Chapter 1

Introduction

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Soft tissue sarcomas represent a heterogeneous group of rare malignancies with an overall incidence of about 5/100,000/year. Incidence tends to vary according to age, ranging from approximately 2/100,000/year in the first two decades to 15–20/100,000/year in the elderly population. Soft tissue sarcomas can occur at any anatomic location; however, approximately half of all sarcomas occur in the limbs (wherein the thigh is by far the most common site), 30% occur intra-abdominally (including the retroperitoneum), and 15% arise in the trunk and in the head and neck region. As will be discussed in more detail, both incidence and site of occurrence are strongly influenced by the specific histotype. For example, alveolar rhabdomyosarcoma occurs most often in children, myxoid liposarcoma occurs most often in the thigh of adults in their third decade, dedifferentiated liposarcoma tends to occur in the retroperitoneum with a peak incidence in the fourth and fifth decades, and myxofibrosarcoma tends to occur in the superficial soft tissues of elderly patients.

Soft tissue sarcomas are aggressive neoplasms capable of local destructive growth, recurrence, and distant metastases, most often to lungs, liver, bone, soft tissue, and brain. Lymph node metastases are comparatively more rare, and tend to be associated with a relatively limited number of distinctive histologies, such as epithelioid sarcoma, clear cell sarcoma, alveolar rhabdomyosarcoma, and succinate dehydrogenase-deficient gastrointestinal stromal tumors (SDH-deficient GISTs). In approximately 20–30% of cases there is local recurrence, whereas about 30–50% of cases metastasize. Five-year overall survival varies between 55 and 65%, regardless of stage and histology.

Mesenchymal tumors have always been regarded as diagnostically challenging, rarity and morphologic heterogeneity representing the main factors affecting diagnostic accuracy. As a consequence, sufficient expertise can be achieved only through access to a large number of cases. To avoid major mistakes, careful evaluation of clinical presentation and integration of immunohistochemistry and molecular genetics whenever relevant are mandatory. As accurate classification increasingly correlates with the choice of specific treatments, every effort should be made to achieve diagnostic accuracy.

Soft tissue sarcomas are currently classified on the basis of the 2013 World Health Organization's (WHO) classification of soft tissue tumors, which has further expanded and refined the concepts that were pioneered in the 2002 WHO classification, and which has collected and distilled all the major advances generated in the past 15 years. WHO classifies the different entities on the basis of histomorphology and includes all available immunophenotypic and genetic data. This perfectly matches a diagnostic approach that integrates sequentially the microscopic features of the lesion with its immunophenotype and its genetic profile. The changes that have occurred since publication of the latest WHO classification will be specifically addressed in the context of the discussion of the single tumor entities; however, it is useful at this stage to summarize the major changes introduced thus far. Soft tissue sarcomas and soft tissue tumors of intermediate malignancy currently recognized by the WHO 2013 classification are listed in Table 1.1.

Table 1.1 Intermediate (locally aggressive and/or rarely metastasizing) and malignant soft tissue tumors recognized by the 2013 WHO Classification of Soft Tissue Tumors

Intermediate Adipocytic Tumors
Atypical lipomatous tumor/well-differentiated liposarcoma
Malignant Adipocytic Tumors
Dedifferentiated liposarcoma
Myxoid liposarcoma
Pleomorphic liposarcoma
Intermediate Fibroblastic/Myofibroblastic Tumors
Superficial fibromatosis
Desmoid-type fibromatosis
Lipofibromatosis
Giant cell fibroblastoma
Dermatofibrosarcoma protuberans and variants
Solitary fibrous tumor
Inflammatory myofibroblastic tumor
Low-grade myofibroblastic sarcoma
Myxoinflammatory myofibroblastic tumor
Infantile fibrosarcoma
Malignant Fibroblastic/Myofibroblastic Tumors
Adult fibrosarcoma
Myxofibrosarcoma
Low-grade fibromyxoid sarcoma
Sclerosing epithelioid fibrosarcoma
Intermediate So-Called Fibrohistiocytic Tumors
Plexiform fibrohistiocytic tumor
Giant cell tumor of soft tissues
Malignant Smooth Muscle Tumors
Leiomyosarcoma

Table 1.1 (cont.)

Malignant Skeletal Muscle Tumors
Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma
Spindle cell/sclerosing rhabdomyosarcoma
Intermediate Vascular Tumors
Kaposiform hemangioendothelioma
Retiform hemangioendothelioma
Papillary intralymphatic angioendothelioma
Composite hemangioendothelioma
Pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma
Kaposi sarcoma
Malignant Vascular Tumors
Epithelioid hemangioendothelioma
Angiosarcoma of soft tissue
Malignant Chondro-Osseous Tumors
Extraskeletal mesenchymal chondrosarcoma
Gastrointestinal Stromal Tumors
Malignant Nerve Sheath Tumors
Malignant peripheral nerve sheath tumor
Epithelioid malignant peripheral nerve sheath tumor
Malignant triton tumor
Malignant granular cell tumor
Ectomesenchymoma
Intermediate Tumors of Uncertain Differentiation
Hemosiderotic fibrolipomatous tumor
Atypical fibroxanthoma
Angiomatoid fibrous histiocytoma
Ossifying fibromyxoid tumor
Mixed tumor
Myoepithelioma
Myoepithelial carcinoma
Phosphaturic mesenchymal tumor
Malignant Tumors of Uncertain Differentiation
Synovial sarcoma
Epithelioid sarcoma
Alveolar soft parts sarcoma
Clear cell sarcoma of soft tissues
Extraskeletal myxoid chondrosarcoma
Ewing sarcoma
Desmoplastic small round cell tumor
Extrarenal rhabdoid tumor
PEComa
Intimal sarcoma
Undifferentiated/Unclassified Sarcomas
Undifferentiated spindle cell sarcoma
Undifferentiated pleomorphic sarcoma
Undifferentiated round cell sarcoma
Undifferentiated epithelioid sarcoma

Adipocytic Tumors

One of the major conceptual shifts introduced after 2002 is the use of a stricter terminological definition of "well-differentiated liposarcoma," which represents the most common liposarcoma subtypes. It has been clarified that the terms **atypical lipomatous tumor** and **well-differentiated liposarcoma** are synonyms, and that the latter term should be used only for lesions that occur in the retroperitoneum/mediastinum or in other anatomic sites where complete resectability is unachievable. The use of the term "atypical lipomatous tumors" for resectable lesions is justified by the fact they never recur and are most often cured by complete (even marginal) surgical excision. In 2002, it was recognized that in **dedifferentiated liposarcoma** (defined as morphologic progression from well-differentiated liposarcoma to high-grade non-lipogenic sarcoma), a low-grade dedifferentiation can also be observed. In 2013, the concept of homologous dedifferentiation (represented by the occurrence of lipogenic, high-grade morphology somewhat mimicking pleomorphic liposarcoma) was fully acknowledged. A major change also involved **myxoid liposarcoma**, which, until 2002, was kept separated from **round cell liposarcoma**. To reflect the fact that both lesions actually represent the ends of a morphologic spectrum of a genetically distinct histology, in 2002 myxoid and round cell liposarcoma merged into a single entity. In 2013 the term "round cell liposarcoma" was eliminated and replaced by **high-grade myxoid liposarcoma** to underscore the fact that clinical outcome depends on the amount of hypercellularity and not on the shape of neoplastic cells, which can be either rounded or spindled.

Fibroblastic/Myofibroblastic Tumors

An important conceptual change in 2002 was represented by the inclusion of **hemangiopericytoma** (HPC) within the WHO's chapter on solitary fibrous tumors, because the borders between those lesions had become increasingly blurred. It was felt that the very concept of HPC was at risk of extinction, because it represented a collection of unrelated, benign as well as malignant, simple lesions sharing an HPC-like vascular network. Most cases (at any location) would currently be reclassified as **solitary fibrous tumors**, and the entity labeled as **lipomatous HPC** is considered a variant of solitary fibrous tumor. As a logical consequence of this conceptual evolution, in 2013 the label "hemangiopericytoma" (HPC) was completely abolished. Currently, the original (still valid) idea generated by Arthur Purdy Stout of the existence of lesions composed mainly of contractile cells organized in a perivascular pattern of growth survives within the label **myopericytoma**.

Fibrosarcoma also experienced a significant remodeling. Whereas it is currently recognized that most superficially located fibrosarcomas actually represent examples of **fibrosarcomatous dermatofibrosarcoma protuberans** (FS-DFSP), **infantile fibrosarcoma** is confirmed as a clinically, pathologically, and genetically distinct entity. However, new distinctive sarcoma subtypes featuring fibroblastic/myofibroblastic differentiation have been introduced. These are **low-grade fibromyxoid sarcoma, myxoinflammatory fibroblastic sarcoma, sclerosing epithelioid fibrosarcoma**, and **low-grade myofibroblastic sarcoma**.

So-Called Fibrohistiocytic Tumors

After reappraisal of malignant fibrous histiocytoma (MFH) and its variants, the label malignant fibrous histiocytoma was abolished in 2013. As discussed in depth in Chapter 7, **pleomorphic MFH**, once the most commonly diagnosed sarcoma, is now synonymous with high-grade undifferentiated pleomorphic sarcoma and it should not exceed approximately 5% of newly diagnosed sarcomas. **Myxoid MFH** is now included within the morphologic spectrum of myxofibrosarcoma. In addition, the so-called **giant cell variant of MFH** appears to be a heterogeneous collection of clinically as well as morphologically distinctive lesions – namely, giant cell tumor of soft tissue, extraskeletal osteosarcoma, and spindle cell sarcoma (most often leiomyosarcoma) featuring osteoclast-like giant cells. The **inflammatory variant of MFH** most often represents examples of inflammatory dedifferentiated liposarcoma. **Angiomatoid MFH**, the latest addition to the MFH family, is no longer considered a malignancy and has therefore been downgraded to the intermediate category. As its line of differentiation remains unknown, it has also been moved to the category of mesenchymal tumors of uncertain differentiation.

The existence of a broader category of **undifferentiated sarcomas** (pleomorphic, epithelioid, round cell, and spindle cell) is now fully acknowledged. Those round cell sarcomas harboring the *CIC-DUX4* or the *BCOR-CCNB3* translocation are temporarily classified under the heading "undifferentiated round cell sarcomas." In consideration of the new data accumulated, these sarcomas are covered in Chapter 6 as separate entities.

Vascular Tumors

In the past two decades, several new entities have been characterized, particularly in the intermediate malignancy category, including **kaposiform, retiform**, and **composite hemangioendotheliomas**. Since the 2002 WHO classification, **epithelioid hemangioendothelioma** (EHE) has been reclassified as malignant because of its considerable metastatic rate that ranges between 15 and 30%. **Endovascular papillary angioendothelioma** (so-called Dabska tumor) has been renamed **papillary intralymphatic angioendothelioma. Pseudomyogenic hemangioendothelioma**, a novel, genetically distinct entity characterized by multifocality as well as relatively indolent clinical behavior, has been added to the group of vascular neoplasms of intermediate malignancy.

Tumors of Uncertain Differentiation

Tumors of uncertain differentiation is a category that contains tumors without a clear line of differentiation or without a normal cellular counterpart. Obviously, several new entities have been described since 1994, including **myoepithelioma of soft tissue** and **PEComa**. Because we now know more about divergent differentiation in various sarcoma subtypes, the category of **malignant mesenchymoma** is also losing ground, as it is currently acknowledged that heterologous differentiation may occur in the context of specific entities such as malignant peripheral nerve sheath tumors (MPNSTs) and dedifferentiated liposarcoma. The morphologically rather elusive category of **intimal sarcoma** was introduced as a new entity in this group.

Principles of Sarcomagenesis

The pathogenesis of the vast majority of soft tissue sarcomas is still unknown and most of them seem to arise de novo without an apparent causative factor. In rare cases, genetic and environmental factors such as radiation, lymphedema (secondary angiosarcoma of the breast), viral infections (human herpesvirus 8 infection is associated with Kaposi sarcoma), exposure to chemicals (vinyl chloride is linked to hepatic angiosarcoma), and immunodeficiency (Epstein-Barr virus infection in immunodeficient subjects is associated with the development of smooth muscle tumors) have been identified as risk factors. It is broadly accepted that trauma does not represent a predisposing factor and that, at best, it can simply draw attention to the presence of a pre-existing mass.

Genetic susceptibility plays a role in a minority of soft tissue sarcomas. Neurofibromatosis type 1 (NF1) and Li-Fraumeni syndromes represent two good examples. In NF1, up to 10% of patients will develop MPNSTs as well as multiple GISTs. The autosomal dominant Li-Fraumeni syndrome (wherein germline mutations of the *TP53* gene occur) has been shown to predispose the development of malignant tumors, one-third of which are represented by bone and soft tissue sarcomas. Recent data have shown that approximately half of patients with sarcoma have putatively pathogenic monogenic and polygenic variation in known and novel cancer genes, among which are *TP53, ATM, ATR, BRCA2*, and *ERCC2*.

In the past two decades, molecular genetics has greatly contributed to the elucidation of some of the molecular mechanisms associated with the development of soft tissue sarcomas. Significant subsets of mesenchymal malignancies are associated with **chromosome translocations**, the presence of which is currently being exploited for diagnostic confirmation (Table 1.2). A smaller group of lesions is characterized by the presence of **simple karyotypes associated with mutations**. Good examples are represented by **desmoid fibromatosis** (the vast majority of which are associated with mutations of either the *CTNNB1* or *APC* gene) and **gastrointestinal stromal tumors** (most often associated with mutations of the *KIT* and *PDGFRA* genes and far less often of the *BRAF, SDH*, and *NF1* genes). A third (large) group of sarcomas exhibits **variably complex karyotypes**. In this context, particularly relevant is the occurrence of gene copy number alterations as observed in well-differentiated/dedifferentiated liposarcoma, wherein the amplification of the *MDM2, CDK4*, and *HMGA2* genes represents the key driver genetic event.

Principles of Pathologic Diagnosis

Sarcomas are currently classified on the basis of their morphology, their immunophenotype, and their molecular status. The integration of conventional morphology with immunohistochemistry and molecular genetics represents the major contribution of the WHO classification since 2002 and this approach has been further confirmed in 2013. For practical reasons, the

Table 1.2 Gene fusions in soft tissue neoplasms

Tumor	Gene fusion	Cytogenetics
Lipoma	*EBF1-LOC204010*	t(5;12)(q33;q14)
	HMGA2-CXCR7	t(2;12)(q37;q14)
	HMGA2-EBF1	t(5;12)(q33;q14)
	HMGA2-LHPF	t(12;13)(q14;q13)
	HMGA2-LPP	t(3;12)(q28;q14)
	HMGA2-NFIB	t(9;12)(p22;q14)
	HMGA2-PPAP2B	t(1;12)(p32;q14)
	HMGA2-LPP	t(3;6)(q27;p21)
	LPP-C12orf9	t(3;12)(q28;14)
Lipoblastoma	*COL1A2-PLAG1*	t(7;8)(q21;q12)
	HAS2-PLAG1	Del(8)(q12;q24)
	PLAG1-RAD51L1	t(8;14)(q12;q24)
	COL3A1-PLAG1	t(2;8)(q31;q12.1)
Chondroid lipoma	*C11orf95-MKL2*	t(11;16)(q13;p13)
Myxoid/round liposarcoma	*FUS-DDIT3*	t(12;16)(q13;p11)
	EWSR1-DDIT3	t(12;22)(q13;q12)
Soft tissue angiofibroma	*AHRR-NCOA2*	t(5;8)(p15;q13)
	GTF2I-NCOA2	t(7;8;14)(q11;q13;q31)
Dermatofibrosarcoma protuberans	*COL1A1-PDGFB*	t(17;22)(q21;q13)
Low-grade fibromyxoid sarcoma	*FUS-CREB3L2*	t(7;16)(q34:p11)
	FUS-CREB3L1	t(7;16)(p11;p11)
	EWSR1-CREB3L1	t(11;22)(p11;q12)
Solitary fibrous tumor	*NAB2-STAT6*	inv(12)(q13;q13)
Infantile fibrosarcoma	*ETV6-NTRK3*	t(12;15)(p13;q25)
Sclerosing epithelioid fibrosarcoma	*FUS-CREB3L2*	t(7;16)(q34:p11)
	FUS-CREB3L1	t(11;16)(p13;p11)
	EWSR1-CREB3L1	t(11;22)(p11;q12)
Myxoinflammatory fibroblastic sarcoma/ Hemosiderotic fibrolipomatous tumor	*MGEA5-TGFBR3*	der(10)t(1;10)(p22;q24)
Inflammatory myofibroblastic tumor	*CARS-ALK*	t(2;11)(p23;p15)
	SEC31A-ALK	t(2;4)(p23;q21)
	ATIC-ALK	inv(2)(p23;q35)
	RANBP2-ALK	t(2;2)(p23;q13)
	CLTC-ALK	t(2;17)(p23;q23)
	TPM3-ALK	t(1;2)(q21;p23)
	TPM4-ALK	t(2;19)(p23;p13)
	PPFIBP1-ALK	t(2;12)(p23;p11)
	RREB1-TFE3	t(X;6)(p11;p24)

Table 1.2 (cont.)

Tumor	Gene fusion	Cytogenetics
Myxofibrosarcoma	*KIAA2026-NUDT11*	t(9;X)(p24;p11)
	CCBL1-ARL1	t(9;12)(q34;q23)
	AFF3-PHF1	t(2;6)(q12;p21)
Tenosynovial giant cell tumor	*COL6A3-CSF1*	t(1;2)(p13;q37)
Pericytoma with t(7;12)t(7;12)	*ACTB-GLI1*	t(7;12)(p22;q13)
Alveolar rhabdomyosarcoma	*PAX3-FOXO1*	t(2;13)(q35;q14)
	PAX7-FOXO1	t(1;13)(p36;q14)
	PAX3-FOXO4	t(X;2)(q13;q36)
	PAX3-NCOA1	t(2;2)(p23;q36)
	PAX3-NCOA2	t(2;8)(q36;q13)
	FOXO1-FGFR1	t(8;13;9)(p11;q14;q32)
Spindle cell rhabdomyosarcoma	*SRF-NCOA2*	t(6;8)(p21;q13)
	TEAD1-NCOA2	t(8;11)(q13;p15)
Angiomatoid fibrous histiocytoma	*EWSR1-CREB1*	t(2;22)(q33;q12)
	FUS-ATF1	t(12;16)(q13;p11)
	EWSR1-ATF1	t(12;22)(q13;q12)
Ossifying fibromyxoid tumor	*EP400-PHF1*	t(6;12)(p21;q24)
	MEAF6-PHF1	t(1;6)(p34;p21)
	ZC3H7B-BCOR	t(X;22)(p11;q13)
Myoepithelioma/ mixed tumor	*EWSR1-ATF1*	t(12;22)(q13;q12)
	EWSR1-PBX1	t(1;22)(q23;q12)
	EWSR1-POU5F1	t(6;22)(p21;q12)
	EWSR1-ZNF444	t(19;22)(q13;,q12)
	EWSR1-KLF17	t(1;22)(p34.1;q12)
	EWSR1-PBX3	t(9;22)(q12.2;q33.3)
	FUS-KLF17	t(1;16)(p34.1;p11)
	LIFR-PLAG1	t(5;8)(p13;q12)
	SRF-E2F1	t(20;6)(q11;p21)
Clear cell sarcoma	*EWSR1-ATF1*	t(12;22)(q13;q12)
	EWSR1-CREB1	t(2;22)(q33;q12)
	IRX2-TERT	del(5)(p15.33)
Synovial sarcoma	*SS18-SSX1*	t(X;18)(p11;q11)
	SS18-SSX2	t(X;18)(p11;q11)
	SS18-SSX4	t(X;18)(p11;q11)
	SS18L1-SSX1	t(X;20)(p11;q13)
Biphenotypic sinonasal sarcoma	*PAX3-MAML3*	t(2;4)(q35;q31.1)
	PAX3-NCOA1	t(2;2)(q35;p.23)
	PAX3-FOXO1	t(2;13)(q35;q14)
Alveolar soft part sarcoma	*ASPSCR1-TFE3*	t(X;17)(p11;q25)
Extraskeletal myxoid chondrosarcoma	*EWSR1-NR4A3*	t(9;22)(q31;q12)
	TAF15-NR4A3	t(9;17)(q31;q12)
	TFG-NR4A3	t(9;3)(q31;q12)
	TCF12-NR4A3	t(9;15)(q31;q21)
	HSPA8-NR4A3	t(9;11)(q31;q24)

Table 1.2 (cont.)

Tumor	Gene fusion	Cytogenetics
Desmoplastic small round cell tumor	*EWSR1-WT1*	t(11;22)(p13;q12)
Ewing sarcoma and Ewing-like sarcomas	*EWSR1-FLI1* *EWSR1-ERG* *FUS-ERG* *EWSR1-ETV1* *EWSR1-ETV4* *EWSR1-FEV* *EWSR1-NFATC2* *EWSR1-PATZ1* *EWSR1-SMARCA5* *EWSR1-POU5F1* *EWSR1-SP3* *FUS-FEV* *CIC-DUX4* *CIC-FOXO4* *BCOR-CCNB3* *FUS-NCATc2*	t(11;22)(q24;q12) t(21;22)(q22;q12) der(21)t(16;21) t(7;22)(p21;q12) t(17;22)(q21;q12) t(2;22)(q35;q12) t(20;22)(q13;q12) inv(22) (q12q12) t(4;22) (q31;q12) t(6;22) (p21;q12) t(2;22)(q31;q12) t(2;16)(q35;p11) t(4;19)(q35;q13) t(X;19)(q13;q13) inv(X) (p11.4p11.22) t(16;20) (p11;q13)
Gastrointestinal stromal tumor	*ETV6-NTRK3*	t(12;15)(p13;q25)
Perivascular epithelioid cell tumor	*SFPQ-TFE3*	t(X;1)(p11;p34)
Soft tissue chondroma	*HMGA2-LPP*	t(3;12)(q28;214)
Mesenchymal chondrosarcoma	*HEY1-NCOA2* *IRFBP2-CDX1*	del(8)(q13;q21) t(1;5)(q42;q32)
Epithelioid hemangioma	*ZFP36-FOSB*	t(19;19)(q13.32; q13.2)
Epithelioid hemangioendothelioma	*WWTR1-CAMTA1* *YAP1-TFE3*	t(1;3)(p36;q25) t(x;11)(p11;q22)
Pseudomyogenic hemangioendothelioma	*SERPINE1-FOSB*	t(7;19)(q22;q13)
Angiosarcoma	*CIC-LEUTX*	t(19;19)(q13.11; q13.2)

classification scheme follows a histogenetic approach, even though currently it is no longer believed that a given mesenchymal neoplasm actually originates from a mature normal counterpart. Interestingly, the list of lesions of unknown histogenesis (i.e., unknown line of differentiation) has increased in size, reflecting the uncertainties surrounding the mechanisms of sarcomagenesis.

Microscopic observation of hematoxylin- and eosin-stained slides obtained from formalin-fixed, paraffin-embedded material still represents the mainstay of sarcoma classification. The amount of information provided by this technically simple step is invaluable. Any other ancillary technique (immunohistochemistry and/or molecular pathology/genetics), even the most sophisticated, certainly represents an important complement to, but under no circumstances a replacement for, classic morphologic observation. It should be also noted that macroscopic observation also plays a fundamental role – first in providing accurate reporting of the status of surgical margins, and second in guiding proper sampling, and therefore acting as the milestone for correct classification. It is very important that any area showing a distinct gross appearance is sampled so that no relevant information is missed. It is also possible that in the near future, similar to what already occurs for osteosarcoma and Ewing sarcoma, the morphologic evaluation of tumor response to systemic treatment will gain significant clinical relevance.

Microscopic Examination of Soft Tissue Sarcomas

The diagnosis of mesenchymal malignancies represents a true challenge. This is largely owing to their rarity, a fact that hampers the chance to develop expert skills outside high-volume referral centers. Moreover, sarcomas relatively often exhibit a tendency to violate some of the common rules of malignancy that we routinely apply to non-mesenchymal cancers. Just imagine a lesion occurring in the forearm of a young adult that is clinically characterized by rapid growth, and that microscopically is composed of a spindle cell proliferation featuring both hypercellularity and high mitotic activity (Fig. 1-1). Understandably, in the absence of specific expertise, these morphologic (and clinical) features would all lead to a diagnosis of malignancy. However, those characteristics actually fit perfectly with the clinicopathologic presentation of nodular fasciitis, an entirely benign myofibroblastic proliferation that, in fact, is frequently mislabeled as a sarcoma. Several other examples of benign tumors mimicking malignant lesions are discussed in this book whenever appropriate (Table 1.3). At the opposite end, try to imagine a deep-seated mass featuring a hypocellular spindle cell proliferation with minimal atypia and irrelevant mitotic activity. The presence of cellular variation as well as of fibromyxoid background is of great help to the expert pathologist to suspect a low-grade fibromyxoid sarcoma (also known as Evans tumor). In less experienced hands, however, most of these cases are unrecognized and so diagnosed as benign (Fig. 1-2). Locally aggressive or malignant soft tissue lesions mimicking benign processes are listed in Table 1.4.

Despite the intrinsic challenge of sarcoma diagnosis, it is still possible to achieve a correct classification in most instances, provided that cases are approached following a rigorous methodology. The diagnosis of sarcoma relies upon the evaluation as well as the integration of four main features:

1. Predominant shape of the neoplastic cells
2. Pattern of growth
3. Quality of the background
4. Architecture of the vascular network

Table 1.3 Clinically benign soft tissue lesions mimicking malignancy

Nodular fasciitis
Proliferative fasciitis
Proliferative myositis
Ischemic fasciitis
Myositis ossificans
Pleomorphic angiectatic hyalinizing tumor
Pseudosarcomatous proliferation of urinary bladder
Cellular schwannoma
Atypical fibroxanthoma
PEComa
Pleomorphic lipoma

Table 1.4 Intermediate and malignant soft tissue lesions mimicking benign tumors

Desmoid fibromatosis
Low-grade fibromyxoid sarcoma
Low-grade myxofibrosarcoma
Low-grade myxoid liposarcoma
Epithelioid hemangioendothelioma
Epithelioid sarcoma, classical type
Low-grade malignant peripheral nerve sheath tumor

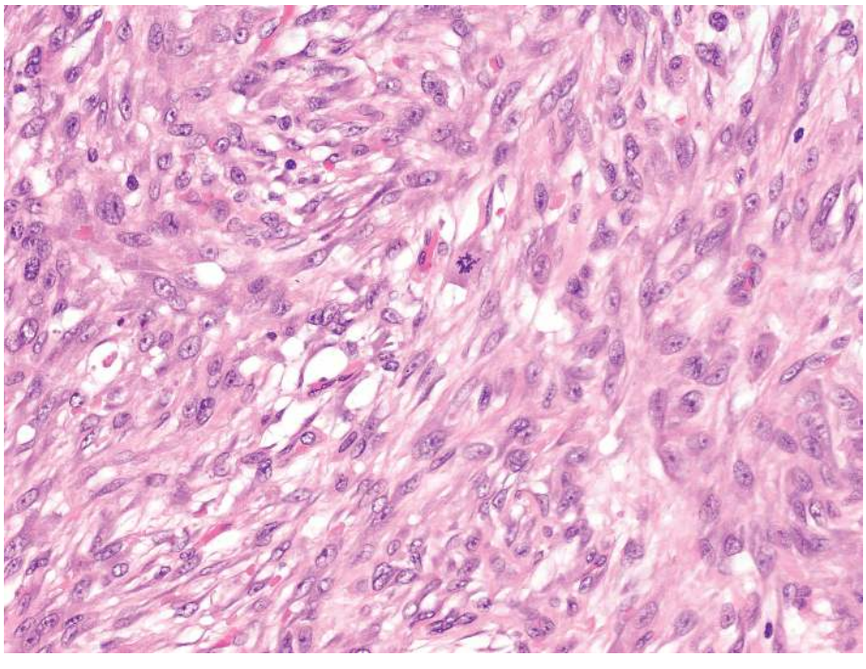

Fig. 1-1. Nodular fasciitis. Hypercellularity and mitotic activity certainly represent worrisome morphologic features. However, they are the morphologic hallmark of this entirely benign mesenchymal neoplasm.

This approach possesses the great merit of reducing dramatically the number of diagnostic options, also allowing a rational choice of ancillary immunohistochemical and molecular tests. Of course, this approach needs some degree of flexibility because numerous entities may at times exhibit a combination of different major morphologic features.

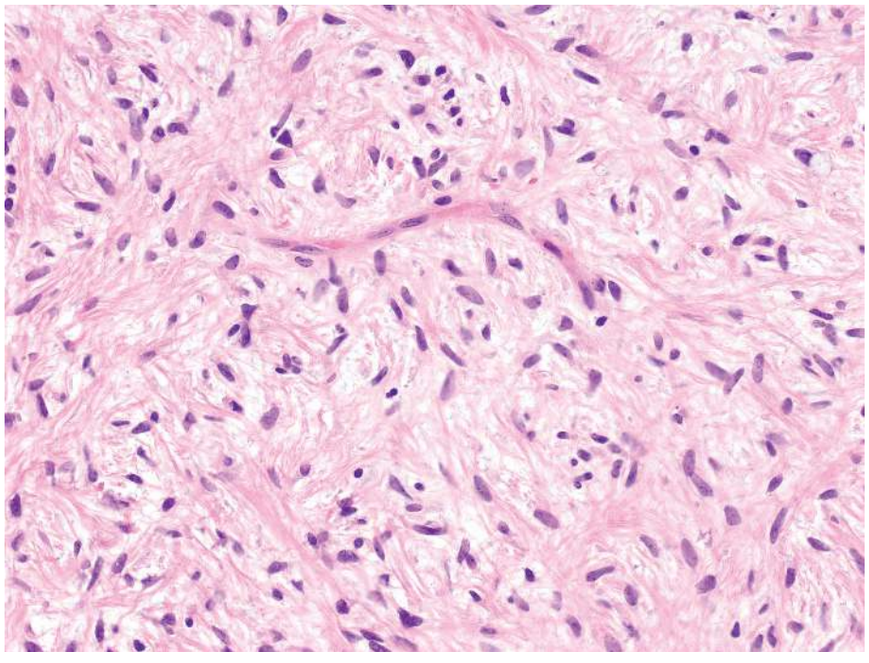

Fig. 1-2. Low-grade fibromyxoid sarcoma. The absence of nuclear atypia contrasts with the significant aggressiveness of this tumor entity.

The Shape of Neoplastic Cells

Neoplastic cells can be classified on the basis of their shape into four main categories: spindle, epithelioid, round, and pleomorphic.

1. **Spindle cells** are defined by the presence of an elongated cytoplasm, harboring oval nuclei that can be *blunt ended* (as typically seen in smooth muscle tumors) (Fig. 1-3), *tapering* (as seen in myofibroblastic tumors) (Fig. 1-4), or *pointed* (as seen most often in neural neoplasms) (Fig. 1-5). Soft tissue malignancies featuring a predominantly spindle cell morphology are listed in Table 1.5 and described in Chapter 4.
2. **Epithelioid cells** are defined by the presence of polygonal, abundant cytoplasm, most often harboring a round-shaped nucleus (Fig. 1-6). Soft tissue malignancies featuring predominantly epithelioid cell morphology are listed in Table 1.6 and described in Chapter 5.
3. **Round cells** are defined by the presence of circular, scanty cytoplasm, harboring centrally located, round nuclei (Fig. 1-7). Soft tissue malignancies featuring predominantly round cell morphology are listed in Table 1.7 and described in Chapter 6.
4. **Pleomorphic cells** are defined on the basis of marked nuclear atypia represented by extreme variation of nuclear size with or without macronucleolation and nuclear hyperchromasia (Fig. 1-8). Soft tissue malignancies featuring a predominantly pleomorphic morphology are listed in Table 1.8 and described in Chapter 7.

Table 1.5 Intermediate and malignant soft tissue neoplasms featuring spindle cell morphology

Dermatofibrosarcoma protuberans (DFSP)
Fibrosarcomatous dermatofibrosarcoma protuberans (FS-DFSP)
Giant cell fibroblastoma
Angiomatoid "malignant" fibrous histiocytoma
Low-grade myofibroblastic sarcoma
Desmoid fibromatosis
Phosphaturic mesenchymal tumor
Gastrointestinal stromal tumor (GIST)
Leiomyosarcoma
Solitary fibrous tumor
Synovial sarcoma
Infantile fibrosarcoma
Malignant peripheral nerve sheath tumor (MPNST)
Spindle cell liposarcoma
Spindle cell/sclerosing rhabdomyosarcoma
Intimal sarcoma
Undifferentiated spindle cell sarcoma

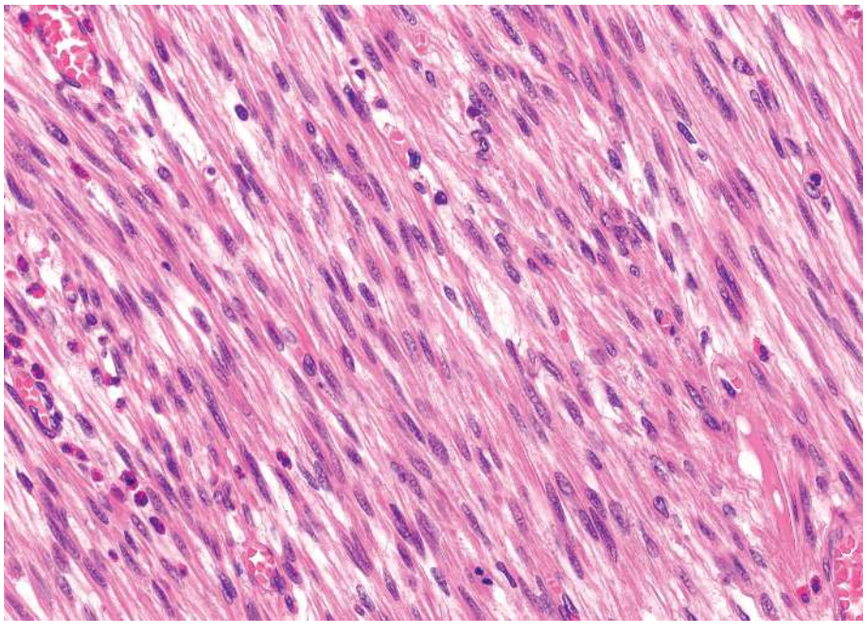

Fig. 1-3. Leiomyosarcoma. In spindle cell sarcomas, spindle cells are elongated. In smooth muscle lesions, nuclei tend to be blunt ended.

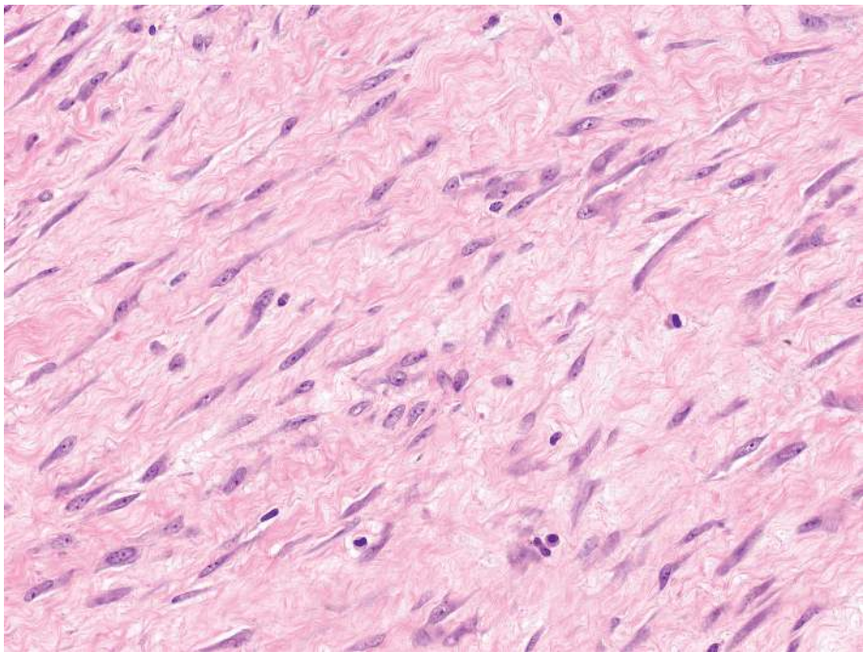

Fig. 1-4. Desmoid fibromatosis. Spindle cells in myofibroblastic proliferation most often exhibit tapering nuclei.

Table 1.6 Intermediate and malignant soft tissue neoplasms featuring epithelioid cell morphology

Epithelioid sarcoma, classical type
Epithelioid sarcoma, proximal type
Malignant rhabdoid tumor
Malignant myoepithelioma (myoepithelial carcinoma)
Pseudomyogenic hemangioendothelioma (can be spindled)
Epithelioid hemangioendothelioma
Epithelioid angiosarcoma
Epithelioid malignant peripheral nerve sheath tumor
Clear cell sarcoma of soft parts
Clear cell sarcoma of gastrointestinal tract (malignant gastrointestinal neuroectodermal tumor)
Sclerosing epithelioid fibrosarcoma
Alveolar soft part sarcoma
PEComa
Epithelioid pleomorphic liposarcoma
Epithelioid GIST
Epithelioid myxofibrosarcoma
Epithelioid leiomyosarcoma
Epithelioid rhabdomyosarcoma
Epithelioid inflammatory myofibroblastic sarcoma
Undifferentiated epithelioid sarcoma

Table 1.7 Malignant soft tissue neoplasms featuring round cell morphology

Ewing sarcoma
CIC-DUX4-associated round cell sarcoma
BCOR-CCNB3-associated round cell sarcoma
Extraskeletal mesenchymal chondrosarcoma
Desmoplastic small round cell tumor
Alveolar rhabdomyosarcoma
Poorly differentiated round cell synovial sarcoma
High-grade myxoid (formerly, round cell) liposarcoma

Table 1.8 Malignant soft tissue neoplasms featuring pleomorphic morphology

Pleomorphic rhabdomyosarcoma
Pleomorphic liposarcoma
Dedifferentiated liposarcoma
Extraskeletal osteosarcoma
Pleomorphic high-grade myxofibrosarcoma
Pleomorphic leiomyosarcoma
Pleomorphic malignant peripheral nerve sheath tumor
Undifferentiated pleomorphic sarcoma

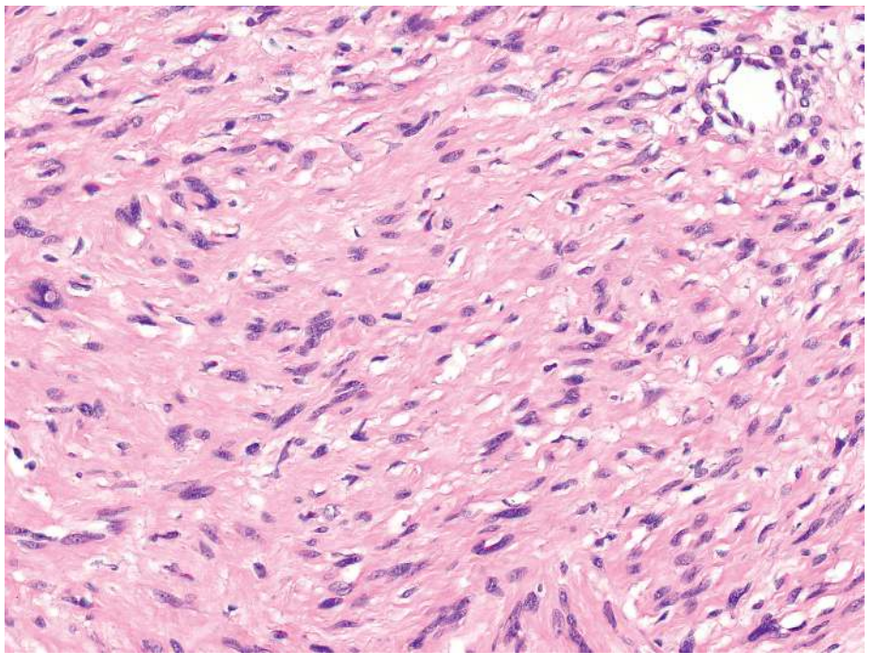

Fig. 1-5. Schwannoma. In neural neoplasms, nuclei tend to be irregularly shaped and often feature a pointed end.

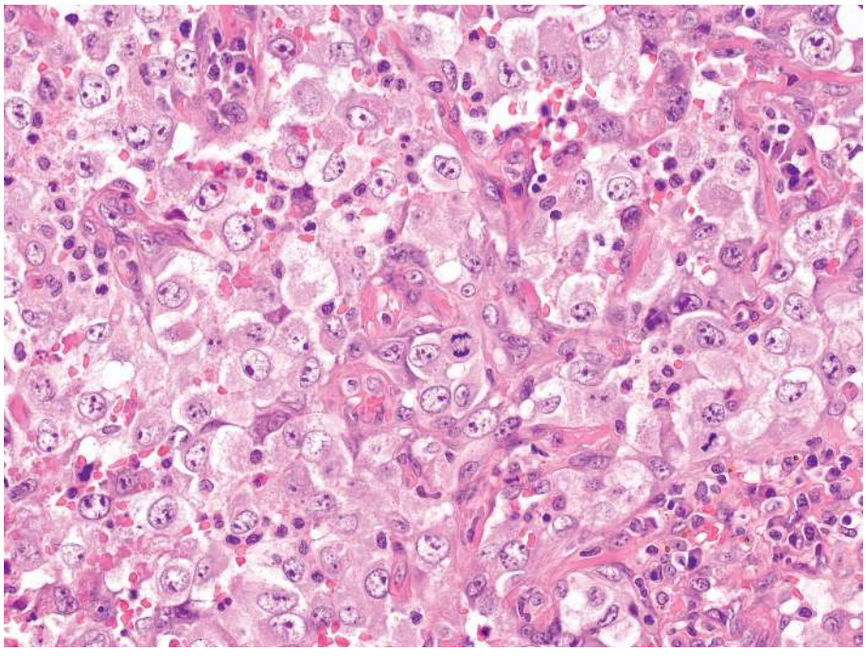

Fig. 1-6. Epithelioid angiosarcoma. Epithelioid cells exhibit abundant polygonal cytoplasm, most often harboring rounded nuclei.

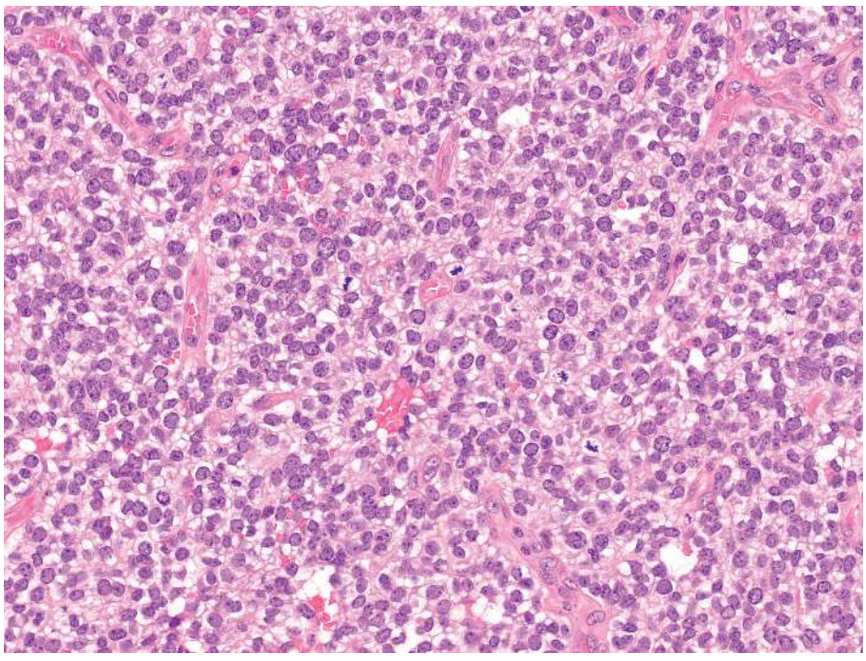

Fig. 1-7. Ewing sarcoma. Round cell sarcomas are characterized by the presence of round nuclei. Cytoplasm tends to be scanty.