# Giant cell-rich solitary fibrous tumour of the lacrimal gland with prominent angiomatoid cystic changes and an underlying NAB2ex3-STAT6ex18 fusion

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## SUMMARY

Giant cell-rich solitary fibrous tumour (GCR-SFT) is a rare variant of SFT with a predilection for the orbital region. Despite its hypervascularity, extensive angiomatoid cystic changes are unusual in GCR-SFT and may pose a diagnostic challenge. A 47-year-old man presented with a right eye proptosis and a protruding tumour of several years' duration with recently accelerated tumour growth. MRI revealed a cystic-solid heterogeneous mass arising from the lacrimal gland and displacing the globe. A subtotal excision of the mass was performed due to unanticipated hypervascularity and intraoperative bleeding. Pathologically, a vascular neoplasm was initially suspected. The diagnosis of GCR-SFT was made following careful evaluation and demonstration of CD34 and STAT6 expression. Molecular studies revealed a pathognomonic but rare NAB2ex3-STAT6ex18 fusion variant as well as a TP53 mutation suggestive of aggressive phenotype. The patient had a complete resolution of the proptosis but the clinical picture remains guarded due to incomplete resection.

## BACKGROUND

Solitary fibrous tumour (SFT) is an uncommon neoplasm of mesenchymal fibroblastic origin known to arise at numerous anatomical locations, with the pleura being one of the most common. Orbital involvement has been increasingly recognised since their first description in 1994,[1 2] probably due to increased awareness of this entity, refined diagnostic histological criteria[3] and advent of STAT6 immunohistochemistry as a specific marker for SFT and a surrogate for the pathognomonic NAB2–STAT6 gene fusion.[4] Accurate diagnosis is largely dependent on having a high index of suspicion and appreciation of the protean radiological and pathological features. While most SFTs are slow-growing indolent tumours, they are notorious for their unpredictable clinical behaviour irrespective of the histology. Complete surgical resection is required to reduce the risk of local recurrences and potential malignant transformation.

Giant cell-rich solitary fibrous tumour (GCR-SFT), formerly known as giant cell angiofibroma, was first described in 1995 as a distinctive orbital tumour in adults.[5] Subsequently, reports of GCR-SFTs at extraorbital locations started to emerge.[6] Currently, GCR-SFT is classified as a histological variant of SFT based on the overlapping clinico-pathological, immunohistochemical and genetic features.[3 7] GCR-SFTs are known to be richly

vascularised, although extensive cystically dilated angiomatoid spaces are unusual. Herein, we report an orbital GCR-SFT displaying such extensive angiomatoid changes reminiscent of a vascular tumour, posing a diagnostic challenge. Awareness of these features is important among radiologists, ophthalmologists and pathologists for optimal preoperative diagnosis and surgical planning.

## CASE PRESENTATION

A 47-year-old man presented with progressive painless protrusion of the right eye for several years associated with blurred vision (figure 1A). Physical examination showed right eye proptosis measuring 30 mm on exophthalmometry (in comparison to 21 mm on the left side). This was accompanied by significant conjunctival chemosis, corneal exposure and dryness, and diffuse punctate erosions. Additionally, a congested protruding swelling was visible laterally, which seemed to be the cause of the globe displacement. Extraocular movements were restricted in all gaze directions. Visual acuity was 20/400 in the affected eye and 20/25 in the opposite eye. No afferent pupillary defect was identified. Visual fields could not be assessed due to poor vision. Fundus examination was normal bilaterally. The patient first noticed the proptosis in 2015 (6 years ago) for which he sought medical attention then lost follow-up. Since then, the lesion had been slowly growing but especially worsening over the past year. No significant medical or surgical history was noted.

## INVESTIGATIONS

The patient first presented at another hospital in 2015 and had a CT scan of the orbit there with no further details available to us. A biopsy was attempted at the time which turned out to be uninformative, yielding non-representative benign lacrimal tissue only. The patient lost follow-up for 6 years, during which the mass was gradually increasing in size. He eventually sought medical attention at our specialised eye centre due to worsening proptosis and decreased vision over the past year. Recent MRI revealed an extraconical antero-lateral 3.8×3.5×2.0 cm solid-cystic mass in the right orbit, showing a heterogeneous intensity and marked contrast enhancement, most likely originating from the lacrimal gland, which appeared inseparable from it (figure 1B,C). The mass abutted the lateral aspect of the eye globe and lateral rectus muscle, resulting in globe displacement and
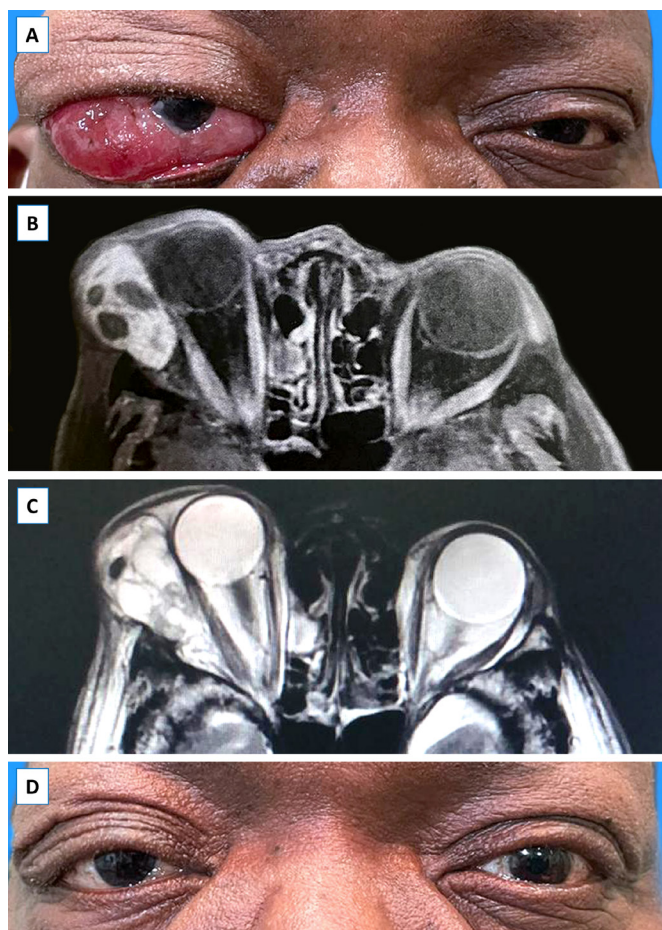
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**Figure 1** (A) Preoperative photograph showing right proptosis and a protruding tumour; (B,C) MRI orbit, T1 and T2, respectively, showing a markedly enhancing solid and cystic lesion abutting the globe and medial rectus muscle; (D) 3 months postoperatively.



**Figure 2** (A) Low magnification view shows cystic/angiomatoid appearance of the tumour (H&E, ×0.4). (B) Pseudovascular cystic spaces (H&E, ×1.5). (C) Small capillary-sized vessels and sinusoid-like spaces (H&E, ×20). (D) Alternating sclerosing and cellular areas with staghorn-like vessels (H&E, ×4). (E) Storiform pattern (H&E, ×10); (F) Spindled cells and multinucleated giant cells (H&E, ×20). (G) Types of multinucleated giant cells with and without nuclear atypia (H&E, ×40). (H) Atypical mitotic figure (H&E, ×40). (I) Cells with vacuolated cytoplasm (H&E, ×40). (J) Intranuclear inclusions (H&E, ×40). (K) Residual lacrimal gland tissue at the periphery of the tumour (H&E, ×10). (L–O) CD34, STAT6, BCL2 and CD99 immunohistochemical stains, respectively (H&E, ×20).

proptosis without evidence of ocular or muscular infiltration. No bone erosion or marrow oedema seen.

## DIFFERENTIAL DIAGNOSIS

In view of the longstanding clinical history and imaging characteristics, particularly the circumscribed non-infiltrative nature of the lesion, a benign/indolent neoplasm was favoured clinically, although malignancy could not be totally excluded. Localising the mass to the extraconal compartment, specifically to the lacrimal gland, further helped narrow down the list of differentials, which included epithelial and non-epithelial neoplasms as well as non-neoplastic mimics. Pleomorphic adenoma, an epithelial neoplasm and the most common benign neoplasm of the lacrimal gland, was on top of the list. Malignant epithelial lesions, on the other hand, were less likely (of which adenoid cystic carcinoma is the most common). A cavernous vascular malformation was also entertained; however, the extraconal location of the mass was atypical for this diagnosis.[8] Lymphoma of the lacrimal gland, such as mucosa-associated lymphoid tissue-type (lymphoma), was at the bottom of the list especially in the absence of extraorbital systemic disease. Finally, a metastatic tumour could not be ruled out. Non-neoplastic conditions of the lacrimal gland (such as sarcoidosis) may mimic neoplasia and were also entertained. SFT was not considered at this point. Eventually, histopathological evaluation was needed to establish a definite tissue diagnosis.
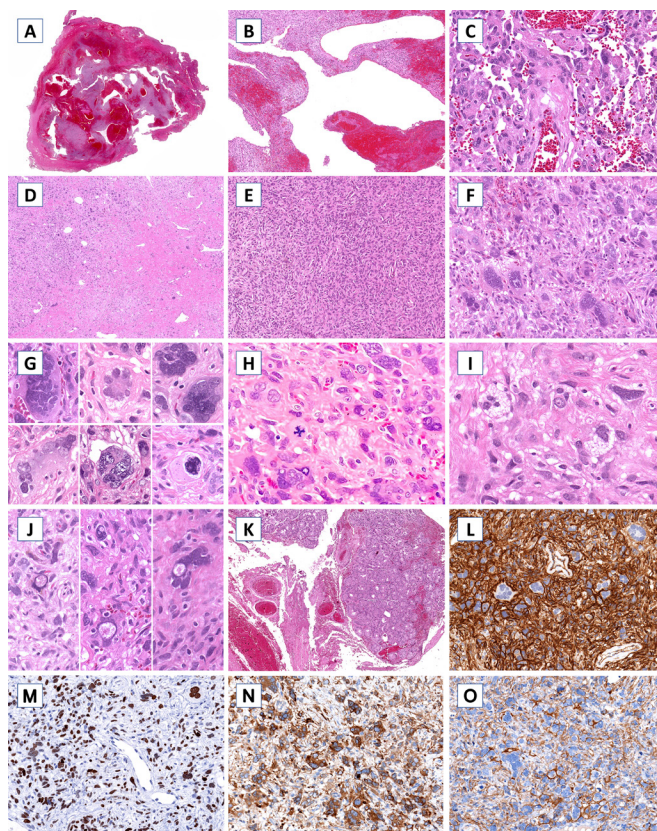
## TREATMENT

The patient underwent surgery under general anaesthesia via upper lid crease anterolateral orbitotomy approach (figure 1D). The procedure proved to be challenging due to intraoperative haemorrhage and adherence of the mass to surrounding structures. Presurgical embolisation was not employed as this was not anticipated. The hypervascularity and bleeding precluded complete removal of the tumour so a subtotal resection was performed instead. At this point, a vascular tumour/malformation was highly suspected clinically. The specimen was sent to histopathology.

On gross pathological examination, the mass measured 3.5×2.0×2.0 cm and its cut surface revealed blood-filled cystic spaces as well as solid areas. Histologically, the tumour showed a prominent angiomatoid appearance in the form of large blood-filled cystic spaces, small capillary-sized vessels and sinusoid-like spaces (figure 2A–C). At first glance, the striking vascularity was alarming for angiosarcoma mandating immunohistochemical evaluation. On closer inspection of the solid tumour component, a 'patternless' pattern with alternating hypocellular and hypercellular areas was appreciated along with staghorn-like vessels

(figure 2D) and a focal storiform architecture (figure 2E). A dual population of cells were apparent: spindled fibroblast-like cells and large multinucleated giant cells (figure 2F), the latter of which showed nuclei nested in the centre of the cell or at the periphery (floret-like or Touton giant cell-like cells) (figure 2G). Some nuclei appeared smudged and degenerative, while others were markedly atypical (figure 2G). However, mitotic activity was disproportionately low (up to 3/10 hpf). After a meticulous search, an occasional atypical mitotic form was identified (figure 2H). Occasional cells had vacuolated cytoplasm superficially resembling lipoblasts (figure 2I).[3] Conspicuous intranuclear pseudoinclusions were seen (figure 2J).[6] Residual lacrimal glandular elements were identified at the periphery of the tumour (figure 2K). Other than angiosarcoma, sarcomatoid carcinoma and undifferentiated pleomorphic sarcoma were also considered. On immunohistochemistry, tumour cells were negative for epithelial, melanocytic, neural, muscular and vascular endothelial markers (CD31 and factor VIII) but were diffusely positive for CD34 (figure 2L). STAT6 showed intense nuclear staining in the mononucleated and multinucleated cells reflective of an underlying NAB2-STAT6 fusion (figure 2M).[7] BCL2 and CD99 were also positive (figure 2N,O). Ki-67 proliferative index was low. This picture was consistent with a GCR-SFT.

Molecular testing confirmed the presence of a fusion variant NAB2e×3-STAT6e×18 (using targeted RNA fusion sequencing). Additionally, a TP53 mutation (c. 437_440delGGGT, p. W146fs) was identified.[3 9]

## OUTCOME AND FOLLOW-UP

Postoperatively, the patient experienced complete remission of the proptosis down to 21 cm with resolution of the conjunctival and corneal changes. Visual acuity was significantly improved at 20/25. Extraocular movements showed full ocular motility with minimal restriction in adduction. After 3 months of follow-up, there was no obvious regrowth of the mass on physical examination; however, the clinical outlook remains guarded in view of the incomplete resection. The patient was referred to an oncologist for further management and for a follow-up MRI to monitor the residual disease.

## DISCUSSION

Orbital SFT is an uncommon mesenchymal neoplasm that is increasingly being recognised and reported mostly due to improved diagnostics and histological criteria. In the most comprehensive review of the English literature to date,[10] 263 orbital SFTs have been identified between 1966 and 2019. SFT comprises a spectrum with diverse histological features encompassing GCR-SFT, which is a rare variant with a predilection for the orbital region, characterised histologically by a spindle-cell proliferation, pseudovascular spaces and multinucleate floret-like giant cells.[11–13]

Although orbital SFTs are richly vascularised, extensive cystic change is unusual and may pose a diagnostic difficulty.[14–19] Rare entirely cystic examples may lead to confusion with other entities such as vascular tumours or even a hydatid cyst in one report.[12 15 18] Another report described three recurrent orbital SFTs containing cysts filled with mucoid material leading the authors to suggest that cystic degeneration may be associated with locally aggressive behaviour.[17] In our case, the cystic nature was due to blood-filled pseudovascular spaces leading to an erroneous initial impression of a vascular neoplasm. Such appearance may be particularly challenging for general radiologists/ophthalmologists/pathologists who are not exposed to ophthalmic oncology cases on a regular basis.

SFTs characteristically harbour inv12(q13q13)-derived NAB2-STAT6 fusions with variable breakpoints resulting in diverse fusion variants that seem to correlate with some clinicopathological features particularly anatomic location of the tumour.[20 21] SFTs in the head and neck, however, have shown more genetic heterogeneity in the NAB2-STAT6 variants with one study demonstrating a NAB2e×6-STAT6e×17 variant in 3 out of 5 orbital GCR-SFT cases.[7] In our case, a rare NAB2e×3-STAT6e×18 fusion variant was detected, which was previously reported in a large SFT in the brain of a 75-year-old patient who had no disease progression 3 years after surgery.[22] Nonetheless, the significance of such fusion variants in the orbit remains to be seen. Additionally, our case showed a TP53 mutation on targeted next-generation sequencing. TP53 mutations have been associated with aggressive behaviour and dedifferentiation in SFT.[21] Our patient had the tumour for at least 6 years without demonstrating aggressive behaviour, such as local infiltration into adjacent structures, but he did report a recent increase in size over the past 1 year which may be related to the acquisition of additional mutations including that of TP53. TERT promoter mutation, another adverse factor, was not detected in this case.[21]

Predicting the clinical course of SFTs is an enigma since histology is not usually predictive of biological behaviour. This is particularly true of orbital SFTs which are inadequately studied due to their rarity. Several risk-assessment models exist for predicting local recurrences and/or distant metastasis in SFTs irrespective of their site.[23 24] Recently, Thompson et al proposed a site-specific model unique to orbital SFTs incorporating age, tumour size, tumour necrosis, mitoses, cellularity, and pleomorphism.[10] Such models, however, may not be fully applicable to our case since the patient is known to have residual disease due to incomplete surgical excision making tumour regrowth inevitable. Our case would have been regarded as 'intermediate risk' based on the Thompson model with a total score of 4: 0 for patient age at initial presentation (≤45 years old), 2 for tumour size (>3 cm), 0 for mitotic activity (≤4 mitoses/2 mm$^2$), 1 for cellularity (moderate to high), 1 for pleomorphism (moderate to high) and 0 for necrosis (absent).[10] Despite the cellular pleomorphism in this case, mitotic activity was disproportionately low.

Complete surgical removal of orbital SFT is the mainstay of treatment, sometimes preceded by preoperative embolisation in order to reduce the risk of intraoperative bleeding as recommended by several papers.[25 26] Angiography may be used preoperatively to assess the tumour vascularity and to better plan for the surgery. Incomplete resection of SFT is a risk factor for local recurrences and/or malignant transformation along with the potential to metastasise sometimes many years later. Some incompletely excised cases may benefit from adjuvant radiotherapy or chemotherapy.

> **Learning points**
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> - Giant cell-rich solitary fibrous tumour should be considered in the differential diagnosis of a cystic orbital lesion.
> - Extensive angiomatoid change in orbital SFT may mimic a vascular neoplasm.
> - Complete surgical excision may be hindered by profuse bleeding necessitating preoperative embolisation.
> - Orbital solitary fibrous tumours harbour heterogenous NAB2-STAT6 fusion variants.

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