

Pathological Spectrum of Solitary Fibrous Tumours: A Study of 25 Cases Diagnosed at a Tertiary Care Institute

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¹ Conception of study

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Abstract

Objective: To evaluate the clinicopathological and immunohistochemical features of Solitary Fibrous Tumor (SFT) in Shifa International Hospital.

Materials and Methods: This is a retrospective descriptive study. All cases of solitary fibrous tumor diagnosed on morphology from January 2012 till June 2018 were retrospectively retrieved from the histopathology department of Shifa International Hospital, Islamabad. The hematoxylin and eosin (H&E) stained slides as well as IHC slides were reviewed. The diagnosis was established on current standard histopathological and IHC criteria provided by the World Health Organization (WHO) Classification of soft tissue tumors.

Approval for the acquisition of the tissue specimens and supporting case information and retrieval of glass slides were obtained by Institutional Review Board & Ethics Committee (IRB & EC) wide reference number IRB # 259-1079-2020 of Shifa Tameer-e- Millat University (STMU).

Results: There were 25 cases of SFT in our study involving 12 males and 13 females. According to WHO 2013 criteria, eleven cases in our study were classified as malignant (44%) while 14 cases were in the benign group (56%). STAT6 was available in our hospital in 2018 and since then all the subsequent cases of SFT in the present study (seven in number) came positive for STAT6 (sensitivity 100%) while CD34 which was done throughout the duration of this study (January 2012-June 2018) was positive in 20 cases (86.9%) and negative in three cases (13%). A follow-up of 16 cases is available. Out of a total of 14 benign cases, follow-up of only seven (50%) cases could be traced and from a total of 11 malignant cases, follow-up of nine (81%) cases could be sought. All benign cases remained disease-free while among the nine malignant cases: three (33.3%) patients died, recurrence was reported in four (44.4%) patients. One (11.1%) patient remained disease-free while one (11.1%) patient is alive and on treatment.

Conclusion: Malignancy in SFT is common and must be evaluated meticulously. STAT6 is a highly sensitive marker for the diagnosis of SFTs. An immunohistochemical panel including STAT6, CD34, CD99, and BCL-2 support morphology. Malignant behavior is common and is evaluated by meticulous analysis of gross/microscopic features and close follow-up of the patient. However further advances in genetics and new tumor markers is in progress and must be followed for the definitive decision on tumor behavior and its subsequent treatment.

Keywords: Solitary Fibrous Tumor (SFT), STAT6, CD34.

Introduction

The first case of solitary fibrous tumor (SFT) was reported in 1870.¹ A study on the clinicopathologic features of SFT was done by England in 1989 on 223 cases.² SFTs are rare mesenchymal tumors representing less than 5% of all neoplasms involving pleura. These arise from the submesothelial connective tissue. More studies reveal SFT may be found in any location of the body with two-thirds arising from the visceral pleura and the remaining one-third from the parietal pleura.^{2,3} These tumors also occur in extrapleural sites such as the meninges of CNS, pericardium, anterior mediastinum, lung, breast parenchyma, nose & paranasal sinuses, orbit, parotid gland, liver, and thyroid gland.⁴

SFT occurs with an equal incidence between men and women and at all ages but peaks in the sixth and seventh decades of life. Paraneoplastic manifestations include clubbing of fingers and hypoglycemia. Paraneoplastic syndromes are more common in tumors larger than 8 cm in size and are seen to resolve with surgical resection.⁵ Grossly these tumors are well-circumscribed, non-encapsulated, solitary, lobulated masses with an average size of 5-8 cm. There is much variation in the size of this tumor from 1 to 36 cm in diameter.⁶ Cut surface is firm, white, and multinodular. According to WHO (2013) criteria for these tumors, the risk factors for SFTs associated with recurrence and disease-specific mortality are a mitotic index of $\geq 4/10$ high-power fields (HPF), high tumor cellularity, high nuclear pleomorphism, atypia, hyperchromasia, and tumor necrosis. Most cases are benign 78-88% while 12-22% are histologically malignant.⁷ Immunohistochemically the SFT generally is vimentin-positive and cytokeratin-negative. In addition, both the benign and malignant varieties of SFT are CD34, CD99, and BCL-2-positive. Further progress was made in 2013 as three groups discovered that the NAB2-STAT6 fusion gene resulted from the binding of transcriptional repressor NAB2 with transcriptional activator STAT6.⁸ This fusion gene is present in all SFTs regardless of their site and clinical behavior (benign/ malignant). The detection of the NAB2-STAT6 fusion gene can help in diagnosing SFT but molecular essays require specialist experts and are expensive. Schweizer in 2013 demonstrated NAB2-STAT6 fusion gene was rapidly detectable by STAT6 immunohistochemistry, which exhibited strong nuclear expression.⁸ STAT6 stain is a highly sensitive and specific marker for the genetic alteration (NAB2-STAT6 gene fusion) found in SFTs and is particularly

useful in differentiating it from other spindle cell neoplasms.⁹ In this study we evaluated the clinicopathological and immunohistochemical features of SFT cases in our hospital.

Materials and Methods

This is a retrospective longitudinal study. All cases of solitary fibrous tumor diagnosed on morphology from January 2012 till June 2018 were retrospectively retrieved from the records of the histopathology department of a tertiary care institute. The hematoxylin and eosin (H&E) stained slides as well as IHC slides were reviewed. The diagnosis was established on current standard histopathological and IHC criteria provided by the World Health Organization (WHO) Classification of soft tissue tumors.⁷

Four-micron thick sections from paraffin blocks were made of each sample and mounted onto glass slides. IHC staining for anti-STAT6 antibody (BioSB antibody, Roche kit) was available in our hospital from 2018 onwards. It was performed on all suspected cases of SFT using the manufacturer's instructions. The quality of expression was graded and interpreted as absent staining, weak expression, or strong expression. The samples were graded based on diffuse (>50%) versus localized (<50% of tumor cells) staining, as well as localization of the stain within the cell (nuclear only, cytoplasmic only, or both nuclear and cytoplasmic).

Approval for the acquisition of the tissue specimens and supporting case information and retrieval of glass slides were obtained by Institutional Review Board & Ethics Committee (IRB & EC).

Results

Clinical Data

There were 25 cases of SFT in our study involving 12 males and 13 females with a mean age of 49 years (range 24-84 years) (Figure 1). These SFTs arose in various body locations including the thorax (8 cases with 3 in the lung, 2 pleura, 2 mediastinum & 1 from the chest wall). The abdomen was the most commonest site of occurrence of this tumor in our study whereas this tumor was also reported one each in the nape of the neck, anterior thigh, retrobulbar mass, parasagittal mass, and 2 in the spinal cord (Figure 2). There were no differences in age and sex between patients with benign and malignant SFTs. Tumor size was in the range of 1->10cm. Tumors

larger than 10cm were mostly malignant (6 cases, 24%) (Figure 3).

Microscopy

The microscopic examination revealed a patternless architecture of bland spindle cells forming hypo and hypercellular areas in a collagenous stroma, areas of hyalinization, and interspersed staghorn-shaped vessels. Eleven cases in our study were classified as malignant (44%) according to WHO 2013 criteria while 14 cases were in the benign group (56%) (Figure 4).

Immunohistochemical findings

STAT6 was available in our hospital in 2018 and since then all the subsequent cases in our study (7 in number) of SFT came positive for STAT6 (sensitivity 100%) while CD34 which was done throughout the duration of this study was positive in 20 cases (86.9%) and negative in 3 cases (13%). Immunohistochemistry was suggested in 2 cases but was not performed (Figure 5).

Follow-up

Follow up of 16 cases is available. Out of a total of 14 benign cases, follow-up of only 7(50%) cases could be traced and from a total of 11 malignant cases, follow-up of 9(81%) cases could be sought. All benign cases remained disease-free while among 9 malignant cases: 3(33.3%) patients died, recurrence was reported in 4(44.4%) patients. One (11.1%) patient remained disease-free while one (11.1%) patient is alive and on treatment.

Discussion

Solitary fibrous tumors are rare mesenchymal tumors most commonly arising in the pleura and representing less than 5% of all neoplasms involving the pleura.² Magdeleinat et al in 2002 carried out a study on 60 cases in which they found pleura to be the most common site and 36.63% cases were malignant out of which two later presented with local recurrence and one with metastasis.⁵ Sung et al in 2005 published a study of 63 cases with 30.2% being malignant with three recurrences and distant metastasis in eight cases.¹⁰ In a study on 10 cases, carried out by Erdag in 2007, the common site of occurrence was trunk and cheek, all were benign and there was no evidence of disease in 9 patients whereas one recurrence was reported.¹¹ In our study eleven cases (44%) out of 25 total cases were found in the abdomen and out of the 8 cases (20%) in the thorax, only two (8%) were arising from pleura. DeVito et al 2015 studied 82 patients and found 49% to be malignant and out of those reported as benign, 11 recurrences were presented in addition

to the two reported as atypical.¹² Our results were comparable to other studies as 44% of cases were malignant and our benign cases (56%) remained symptom-free. In our study follow-up of only 9 out of 11 malignant cases could be traced which showed 4 cases (44.4%) of recurrence and 3 patients (33.3%) succumbing to the disease. This may be due to presentation at a higher stage of the tumor.

In a study carried out by Han et al in 2015 out of 53 cases studied for STAT6, CD34, and CD99 expression, 51 (96.2%) were STAT6 positive, and 47 (88.7%) showed CD34 positivity and CD99 was positive in 50 (94.3%) cases.¹³ In the present study STAT6 was positive in all cases tested (sensitivity 100%) while CD34 was positive in 20 cases (86.9%) and negative in 3 cases (13%). The three cases in which CD34 came negative in this study were recurrent malignant tumors, otherwise, it was positive in both benign and malignant tumors. Immunohistochemistry was suggested in 2 cases but was not performed. Fletcher in 2013 observed that CD34 is positive in many cases of SFT but approximately 5-10% are negative⁸. The lost expression of CD34 is noted in high-grade foci or recurrent tumors.¹⁴ This process of conversion of CD34 positive to negative areas may be related to malignant transformation.¹⁵ CD34 is not entirely specific for SFT as it can be expressed in a variety of mesenchymal tumors like dermatofibrosarcoma protuberans, hemangiopericytoma, and gastrointestinal stromal tumor (GIST), but still it is highly sensitive for SFT.^{16,17} SFT of CNS is a different neuropathological entity from Soft tissue SFT, and WHO 2007 CNS classification has retained the SFT/Hemangiopericytoma terminology for this entity only. Tumors with SFT phenotype are grade I while those of HPC phenotype are grade II & III. A study done on meningeal SFT/HPC tumors by Zubair et al. showed that the majority of the tumors were of grade II & III. These cases required not only complete surgical resection but also adjuvant radiotherapy. They observed that patients who had not received radiotherapy had a high recurrence rate.¹⁸ Different NAB2-STAT6 fusion types seem to be associated with clinicopathologic subtypes of SFT. NAB2ex4-STAT6 ex2/3 variant is found in classic SFT while NAB2ex6-STAT6 ex16/17 is found in SFT showing aggressive behavior.¹⁹ The finding of fusion variants requires designing future molecular targeted therapies as conventional chemotherapeutic agents have demonstrated limited efficacy in treatment strategy.²⁰

A study by Patrick on 26 cases of SFTs arising in dermis or sub-cutis found that cutaneous SFTs are more common in females mostly occurring in the head region. These tumors are of low grade and behave in a benign manner. However, more studies are required to confirm this. He recommends that a proper histomorphology and IHC would differentiate it from other CD34 tumors arising in the skin.²¹ In my study most of the SFT cases were reported in the abdomen and none in subcutaneous tissue were seen.

In a study comprising 41 patients diagnosed with SFT, it was concluded that this tumor when occurring in limbs had a better prognosis. This study also noted an association between *TERT* promoter mutations and histologically malignant features.²²

The H&E staining showed typical histological features, which were spindle tumor cells with hypo and hypercellular areas in a collagenous stroma. This patternless architecture was separated by branching staghorn-like vessels which were similar to other studies. The risk factors for SFTs associated with recurrence and malignancy are the mitotic index of $\geq 4/10$ high-power fields (HPF), high tumor cellularity, high nuclear pleomorphism, atypia, hyperchromasia, and tumor necrosis as are specified by WHO (2013) criteria for these tumors.^{7,21} The findings of various studies are compared in Table 1.

Table 1: Comparison of various studies (NED* No evidence of disease)

Studies	No. of cases	Commonest sites	Benign/Malignant	Follow-up
1 Magdeleinat et al. 2002	60	Pleura	63.3% Benign 36.6% Malignant	Benign; No recurrence Malignant; 2 local recurrences, 1 metastasis
2 Sung et al. 2005	63	Pleura	69.8% Benign 30.2% Malignant	Malignant; 3 recurrences, 8 Metastasis
3 Erdag et al. 2007	10	Trunk & cheek	All benign	NED* in 9, 1 recurrence
4 De Vito et al. 2015	82	Pleura	51% Benign 49% Malignant	Benign; 2 Atypical benign & 11 benign had recurrence
5 Current study 2018	25	Abdominal	56% Benign 44% Malignant	Benign; No recurrence Malignant; 3 died, 4 recurrences, 1 disease-free

Conclusion

Malignancy in SFT is common and must be evaluated meticulously. STAT6 is a highly sensitive marker for the diagnosis of SFTs. An immunohistochemical panel including STAT6, CD34, CD99, and BCL-2 support morphology. Malignant behavior is common and is evaluated by meticulous analysis of gross/microscopic features and close follow-up of the patient. However, further multi-center studies are suggested to analyze the biologic and clinical behavior of this tumor with follow-up of patients.

A limitation of our study was many patients were lost in follow-up. A long-term follow-up is required to evaluate the rate of recurrence, overall survival, and clinical behavior of this tumor. More studies are required to further evaluate the genetics of this tumor as it would help in devising a targeted therapy.

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