Rare Occurrence of an Intraocular Choroidal Solitary Fibrous Tumor/Hemangiopericytoma

Lorenzo Rinaldo^a Sarah Chao Ying Xu^a Scott D. Eggers^c Diva R. Salomão^{b, d}
John J. Chen^{b, c} Aditya Raghunathan^d

Departments of ^aNeurosurgery, ^bOphthalmology, ^cNeurology and ^dLaboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Established Facts

- Already known fact 1: Intraocular solitary fibrous tumor (SFT) and hemangiopericytoma (HPC) are very rare.
- Already known fact 2: SFT and HPC are now considered part of the same tumor entity, characterized by the *NAB2-STAT6* fusion gene.

Novel Insights

- New information 1: SFT/HPC shows nuclear STAT6 expression by immunohistochemistry, consistent with the *NAB2-STAT6* fusion.
- New information 2: The STAT6 immunostain helps distinguish SFT/HPC from other intraocular spindle cell tumors, particularly melanoma.

Keywords

Intraocular tumor · Choroidal lesion · Solitary fibrous tumor · Hemangiopericytoma · *NAB2-STAT6*

Abstract

Purpose: Tumors previously diagnosed as solitary fibrous tumors (SFT) and hemangiopericytomas (HPC) are characterized by the *NAB2-STAT6* fusion gene, leading to nuclear STAT6 expression, and are now considered part of one SFT/HPC tumor entity by the 2016 World Health Organization Classification of Tumors of the Central Nervous System. We

present the first primary choroidal SFT/HPC with the diagnosis confirmed by STAT6 expression. **Procedures:** A 51-year-old man underwent enucleation for a choroidal mass, which revealed a spindle cell neoplasm involving the optic nerve, without extrascleral extension. Immunohistochemical stains for S-100, melan-A, tyrosinase, and HMB45 were all negative; however, detection of monosomy 3 by FISH favored a choroidal spindle cell melanoma. Four years later, he presented

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with hepatic metastases of a spindle cell tumor, and a year later with an epithelioid malignancy involving the calvarium.

Results: The calvarial tumor showed nuclear STAT6 immunoreactivity, supporting the diagnosis of SFT/HPC. Retrospectively, the choroidal and hepatic masses were also found to demonstrate nuclear STAT6 expression, supporting the diagnosis of a primary choroidal SFT/HPC with metachronous metastases to the liver and calvarium. **Conclusions:** This case highlights the significance of considering SFT/HPC in the diagnosis of intraocular spindle cell tumors and the importance of STAT6 immunohistochemistry in the evaluation of such tumors.

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Introduction

Solitary fibrous tumor (SFT) is an uncommon mesenchymal neoplasm [1]. While previously thought to be an entity separate from hemangiopericytoma (HPC), recent studies have shown that both tumors express a fusion gene consisting of the transcriptional repressor NGFI-A Binding Protein 2 (*NAB2*) and the transcriptional activator Signal Transducer and Activator of Transcription 6 (*STAT6*; *NAB2-STAT6*) [2–4], supporting a common pathophysiologic mechanism between these previously distinct pathologic entities. The 2016 World Health Organization Classification of Tumors of the Central Nervous System considers SFT and HPC to encompass a histologic spectrum of the same tumor, now designated as SFT/HPC. The STAT6 immunohistochemical stain is a highly specific surrogate for the presence of the *NAB2-STAT6* fusion [3, 5], and multiple studies have demonstrated 100% specificity for STAT6 nuclear expression among SFT/HPCs arising in meningeal and nonmeningeal locations [6–8].

While SFTs were first characterized as tumors of the pleural cavity [9], SFTs and HPCs have since been observed throughout the body, including orbital, intraperitoneal, and intracranial compartments [10–13]. Intraocular SFT/HPC is rare, with only 4 cases of intraocular tumors diagnosed as either SFT or HPC having been reported in the literature [14–17]. Herein, we describe the case of a patient with a tumor occurring in the choroid, which was initially favored to be a spindle cell melanoma and was retrospectively identified as an SFT/HPC after the patient had developed delayed and metachronous metastases to the liver and calvarium.

Case Report

Clinical Summary

A 51-year-old man presented for a routine ophthalmic examination and was found to have a choroidal lesion adjacent to the optic disc. He had a history of testicular seminoma diagnosed 10 years previously and treated with orchiectomy and radiation therapy. On examination, his best corrected visual acuity was 20/20 on the right eye (OD) and 20/20-1 on the left (OS). There was no afferent pupillary defect. Intraocular pressures measured 17 mm Hg OD and 19 mm Hg OS. Dilated fundus examination showed a 2- to 3-fold disc diameter, yellow, elevated choroidal mass adjacent to the optic disc with associated inferonasal disc edema (Fig. 1a). There was adjacent choroidal atrophy, which had been noted on a routine examination 6 years prior. Visual fields showed a small superotemporal defect in the left eye. B-scan ultrasonography depicted an elevated mass of $4.9 \times 4.6 \times 2.6$ mm with medium-high to high reflectivity and a small area of probable calcification (Fig. 1b). The lesion was without extrascleral extension. Magnetic resonance imaging (MRI) of the orbit showed the choroidal mass to be adjacent to the left optic nerve without frank extension along the optic nerve (Fig. 1c, d). Systemic evaluation for an infectious, inflammatory, or neoplastic etiology was unrevealing. The lesion was favored to be a unifocal choroidal granuloma and was considered less likely to be a metastasis. Melanoma was thought to be unlikely because of the high reflectivity on ultrasound. Positron emission tomographic scan at the time did not reveal any hyperintensity in the intraocular mass nor were any additional systemic hypermetabolic lesions identified.

He underwent empiric treatment with intravitreal bevacizumab followed by photodynamic therapy without improvement. He then underwent pars plana vitrectomy with biopsy, which showed a minute fragment of fibrous tissue with pigmented choroidal cells but did not show identifiable neoplastic cells. The mass continued to grow, and he underwent a second biopsy a year later, which showed rare spindle cells. With progressively worsening vision and the concern for a malignancy, the decision was made for enucleation of the left eye. Given the lack of extrascleral extension, it was decided to forgo adjuvant therapy, and the patient was subsequently managed with observation alone.

The patient had an unremarkable clinical recovery following this surgery. Four years subsequently, he presented to the emergency department with renal colic. Abdominal MRI at this time demonstrated parapelvic and cortical renal cysts, including a small hemorrhagic cyst, but did not reveal any hepatic masses. A follow-up abdominal MRI 6 months later revealed 2 T2-hyperintense hepatic masses (Fig. 2a). Ultrasound-guided, fine-needle aspiration biopsies were negative for malignancy, and the lesions were managed as expected. The masses continued to grow over the next few months, prompting a needle biopsy. He was then treated with stereotactic body radiation therapy and hepatic wedge resection with intraoperative radiofrequency ablation.

One year later, the patient presented to the emergency department with progressive left-sided weakness and sensory loss. He was noted to have a firm, immobile, subcutaneous mass underlying the right parietal scalp, which he attributed to remote minor trauma. MRI of the head demonstrated a 6.7-cm right parietal transcalvarial mass with extracranial, intracranial/extra-axial, and intracranial/intra-axial components, showing heterogeneous post-contrast enhancement and magnetic resonance venography-

Fig. 1. Fundal photograph (a) demonstrating an elevated yellow choroidal lesion adjacent to the optic nerve and an area of choroidal atrophy. It measured $2.6 \times 4.9 \times 4.6$ mm on B-scan ultrasound (b) with medium-high to high reflectivity. Axial MRI image of the orbit with contrast also demonstrates the left choroidal lesion with no extension along the optic nerve (c, d; white arrow).

confirmed occlusion of the superior sagittal sinus (Fig. 2c). He underwent a biparietal craniotomy with extensive resection of the hemorrhagic, encapsulated-appearing intra- and extracranial mass with minimal residual tumor deliberately left adjacent to the motor cortex to minimize the risk of permanent neurologic deficits. Postoperatively, the patient awoke with bilateral supplementary motor area syndrome with predominant lower extremity weakness. This showed gradual amelioration, and he was discharged to inpatient rehabilitation where he continued to recover neurologically.

A follow-up MRI performed 6 months following neurological surgery demonstrated progression of the residual parietal tumor. In addition, abdominal MRIs performed at this time also revealed innumerable hepatic lesions (Fig. 2b). The patient received salvage therapy, including Gamma Knife radiosurgery, targeting the brain lesion and sunitinib protein tyrosine kinase inhibitor therapy. The patient died 8 years after the initial identification of the intraocular mass and 9 months following the last surgical procedure. Postmortem examination was not performed due to lack of consent.

Histologic and Immunohistochemical Staining

The formalin-fixed, paraffin-embedded (FFPE) tissue sections were stained with hematoxylin and eosin for routine histologic review. Immunohistochemical staining was performed on FFPE sections using antibodies directed against CD31 (clone JC/70A; Dako; 1:350), CD34 (clone QBEnd/10; Novocastra; 1:50), CD56 (clone

123C3; Dako; 1:100), c-Kit (clone YR145; Cell Marque; 1:200), chromogranin (clone LK2H10; Biocare; 1:100), DOG-1 (clone K9; Novocastra; 1:100), HMB45 (clone HMB45; Dako; 1:400), melan-A (clone A103; Dako; 1:50), S-100 protein (polyclonal; Dako; 1:4,000), STAT6 (polyclonal, S-20; Santa Cruz Biotechnology; 1:100), synaptophysin (clone 27G12; Novocastra; 1:50), tyrosinase (clone T311; Novocastra; 1:500), and vimentin (clone v9; Dako; 1:500).

Fluorescence in situ Hybridization

Three consecutive FFPE tissue sections were cut at $5 \mu\text{m}$ and mounted on positively charged glass slides. Target areas were identified on a reference hematoxylin-and-eosin-stained slide by a pathologist, and target areas were etched with a diamond-tipped etcher on the back of the unstained slides. The assay was performed using a commercially available chromosome 3 centromere probe (D3Z1; Abbott Molecular) and a laboratory-developed *BCL6* (3q27.2) probe. Following hybridization of the probe set to the appropriate target areas, two technologists analyzed 100 interphase nuclei each (for 200 cells in total). A threshold of over 23% nuclei showing only one signal per probe was used as an indicator of monosomy of chromosome 3.

Pathological Findings

The enucleation revealed a fibrotic, hemorrhagic mass centered in the choroid with invasion into the optic nerve and sclera

Fig. 2. **a** Gadolinium-enhanced MRI of the abdomen demonstrates 3 discrete hepatic metastases (white arrows). **b** A subsequent scan after hepatic wedge resection and radiofrequency ablation demonstrates progression with innumerable lesions. **c** A year later, preoperative gadolinium-enhanced, T1-weighted coronal MRI demonstrates a predominantly right-sided biparietal lesion with extracranial and intracranial components.

without extrascleral extension (Fig. 3a). It was composed of short fascicles of malignant cells with elongated and spindle-shaped nuclei, with areas showing pericellular collagen deposition (Fig. 3b). Multiple scattered mitotic figures were present (Fig. 3c, arrows), and there was no necrosis. On immunohistochemical staining, the neoplastic cells were positive for vimentin, negative for CD34, as well as negative for S-100, melan-A, tyrosinase, and HMB45. Ultrastructural evaluation by electron microscopy could not be performed due to suboptimal tissue fixation. On fluorescence in situ hybridization, 140 of 200 (70%) tumor nuclei demonstrated one D3Z1 and one BCL6 signal, indicative of monosomy of chromosome 3. Although S-100, melan-A, tyrosinase, and HMB45 would have been expected to show expression in a choroidal melanocytic tumor [18–20], the malignant spindle cell neoplasm was favored to represent a spindle cell melanoma [5, 21].

The needle biopsy from the hepatic mass, performed 4 years later, revealed a spindle cell neoplasm (Fig. 3e). On immunohistochemical staining, these spindle cells showed focal minimal staining for CD34 and were negative for S-100, melan-A, tyrosinase, c-Kit, DOG-1, and CD31.

Resection of the calvarial lesion was performed approximately 1 year later and demonstrated sheets of predominantly epithelioid cells with high nucleus-to-cytoplasmic ratios and focal regions also showing cells with vaguely spindle-shaped nuclei (Fig. 3g). The tumor showed brisk mitotic activity and focal areas of necrosis. On

immunohistochemical staining, these cells were diffusely positive for STAT6 (Fig. 3h); they were also positive for the neuroendocrine markers synaptophysin (diffusely), CD56 (focally), and chromogranin (very focally), and were negative for CD34. As STAT6 immunoreactivity is a well-established surrogate for the presence of the *NAB2-STAT6* fusion [22], this finding supported the diagnosis of SFT/HPC. At this time, STAT6 immunostains were also performed on the original choroidal mass and the hepatic mass, both of which showed strong nuclear STAT6 expression (Fig. 3d and f, respectively). The original diagnosis of the choroidal mass was amended to SFT/HPC, and the hepatic mass was also diagnosed as SFT/HPC. Since the hepatic and calvarial masses had been demonstrated to have developed after the choroidal mass, the findings support these masses to represent metachronous metastases of the choroidal SFT/HPC.

Discussion

To our knowledge, this represents the fifth reported case to date of an SFT or an HPC occurring within the choroid and the first case in this location with demonstration of STAT6 immunoreactivity. The clinical course

Fig. 3. On histopathological evaluation, the choroidal mass invades into but not through the sclera and involves the optic nerve (**a**). It is composed of short fascicles of malignant cells with elongated, spindle-shaped nuclei, focally with pericellular collagen deposition (**b**). Multiple mitotic figures are identified (**c**, arrows). This tumor was retrospectively demonstrated to show STAT6 nuclear expression (**d**). The liver is involved by a malignant spindle cell neoplasm (**e**), which also retrospectively demonstrated STAT6 nuclear expression (**f**). The calvarial mass is composed of malignant epithelioid cells, showing brisk mitotic activity (**g**) and also shows nuclear expression of STAT6 (**h**). These overall findings support the diagnosis of a choroidal SFT/HPC with metachronous metastases to the liver and calvarium.

of our patient highlights the potential for SFT/HPCs to metastasize in a delayed but highly aggressive fashion. It also highlights the potential for choroidal SFT/HPCs to be misdiagnosed as an amelanotic or spindle cell melanoma.

Including our case with others previously reported, choroidal SFT/HPC tumors occur in a wide age range and

with relatively equal frequency in both sexes (3 female and 2 male patients) [14–17]. In 3 of the cases, patients underwent enucleation, 2 after evidence of local invasion without distant metastasis [14, 17] and the other over concern that the lesion represented a malignant melanoma [15]. In one other case, the patient was treated with xenon arc photocoagulation to reduce subretinal fluid,

and the tumor remained stationary until her death, 8 years later, from complications of alcoholic cirrhosis [16]. In our case, the primary ocular SFT/HPC was relatively bland-appearing when compared to the liver and meningeal metastases. Because of the absence of extrascleral invasion, the patient did not receive adjuvant chemo- or radiotherapy after enucleation.

Pathological evaluation of the original ocular lesion in our case was initially thought to represent a choroidal melanoma. In retrospect, the presence of collagen surrounding the tumor cells should have raised a question in the original diagnosis [23]. While SFT/HPCs have only rarely been reported in this location, the frequency with which intraocular SFT/HPCs are erroneously diagnosed as melanomas is unknown, and STAT6 testing may be of benefit in cases with unusual findings or equivocal immunoprofile. In our case, for example, B-scan ultrasonography revealed a lesion with medium-high to high reflectivity in contrast to the usual low-to-medium internal reflectivity of choroidal melanomas [24]. In addition, the choroidal tumor cells did not express markers of melanocytic differentiation on immunohistochemical staining [18–20]. We could not find any study within the literature evaluating STAT6 immunohistochemistry in uveal melanomas, or indeed any other intraocular melanomas. Thus, consideration of SFT/HPC in the differential diagnosis of spindle intraocular lesions and subsequent testing for STAT6 immunoreactivity may be of benefit in cases with unusual features for a diagnosis of melanoma such as ours.

While the rarity of SFT/HPCs has limited the study of adjuvant therapies, a number of small case series have observed prolonged tumor-free survival when radiation is combined with surgical resection [25–27], suggesting that adjuvant therapy may be of benefit after gross total resection in certain patients. The role of chemotherapy is even less defined, particularly as it has typically been reserved for salvage therapy in progressive SFT no longer amenable to resection. Nevertheless, a number of regimens have demonstrated efficacy in halting progression [28–30], allowing for a possible role for adjuvant chemotherapy. To aid in patient selection for adjuvant therapy, prognostic features associated with SFT recurrence – independent of site of origin – include tumor size, hypercellularity, mitoses, and necrosis [27, 31, 32]. Notwithstanding, our patient had a subcentimeter primary tumor that exhibited relatively few mitotic figures and had no evidence of focal necrosis but, nevertheless, experienced multiple recurrences, reinforcing the highly unpredictable nature of these lesions.

We report only the fifth known case of a choroidal SFT/HPC. This case highlights how an SFT/HPC can be mistaken for an amelanotic, spindle cell melanoma, discussing the differences. In addition, we demonstrate nuclear STAT6 expression for the first time in an intraocular SFT/HPC, suggesting the presence of the *NAB2-STAT6* fusion gene in tumors from this region [22] and supporting the addition of STAT6 immunohistochemistry while evaluating intraocular tumors in certain cases. This case suggests that SFT/HPC be considered in the differential diagnosis for choroidal spindle cell lesions and, given the highly aggressive clinical course in our case, suggests increased surveillance in such cases.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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