# Intracranial Solitary Fibrous Tumor in A 25-Year-Old Woman

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**Abstract**

**Introduction:** Intracranial solitary fibrous tumors (ISFTs) are extremely rare spindle cell tumors originating from dendritic mesenchymal cells expressing CD34 antigens that are usually benign, although malignant transformation had been reported. The knowledge of natural course and prognostic factors of ISFTs is still limited and the tumor is easily misdiagnosed.

**Case Presentation:** An intra-cranial extra-axial tumor tissue resection from a 25-year-old woman was evaluated in the Surgical Pathology Laboratory. Histologic findings (cellular spindle cell tumor with 'patternless' pattern, staghorn blood vessels and <5 mitoses per 10 hpf) and immunophenotype (positive for CD34, weakly and focally positive for STAT6) suggested a diagnosis of intracranial solitary fibrous tumor WHO Grade II.

**Discussion:** ISFTs have very low incidence in the CNS and are difficult to distinguish radiologically from meningiomas, thus post operative pathological examination and immunohistochemistry markers evaluations are the mainstay for diagnosis. ISFT is associated with NAB2-STAT6 gene fusion and may exhibits a wide spectrum of histological features. STAT6 immunohistochemistry is considered as one of the most sensitive diagnostic methods, while the evaluation of CD34 expression can be used as alternative diagnostic method despite having lower sensitivity.

## Introduction

Solitary fibrous tumors (SFTs) are extremely rare spindle-cell mesenchymal neoplasms expressing CD34 antigens that was first described as a tumor arising from the pleura.[1] SFTs have subsequently been found in many different locations, although SFTs involving the central nervous system (CNS) is very rare,[2,3] most likely because of the low content of true connective tissue elements in the CNS.[4] The first cases of intracranial solitary fibrous tumors (ISFTs) were reported by Carneiro et al. in 1996. They reported seven cases of meningeal SFT that could be distinguished from fibrous meningioma based on morphologic and immunohistochemical grounds.[5] Since then, there are less than three hundred cases of SFTs that have been reported at various sites within the CNS in the English literature,[3] and ISFTs was reported to account for ~0.09% of all meningeal tumors.[2]

Solitary fibrous tumors in the CNS can affect both cranial and spinal meninges and may involve spinal nerve roots. The tumors are seen primarily in adults and may show invasion of brain parenchyma or nerve roots as well as the skull base.[3] Most CNS SFTs are intracranial, and just over one-fifth of tumors involve the spine. In decreasing frequency, ISFTs involve the

supratentorial compartment, infratentorial compartment, pontocerebellar angle, sellar and parasellar regions, and cranial nerves. Intraspinal tumors are mainly located in the thoracic and cervical segments.[4,6]

Intracradial solitary fibrous tumors (ISFTs) are usually benign, however, a growing body of literature demonstrates an unpredictable clinical course and an uncertain prognosis, where anaplastic or malignant transformation of benign ISFTs resulting in multiple local and distant recurrences has been described.[4] There has been changes in WHO classification and diagnostic criteria for SFT over the years. Current WHO Classification of Soft Tissue and Bone Tumors has classified SFT as a fibroblastic neoplasm with intermediate (rarely metastasizing) behavior.[7] The knowledge of natural course and prognostic factors of ISFTs is still limited. ISFT has also often been easily misdiagnosed with other types of brain tumors given that it has a very low incidence in the CNS and shows resemblance to meningioma or hemangiopericytomas, and thus remains a diagnostic challenge.[8,9] For that reason, this article intended to contribute the pathologic findings and results of immunohistochemical studies of a 25-year-old woman with ISFT.

## Case Report

### *Pathologic Findings*

An intra-cranial extra-axial tumor tissue resection from a 25-year-old woman was evaluated in the Surgical Pathology Laboratory. Routine H&E staining, special staining and immunohistochemical studies were performed after formalin fixation and paraffin-embedding. Light microscopy examination of the sections showed a cellular spindle cell tumor with “patternless” pattern and staghorn blood vessels. The neoplastic short spindle cells featured elongated nuclei. There was extensive background cautery artefact, which hampers assessment of mitotic activity. Mitotic activity was not readily identified (less than 5 mitoses per 10 high-power field). No definite necrosis was identified. No heterologous cartilaginous or “grungy” calcified matrix identified.

Immunohistochemical studies found that the neoplastic cells were positive for CD34. The neoplastic cells were only weakly and focally positive for STAT6. The neoplastic cells were negative for AE1/AE3, CAM 5.2, ERG, TLE1, SOX10, EMA and PR stains. INI1 immunohistochemistry was non-contributory. However, while there was complete lack of expression in the neoplastic cells, there was also lack of expression in the internal control (such as smooth muscle cells and endothelial cells). Thus, the lack of INI1 expression in the neoplastic cells may be caused by poor specimen immunoreactivity, possibly due to cautery artefact and/or specimen fixation issue, rather than true aberrant loss of expression in tumor cells.

## Discussion

A diagnosis of intracranial solitary fibrous tumor WHO Grade II was suggested in a 25-year-old woman with an intracranial extra-axial tumor based on histologic findings and results of immunohistochemical studies. The majority of ISFTs are found in females. The tumors grow slowly, and certain patients may develop the symptoms of episodic headaches, gait imbalance, dizziness, sensory disturbance, hemiplegic paralysis or epileptic seizure, while other patients may be asymptomatic, with no distinctive local symptoms. Only when the lesions become large enough or infringe into the important functional areas, will clear clinical symptoms arise.[2]

Forming a pre-operative diagnosis for ISFTs is quite challenging due to the atypical symptoms and imaging manifestations. ISFTs are difficult to distinguish radiologically from meningiomas because of their overlapping imaging features.[10] Therefore, post-operative pathological examination and immunohistochemistry markers evaluations are the mainstay for diagnosis. The microscopic histology of ISFTs is similar to the SFTs in other parts of the body. The SFT tissue mainly exhibits a proliferation of spindle cells with a variety of growth patterns.[2] These spindle cells tend to be bundled in barely undulating fascicles and lack any specific arrangement, and thus often result in a “patternless pattern.” Deposition of collagen substance is increased in the cell sparse area. Crack or staghorn-like vascular is often prominent in the cell-intensive areas, characterized by small and/or large branching vascular spaces.[9] The current patient showed cellular spindle cell tumor with ‘patternless’ pattern and staghorn blood vessels.

The new World Health Organization Classification uses a 3-tiered grading system to help determine the prognosis of SFT. Grade I define benign lesions that correspond to the classic SFT pattern with relatively low cellularity, rich collagen, spindle cell lesion. Both Grades II and III define malignant lesions. Tumors with less collagen, more cellularity, hemangiopericytoma pattern and "staghorn" vasculature, with less than 5 mitoses per 10 high-power fields were defined as Grade II lesions, while Grade III lesions showed more than 5 mitoses per 10 high-power fields.[11] The lesions from this patient was classified as WHO grade II SFT because it showed cellular spindle cell tumor with “patternless” pattern, which was a storiform arrangement of spindle cells combined with a hemangiopericytoma-like appearance and increased vascularity of the lesion, staghorn blood vessels, and <5 mitoses per 10 hpf.

Immunohistochemical examinations are considered essential for proper diagnosis of ISFTs. The important immunohistochemical characteristics for successful diagnosis and treatment of SFTs include STAT6, CD34, CD31, ERG, Bcl-2 protein, and vimentin,[1,4] whereas it is usually negative for cytokeratin, EMA, SMA, PR, S-100 and GFAP.[9,12] Immunohistochemical studies in this patient found that the neoplastic cells were strongly and diffusely positive for CD34, whilst only weakly and focally positive for STAT6, and negative for ERG. The neoplastic cells were also found to be negative for AE1/AE3, CAM 5.2, TLE1, SOX10, EMA and PR stains, thus excluding the differential diagnosis such as metastasis and meningioma.[9,12-14]

Studies in molecular pathology have found that transcription repressor NAB2 and the transcription activator STAT6 are two adjacent genes located on the q13 band of 12$^{th}$ chromosome,[15] and furthermore, almost all SFTs have detected NAB2 and STAT6 fusion genes.[16] Over-expression of NAB2-STAT6 gene fusion was reported to induce cell proliferation, activates EGR1 target genes and their promoters, promotes gene expression, and disrupts EGR1-related metabolic balance, which is a decisive factor in the mutation process of SFT.[8] Accumulating evidence after the discovery of NAB2-STAT6 fusion gene has found that STAT6 nuclear staining is extremely sensitive and specific in ISFTs, which made STAT6 immunohistochemistry a powerful and key diagnostic modality for this neoplasm.[10] The STAT6 immunostaining can also help to exclude the possible diagnosis of meningiomas, because it is totally negative in this type of

intracranial tumor. However, absence of STAT6 nuclear expression by IHC staining may not exclude the possibility of ISFT.[17]

Combination with other immunohistochemistry markers might be helpful to establish a diagnosis in STAT6-negative ISFTs, although their specificities for ISFTs are not so high as STAT6.[18] Positive expression of CD34 was regarded as the most prominent characteristic of ISFTs and was often used for differential diagnosis before the discovery of STAT6-NAB2 fusion gene.[6] CD34 is a transmembrane glycoprotein that had been identified in endothelial cells, hematopoietic stem and progenitor cells, and fibroblast-related mesenchymal cells.[19] Previous studies reported that SFT had a diffuse and strong positivity for CD34 in 80% to 100% of cases,[20] whereas other studies also reported that 5%–10% of SFTs were negative for CD34.[17,21] However, the specificity of CD34 for ISFT is quite low,[13] and this marker can be also detected in other type of brain tumors.[17] The sensitivity of STAT6 for ISFTs was reported to be 96.6% in current literature,[17] whereas CD34 was reported to have 87.5% sensitivity.[8]

## Conclusion

T Intracranial SFTs are an extremely rare mesenchymal neoplasms originating in the meninges. They have low incidence in the CNS and are difficult to distinguish radiologically from meningiomas, thus post-operative pathological examination and immunohistochemistry markers evaluations are the mainstay for diagnosis. STAT6 immunohistochemistry is considered as one of the most sensitive diagnostic methods, while the evaluation of CD34 expression can be used as alternative diagnostic method despite having lower sensitivity.

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