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Retrospective Study

Clinical Characteristics and Prognosis of Orbital solitary fibrous tumor in a Chinese Tertiary Eye Hospital

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Abstract

BACKGROUND

Solitary fibrous tumor (SFT) is predominant within the pleura but very rare in orbit , which is why the diagnosis of orbital SFT poses challenges in clinical practice. Accordingly, an integrated approach that incorporates specific clinical, histological, Histopathological and immunohistochemical examination (HPE and IHC), and molecular analyses is warranted.

AIM

To retrospectively explore the clinical and imaging characteristics, treatment, outcomes of a series of patients with orbital solitary fibrous tumor.

METHODS

We conducted a retrospective noncomparative and consecutive review of a series of patients diagnosed with a histopathologic orbital SFT treated at a single institution. All data on demographics, clinical characteristics, imaging, treatment, postoperative HPE and IHC, and prognosis were collected.

RESULTS

In total, 13 patients were enrolled, 7 (53.8%) of whom were grouped in the superomedial quadrant of the orbit. CT scan revealed solitary ovoid lesions in 10 (76.9%) patients and irregular lesions in 3 (23.1%) patients. MRI results were as follows: On T1 weighted images (T1WI), 3 (23.1%) patients had hypointense mixed signals, whereas 10 (76.9%) patients showed isointense mixed signal; on T2 weighted images (T2WI), 3 (23.1%) patients, 4 (30.8%) patients, and 6 (46.2%) patients exhibited hypointense mixed signals, isointense mixed signals, and hyperintense signals, respectively. Notably, 12(92.3%) patients showed significant enhancement, whereas with patchy no enhancement lesions in the tumor. All patients were treated through surgery. IHC analysis demonstrated that the tumor cells were immunoreactive for

CD34, CD99, STAT-6, and Vimentin in all patients. The lesions showed Ki-67 positivity <5% in 1 (7.7) patient, 5%-10% in 10 (76.9%) patients, >10% in 2 (15.4%) patients. Two (15.4%) patients exhibited tumor recurrence.

CONCLUSION

The clinical manifestations and radiologic characteristics of orbital SFT are diverse and not specific. The accuracy of diagnosis and treatment require detailed radiological and HPE/IHC evaluation.

Key Words: orbit; solitary fibrous tumor; diagnostic imaging; immunohistochemistry; surgical therapy

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Core Tip: The clinical manifestations of orbital solitary fibrous tumor (SFT) are diverse and not specific. In most cases, the lesions occur outside the muscular cone, are localized at the superomedial quadrant and inferomeddial quadrant of the orbit. The mean CT values of lesions are variable, the signal of lesions on MRI is uncertain. Contrast-enhanced image performance showed most part of lesions were significant enhancement, whereas there were patchy slight enhancement lesions in them. Delineating SFT from histologic mimics requires nuclear staining of STAT6 as a diagnostic adjunct in conjunction with CD34 positivity. Ki-67 Labelling index maybe extremely low, malignant forms with an enhanced propensity for local recurrence have been reported.

INTRODUCTION

A solitary fibrous tumor (SFT) is a rare spindle-cell tumor of mesenchymal origin, first described in the pleura by Klemperer and Rabin in 1931 [1]. Original reports demonstrated that SFT is of submesothelial origin. However, there is controversy regarding its histogenesis and the etiology of the neoplasm remains largely unknown. Although the majority are benign, increasing evidence indicates the aggressive nature of the tumors. SFT is predominant within the pleura but very rare in orbit [2], which is why the diagnosis of orbital SFT poses challenges in clinical practice. Therefore, an integrated approach that incorporates specific clinical, radiological, HPE/IHC, and molecular analyses is warranted [3]. Since this disease is relatively rare, most scholars focus on case reports or serial case studies. Due to the relatively limited number of cases, understanding this disease may be limited. The present work reviews the clinical characteristic features and treatment experience of 13 orbital SFT patients in a Chinese Tertiary Eye Hospital, aiming to improve the accuracy of diagnosis and treatment.

MATERIALS AND METHODS

A retrospective chart review was conducted on subjects with orbital SFT. A total of 13 patients diagnosed with orbital SFT via postoperative Histopathological and immunohistochemical examination (HPE and IHC) were identified between January 2012 and March 2019 in Hebei Eye Hospital. Patient charts and medical information were retrieved from the electronic medical records of Hebei Eye Hospital. Data on demographics, relevant medical and family history, clinical presentation, radiological, HPE/IHC, treatments, and prognosis were reviewed for all the subjects. The study followed the tenets of the Declaration of Helsinki. The ethics committee of the Hebei Eye Hospital approved all study protocols. All patients gave written informed consent before the procedures. They were fully informed about the study and provided data voluntarily for analysis. All data were recorded and stored in compliance with ethical and data protection guidelines. All imaging examinations were performed under uniform conditions. An ophthalmologist who specialized in

orbital diseases and a general neuroradiologist reviewed the CT and MRI at a conference. Two senior pathologists reviewed data on pathological examination. Patients with severe MRI artifacts due to the presence of metal implants in adjacent sites and incomplete clinical case data were excluded.

RESULTS

Demographic information, relevant medical and family history

Thirteen patients were reviewed 7 (53.8%) males and 6 (46.2%) females. The mean and median age of subjects at initial presentation was 45.2 (range 19-72) years and 43.0 years, respectively. Patients presented with the following systemic conditions: Hypertension (n = 3, 23.1%), iron deficiency anemia (n = 1, 7.7%), chronic bronchitis (n = 1, 7.7%), sinusitis (n = 1, 7.7%). Their family members had no history of this disease (Table 1).

Clinical characteristics

Patients predominantly presented with proptosis (n = 7, 53.8%). Subsequently, other symptoms appeared, including eyelid swelling (n = 2, 15.4%), painful mass (n = 2, 15.4%), epiphora (n = 1, 7.7%), and visual disturbances (n = 1, 7.7%), respectively. Nine (69.2%) patients exhibited visual acuity above 20/60, 1 (7.7%) patient showed 20/100 visual acuity, 3 (23.1%) patients had visual acuity lower than 20/200. Hertel exophthalmometry readings showed the median proptosis of the affected eye was 4 mm (range 1-6 mm), towered over the contralateral eye. Seven (53.8%) patients showed non axial proptosis as follows: Inferolateral (n = 3, 23.1%), inferomedial (n = 1, 7.7%), superomedial (n = 1, 7.7%), superior (n = 1, 7.7%), inferior (n = 1, 7.7%), respectively. Six (46.2%) patients presented with impaired control of eye movement. Nine (69.2%) patients exhibited palpable masses. One (7.7%) patient had noticeable tenderness. Six (46.2%) patients had secondary lesions. Two (15.4%) recurrent patients had optic nerve atrophy; 2 (15.4%) patients exhibited lacrimal

duct obstruction; 1 (7.7%) patient had corneal perforation secondary to exposure keratitis due to severe proptosis (Table 2).

The location of the lesions on orbital imaging examination

Orbital CT and MRI were applied to establish the location of the lesions. With the optic nerve as the original point, we classified the orbit into four quadrants. The mass was located in the superomedial quadrant (n = 7, 53.8%), the inferomedial quadrant (n = 3, 23.1%), the inferolateral quadrant (n = 2, 15.4%), superolateral quadrant (n = 1, 7.7%), respectively (Table 3). The lesions: (i) adhered closely to the extraocular muscles (n = 7, 53.8%); (ii) adhered to the optic nerve (n = 3, 23.1%), while 1 patient was the recurrent case; (iii) compressed the lacrimal sac (n = 2, 15.4%); (iv) spread to the brain, nasal cavity, and eyelids (n = 1, 7.7%) and this patient was the recurrent case, respectively.

Orbital Ultrasonography characteristics

The results of ultrasonographic manifestations are as follows: 1 (7.7%) patient had hypoechoic masses; 3 (23.1%) patients had moderate masses; 9 (69.2%) patients had mixed echogenic masses; 11 (86.4%) patients had a non-uniform echo, while 2 (15.4%) patients had relatively uniform echo; 9 (69.2%) patients had a clear boundary of the lesion, whereas 4 (30.8%) patients had an unclear boundary of the lesion; 10 (76.9%) patients exhibited ovoid mass, 3 (23.1%) patients had irregular mass; 12 (92.3%) patients had abundant branching blood flow signals in the mass, include 1 (7.7%) recurrent case; another (7.7%) recurrent patient had small flaky blood flow signals in the mass (Figure 1).

Orbital CT characteristics

According to the morphology of lesions, 10 (76.9%) patients had a solitary ovoid mass, whereas 3 (23.1%) patients had irregular mass. Nine (69.2%) patients had well-defined lesion boundaries, whereas 4 (30.8%) patients had unclear lesion boundaries. The

arithmetic mean CT value of the tumor was 45.9 Hu (range 22.8-64.4Hu). Regarding the standard deviation of CT value, 4 (30.8%) patients and 9 (69.2%) patients showed a lower and a higher value than 10% of their own CT value, respectively. The largest and the smallest lesions measured 2.7cm*2.9 cm *4.1cm and 1.0cm*1.3cm*1.4cm, respectively (Figure 2). Nine (69.2%) patients showed compressive bone change.

Orbital MRI characteristics

Following T1 weighted images (T1WI), 3 (23.1%) patients showed hypointense mixed signals, whereas 10 (76.9%) patients showed isointense mixed-signal; 10 (76.9%) patients and 3 (23.1%) patients had homogeneous and uneven signal intensity, respectively. 4 (30.8%) patients showed vessel-emptied signals. Following T2 weighted images (T2WI), 3 (23.1%) patients showed hypointense mixed signals, 4 (30.8%) patients showed isointense mixed signals, and 6 (46.2%) patients showed hyperintense signals; 2 (15.4%) patients showed relatively homogeneous signals, whereas 11 (86.4%) patients showed uneven signals. Contrast-enhanced image performance showed most part of the tumors were significant enhancement, whereas there were patchy slight enhancement lesions in those tumors, in twelve (92.3%) patients. One recurrent patient presented with significant enhancement at the edges of the lesion and in tissues surrounding the lesion (Figure 3).

The choice of the surgical approach

All patients were managed by surgery. The choice of the surgical approach was determined by the location, size, and relationship to surrounding tissue. As such, 2 (15.4%) patients underwent lateral orbitotomy, while 2 (15.4%) patients the lesion adhered to the optic nerve; 2 (15.4%) patients underwent lateral orbitotomy-medial conjunctival procedure, while 1 (7.7%) patient the lesion adhered to the optic nerve, and 1 (7.7%) patient the lesion spread to the brain, nasal cavity, eyelids; 9 (69.2%) patients underwent anterior orbitotomy. In addition, 9 (69.2%) patients were managed as follows: 3 (23.1%) via transcutaneous superomedial routes; 1 (7.7%) *via*

transcutaneous superolateral routes; 3 (23.1%) via frontoethmoidal medial orbitotomy, while 2 (15.4%) patients the lesion compressed the lacrimal sac; 1 (7.7%) by transcaruncular medial orbitotomy; 1 (7.7%) by transconjunctival orbitotomy. Eleven (86.4%) patients had the lesions completely removed. However, one recurrent patient the lesion adhered to the optic nerve underwent a majority resection, whereas another recurrent patient the lesion spread to the brain, nasal cavity, eyelids, underwent mass resection combined with orbital exenteration.

Post-operative complications

Post-operative complications were found in 4 (30.8%) patients. 2 (15.4%) patients presented with impaired control of eye movement. 1 (7.7%) patient had impaired visual function. 1 (7.7%) patient presented with severe ocular malformation.

Histopathological and immunohistochemical characteristics

Among the excised tumors, 8 (61.5%) patients had capsules or pseudocapsules, whereas 5 (38.5%) patients had no capsules. The tumor sections were gray-white in 6 (46.2%) patients and gray-red in 7 (53.8%) patients. Eight (61.5%) patients had brittle tumors, while 5 (38.5%) patients had tough tumors. HPE showed that the tumor comprised haphazardly arranged spindle cells with bland nuclei and inconspicuous nucleoli. IHC showed that all patients had tumor cells with diffuse immunoreactivity for CD34 and CD99. All patients tested positive for STAT-6 and Vimentin. The lesions showed Bcl-2 positivity in 11 (86.4%) patients. The lesions showed Bcl-2 positivity in 11 (86.4%) patients, S-100 negativity in 13 patients (100%), SMA negativity in 11 patients (86.4%). Ki-67 positivity of the lesions was <5% in one patient, 5%-10% in 10 (76.9%) patients, >10% in 2 (15.4%) patients (Figure 4).

Prognosis

Median follow-up was 36 (range 18-96) months. Two (15.4%) patients exhibited tumor recurrence, which lasted 36 mo and 28 mo post-surgery, respectively. No patient died.

DISCUSSION

Recent reports have found SFT in diverse bodily locations and are thought to present a vast array of clinical and radiological features [4]. Orbital SFT is a type of extrapleural SFT, considered as a rare type of orbital tumor with unclear clinical characteristics. Recent understanding of the orbital SFT demonstrates that it is more aggressive than a pleural form with a substantially unpredictable prognosis [3]. As such, exploring the clinical characteristics and development mechanisms of this tumor is of profound clinical significance.

There is no evidence on whether orbital SFT is linked to sex and side of affected eye predilection. Based on the findings from previous studies and the present results, adult cases seem to account for the majority. Meanwhile, children patients have been reported previously [5]. The clinical manifestations are diverse and do not significantly differ from other orbital tumors. The common manifestations of orbital SFT include proptosis and eyeball dislocation, and some patients may present with eyelid swelling, visual disturbances, a palpable painless mass, epiphora, and ptosis, periorbital spontaneous pain or tenderness [6].

Orbital SFT mostly presents as a soft-tissue mass on CT, round or oval; the density of the lesions is uneven. In most cases, the lesions occur outside the muscular cone and are localized at the superomedial quadrant and inferomeddial quadrant of the orbit. Tumors mostly develop on the outside of the muscular cone, and in partial cases, the lesions may be associated with or within the orbital muscle cone. In the present study, the mean CT values ranged between 22.8 Hu and 66.4 Hu, demonstrating the variability in the mean CT values of the tumors on CT scans. Remodeling of the adjacent bones is associated with long-standing orbital SFT [6], due to the compression of the lesions. In addition, mounting evidence shows that the disease can spread to the nasal cavity or the brain in recurrent or long-standing cases.

Although not pathognomonic, CT and MRI reports show that homogeneous or heterogeneous-attenuated enhancement is the most prominent feature of SFT. And it

can see a markedly enhancing mass showing similar characteristics to those of the internal carotid artery on postcontrast CT or MRI [7]. Most tumors could be significantly enhanced and a majority of cases showed heterogeneous enhancement, though unenhanced lamellar regions were also revealed. In some recurrent cases, most lesions may be not enhanced, except for cystic enhancement around the lesion. The present study found that the MRI signals of orbital SFT were relatively complex in practice, mostly medium or low signal on T1WI but could show arbitrary signal on T2WI, which may be related to the tumor composition. Orbital SFT showed a variable intensity on T2WI. Kurtosis in the histogram analysis on T2WI had a strong correlation with the amount of collagenous tissue[8].

Due to the uncertainty of lesion signal on MRI, it is necessary to distinguish between orbital hemorrhage and schwannoma. Moreover, the lesions in hemorrhage are not enhanced on MRI, and the composition of orbital schwannoma is complex. Secondary degenerative changes of the tumor, including cyst formation, hyalinization, hemorrhage, are relatively common and are suggested to contribute to extremely complex MRI findings of schwannomas. However, the schwannoma boundary is very clear. Other orbital tumors for differential consideration include histiocytomas, giant cell angiofibromas, and hemangiopericytomas [9].

SFT is originally confused for other lesions such as fibrous histiocytoma, giant angiofibroma, *etc.* It is thought to be a separate entity from hemangiopericytoma. Currently, the clinical diagnosis of SFT is getting more accurate with much greater frequency. The typical SFT phenotype is spindle-shaped tumor cells and the alternately arranged sparse and dense cells separated by eosinophilic collagen fiber bands and staghorn hemangiopericytoma-like vessels [10]. Immunohistochemical markers are fundamental for successful diagnosis. The diagnosis of SFT depends on the diffuse and intense positivity of CD34 staining through IHC. SFT is highly sensitive to CD34 but shows weak specificity. Although Bcl-2 expression is extremely high in SFT, it is negative in most malignant mesotheliomas. In this view, integrating these two immunohistochemical markers would increase the diagnostic accuracy [11, 12]. In the

present study, the immunohistochemistry (CD34+, Bcl-2+) was consistent with most cases of orbital SFT in previous reports. But we found that Bcl-2 was negatively expressed in 2 cases at the same time. Furthermore, the immunohistochemical staining method using the STAT6 protein is key in the rapid detection of the NAB2-STAT6 gene fusion status in tumor cells, and it is highly sensitive and specific for SFT diagnosis. Mounting evidence indicates that the fusion of NAB2 and STAT6 genes can trigger the entry of cytoplasmic STAT6 protein into the nucleus such that the nucleus strongly expresses the STAT6 protein. STAT6 also has a great auxiliary effect for the accurate distinction of SFT in morphologically similar tumors [13]. Therefore, the combined application of vimentin, STAT6, CD34, and other markers may guide the accurate SFT diagnosis.

The Ki-67 Labelling index is very low, orbital solitary fibrous tumors routinely exhibit a benign course. But malignant forms with an increased propensity for local recurrence have also been reported [12]. There is evidence on the correlation of Ki67 protein (pKi67) expression with the proliferative activity of intrinsic cell populations in malignant tumors, permitting its application as a marker of tumor aggressiveness [14]. Owing to the high expression rate in orbital SFT, and contributes to the development and epithelial-mesenchymal transition and metastasis in cancer, vimentin much focus must be diverted to explore the recurrence or metastasis of this tumor. Vimentin, a key component of the cytoskeleton, plays critical biological functions at the cellular and organismal levels [15].

Owing to the rarity of the orbital SFT, limited studies have investigated the various treatment modalities. But as with many soft tissue tumors, the mainstay of treatment for orbital SFT is en bloc surgical resection with negative margins. The choice of surgical approach is related to the lesion location. Orbital division based on the anatomical location of the coordinate system of four quadrants is valuable. Usually, a lateral orbitotomy is administered for lesions located in the superomedial or inferomedial quadrant, behind the globe, or within the muscle cone. In patients with an unclear boundary of lesions, incomplete or no capsule, non-contact excision and thorough

rinsing of the operation area after extensive excision may reduce the recurrence rate of the lesion. If the initial excision is incomplete, the recurrent tumor tends to spread into surrounding tissues and bone, rendering a second excision much more difficult [9]. For recurrent cases, more extensive excision is required, and the margin should be examined if necessary.

Significantly, our examination of flow void-like intensity in preoperative T1WI demonstrated that 4 patients exhibited vessel-emptied signals corresponding to the abnormal arterial components within the tumor tissue. It was deduced that surgical resection in orbital SFT may be very dangerous. Nevertheless, to avoid accidental intraoperative hemorrhage, surgical resection should be performed carefully. If necessary, surgeons should consider embolization before commencing surgical resection.

Currently, there is little evidence on whether adjuvant chemotherapy and radiation therapy following complete surgical resection are beneficial, which limits their routine application [16,17]. In our cohort, there was no evidence of malignant transformation in recurrent cases, as such the subjects were not managed using radiotherapy or chemotherapy.

In the present investigation, the lesions grew more rapidly and invasive after recurrence. For the two patients with tumor recurrence, it is possible that the tumor has no capsule and is located above the orbit. The surgery scope is limited by factors such as the levator palpebral muscle and the trochlear nerve. Recently, a study showed the recurrence rate of transorbital approach operations was 83.3 %, and the recurrence rate of transfronto-orbital approach operations was 17.6 % [18]. The fairly high local recurrence rate underscores their aggressive potential and uncovers the importance of prospective recognition [19]. In the cohort of recurrent orbital hemangiopericytoma/SFT, the median time to recurrence was 4 years, underscoring the importance of careful continued follow-up [20].

CONCLUSION

The clinical manifestations of orbital SFT are diverse and not specific. The lesions also show uneven density. The radiological features are variable, few features are more consistent. Complete gross resection or more aggressive wide excision are preferred in most cases. In patients with an unclear boundary of lesions, incomplete or no capsule, non-contact excision and thorough rinsing of the operation area after extensive excision may reduce the recurrence rate of the lesion. Delineating SFT from histologic mimics requires nuclear staining of STAT6 as a diagnostic adjunct in conjunction with CD34 positivity. Although the Ki-67 Labelling index may be extremely low, malignant forms with an increased propensity for local recurrence have been reported.

ARTICLE HIGHLIGHTS

Research background

Solitary fibrous tumor (SFT) is predominant within the pleura but very rare in orbit , which is why the diagnosis of orbital SFT poses challenges in clinical practice.

Research motivation

Unspecific symptoms and a wide range of clinical manifestations can significantly hamper the establishment of a definitive diagnosis and treatment.

Research objectives

This study aimed to retrospectively explore the clinical and imaging characteristics, treatment, outcomes of a series of patients with orbital solitary fibrous tumor.

Research methods

This retrospective analysis of the patients diagnosed with a histopathologic orbital SFT treated at a single institution. All data on demographics, clinical characteristics, imaging, treatment, postoperative HPE and IHC, and prognosis were collected.

Research results

In total, 13 patients were enrolled, 7 (53.8%) of whom were grouped in the superomedial quadrant of the orbit. Notably, 12(92.3%) patients showed significant enhancement, whereas with patchy no enhancement lesions in the tumor. IHC analysis demonstrated that the tumor cells were immunoreactive for CD34, CD99, STAT-6, and Vimentin in all patients. The lesions showed Ki-67 positivity <5% in 1 (7.7) patient, 5%-10% in 10 (76.9%) patients, >10% in 2 (15.4%) patients. Two (15.4%) patients exhibited tumor recurrence.

Research conclusions

The clinical manifestations and radiologic characteristics of orbital SFT are diverse and not specific. The accuracy of diagnosis and treatment require detailed radiological and HPE/IHC evaluation.

Research perspectives

According to the comprehensive analysis of clinical data, the clinical symptoms, therapeutic efficacy, and prognosis of orbital SFT were observed.

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