original article

Orbital solitary fibrous tumors: a multi-centered histopathological and immunohistochemical analysis with radiological description

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BACKGROUND: Solitary fibrous tumors (SFT), formerly called hemangiopericytoma, are rare tumors derived from mesenchymal cells originally described in the pleura, but these tumors may affect extraserosal tissues including the lacrimal gland and orbit.

OBJECTIVE: Conduct a multi-centered clinical, radiological and histopathological analysis of 17 orbital SFT cases.

DESIGN: A retrospective case series.

SETTING: Three eye centers in two countries.

PATIENTS AND METHODS: The data collected from the charts of 17 adult patients presenting with tissue diagnosis of orbital hemangiopericytoma or SFT from January 2003 to December 2018 included demographics, clinical imaging and histopathological information including immunohistochemical (IHC) characteristics.

MAIN OUTCOME MEASURES: The demographic characteristics, clinical presentation, and histopathological patterns or variants of SFT were analyzed.

SAMPLE SIZE: 17 adult patients.

RESULTS: Mean age was 45 years (range 23-80 years). Male to female ratio was 3:1. The right eye was affected in 12 (70.5%) patients. Commonest presentation was proptosis in 13/17 (76% of patients). Other symptoms were impaired motility (29%) and ptosis (11%). Lesions mostly affected the medial orbit (35%), then orbital apex in 11%. The histopathological classic pattern-less variant was the commonest. One case with aggressive behavior, multiple recurrences and atypical features was encountered. Immunohistochemical (IHC) markers used included CD34 expression in all cases, Bcl-2 expression in 10/11, CD99 in 9/9 and Vimentin in 4/4. STAT6 was used in 2 cases.

CONCLUSIONS: SFTs are rare tumors affecting the orbit in both genders equally in their mid-forties, but showed male predominance in our analysis with a predominant classic histopathological pattern. Tissue diagnosis is essential and requires IHC studies for confirmation.

LIMITATIONS: Sample size is relatively small owing to the rarity of this tumor in the orbit.

CONFLICT OF INTEREST: None.

Solitary fibrous tumors (SFTs) are uncommon, but frequently nonaggressive tumors that originate from the mesenchyme and mostly affect the pleura and the peritoneum.[1] The tumor has been reported to affect extra-pleural tissue and rarely involves the head and neck area (including the orbit) (6% of cases).[2] SFTs have histopathological overlapping features with giant cell angiofibroma (GCA) as part of what has been known as SFT- hemangiopericytoma (HPC) spectrum, and thus requires immunohistochemical (IHC) staining for proper identification.[3] Historically, CD34 reactivity has been described by Westra et al.[1] Recently STAT6 became more reliable in detecting SFTs.[4] Orbital SFTs classically cause unilateral painless proptosis, and are more common in the mid-40s (range 9–76 years). Every part of the orbit can be affected including the lacrimal gland.[5,6] Surgical excision and long-term follow-up are the treatment of choice. Recurrent SFT and aggressive behavior transformation are probably due to incomplete excision.[7]

PATIENTS AND METHODS

We report a retrospective case series of consecutive adult patients with periocular/orbital lesions (18 years or older) who had a histopathologically verified tissue diagnosis of solitary fibrous tumor and presented to King Abdulaziz University Hospital (KAUH), King Khaled Eye Specialist Hospital (KKESH), Riyadh, Saudi Arabia, as well as the orbital unit of university of Naples Federico II, Naples, Italy between January 2003 and December 2018. The information collected included demographic data, clinical information, imaging studies and histopathological and immunohistochemical (IHC) features. We conducted a literature review to highlight the specific histopathological and IHC characteristics of SFTs as well as the treatment and prognostic factors. The study was approved by the Human Ethics Committee and Institutional Review Board at KKESH (expedited approval since it was a retrospective study) with collaborative agreement between KKESH and other centers and it adhered to the ethical principles outlined in the Declaration of Helsinki as amended in 2013. An informed written general consent was obtained from all patients for investigations and treatment, which includes permission for anonymous use of their data for publication.

RESULTS

The 17 patients who presented to our facilities were diagnosed with periocular and orbital SFT. The mean age of presentation was 45 years (range 23-80 years). Out of the 17 patients, 13 were males (76%) and 4 were females (24%). Twelve of our patients had their right side affected (70.5%) and 5 had their left side affected (29.5%). None of the patients presented with bilateral disease. The most common presenting symptom was proptosis which was observed in 13 patients (76%). Other clinical signs included impaired ocular motility seen in 5 patients (29%), papilledema in 3 patients (17%) and ptosis in 2 patients (11%). One patient (5%) showed choroidal folds upon fundus examination. The tumor mostly affected the medial side of the orbit in 6 patients (35%). The apex was involved in 2 cases (11%), 1 tumor was intraconal (5%) and 1 was seen in the lacrimal gland (5%).

Biopsies of all 17 patients were obtained with multiple approaches. Seven patients underwent lateral orbitotomy (41%), 6 underwent anterior orbitotomy (35%), 3 had transconjunctival approach (17%) and 1 underwent supero-medial orbitotomy (5%). Grossly, the mass was mostly nodular and firm in consistency with a size ranging from 1 cm to 3.5 cm in largest diameter and a median of 2.5 cm in diameter. The cut surface of the mass upon sectioning was generally smooth, yellowish to tan in color, and often showing cystic spaces that have shown relatively clear fluid.

Histopathologically, the tumors shared the common features of hypo- and hyper-cellular areas of spindle-

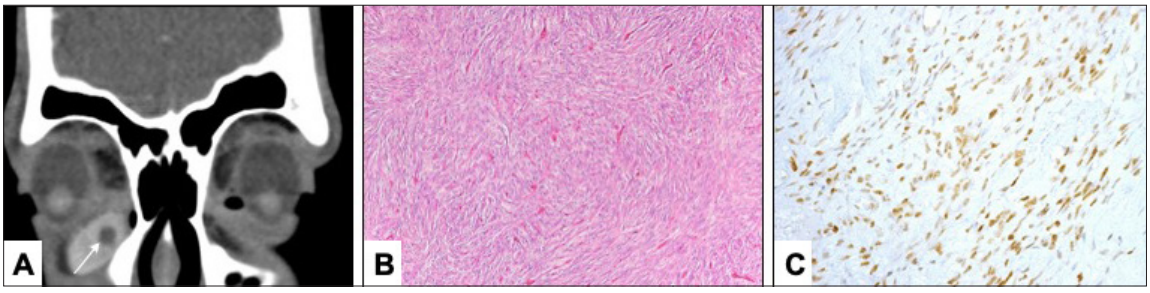

Figure 1. A: Coronal computerized tomography (CT) scan (post-contrast) showing right eye proptosis and displacement of the globe laterally with well-defined highly contrast-enhancing lesion in the extraconal space in the inferior nasal part of the orbit, measuring 4×2.5 cm, causing thinning of the medial wall of the orbit with focal central fat content (white arrow). B: Spindle-shaped cells with irregular vascular channels surrounded by partially cellular and partially hyalinized tissues with classic storiform pattern in the same patient. There was no evidence of pleomorphism, mitosis or necrosis (Original magnification ×100 hematoxylin & eosin). C: The diagnosis of solitary fibrous tumor was confirmed by expression of STAT6 by the proliferating cells (Original magnification ×400 STAT6).

shaped cells separated by collagen fibers of variable thickness with a storiform pattern (**Figure 1**). The tumors were morphologically identified by the pathologists. Other similar appearing tumors such as fibrous histiocytoma were excluded based on IHC staining. Vascular proliferation was noted in all cases, some of which demonstrated the typically-shaped staghorn vessels (**Figure 2**). Hyalinized stroma was also noted. One case involving the lacrimal gland showed areas of entrapped glandular tissue with ductal dilatations and changes mimicking pleomorphic adenoma. Another two cases showed multinucleated tumor giant cells (**Figure 3**). Almost half of our cases (47%) were of the classic pattern-less variant. Other rare variants encountered were the myxoid type noted in 2 cases where one was considered to show an aggressive behavior with significant atypia and moderate mitosis, while the other was of the pseudoangiomatous type (**Figure 4**). The histopathological variant profile is represented in **Figure 5**. Immunohistochemical (IHC) markers were used to confirm SFT diagnosis depending on their availability and the year of presentation. CD34 was used in 16 cases and all showed positive expression delineating the typical vascular spaces. Other IHC stains that showed positive expression were Bcl-2 (10 out of 11 cases), CD99 (9 out of 9 cases) and vimentin (4 out of 4 cases). STAT 6 was used in 2 cases and both showed positive immunoreactivity in the nucleus. Tissue blocks were not available for all cases to perform STAT6 on the rest. Protein S-100 was used in 11 cases and 9 showed negative expression (82%). Actin and desmin were negative in all cases where the stain was used (6 out of 6 and 4 out of 4 respectively). Cytokeratin stain was performed in 3 cases with negative expression by the tumor cells; however, the stain was helpful in outlining the entrapped lacrimal gland acini and dilated ducts in the case mentioned above. We only had the details of the radiological testing in 5 cases, where the tumor generally showed a well-defined, heterogeneous density mass with marked contrast enhancement.

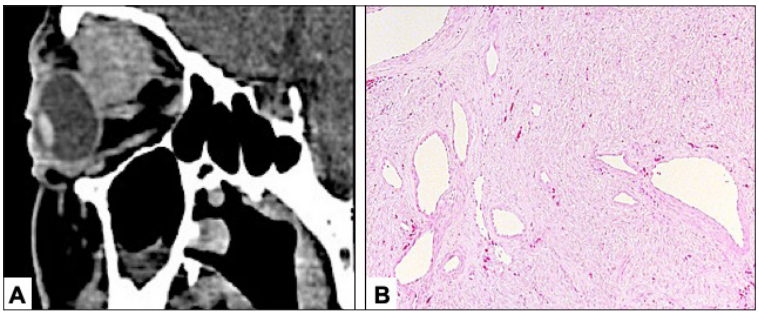

Figure 2. A: Sagittal CT scan of the left orbit showing a round fairly well-defined mildly enhancing soft tissue density mass lesion measuring 2.66×1.84 cm located mainly intraconally extending to the extraconal space. It was located above the left optic nerve displacing the globe inferiorly and causing thinning and slight erosion of the left superior orbital floor with no intracranial extension. B: Several dilated and staghorn-shaped blood vessels with surrounding cellular spindle cell stroma (Original magnification ×100 hematoxylin & eosin).

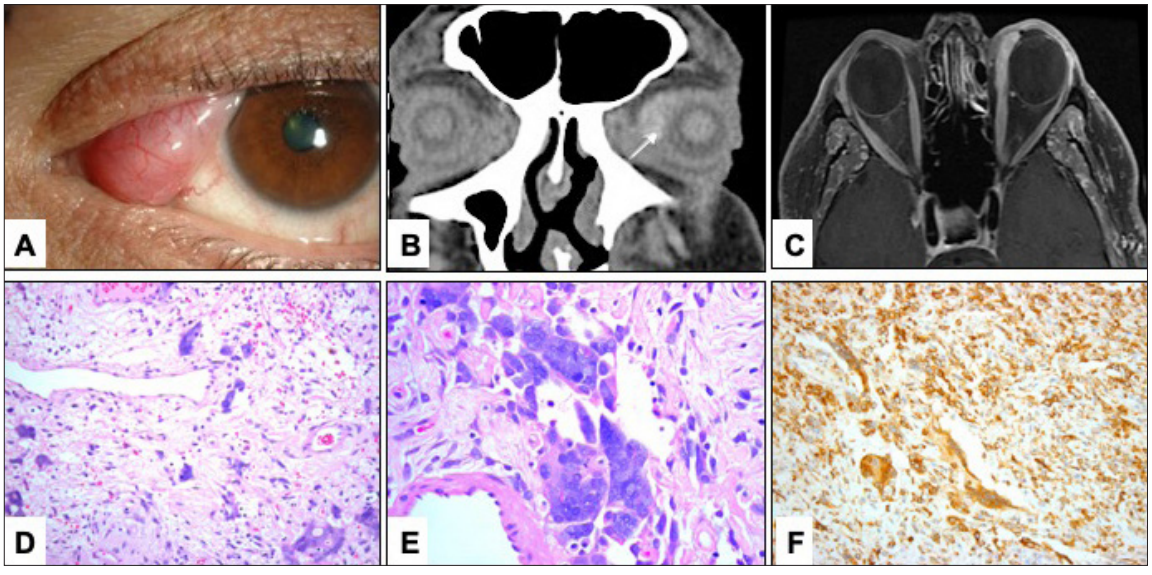

Figure 3. A: The clinical appearance of a slowly progressive painless medial canthal mass in the left orbit of a 53-year old male over 3 years presenting as a protruding soft mass in the subconjunctival area of the left eye supero-nasally. B & C: Coronal CT scan and axial MRI of the left orbit showing contrast-enhancing extraconal mass nasally at the medial rectus muscle insertion extending along the muscle sheath to the belly of the muscle (white arrow in the CT image). D & E: The solitary fibrous tumor in this case showing spindle-shaped cells and numerous giant cells (Original magnification ×200 in D and ×400 in E hematoxylin & eosin). F: The tumor spindle cells showed diffuse positive expression of Bcl-2 (Original magnification ×200).

DISCUSSION

SFTs are slowly growing, rarely encountered mesenchymal tumors. They are composed of spindle-shaped cells and known to affect primarily the pleura.[1,5] Historically, SFTs were diagnosed as hemangiopericytomas (HPCs) and giant cell angiofibromas (GCAs).[8] In the past, SFT, HPC, and GCA were considered different entities and traditionally were separated.[9] Because of the overlapping morphology and the similarities in IHC staining, debates have been raised about whether these tumors are distinct from each other or if they should be considered under one spectrum.[10,11] Goldsmith et al have proposed that HPC should be included under the umbrella of SFT.[9] More recently, Furusato et al suggested the same.[11] At present, SFTs are sets of tumors with a highly variable histopathological feature ranging from highly packed cells, and therefore, called "cellular" to the classical spindle-shaped, and thus, called "classic".[12] SFTs have been recognized in multiple extra-serosal tissues including the upper respiratory tract, paranasal and nasal sinuses, the salivary glands, thyroid, lung, mediastinum, pericardium, peritoneum, spine, soft-tissue, lacrimal gland, and orbit.[13] Both genders are equally involved, and it is more common in the mid-40s (range 9–76 years).[6] However, this was not seen in our patients as 76% of them were males. All orbital spaces can be affected including intraconal and extraconal spaces of the orbit and the lacrimal gland which has been observed in our patients. Other periocular and orbital sites reported include the lacrimal sac, eyelids, conjunctiva, and sclera.[14,15]

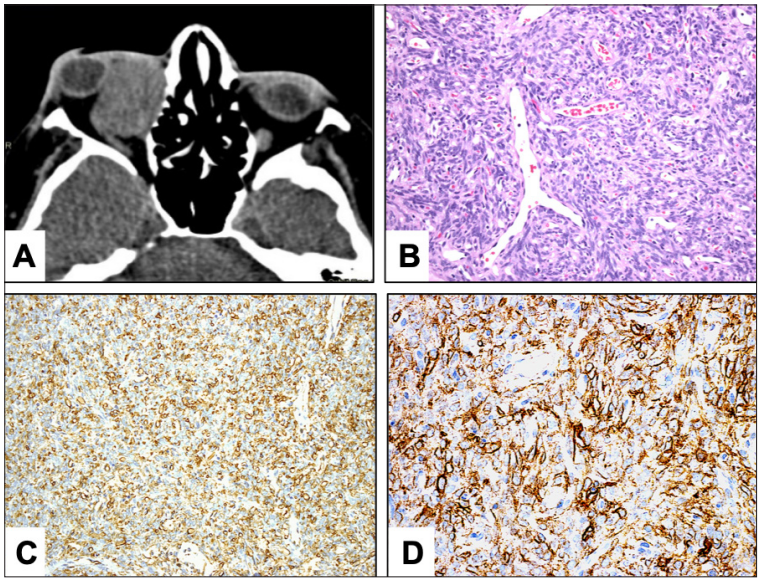

Figure 4. A: Axial CT scan of the right orbit with contrast showing a well-defined mildly enhanced soft tissue density mass. B: The spindle cells in the same case showing hemangiopericytoma areas with staghorn-shaped blood vessels (Original magnification ×200 hematoxylin & eosin). C: The cells diffusely express CD34 confirming the pseudoangiomatous pattern (original magnification ×200). D: The diffuse expression of CD99 by the proliferating cells (original magnification ×400).

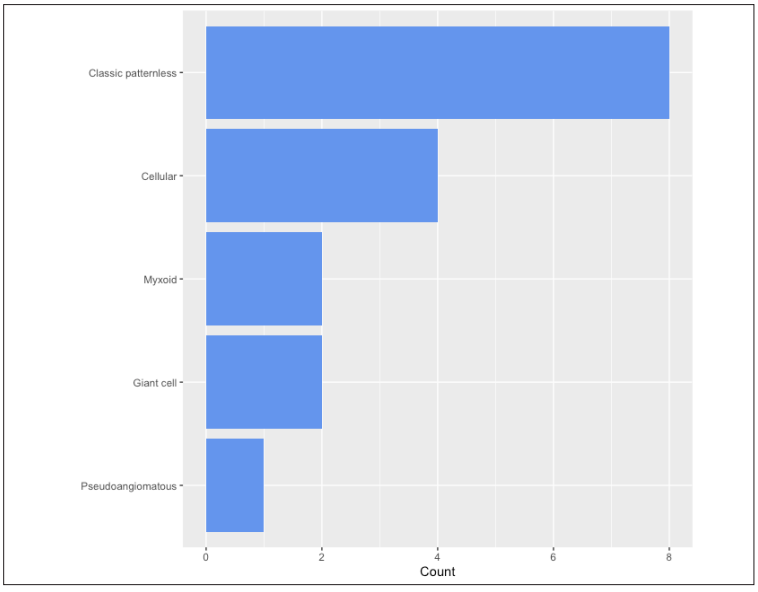

Figure 5. Distribution of the histopathological types in 17 cases of orbital solitary fibrous tumors.

The most common presentation is an orbital mass.[11] Proptosis is also a common presentation.[14,15] Other symptoms include limitation of extraocular muscle motility, globe displacement, diplopia, and blurred vision.[5,13] Similarly, these symptoms were observed in our patients in addition to ptosis. The patients who presented with papilledema and choroidal folds had intraconal and/or apical lesions thus causing globe indentation with choroidal folds and a pressure effect on the optic nerve, respectively.

Microscopic findings are very helpful in differentiating between SFTs subsets, as the cellular SFT, which was previously designated as HPC, shows tightly packed spindle cells and small branching vessels or staghorn vessels.[9,12] On the other hand, the classical SFT, which was designated previously as the true SFT, exhibits randomly oriented spindle cells (pattern-less appearance) as well as hypercellular and hypocellular ground of thick collagen bands.[6,16,17] The presence of mature adipose tissue in combination with the cellular type gives us the fat-forming variant of SFT. This variant is known to have a benign course and was previously known as lipomatous hemangiopericytoma.[18] Furthermore, giant cell-rich SFTs (previously known as giant cell angiofibromas) have been described in multiple studies as a spindle-shaped cell on a ground of thick collagen with multiple multinucleated giant cells; this was observed in two of our cases.[5,19] Lacrimal gland SFTs might have some

additional histopathological feature that has been also described in SFT involving the salivary gland(s), which is the entrapment of the gland tissue with dilated ductal structures, which might be similar in appearance to pleomorphic adenoma.5 Feasel et al analyzed 26 superficial solitary fibrous tumors for pathological studies.[20] Most of their cases (70%) were in the cellular end of the spectrum which also featured irregular fascicles of spindled cells with staghorn-like vessels and variable amounts of collagen.[20] However, 23% of our cases showed a cellular pattern, whereas classic patternless was the main variant noted in our study (47%), where the tumor cells are oval or spindle in shape with small vesicular nuclei and intervening collagen fibers that are arranged in pattern-less configuration. In these classic SFTs, a combination of hypercellular areas showing numerous tumor cells as well as other areas with more stromal collagenous components and fewer tumor cells are observed. The nuclear atypia in these classic SFTs is absent or minimal with few mitotic figures. In contrast to our cases, necrosis and focal atypia were present in 3 of their cases.[20] Aggressive SFTs are characterized by nuclear pleomorphism, high cellularity, necrosis, hemorrhage, and mitotic figures of ≥4/10 HPFs. Also, a large tumor >15 cm or equal is a sign of an aggressive behavior.[8] As expected, Smith et al reported that less than <15 cm tumors were associated with low mitotic index and were of low metastatic risk.[8] Furthermore, some suggested that 5 cm tumor size is of potential risk, which is applicable on our cases that had a largest tumor diameter of 3.5 cm.[8] Importantly, Furusato et al reported that p53 and Ki-67 have been associated with worse outcome and higher mitotic index.[11] The classic pattern-less histopathological variant was the most common type of SFT encountered in our series. However, we encountered one case with aggressive behavior evident by multiple recurrences, histopathological atypical features, and cellular pleomorphism. Historically SFT has a strong immunoreactivity to CD34, CD99, and variable reactivity to Bcl-2.[1,16] Furthermore, SFT shows negative immune-reactivity to desmin, keratin, factor VIII, EMA, S-100 protein, and SMA.[21,22] Thus, we were able to have the tissue diagnosis confirmed in all our cases based on descriptions in the literature where CD34, CD99, Bcl-2, and vimentin were positively reactive, while S-100 protein, actin, and desmin showed negative reactivity in almost all our patients. However, negative reactivity to CD34 does not exclude SFTs.[23,24] The NAB2-STAT6 gene fusion is currently an important factor in the pathogenesis of SFTs, and is caused by intra-chromosomal rearrangements on chromosome 12q.[25] It has been associated with nuclear STAT6 expression. Some researchers suggested that STAT6 is the gold standard for SFTs nowadays, but this has been controversial since conversely, some reports found that nuclear STAT6 is not actually identified all the time.[26-28] Thus, a combination of STAT6 and CD34 is important.[29] The malignant or aggressive form of SFT is CD34 negative, STAT6 positive, and S-100 positive.[30] Schwannoma, which is an important differential diagnosis, and other neural tumors are focally stained with Bcl-2 and CD34 and show strong positivity to S100 protein.[31,32] Fibrous histiocytoma (FH) is another important differential diagnosis as it exhibits variable reactivity to Bcl-2 and CD34 but with very strong positivity to keratins and alpha-1-antichymotrypsin.[33] Epithelial membrane antigen (EMA) is not reactive with FH.[31]

Orbital SFTs classically appear as an oval well-defined masses.[34] On magnetic resonance imaging (MRI) T1-weighted images (T1W1), SFTs tend to show a homogenous iso-intense appearance in contrast to the gray matter. While on T2-weighted images (T2W2), they frequently exhibit a heterogeneous hypo- or isointense appearance.[35] SFT appears on CT as an iso-dense well-defined mass, in contrast to the extraocular muscle, and has a good enhancement after the contrast injection which is similarly observed in our cases.[35] Those CT findings are not specific, yet CT is essential to rule out bone involvement, while soft tissue involvement is better detected by MRI.[36] Even though histopathological studies are the key to the diagnosis, radiological studies have some importance in the preoperative and postoperative evaluation. MRI was the best radiological study to confirm the location as well as the extension of the mass, and for follow-up postoperatively.[35]

The main differential diagnosis of orbital masses on MRI includes orbital Inflammatory pseudotumor (OIP), schwannoma, orbital lymphoma, and cavernous hemangiomas (CH). OIP appears as an ill-defined mass and has an iso-intense signal on T1W1 and hypo-intense signals on T2W2 with marked homogeneous enhancement after contract administration.[35] CH is the most common vascular orbital lesion in adults, more commonly in the intraconal space and appears as a well-defined mass. Both CH and schwannoma have an iso-intense signal on T1W1 and hyper-intense signal on T2W2, thus the enhancement pattern is the best way in discriminating these two entities since CH has a progressive enhancement pattern and starts from a small point then progressively involves the whole lesion, while schwannoma starts from a large area with a homogeneous enhancement.[37] Lymphoma appears as a well-defined mass with an iso-intense signal on T1W1 and iso-hyperintense signal on T2W2 with a uniform enhancement.[38] **Table 1** summarizes the main differential diagnoses of orbital

Table 1. Main features in the differential diagnosis of orbital solitary fibrous tumors based on magnetic resonance imaging (MRI) findings.[35,37,38]

Features	Solitary fibrous tumor	Cavernous haemangioma	Schwannoma	Inflammatory pseudotumor	Lymphoma
Distribution	Intraconal or Extraconal space	Frequently intraconal space	Intraconal or Extraconal space	Intraorbital or Extraorbital involvement	Extraconal location only or extra and intraconal together
Mass appearance	Oval well-defined mass	Well-defined margins, oval shape mass	Well-defined margins	Ill-defined mass	Well-defined margins
T1-weighted MRI image	Isointensity to muscle	Isointensity to muscle	Isointensity to muscle	Isointensity to muscle	Isointensity to muscle
T2 weighted MRI image	Iso-hypointensity to muscle	Marked hyperintensity to muscle	Mildly hyperintensity to muscle	Variable, Hypointensity to muscle	Iso-hyperintensity to muscle
Enhancement pattern	Heterogeneous marked enhancement after the contract administration	Starts as a point of enhancement then progressively enhanced after contrast injection "progressive enhancement"	Frequently homogeneous enhancement	Marked homogeneous enhancement	Uniformly enhanced after the contrast administration
Diffusion weighted MRI image	Non-restricted	Non-restricted	Non-restricted	Non-restricted	Restricted

SFT based on MRI findings.[35,37,38]

The treatment of choice is complete surgical excision with a long-term follow up.[39] Recurrence after surgery has been reported.[12] Incomplete surgical excision is probably the most important cause of recurrence.[40] Regardless of the histologic subtype, surgical excision remains the best approach.[41] The need for adjuvant therapy is still a controversial issue that needs to be investigated. Those who are treated with chemotherapy had worse outcomes in contrast to untreated patients. However, this could be caused by a selection bias, in which patients with an aggressive disease have been selected, thus worse results were expected as described by DeVito et al.[41] Furthermore some studies mentioned that many patients do not respond to chemotherapy.[42] Conversely, Park et al reported in a retrospective study that those with advanced SFTs who were treated with traditional chemotherapy had more stable disease. Advanced SFTs means unresectable metastatic disease as defined by Park et al[43] Radiotherapy has no role as an adjuvant therapy as reported in several studies.[41,44] Nevertheless, for patients having a malignant disease or positive surgical margins, adjuvant radiation may be helpful.[45] Patient outcomes depends on several factors, one being the nature of the disease, and whether it is malignant or benign, as the malignant form has a worse outcome.[41] Positive tumor margin after resection is considered to be the worse prognostic factor, in which cases, metastasis is prevalent.[2] Whatever the management plan, clinical follow up is essential for any patient.

In conclusion, SFTs are a relatively rare tumor that can affect the orbit and are known to affect both genders equally in their mid-40s. In our multi-centered analysis of orbital SFT, we observed a male predominance with similar mean age and clinical presentation to previously reported data. Radiological imaging aids in the diagnosis in some cases. Histopathological tissue diagnosis is essential and requires the use of IHC studies for confirmation of the diagnosis.

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