

Retinal Vascular Proliferation as an Ocular Manifestation of von Hippel-Lindau Disease

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Objectives: To describe the features, natural history, and management of an unusual manifestation of ocular von Hippel-Lindau disease in the form of fine vascular proliferation.

Methods: Case series of 14 patients with definite or presumed von Hippel-Lindau disease.

Results: Retinal vascular proliferation consisting of fine superficial vessels was found in 16 eyes of 14 patients with von Hippel-Lindau disease. The lesion was often found in a juxtapapillary location and associated with a fibrovascular component and/or a macular epiretinal membrane. In cases with follow-up (12 patients; mean [SD] follow-up, 10.9 [7.5] years), the lesion was stable in 7 of 13 eyes but showed growth and progression re-

sulting in vision loss in the remainder. In 5 eyes, surgical intervention with pars plana vitrectomy, membrane peel, and excision of the fibrovascular lesion resulted in visual improvement in all of the cases.

Conclusions: Ocular von Hippel-Lindau disease can uncommonly manifest as vascular proliferation that consists of fine, superficial, juxtapapillary vessels that are often associated with fibrovascular proliferation and epiretinal membrane formation. The natural history of this lesion is variable and can result in vision loss from tractional effects in progressive cases. Vision-threatening cases may be successfully managed by surgical excision.

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AFFECTING ABOUT 1 IN 40 000 individuals,¹ von Hippel-Lindau (VHL) disease is a rare, multisystem, dominantly inherited cancer syndrome. Tumors related to VHL are not found congenitally but develop later in life when a somatic cell in susceptible tissues acquires a second mutation in the remaining functional copy of the VHL gene. This second hit² then results in the loss of VHL protein function, which culminates in the development of a tumor typical of VHL disease. The reasons only some tissues are susceptible to tumor formation and what determines the phenotype of the tumor formed are not well understood.

The hallmark lesion of ocular VHL disease is the retinal capillary hemangioblastoma (RCH), which occurs in 2 of every 5 patients with VHL disease.³ An RCH is typically a circumscribed, round, orange-red vascular lesion that is located either in a juxtapapillary location or, more commonly, in the peripheral retina.⁴ The RCHs are usually supplied and drained by dilated afferent and efferent vessels and can be seen to fill uniformly on fluorescein an-

giography. Vision loss resulting from RCHs often occurs as a result of exudative effects; peripheral tumors may be treated successfully with laser photocoagulation, cryotherapy, photodynamic therapy, and various forms of radiation, whereas juxtapapillary tumors in many cases still lack definitive therapy.⁵

Other less common, nonangiomatous retinal lesions associated with VHL disease have been previously described in the literature. These have been called *retinal vascular hamartomas*⁶ and *vascularized glial veils*.⁷ In this case series, we describe 14 patients with a consistent pattern of vascular proliferation that is variably associated with a fibrovascular component and epiretinal membrane and is clearly distinct from the hallmark RCH lesion associated with ocular VHL disease. The clinical phenotype, natural history, visual morbidity, pathological findings, and successful management are described.

METHODS

Of the 14 patients in the case series, 12 were enrolled in an institutional review board-

Table. Demographic Characteristics and Systemic von Hippel-Lindau Disease Involvement in 14 Patients With Documented von Hippel-Lindau Disease and Retinal Vascular Proliferation

Patient No./ Age, y/Sex ^a	Basis of VHL Disease Diagnosis	VHL Gene Mutation, Effect on VHL Protein	VHL Family History	Systemic Manifestations of VHL Disease at Most Recent Visit			
				Pancreas	CNS	Renal	Other
1/69/F	Clinical, genetic	Missense mutation in codon 184, exon 3, leucine to proline substitution	+	+	+	+	-
2/44/F	Clinical, genetic	Missense mutation in codon 188, exon 3, leucine to valine substitution	+	+	-	-	-
3/38/F	Clinical, genetic	Missense mutation in codon 161, exon 3, arginine to glutamine substitution	+	-	-	-	Pheochromocytoma
4/38/F	Clinical, genetic	Partial deletion, protein truncating mutation	-	+	+	+	Endolymphatic sac tumor
5/34/F	Clinical, genetic	Partial deletion, protein truncating mutation	-	+	+	+	-
6/34/F	Clinical, genetic	Missense mutation in codon 78, exon 1, asparagine to aspartic acid substitution	+	+	+	+	Epididymal cyst
7/34/M	Clinical, genetic	Single-nucleotide deletion at nucleotide 739, protein truncating mutation	+	+	-	+	-
8/29/F	Clinical, genetic	Nonsense mutation in codon 161, exon 3, arginine to stop codon, protein truncating mutation	+	+	+	-	Endolymphatic sac tumor
9/25/F	Clinical	ND	+	+	+	+	-
10/22/M	Clinical, genetic	Partial deletion, protein truncating mutation	+	+	+	+	-
11/19/F	Genetic	Missense mutation in codon 167, exon 3, arginine to glutamine substitution	+	-	-	-	-
12/16/M	Clinical, genetic	Partial deletion, protein truncating mutation	+	-	-	-	-
13/8/M	Presumed VHL disease	ND	+	-	-	-	-
14/5/F	Presumed VHL disease	ND	+	-	-	-	-

Abbreviations: CNS, central nervous system; ND, not done; VHL, von Hippel-Lindau; +, positive; -, negative.

^aAll of the patients were white.

approved study protocol at the National Cancer Institute, National Institutes of Health. These patients were evaluated for systemic manifestations of VHL disease, and only patients who met clinical diagnostic criteria for VHL disease were enrolled. Of these 12 patients, 11 underwent genetic testing for mutation in the germ-line VHL gene. One patient was not tested. The 2 remaining patients outside of this study protocol (patients 13 and 14) were referred from other clinical centers with a family history of VHL disease (first-degree relative) and suggestive ophthalmic findings. These 2 patients (aged 5 and 8 years) had no other systemic VHL manifestations, and genotype analysis had not been performed. Some of these cases have been described briefly in a prior article.⁸

RESULTS

DEMOGRAPHICS, SYSTEMIC MANIFESTATIONS, AND GENOTYPE OF THE PATIENTS WITH VHL DISEASE

Patient demographics are summarized in the **Table**. Ten patients (71%) were female and all of the patients were white. The mean (SD) age (on last follow-up visit) was

29.6 (16.2) years, with a range of 5 to 69 years. Of 14 patients, 12 had longitudinal follow-up for a mean (SD) period of 10.9 (7.5) years (range, 5 months to 25 years).

In 12 of 14 patients, the diagnosis of VHL disease was made based on clinical criteria⁹ and/or by documentation of a germ-line mutation in the VHL gene (Table). All of the patients older than 22 years had at least 1 typical visceral or central nervous system VHL lesion. Of the 11 patients with a documented germ-line mutation in the VHL gene, 5 (45%) were missense mutations and 6 (55%) had a partial deletion (n=4), nonsense mutation (n=1), or single-nucleotide deletion resulting in a truncated VHL protein product (n=1).

CASE DESCRIPTIONS OF RETINAL VASCULAR PROLIFERATION ASSOCIATED WITH VHL DISEASE

The following 5 cases illustrate the range of phenotypes seen with this particular lesion.

Patient 1 was a 69-year-old white woman with a typical RCH in her left eye from age 13 years that was treated

with radiation. The eye subsequently became phthisical with no light perception. In the decades following treatment, no radiation-associated changes were found in her contralateral eye. At age 62 years, this eye had good visual acuity (20/20) without any RCHs. On the right optic disc, fine superficial retinal vessels on the surface of the optic nerve extending from the optic cup to the rim of the optic nerve were observed (**Figure 1**). No signs of exudation and fibrovascular proliferation were associated with these vessels. The patient was examined 6.5 years later at age 69 years; no interval changes in the features of the lesion were detected.

Patient 3 was a 38-year-old white woman with no evidence of RCHs in either eye. At age 29 years, her right eye had a fine network of superficial retinal vessels in the inferior juxtapapillary region, extending radially from the nerve margin (**Figure 2A**). There was no evidence of exudation, and fluorescein angiography showed slow filling of the vessels without leakage. A fine epiretinal membrane was seen extending temporally across the macula, distorting perifoveal retinal vessels and producing the appearance of a foveal pseudohole (**Figure 2B**). Visual acuity was 20/20 OD. Her contralateral eye was normal. When the patient was reexamined 9 years later at age 38 years, there were no interval changes in the lesion or in visual acuity.

Patient 10 was a 22-year-old white man who had been initially examined at age 12 years. At that time, his left eye had a large juxtapapillary vascular complex extending from the nerve along the superior arcade that was associated with dense fibrovascular tissue. The complex extended across the vitreoretinal surface, exerting traction on the retinal surface and causing macular retinal striae (**Figure 3A**). Visual acuity at this time was 20/20 OS; no RCHs were present. Fluorescein angiography demonstrated filling of the vascular proliferation in the early frames and diffuse leakage of dye from the entire fibrovascular complex in the late frames (**Figure 3B and C**). No lesions resembling juxtapapillary RCHs were seen. During the next 29 months, this fibrovascular complex enlarged, extending into the center of the macula and causing a decrease in visual acuity to 20/80 (**Figure 3D**). The patient underwent pars plana vitrectomy and membrane peel, during which the fibrovascular complex was dissected from the vitreoretinal surface and removed completely. The excised specimen was submitted for pathological analysis. When the patient was reexamined 7 years after his surgery, there was no recurrence of the lesion (**Figure 3E**). Visual acuity increased to 20/63 postoperatively. In the patient's contralateral right eye, 3 typical peripheral RCHs were observed during this 7-year follow-up. At age 14 years, he was also noted to have a small patch of superficial retinal vessels in the inferior retinal quadrant near the equator of the right eye that resembled an arteriovenous anastomosis (**Figure 3F**). This lesion was ablated with argon laser photocoagulation.

Patient 4 was a 38-year-old white woman who was examined after a craniotomy at age 24 years and noted to have mild bilateral papilledema and visual acuities of 20/20 OU. She had a typical peripheral RCH in her left eye that had been treated previously with argon laser photocoagulation. No other vascular abnormality was present.



Figure 1. Right optic nerve of patient 1, with fine superficial retinal proliferative vessels (arrow) extending from the central surface to the peripheral surface of the nerve. No epiretinal membrane or fibrovascular proliferation is associated with the neovascular vessels.

When examined 1 year later, her right eye was found to have developed new fine, juxtapapillary, superficial retinal vessels that covered the surface of the optic nerve and extended into the nasal macula (**Figure 4A**). The vessels were associated with a mild degree of fibrovascular proliferation that exerted traction on the macula, resulting in striae and a decreased visual acuity of 20/50 OD. Fluorescein angiography showed filling of the vessels in the early phase and slow leakage and staining of the fibrovascular complex in the late phase (**Figure 4B and C**). At this time, the contralateral left eye appeared normal. The patient underwent pars plana vitrectomy during which the fibrovascular complex was completely excised, with a recovery of visual acuity to 20/20 OD. She was reexamined 11 years later at age 36 years with no lesion recurrence (**Figure 4D**). However, at this time, her left eye was noted to have a new area of juxtapapillary retinal vessel proliferation on the nasal border of the optic nerve. The retinal vessels extended nasally and lacked a fibrovascular component (**Figure 4E**), but they were associated with a fine macular epiretinal membrane (**Figure 4F**). Visual acuity remained 20/20 OS. On reexamination 2 years later at age 38 years, no further structural or visual acuity changes were noted in either eye.

Patient 8 was a 29-year-old white woman with a history of poor vision in her left eye from age 5 years. At that time, no typical RCHs were found but she was noted to have a large peripapillary fibrovascular complex in her left eye that extended into the macula. No treatment was rendered. At age 29 years, visual acuity was 20/500 OS. On examination, a papillary fibrovascular stalk could be seen extending from the nerve into the vitreous (**Figure 5**) and also onto the center of the macula, exerting tractional effects on retinal vessels in the major vascular arcades. Areas of chronic pigmentary change were also present in the macula. No vascular lesions were observed in the right eye.

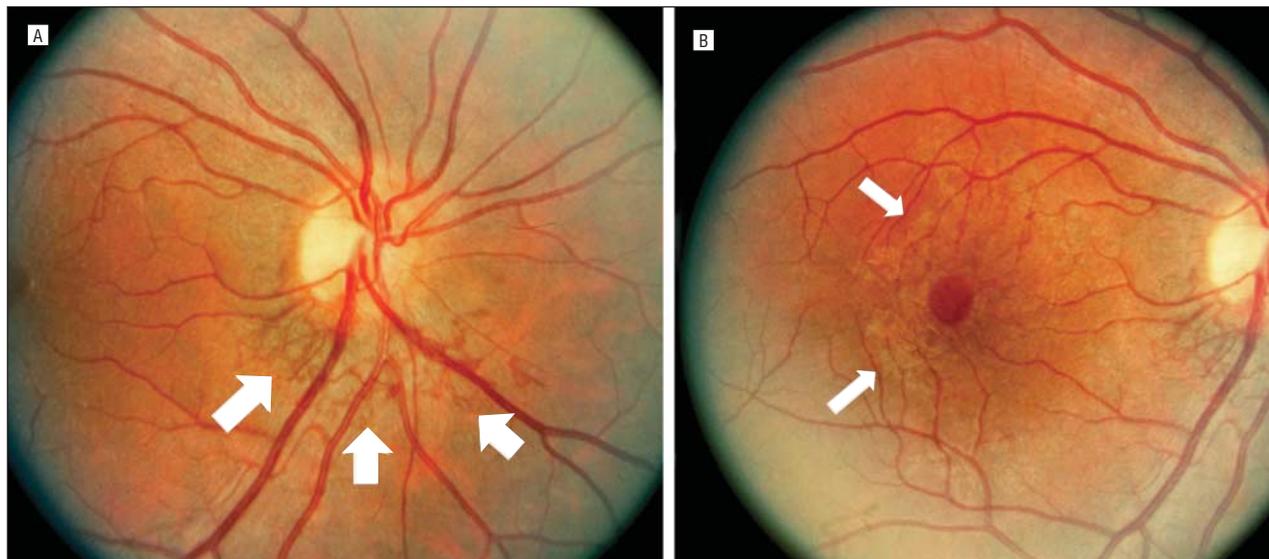


Figure 2. Right optic nerve (A) and macula (B) of patient 3. A, Fine juxtapapillary retinal vessels are found from the 4-o'clock to 8-o'clock positions along the optic nerve margin (arrows). B, An epiretinal membrane extending temporally across the macula is seen (arrows), with an appearance of a pseudohole in the fovea.

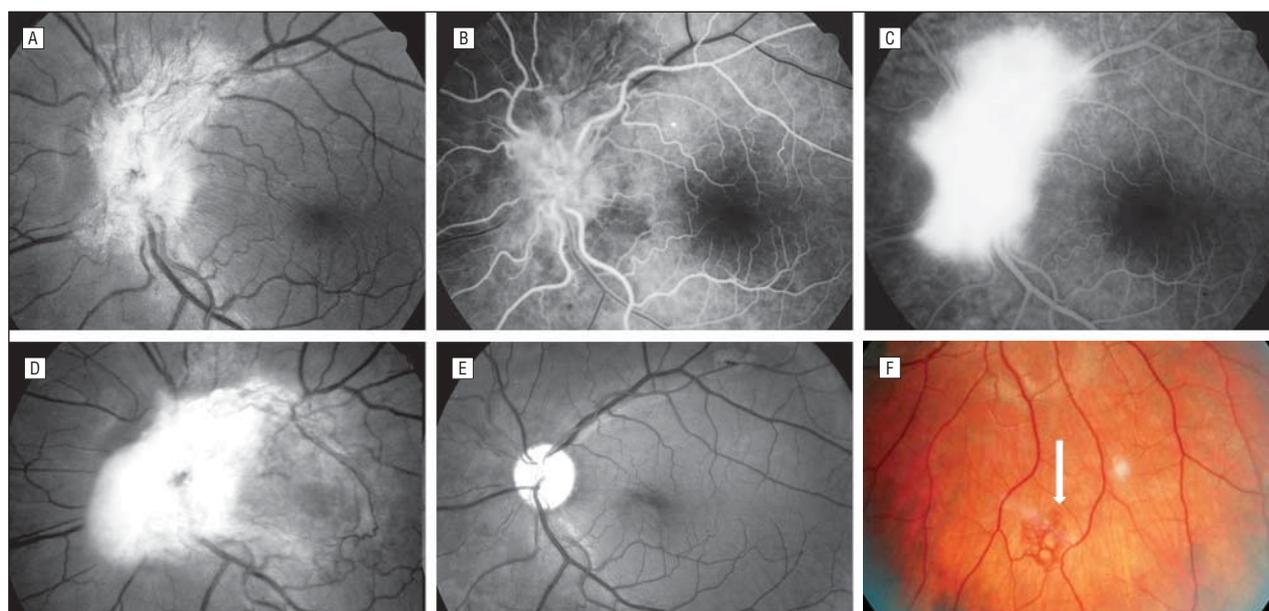


Figure 3. Patient 10. A, At age 12 years, a red-free photograph of the left eye shows retinal vascular proliferation extending from the optic disc to the superior arcade, associated with a large fibrovascular component, causing macular striae. Also at age 12 years, fluorescein angiograms show slow filling of the neovascular vessels in the early phase (B) and late staining and leakage in the late phase (C). D, At age 15 years, a red-free photograph shows that the fibrovascular complex has increased in height as well as area and now extends into the macula. E, At age 22 years, 7 years after surgical removal of the fibrovascular complex, a red-free photograph documents the absence of lesion recurrence. F, A color photograph of the contralateral right eye at age 14 years shows extrapapillary retinal vascular proliferation forming an arteriovenous anastomosis (arrow).

OCULAR FEATURES OF RETINAL VASCULAR PROLIFERATION

The prevalence of this rare VHL association is low; 12 of 14 patients in this series were part of a systemic VHL disease study at the National Cancer Institute, which screened 890 patients and identified 335 patients with ocular VHL disease.⁴ The overall prevalence of this lesion type may thus be estimated at 1.3% among all patients with VHL disease and at 3.6% among patients with ocular VHL disease.

Ocular features in the 14 affected patients are summarized in eTable 1 (available online at [\[.archophthalmol.com\]\(http://www.archophthalmol.com\)\). Fine vascular proliferation was unilateral in 12 of 14 patients \(86%\). Among affected eyes \(n=16\), all lesions but 1 \(94%\) were juxtapapillary in location. In 14 of 16 affected eyes \(88%\), the lesion was associated with either a fibrovascular component or the presence of a macular epiretinal membrane. These fine superficial vascular proliferations are clearly distinct in their clinical properties from neovascular vessels arising from diabetic retinopathy, sickle cell retinopathy, or ischemic retinopathies \(pathological findings absent from patients in this series\); they are not associated with ischemic changes elsewhere in the retina and do not ex-](http://www</p>
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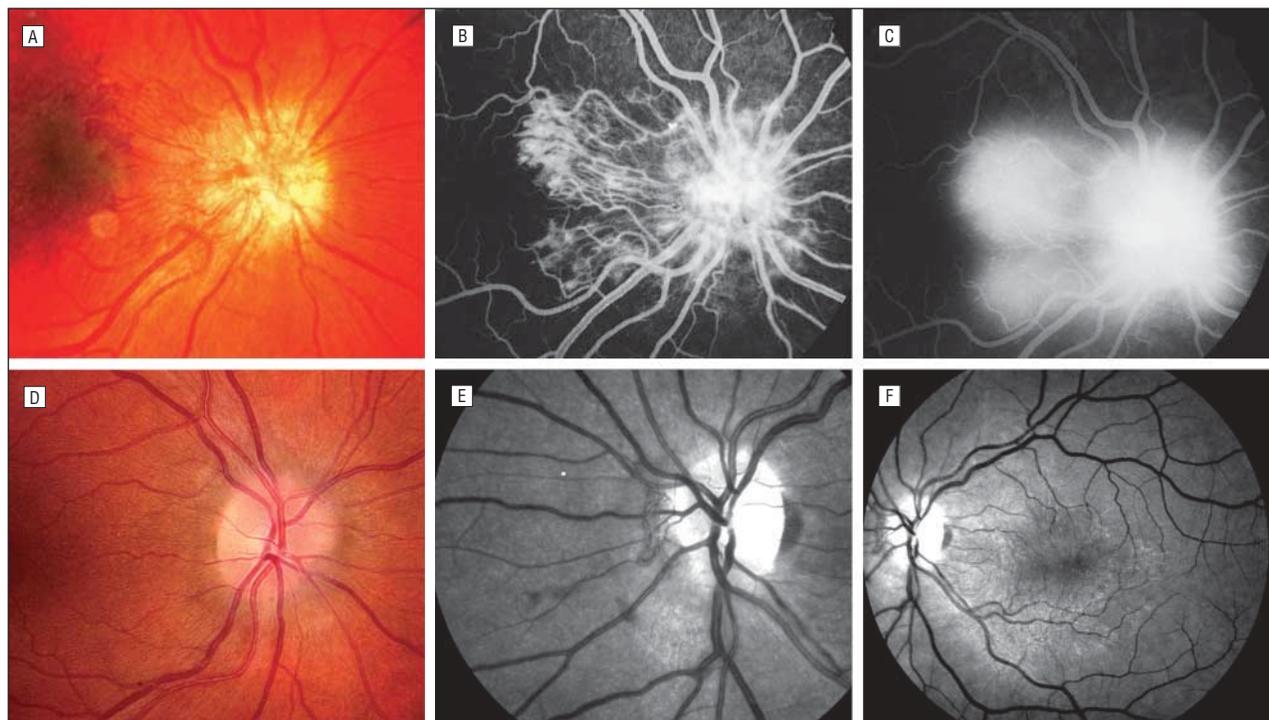


Figure 4. Patient 4. A, At age 25 years, a color photograph of the right eye shows superficial retinal vessels extending over the entire optic disc and into the nasal macula. Also at age 25 years, fluorescein angiograms show filling of the vessels in the early phase (B) and late staining and leakage in the late phase (C). D, At age 36 years, a color photograph of the right eye shows complete resolution of the fibrovascular complex without recurrence. E, Also at age 36 years, a red-free photograph of the left nerve shows fine retinal vessels extending nasally from the edge of the optic disc margin. F, Again at age 36 years, a red-free photograph shows the epiretinal membrane in the left macula.

hibit any exudative or hemorrhagic features. While these vessels appear to fill readily and completely from existing retinal vessels in the transit phase on fluorescein angiography, they do not leak prominently unless associated with a significant fibrovascular component, in which case late staining can be observed. Areas of ischemic non-perfusion were not observed. Visual loss associated with these lesions occurred from disruption of the macular architecture arising from tractional forces exerted by the fibrovascular complex or from an associated epiretinal membrane. However, tractional retinal detachments per se were absent. The presence of this lesion did not preclude the presence of more typical RCHs in the same eye; 5 of 16 affected eyes (31%) had 1 or more RCHs.

In this case series, the age at which VHL-associated vascular proliferative lesions were first detected ranged from 3 to 62 years (mean [SD], 20.6 [15.6] years). On average, the lesions tended to appear early in life, manifesting in about one-third of patients during each of the first decade of life (4 of 14 patients [29%]) and the second decade of life (5 of 14 patients [36%]), making it largely a lesion of childhood and adolescence. Among the older patients in the series, early records were unavailable and the time of onset of the lesion cannot be determined precisely. However, in 1 patient (patient 4), new lesions were documented to arise de novo between ages 25 and 36 years.

The natural history of this particular lesion in this series was variable and was unlike that seen in retinal neovascularization from other causes. In 7 of 16 eyes (44%), there was stability in the structure of the lesion over many years of observation with maintenance of good visual acu-

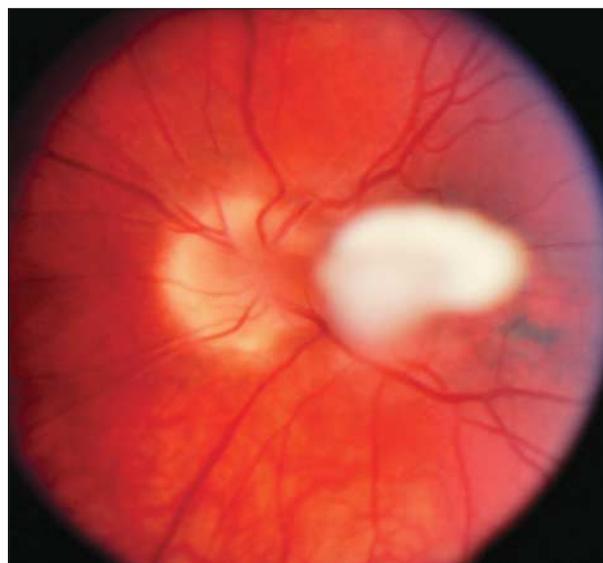


Figure 5. A color fundus photograph of the left eye of patient 8 shows a large fibrovascular stalk arising from the optic disc and chronic tractional effects on the macula.

ity ($\geq 20/25$) without intervention. In cases of progression, visually significant sequelae resulted from growth of the fibrovascular complex toward the macula and along the major arcades and from formation of a macular epiretinal membrane. The end stage of the progression, left untreated, is likely to be the formation of a large fibrotic peripapillary lesion associated with chronic scarring and distortion of the macula as seen in patient 8.

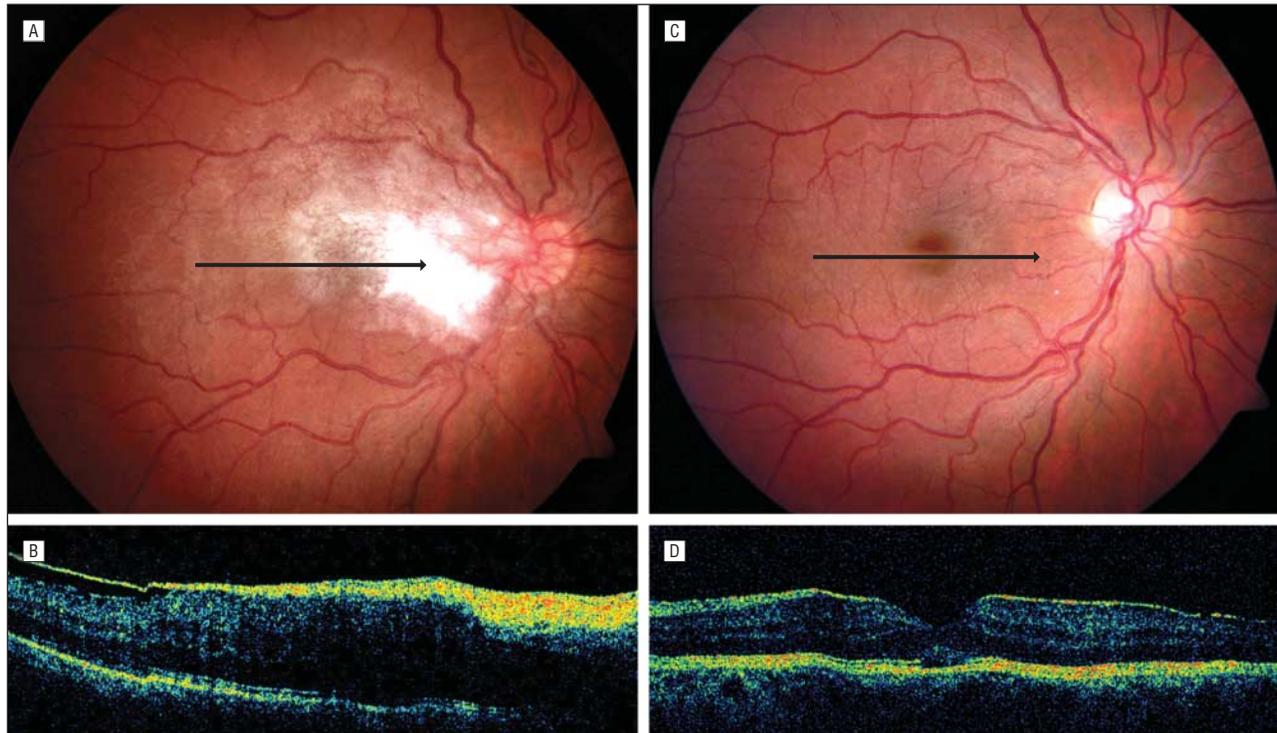


Figure 6. Patient 11. A, A color photograph shows a fibrovascular complex and associated epiretinal membrane. B, Optical coherence tomographic image of a horizontal scan through the macula shown in A. C, A color photograph shows the same eye after surgical excision of the entire fibrovascular complex and epiretinal membrane. D, Optical coherence tomographic image of a horizontal scan through the macula shown in C. The horizontal arrows in A and C indicate the position and direction of the optical coherence tomographic scans shown in B and D, respectively.

From this small group of patients, patient demographics (age, age at onset, and race) and nature of the VHL germline mutation could not be clearly associated with the laterality, phenotype, or natural history of the lesion.

MANAGEMENT OF VHL-ASSOCIATED RETINAL VASCULAR PROLIFERATION

In 5 eyes of 5 patients (patients 4, 10, 11, 13, and 14), retinal vascular proliferations were associated with a large fibrovascular component and were managed surgically. In all of the cases, pars plana vitrectomy was first performed, followed by the dissection and excision of the entire fibrovascular complex from the vitreoretinal surface. The procedures were not complicated by significant hemorrhage, and complete removal of the lesion was accomplished in all of the cases. Retinal anatomy of the fovea was largely preserved in all of the cases, and the underlying intraretinal vasculature was unaffected (for example, in patient 11, **Figure 6A**). Pre-surgical (Figure 6A and B) and postsurgical (Figure 6C and D) optical coherence tomography in patient 11 demonstrated the fibrovascular complex as a hyperreflective layer that was limited to the vitreoretinal surface. There was traction on the underlying retinal tissue, resulting in thickening and obliteration of the foveal contour. Postsurgically, excision of the complex restored the overall shape of the foveal contour, leaving behind only a small disruption in the outer retinal lamination (corresponding perhaps to the inner segments at the base of the foveal pit) and a small residual macular epiretinal membrane. In these cases, visual acuity outcomes were improved (eTable 2) without significant postoperative complications or recurrences.

HISTOPATHOLOGICAL ANALYSIS OF VHL-ASSOCIATED RETINAL VASCULAR PROLIFERATION

In 1 case (patient 10), histopathological analysis of the surgically excised fibrovascular complex revealed a small piece of fibrovascular membrane composed of loose connective tissue with a few small thin-walled vessels. Immunohistochemical analysis showed positivity for vascular endothelial growth factor highlighting the vascular endothelial cells (**Figure 7**).

COMMENT

Uncommon angiomatous retinal lesions associated with VHL disease have been previously reported.¹⁰ Also, some infrequent nonangiomatous VHL retinal lesions have also been described. These include paired retinal arterioles and venules called *twin vessels*¹¹; flat, sessile, vascular tufts that form arteriovenous anastomoses termed *retinal vascular hamartomas*^{6,7}; and juxtapapillary vascularized fibrovascular membranes termed *vascularized glial veils*.⁷ This last entity most closely resembles the juxtapapillary lesion type featured in this case series, whereas the peripheral lesion in patient 10 is similar to the previously described retinal vascular hamartoma. Here, we have provided a larger number of cases with a more detailed description of the lesion phenotype, its natural history, histopathological findings, and surgical management. We also have preferred the term *retinal vascular proliferation* to *vascularized glial veils* to include lesions that do

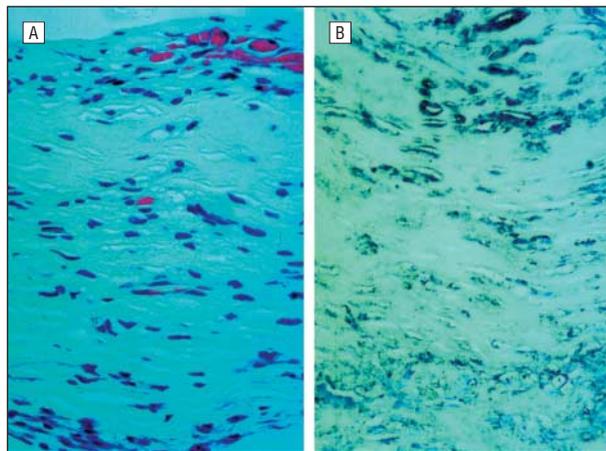


Figure 7. Photomicrographs of a fibrovascular membrane excised from the left eye of patient 10, showing fibrous tissue with small blood vessels (hematoxylin-eosin, original magnification $\times 200$) (A), with positive staining for vascular endothelial growth factor in the vascular endothelium and some collagens of the membrane (dark areas, avidin-biotin-complex immunoperoxidase, original magnification $\times 200$) (B).

not have, or have yet to develop, a significant fibrovascular component. The lesions consist of a proliferation of vessels in the superficial retina that are filled from existing, normal retinal vessels. Throughout the entire spectrum of lesion phenotypes, no angiomatous component was identified.

The pathogenic mechanisms underlying this particular VHL-associated lesion are unclear. It is unlikely that they result from particular mutations in the germ-line VHL gene; from the 11 genotyped patients in our series, there was no consistent pattern of mutational genotypes (Table). It has been proposed that an RCH arises in VHL disease as a result of a second hit in an initial stromal cell that inactivates both VHL alleles. This loss of VHL protein function then results in an overproduction of downstream growth factors such as vascular endothelial growth factor and platelet-derived growth factor B chain that in turn stimulate the proliferation of surrounding pericytes and endothelial cells, culminating in an RCH.^{12,13} It is possible that in the retinal vascular proliferations in this series, this second hit may have occurred in a different retinal precursor cell that undergoes transformation into a phenotypically distinct lesion. The presence of abundant vascular endothelial growth factor, as found in our histopathological analysis, may be similarly involved in lesion formation and growth. Future molecular analysis of the lesion tissue may be useful in addressing this hypothesis.

Our series may be limited by its retrospective nature and short follow-up in some cases. However, the mean follow-up for the whole series was more than 10 years. Three patients who underwent vitrectomy with membrane peeling were followed up for less than 12 months, but stability of vision and examination results was maintained during each patient's follow-up period. In addition, the 2 patients with long-term follow-up after vitrectomy have demonstrated visual stability without recurrence of retinal neovascularization for more than 9 years.

Taking into account these limitations, we recommend that early, nonvisually significant lesions be observed as they can sometimes have a benign natural history. For lesions

that grow and encroach on the macula, surgical removal is recommended to successfully restore macular architecture and aid visual recovery. Surgical excision should be undertaken promptly in a child for whom amblyopia is a concern; deferring intervention may result in chronic macula scarring and very poor visual acuity.

In summary, we have described a series of patients with VHL disease with a rare ocular lesion that differs in phenotype, natural history, and management considerations from the more commonly observed RCH lesions. Specifically, our series of patients with VHL disease developed superficial retinal vascular proliferation as a primary process in the absence of retinal ischemia, with many developing a secondary fibrovascular component and epiretinal membrane formation. The pathogenesis of this VHL lesion is unclear but likely involves the up-regulation of vascular endothelial growth factor following loss of VHL protein function. In cases of documented progression, these lesions may be successfully addressed by surgical excision with vitrectomy and membrane peeling.

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