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CASE REPORT

Multiple Recurrence of Primary Orbital Synovial Sarcoma: Report of Two Cases and Literature Review

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ABSTRACT

Synovial sarcoma (SS) is typically an aggressive malignant soft tissue tumor that mostly affects adolescents and young adults. It is extremely rare in orbit and carries a high risk of recurrence and metastasis, posing a challenge to ophthalmologists in diagnosing and managing. We present two primary orbital synovial sarcoma cases with unilateral exophthalmos and limited motility. Both male patients underwent reoperation in our hospital since tumor recurrence; the pathologic diagnoses were biphasic type and occult type, respectively. Both cases were positive for EMA and CK, and SOX-9 and INI-1 were newly discovered immune markers. *Fluorescence in situ hybridization* analysis (FISH) revealed a translocation of t (X; 18) (p11.2; q11.2) that was detected in case 1 but not in case 2. Both patients initially refused adjuvant therapy, developed multiple recurrences and metastasis, and eventually died of distant metastasis. We provided clinical features, imaging findings, histopathology, treatments, outcomes of these very rare cases, and a literature review, underlining the timely diagnosis and management.

KEYWORDS

Diagnosis; orbit; synovial sarcoma; treatment; tumor recurrence; metastasis

1 Introduction

Synovial sarcoma (SS) is a highly malignant soft tissue sarcoma that differentiates into mesenchymal tissue and epithelium. It accounts for approximately 10% of all soft tissue tumors and has an unknown source and cell of origin, variable clinical behavior, and unique genetic features [1]. It can develop at any age and location, most commonly in the extremities of adolescents and young adults; males are more commonly afflicted [2]. SS involving orbit is exceedingly rare; only 13 cases have been well documented to date, and SS from all sites has a high risk of recurrence and metastasis [3]. However, a correct diagnosis and systemic management pose a challenge for an ophthalmologist. Here, we present two primary orbital SS to expand the medical literature about this rare condition. To our knowledge, case 2 is the first case of occult SS in orbit. In addition, we also review the literature of previously published SS cases, with an emphasis on timely diagnosis and treatment.

2 Case Report

Two cases of orbital SS have been reviewed, which were accessioned in the database of the Ophthalmology Department and Pathology Department of West China Hospital of Sichuan University from 2009 to 2021.

2.1 Case 1

A 56-year-old man presented with a 2-year history of proptosis of the right eye (Fig. 1A). He underwent surgery in another hospital one year ago, and the pathologic diagnosis was SS. On ophthalmologic examination, the visual acuity was light perception in the right eye and count finger/40 cm in the left eye. A poorly defined, nonmobile soft mass in the nasal region of the right orbit was palpated, and proptosis was identified. The edema of the inferior bulbar conjunctiva, the disappeared pupillary reaction, and limited ocular motility in all directions were presented. The computed tomography (CT) imaging indicated a 4.8 cm × 2.6 cm soft tissue mass in the right medial orbit in close relation to ocular muscles and optic nerve without invading the eyeball and orbital wall (Figs. 1C and 1D). A routine orbitotomy was performed from the upper edge of the orbit and the tumor was removed as completely as possible (Fig. 2A). Subsequently, the hematoxylin-eosin (HE) and immunohistochemical staining indicated the tumor was mainly composed of spindle-shaped cells and epithelioid cells with positive staining of TLE-1, EMA and CK (Figs. 2A–2F). The histopathology confirmed the diagnosis of biphasic SS with molecular translocation t (X; 18) (p11.2; q11.2) of the SS18-SSX gene. Although adjuvant radiation and chemotherapy were recommended, the patient refused. Since then, the patient has had five relapses, accepted five tumor resections and one gamma knife radiosurgery over three years, and finally received chemotherapy and radiotherapy. Nevertheless, he died of lung metastases 11 months after adjuvant therapy, as reported by telephone follow-up.

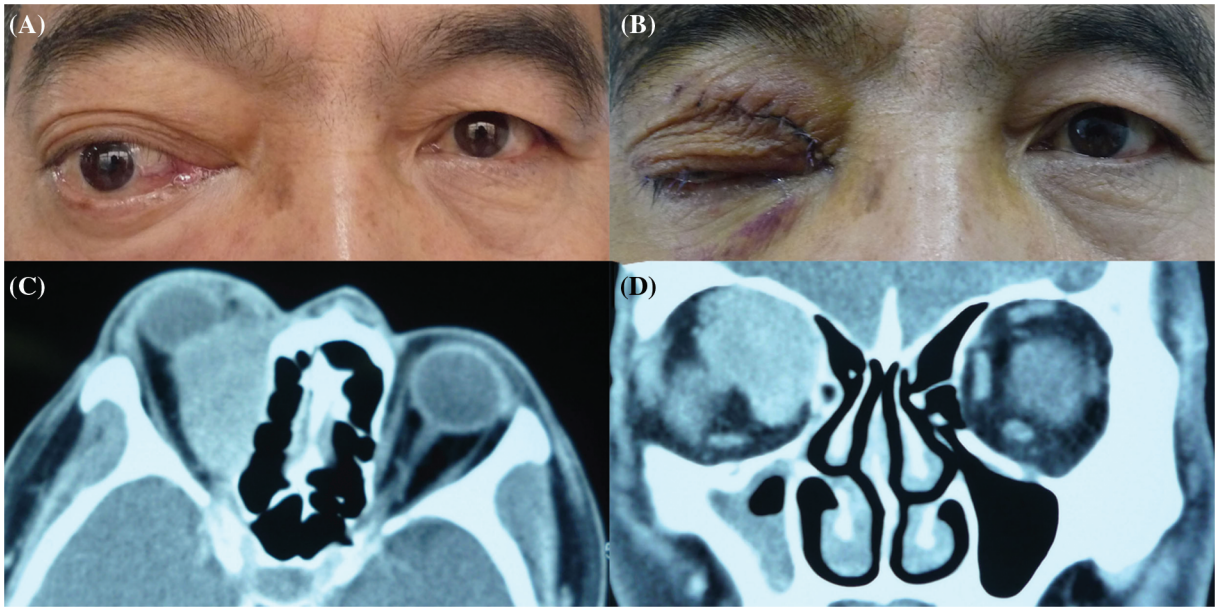

Figure 1: (A) The preoperative image showed proptosis of the right eye. (B) The postoperative image showed that the right eyelid closed entirely. (C) and (D) Orbital CT scan demonstrated a large, homogeneous mass surrounding the optic nerve and the medial rectus muscle in the right orbit

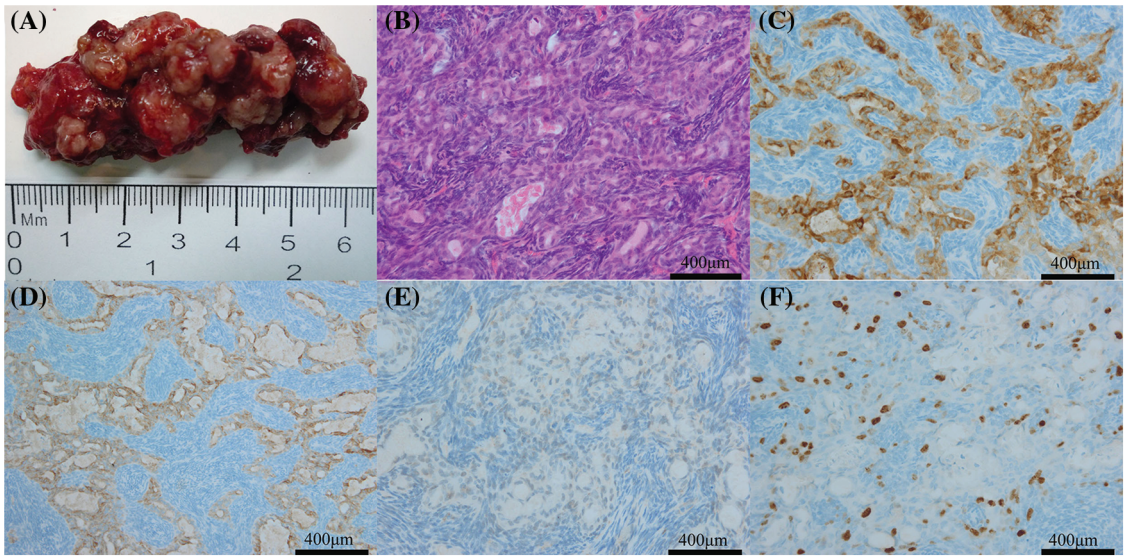

Figure 2: Gross specimens and pathological images of the tumor specimen. (A) The resected tumor showed grey-white, dark red with a total volume of about 6 cm × 2.5 cm × 2 cm. (B) The tumor was composed of spindle cells arranged in sheets or fascicles and epithelial cells arranged in nests or gland-like structures (HE, original magnification × 400). (C) Tumor cells revealing cytoplasmic positivity of EMA immunostaining (EMA, original magnification × 400). (D) Tumor cells revealing cytoplasmic positivity of CK7 immunostaining (CK7, original magnification × 400). (E) Tumor cells revealing cytoplasmic positivity of TLE-1 immunostaining (TLE-1, original magnification × 400). (F) Ki67 immunostaining demonstrated that approximately 20% of tumor cells showed strong nuclear positivity (Ki67, original magnification × 400)

2.2 Case 2

A 28-year-old man sought treatment for tumor recurrence of the right orbit. Three years and eight months ago, he underwent two operations and adjuvant radiation in another hospital. The pathologic diagnosis was mesenchymal chondrosarcoma. His best corrected visual acuity was 20/20 in both eyes, and the right eye showed an obvious proptosis with limited motility in horizontal directions. The remainders of the ophthalmic examination results were normal. An orbital CT scan revealed a right retrobulbar soft mass near the lateral wall with calcification and bone involvement (Fig. 3A). A lateral orbitotomy and complete tumor resection were performed. Histological examination showed a small round spindle cell proliferation with positive staining of CD99, EMA, CK19, INI-1 and SOX-9, but without the translocation of t (X; 18) (p11.2; q11.2). Thus, the final diagnosis is occult SS. After the operation, the patient did not receive radiotherapy or chemotherapy. Since then, he has had four relapses (Figs. 3B–3F). The malignant tumor developed intracranial extension at the fourth relapse, and then he accepted tumor resections in orbit and brain combined with regular adjuvant radiotherapy and chemotherapy (gemcitabine, pirarubicin and ifosfamide). Unfortunately, he died of brain metastases after a two-month follow-up.

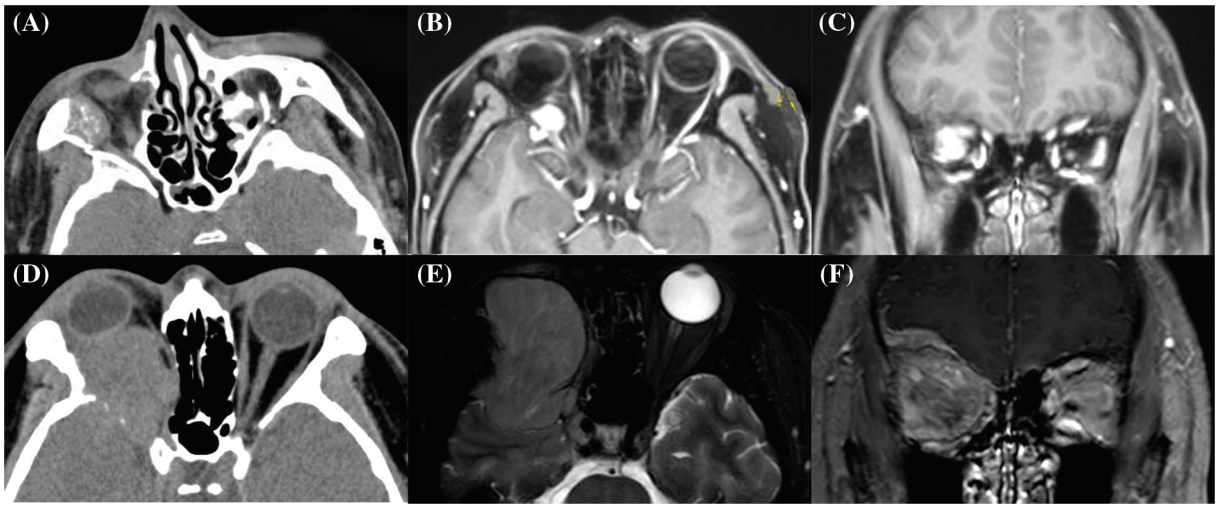

Figure 3: Orbital imaging of tumor recurrence. (A) Orbital CT scan of the second tumor recurrence revealed a 2.4 cm × 1.2 cm right orbital mass with calcification and bone absorption. (B) and (C) Orbital magnetic resonance imaging (MRI) scan of the third recurrence revealed a 1.4 cm × 1.1 cm soft mass near the lateral orbital wall with mild enhancement. (D) Orbital CT scan of the fourth recurrence showed a huge right orbital mass with bone destruction of the orbital roof, lateral wall and sphenoid bone, partly protruding into the middle cranial fossa. (E) and (F) Head MRI scan revealed a 5.8 cm × 3.7 cm heterogeneous mass with bone destruction of each orbital wall, involving the frontal and temporal lobes

3 Discussion

Orbital SS is a very rare malignant entity. Among the 13 current reports of orbital SS (including our cases), 11 were primary SS (Appendix A) and 2 were metastatic SS [4,5]. The age of patients ranged from 1.5 to 56 years (median: 26.9 years), and the female was more susceptible, unlike any other part of the body. However, orbital lesions in these reported cases do not have any distinguishing characteristics.

SS is categorized into 3 main types: the monophasic type contains only spindle cells, the biphasic type contains epithelial and spindle cell components in varying proportions, and the poorly differentiated type contains monophasic and biphasic regions as well as poorly differentiated areas [6]. Of 13 cases with available histopathological information, the biphasic type is the most common and the poorly differentiated type is the rarest. It is worth noting that we reported a rarer type; this is the first case of occult SS occurring in orbit.

As observed in case 2, SS is commonly missed or misdiagnosed; the patient was initially considered to have mesenchymal chondrosarcoma. The pathologic differential diagnosis of SS includes malignant peripheral nerve sheath tumor, fibrosarcoma, leiomyosarcoma, mesenchymal chondrosarcoma and other small round blue cell tumors. Traditionally, the diagnosis of biphasic SS depends on its unique histological morphology, but other types need to be supported by immunohistochemical and molecular genetic studies.

Positivity for EMA, CK, and Vimentin is the most valuable and sensitive marker for the diagnosis of SS. TLE-1 is highly sensitive but not specific to SS [7]. Other positive expressions include Calponin, Bcl-2, CD-99, S-100, collagen IV, Synaptophysin, SOX10 and AE1/AE3, and negative stains for α-SMA, desmin, Factor VIII, CD34 and MPO could also be helpful to rule out other mesenchymal tumors. Interestingly, we found the tumor in our case 2 positive staining for SOX-9 and INI-1, which has never been reported.

Currently, the newly discovered translocation t (X;18) (p11.2; q11.2) is diagnostic and is present in more than 90% of SS and does not occur in other forms of sarcomas [6,8].

SS carries a high risk of local recurrence and distant metastasis that most often occur in the lungs, brain, lymph, and bone marrow [5,9]. Some favorable prognosis factors include younger patient age, smaller tumor size (<5 cm), combined with chemoradiotherapy, negative surgical margin, extremity location, and SS18-SSX2 fusion gene, while unfavorable prognosis factors include the poorly differentiated subtype, the presence of metastasis, lymph node positivity and SS18-SSX1 fusion gene [3,9–11].

Surgical resection with a negative margin remains the standard initial treatment for SS; however, it is difficult to obtain negative surgical margins due to the poorly defined form of the tumor and its adherence to critical issues such as the extraocular muscles or optic nerve. Exenteration could be considered if the tumor is large or if tumor-free margins are difficult to identify. Postoperative radiotherapy is recommended for patients with positive margins to prevent tumor relapse or metastasis. Palmerini et al. [12] retrospectively studied radiotherapy and prognosis in 250 adult SS patients. They found that patients who received radiotherapy had a higher 5-year local control rate than those who received surgery alone (85% *vs*. 67%). The role of chemotherapy for SS is controversial. Several studies suggested that neoadjuvant/adjuvant chemotherapy does not significantly improve the survival of soft tissue sarcoma patients [13,14]; other studies suggested that chemotherapy is not recommended for low-risk SS but is recommended for high-risk patients [15]. Among the 11 patients reported previously, 8 cases had no recurrences or metastasis with follow-up time ranging from 6 to 84 months, possibly due to negative surgical margin or incomplete resection with adjuvant therapy. In our cases, both patients underwent multiple operations with adjuvant chemoradiotherapy; however, they initially refused chemoradiation and eventually died of metastasis. Thus, only surgical resection is not enough, timely postoperative adjuvant therapy is essential for local control and distant metastasis. Some clinical trials focusing on immunotherapeutic strategies are underway, including SS18-SSX specific vaccine and genetically engineered lymphocytes treating patients with NY-ESO-1 positive tumors [16,17]. With the discovery of potential therapeutic targets, molecular-targeted drugs are increasing and have shown good efficacy, tyrosine kinase inhibitors such as Pazopanib and Apatinib are inhibiting VEGF1, VEGF2, VEGF3 and PDGFRα, PDGFRβ, c-Kit to inhibit tumor growth activity [18,19].

4 Conclusion

Orbital SS is extremely rare and easily misdiagnosed. The diagnosis should be made by combining histopathology, immunohistochemistry, and molecular genetics. SS18-SSX fusion gene testing is the golden standard of diagnosis, however, due to the current high cost, high equipment requirements and failure to detect SS18-SSX in a few SS cases, exploring more economical and effective methods for SS identification is still necessary. Patients with orbital SS need to be treated with free-marginal surgery combined with adjuvant radiotherapy or chemotherapy, the latter should be added for high-risk SS or metastasis SS. However, we also need further studies to explore new immunotherapy and gene therapy to improve the survival rate.

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Author's Contribution: YW: Conceptualization, methodology, data collection, writing original draft and review and editing, YJW: Investigation, review and editing, WMH: Surgery, conceptualization, supervision, review and editing.

Ethics Approval and Informed Consent Statement: Informed written consent has been obtained from the patients in this case report to publish this paper. The present study involved human participants, and it was

conducted considering ethical responsibilities according to the World Medical Association and the Declaration of Helsinki.

Availability of Data and Materials: There is no additional data regarding this study and all available data and materials have been shared within the case report.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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Appendix A:

Table 1: Reported cases of primary orbital SSs

Case	Author	Age sex	Clinical history	Location	Imaging	Histopathology	Immune markers	Molecular genetics	Treatment	Follow-up
1	Thomas et al. [1]	54,M	7-year-history of painless exophthalmia	Right orbit and posterosuperior	-	Biphasic	-	-	RT to decrease exophthalmia; Exenteration	No recurrences and metastasis after 4 years
2	Ratnatunga et al. [2]	21, F	5-year-history of painless mass with the displacement of the eyeball and limited adduction	Left orbit: subconjunctival mass, adherent to the medial rectus muscle and extending posteriorly into the retrobulbar region	-	Biphasic	EMA, pankeratin	-	Incomplete excision	-
3		42, F	8-month-history of swelling	Left orbit: adherent to the tendon sheath of the superior oblique muscle	-	Biphasic	EMA, pankeratin	-	Incomplete excision	-
4	Shukla et al. [3]	32, F	5-year-history of recurrent swelling and pain, diplopia, and decreased vision, motility restriction	Left orbit: encroaching the cornea	CT: 4 × 2.5cm well-defined enhancing mass with calcifications, involving the globe, and the medial, lateral, and superior recti muscles	Biphasic	pan-cytokeratin, EMA, vimentin, CD99, S-100	-	Incomplete excision; RT	-
5	Hartstein et al. [4]	14,M	1-month-history of painless proptosis	Left orbit	CT: well-circumscribed intraconal mass	Biphasic	vimentin, collagen IV, cytokeratin, EMA	t (X; 18)	Exenteration	No recurrences after 18 months
6	Kusuma et al. [5]	18, F	18-month-history of a slowly enlarging mass	Right medial canthus	CT: mass extended into the right lateral nasal dorsum	Monophasic	vimentin, EMA; cytokeratin, S-100	-	Complete excision; RT	No recurrences after 7 years
7	Liu et al. [6]	1.5, F	1-month-history of painless swelling in left eyelid, proptosis, inflamed conjunctiva, and limited ocular motility	Left upper eyelid, nasal portion, adherent to the medial rectus muscle	CT: orbital mass with unclear border	Poorly differentiated	pan cytokeratin, EMA, vimentin, CD99, Ki67 60%	t (X; 18)	Orbitotomy with tumor resection; CT	No recurrences and metastasis after 1 year

(Continued)

Table 1 (continued)

Case	Author	Age sex	Clinical history	Location	Imaging	Histopathology	Immune markers	Molecular genetics	Treatment	Follow-up
8	Stagner et al. [7]	31, F	Fullness in her temporal left lower eyelid, left facial, orbital and periorbital pain for more than a decade; proptosis, upward displacement of the globe, and eyelid ptosis	Left inferior orbit, adherent to the inferior rectus and oblique muscles	CT and MRI:2.5 × 1.5 × 2.8 cm well-defined mass with calcifications, adherence to the inferior rectus and oblique muscles	Poorly differentiated	TLE1, CD99, EMA, synaptophysin	t (X; 18)	Subtotal excision; RT	No recurrences after 6 months
9	Xu et al. [8]	6, F	1-week-history of painless proptosis, motility restriction	Right orbit	CT and MRI: 4 × 5.5 × 6.5 cm mass in the lateral orbital wall extending into the orbit, the intracranial, and the temporal fossa, with bone destruction	Monophasic	vimentin, CD99, Calponin, Bcl-2	-	Complete excision; CT	No recurrences and metastasis after 1 year
10	Portelli et al. [9]	24, F	1-year-history of painful cystic lesion	Left superonasal orbit	B ultrasound:1.4 × 0.75 cm hypoechogenic uniform roundish lesion	Monophasic	EMA, AE1/AE3, S-100, Bcl-2	t (X; 18)	Complete excision	No recurrences and metastasis after 20 months
11	Gervasio et al. [10]	23, F	1-year-history of right upper eyelid mass, pain, headache, eyelid swelling, right upper eyelid ptosis	right superomedial orbit	CT: 2 × 1.5 × 1 cm, well-circumscribed, extraconal, heterogeneously enhancing, ovoid mass	Monophasic	TLE-1,EMA, S-100, SOX10,Ki67 1%–15%	ss18 rearrangement	Complete excision; RT	under treatment

Abbreviations: M, male; F, female; RT, radiotherapy; CT, chemotherapy

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