Current Concepts in Pathology of Soft Tissue Sarcoma

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Abstract Soft tissue sarcomas (STS) constitute a heterogeneous category of soft tissue neoplasia composed mostly of uncommon tumors of diverse histology, different biology and varied outcomes. Substantial developments in immunohistochemistry (IHC), cytogenetics and molecular genetics of STS have caused a significant change in the classification and diagnosis of these tumors with a direct implication for clinical management and prognosis. In this review we discuss newer developments impacting diagnosis and prediction.

Keywords Sarcoma · Soft tissue · Immunohistochemistry · Grading · Molecular · Pathology

Introduction

A large majority of soft tissue tumors are benign with a very high cure rate after surgical excision. Malignant mesenchymal neoplasms account for <1% of overall human burden of malignant tumors but they are life threatening and pose significant diagnostic and therapeutic challenges. Close interaction of surgeons, oncologists and surgical pathologists has brought about a significant disease free survival for tumor which previously almost invariably fatal. The overall 5 year survival rate for STS in the limbs is now in order of 65–75%.

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WHO Classification of Soft Tissue Tumors

The WHO classification (2002) of soft tissue tumors incorporates detailed clinical, histological and genetic data. The usual approach to soft tissue tumor classification is by presumed cell lineage. Tumors are categorized into adipocytic, fibroblastic or myofibroblastic, so called fibrohistiocytic, smooth muscle, pericytic, skeletal muscle, vascular, chondro-osseous and lastly “of uncertain differentiation” category.

Further the WHO working group divides STS into four categories: Benign, Intermediate (locally aggressive), Intermediate (metastasizing) and malignant [1, 2]. Benign soft tissue tumors do not recur locally and almost always cured by complete local excision.

Intermediate (locally aggressive) STS recur locally and are associated with an infiltrative locally destructive growth pattern. Lesions in this category do not have any evident potential to metastasize and typically require wide excision to ensure local control. Intermediate (rarely metastasizing) soft tissue tumor as often locally aggressive but in addition show well documented ability to give rise to distant metastasis in occasional cases. The risk of such metastasis is <2% and is not predictable on the basis of histomorphology. Malignant soft tissue tumors have significant risk of distant metastasis (ranging from 20% to almost 100% depending upon histological type and grade) in addition to the potential for locally destructive growth and recurrence [2, 3].

Grading Unlike with other tumors the staging of STS is largely determined by grade. Unfortunately there is no generally agreed up on scheme for grading STS [4, 5]. The most widely used STS grading systems are French Federation of Cancer Centers Sarcoma Group (FNCLCC) [6] and National Cancer Institute (NCI) [5]. Both systems have 3 grades and are based on mitotic activity, necrosis and differentiation which

correlate well with the prognosis. However in addition to these criteria, the NCI system requires the quantification of cellularity and pleomorphism for certain subtypes of sarcomas which is difficult to determine objectively. The FNCLCC system is easier to use and appears slightly better in predicting prognosis than NCI system [6] (Table 1). The TNM staging system recommends the FNCLCC system but effectively collapses into high grade and low grade [7, 8], which means that FNCLCC grade 2 tumors are considered “high grade” for the purposes of stage grouping.

Grading of malignant peripheral nerve sheath tumor, embryonal and alveolar rhabdomyosarcoma, angiosarcoma, extraskeletal myxoid chondrosarcoma, alveolar soft part sarcoma, clear cell sarcoma, and epithelioid sarcoma is not recommended [3].

Morphological Categories While approaching soft tissue tumors the pathologist must look into architectural pattern, appearance of the cells, and the characteristics of the stroma. These categories can lend themselves to the development of a number of different diagnostics categories which can be further differentiated on the basis of morphological features as well as Immunohistochemical characteristics (Table 2).

Pitfalls in the Diagnosis of STS Certain reactive processes may mimic sarcomas. Therefore it is important to determine whether the lesion under study is a reactive process or a neoplasm. Some reactive lesions display a distant zonal quality. For example in nodular fasciitis and ischemic fasciitis one encounters a cuff of proliferating fibroblasts that surround a

central hypocellular zone of fibrinoid change. Cells comprising reactive lesions often have the appearance of tissue culture fibroblasts with large vesicular nuclei, prominent nuclei and cytoplasmic basophilia. No atypical mitosis or nuclear atypia is usually seen.

It is not always possible to classify soft tissue tumors precisely based on biopsy material, especially FNA and core needle biopsy specimens. Although pathologists should make every attempt to classify lesions in small biopsy specimens, on occasion stratification into very basic diagnostic categories, such as lymphoma, carcinoma, melanoma, and sarcoma, is all that is possible. In some cases, precise classification is only possible in open biopsies or resection specimens.

Histologic classification of soft tissue tumors is sufficiently complex that, in many cases, it is unreasonable to expect a precise classification of these tumors based on an intraoperative consultation. Intraoperative consultation is useful in assessing if “lesional” tissue is present and in constructing a differential diagnosis that can direct proper resection of tissue. The role of frozen section in STS is limited only to assure the surgeon that he has obtained representative, adequate and viable tissue for diagnosis or to evaluate the margins.

Grading of sarcomas in small needle core biopsies is also frequently erroneous. Inappropriate sampling may lead to high grade lesion being diagnosed as low grade sarcoma. Core biopsy containing necrosis usually implies high grade sarcoma but necrosis should be coagulative and distinguished from hyaline change. Further necrosis reflective of prior therapy or surgical intervention does not upgrade a lesion. Grading becomes unreliable if chemotherapy and radiotherapy is given prior to biopsy [9].

Pathologists must proceed cautiously and consider IHC results in the context of all available data in a given case of soft-tissue tumors and to the demonstrated tendency to aberrant antigen expression in soft-tissue tumors. Pathologists must be aware not only of the typical profile and reported antigenic infidelities of a particular entity, but also of the pitfalls that can be introduced by technical factors, such as tissue processing and fixation as well as the IHC procedures. It is estimated that. IHC in fact adds confusion to the diagnostic process in 5% to 10% of cases [10].

Immunohistochemistry in Diagnosis and Prognosis of Soft Tissue Tumours With the implementation of immunohistochemistry, cytogenetics and molecular genetic analysis significant changes have been made regarding the classification and diagnosis of STS. These changes are relevant because they have direct implications for clinical management and prognosis. Many new entities have been recognized of which desmoplastic small round cell tumor and intimal sarcomas are examples. Some sarcoma entities lost in importance (e.g., the so-called malignant fibrous histiocytoma, hemangiopericytoma, and fibrosarcoma categories) [3].

Table 1 FNCLCC grading system: definition of parameters

Tumour Differentiation	
Score 1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., well differentiated liposarcoma and leiomyosarcoma).
Score 2	Sarcomas for which histological typing is certain (e.g. myxoid liposarcoma & conventional leiomyosarcoma)
Score 3	Embryonal and undifferentiated sarcomas, Pleomorphic sarcomas, synovial sarcomas, osteosarcomas, PNET)
Mitotic Count	
Score 1	0–9 mitoses per 10 HFP*
Score 2	10–19 mitoses per 10 HFP*
Score 3	≥20 mitoses per 10 HFP*
Tumor Necrosis: determined on histologic sections	
Score 0:	No tumor necrosis
Score 1:	Less than or equal to 50% tumor necrosis
Score 2:	More than 50% tumor necrosis
Histological grade	
Grade 1	Total score 2,3
Grade 2	Total score 4,5
Grade 3	Total score 6,7,8

Table 2 STS: morphological categories and IHC parameters

Morphological category	IHC parameters
Fascicular Spindle Cell Sarcomas	
Fibrosarcoma	Vimentin
Leiomyosarcoma	SMA, HHF 35, Calponin, Desmin +/-
Spindle cell RMS	Desmin+, Myogenin+
Synovial sarcoma	S-100 +/-, EMA+
MPNST	S-100 +, EMA-
Solitary fibrous tumor	CD34+, CD99-, CD31-
Myxoid Soft Tissue Sarcomas	
Myxoid liposarcoma	MDM 2 +, CD34 +/-, novel IHC antibody to the TLS/EWS-CHOP chimeric oncoproteins
Myxoid chondrosarcoma	Vim +, Synaptophysin +/-, EMA +/-
Myxoid DFSP	CD34
Myxoid MFH (myxofibrosarcoma)	CD34 +, HMGA1 and HMGA2
Botryoid Embryonal RMS	Desmin, Myogenin
Myxoid leiomyosarcoma	SMA, HHF 35, Desmin, Myogenin
Epithelioid Soft Tissue Sarcomas	
Alveolar soft part sarcoma	Desmin, SMA
Epithelioid sarcoma	CK, EMA, Vimentin, CD34 +/-
Epithelioid angiosarcoma	CD31, Factor VIII, CD34, FLI-1
Epithelioid hemangioendothelioma	CD31, Factor VIII, CD34, FLI-1
Extra gastrointestinal stromal tumor	CD117, CD34 +/-
Malignant Rhabdoid tumor	Polyphenotypic, Loss of INI1 protein
Malignant mesothelioma	Calretinin, Thrombomodulin
Synovial sarcoma	EMA, Cytokeratin, S100 +/-
Sclerosing epithelioid fibrosarcoma	Vimentin
Clear cell sarcoma	HMB45, Melan1 <i>EWSR1-ATF</i> fusion
Round Cell Soft Tissue Sarcomas	
Alveolar RMS	Desmin, Myogenin
Desmoplastic small round cell tumor of childhood	Polyphenotypic
Embryonal RMS	Desmin, Myogenin
Extraskeletal ES/PNET	CD99, FLI-1
Round cell liposarcoma	S-100
Small cell osteosarcoma	Vimentin
Malignant hemangiopericytoma	CD34
Pleomorphic Sarcomas	
Pleomorphic undifferentiated sarcoma	Vimentin
Malignant fibrous histiocytoma	Alpha 1 antitrypsin, alpha-1-antichymotrypsin
Pleomorphic liposarcoma	MDM2 and CDK4
Pleomorphic RMS	Desmin, Myogenin
Pleomorphic MPNST	S100
Pleomorphic leiomyosarcoma	SMA, SMA, Desmin

Table 2 (continued)

Morphological category	IHC parameters
Pleomorphic angiosarcoma	CD31, Factor VIII, CD34, FLI-1
Chondro-Osseous STS	
Mesenchymal Chondrosarcoma	S-100
Extra skeletal osteosarcoma	Vimentin
Clear Cell Lesions	
Clear cell sarcoma of soft tissue	S-100, HMB45, NSE, CD57, <i>EWSR1-ATF</i> fusion gene
Clear cell myomelanocytic tumor	HMB45, MelanA +/-, SMA +/-

Immunohistochemistry (IHC) plays an important role in STS diagnosis. The diagnostic approach consists in ruling out a nonmesenchymal tumor, followed by trying to define mesenchymal cell lineage. A panel of immunostains, rather than single marker, should always be performed. This approach greatly eliminates the potential for misdiagnosis owing to anomalous expression of antigens (eg, cytokeratin in angiosarcoma) [11]. The routine use of a small, carefully selected panel based on patterns as enumerated in Table 2 is time and cost effective. The extent of sub-categorization of tumors should be driven by clinical relevance. For instance in cases of pleomorphic sarcoma treatment protocols do not discriminate between histologic subtypes with the possible exception of pleomorphic rhabdomyosarcoma(RMS) which may be treated according to an RMS protocol, and Leiomyosarcoma for which oncologists often use a specific chemotherapeutic agent. How far should one go with ancillary studies in trying to determine specific lineage and what are the clinical/prognostic implications is a question best answered by need driven requirements of treating oncologists [12] Fig. 1.

There is little disagreement over the importance of separating pleomorphic sarcoma from pleomorphic nonmesenchymal malignancies. The main differentials are metastatic sarcomatoid carcinoma, metastatic melanoma, and, in some instances, an unusual hematolymphoid tumor with spindle cell features. The initial battery of IHC markers should always include a broad keratin (pancytokeratin), S100, and vimentin. A positive keratin result indicates primary carcinoma, positive S100 stain should be followed by additional melanoma markers. Hodgkin's lymphomas, large cell lymphomas including anaplastic large cell lymphoma, and follicular dendritic cell tumor are distinguished using leucocyte common antigen (LCA) and CD30. It is important to remember that some of these tumors may be negative for leukocyte common antigen [11].

Synovial sarcoma is a unique soft tissue sarcoma showing both mesenchymal and epithelial differentiation. Despite its name, it is neither related to nor does it arise from synovial cells. Microscopically, biphasic, monophasic spindle cell,

Fig. 1 a. Vascular network highlighted in CD 34 stain in a sclerosing epithelioid fibrosarcoma b. Dermatofibrosarcoma protuberans showing diffuse CD 34 expression c. Diffuse desmin expression in a pleomorphic

rhabdomyosarcoma, d. HMB 45 in amelanotic melanoma, e. Diffuse CD117 in GIST and f. Focal SMA in GIST

poorly differentiated, calcifying/ossifying and myxoid subtypes have been described [13]. Immunohistochemistry is particularly useful in the diagnosis of the monophasic spindle cell variant, which is more difficult to distinguish from other spindle cell sarcomas on morphologic grounds alone. Epithelioid sarcoma is a rare soft tissue sarcoma showing epithelial differentiation. Cytokeratins and EMA are strongly positive in almost all cases, mostly coexpressed with vimentin. CD34 is positive in about 50% with a strong membranous staining pattern. When positive, this stain is helpful in excluding carcinomas which are CD34 negative.

Despite their similar IHC staining profiles, clear cell sarcoma of soft tissue is clinically and genetically distinct from cutaneous melanoma. Like the latter, it is positive for melanocytic markers S100, HMB-45, and less consistently positive for melan 1. Melanocytic stains are helpful in separating clear cell sarcoma from other soft tissue sarcomas, distinction from cutaneous melanomas is based on tumor morphology, location, or genetic confirmation of the *EWSR1-ATF* fusion gene, which has been found in clear cell sarcoma but never in cutaneous melanoma.

Immunohistochemistry plays a major role in the differential diagnosis of round cell tumors including Ewing's sarcoma/Primitive Neuroectodermal Tumors (ES/PNET), alveolar rhabdomyosarcoma, desmoplastic small round cell tumor, poorly differentiated synovial sarcoma, and Merkel cell carcinoma. Strong CD99 membrane immunopositivity is usually seen in most ES/PNET. However, as with most differentiation markers, CD99 tends to be very sensitive but not specific [14].

Pathologists must proceed cautiously and consider IHC results in the context of all available data in a given case being aware of the demonstrated tendency to aberrant antigen expression in soft-tissue tumors. Pathologists must be aware not only of the typical profile and reported antigenic infidelities of a particular entity, but also of the pitfalls that can be introduced by technical factors, such as tissue processing and fixation as well as the IHC procedures. It is estimated that IHC in fact adds confusion to the diagnostic process in 5% to 10% of cases [10].

It is hoped that detection of tumor-specific alterations and validation through genetic analysis on larger samples will lead to development of new IHC antibodies. These new markers detect tumor-specific fusion proteins that are either over expressed or aberrantly expressed as a result of a translocation. Examples of such antibodies are ALK-1, WT-1, and FLI-1.

Molecular Pathology of STS Molecular genetics of STS has developed at a rapid pace in recent years. Methodological advances including molecular ancillary techniques comprising of a vast array of polymerase chain reaction-based techniques, fluorescence in situ hybridization (FISH), conventional and array-based comparative genomic hybridization, expression arrays, direct genome sequencing, and DNA methylation analysis have allowed better understanding of biology, identified new histogenetic concepts and built up robust diagnostic methods [15]. The more current textbooks including the current World Health Organization

Table 3 Standard reporting system for STS (based on AJCC/UICC/TNM)

(A) Procedures
Biopsy
Resection
Intralesional resection
Marginal resection
Wide resection
Radical resection
Other (Specify)
Not specified
(B) Tumor site
Specify (If known)
Not specified
(C) Tumor size
Greatest dimension _____ cm
Additional dimension _____ cm
Cannot be determined
(D) Macroscopic Extent of tumor (Select All that apply)
Superficial
Dermal
Subcutaneous
Deep
Fascial
Subfascial
Intramuscular
Mediastinal
Intraabdominal
Retroperitoneal
Head & neck
Other (specify)
Cannot be determined
(E) Histological type (WHO, classification of STT)
Specify
Cannot determined
(F) Mitotic rate
Specify ___/10HFP
(G) Necrosis
Not identified
Present-extent _____%
(H) Histological Grade (FNCLCC)
Grade I
Grade II
Grade III
Ungraded Sarcoma
Cannot be determined
(I) Margins
Positive/Negative
Indicate distance from all margins <1.5 cm
(J) Lymphovascular Invasion
Not identified
Present

Table 3 (continued)

Indeterminate
(K) Ancillary studies
IHC
Cytogenetics
Molecular Pathology
Others
(L) Pre-resection Treatment
No therapy
CT
RT
Therapy performed, type not specified
Unknown
(M) Treatment effect
Present specified _____
Not specified
(N) TNM code
(O) Comments

edition on tumors of soft tissue and bone reserve specific sections to include recent cytogenetic and molecular data [3]. The majority of sarcomas carry nonspecific genetic changes in a background of a complex karyotype. Many of these alterations have been detected in a small number of cases and confirmatory tests are not yet commercially available. Their diagnostic utility is therefore limited with the exception of some fluorescence in situ hybridization probes, which are being used with increasing frequency, in particular for the diagnosis of synovial sarcoma, ES/PNET, and alveolar rhabdomyosarcoma.

Soft tissue sarcomas can be divided in two categories: those with simple karyotypes and those with complex karyotypes [15]. Of the soft tissue sarcomas with relatively simple karyotypes, 15–20% bear specific reciprocal translocations which can be used as diagnostic markers. Some others are characterized by specific somatic mutations (e.g., cKIT and platelet-derived growth factor receptor alpha in gastrointestinal stromal tumor (GIST) [16] or specific amplifications (e.g., MDM2 and CDK4 amplification in the well-differentiated/ dedifferentiated liposarcoma category [17], MYCN amplification in Neuroblastoma, Translocation FKHR (FOXO1A) in alveolar rhabdomyosarcoma [18].

The Ewing sarcoma breakpoint region 1 (EWSR1; also known as EWS) represents one of the most commonly involved genes in sarcoma translocations. In fact, it is involved in a broad variety of mesenchymal lesions which includes Ewing's sarcoma/peripheral neuroectodermal tumor, desmoplastic small round cell tumor, clear cell sarcoma, angiomatoid fibrous histiocytoma, extraskeletal myxoid chondrosarcoma, and a subset of myxoid liposarcoma. 14 EWSR1 maps on 22q12, and its coding sequence includes 17 exons. 19 EWSR1

rearrangement can be visualized by FISH. However, as in most instances a split-apart approach is used, the results of molecular genetics must be evaluated in context with morphology [19].

Soft tissue sarcomas with complex karyotypes account for about 50% of sarcomas. This sarcoma category includes most of spindle cell/pleomorphic sarcomas (myxofibrosarcoma, pleomorphic liposarcoma, etc.) as well as leiomyosarcomas, malignant peripheral nerve sheath tumors, and many other neoplasms [6]. Sarcomas with non-EWS translocations are spindle, polygonal or small round cell tumours with varying behaviour, which mostly occur in children or young adults. They include synovial sarcoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, dermatofibrosarcoma protuberans, low-grade fibromyxoid sarcoma, infantile fibrosarcoma and inflammatory myofibroblastic tumour [13].

In recent years, a characteristic translocation (X;17) resulting in a *ASPL-TFE3* fusion gene has been found in alveolar soft part sarcoma [14, 20]. This fusion gene is not exclusive to alveolar soft part sarcoma but is also present in a pediatric variant of renal cell carcinoma [21]. A new immunohistochemical stain for TFE3 protein has been developed, which detects the over-expressed TFE3 protein in alveolar soft part sarcoma and in other *ASPL-TFE3* fusion gene-positive tumors [21].

Apart from the obvious relevance of specific genetic aberrations for establishing a correct diagnosis, which is a prominent prognostic parameter in itself, the importance of the genetic aberrations on clinical outcome of STS is elusive. The currently used prognostication systems rely on relatively crude clinical parameters, such as tumor size, and histopathologic parameters such as morphologic subtype, grade, necrosis, vascular invasion, and growth pattern, all of which suffer from inter-observer variability there is no reason to believe that the pattern of genetic aberrations should be of less importance for the management of soft tissue sarcomas than for that of leukemias and lymphomas, where genomic analyses today constitutes an integral part of the routine diagnostic and prognostic profiling. However, there is clearly a need for further analyses, using cytogenetic as well as high resolution genomic techniques, on larger series of morphologically well-characterized tumors from patients with adequate follow-up to establish the spectrum of aberrations occurring within each type of soft tissue sarcoma, as well as to allow proper evaluation of the prognostic importance of characteristic genomic changes.

GIST is one of the examples in oncopathology where the understanding of the genetics of the tumor has lead to major changes in treatment following the development of specific tyrosine kinase blockers. Resistant mechanisms which develop in the course of the treatment are of keen interest for molecular pathologist and of importance for the patients. The role of predicting response of targeted therapy has been

well established for KIT and PDGFRA mutations in gastrointestinal stromal tumors [22].

Biomarker-integrated approaches of targeted therapy for a number of solid tumors have been developed. Chemotherapeutic agents are designed to modulate, inhibit, or otherwise interfere with the function of specific molecular targets that are crucial to the malignancy of tumors, and thereby produce a positive clinical response. The role of the vascular endothelial growth factor and its receptor in angiosarcoma, epithelioid hemangioendothelioma and hemangiopericytoma/solitary fibrous tumor has been evaluated. Several phase II trials in advanced soft tissue sarcoma patients have investigated the efficacy of bevacizumab, an anti-VEGF antibody, as well as sunitinib, sorafenib, and pazopanib, VEGFR tyrosine kinase inhibitors. Although response rates and progression-free survival periods were generally low, several angiosarcoma, epithelioid hemangioendothelioma and hemangiopericytoma/solitary fibrous tumour patients demonstrated response or durable disease stabilization on these therapies [23].

Standard reporting protocol (Table 3) recommended by College of American Pathologists should be used for histological reporting to allow generation of uniform and comprehensive reports [8]. In conclusion the histological diagnosis of STS is complex, and is aided by the use of immunohistochemistry which has been well established in routine pathological practice. The application of molecular and immunohistochemical techniques needs to be under strict protocol and results should be interpreted in the morphological context in order to avoid disastrous mistakes in tumor classification.

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