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Recent advances in the diagnosis of soft tissue tumours

INGA-MARIE SCHAEFER AND CHRISTOPHER D. M. FLETCHER

Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

Summary

Soft tissue tumours are relatively rare, but are diagnostically challenging as they comprise a large spectrum of diagnostic entities. Substantial advances have been made in recent years in identifying the underlying recurrent chromosomal and genomic alterations in a significant subset of soft tissue tumours, and this continues to enrich our understanding of the biological mechanisms of tumour development and progression. Ongoing validation and integration of these findings into existing pathological-diagnostic algorithms has led to re- or subclassification of diagnostic categories and will continue to shape a more nuanced (and hopefully clinically relevant) tumour classification system in the future. This review provides a selective overview of recent diagnostic or conceptual advances in the categories of peripheral nerve sheath tumours, vascular and adipocytic tumours, round cell and myogenic sarcomas, and gastrointestinal stromal tumours, as well as their underlying molecular mechanisms, some of which have been translated successfully into useful immunohistochemical stains. A thorough and critical validation of newly identified diagnostic markers—acknowledging the fact that some genetic alterations may not necessarily be tumour-specific—and ongoing correlation with clinical and prognostic implications will be necessary in this regard.

Key words: Sarcoma; soft tissue; genomic alteration; immunohistochemical marker; classification.

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INTRODUCTION

Recent advances in the past few years have substantially changed and will continue to influence our perception of many soft tissue tumours, in particular peripheral nerve sheath tumours, epithelioid vascular and adipocytic tumours, round cell sarcomas, myogenic sarcomas, and gastrointestinal stromal tumours (GISTs). A better understanding of potential molecular drivers in these neoplasms offers the opportunity to refine current classification systems in order to take into account distinct prognostic or therapeutic implications. Loss of function of certain tumour suppressors and oncogenic fusion events are increasingly being detected, in part attributable to improved sensitivity of targeted sequencing approaches, bioinformatics algorithms for rearrangement detection, and molecular/cytogenetic analyses, along with their integration into the clinical diagnostic setting at an increasing number of institutions.

Herein we discuss newly characterised and refined diagnostic concepts or entities as part of the expanding spectrum of soft tissue tumours, driven by recurrent genomic and chromosomal alterations, and review presently available diagnostic markers. Table 1 provides an overview of the selected tumour types, associated molecular alterations, and diagnostic correlates.

BIOLOGICAL SPECTRUM OF PERIPHERAL NERVE SHEATH TUMOURS

Malignant peripheral nerve sheath tumours (MPNSTs) arise in the sporadic setting or in association with neurofibromatosis type 1 (NF1), each accounting for ~50% of cases, and around 10% of cases develop post-radiation. Most MPNSTs are aggressive tumours, with 5-year survival rates of 35–50%.[1] Despite the presence of established diagnostic criteria for MPNSTs (which include identifiable origin from a peripheral nerve or neurofibroma, immunohistochemical/ultrastructural evidence of Schwann cell differentiation, or a background of NF1), their diagnosis can be very challenging, especially in the absence of NF1 or an evident nerve of origin. Expression of neural markers (S100, SOX10, and GFAP) is usually limited in extent and less than 50% of MPNSTs express any of these markers, highlighting the need for more specific diagnostic tools.

In some cases, MPNST shows biological progression from conventional to atypical neurofibroma, and low grade, intermediate grade, and finally high grade MPNST, and current research endeavours aim at further clarifying the order of underlying molecular events. As an example, *CDKN2A* inactivation (leading to p16 loss of function) has been identified not only in MPNST, but is already present in a subset of atypical neurofibromas which credentials these tumours as precursor lesions.[2] In addition, recent methylation-based studies showed that atypical neurofibromas and MPNST share overlapping methylation profiles.[3] However, despite the existence of diagnostic criteria, benign and evolving malignant PNSTs occasionally represent a spectrum of disease which makes their correct diagnosis (with direct implications for clinical management) challenging in certain situations.

A recent consensus approach proposed a modified nomenclature for the spectrum of PNSTs in NF1 patients[4] and identified common diagnostic challenges, such as the inconsistent distinction of atypical neurofibroma versus low-grade MPNST for which clear diagnostic guidelines and a better understanding of the underlying genetic differences are required. However, this classification system, which is based

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Table 1 Overview of recently characterised entities and related biomarkers

Tumour type	IHC	Staining pattern	% of cases	Other useful markers	Genetics
Neural tumours					
MPNST	H3K27me3	Loss	30% low grade, 60% intermediate grade, 80% high grade	S-100, SOX10, GFAP (all subset only, <50% of cases)	*SUZ12* or *EED* mutation (PRC2 inactivation); *NF1*inactivation
Epithelioid MPNST	SMARCB1	Loss	70%	S-100 (strong, diffuse)	
Vascular tumours					
Epithelioid haemangioendothelioma	CAMTA1; TFE3	Overexpression	90%; 5%	CD31, ERG	*WWTR1-CAMTA1* fusion; *YAP1-TFE3* fusion
Epithelioid haemangioma	FOSB	Overexpression	50%	CD31, ERG	*ZFP36-FOSB* fusion; *WWTR1-FOSB* fusion; *FOS* rearrangement
Pseudomyogenic haemangioendothelioma	FOSB	Overexpression	96%	CD31, ERG, keratin	*SERPINE1-FOSB* fusion
Adipocytic tumours					
Atypical spindle cell lipomatous tumour	RB1	Loss	60%	CD34, desmin, S-100 (subset)	13q14 deletion
Round cell sarcomas					
Ewing's sarcoma	NKX2-2	Nuclear overexpression	>90%	CD99 (diffuse, membranous)	*EWSR1-FLI (90%); ESWR1-ERG (5%);* others
Sarcoma with *CIC* rearrangement	WT1, ETV4	Nuclear overexpression	>90%	CD99 (limited)	*CIC-DUX4* fusion (rarely *CIC-FOXO4* fusion)
Sarcoma with *BCOR* rearrangement	BCOR	Nuclear overexpression	>90%	CD99 (variable)	*BCOR-CCNB3* fusion (*BCOR-MAML3*; *ZC3H7B-BCOR*)
Myogenic sarcomas					
Spindle cell/sclerosing rhabdomyosarcoma	MYOD1	Overexpression	100%	Desmin, myf-4	*MYOD1* mutation (p.L122R)
GIST					
SDH-deficient GIST	SDHB (SDHA)	Loss	~90% of *KIT/PDGFRA* wild-type GIST	KIT, DOG1	*SDHA/SDHB/SDHC/SDHD* mutation/*SDHC* hypermethylation

GIST, gastrointestinal stromal tumour; IHC, immunohistochemistry; MPNST, malignant peripheral nerve sheath tumour; NF1, neurofibromatosis type 1; PRC2, polycomb repressive complex 2; SDH, succinate dehydrogenase complex.

on nuclear atypia, cellularity, mitotic rate, and necrosis, needs to be validated in practice. Consensus guidelines that apply to sporadic MPNSTs remain to be established.

H3K27me3 loss in the differential diagnosis of MPNST

In 2014, two groups independently identified recurrent inactivating mutations of the polycomb repressive complex 2 (PRC2) components *SUZ12* or *EED* in ~80% of MPNSTs, which result in PRC2 loss of function and thereby loss of the chromatin mark H3K27me3 (i.e., trimethylation of histone 3 at lysine 27), with subsequent oncogenic RAS pathway activation and presumed cooperation with *CDKN2A* and *NF1* inactivation.[5,6] Based on these compelling observations, our group and others have validated H3K27me3 loss as a seemingly very specific (although not fully sensitive) immunohistochemical marker for the diagnosis of MPNST.[7–9] We found that H3K27me3 expression is lost in ~30% of low grade, ~60% of intermediate grade, and ~80% of high grade MPNST and that, in contrast, other spindle cell neoplasms in the differential diagnosis (including benign peripheral nerve sheath tumours) typically retain H3K27me3 expression (Fig. 1).[7]

These findings suggest that PRC2 inactivation is not an initiating event in MPNST development, but likely occurs during progression from low/intermediate to higher grade tumours. Notably, almost all radiation-associated MPNSTs, but none of the epithelioid MPNSTs tested, showed loss of H3K27me3 expression.[7,8] Therefore, H3K27me3 loss is a highly useful diagnostic marker with well-characterised implications for tumour biology and genomic progression in this type of sarcoma.

In a recent study, five cases of prepubertal paediatric nodular melanomas arising in congenital melanocytic naevi were reported to show markedly decreased H3K27me3 expression (i.e., loss in 50% to >80% of tumour cells) whereas expression was retained in the adjacent naevus and normal tissue.[10] In contrast, all ten adult melanomas tested in this study showed retained expression.[10] PRC2 inactivating mutations have not been reported to be frequent in melanomas and the investigators hypothesise that epigenetic mechanisms may lead to H3K27me3 loss in these tumours.[10]

Of note, H3K27me3 also highlights the inactivated X chromosome in female non-neoplastic (and possibly also neoplastic) cells and therefore may also aid in clarification of sample identity in the routine pathology setting (Fig. 1).[11]

SMARCB1 loss in epithelioid schwannoma and epithelioid MPNST

Epithelioid MPNSTs are biologically distinct from MPNST with spindled morphology and they usually do not arise in association with NF1. They exhibit distinct epithelioid cytomorphology with a strikingly lobulated growth pattern and, in contrast to conventional MPNSTs, show strong and diffuse expression of S100 protein. A significant subset of epithelioid MPNSTs (~70%) lack SMARCB1 expression.[12] SMARCB1 constitutes a component of the SWI/SNF1 chromatin remodelling complex, a master regulator of

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