybridization analysis has revealed frequent chromosomal gains, such as the gain of 8q23, seen in about half of osteosarcomas.[3,40,103] A high incidence of loss of heterozygosity has also been seen.[22,103] CDK4 with or without MDM2 is commonly amplified in aggressive osteosarcomas. Patients with hereditary retinoblastoma (RB) and Li Fraumeni syndrome have an increased risk of developing osteosarcomas. RB1 alterations have also been seen in up to 40% of sporadic osteosarcomas, whereas TP53 alterations have been seen in up to 35% of osteosarcomas. Many genetic aberrations have been found in high frequency, some of which may offer prognostic value.[22,40,42]

Prognostic implications

The overall survival, with a multidisciplinary therapeutic management approach, for osteosarcomas is about 80% to 90%.[22] Parosteal osteosarcoma carries an excellent prognosis, with a greater than 90% 5-year survival, whereas small cell osteosarcomas have slightly worse outcomes compared with conventional osteosarcomas.[22,104] Elderly patients with polyostotic Paget disease are at increased risk for developing osteosarcomas that have particularly unfavorable outcomes.[22]

Malignant Peripheral Nerve Sheath Tumor

MPNST accounts for up to 5% of all soft tissue tumors and can be found in the setting of NF1 or arising from a peripheral nerve or benign nerve sheath tumor. Individuals

with NF1 have about a 50% chance developing MPNST, with a higher chance of development associated with plexiform neuromas. MPNST can be variably painful, most commonly involving a major nerve, such as the sciatic nerve, which often presents with neuropathic symptoms. Microscopically, they typically show a fascicular or whorling growth pattern of spindled cells, with alternating hypercellular and hypocellular areas and prominent, branching, HPC-like vasculature. The neoplastic cells are usually more concentrated and appear more epithelioid adjacent to the blood vessels. Up to about 15% of MPNST have heterologous elements, and the term malignant Triton tumor is used for an MPNST with skeletal muscle differentiation.[22,46,105]

Ancillary studies

Although MPNST can stain positively for S100 in up to about 50% of cases, a diffusely strong immunoreactivity is very uncommon, so other tumors within the differential diagnosis, such as melanoma, dendritic cell sarcoma, and cellular schwannoma, should be considered in that setting. Helpful histologic features include perivascular hypercellularity, tumor herniation into vascular lumens, necrosis, and expression of p75NTR, all of which are frequently associated with MPNST.[105] Glial fibrillary acidic protein (GFAP) shows positive immunoreactivity in up to 30% of MPNST.[22] Complete loss of SOX10, neurofibromin, or p16 immunoreactivity, and the presence of EGFR expression are also helpful in differentiating MPNST from a cellular schwannoma.[105] MPNSTs usually have a complex karyotype, and many have biallelic NF1 or CDK2NA gene mutations.[22]

Prognostic implications

MPNSTs with higher grade, diameter greater than 5 cm, recurrent disease, arising within the trunk region, and Triton tumors are associated with more aggressive behavior, whereas sporadic MPNSTs seem to have an overall better prognosis. Certain chromosomal arm gains and losses also seem to have prognostic significance, none of which have been found to be more associated with NF1 when compared with sporadic MPNSTs.[7,10,83]

Epithelioid Sarcoma

ESs account for up to 1% of all soft tissue sarcomas, occurring most commonly in adolescents and young adults, classically arising within acral sites with a pseudogranulomatous growth pattern. Another subtype, the “large cell” variant or proximal-type ES, usually arises within truncal regions. Histologically, the neoplastic cells may have a vaguely granulomatous growth pattern of predominantly plump epithelioid to spindled cells containing eosinophilic cytoplasm, most often with associated central or geographic necrosis.[22,106]

Ancillary studies

Most ES show positive immunoreactivity with CK 8 and 19, but are negative to focally positive for CK 5/6.[22,106] Unlike a sarcomatoid carcinoma, most ES are positive for CD34. Most also have a loss of SMARCB1 (INI1) protein expression, which likely plays an important role in the pathogenesis of these tumors.[80,107]

Prognostic implications

The overall 5-year survival for ES approaches 80%, whereas the reported 10-year overall survival is up to about 62%.[106,108–110] Metastatic disease may occur in about half of the cases, with a predilection for the lungs.[106,109,110] Unlike most sarcomas, ES is most commonly metastatic to regional lymph nodes. Factors associated with worse outcomes include tumor size of greater than 5 cm, male gender, older age,

multifocality, high mitotic activity, nodal involvement, and proximal, axial, or deep soft tissue location.[22,106,110,111]

SARCOMAS WITH LOW METASTATIC POTENTIAL

Solitary Fibrous Tumor

The distinction between a SFT and an HPC has become increasingly ill-defined, so much so that the term HPC is no longer considered a separate entity for soft tissue tumors.[20,21,61] SFT (**Fig. 10**) is a mesenchymal tumor, likely fibroblastic, with the characteristic "hemangiopericytoma-like" prominent branching vascular pattern.[20–22] Most patients are middle-aged adults, with a median age of 50, and tumors can arise from any location, mostly occurring within subcutaneous tissue as a slow-growing painless mass.[3,17] Rarely, large tumors have been found to secrete hormones, leading to a paraneoplastic syndrome.[112–114] Histologic evaluation usually shows a patternless architecture with alternating hypocellular and hypercellular areas, with the classical prominent branching vasculature. Thick stromal and perivascular collagen bands are also characteristically seen. For a benign SFT, mitotic rate should be low, with less than 4 mitoses per 10 HPF. Cytologic atypia, infiltrative margins, high cellularity, and greater than 4 mitoses per HPF are features of a malignant SFT.[22]

Ancillary studies

Cytogenetic aberrations are uncommon in SFTs that are less than 10 cm in diameter. Some studies have reported near diploid or pseudodiploid karyotypes, balanced translocations, and recurrent genomic imbalances. The recurrent *NAB2-STAT6* fusion has been recently identified by integrative sequencing and has been established as the hallmark defining driver mutation of SFT.[115–120] STAT6 immunohistochemistry can also be a useful marker in the diagnosis of SFT, especially in cases with unusual morphology or location, and limited material.[115,120–122]

Prognostic implications

Only a minority of SFT behaves aggressively, with approximately 80% to 90% following a benign course.[22] SFTs that arise within the mediastinum, pelvis, and

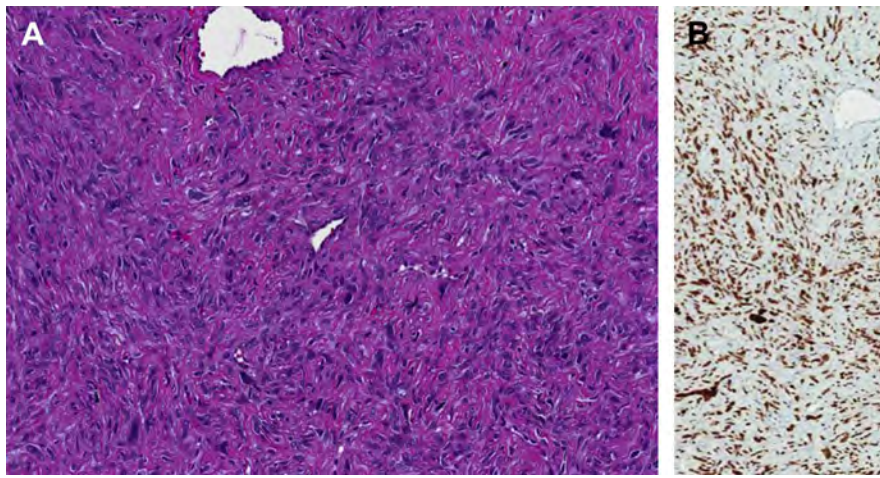

Fig. 10. Malignant SFT (*A*) (hematoxylin-eosin, original magnification ×4), showing positive nuclear immunoreactivity for STAT6 (*B*) (Original magnification ×2).

abdominal regions, and the histologically malignant SFTs are associated with more aggressive behaviors. The fusion variant *NAB2ex6-STAT6ex16/17* is associated with deep-seated extrapleural SFTs, and aggressive behavior.[121]

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) is a spindle cell tumor that most often arises within the soft tissue or viscera of children or young adults.[22] It is characterized by a variably cellular infiltrate of lymphocytes, eosinophils, and plasma cells, often within a myxoid or edematous background.[22]

Ancillary studies

IMT is variably positive for SMA, desmin, and focally positive for CD68.[22] Approximately one-third of cases may have keratin reactivity, and up to about 60% are ALK positive.[123,124] S100 and skeletal muscle markers are negative in these tumors.[22,124]

Prognostic implications

The likelihood of metastatic disease is usually low, with only rarely reported cases of distant metastasis. Most ALK-negative tumors are associated with an increased likelihood of metastasis; however, the round cell morphology, often associated with specific ALK fusion partners, such as RANBP2, has a greater chance of progressing to metastatic disease.[22,123–126] Aneuploidy is also a negative prognostic factor.[7,8,20,22,127]

Low-Grade Myofibroblastic Sarcoma

Low-grade myofibroblastic sarcoma, also known as myofibrosarcoma, most commonly occurs in adults with a possible predilection for the extremities or head and neck regions. They usually have fibromatosis-like features and are characterized by a diffusely infiltrative growth pattern of spindled cells, with at least focal nuclear atypia and pale to eosinophilic cytoplasm, arranged in a storiform or fascicular growth pattern.[22]

Ancillary studies

Low-grade myofibroblastic sarcomas are variably positive for smooth muscle markers and may stain positive for calponin, or sometimes with focal reactivity for CD34.[22]

Prognostic implications

Very few genetic aberrations have been reported, with overall less complex karyotypes when compared with other higher-grade sarcomas.[20,22,51,93] Although not diagnostic, gene rearrangement studies may be considered for differentiating low-grade myofibroblastic sarcoma from fibromatosis.[7,22,58] Overall, frequency of metastatic disease is very rare.[22]

Myxoinflammatory Fibroblastic Sarcoma

Myxoinflammatory fibroblastic sarcoma is characterized by large epithelioid fibroblasts within a myxoid matrix, containing prominent mixed inflammatory cells. The great majority occur in the distal extremities, especially common in the fingers, involving tenosynovial structures, usually in middle-aged individuals.[128–130] Morphologic evaluation reveals variable nuclear atypia, often with large bizarre epithelioid cells, prominent viral inclusion-like nucleoli, and sometimes with vacuolated cytoplasm.[22,128,129,131,132]

Ancillary studies

Myxoinflammatory fibroblastic sarcomas are variably positive for CD68, CD34, and SMA and may be focally positive for keratin markers.[22] They characteristically have t(1;10) breakpoints leading to the upregulation of FGF8.[22,51,58]

Prognostic implications

Myxoinflammatory fibroblastic sarcomas are considered locally aggressive tumors, with widely variable local recurrence rates reported from 20% to 70%.[22] Up to one-third of cases eventually require amputation due to repeated local recurrences.[29,130,132–134] Metastatic disease is rare, usually involving local bone or regional lymph nodes, with extremely uncommon distant metastatic disease.[83,128,129,131,132,135–137]

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP), a low-grade fibroblastic neoplasm that usually presents in middle aged-adults, although rare, is one of the most common dermal sarcomas.[22,138] Most are sporadic, occurring in proximal extremities or trunk regions, less commonly in the head and neck or other regions, and usually present as a cutaneous plaque or nodule.[138] Histologic evaluation reveals a dense dermal proliferation of uniform spindled cells, with elongated or plump nuclei, minimal nuclear atypia, and few mitoses, arranged in a storiform pattern of growth.[22]

Ancillary studies

DFSP is usually CD34 positive and factor XIIIa negative, but may lose CD34 reactivity often with increased TP53 expression.[22,138] Gene rearrangement studies characteristically show supernumerary ring chromosomes, containing sequences from chromosomes 22 and 17, carrying the COL1A1-PDGFB (platelet-derived growth factor B-chain) fusion gene, which can be detected by FISH (preferred) or RT-PCR.[22,51] The resultant COL1A-PDGFRB fusion protein results in a functional PDGFB receptor on the cell surface that can be stimulated, driving tumor growth.[7,51,93,138–140]

Prognostic implications

Approximately 10% to 15% progress to higher-grade fibrosarcomatous DFSP, typically exhibiting fascicular architecture, which increases the metastatic potential of the tumor.[138,140,141] Tyrosine kinase inhibitors, such as imatinib mesylate, interfere with the activation of PDGFRB and are especially useful in the setting of unresectable or metastatic disease.[7,51] Molecular testing is available to help identify patients who may have clinical response.[138,139,142,143] Local recurrence rates for DFSP are lowest if wide margins can be achieved.[22,143] They very rarely metastasize unless fibrosarcomatous progression is present.[22,144–146]

Kaposi Sarcoma

Kaposi sarcoma (KS) is a locally aggressive vascular proliferation (**Fig. 11**) induced by the human herpes virus 8 (HHV8), which is also known as Kaposi sarcoma–associated herpes virus.[22,147] It characteristically presents a red-purple to brown skin patch, plaque, or nodule, usually involving the distal extremities.[3,147,148] Currently, 4 clinical forms of KS are recognized, including the classic indolent form, the endemic African form, the iatrogenic form arising in association with solid organ transplantation, and the AIDS-associated form of KS, all of which are morphologically identical.[3,147–150]

Ancillary studies

The neoplastic cells are positive for endothelial markers, including CD31, CD34, and ERG, as well as lymphatic markers such as D2-40.[151] HHV8 is nearly always positive by immunohistochemistry; however, rare cases may require PCR for confirmation.[22,148,149,152–154]

Prognostic implications

The classic KS has an indolent clinical course with only rare metastatic disease involving lymph nodes or visceral organs.[3,147] A rare form of endemic KS, the

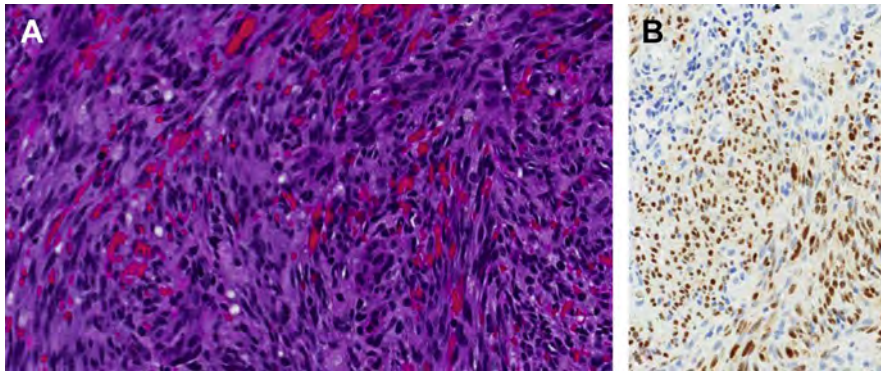

Fig. 11. KS, high power (*A*) (hematoxylin-eosin, original magnification ×20), showing the characteristic positive nuclear immunoreactivity for HHV8 (*B*) (Original magnification ×10).

lymphadenopathic variant, is rapidly progressive with a high mortality.[22] The AIDS-associated KS is overall the most aggressive form, with more widespread organ involvement, mostly involving the lungs and gastrointestinal tract.[22] The iatrogenic form is the least predictable, often improving after adjustment of immunosuppressive therapy.[3,147,151,155] New therapeutic approaches have focused on the control of HHV8 for prevention and treatment of KS. For example, antiherpes medications, such as ganciclovir, have been found to reduce the risk of KS among transplant patients, as well as in HIV-positive individuals.[147,148,155,156] In addition, targeted therapy, including inhibitors of angiogenesis, vascular endothelial growth factor, tyrosine kinase, and matrix metalloproteinases are being investigated or are under development.[147,152]

Chordoma

Chordoma is a low-grade malignant tumor showing notochordal differentiation. It is the most common primary malignancy of the sacrum; however, it more commonly arises within the base of the skull.[3,22,157] They typically present as slow-growing tumors, and morphologically are composed of epithelioid cells arranged in nests or cords with clear to eosinophilic cytoplasm (**Fig. 12**), with the so-called physaliphorous cells, which contain vacuolated cytoplasm.[22] Chordomas morphologically exhibit a lobulated appearance with tumor cells separated by fibrous septa and embedded within abundant extracellular myxoid matrix.[22] A rare variant, chondroid chordoma, contains a hyaline cartilage component, which can potentially be misdiagnosed as chondrosarcoma.[158,159]

Ancillary studies

Brachyury is a nuclear immunohistochemical marker that is specific for chordoma, and negative in chondrosarcoma.[22,158,160] Other helpful positive immunohistochemical markers for chordoma include keratin, EMA, and S-100 protein.[158,160,161] A loss of PTEN and INI-1 expression may also be useful in the diagnosis of chordoma.[158,161–165]

Prognostic implications

Dedifferentiated chordoma is a high-grade and biphasic tumor consisting of a conventional chordoma with an associated high-grade undifferentiated spindle cell sarcoma.[22,166–168] The dedifferentiated component loses expression of the above diagnostic immunohistochemical markers.[22,167–169] Imatinib may be useful for

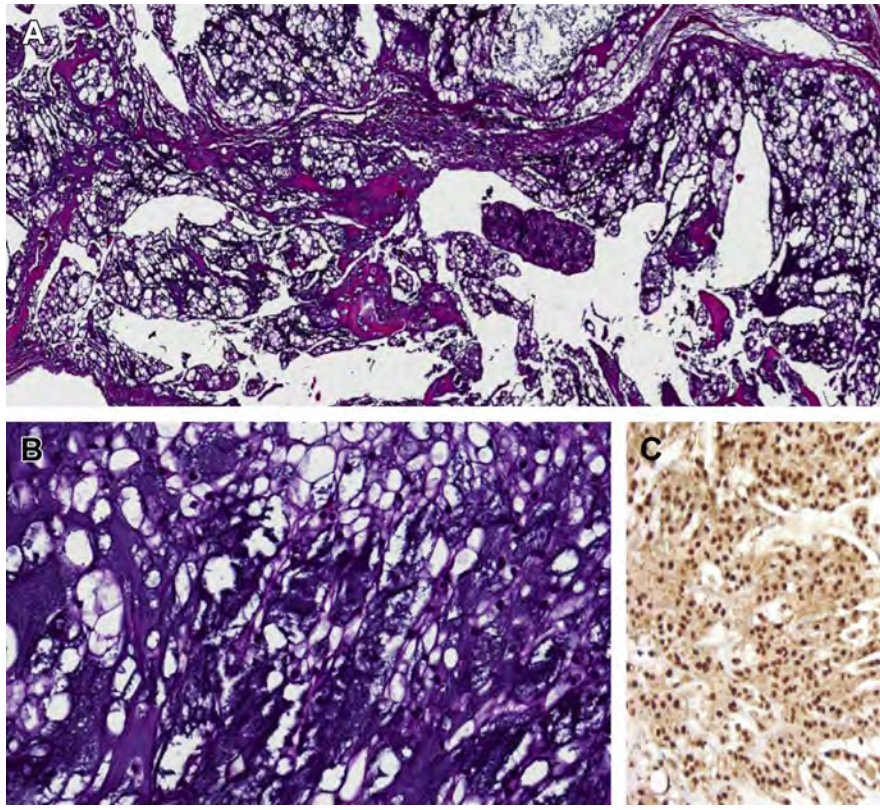

Fig. 12. Chordoma, low power (*A*) (hematoxylin-eosin, original magnification ×2) and high power (*B*) (hematoxylin-eosin, original magnification ×40), showing positive immunoreactivity for brachyury (*C*) (Original magnification ×4).

stabilization of disease or for pain reduction in locally advanced or metastatic disease if the tumor expresses platelet-derived growth factor receptor-β (PDGFR-β).[158,161,163]

Gastrointestinal Stromal Tumors

GIST is the most common mesenchymal tumor that occurs in the gastrointestinal tract and is thought to be of interstitial cell of Cajal differentiation. More than half of cases are sporadic and involve the stomach, with a clinical spectrum that ranges from benign to malignant.[170] GISTs most often have spindle cell morphology, but also frequently exhibit epithelioid cell histology. If spindle cell morphology is present, the pallisading vacuolated and sclerosing subtypes are the most common, although, with the epithelioid morphology, sclerosing, hypercellular, or discohesive histologic findings may most often be seen.[22,170]

Ancillary studies

GIST is classically strongly immunoreactive for CD117 (c-KIT). A more recent and equally specific immunomarker, DOG1, usually reacts with the approximately 5% of GISTs that are negative for CD117.[22] GISTs with spindle cell morphology are usually also positive for CD34 and rarely focally immunoreactive with smooth muscle markers, keratins, or S100.[22] GIST is characterized by activating oncogenic mutations,

classically either KIT or PDGFRA.[22,51] Most GISTs harbor a mutation in KIT exon 9, KIT exon 11, or PDGFRA exon 18.[51] The few cases of GIST that are associated with the Carney triad and Carney-Stratakis syndrome typically show mutations in SDH-related genes and have a distinct morphology.[51]

Prognostic implications

Tumor size, mitotic activity, and anatomic site are currently the tumor parameters that are best used as prognostic indicators to separate patients into prognostic groups.[22,170] A Ki67 proliferative index may also be a useful tool, especially in borderline cases.[171] Mutational analysis, currently most often performed by PCR methods, is now essential for selection of therapy and for prognostic value.[51] Tyrosine kinase inhibitors, such as imatinib mesylate, have been successfully used in the treatment of GIST.[8,51,170] Recently, BRAF V600E mutations were identified in cases lacking KIT and PDGFRA mutations,[51] which may respond to BRAF therapy.[172,173] SDH-deficient GISTs have less predictable prognosis, but GISTs that arise in association with NF1 are typically multifocal with favorable outcomes.[22]

LOCALLY AGGRESSIVE SOFT TISSUE TUMORS

Atypical Lipomatous Tumor

ALT is a locally aggressive tumor with adipocytic differentiation (**Fig. 13**). This term is now preferred over the term "well-differentiated liposarcoma"; the latter has fallen out of favor due to the fact that these tumors have no metastatic potential, unless they undergo dedifferentiation.[22] Certain tumors that are deemed unresectable, usually ones located in the mediastinum or retroperitoneum, typically have locally aggressive and uncontrollably recurrent disease with a higher likelihood of eventual dedifferentiation, so the term well-differentiated liposarcoma may be justifiable in such cases.[22]

Ancillary studies

MDM2 and CDK4 testing are useful in the diagnosis of ATL and are usually negative in myxoid and pleomorphic sarcomas.[22] Gene amplification or protein overexpression of these markers can be detected by FISH or immunohistochemistry, respectively.[47,51,58]

Prognostic implications

Radiation therapy is frequently used in the management of ALT or well-differentiated liposarcoma, especially in cases with positive margins or tumors greater than 5 cm; however, there may be no significant effect on overall survival with the addition of radiation therapy, compared with surgery alone when located in the extremities.[174,175]

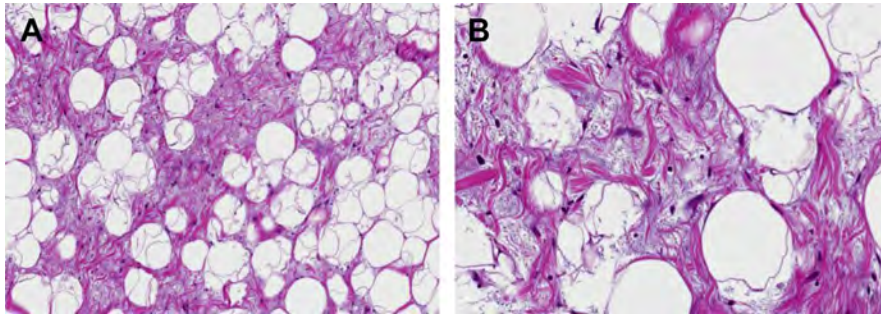

Fig. 13. Atypical lipomatous tumor, low power (*A*) (hematoxylin-eosin, original magnification ×4) and high power (*B*) (hematoxylin-eosin, original magnification ×40).

Dedifferentiation occurs in up to 10% of atypical lipomatous tumors, which then gives the tumor metastatic potential, at which point it is diagnosed as a dedifferentiated liposarcoma.[3,7,44,58,83]

Fibromatosis

Locally aggressive forms of fibromatosis include desmoid-type fibromatosis, palmar/plantar fibromatosis, and lipofibromatosis.[22] Desmoid-type fibromatosis (**Fig. 14**) typically arises within deep soft tissue and is rarer than the superficial forms.[176–179] Pathogenesis is thought to be multifactorial, with likely genetic factors.[22] Palmar and plantar fibromatosis occur more commonly in men with increasing incidence with age.[22,69] Lipofibromatosis is an exceedingly rare pediatric tumor usually arising within the hand or foot, or less commonly in the head and neck or truncal regions.[22] Each of these forms of fibromatosis has a high rate of local recurrence, but no metastatic potential.[176–178,180,181] Desmoid-type fibromatosis is a proliferation composed of uniform whorling spindled cells with infiltrative borders, often with prominent vasculature, perivascular edema, and a variable mitotic rate.[22,69,177,178,182–184]

Ancillary studies

Desmoid-type, palmar, and plantar fibromatosis usually have nuclear immunoreactivity for β–catenin and variable immunoreactivity for SMA and are usually negative for desmin, caldesmin, and S100.[22,183] Lipofibromatosis usually has a similar-appearing fibrous component with abundant mature adipose tissue, usually greater than 50% of the tumor.[22] The mutations in the gene encoding for β-catenin (CTNNB1) and APC gene mutations occur in the large majority of desmoid-type fibromatosis, resulting in the accumulation of β-catenin protein within the nucleus.[22,183] Gene rearrangement studies have shown clonal chromosomal aberrations in the minority of fibromatosis cases.[22]

Prognostic implications

Although desmoid-type fibromatosis has no metastatic potential, rare cases have been fatal due to local growth effects.[177,182,185] Unfortunately, the ability to achieve adequate margins after resection does not seem to correlate well with the rate of local recurrence, making the likelihood of recurrent disease somewhat unpredictable.[22] For palmar and plantar fibromatosis, on the other hand, the rate of local recurrence is closely related to adequacy of margins.[22] Prognostic implications of the reported gene mutations or chromosomal aberrations are currently unclear.[22,51,58,183]

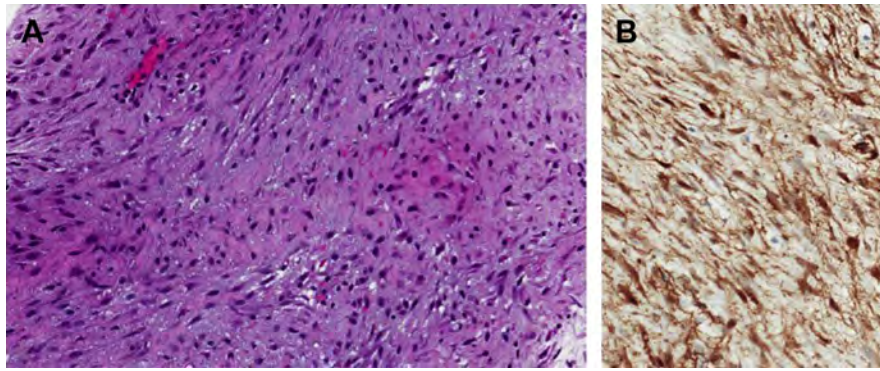

Fig. 14. Desmoid-type fibromatosis, low power (*A*) (hematoxylin-eosin, original magnification ×10), showing nuclear immunoreactivity for β-catenin (*B*) (Original magnifications ×10).

BENIGN SOFT TISSUE AND BONE TUMORS

Benign soft tissue tumors are a great deal more common than benign bone tumors and are far more common than sarcomas, with only about one out of every hundred overall soft tissue tumors found to be malignant.[22] They can be categorized based on their histologic differentiation, usually as tumors of adipocytic, cartilaginous, osteogenic, fibrogenic, fibrohistiocytic, vascular, perivascular, or neural differentiation (**Table 4**),[22] while benign bone tumors are currently most commonly classified as chondrogenic, osteogenic, fibrogenic, fibrohistiocytic, or vascular differentiation.[22] The most common benign soft tissue tumors are adipocytic, followed closely by fibrogenic tumors (**Table 5**).[20,22] A tumor should only be considered benign after ensuring that the pathologic diagnosis fits the clinical picture. This process involves gathering appropriate clinical and radiologic information, followed by adequate tissue sampling for pathologic evaluation, possibly with the aid of ancillary studies. If uncertainty persists, additional sampling or close follow-up is indicated.

GIANT CELL TUMORS

Tenosynovial Giant Cell Tumor

Tenosynovial giant cell tumors are a group of neoplastic disorders that involve synovium-lined tendon sheaths, synovial joints, and adjacent soft tissue. They are divided into localized and diffuse subtypes. The localized type is also known as nodular tenosynovitis. It presents as discrete nodules primarily affecting the tenosynovium of hands and feet (75% are in digits).[22] The nodule is grossly well circumscribed and encapsulated. The cut section shows a lobulated and tan-brown appearance. The tumor is composed of a polymorphous population of cells including osteoclast-like giant cells, larger mononuclear histiocytes, smaller mononuclear stromal cells, and macrophages that either engulf fatty content (xanthoma cells or foamy cells) or are hemosiderin-laden (pigmented). Lymphoplasmacytic infiltration is usually a minor component. Fibrous and collagenous stroma can be seen. The diffused type is also called pigmented villonodular tenosynovitis. The intra-articular lesions and the extra-articular affect the knee. The diffuse type tumors have larger and more numerous giant cells. The intra-articular lesions has typical villous pattern.

Ancillary studies

The larger mononuclear cells are positive for clusterin, while the smaller histiocytes are positive for CD68. There is also a high level of *CSF1* expression of the tumor cells resulted by the translocation of *CLO6A3* with CSF1 gene.[22]

Prognostic implications

Local type is a benign lesion with local recurrence.

Giant Cell Tumor of Bone

Giant cell tumor of bone is a benign but locally aggressive tumor. The tumor is composed of numerous characteristic giant cells that are large and osteoclast-like (**Fig. 15**). These cells are impressive morphologically; however, they are the background cells reactive to the true neoplastic cells, which are primitive mesenchymal stromal cells. The neoplastic cells are mononuclear and express receptor activator for nuclear factor -κB ligand RANKL, the master regulator of osteoclast differentiation.[22] Macrophages and osteoclasts express RANK. The interaction between the neoplastic mononuclear stromal cells and macrophages/osteoclasts by an RANKL-dependent mechanism via the stimulation of macrophage-colony stimulation factor results in neoplastic proliferation and induces osteoclast formation.[22] During this

Table 4
Common histological, immunohistochemical, and molecular findings of selected benign soft tissue tumors

Classification/ Tumor Type	Histology	Immunohistochemical	Molecular
Adipocytic			
Lipoma	Well-circumscribed, mature white adipocytes	MDM2 (–), S100 (+), leptin (+), HMGA2 (+)	MDM2 (–) HMGA2 aberrations
Lipoblastoma	Diffuse or local, lobular embryonal adipocytic cells, and fibrovascular septa	S100 (+), CD34 (+), desmin (+/–)	PLAG1
Angiolipoma	Mature adipocytes, thin capillary-sized vessels containing fibrin thrombi	S100 (+), HMGA2 (+/–)	HMGA2
Spindle cell/pleomorphic lipoma	Mature adipocytes, admixed bland spindled cells/multinucleated (often "floret-like") giant cells, thick ropelike collagen fibers, myxoid matrix	CD34 (+) spindled cells, S100 (–/+), desmin (–/+)	Losses involving 13q, 16q, 6q, 10p
Chondroid lipoma	Mature adipocytes, admixed small round lipoblasts, chondromyxoid matrix	S100 (+/–), PAS (+)	Fusion of C11of 95 (11q13) and MKL2 (16p13.3)
Hibernoma	Variable amount of polygonal, multivacuolated cells with small central nucleus, and granular cytoplasm (brown fat)	S100 (+/–), CD34 (–), desmin (–/+), UCP1 (+)	11q aberrations UCP1 expression
Cartilagenous			
Soft tissue chondroma	Lobulated mature hyaline cartilage, often hypercellular, with groups of chondrocytes	—	12q13, +5, +8, HMGA2
Fibrogenic			
Nodular fasciitis	Plump spindled fibroblasts/myofibroblasts, frequent mitoses, lacking nuclear hyperchromasia or pleomorphism, occasional osteoclast-like giant cells, tissue culture-like growth pattern	Actin (+) strong/diffuse, Desmin (–) CD68 (+) giant cells	MYH9-USP6 fusion

Elastofibroma	Fibrocollagenous tissue with abnormally prominent elastic fibers	Elastin (+), tropoelastin (+)	Chromosome 1 aberrations, Xq12–22 gain
Myositis ossificans	Localized nodular fasciitis-like proliferation with osteoblasts and osteoclasts rimming irregular sheets of bone formation	Actin (+), desmin (+/–)	Limited data
Cellular angiofibroma	Uniform, spindled cells, numerous small-to-medium, thick-walled vessels, variably fibrous to edematous stroma	CD34 (+/–), actin (–/+), desmin (–/+)	AHRR-NCOA2
Gardner fibroma	Hypocellular, haphazard, thick collagen fibers	CD34 (+), nuclear β-catenin (+/–) actin (–), desmin (–)	Associated with Gardner-type FAP
Fibrohistiocytic			
Tenosynovial giant cell tumor, localized type	Lobulated, variable proportions of multinucleated giant cells and variably sized mononuclear cells with pale cytoplasm, hemosiderin deposits, and variably hyalinized stroma, arising from synovium	Clusterin (+) in larger mononuclear cells CD68 (+), CD45(+), and CD163(+) smaller cells CD68 (+), CD45 (+), tartrate-resistant acid phosphatase (+) giant cells	CSF1-COL6A3
Deep benign fibrous histiocytoma	Well-circumscribed, cellular spindled cells, storiform pattern, vesicular nuclei, many with prominent branching vascular pattern	CD34 (+), SMA (+/–)	Limited data
Neural/perineural			
Schwannoma	Majority are biphasic with compact spindled cells (Antoni A) and looser areas (Antoni B) with pallisading verocay bodies	S100 (+), collagen IV (+), laminin (+), GFAP (+/–), SOX-10 (+)	Chromosome 22 losses, NF2, SMARCB1
Neurofibroma	Loosely arranged small, spindled cells, with collagen fibers and myxoid material	S100 (focal +), GLUT1 (+), claudin-1 (+), EMA (+/–) in perineural-like cells	NF1
Perineurioma	Spindled cells with storiform growth pattern, perivascular whorls, in collagenous stroma	EMA (+), GLUT1 (+/–), claudin-1 (+/–) S100 (–), GFAP (–)	Chromosome 22 losses, NF2

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Table 4
(*continued*)

Classification/ Tumor Type	Histology	Immunohistochemical	Molecular
Granular cell tumor	Nested to trabecular large ovoid cells with eosinophilic, granular cytoplasm, ill-defined borders. Often associated with pseudo-epitheliomatous hyperplasia of overlying epithelium	S100 (+), CD68 (+), CD63 (+), MITF (+/–), TFE (+/–), HMB45 (–), GFAP (–)	Limited data Malignant granular cell tumors may show partial loss of 5p
Smooth muscle			
Leiomyoma	Spindled cells with eosinophilic cytoplasm, cigar-shaped nuclei, arranged in fascicular growth pattern	Actin (+), desmin (+), h-caldesmon (+), S100 (–) Abdominal or inguinal tumors usually ER, PR, and WT1 (+)	Not well-described in soft tissue. Likely variable clonal chromosomal changes
Skeletal muscle			
Rhabdomyoma	Unencapsulated, lobular, large polygonal cells with abundant eosinophilic granular cytoplasm, cross-striations, or rodlike inclusions, round vesicular nuclei, and well-defined cell borders	Actin (+), desmin (+), myogenin (+)	Few reports of sonic hedgehog pathway activation
Vascular			
Hemangiomas	Multiple dilated, predominantly thin-walled, variably sized vascular channels, commonly with hemosiderin deposition, and fibrotic or myxoid stroma	WT1 (+), ERG (+), CD31 (+), CD34 (+) Epithelioid variant CK (focal +/–)	Limited data
Lymphangioma	Cystic, variably sized, lymphatic channels, lined by flattened endothelium, commonly empty or filled with proteinaceous fluid or lymphocytes	Podoplanin/D2-40 (+), PROX1 (+), CD31 (+), CD34 (+/–)	Limited data

Perivascular			
Glomus tumor	Nested small uniform, rounded cells with central round nuclei, amphophilic to eosinophilic cytoplasm, sharply defined cell borders, surrounding capillary-sized vessels	SMA (+), caldesmon (+), collagen IV (+, pericellular)	Hereditary tumor syndrome cases associated with GLMN or NF1
Myopericytoma	Nodular or lobular, uniform oval spindled myoid cells, with multilayered, concentric perivascular growth. Neoplastic cells with plump, spindled nuclei and eosinophilic cytoplasm	Perivascular cells SMA (+), caldesmon (+) Neoplastic cells desmin (focal +/–), CD34 (focal +/–)	ACTB-GLI1 fusion
Angioleiomyoma	Spindled cells with eosinophilic cytoplasm, cigar-shaped nuclei, arranged in fascicular pattern with intervening vascular channels	Actin (+), calponin (+), caldesmon (+/–)	Variable, most commonly with 22q11.2 loss or Xq gain
Uncertain differentiation			
Acral fibromyxoma	Spindled to stellate-shaped fibroblasts within collagenous or myxoid stroma, loose fascicular to storiform patterns, usually with numerous vessels and mast cells	CD34 (+), EMA (+/–)	GNAS (–)
Intramuscular myxoma	Spindled to stellate-shaped fibroblasts within abundant, often vacuolated, myxoid stroma, and sparse small vessels	CD34 (+/–), desmin (+/–), actin (+/–)	GNAS
Deep angiomyxoma	Spindled to stellate myoid cells, with loose myxoedematous to collagenous stroma	ER/PR (+/–), CD34 (+/–), actin (+/–), desmin (+/–), HMGA2 (+/–)	12q13–15, HMGA2

Data from Refs.[22,23,51,54,58,93,103,186–189]

Table 5
Common histologic, immunohistochemical, and molecular findings of selected benign bone tumors

Classification/Tumor Type	Histology	Immunohistochemical	Molecular
Chondrogenic			
Osteochondroma	Perichondrium, cartilage, and bone layers. Continuous cortical and medullary bone with stalk	—	EXT1 or EXT2 Negative for IDH1 or IDH2 mutations
Chondromas	Encondroma: Hypocellular, avascular, with prominent hyaline cartilage matrix Periosteal chondroma: Similar, but beneath periosteum, occasional with mild nuclear pleomorphism	—	IDH mutations
Chondromyxoid fibroma	Peripherally, spindled cells with fibrous stroma. Centrally, stellate and chondrocyte-like cells with chondromyxoid stroma	—	Chromosome 6 aberrations
Osteogenic			
Osteoma	Compact, spongious, or mixed lamellar bone, with osteoblastic remodeling, in a well-vascularized, moderately cellular, fibrous stroma	—	Limited data
Osteoid osteoma	Small (<2 cm) tumor with central (nidus) of osteoblastic activity, producing osteoid and often bone	—	Rare reports of clonal chromosomal aberrations
Osteoblastoma	Similar to osteoid osteoma, except >2 cm and richly vascular	—	Variable reported, limited data
Fibrohistiocytic			
Nonossifying fibroma	Large proliferation of bland spindled fibroblasts, with storiform growth pattern, extending into medullary cavities	—	Limited data

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Table 5
(*continued*)

Classification/Tumor Type	Histology	Immunohistochemical	Molecular
Benign fibrous histiocytoma	Identical histologic findings as nonossifying fibroma, but different clinical and radiologic presentation (smaller, usually involving nonmetaphyseal long bones or pelvis)	—	Limited data
Notochordal			
Benign notochordal cell tumor	Well-defined tumor with vacuolated cells, small centrally or peripherally located round or oval nuclei, and no nuclear atypia. Lacks the lobular architecture, fibrous bands, and myxoid matrix seen in chordoma	S100 (+), EMA (+), keratin (+), brachyury (+)	Limited data
Undefined neoplastic nature			
Aneurysmal bone cyst	Well-circumscribed, cystic spaces filled with blood, separated by cellular fibrous septa containing bland fibroblasts, scattered multinucleated osteoclast-like cells and woven bone rimmed by osteoblasts, often mitotically active	—	USP6 fusion with CDH11, TRAP150, ZNF9, OMD, or COLA1

Data from Fletcher CDM, World Health Organization, International Agency for Research on Cancer. WHO classification of tumours of soft tissue and bone. World Health Organization classification of tumours. 4th edition. Lyon (France): IARC Press; 2013. p. 468; and Letson GD, Muro-Cacho CA. Genetic and molecular abnormalities in tumors of the bone and soft tissues. Cancer Control 2001;8(3):239–51.

process, tumor-associated macrophage-like osteoclast precursors, which are also mononuclear cells, are recruited by tumoral stromal cells to participate in osteoclast differentiation and activation. Because osteoclast formation is the major consequence of GCTB, inhibition of osteoclast formation and activity is the key therapeutic approach. For example, bisphosphonate inhibits osteoclast-mediated resorption of bone/osteolysis and anti-RANKL antibody targets the RANKL-dependent mechanism of GCTB formation.[186,190–193]

Osteoprotegerin (OPG) is a soluble decoy receptor that is produced by osteoblasts to inhibit osteoclast differentiation through its binding to RANKL, which prevents

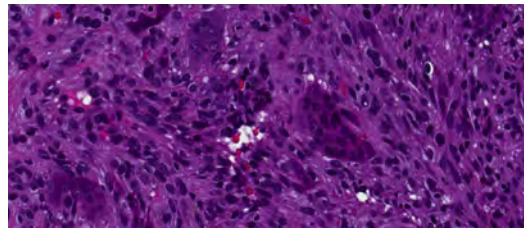

Fig. 15. Giant cell tumor of bone, high power (hematoxylin-eosin, original magnification ×40).

RANK binding. OPG expression reflects a protective mechanism of the skeleton to compensate increased bone resorption. Bone remodeling is mainly controlled by the balance of RANKL/OPG. Osteoprotegerin ligand (OPGL), also named receptor activator of RANKL, is also expressed in the stromalike tumor cells of GCTB. The ratio of OPGL/OPG by tumor cells may contribute to the degree of osteogenesis and bone resorption.[194]

Grossly, the tumor is red-brown with hemorrhage. Yellow areas reflect lipid-laden macrophage-rich areas. Histologically, the tumor is composed of numerous giant cells with multinucleation and scattered mononuclear cells that are round or spindle shaped. Lipid-laden or hemosiderin-laden macrophages are also present. The tumor is mainly solid and may contain cystic areas. Secondary aneurysmal bone cyst component is seen in 10% of GCTB.[22] The tumor may be mitotically active; however, a benign giant cell tumor typically does not have atypical mitosis or significant nuclear atypia. The latter is associated with a malignant transformation of GCTB. One diagnostic pitfall is to avoid misdiagnosing an osteosarcoma when a pathologic fracture is in association with a malignant giant cell tumor.

Ancillary studies

Giant cell tumor of soft tissue is positive for CD68, with some mononuclear cells showing SMA positivity.[190,191,195,196] A ligand for RANKL is also expressed by the mononuclear cells and is important for osteoclastic recruitment.[190,197,198]

Prognostic implications

Local recurrence rates of up to 12% have been reported with only rare cases of metastatic disease reported.[196,197,199–202] Although complete resection improves local recurrence rates, prognostic factors are otherwise currently unknown.[22,190,202]

Giant Cell Tumor of Soft Tissue

Giant cell tumor of soft tissue is clinically and histologically similar to giant cell tumor of bone. It most often presents in middle-aged adults, usually as a superficial painless extremity soft tissue tumor, less often affecting the trunk or head and neck regions.[22] Morphologic evaluation shows a multinodular proliferation of cellular nodules containing mononuclear and multinuclear osteoclast-like giant cells, often with frequent mitoses, within a richly vascular stroma.[22] About half of these tumors present with metaplastic bone formation, and other common histologic features include cystic changes, stromal fibrosis, stromal hemorrhage, and foamy macrophages.[22,190]

SUMMARY

Recent advances in immunohistochemical markers, cytogenetics, and molecular pathology techniques summarized here have improved the diagnosis and management of sarcomas. The most recent version of the WHO classification of soft tissue and bone tumors better defines pathological diagnostic criteria, allowing for more reproducible diagnoses. Ongoing improvements in our understanding of the molecular characteristics of tumors will undoubtedly continue to shed light on the factors that influence the pathogenesis of soft tissue and bone tumors and optimize the management of sarcomas.

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