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Clinical Profiles of Retinal Vasoproliferative Tumors

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Abstract

Purpose: To describe the clinical features and treatment outcomes of patients with retinal vasoproliferative tumors. **Methods:** This retrospective case series comprised patients diagnosed with a retinal vasoproliferative tumor. Electronic medical records were reviewed, and patients' demographic details, clinical presentation, and treatment outcomes were analyzed. **Results:** Nineteen eyes of 19 patients with vasoproliferative tumors were included. The mean age (±SD) at presentation was 37.0 ± 16.95 years. No eye had bilateral tumors, and 1 eye had multiple tumors. Three eyes (15%) had primary tumors, while 16 (84%) had secondary tumors. Primary tumors mainly affected the inferotemporal quadrant (n = 3). Secondary tumors involved the inferior quadrant (n = 4), inferotemporal quadrant (n = 5), and inferonasal quadrant (n = 5). Secondary tumors were associated with Coats disease (n = 6), intermediate uveitis (n = 3), traumatic chorioretinopathy (n = 2), familial exudative vitreoretinopathy (n = 2), retinal vasculitis (n = 2), and retinal vascular occlusion (n = 1). Retinochoroidal features included intraretinal and subretinal exudates, subretinal fluid, intraretinal hemorrhaging, vitreous hemorrhaging, cystoid macular edema, vitritis, preretinal fibrosis, dilated feeding vessel, epiretinal membranes, and tractional retinal detachment. Treatment modalities included cryotherapy, laser photocoagulation, and local steroids. The mean follow-up was 25.3 months, during which 18 eyes had tumor regression and 1 had a worsening condition. **Conclusions:** Secondary vasoproliferative tumors were more frequently observed than primary tumors, often presenting as unilateral, unifocal tumors situated posterior to the equator in the inferior fundus. Conventional treatment approaches, such as cryotherapy and laser photocoagulation, were effective at tumor regression and often required multiple sessions.

Keywords

eye, retina, tumor, vasoproliferative tumor

Introduction

Acquired retinal tumors containing both vascular and glial components were first described in 1983 by Shields et al[1] in a series of 12 cases. The initial term they used for the condition was *acquired retinal hemangioma*. In 1995, they presented a series of 103 patients, renaming the lesions *vasoproliferative tumors of the retina* and proposing a comprehensive classification of vasoproliferative tumors.[2] Hiscott and Mudhar[3] suspected an association between these tumors and proliferative vitreoretinopathy and termed the entity *reactive retinal glioangiosis*. Vasoproliferative tumors are benign tumors of unknown origin, mainly occurring in healthy patients between 40 years and 60 years of age[4] and that can be primary/idiopathic or secondary to underlying conditions such as Coats disease, uveitis, and retinal vasculitis.

Vasoproliferative tumors are highly vascularized, pink on indirect fundus examination, and associated with intraretinal hemorrhaging and intraretinal or subretinal exudates.[4] On histopathologic examination, they show a prominent presence of glial cell proliferation and display characteristic traits consistent with a pilocytic astrocytoma. In addition, smaller blood vessels are present that primarily supply the essential nutrients required for the gradual growth of the primary glial component.[5] Vasoproliferative tumors can cause visual impairment as a result of excessive exudation,

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Table 1. Patient Characteristics at Baseline and Treatment Outcomes of Individual Tumors.

Pt	Age (Y)	Sex	Eye Involved	Type of Tumor	Primary Treatment	Distance BCVA (Snellen)		6-Month Outcome
						Baseline	Final	
1	38	Male	OS	Primary	Cryotherapy	6/9	6/19	Regressed
2	49	Female	OS	Primary	Cryotherapy	6/19	6/60	Regressed
3	15	Male	OD	Secondary	BB + cryotherapy + sub-Tenon steroid	HM+	LP PR accurate	Regressed
4	20	Male	OS	Secondary	IVT steroid	6/9.5	6/9.5	Regressed
5	15	Male	OD	Secondary	Cryotherapy + systemic steroids	6/6	6/6	Regressed
6	60	Male	OS	Secondary	Cryotherapy + anti-VEGF	HM+	LP PR accurate	Regressed
7	55	Male	OS	Secondary	Cryotherapy + systemic steroids	6/6	6/6	Worsened
8	17	Male	OS	Secondary	Cryotherapy	HM+	LP PR accurate	Regressed
9	27	Male	OD	Secondary	Cryotherapy + laser PHC + anti-VEGF	6/9.5	6/19	Regressed
10	18	Male	OS	Secondary	Cryotherapy + IVT steroids	6/38	6/60	Regressed
11	53	Female	OS	Secondary	Cryotherapy	6/9.5	6/9.5	Regressed
12	28	Male	OS	Secondary	Cryotherapy	6/6	6/6	Regressed
13	53	Male	OD	Secondary	Cryotherapy	6/6	6/6	Regressed
14	22	Male	OD	Secondary	Cryotherapy	HM+	1/60	Regressed
15	39	Male	OD	Secondary	Cryotherapy	6/60	6/15	Regressed
16	29	Female	OD	Secondary	Cryotherapy	6/38	6/9.5	Regressed
17	55	Male	OD	Secondary	IVMP + oral steroids	CF	CF	Regressed
18	65	Female	OS	Primary	Cryotherapy	CF @ 0.50 m	CF @ 0.50 m	Regressed
19	45	Male	OS	Secondary	Cryotherapy+ systemic steroids	6/6	6/6	Regressed

Abbreviations: anti-VEGF, antivascular endothelial growth factor; BB, belt buckling; BCVA, best-corrected visual acuity; CF, counting fingers; HM, hand motions; IVMP, intravenous methylprednisolone; IVT, intravitreal; LP, light perception; PHC, photocoagulation; PR, projections of rays; Pt, patient.

hemorrhage, or secondary retinal detachment (RD) involving the macular area. Treatment options include laser photocoagulation, cryotherapy, plaque radiotherapy to control exudation,[4] and vitrectomy for associated tractional RD (TRD) or macular pucker.[6]

Walinjkar et al[7] found a predominance of secondary vasoproliferative tumors that required more treatments and had a greater likelihood of recurrence after regression. The authors recommended close follow-up to address the potential complications and emphasized the need for larger studies to determine the optimum treatment modalities. The current study assessed the long-term outcomes of vasoproliferative tumors and explored the treatment alternatives.

Methods

This retrospective case series comprised patients diagnosed with a vasoproliferative tumor between 2011 and 2018. All patients provided written informed consent for their examination and treatment, and the study conformed to the principles outlined in the Declaration of Helsinki. The Institutional Review Board, Vision Research Foundation, approved the study.

The medical records of patients diagnosed with a vasoproliferative tumor were reviewed. Collected data included patient demographics, which eye was affected, the results of ocular examinations, characteristics associated with the tumor, treatments administered, complications, and the progression of each patient's condition. The study included cases diagnosed as a primary or secondary vasoproliferative tumor with a minimum follow-up of 6 months. Eyes with other pathologies such as diabetic retinopathy, hypertensive retinopathy, cataract, glaucoma, and unrelated conditions were excluded.

A diagnosis of vasoproliferative tumor was based on a comprehensive eye examination that included an assessment of visual acuity (VA), refraction, applanation tonometry, and a dilated fundus examination. This was followed by spectral-domain optical coherence tomography (OCT) in eyes with cystoid macular edema (CME) or retinal fluid as well as fundus fluorescein angiography (FFA). Tumor size was measured in millimeters using calipers on an ultrasound machine (Alcon Laboratories).

The mean, median, and range for continuous and ordinal scale data were calculated, with all mean values ± SD. The best-corrected VA (BCVA) was evaluated using the Snellen chart and then converted to logMAR notation for analysis. Findings related to ocular conditions and tumor-associated features were expressed as percentages.

Results

Table 1 shows the characteristics and treatments of the 19 patients (19 eyes) included in the analysis. The mean age of the 4 women and 15 men at the time of presentation was 37.0 ± 16.95 years (range, 15-66). Three of 19 cases were primary vasoproliferative

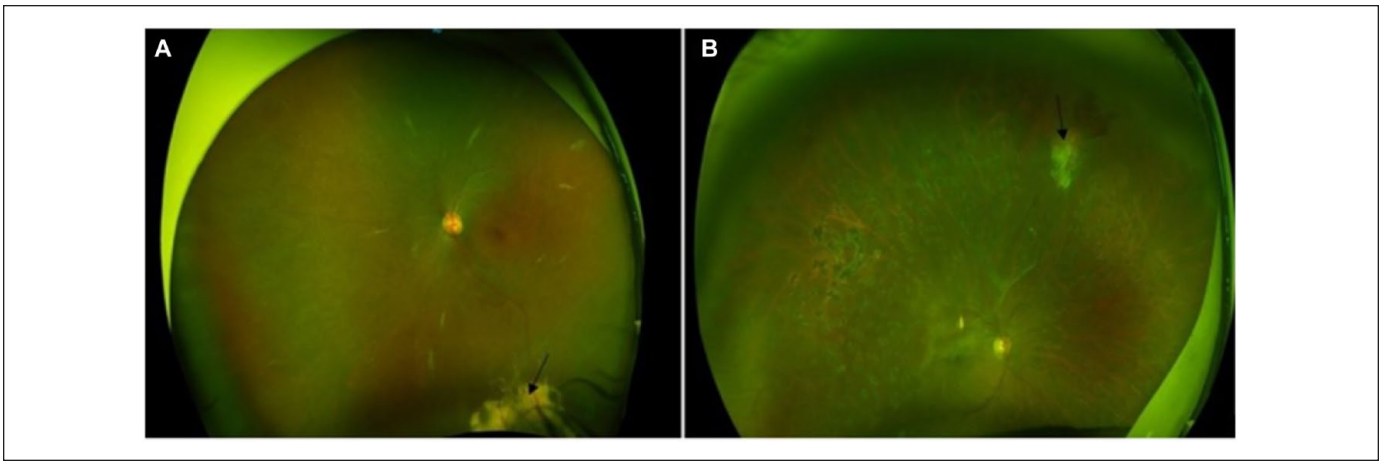

Figure 1. Optos imaging of vasoproliferative tumors (black arrows). (A) A secondary vasoproliferative tumor is seen in the inferior quadrant of the left eye. A telangiectatic vessel is accompanied by a major artery and vein directed toward the lesion. (B) A secondary vasoproliferative tumor located superiorly with large vascular channels is seen in the right eye.

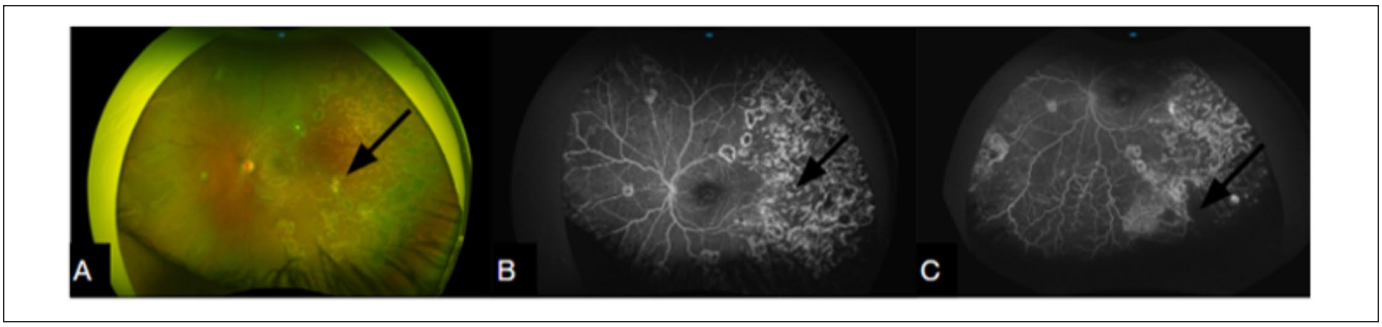

Figure 2. Optos imaging of a 45-year-old man with a vasoproliferative tumor secondary to Coats disease. (A) The tumor is located along the inferior arcade (black arrow). (B) Widefield fundus fluorescence angiography shows hyperfluorescence of the lesion that increases in intensity. (C) Areas of capillary nonperfusion are seen in the inferior quadrant.

tumors, and the remaining 16 were secondary vasoproliferative tumors (Figure 1). No patient had bilateral tumors, and only 1 eye in the secondary tumor group had multiple tumors.

The mean BCVA at presentation was 1.05 ± 1.20 logMAR, and the mean final BCVA was 1.07 ± 1.27 logMAR. The most common systemic association was hypertension, found in 4 patients, followed by diabetes mellitus in 2 patients. The mean intraocular pressure was 13.36 ± 3.11 mm Hg (median, 12; range, 12-25). Myopia was the most commonly associated refractive error, observed in 6 eyes, followed by hyperopia in 5 eyes and emmetropia in 5 eyes. An anterior segment examination showed a relative afferent pupillary defect in 3 eyes, a sluggish pupillary reaction in 2 eyes, exotropia in 3 eyes, and an anterior chamber inflammatory reaction in 2 eyes.

Most tumors were located in the inferotemporal quadrant (primary [n = 3]; secondary [n = 5]) followed by the inferior quadrant (primary [n = 0]; secondary [n = 4]) and the inferonasal quadrant (primary [n = 0]; secondary [n = 5]). In all eyes, the tumor was located anterior to the equator. The mean tumor height at presentation was 1.08 ± 1.72 mm, the mean horizontal basal diameter was 0.58 ± 1.44 mm, and the mean vertical basal diameter was 0.77 ± 1.88 mm. OCT examination showed CME in 6 eyes, with a mean foveal thickness of 138.57 ± 221.96 μm at baseline and 121.26 ± 186.50 μm at the follow-up visit. Five of the 6 eyes with CME had regression of the CME at the follow-up visit. The FA examination showed blocked fluorescein in 1 eye, areas of hyperfluorescence in 2 eyes, tortuous vessels in 2 eyes, leakage in 3 eyes, areas of capillary nonperfusion in 2 eyes, and neovascularization elsewhere in 2 eyes (Figure 2).

Table 2 shows the tumor-associated findings at baseline. The most common finding on fundus examination was intraretinal and subretinal exudation (primary [n = 2]; secondary [n = 6]) followed by intraretinal hemorrhage (primary [n = 1]; secondary [n = 6]), subretinal fluid (SRF) (primary [n = 1]; secondary [n = 6]), vitreous hemorrhage (primary [n = 1]; secondary [n = 4]), and CME (primary [n = 0]; secondary [n = 5]). Other findings, such as CME, vitritis, and TRD, were found exclusively in the group with secondary tumors.

Table 3 shows the treatment modalities for the secondary tumor group. At the baseline visit, all eyes received treatment and none was placed under observation. During the follow-up period, 3 of 19 eyes did not require further treatment. Of the 10 eyes that did require further treatment, 5 received 2 sessions of cryotherapy, 2 received 3 cryotherapy sessions, 1 received 3

Table 2. Tumor-Associated Findings at Baseline.

Parameter	Number (%)	
	Primary (n = 3)	Secondary (n = 16)
Intraretinal/subretinal exudates	2 (67)	6 (38)
Intraretinal hemorrhage	1 (34)	6 (38)
Subretinal fluid	1 (34)	2 (13)
Vitreous hemorrhage	1 (34)	4 (25)
Preretinal fibrosis	1 (34)	1 (17)
Cystoid macular edema	0	5 (94)
Dilated feeding vessel	1 (34)	4 (25)
Vitritis	0	2 (13)
Epiretinal membrane	1 (34)	4 (25)
Tractional retinal detachment	0	2 (13)

Table 3. Treatment Modality in Secondary Retinal Vasoproliferative Tumors.

Pt	Age (Y)	Sex	Eye Involved	Underlining Etiology	Baseline Treatment	Retreatment During FU
1	15	Male	OD	Traumatic chorioretinopathy + Coats disease	BB + cryotherapy + sub-Tenon steroid	1 cryotherapy session
2	20	Male	OS	Traumatic chorioretinopathy	IVT steroid	2 laser PHC sessions
3	15	Male	OD	Coats disease	Cryotherapy + systemic steroids[a]	None
4	60	Male	OS	Intermediate uveitis	Cryotherapy + anti-VEGF	3 cryotherapy sessions
5	55	Male	OS	Coats disease	Cryotherapy + systemic steroids[a]	1 cryotherapy session
6	17	Male	OS	Intermediate uveitis	Cryotherapy	2 cryotherapy sessions
7	27	Male	OD	FEVR	Cryotherapy+ laser PHC+ anti-VEGF	3 doses of anti-VEGF + 2 cryotherapy sessions
8	18	Male	OS	FEVR	Cryotherapy + IVT steroids	2 cryotherapy sessions
9	53	Female	OS	Coats disease	Cryotherapy	3 cryotherapy sessions
10	28	Male	OS	Intermediate uveitis	Cryotherapy	1 cryotherapy session
11	53	Male	OD	Coats disease	Cryotherapy	2 laser PHC sessions
12	22	Male	OD	Retinal vascular occlusion	Cryotherapy	1 cryotherapy session
13	39	Male	OD	Retinal vasculitis	Cryotherapy	1 cryotherapy session
14	29	Female	OD	Retinal vasculitis	Cryotherapy	2 cryotherapy sessions
15	55	Male	OD	Coats disease	IVMP + oral steroids	None
16	45	Male	OS	Coats disease	Cryotherapy + systemic steroids[a]	None

Abbreviations: anti-VEGF, antivascular endothelial growth factor; BB, belt buckling; FEVR, familial exudative vitreoretinopathy; FU, follow-up; HM, hand motions; IVMP, intravenous methylprednisolone; IVT, intravitreal; PHC, photocoagulation; Pt, patient.
[a]Systemic steroids were given in an attempt to reduce the tumor vascularity and exudation.

antivascular endothelial growth factor (anti-VEGF) injections, and 2 had laser photocoagulation.

Conclusions

Vasoproliferative tumors are relatively rare and have gained recognition as a distinct clinical entity in the differential diagnosis of intraocular tumors.[1–3] They are most frequently found in the lower or outer quadrant of the retinal periphery, manifesting as yellow, orange, or red lesions and typically appearing in individuals in their fifth or sixth decades.[6–10]

Primary tumors are typically solitary, small, and situated near the ora serrata retinae.[2–4] Secondary tumors are more often multifocal, bilateral, and believed to be a reactive vascular response to a variety of ocular insults.[2–4] Secondary vasoproliferative tumors are more common than primary tumors, with our study identifying 16 cases of secondary tumors and 3 cases of primary tumors. All tumors presented unilaterally. In our study, a higher proportion of men had secondary tumors, whereas a study by Shields et al[2] found women to be more prone to developing aggressive, multiple, or diffuse tumors. Our findings are in alignment with results in the previous literature, indicating that a younger population is affected by secondary tumors that often involve both eyes, present as unifocal lesions, and result in overall poorer VA.[2]

As seen in our study, FA may prove challenging, with varying quality resulting from the predominantly peripheral location of most lesions.[2,6,11] Rapid arterial phase filling of tumors through nondilated or minimally dilated retinal feeding arterioles was typically seen. In the venous phase, diffuse leakage (n = 2) and

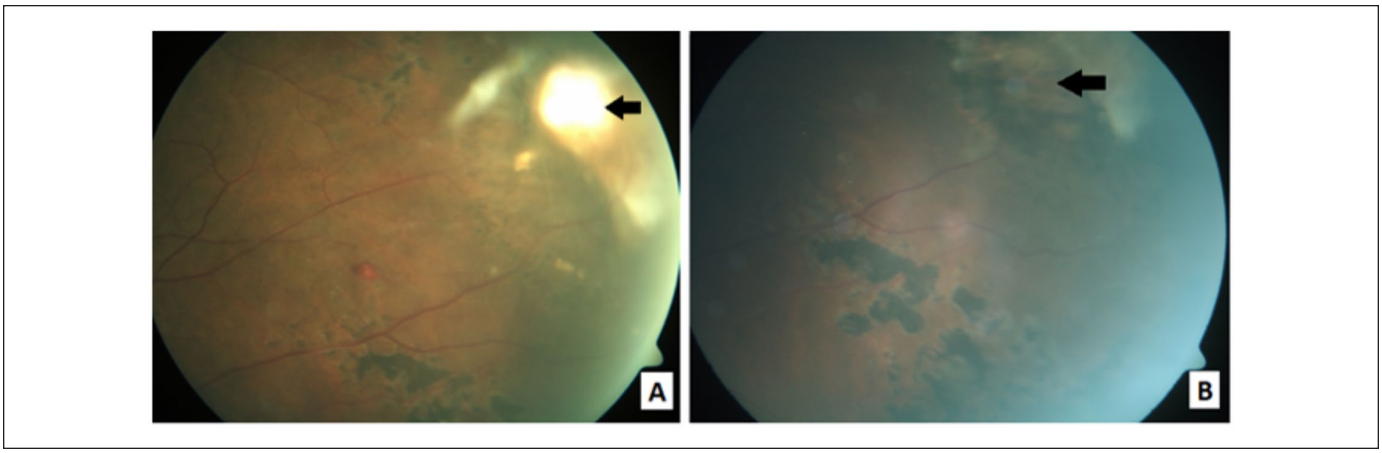

Figure 3. (A) Fundus imaging of the left eye before treatment of a vasoproliferative tumor (black arrow) secondary to adult-onset Coats disease in a 55-year-old man. (B) Regression of the tumor (black arrow) is seen after treatment with cryotherapy and systemic steroids.

staining of the mass with SRF (n = 2) were observed, persisting into late angiograms. Additional findings included blocked fluorescein (n = 1), areas of hyperfluoresence (n = 2), capillary nonperfusion (n = 2), and neovascularization elsewhere (n = 2).

In the study by Shields et al,[2] 51% of tumors required treatment. In our study, almost all eyes required treatment, likely because the majority of tumors were secondary. Cryotherapy was the predominant treatment approach and was exclusively used in 10 eyes (primary [n = 3]; secondary [n = 7]). Nine eyes with secondary tumors received a combination treatment, such as buckling with cryotherapy and a sub-Tenon steroid (n = 1), cryotherapy and systemic steroids (n = 3), intravitreal (IVT) steroids (n = 1), cryotherapy and anti-VEGF (n = 1), cryotherapy with anti-VEGF and laser photocoagulation (n = 1), cryotherapy and IVT steroids (n = 1), or intravenous pulse methylprednisolone and oral steroids (n = 1). Cryotherapy seems to be sufficient for treating small tumors (<2.0 mm), whereas larger tumors are challenging to treat because the tumor's size may hinder complete treatment with a single session.[11–13] Irvine et al[14] reported that repeated cryotherapy treatments may be necessary for patients with tumors larger than 2.0 mm. In our study, of the 19 eyes requiring retreatment, 7 had cryotherapy, 5 (primary [n = 1]; secondary [n = 4]) had 2 sessions of cryotherapy, and 2 (secondary) had 3 cryotherapy sessions.

The mean BCVA at presentation was 1.05 ± 1.20 logMAR, and the final BCVA was 1.07 ± 1.27 logMAR. Of the 19 eyes, 5 (26%) did not have vision impairment, 4 (21%) had moderate vision impairment, and 9 (47%) had severe vision impairment. We administered treatment even to patients with initially good vision (n = 5) and moderate vision impairment (n = 4) given indications suggesting potential risks to VA. These indications included proximity of the tumor to the macula (n = 1), massive exudation (n = 9), vitritis (n = 3), vascular abnormalities (n = 2), and CME (n = 2) in addition to reported symptoms of blurred and distorted vision (n = 9). Heimann et al[4] stated that VA can be significantly impaired by vasoproliferative tumors due to the presence of vitreoretinal changes. We believe the anatomic location of the tumor and the associated vitreoretinal abnormality would have resulted in impaired vision in those patients. It is crucial to actively seek and identify these cases when patients present with remote macular exudates.[13]

Limitations of this study include its retrospective nature and small sample. The mean follow-up was 25.3 months (median, 12.5; range, 2-105), during which the tumor regressed in 18 eyes and the condition worsened in 1 eye. Ninety-five percent of cases regressed well (Figure 3), with clinical features suggestive of tumor regression, including a reduction in or resolution of retinal exudation, SRF, CME, and hemorrhaging. However, 1 eye in the secondary tumor group had tumor recurrence 3 months after complete regression. It is crucial to closely monitor cases of secondary vasoproliferative tumors because of their tendency to recur.

Complications seen at follow-up visits included 2 eyes in the secondary group that developed TRD after the initial cryotherapy treatment and required management with a vitrectomy and 2 eyes from the secondary tumor group that developed complicated cataract and were treated with lensectomy. In addition, 1 eye with silicone oil (SO) tamponade developed an early cataract that was managed with phacoemulsification and SO removal. Furthermore, 5 eyes (primary [n = 1]; secondary [n = 4]) presented with a vitreous hemorrhage after initial cryotherapy treatment, all of which were managed with anti-VEGF therapy. Notably, 2 eyes with secondary tumors had a decline in VA from hand motions+ to light perception/accurate projections of rays, despite treatment with belt buckling and cryotherapy as well as laser photocoagulation.

This study emphasizes that macular function and VA can be significantly affected by retinal vasoproliferative tumors and that regular monitoring is required. These tumors can manifest as primary or secondary tumors, with the 2 types sharing similar features and complications. Prompt diagnosis, in particular in younger patients before the onset of fibrosis and exudation, is essential for maintaining or improving vision.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board, Vision Research Foundation, approved the study.

Statement of Informed Consent

Informed consent, including permission for publication of all photographs and images included herein, was obtained before the procedure was performed.

Declaration of Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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