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OCULOPLASTICS AND ORBIT

Ocular adnexal (orbital) solitary fibrous tumor: nuclear STAT6 expression and literature review

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Abstract
Purpose To report the clinico-pathological features of solitary fibrous tumor occurring in the ocular adnexa (OA) in a single center. To assess the presence of *NAB2–STAT6* genes fusion in OA solitary fibrous tumor detected by nuclear overexpression of STAT6.
Methods Retrospective study including orbital and OA solitary fibrous tumors treated between 2006 and 2014 in our center. The clinical, radiological, and histopathological findings were evaluated. STAT6 expression was assessed by immunohistochemistry.
Results Five patients were identified and presented with a chronic OA mass. The tumors were radiologically well delimited, highly vascularized and without bone erosion. All the patients underwent complete surgical excision. Pathological examination confirmed solitary fibrous tumor in all cases. All tumors demonstrated a nuclear expression of STAT6. There were no recurrences, with a mean follow-up of 5 years after surgery.

Our review demonstrated that proptosis was the most common presentation occurring in 60 % of the cases. In the ocular adnexa, adverse histological criteria were found in 19.7 % of the tumors, and recurrences were observed in 48 % of these cases. Thirty-six percent of patients presented at least one local recurrence, and metastastic spread was found in 2.4 % of the cases. Tumor-related death was described in two cases.
Conclusion Ocular adnexal SFT are rare and usually present as a chronic orbital mass with proptosis. In the OA, solitary fibrous tumor demonstrates STAT6 nuclear expression, as documented in other locations. Recurrences are unusual and metastasis exceptional. Initial surgical resection should be complete in order to avoid recurrence.

Keywords Solitary fibrous tumor · Orbit · STAT6 · NAB2

Introduction

Solitary fibrous tumor (SFT) was probably initially reported in the pleura in 1760 by Lieutaud [1], but the first accurate pathological description was reported in 1931 by Klemperer and Rabin [2]. At that time, the tumor was named "localized mesothelioma" and was opposed to the diffuse pleural mesothelioma [3, 4]. Although more commonly arising in the pleura, SFT can occur in many sites, including meninges, oral cavity, pericardium, peritoneum, kidney, and liver [5–7]. In the ocular adnexa (OA), including orbit, eyelid, lacrimal gland, lacrimal sac, and conjunctiva, it has rarely been reported, with less than 130 cases documented to date in the English literature [8–85]. As most reported cases occurring in the OA are isolated case reports, the precise management of these tumors of intermediate malignancy level is not clearly defined. The behavior is often unpredictable, and does not always correlate with histological findings.

The recent identification of *NAB2-STAT6* genes fusion using whole exome sequencing represents a breakthrough in the understanding of SFT pathogenesis [86, 87]. NAB2 (NGFI-A binding protein 2) is a transcriptional repressor of the transcription factor EGR1. STAT6 (signal transducer and

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activator of transcription 6) is a transcriptional activator involved in interleukin 4 signaling. *NAB2* and *STAT6* are both located closely to each other on the chromosomal band 12q13. Their fusion leads to the production of a chimeric protein that has been shown in vitro to induce cellular proliferation through the activation of early growth response genes (EGR1) [86, 87]. As the inversion can be difficult to detect using by conventional in-situ hybridization, Doyle and al. demonstrated that nuclear expression of the carboxy terminal part of STAT6 was highly sensitive and specific of SFT, allowing the distinction between those tumors from histologic mimics [88]. In the normal bronchial epithelium, STAT6 predominantly localizes to the cytoplasm [89], but in meningeal SFT with *NAB2–STAT6* fusion detected by sequencing or Duolink in-situ assay, a nuclear localization of STAT6 was demonstrated [90] .

We present here a clinico-pathological study including all the cases of OA SFT that occurred between 2006 and 2013 in our institution. We also assess the expression of STAT6, which has not been extensively evaluated in orbital solitary fibrous tumor.

Material and methods

Clinical analysis

We conducted a single-center, retrospective, non-comparative case review study of all patients who presented between 2006 and 2014 with histological diagnosis of SFT. Patient files were reviewed to retrieve clinical data including patient demographics (age, sex, race), past medical history, symptoms, clinical presentation, radiological findings, treatment modalities, and outcomes. All patients were operated by the same surgeon (MH). This study was approved by the Swiss Federal Department of Health (authorization no 035.0003-48) and is in accordance with the Declaration of Helsinki.

Histopathologic analysis

The tumors were formalin-fixed, macroscopically processed, and dehydrated through graded alcohol followed by paraffin inclusion. Sections of 5 μm were cut, and hematoxylin–eosin and periodic acid-Schiff stains were performed.

Immunohistochemistry was performed on formalin-fixed paraffin-embedded (FFPE) tissue sections representative of the solitary fibrous tumor. After epitope retrieval at pH 6.0 or pH 9.0, endogenous peroxidase was blocked by 4 % hydrogen peroxide for 10 min. The sections were incubated with several anti-human antibodies (anti-CD34, mouse monoclonal, DAKO, 1:300; anti-BCL2, mouse monoclonal, DAKO, 1:100; anti-STAT6 against the carboxy terminal part, rabbit polyclonal, Santa Cruz, sc-621, 1:1000). A streptavidin/biotin detection method with 3.3'-diaminobenzidine tetrachloride (DAB) was used for signal detection (DAKO Envision™+System/ HRP Dual Link). The percentage of immunoreactive cells was graded by two independent observers in the following manner: 0 %–10 %, 1+;10–50 %, 2+; 50–100 %, 3+.

Literature review strategy

Systematic review of the literature was undergone using Pubmed, Web of Science using the key words "solitary fibrous tumor", "orbit", "eyelid", "conjunctiva", "ocular adnexa", "lacrimal gland", "lacrimal sac", and "NAB2–STAT6".

Statistical analysis

Statistical analysis was performed using JUMP 8.0 software.

Results

Clinical findings

There were four women and one male with a mean age of 36 years (26–68 years). Past medical history was unremarkable. The clinical and radiological findings are summarized in Table 1. The patients presented with a unilateral, indolent mass that was slowly progressing over months in four cases (patients 2–5), and in one case the patient (1) noticed a periocular mass 2 years ago with a recent and rapid increase in size during pregnancy (Fig. 1). Patient 4 complained of unilateral tearing (Fig. 2). In all patients, visual acuity was 1.0 (decimal scale), ocular motility was not limited and intraocular examination was unremarkable. There was no proptosis. In patient 4, there was no obstruction of the lacrimal drainage system.

Four patients underwent preoperative MRI, and presented well-defined, non-infiltrative tumors with an isointense T1-weighted signal. Within these tumors, hypointense flow voids could be observed. All the tumors demonstrated a strong contrast enhancement, which was homogenous in three cases and heterogenous in one case. On T2-weighted signal, the tumors showed a variable signal, isointense in two cases and slightly hyperintense in one case. One patient underwent CT scan, in which there was no bone erosion.

All patients had surgical resection through an anterior orbital access. Surgery allowed a complete resection in all the cases. Patient 1 underwent preoperative arterial embolization of the infra-orbital artery.

After surgery, all patients retained 1.0 visual acuity, full range of extra ocular movements, and symmetric exophthalmometric readings. Tearing disappeared after surgery for patient 4. No postoperative complication was

Table 1 Clinical and radiological presentation

Patient	Age	Sex	Clinical presentation	Symptoms duration (months)	Radiological findings
1	28	F	Left inferior orbital mass	24	T1: isointense signal Proeminent hypointense vessels. No bone erosion. Contrast enhancement : strong and homogenous T2: isointense signal
2	68	F	Right superior orbital mass	24	Isodense, well defined mass without bone erosion. Contrast enhancement: homogenous.
3	26	F	Left supero-temporal orbital mass with subconjonctival procidence in the lateral canthus	12	T1: isointense signal with hypointense vascular channels. No bone erosion, no infiltration of adjacent fat Contrast enhancement: strong, heterogenous T2 : heterogenous, isointense and hypointense signal
4	29	F	Right tearing and right medial orbital mass.	1	T1: isointense signal with focal hypointense areas No bone erosion, no infiltration of adjacent tissue Contrast enhancement: strong, homogenous. T2: slightly hyperintense, homogenous signal.
5	29	M	Right medial canthal mass appeared after trauma.	20	T1: isointense signal. No bone erosion, no infiltration of adjacent tissue. Contrast enhancement: strong and homogenous T2: heterogenous signal with discret hyperintense signal

reported. Local recurrence did not happen in any of our patients, with a mean follow-up of 5 years (1–7 years).

Histopathological findings

Microscopic examination showed in all cases a proliferation of spindle cells with minimal to mild pleomorphism, organized in sheets or in whorls. The histopathological findings are summarized in Table 2. Most of the tumors were densely cellular; less cellular areas with a loose, focally myxoid stroma could be identified in two cases. The cells were separated by collagen bundles that were locally thickened (Fig. 3). Capsular infiltration was noted in one case. No cases harbored more than 2 mitoses/10

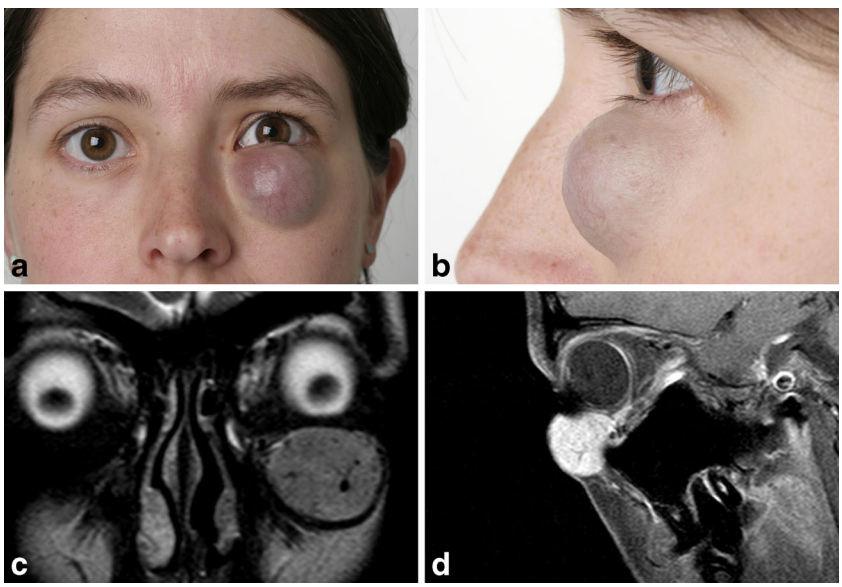

Fig. 1 Case 1, patient with left inferior orbital solitary fibrous tumor. **a** Clinical photography during initial presentation showing a firm bluish mass. **b** Profile photography. **c** Coronal T2 MRI image showing a well-defined, iso-intense masse, with area of mild hyperintense intensity. **d** Sagittal T1 MRI image depicting a marked enhancement after Gadolinium injection

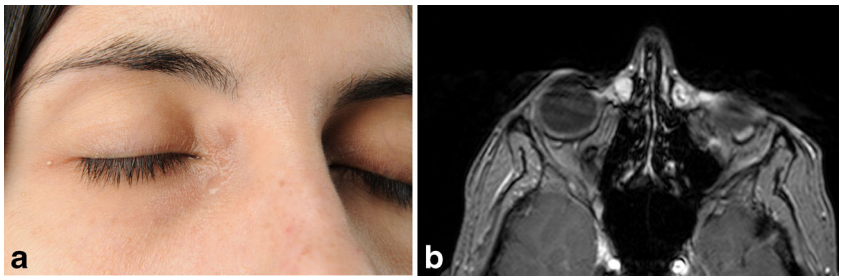

Fig. 2 Case 4, patient with right orbital solitary fibrous tumor. **a** Clinical photography of a patient with right internal orbital mass complaining of tearing. **b** Axial T1 MRI image showing an intense enhancement after gadolinium injection

HPF, and no necrosis could be identified. In three cases, branching, staghorn vessels could be observed. Occasional giant cells were found in three cases. In one case, embolic material surrounded by macrophages and neutrophils could be found within the vessels.

On immunohistochemistry, all the tumors expressed diffusely CD34 (+++) and STAT6 (+++) (Fig. 4). STAT6 expression was strongly expressed in the nuclei. BCL2 was found diffusely expressed in three cases (+++) and in a smaller proportion of cells in one case (++).

Discussion

The occurrence of solitary fibrous tumor in the OA is rare, with 130 documented cases to date, including the cases described in our study (summarized in Table 3). Women appear to be slightly more commonly involved (53 %; 65/122) than men (47 %, 57/122). Orbital SFT can occur in all age groups, ranging from 5 years old [68] to 94 years old [60], but they peak in the fourth decade, with a mean age of 41.6 (±1.79 SEM) years old.

Our retrospective analysis demonstrated that orbit is the most frequent site affected, with proptosis the most common presentation, occurring in 60 % of the patients (74/124). Patients noticed a mass in 40 % of the cases (50/126). Ptosis and tearing, as presented in our study, were rather uncommon findings, occurring in respectively 3.2 % (4/126) and 1.6 % of the cases (2/126). Two patients presented with palpebral mass [82, 84] and one with tumor of the conjunctiva [83]. Most of the tumors were extraconal (92.9 %, 105/113). In reviewing 97 cases with available information, SFT manifested a slow, indolent growth with mean symptom duration of 3.2 years (±6.6 months SEM). In the previous reported cases, visual acuity was always conserved, except in cases with optic nerve function impairment due to mechanical distension [52, 73] or tumor development on optic nerve sheath [71, 78].

In our study, one of our patients presented a sudden increase in tumor size during her pregnancy, as already documented in the literature [43]. The identification of estrogen as well as progesterone receptors in SFT [91] might explain the abrupt change in tumor volume observed in these patients during their pregnancy.

On CT and MR images, the majority of SFTs appeared ovoid in configuration and had well-defined margins [92–94]. On MR imaging, all SFT showed isointense signal intensity on T1-weighted images compared to cerebral grey matter [92–94]. On T2-weighted images, SFT appeared heterogeneous and have been described as isointense [92], hypointense [92, 93], or mixed iso-hyperintense [94]. On both CT and MR imaging, SFT showed marked enhancement after contrast injection [92–94]. The time intensity curve often showed an early washout pattern, characteristic of SFT on MR imaging [92, 93]. SFT can also present as a cystic lesion [46, 72, 73, 77] or can demonstrate intra-tumoral calcification [61, 72].

The principal radiological differential diagnosis of SFT needs to be established with cavernous hemangioma. Cavernous hemangioma appears isointense on T1-weighted images, as with SFT, but unlike SFT is markedly hyperintense

Table 2 histopathological analysis

Patients	1	2	3	4	5
Cellularity	+++	++	++	+++	++
Mitoses/10 HPF	1	2	0	1	0
Capsular infiltration	Yes	No	No	No	No
Necrosis	No	No	No	No	No
Cellular pleomorphism	Mild	Mild to moderate	Mild	Mild	Mild
Giant cells	Occasional	Occasional	Absent	Absent	Occasional
BCL2	+++	+++	++	+++	+++
CD34	+++	+++	+++	+++	+++
STAT6	+++	+++	+++	+++	+++

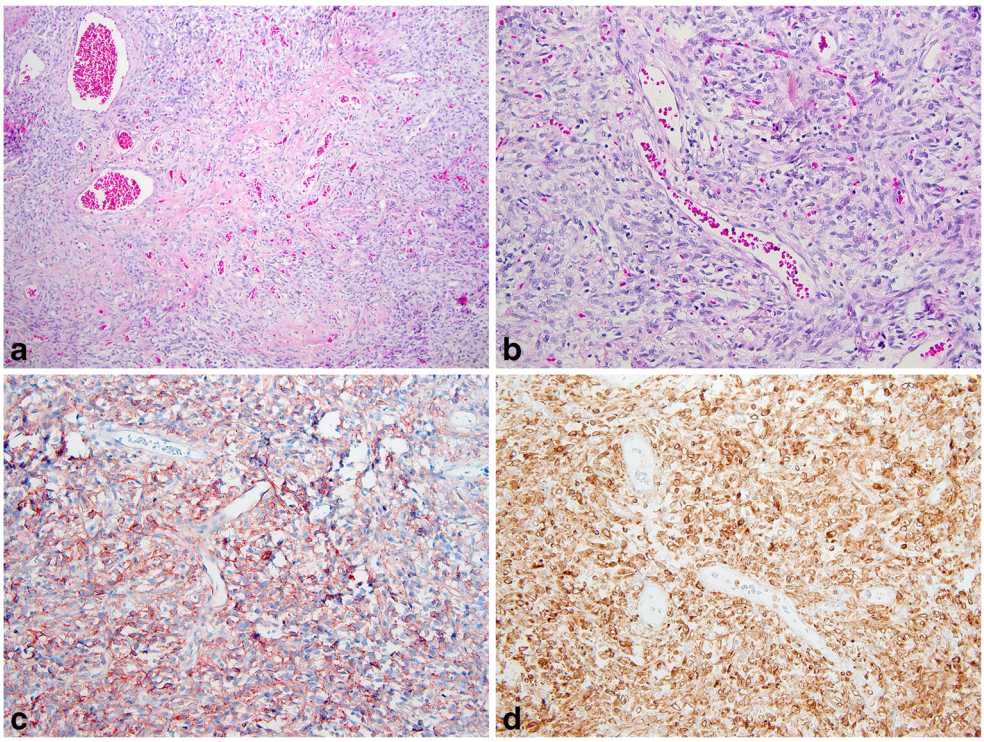

Fig. 3 **a** Hematoxylin & eosin, 63×. SFT are populated by sheets of spindle cells containing localized, dense collagenous areas. **b** Hematoxylin & eosin, 126×. The stroma harbours branching, staghorn-shaped vessels. The cellular pleomorphism is mild. **c** CD34 immunohistochemistry, 126×. The tumor cells diffusely express CD34. **d** BLC2 immunohistochemistry, 126×. There is also a diffuse and strong expression of BCL2

on T2-weighted images compared to extraocular muscle [95]. SFT often shows a feeder artery forming a pedicle which enters the tumor and branches radially, a finding that is uncommon in cavernous haemangioma [96].

The microscopic diagnosis of SFT relies on the identification of sheets of spindle cells admixed with branching, staghorn vessels with an alternation of cellular areas and less cellular areas. The stroma contains thickened collagen bundles. Adverse prognosis criteria previously described include: size superior to 5 cm, hypercellularity, elevated mitotic index (>4 mitosis/10 HPF), cellular pleomorphism, infiltrated surgical margin, and necrosis [97]. In

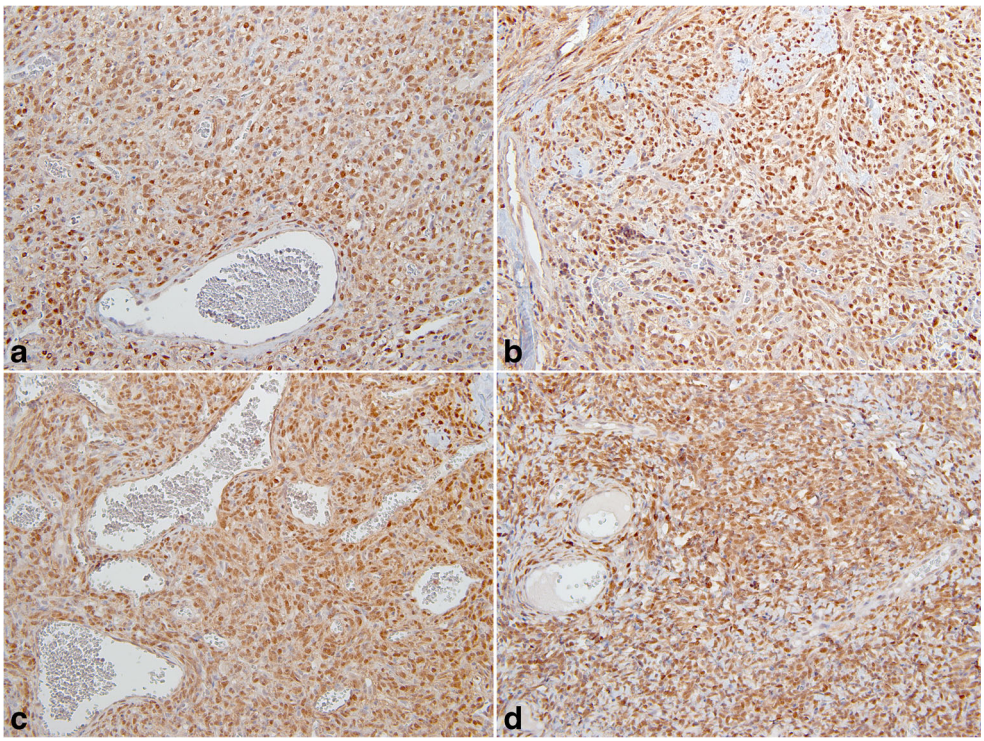

Fig. 4 **a**–**d**. STAT6 immunohistochemistry, 126×. All the tumors demonstrated a diffuse and strong nuclear expression of the carboxy terminal part of STAT6

Table 3 Review of the literature

Mean age at presentation	41.6±1.8 (SEM)
Female	53.3 % (65/122)
Clinical presentation	
- proptosis	59.2 % (74/125) [8, 15, 16, 18–20, 22, 24–31, 33–38, 40–46, 48, 49, 52, 54, 55, 57–64, 66, 68, 71–76, 78, 79]
- palpable mass	39.7 % (50/126) [8, 17, 20, 23, 34, 35, 38, 41, 46–48, 50, 53, 56, 59, 63, 65–67, 69–71, 73, 77, 80, 81]
- ptosis	3.2 % (4/126) [40, 48, 59]
- tearing	1.6 % (2/126) [8, 64]
- other	3.2 % (4/126) [24, 32, 48, 73]
Localisation	
- intraconal	7.3 %
- extraconal	92.9 % (105/113)
−orbital	
−orbital lacrymal gland	5.5 % (7/126) [34, 40, 41, 69, 85]
-eyelid	1.6 % (2/126) [82, 84]
-conjunctiva	[83]
-lacrymal sac	[50]
Symptoms duration (years)	3.2 (± 6.6 months)
Adverse histopathological factors	17.2 % (17/99)
(at least one adverse prognostic factor: size>5 cm, >4mitosis/10 HF, necrosis, pleomophism)	[16, 17, 20, 33, 36–38, 49, 62, 64, 66, 67, 71, 73, 75]
Treatment	
-surgery	100 % (130/130)
-adjunctive radiotherapy	8.2 % (10/121) [17, 30, 41, 56, 66, 68, 74, 75]
Immunochemistry	
-CD34+	99.2 % (123/124) [8–27, 29–44, 46–52, 54–60, 62–81]
-CD99+	92 % (46/51) [30, 40, 42, 46–48, 56–58, 61, 63–66, 68, 69, 71, 72, 78–80]
-Bcl2+	79.5 % (35/45) [8, 30, 37, 46–48, 57, 58, 61, 63, 65, 66, 68, 71, 74, 75, 77–80]
Recurrence	36.5 % (31/85) [8, 17, 29, 30, 36, 38, 41, 45, 49–51, 56, 57, 59, 64, 66, 68, 71, 73, 75]
Time to first recurrence (month)	16.06±3.87 (SEM)
Metastasis	2.4 % (2/87) [56, 64]
Death due to SFT	2.5 % (2/81) [38, 64]
Follow-up (mean, months)	37.3±6.34 (SEM)

the orbit, our review demonstrated that at least one adverse histological criteria was found in 19.7 % of the tumors (23/86), and recurrences were observed in 48 % of these cases (11/23). Four patients presented a transformation into fibrosarcoma after multiple recurrences [17, 30, 38, 66]. Previous study reported that adverse prognostic factors were associated with an aggressive clinical behavior, but were not by themselves predictive of such a behavior [5]. The immunohistohemical profile of SFT includes expression of CD34, CD99, and variable expression of BLC2. Strong and homogenous presence of CD34 within SFT was first described in 1994 [19]. In the previous reported cases, tumors showed intense and diffuse CD34 and CD99 reaction in more than 90 % of the cases (Table 3).

The recent identification of *NAB2–STAT6* inversion on chromosome 12 not only constitutes an important step in the mechanistic understanding of the molecular pathogenesis of SFT, but also enhances the possibilities of its diagnosis. Doyle and al. analyzed the presence of the carboxy terminal STAT6 portion in cell nucleus and confirmed its presence in 98 % of cases [88]. Other mesenchymal tumors tested in the same study did not show STAT6 reactivity. In our patients, all tumors were expressing STAT6 in the nuclei, strongly suggesting the presence of *NAB2–STAT6* inversion. A recent series, yet unpublished, also confirmed STAT6 expression in 12 orbital SFT [98].

All OA SFT reported in the literature were treated with surgical resection, except for two cases where

exenteration was necessary due to cranial bone invasion [38, 75]. In both cases, tumor recurred months after surgery in the orbit. Nine patients with orbital SFT were treated with complementary radiotherapy [17, 30, 41, 56, 66, 68, 74, 75], with doses ranging from 40 Gy [56] to 50.4 Gy [66]. In six incompletely resected or recurrent SFT, complementary radiotherapy did not prevent further recurrences [56, 68].

According to Houdt et al. [99], orbital and extra-orbital SFT have a recurrence rate of 29 % at 5 years, a general metastatic rate of 34 %, and a mortality rate of 16 % (Table 3). In our review, we identified 31 patients (31/85) with at least one local recurrence (36 %, mean follow-up of 37 months). Two patients developed metastasis (2.4 %) [56, 64], and in two patients death was attributed to SFT. The rate of local recurrence appears to be similar between orbital and non-orbital SFT, but metastasis rate is much higher in non-orbital SFT, possibly due the earlier clinical detection of orbital SFT. In the two patients with orbital SFT and metastatic behavior, the tumor had initially not been completely resected and recurred several times. In previously published cases, metastasis only occurred in cases with local recurrence and loss of local tumor control. Based upon these findings, it appears that one evaluation seems to be particularly relevant for incompletely resected tumor. The role of systemic follow up of incompletely resected tumors seems to be less important, but further studies are required to address this issue.

Local recurrences developed as soon as 3 months after surgery to 20 years (mean of 16 months). In most cases of local recurrence, SFT was initially described as incompletely excised. However, recurrences have been described even with complete surgery, suggesting that other unknown factors have to be incriminated in the malignant and invasive transformation of those tumors [75].

Considering that SFT arising in the OA seem to be associated with a lower metastatic spread than systemic SFT, we sought to evaluate if OA SFT and systemic SFT share common pathogenic mechanisms. In other tumors such as extranodal marginal zone lymphoma, different translocations have been demonstrated in different location [100, 101].

This article aims to present our experience with SFT and a large review of the literature, as well as an update of the new molecular aspects of this condition. We demonstrate that SFT can have different clinical presentation, proptosis being the more common, with slow and chronic growth without local inflammation. The identification of *NAB2–STAT6* inversion specific of SFT can be detected by immunohistochemistry in orbital SFT. Complete surgical excision seems to reduce the local recurrence rate. The fact that recurrences can develop as long as 14 years after the surgery underlines the need for a long-term local follow-up.

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