

Rapid symptomatic and structural improvement of a retinal astrocytic hamartoma in response to anti-VEGF therapy: A case report

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ABSTRACT

Purpose: To describe a patient with bilateral peripapillary astrocytic hamartomas with exudation of subretinal fluid into the macula and loss of vision without evidence of choroidal neovascularization. The patient rapidly responded to intravitreal bevacizumab injections resulting in reduced subretinal fluid and clinical improvement. **Observation:** A 70-year-old female presented with worsening vision in her left eye due to subretinal fluid exudation from a peripapillary astrocytic hamartoma. The patient was treated with two doses of bevacizumab with rapid improvement in vision and resolution of subretinal fluid. Genetic testing was negative for common pathogenic variants for tuberous sclerosis and neurofibromatosis, which are highly associated with bilateral optic nerve and retinal astrocytic hamartomas.

Conclusion: Astrocytic hamartomas with exudation may be responsive to bevacizumab suggesting a dependence of these lesions on vascular endothelial growth factor (VEGF) independent of secondary choroidal neovascularization. Furthermore, this case describes a patient with bilateral astrocytic hamartomas without genetic or clinical confirmation of associated phakomatoses, such as tuberous sclerosis and neurofibromatosis.

1. Introduction

Retinal astrocytic hamartomas are glial cell tumors of the eye that are often pathologic consequences of phakomatoses, such as tuberous sclerosis (TSC).^{1,2} These lesions are frequently asymptomatic but when proximal to the macula or optic nerve lead to complications including exudative retinal detachment or choroidal neovascularization that reduce visual acuity.^{3–5} Medical treatment for symptomatic hamartomas included mTOR inhibitors such as sirolimus, while other studies have suggested the use of anti-VEGF biologics to limit complications from exudative choroidal neovascularization.^{4,6–9} Here, we demonstrate a patient with a symptomatic hamartoma due to accumulation of subretinal fluid without evidence of choroidal neovascularization that resolved rapidly in response to bevacizumab.

2. Case report

A 70-year-old woman with a history of hyperlipidemia, on atorvastatin, presented with blurry vision of the right eye (OD, 20/30) and unperturbed left eye (OS, 20/25). Her slit lamp exam was notable for bilateral (OU) nuclear sclerosing cataracts but was otherwise

unremarkable. Her fundus exam revealed peripapillary lesions with elevated margins and mulberry clusters of the optic disc OU with numerous exudates and calcified bodies OD (Fig. 1A). The patient was referred to genetics but was lost to follow-up for 8 years, at which point she presented reporting new distortions of her vision OS leading to reading difficulties.

Her visual acuity OS decreased (20/40) and her fundus exam demonstrated relative stability of lesion size but appearance of temporal exudates OS (Fig. 1B). Optical coherence tomography (OCT) imaging was remarkable for lesions with classic astrocytic hamartoma architecture derived from the retina nerve fiber layer (RNFL), such as “moth-eaten spots” and numerous calcifications with foveal subretinal and intraretinal fluid OS (Fig. 1C). This correlated with the enlarged blind spot OS demonstrated by automated visual field perimetry (Fig. 2). Fluorescein angiography and OCT-angiography demonstrated no choroidal neovascularization suggesting the subretinal fluid originated directly from the adjacent tumor (Fig. 3A and B).

While no choroidal neovascularization was documented in this case, we elected to trial bevacizumab injections since exudation from the tumor itself may be responsive to anti VEGF agents due to their anti-permeability effect.^{10,11} The patient responded with decreased

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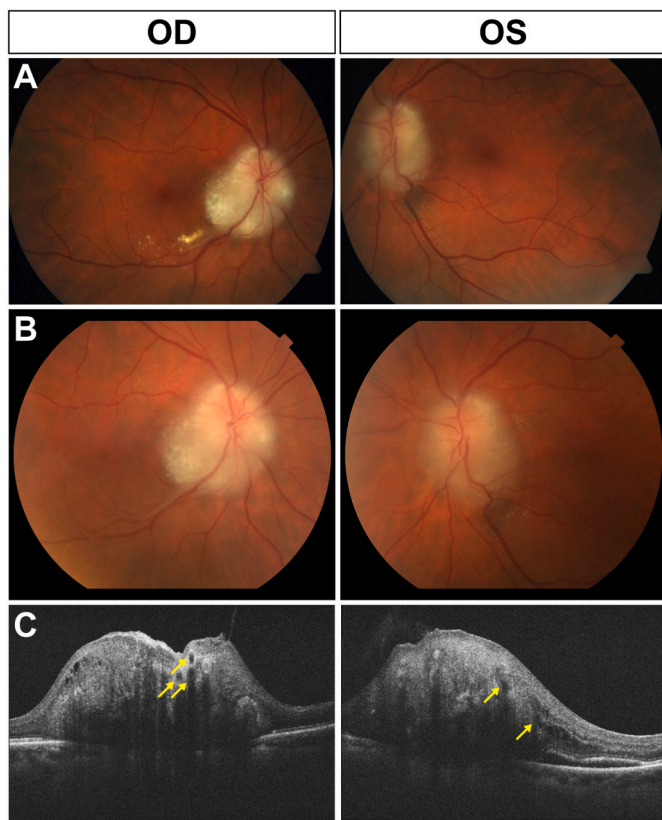


Fig. 1. (A) Fundus photos showing bilateral optic nerve mulberry cluster lesions with retinal calcifications upon original presentation and (B) follow-up 8 years later. (C) Optical coherence tomography of lesions OD and OS displaying optically empty spaces “moth-eaten spots” (yellow arrows), posterior shadowing, and derivation entirely from the RNFL. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

subretinal fluid and improved visual acuity OS following a single dose of bevacizumab which remained stable with 2 subsequent monthly injections (Fig. 4A and B). Furthermore, the lesion size appeared to decrease with collapse of “moth spots” noted in earlier OCT images (Fig. 4B,D), suggesting intratumoral reduction of fluid.

She was referred to medical genetics and received genetic testing including Invitae TSC, RASopathies, and Noonan spectrum disorder panels that were negative for the top 30 candidate genes including TSC1, TSC2, and NF1. Pedigree analysis, including her children, demonstrated no family history of phakomatoses. Furthermore, an extensive review of systems was performed that was negative for all systemic signs of putative genetic disease, such as seizures or café au lait macules, with the only notable positive being a history of skin rash, which was noted as rosacea.

3. Discussion

We present a case of bilateral retinal astrocytic hamartomas (RAH) in a patient currently without any genetic diagnoses who exhibited functional and anatomical improvement in response to anti-VEGF therapy. We would like to highlight that, although our patient did not have evidence of neovascularization, she responded rapidly with functional and structural improvement in response to bevacizumab.

Retinal astrocytic hamartomas are lesions arising from the RNFL containing “optically empty spaces” on OCT imaging, and are frequently asymptomatic.^{3,12} However, there have been documented cases of symptomatic hamartomas owing to accumulation of subretinal fluid (SRF), neovascular glaucoma, or development of retinal traction.^{3,4,13,14} Multiple studies have highlighted the putative importance of VEGF to these tumors due to the appearance of neovascularization and the decreased burden of the lesion with response to anti-VEGF therapies.^{9,15} Other treatment options for RAH-associated SRF includes photodynamic therapy (PDT) and sirolimus. However, given the peripapillary nature of the lesion, the risk of PDT was deemed too high. While oral mTOR inhibitors have been reported to successfully decrease RAH size and exudation, we decided to attempt local therapy to avoid potential systemic toxicities given that the patient’s symptoms were more likely a result of the SRF associated with the RAH and not the size of the lesion

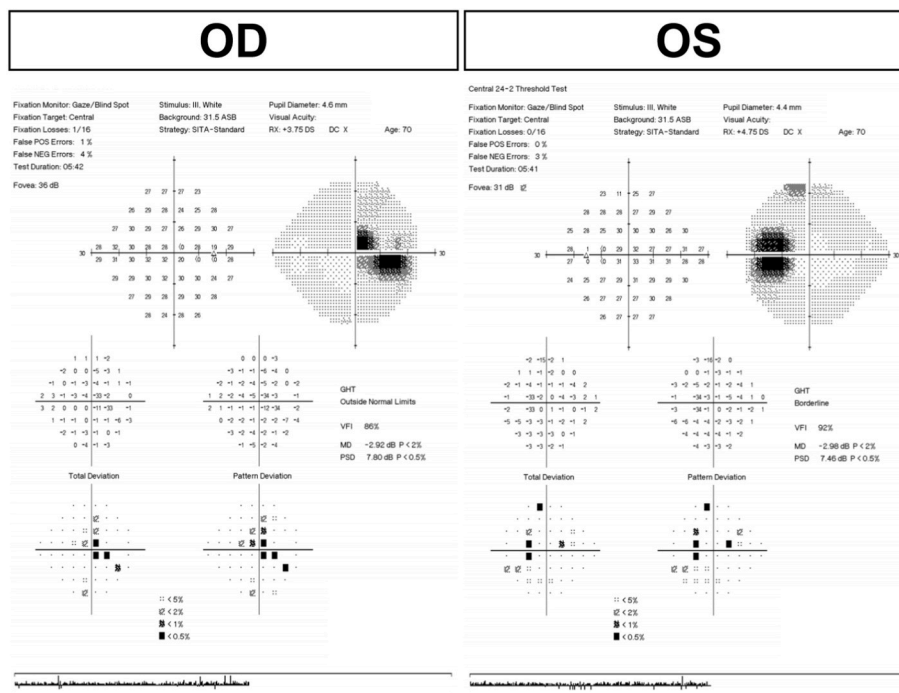


Fig. 2. Humphrey visual field (HVF) reports, 24-2 SITA-Standard obtained in 2021 showing bilateral enlarged blind spots.

itself.^{6,7,16}

Our study demonstrates the symptomatic visual distortions secondary to SRF accumulation directly from a hamartoma resolved in response to anti-VEGF therapeutics. There have been documented cases of spontaneous SRF resolution in hamartomas without intervention.¹⁷ However, the timing of the resolution in close approximation to bevacizumab delivery combined with the continued reduction in size of the tumor with repeated doses makes this less likely. This supports the notion that astrocytic hamartomas may be intrinsically associated with VEGF signaling for their structure and exudative properties independent of their ability to promote neovascularization. More broadly, this suggests that hamartomas can exhibit clinical improvement in response to anti-VEGF therapy without requiring any evidence of pre-retinal or choroidal neovascularization.

Bilateral retinal hamartomas are often a symptom of underlying genetic disorders, such as TSC or neurofibromatosis (NF).^{1-3,18-20} In fact, nearly all previous case reports describing a response of astrocytic hamartomas to anti-VEGF therapy occurred in patients with confirmed diagnosis of TSC.^{8,9,15,21,22} While bilateral or multifocal retinal astrocytic hamartomas are often indicative of underlying systemic genetic disease, such as TSC or NF1, the patient in this case report has yet to obtain a definitive genetic or clinical diagnosis.^{1-3,18-20} Both TSC and NF1 are autosomal dominant diseases but nearly two-thirds of TSC cases and half of NF1 cases are thought to be sporadic.^{23,24} Interestingly, 10 to 15% of TSC patients receive negative results on conventional genetic testing, such as the Invitae panels used in this report, despite still meeting clinical TSC diagnosis criteria.²⁵ This could be explained by TSC variants that are missing in conventional genetic panels or potential somatic mosaicism, which has been reported to occur in up to 3% of patients diagnosed with definitive TSC.^{24,26} In a retrospective

consecutive case series, TSC patients with ocular findings such as hamartomas were shown to frequently harbor a history of epilepsy, cortical tubers, and dermatologic findings such as hypomelanotic macules.²⁷ Similarly, diagnosis of NF1 is often made clinically based on presence of cutaneous findings of café au lait macules, inguinal or axillary freckling, or neurofibromas, or ocular findings of Lisch nodules and does not require a genetic diagnosis.²³ However, this patient has no documented history of seizures, her most recent brain MRI exhibited no gross anatomical pathology, no anterior segment exam findings other than cataracts, and no dermatologic diagnoses other than rosacea. NF2, which was not included in the genetic screening panel for this patient, has also been shown to lead to combined hamartomas and retinal astrocytic hamartomas.^{28,29} While this patient does not harbor the predominant clinical manifestations of NF2, such as bilateral acoustic schwannomas, she is currently being followed up for NF2 diagnostic testing.

Elucidating the potential underlying genetic disease of this patient is not only beneficial to optimize her future medical care, but can also delineate putative pathophysiologic mechanisms of RAH. Currently, case reports describing a response of RAH to anti-VEGF therapy have occurred exclusively in patients with a TSC diagnosis, and therefore have led to hypotheses regarding TSC regulation of the hypoxia inducible factor (HIF)-VEGF axis as a central dependence of this tumor.²² This case suggests there could be a dependence of RAH on VEGF independent of TSC mutation status. Furthermore, parsing the potential underlying genetic disorder is important to eventually determine whether genetic background impacts the response of retinal astrocytic hamartomas to anti-VEGF therapeutics.

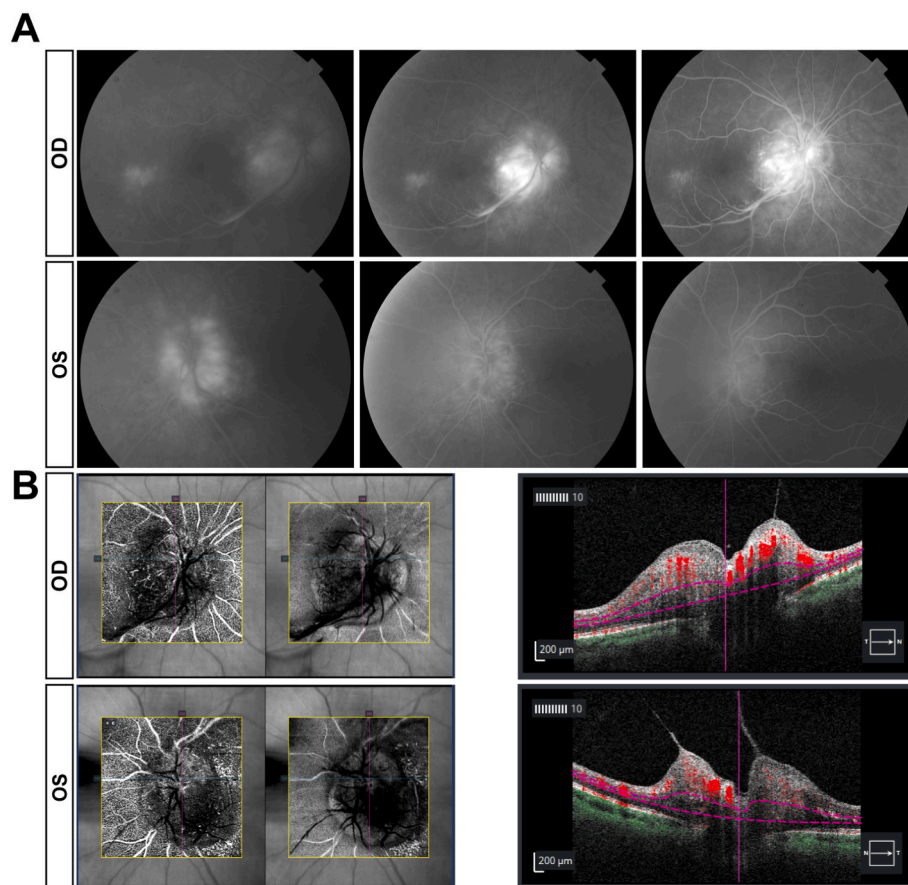


Fig. 3. (A) Fluorescein angiography (FA) showing staining without clear leakage or sign of choroidal neovascularization. (B) Optical coherence tomography angiography (OCT-A) demonstrates the lack of choroidal neovascularization proximal or distal to the astrocytic hamartomas OD and OS.

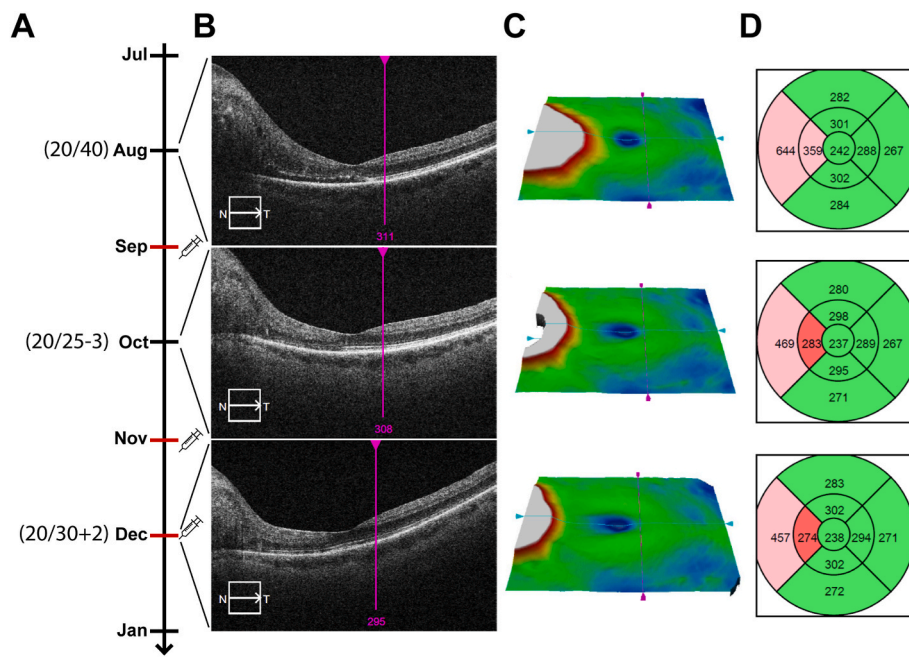


Fig. 4. (A) Timeline of the treatment of the astrocytic hamartoma OS with bevacizumab injections noted by a syringe schematic and highlighting of the month of injection in red. (B) Response of the lesions to injections was tracked with optical coherence tomography (OCT) of the peripapillary RNFL and (C–D) OCT thickness map demonstrating rapid and stable reduction in subretinal and intraretinal fluid and decreased size of the lesion. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Conclusions

Symptomatic astrocytic retinal hamartomas with associated subretinal fluid may respond to anti-VEGF therapeutics independent of the presence of neovascularization.

Patient consent

Informed consent was not required by the institutional review board.

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Authorship

All authors attest that they meet current ICMJE criteria for authorship.

Declaration of competing interest

All authors have no financial disclosures.

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