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

Hind Manaa Alkatan, Abrar K. Alsalamah, Abdulrahman Almizel, Khalid M. Alshomar, Azza MY Maktabi, Sahar M. ElKhamary, Charles G. Eberhart, Adriana Iuliano, Vittoria Lanni, Diego Strianese

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. The 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 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. The tumor has been reported to affect extra-pleural tissue and rarely involves the head and neck area (including the orbit) (6% of cases). 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. Historically, CD34 reactivity has been described by Westra et al. Recently STAT6 became more reliable in detecting SFTs. 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. Surgical excision and long-term follow-up are the treatment of choice. Recurrent SFT and aggressive behavior transformation are probably due to incomplete excision.

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 intracanal (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-like 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. The diagnosis of solitary fibrous tumor was confirmed by expression of STAT6 by the proliferating cells.
SFT CASES

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.\textsuperscript{1,5} Historically, SFTs were diagnosed as hemangiopericytomas (HPCs) and giant cell angiofibromas (GCAs).\textsuperscript{9} In the past, SFT, HPC, and GCA were considered different entities and traditionally were separated.\textsuperscript{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.\textsuperscript{10,11} Goldsmith et al have proposed that HPC should be included under the umbrella of SFT.\textsuperscript{9} More recently, Furusato et al suggested the same.\textsuperscript{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”.\textsuperscript{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.\textsuperscript{13} Both genders are equally involved, and it is more common in the mid-40s (range 9–76 years).\textsuperscript{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.\textsuperscript{14,15}

The most common presentation is an orbital mass.\textsuperscript{11} Proptosis is also a common presentation.\textsuperscript{14,15} Other symptoms include limitation of extraocular muscle motility, globe displacement, diplopia, and blurred vision.\textsuperscript{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 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 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.

Figure 5. Distribution of the histopathological types in 17 cases of orbital solitary fibrous tumors.
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. 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 hypointense appearance in contrast to the grey matter.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.36 Those CT findings are not specific, yet CT is essential to rule out bone involvement, while soft tissue involvement is better detected by MRI.37 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.38

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 contrast administration.39 CH is the most common vascular orbital lesion in adults, more commonly in the intracanal 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.40 Lymphoma appears as a well-defined mass with an iso-intense signal on T1W1 and iso-hyperintense signal on T2W2 with a uniform enhancement.41 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 Extracanal space | Frequently intraconal space | Intraconal or Extraconal space | Intraorbital or Extraconal involvement | Extracanal 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 contract 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.40 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 depend 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.
REFERENCES

1. Westra WH, Gerald WL, Rosai J. Solitary fibrous tumor. Consistent CD34 immunoreactivity and occurrence in the orbit. Am J Surg Pathol 1994;18(10):992-8.

2. Gold JS, Antonescu CR, Hajdu C, et al. Clinicopathologic correlates of solitary fibrous tumors. Cancer 2002;94(4):1057-68.

3. Gengler C, Guillou C. “Solitary Fibrous Tumor and Haemangiopericytoma: Evolution of a Concept.” Histopathology 2006;48:63-74.

4. Yoshida A, Tsuma K, Ohno M, et al. STAT6 immunohistochemistry is helpful in the diagnosis of solitary fibrous tumors. Am J Surg Pathol 2014;38(4):552-9.

5. Alkatan HM, AlJarallah OJ., Fathuddin AA, et al. Solitary fibrous tumor of the lacrimal gland: a clinicopathological review of all reported cases in comparison to the salivary gland and a unique case report showing lacrimal gland entrapment mimicking pleomorphic adenoma. PONTE Int Sci Res J 2016;7(2):10.

6. Krishnakumar S, Subramanian N, Mohan ER, et al. Solitary fibrous tumor of the orbit: a clinicopathologic study of six cases with review of the literature. Surv Ophthalmol 2003;48(5):544-5.

7. Graue GF, Schubert HD, Kazim M. Correlation between clinical features, imaging and pathologic findings in recurrent solitary fibrous tumor of the orbit. Orbit 2013;32(6):375-80.

8. Smith SC, Gooding WE, Ellkins M, et al. Solitary Fibrous Tumors of the Head and Neck: A Multi-Institutional Clinicopathologic Study. Am J Surg Pathol 2017;41(12):1642-1656.

9. Goldsmith JD, Van der rijn M, Syed N. Orbital hemangiopericytoma and solitary fibrous tumor: a morphologic continuum. Int J Surg Pathol 2001;9(6):295-302.

10. Jung SK, Paik JS, Park GS, Yang SW. CD34 + tumors of the orbit including solitary fibrous tumors: a six-case series. BMC Ophthalmol 2012;17(1):53.

11. Furusato E, Valenzuela IA, Fanburg-smith JC, et al. Orbital solitary fibrous tumors: an encompassing terminology for hemangiopericytoma, giant cell angiofibroma, and fibrous histiocytoma of the orbit: reappraisal of 41 cases. Hum Patholl 2011;42(1):120-8.

12. Kunzel J, Hainz M, Ziebert T, et al. Head and neck solitary fibrous tumors: a rare and challenging entity. Eur Arch Otorhinolaryngol 2016;273(6):1589-98.

13. Bernardin FP, De concilis C, Schnei der S, et al. Solitary fibrous tumor of the orbit: is it rare? Report of a case series and review of the literature. Ophthalmology 2003;110(7):1442-8.

14. Kim HJ, Kim HJ, Kim YD, et al. Solitary fibrous tumor of the orbit: CT and MR imaging findings. AJNR Am J Neuroradiol 2008;29(5):857-62.

15. Gupta S, Verma R, Sen R, et al. Solitary fibrous tumor of the orbit. Asian J Neurosurg 2016;11(1):78.

16. Savino G, Alberti B, Colucci D, et al. Atypical presentation of a case of solitary fibrous tumor of the orbit. Orbit 2009;28(2-3):176-8.

17. Ali SZ, Hoon V, Hoda S, et al. Solitary fibrous tumors: a cytologic-histologic study with clinical, radiologic, and immunohistochemical correlations. Cancer 1997;81(2):116-21.

18. Pitchamuthu H, Gonzalez P, Kyle P, Rob erts F. Fat-forming variant of solitary fibrous tumor of the orbit: the entity previously known as lipomatous haemangiopericytoma. Eye (Lond) 2009;23(6):1479-81.

19. Yuzawa S, Tanikawa S, Kunibe I, et al. A case of giant cell-rich solitary fibrous tumor in the external auditory canal. Pathol Int 2016;66(12):701-705.

20. Parrozzani P, Ai-Abrahemi A, Fritchke C, Ziek RT. Superficial Solitary Fibrous Tumor: A Series of 26 Cases. Am J Surg Pathol 2018;42(6):778-785.

21. Ali MU, Honavar SG, Naik MN, Vemuganti GK. Orbital solitary fibrous tumor: A clinicopathologic correlation and review of literature. Ophthal Clin Pract 2015;143(5):672-82.

22. Kayser K, Trott J, Böhm O, et al. Localized fibrous tumors (LFTs) of the pleura: clinical data, asbestos burden, and syntactic structure analysis applied to newly defined anaplastic growth-regulatory effectors. Pathol Pract Res Pract 2006;2011(12):791-801.

23. Thwy K, Ng W, Noujaim J, et al. The Current Status of Solitary Fibrous Tumor: Diagnostic Features, Variants, and Genetics. Int J Surg Pathol 2016;24(4):281-92.

24. Vogels RJ, Vletter M, Versleijen-jonkers YM, et al. Solitary fibrous tumor - clinicopathological, immunohistochemical and molecular analysis of 28 cases. Diagn Pathol 2014;9:224.

25. Koelsche C, Schweizer L, Remmer M, et al. Nuclear relocation of STAT6 is a strong indicator for the diagnosis of solitary fibrous tumor. Histopathology 2014;65(5):613-22.

26. Demicco EG, Harms RW, Patel RM, et al. Extensive survey of STAT6 expression in a large series of mesenchymal tumors. Am J Clin Pathol 2015;143(5):672-82.

27. Kao YC, Lin PC, Yen SL, et al. Clinicopathological and genetic heterogeneity of the head and neck solitary fibrous tumors: a comparative histological, immunohistochemical and molecular study of 36 cases. Histopathology 2016;68(4):492-501.

28. Edriwicrema LS, Burstine M, Saber MS, Rao N. Malignant solitary fibrous tumor of the orbit: Spectrum of histologic features. Am J Ophthalmol Case Rep 2017;5:7-10.

29. Suster S, Fisher C, Moran CA. Expression of bcl-2 oncoprotein in benign and malignant scalp cell tumors of soft tissue, skin, serosal surfaces, and gastrointestinal tract. Am J Surg Pathol 1996;20(7):863-72.

30. Miettinen M, Shekittka KM, Sobin LH. Schwannomas in the colon and rectum: a clinicopathologic and immunohistochemical study of 20 cases. Am J Surg Pathol 2001;25(7):846-55.

31. Hornick, J.L. Practical soft tissue patholo gy: a diagnostic approach. 1st ed. Saunders; 2013; 38-43.

32. Yang YY, Hsu YY, Huang TL. Orbital solitary fibrous tumor. Tzu Chi Med J 2015;27(1):35-7.

33. Yang BT, Wang YZ, Dong JY, et al. MRI study of solitary fibrous tumor in the orbit. AJR Am J Roentgenol 2012;199(4):W506-11.

34. Cal sina M, Filipone E, Patwardhan M, et al. Solitary orbital myofibroma: clinical, radiographic, and histopathologic findings. A report of two cases. Orbit 2011;30(4):180-2.

35. Xian J, Zhang Z, Wang Z, et al. Evaluation of MR imaging findings differentiating cavernous haemangiomas from schwannomas in the orbit. Eur Radiol 2010;20(9):2221-8.

36. Priego G, Majos C, Climent F, Muntane A. Orbital lymphoma: imaging features and differential diagnosis. Insights Imaging 2012;3(4):337-44.

37. Tall ES, Chen EC, Nijhawan N, et al. Solitary fibrous tumor of the orbit: a case series. Orbit 2008;27(6):426-31.

38. Le CP, Jones S, Valenzuela AA. Orbital solitary fibrous tumor: a case series with review of the literature. Orbit 2014;33(2):145-51.

39. Devito N, Henderson E, Han G, et al. Clinical Characteristics and Outcomes for Solitary Fibrous Tumor (SFT): A Single Center Experience. PLoS ONE 2015;10(10):e0140362.

40. Chamberlain MC, Glantz MJ. Sequential salvage chemotherapy for recurrent intracranial hemangiopericytoma. Neurosurgery 2008;63(4):720-6.

41. Park MS, RavI V, Conley A, et al. The role of chemotherapy in advanced solitary fibrous tumors: a retrospective analysis. Clin Sarcoma Res 2013;3(1):7.

42. Van houdt WJ, Westerveld CM, Vrijen hoek JE, et al. Prognosis of solitary fibrous tumors: a multicenter study. Ann Surg Oncol 2013;20(13):4090-5.

43. Bowe SN, Wakeley PE, Ozer E. Head and neck solitary fibrous tumors: diagnostic and therapeutic challenges. Laryngoscope 2012;122(8):1748-55.