Review Article

Fibroblastic sarcomas of the mediastinum

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Abstract: Primary mediastinal fibroblastic sarcomas constitute a rare, heterogeneous group of neoplasms, mainly including solitary fibrous tumor (SFT) (benign and malignant), low grade fibromyxoid sarcoma (LGFMS), adult fibrosarcoma (FS), myxofibrosarcoma, sclerosing epithelioid FS, etc. Although morphologically diverse, they frequently have similar clinical and radiological features. Overlapping of histological features among these neoplasms can make it challenging for pathologists to come to an accurate diagnosis. In addition, other mesenchymal neoplasms and spindle cell neoplasms of the epithelial cell origin can occur in the mediastinum. Immunostaining and molecular testing are important ancillary studies to confirm or rule out primary mediastinal fibroblastic neoplasms. SFT and LGFMS occur more often than adult FS in the mediastinum and both have reliable immunostaining markers STAT6 and MUC4, respectively, and unique molecular changes. The incidence of adult FS has decreased dramatically due to recognition of morphologically and genetically distinctive subtypes of fibroblastic sarcoma and better understanding of mesenchymal and non-mesenchymal mimickers. Adult FS is extremely rare and a diagnosis of exclusion. Adult FS can be rendered only after careful histological examination and thorough ancillary studies have ruled out all its mimickers. This article is focused on reviewing clinicopathological features, immunostaining, molecular changes, prognosis and differential diagnosis of SFT, LGFMS, and adult FS. Correct diagnosis is crucial for oncologists to make appropriate clinical management plans.

Keywords: Fibroblastic sarcoma of the mediastinum; solitary fibrous tumor (SFT); low grade fibromyxoid sarcoma (LGFMS); adult fibrosarcoma (adult FS)

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Introduction

Primary sarcomas of the mediastinum are rare, accounting for only 1.4% of soft tissue sarcomas (1) and constitute 2% to 8% of primary mediastinal malignancies (2,3). Patients may have symptoms and ominous signs due to the location of these tumors adjacent to vital structures. Almost all entities arising from peripheral soft tissues can be encountered in the mediastinum except for organ-specific tumors, such as gastrointestinal stromal tumors. This article will be focused on some fibroblastic sarcomas of the mediastinum, including solitary fibrous tumor (SFT) (benign and malignant), low grade fibromyxoid sarcoma (LGFMS), and adult fibrosarcoma (FS). Infantile FS is a distinct entity with different clinicopathological and genetic findings and beyond the scope of this article. Sclerosing epithelioid sarcoma and myxofibrosarcoma are extremely rare in the mediastinum and will not be discussed here.

SFT

SFT is usually a well-circumscribed fibroblastic tumor consisting of an admixture of spindle cells and thick collagen stroma with at least focal areas of branching

Table 1 Review of some single case reports of mediastinal SFT in the English literature

Reference	Case #	Age (y)/sex	Clinical presentation	Location	Size (cm)	Gross	Histology
Weidner, 1991 (8)	1	62/F	Asymptomatic, mass by routine X-ray, well circumscribed by CT	Anterior mediastinum	5.4	Firm, gray-white with a smooth capsule	Typical morphology with rare mitoses, no necrosis or atypia
Bortolotti *et al.*, 1992 (9)	2	60/M	Pericardial effusion, large mass anterior to the ascending aorta and pulmonary trunk by CT	Intrapericardial	14	White with whorled appearance and scattered hemorrhage	Typical morphology with no mitoses
Iwata *et al.*, 2007 (10)	3	74/F	Asymptomatic, incidentally detected by a routine X-ray	Thymus	5.3	Invading into the left lung and pericardium	Typical morphology, no significant mitoses or pleomorphism
Gannon *et al.*, 2007 (11)	4	62/F	Stridor	Anterior mediastinum	10.5	Firm and circumscribed with no cardiac or lung involvement	Typical morphology with HPC-like blood vessels
Liu *et al.*, 2007 (12)	6	61/M	Asymptomatic, detected by CT	Posterior mediastinum	9.5	Lobulated and well circumscribed, rubbery with white-tan appearance	Typical morphology with fat component
Zhao *et al.*, 2012 (13)	7	55/M	Shortness of breath, jugular vein engorgement, right pleural effusion	Anterior mediastinum with the right atrial involvement	6	Firm and white-grey, attached to the interior wall of the right atrium	Malignant SFT
Xiang *et al.*, 2017 (14)	8	42/M	Dry cough over 12 months, solid mass detected by CT	Anterior mediastinum	6	Firm and grey, involvement of the pericardium and right upper lobe of the lung	Malignant SFT
Webb *et al.*, 2017 (15)	9	32/M	Chest pain for 6 months, recently developed dysphagia, cough, and dyspnea	Middle mediastinum	18	Tan-red to yellow lesion, multicystic and partially necrotic	Increase cellularity and mitoses, classified as high risk

SFT, solitary fibrous tumor.

staghorn blood vessels. It was originally thought to be a neoplasm of pleura, other serosal surfaces, and mediastinum. However, it is now recognized as a tumor that commonly affects deep soft tissue and can virtually occur at any location including the meninges (4-7). SFTs can arise in the anterior and posterior mediastinal connective tissue, thymic tissue, pericardium, heart, etc. (6,8-16) without any involvement of the pleura. SFT commonly occur in the anterosuperior and posterior mediastinum and rarely in the middle mediastinum. Most patients are asymptomatic and mediastinal masses are detected incidentally on an imaging study performed for an unrelated condition. Symptomatic patients commonly present with cough, chest pain, dyspnea and other discomfort. Extrathoracic findings associated with mediastinal SFT include clubbing, osteoarthropathy, and hypoglycemia (caused by an insulin-like growth factor produced by the tumor cells). These manifestations are more likely to be seen in patients with large mediastinal masses.

Mediastinal SFTs are rare and the exact incidence is unknown. Review of two larger case series (6,16) and single case reports (summarized in *Table 1*) together (total 34 cases excluding one case without designating sex in Witkin *et al*. series) shows a wide age range (27 to 81 years) with a peak of incidence in the fifth and sixth decades with male predominance (a male to female ratio of 2:1). The tumors range from 3.0 to 24.0 cm in size and are usually encapsulated firm masses with lobulated and whorled appearance. The cut surface is white to gray, often

associated with focal cystic degeneration. Microscopic examination (*Figure 1*) shows spindle cell proliferation with areas of hypocellularity and hypercellularity, dense collagenization, and myxoid change. Tumor cells have relatively bland nuclear features with indistinct cell borders and are randomly arranged in strands between thick and keloid-like collagen bundles. A hemangiopericytoma-like blood vessel pattern can be present at least focally in most cases. Mitoses are scarce, usually between 1 and 3 per 10 high power fields. Fat-forming variant of mediastinal SFT have also been described (12). Malignant SFTs are usually characterized by hypercellularity, increased mitotic activity (≥4 mitoses/10 hpf), nuclear atypia and necrosis (17). Malignant lesions tend to be larger and show infiltrative growth borders. The cells of SFT are positive for CD34 (90% to 95% cases) and CD99 (70% cases) and variably positive for EMA, Bcl-2, and SMA (20% to 35% cases). Recent study demonstrated nuclear expression of STAT6 in 98% of 60 SFTs (40 benign, 5 atypical and 15 malignant) with polyclonal antibody (18) and 100% of 54 and 45 SFTs respectively using monoclonal antibody (19,20). STAT6 is a useful diagnostic marker to distinguish SFT from other spindle cell neoplasm or histologic mimics. SFTs harbor a recurrent intrachromosomal fusion between the *NAB2* and *STAT6* genes on chromosome 12 (*NAB2-STAT6*) (21-23), which can be detected by RT-PCR. However, the close proximity of these genes makes the fusion difficult to be detected by conventional chromosomal banding or fluorescence *in situ* hybridization (FISH) techniques. The diagnosis of conventional SFTs is straightforward in well-sampled materials. Diagnostic challenges more often occur in fat-forming and giant cell-rich variants of SFTs and malignant SFTs. STAT6 immunostaining and RT-PCR of *NAB2-STAT6* fusion gene should be helpful for rendering a diagnosis of SFT (24).

Complete surgical excision with negative margins is the treatment choice for both benign and malignant SFT. Limited data that is available suggests that mediastinal SFTs are more aggressive than SFTs of the pleura (6,25), but larger studies are necessary. Aggressive or malignant behavior generally is characterized by local recurrence, intrathoracic spread, and distant metastases. Recurrence can occur years later after the initial excision highlighting the necessity of long-term follow-up. Although long-term follow-up of mediastinal SFT is rarely reported, pleuropulmonary SFT generally shows a benign clinical course, but a subset will recur or metastasize, with an estimated 5-year progression rate in the range of 8.5% (26). Morphological features are not always reliable for predicting tumor behavior, but most histologically benign SFTs do not recur or metastasize after complete excision. Malignant SFT shows a higher metastatic potential than predominantly fibrous SFT (20% to 30% *vs*. 5%) (27,28). Recently, a proposed risk stratification model using age (≥55 years), size (≥15 cm), mitotic index (≥4 per 10 HPF) and necrosis (≥10%) was developed to predict a high risk of metastasis (29). Molecular predictors of behavior for SFT remain to be identified.

LGFMS

LGFMS is a malignant fibroblastic tumor with deceptively benign spindle cell proliferation, contrasting fibrous and myxoid areas and late metastasis. Hyalinizing spindle cell tumor (HSCT) with giant rosettes is now considered a histological variant of LGFMS as they both share the same genetic abnormalities (30-34). LGFMS typically involves the proximal extremities and trunk. It was first reported by Evans in 1987, who described two female patients with lung metastases. Both patients had histories of resections of bland-appearing soft tissue tumors located in the soft tissues of the scapular area and the axillary–chest wall area, respectively (30). Later, Evans expanded his original series with up to 33 cases published in two series (31,32), that showed the typical histological findings and other unusual features. The exact incidence of LGFMS is unknown because these have been misdiagnosed as other mesenchymal tumors including benign fibrous tissue, desmoid-type fibromatosis, peripheral nerve sheath tumor, monophasic synovial sarcoma, and gastrointestinal stromal tumors (35).

Only rare cases of primary mediastinal LGFMS have been reported in the English literature (36-39) and occurred in the anterior mediastinum (3 cases), the superior mediastinum (1) and the epicardium/right heart (1) (*Table 2*). The age of patients ranged from 19 to 50 years with male to female ratio 3:1. Tumor size ranged from 7 to 20 cm. Gross examination showed a well circumscribed firm mass with lobular appearance (3 cases), necrosis (1 case), calcification (1 case) and hemorrhage (1 case). The tumor involved the anterior portion of the superior vena cava (1 case), the right heart epicardium (1 case), and chest wall (1 case). Histologically, all these cases displayed areas of characteristic hypocellular myxoid and hyalinized zones (*Figure 2* and *Table 3*). Three cases had giant rosettes (collagenous center surrounded by a cuff of tumor cells).

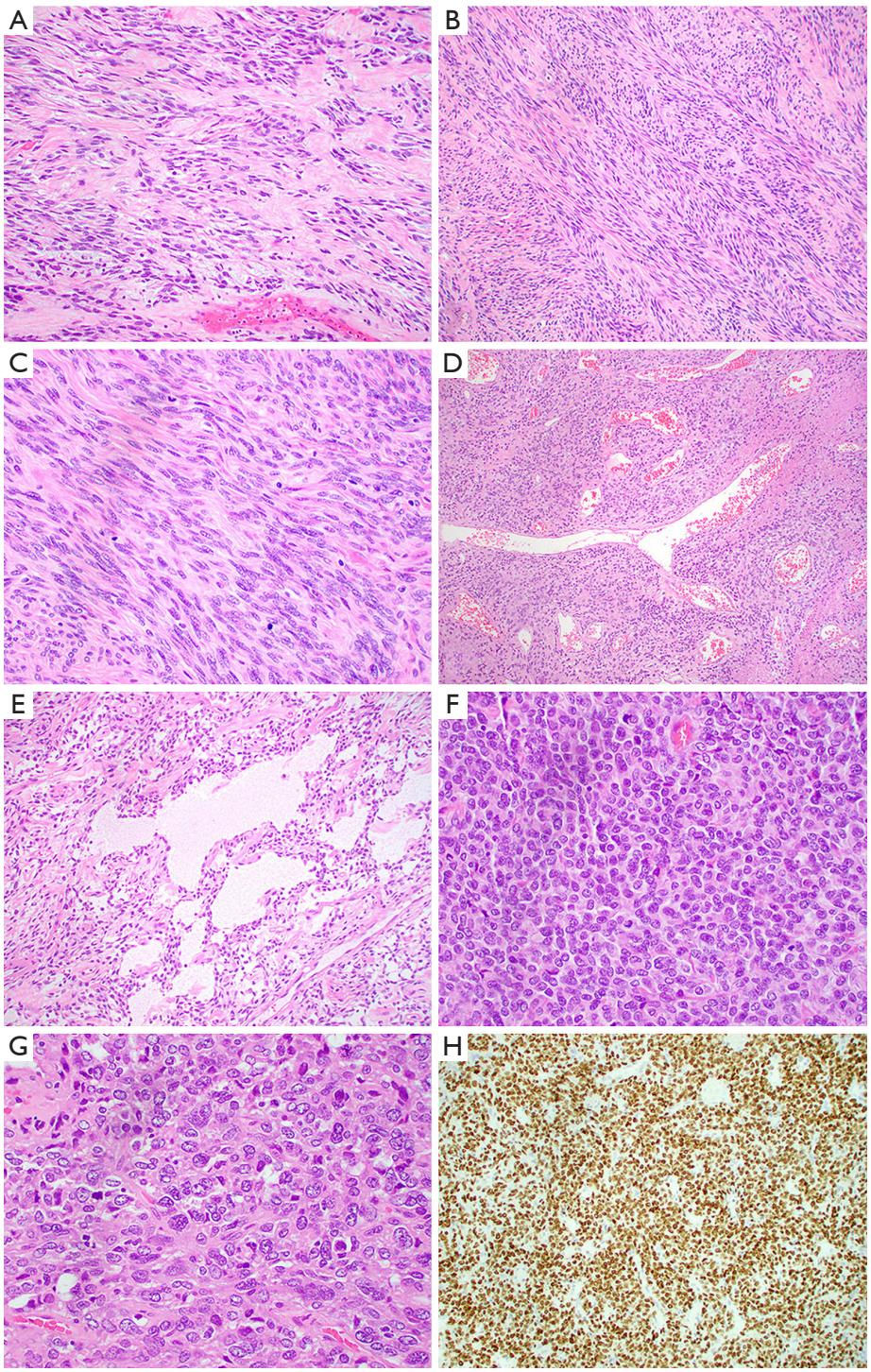

Figure 1 Solitary fibrous tumor (SFT). (A) Spindle cell proliferation with variable amount of collagen in the background, fibrous form of SFT (200×); (B) fascicular growth pattern can be present (200×); (C) spindle cells have elongated monomorphic nuclei, inconspicuous nucleoli, and indistinct pale cytoplasm. A few mitotic figures are present (400×); (D) staghorn blood vessel and perivascular hyalinization are present (100×); (E) small cystic change (200×); (F) hypercellular area with round to oval monomorphic nuclei, little intervening fibrosis and increased mitosis (400×); (G) malignant SFT with nuclear enlargement and marked pleomorphism (400×); (H) lesional cells in SFT show diffuse nuclear positivity for STAT6 (200×).

Table 2 Clinical features of LGFMS

Reference	Case #	Age (y)/sex	Mediastinum	Number of tumor	Tumor size (cm)	Clinical presentation and imaging findings	Excision	Local recurrence and follow-up (month)
Takanami *et al*., 1999 (37)	1	35/M	Anterior	Single	9	Gradually enlarging mass for 7 years, detected by X-ray	Yes. Excised with the portion of the sternum, the head of the left clavicle, and partial left first rib	Yes/108, recurrent tumor (6.0 cm) in the same location has the exact histology as the primary, Wider excision performed
Galetta *et al*., 2004 (36)	2	41/M	Anterior	Single	8	Abnormal mediastinal shadow on a routine X-ray, close contact with SVC and the ascending aorta by CT	Yes. Radically excised with a portion of SVC and mediastinal fat	No/35, irradiated with 60 Gy
Jakowski *et al*., 2008 (38)	3	44/F	Epicardium/ right heart	Single	12	Vague retrosternal discomfort for a few months, a large mass involving the right heart by echocardiogram and MRI	Yes. Completely excised with a 1-cm portion of uninvolved right atrial wall	No/7
Maeda *et al*., 2009 (39)	4	19/F	Anterior	Single	23.5	A mass since the age of 5, massive left-sided pleural effusion and atelectasis of the left hemithorax	Yes. Completely excised	Yes/60, lobulated masses in the anterior medisrtinum, chest wall, and at the base of the diaphragm, same gross findings as the primary mass, pleural effusion
Maeda *et al*., 2009 (39)	5	50/M	Superior	Single	13	A mass detected 10 months ago by a routine X-ray, chest pain 4 months before the surgery	Yes. Resected together with the first rib, the chest wall, right subclavian artery, etc.	No/60

LGFMS, low grade fibromyxoid sarcoma.

The bland spindle cells were arranged in a storiform or fascicular pattern with rare mitoses and slight nuclear pleomorphism. Vasculature is either focally or diffusely present. Lesional cells are positive for vimentin (diffuse) and SMA (focal) and negative for S100, CK, desmin, CD34, and EMA. The diagnosis can be confirmed by FISH with FUS dual-color break-apart probes or by EM, which shows numerous intermediate filaments and dilated rough endoplasmic reticulum in the spindled cells, indicating the fibroblastic origin. More recently, diffuse and strong cytoplasmic staining for MUC4 has been demonstrated to be a highly sensitive and specific immunohistochemical marker of genetically confirmed LGFMS (40,41). In these studies, all the histologic mimickers of LGFMS were negative for MUC4, except for 30% of monophasic synovial sarcomas analyzed. Some authors consider MUC4 expression, even without confirmatory FISH studies, as a sufficient ancillary test for the diagnosis of LGFMS. The majority of LGFMS harbor a common t(7;16)(q34; p11) resulting in the fusion gene *FUS-CREB3L2* while a minority of cases contain t(11;16)(p11;p11) resulting the fusion gene *FUS-CREB3L1* (34).

All the mediastinal LGFMS cases are essentially identical to their counterparts in the extremities and trunk (32,34). The natural history of LGFMS in the mediastinum also appears to be similar to that of their counterparts elsewhere, with potential for late (greater than 5 years) local recurrence (*Table 2*). Distant metastases have not yet been reported; this could be due to limited case number and a short period of follow-up. However, the

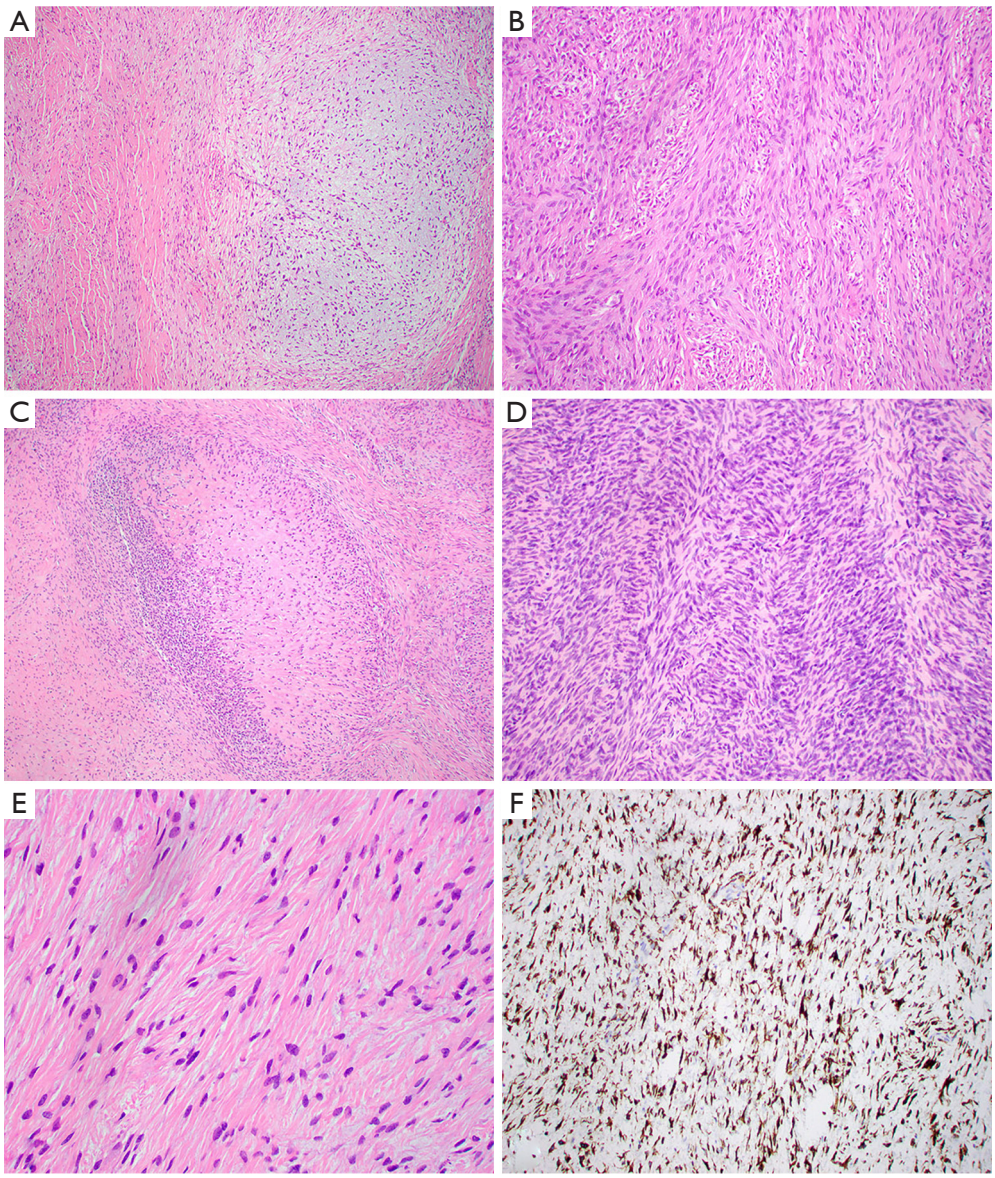

Figure 2 Low grade fibromyxoid sarcoma (LGFMS). (A) Classic feature of LGFMS with alternating fibrous and myxoid areas (100×); (B) fascicular and vaguely whorled growth of lesional cells (200×); (C) giant collagen rosette characterized by hyalinized collagen surrounded by epithelioid cells (100×); (D) occasional, herringbone growth pattern can occur (200×); (E) bland, short spindle cells with oval and elongated nuclei, fine chromatin, inconspicuous nucleoli, and scant cytoplasm (200×); (F) lesional cells are diffusely positive for MUC4 (100×).

potential for late metastatic spread to the lung and pleura is high, necessitating long-term follow-up for all patients with LGFMS (32,34). Some cases reported outside the mediastinum have unusual cytomorphological features and growth patterns such as hypercellular areas with moderate nuclear pleomorphism, round cell morphology, increased mitoses, and fascicular-herringbone pattern (*Figure 2D*). Areas of sclerosing epithelioid FS and dedifferentiation with predominantly round cells and numerous mitotic figures have been reported (32). Although dedifferentiation resulted in short survival, unusual morphological features did not have effect on tumor behavior or prognosis. Another large study of 73 cases also showed LGFMS with occasional presence of intermediate- to high-grade sarcoma, which did not have a worse outcome in short term follow-up (33).

Table 3 Gross examination, morphological features and ancillary studies of LGFMS

Case #	Gross examination	Morphology	IHC and molecular study
1	Well capsulated	Typical LGFMS, bland-appearing fibroblastic cells in fibrous and myxoid areas, slight nuclear pleomorphism, rare mitotic figures, mostly a whorled pattern	None
2	Firm mass with pseudo-capsule and infiltration of the anterior-external wall of the SVC, gray-white on the cut surface	LGFMS with giant rosettes, vascularized, myxoid and hyalinized areas, large rosette-like structures, a few mitotic figures,	Positive for vimentin, negative for S100, CK, desmin, CD34, and EMA
3	A well-circumscribed oval mass with no extension into the myocardium, uncapsulated, lobulated pink-tan tissue with approximately 30% of necrosis on the cut surface	LGFMS with numerous giant rosettes, admixture of hypocellular myxoid and hyalinized areas, storiform or fascicular growth pattern, uniform nuclei with indistinct nucleoli, 1 to 2 mitoses per 50 HPF, necrosis with dystrophic calcification, focally vascularized	Positive for vimentin, CD99 (weak), SMA (focal), negative for CD34, EMA, MSA, AE 1/3, desmin, and S100, FUS gene rearrangement positive
4	A well-circumscribed lobulated mass with multiple nodular calcifications, encapsulated, white-yellow	LGFMS with giant rosettes, hypercellular, hypocellular myxoid and hyalinized zones, each zone has abundant small- and medium-sized blood vessels	None
5	A solid-hard, well-circumscribed, and encapsulated whitish mass, firmly attached to the chest wall, multilobular, hemorrhage	Typical LGFMS, hypocellular myxoid stroma in the lateral portion of the mass, hypercellular with a whorled arrangement of spindle cells and variable vascularity in the medial portion of the mass	None

LGFMS, low grade fibromyxoid sarcoma.

Adult FS

Adult FS (or FS) was described as a "*malignant tumor, composed of fibroblasts with variable collagen and, in classical cases, a herringbone architecture*" by the World Health Organization (WHO) (42). Although it was once considered as the most common adult sarcoma, changes in the diagnostic criteria have made it a rare entity. There is considerable doubt about the veracity of demographic and clinicopathologic features of FS in the older literature without immunostaining and electron microscopy studies (43). Proper classification of soft tissue tumors with morphological features, new immunostaining markers and characteristic molecular changes has resulted in marked decline in the number of adult FS because numerous cases formerly diagnosed as FSs were actually dedifferentiated liposarcoma (DDL), fibromatosis, fibrosarcomatous DFSP, LGFMS, malignant peripheral nerve sheath tumor (MPNST), synovial sarcoma, etc. (43-45). A 2010 review for adult-type FS from a single institution over a 48-year period by Bahrami and Folpe revealed that true adult FS accounts for <1% of approximately 10,000 adult soft tissue sarcomas diagnosed from 1960 to 2008 at Mayo clinic (43).

Mediastinal adult FS is an extremely rare tumor. Only 26 cases of 163 cases previously diagnosed as adult FS over a 48-year period met WHO diagnostic criteria; one case possibly arose from the mediastinum (43). Another large study of 39 low grade FS cases (not otherwise specified) published in 2006 revealed that 6 tumors involved the thorax without mentioning the mediastinum specifically (44). Review of the older English literature from 1955 to 1991 show 7 reported mediastinal FS cases (46-48); it is unclear how many of these would meet the modern definition (48). However, one case of mediastinal FS was confirmed by morphological features and electron microscopy (48). The 34-year-old white female developed chest pain with cough, dyspnea, and dysphagia. Imaging revealed a bulky mass (19.0 cm) in the anterior mediastinum. Grossly, it was well-circumscribed and encapsulated with grey-white appearance on the cut surface. Histological examination revealed cellular, intersecting fascicles composed of plump to spindle cells with a moderate degree of atypia and numerous mitotic figures. Electron microscopy displayed loosely arranged fibroblast-like cells with prominent endoplasmic reticulum and varying amount of collagen fibers around the cells (48).

Due to the rarity of mediastinal adult FS, review of this neoplasm must be extrapolated from studies reported at other body sites (43-45). FS most often arises from the deep soft tissues of the extremities, truck, head and neck. It is uncommon in the visceral organs and retroperitoneum, where sarcomatoid carcinoma and low

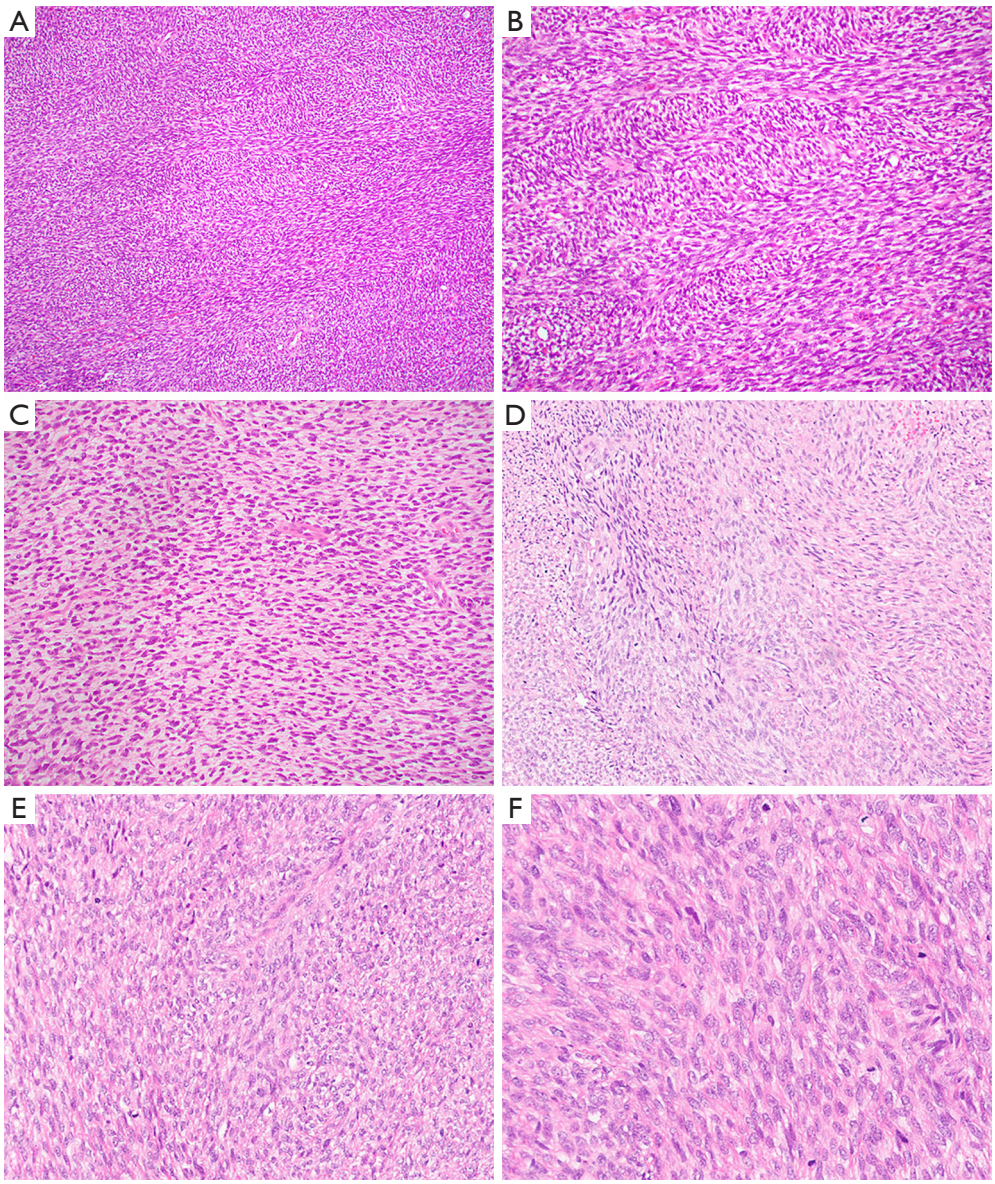

Figure 3 Adult FS. (A,B,C) FS with a striking herringbone pattern consists of relatively uniform, hyperchromatic spindled cells (A, 100×; B, 200×). Area with no particular pattern and less cellularity. Increased mitosis, nuclear pleomorphism and delicate intercellular collagen (C, 200×); (D,E,F) radiation induced adult FS in the right subclavicular area showing intersecting fascicles of atypical spindle cell proliferation (D, 50×), moderate nuclear pleomorphism, irregular nuclear contour, small nucleoli, increased mitosis and scant collagen in the background (E, 100×; F, 200×). FS, fibrosarcoma.

grade dedifferentiated liposarcoma should be ruled out respectively. Adult FS most commonly occurs in middle-aged and older adults (median age, 50 years), with a slight male predominance. Histological examination of adult FS reveals relatively monophasic spindle cells with no more than a moderate degree of pleomorphism (*Figure 3*). The lesional cells resemble normal fibroblasts and are arranged in fascicles that intersect each other at acute angles, resulting in a herringbone pattern and at times a storiform growth pattern. Lesional cells have elongated hyperchromatic nuclei, variably prominent nucleoli and scanty cytoplasm with variable mitotic activity. The amount

of stromal collagen can range from a delicate intercellular network to areas with keloid like sclerosis or hyalinization. Fibromatosis-like areas may be present in some FS. Immunohistochemically, the prototypical FS should be positive for vimentin and type I collagen. The presence of focal immunoreactivity for SMA and laminin indicate myofibroblastic differentiation.

FSs are aggressive. The survival rate in one large series was 41% at 5 years and 29% at 10 years (49). Increased mitoses and hypercellularity were associated with an increased incidence of metastases (49). Another series study of strictly defined adult FS disclosed that at least 80% of tumors were high-grade (FNCLCC grade 2 or 3). One of the four low-grade lesions progressed to a high-grade sarcoma when it recurred. Multiple local recurrences, lymph node and parenchymal metastasis occurred. The overall survival rate was <70% at 2 years and <55% at 5 years. Due to the limited number of FS cases, no correlation could be made between clinicopathological features (such as grading, tumor size) and prognosis (43).

Differential diagnoses

A wide range of spindle cell mesenchymal neoplasms can occur in the mediastinum. The main differential diagnoses for mediastinal SFT include spindle cell thymoma, desmoplastic mesothelioma, monophasic synovial sarcoma, spindle cell lipoma and LGFMS. Spindle cell thymomas are composed of relatively benign spindle to ovoid epithelial cell nests separated by bands of collagen. Other features include lack of mitotic figures and the presence of small immature T lymphocytes (50). Tumor cells are uniformly positive for cytokeratin and P63 (strong and diffuse) and negative for STAT6. Desmoplastic mesothelioma commonly arises from the pleura and consists of atypical cells in a storiform or nonspecific pattern with a dense collagenous background. Atypical cells are positive for CK5/6, WT1, D2-40 and calretinin. Monophasic synovial sarcoma can mimic cellular SFT (previously called hemangiopericytoma) and malignant SFT. They both can display HPC-like or staghorn vascular patterns. Monophasic synovial sarcoma is composed of relatively uniform spindle cells with a high N/C ratio, oval and vesicular nuclei, scant cytoplasm and indistinct cell borders. The tumor cells grow as sheets or fascicles with hyalinized or wiry collagen in the background (50). The mitotic rate is highly variable and dystrophic calcifications are relatively common. The spindle cells are positive for TLE1 (diffuse to patchy), cytokeratin (focal), EMA (focal), and CD99. Majority of synovial sarcoma contain a characteristic t(X;18) balanced translocation, which can be detected by FISH of *SYT* (*SS18*) gene or RT-PCR of the *SS18-SSX* fusion gene. Spindle cell lipoma can also be a diagnostic pitfall for fat-forming SFT. It is typically composed of short stubby spindle cells, distinctive ropy collagen, and a variable adipose component with lack of HPC-like blood vessels. It is usually strongly and diffusely positive for CD34 and negative for STAT6 (18). SFT can be confused with LGFMS, particularly on core biopsies, as both show a benign-looking spindle cell proliferation with collagen in the background. LGFMS is diffusely positive for MUC4 and almost never expresses CD34 or STAT6 (40).

It is important to distinguish LGFMS from benign neoplasms due to LGFMS late metastatic spread. LGFMS can shows hypocellular areas of bland spindle cell morphology with abundant collagenized stroma. The main differential diagnosis of LGFMS includes typical SFT, desmoid fibromatosis, neurofibroma, and MPNST in the mediastinum. Fibrous forms of SFT are composed of variable bland oval spindle cells with no specific growth pattern and variable hyalinized stromal collagen. The stroma may have a variable degree of myxoid change. These features can overlap with LGFMS. However, staghorn blood vessels and medium-sized round vessels with variable perivascular hyalinization are a common feature for SFT (7). Instead LGFMS have curvilinear capillary vessels or arcades of blood vessels, occasionally with perivascular hyalinization in the myxoid areas (34). A subset of LGFMS can have areas of a fascicular growth pattern reminiscent of desmoid fibromatosis (34). Fibromatosis can occur in the mediastinum (51). It has infiltrative borders, but entirely lacks metastatic potential. It displays long fascicles of uniform bland myofibroblastic cells admixed with well-formed medium-sized blood vessels with muscular wall. It does not have the curvilinear blood vessels commonly present in the myxoid areas of LGFMS. Between 70% to 80% of desmoid fibromatosis shows nuclear staining of beta-catenin. LGFMS with focal myxoid change and lack of alternating fibrous and myxoid areas can resemble neurofibroma. Neurofibromas occur in association with nerves in the paraspinal region and present as mass forming lesions in the posterior mediastinum (52). Both show spindle cell proliferation with whorled or vaguely whorled growth pattern and variably myxoid or collagenous stroma. However, neurofibroma is composed of elongated spindle cells with wavy or buckled hyperchromatic nuclei,

admixed with a population of short spindle cells. LGFMS consists of bland, short spindle cells with ovoid nuclei and fine chromatin. Heterogeneous cells of neurofibroma are highlighted by S100 (Schwann cells) and CD34 (fibroblasts). MPNST is often associated with a large nerve at the posterior mediastinum and typically show a more fascicular growth pattern than LGFMS with perivascular hypercellularity, tapering nuclei, and rare focal expression of S100.

It is not uncommon that monophasic SS, cellular SFT and MPNST were misdiagnosed as adult FS. As mentioned earlier, only 26 cases (16%) of the 163 putative FSs reported by Bahrami and Folpe met diagnostic criteria for FS. Some previously diagnosed FS cases were reclassified as synovial sarcoma (21 cases, 13%), SFT (14 cases, 9%) and MPNST (8 cases, 5%) (43). This is not surprising because some monophasic SSs consists of tight intersecting fascicles with a herringbone (FS-like) appearance; of note it should be remembered that monophasic SS was not recognized as a definite entity until the mid-1980s (45). However, the presence of HPC-like blood vessels, wiry collagen, stromal calcification and mast cells should always raise consideration of SS. Molecular studies of t(X;18)(p11;q11) should help to confirm or rule out SS. TLE1 immunostaining is not specific, but absence of TLE1 staining helps to rule out SS. Cellular SFT has a monotonous appearance with moderate to high cellularity, round to oval nuclei and little intervening fibrosis, resembling FS and monophasic SS. However, staghorn blood vessels, myxoid or microcystic change, nuclear palisading, and interstitial mast cells are commonly observed in SFT. Malignant SFT can show dedifferentiation. However, unlike FS, lesional cells in SFT are positive for CD34 and STAT6 (18). MPNST can occur in the posterior mediastinum and shows fascicles of monotonous spindle cells with a "herringbone" pattern, mimicking FS (50). It also reveals alternating hypercellular and hypocellular zones with accentuated perivascular cellularity. Lesional cells are focally positive for S100 in 50% cases (53), and patchy positive for SOX10 (54). The majority of both sporadic (95%) and radiotherapy-related (91%) MPNSTs showed loss of H3K27me3 expression (55). Other mimickers such as cellular schwannoma, fibromatosis, LGFMS, and dedifferentiated liposarcoma might be misdiagnosed as adult FS (43). Morphological features of fibromatosis and LGFMS have been discussed above. Schwannoma most commonly occurs in the posterior mediastinum and presents as a well circumscribed mass. Lesional cells are diffusely positive for S100 and SOX10. Finally, low grade dedifferentiated liposarcoma may show spindle cell morphology which mimics FS. If well-differentiated liposarcoma is present in the background, the diagnosis of low grade dedifferentiated liposarcoma can generally be rendered without difficulty. For difficult cases, dedifferentiated liposarcoma typically shows expression of CDK4 and MDM2 and *MDM2* amplification by FISH (34).

Conclusions

In summary, SFT and LGFMS show unique clinicopathological and molecular features that separate them from adult FS. Immunostaining and molecular testing are very helpful for rendering a definitive diagnosis of SFT and LGFMS. In contrast, adult FS is inherently a diagnosis of exclusion (43). A large number of mesenchymal and nonmesenchymal tumors may mimic adult FS, including MPNST, monophasic synovial sarcoma, SFT, spindle cell melanoma, sarcomatoid carcinoma, etc. Diagnosis of adult FS should be rendered only with the greatest of trepidation after all mimickers have been excluded through taking into account the clinical information, morphological features, immunostaining, molecular testing and possible electron microscopy study (43). So far there are no distinct immunohistochemical markers or molecular features that are pathognomonic for the diagnosis of adult FS and the underlying molecular genetics remain to be fully explored.

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Footnote

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