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Case report

Optic nerve head reactive retinal astrocytic tumor treated with photodynamic therapy

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ABSTRACT

Purpose: To describe the unusual presentation and the treatment course of a case of bilateral optic nerve head reactive retinal astrocytic tumor (RRAT).

Observations: A 29 year-old woman with bilateral optic disc masses presented with declining vision refractory to anti-vascular endothelial growth factor (VEGF) injections. After total loss of vision in her left eye, diagnostic enucleation and histopathology was consistent with RRAT. Staged photodynamic therapy (PDT) treatments over a period of four months in the better seeing eye resulted in stabilization of vision, improvement in intraretinal and subretinal fluid, and shrinkage of the optic disc mass.

Conclusions: In this unusual case of bilateral vision-threatening optic nerve head RRAT that were refractory to multiple therapies including anti-VEGF injections, PDT demonstrated safety and efficacy. Diagnostic work-up included whole exome sequencing (WES) that was negative for mutations in genes related to von-Hippel-Lindau (VHL), neurofibromatosis, tuberous sclerosis, and hypoxia-inducible factor (HIF)-2α.

1. Introduction

Reactive retinal astrocytic tumors (RRAT), also known as vasoproliferative tumors of the retina (VPTR), were originally called "presumed acquired retinal hemangiomas" by Shields et al.[1] Subsequently, Shields et al. renamed these tumors "vasoproliferative retinal tumors" based on histopathology demonstrating that these lesions were not true hemangiomas.[2] They differentiated primary tumors (approximately 75% of cases) and those secondary to ocular diseases such as uveitis (approximately 25% of cases). The majority of these tumors were located in the retinal periphery, most often in the inferior, temporal, or inferotemporal regions, with uncommon bilateral involvement. While these tumors have rarely been reported at the optic disc, they were usually unilateral.[2,3] RRAT typically appear as pink-to-yellow lesions, and are associated with retinal exudates and edema, which may lead to visual complaints including photopsias.[4,5]

More recently, Poole Perry et al.[6] argued for a change in the nomenclature based on the histopathology of four enucleated eyes demonstrating glial fibrillary acidic protein (GFAP)-positive spindle cells with a relatively sparse microvasculature, suggesting a predominance of reactive astrocytes. As a result, they proposed the term "reactive retinal astrocytic tumor," the name utilized in the current report. Their naming suggestion has been supported by subsequent gene expression profiling.[7]

We discuss an unusual case of a young woman presenting with progressive bilateral vision loss and bilateral optic nerve head masses. Whole exome sequencing (WES) was negative for mutations in von Hippel-Lindau (VHL) and hypoxia-inducible factor (HIF)-2α. Histopathology was consistent with RRAT. The remaining eye was treated successfully with photodynamic therapy (PDT) after progression to recalcitrant macular exudation despite high-frequency intravitreal anti-vascular endothelial growth factor (VEGF) and intravitreal steroid therapy.

1.1. Case report

A 29-year-old woman with declining vision in her left eye was initially seen by us in 2011 with a 15-year history of headaches associated with bilateral optic nerve head swelling and possible masses (Fig. 1). Her visual acuity was 20/20 OD and 20/150 OS. At the age of 14, she had been diagnosed with pseudotumor cerebri, and had undergone an extensive negative work-up and a left-sided optic nerve sheath fenestration without improvement.

Our initial working diagnosis was VHL syndrome. However, WES

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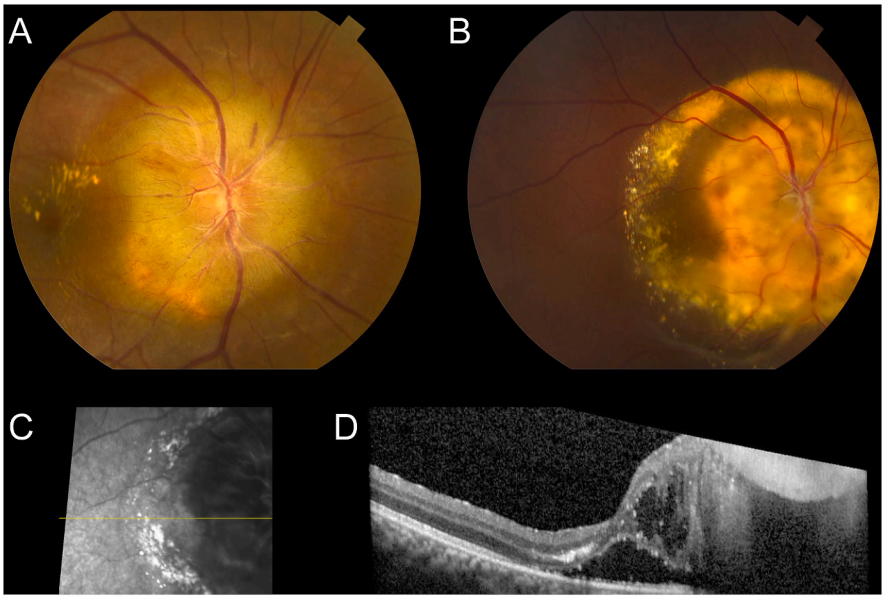

Fig. 1. Imaging of the patient's right eye. Color fundus photo of the right optic nerve head **(A)** at initial presentation in 2011 (patient was 29 years-old). Color fundus photo of right eye **(B)** in early 2017. Infrared **(C)** image of right eye with yellow line indicating location of spectral-domain optical coherence tomography B-scan **(D)** in 2014. Note the intraretinal and subretinal fluid nasal to the fovea in the B-scan. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

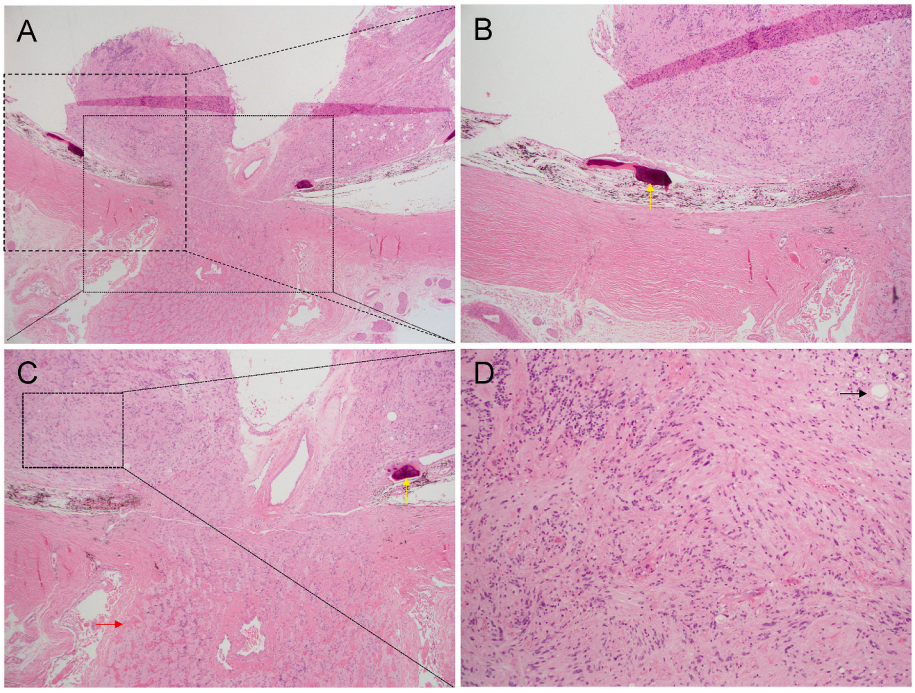

Fig. 2. Histopathology of the left optic nerve head tumor with hematoxylin and eosin staining. Note retinal pigment epithelium (RPE) osseous metaplasia (yellow arrows) **(A–C)**. Black boxes demarcate borders of enlarged images in **(B** and **C)**. There is no invasion of the tumor into the optic nerve (red arrow) **(C)**. Black box **(C)** shows area enlarged in **(D)**, which demonstrates spindle proliferation of astrocytes and scant vessels (black arrow). This tumor was positive for S100 and GFAP (not shown), consistent with astrocytic proliferation. Rosenthal fibers were not present. Magnification = 10× **(A)**, 40x **(B** and **C)**, and 100x **(D)**. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

was negative for mutations in genes related to VHL, neurofibromatosis, and tuberous sclerosis. While the bilaterality and appearance of her lesions were similar to those observed in HIF-2α paraganglioma-somatostatinoma-polycythemia syndrome,[8] WES was also negative for a HIF-2α genetic mutation.

Over the next several years, the patient moved between several academic institutions, receiving monthly and, most recently, biweekly alternating bevacizumab and aflibercept intravitreal injections, as well as bimonthly Ozurdex injections. Only a small initial response was seen in the better eye. The lesions progressed to involve the papillomacular bundle. In early 2017, her vision had declined to 20/400 OD and no light-perception OS (Fig. 1). We performed a diagnostic enucleation of her left eye, with resulting pathology consistent with RRAT (Fig. 2). Genetic profiling of the mass did not show somatic HIF-2α mutation.

In late 2017, the patient was offered her first treatment of PDT, targeting an area nasal to the optic nerve with a resulting best corrected visual acuity 20/200 one month following treatment (Fig. 3). She subsequently received two more treatments to tissue surrounding the optic nerve superiorly, temporally, and inferiorly. This resulted in symptomatic improvement in vision and stabilization at 20/150, along with improvement of intra- and subretinal fluid and shrinkage of the tumor. Although the patient received several intravitreal anti-VEGF injections (aflibercept and bevacizumab) in the months following her last PDT treatment, the lesion has continued to decrease in size over the following two years without additional interventions.

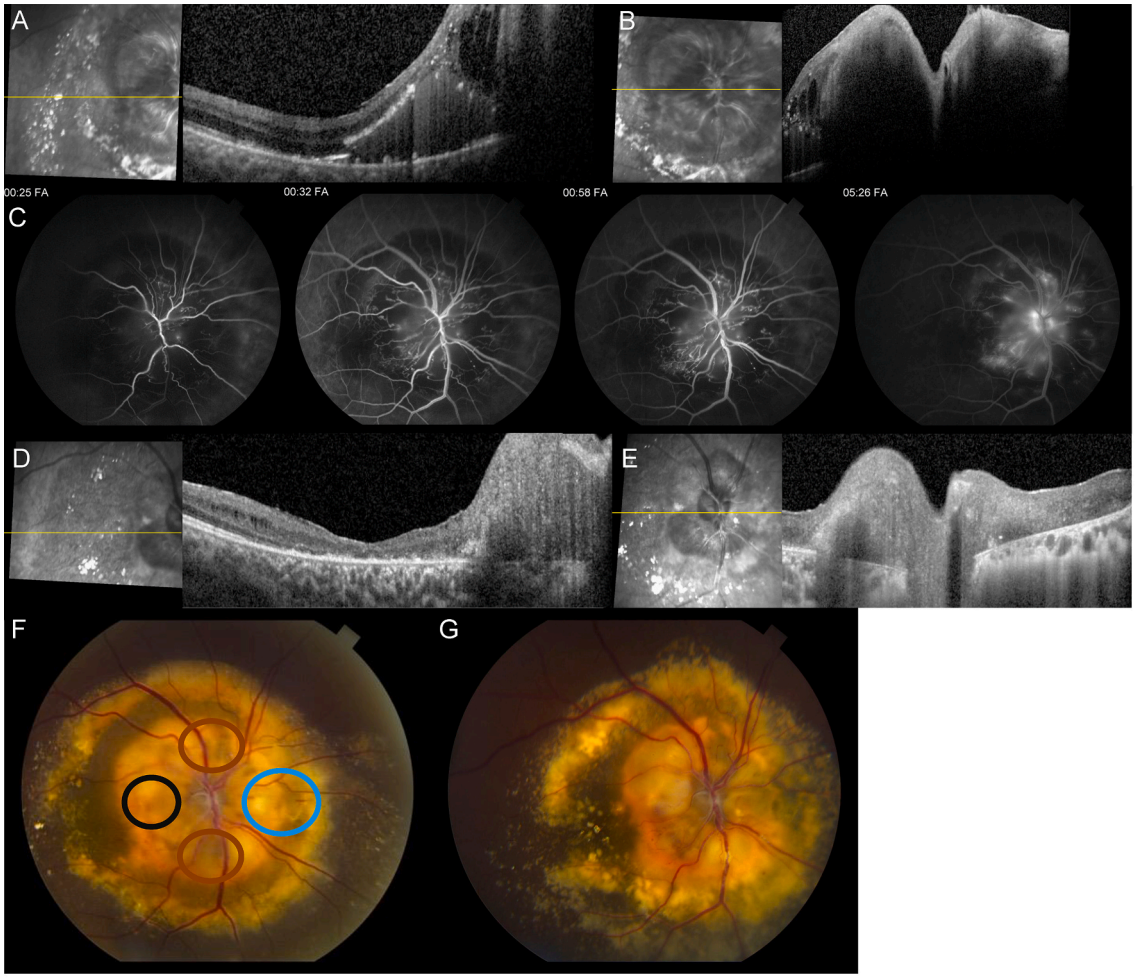

Fig. 3. Clinical imaging before and after photodynamic therapy (PDT). Infrared (IR) fundus image of the right macula **(A)** and optic nerve **(B)** prior to PDT treatment. Yellow lines mark locations of associated optical coherence tomography (OCT) B-scans. Note substantial subretinal and intraretinal fluid in B-scan associated with **(A)** as well as the size of the optic nerve mass in B-scan associated with **(B)**. Fluorescein angiography **(C)** prior to PDT treatment demonstrating areas of capillary drop-out as well as scattered telangiectatic vessels, which leak in late frames. IR and OCT B-scans of the macula **(D)** and optic nerve **(E)** depict significant improvement in edema twelve months after the last PDT session as well as significant improvement in size of the optic nerve mass. Color fundus photography pre- **(F)** and post-PDT **(G)** displaying slight apparent decrease in size of the lesion. The blue, green, and black circles approximately mark the sites of the first, second, and third PDT treatments respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2. Discussion

We present a young woman with bilateral optic nerve head tumors refractory to multiple interventions including frequent anti-VEGF injections. Her blind left eye was diagnostically enucleated, with immunohistochemistry positive for GFAP and S100 and histopathology consistent with RRAT. Right eye PDT was successful in stabilizing vision and shrinking the tumor.

There is controversy regarding the true nature of RRAT. Histopathology done by Poole Perry et al.[6] demonstrated a relative paucity of the microvasculature compared to previous reports.[2,5] This was also seen in our specimen. A change in the nomenclature from vasoproliferative tumor of the retina to the term "reactive retinal astrocytic tumor" has been suggested. Shields et al. have argued that the observed predominance of gliosis and relative lack of blood vessels is secondary to treatments including cryotherapy and multiple injections of anti-VEGF agents.[9] By the time advanced cases were enucleated, they postulated that the vascular components would have regressed. Countering that argument, genetic profiling of these lesions demonstrated upregulation of genes seen in reactive astrocytes despite a general lack of upregulation of vascular and angiogenesis-related genes.[7]

There are several entities in the differential diagnosis of similar lesions. The initial appearance of apparent papilledema suggested a diagnosis of pseudotumor cerebri, leading to an optic nerve sheath biopsy with fenestration. However, the early age of onset and bilateral nature of the masses in the current patient were suggestive of a genetic cause. A strong resemblance to lesions observed in HIF-2α paraganglioma-somatostatinoma-polycythemia syndrome was noted.[8] These somatic gain-of-function mutations in HIF-2α are associated with optic disc edema and fibrosis, bilateral dilated capillaries, and retinal exudates. Another potential diagnosis was bilateral hemangioblastomas associated with VHL syndrome, an entity also involving dysregulation of the HIF pathway. Classically, these tumors are found in young patients, who present with one or multiple tumors that can be bilateral and located anywhere in the retina.[10] In contrast, RRATs occur sporadically in older patients, are unilateral, and are most often found in the retinal periphery.[2] However, bilateral RRAT has been reported in the past (found in 4% of patients with primary RRAT, and 20% of patients with secondary RRAT).[2,3] In addition, there are indications of a possible genetic etiology of RRAT as bilateral lesions have been reported in a pair of 58 year-old monozygotic female twins.[11] While it is important to note that histopathology cannot definitively distinguish between RRAT and the ocular lesions observed in HIF-2α paraganglioma-somatostatinoma-polycythemia syndrome, the patient's

histopathology was reviewed by several ocular pathologists who believed it to be more consistent with RRAT. In addition, our patient did not have systemic mutations in either the HIF-2α or VHL genes, the optic nerve mass did not show HIF-2αsomatic mutations, and the patient did not present with evidence of a paraganglioma, a somatostatinoma, or polycythemia.

Another entity that was considered was retinal astrocytic hamartoma, which often presents bilaterally at the optic disc and is commonly associated with tuberous sclerosis complex.[12] While these lesions are typically considered benign and relatively stable, aggressive cases necessitating enucleation have been documented.[13] When these aggressive tumors are associated with tuberous sclerosis, they have been reported to occur adjacent to the optic disc with invasion of the optic nerve, but generally require enucleation early in childhood or adolescence and have histopathology characteristically demonstrating the presence of populations of giant cells resembling those seen in subependymal giant cell astrocytoma as well as significant necrosis, none of which were observed in the current case.[13] In cases of aggressive retinal astrocytic hamartoma not associated with tuberous sclerosis, enucleation may be required at an older age but the lesions are generally unilateral.[13] Overall given the histopathology and negative genetic testing for tuberous sclerosis and neurofibromatosis, retinal astrocytic hamartoma was considered lower on the differential diagnosis.

A variety of treatment modalities have been used for RRAT. These include cryopexy, anti-VEGF injections, and plaque radiotherapy, which have all demonstrated effectiveness in shrinking peripheral lesions as well as stabilizing or improving vision.[4,5,14] Success using PDT has also been reported in peripheral tumors.[15] In our case, years of anti-VEGF and steroid treatments failed to halt lesion growth and exudation, or improve visual acuity, but PDT resulted in resolution of fluid as well as tumor regression. Use of verteporfin in close proximity to the optic nerve (within 200 μm of the temporal edge of the optic disc) is specifically prohibited on the package labeling for fear of optic nerve vascular compromise and resulting vision loss.[16] However, PDT has been utilized at the optic nerve in other conditions without subsequent evidence of optic nerve damage.[17] In our case, to minimize this risk, staged treatments were guided by fluorescein angiography to tissue adjacent to the nerve.

In conclusion, we describe a unique presentation of bilateral optic disc RRAT refractory to steroids and anti-VEGF injections, where staged treatment with PDT was effective and safe.

Patient consent

The patient consented to publication of the case in writing.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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