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Review Article

Solitary Fibrous Tumor of the Limbs – Our Experience and Current Knowledge

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Abstract

Extra pleural solitary fibrous tumors are a very rare category of soft tissue derived neoplasm, that can occur anywhere in the body and that are most frequently benign. Their microscopic characteristics consist in a collagenous stroma and spindled-shaped cells disposed around dilated vasculatures that stain positive for CD34 and STAT6 in the immunohistochemistry analysis. We evaluated the current literature findings and compared them to our experience in treating a 68-year-old woman with a history of diabetes mellitus type 2, blood hypertension and chronic kidney disease presented with dull pain and discomfort on the posterior aspect of the right arm. After MRI evaluation, the patient underwent a block excision of the tumor, followed by surgical pathology examination coupled with immunohistochemistry (IMC) assessment, with a diagnostic for benign extra pleural solitary fibrous tumor. The postoperative evolution was uneventful, and at the 6- and 12-month post-op follow-up, the patient remained asymptomatic and no tumoral recurrence was signaled on the follow-up whole-body CT.

Keywords: Extra Pleural Solitary Fibrous Tumor; Immunohistochemistry; CD34; STAT6

Introduction

Solitary fibrous tumors (SFTs) represent a rare category of mesenchymal derived neoplasms, that was firstly described in 1931 by Klemperer [1], as a benign mesothelioma in the pleura. SFTs comprise less than 2% of soft tissue tumor types [2]. Previously known as hemangiopericytomas, today with help from modern diagnostic capabilities (immunohistochemistry, molecular biology), this term was abandoned.

SFTs affect usually adult people in the 5th decade, having no evident predilection for gender. Extra pleural SFTs are usually encountered at patients aged between 20 and 70 years old, with rare cases being encountered in children and teenagers [3-5]. SFTs are ubiquitous in the human body, although the most common site of origin is the pleura. Extra pleural tumors have been rarely described, especially at cranial and visceral level (orbit, neck, thyroid gland, mediastinum, retroperitoneum, bladder, and kidneys) [6-9].

Limb localization is infrequent for this type of neoplasm, with a slight predilection for soft tissue of the proximal part of extremities [10].

Materials and Methods

We evaluated the available English literature and articles of case and series of case presentations and focused on the clinical, etiological, pathogenesis, morphological and imagistic traits of the tumor in order to find a better way to identify (diagnose) and successfully treat extra pleural SFTs.

Clinical features

Extra pleural SFT is found under 2013 WHO classification of bones and soft tissue neoplasm as a fibroblastic/myofibroblastic neoplasm with intermediate to rarely metastasizing behavior [11].

Clinically, SFTs present themselves as large, soft, encapsulated, pain-free masses that determine symptoms by compression of adjacent structures, often reported as incidental findings [11-13]. Intra-abdominal and pleural localization of the tumor has been found to correlate with larger masses than those found in extremities, trunk or head, but this might be due to the wider space of the anatomical cavity development site than due to the biological features [14].

Sometimes clinical presentation may rarely include hypoglycemia due to neoplasm cells secreting insulin-like growth factor [15,16].

We also encountered a 68-year-old woman that presented in our service with a long history of blood hypertension, diabetes mellitus type 2 and chronic kidney disease and a 6-month history of painful growing mass on the posterior distal aspect of the right arm.

Clinically, a large, soft, mobile mass could be palpated, with no simultaneous alteration of mobility or strength of the right triceps brachii and with no pathological change of the overlying tissues and skin.

Imaging

Imaging tools lack specificity for SFTs, but can orient the diagnosis with some tumors showing internal calcifications on radiographs [17]. Ultrasonography shows heterogeneous tissues with internal vascularity on Doppler images, but their appearance is non-specific [17-22].

The majority of the tumors show hypointense or isointense T1 signal on MRI and the low T2-weighted signal intensity is helpful in identifying the fibrous content of the tumor [20,23]. Malignant territories within the tumor tend to appear as intermediate to high signal intensity on T-weighted slices, which correspond to increased vascularity and edema [24].

CT scans can show local invasion of tissues and eventual metastases in malignant instances.

PET-CT findings were reported in only a few cases and showed a hypermetabolic 18-F radiotracer uptake in both malignant and benign tumors [25-27].

After carrying out arm x-ray and ultrasound examinations on our patient, which proved nonspecific, a contrast MRI of the right arm and elbow was performed. The results showed a 10x5.3x2.8 cm long encapsulated tumoral mass, adjacent to the long and lateral heads of the triceps brachii. It exhibited low to isointense signal on native T1 and T2 weighted images and high intensity on gadolinium enhanced images (Figures 1,2,3).

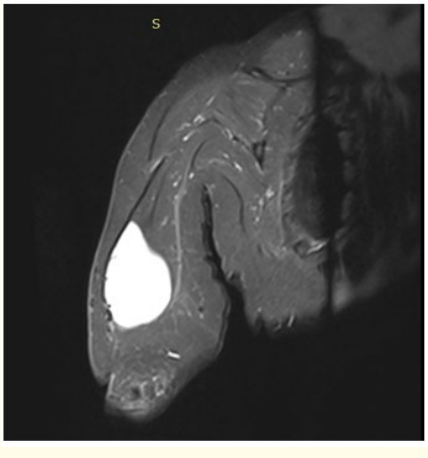

Figure 1: Coronal section of contrast-enhanced T1-weighted MR image of the right arm that shows hypercaptant 10 cm long tumor, adjacent to the triceps brachii

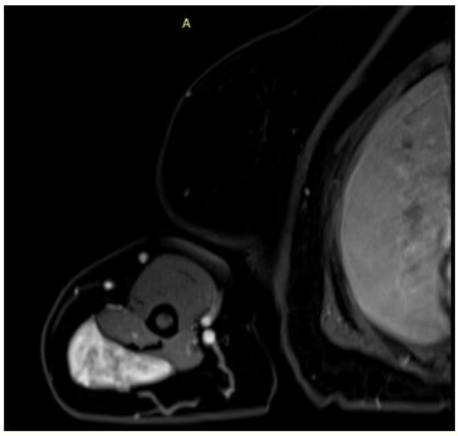

Figure 2: Transverse section of contrast-enhanced T1-weighted with fat saturation MR image of the right arm that shows hypercaptant 5.3x2.8 cm tumor, adjacent to the triceps brachii. Intense mottling and hypointense foci are present on cross section.

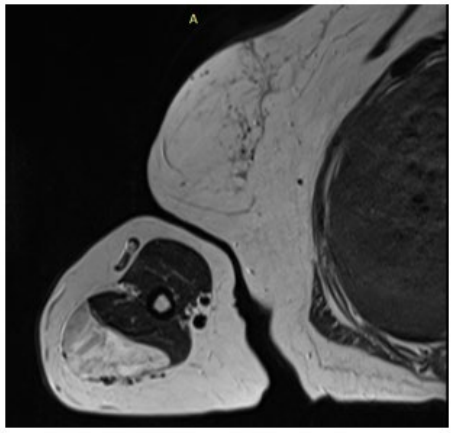

Figure 3: Transverse section of native T2-weighted MR image of the right arm that shows 5,3x2.8 cm tumor, adjacent to the triceps brahii. Intense mottling and hypointense foci are present on cross section.

The tumor displayed heterogeneous structure and clear margins of delineation, tortuous vasculature, with no signs of invasion in the neighboring tissues.

Treatment

The treatment is represented by complete in-bloc excision and despite negative surgical margins local or distant recurrences can be found in lungs, bones and liver in a minority of patients [11,28,29], thus needing long term follow up for potential local recurrence or metastases [30]. Adjuvant radiotherapy is sometimes employed in malignant SFTs management, with good results [31].

The appearance of metastasis is associated with poor prognosis, with some data suggesting the median of survival being of 22-46 months [32].

A total in-block resection of the tumor was performed (Figures 4 and 5) and samples were sent to the pathology department for macro and microscopic analysis. Gross specimen examination revealed a neatly encapsulated, pseudo lobular rubbery tumor, with convoluted blood vessels. On dissection it presented a greyish cross section with various cystic cavities inside (Figures 6 and 7).

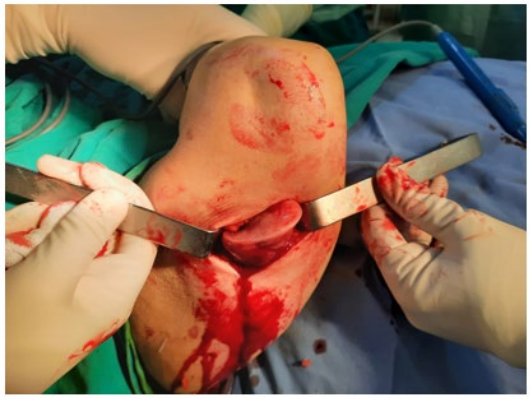

Figure 4: Intraoperative picture – posterior longitudinal incision of the right arm with obvious tumoral expression.

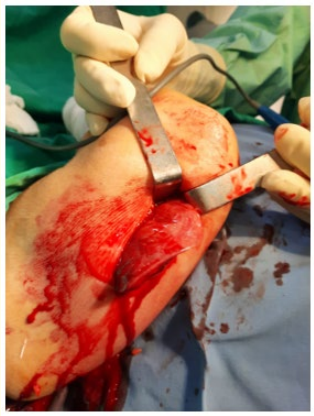

Figure 5: Intraoperative picture – posterior longitudinal incision of the right arm with obvious tumoral expression.

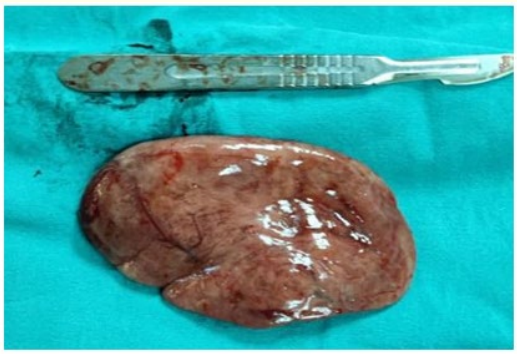

Figure 6: Macroscopic aspect of the resected specimen-neatly encapsulated, pseudo lobular greyish mass with rich vasculature with hilum present at the inferior margin of the specimen.

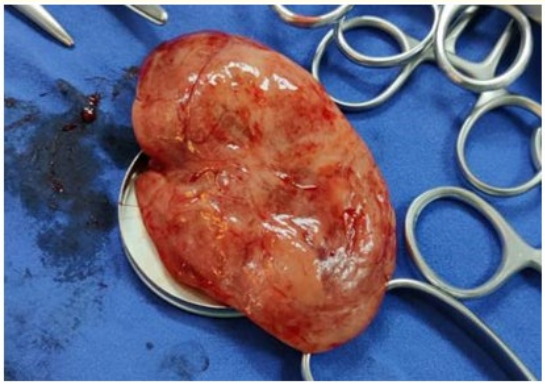

Figure 7: Macroscopic aspect of the resected specimen – neatly encapsulated, pseudo lobular greyish mass with rich vasculature with hilum present at the inferior margin of the specimen.

Etiology, pathological and microscopic features

The etiology of extra pleural SFT is not clearly defined currently, but there has been an association showed for smokers and asbestos exposure in patients [33]. Various abnormalities in structural and numerical karyotypic aberrations have been reported in various studies, which include a gain of 5,8,13 and 21 chromosomes and partial deletion or complete loss of 1,9,13,15,17,18 and X chromosomes [34-38].

It has been discovered that a gene mutation (NAB2-STAT6 fusion) is one of the mechanisms implicated in the etiology and pathogenesis of this tumor type, therefore the heighted expression of STAT6 marker proves a valuable asset in diagnosing SFTs [39]. Microscopically, SFTs consist of round to spindle-shaped fibroblast-like cells with eosinophilic cytoplasm, rich vasculature with branching staghorn pattern, hyalinized fibrous stroma and possibly, foci of hemorrhage and necrosis [40]. Malignant variants of SFTs display on most occasions' cellular atypia, high mitotic activity and necrosis. CD34 and STAT6 staining at the immunohistochemistry (IMC) analysis, alongside immunophenotypic classification decide the final diagnosis. Malignant SFTs have been reported in 10 to 15% of cases [41], occasionally exhibiting increased aggression and quick dissemination.

Two major risk assessment stratification schemes have been adopted for SFTs in the literature (tapias and Demicco) [42], which take into account the age of the patient, mitotic activity, tumor size, necrosis, hemorrhage and cellularity.

Our microscopic findings indicated areas with high cellularity of fusiform to ovoid-shaped cells, with fascicular and perivascular positioning, having eosinophilic cytoplasm, and small nuclei with visible nucleoli. In addition, the sample exhibited rich, staghorn-shaped vessels, with hyalinized vessel walls located in poor cellularity areas. Overall, very few mitoses and no necrosis were present (Figures 8,9,10).

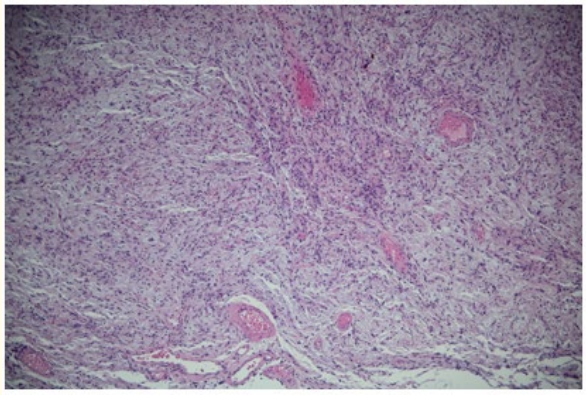

Figure 8: Hematoxylin and eosin-stained slide reveals typical microscopic pattern of a benign solitary tumor. Centrally, there is an area of condensed, high cellularity of fibroblasts and a few hyalinized thick-walled vessels on cross section (H&E x20).

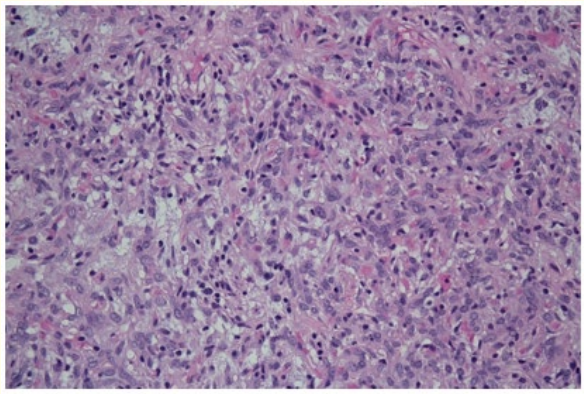

Figure 9: Hematoxylin and eosin-stained slide reveals typical microscopic pattern of a benign solitary fibrous tumor. Spindle to ovoid- shaped fibroblasts, small nuclei with visible nucleoli, no atypia, very few mitoses, no necrosis (H&E x40).

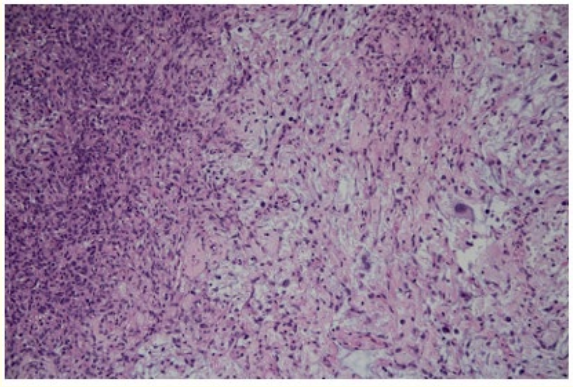

Figure 10: Hematoxylin and eosin-stained slide reveals typical microscopic pattern of a benign solitary fibrous tumor. To the left there is an area of condensed, high cellularity of fibroblasts. Loosely arranged cell clusters with rich collagenous stroma fill the rest of the picture (H&E x20).

On the immunohistochemistry assay, the results came back as follows:

- CD34 and CD99/MIC2 intensely positive in tumoral cells (Figures 11 and 12)
- STAT6 positive in some tumoral cell clusters
- Desmin positive in vessel walls and negative in tumoral cells
- HHV8 and EMA negative
- Ki67 proliferation index of 3%

Having considered clinical, imaging, morphological and immunohistochemical evidence, the diagnosis of benign primary extra pleural solitary fibrous tumor of the arm was made.

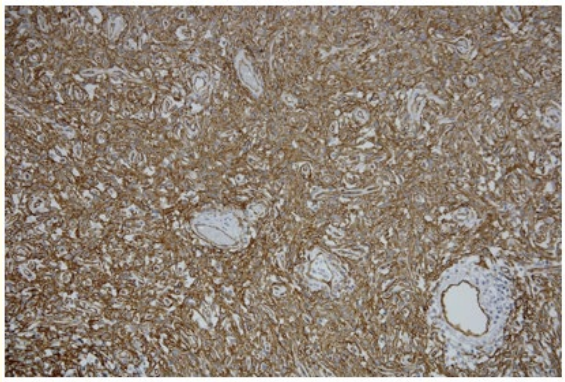

Figure 11: CD 34 positive immunohistochemical stained slide (H&E x20).

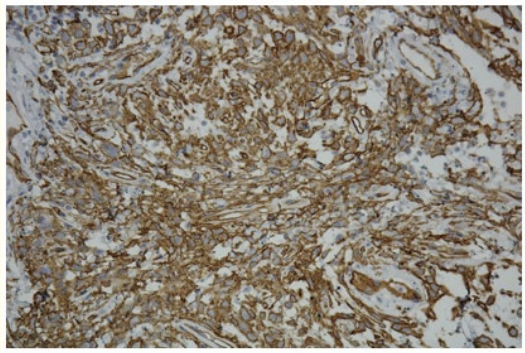

Figure 12: CD34 positive immunohistochemical stained slide (H&E x40).

Discussion

Solitary fibrous tumors are ubiquitous, first described in 1931 and named hemangiopericytomas. The ever-increasing differential diagnosis with other look-alike soft tissue tumors has since put SFTs in a group of their own, with specific microscopic and immunophenotypic characteristics [43]. Extra pleural sites of origin are rare instances, with an incidence of 0.2/100000 people-year [44], being even rarer at limb level. Another case of benign arm SFT was reported in 2015 in Saudi Arabia, in a 30-year-old

male, with good outcome at 3 years postop follow up [45]. No risk factors for SFT apparition have ever been discovered. The patient in our case was slightly older than the average patient (5TH decade of life) presenting with this kind of pathology. Most often the tumor is slow growing and painless. X-rays and ultrasound assessment are most of the time not specific, so the diagnostic imaging is made after MRI scanning. As it is in our case, T1-weighted images are hypo/isointense and variable on T2-weighted images with marked heterogeneity, caused by possible hemorrhage or necrotic foci [46]. The tumor is usually well delineated from the surrounding tissues, has a rich vasculature, which causes positive enhancement on gadolinium MRI images. Large tumors tend to compress and displace other tissues and organs. However, the final diagnosis and malignity status are based on microscopic, immunohistochemical and immunophenotypic analysis.

Macroscopically, SFTs are pseudo lobulated, firm, rubbery masses, rich in tortuous vessels, which converge in a hilum. On cross section, hemorrhage, large cysts or necrosis can be found. In our case, the tumor had large dimensions (10x5cm), with a neat glossy aspect, pseudo lobulated, with dilated vasculature and yellow cysts on the inside.

At microscopic level, there is a huge variety of patterns that create difficulties in differentiating SFTs from other close-related tumor, like Ewing sarcoma [47], mesenchymal chondrosarcoma, synovial sarcoma [48], low grade fibro myxoid sarcoma, round cell liposarcoma.

The typical findings on hematoxylin and eosin (H&E) staining are similar to the ones in this case: spindled to ovoid cells with eosinophilic cytoplasm and vesicular nuclei with visible nucleoli, grouped in patches of high cellularity and areas of rich vasculature with staghorn branching pattern and hyalinized vessel walls, collagenous stroma. In the case of malignant SFTs, necrosis, high mitotic activity and cellular atypia are present [49].

Solitary fibrous tumors cells stain intensely positive for CD34, uneven positive for STAT6 and stain negatively for desmin [50]. In case of malignant cells, the nuclear antigen ki67 is overly-expressed and the cells stain positive for this marker, which is an indirect sign of the degree of mitotic activity and tumor aggressiveness [51]. In this case, the cells stained CD34, STAT6 positive and desmin, SMA negative, with a very low ki67 proliferation index of 3%. These microscopic characteristics credit the studied specimen as low risk for further proliferation on Demicco risk stratification model [52]. As for other markers tested during IMC, the tumor cells stained CD99/MIC2 positive, and CD31, ERG, FLI1, SMA negative, reaffirming the diagnosis.

Different variants of NAB2-STAT6 gene fusion can be detected by polymerase chain reaction analysis.

Considering treatment options, total surgical excision is the gold standard therapy for benign SFTs [53]. Adjuvant radiotherapy has been proven to be helpful, especially in cases of high risk of local recurrences [31]. Chemotherapy has not been shown to be efficient on solitary fibrous tumors and it should not be administered [54].

Even in the case of benign tumors, a minimum of 5 years follow up period is recommended, in which clinical and CT scan exams should be performed regularly. However, Baldi et al. found an average time to recurrence of 12 years after the primary lesion [55], fact that can only encourage adequate and regular check-up visits.

Conclusion

After the surgery, the evolution of our patient was uneventful. At 12 months post-op follow-up, the patient is asymptomatic. Full body CT scan was performed at 6- and 12-months post-surgery with no evidence of local recurrence or metastasis.

To our knowledge, this is one of very few arm solitary fibrous tumor ever reported.

Giving the uncommonness of this type of tumor and the unusual location, diagnosing it was challenging. Only after careful examination, involving a plethora of imaging, microscopic and IMC techniques, had a final decision been achieved. In addition to that, SFTs share a lot of microscopic traits with other types of soft tissue tumors, which can mislead the diagnostic process and the treatment. Early total resection of the tumor is very important for patient's prognosis, alongside careful assessment of malignity. Close clinical and imaging follow-up after discharge is paramount for avoiding local recurrence or metastases.

In conclusion, although this pathology is very infrequent, when faced with big, painless masses in the extremities, that have the same MRI pattern as the one described before, the possibility of a SFT should be accounted for in order to reach an accurate diagnosis.

This section is not mandatory but can be added to the manuscript if the discussion is unusually long or complex.

Patient Consent for Publication

The patient signed a written informed consent allowing the publication, use of personal information and pictures provided in this paper.

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