CHAPTER
21 Soft Tissue Sarcomas

GENERAL CONSIDERATIONS

Soft tissue is defined as extraskeletal tissue of the body exclusive of glial tissue, lymphoid tissue and supporting tissue of various parenchymatous organs. This chapter also include neuroectodermal tumors. Gastrointestinal stromal tumors (GIST) are presented in chapter 13.

Incidence

Soft tissue sarcomas are rare malignant tumors constituting about 1% of all cancers. Benign soft tissue tumors outnumber malignant ones 100 times in hospital series. In pediatric series, soft tissue sarcomas contribute 5-10% of all cancers. There is a wide range of age incidence depending on histologic type (Table 21-1) and 15% of cases affect children below the age of 15 years. There is a minimal male predominance of 1.1:1. The most common sites of origin (59%) are the lower extremity and retroperitoneum (Table 21- 2).

Etiology

1. Chemicals: asbestos exposure predisposes to mesotheliomas. Dioxin herbicides used in Vietnam war as defoliant predisposed to soft tissue sarcomas. Exposure to vinyl chloride predisposes to hepatic angiosarcomas.

2. Radiation: about 2% of patient treated with irradiation will develop sarcomas 10 years later, commonly (70%) malignant fibrous histiocytoma.

3. Immunosuppression: AIDS-related or iatrogenic, predisposes to Kaposi sarcoma in adults and leiomyosarcoma in children.

4. Sarcoma hereditary syndromes: Four syndromes are associated or complicated with soft tissue sarcomas: (a) Neurofibromatosis type 1 (associated malignant peripheral nerve sheath tumor, (MPNST), (b) Carney syndrome (associated multiple myxomas) (c) Gardner syndrome (associated mesenteric fibromatosis) and (d) Li-Fraumeni syndrome, a germline mutation of TP53 gene (associated with rhabdomyosarcoma in childhood).

5. Chronic lymphedema: such as after mastectomy, predisposes to lymphangiosarcoma (Stewart-Treves syndrome).

Pathogenesis

Soft tissue sarcomas are considered to arise from mesenchymal stem cells committed to a specific tissue lineage. Two exceptions are neurofibrosarcoma and peripheral primitive neuroectodermal tumor (PNET) which are neuroectodermal in origin. The primitive mesenchymal cell may differentiate along one of 4 different pathways: (1) a single cell type (monophasic), (2) two cell types (biphasic), (3) multiple cell types (mesenchymoma) or (4) remain undifferentiated (unclassified tumor). Examples of biphasic sarcomas are ectomesenchymoma (rhabdomyo-

Table 21-1 Median Age of Soft Tissue Sarcomas

Histologic Type	Age/ Years
Malignant Fibrous histiocytoma	60
Liposarcoma	53
Fibrosarcoma	45
Malignant Peripheral nerve Sheath tumor (MPNST)	40
Synovial Sarcoma	27
Rhabdomyosarcoma	10

Table 21-2 Site Distribution of Soft Tissue Sarcomas

	Hashimoto et al 1992	Connier et al 2009
Extremities	52%	59%
Trunk	16%	19%
Retroperitoneum	20%	15%
Head and Neck	12%	9%

sarcoma and PNET) and Triton tumor (rhabdomyosarcoma and neurofibrosarcoma).

Molecular Oncogenesis

1. Oncogene activation: This is accomplished through different mechanisms (Chromosomal translocations, mutations, amplification or complex chromosomal aberrations). Chromosomal translocations result in the formation of fusion genes (Table 21-3). The protein products of fusion genes, are commonly transcription factors or have a protein kinase activity, resulting in cellular proliferation. These molecular changes (detected by FISH technique) help to explain sarcoma histogenesis, as well as, diagnosis and precise typing. Moreover, molecular studies are valuable to select patients who would benefit antikinase from targeted therapy (Gleevec therapy for dermatofibrosarcoma with protein kinase expression).

2. Tumor Suppressor gene inactivation: This plays a key role in sarcoma oncogenesis. Thus, loss of p53 formation will lead to genomic instability, and mutation or deletion of RB gene will dysregulate the cell cycle. Such mechanisms are operable in both pediatric and adult soft tissue sarcomas.

Macroscopy

The gross appearance of most soft tissue sarcomas is not distinctive except for desmoid tumor (fibrotic), liposarcoma (yellow color or myxoid) and angiosarcoma (hemorrhagic). Most sarcomas arise deep in relation to muscle with the size exceeding 5 cm. In contrast, the majority of subcutaneous tumors 2 cm or less in diameter are benign pseudosarcomas (e.g. nodular fasciitis). Soft tissue sarcomas are usually pseudo-encapsulated, fleshy tumors with areas of necrosis. Low-grade sarcomas grow by expansion, pushing adjacent structures creating a psendocapsule, whereas, high-grade sarcomas invade adjacent tissue. Because of these microscopic projections of tumor beyond the apparent capsule, local recurrence follows a "shelling out" procedure in 80% of cases.

Classification

Soft tissue sarcomas are traditionally classified according to their histologic resemblance to normal adult or embryonic cells. However, since cancer arises from stem cells rather than adult cells, sarcomas should be classified according to the line of differentiation of cancer stem cell. The multipotency of stem cells explain the histologic diversity of tumors and multiphenotypic features of some soft tissue sarcomas.

Histogenetically, soft tissue sarcomas include 3 main groups, namely, (1) tumors of mesenchymal stem cell origin (mesodermal) with distinctive immunophenotype (vimentin, actin and desmin positivity), (2) tumors of neuroectodermal origin which present in soft tissue, also identified by specific markers (chromogranin, S-100 and neurofilament protein) and (3)

Table 21-3 Chromosomal Translocations and their Associated Gene Fusion in Soft Tissue Sarcomas

Sarcoma Type	Translocation	Gene fusion	Frequency (%)
Ewing/PNET	T(11;22)	EWS-FLI-1	95
DSRCT	T(11;22)	EWS-WT-1	100
Round cell liposarcoma	T(12;16)	TLS-CHop	95
Myxoloposarcoma	T(9;22)	EWS-CHN (TEC)	75
Synovial sarcoma	T(X;18)	SS18-SSX1	65
Alveolar rhabdomyosarcoma	T(2;13)	PAX-3-FKHR	75
DFSP	T(17;22)	COL1A1-PDGFB	90
Infantile fibrosarcoma	T(12;15)	ETV6-NTRK3	75

Abbreviations: PNET Primitive neuroectodermal tumor, DSRCT Desmoplastic small round cell tumor, DFSP Dermatofibrosarcoma protuberans

rare tumors of uncertain differentiation which lack distinctive morphologic or immophenotypic features, and hence, are considered unclassified.

Soft tissue sarcomas include more than 50 histologic types, hence creating diagnostic difficulties to pathologists. Disagreements in histologic typing is rather high (almost 30%) even among experts, hence, the importance of objective methods (molecular or immune markers) to improve the accuracy of histologic diagnosis.

The WHO classification is generally followed for histologic typing of soft tissue sarcomas (Table 21-4). The frequency of sarcoma types varied with time. Thus, 20 years ago, fibrosarcoma was the most common tumor, but, 10 years ago, malignant fibrous histiocytoma (MFH) predominated, contributing 28% of cases. This high figure is probably an over diagnosis. Thus, recent studies involving gene expression analysis, EM and immunophenotyping, revealed that MFH is a heterogeneous group and include pleomorphic subtypes of other malignancies (spindle cell carcinoma, melanoma, pleomorphic liposarcoma and pleomorphic rhabdomyosarcoma). Moreover, most MFH are negative for specific histiocytic markers (CD 68). Accordingly, before making the diagnosis of storiform pleomorphic MFH, other pleomorphic tumors must be excluded by markers studies (CK, S-100 and Desmin). If all markers studies are negative, the WHO recommends to call the tumor undifferentiated pleomorphic sarcoma (Fletcher et al, 2002) and this may represent a final dedifferentiated state of all sarcomas. At present, Leiomyosarcoma, rhabdomyosarcoma and liposarcoma predominate over (MFH)

Undifferentiated soft tissue sarcomas are positive only for vimentin, but negative for other specific soft tissue markers. Four morphologic variants are recognized, namely: round cell (Ewing tumor-like), spindle cell, epithelioid cell and pleomorphic cell (formely storiform pleomorphic MFH)

Soft tissue sarcomas show striking differences in children as compared to adults, both in site distribution, frequency of histologic types, management and prognosis (Table 21-5).

Table 21-4 Classification and Frequency of Soft Tissue Sarcomas

Histologic type	Hashimoto et al 1116 Pts, 1992 (%)	Coindre et al 1240 Pts, 2001 (%)
MFH	25	28
Liposarcoma	12	15
Leiomyosarcoma	9	12
Synovial sarcoma	7	10
MPNST	6	6
Rhabdomyosarcoma	10	5
Fibrosarcoma	5	3
PNET	3	2
Unclassified	-	11
Others	24	8

Abbreviations: MFH Malignant fibrous histiocytoma, MPNST Malignant peripheral nerve sheath tumor, PNET Primitive neuroectodermal tumor.

Grading

The grading system of French Federation of Cancer (FNCLCC) is recommended due to its high predictive power and interobserver agreement (Guillou and Coindre, 1998). It is based on 3 parameters (differentiation, mitotic count and tumor necrosis), each is given a score (from 0 to 3) and then the scores are summed to produce a three tier grade (Table 21-6). The metastatic potential of sarcoma grades are 10% for grade 1, 30% for grade 2 and 60% for grade 3.

Table 21-5 Comparison of Pediatric and Adult Soft Tissue Sarcomas

Feature	Pediatric	Adult
% of cancers	10%	1%
Most common site	Head and Neck (37%)	Extremities (66%)
Common types	Rhabdomyosarcoma Neuroblastoma, PNET	MFH Liposarcoma Leiomyosarcoma
Prognostic factor	Tumor site	Tumor grade
Preferred therapy	Multi-modality	Surgery

Table 21-6 The Updated FNCLCC[a] System for Grading Soft Tissue Sarcomas

Parameter	Score 1	Score 2	Score 3
Differentiation	Well-differentiated Liposarcoma leiomyosarcoma	Myxoliposarcoma Fibrosarcoma Conventional leiomyosarcoma	Pleomorphic Sarcomas, Synovial sarcoma Ewing/PNET
Mitosis/10 HPF	0-9	10-19	20 or more
Necrosis	<50%	>50%	--
Sum of scores	Grade		5-year survival (%)
2 or 3	1 Low grade		80
4 or 5	2 } High grade		40
6 – 8	3 }		

(Guillou and Coindre, 1998), Abbreviations: FNCLCC French Federation of Cancer Centers, Pleomorphic sarcomas include: pleomorphic FHS, pleomorphic liposarcoma and pleomorphic rhabdomyosarcoma, HPF high power microscopic field, The score is zero if necrosis is absent.

The prognostic significance of the FNCLCC system has been firmly established, hence, it has been incorporated in staging of soft tissue sarcomas. For staging purposes the three grades are converted into two grades only (low grade and high grade). Low grade is G1, whereas, high grade includes (G2 and G3) as shown in (Table 21-6).

This grading system is inapplicable for some soft tissue sarcomas including: GIST, Desmoid, Kaposi sarcoma, mesothelioma, infantile fibrosarcoma, inflammatory myofibroblastic tumor, dermatofi-brosarcoma and sarcomas of parenchymal organs.

Spread

1. Local spread: in extremities, a sarcoma starts as an intracompartmental tumor (Tl) then becomes extracompartmental (T2) after crossing fascial boundaries. In the abdomen or chest, a sarcoma directly invades vital organs or structures.

2. Lymphatic spread: the overall incidence of lymph node metastases is generally low (about 2.5%), but highest in neuroblastoma (25%) and relatively high in rhabdomyosarcoma, synovial sarcoma (15%), as well as, malignant fibrous histiocytoma MFH and epithelioid sarcoma.

3. Hematogenous spread to the lungs occurs in 30% of cases,

4. Transcavitary spread occurs in sarcomas of abdomen or chest.

Staging

The updated staging system of AJCC/UICC (Table 21-7 and Fig 21-1) is most widely accepted worldwide (Edge, 2010). This system is based on tumor grade and metastatic spread (GNM), hence, provides more prognostic information than the previous Enneking system (1980) which was based on tumor grade and local compartmental spread (GTM). Clinical staging is assisted by plain radiographs to rule out a primary bone tumor, MRI for precise assessment of anatomic extent and PET scan to detect unsuspected metastases. This staging system is inapplicable for rhabdomyosarcoma which has it own staging system based on anatomic site and extent of the tumor.

Prognosis

There are two risks facing the patient with soft tissue sarcoma, namely: local recurrence in about 20% of cases and distant metastases in 50% of cases. These mishaps usually occur within 2 to 3 years after initial therapy. However, for a given patient the risk varies according to prognostic factors which are classified into established and potential factors,

1. Established prognostic factors are listed in (Table 21-8 and Table 21-9). The histologic type and grade are good indicators of distant metastases, whereas, tumor size and surgical margin predict the risk of recurrence.

2 . Potential prognostic factors include molecular and immunohistochemical studies such as: p53 overexpression, pRb inactivation, PDGFR, VEGF, IGF-1, KI-67 proliferation index and cyclin D1 expression.

Table 21-7 The Updated GNM Staging of Soft Tissue Sarcomas (AJCC/UICC)

Tumor Categories (T)	
T1	< 5 cm
T2	> 5 cm
Location Categories	
A	Superficial
B	Deep
Metastasis Categories (N, M)	
No	No metastases
N1	Lymph node metastases
M1	Distant metastases
Stage	
I	Non metastatic, low grade
II	Non-metastatic, high grade
III	Lymph node metastases
IV	Distant metastases

(Edge, 2010). Abbreviation: AJCC American Joint Committee on Cancer, UICC International Union Against Cancer

Table 21-8 Prognostic Groups of Soft Tissue Sarcomas Based on Histologic Type

Group	5-year Survival (%)
Favorable (>80%)	
Dermatofibrosarcoma	95
Low-grade fibromyxoidsarcoma	95
Embryonal rhabdomyosarcoma	90
Atypical lipomatous tumor	80
Infantile fibrosarcoma	80
Intermediate (50-80%)	
Myxoid liposarcoma	75
Leiomyosarcoma (extremities)	65
Unfavorable (< 50%)	
Adult fibrosarcoma	45
Malignant fibrous histiocytoma	45
Synovial sarcoma	45
Ewing / PNET	40
Alveolar rhabdomyosarcoma	40
Leiomyosarcoma (retroperitoneum)	29
Pleomorphic liposarcoma	25
Desmoplastic small round cell tumor	25
Angiosarcoma	12
Pleomorphic rhabdomyosarcoma	10

Table 21-9 Established Prognostic Factors of Soft Tissue Sarcomas

Factor	5-Year survival (%)
Histologic	
Type (Table 21-8)	
Favorable	> 80
Intermediate	50-80
Unfavorable	< 50
Tumor Grade	
Low	80
High	40
Anatomic site	
Extremities	81
Retroperitoneim	70
Head and neck	16
Tumor size	
<5 cm	89
5-10 cm	79
>10 cm	69
Surgical Margins	
Negative	88
Positive	64

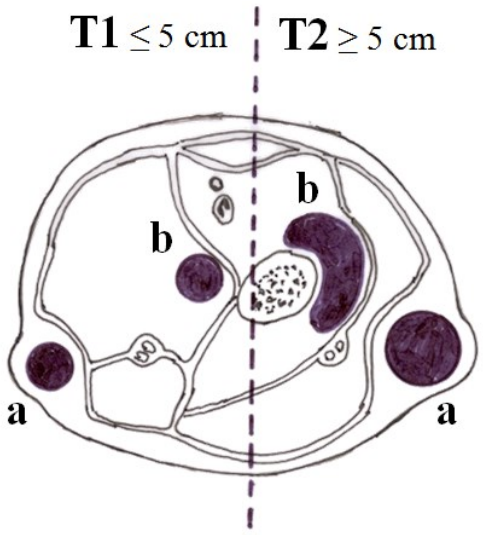

Fig 21-1 *Tumor categories of soft tissue sarcomas. T1. Size <5 cm, T2. Size >5 cm, a. Superficial Tumor b. deep tumor, in relation to superficial fascia.*

SPECIAL CONSIDERATIONS

FIBROBLASTIC TUMORS

Fibromatosis

Fibromatosis is a group of well-differentiated fibroblastic soft tissue tumors with locally infiltrative features and intermediate malignancy. The aggressive clinical behavior is characterized by repeated local recurrences (about 60%) but lack of distant metastases.

Fibromatosis affects all ages. It may be congenital (e.g. fibromatosis coli and infantile myofibromatosis), affect infants below 2 years of age (infantile digital fibromatosis) or may develop in adults usually between the age of 30-40 years. Fibromatosis in adults is divided into two clinicopathologic forms, namely superficial and deep (Table 21-10)

Macroscopy

Fibromatosis typically arises within muscle. It appears as a gray-white mass of rubbery consistency, trabeculated surface and ill-defined peripheral margin (p 21-1).

Histopathology

Most of the proliferating cells have features intermediate between those of fibroblasts and smooth muscle cells. This myofibroblastic differentiation is confirmed by EM studies (actin filaments with focal densities) and immunopathology (positive actin marker). Fibromatosis has to be distinguished from fibrosarcoma. In fibromatosis the amount of collagen in the stroma is more abundant than the cellular component, anaplasia and mitotic activity are almost absent (P 21-2). Conversely, in fibrosarcoma there is hypercellularity, as well as, anaplasia and active mitosis. A distinctive type of familial multiple fibromatosis affects mainly children, but not present at birth.

Table 21-10 Classification of Fibromatosis According to site

Superficial fibromatosis
Palmar (Dupuytren contracture)
Plantar (Ledderhose disease)
Penile (Peyronie disease)
Infantile digital
Deep fibromatosis
Abdominal wall: (Desmoid)
Extra-abdominal: (Sternomastoid tumor, trunk, mesenteric/ Retroperitoneum and extremities)
Multiple : (Juvenile and adult subtypes)

(Folpe and Inwards, 2010)

Fibrosarcoma

In the past, it was the most ommon sarcoma because many tumors were classified as fibrosarcoma, but at present it accounts for only 5% of soft tissue sarcomas. Fibrosarcoma tends to originate at Inter- and intramuscular fibrous tissue, fascia, tendons and aponeuroses (P 21-3A). Histologically, it is composed of short bundles of spindle shaped fibroblasts, with well defined cell borders and variable mitotic activity. Hypercellularity and collagen production are evident. Interlacing bundles classically form a herringbone pattern (Fig 21-2, P 21-3B). The 5-year survival is about 45%.

There are 4 variants of fibrosarcoma, all having a more favorable prognosis than the conventional one *(1) Low-grade fibromyxoid sarcoma is* characterized by areas of hypercellulasity alternating with hypocellular areas rich in collagen. Tumor cells may by arranged around dense collagen islands forming giant pseudorosettes (P 21-3C) *(2) Sclerosing epithelioid fibrosarcoma* shows dense fibrous stroma separating small groups of fibroblasts simulating carcinoma pattern, (P 21-3D) *(3) Myxofibrosarcoma* (previously classified as myxoid MFH) is at present considered a variant of fibrosarcoma. Histologically, myxofibrosarcoma lacks the giant cells of fibrous histiocytoma (P 21-3E and P 21-4), and *(4) Infantile fibrosarcoma* (also named congenital fibrosarcoma because 30% of cases are present at birth). It develops in infants below the age of 2 years and presents as large tumor mass in extremities. Despite hypercellularity and

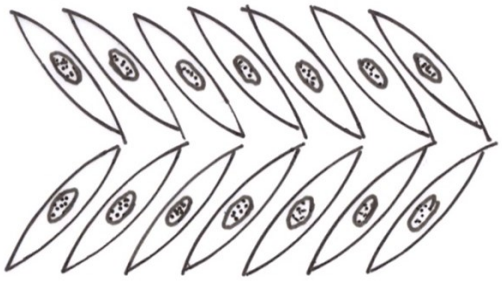

Fig 21-2 *Hering-bone pattern of conventional fibrosarcoma. Fibroblasts meet at an acute or right*

mitotic activity, prognosis is most favorable (5-years survival 80%),

Inflammatory Myofibroblastic Tumor

It was previously known as inflammatory pseudotumor, but now considered as a true neoplasm. It affects mainly children and young adults and the main sites are the lungs, mesentery and omentum. It is composed of myofibroblastic spindle cells accompanied by inflammatory cells (P 21-5). It is vimentin+, actin+, desmin+, ALK-1+ CD99+ (50%). About 25% of cases recur and 5% metastasize.

Differential Diagnosis

A number of *reactive fibroblastic* lesions of infancy produce tumor-like masses which may be misdiagnosed as fibrosarcoma. Some of these lesions are only seen in infants below the age of 2 years (Table 21-11 and P 21-6). In adults, the reactive pseudotumors may have an obvious cause, such as: postsurgical keloids (P 21-7), postendoscopy nodules, postradiation fibrosis, and ischemic fasciitis (atypical decubital fibroplasia). Other lesions are idiopathic and spontaneous such as *nodular fasciitis* (P 21-8). All these lesions are superficially located in subcutaneous tissue and small in size (2-3 cm). It is a wise policy not to diagnose sarcomas in superficial small mass lesions.

Fibrohistiocytic Tumors

These biphasic mesenchymal tumors (fibrous histiocytoma) show both fibrocytic and histiocytic cell differentiation. They exhibit a wide range of cytomorphology (Fig 21-3) and biologic behavior including: (1) *Benign:* dermatofibroma (P 21-9), deep benign fibrous histiocytoma and localized tenosynovial giant cell tumor (P 21-10) (2) *Borderline:* dermatofibrosarcoma (P 21-11), diffuse tenosynovial giant cell tumor, plexiform fibrohistiocytic tumor and giant cell tumor of soft tissue parts, and (3) *Malignant fibrous histiocytoma (MFH), which at present is renamed undifferentiated pleomorphic sarcoma*

Table 21-11 Fibrous Proliferations of Childhood

Fibrous hamartoma of infancy
Infantile digital fibromatosis
Juvenile hyaline fibromatosis
Fibromatosis colli
Calcifying aponeurotic fibroma

(Fletcher et al, 2013)

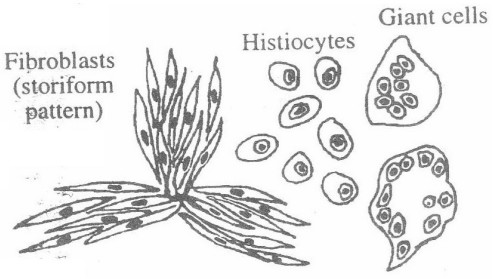

Fig 21-3 *Malignant fibrous histiocytoma cell types. In a storiform pattern, fibroblasts radiate from a central point.*

In the past, malignant fibrous histiocytoma (MFH) was the most common soft tissue sarcoma (Table 21-4), but this is rather an overdiagnosis. Enzinger(1995) classified MFH into 4 main subtypes, namely: storiform pleomorphic, myxoid type, giant cell type and inflammatory type. Recently, significant changes were made in both terminology and reclassification under other sarcoma entities (Fletcher et al, 2013/ Folpe and Inwards, 2010)

1. The *storiform-pleomorphic type* is a high grade tumor (5-year survival 50%) most common variant, composed of different cell shapes (Fig 21-3) and CD68 is expressed in giant cells. At present it is named undifferentiated pleomorphic sarcoma and represent an end stage of progression (dedifferentiation) of any sarcoma.
2. The *myxoid type*, it is composed of fibroblastic proliferation with myxoid areas is at present reclassified as myxofibrosarcoma (P 21-3).
3. The *giant cell type* contains giant cells of osteoclastic type, hence, it is at present considered a tumor of borderline malignancy and called giant cell tumor of soft parts.
4. The *inflammatory type* which is rich in Histiocytes and inflammatory cells is included at present in the histiocytosis family of tumors under the terms xanthogranuloma and hemophagocytic lymphohitiocytosis (Chapter 26).

LIPOSARCOMA

Liposarcoma contributes 20% of all soft tissue sarcomas. The cardinal diagnostic histologic feature is the presence of lipoblasts, a primitive small round cells with multiple cytoplasmic vacu-

oles. The characteristic phenotype is immunorectivity to S-100, MDM-2 and CDK-4. Five histologic types of liposarcomas are recognized.

1. Well differentiated liposarcoma (WDL)/Atypical lipomatous tumor (ALT): Both are low grade, constitute 45% of cases and show the same histology (P21-12). Focal fibroblastic areas or inflammation may be observed. The term WDL is often used for deep masses with difficult resectability (e.g. retroperitoneum and mediastinum), whereas, ALT is reserved for more superficial tumors (e.g. subcutaneous) that are amenable to complete surgical excision.

2. Myxoid liposarcoma (MLS): This low grade liposarcoma constitutes about 35% of cases. The diagnostic histologic feature is arborizing blood vessels in myxoid stroma (P21-13).

3. Dedifferentiated liposarcoma (DL). Accounts for up to 10% of cases and is a neoplasm of intermediate malignancy (5-year survival 70%). It is defined as a well differentiated low grade liposarcoma having a component of non-lipogenioc sarcoma. The dedifferentiated compoinent may be low grade (fibromyxoid, myogenic or neurogenic) or more commonly high grade (round cell, spindle cell or pleomorphic cell). Dedifferentiated areas show intense MDM-2 nuclear immunoreactivity.

4. Round cell liposarcoma (RL): Accounts for about 5 % of cases. It is high grade sarcoma in which round cells constitute > 75% of tumor area (P21-14).

5. Pleomorphic liposarcoma (PL): Accounts for about 5% of cases. It is a high grade tumor showing marked cellular pleomorphism including round, spindle, epithelioid and giant cells (P21-15).

Prognosis

In the series reported by Enzinger (1995), the 5-year survival of well-differentiated and myxoid variants was about 80%, whereas, in the pleomorphic and round cell types it was only 20% (Fig 21-4). Another significant factor affecting survival rate is the location of the tumor. Thus, the 5-year survival of patients with retroperitoneal tumors was 39%, as compared to 71 % in patients with tumors of extremities.

Differential Diagnosis

The important differential diagnoses of liposarcoma are: lipoblastoma in infants, and spindle cell lipoma in adults. *Lipoblastoma* shows myxoid stroma with arborizing blood vessels which overlap histologically with myxoliposarcoma (P21-16). However, the lobulated pattern of the tumor supports a benign nature and helps reaching the correct diagnosis. *Spindle cell lipoma* (including pleomorphic lipomas) shows a biphasic structure with spindle cells, as well as, giant cells with peripheral nuclei (floret-like) and lack of mitotic activity (P 21-17).

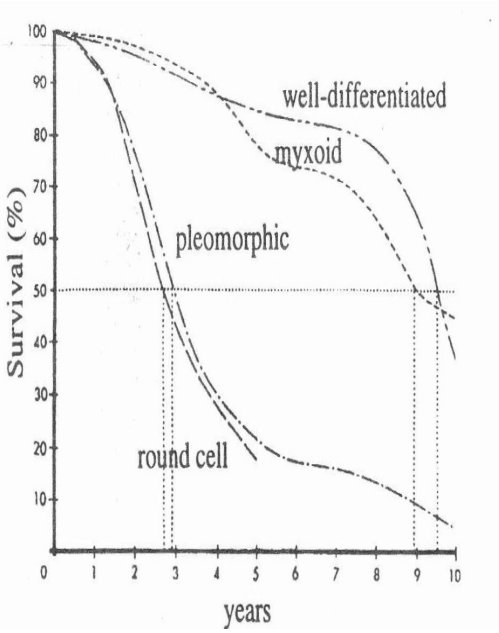

Fig 21-4 *Survival rates of liposarcoma subtypes. Well-differentiated liposarcoma (atypical lipomatous tumor) and myxoliposarcoma are favorable subtypes,*

RHABDOMYOSARCOMA (RMS)

It is the most common soft tissue sarcoma in children and young adults. It displays a wide range of histologic cell types (Fig 21-5) and is definitely rare in persons older than 45 years. It is classified into 3 main subtypes, namely: embryonal, alveolar and pleomorphic (Enzinger, 1995 and Fletcher 2013).

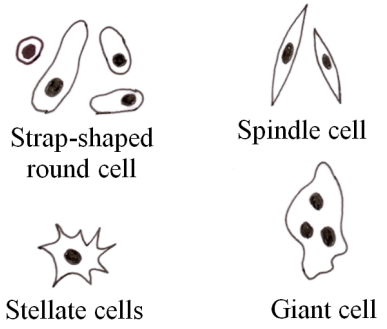

Fig 21-5 *Histologic cell types observed in rhabdomyosarcoma.*

1. Embryonal rhabdomyosarcoma is the most common (60% of cases), affects mainly children and occurs predominantly in the head and neck region. Microscopically, it bears a close resemblance to the various stages in the development of muscle tissue (Fig 21-5). Rhabdomyoblasts with strap-shaped eosinophilic cytoplasm (positive for desmin) are characteristic (P 21-18 and 21-19). The 5-year survival with modern chemotherapy is about 60%.

Three variants of embryonal rhabdomyosarcoma are recognized: (a) *botryoid* RMS is characterized by a polypoid grape-like growth, with subepithelial hypercellularity and abundant myxoid stroma (P 21-20). It is most frequently seen in mucosa-lined hollow structures such as the urinary bladder, vagina and nasopharynx, (b) *spindle cell* RMS is characterized by its more favorable clinical behavior (5-year survival 90%), and (c) *ectomesenchymal* RMS is characterized by the presence of primitive neuroectodermal elements in addition to the rhabdomyoblastic component.

2. Alveolar RMS is the second most common type, accounting for about 20% of all cases and affects most often persons between 10 and 25 years. It commonly affects the extremities. Histologically, tumor cells show an alveolar pattern delineated by fibrous septa (P 21-21). A balanced chromosomal translocation t (2; 13) is considered diagnostic. The prognosis is unfavorable, with 5-year survival of only 25%. For prognostic purposes, mixed forms of RMS with embryonal and alveolar features are best classified as alveolar RMS since the latter is the more aggressive component.

3. Pleomorphic RMS, also known as the classic type, accounts for less than 5% of cases. The median age incidence is over the age of 50 years. It is primarily a tumor of large muscles of extremities, particularly the muscles of the thigh. Histologically, it is characterized by pleomorphic giant cells resembling MFH and other pleomorphic sarcomas (P 21-22 to P 21-24). Positivity to desmin may help in the differential diagnosis.

Differential Diagnosis

Proliferative myositis is the main lesion to be misdiagnosed as rhabdomyosarcoma. This reactive lesion of obscure etiology (possibly traumatic) commonly affects trunk muscles of adults. The lesion stows spindle cells and giant cells with abundant eosinophilic cytoplasm (ganglion-like cells) which may be confused with rhabdomyoblasts (P 21-25). However, these cells are negative for desmin.

LEIOMYOSARCOMA

In series that include leiomyosarcomas of gastrointestinal tract and uterus, these tumors are often the most common soft tissue sarcoma. But, if GI and gynecologic leiomyosarcomas are excluded, true soft tissue leiomyosarcomas account for only about 12% of cases. Leiomyosarcoma affects mainly elderly patients, with a median age of 60 years. However, recently, there have been reports of these tumors in immunosuppressed children (AIDS or post-transplant), possibly related to EBV infection.

Leiomyosarcoma is most common in the skin, deep soft tissue of extremities and the retroperitoneum. Cutaneous tumors are detected early and have a favorable prognosis. Conversely, leiomyosarcomas of deep soft tissue often arise in the walls of veins, are detected late and carry an unfavorable prognosis.

Histologically, leiomyosarcoma is composed of spindle cells, arranged in interdigitating bundles crossing each other at right angle (Fig 21-6). The cells have blunt-ended cigar-shaped nuclei (P 21-26 and P 21-27). A vascular pattern or merging of the tumor with blood vessel wall is characteristic. Positivity of cytoplasm to desmin is a typical immunohistochemical feature. Evans (1985) classified the tumors into low and high grade according to the mitotic activity (high-grade tumors have more than 10 mitoses per 10 high power fields). This classification has important prognostic implications.

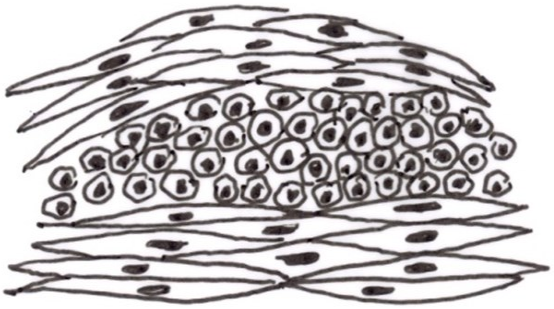

Fig 21-6 *The interdigitating pattern diagnostic of leiomyosarcoma. Tumor cell bundles cross each other at right angle and appear as alternating spindle and round cells .*

VASCULAR SARCOMAS

This class includes malignant tumors of blood or lymph vessels which are difficult to separate from each other. They are classified into vascular and perivascular tumors. The former represent a true neoplastic endothelial proliferation, whereas, perivascular tumors includes round or spindle cell patterns around normal vascular channels.

Vascular Tumors

This includes two main subtypes of different biological behavior, namely hemangioendothelioma (a locally malignant recurrent tumor) and hemangiosarcoma (a highly malignant and metastasizing sarcoma).

1. Hemangioevdothelioma: Endothelial proliferation (CD 34 positive) is limited to vessel wall or its lumen. Immature tumor cells are elongated and contain a single paranuclear vacuole containing red blood cells. In addition to the *conventional* type, three variants are recognized, namely *postradiation* hemangioendothelioma and *Juvenile papillary* endothelioma or Dabska tumor (P 21-28) and *epithelioid* endothelioma in adults

2. Angiosarcoma is a frankly malignant tumor of vascular endothelium, affecting both blood vessels and lymphatics. It is a rare tumor (1% of sarcomas) which may arise in the skin typically as multicentric lesions in elderly men (P 21-29). It may also arise as multiple chest and arm lesions in patients with chronic lymphedema after mastectomy (Stewart-Treves syndrome). Other sites include the breast, liver, lung and myocardium. Histologically, it is composed of anastomosing vascular channels, lined by atypical large endothelial cells with irregular hyperchromatic nuclei which show papillary intraluminal projections (P 21-30). Tumor cells are positive for CD 34 and factor VIII related antigen. The prognosis is generally poor (12% 5-y survival).

Perivascular Tumors

Perivascular tumors are a heterogeneous group characterized by oval or spindle cells around blood uessels. They are classified info three groups according to their biological behavior (Table 21-12).

The WHO considered hemangiopericytoma to represent the early phase of *solitary fibrous tumor* (SFT), hence, the term hemangiopericytoma is obsolete. SFT is observed into two main clinical settings namely: pleural and extrapleural (in meninges, nasopharynx, soft tissue of trunk and exterimites). The tumor is characterized by spindle cells which are (CD34+, CD99+, actin-) arranged around branching (staghorn) blood vessels (P 21-31A). About 10% of SFT are aggressive, especially large tumors (>10 cm).

Table 21-12 Classification of perivascular Tumors

Benign
Glomus tumor*
PEComas*
Angiomyolipoma
Angiomyoma and angiomyoblastoma
Myopricytoma
Intermediate (Recurrent or rarely metastasizing)
Solitory fibrous tumor
Nasal angiofibroma
Malignant
Kaposi sarcoma

(Fletcher et al, 2013 and Folpe and Inwards, 2010) * Malignant variant are rare

Glomus tumor is the most common in hands and feet. Histologically (P 32-31B), it is composed of cavernous spaces with hyaline wall surrounded by rounded cells (actin-, CD34+). The grand majority of Glomus tumor are benign.

Myopericytoma is a benign pediatric tumor, composed of myoid spindle cells (actin+) arranged around branching staghorn blood vessel.

PEComa (perivascular epithelioid cell tumor) is a rare neoplasm of uncertain differentiation. It is most commonly observed in the lung, liver, and Retroperitoneum. Histologically, it is characterized by perivascular arrangement of clear cells, with a peculiar myomelanocytic phenotype (actin+, Melan-A+).

Perivascular tumors must be distinguished from other sarcomas with pericyctic pattern. Examples include: (1) Synovial sarcoma, (2) Solitary fibrous tumor, (3) Mesenchymal chondrosarcoma, and (4) phosphaturic mesenchymal tumor (which shows giant cells and calcific areas.

NEUROECTODERMAL TUMORS

Four soft tissue sarcomas arise from neural crest, including two pediatric tumors (extraskeletal Ewing/PNET and neuroblastoma) and two adult tumors (malignant paraganglioma and neurofibrosarcoma MPNST).

Extraskeletal Ewing/ PNET

This primitive neuroectodermal tumor primarily affects adolescents and is rarely encountered after the age of 40 years. The most common locations are chest wall (Askin tumor), paravertebral area, pelvis and extremities. Histologically, it is characterized by sheets of uniform small round cells with central nuclei and scanty cytoplasm (P 21-32). The nuclei have a fine chromatin pattern with indistinct nucleoli. The tumor has a rich vascular stroma, with septa containing thick-walled vessels. Immunohistochemically, it is positive for chromogranin and CD99. Cytogenetically, it is characterized by a chromosomal translocation t (11;22) (q24; ql2). With recently advanced chemotherapy, a 5-year survival rate of 40% has been achieved.

Neuroepithelioma

This tumor is a variant of primitive neuroectodermal tissue (PNET) which rarely arise in soft tissue. Histologically, it is characterized by the presence of numerous pseudorosettes of Homer-Wright type (P 21-33). This feature is considered by Fletcher (2007) to indicate well differentiation in PNET. However, the prognostic significance of the quantity of rosettes in the tumor is still unsettled.

Neuroblastoma

Neuroblastoma and ganglioneuroblastoma are malignant tumors of the sympathetic nervous system (P 21-34) typically affecting infants and young children (peak age 2 years). The site distribution is abdominal in 68% of cases (adrenal gland 38% and extra-adrenal 30%), chest 20%, pelvis 3.4%, head and neck 3.6% and unknown 5%. Neuroblastoma is further discussed among neoplasms of the adrenal gland (Chapter 19).

Paraganglioma

Tumors of the autonomic nervous system are neoplasms of the adults (mean age 50 years). Sexes are affected equally except for vagal and jugulotympanic paragangliomas in which females predominate. The tumors are commonly sporadic, but rarely familial (e.g. with VHL and MEN-2 syndromes). Paragangliomas are classified anatomically into two main groups:

1. *Paraganglia of head and neck* (including aorticopulmonary paraganglia). These are associated with the parasympathetic system, are chromaffin negative, function mainly as chemoreceptors and does not secrete catecholamines. This group includes: the jugulotympa-nic paraganaglia (glomus jugulare), vagal, carotid body, orbit, pharynx, larynx, and aortic bodies (Chapter 4).

2. *Thoraco-abdominal paraganglia* (sympathoadrenal): These are associated with the sympathetic system, are chromaffin positive, may secrete catecholamines. This group affects: the adrenal medulla (pheochromocytoma), paravertebral paraganglia, organ of Zukerkandl and urinary bladder.

Grossly, the tumors are pseudoencapsulated and appear gray brown in color. Histologically, they are composed of nests of chief cells (Zellballen) with abundant granular cytoplasm, enclosed by fibrovascular stroma (P 21-35). Pleomorphism is not an indication of malignancy. The latter is only confirmed by the presence of metastases. The chief cells are immunoreactive to, S-100 (stromal cells) and chromogranin. Electron microscopy reveals characteristic dense core neurosecretory granules in the cytoplasm.

Biologically, 70% of paragangliomas are benign, 20% are of borderline malignancy and about 10% are malignant. However, the incidence of malignancy varies according to the anatomic site, being 5% in jugulotympanic paraganglia, 10% in adrenal pheochromocytoma, and 35% in paravertebral paraganglia.

Neurofibrosarcoma (MPNST)

This sarcoma arises from neurilemmal or Schwann stem cells. It is also known by other names: malignant schwannoma, and recently, malignant peripheral nerve sheath tumor (MPNST). It constitutes about 6% of soft tissue sarcomas. Approximately 50% arise in patients with neurofibromatosis type I through a malignant change of nerve trunk neurofibroma, the remainder occur sporadically (P 21-36).

Histologically, it is composed of spindle cells which may show characteristic serpentine (wavy pattern) or palisade arrangement (Fig 21-7 and P 21-38). Immunohistochemically, vimentin and S-100 are variably present. The prognosis is relatively poor, with a 5-year survival rate of about 40%.

Granular Cell Tumor

Granular cell tumors are neuroectodermal in origin. Most of such tumors encountered are benign but rarely malignant tumors are observed (P 21-39). The malignant nature is

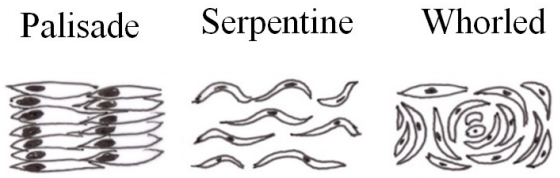

Fig 21-7 *Diagnostic pattern of MPNST*

established by bulky size, mitotic activity and lymph node metastases.

Differential Diagnosis

The main differential diagnosis of MPNST is neurofibroma (P 21-40). The small size, hypocellularity and lack of mitotic activity are important diagnostic features.

Table 21-13 Soft Tissue Sarcomas of Uncertain Differentiation

Locally recurrent (3-30%)
Myxoma
Hemangiosideratic fibrolipomatous tumor
Rarely metastasizing (<10% metastases)
Angiomatoid fibrous histiocytoma
Ossifying fibromyxoid tumor
Myoepithelioma (parachordoma)
Phosphaturic Mesenchymal tumor
Malignant (>10% metastases)
Synovial sarcoma
Alveolar soft part sarcoma
Epithelioid sarcoma
Clear cell sarcoma (melanoma)
Desmoplastic small round cell tumor
Extrarenal rhabdoid tumor
Perivascular epithelioid cell tumor (PEComa)

(Fletcher et al, 2013/Folpe and Edwards, 2010)

SARCOMAS OF UNCERTAIN DIFFERENTIATION LINEAGE

In this class tumor cells lack any resemblance to normal or embryonic human cells. Hence they are given terms descriptive of their cytomorphology. These tumors have diverse biologic behavior (Table 21-3) and apart from synovial sarcoma they are rarely encountered in practice.

1. Synovial Sarcoma

It affects young adults (25-35 years), more common in men and the common sites are soft tissue of extremities. The tumor is biphasic, showing both epithelial and mesenchymal spindle cell elements (P 21-41 and P 21-42). Tumor cells have primitive blastoid nuclei and show areas of hypercellularity alternating with areas of hypocellularity. Translocation t(18; X) is characteristic. Immunoreactivity is EMA+, CK+ (90%), CD99+, BCL 2+, vimentin+ and CD34 -. The tumor is not of synovial origin since normal synovium is cyto-keratin negative.

The 5-year survival is about 50%. Favorable prognostic factors include: small tumors (less than 5 cm), peripheral locations, young age, monophasic epithelial type, low mitotic activity, massive stromal calcification and absent necrosis.

2. Alveolar Soft Part Sarcoma

Common sites are the lower extremity, oral cavity, mediastinum and retroperitoneum. It shows nested pattern, large granular cytoplasm and fibrovascular trabeculae (P 21-43). It is positive for the myogenic marker Myo-Dl as well as PAS stain. Electron microscopy reveals membrane-bound rhomboid crystals (P21-44).

3. Epithelioid Sarcoma

Commonly arises in upper extremity. It is composed of epithelioid cells with eosinophilic cytoplasm and prominent nucleoli and focal necrosis (P 21-45). It is positive for cytokeration, vimentin and CD 34 (50%). Recurrence sate at 10 years is 80%.

4. Desmoplastic Small Round Cell Tumor

It is most common in retroperitoneum, rarely intrathoracic, commonly affecting young patients. Histologically, It is composed of undifferentiated small round cells associated with prominent fibrotic stroma (P 21-46). Paradoxical coexpression of cytokeratin and desmin by immunohistochemistry is characteristic. Prognosis is very poor (25% 5-year survival).

5. Myxoma

It is composed of stellate cells in myxoid stroma (P21-47). Local recurrence rate is variavle according to the site being only 3% in sporadic solitary cardiac myxoma, 10% in familial multiple cardiac myxomas (Carney syndrome), as well as, soft tissue myxomas, 25% in maxillary myxoma and 30% in the

aggressive angiomyxoma of the vulva and perineum.

6. Inflammatory Myxohyaline Tumor

It is a low-grade sarcoma that typically affects the distal extremities. It is characterized by inflammation, spindle cells, myxoid areas and bizarre giant cells (Reed-Sternberg like). Tumor cells are positive for vimentin, CD68 and CD 34. Recurrence rate is 22%.

7. Extrarenal Rhabdoid Tumor

It affects infants 1-3 years. The cells have eosinophilic cytoplasm (intermediate filaments) which is positive for vimentin, cytokeratin, CD99, but negative for desmin and CD34.

8. Giant cell Tumors of Soft Tissue

It is composed of osteoclast-like giant cells (reactive in nature positive for CD68) and neoplastic stroma cells (positive for p63).

9. Myoepithelioma (Parachordoma)

Parachordoma was previously applied to tumors with similar histology to chordoma but affecting soft tissue. Recently, such tumors proved to be myoepithelioma .(CK+ve and S100 +ve).

10. Ossifying fibromyxoid tumor

This tumor is composed of lobules of ovoid to fusiform cells surrounded by a partial shell of mature lamellar bone (P 21-48). The stroma is fibromyxoid. Tumor cells are positive for vimentin, S-100 and desmin. Local recurrence was reported in 27% of cases, but, metastases are rare.

11. Perivascular epithelioid cell tumor (PEComa)

This family of tumors, including angiomyolipoma, also known as sugar tumors, affects the lung, abdominal and female genital organs. Histologically, it is characterized by perivascular epithelioid cells with granular or clear cytoplasm (rich in glycogen) and small central nuclei (P 21-49). A paradoxical myomelanocytic phenotype is characteristic of this tumor (coexpression of actin, Melan-A and HMB-45). The majority of tumors are benign, but few are metastasizing.

12. Angiomatoid fibrous histiocytoma

This tumor commonly arises in subcutaneous tissues of extremities and appears grossly vascular and hemorrhagic. It shows pseudovascular spaces (not lined by endothelium) filled with blood. There is associated lymphoplasma cell infiltrate in the stroma. Immunoreactivity is complex, desmin positive (50%) and EMA positive (40%). The positivity to CD68 does not indicate histiocytic origin because it is rather unreliable marker. The tumor has a very low recurrence rate (6%) and metastatic (1%) potentials.

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