CASE REPORT

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# Solitary fibrous tumor developing in the right retroperitoneal space

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## Abstract

Solitary fibrous tumor (SFT) is a rare mesenchymal tumor that is quite aggressive and prone to recurrence and metastasis. Most SFTs are benign, but the identification of the histological features that define the dedifferentiation of SFTs can predict the aggressiveness of the tumor and the presence of a reserved prognosis. We present a rare case of conventional SFTs with features of malignancy and highlight the diagnostic and therapeutic difficulties related to this case. Computed tomography aspect suggested a possible gastrointestinal stromal tumor. Surgical intervention was performed through median laparotomy and a tumor of approximately 15/12 cm was found, developed from the level of the right retroperitoneal space, and pushing anteriorly the ascending colon, cecum, and terminal ileum. The immunohistochemical aspect correlated with the histopathological one suggests a SFT most likely malignant. In conclusion, the early diagnosis of SFTs is essential in establishing an appropriate treatment. Immunohistochemistry is indispensable in establishing the diagnosis of SFTs.

***Keywords***: solitary fibrous tumor, immunohistochemistry, early diagnosis.

## Introduction

Solitary fibrous tumor (SFT) is a rare mesenchymal tumor that is quite aggressive and prone to recurrence and metastasis. The identification of nerve growth factor-inducible A (NGFI-A) binding protein 2 (*NAB2*)–signal transducer and activator of transcription factor 6 (*STAT6*) gene fusion [1–4] led to the conclusion that hemangiopericytoma (HPC) and SFT represent a single disease. SFTs have various locations, the one in the retroperitoneal space being the least reported. The immunohistochemical (IHC) examination is essential to make the differential diagnosis with spindle cell lipoma, schwannoma, liposarcoma, dermatofibrosarcoma, malignant peripheral nerve sheath tumor (MPNST), gastrointestinal stromal tumor (GIST), and synovial sarcoma. However, although SFT presents distinct IHC characteristics, in some cases genetic examination is also necessary. Most SFT [5, 6] are benign, but the identification of the histological features that define the dedifferentiation of SFT can predict the aggressiveness of the tumor and the presence of a reserved prognosis.

## Aim

The authors present a rare case of conventional SFT with features of malignancy and highlight the diagnostic and therapeutic difficulties related to this case.

## Case presentation

C.I. patient, aged 74, female, was admitted to the Second Surgical Clinic, Emergency County Hospital, Craiova, Romania, by transfer from the Gastroenterology Clinic, for pain in the right iliac fossa, paresthesia in the right pelvic limb. The objective clinical examination revealed the presence of a tumor formation located in the right iliac fossa 15/20 cm, regular surface, ovoid shape, hard consistency, slightly sensitive to palpation, mobile on the deep planes. The patellar and achilleas osteotendinous reflexes were present, as were the abdominal skin reflexes. Digital rectal exam was normal. The biological paraclinical explorations have relevant values: hemoglobin 12.7 g/dL; white blood cell (WBC) count 7800/mm$^3$; Quick time (QT) 101%; international normalized ratio (INR) 1.2; glycemia 98 mg/dL; serum glutamic oxalo-

acetic transaminase (SGOT) 12 IU; serum glutamic pyruvic transaminase (SGPT) 16 IU; urea 47 mg%; creatinine 1.08 mg%; urinalysis normal; total bilirubin 0.57 mg%; carcinoembryonic antigen (CEA) 4 ng/dL; carbohydrate antigen 19-9 (CA19-9) 21 IU/L.

Electrocardiography (ECG): sinus rhythm, QRS axis normal, without abnormal repolarization.

The colonoscopy performed in the Gastroenterology Clinic showed a normal appearance of the colon and rectal mucosa.

Chest computed tomography (CT) showed normal appearance of the lung, mediastinum.

Abdomen and pelvis CT scan revealed the presence of a tumor formation in the right flank, with development in the right retroperitoneal space, well delimited, with dimensions of 13/10/12 cm, inhomogeneous iodophilia, mass effect on the ascending colon, intestinal loops, right common iliac vessels, right psoas muscle and compression on the broad abdominal muscles on the right side (Figure 1, A–C).

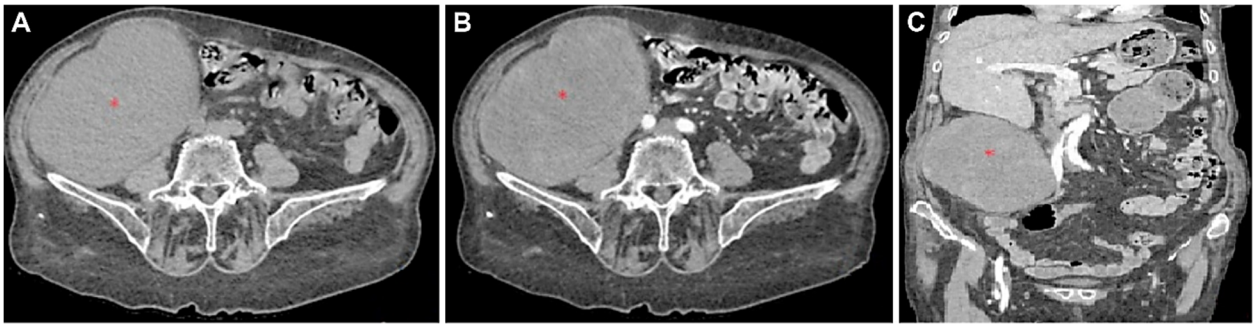


**Figure 1 –** ***CT examination revealed a well-defined tumoral mass, located in the right flank of the abdomen, near the ascending colon and the right lobe of the liver, with a homogeneous appearance on the native acquisition (A), and a relatively inhomogeneous contrast enhancement (B – arterial phase, axial plane; C – venous phase, coronal plane), measuring 13.2/9.5/12.4 cm in all three planes, generating mass effect on the ascending colon, ileal loops, right common iliac vessels, right psoas muscle, right antero-lateral muscles of the abdomen, with no macroscopic signs of tumoral invasion and no suspicious adjacent lymph nodes – CT aspect suggested a possible gastrointestinal stromal tumor. CT: Computed tomography.***

Surgical intervention was performed through median laparotomy and a tumor of approximately 15/12 cm was found, developed from the level of the right retroperitoneal space, and pushing anteriorly the ascending colon, cecum, and terminal ileum (Figure 2). Intraoperatively, the cecum, the ascending colon together with the terminal ileum were mobilized, the ureter and the common iliac and ovarian vessels were highlighted, and the tumor excision was divided, with free resection blades together with part of the postero-lateral abdominal muscles. The muscle defect was partially closed.

The macroscopic aspect of the resection piece showed the presence of an encapsulated oval tumor formation with dimensions of 15/8.5/8 cm, greyish-white in section, arranged in swirls with areas of necrosis, firm consistency (Figure 3).

The histopathological (HP) examination revealed an encapsulated tumor proliferation with densely cellular areas consisting of fusiform mesenchymal cells arranged in bundles of variable size, some with acidophilic cytoplasm, alternating with looser, hypocellular areas (zones), with abundant interstitial collagen and with moderate mitotic activity [5–6 mitoses/10 high-power fields (HPFs)]. On another section, hemorrhagic areas are also observed. HP appearance is suggestive of peripheral nerve mesenchymal tumor – most likely schwannoma (Figure 4).

IHC examination (Figures 5–13): S100 protein – negative in tumor cells, but positive in rare interstitial mesenchymal cells; cluster of differentiation (CD)56 – positive in tumor cells; B-cell lymphoma-2 (Bcl-2) – focally positive in tumor cells; CD34 – intensely positive in tumor cells; smooth muscle actin (SMA) – negative in tumor cells, positive in smooth muscle cells from the walls of blood vessels; glial fibrillary acidic protein (GFAP) – negative in tumor cells; vimentin (VIM) – intensely positive in tumor cells; CD117 – negative in tumor cells; CD99 – positive in tumor cells; discovered on GIST1 (DOG1) – negative in tumor cells; factor XII (FXII) – negative in tumor cells; Ki67 proliferation index – 35% in tumor cells. IHC aspect correlated with the HP one suggests a SFT, most likely malignant.

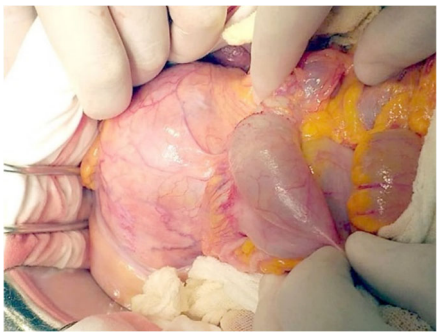

**Figure 2 –** ***The intraoperative aspect of solitary fibrous tumor. It is observed how the tumor, developed in the right retroperitoneal space, pushes anteriorly the ascending colon, the cecum and the terminal ileum.***

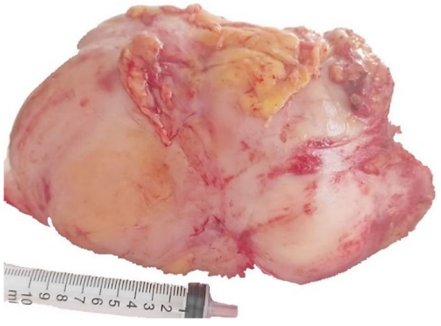

**Figure 3 –** ***The macroscopic appearance of the right retroperitoneal tumor highlights an ovoid, encapsulated, greyish-white tumor formation on section.***

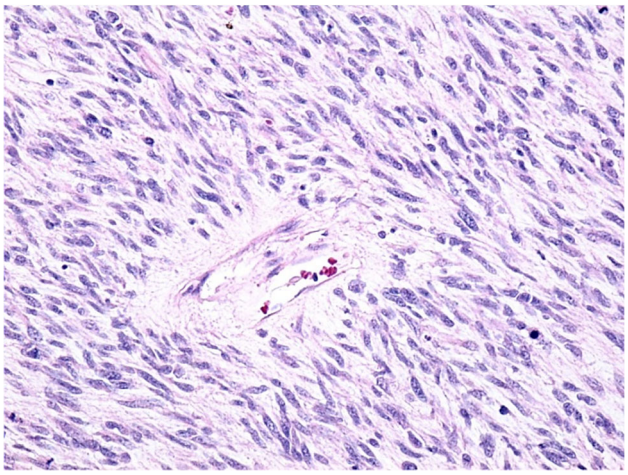

**Figure 4** – *The examined fragments show a tumor proliferation with densely cellular areas made up of fusiform mesenchymal cells arranged in bundles of variable size, some with acidophilic cytoplasm, alternating with main axes, hypocellular areas with abundant interstitial collagen, with moderate mitotic activity (5–6 mitoses/10 HPFs). HE staining, ×200. HE: Hematoxylin–Eosin; HPF: High-power field.*

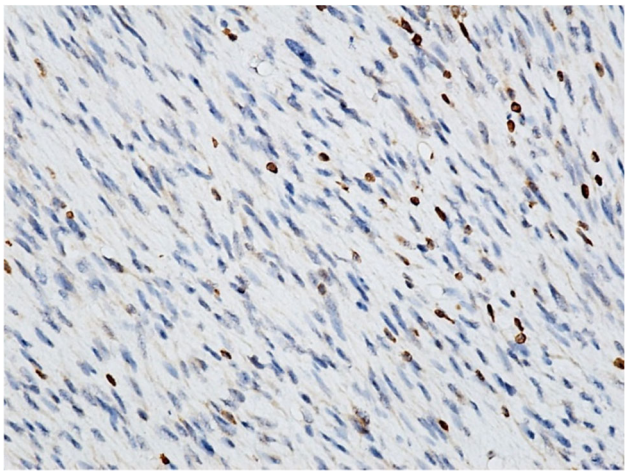

**Figure 5** – *Bcl-2 cytoplasmic immunolabeling (non-specific), with variable positivity in intensity and cellularity in tumor proliferation, focally positive in tumor cells. Immunostaining with anti-Bcl-2 antibody, ×200. Bcl-2: B-cell lymphoma-2.*

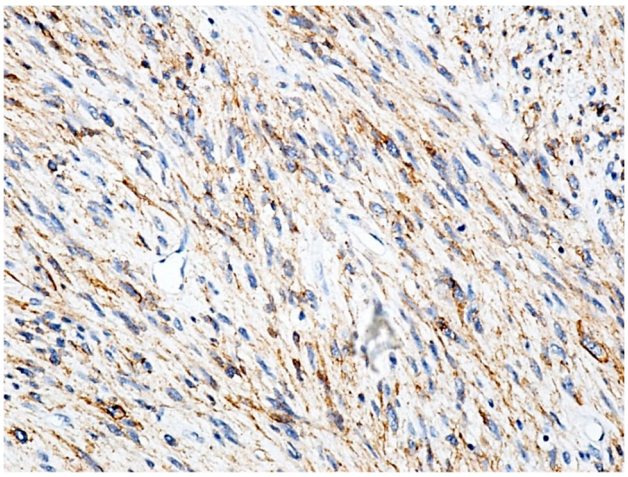

**Figure 6** – *CD56 diffuse membrane immunolabeling at the level of target tumor cells, positive in tumor cells. Immunostaining with anti-CD56 antibody, ×200. CD56: Cluster of differentiation 56.*

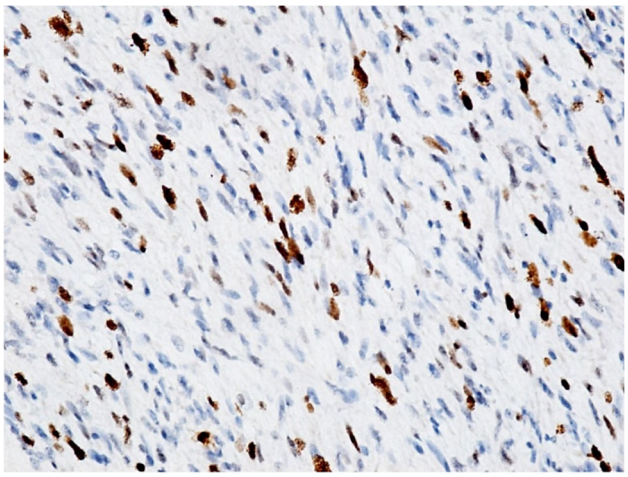

**Figure 7** – *Ki67 proliferation index 35% in tumor cells. Immunostaining with anti-Ki-67 antibody, ×200.*

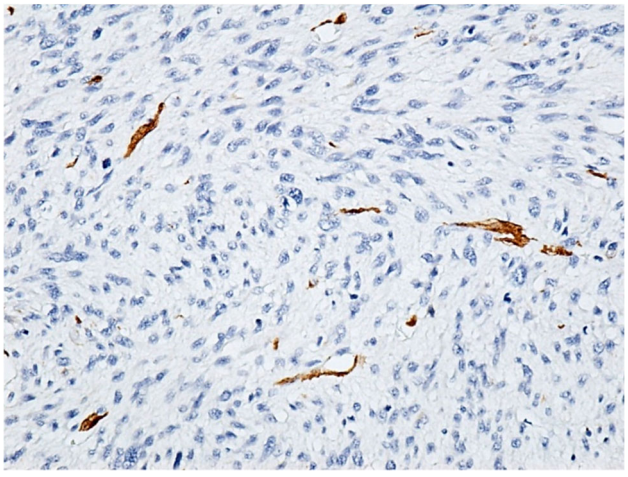

**Figure 8** – *SMA cytoplasmic immunolabeling, negative in tumor cells but positive in rare interstitial mesenchymal cells. Immunostaining with anti-SMA antibody, ×200. SMA: Smooth muscle actin.*

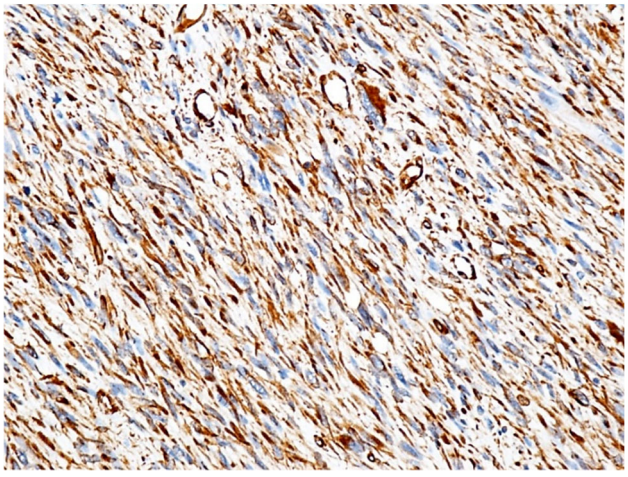

**Figure 9** – *VIM cytoplasmic immunolabeling, intense and diffuse positive in mesenchymal tumor proliferation. VIM intensely positive in tumor cells. Immunostaining with anti-VIM antibody, ×200. VIM: Vimentin.*

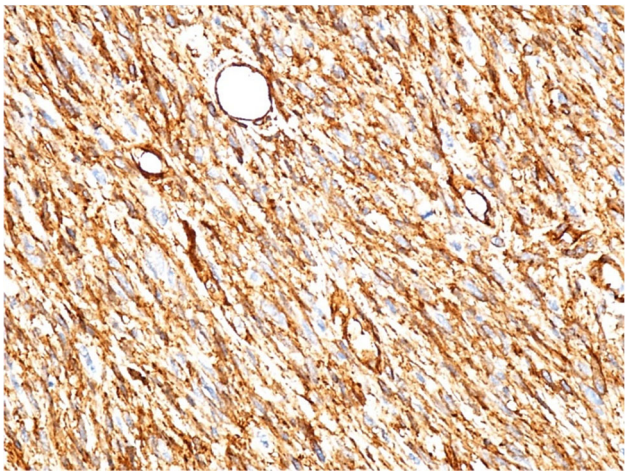

**Figure 10 –** ***CD34 intensely positive in tumor cells. CD34-positive round or oval cells. Membrane immunolabeling, intensely positive, diffuse, extensive (specific immunolabeling). Immunostaining with anti-CD34 antibody, ×200. CD34: Cluster of differentiation 34.***

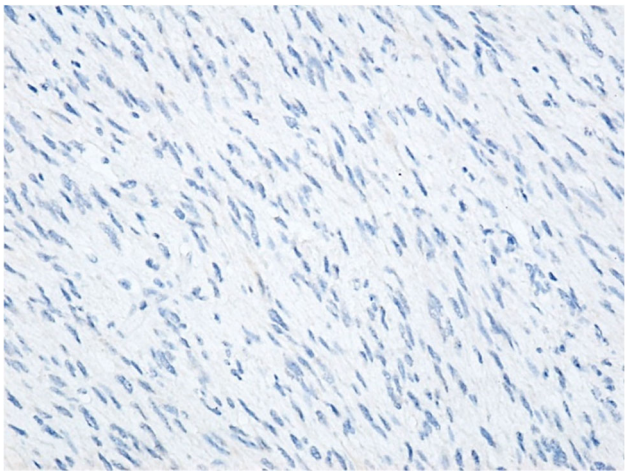

**Figure 11 –** ***CD117 cytoplasmic immunolabeling, negative in tumor proliferation, negative in tumor cells. Immunostaining with anti-CD117 antibody, ×200. CD117: Cluster of differentiation 117.***

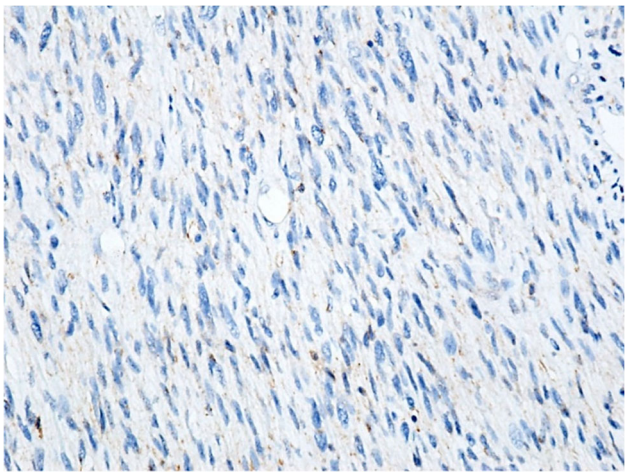

**Figure 12 –** ***CD99 cytoplasmic and membrane immunolabeling (non-specific) intensely positive but with a focal aspect in proliferation, positive in tumor cells. Immunostaining with anti-CD99 antibody, ×200. CD99: Cluster of differentiation 99.***

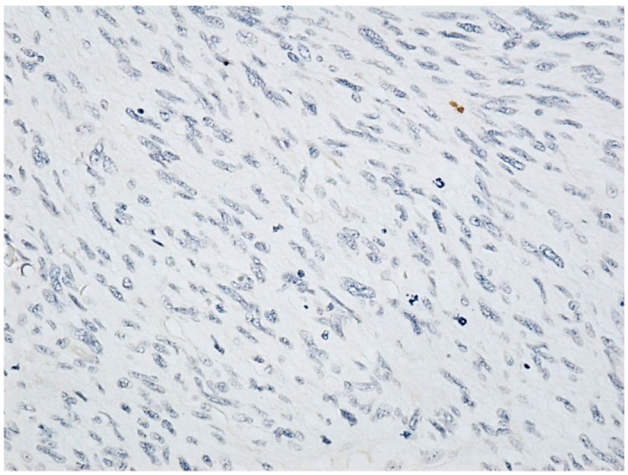

**Figure 13 –** ***S100 protein cytoplasmic immunolabeling, negative in tumor cells, but positive in rare interstitial mesenchymal cells. Immunostaining with anti-S100 antibody, ×200.***

Genetic examination: *KIT* gene mutations in exons 9, 11, 13 and 17 and platelet-derived growth factor receptor alpha (*PDGFRA*) gene mutations. Technique used: deoxyribonucleic acid (DNA) extraction followed by real-time polymerase chain reaction (PCR) (IVDEnteroGen kit). The kit detects 19 mutations (one mutation in exon 9, eight mutations in exon 11, one mutation in exon 13 and nine mutations in exon 17) and one *PDGFRA* gene mutation, corresponding to *D842V* in exon 18. Conclusion: GIST wild-type negative. Note: At least 2–3% of cells must carry *KIT* or *PDGFRA* mutations for this kit to detect them. *KIT* mutations are present in over 80% of GISTs, and *PDGFRA* mutations are present in 5–10% of GISTs.

The postoperative evolution was favorable without incidents. The patient was discharged after 10 days, with recommendations to perform oncological treatment.

## Discussions

SFT is a mesenchymal tumor of fibroblastic origin that can develop in any region of the body. From a histological point of view, SFTs are composed of fibroblast-like tumor cells arranged in hyalinized collagenous stroma and with a diffuse expression of CD34. Unconventional subtypes have also been described but with distinct morphological features: lipomatous, myxoid and dedifferentiated variants. The 2013 Classification of Soft Tissue Tumors of the *World Health Organization* (*WHO*) defined SFT as a rarely metastasizing tumor [7, 8]. Most SFTs have a favorable evolution, but 10–20% of them behave like recurrent tumors with the potential for metastasis [1]. Histological studies performed on SFT (increased mitotic activity, hypercellularity, nuclear atypia, pleomorphism) showed that the reserved prognostic factors of SFT were patient age, tumor size and mitotic activity [1]. However, there are few genetic studies that assess the behavior of SFT. However, there are few genetic studies that assess the behavior of SFT. SFT was initially considered to be a mesenchymal tumor, distinct from HPC, but the identification of the *NAB2–STAT6* gene fusion, located on the chromosomal region 12q13, present in both tumors, showed that it actually represents a single

entity. IHC detection of the STAT6 protein has proven to be very useful in the diagnosis of SFT/HPC [2, 6]. Clinical-pathological parameters are currently used to assess the prognosis of SFT, but the molecular determinants of malignancy remain unknown.

SFTs have a maximum incidence in patients aged between 50 and 60 years, and the presence of this tumor in children and adolescents is very rare. In 30% of cases, SFTs are located in the pleura. Other locations of SFT are cervical meninges (27%), pleural cavity (20%), thorax (10%), upper and lower limbs (8%), head (5%) [9]. The size of the tumor varies between 1–40 cm, with an average size of 5–8 cm. Small tumors are found in the head and neck, while tumors in the abdominal cavity reach large sizes without showing any obvious symptoms [4]. The tumor presented by us, with development in the right retroperitoneal space, had dimensions of 15/12 cm. Some SFT present with a paraneoplastic hypoglycemic syndrome (Doege–Potter syndrome) resulting from an excessive production of insulin-like growth factor 2 (IGF2) [10–12].

Regular SFTs are often well demarcated and encapsulated, which on section are whitish, multinodular. Myxoid and hemorrhagic changes can be seen in rare cases. Malignant tumors and those with aggressive behavior have infiltrative borders and necrotic areas [9, 13].

SFTs are tumors that, from a histological point of view, are composed of ovoid or fusiform cells and the stroma contains staghorn-shaped branched blood vessels. Common SFTs are composed of a few fusiform cells, arranged in short bands, with fusiform nuclei and reduced cytoplasm [14, 15]. At the level of the vascular channels of the SFT, perivascular fibrosis is not observed [4]. Vascularization similar to HPC tumors can be observed, but also in other mesenchymal tumors including soft tissue sarcomas [1, 16]. From a morphological point of view, in general, SFTs show a low mitotic activity and are devoid of a significant nuclear polymorphism or necrosis [8]. There are several morphological variants of SFT: dedifferentiated, fat-forming and giant cell-rich variants. Lipomatous HPC contains a lot of mature adipocytes, being mainly found in soft tissue but also in other places, such as retroperitoneal space, thigh and paratesticular soft tissue [16–18]. SFT with giant cells presents cells with multiple nuclei, located predominantly around blood vessels. However, extraorbital locations have also been reported, such as head and neck, inguinal region, retroperitoneal space, vulva, back, and hip [19]. The dedifferentiated SFT variant is very rare and presents itself as a transitional variant and the most frequent component of dedifferentiated SFT is form of undifferentiated pleomorphic sarcoma or spindle cell sarcoma [20, 21]. Dedifferentiation can be observed in primary or recurrent tumors. Occasionally, squamous and neuroendocrine dedifferentiation has been reported [20].

Features suggestive of malignancy include advanced age, large tumors, high cellularity, high mitotic activity (≥4 mitoses/10 HPFs or >2 mitoses/2 $mm^2$), nuclear pleomorphism, necrobiosis and infiltrative margins [4, 17]. Tumors that have lost malignant histological features on primary resection specimens may become malignant features during recurrences or metastases [21]. In extra-pleural and extra-meningeal tumors, Pasquali *et al.* [22] found that reduced survival in these patients was associated with hypercellularity and nuclear pleomorphism; hypercellularity, high mitotic index and nuclear pleomorphism would be associated with tumor recurrence. Demicco *et al.* [23] found that the factors predicting metastasis would be the age of the patients, the size of the tumor and the rate of the mitotic index. The size of the tumor in general is considered to be an unfavorable prognostic factor for patients with SFT, but SFT can grow and reach considerable sizes without presenting an aggressive behavior [22]. Kim *et al.* [24] found that the only reserved prognostic factor of different locations of SFT would be the mitotic index rate (>4 mitoses/10 HPFs). Yamada *et al.* [21] identified that dedifferentiation would be a major prognostic factor and hypoglycemia, intra-abdominal and cervico-meningeal locations would be associated with a reserved prognosis. Determination of tumor protein p53 (TP53) and telomerase reverse transcriptase promoter mutations ($TERTp^{mut}$) [25, 26] would be associated with the risk of metastasis and tumor recurrence.

For the IHC diagnosis of SFT, the determination of the following IHC markers is used: CD34, CD99 and Bcl-2, their expression being in approximately 90% of cases. The IHC expression of CD34 is observed in 81–95% of SFTs [27], but the expression of this IHC marker disappears in malignant tumors and in dedifferentiated tumors. Bcl-2 has a high sensitivity, while CD99 has a slightly lower sensitivity, and the specificity of these markers is quite low [28]. In the case presented by us, Bcl-2, CD34 and VIM were positive in the tumor cells. STAT6 IHC staining proved to be a good marker with very good sensitivity and specificity, being also present in malignant SFT [29]. In recent studies, an expression of the STAT6 IHC marker was observed in 92% of the studied patients [4]. STAT6 IHC staining can also be present in other soft tissue tumors: low-grade fibromyxoid sarcoma, undifferentiated pleomorphic sarcoma, synovial sarcoma, ovarian fibroma, neurofibroma, desmoid fibromatosis, myxoid liposarcoma, well-differentiated liposarcoma and dedifferentiated liposarcoma [9, 30]. STAT6 IHC expression was also found in non-neoplastic tissues, such as scar tissue and adipose tissue [30]. In SFT, genetic studies have identified an aberrant expression of the glutamate ionotropic receptor $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) type subunit 2 (GRIA2) protein and an over-expression of the *GRIA2* gene [3]. GRIA2 protein in most cases is expressed in the epithelium of several organs and central nervous system tissue, but it can also be expressed in soft tissue neoplasms, such as SFT or fibrosarcoma with dermal starting point [27]. In the studies carried out by Ouladan *et al.* [31], it was found that aldehyde dehydrogenase 1 (ALDH1) can be a marker for SFT, especially to differentiate meningeal SFT from synovial sarcoma and meningioma. In the case of SFT locations in the peritoneal or pleural cavity, a multifocal expression of cytokeratins (CKs) was found [32]. Also, in some cases, focal expression was observed for $\alpha$-SMA, epithelial membrane antigen (EMA), neuron-specific enolase (NSE) and $\beta$-actin [32]. S100 protein, CD31, desmin, h-caldesmon are usually negative [32]. CD56, SMA and S100 protein immunohistochemistry performed by us to establish the diagnosis of SFT was negative in tumor cells. TP53 IHC expression is observed in malignant cases [25].

To establish a correct diagnosis of SFT, it is necessary to integrate clinical, pathological, IHC and genetic data [9]. Monophasic and poorly differentiated synovial sarcomas can mimic SFT [8]. CD34 staining is usually absent in synovial sarcomas. SFT can also have a low expression of transducin-like enhancer of split 1 (TLE1), but high nuclear expression of TLE1 is found in synovial sarcomas. Molecular studies for the *t*(X;18) translocation are recommended in this case to confirm the diagnosis [14]. Tumor cells in MPNST may show HPC-like vasculature, but STAT6 negativity and the expression of GFAP, sex-determining region Y (SRY)-related high mobility group box-10 (SOX-10) and S100 protein are in favor of MPNST diagnosis [6]. Although intrapulmonary SFTs are uncommon tumors, they must be differentiated from sarcomatoid carcinoma. Diffuse expression for CKs observed in abdominal SFT can pose a differential diagnosis problem. Also, SFT must be differentiated from leiomyosarcoma, leiomyoma, inflammatory myofibroblastic tumor (IMT) and adenofibroma, in which the presence of CD34 and STAT6 markers has a very important role in establishing the diagnosis of SFT [11]. Lipomatous SFT or fast-forming SFTs must be differentiated from spindle cell lipoma where retinoblastoma 1 (*RB1*) gene loss is observed and also must be differentiated from malignant lipomatous tumors, in which cyclin-dependent kinase 4 (CDK4) and p16 are used for diagnosis of well-differentiated and dedifferentiated malignant lipomatous tumors [6, 12, 13, 16, 18, 19]. From a HP point of view, SFTs can be confused with cellular schwannomas in which the presence of a thick fibrous capsule, foamy macrophages, lymphoid infiltrates, and S100 protein expression favors the diagnosis of schwannoma [6, 12, 13]. In angiofibroma of soft tissue, the tumor cells can present an expression of the CD34 marker. Desmin, EMA but the presence of STAT6 is negative, the molecular diagnosis is established by *t*(p15;q13) translocation resulting in aryl hydrocarbon receptor repressor (*AHRR*)–nuclear receptor coactivator 2 (*NCOA2*) gene fusion [33]. Cellular angiofibroma and deep fibrous histiocytoma show hyalinized blood vessels, HPC-like vessels but variable expression for CD34, $\alpha$-SMA, and STAT6 is negative [34]. In the case of abdominal SFTs, they must be differentiated from GISTs, in which CD34 expression is shared by SFTs and GIST, but in most of the GISTs the CD117 and DOG1 markers are present and the STAT6 marker is absent [8]. For the differential diagnosis between SFT and meningothelial meningioma, it is useful to determine the expression of CD34 and STAT6, which is negative in meningioma [35]. Myxoid changes in SFT that can be found in myxofibrosarcoma, fibromyxoid sarcoma and liposarcoma must also be excluded, in which a careful examination can establish the diagnosis, although in some cases CD34 and STAT6 expression can be reported [14]. Soft tissue tumors with epithelioid morphology (epithelioid sarcoma, epithelioid angiosarcoma) and prostate stromal tumors with undefined malignant potential (STUMP) and prostate stromal sarcomas (PSS) can pose differential diagnostic problems, but STUMP and PSS lack nuclear expression for STAT6 [16, 18, 19].

The molecular studies performed on SFT have identified recurrent fusion of two genes (*NAB2* and *STAT6*) located on chromosome 12, in most cases of SFT [1–3]. *NAB2* and *STAT6* play important roles in collagen formation, vessel formation and in fibroblastic activation. The studies of Robinson *et al.* [1] found that two out of three SFTs with *NAB2ex4–STAT6ex2/3* gene fusion variant were discovered in patients with pleuro-pulmonary SFTs and in most extra-thoracic SFTs, *NAB2ex6–STAT6ex10/17* gene fusion variant. Yamada *et al.* [21] and Park *et al.* [25] found that the association between the gene fusion variants and the tumor can to some extent influence the behavior of SFT. In two studies, $TERTp^{mut}$ [25, 26] were found in malignant SFTs. Many of the kinases and growth factors [platelet-derived growth factor (PDGF)-$\alpha$, PDGF-$\beta$, insulin-like growth factor 1 receptor (IGF1R), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), IGF2, c-Met, c-Kit, c-erbB2, phosphatase and tensin homolog (PTEN), ribosomal protein S6 (rpS6), p4EBP–EGFR, Erb-B2 receptor tyrosine kinase 2 (ERBB2), fibroblast growth factor receptor 1 (FGFR1), and Janus kinase 2 (JAK2)], which are overexpressed in SFTs, these markers lead to the activation of Akt/mammalian target of rapamycin (mTOR) pathway and seem to be associated with necrobiosis [36]. The genetic study carried out by us revealed a mutation in exon 9, eight mutations in exon 11, a mutation in exon 13 and nine mutations in exon 17. In recent studies, it was identified that 41% of malignant SFTs present TP53 mutations [25] and the same in dedifferentiated SFTs [21, 25].

In a study carried out on malignant SFTs, it was found that they present an increased rate of local recurrence and distant metastasis [37]. Also, SFTs located in the cervical meninges and pelvic–subperitoneal space are associated with an increased risk of recurrence [38]. In the study by Barthelmeß *et al.* [4], it was observed that local recurrences appeared in 13 out of 39 cases. In the study by Demicco *et al.* [23] on extra-thoracic SFTs, the median overall survival duration was between 59 and 94 months, the 5-year survival rate was 89%, and the 10-year survival rate was 73%.

The treatment of these SFTs consists of wide surgical excision, chemotherapy and radiotherapy are not necessary in ordinary cases [39]. In some cases of SFT, it has been suggested that adjuvant radiotherapy would have a beneficial effect in preventing the local extension of the SFT [39]. Cervical meningeal tumors (*WHO* grade 1) are treated only by surgical removal, while *WHO* grades 2 and 3 meningeal tumors benefit from adjuvant radiotherapy [40]. A multi-disciplinary approach is indicated for meningeal tumors [40].

## Conclusions

The early diagnosis of SFTs is essential in establishing an appropriate treatment. Also, immunohistochemistry is indispensable in establishing the diagnosis of SFTs. In tumors where *NAB2–STAT6* gene fusion and IHC expression is present, molecular studies are necessary in cases where IHC is inconclusive.

### Conflict of interests

The authors declare that they have no conflict of interests.

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