

Role of Immunohistochemistry in the Diagnosis of Solitary Fibrous Tumor, a Review

Bitá Geramizadeh¹, Mahsa Marzban², Andrew Churg³

1. Dept. of Pathology, Transplant Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

2. University of British Columbia, Vancouver, BC, Canada

3. Dept. of Pathology, Vancouver General Hospital and University of British Columbia, Vancouver, BC, Canada

KEY WORDS

Solitary fibrous tumor
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ABSTRACT

Background: Solitary fibrous tumor (SFT) is a mesenchymal tumor which is most commonly seen in the pleura; however it can be seen in other organs such as the meninge, gastrointestinal tract, soft tissue, bone, and skin. SFT should be differentiated from other mesenchymal tumors in these organs. Immunohistochemistry plays a pivotal role for the histopathologic diagnosis of this tumor. Currently, new markers have been introduced which has been very useful for definite diagnosis of SFT along with other markers in each specific location which are negative in SFT.

Methods: Here we review the reported positive and negative immunohistochemical markers of SFT in the English literature with the emphasis on the useful markers in each specific organ. We explored the English literature from 1990 through 2015 via PubMed, Google, and Google scholar using the following search keywords: Solitary fibrous tumor, Solitary fibrous tumor and immunohistochemistry, Solitary fibrous tumor and diagnosis, Solitary fibrous tumor and histogenesis, Solitary fibrous tumor and prognosis, Solitary fibrous tumor and hemangiopericytoma, Solitary fibrous tumor and differential diagnosis, Solitary fibrous tumor and markers.

Results: The most important and valuable positive markers in SFT are CD34, CD99, Bcl-2 and STAT-6. There are consistently negative markers in this tumor as well, used according to the tumor location, such as EMA and S100

Conclusion: Immunohistochemistry is very useful for the diagnosis of solitary fibrous tumor and for its differentiation with other spindle cell mesenchymal tumor in different locations.

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Corresponding Information: Bitá Geramizadeh, Dept. of Pathology, Transplant Research Center, Shiraz, Iran Telephone: 0098-9173143438
Email: geramib@gmail.com, geramib@sums.ac.ir

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Introduction

Solitary fibrous tumor (SFT) is a spindle cell mesenchymal tumor of poorly understood origin. It was first mentioned in pleura in 1870 (1), however the first description of this tumor was in 1931 by Klemperer, who called it “localized

fibrous mesothelioma” (2). Although initially regarded as a pleural tumor, it is now recognized that SFT occur in, skin, nervous system, soft tissue, liver, lung, kidney, and thyroid (3).

The usual histomorphology of SFT is variable, ranging from a paucicellular to a moderate to highly cellular tumor, composed of round

to spindle-shaped cells with little cytoplasm, between prominent eosinophilic bands of collagen often arranged in a short storiform pattern, along with thin-walled branching vessels showing a staghorn hemangiopericytoma-like configuration (Fig. 1). Hypocellular and hypercellular areas can be seen (1-3).

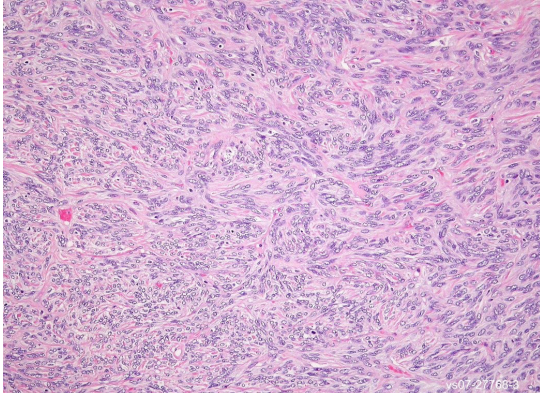


Fig. 1

Sections show a moderately cellular SFT composed of bland spindle-shaped cells with little cytoplasm, running between bands of collagen arranged in a short storiform pattern. (H&E X 250)

SFT and hemangiopericytoma (HPC) have been originally regarded as separate entities, but according to the 2013 WHO classification of soft tissue tumors, they are now considered as one neoplasm, except for the central nervous system where meningeal HPC is still considered a separate entity (4).

This tumor is the most common in the middle-aged adults (20-70 yr). Rare cases in paediatric age groups have also been reported (5).

Clinical manifestations are highly variable according to the location of the tumor (6). Clinical behavior, can often be predicted by features, such as hypercellularity, high mitotic figures (>4/10HPF), cytologic atypia, tumor necrosis, infiltrative margins (4). Absence of these criteria is not a definite predictor of benign behavior and some SFTs with completely bland histomorphologic findings can have an aggressive course. Immunohistochemistry is not widely accepted to be predictive of malignancy (6).

Data Acquisition

In this review, we explored the English literature from 1990 through 2015 via PubMed, Google, and Google scholar using the following search keywords:

- 1) Solitary fibrous tumor
- 2) Solitary fibrous tumor and immunohistochemistry
- 3) Solitary fibrous tumor and diagnosis
- 4) Solitary fibrous tumor and histogenesis
- 5) Solitary fibrous tumor and prognosis
- 6) Solitary fibrous tumor and hemangiopericytoma
- 7) Solitary fibrous tumor and differential diagnosis
- 8) Solitary fibrous tumor and markers

Positive Markers for SFT

CD34 and Bcl-2

The most important and consistent positive immunohistochemical markers useful for the first line of diagnosis in SFT are CD34 and Bcl-2 (Fig. 2).

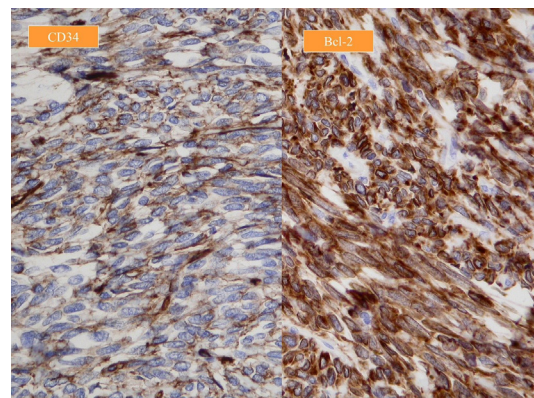


Fig. 2

CD34 and Bcl-2 are positive in the tumor shown in Figure 1. (X 400)

A combination of positive CD34 and Bcl-2 is highly characteristic of SFT. CD34 positivity has been reported in 95 to 100% of the cases. Therefore to call a tumor "SFT" CD34 should be positive. The only exception to this is malignant and dedifferentiated cases of SFT in which the percentage of CD34 positivity is

lower, but still significant (83%) (7-10). In such cases, cytokeratin (CK) will be positive and CK positivity accompanied with negative CD34 is an indication for this tumor to be dedifferentiated or malignant and to behave aggressively, in which the tumor is still recognizable as SFT but has cytologically malignant features (11).

In various locations of the body, Bcl-2 has been reported positive in 50-100% of the SFTs (11, 12). A double negative CD34, and Bcl-2 makes the diagnosis of SFT highly unlikely (9).

STAT-6

NAB2-STAT6 fusion genes are specific for SFTs and the detection of the fusion gene can be helpful in diagnostically challenging cases. However, the molecular tests are costly, and are not available in every laboratory. Recently, the use of immunohistochemistry for STAT6, as a surrogate for detecting the fusion gene has been introduced. It has been showed a strong nuclear STAT6 immunoreactivity that was highly sensitive and specific for SFTs (13, 14) (Fig. 3).

By using this marker, SFT can be accurately

differentiated from other histologic mimics such as meningeal hemangiopericytoma. Intense and diffuse nuclear staining of STAT-6 is highly characteristics of SFT, seen in more than 90% of the cases (15, 16). Less than 10% of other spindle cell tumors in different locations of the body have been positive with STAT-6, most of which do not show as diffuse and intense staining as SFT (16, 17).

Useful Immunohistochemical Markers according to the specific location: (Table-1)

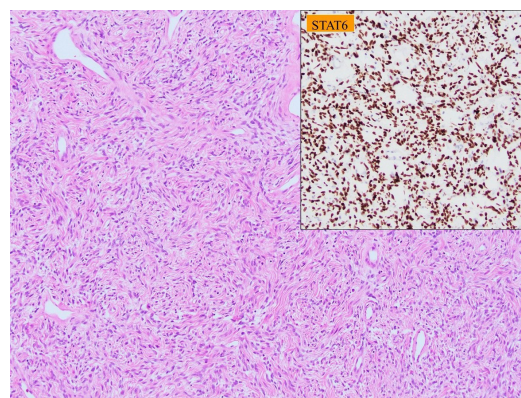


Fig. 3
SFT with diffuse nuclear positivity for STAT6 (inset)

Table 1

Percentage of positivity of different markers in benign SFTs in different locations of the body

Marker	Pleura ¹⁸⁻²⁶	Meninges ²⁷⁻³⁵	Soft tissue ³⁶⁻⁴¹	Skin ^{20,42, 43}	GI tract ⁴⁴⁻⁴⁶
STAT-6	95-100%	91%	99-100%	NR	NR
CD34	90-100%	92-100%	85-100%	80%-1005	100%
CD99	88.6%	100%	89-100%	60-100%	NR
Bcl-2	94.3-100%	89-100%	85-100%	60-100%	NR
Beta-catenin	77-100%	100%	22-67%	NR	24%
Vimentin	100%	NR	NR	NR	NR
Calretinin	0-13%	NR	NR	NR	NR
Desmin	0	NR	NR	NR	NR
cytokeratin	0-3.5%	0	NR	0	NR
EMA	0	0-29%	NR	0	NR
CK5/6	NR	0	NR	NR	NR
D2-40	NR	NR	NR	NR	NR
Claudin-1	NR	0	NR	NR	NR
SMA	0	NR	NR	30%	0
CD117	3.4%	NR	NR	NR	0
S100	0	0-26%	NR	0	0
P53	0-79.6	NR	NR	NR	NR
Ki-67	0-2%	NR	NR	NR	NR

Pleuropulmonary SFT

The first report of SFT was from the pleura and overall the most common site of this tumor is pleura. However, SFT is not a common tumor in the pleura and comprises less than 5% of pleural neoplasms, so it should be differentiated from other more common pleural tumors (3). It most commonly arises from the visceral pleura and very rarely from the parietal pleura. The most common neoplasm that must be differentiated from SFT in the pleura is localized malignant mesothelioma especially the desmoplastic subtype (18, 19).

The best positive markers in mesothelioma that are mostly negative in SFT are cytokeratin (CK), calretinin, WT-1, CK5/6 (20). Cytokeratin is mostly negative in SFT (21, 22). Calretinin is also mostly negative in SFTs, and it's uncommon to be positive for calretinin (up to 13%) (23).

D2-40 is another marker which has been reported to be helpful in the diagnosis of pleural mesothelioma, which is mostly negative in SFT, however very rare reports of focal reactivity has been reported in SFT (24).

Intrapulmonary SFT is very rare and immunohistochemical findings are very similar to those in pleural SFT. Intrapulmonary SFT are keratin and TTF-1 negative (25, 26).

Meningeal SFT

Another common location of SFT is the nervous system i.e. meningeal SFT, which are most commonly intracranial, however less than 20% are intraspinal. The two most important differential diagnoses in the meninges are hemangiopericytoma (HPC) and fibroblastic meningioma (27).

Hemangiopericytoma is an aggressive tumor which, according to the 2007 WHO classification of CNS tumors, is still viewed as a separate tumor from SFT of the meninges (28). However, the presence of NAB2-STAT6 fusion gene and STAT6 protein expression by

immunohistochemistry in both SFT and HPC suggest that these are probably the same entity. STAT6 reactivity has been reported in 95 to 100% of meningeal HPC and 100% of SFTs (29). Bcl-2, CD34 and CD99 are frequently positive in meningeal HPC, similar to SFT (80-100%) (30, 31). Many of the previously diagnosed meningeal HPC has in fact been SFT and that HPC cases represent malignant or aggressive SFTs (32).

Another important differential diagnosis of SFT in the nervous system is meningioma (fibroblastic type). Immunohistochemistry plays a pivotal role for this differential diagnosis, because in all of the previous studies, EMA and S100 have been consistently negative in SFT, as opposed to meningioma which is consistently reactive with S100 and EMA. Meanwhile meningiomas are reported to be consistently nonreactive for CD34, CD99 and Bcl-2. Claudin-1 has been also reactive in more than 70% of the meningiomas and consistently negative in meningeal SFTs (34).

The MIB-1 index has been proposed as an acceptable criterion for prediction of aggressive behavior in CNS SFTs (35).

Soft tissue and bone SFT

As it has been mentioned above, according to the WHO classification (2013) (4), HPC and SFT are considered to be the same entity. Immunohistochemistry of soft tissue SFT is fairly similar to meningeal SFT i.e. both are consistently positive with CD34, CD99 and Bcl-2, although the average Ki67 positivity is higher in meningeal SFT (36, 37).

STAT6 is both a sensitive and specific marker in soft tissue SFTs as is true in other locations (13, 38, 39). In other studies, this marker was completely negative in many of the soft tissue tumors with spindle cell morphology (13). Table-2 shows some of the soft tissue tumors with reported percentage of nuclear positivity of STAT6 (13, 38, 39). There are a number of other genes that are up-regulated in SFTs in comparison

with other histological mimics in soft tissue. The most frequently and highly over expressed is GRIA2, which encodes an AMPA selective ionotropic glutamate receptor subunit thought to mediate increased cell proliferation. GRIA2 has been absent in normal fibroblasts. Vivero et al. have investigated GRIA2 expression in some soft tissue tumors by immunohistochemical analysis. The marker was positive in 89% of SFTs, but more than 99% of all other histologic mimics mentioned in Table 2 has been nonreactive with this marker (40).

Another important issue in differential diagnosis of this tumor is fibromatosis, because of the probability of SFT to show nuclear positivity with β -catenin which should be interpreted cautiously. However, presence of nuclear STAT-6 in SFT and consistently negative STAT-6 in fibromatosis is very helpful for this differential diagnosis in equivocal cases (41).

Cutaneous SFT

There are a group of spindle cells in the

dermis that are CD34 positive called “dermal dendrocytes”. Proliferation of these cells will cause different types of tumors including SFT. These tumors consist of dermatofibrosarcoma protuberans (DFSP), and spindle cell lipoma, which show great histopathologic overlap (42). These CD34 positive tumors must be differentiated from SFT when it arises from the dermis (20). Both of these tumors are consistently non-reactive with CD99 and Bcl-2 (43). Another dermal tumor which shows histologic overlap with SFT is fibrous histiocytoma. This tumor is most commonly CD34 negative, as opposed to SFT (20). Neural tumors such as Schwannoma can be easily differentiated by positivity with S100 which is non-reactive with tumor cells in SFT (20).

Gastrointestinal SFT

There are four main tumors in the gastrointestinal tract (GI) which can be differentiated by using immunohistochemical markers; i.e., gastrointestinal stromal

Table 2
STAT-6 nuclear positivity in different spindle cell tumors

Tumor type	Percentage of positive nuclear staining
Solitary fibrous tumor, benign ^{9,13}	100%
Cellular angiofibroma ^{13,38}	0
Myofibroblastoma ^{13, 38}	0
Spindle cell lipoma ^{13,38}	0
Benign fibrous histiocytoma ^{13,38}	0
DFSP ^{13, 38}	0
Desmoid type fibromatosis ^{13,38, 39}	0-7.6%
Monophasic synovial sarcoma ^{13,38}	0
Mesenchymal chondrosarcoma ^{13,38}	0
High grade fibromyxoid sarcoma ¹³	28.5%
Lieomyoma ¹³	0
Leiomyosarcoma ¹³	0
Schwannoma ¹³	0
Neurofibroma ¹³	0
MPNSD ¹³	0
Dedifferentiated liposarcoma ^{13, 39}	0-12%
Ewing's sarcoma ¹³	0
Nodular fasciitis ¹³	0
Unclassified sarcoma ³⁹	12.3%

tumor (GIST), desmoid type fibromatosis, leiomyosarcoma and schwannoma (44). CD-117 is the best marker for the diagnosis of GIST and exclusion of SFT, because most of the GISTs are both CD34 and CD99 positive (45). Desmoid type fibromatoses are mostly positive with smooth muscle actin which is rarely positive in SFT; this is the opposite of CD34 which is consistently negative in desmoid type fibromatosis (46). Leiomyosarcoma and schwannoma in the GI tract can be differentiated from SFT by being positive with SMA and S100 respectively (44).

Other locations

SFTs have been reported from salivary gland especially as a parotid gland tumor, which should be differentiated from other mesenchymal tumors of this organ such as schwannoma, desmoid tumor, DFSP, and leiomyosarcoma using the three most important markers that have been mentioned before i.e. CD34, CD99 and Bcl-2 (15, 47). O'regan et al. have reported the same experience in 21 cases of SFT in the oral cavity i.e. all were reactive with CD34, CD99 and Bcl-2 but nonreactive with EMA, CK, S-100 and SMA (48) Blandamura et al. (49) have reported similar results for eye and peri-ocular SFT (49).

Role of Immunohistochemistry for prediction of the behavior and prognosis in SFT

Malignant SFT is rare and malignancy has been reported in 12% to 37% of the cases. Several histomorphologic findings were reported to be important for prediction of malignancy and disease free survival, including high cellularity, mitotic activity (Some studies report that presence of mitosis per se is a poor prognostic indicator however most of the previous studies have emphasized that >4 mitosis /10 HPF is predictor of malignant and aggressive behaviour), with hemorrhage and necrosis (50). There are reports about the role of immunohistochemical biomarkers in prediction of behaviour in SFTs such as P53, and Ki67, however it has not been

widely accepted (21, 50).

Dedifferentiation has also been reported as a poor prognostic factor. It means that in a tumor, in addition to typical features of benign-appearing SFT there is an abrupt transition to nondistinctive high-grade sarcoma. This can be round or spindle shaped cells or epithelioid (51). There are reports of CD34 loss and P53 expression in these dedifferentiated SFTs (52). Besides, Ki67 shows a significant increase in dedifferentiated SFTs (51, 52).

Conclusion

SFT is a mesenchymal spindle cell tumor which is most commonly seen in the pleura; however it can be seen in various extrapleural organs and should be differentiated from other spindle cell mesenchymal tumors. Immunohistochemical markers are very important for the histopathologic diagnosis of this tumor; especially CD34, Bcl-2 and STAT-6. There are also consistently negative markers in this tumor which can be used according to the location.

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