

Review

Solitary fibrous tumor: An evolving and unifying entity with unsettled issues

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Summary. Solitary fibrous tumor (SFT) is a distinct fibroblastic neoplasm of intermediate biological potential, prototypically presenting as a pleura-associated tumor characterized by patternless proliferation of generally banal oval to spindle cells with hemangiopericytoma-like staghorn vessels in fibrocollagenous stroma. Over the past decades, the clinicopathological spectrum of SFT has been ever-expanding with the incorporation of cases exhibiting myxoid, giant cell-containing, and fat-forming histology, as well as those from extrathoracic sites, including the meninx. Atypical, frankly malignant and even dedifferentiated variants have also been recognized in a subset of SFTs. Notably, the recent groundbreaking discovery of the disease-defining *NAB2-STAT6* gene fusion, resulting from intrachromosomal inversion involving 12q13.3, has largely unified tumors with the aforementioned variations. The derived immunohistochemical detection of nuclear STAT6 expression has high diagnostic value in distinguishing SFTs from histologic mimics, although some relevant pitfalls have been proposed as a precaution. *NAB2-STAT6* fusions yield numerous transcript subtypes associated with the clinicopathological variations. Despite mostly following a favorable course, SFT is notoriously difficult for prognostication because of the propensity for late relapse

or even metastases in 10-40% of cases, which prompts several proposed schemes incorporating age, size, mitosis, and/or necrosis as factors for risk stratification. Mitotic figures >4/10 HPFs, *TERT* promoter and/or *TP53* mutations have been considered as variables that are better correlated with aggressiveness. Although radiotherapy and chemotherapy provide unsatisfactory responses, a better understanding of SFT tumorigenesis may pave the way for new treatment modalities. In this review, we comprehensively discuss the recent advances of SFTs in diagnostic and molecular pathology.

Key words: Solitary fibrous tumor, Hemangiopericytoma, NAB2, STAT6, TERT

Introduction

Solitary fibrous tumor (SFT) is a relatively uncommon mesenchymal tumor of fibroblastic differentiation with intermediate biological potential and occurs in ubiquitous anatomical locations (Fletcher et al., 2013). The incidence of SFT is estimated to be less than 2% of all soft tissue tumors and approximately 0.2 per 100,000 persons per year (Kayani et al., 2018). Indeed, SFT has undergone ever-changing evolutions in its cellular lineage, clinicopathological spectrum expansion, risk stratification, and diagnostic armamentarium. Till recently, the diverse variants of SFTs were unified as a distinct molecularly defined tumor entity owing to the hallmark *NAB2-STAT6* gene fusion identified in 2013 (Chmielecki et al., 2013;

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Robinson et al., 2013). The groundbreaking discovery of the intrachromosomal inversion at 12q13.3, causing the *NAB2* (NGFI-A binding protein 2) and *STAT6* (signal transducer and activator of transcription 6, interleukin-4 induced) gene to fuse in frame in >90% of cases, has facilitated subsequent immunohistochemical detection of nuclear STAT6 expression as a novel diagnostic adjunct of SFT with superb sensitivity and specificity (Doyle et al., 2014a; Yoshida et al., 2014).

Approximately 1.5 centuries ago, SFT was initially described as a primary spindle cell neoplasm of the pleura and then hypothesized to be a "localized mesothelioma" (Wagner, 1870; Klemperer and Rabin, 1931). This misconception prevailed until the 1960s and was perhaps attributable to subsequent tissue culture studies displaying the proliferation of cells with mesothelial cytological features, as well as ultrastructural analyses claiming the observation of epithelial-like mesothelial phenotypes (Stout and Murray, 1942a; Foster and Ackerman, 1960; Luse and Spjut, 1964; Kawai et al., 1978). A consensus on the differentiation lineage of SFT toward mesenchymal cells was eventually reached in the late 1980s because SFT was found to have an intact overlying mesothelium and to express strong vimentin without cytokeratin reactivity in the predominantly spindle tumor cells showing ultrastructural fibroblastic characteristics (Hernandez and Fernandez, 1974; Said et al., 1984; Al-Izzi et al., 1989). Moreover, a more complex phenotype made up of cells showing fibroblastic, myofibroblastic and smooth muscle cell derivations has been described in SFTs of the prostate, in line with the categorization of SFTs into fibroblastic/myofibroblastic tumors in the current WHO classification (Fletcher et al., 2013; Gharaee-Kermani et al., 2014).

Regarding the awareness of protean morphologic variations in SFT, giant cell angiofibroma (GCA) and the vanishing hemangiopericytoma (HPC), originally coined independently of SFT, deserve particular remarks (Gengler and Guillou, 2006). In 1995, Dei Tos et al. designated GCA as distinctive orbital tumors featuring multinucleated giant stromal cells (Dei Tos et al., 1995), which, though not confined to the orbit, indeed exhibit considerable morphological overlap with SFTs and have been subsumed merely into a histological variant of SFT in the World Health Organization (WHO) classification of soft tissue and bone tumors since 2006 (Fletcher, 2006). Although obsolete in the latest WHO tumor classification in 2013, HPC was initially reported in 1942 (Stout and Murray, 1942b) to delineate a broad range of soft tissue neoplasms that were presumed to arise from pericytes and to share prominent staghorn branching vessels. In somatic soft tissue and bone, heterogeneous mesenchymal neoplasms with HPC-like vessels can be generally divided into three categories: (1) bona fide SFTs, including its various histological subtypes, as defined by the hallmark *NAB2-STAT6* fusion; (2) numerous SFT-mimicking entities with HPC-like vessels but definite clinicopathological and/or molecular features, e.g., synovial sarcoma, mesenchymal

chondrosarcoma, infantile fibrosarcoma, etc.; and (3) tumors with genuine pericytic differentiation, e.g., glomus tumor, myopericytoma/myofibroma, and sinonasal HPC/glomangiopericytoma (Gengler and Guillou, 2006). For meningeal neoplasms, SFT used to be a term that only referred to those apparently fibrotic tumors akin to the classical extracranial SFT. Recently, adopting the notion used in soft tissue tumors, the latest 2016 version of the WHO classification of tumors of the central nervous system has considered SFT and HPC as synonyms of a single tumor entity (Louis et al., 2016), while the usage of HPC is not obsolete. Notably, meningeal SFT/HPC are different from extracranial counterparts in risk stratification criteria with their own 3-tier grading system and mitotic cutoff set at 5/10 HPFs rather than 4/10 HPFs.

Clinical and radiographic features

Mainly affecting middle-aged adults without sex predilection, SFTs show a peak incidence at an age between the 3rd and 6th decades of life with a broad age range (5-87 years) (Fletcher et al., 2013). Ubiquitously occurring throughout the body, extracranial SFTs may arise from somatic soft tissues, the head and neck region outside the meninx, and body cavities, such as the intrathoracic pleural/mediastinal cavity, abdominopelvis, and retroperitoneum. A small subset of body cavity-associated SFTs may involve various visceral organs where SFTs are thought to originate from the overlying serosa. Frequent sites of visceral SFTs include the lung, gastrointestinal tract, liver, pancreas, kidney, and urinary bladder, among others. In contrast, SFTs occur rarely in the external genitalia and gynecological organs (Strickland et al., 2016; Tardio et al., 2018). The penis represents the least common male genitourinary organ from which SFTs arise. Primary cutaneous SFT is extremely rare but could be found from the scalp to toes with a benign or malignant appearance (Erdag et al., 2007; Creytens et al., 2016; Feasel et al., 2018). In our prospectively maintained database of 263 SFTs accrued from multiple centers, the primary tumor locations, albeit with referral bias, exhibit generally equal distributions among the meninx (23%), the head and neck (22%), intrathoracic sites (21%), retroperitoneum/abdominopelvis (17%) with or without involving visceral organs, and the extremities and external trunk (16%).

The majority of SFTs manifest as a well-delineated, slowly growing and painless mass, which can be asymptomatic or cause variable compression symptoms depending on the tumor size and anatomic locations. A subset (~5%) of large tumors may develop paraneoplastic hypoglycemia (a.k.a. Doege-Potter syndrome), which tends to be more common in malignant and retroperitoneal/pelvic SFTs (Kayani et al., 2018) and results from ectopic secretion of insulin-like growth factor II (IGF- II) with ensuing hypoinsulinemic hypoglycemia (Hajdu et al., 2010; Han et al., 2017).

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Other reported paraneoplastic manifestations include seborrheic keratosis (Stein et al., 2004), clubbing digits, hypertrophic osteoarthropathy, and arthralgia (Kayani et al., 2018), as well as, much more rarely, an elevated serum β -human chorionic gonadotropin level (Yabuki et al., 2016).

Radiologically, SFTs are variable and generally nonspecific, while a prominent blood supply is frequently demonstrated, given their abundant vascularity. Computed tomography is the standard imaging modality for detecting SFT, which usually reveals a well-demarcated mass that is often isodense to the skeletal musculature with prominent avid blood vessels and heterogeneous contrast enhancement (Fig. 1A,B) (Rosado-de-Christenson et al., 2003; Chick et al., 2013; Keraliya et al., 2016). On magnetic resonance

imaging, SFTs consistently exhibit a homogeneous low-to-intermediate signal intensity on T1-weighted imaging and a nonhomogeneous signal intensity on T2-weighted imaging (Fig. 1C,D). Larger or malignant cases may present with a more heterogeneous appearance due to fibrosis, hemorrhage, necrosis, myxoid and cystic degeneration or calcifications. The increased uptake on fluorine-18-fluorodeoxyglucose (^{18}F -FDG) positron emission tomography may be worrisome for malignant SFT, but its imperfect sensitivity limits its diagnostic utility (Tazeler et al., 2016).

Pathologic features

Grossly, SFTs are generally well circumscribed with or without fibrous pseudocapsules and have a soft,

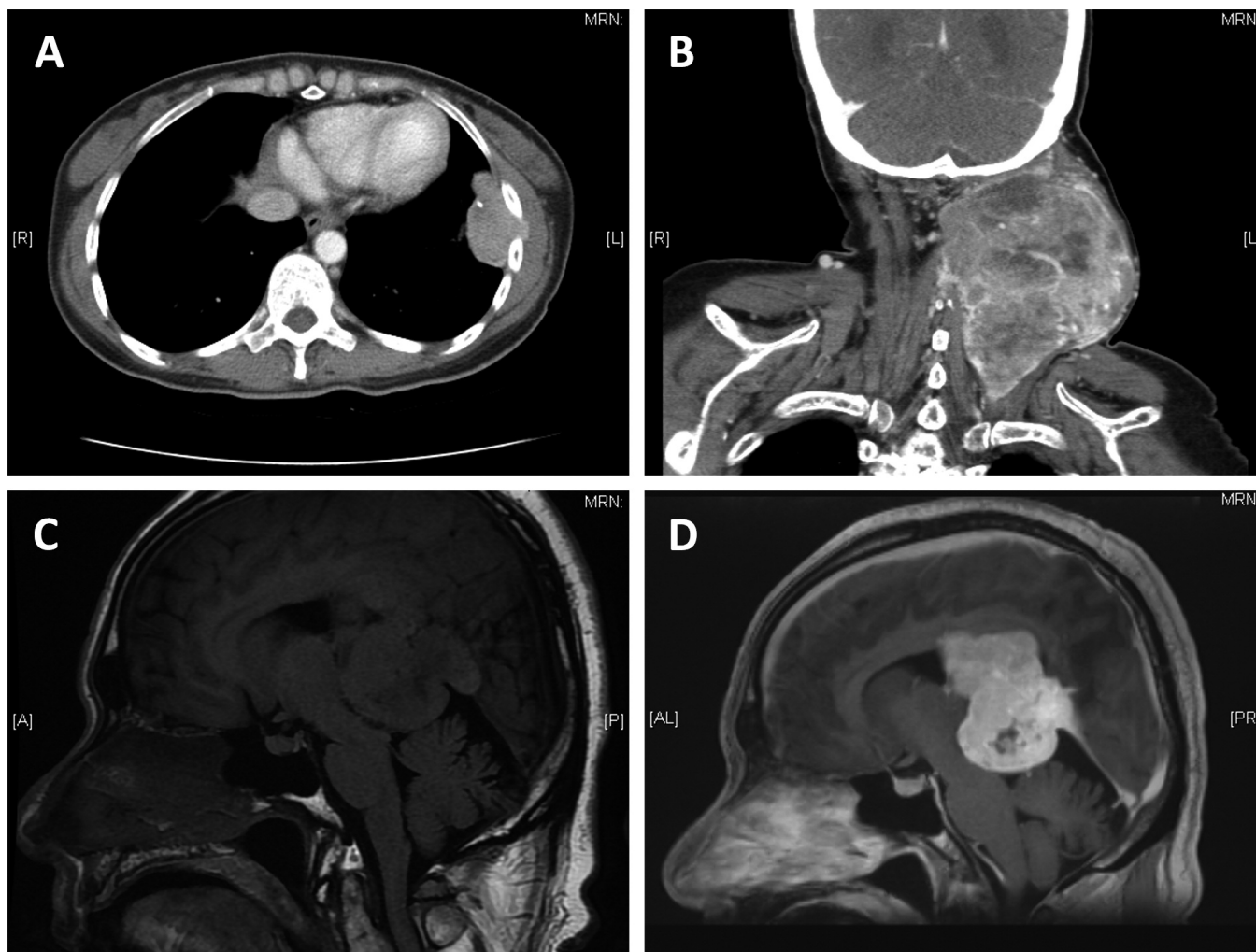


Fig. 1. Imaging characteristics of SFTs. Computed tomography shows a pleura-based, demarcated mass with homogenous low density, focal calcification and mild enhancement (A) and a large and heterogeneous mass with prominent vascularity in the paraspinal region of the neck (B). Magnetic resonance imaging discloses a pineal mass with a relatively homogeneous low-to-intermediate signal intensity on T1-weighted imaging (C), which has been shown to attach to the tentorium and exhibits intense contrast enhancement (D).

rubbery to firm consistency depending on relative proportion of cellularity to the collagenous stroma. The section surfaces are often multinodular, whitish or tan with infrequent secondary myxoid changes, while areas of hemorrhage and necrosis are more common in malignant cases (Fig. 2). The sizes of SFTs range widely from <1 cm to >30 cm and are related to the tumor sites. In our database, the abdominopelvis/retroperitoneum SFTs exhibit the largest median dimensions (median, 11.3 cm), followed by the thoracic cavity (median, 7.9 cm) and somatic soft tissues (median, 4.7 cm). SFTs in the head and neck usually present with a small size (median, 2.5 cm).

Microscopically, SFTs prototypically exhibit a patternless proliferation of ovoid to spindle-shaped tumoral cells with a prominent branching, thin-walled,

HPC-like vasculature (Fig. 3A). The patternless growth denotes a haphazard arrangement of bland tumor cells scattered within collagenous stroma with alternating cellularity (Fig. 3B). The plump spindle to ovoid tumoral cells have scanty pale cytoplasm, indistinct borders, vesicular nuclei and inconspicuous nucleoli. In general, most cases fall within a histological spectrum from paucicellular sclerotic lesions to hypercellular tumors without appreciable intervening stroma. In classical fibrous SFTs, the collagenous matrix can be deposited among tumor cells or in the form of perivascular hyalinization (Fig. 3C). Exaggerated cases even have thick keloid-like fibers and amianthoid bands assuming a sunburst configuration (Fig. 3D). In contrast, cellular SFTs have a scant intervening stroma amid tumoral cells, which instead intimately surround the abundant thin-

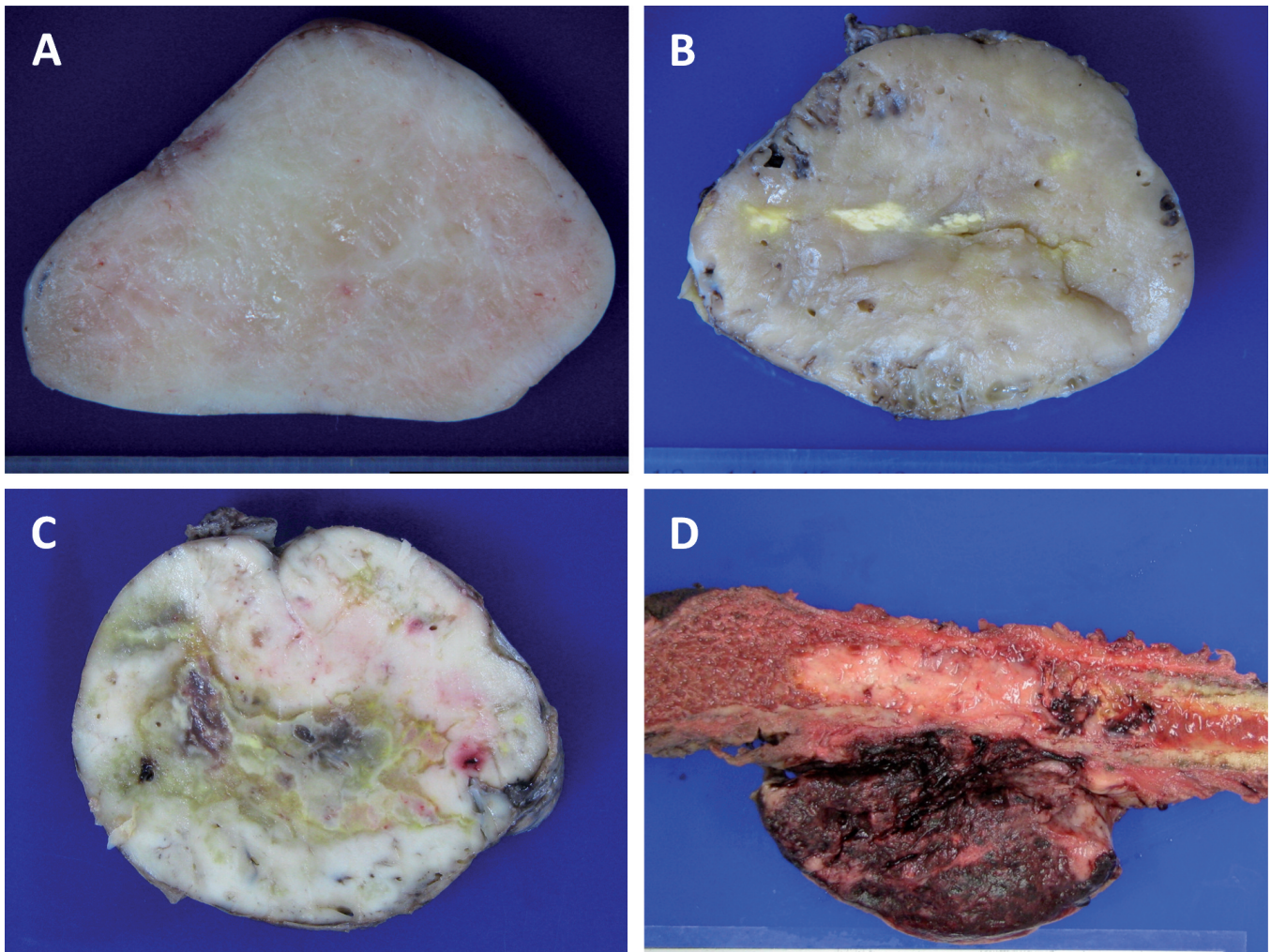


Fig. 2. The gross appearance of SFT: a circumscribed, firm and whitish pleural tumor, histologically exhibiting fibrous SFT (A), an encapsulated, tan-colored mass with microcystic spaces and areas of yellowish discoloration arising from somatic soft tissue, corresponding to cellular SFT (B), and a demarcated, variegated, gray-white mass with central myxoid change, hemorrhage and yellow areas, confirmed to be a fat-forming SFT (C). A recurrent malignant SFT displays a fleshy texture and tan coloration with extensive hemorrhage, focal necrosis and bone invasion (D).

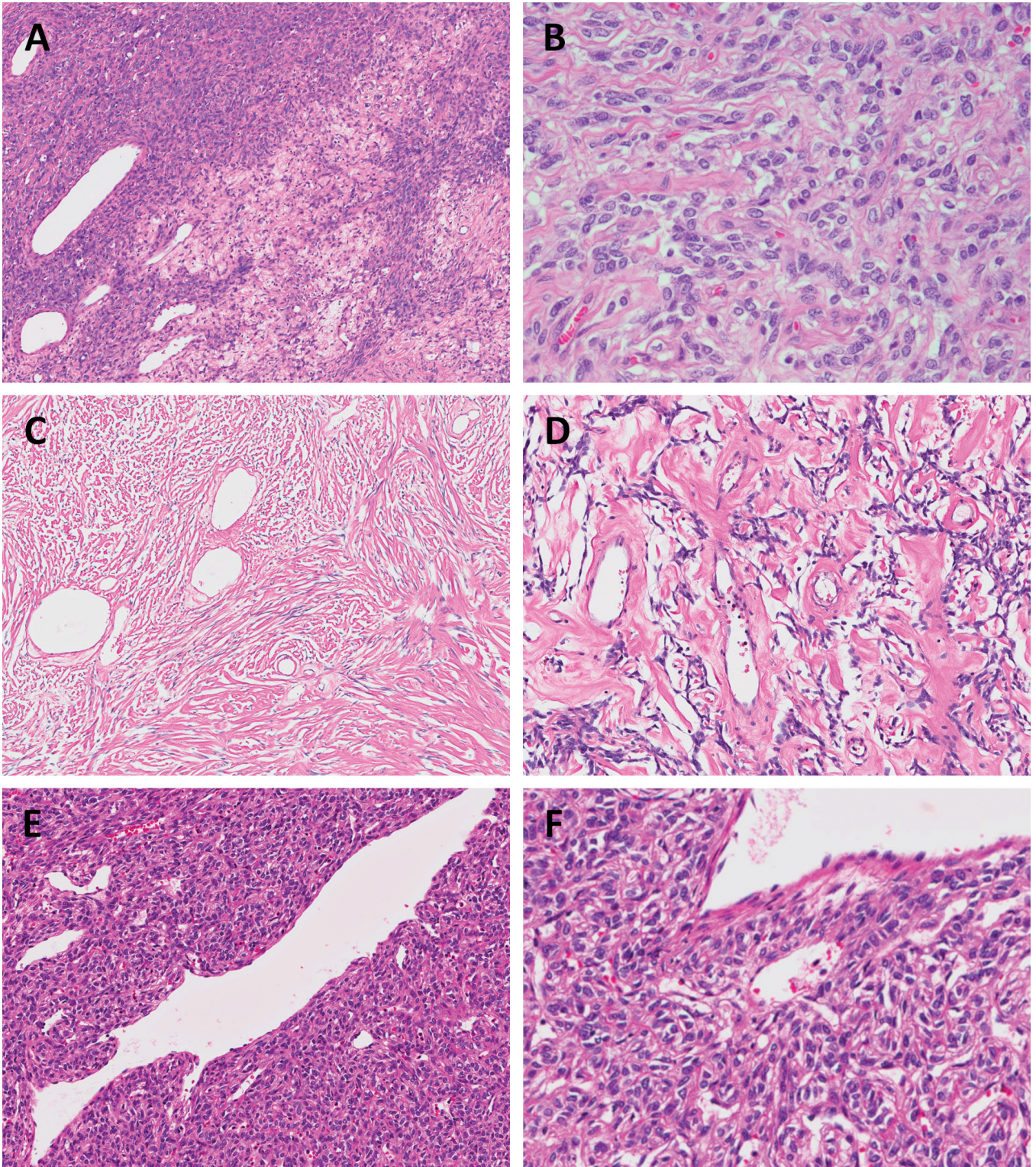


Fig. 3. Typical histologic features of SFTs. Most SFTs show alternating or variable cellularity at low power (**A**) and a patternless arrangement of short spindle to ovoid tumoral cells with indistinct cell borders, vesicular nuclei and inconspicuous nucleoli (**B**). Fibrous SFT is characterized by paucicellular proliferation of slender spindle-shaped tumoral cells in prominently sclerotic stroma (**C**) and may exhibit striking perivascular hyalinization and keloid-like collagen bundles (**D**). Cellular SFT has overtly increased cellularity and comprises ovoid to round tumoral cells growing randomly around delicate small and ectatic, branching larger blood vessels with scant stromal matrix, imparting a hemangiopericytoma-like vasculature (**E**, **F**). Hematoxylin-eosin (H&E). A, C, x 100; D, E, x 200; B, F, x 400.

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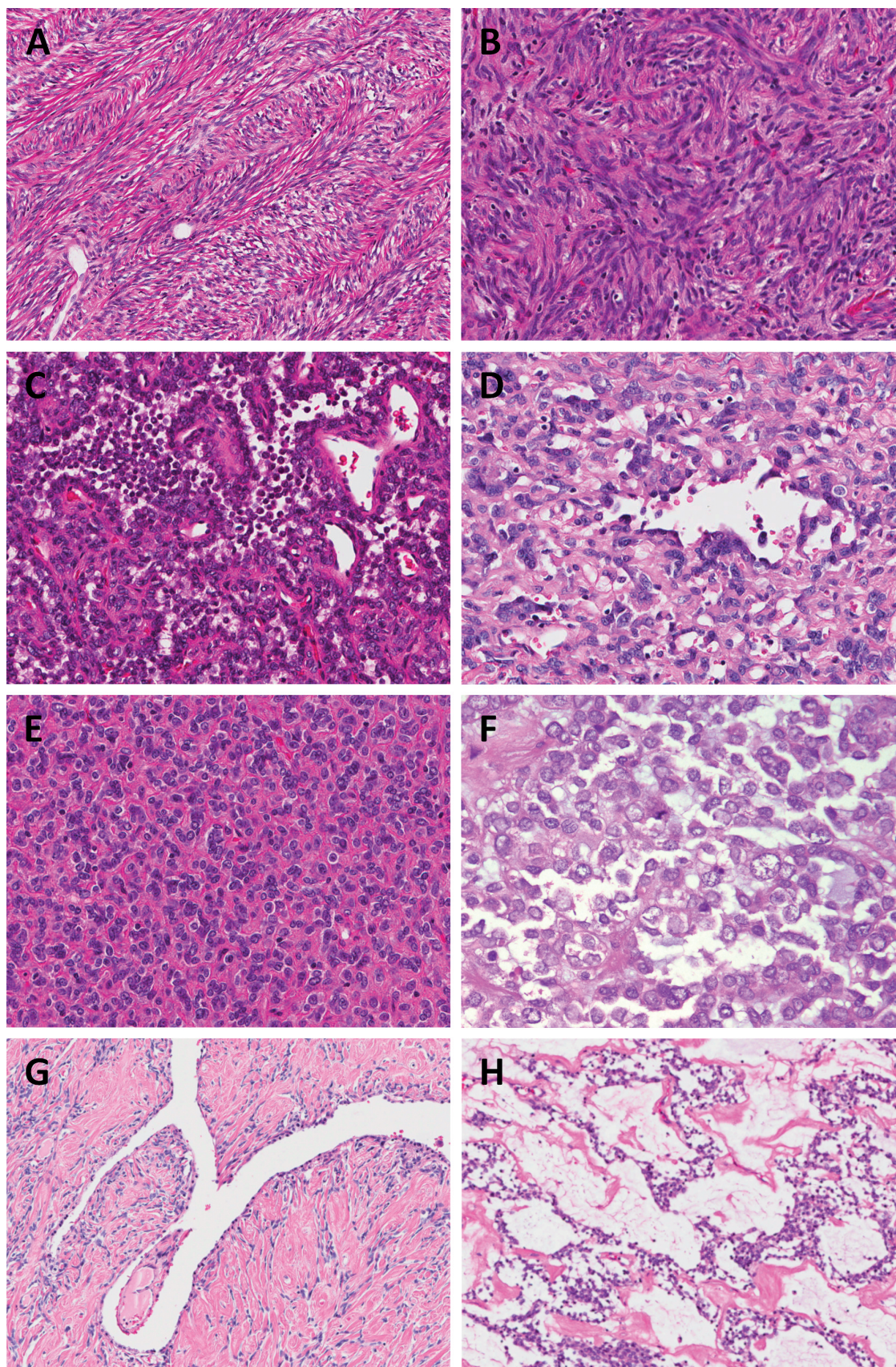


Fig. 4. The wide morphological spectrum of SFTs, including long fascicles (A), a storiform pattern (B), pseudopapillae (C), and pseudovascular spaces formed by multinucleated stromal cells (D), can coexist with classical patternless growth in varying proportions within a given tumor. Some SFTs are composed of a predominance of round (E) or epithelioid (F) cytology, mimicking round cell sarcomas or epithelial neoplasms, respectively. Entrapment of original epithelial structures can be observed and imparts a phyllodes-like appearance in this pulmonary SFT (G). Edematous/myxoid alteration is not uncommon and may result in a microcystic or reticular pattern (H). H&E. A-C, E, x 200; D, F, x 400; G, H, x 100.

walled capillaries that merge imperceptibly into staghorn vessels of larger caliber, exhibiting a morphological equivalence to HPC (Fig. 3E,F). Occasionally, a long fascicular or storiform growth pattern, albeit commonly present in focal areas, may predominate in a subset of SFTs (Fig. 4A,B), and the formation of pseudopapillae due to the dropout of surrounding tumor cells is unusual (Fig. 4C). Previously coined as GCA, orbital SFTs frequently present with multinucleated giant cells growing around pseudovascular spaces (Fig. 4D), while this feature may appear focally or diffusely in SFTs arising elsewhere. A round cell cytomorphology can be observed regionally or extensively in some cases (Fig. 4E), potentially mimicking round cell neoplasms, especially in limited specimens. In addition, SFTs may display epithelioid cytomorphology (Fig. 4F) (Marchevsky et al., 2003; Martorell et al., 2007). Moreover, entrapment of non-neoplastic epithelial cells in SFTs may be appreciated particularly in those arising in visceral organs, such as lung, salivary gland, thyroid gland, prostate, etc, yielding a fibroadenomatous or phyllodes-like appearance (Fig. 4G) (Westra et al., 2000; Tanahashi et al., 2006; Tapia et al., 2011; Rao et al., 2013). Focal edematous or myxoid change is not uncommon and could result in a reticular pattern and/or microscopic or gross cystic spaces (Fig. 4H).

In addition, another three histological variants of SFT merit particular emphasis. Fat-forming SFTs were originally reported under the rubric of “lipomatous HPC” by Nielsen et al. (1995), while it is currently defined as a morphological variant of SFT with the best documentation of divergent differentiation by the latest WHO classification (Fletcher et al., 2013). Although adipocytic cells may vary in the amount and degree of maturation, most fat-forming SFTs exhibit mature adipocytes amid bland-appearing spindle cells (Fig. 5A), without notable differences in the occurrence of location, age range, and gender, and follow a favorable clinical course (Nielsen et al., 1995; Folpe et al., 1999; Guillou et al., 2000). However, fat-forming SFTs can behave aggressively, either showing malignant features in the non-adipocytic fibrotic component, such as increased mitotic figures or high-grade nuclear atypia, or rarely presenting multivacuolated lipoblasts (Guillou et al., 2000; Lee and Fletcher, 2011). In this scenario, particularly when dealing with abdominopelvic/retroperitoneal lesions, *MDM2* fluorescence in situ hybridization (FISH) or *CDK4*/*MDM2* immunohistochemistry are warranted to exclude an atypical lipomatous tumor or a dedifferentiated liposarcoma (Ceballos et al., 1999; Lee and Fletcher, 2011). In this regard, SFT-like histology has been well described in dedifferentiated liposarcoma (Huang et al., 2005), and 15% of well differentiated/dedifferentiated liposarcomas share nuclear *STAT6* expression with SFTs through a different coamplification mechanism owing to the physical proximity of *STAT6* and *CDK4* on 12q13 (Doyle et al., 2014b).

Focal myxoid and edematous stromal change are not

uncommon in classical SFTs, while such a myxoid component should account for at least 50% of the surface areas examined to be deemed a myxoid SFT variant, with only 14 cases being reported to date (de Saint Aubain Somerhausen et al., 1999; Lau et al., 2009; Dantey and Cooper, 2013; Han et al., 2013; Lee et al., 2015). Myxoid SFTs pose a tremendous challenge in differential diagnosis, which encompasses a variety of myxoid oval-to-spindle cell mimics with abundant thin-walled blood vessels (Fig. 5B), such as monophasic myxoid synovial sarcoma or sarcomas with *BCOR* gene abnormalities (Kao et al., 2016). Adequate sampling and meticulous searches for telltale classical components with patternless growth of nondescript spindle cells represent the key to arrive at a correct diagnosis in conjunction with *STAT6* immunohistochemistry. Again, most myxoid SFTs pursue a benign or indolent course.

As a very minor subset of SFTs (0.8%), the dedifferentiated variant may de novo exhibit an abrupt transition from the typical fibrous, cellular or, more rarely, fat-forming area into an anaplastic component, or secondarily develop during recurrence of the originally classical SFTs (Mosquera and Fletcher, 2009; Collini et al., 2012). The dedifferentiated component is characterized by solid sheets of poorly differentiated round cells or bundles or storiform structures of high-grade, mitotically active spindle to pleomorphic cells (Mosquera and Fletcher, 2009). Only a handful of SFTs displaying heterologous rhabdomyosarcomatous and osteosarcomatous dedifferentiation have been reported (Collini et al., 2012; Thway et al., 2013) without molecular confirmation or demonstration of nuclear *STAT6* expression. Herein, we provide a bona fide retroperitoneal dedifferentiated SFT presenting with an overwhelming rhabdomyosarcomatous component (Fig. 5C) and molecular confirmation of the *NAB2ex3-STAT6ex18* fusion (Fig. 5D). In a very recent series, two SFTs were reported to dedifferentiate into a peculiar neuroendocrine and squamous cell carcinomatous histology in a synchronous or metachronous manner, respectively, with molecular confirmation by targeted RNA-sequencing (Lu et al., 2018). Compared with the classical SFT component, *CD34* and *STAT6* expression oftentimes decreases in the dedifferentiated component, adding another layer of complexity in the diagnosis. Instead, the dedifferentiated component may overexpress *p53* and *p16* (Mosquera and Fletcher, 2009; Subramaniam et al., 2011; Akaike et al., 2015; Dagrada et al., 2015). Clinically, dedifferentiated SFTs more frequently affect elderly patients (median, 60 years) and behave more aggressively, with higher rates of recurrence, metastasis and mortality (Mosquera and Fletcher, 2009; Collini et al., 2012).

Risk assessment

Although the majority of SFTs behave in a benign fashion, approximately 10-40% of cases may follow an aggressive course or even develop relapsed disease as

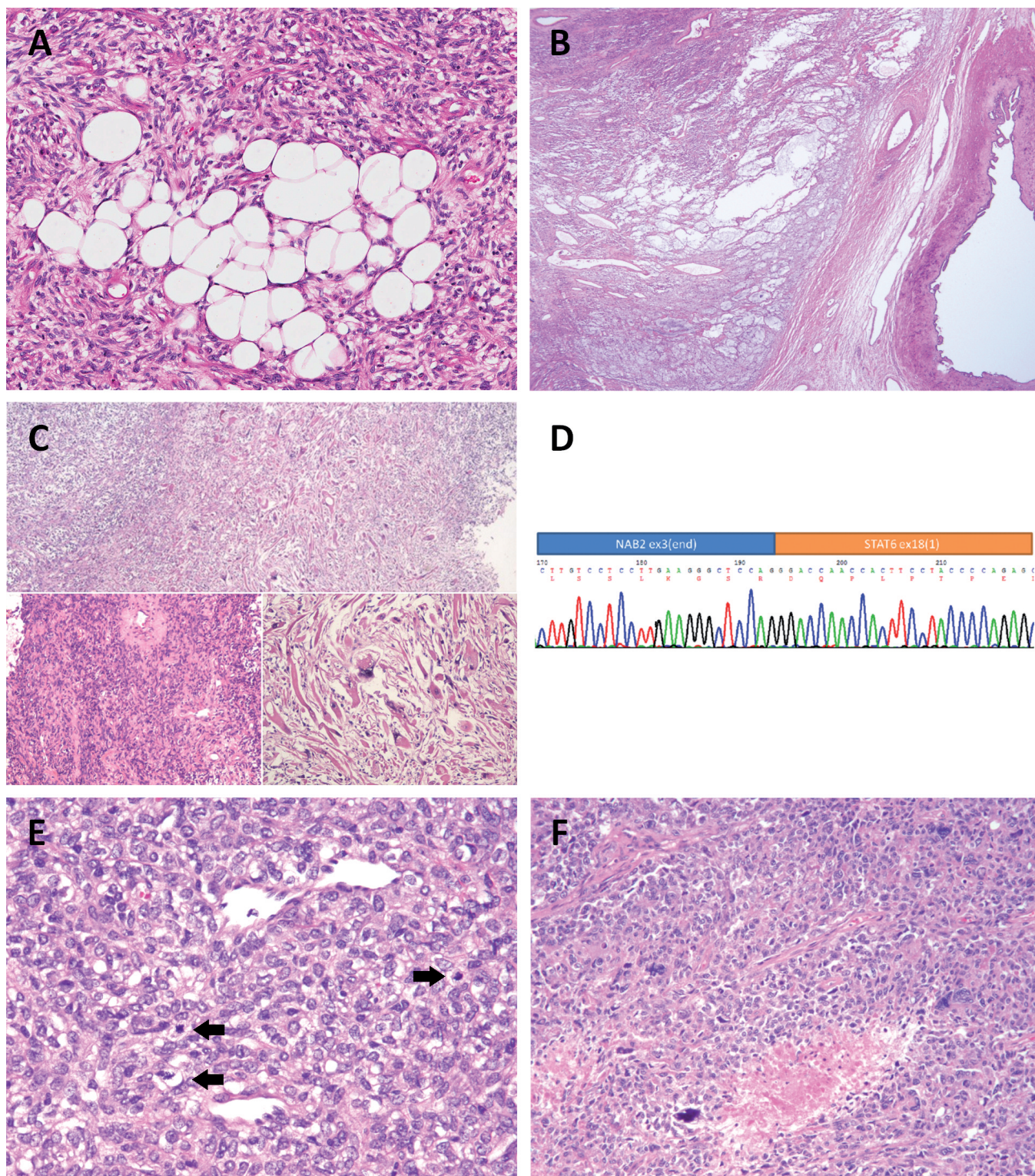


Fig. 5. Histologic variants of SFT and malignant SFTs. An SFT with fat cells, usually mature, is designated as a fat-forming SFT (A). Myxoid SFT shows a prominent myxoid change with a reticular arrangement of spindle cells (B). A heterologous dedifferentiated SFT (C) shows a conventional SFT area (left lower) that transitions into predominant anaplastic spindle tumoral cells containing heterologous rhabdomyosarcomatous cells (right lower) with increased expression of myogenin and reduced staining intensity of nuclear STAT6 (not shown), which harbors the NAB2ex3-STAT6ex18 fusion (D). A malignant SFT features brisk mitotic activity (arrows) (E) with or without nuclear pleomorphism and necrosis (F). H&E. A, C- right lower, F, x 200; B, C-upper, x 40; C- left lower, x 100; E, x 400.

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late as >10 years after the primary resection, requiring long-term surveillance for all patients. Owing to the unsatisfactory prognostic predictability, numerous investigators have endeavored to tackle this problem by extensively examining a variety of clinical and histological factors (Enzinger and Smith, 1976; England et al., 1989; Vallat-Decouvelaere et al., 1998; Gold et al., 2002; Gholami et al., 2017) or their combination into various proposed risk models (Demicco et al., 2012, 2017; Pasquali et al., 2016; Salas et al., 2017) (Table 1). Nevertheless, variations in the cohort and follow-up durations, which are oftentimes inadequate regarding the relatively indolent behavior of SFTs, have been considered responsible for the inconsistency in the prognostic weightiness of some parameters among different studies.

Overall, high mitotic counts with a general consensus cutoff set at >4/10 HPFs represent the strongest single prognosticator (Fig. 5E). In contrast, necrosis, nuclear pleomorphism, or hypercellularity is not uniformly accepted as a reliable prognosticator (Fig.

5F). The reported incidence of histologically malignant SFT ranges from 10% to 36% (England et al., 1989; Kayani et al., 2018). Notably, the merit of high mitotic counts is repeatedly reflected by its reproducible independent associations with shorter progression-free survival and/or tumor-associated mortality, as well as its constant inclusion in various risk models. However, it must be noted that SFTs falling short of this mitotic threshold are by no means unlikely to suffer disease relapse.

Tumor location is another essential prognostic factor. For example, meningeal SFT is known to more frequently develop local recurrence, distant metastasis and disease-specific death (Ambrosini-Spaltro and Eusebi, 2010; Tai et al., 2015; Kim et al., 2017), partly attributable to the lower amenability to complete resection in this anatomical location. Regarding the extracranial head and neck region, SFTs have a considerably high local recurrence rate (up to 40%) with common infiltrative growth (49%) and osseous invasion (82%), while only infrequent cases metastasize or cause

Table 1. Recent studies regarding the survivals and prognostic factors in extracranial solitary fibrous tumors.

Studies	Demicco et al., 2012 & 2017			Salas et al., 2017			Gholami et al., 2017		
Case number	101			162			219		
follow-up (median, month)	48			33			73		
Overall	10%			12%			5%		
LR	LR rate			19% (10-year)			4% (5-year)		
	Not available			39% (20-year)			7% (10-year)		
Overall	26%			17%			14%		
MR	MR rate			31% (10-year)			13% (5-year)		
	26% (5-year)			50% (20 years)			16% (10-year)		
	45% (10-year)			77% (10-year)			91% (5-year)		
OS rate	89% (5-year)			52% (20 year)			89% (10-year)		
	73% (10-year)								
Risk factor	Score	MR/OS	Score	LR	MR	OS	LR	MR	OS
Age (years)	0	<55	0	≥60	<60	<60			
	1	≥55	1	<60	≥60	≥60			
Location			0	Others	Others		Significant*		Significant*
			1	Viscera	Limb				
Size (cm)	0	<5						Significant (≥8)	
	1	5 to <10							
	2	10 to <15							
	3	≥15							
Mitoses (/10 HPFs)	0	0	0		≤4	≤4			
	1	1-3	1		>4	>4			
	2	≥4							
Necrosis	0	<10%							
	1	≥10%							
Radiation therapy			0	Yes					
			1	No					
Margin									Significant#
Risk stratification	Score	MR/OS	Score	LR	MR	OS	LR	MR	OS
	0-3	Low	0	Very low	Very low	Low			
	4-5	Intermediate	1	Low	Low	Intermediate			
	6-7	High	2	Intermediate	Intermediate	High			
			3	High	High			Not done	

LR, local recurrence; MR, metastatic recurrence; OS, overall survival; HPF, high power field. *thoracic and abdominal cavity and retroperitoneum: unfavorable. #R2 resection: unfavorable.

death from disease, highlighting its intermediate malignant potential (Smith et al., 2017). In addition, abdominopelvic/retroperitoneal and visceral locations have been well documented to associate with disease recurrence (Gholami et al., 2017; Salas et al., 2017). Despite different cutoffs applied in various studies, age (age >55 or 60 years) and tumor size (>8, 10 or 15 cm) are crucial clinical parameters that are significantly correlated with prognosis (Demicco et al., 2012; Gholami et al., 2017; Kim et al., 2017; Salas et al., 2017). Although the prognostic impact of microscopic margin status remains controversial, R2 resection, representing grossly residual disease after resection, is usually an unfavorable factor (Gold et al., 2002; Gholami et al., 2017).

As there is no single optimal clinicopathological factor to robustly predict the outcome of SFTs, Demicco et al. initially proposed a 3-tier risk model in which age (<55 or ≥55 years), tumor size (<5, 5 to <10, 10 to <15, ≥15 cm) and mitotic figures (0, 1-3, ≥4 per 10 HPFs) were accordingly assigned different scores and summed up to define risk levels, namely, low-risk (0-2), moderate-risk (3-4), and high-risk (5-6) (Demicco et al., 2012). Very recently, tumor necrosis (≥10%) was subsequently enrolled as the 4th variable in the updated 3-tier risk model to reinforce its discriminative capability among the risk groups (Table 1) (Demicco et al., 2017). Almost simultaneously, the French Sarcoma Group also proposed a prognostic model with internal and external validation for SFTs stratified according to the score of their unfavorable factors from 0 to 3 to predict local recurrence incidence (LRI), metastatic recurrence incidence (MRI) and overall survival (OS) (Salas et al., 2017). They not only noted a delayed relapse with apparently increased LRI and MRI between 10 and 20 years but also recognized the localization of the viscera, radiotherapy

and age for LRI, mitotic count (>4/10 HPFs), tumor localization other than limb and age (≥60 years) for MRI, and age and mitotic count for OS (Table 1).

Immunohistochemistry

In the pre-STAT6 era, the diagnosis of SFT has mostly relied on the constellation of CD34, bcl-2, and CD99 (Fig. 6A) (van de Rijn et al., 1994; Westra et al., 1994; Chan, 1997), and this nonspecific panel can aid in the diagnosis of approximately 85-90% of SFTs in a proper histomorphological context. As a transmembranous glycoprotein, CD34 was initially discovered to be expressed by hematopoietic stem cells and vascular endothelial cells (Natkunam et al., 2000; Miettinen, 2014). Later, it became explicit that CD34 was expressed in a broad variety of mesenchymal tissues and is widely accepted as a biomarker indicative of a specialized fibroblastic phenotype in the dermis and perineurial cells. In diagnostic practice, spindle cell neoplasms may enter the differential diagnosis of SFTs because of their common CD34 expression and overlapping histomorphological features, such as cellular angiofibroma, deep fibrous histiocytoma, dermatofibrosarcoma protuberans, mammary-type myofibroblastoma, gastrointestinal stromal tumor, perineurioma, and spindle cell lipoma, among others. However, the tumor cells of cellular SFTs often do not show CD34 positivity diffusely, as observed in the classical counterpart, and this variation is especially noted in meningeal cases (Yalcin and Tihan, 2016).

To variable degrees, SFTs may express immunohistochemical markers used in distinguishing other histological mimickers. For instance, CD10 has been reported to be present in up to 65% of HPCs to varying extents, and an unawareness of this pitfall may

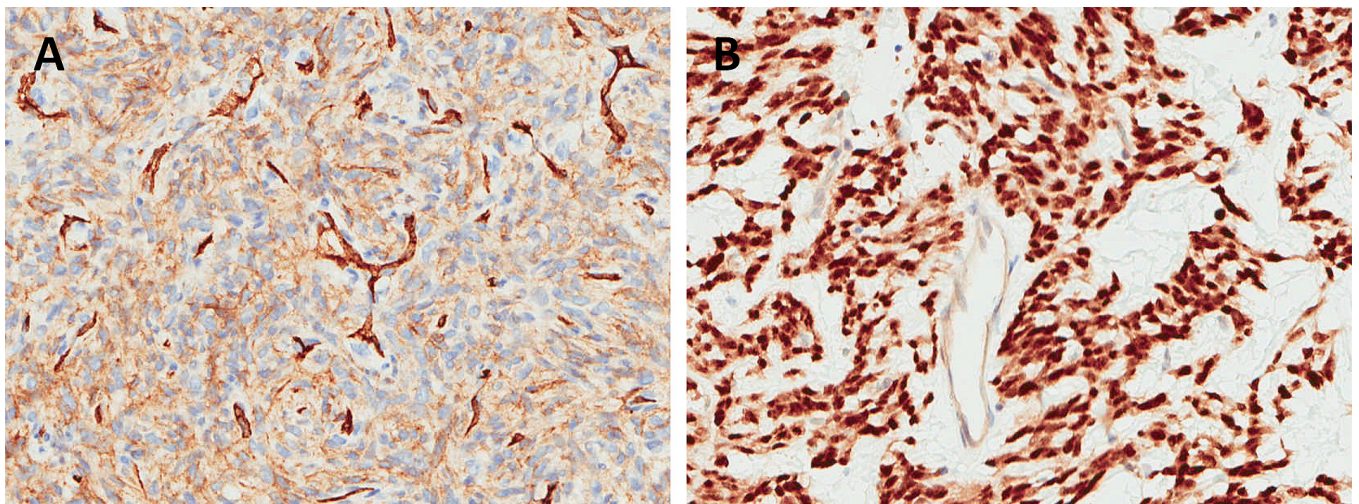


Fig. 6. Immunohistochemical staining of SFT. The tumoral cells usually express CD34, despite being weaker and patchy in comparison with endothelial cells in this case (A). Diffuse and strong nuclear STAT6 positivity is a diagnostic feature for SFT (B). Note the endothelial cells are negative. Diaminobenzidine (DAB). x 400.

potentially lead to the misdiagnosis of cellular SFTs as low-grade endometrial stromal sarcomas (Bhargava et al., 2005). Initially, considered a marker for synovial sarcoma, TLE1 was observed in less than one-third of SFTs with exceptionally strong and diffuse expression, as observed in genuine synovial sarcomas (Kosemehmetoglu et al., 2009; Foo et al., 2011). In contrast to malignant peripheral nerve sheath tumors, SFTs always retain H3K27me3 immunoreactivity (Schaefer et al., 2016; Asano et al., 2017). Although desmin is mostly negative in SFTs, one should otherwise consider the very rare heterologous rhabdomyosarcomatous dedifferentiation of SFTs (Cretyens et al., 2018). When dealing with abdominopelvic/retroperitoneal masses, pathologists should be cognizant of the occasional nuclear reactivity of PAX8 and PAX2 in 27% (11 of 41) and 12% (5 of 41) of SFT cases, respectively, with diffuse expression detected in nearly one half of cases (McDaniel et al., 2016), which may result in confusion with renal spindle cell tumors.

Adding to the diagnostic fidelity of SFTs, STAT6 immunohistochemistry, beyond question, takes precedence over other markers. Regardless of histological variants, the superb sensitivity and specificity of STAT6 nuclear expression, which is usually diffuse and intense (Fig. 6B), has been confirmed in >90% to 100% of SFTs (Schweizer et al., 2013; Doyle et al., 2014a; Koelsche, et al., 2014b; Yoshida et al., 2014; Demicco et al., 2015), except for dedifferentiated SFTs, which frequently exhibit an absence or reduced expression of STAT6 (Schneider et al., 2017). Notably, nuclear STAT6 immunostaining is occasionally observed in dedifferentiated liposarcoma (9%, 12/134), deep fibrous histiocytoma (10%, 1/10), nodular fasciitis (2%, 1/63), low-grade fibromyxoid sarcoma (9%, 2/23), myxoid/round cell liposarcoma (2%, 1/46), ovarian fibroma (1/2, 50%) and undifferentiated pleomorphic sarcoma (2%, 2/130) (Doyle et al., 2014b; Demicco et al., 2015). In contrast, other CD34-positive or negative spindle cell tumors entering the diagnosis of SFT are negative for nuclear STAT6, including cellular angiofibroma, dermatofibrosarcoma protuberans, desmoid tumor, gastrointestinal stromal tumor, malignant peripheral nerve sheath tumor, meningioma, perineurioma, spindle cell lipoma, and others. In routine practice, 2-3% of SFTs may present with typical histology and CD34 reactivity but a lack of STAT6 expression. In this setting, several novel markers have recently been reported to be useful, including GRIA2 and ALDH1. *GRIA2* encodes the glutamate ionotropic receptor AMPA type subunit 2 (Mohajeri et al., 2013), and its expression sensitivity reaches 80% (84 of 105) of SFTs, including malignant and dedifferentiated cases (Vivero et al., 2014). However, it should be underlined that *GRIA2* is frequently expressed in dermatofibrosarcoma protuberans (75%, 15/20). Another expression profiling-derived diagnostic marker is ALDH1 (aldehyde dehydrogenase 1), a stem cell trait marker that is

differentially upregulated in SFT compared with other soft tissue tumors types (Bouvier et al., 2013). By immunohistochemistry, ALDH1 was frequently expressed in 85% of SFT but occasionally observed in synovial sarcomas (7%) and meningiomas (16%) (Bouvier et al., 2013; Macagno et al., 2016). In a large study of 454 soft tissue tumors, coexpression of nuclear STAT6 and cytoplasmic ALDH1 was found to be the most sensitive and specific marker panel in the differential diagnosis of SFTs (Ouladan et al., 2015).

Differential diagnosis

The differential diagnoses of SFT encompass a broad array of benign to malignant histological mimics with oval to spindle cells and staghorn vessels of various calibers. As such, the diagnosis of SFT is better approached in the context of the anatomical locations of tumors as well as the dominant histological pattern (Table 2). When the possibility of SFT is kept in mind, the application of STAT6 immunohistochemistry should largely resolve most diagnostic challenges.

For intracranial SFTs, meningiomas, beyond dispute,

Table 2. The differential diagnoses of solitary fibrous tumor.

Predominant fibrous pattern
Mammary-type myofibroblastoma
Angiofibroma of soft tissue
Pleomorphic hyalinizing angiectatic tumor
Desmoid fibromatosis
Perineurioma
Predominant cellular pattern (hemangiopericytoma-like)
Deep fibrous histiocytoma
Cellular angiofibroma
Cellular schwannoma
Monophasic synovial sarcoma
Infantile fibrosarcoma
Phosphaturic mesenchymal tumor
Sinonasal hemangiopericytoma
Glomus tumor and myopericytoma
Giant cell-rich pattern (giant cell angiofibroma)
Giant cell fibroblastoma
Predominant myxoid pattern (myxoid SFT)
Low-grade fibromyxoid sarcoma
Cellular myxoma
Myxoid nerve sheath tumor
Myxoid dermatofibrosarcoma protuberans
Myxofibrosarcoma
Fat-forming SFT
Spindle cell lipoma
Atypical spindle cell lipomatous tumor
Mammary-type myofibroblastoma
Dedifferentiated liposarcoma
Malignant/dedifferentiated SFT
Malignant peripheral nerve sheath tumor
Leiomyosarcoma
Undifferentiated pleomorphic sarcoma
Spindle cell/desmoplastic mesothelioma
Spindle cell melanoma
Sarcomatoid carcinoma

represent the most important differential diagnosis. The tumor cells of meningiomas may range from ovoid to spindle, which, unlike SFTs, tend to grow in a syncytial pattern with focal cellular whirling or fibrous fascicular architectures and typical nuclear pseudoinclusions or psammomatous calcifications. Angiomatous and fat metaplastic meningiomas are rare variants that may impart the appearance of classical or fat-forming SFTs. A limited but apropos immunohistochemical panel, including EMA and S100 for meningioma and CD34 and STAT6 for SFTs, may aid in the differential diagnosis. In the nasal cavity and paranasal sinuses, SFT should be distinguished from the sinonasal glomangiopericytoma, a borderline/low-grade mesenchymal neoplasm exclusively occurring in this region. Sinonasal glomangiopericytoma is composed of ovoid to plump spindle cells with distinct cell borders, which proliferate around a delicate staghorn vascular network in the form of uniformly cellular solid sheets or fascicles without obvious collagen deposition and alternating cellularity typically observed in SFTs. Immunohistochemically, sinonasal glomangiopericytomas show diffuse strong reactivity to smooth muscle actin and variable h-caldesmon expression, but they do not exhibit desmin and hence are considered a tumor of pericytic derivation. The absence of CD34 and STAT6 immunoreactivity may help differentiate from SFTs. The recent discovery of heterozygous activating mutations of *CTNNB1* in >90% of sinonasal glomangiopericytomas, leading to nuclear expression of β -catenin, certainly adds another layer of confidence in the diagnosis of this tumor (Lasota et al., 2015), although mutation-driven nuclear entry of β -catenin has also been reported in juvenile nasopharyngeal angiofibroma. Among tumors commonly originating from thoracic or abdominopelvic cavities, it is relevant to bear in mind desmoplastic mesothelioma, monophasic synovial sarcoma, and dedifferentiated liposarcoma in the differential diagnosis of SFTs for the sake of their prominent collagen matrix, frequent staghorn vessels, or occasional but notable expression of nuclear STAT6, resulting in histological and immunophenotypic overlap. The mimicry of the latter two tumor types in the diagnosis of SFTs has been mentioned in previous or following sections. Despite being utilized as a mesothelial marker, calretinin expression has been reported in 13% of SFTs (Barak et al., 2012), a pitfall leading to the misdiagnosis of SFTs as desmoplastic mesothelioma with decreased or absent expression of cytokeratin. As such, a broad panel of mesothelial markers, such as D2-40, WT-1 and GLUT1 plus CD34 and STAT6, may enable the clear distinction of SFTs from desmoplastic mesothelioma. It is exceedingly rare for SFTs to arise from the external genitalia, where a peculiar group of CD34-positive mesenchymal neoplasms may occur, including mammary-type myofibroblastoma and cellular angiofibroma, which have an intimate genetic kinship of sharing the inactivated *RB* gene caused by mono-allelic or biallelic deletion (Tardio et al., 2017). Among these,

mammary-type myofibroblastoma features distinct fascicles of myofibroblastic spindle cells with a pale eosinophilic cytoplasm in the more collagenous fibrous stroma, while cellular angiofibroma is characterized by small to medium-sized vessels with variably hyalinized walls surrounded by sheets or vague bundles of proliferative oval to spindle cells. The majority of mammary-type myofibroblastoma exhibit desmin, while this seems infrequent in cellular angiofibroma. Both mammary-type myofibroblastoma and cellular angiofibroma may contain variable amounts of fat cells, imparting a morphological similarity to fat-poor spindle cell/pleomorphic lipoma, another member of the CD34-positive, *RB*-deficient family of tumors that lack nuclear STAT6 expression.

From the perspective of morphological resemblance, it is of diagnostic relevance to reiterate several mesenchymal tumors with a prominent staghorn vasculature but defining molecular pathogenesis, namely, monophasic synovial sarcoma, mesenchymal chondrosarcoma, phosphaturic mesenchymal tumor and infantile fibrosarcoma. Monophasic synovial sarcoma usually presents with long herringbone-like fascicles with overlapped tumoral nuclei, while alternating cellularity with increased myxoid to hyalinized stroma reminiscent of SFT is not infrequent. In most cases, diffuse strong expression of TLE1, CD34 negativity, and a lack of nuclear STAT6 reactivity argue against the diagnosis of SFT, while demonstration of the gene rearrangement of *SS18* or *SS18L1* by FISH or detection of their fusions with *SSX1*, *SSX2* or *SSX4* by RT-PCR may allow the definite diagnosis of synovial sarcoma. Mesenchymal chondrosarcoma is a biphasic tumor characterized by undifferentiated small round cells interspersed with HPC-like vessels and variable islands, nodules to sheets of well-differentiated neoplastic hyaline cartilage, which not only occur in the skeleton but also in various extraosseous sites, including meninges. In the setting of limited biopsy material devoid of the chondroid component, the distinction of mesenchymal chondrosarcoma from cellular SFT, especially for cranial cases, is not straightforward by histological evaluation. Fortunately, mesenchymal chondrosarcoma is nuclear STAT6-negative, and the detection of its hallmark *HEY1-NCOA2* fusion is only required for differentiation from other STAT6-negative small round cell malignancies with staghorn vessels. Phosphaturic mesenchymal tumor (PMT) is a very rare intraosseous or soft tissue tumor of intermediate malignancy, and it is usually associated with tumor-induced phosphaturia and osteomalacia induced by overexpressed fibroblast growth factor-23 protein. Despite embracing a plethora of morphologic appearances, the most common mixed connective tissue variant of PMT is characterized by bland spindled or ovoid cells with a thin-walled staghorn vasculature within a palely basophilic matrix with characteristic grungy calcification and varying amounts of osteoclast-like giant cells and metaplastic adipocytes.

Pathognomonic *FN1-FGFR1* or *FN1-FGF1* fusions are present in 42% and 6% of PMTs (Lee et al., 2016). However, molecular testing is seldom required to differentiate PMT from SFT, as the former is consistently negative for CD34 and nuclear STAT6 (Agaimy et al., 2017). Presenting in the first year of life in almost all cases, infantile fibrosarcoma is chiefly composed of hypercellular elongated spindle cells arranged in a herringbone fashion without specific diagnostic immunohistochemistry except for the

recurrent *ETV6-NTRK3* fusion in ~70% of cases and the recently unraveled minor *EML4-NTRK3* variant (Church et al., 2018). A subset may predominantly exhibit high-grade round cells around staghorn vessels and bear a histological resemblance to cellular SFT. However, SFT is essentially a tumor of adults, and clinicopathological correlation and STAT6 immunohistochemistry may aid in excluding SFTs from key differential considerations of pediatric spindle cell neoplasms (Tan et al., 2018).

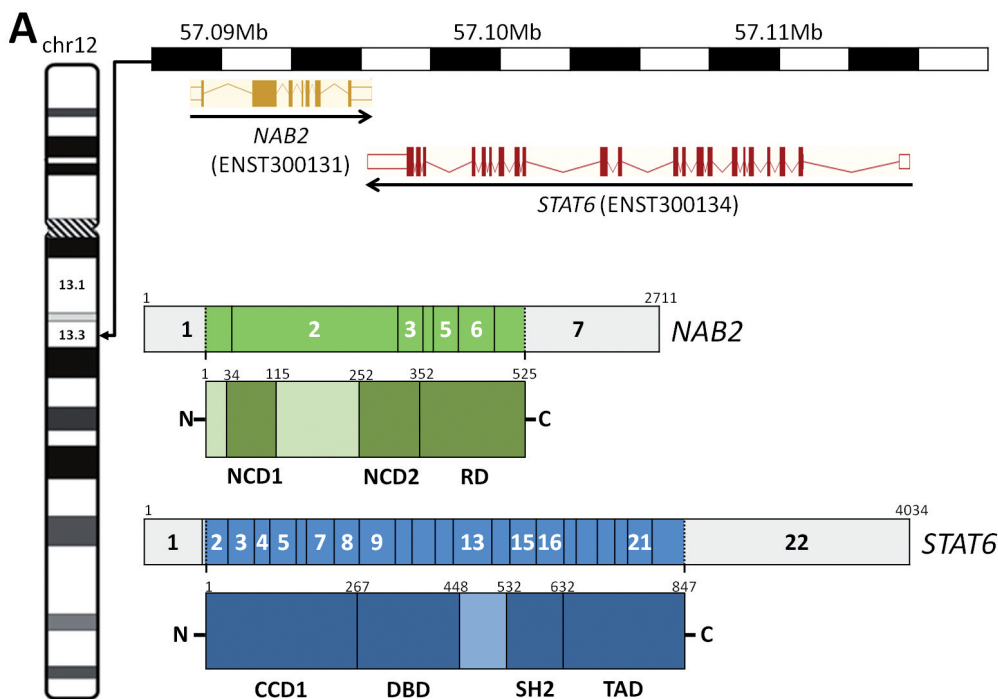
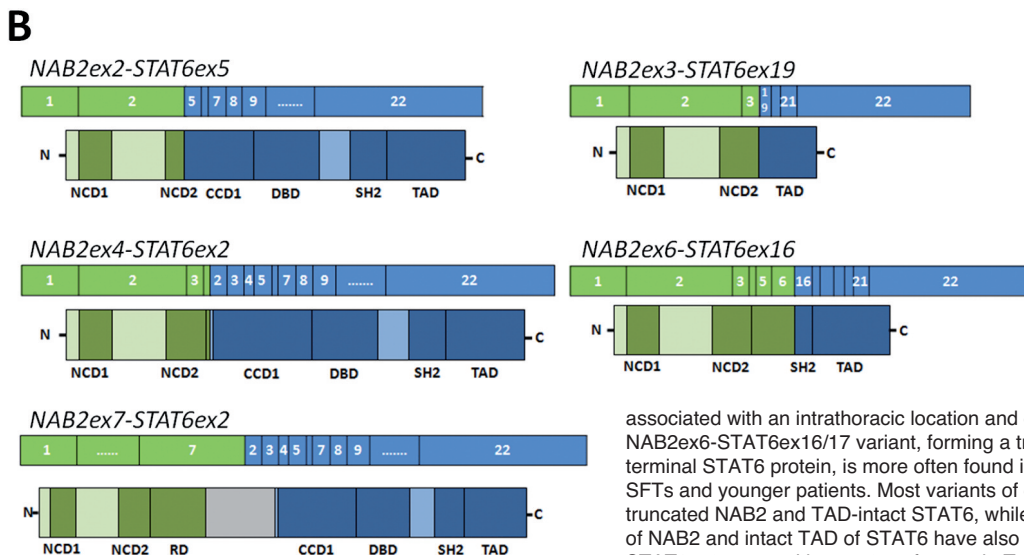


Fig. 7. A. The pathognomonic NAB2-STAT6 fusion of SFT derives from an intrachromosomal inversion at chromosome 12q13.3, bringing NAB2 and STAT6 in opposite transcriptional directions into a chimeric fused gene. The exon compositions and protein structures of NAB2 and STAT6 are depicted in the figures. (NCD: NAB conserved domain, RD: repressor domain, CCD: coiled-coil domain, DBD: DNA-binding domain, SH2: Src homology 2, TAD: transcriptional activation domain). **B.** Schematic illustration of chimeric transcripts and fusion proteins of NAB2-STAT6. The common NAB2ex4-STAT6ex2 fusion variant, creating a truncated NAB2 and nearly full-length STAT6 chimeric protein, is



associated with an intrathoracic location and older age. The other common NAB2ex6-STAT6ex16/17 variant, forming a truncated NAB2 and short C-terminal STAT6 protein, is more often found in extrathoracic and meningeal SFTs and younger patients. Most variants of chimeric proteins contain RD-truncated NAB2 and TAD-intact STAT6, while rare variants with full-length RD of NAB2 and intact TAD of STAT6 have also been identified, such as NAB2ex7-STAT6ex2 reported in 3%~8% of cases in Table 3.

Genetic alterations

Karyotyping and copy number variations

Cytogenetic data on SFTs are relatively sparse in the literature, most of which has reported near-diploid karyotypes with few chromosomal aberrations, typical of gene fusion-driven mesenchymal tumors (Donner et al., 1999; Torabi et al., 2008; Mohajeri et al., 2013). Common recurrent alterations include rearranged 4q13, 9p22–23 and 12q13–15, gains in chromosomes 5, 8, 12, and 21, as well as chromosomal losses mapped to 1 and 13q. High-resolution array-based comparative genomic hybridization, single-nucleotide polymorphism array, and next-generation sequencing data have also revealed simple genomic aberrations of SFT with only occasional low-copy number variations, consisting mostly of losses of 13q or gains of 8p, as reflected by a lack of copy number abnormalities detected in nearly 70% of cases (Bertucci et al., 2013a; Chmielecki et al., 2013; Mohajeri et al., 2013; Robinson et al., 2013). Even less is known about the genetic alterations of malignant and dedifferentiated SFTs, while these tend to harbor more complex karyotypes (Hoshino et al., 2007; Dagrada et al., 2015). Notably, all dedifferentiated SFTs exhibit losses in chromosome 13, spanning the *RB1* gene, as well as 16q losses with a minimal common region of deletion mapped to chromosomal band 16q23.1 (Dagrada et al., 2015).

Recurrent NAB2-STAT6 fusions

In keeping with a genetically simple neoplasm, SFT harbors the pathognomonic *NAB2-STAT6* fusion as its genetic hallmark, which was simultaneously unraveled

by two groups using whole-transcriptome sequencing in 2013 (Chmielecki et al., 2013; Robinson et al., 2013). Beyond the resolution of conventional karyotypic and FISH technology, this gene fusion results from a very subtle intrachromosomal inversion at 12q13.3 and renders the neighboring *NAB2* and *STAT6* genes in frame and oriented in the same direction of transcription (Fig. 7A). Nearly all SFTs harbor this unique fusion, and more than 40 variants of fusions have been discovered to date (Nakada et al., 2016) (Table 3).

On the forward strand of chromosome 12, *NAB2* spans 6,583 bps (hg38) and comprises 7 exons that encode a 2,711-bp transcript and 525 amino acids (ENST00000300131; Fig. 7A). Spanning 16,010 bps (hg38), *STAT6* is located on the reverse strand of chromosome 12 and has 22 exons that encode a 4,034-bp transcript and 847 amino acids (ENST00000300134; Fig. 7A). As a member of the family of NAB proteins, *NAB2* comprises an N-terminal NAB conserved domain 1 (NCD1), a NAB conserved domain 2 (NCD2) and a transcriptional repressor domain (RD) at its C-terminus. To function as a transcriptional repressor in the nucleus, the wild-type *NAB2* first forms homo-polymers with itself or heteropolymers with other EGR (early growth response) proteins through NCD1, which in turn interact with the nucleosome remodeling and deacetylase (NuRD) complex, partly through its C-terminal NCD2 and RD domains. *STAT6* is a member of the STAT family of transcription factors and comprises a coiled-coil domain 1 (CCD1), a DNA-binding domain (DBD), a Src homology 2 (SH2) domain and a transcriptional activation domain (TAD) at its C-terminus. In response to physiological stimuli from cytokines and growth factors, activated membranous receptor kinases result in phosphorylation and homo- or hetero-dimerization of

Table 3. The summary of NAB2-STAT6 variants in solitary fibrous tumors from two studies and the COSMIC database.

Fusion variant	Robinson et al. 2013		Tai et al. 2015		COSMIC	
	Number	Percent	Number	Percent	Number	Percent
2-2	0	0%	0	0%	9	4%
2-5	1	2%	0	0%	8	3%
2-1/4	1	2%	0	0%	3	1%
3-19	0	0%	2	3%	3	1%
3-2/17/18/20	0	0%	1	1%	4	2%
4-2	3	6%	33	42%	95	41%
4-1/3/4/18	1	2%	1	1%	11	5%
5-1/2/16/17/81	0	0%	0	0%	8	3%
6-1/2/3/15	3	6%	1	1%	4	2%
6-16	32	62%	16	22%	53	23%
6-17	6	12%	16	22%	17	7%
6-18	0	0%	1	1%	7	3%
7-1/14/16/18/20	1	2%	0	0%	5	2%
7-2	4	8%	2	3%	6	3%
Total	52	100%	73	100%	233	100%
Non-exon/exon	5	10%	3	4%	27	12%

STAT family members, enabling their nuclear translocation to act as transcription activators.

At the RNA level, the chimeric *NAB2-STAT6* transcripts in the vast majority (93%-97%) of SFTs harbor 5' exons of *NAB2* and 3' exons of *STAT6* (Fig. 7B), and the reciprocal *STAT6-NAB2* fusion transcript is also detectable in nearly 50% of cases (Robinson et al., 2013). Most of the *NAB2-STAT6* fusion subtypes have breakpoints at the boundaries of juxtaposed exons, while a small subset (4-12%) appear to undergo more complex gene rearrangements, incorporating intervening sequences from introns or untranslated regions between the distal *NAB2* exon and proximal *STAT6* exon. All fusion transcripts retain the reading frame to maintain the function of the C-terminal transactivation domain of *STAT6*. However, the reciprocal transcripts can be in and out of the reading frame, presenting exact *STAT6-NAB2* reciprocals, shorter variants that miss one to several *STAT6* exons or both. The chimeric *NAB2-STAT6* proteins identified thus far exhibit a truncation of the transcriptional repressor domain of *NAB2* in most SFTs and retain the transcriptional activation domain of *STAT6* in nearly all cases, the biologic consequences of which have been verified to induce nuclear entry of the fused protein to increase cell proliferation by transactivating *EGR1* target genes (Robinson et al., 2013). Compared with *EGR1* per se, the chimeric *NAB2-STAT6* protein is tenfold more efficient in upregulating *EGR1* target genes, which was initially thought to be attributable both to the derepression of inhibition by the repressor domain of *NAB2* and contribution of the transactivation domain of *STAT6*. However, no significant promoting effect has been observed in parallel experiments using a *STAT6* response element reporter, indicating that the *NAB2-STAT6* fusion protein functions chiefly through *EGR1* target genes instead of *STAT6* target genes. Highly significant overexpression of *EGR1* target genes are observed in SFT, including *NAB2*, *NAB1*, *IGF2*, *FGF2*, *PDGFR*, and receptor tyrosine kinases, such as *FGFR1* and *NTRK1*. Overall, the net effect of the *NAB2-STAT6* fusion is to convert wild-type *NAB2* from a transcriptional repressor into an oncogenic transcriptional activator, which results in a feedforward loop by constitutive *EGR1*-mediated transactivation to drive neoplastic progression.

The finding that nearly all SFTs and so-called HPCs harbor the *NAB2-STAT6* fusion, e.g., in the meningeal setting, provides compelling molecular evidence to argue for unifying these tumors into a single entity regardless of their ubiquity in location (Schweizer et al., 2013; Yuzawa et al., 2016). More recently, recurrent *NAB2ex4-STAT6ex2* fusions were also detected in the so-called "pulmonary adenofibroma", which histologically features a centrally hyalinized, frond-like stroma with paucicellular to alternating cellular *STAT6*-positive spindle cells lined by a TTF-1-positive cuboidal to columnar epithelium. This finding indicated that pulmonary adenofibroma is indeed a peculiar variant of

intrapulmonary SFT (Fusco et al., 2017). The correlation between *NAB2-STAT6* fusion subtypes and clinicopathological variables of SFTs has been analyzed in some studies (Barthelmeß et al., 2014; Tai et al., 2015), revealing significant difference between tumors with various fusion subtypes in their tumor locations, ages at presentation, and mitotic activity. Among all fusion subtypes reported to date, *NAB2ex4-STAT6ex2* and *NAB2ex6-STAT6ex16/17* represent the two predominant variants, accounting for approximately 70% of cases. The former exhibits preponderance in intrathoracic sites (up to 80%) of the elderly, with greater sizes and indolent behaviors, while the latter, encoding a chimeric protein without *STAT6* DNA-binding domain, is consistently associated with younger age, cellular histology, and extrathoracic locations, but variably with higher mitotic counts and smaller sizes. Similar to extrathoracic and head and neck counterparts, nearly two thirds of meningeal SFT/HPCs show *NAB2ex5/6-STAT6ex16/17* fusions (Tai et al., 2015; Huang et al., 2016; Nakada et al., 2016; Yuzawa et al., 2016), while the aggressive behavior of meningeal SFTs cannot be explained solely by the fusion subtypes (Tai et al., 2015; Yuzawa et al., 2016).

TERT promoter and miscellaneous mutations

Little is known about recurrent genetic alterations other than the *NAB2-STAT6* fusion in SFTs. The *TERT* promoter mutation was first unraveled in melanomas, which acquire hotspot C228T (chr 5: 1,295,228 C>T, hg19) and C250T (chr 5: 1,295,250 C>T, hg19) somatic mutations at -124 bp and -146 bp from the ATG start site, respectively (Horn et al., 2013; Huang et al., 2013). These promoter mutations confer de novo consensus binding motifs for E-twenty-six (ETS) transcription factors, hence elevating *TERT* transcriptional activity by two- to fourfold in reporter assays (Huang et al., 2013). A subsequent study showed general prevalence rates of the *TERT* promoter mutation of 11% (36/341) in soft tissue sarcomas, but wide variability among different sarcoma histotypes, with myxoid liposarcoma being the most commonly mutated in up to 74% (29/39) of cases tested. In stark contrast, *TERT* promoter mutations have been infrequently detected in other sarcoma types, such as malignant peripheral nerve sheath tumors (2/35; 6%) and synovial sarcomas (1/25; 4%) (Koelsche et al., 2014a). Specifically, for SFTs, their reported frequencies of *TERT* promoter mutation range from 13 to 29%, with a predominance (> 90%) of C228T/A (Koelsche et al., 2013, 2014a; Bahrami et al., 2016; Demicco et al., 2018). Akaike et al. reported that *TERT* promoter mutations in 5 of 40 cases (13%) were associated with a shorter disease-free survival rate ($P = 0.007$) (Akaike et al., 2015). Notably, a large series (Bahrami et al., 2016) on *TERT* promoter mutations in SFTs reported an overall prevalence rate as high as 28% (26/94), with a twofold greater frequency in thoracic (42%, 13/31) compared with extrathoracic sites (21%, 13/63). *TERT* promoter

mutations are strongly associated with older age (56 versus 65 years, $P=0.006$), larger tumor size (6 versus 13 cm, $P=0.000002$), higher risk classification (2%, 39%, 70% for low-risk, moderate-risk and high-risk SFTs, $P=2.9 \times 10^{-9}$), and a worse event-free survival ($P=0.0082$) and carry a 3.43-fold increased risk of failure events ($P=0.01$) in Cox models. These associations of the *TERT* promoter mutation with adverse clinicopathological factors and a worse prognosis are partly similar to a recent large study in which significance was only observed in the prediction of shorter metastasis-free survival in intermediate risk category SFTs with imperfect risk prediction (Demicco et al., 2018).

Whole-genome sequencing revealed a very low mutation burden in SFTs with an average of 22.5 nonsynonymous somatic mutations per tumor (median 19; range of 12–41; median rate of 0.66 mutations per Mb) (Chmielecki et al., 2013). The sequencing studies identified no significant point mutations, either germline or somatic, in frequently mutated cancer-associated genes, such as *KRAS*, *BRAF* and *PIK3CA* (Chmielecki et al., 2013; Robinson et al., 2013). However, deletions or mutations of the *TP53* gene locus at 17p13 have been described in dedifferentiated or malignant SFTs (Mosquera and Fletcher, 2009; Subramaniam et al., 2011; Akaike et al., 2015; Dagrada et al., 2015). Mutations of *PDGFRB* have been observed in 3/40 conventional SFTs (Akaike et al., 2015).

Gene expression profiling

Microarray-based expression profiling studies have identified a distinct transcriptional signature of SFTs that form a tight genomic cluster distinct from all other sarcoma subtypes with closer kinship to genetically simple tumor types than to genetically complex sarcomas (Hajdu et al., 2010; Bertucci et al., 2013b; Mohajeri et al., 2013). However, the unsupervised clustering analyses failed to detect distinct subgroups within SFTs per se and did not validate the role of anatomical locations in differential transcriptional regulation. The listed differentially expressed genes of SFTs range from 1662 to 3401 in number and include those encoding receptor tyrosine kinases (e.g., *FGFR1*, *DDR1*, *ERBB2*, *INSR*), nonkinase genes (e.g., *ADLH1A*, *IGF2*, *CHI3L1*, *GRIA2*, *ApoD*), various collagen proteins (e.g., *COL4A1*, *COL16A1*, *COL11A1*, *COL6A3*, *COL14A1*, *COL17A1*), retinoic acid receptors (*RARA*, *RARG*), homeobox family of transcription factors (*HOXA2-3-4*, *HOXB2-3-5-16*, *HOXC5*), and histone deacetylases (*HDAC1*, 3, 4, 5 and 11) (Hajdu et al., 2010). Most differentially expressed genes lack any DNA copy number alterations (Bertucci et al., 2013b). Accounting for hypoglycemia in Doege-Potter syndrome-associated SFTs, overexpressed *IGF2* is caused by a loss of imprinting (Hajdu et al., 2010) and activates downstream signaling pathways through insulin receptor (IR) rather than *IGF1* receptor (*IGF1R*),

which exhibits only negligible expression. Several upregulated genes and associated ontologies are implicated in the maintenance of progenitor/stem cells traits, such as *ALDH1A*, retinoic acid receptors-encoding genes, and *HOX* genes.

Prognosis and current treatment

To date, surgical intervention with adequate margins and long-term follow-up still remain the standard of care in managing patients with SFTs (Kayani et al., 2018), with recurrence-free survival exceeding 90% for completely resected cases and overall recurrence or metastatic rates of 5% to 10% according to early studies (Kayani et al., 2018). More recently, studies with longer follow-up durations have documented a tendency of increased late recurrence 10 years after primary surgery, and overall recurrence and metastatic rates have been estimated to be 5–12% and 14–26%, respectively (Demicco et al., 2017; Gholami et al., 2017; Salas et al., 2017). These figures illustrate that most SFTs pursue a relatively indolent course, while even the histologically benign-appearing lesions may still pose a therapeutic challenge because of the late recurrence potential.

In isolated case reports, neoadjuvant radiotherapy aiming at tumor shrinkage has been used to control local symptoms or enable surgical excision (Kayani et al., 2018). For high-risk, inoperable or local recurrent SFTs, adjuvant radiation therapy can be considered but falls short of a consistent survival benefit among different studies. Stereotactic radiosurgery appears to be a reasonable therapeutic modality for the local control of recurrent, unresectable intracranial SFTs, but it is still unsatisfactory for the high probability of local recurrence and distant metastases (Cohen-Inbar et al., 2017). In contrast, combined surgery and radiotherapy have achieved better local control of soft tissue SFTs (Bishop et al., 2018).

The therapeutic efficacy of systemic chemotherapy in advanced or metastatic SFTs is not recognized, barely achieving low rates (0–20%) of complete or partial responses to conventional chemotherapies, including doxorubicin, gemcitabine, and paclitaxel-based regimens, with wide variations in outcomes between stable disease (27–90%) and disease progression (10–53%) (Park and Araujo, 2009; Constantinidou et al., 2012; Stacchiotti et al., 2013a). Regarding newer chemotherapeutic agents, temozolomide and dacarbazine show significant antitumoral activity in xenografts (Stacchiotti et al., 2013b). In addition, the combination of temozolomide and bevacizumab or dacarbazine monotherapy exhibit 79% and 38% of partial response rates, respectively, in a small series (Park et al., 2011). Moreover, doxorubicin/dacarbazine combination therapy, trabectedin and eribulin have been shown to be effective in inhibiting patient-derived xenografts of dedifferentiated SFTs (Stacchiotti et al., 2017). Regarding targeted therapies, receptor tyrosine kinase

inhibitors, such as imatinib (De Pas et al., 2008), sunitinib (George et al., 2009; Stacchiotti et al., 2012), pazopanib (Stacchiotti et al., 2014) and dasatinib (Schuetze et al., 2017), have been attempted in limited cases, requiring future large-scale studies to evaluate their therapeutic efficacy. The anti-PD-1 checkpoint immunotherapy, pembrolizumab, may be effective in treating SFTs (Boothe et al., 2017; Toulmonde et al., 2018).

Conclusion

In summary, current understanding of SFT has undergone continued conceptual evolutions in histological classification and prognostication, immunohistochemical characterization, and molecular discovery and diagnosis since its first debut nearly 150 years ago. SFT is now recognized as a unique mesenchymal tumor of intermediate biological potential characterized by the pathognomonic *NAB2-STAT6* gene fusion. This genetic hallmark not only highly prevails among SFTs originating from ubiquitous anatomic sites, but it also assimilates SFTs with classical histology and diverse variants, including the formerly distinct GCA and so-called HPC, into the same tumor entity. The chimera of truncated NAB2 and STAT6 proteins consequently results in nuclear entry of the fusion protein to activate a variety of EGR1-related genes in need of further clinical and biological characterization. However, the aberrant nuclear STAT6 expression, detectable by immunohistochemistry, has become a sensitive and specific feature in the diagnosis of SFTs. The risk assessment for tumor relapse remains a challenging issue in the clinical management of SFTs, for which recently proposed risk models, incorporating patient age, tumor size, mitotic count, and/or tumor necrosis, still require large-scale prospective validation in independent studies. In addition to surgical intervention with curative intent, therapeutic options for advanced or malignant SFTs are very limited owing to generally poor responses to conventional radio-therapeutic and chemotherapeutic modalities. Although the efficacy of targeted therapies for SFTs awaits further investigation, the application of *NAB2-STAT6* hallmark to establish accurate diagnosis and further elucidation of its biology in orchestrating the transcriptional program may collectively lead to the potential incorporation of molecular signatures into the risk classification and future identification of more druggable targets in precision medicine of SFTs.

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References

- Agaimy A., Michal M., Chiosea S., Petersson F., Hadravsky L., Kristiansen G., Horch R.E., Schmolders J., Hartmann A., Haller F. and Michal M. (2017). Phosphaturic mesenchymal tumors: Clinicopathologic, immunohistochemical and molecular analysis of 22 cases expanding their morphologic and immunophenotypic spectrum. *Am. J. Surg. Pathol.* 41, 1371-1380.
- Akaike K., Kurisaki-Arakawa A., Hara K., Suehara Y., Takagi T., Mitani K., Kaneko K., Yao T. and Saito T. (2015). Distinct clinicopathological features of NAB2-STAT6 fusion gene variants in solitary fibrous tumor with emphasis on the acquisition of highly malignant potential. *Hum. Pathol.* 46, 347-356.
- Al-Izzi M., Thurlow N.P. and Corrin B. (1989). Pleural mesothelioma of connective tissue type, localized fibrous tumour of the pleura, and reactive submesothelial hyperplasia. An immunohistochemical comparison. *J. Pathol.* 158, 41-44.
- Ambrosini-Spaltro A. and Eusebi V. (2010). Meningeal hemangiopericytomas and hemangiopericytoma/solitary fibrous tumors of extracranial soft tissues: A comparison. *Virchows Arch.* 456, 343-354.
- Asano N., Yoshida A., Ichikawa H., Mori T., Nakamura M., Kawai A. and Hiraoka N. (2017). Immunohistochemistry for trimethylated H3K27 in the diagnosis of malignant peripheral nerve sheath tumours. *Histopathology* 70, 385-393.
- Bahrami A., Lee S., Schaefer I.M., Boland J.M., Patton K.T., Pounds S. and Fletcher C.D.M. (2016). TERT promoter mutations and prognosis in solitary fibrous tumor. *Mod. Pathol.* 29, 1511-1522.
- Barak S., Wang Z. and Miettinen M. (2012). Immunoreactivity for calretinin and keratins in desmoid fibromatosis and other myofibroblastic tumors: A diagnostic pitfall. *Am. J. Surg. Pathol.* 36, 1404-1409.
- Barthelmeß S., Gedder H., Boltze C., Moskalev E.A., Bieg M., Sirbu H., Brors B., Wiemann S., Hartmann A., Agaimy A. and Haller F. (2014). Solitary fibrous tumors/hemangiopericytomas with different variants of the NAB2-STAT6 gene fusion are characterized by specific histomorphology and distinct clinicopathological features. *Am. J. Pathol.* 184, 1209-1218.
- Bertucci F., Bouvier-Labit C., Finetti P., Adelaide J., Metellus P., Mokhtari K., Decouvelaere A.V., Miquel C., Jouvet A., Figarella-Branger D., Pedetour F., Chaffanet M. and Birnbaum D. (2013a). Comprehensive genome characterization of solitary fibrous tumors using high-resolution array-based comparative genomic hybridization. *Genes Chromosomes Cancer* 52, 156-164.
- Bertucci F., Bouvier-Labit C., Finetti P., Metellus P., Adelaide J., Mokhtari K., Figarella-Branger D., Decouvelaere A.V., Miquel C., Coindre J.M. and Birnbaum D. (2013b). Gene expression profiling of solitary fibrous tumors. *PLoS One* 8, e64497.
- Bhargava R., Shia J., Hummer A.J., Thaler H.T., Tornos C. and Soslow R.A. (2005). Distinction of endometrial stromal sarcomas from 'hemangiopericytomatous' tumors using a panel of immunohistochemical stains. *Mod. Pathol.* 18, 40-47.
- Bishop A.J., Zagars G.K., Demicco E.G., Wang W.L., Feig B.W. and Guadagnolo B.A. (2018). Soft tissue solitary fibrous tumor: Combined surgery and radiation therapy results in excellent local control. *Am. J. Clin. Oncol.* 41, 81-85.
- Boothe J.T., Budd G.T., Smolkin M.B. and Ma P.C. (2017). Durable near-complete response to anti-PD-1 checkpoint immunotherapy in a refractory malignant solitary fibrous tumor of the pleura. *Case.*

- Rep. Oncol. 10, 998-1005.
- Bouvier C., Bertucci F., Metellus P., Finetti P., Maues de Paula A., Forest F., Mokhtari K., Miquel C., Birnbaum D., Vasiljevic A., Jouvet A., Coindre J.M., Loundou A. and Figarella-Branger D. (2013). ALDH1 is an immunohistochemical diagnostic marker for solitary fibrous tumours and haemangiopericytomas of the meninges emerging from gene profiling study. *Acta. Neuropathol. Commun.* 1, 10.
- Ceballos K.M., Munk P.L., Masri B.A. and O'Connell J.X. (1999). Lipomatous hemangiopericytoma: A morphologically distinct soft tissue tumor. *Arch. Pathol. Lab. Med.* 123, 941-945.
- Chan J.K. (1997). Solitary fibrous tumour--everywhere, and a diagnosis in vogue. *Histopathology* 31, 568-576.
- Chick J.F., Chauhan N.R. and Madan R. (2013). Solitary fibrous tumors of the thorax: Nomenclature, epidemiology, radiologic and pathologic findings, differential diagnoses, and management. *AJR. Am. J. Roentgenol.* 200, W238-248.
- Chmielecki J., Crago A.M., Rosenberg M., O'Connor R., Walker S.R., Ambrogio L., Auclair D., McKenna A., Heinrich M.C., Frank D.A. and Meyerson M. (2013). Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors. *Nat. Genet.* 45, 131-132.
- Church A.J., Calicchio M.L., Nardi V., Skalova A., Pinto A., Dillon D.A., Gomez-Fernandez C.R., Manoj N., Haimes J.D., Stahl J.A., Dela Cruz F.S., Tannenbaum-Dvir S., Glade-Bender J.L., Kung A.L., DuBois S.G., Kozakewich H.P., Janeway K.A., Perez-Atayde A.R. and Harris M.H. (2018). Recurrent EML4-NTRK3 fusions in infantile fibrosarcoma and congenital mesoblastic nephroma suggest a revised testing strategy. *Mod. Pathol.* 31, 463-473.
- Cohen-Inbar O., Lee C.C., Mousavi S.H., Kano H., Mathieu D., Meola A., Nakaji P., Honea N., Johnson M., Abbassy M., Mohammadi A.M., Silva D., Yang H.C., Grills I., Kondziolka D., Barnett G.H., Lunsford L.D. and Sheehan J. (2017). Stereotactic radiosurgery for intracranial hemangiopericytomas: A multicenter study. *J. Neurosurg.* 126, 744-754.
- Collini P., Negri T., Barisella M., Palassini E., Tarantino E., Pastorino U., Gronchi A., Stacchiotti S. and Pilotti S. (2012). High-grade sarcomatous overgrowth in solitary fibrous tumors: A clinicopathologic study of 10 cases. *Am. J. Surg. Pathol.* 36, 1202-1215.
- Constantinidou A., Jones R.L., Olmos D., Thway K., Fisher C., Al-Muderis O. and Judson I. (2012). Conventional anthracycline-based chemotherapy has limited efficacy in solitary fibrous tumour. *Acta Oncol.* 51, 550-554.
- Creytens D., Ferdinande L. and Van Dorpe J. (2016). Histopathologically malignant solitary fibrous tumor of the skin: A report of an unusual case. *J. Cutan. Pathol.* 43, 629-631.
- Creytens D., Ferdinande L. and Van Dorpe J. (2018). Multifocal cytokeratin expression in a dedifferentiated solitary fibrous tumor with heterologous rhabdomyosarcomatous differentiation: A challenging diagnosis! *Int. J. Surg. Pathol.* 26, 423-427.
- Dagrada G.P., Spagnuolo R.D., Mauro V., Tamborini E., Cesana L., Gronchi A., Stacchiotti S., Pierotti M.A., Negri T. and Pilotti S. (2015). Solitary fibrous tumors: Loss of chimeric protein expression and genomic instability mark dedifferentiation. *Mod. Pathol.* 28, 1074-1083.
- Dantey K. and Cooper K. (2013). Myxoid solitary fibrous tumor: A study of three cases. *Int. J. Surg. Pathol.* 21, 358-362.
- De Pas T., Toffalorio F., Colombo P., Trifiro G., Pelosi G., Vigna P.D., Manzotti M., Agostini M. and de Braud F. (2008). Brief report: Activity of imatinib in a patient with platelet-derived-growth-factor receptor positive malignant solitary fibrous tumor of the pleura. *J. Thorac. Oncol.* 3, 938-941.
- de Saint Aubain Somerhausen N., Rubin B.P. and Fletcher C.D.M. (1999). Myxoid solitary fibrous tumor: A study of seven cases with emphasis on differential diagnosis. *Mod. Pathol.* 12, 463-471.
- Dei Tos A.P., Seregard S., Calonje E., Chan J.K. and Fletcher C.D.M. (1995). Giant cell angiofibroma. A distinctive orbital tumor in adults. *Am. J. Surg. Pathol.* 19, 1286-1293.
- Demicco E.G., Park M.S., Araujo D.M., Fox P.S., Bassett R.L., Pollock R.E., Lazar A.J. and Wang W.L. (2012). Solitary fibrous tumor: A clinicopathological study of 110 cases and proposed risk assessment model. *Mod. Pathol.* 25, 1298-1306.
- Demicco E.G., Harms P.W., Patel R.M., Smith S.C., Ingram D., Torres K., Carskadon S.L., Camelo-Piragua S., McHugh J.B., Siddiqui J., Palanisamy N., Lucas D.R., Lazar A.J. and Wang W.L. (2015). Extensive survey of STAT6 expression in a large series of mesenchymal tumors. *Am. J. Clin. Pathol.* 143, 672-682.
- Demicco E.G., Wagner M.J., Maki R.G., Gupta V., Iofin I., Lazar A.J. and Wang W.L. (2017). Risk assessment in solitary fibrous tumors: Validation and refinement of a risk stratification model. *Mod. Pathol.* 30, 1433-1442.
- Demicco E.G., Wani K., Ingram D., Wagner M., Maki R.G., Rizzo A., Meeker A., Lazar A.J. and Wang W.L. (2018). TERT promoter mutations in solitary fibrous tumor. *Histopathology* 73, 843-851.
- Donner L.R., Silva M.T. and Dobin S.M. (1999). Solitary fibrous tumor of the pleura: A cytogenetic study. *Cancer. Genet. Cytogenet.* 111, 169-171.
- Doyle L.A., Vivero M., Fletcher C.D.M., Mertens F. and Hornick J.L. (2014a). Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. *Mod. Pathol.* 27, 390-395.
- Doyle L.A., Tao D. and Marino-Enriquez A. (2014b). STAT6 is amplified in a subset of dedifferentiated liposarcoma. *Mod. Pathol.* 27, 1231-1237.
- England D.M., Hochholzer L. and McCarthy M.J. (1989). Localized benign and malignant fibrous tumors of the pleura. A clinicopathologic review of 223 cases. *Am. J. Surg. Pathol.* 13, 640-658.
- Enzinger F.M. and Smith B.H. (1976). Hemangiopericytoma. An analysis of 106 cases. *Hum. Pathol.* 7, 61-82.
- Erdag G., Qureshi H.S., Patterson J.W. and Wick M.R. (2007). Solitary fibrous tumors of the skin: A clinicopathologic study of 10 cases and review of the literature. *J. Cutan. Pathol.* 34, 844-850.
- Feasel P., Al-Ibraheemi A., Fritchie K., Zreik R.T., Wang W.L., Demicco E., Saeb-Lima M., Goldblum J.R., Rubin B.P., McKenney J.K., Ko J.S. and Billings S.D. (2018). Superficial solitary fibrous tumor: A series of 26 cases. *Am. J. Surg. Pathol.* 42, 778-785.
- Fletcher C.D.M. (2006). The evolving classification of soft tissue tumours: An update based on the new WHO classification. *Histopathology* 48, 3-12.
- Fletcher C.D.M., Bridge J.A. and Lee J.C. (2013). Extrapleural solitary fibrous tumor. In: WHO classification of tumours of soft tissue and bone. 4th ed. Fletcher C.D.M., Bridge J.A., Hogendoorn P.C.W. and Mertens F. (eds). International Agency for Research on Cancer. Lyon. pp 80-82.
- Folpe A.L., Devaney K. and Weiss S.W. (1999). Lipomatous hemangiopericytoma: A rare variant of hemangiopericytoma that may be confused with liposarcoma. *Am. J. Surg. Pathol.* 23, 1201-

Solitary fibrous tumor

- 1207.
- Foo W.C., Cruise M.W., Wick M.R. and Hornick J.L. (2011). Immunohistochemical staining for TLE1 distinguishes synovial sarcoma from histologic mimics. *Am. J. Clin. Pathol.* 135, 839-844.
- Foster E.A. and Ackerman L.V. (1960). Localized mesotheliomas of the pleura. The pathologic evaluation of 18 cases. *Am. J. Clin. Pathol.* 34, 349-364.
- Fusco N., Guerini-Rocco E., Augello C., Terrasi A., Ercoli G., Fumagalli C., Vacirca D., Braidotti P., Parafioriti A., Jaconi M., Runza L., Ananthanarayanan V., Pagni F., Bosari S., Barberis M. and Ferrero S. (2017). Recurrent NAB2-STAT6 gene fusions and oestrogen receptor- α expression in pulmonary adenofibromas. *Histopathology* 70, 906-917.
- Gengler C. and Guillo L. (2006). Solitary fibrous tumour and haemangiopericytoma: Evolution of a concept. *Histopathology* 48, 63-74.
- George S., Merriam P., Maki R.G., Van den Abbeele A.D., Yap J.T., Akhurst T., Harmon D.C., Bhuchar G., O'Mara M.M., D'Adamo D.R., Morgan J., Schwartz G.K., Wagner A.J., Butrynski J.E., Demetri G.D. and Keohan M.L. (2009). Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. *J. Clin. Oncol.* 27, 3154-3160.
- Gharaee-Kermani M., Mehra R., Robinson D.R., Wei J.T. and Macoska J.A. (2014). Complex cellular composition of solitary fibrous tumor of the prostate. *Am. J. Pathol.* 184, 732-739.
- Gholami S., Cassidy M.R., Kirane A., Kuk D., Zanchelli B., Antonescu C.R., Singer S. and Brennan M. (2017). Size and location are the most important risk factors for malignant behavior in resected solitary fibrous tumors. *Ann. Surg. Oncol.* 24, 3865-3871.
- Gold J.S., Antonescu C.R., Hajdu C., Ferrone C.R., Hussain M., Lewis J.J., Brennan M.F. and Coit D.G. (2002). Clinicopathologic correlates of solitary fibrous tumors. *Cancer* 94, 1057-1068.
- Guillo L., Gebhard S. and Coindre J.M. (2000). Lipomatous hemangiopericytoma: A fat-containing variant of solitary fibrous tumor? Clinicopathologic, immunohistochemical, and ultrastructural analysis of a series in favor of a unifying concept. *Hum. Pathol.* 31, 1108-1115.
- Hajdu M., Singer S., Maki R.G., Schwartz G.K., Keohan M.L. and Antonescu C.R. (2010). IGF2 over-expression in solitary fibrous tumours is independent of anatomical location and is related to loss of imprinting. *J. Pathol.* 221, 300-307.
- Han H., Ahn S., Hwangbo W. and Chae Y.S. (2013). Myxoid solitary fibrous tumor of the central nervous system. *Korean. J. Pathol.* 47, 505-506.
- Han G., Zhang Z., Shen X., Wang K., Zhao Y., He J., Gao Y., Shan X., Xin G., Li C. and Liu X. (2017). Doege-Potter syndrome: A review of the literature including a new case report. *Medicine (Baltimore)* 96, e7417.
- Hernandez F.J. and Fernandez B.B. (1974). Localized fibrous tumors of pleura: A light and electron microscopic study. *Cancer* 34, 1667-1674.
- Horn S., Figl A., Rachakonda P.S., Fischer C., Sucker A., Gast A., Kadel S., Moll I., Nagore E., Hemminki K., Schadendorf D. and Kumar R. (2013). TERT promoter mutations in familial and sporadic melanoma. *Science* 339, 959-961.
- Hoshino M., Ogose A., Kawashima H., Kudo N., Hotta T., Umezu H., Tohyama T., Nakade K., Beppu H. and Endo N. (2007). Malignant solitary fibrous tumor of the soft tissue: A cytogenetic study. *Cancer Genet. Cytogenet.* 177, 55-58.
- Huang H.Y., Brennan M.F., Singer S. and Antonescu C.R. (2005). Distant metastasis in retroperitoneal dedifferentiated liposarcoma is rare and rapidly fatal: A clinicopathological study with emphasis on the low-grade myxofibrosarcoma-like pattern as an early sign of dedifferentiation. *Mod. Pathol.* 18, 976-984.
- Huang F.W., Hodis E., Xu M.J., Kryukov G.V., Chin L. and Garraway L.A. (2013). Highly recurrent TERT promoter mutations in human melanoma. *Science* 339, 957-959.
- Huang S.C., Li C.F., Kao Y.C., Chuang I.C., Tai H.C., Tsai J.W., Yu S.C., Huang H.Y., Lan J., Yen S.L., Lin P.C. and Chen T.C. (2016). The clinicopathological significance of NAB2-STAT6 gene fusions in 52 cases of intrathoracic solitary fibrous tumors. *Cancer Med.* 5, 159-168.
- Kao Y.C., Sung Y.S., Zhang L., Huang S.C., Argani P., Chung C.T., Graf N.S., Wright D.C., Kellie S.J., Agaram N.P., Ludwig K., Zin A., Alaggio R. and Antonescu C.R. (2016). Recurrent BCOR internal tandem duplication and YWHAE-NUTM2B fusions in soft tissue undifferentiated round cell sarcoma of infancy: Overlapping genetic features with clear cell sarcoma of kidney. *Am. J. Surg. Pathol.* 40, 1009-1020.
- Kawai T., Yakumaru K., Mikata A., Kageyama K., Torikata C. and Shimamoto Y. (1978). Solitary (localized) pleural mesothelioma. A light- and electron-microscopic study. *Am. J. Surg. Pathol.* 2, 365-375.
- Kayani B., Sharma A., Sewell M.D., Platinum J., Olivier A., Briggs T.W. and Eastwood D.M. (2018). A review of the surgical management of extrathoracic solitary fibrous tumors. *Am. J. Clin. Oncol.* 41, 687-694.
- Keraliya A.R., Tirumani S.H., Shinagare A.B., Zaheer A. and Ramaiya N.H. (2016). Solitary fibrous tumors: 2016 imaging update. *Radiol. Clin. North. Am.* 54, 565-579.
- Kim J.M., Choi Y.L., Kim Y.J. and Park H.K. (2017). Comparison and evaluation of risk factors for meningeal, pleural, and extrapleural solitary fibrous tumors: A clinicopathological study of 92 cases confirmed by STAT6 immunohistochemical staining. *Pathol. Res. Pract.* 213, 619-625.
- Klemperer P. and Rabin C.B. (1931). Primary neoplasms of the pleura: A report of five cases. *Arch. Pathol.* 111, 385-412.
- Koelsche C., Sahn F., Capper D., Reuss D., Sturm D., Jones D.T., Kool M., Northcott P.A., Wiestler B., Bohmer K., Meyer J., Mawrin C., Hartmann C., Mittelbronn M., Platten M., Brokinkel B., Seiz M., Herold-Mende C., Unterberg A., Schittenhelm J., Weller M., Pfister S., Wick W., Korshunov A. and von Deimling A. (2013). Distribution of TERT promoter mutations in pediatric and adult tumors of the nervous system. *Acta Neuropathol.* 126, 907-915.
- Koelsche C., Renner M., Hartmann W., Brandt R., Lehner B., Waldburger N., Alldinger I., Schmitt T., Egerer G., Penzel R., Wardelmann E., Schirmacher P., von Deimling A. and Mechttersheimer G. (2014a). TERT promoter hotspot mutations are recurrent in myxoid liposarcomas but rare in other soft tissue sarcoma entities. *J. Exp. Clin. Cancer Res.* 33, 33.
- Koelsche C., Schweizer L., Renner M., Warth A., Jones D.T., Sahn F., Reuss D.E., Capper D., Knosel T., Schulz B., Petersen I., Ulrich A., Renker E.K., Lehner B., Pfister S.M., Schirmacher P., von Deimling A. and Mechttersheimer G. (2014b). Nuclear relocation of STAT6 reliably predicts NAB2-STAT6 fusion for the diagnosis of solitary fibrous tumour. *Histopathology* 65, 613-622.
- Kosemehmetoglu K., Vrana J.A. and Folpe A.L. (2009). TLE1 expression is not specific for synovial sarcoma: A whole section study of 163 soft tissue and bone neoplasms. *Mod. Pathol.* 22, 872-

- 878.
- Lasota J., Felisiak-Golabek A., Aly F.Z., Wang Z.F., Thompson L.D. and Miettinen M. (2015). Nuclear expression and gain-of-function beta-catenin mutation in glomangiopericytoma (sinonasal-type hemangiopericytoma): Insight into pathogenesis and a diagnostic marker. *Mod. Pathol.* 28, 715-720.
- Lau S.K., Weiss L.M. and Chu P.G. (2009). Myxoid solitary fibrous tumor: A clinicopathologic study of three cases. *Virchows Arch.* 454, 189-194.
- Lee J.C. and Fletcher C.D.M. (2011). Malignant fat-forming solitary fibrous tumor (so-called "lipomatous hemangiopericytoma"): Clinicopathologic analysis of 14 cases. *Am. J. Surg. Pathol.* 35, 1177-1185.
- Lee J.Y., Park S.E., Shin S.J., Kim C.W., Kim S.S. and Kim K.H. (2015). Solitary fibrous tumor with myxoid stromal change. *Am. J. Dermatopathol.* 37, 570-573.
- Lee J.C., Su S.Y., Changou C.A., Yang R.S., Tsai K.S., Collins M.T., Orwoll E.S., Lin C.Y., Chen S.H., Shih S.R., Lee C.H., Oda Y., Billings S.D., Li C.F., Nielsen G.P., Konishi E., Petersson F., Carpenter T.O., Sittampalam K., Huang H.Y. and Folpe A.L. (2016). Characterization of FN1-FGFR1 and novel FN1-FGF1 fusion genes in a large series of phosphaturic mesenchymal tumors. *Mod. Pathol.* 29, 1335-1346.
- Louis D.N., Perry A., Reifenberger G., von Deimling A., Figarella-Branger D., Cavenee W.K., Ohgaki H., Wiestler O.D., Kleihues P. and Ellison D.W. (2016). The 2016 World Health Organization classification of tumors of the central nervous system: A summary. *Acta Neuropathol.* 131, 803-820.
- Lu C., Alex D., Benayed R., Rosenblum M. and Hameed M. (2018). Solitary fibrous tumor with neuroendocrine and squamous dedifferentiation: A potential diagnostic pitfall. *Hum. Pathol.* 77, 175-180.
- Luse S.A. and Spjut H.J. (1964). An electron microscopic study of a solitary pleural mesothelioma. *Cancer* 17, 1546-1554.
- Macagno N., Figarella-Branger D., Mokthari K., Metellus P., Jouvett A., Vasiljevic A., Loundou A. and Bouvier C. (2016). Differential diagnosis of meningeal SFT-HPC and meningioma: Which immunohistochemical markers should be used? *Am. J. Surg. Pathol.* 40, 270-278.
- Marchevsky A.M., Varshney D. and Fuller C. (2003). Mediastinal epithelioid solitary fibrous tumor. *Arch. Pathol. Lab. Med.* 127, e212-e215.
- Martorell M., Pérez-Vallés A., Gozalbo F., Garcia-Garcia J.A., Gutierrez J. and Gaona J. (2007). Solitary fibrous tumor of the thigh with epithelioid features: a case report. *Diagn. Pathol.* 18, 19.
- McDaniel A.S., Palanisamy N., Smith S.C., Robinson D.R., Wu Y.M., Chinnaiyan A.M., McHugh J.B., Greenson J.K. and Kunju L.P. (2016). A subset of solitary fibrous tumors express nuclear PAX8 and PAX2: A potential diagnostic pitfall. *Histol. Histopathol.* 31, 223-230.
- Miettinen M. (2014). Immunohistochemistry of soft tissue tumours - review with emphasis on 10 markers. *Histopathology* 64, 101-118.
- Mohajeri A., Tayebwa J., Collin A., Nilsson J., Magnusson L., von Steyern F.V., Brosjo O., Domanski H.A., Larsson O., Sciort R., Debiec-Rychter M., Hornick J.L., Mandahl N., Nord K.H. and Mertens F. (2013). Comprehensive genetic analysis identifies a pathognomonic NAB2/STAT6 fusion gene, nonrandom secondary genomic imbalances, and a characteristic gene expression profile in solitary fibrous tumor. *Genes Chromosomes Cancer* 52, 873-886.
- Mosquera J.M. and Fletcher C.D.M. (2009). Expanding the spectrum of malignant progression in solitary fibrous tumors: A study of 8 cases with a discrete anaplastic component--is this dedifferentiated SFT? *Am. J. Surg. Pathol.* 33, 1314-1321.
- Nakada S., Minato H. and Nojima T. (2016). Clinicopathological differences between variants of the NAB2-STAT6 fusion gene in solitary fibrous tumors of the meninges and extra-central nervous system. *Brain Tumor. Pathol.* 33, 169-174.
- Natkunam Y., Rouse R.V., Zhu S., Fisher C. and van De Rijn M. (2000). Immunoblot analysis of CD34 expression in histologically diverse neoplasms. *Am. J. Pathol.* 156, 21-27.
- Nielsen G.P., Dickersin G.R., Provenzal J.M. and Rosenberg A.E. (1995). Lipomatous hemangiopericytoma. A histologic, ultrastructural and immunohistochemical study of a unique variant of hemangiopericytoma. *Am. J. Surg. Pathol.* 19, 748-756.
- Ouladan S., Trautmann M., Orouji E., Hartmann W., Huss S., Buttner R. and Wardelmann E. (2015). Differential diagnosis of solitary fibrous tumors: A study of 454 soft tissue tumors indicating the diagnostic value of nuclear STAT6 relocation and ALDH1 expression combined with in situ proximity ligation assay. *Int. J. Oncol.* 46, 2595-2605.
- Park M.S. and Araujo D.M. (2009). New insights into the hemangiopericytoma/solitary fibrous tumor spectrum of tumors. *Curr. Opin. Oncol.* 21, 327-331.
- Park M.S., Patel S.R., Ludwig J.A., Trent J.C., Conrad C.A., Lazar A.J., Wang W.L., Boonsirikamchai P., Choi H., Wang X., Benjamin R.S. and Araujo D.M. (2011). Activity of temozolomide and bevacizumab in the treatment of locally advanced, recurrent, and metastatic hemangiopericytoma and malignant solitary fibrous tumor. *Cancer* 117, 4939-4947.
- Pasquali S., Gronchi A., Strauss D., Bonvalot S., Jeys L., Stacchiotti S., Hayes A., Honore C., Collini P., Renne S.L., Alexander N., Grimer R.J., Callegaro D., Sumathi V.P., Gourevitch D. and Desai A. (2016). Resectable extra-pleural and extra-meningeal solitary fibrous tumours: A multi-centre prognostic study. *Eur. J. Surg. Oncol.* 42, 1064-1070.
- Rao N., Colby T.V., Falconieri G., Cohen H., Moran C.A. and Suster S. (2013). Intrapulmonary solitary fibrous tumors: clinicopathologic and immunohistochemical study of 24 cases. *Am. J. Surg. Pathol.* 37, 155-166.
- Robinson D.R., Wu Y.-M., Kalyana-Sundaram S., Cao X., Lonigro R.J., Sung Y.-S., Chen C.-L., Zhang L., Wang R., Su F., Iyer M.K., Roychowdhury S., Siddiqui J., Pienta K.J., Kunju L.P., Talpaz M., Mosquera J.M., Singer S., Schuetze S.M., Antonescu C.R. and Chinnaiyan A.M. (2013). Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. *Nat. Genet.* 45, 180-185.
- Rosado-de-Christenson M.L., Abbott G.F., McAdams H.P., Franks T.J. and Galvin J.R. (2003). From the archives of the AFIP: Localized fibrous tumor of the pleura. *Radiographics* 23, 759-783.
- Said J.W., Nash G., Banks-Schlegel S., Sassoon A.F. and Shintaku I.P. (1984). Localized fibrous mesothelioma: An immunohistochemical and electron microscopic study. *Hum. Pathol.* 15, 440-443.
- Salas S., Resseguier N., Blay J.Y., Le Cesne A., Italiano A., Chevreau C., Rosset P., Isambert N., Soulie P., Cupissol D., Delcambre C., Bay J.O., Dubray-Longeras P., Krengli M., De Bari B., Villa S., Kaanders J., Torrente S., Pasquier D., Thariat J.O., Myroslav L., Sole C.V., Dincbas H.F., Habboush J.Y., Zilli T., Dragan T., Khan R.K., Ugurluer G., Cena T., Duffaud F., Penel N., Bertucci F., Ranchere-Vince D., Terrier P., Bonvalot S., Macagno N., Lemoine

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- C., Lae M., Coindre J.M. and Bouvier C. (2017). Prediction of local and metastatic recurrence in solitary fibrous tumor: Construction of a risk calculator in a multicenter cohort from the French sarcoma group (FSG) database. *Ann. Oncol.* 28, 1979-1987.
- Schaefer I.M., Fletcher C.D.M. and Hornick J.L. (2016). Loss of H3K27 trimethylation distinguishes malignant peripheral nerve sheath tumors from histologic mimics. *Mod. Pathol.* 29, 4-13.
- Schneider N., Hallin M. and Thway K. (2017). STAT6 loss in dedifferentiated solitary fibrous tumor. *Int. J. Surg. Pathol.* 25, 58-60.
- Schuetze S.M., Bolejack V., Choy E., Ganjoo K.N., Staddon A.P., Chow W.A., Tawbi H.A., Samuels B.L., Patel S.R., von Mehren M., D'Amato G., Leu K.M., Loeb D.M., Forscher C.A., Milhem M.M., Rushing D.A., Lucas D.R., Chugh R., Reinke D.K. and Baker L.H. (2017). Phase 2 study of dasatinib in patients with alveolar soft part sarcoma, chondrosarcoma, chordoma, epithelioid sarcoma, or solitary fibrous tumor. *Cancer* 123, 90-97.
- Schweizer L., Koelsche C., Sahn F., Piro R.M., Capper D., Reuss D.E., Pusch S., Habel A., Meyer J., Gock T., Jones D.T., Mawrin C., Schittenhelm J., Becker A., Heim S., Simon M., Herold-Mende C., Mechttersheimer G., Paulus W., König R., Wiestler O.D., Pfister S.M. and von Deimling A. (2013). Meningeal hemangiopericytoma and solitary fibrous tumors carry the NAB2-STAT6 fusion and can be diagnosed by nuclear expression of STAT6 protein. *Acta Neuropathol.* 125, 651-658.
- Smith S.C., Gooding W.E., Elkins M., Patel R.M., Harms P.W., McDaniel A.S., Palanisamy N., Uram-Tuculescu C., Balzer B.B., Lucas D.R., Seethala R.R. and McHugh J.B. (2017). Solitary fibrous tumors of the head and neck: A multi-institutional clinicopathologic study. *Am. J. Surg. Pathol.* 41, 1642-1656.
- Stacchiotti S., Negri T., Libertini M., Palassini E., Marrari A., De Troia B., Gronchi A., Dei Tos A.P., Morosi C., Messina A., Pilotti S. and Casali P.G. (2012). Sunitinib malate in solitary fibrous tumor (SFT). *Ann. Oncol.* 23, 3171-3179.
- Stacchiotti S., Libertini M., Negri T., Palassini E., Gronchi A., Fatigoni S., Poletti P., Vincenzi B., Dei Tos A.P., Mariani L., Pilotti S. and Casali P.G. (2013a). Response to chemotherapy of solitary fibrous tumour: A retrospective study. *Eur. J. Cancer* 49, 2376-2383.
- Stacchiotti S., Tortoreto M., Bozzi F., Tamborini E., Morosi C., Messina A., Libertini M., Palassini E., Cominetti D., Negri T., Gronchi A., Pilotti S., Zaffaroni N. and Casali P.G. (2013b). Dacarbazine in solitary fibrous tumor: A case series analysis and preclinical evidence vis-a-vis temozolomide and antiangiogenics. *Clin. Cancer. Res.* 19, 5192-5201.
- Stacchiotti S., Tortoreto M., Baldi G.G., Grignani G., Toss A., Badalamenti G., Cominetti D., Morosi C., Dei Tos A.P., Festinese F., Fumagalli E., Provenzano S., Gronchi A., Pennacchioli E., Negri T., Dagrada G.P., Spagnuolo R.D., Pilotti S., Casali P.G. and Zaffaroni N. (2014). Preclinical and clinical evidence of activity of pazopanib in solitary fibrous tumour. *Eur. J. Cancer* 50, 3021-3028.
- Stacchiotti S., Saponara M., Frapolli R., Tortoreto M., Cominetti D., Provenzano S., Negri T., Dagrada G.P., Gronchi A., Colombo C., Vincenzi B., Badalamenti G., Zuco V., Renne S.L., Collini P., Morosi C., Dei Tos A.P., Bello E., Pilotti S., Casali P.G., D'Incalci M. and Zaffaroni N. (2017). Patient-derived solitary fibrous tumour xenografts predict high sensitivity to doxorubicin/dacarbazine combination confirmed in the clinic and highlight the potential effectiveness of trabectedin or eribulin against this tumour. *Eur. J. Cancer* 76, 84-92.
- Stein R.H., Herman S.D., Phelps R.G. and Sapadin A.N. (2004). Flurid eruption of seborrheic keratoses associated with elevated insulin-like growth factor, hypoglycemia, and solitary fibrous tumor of the pleura. *Int. J. Dermatol.* 43, 944-947.
- Stout A.P. and Murray M.R. (1942a). Localized pleural mesothelioma. *Arch. Pathol.* 34, 951-964.
- Stout A.P. and Murray M.R. (1942b). Hemangiopericytoma: A vascular tumor featuring zimmermann's pericytes. *Ann. Surg.* 116, 26-33.
- Strickland K.C., Nucci M.R., Esselen K.M., Muto M.G., Chopra S., George S. and Howitt B.E. (2016). Solitary fibrous tumor of the uterus presenting with lung metastases: A case report. *Int. J. Gynecol. Pathol.* 35, 25-29.
- Subramaniam M.M., Lim X.Y., Venkateswaran K., Shuen C.S., Soong R. and Petersson F. (2011). Dedifferentiated solitary fibrous tumour of the nasal cavity: The first case reported with molecular characterization of a TP53 mutation. *Histopathology* 59, 1269-1274.
- Tai H.C., Chuang I.C., Chen T.C., Li C.F., Huang S.C., Kao Y.C., Lin P.C., Tsai J.W., Lan J., Yu S.C., Yen S.L., Jung S.M., Liao K.C., Fang F.M. and Huang H.Y. (2015). NAB2-STAT6 fusion types account for clinicopathological variations in solitary fibrous tumors. *Mod. Pathol.* 28, 1324-1335.
- Tan S.Y., Szymanski L.J., Galliani C., Parham D. and Zambrano E. (2018). Solitary fibrous tumors in pediatric patients: A rare and potentially overdiagnosed neoplasm, confirmed by STAT6 immunohistochemistry. *Pediatr. Dev. Pathol.* 21, 389-400.
- Tanahashi J., Kashima K., Daa T., Kondoh Y., Suzuki M., Kerakawauchi H. and Yokoyama S. (2006). Solitary fibrous tumor of the thyroid gland: report of two cases and review of the literature. *Pathol. Int.* 56, 471-477.
- Tapia J.L., Goodloe S. 3rd, Margarone J.E. 3rd, Markiewicz M.R. and Aguirre A. (2011). Solitary fibrous tumor with entrapment of minor salivary gland tissue: an unusual presentation that requires exclusion of pleomorphic adenoma. *Head Neck Pathol.* 5, 314-320.
- Tardio J.C., Machado I., Alemany I., Lopez-Soto M.V., Nieto M.G. and Llombart-Bosch A. (2018). Solitary fibrous tumor of the vulva: Report of 2 cases, including a de novo dedifferentiated solitary fibrous tumor diagnosed after molecular demonstration of NAB2-STAT6 gene fusion. *Int. J. Gynecol. Pathol.* 37, 547-553.
- Tazeler Z., Tan G., Aslan A. and Tan S. (2016). The utility of 18F-FDG PET/CT in solitary fibrous tumors of the pleura. *Rev. Esp. Med. Nucl. Imagen. Mol.* 35, 165-170.
- Thway K., Hayes A., Ileremia E. and Fisher C. (2013). Heterologous osteosarcomatous and rhabdomyosarcomatous elements in dedifferentiated solitary fibrous tumor: Further support for the concept of dedifferentiation in solitary fibrous tumor. *Ann. Diagn. Pathol.* 17, 457-463.
- Torabi A., Lele S.M., DiMaio D., Pinnt J.C., Hess M.M., Nelson M. and Bridge J.A. (2008). Lack of a common or characteristic cytogenetic anomaly in solitary fibrous tumor. *Cancer Genet. Cytogenet.* 181, 60-64.
- Toulmonde M., Penel N., Adam J., Chevreau C., Blay J.Y., Le Cesne A., Bompas E., Piperno-Neumann S., Cousin S., Grellety T., Ryckewaert T., Bessede A., Ghiringhelli F., Pulido M. and Italiano A. (2018). Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas: A phase 2 clinical trial. *JAMA Oncol.* 4, 93-97.
- Vallat-Decouvelaere A.V., Dry S.M. and Fletcher C.D.M. (1998). Atypical and malignant solitary fibrous tumors in extrathoracic locations: Evidence of their comparability to intra-thoracic tumors. *Am. J. Surg. Pathol.* 22, 1501-1511.

- van de Rijn M., Lombard C.M. and Rouse R.V. (1994). Expression of CD34 by solitary fibrous tumors of the pleura, mediastinum, and lung. *Am. J. Surg. Pathol.* 18, 814-820.
- Vivero M., Doyle L.A., Fletcher C.D.M., Mertens F. and Hornick J.L. (2014). GRIA2 is a novel diagnostic marker for solitary fibrous tumour identified through gene expression profiling. *Histopathology* 65, 71-80.
- Wagner E. (1870). Das tuberkelähnliche lymphadenom (der cytogene oder reticulirte tuberkel). *Arch Heilk (Leipzig)* 11, 497.
- Westra W.H., Gerald W.L. and Rosai J. (1994). Solitary fibrous tumor. Consistent CD34 immunoreactivity and occurrence in the orbit. *Am. J. Surg. Pathol.* 18, 992-998.
- Westra W.H., Grenko R.T. and Epstein J. (2000). Solitary fibrous tumor of the lower urogenital tract: a report of five cases involving the seminal vesicles, urinary bladder, and prostate. *Hum. Pathol.* 31, 63-68.
- Yabuki H., Sakurada A., Niikawa H., Notsuda H., Endo C., Matsuda Y., Noda M., Saito R., Yamashita S., Arai Y. and Okada Y. (2016). Serum β -hCG as an indicator of recurrence after the complete resection of a malignant solitary fibrous tumor of the pleura. *Ann. Thorac. Surg.* 102, e551-e553.
- Yalcin C.E. and Tihan T. (2016). Solitary fibrous tumor/hemangiopericytoma dichotomy revisited: A restless family of neoplasms in the CNS. *Adv. Anat. Pathol.* 23, 104-111.
- Yoshida A., Tsuta K., Ohno M., Yoshida M., Narita Y., Kawai A., Asamura H. and Kushima R. (2014). STAT6 immunohistochemistry is helpful in the diagnosis of solitary fibrous tumors. *Am. J. Surg. Pathol.* 38, 552-559.
- Yuzawa S., Nishihara H., Wang L., Tsuda M., Kimura T., Tanino M. and Tanaka S. (2016). Analysis of NAB2-STAT6 gene fusion in 17 cases of meningeal solitary fibrous tumor/hemangiopericytoma: Review of the literature. *Am. J. Surg. Pathol.* 40, 1031-1040.

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