Original Article

Clinical features and treatment outcomes of vasoproliferative tumors in Indian participants

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Purpose: The aim of the study was to describe the clinical features and treatment outcomes of vasoproliferative tumors (VPT) in Indian participants. **Methods:** This study design was a retrospective case series in a tertiary eye care center. Case records of patients diagnosed with VPT from 2011 to 2015 were reviewed, and their demographic details, clinical presentation, and treatment outcomes were documented. Baseline and follow-up visual acuity and tumor dimensions were statistically compared by applying paired *t*-test. Statistical analysis used SPSS version 14. **Results:** Twenty-two tumors from 19 eyes of 17 patients were included. Mean age at presentation was 43.5 years (range: 15–68 years). Mean presenting best-corrected visual acuity (BCVA) was + 1.10 logMAR. Sixty-eight percent eyes had secondary tumors. Most common association of secondary VPT was Coats disease followed by retinal vasculitis, polypoidal choroidal vasculopathy, familial exudative vitreoretinopathy, and traumatic chorioretinopathy. Ten tumors (45%) involved the inferior quadrant. Tumor-associated features were intra/subretinal exudates, vitritis, subretinal fluid, vitreous hemorrhage, preretinal fibrosis, epiretinal membrane, and subretinal blood. Treatment included cryotherapy, intravitreal or oral steroids, laser photocoagulation, cryotherapy with encirclage, cryotherapy with anti-vascular endothelial growth factor, and observation. Complications included tumor recurrence, retinal detachment, raised intraocular pressure, neovascularization of iris, and cataract. Ninety-five percent VPT regressed at mean 21 months (Median: 17 months; Range: 3–64 months). Mean final BCVA was + 1.21 logMAR. **Conclusion:** VPTs are commonly unilateral, unifocal, and located anterior to equator in inferior fundus. Secondary tumors are more common than primary tumors. Treatment achieves tumor regression in majority of cases.

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Vasoproliferative tumor (VPT) of the retina is a well-documented entity described clinically as yellow to reddish, globular mass lesion in the periphery. Henkind and Morgan[1] first described these tumors histopathologically in enucleated eyes having Coats'-like features with severe ocular disease. Shields *et al*.[2] coined the term "VPT" and proposed a comprehensive classification system of these tumors. Since then, there have been various reports on VPT from across the world.[3-8] The purpose of this study is to describe the clinical features and treatment outcomes of VPT in Indian participants and how they differ from that described in published literature.

Methods

This study is a retrospective case series of patients diagnosed with VPT in a tertiary eye care center in India from 2011 to 2015. A written informed consent was signed by all patients for examination and treatment. This study adhered to the tenets of the Declaration of Helsinki. Case records of patients with VPT were screened for demographic details, ocular examination findings, tumor-associated features, treatment, complications, and follow-up course. The data collected on continuous and ordinal scale were expressed as mean, median, and range. Best-corrected visual acuity (BCVA) was measured in Snellen visual acuity and was converted to logMar for the ease of comparison and determining statistical significance. Tumor dimensions were measured in millimeters using calipers in ultrasound machine (Alcon Laboratories, Worth, Tx, USA).

Comparison between the baseline and follow-up characteristics of tumors and between primary and secondary tumors was done by converting the data into percentages. Baseline and follow-up visual acuity and tumor dimensions were statistically compared by applying paired *t*-test using SPSS software version 14 (SPSS Inc. 233 South Wacker Drive, 11th Floor Chicago, IL 60606-6412). $P < 0.05$ was considered statistically significant. Primary outcome measures were to study the anatomical and functional response to the treatment.

Results

Twenty-two tumors in 19 eyes of 17 patients were included in the study. Table 1 summarizes the patient characteristics at

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Table 1: Patient characteristics at baseline and treatment outcomes of individual tumors

Patient number	Age	Gender	Laterality	Number of tumors	Tumor number	Primary treatment given	Visual outcome		Anatomical outcome
							Baseline visual acuity	Final visual acuity	
1	28	Female	UL	1	1	Observation	PL, PR	PL, PR	Regressed
2	38	Male	UL	1	2	Cryotherapy	20/32	20/40	Regressed
3	49	Female	UL	1	3	Cryotherapy	20/63	20/400	Regressed
4	31	Female	UL	2	4	Cryotherapy	20/63	Lost to follow up	Lost to follow up
					5	Cryotherapy			
5	48	Male	BL	1	6	Cryotherapy	20/20	20/32	Regressed
				1	7	Laser photocoagulation	20/20	20/32	Regressed
6	55	Female	UL	1	8	Patient not willing for treatment was advised cryotherapy	20/125	HM	Tumor worsened
7	15	Male	UL	1	9	Cryotherapy with cerclage	HM	PL, PR	Regressed
8	20	Male	UL	1	10	Intravitreal steroid	20/32	20/32	Regressed
9	15	Male	UL	3	11	Systemic steroids	20/20	20/20	Regressed
					12	Systemic steroids			Regressed
					13	Laser photocoagulation			Regressed
10	60	Male	UL	1	14	Cryotherapy with anti-VEGF	HM	PL, PR	Regressed
11	48	Male	UL	1	15	Cryotherapy	20/400	20/400	Regressed
12	55	Male	UL	1	16	Systemic steroids	20/20	20/20	Regressed
13	52	Male	UL	1	17	Cryotherapy	HM	20/400	Regressed
14	17	Male	UL	1	18	Cryotherapy	HM	PL, PR	Regressed
15	66	Female	UL	1	19	Observation	20/400	20/400	Regressed
16	65	Female	UL	1	20	Cryotherapy	20/63	20/63	Regressed
17	38	Male	UL	2	21	Laser photocoagulation	20/20	20/20	Regressed
					22	Cryotherapy	20/20	20/20	Regressed

UL: Unilateral, BL: Bilateral, PL: Perception of light, PR: Projection of rays, HM: Hand movements, VEGF: Vascular endothelial growth factor

presentation with treatment outcomes. Mean age of patients was 43.5 years (range: 15–68 years). Majority of patients ($n = 11$) in our study were males, the male: female ratio being 2:1. One patient with secondary VPT had a history of treatment with systemic antitubercular therapy for granulomatous uveitis of suspected tubercular etiology, whereas another patient had a history of treatment with systemic steroids and immunomodulators for posterior uveitis. Hypertension was the most common systemic association found in 29% ($n = 5$) patients followed by hypercholesterolemia (6%, $n = 1$). One patient (6%) had hypertension and diabetes mellitus.

Table 2 summarizes the ophthalmic findings at presentation. At presentation, mean IOP was 15.5 mmHg (median = 14.5 mmHg, range = 8–25 mmHg). Hypermetropia was the most commonly associated refractive error in 47% eyes, followed by myopia (37%) and emmetropia (16%). Anterior segment examination was unremarkable in most (58%, $n = 11$) of the eyes. Relative afferent pupillary defect (26%, $n = 5$) was the most common anterior segment abnormality followed by exotropia (16%, $n = 3$) and cataract (11%, $n = 2$). Anterior chamber inflammatory reaction, neovascularization of iris, cornea haze, shallow anterior chamber angles, sluggish pupil reaction, and nystagmus were found in one eye (5%) each. Secondary tumors ($n = 15$) outnumbered primary tumors ($n = 7$) in the ratio of 2:1 (15:7). All except two patients had unilateral disease. Sixteen eyes had a single tumor; two eyes with secondary VPT and one eye with primary VPT had multiple tumors. Majority of tumors were located in inferior quadrant. In all but one case, tumor was anterior to equator. Mean basal diameter at presentation was 6.3 mm (median = 6.3 mm; range = 5.8–6.8 mm). Mean tumor height at presentation was 2.88 mm (median = 2.8 mm; range = 2.0–4 mm).

Table 3 summarizes tumor-associated findings at presentation. Most common tumor-associated finding was retinal exudates [Fig. 1]. Vision-threatening features included epimacular membrane, cystoid macular edema (CME), and exudation involving macula. Most common etiology of secondary VPT was Coats' disease ($n = 2$, 15%) followed by retinal vasculitis ($n = 2$, 15%), polypoidal choroidal vasculopathy ($n = 2$, 15%), familial exudative vitreoretinopathy ($n = 2$, 15%) [Fig. 2], intermediate uveitis ($n = 2$, 15%), papillitis ($n = 2$, 15%), and glaucoma with traumatic choroioretinopathy ($n = 1$, 7%). One case of primary tumor had associated Fuchs endothelial dystrophy.

Table 4 summarizes the treatment details. Fifty-five percent tumors ($n = 12$) were advised cryotherapy as a primary modality [Fig. 3], either alone or in combination with circlage and anti-vascular endothelial growth factor (VEGF). Systemic steroids were used in two patients with secondary VPTs in an attempt to reduce the tumor vascularity and exudation. Mean follow-up duration was 21 months (median: 17 months; Range: 3–64 months). Out of 22 tumors (19 eyes), twenty tumors (18 eyes) were evaluated at final follow-up. One patient with two primary tumors in the left eye was lost to follow-up. One

Table 2: Ocular examination details at baseline (figures in brackets indicate percentage)

Parameter	Primary (*n*=15)	Secondary (*n*=7)	Total (*n*=22)
Laterality (*n*=17)			
Unilateral	4 (80)	11 (92)	15 (88)
Bilateral	1 (20)	1 (8)	2 (12)
Number of tumor per eye (*n*=19)			
Single	5 (83)	11 (85)	16 (84)
Multiple	1 (17)	2 (15)	3 (16)
Quadrant involved (*n*=22)			
Temporal	1 (14)	4 (27)	5 (23)
ITQ*	1 (14)	6 (40)	7 (32)
Inferior	5 (71)	5 (33)	10 (45)
AP tumor location (*n*=22)			
Anterior to equator	6 (86)	15 (100)	21 (95)
Posterior to equator	1 (14)	0	1 (5)

*ITQ: Inferotemporal quadrant, AP: Antero-posterior

Table 3: Tumor-associated findings at baseline (figures in brackets indicate percentage)

Parameter	Primary (*n*=7)	Secondary (*n*=15)	Total (*n*=22)
Intraretinal/subretinal exudates	5 (71)	9 (60)	14 (63)
Subretinal fluid	1 (14)	4 (27)	5 (23)
Intraretinal/subretinal blood	1 (14)	2 (14)	3 (14)
Vitreous hemorrhage	1 (14)	2 (14)	3 (14)
Preretinal fibrosis	0	3 (20)	3 (14)
CME	0	1 (7)	1 (5)
Dilated feeding arteriole/ draining venule	0	3 (20)	3 (14)
Vitritis	0	7 (47)	7 (32)
Epiretinal membrane	0	3 (20)	3 (14)
Sclerosed vessel	0	3 (20)	3 (14)
Tractional retinal detachment	0	1 (7)	1 (5)

CME: Cystoid macular edema

patient was advised cryotherapy; however, the patient was not willing for the same and at 5 months, she presented with worsening of tumor and four-line deterioration of vision. Of twenty tumors, it was found that 3 out of 5 (60%) primary tumors and 4 out of 15 (27%) secondary tumors required retreatment at first follow-up. Three primary tumors needed one retreatment session each; two secondary tumors needed three retreatment sessions, one secondary tumor needed two retreatment sessions, and one secondary tumor needed one retreatment session; however, the tumor did not regress, and eye was best left alone. Tumor recurrence after complete regression was noted in two (10%) cases, both of which were secondary VPT. Two cases treated with cryotherapy developed rhegmatogenous retinal detachment (RD) and were managed with vitreous surgery. Of these, one case had secondary VPT associated with traumatic chorioretinopathy. He was treated with cryotherapy and belt buckling. Rhegmatogenous RD occurred 4 months after primary treatment and was treated with vitreous surgery and silicone oil tamponade. Another

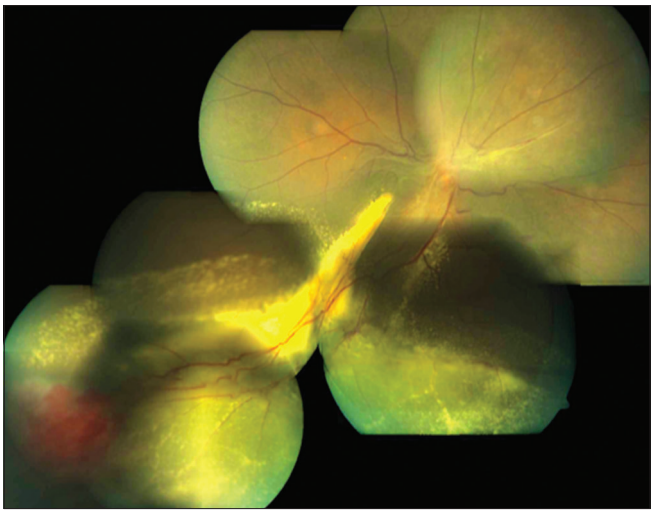

Figure 1: A 55-year-old female presented with diminution of vision since 6 months. Examination revealed primary vasoproliferative tumor with secondary retinal detachment, subretinal exudation, and epiretinal membrane

case developed rhegmatogenous RD 33 months after primary cryotherapy and was treated with vitreous surgery and silicone oil tamponade. Raised IOP was found in two cases, and both were controlled with medical management. One eye with secondary VPT developed neovascularization of iris 13 months after last treatment session and was treated with intracameral anti-VEGF. In one eye with secondary VPT, lensectomy was performed for complicated cataract. At final follow-up, 95% (n = 20) tumors regressed well. Mean BCVA at baseline was +1.10 logMAR. Mean BCVA at final follow-up was +1.21 logMar. At final follow-up, mean basal diameter was 5.5 mm including the dimensions of regressed tumors. (median: 5.45 mm; range: 4.8–6.8 mm) and mean tumor height was 2.33 mm (median: 2.15 mm; range 1.8–3.4 mm). The difference in the visual acuity at baseline and final follow-up was not statistically significant (P = 0.51). The difference in the mean basal dimensions at baseline and final follow-up was statistically significant (P = 0.03).

Discussion

VPT represents the reactive process of retina, retinal pigment epithelium, and choroid in response to an intraocular insult. It has been proposed that vascular anomalies are present in dormant state since birth and they become active by local stasis and hypoxia.[1,9-14] However, there are hardly any reports about this ocular entity from the Indian subcontinent. This study describes the clinical features, treatment outcomes, and complications of VPT in Indian participants. Males outnumbered females in a ratio of 2:1 in our study. This is in accordance with the existing data.[4] There are reports suggesting the preponderance of these tumors in females after the fifth decade.[4,15] This was also observed in our study. However, there are reports suggesting that young females have relatively aggressive, multiple, or diffuse tumors.[2] However, the exact cause is still uncertain.

Most of the tumors in our study were unilateral, unifocal, and located anterior to equator, in the inferior fundus, which is also noted by other workers.[2] This is supported by the

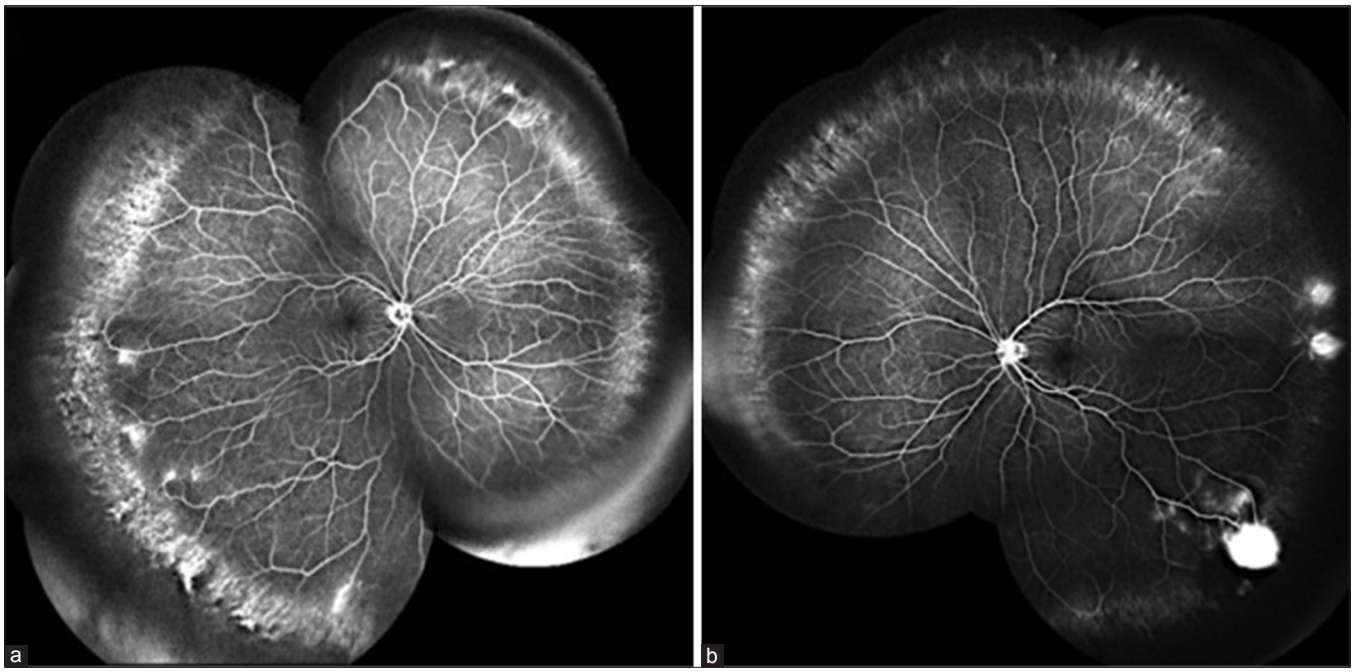

Figure 2: An asymptomatic 38-year-old male presented for a routine checkup when he was discovered to have familial exudative vitreoretinopathy (a) with secondary Vasoproliferative tumors in the left eye. (b) Wide-field fundus fluorescein angiography reveals peripheral avascular retina in both eyes with incipient neovascularization in the right eye (a)

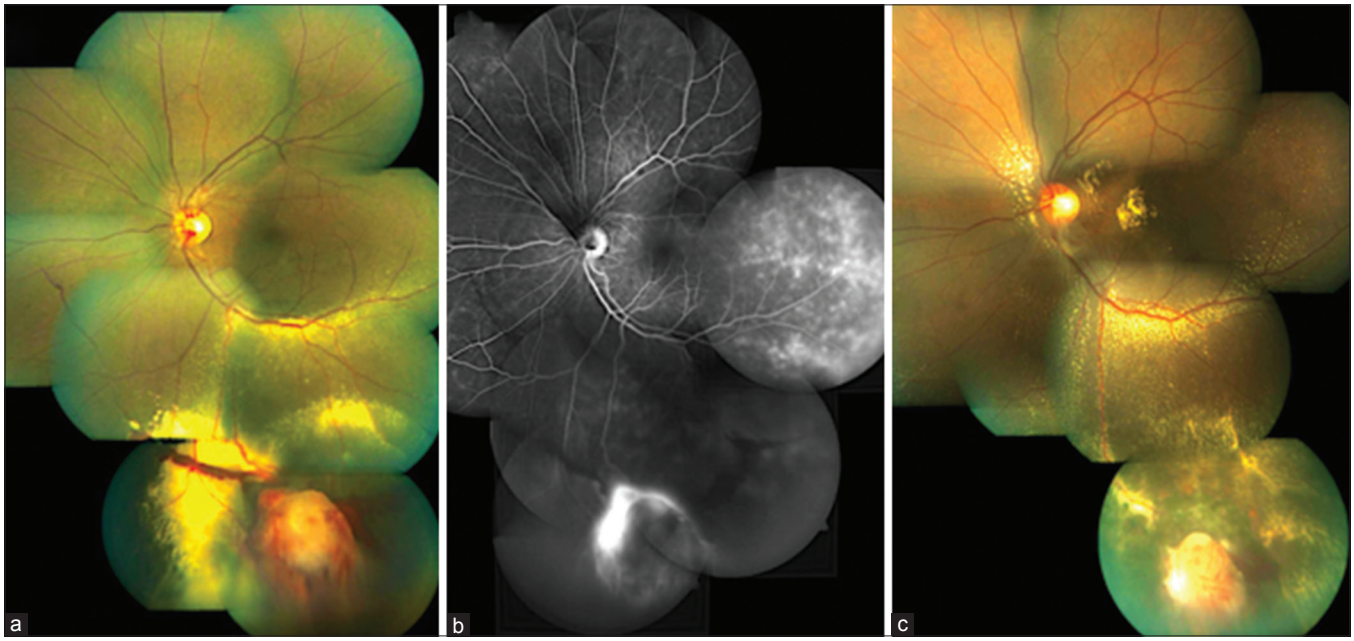

Figure 3: A 38-year-old female presented with diminution of vision with vasoproliferative tumor, subretinal exudation, and subretinal hemorrhage in the left eye (a). Clinical findings were confirmed on fluorescein angiography (b). Following treatment with cryotherapy, tumor regression (yellowish appearance, fibrotic changes), and significant reduction of exudation was noted (c)

existing literature that primary tumors tend to be solitary.[2] Few patients in our study did not have any visual impairment whereas majority patients presented with mild-to-profound visual impairment. This can be attributed to the fact that although VPT is benign retinal tumors of peripheral location, tumor-related complications may involve the macula and cause visual impairment.[4] In our case series too, there were cases of epiretinal membrane (ERM), CME, preretinal fibrosis, tractional RD, vitritis, and vitreous hemorrhage. In our case series, secondary tumors were more common than primary tumors. This is in contrast to most of the literature from the published reports.[2-4]

In contrast to the report by Shields[2] where 51% tumors required treatment, 86% cases in our study were advised treatment. This could be explained by the predominance

Table 4: Details of treatment modalities used (figures in brackets indicate percentage)

Parameter	Treatment modality	Primary (*n*=7)	Secondary (*n*=15)	Total (*n*=22)
Treatment	Cryotherapy	5 (71)	4 (27)	9 (41)
	Laser	1 (14)	2 (13)	3 (14)
	Systemic steroids*	0	3 (20)	3 (14)
	Local steroids	0	1 (7)	1 (5)
	Anti-VEGF (combined with cryotherapy)	0	1 (7)	1 (5)
	Belt buckle (combined with cryotherapy)	0	1 (7)	1 (5)
	Observation	1 (14)	2 (13)	3 (14)
	Noncompliant to treatment	0	1 (7)	1 (5)

*Systemic steroids were used in two patients with secondary VPTs in an attempt to reduce the tumor vascularity and exudation. VEGF: Vascular endothelial growth factor

of secondary tumors at presentation. Cryotherapy was the preferred treatment modality for most tumors in our series.

In our series, mean duration of follow-up was 21 months (median: 17 months; range: 3–64 months). Three cases of primary VPT required retreatment for residual tumor activity. Irvine *et al*.[16] noted that repeated treatment may be needed in patients treated with cryotherapy if the tumor thickness exceeds 2 mm. Rhegmatogenous RD was noted in two cases treated with cryotherapy. It is possible that after cryotherapy, there are chances of rhegmatogenous RD due to the occurrence of break adjacent to scar area and hence it is prudent to avoid heavy cryotherapy to the surrounding areas and edges. Three cases in our study had raised IOP on follow-up visits. Of these, one case had prior treatment with intravitreal steroids, one had neovascular glaucoma, whereas another had prior treatment with intravitreal anti-VEGF and cryotherapy. One case of VPT secondary to uveitis developed complicated cataract along with neovascular glaucoma. Complicated cataract was noted in one case of secondary VPT which later developed neovascular glaucoma. It was treated with lensectomy with intracameral anti-VEGF injection and pupilloplasty. One eye with silicone oil tamponade developed early cataract and was treated with phacoemulsification and silicone oil removal.

At final follow-up visit, 95% cases regressed well. Clinical features suggestive of tumor regression included reduction/resolution of retinal exudation, CME, subretinal fluid, and hemorrhage. Reduction of tumor size and fibrotic changes in the tumor were other features indicating tumor regression. However, tumor recurrence was noted in two cases; both of these were secondary tumors. One case was secondary VPT in eye with uveitis, developed recurrence at 18.5 months whereas one case was secondary to Eales disease, developed recurrence at 2.5 months. Hence, cases of secondary VPT must be closely followed up even after tumor regression.

It was found that the mean BCVA in our study was slightly less as compared to the mean initial BCVA. This is because two cases on follow-up presented with the progression of ERM and exudative RD involving macula, which although was treated adequately left residual visual impairment; one case had progression of posterior capsular opacity. Thus, these tumors must be closely followed up to look for macular complications involving early treatment.

The limitation of our study lies in its retrospective nature and small sample size. Furthermore, the criteria of preferring one treatment modality over others were not defined before the study. Hence, we could not evaluate the efficacy of treatment modality with respect to the dimensions of tumor or compare the efficacy of one treatment modality with the other. However, this case series adds to the existing knowledge of VPTs and describes the clinical presentation and treatment outcomes in Indian participants as compared to other case series reported in the Western population. However, we do accede to the possibility of a referral bias as the study was conducted in a tertiary care setting. We recommend that large studies and trials are needed to formulate the appropriateness of various treatment modalities in these tumors.

Conclusion

VPTs are rare tumors of retina, with peripheral predilection. They are benign, however, can cause remote effects on macula with vision-threatening complications. To the best of our knowledge, this is the first case series in Indian participants describing the clinical features and treatment outcomes in eyes with VPT. We found that, secondary tumors are more common in Indian participants having relatively worse visual and anatomical outcomes, requiring more number of treatment sessions with an increased tendency to recur after complete regression. Bilaterality, postequatorial location, and multifocal VPTs are rare. Treatment achieves tumor regression in the majority of cases. We recommend close follow-up to look for recurrences, development of neovascular glaucoma, and rhegmatogenous RD even after complete regression of these tumors so that these eyes can be salvaged with reasonably good anatomical and visual outcomes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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