Case Report

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Retinal vascular proliferation with fibrotic regression in von Hippel–Lindau disease

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Abstract:

In this study, we report a rare case of retinal vascular proliferation (RVP) in von Hippel–Lindau (VHL) disease, followed by a literature review. A 12-year-old boy presented with a left cerebellar hemangioblastoma and right eye blurred vision for 1–2 years. Fundus examination found no capillary hemangioblastoma lesion but a broad epiretinal fibrovascular membrane, which caused significant traction to the right macula. The genetic testing identified a pathogenic missense mutation (c. 223A > G) within the *VHL* gene, confirming VHL disease. RVP is a less common, poorly understood condition that can occur in VHL disease apart from the typical retinal capillary hemangioblastoma. The surface vasculature of the fibrovascular membrane regressed over an observation period of 3 years, and pars plana vitrectomy was eventually conducted at the age of 15 years to remove the fibrovascular membrane. Nevertheless, his visual acuity remained at 20/200 at postoperative 1 year due to the development of cataracts. In our literature review, we analyzed 39 reported cases of RVP, of which 90% had unilateral lesions, 70% had lesions at the juxtapapillary location, and 50% had a visual acuity <20/40. The mean onset age was 24 years. An intervention was performed in 39% of the cases and 78% experienced improved vision posttreatment. In conclusion, RVP likely starts as mainly vascular proliferation and eventually regresses spontaneously to fibrotic tissue formation. Unlike typical retinal capillary hemangioblastoma, vision can improve after an intervention, even in eyes with juxtapapillary lesions.

Keywords:

Fibrovascular proliferation, retinal capillary hemangioblastoma, retinal neovascularization, retinal vascular proliferation, von Hippel–Lindau disease

Introduction

Von Hippel–Lindau (VHL) disease is a rare, dominantly inherited, multisystem neoplastic syndrome stemming from the mutations in the *VHL* tumor-suppressor gene, located on chromosome 3, resulting in aberrant VHL protein production.[1,2] The VHL protein plays a pivotal role in the degradation of hypoxia-inducible factor-α (HIF-α), the oxygen-labile component of HIF. Mutations in *VHL* tumor-suppressor gene lead to uncontrolled upregulation of HIF-α, which, in turn, upregulates proangiogenic factors, such as vascular endothelial growth factor (VEGF).[2,3]

In the initial stages, VHL disease manifests most commonly as central nervous system hemangioblastomas and retinal hemangioblastomas, the latter detected in up to 50.4% of patients, making ophthalmologists integral in primary VHL diagnosis.[3] As the lesion progresses, visual impairment may ensue due to tractional retinal detachment, macular puckering, macular edema, or vitreous hemorrhage.[4] VHL disease may also manifest as retinal vascular proliferation (RVP), a less common

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condition that has scarcely been reported and remains poorly understood.[3,5]

Here, we present an unusual clinical manifestation of a large fibrovascular lesion over the macula in a young boy with VHL disease. Furthermore, we review the literature on this rare condition, offering insights into its clinical presentation and outcomes.

Case Report

A 12-year-old male patient initially presented at our institution's emergency department with complaints of severe headache, vomiting, and ataxia. Imaging studies indicated a left cerebellar hemangioblastoma, which resulted in obstructive hydrocephalus. The patient's mother denied any family history of VHL disease or other hereditary or systemic ailments. The tumor was successfully excised through surgical intervention.

Furthermore, the patient reported experiencing the right eye blurred vision for 1–2 years, prompting referral to an ophthalmologist for comprehensive assessment. The patient exhibited a visual acuity of 20/200 in the right eye and 20/100 in the left eye, with a bilateral intraocular pressure (IOP) of 23 mmHg. The initial IOP and visual acuity measurements may have been influenced by the young age and the poor compliance during the initial visit, as the patient had a poor systemic condition with obstructive hydrocephalus.

The anterior segment displayed unremarkable findings in both eyes. Fundoscopy revealed the presence of a broad epiretinal fibrovascular membrane extending from the optic disc to the macula, inducing severe traction in the right eye [Figure 1a]. Intraretinal or subretinal exudation was not detected. Spectral-domain optical coherence tomography (OCT) of the right macula indicated retinal distortion due to traction from the neovascular tissue [Figure 1b], whereas OCT scans of the left macula yielded unremarkable findings. Genetic testing identified a pathogenic missense mutation (c. 223A > G) in the *VHL* gene. Surgery was recommended due to the observed macular traction and poor vision. However, considering the patient's young age and newly diagnosed VHL disease, the family refused ophthalmic surgery and prioritized the management of other systemic conditions.

The patient was monitored for a 3-year period, during which the fibrovascular membrane persisted, with regressed vasculature on its surface [Figure 1c and d]. Notably, visual acuity of the right eye remained poor at 20/200, while the left eye exhibited normal visual acuity of 20/20. IOP measurements were 17 mmHg in the right eye and 16 mmHg in the left eye. Due to the persistent macular traction and poor visual acuity, along with the stabilization of the patient's systemic conditions, the family consented to surgical intervention. The patient subsequently underwent pars plana vitrectomy with excision of the fibrovascular membrane. During the surgery, we induced posterior vitreous detachment and removed the RVP membrane without peeling the internal limiting membrane. After epiretinal membrane removal, a complete fluid-air exchange was performed, followed by the instillation of 20% sulfur hexafluoride gas (SF6) as a long-acting tamponade agent. At 1-year postoperation, OCT revealed reduced macular traction [Figure 1e and f], and the patient's vision remained at 20/200 despite the development of a cataract.

Discussion

Primary RVP is a rare manifestation of VHL disease.[3,5-7] Different from retinal capillary hemangioblastoma, which typically manifests as conspicuous feeder and drainage vessels accompanied by aneurysmal dilatation, RVP lesions are characterized by fine superficial nonaneurysmal vascular proliferation. Moreover, they often display a certain degree of spontaneous fibrotic regression.[4] Wong *et al*.[5] reported that only 1.3% of all 890 patients with VHL developed RVP, whereas this prevalence increased to 3.6% among the 335 patients with ocular involvement in VHL disease. Diverse forms of angiomatous or nonangiomatous retinal lesions have been previously reported, such as RVP, twin vessels, vascularized glial veils, and retinal vascular hamartomas.[7,8] However, the absence of systematic reviews and standardized nomenclature for these lesions remain a challenge. Consequently, we extensively reviewed the literature, summarizing the limited 39 cases of RVP along with their clinical presentations and outcomes [Table 1].

Among the 39 patients, 36 (92%) presented with unilateral RVP. The 39 patients comprised 26 women and 13 men, with ages at presentation ranging from 3–62 years and a median age of 23.7 years. Juxtapapillary RVP was detected in 19 of the 27 eyes (70%) with available details. Moreover, 17 of the 27 eyes (63%) presented with RVP accompanied by various degrees of fibrous proliferation. Concurrent typical retinal capillary hemangioblastoma was detected in only 30% of the eyes.

The mechanisms underlying the pathophysiology and natural progression of RVP remain obscure. Histopathological examination of excised fibrovascular proliferative membranes revealed the presence of small, thin-walled vessels within loose connective tissue that stained positive for VEGF in immunohistochemical assays.[5] Kreuz *et al*.[6] also documented immature capillary proliferation and fibrotic areas in RVP, differentiating it

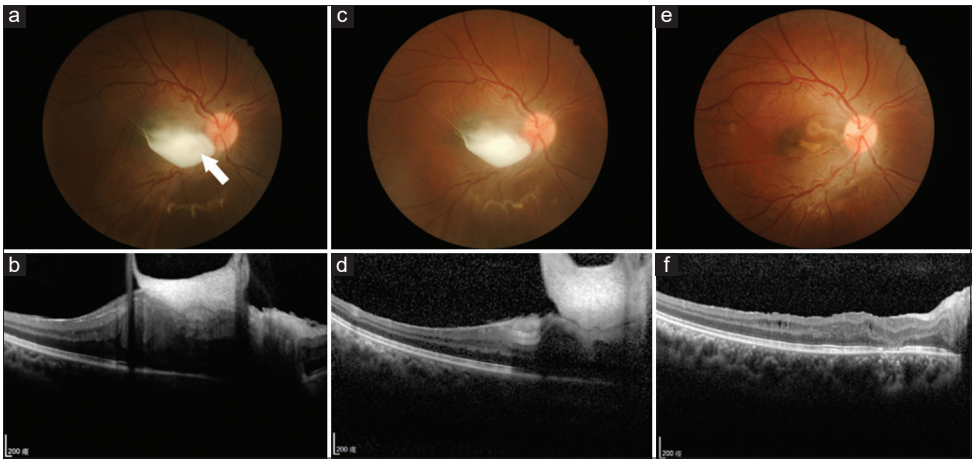

Figure 1: A teenage boy with von Hippel–Lindau disease and associated retinal vascular proliferation. (a) A fibrotic "retinal veil" with thin nonangiomatous vasculature on its surface can be seen in the color fundus photograph (arrow). (b) The horizontal optical coherence tomography slab (a) indicates a thick epiretinal membrane with significant macular traction. Surgical removal was offered; however, the family declined due to the patient's young age and unstable systemic condition. (c) After 3 years of observation, the vasculature on the surface regressed, but the macular traction persisted, as shown in (d). Surgery was ultimately performed after the systemic condition stabilized. Fundus examination 1 year after pars plana vitrectomy confirming the absence of fibrovascular membrane over the macula. (e) Spectral-domain optical coherence tomography scan 1 year after PPV shows significant improvement of macular traction in (f)

Table 1: Clinical characteristics of retinal vascular proliferation in patients with von Hippel–Lindau disease

	Patient, *n*	Male: female	Onset age, mean (range), years	Family history of VHL	VHL gene mutation	Concurrent retinal capillary hemangioblastoma
Wong *et al*.[5][a]	14	4:10	21 (3–62)	12	11; 3 without info	5
Schmidt and Neumann[7]	5	3:2	33 (24–58)	4; 1 without info	All 5 without info	1
Chew[3][b]	17	5:12	25 (5–68)	3[b]	1; 16 without info	0[b]
Kreuz *et al*.[6]	1	0:1	13	+	+	1
Arnold *et al*.[9]	1	0:1	44	+	+	1
Current case	1	1:0	12	–	+	0
Summary of the reported cases	39	13:26	24 (3–62)	21/24 (92)[c]	15/24 (63)[c]	8/27 (30)[c]

[a]Sixteen eyes of 14 patients, [b]Clinical manifestations of the lesion were reported in three patients, [c]*n*/total *n* (%) calculated by the cases with available information. Data are presented as the number of patients or eyes unless indicated otherwise. +=Positive, –=Negative, VHL=Von Hippel-Lindau, Info=Information

from retinal capillary hemangioblastomas. A second somatic hit inactivating both VHL alleles has been proposed as a causative mechanism, potentially giving rise to the distinct lesions.[10]

In the present case and some previous studies, a spontaneous regression of the vascular tissue was observed, suggesting that vascular proliferation is the initial manifestation, followed by fibrotic regression, and that the clinical presentations of RVP lie on a spectrum ranging from mainly vascular proliferation to the formation of a fibrotic membrane. Wong *et al*.[5] reported that out of 16 affected eyes, 2 exhibited only RVP, while the majority showed fibrotic proliferation. Similarly, Schmidt and Neumann.[7] documented five eyes with RVP without fibrotic tissue. Chew[3] also described 2 out of 3 eyes with detailed clinical manifestations showing RVP with fibrous proliferation. Overall, we have compiled case series data in Table 2.

Among the 27 eyes with known clinical manifestations, 17 (63%) exhibited RVP with fibrotic proliferation, while 10 (37%) had only RVP. In our case, vascular regressed with fibrovascular membrane persisted after a 3-year follow-up without intervention. Additional case studies and molecular analyses of the tissues may further validate this hypothesis in future.

Over half of the reported cases underwent no intervention, with 71% of those patients maintaining stable vision and 29% demonstrating worsening visual acuity over an extended follow-up period. However, the persistence of the fibrovascular membrane can lead to distortion of the retina and, eventually, decreased visual acuity. Among the patients that underwent intervention, eight underwent vitrectomy and excision of the fibrovascular complex, of which seven (88%) experienced improved vision after surgery. In one case, anti-VEGF therapy was administered 5 days before vitrectomy, resulting in a partially regressed vascular membrane and improved macular anatomy at the time of surgery, thus making preoperative anti-VEGF therapy a considerable adjunctive treatment, particularly in cases with a prominent vascular component.[6] The sole patient

Table 2: Clinical manifestations and visual outcomes of retinal vascular proliferation in patients with von Hippel–Lindau disease

	Unilateral RVP	Juxtapapillary: Peripheral RVP	RVP with fibrous proliferation	Presenting visual acuity	Management	Indication for intervention	Visual outcomes	
							Eyes without intervention	Eyes with intervention
Wong *et al*.[5]a	12	15:1	14	>20/40 (3); ≤20/40 (1); NR (12)	Observation (11); PPV (5)	Worsening of vision (2)[d]	Stable (7); worsened (4)	Improved (5)
Schmidt and Neumann[7]	5	0:5	0	NR (5)	Observation (1); NR (4)	–	Stable (1)	–
Chew[3]	16	3:0b	2b	>20/40 (8); ≤20/40 (9)	Observation (2); PPV (1); NR (14)	Worsening of vision (1)	Stable (2)[b]	Improved (1)[b]
Kreuz *et al*.[6]	1	0:1	1	20/100	IVB + PPV (1)	Worsening of vision (1)	–	Improved (1)
Arnold *et al*.[9]	1	0:1	0	20/30	PRP (1)	Worsening of vision (1)	–	Worsened (1)
Current case	1	1:0	1	20/200	PPV (1)	Persistent traction (1)	–	Stable (1)
Summary of the reported cases	36/39 (92)	Juxtapapillary: 19/27 (70); Peripheral: 8/27 (30)[c]	17/27 (63)[c]	>20/40: 12/24 (50); ≤20/40: 12/24 (50)[c]	Observation: 14/23 (61); PPV: 8/23 (35); PRP: 1/23 (4)[c]	Worsening of vision 5/6 (83); Persistent traction: 1/6 (17)	Stable: 10/14 (71); Worsened: 4/14 (29)	Improved: 7/9 (78)[c]; Worsened: 1/9 (11); Stable: 1/9 (11)

*a*Sixteen eyes of 14 patients, [b]Clinical manifestations of the lesion were reported in 3 patients, [c]*n*/total *n* (%) calculated by the cases with available information, [d]Visual acuity after intervention was only mentioned in 2 patients. Data are presented as the number of patients or eyes unless indicated otherwise. –=Negative, NR=Not recorded, PPV=Pars plana vitrectomy; IVB=Intravitreal injection of bevacizumab, PRP=Panretinal laser photocoagulation

treated with argon laser photocoagulation experienced a decline in visual acuity postmanagement from 20/30 to 20/200.[9] The overall visual outcomes among the reported cases with follow-up details were as follows: 11/23 (48%) remained stable, 5/23 (22%) worsened, and 7/23 (31%) improved.

Our literature review is limited by its retrospective nature and the absence of extended follow-up in some cases. Given these limitations, patients with unaffected vision should be closely observed because benign outcomes are plausible. However, if the lesion exhibits growth and affects visual acuity or obscures the macula, pars plana vitrectomy is recommended due to its favorable surgical outcomes and potential for promoting visual recovery.

In conclusion, we present a pediatric case with RVP that was characterized by nonaneurysmal vascular proliferation and spontaneous fibrotic regression, which distinguished it from retinal capillary hemangioblastoma. Furthermore, these RVP lesions tend to present unilaterally and can have a favorable prognosis despite their juxtapapillary location.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of patient consent

This study was conducted in accordance with the ethical standards of the institutional review board and conformed to the principles outlined in the Declaration of Helsinki.

The authors certify that they have obtained appropriate consent forms from the legal guardians of the patient (s). In the form, the guardians have given the consents for the images and other clinical information of the patient (s) to be reported in the journal. The guardians understand that the names and initials of the patient (s) will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Conflicts of interest

Prof. Chi-Chun Lai, an editorial board member of the Taiwan Journal of Ophthalmology, had no role in the peer review process or the decision to publish this article. The other authors declare no conflicts of interest in writing this paper.

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