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Case Report

Solitary fibrous tumor of the orbital region: report of a case with emphasis on the diagnostic utility of STAT-6

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Summary

Solitary fibrous tumor (SFT) is a relatively rare soft tissue neoplasm originally described in the pleura. Since its first description, several cases arising in extra-pleural superficial and deep soft tissues have been reported in the literature. SFT arising in the head and neck region is quite rare, representing about the 6% of all SFTs, and the sinonasal tract is the most common involved region, followed by the orbit, the oral cavity and the salivary glands. Herein, we report the clinico-pathologic features of a rare case of SFT of the orbital region, emphasizing the diagnostic role of the immunomarker STAT-6. A 52-year-old female presented to our hospital with a nodular mass in the left orbital region. Histological examination revealed a uniformly hypercellular tumor composed of pale to slightly eosinophilic bland-looking spindle cells arranged in intersecting short fascicles with interspersed stellate-shaped, keloid-type collagen fibers. Notable hypocellular areas, perivascular hyalinization and hemangiopericytoma-like branching vascular pattern were absent. Immunohistochemically, neoplastic cells were diffusely positive for vimentin, CD34 and STAT-6. The introduction of STAT-6 in daily diagnostic practice is helpful to confidentially render a diagnosis of SFT even in the presence of unusual morphology and site.

Key words: solitary fibrous tumor, soft tissue tumor, spindle cell lesion, orbit, STAT-6

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Introduction

Solitary fibrous tumor (SFT) is a relatively rare soft tissue neoplasm originally described in the pleura [1]. Since its first description, several cases arising in extra-pleural superficial and deep soft tissues have been reported in literature [2-4]. SFT may also arise in visceral sites, including kidney, mammary gland, liver, pancreas and gastrointestinal tract [5-10]. SFTs of the head and neck region are relatively uncommon, and the orbit is the second most common site (25% of cases) after the sinonasal tract (30% of cases) [11]. More rarely the tumor may occur in the oral cavity (15% of cases) or salivary glands (14% of cases) [11]. Orbital SFT usually arises as a unilateral progressive slow-growing tumor, clinically detectable for the onset of proptosis, eyelid swelling or palpable mass [12-14]. Other symptoms, such as visual deficit and ptosis, depend on the size and exact location of the neoplasm [14]. The most common histological features of classic pleural and extra-pleural SFT are: i) bland-looking spindle to ovoidal cells arranged in a "patternless" growth pattern; ii) rich vascular component composed by small- to medium-sized branching vessels, often with perivascular hyalinization and hemangiopericytoma-like pattern;

iii) presence of hypercellular areas alternating with hypocellular ones; iv) thin and thick collagen fibers among neoplastic cells; v) mitotic count ≤ 4 mitoses x 10 high-power fields (HPF) [4,6].

Although the majority of "*histologically benign*" SFTs have a benign clinical behavior, histopathology alone cannot predict the clinical outcome. It is estimated that about 10-15% of "*histologically benign* SFTs" tend to locally recur and metastasize [4,6,11], whereas some cases of "*histologically malignant SFTs*" (defined by the presence of more than 4 mitoses/10 HPF, often combined with hypercellularity, necrosis, infiltrative margins and cellular pleomorphism) exhibit a benign clinical course [4,6,11]. The diagnosis of SFT in its typical pleural site is usually straightforward, but diagnostic problems may arise when the tumor occurs in an unexpected site and the pathologist is faced with small biopsies. Interestingly, the vast majority of SFTs present the inv12(q13q13)-derived *NAB2-STAT6* fusion, which represents the "*molecular hallmark*" of SFT [15]; STAT-6 nuclear expression is a reliable immunohistochemical surrogate for the presence of *NAB2-STAT6* fusion gene, thus representing the most useful diagnostic tool in daily practice [16].

Herein, we report the clinico-pathologic features of a rare case of SFT of the orbital region, emphasizing the diagnostic role of the immunomarker STAT-6.

Clinical and histological findings

A 52-year-old female presented to the Eye Clinic of our hospital with a painless, firm in consistency, nodular mass in the left orbital region (Fig. 1A). No history for neoplasms was reported. On physical examination, a mild extra-rotation of the left eyeball was the only sign present. The mass was not adherent to deep structures. MR imaging showed a solid and well circumscribed mass that exhibited a mild hyperintense T1 signal and a hypointense T2 signal (Fig. 1B) and was located on the lower side of the inner canthus of the left eye, beneath the elevator muscle of the eyelid. The lesion was surgically excised and submitted for histological examination. The patient is well with no recurrence of disease after a 1-year follow-up period.

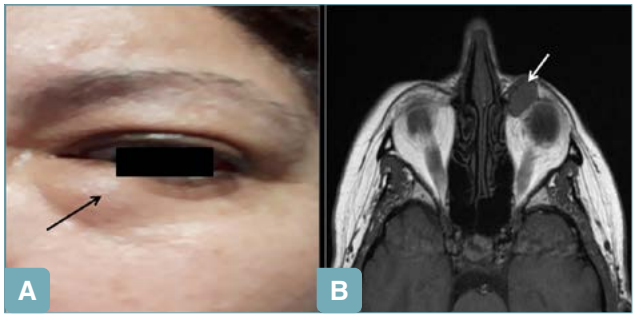

Figure 1. (A) Clinically, a nodular mass (arrow), firm in consistency is evident in the left orbital region; (B) MR imaging showing a solid mass with well circumscribed borders, exhibiting a mild hypointense T2 signal (arrow).

On gross examination, the tumor, measuring 1.8 cm in its greatest diameter, appeared well circumscribed and whitish in color on cut surface. The surgical sample was fixed in neutral-buffered 10% formalin, dehydrated using standard techniques, embedded in paraffin, cut to 5 µm, and stained with hematoxylin and eosin (H&E). Histological examination revealed a uniformly hypercellular lesion with pushing margins (Fig. 2A), composed of pale to slightly eosinophilic bland-looking spindle cells arranged in intersecting short fascicles. A striking finding was the deposition of stellate-shaped, keloid-type collagen fibers among neoplastic fascicles (Fig. 2B). Only a few small- to medium-sized blood vessels were seen. Neither perivascular hyalinization nor hemangiopericytoma-like branching vascular pattern were seen. Only a few mitotic figures (up to 3 mitoses/10 HPF) were detected but atypical mitoses, necrosis, cellular pleomorphism and extension into the surrounding soft tissues were absent. Immunohistochemically, neoplastic cells were diffusely positive for vimentin, CD34 (Fig. 2C) and STAT-6 (Fig. 2D). No staining was obtained with S-100 protein, α-smooth muscle actin, desmin, pancytokeratins, EMA, HMB45, MUC4, CD31 and ERG. Based on both morphological and immunohistochemical features, a diagnosis of "*solitary fibrous tumor"* was rendered. In the pathology report it was added that morphological features predictive of aggressive clinical behavior, such as more than 4 mitoses/10 HPF, hypercellularity, cellular pleomorphism, necrosis and infiltrative margins, were lacking.

Discussion

SFTs arising in the head and neck region are quite rare, representing about the 6% of all SFTs [11]. The sinonasal tract is the most common involved region, followed by the orbit, the oral cavity and the salivary glands [11]. It is likely that a subset of tumors, previously diagnosed as hemangiopericytomas, giant cell angiofibromas or orbital fibrous histiocytoma [17], could be currently re-classified as SFT by means of immunohistochemistry. As radiological imaging, as in our case, is not specific, showing solid, nodular masses with well circumscribed borders [11], a correct diagnosis

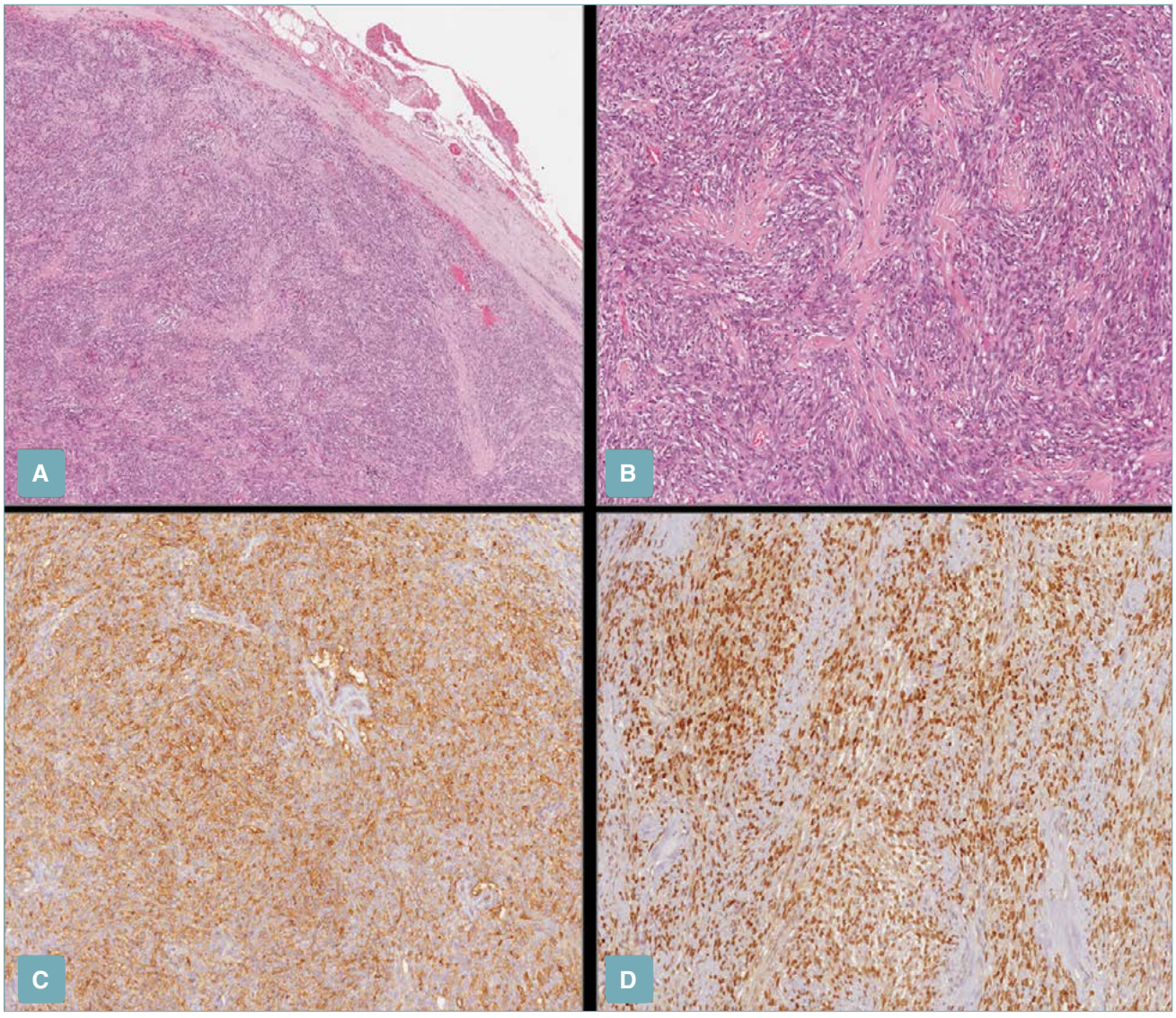

Figure 2. Histological examination. (A) Low magnification showing an uniformly hypercellular tumor with pushing borders, circumscribed by a fibrous pseudo-capsule (H&E staining; 50x magnification). (B) Higher magnification showing moderately eosinophilic bland-looking spindle cells arranged in intersecting short fascicles with interspersed stellate-shaped, keloid-type collagen fibers (H&E staining; 100x magnification); (C,D) Neoplastic cells are positively stained with CD34 (C) and STAT-6 (D) (immunoperoxidase staining; 100x magnification).

of SFT is still histologically-based. Unfortunately, this diagnosis may be challenging, especially when tumor occurs at unexpected sites and/or when pathologist is evaluating small biopsies or unusual morphological features [6]. As SFT often exhibits a wide morphological spectrum, as well as overlapping histological and immunohistochemical features with other benign or malignant spindle cell tumors, its diagnosis may be under-recognized, especially if the pathologist is not familiar with soft tissue tumors.

SFT is a well circumscribed neoplasm, typically composed of spindle to ovoid or epithelioid cells arranged in variable growth patterns (short intersecting fascicles; "*patternless*"; focal herringbone, storiform or leiomyomatous-like patterns). The presence of alternating hypercellular and hypocellular areas is also one of the diagnostic clues. The deposition of collagen fibers intermingling with neoplastic cells may vary, ranging from deeply collagenized to predominantly myxoid tumors. Vascularization is also variable, with different

sized- and shaped-vessels (small to large, round to branching vessels with hyalinized walls) often within the same tumor. Because of its spindle cell appearance, SFT may potentially be confused with several benign (spindle cell lipoma, intranodal palisaded myofibroblastoma, nodular fasciitis, leiomyoma, schwannoma and inflammatory myofibroblastic tumor/inflammatory pseudotumor) and malignant (malignant peripheral nerve sheath tumor, leiomyosarcoma, monophasic fibrous synovial sarcoma, low-grade myofibroblastic sarcoma and desmoid-type fibromatosis) tumors.

In our case, the tumor was composed of bland-looking spindle cells arranged in short fascicles with interspersed stellate-shaped, keloid-like collagen fibers. Apart from the unexpected site, it was the absence of both alternating hypercellular/hypocellular areas and the characteristic branching blood vessels with perivascular hyalinization, that caused difficulties in recognizing SFT. The main differential diagnosis was fat-free/low spindle cell lipoma and myofibroblastoma with which SFT shares a diffuse CD34 staining. However, the former tumor usually have, at least focally, myxoid areas with ropey collagen fibers and short spindle cells with long and thin bipolar cytoplasmic processes. Myofibroblastoma usually exhibits a variable, often diffuse, expression of myogenic markers, such as desmin and α-smooth muscle actin. In our case, the diffuse nuclear expression of STAT-6 was helpful for correct diagnostic interpretation. In the past, the combination of the typical morphology and immunohistochemical positivity for CD34, CD99 and BCL-2 was mandatory for diagnosis of SFT [3]. However, it is currently known that, in spite of its high sensitivity, CD34 is not a specific immunomarker of SFT, as it can be negative in 10% of SFTs, especially if tumor is "*histologically malignant*" [3]; moreover, CD99 and BCL-2 are usually expressed by many other neoplasms [18]. Recently, the fusion transcript, NAB2-STAT-6, and its variants, have been shown to be "*molecular hallmarks*" of SFT [15,19], resulting from an intrachromosomal inversion-derived gene fusion (NAB2-STAT6) that drives STAT-6 nuclear expression, easily identified by means of immunohistochemistry on paraffin-embedded tissues [16,20]. The recent introduction of STAT-6 in the daily diagnostic practice, as a highly specific immunohistochemical marker of SFT, allowes pathologists to confidentially render a diagnosis of SFT even on small pre-operative needle biopsies.

Histology alone cannot predict the clinical course of SFT and, to the best of our knowledge, only limited-follow-up data on orbital SFT are available in the literature, with the majority of cases published as single case reports or short case series without follow-up [14]. The most important prognostic factor seems to be radical surgical excision and the extent of resection might be the most predictive factor for local recurrence [14]. In our case, SFT was classified as "*histologically benign*" as the adverse morphological features, such as high mitotic index (> 4 mitoses/10HPF), nuclear pleomorphism, hypercellularity and necrosis, were lacking. In conclusion, we report a case of SFT arising in the orbital region, emphasizing that a correct diagnosis can be obtained if the pathologist is aware that this tumor can occur anywhere. Although some characteristic morphological features of SFT, such alternating hypercellular/hypocellular areas and hemangiopericytomatous vasculature, are lacking, a diffuse nuclear expression of STAT-6 is helpful in confirming correct diagnosis. Accordingly, we recommend that STAT-6 be included in the immunohistochemical panel when pathologists are faced with a bland-looking spindle cell tumor.

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