Title
MANAGEMENT OF RETINAL HEMANGIOBLASTOMA IN VON HIPPEL-LINDAU DISEASE.

Journal
Retina, 39(12)

ISSN
0275-004X

Authors
Wiley, Henry E
Krivosic, Valerie
Gaudric, Alain
et al.

Publication Date
2019-12-01

DOI
10.1097/iae.0000000000002572

Peer reviewed

Published in final edited form as:

Retina. 2019 December ; 39(12): 2254–2263. doi:10.1097/IAE.0000000000002572.

Management of Retinal Hemangioblastoma in von Hippel-Lindau Disease

Henry E. Wiley, MD[1], **Valerie Krivosic, MD**[2,3], **Alain Gaudric, MD**[2,3], **Michael B. Gorin, MD, PhD**[4], **Carol Shields, MD**[5], **Jerry Shields, MD**[5], **Mary E. Aronow, MD**[6], **Emily Y. Chew, MD**[1]

[1]National Eye Institute, National Institutes of Health, Bethesda, MD

[2]Service d'Opthalmologie, APHP, Hôpital Lariboisière, Université Paris-Diderot, Sorbonne Paris Cité. France

[3]Centre de Référence des Maladies Vasculaires Rares du Cerveau et de l'OEil (CERVCO), Hôpital Lariboisière, APHP, Paris, France

[4]Jules Stein Eye Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA

[5]Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA

[6]Ocular Oncology Service, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA

Abstract

Purpose: To review the current state of diagnosis and management of retinal hemangioblastoma (RH) and retinal vascular proliferation arising from von Hippel-Lindau (VHL) disease.

Methods: A review of the literature was performed. Consensus was reached among authors regarding current practice, with reference to published data where possible.

Results: VHL disease and its ocular manifestations are relatively rare, and there is limited evidence in the literature on which to base management. There was consensus on core principles, including: 1.) Recognition and diagnosis of VHL disease when present, with appropriate referral for care of this potentially lethal systemic condition; 2.) Regular ophthalmic evaluation for individuals with VHL disease, to identify and offer timely treatment for new or active RH; 3.) Ablative treatment of RH that can be safely destroyed, to lower risk of vision loss; 4.) Observation or consideration of non-ablative treatments for RH that cannot be safely destroyed; and 5.) Observation of asymptomatic retinal vascular proliferation, with consideration of vitrectomy for lesions exerting effects on vision.

Corresponding author: Henry E. Wiley, MD, National Eye Institute, 10 Center Drive, Building 10, CRC, Room 3-2531, Bethesda, MD 20892-1204, wileyhe@nei.nih.gov.

Conflict of interest disclosure:
No conflicting relationship or proprietary interest exists for any author.

This manuscript describes off-label use of VEGF antagonists (such as ranibizumab, bevacizumab, aflibercept, and pegaptanib), corticosteroids, and photodynamic therapy with verteporfin for treatment of ocular VHL disease.

Conclusion: Ocular outcomes can be gratifying in many cases with appropriate management. Improved understanding of the molecular basis for the disease creates an opportunity for rational design of better therapies.

Summary statement:

We review the diagnosis and management of retinal hemangioblastoma and retinal vascular proliferation in the setting of von Hippel-Lindau disease, with emphasis on diagnosis of the underlying systemic disease when present, timely detection of ocular lesions, and use of ablative therapy for those retinal hemangioblastomas that can be safely destroyed.

Keywords

pVHL; Retinal capillary hemangioma; Retinal capillary hemangioblastoma; Retinal hemangioblastoma; Retinal hemangioma; Retinal vascular proliferation; Von Hippel-Lindau disease

Von Hippel–Lindau (VHL) disease is an autosomal dominantly-inherited condition in which mutations in the VHL gene lead to development of characteristic benign and malignant neoplasms or cysts in the central nervous system and viscera. The cardinal manifestation of ocular VHL disease is the retinal hemangioblastoma (RH, also appearing in the literature as retinal capillary hemangioma, retinal capillary hemangioblastoma, or retinal angioma), a benign neoplasm with vascular features originating in the retina or optic disc that can lead to vision loss from retinal exudation, fibrosis, vitreous and subretinal hemorrhage, or retinal detachment. Retinal vascular proliferation, characterized by epiretinal growth of fibrovascular tissue, is a less common feature.

Solitary RH can occur in the absence of VHL disease, but the presence of this tumor should prompt consideration of the systemic disorder, given the life-threatening nature of some of its characteristic lesions, such as renal cell carcinoma, pheochromocytoma, and central nervous system hemangioblastoma. Core principles of management include: 1.) Recognition and diagnosis of VHL disease when present, with appropriate referral for comprehensive care, ideally to a multispecialty team familiar with this complex and potentially lethal systemic condition; 2.) Ocular surveillance for individuals with VHL disease, via regular ophthalmic evaluation, to identify and offer timely treatment for new or active RH as early as possible; 3.) Ablative treatment of RH that can be safely destroyed, to lower risk of vision loss from progressive growth, exudation, and scarring; 4.) Observation or consideration of non-ablative treatments for RH that cannot be safely destroyed (such as those growing in proximity to the optic disc and fovea); and 5.) Observation of asymptomatic retinal vascular proliferation, with consideration of vitrectomy for lesions exerting macular traction and consequent effects on vision.

Diagnosis of Retinal Hemangioblastoma and VHL Disease

VHL disease is caused by mutation in the VHL tumor suppressor gene, located on chromosome 3 (3p25–26), which codes for a protein (pVHL) that has been shown to play an important role in cellular oxygen-sensing.[1,2] Most individuals with VHL disease inherit a

mutant copy of the VHL gene from an affected parent, and a wild-type (normal) copy of the gene from the other parent. Occasional cases result from de novo germline or somatic cell mutation of the VHL gene, and accordingly present in the absence of a family history of the disease. Neoplasia in VHL disease results from the somatic inactivation of the normal allele in one or more cells of an individual with a germline (typical) or somatic (rare) mutation in the other allele, in accordance with Knudson's two-hit model for tumorigenesis.[3] The clinical diagnosis of VHL disease is classically based on the following criteria: (1) Positive family history AND presence of a central nervous system hemangioblastoma, RH, pheochromocytoma, OR clear cell renal carcinoma; OR, (2) in the absence of a family history, presence of two or more central nervous system hemangioblastomas or RH, OR one central nervous system hemangioblastoma or RH, AND a visceral tumor (with the exception of epididymal and renal cysts, which are common in the general population).[4,5] Manifestations of VHL disease are heterogeneous, and even those not meeting criteria above should be further evaluated for the condition in the setting of clear cell renal cell carcinoma occurring before age 40; multiple clear cell renal cell carcinomas; central nervous system hemangioblastoma occurring before age 30; pheochromocytoma or pancreatic neuroendocrine tumor occurring before age 40; multiple pheochromocytomas or pancreatic neuroendocrine tumors; endolymphatic sac tumor; multiple pancreatic serous cystadenomas; epididymal papillary cystadenoma; multiple pancreatic cysts in association with another VHL disease-associated lesion; two or more VHL disease-associated lesions; family history of the disease; or one or more VHL-associated lesions plus family history of a VHL disease-associated lesion.[5] Genetic testing has become standard to confirm the diagnosis, and can be especially helpful in certain situations, such as when a patient presents with one or more central nervous system hemangioblastomas or RH in the absence of a family history or visceral lesions. Genetic testing is also important to establish the diagnosis in at-risk family members of a patient with VHL disease, given the latency and heterogeneity of clinical manifestations but a penetrance of over 90% by age 65.[6] It is important to understand the sensitivity of the genetic testing methods used in any particular case, and to bear in mind that even the most comprehensive approaches can be falsely negative, underscoring the importance of interpreting results in the context of clinical evaluation.

RH can arise in association with the optic disc (designated as juxtapapillary or epipapillary RH), or within retina elsewhere (designated as extrapapillary RH). Extrapapillary RH starts as a tiny red or gray intraretinal dot, measuring less than a few hundred microns in diameter, with an ophthalmoscopic appearance similar to a microaneurysm or punctate intraretinal hemorrhage (Figure 1). Fluorescein angiography (FA), particularly with use of wide-field imaging, is a sensitive means for identifying these lesions, which exhibit early and late hyperfluorescence.[7-9] It is only with increasing size that extrapapillary RH display more distinctive prototypical features, such as increasing nodularity; feeding and draining blood vessels that become progressively dilated and tortuous; associated exudation consisting of retinal edema, subretinal fluid, and/or lipid; and early hyperfluorescence with progression to late leakage on FA (Figure 2). RH originate as a mass within the inner retina, manifesting hyper-reflective thickening of these layers on optical coherence tomography (OCT) scanning,[8] and can displace outer retinal layers with increasing size. Juxtapapillary RH can exhibit more subtle features, sometimes appearing only as a localized fullness of the inner

retina at the border of the neural rim, and feeding and draining vessels are usually absent in these lesions, but FA allows ready visualization of associated hyperfluorescent staining and leakage (Figure 3). The typical features of RH more than a few hundred microns in diameter, as characterized on ophthalmoscopy, FA, and OCT, are readily recognized and allow for diagnosis in most cases. The lesion that most closely resembles RH is the vasoproliferative tumor of the ocular fundus,[10,11] and occasionally it can be difficult to differentiate the primary form of vasoproliferative tumor from an extrapapillary RH in the case of a solitary lesion in an individual not known to have VHL disease.

The presence of a solitary RH may reflect a sporadic occurrence or presence of underlying VHL disease. The probability of VHL disease in an individual with a solitary RH has been modeled and depends on the age at diagnosis (with higher risk of having VHL disease in younger individuals),[12] but we typically pursue systemic evaluation and genetic testing even in older individuals without suggestive medical or family history. Many such patients will not have VHL disease,[13] but the potentially life-threatening consequences of missing a case weigh in favor of evaluation. Presence of more than one RH (whether in the same eye or in different eyes) satisfies clinical criteria for diagnosis of VHL disease, as listed above, and should prompt appropriate referral, ideally to a team with expertise in neurosurgery, neuroradiology, urologic and endocrine surgical oncology, otolaryngology, pathology, genetics, and rehabilitation medicine. An ophthalmologist in this setting must be comfortable with the surveillance and treatment of ocular manifestations of VHL disease, and committed to collaboration in multispecialty care.

Approach to Management of Ocular VHL Disease

The goal of treatment for extrapapillary RH is typically destruction of the tumor, to prevent further growth or exudation. Rarely, we observe extrapapillary RH with features suggesting inactivity or partial regression, following the eye closely and maintaining a low threshold for offering ablative treatment for any indication of growth or activity, but destruction of the lesion to prevent future problems is almost always preferable. Large case series demonstrate that small tumors can be readily ablated, prior to any vision loss and with minimal risks of treatment;[14,15] in contrast, larger lesions can be much more difficult to neutralize, and injury caused by treatment often results in a variable acute exudative response that can occasionally cause retinal detachment and threaten vision. Accordingly, a core principle of our approach to management is to identify RH as early as possible, to offer timely treatment. The success of this approach hinges on adequate surveillance for appearance of RH, with acknowledgment that the smallest and most readily-treated tumors do not typically cause symptoms to help bring them to attention.

Annual ophthalmic evaluation is indicated for individuals with VHL disease, starting in early childhood. The age for first examination has not been well-established, but it is rare to find a RH readily visible by ophthalmoscopy in a child under 4 years old. Evaluation of the retina by indirect ophthalmoscopy and extended slit-lamp biomicroscopy by a skilled examiner is generally sufficient to identify all but the smallest and subtlest lesions. Ancillary imaging, when feasible, is helpful to optimize detection rate, particularly in children and in other cases in which cooperation with extended ophthalmoscopy is limited. We commonly

utilize color fundus photography, wide-field photography, and wide-field FA to help detect small tumors. We do not use OCT for identification of extrapapillary RH, but it can be very helpful for detection of juxtapapillary RH and characterization of any RH-associated macular edema, epiretinal membrane, or subretinal fluid (Figure 3), and may occasionally help characterize unexpected features.[8] Identification of extrapapillary RH usually warrants prompt intervention and close subsequent surveillance, tailored to the circumstances. Treated tumors are followed closely after attempted ablation, to monitor for expected regression or signs of regrowth, or persistent or recurrent exudation. Some eyes manifest new tumors more frequently than others, and must be watched closely. Care should be taken to maintain surveillance of the entire retina in both eyes, and not to focus attention solely on known or treated lesions. A systematic approach to screening minimizes risk of missing new tumors, and use of imaging modalities such as color fundus photography and wide-field FA, when feasible, can increase sensitivity of detection.[7-9]

The approach above works well for most RH, but in some cases ablative therapy is either not safe or not effective. Management is most difficult for juxtapapillary RH, particularly those situated in the papillomacular bundle, for which ablative treatments often pose an unacceptable risk for harm to central vision, and for RH that are large, refractory to prior therapy, and/or associated with epiretinal proliferation or retinal detachment. Use of intravitreal vascular endothelial growth factor (VEGF) antagonists or photodynamic therapy to try to limit tumor exudation, or vitreoretinal surgery for management of RH in the setting of retinal detachment, epiretinal traction, or intraocular hemorrhage can be attempted in certain situations and is further discussed below.

Ablative Treatment of Extrapapillary Retinal Hemangioblastoma

Thermal laser photocoagulation, cryotherapy, radiotherapy (brachytherapy, external beam radiotherapy, and proton beam radiotherapy), photodynamic therapy with verteporfin infusion, and transpupillary thermotherapy have all been employed for attempted destruction of RH amenable to such treatment. The feasibility and success of treatment depend on a number of factors, including tumor size, tumor location, degree of exudation, presence of retinal detachment, associated epiretinal fibrosis or hemorrhage, associated chorioretinal scarring (such as from previous laser photocoagulation or cryotherapy), position relative to location of a scleral buckle in previously operated eyes, the features of other viable RH inside the eye, associated retinal vascular changes or vascular proliferation, and response to any previous treatment.

Extrapapillary RH up to 1.5 mm (one disc diameter) in diameter can reliably be ablated using thermal laser photocoagulation across one or more treatment sessions.[7,14-20] In one series of 174 RH in 86 eyes (68 patients) treated with laser photocoagulation, successful ablation was reported for 18/18 (100%) tumors with diameter of 1.5 mm or less, compared with 8/17 (47%) larger RH.[14] In another series of 304 RH in 100 eyes (74 patients) treated with laser photocoagulation, successful destruction was achieved in 271/271 (100%) RH with diameter of 1.5 mm or less, over a mean of 1.3 laser sessions, compared with 24/33 (73%) larger RH, over a mean of 3.5 sessions.[15] Various laser types, including argon green, diode, yellow dye, and krypton, have all shown efficacy in published series.[7,14-20] It has

been theorized that vascular lesions such as RH may absorb yellow light more readily than other laser wavelengths based on the absorption spectrum of oxyhemoglobin,[21] and that use of blue-green laser immediately after intravenous infusion of fluorescein sodium dye may similarly allow for better uptake of laser energy by these vascular lesions,[7,17] but no randomized comparison of ablative laser type or technique has been reported. The treatment technique for small tumors involves a longer burn duration (usually 0.2 to 0.4 seconds) than would be typical for panretinal photocoagulation or laser retinopexy, with power sufficient to create prominent whitening, and with application of burns sufficient to blanch the entire tumor surface. Some apply laser burns surrounding the RH or to feeding and draining blood vessels, but this was not necessary to achieve ablation of small tumors in the series by Krivosic et al described above.[15] The appearance of focal intraretinal or preretinal hemorrhage on the tumor surface immediately following laser photocoagulation is common, but vitreous hemorrhage for lesions of this size is rare. After successful treatment, the lesion evolves a variable chorioretinal scar (Figure 4), sometimes associated with a shrunken, fibrotic vestige of the lesion, and other times with disappearance of the RH. A regressed but visible lesion corresponding to the original RH is compatible with destruction sufficient to prevent further growth or exudation, but treated areas must be followed over time for any sign of persistent viability. Assessment for re-treatment is advisable within 3 to 6 months after laser application, and the technique for re-treatment is the same.

Extrapapillary RH between 1.5 and 4.5 mm in diameter are more difficult to destroy using thermal laser photocoagulation. Multiple sessions are almost always needed to achieve success, and some lesions persist after a number of treatment sessions.[14,15] There is variation in technique, given the limitations of all current methods and absence of any systematic prospective comparisons. Direct treatment of the tumor typically involves application of long-duration burns (usually 0.4 to 0.7 seconds) using a power setting lower than that needed for a typical panretinal photocoagulation or laser retinopexy spot, with a goal of maximizing penetration over the course of the burn. Some of us routinely apply blue-green laser photocoagulation shortly after intravenous infusion of fluorescein sodium dye for RH of this size,[7,15] on the hypothetical grounds mentioned above. Although not common practice, some have advocated for treatment of feeding arterioles with goal of tumor hypoperfusion or nonperfusion, with or without subsequent direct treatment of the tumor.[20] Appearance of hemorrhage on the tumor surface is common with direct treatment, as for smaller lesions, but vitreous hemorrhage is uncommon. Increasing tumor height, exudation, epiretinal fibrosis, or pre-existing vitreous hemorrhage can impair placement of adequate treatment. Some of us occasionally re-treat as soon as hours after an initial session,[15] while others space treatments by up to several months. Trans-scleral cryotherapy is often effective for RH in this size range, either as treatment applied to lesions refractory to previous laser photocoagulation, or as first-line therapy. Some of us often use cryotherapy as first-line treatment for RH greater than 1.5 mm in diameter, especially in the setting of features that make laser photocoagulation less effective, and for lesions with prominent feeding and draining vessels (Figure 5). Treatment can be applied trans-conjunctivally for anterior tumors, or trans-sclerally after conjunctival incision to enable appropriate probe placement for more posterior lesions. The technique varies, with some using a single freeze-thaw cycle (typically in the context of treating tumors already partly-regressed from prior laser

photocoagulation,[15] and others using a double freeze-thaw method.[14] Transvitreal cryotherapy at vitrectomy is utilized by some and has the advantages of removal of vitreous that can otherwise contribute to post-treatment fibrotic changes and more localized delivery to the tumor with less injury to the choroid, but these potential benefits must be weighed against the risks of a more invasive procedure. Use of photodynamic therapy with verteporfin infusion for attempted ablation of RH this size has been described with occasional success,[22,23] but it is probably best considered a non-ablative modality that allows for limited control of growth and exudation in most cases.

Complete disappearance of a treated RH more than 1.5 mm in diameter is not common, and it can be difficult to judge whether a variably regressed-appearing tumor retains viability for further growth or exudation. Encouraging signs include a decrease in tumor size, decrease in redness or vascularity, resolution of any subretinal fluid and hard exudation, normalization of the caliber and decrease in the tortuosity of any feeder vessels, and an underlying chorioretinal scar. An absence of hyperfluorescent filling on FA also suggests adequate destruction of a tumor, but hyperfluorescent staining of regressed lesions is common and does not by itself indicate potential for growth or activity, limiting the utility of FA for assessment of viability. The only definitive measure for success is documentation of no re-growth or recurrent exudation over long-term follow up. Occasionally a quiescent and regressed-appearing tumor can manifest new signs of growth and/or activity years after ablative therapy.

Extrapapillary RH greater than 4.5 mm in diameter pose a difficult challenge, with decreasing rates of success and increasing risks of treatment with increasing tumor size. Thermal laser photocoagulation and photodynamic therapy are almost always ineffective for these tumors, even across multiple treatment sessions, and there is no consensus on how these lesions should be managed. Some have found that cryotherapy can sometimes be effective for lesions this size, in cases where it can be used with sufficiently low risk, but there is concern about the degree of exudation and vitreous contracture that can occur after treatment. Some of us consider brachytherapy for these large, high-risk tumors, while others typically offer vitrectomy with endocryotherapy or with excision of the tumor (Figure 6). Kreusel et al reported their experience using ruthenium-106 brachytherapy for treatment of 25 eyes (24 patients), with a mean diameter of 3.8 mm among treated RH.[24] Ablation of 23 of 25 tumors was reported using a single treatment session. However, the outcome was poor in 9 eyes, with decrease in visual acuity from exudative or tractional retinal detachment. Use of external beam radiation has been described in case reports, but has not resulted in long-term outcomes favorable enough to result in common use.

Acute exudation in response to ablative treatment is not often vision-threatening for RH less than 1.5 mm in diameter, except for posterior lesions close to the macula, but can be a significant issue in larger RH. Severe cases can result in rapid progression to exudative retinal detachment (Figure 5B). The magnitude of this response is variable, and can be difficult to predict, but anecdotally seems to correlate with factors such as increasing tumor size, amount of pre-existing exudation, prominence of feeding and draining vessels, and use of cryotherapy (compared to thermal laser photocoagulation or photodynamic therapy). In our experience, subretinal fluid often occurs within hours following treatment. In mild cases,

fluid remains localized in the region around the treated tumor until resolution weeks later; in more severe cases, frank exudative retinal detachment evolves around the tumor, with dependent migration of subretinal fluid in the days following treatment and slow resolution weeks to months later. In cases where the central macula is involved, impairment of visual acuity usually abates with slow resolution. In rare cases, we have seen conversion to rhegmatogenous retinal detachment when vigorous accumulation of exudation causes retinal tearing at sites of pre-existing chorioretinal scars (as from previous laser treatment), and we observe exudative retinal detachment closely until resolution. Risk of post-treatment exudation should not deter necessary ablative therapy or temper the intensity of treatment in most cases, because eyes with RH at risk for such exudation are also at high risk for vision loss without treatment. However, a patient must understand the risks and the need for surveillance after treatment. Extrapolating from the utility of systemic corticosteroids for mitigation of edema related to excision of central nervous system hemangioblastomas in VHL disease,[25] some of us use a short course of systemic corticosteroids when treating RH that may cause consequential post-treatment exudation. Our impression has been that this intervention mitigates subretinal fluid accumulation, but this is unproven and we are not aware of any controlled comparison. Those of us who use this approach tailor the steroid dose to the anticipated risk of exudation, typically giving prednisone up to 1 mg/kg/day (or equivalent) for one to three days, beginning on the day of treatment, with rapid taper to discontinuation within four to seven days after treatment. In our experience, longer courses do not speed resolution of subretinal fluid, and we usually avoid administration for longer than a week. The benefits and risks of systemic corticosteroid use must be weighed in the context of systemic manifestations of VHL disease and any comorbid conditions, and we consult other members of the managing medical team when warranted.

Surgical Management of Eyes with Large Extrapapillary Retinal Hemangioblastoma

Vitrectomy and scleral buckling can be useful for management of ocular VHL disease in a number of circumstances, usually in the setting of rhegmatogenous or tractional retinal detachment, epiretinal or vascular proliferation affecting central vision, or vitreous hemorrhage, but require careful attention to a number of considerations and risks. In our experience, eyes with RH manifesting exudation, hemorrhage, or associated epiretinal or vascular proliferation are at risk for development of proliferative vitreoretinopathy following vitrectomy. This risk may be compounded by the effects of any ablative treatment applied to RH surrounding surgery, with its attendant compromise of the blood-ocular barrier. In some cases, RH may be too large to respond to any laser photocoagulation or cryotherapy applied at surgery, and surgical excision of the tumor may be considered (Figure 6). Excision of an RH requires attention to intraocular hemostasis, which can include treatment of the lesion with endolaser photocoagulation, followed by diathermy to feeding vessels under high intraocular pressure prior to excision, or ligation of feeder vessels with intraocular suture prior to excision.[26,27] Retinopexy is applied to the region of retinectomy, with use of gas or oil tamponade. The posterior hyaloid in these eyes may be tightly adherent to the retina, especially in younger patients, making removal difficult, and retained posterior hyaloid may serve as a scaffold for epiretinal or vascular proliferation with consequent traction or

evolution to proliferative vitreoretinopathy. Some severely-affected eyes in need of surgical intervention seem prone to development of new RH, and in some cases, growth of new tumors may threaten stabilization achieved with prior surgery. Encircling scleral buckling can be useful to support the peripheral retina in the setting of vitrectomy given the complicating factors above, but is not often useful without vitrectomy because of the features complicating retinal detachment in these eyes.

Gaudric et al reported a series of 23 eyes (21 patients) who underwent vitreoretinal surgery for severe ocular VHL disease.[27] Fourteen eyes received ablative therapy at surgery, consisting of laser endophotocoagulation or trans-scleral cryotherapy, and 9 eyes had retinectomy with excision of RH. Among the 14 eyes in the laser/cryotherapy group, an average of 1.7 surgeries was performed, and mean follow up was 4 years. The retina was attached in 13 of 14 eyes at 6 months following surgery. Three of 14 eyes went blind during follow up (from neovascular glaucoma or exudative retinal detachment), and median visual acuity in the remaining 11 eyes was 20/50 (20/320 to 20/20) at 18 months after surgery. Among the 9 eyes in the RH excision group, an average of 2 surgeries was performed, and mean follow up was 8 years. The retina was attached in 8 of 9 eyes at 6 months following surgery. Four of 9 eyes went blind during follow up (from neovascular glaucoma and RH growth), and visual acuity in the remaining 5 eyes ranged from counting fingers to 20/320 at 18 months post-operatively.

Krzystolik et al recently reported a series of 23 eyes (23 patients) managed with vitrectomy for severe ocular VHL disease.[28] Eyes were severely affected, with baseline logarithm of the minimum angle of resolution (logMAR) of 2.28 (20/3,810) and all RH were larger than 3 mm in diameter. Nine eyes were managed with laser photocoagulation or cryotherapy of RH without excision, and 14 eyes received retinectomy with excision of RH. Twelve months after surgery, logMAR was 1.09 (20/246) in the laser/cryotherapy group and, and 2.3 (20/3,990) in the excision group. The retina was reported to be attached in all cases at one month after surgery, but retinal detachment is listed among post-operative complications in 16 of 23 eyes, and neovascular glaucoma is listed in 14 of 23 eyes. New RH developed in 17 of 23 eyes by 24 months post-operatively, highlighting the frequency of new tumor formation in these eyes.

Treatment of Juxtapapillary Retinal Hemangioblastoma

Management of juxtapapillary RH is complicated by the adverse effects on vision that can result from attempted ablation of the tumor, particularly those situated within or near the papillomacular bundle. Decrease in visual acuity, altitudinal visual field loss, and development of central scotomata have been associated with treatment of such tumors using thermal laser photocoagulation.[29] Photodynamic therapy with verteporfin seems to offer a better safety profile than laser photocoagulation, but does not usually result in ablation of the tumor.[22,30] Given limitations to existing therapies, observation can be a viable strategy. Some juxtapapillary RH do not cause significant exudation, or produce exudation that spares the macula, and observation makes good sense in these circumstances. Even in cases where macular exudation affects central vision, observation can be compatible in some eyes with maintenance of good vision over years, often with waxing/waning of intraretinal fluid, and

sometimes with very slow growth of the tumor. In the absence of safe ablative options, treatment is usually confined to an attempt to minimize exudation affecting central vision. Photodynamic therapy, proton beam therapy, or use of intravitreal VEGF antagonists or corticosteroids can be used individually or in combination to decrease exudation in some cases, but risks of treatment must be weighed, and benefit is often limited.[22,29-33]

Management of Retinal Vascular Proliferation

Foci of juxtapapillary or extrapapillary retinal vascular proliferation are occasionally present in patients with VHL disease. They do not seem to carry the same risks of vitreous hemorrhage and tractional retinal detachment as does retinal neovascularization in ischemic retinopathies, and they sometimes regress spontaneously.[34] Those lesions that progress to exert tractional effects on the macula or overgrow the fovea with effects on central vision can be removed at vitrectomy. In some cases, the complexes regrow after successful excision. It is important to distinguish retinal vascular proliferation from RH, which can be challenging with lesions that exhibit a more saccular or nodular appearance on ophthalmoscopy and have a close association with the underlying retina on OCT. Retinal vascular proliferation can cause retinal thickening via mechanical effects, but does not usually produce exudation. Importantly, it does not typically regress with laser photocoagulation, probably partly because of its epiretinal location. RH can incite retinal vascular proliferation over their surface, creating hybrid lesions, but the tumor component resides in the retina and cannot be excised without retinectomy.

The Role of Anti-angiogenic Pharmacotherapy

There was hope after introduction of ocular VEGF antagonists, including bevacizumab, ranibizumab, pegaptanib, and aflibercept, that VEGF blockade might allow for involution of RH, given their nature as vascular tumors arising from cells with inappropriate activation of the response to hypoxia, which includes upregulation of VEGF expression. Use of VEGF antagonists in ocular VHL disease has been reported in case series and small, uncontrolled clinical trials. In one prospective study, Dahr et al tested intravitreal pegaptanib sodium (3 mg) in 5 eyes (5 patients) with ocular VHL disease characterized by juxtapapillary or large extrapapillary RH.[32] Pegaptanib sodium, a pegylated aptamer blocking the $VEGF_{165}$ isoform, was administered every 6 weeks for at least 6 injections, and 2 of 5 patients completed the course of treatment and one year of follow-up. These two patients demonstrated a decrease in RH-associated exudation, but no change in tumor size. The other 3 patients experienced progression and did not complete the treatment course. In another prospective trial, Wong et al tested intravitreal ranibizumab (0.5 mg) in 5 eyes (5 patients) with RH not amenable or responsive to standard treatments.[33] Ranibizumab, a humanized monoclonal antibody fragment blocking all VEGF-A isoforms, was given every 4 weeks for 6 months, with additional treatment considered through one year. Participants received a mean of 10 injections over an average of 47 weeks. Visual acuity decreased by 9 (± 20) letters and there was no consistent improvement in RH exudation or tumor size.

We occasionally use intravitreal VEGF antagonists in an attempt to control RH-associated exudation in cases where ablative therapy is not feasible (as mentioned above for

juxtapapillary lesions) or has failed, and some but not all eyes can exhibit at least modest improvement in intraretinal edema or subretinal fluid, as suggested by case reports.[35-39] It is possible that use of anti-VEGF drugs as prelude to ablation of extrapapillary RH could increase the probability of successful destruction in some cases, but this has not been well-evaluated. In retrospect, it is perhaps not surprising that VEGF blockade alone does not induce RH regression, and has a typically modest effect on tumor exudation. The hypoxia inducible factors (HIF) that are upregulated by pVHL dysfunction and serve as master regulators of the cellular response to hypoxia are transcription factors known to alter the expression of hundreds of genes. There is hope that rational design of pharmacotherapies targeting multiple HIF-regulated pathways or HIF itself may still someday offer an alternative to present destructive therapies.

Conclusions

Management of ocular VHL disease involves diagnosis of the systemic disease via medical and genetic testing, with referral to a multispecialty team for care, and surveillance with early treatment, when possible, for any RH. RH arising outside the posterior pole are readily destroyed by one or more sessions of appropriate laser photocoagulation when small, but become increasingly hard to treat at larger sizes. RH arising in proximity to the optic disc and fovea can be difficult to manage because of the risks of ablative therapy for central vision. There is a role for cryotherapy, vitreoretinal surgery, photodynamic therapy, radiotherapy, and intravitreal injection of anti-VEGF agents in select cases of ocular VHL disease. The prognosis for the most severely-affected eyes is poor, but many individuals manifesting milder ocular VHL disease and receiving timely and appropriate treatment can retain good vision. In a large cohort of patients with VHL disease comprising 890 individuals among 220 unrelated pedigrees, 335/890 (38%) had ocular involvement, and approximately 20% of those manifesting ocular VHL disease had some degree of at least unilateral visual impairment.[40] There is hope that recent understanding of the molecular basis for VHL disease will allow for rational design of non-ablative strategies to arrest RH growth, or even induce regression of these tumors, with improvement in outcomes for these eyes.

Acknowledgments

Financial support:

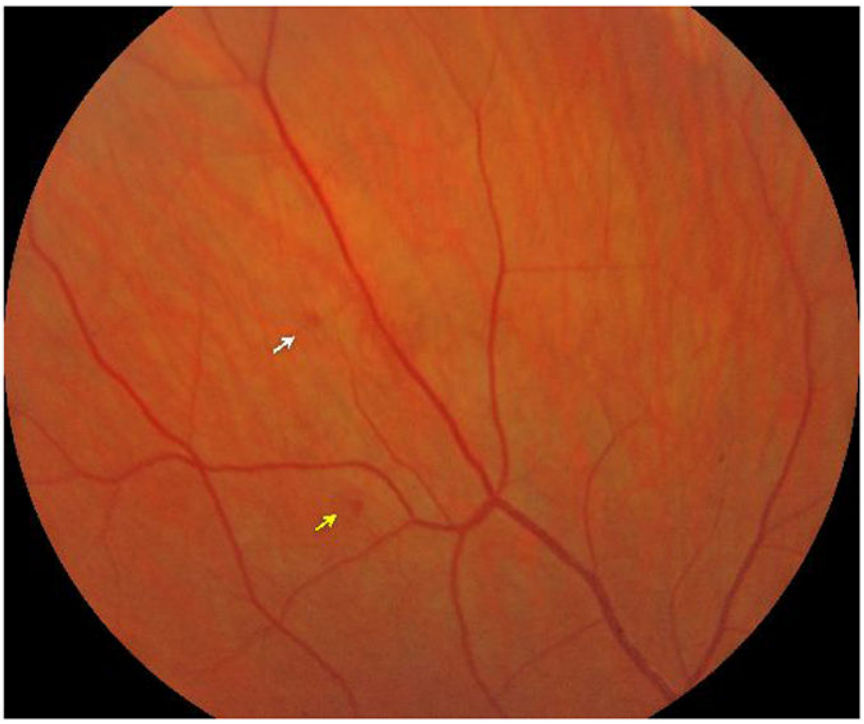
This project has been funded with Federal funds from the National Eye Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN263201200001C.

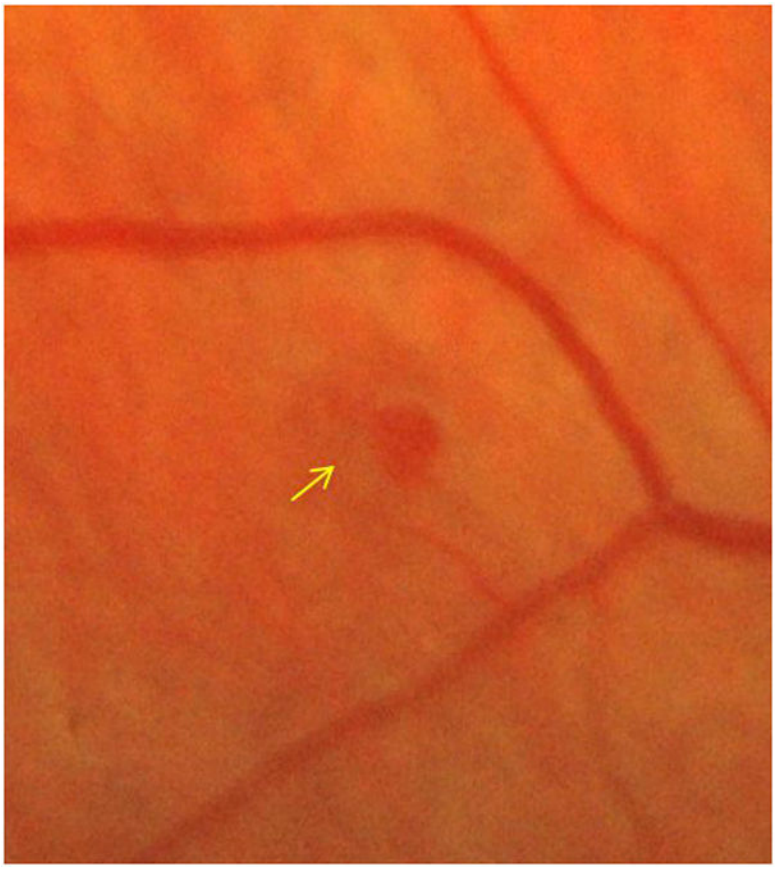
References

1. Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel–Lindau disease tumour suppressor gene. Science 1993;260:1317–20. [PubMed: 8493574]
2. Maxwell PH, Wiesener MS, Chang GW, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature 1999;399:271–5. [PubMed: 10353251]
3. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971;68:820–3. [PubMed: 5279523]
4. Melmon KL, Rosen SW. Lindau's disease. Review of the literature and study of a large kindred. Am J Med 1964;36:595–617. [PubMed: 14142412]

5. Schmid S, Gillessen S, Binet I, et al. Management of von hippel-lindau disease: an interdisciplinary review. Oncol Res Treat 2014;37:761–71. [PubMed: 25531723]
6. Maher ER, Iselius L, Yates JR, et al. Von Hippel-Lindau disease: A genetic study. J Med Genet 1991;28:443–47. [PubMed: 1895313]
7. Gorin MB. Von Hippel-Lindau disease: clinical considerations and the use of fluorescein-potentiated argon laser therapy for treatment of retinal angiomas. Semin Ophthalmol 1992;7:182–91. [PubMed: 10147715]
8. Schoen MA, Shields CL, Say EA, et al. Clinically invisible retinal hemangioblastomas detected by spectral domain optical coherence tomography and fluorescein angiography in twins. Retin Cases Brief Rep 2016;0:1–5.
9. Chen X, Sanfilippo CJ, Nagiel A, et al. Early detection of retinal hemangioblastomas in von Hippel-Lindau disease using ultra-widefield fluorescein angiography. Retina 2018;38:748–54. [PubMed: 28368975]
10. Shields CL, Shields JA, Barrett J, et al. Vasoproliferative tumors of the ocular fundus. Classification and clinical manifestations in 103 patients. Arch Ophthalmol 1995;113:615–23. [PubMed: 7748132]
11. Shields CL, Kaliki S, Al-Dahmash S, et al. Retinal vasoproliferative tumors: comparative clinical features of primary vs secondary tumors in 334 cases. JAMA Ophthalmol 2013;131:328–34. [PubMed: 23494037]
12. Singh A, Shields J, Shields C. Solitary retinal capillary hemangioma: hereditary (von Hippel-Lindau disease) or nonhereditary? Arch Ophthalmol. 2001;119:232–4. [PubMed: 11176984]
13. Singh AD, Nouri M, Shields CL, et al. Retinal capillary hemangioma: a comparison of sporadic cases and cases associated with von Hippel-Lindau disease. Ophthalmology 2001 10;108:1907–11. [PubMed: 11581072]
14. Singh AD, Nouri M, Shields CL, Shields JA, Perez N. Treatment of retinal capillary hemangioma. Ophthalmology. 2002;109:1799–806. [PubMed: 12359597]
15. Krivosic V, Gaudric A, Kasami-Levy C, et al. Laser photocoagulation for peripheral retinal capillary hemangioblastoma in von Hippel-Lindau Disease. Ophthalmology Retina 2017;1:59–67. [PubMed: 31047395]
16. Annesley WH, Leonard BC, Shields JA, et al. Fifteen year review of treated cases of retinal angiomatosis. Trans Sect Ophthalmol Am Acad Ophthalmol Otolaryngol 1977;83:446–53.
17. Lane CM, Turner G, Gregor ZJ, Bird AC. Laser treatment of retinal angiomatosis. Eye 1989;3:33–8. [PubMed: 2591596]
18. Blodi CF, Russell SR, Pulido JS, Folk JC. Direct and feeder vessel photocoagulation of retinal angiomas with dye yellow laser. Ophthalmology 1990;97:791–7. [PubMed: 2374684]
19. Rosa RH, Goldberg MF, Green WR. Clinicopathologic correlation of argon laser photocoagulation of retinal angiomas in a patient with von Hippel–Lindau disease followed for more than 20 years. Retina 1996;16:145–56. [PubMed: 8724960]
20. Schmidt D, Natt E, Neumann HP. Long-term results of laser treatment for retinal angiomatosis in von Hippel–Lindau disease. Eur J Med Res 2000;5:47–58. [PubMed: 10720563]
21. Mainster MA. Wavelength selection in macular photocoagulation. Tissue optics, thermal effects, and laser systems. Ophthalmology 1986 7;93:952–8. [PubMed: 3763141]
22. Sachdeva R, Dadgostar H, Kaiser PK, et al. Verteporfin photodynamic therapy of six eyes with retinal capillary haemangioma. Acta Ophthalmol 2010;88:e334–40. [PubMed: 20946329]
23. Papastefanou VP, Pilli S, Stinghe A, et al. Photodynamic therapy for retinal capillary hemangioma. Eye 2013;27:438–42. [PubMed: 23288135]
24. Kreusel KM, Bornfeld N, Lommatzsch A, et al. Ruthenium-106 brachytherapy for peripheral retinal capillary hemangioma. Ophthalmology 1998;105:1386–92. [PubMed: 9709747]
25. Lonser RR, Oldfield EH. Microsurgical resection of spinal cord hemangioblastomas. Neurosurgery 2005;57:372–6. [PubMed: 16234688]
26. Schlesinger T, Appukuttan B, Hwang T, et al. Internal en bloc resection and genetic analysis of retinal capillary hemangioblastoma. Arch Ophthalmol 2007;125:1189–93. [PubMed: 17846357]

27. Gaudric A, Krivosic V, Duguid G, et al. Vitreoretinal surgery for severe retinal capillary hemangiomas in von Hippel–Lindau disease. Ophthalmology 2011;118:142–9. [PubMed: 20801520]
28. Krzystolic K, Stopa M, Kuprjanowicz L, et al. Pars plana vitrectomy in advanced cases of von Hippel-Lindau eye disease. Retina 2016;36:325–34. [PubMed: 26308528]
29. Garcia-Arumí J, Sararols LH, Cavero L, et al. Therapeutic options for capillary papillary angiomas. Ophthalmology 2000;107:48–54. [PubMed: 10647718]
30. Schmidt-Erfurth UM, Kusserow C, Barbazetto IA, et al. Benefits and complications of photodynamic therapy of papillary capillary angiomas. Ophthalmology 2002;109:1256–66. [PubMed: 12093647]
31. Seibel I, Cordini D, Hager A, et al. Long-term results after proton beam therapy for retinal papillary capillary hemangioma. Am J Ophthalmol 2014;158:381–6. [PubMed: 24844975]
32. Dahr SS, Cusick M, Rodriguez-Coleman H, et al. Intravitreal anti-vascular endothelial growth factor therapy with pegaptanib for advanced von Hippel–Lindau disease of the retina. Retina 2007;27:150–8. [PubMed: 17290195]
33. Wong WT, Liang K, Hammel K, et al. Intravitreal ranibizumab therapy for retinal capillary hemangioblastoma related to von Hippel–Lindau Disease. Ophthalmol 2008;115:1957–64.
34. Wong WT, Yeh S, Chan CC, et al. Retinal vascular proliferation as an ocular manifestation of von Hippel–Lindau disease. Arch Ophthalmol 2008;126:637–43. [PubMed: 18474773]
35. Ziemssen F, Voelker M, Inhoffen W, et al. Combined treatment of a juxtapapillary retinal capillary haemangioma with intravitreal bevacizumab and photodynamic therapy. Eye 2007;21:1125–6. [PubMed: 17545966]
36. de Klerk TA, Steel DH. Use of intravitreal bevacizumab in a patient with a Von Hippel-Lindau-associated retinal haemangioblastoma of the optic nerve head: a case report. J Med Case Rep 2008;2:182. [PubMed: 18510737]
37. Ach T, Thiemeyer D, Hoeh AE, et al. Intravitreal bevacizumab for retinal capillary haemangioma: longterm results. Acta Ophthalmol 2010;88:e137–8. [PubMed: 19681788]
38. Mennel S, Meyer CH, Callizo J. Combined intravitreal anti-vascular endothelial growth factor (Avastin) and photodynamic therapy to treat retinal juxtapapillary capillary haemangioma. Acta Ophthalmol 2010;88:610–3. [PubMed: 19222401]
39. Slim E, Antoun J, Kourie HR, et al. Intravitreal bevacizumab for retinal capillary hemangioblastoma: A case series and literature review. Can J Ophthalmol 2014;49:450–7. [PubMed: 25284102]
40. Wong WT, Agrón E, Coleman HR, et al. Clinical characterization of retinal capillary hemangioblastomas in a large population of patients with von Hippel–Lindau disease. Ophthalmology 2008;115:181–8. [PubMed: 17543389]





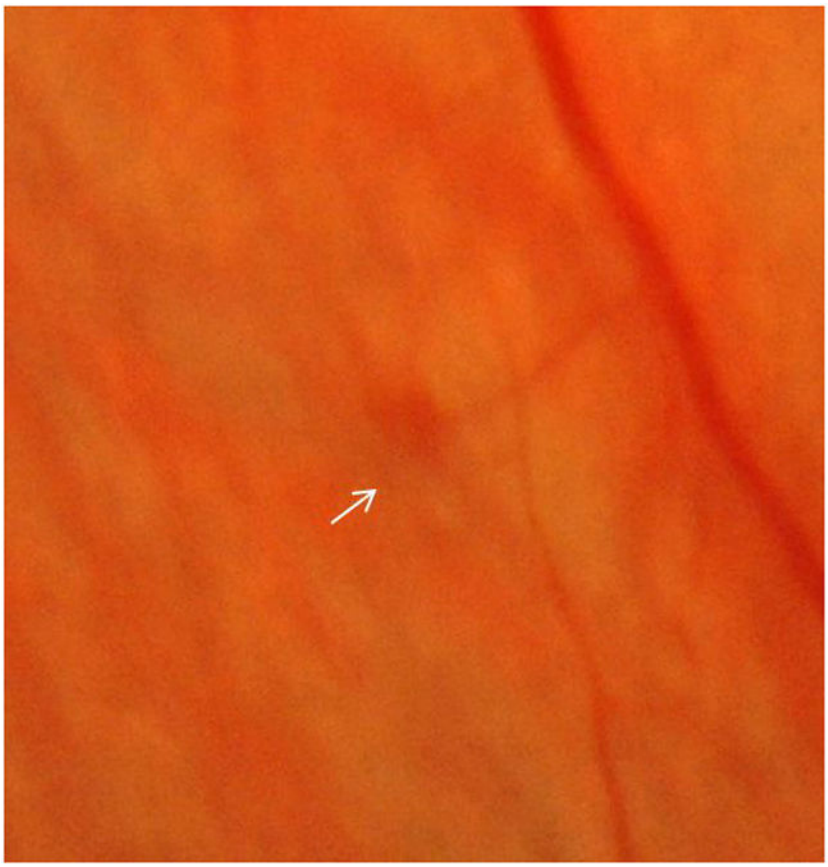
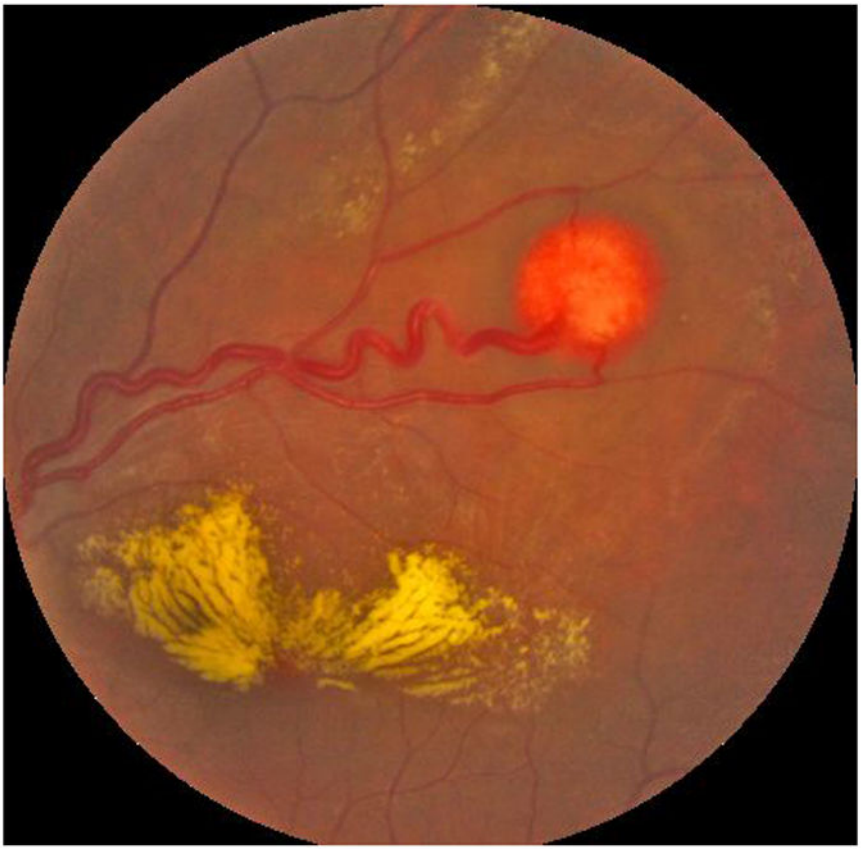


Figure 1. Early extrapapillary retinal hemangioblastomas.

A. Two small retinal hemangioblastomas (white and yellow arrows) are similar in appearance to a small intraretinal hemorrhage or large microaneurysm. **B, C.** Magnified views of each of the hemangioblastomas shown in A illustrate the subtle feeding and draining vessels that help differentiate these from other lesions. They exhibit hyperfluorescence on fluorescein angiography (not shown).



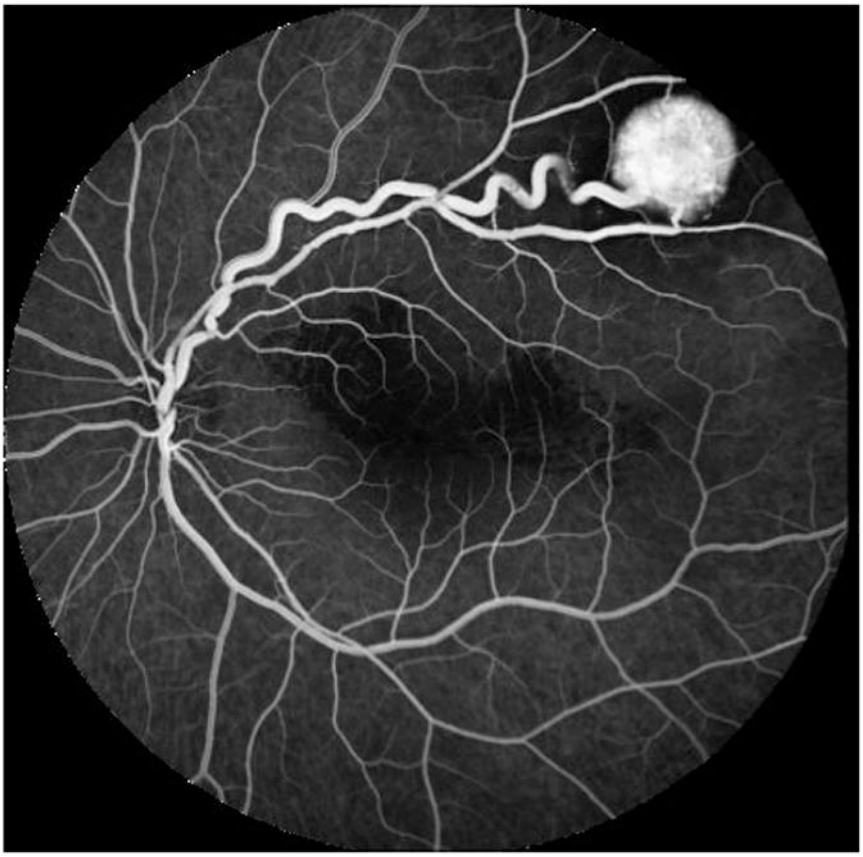
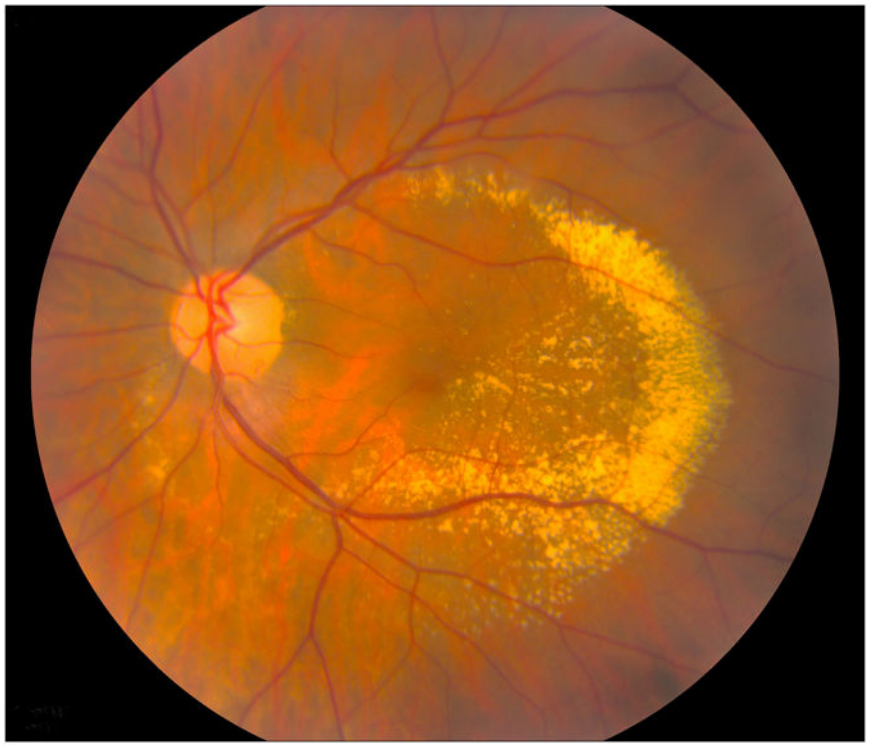
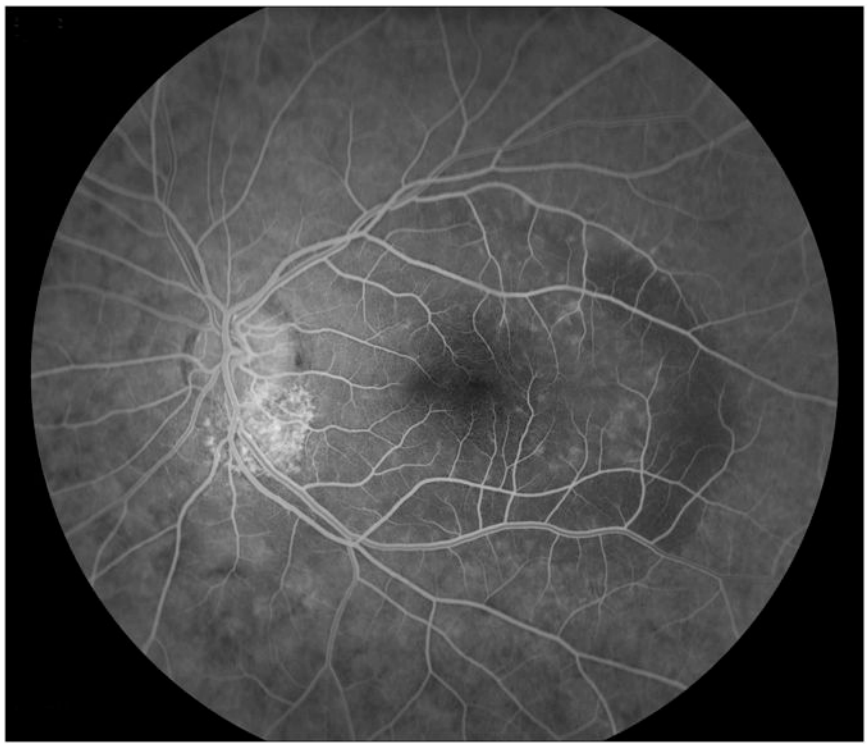


Figure 2. Extrapapillary retinal hemangioblastoma with exudation.

A. A sizeable retinal hemangioblastoma superotemporal to the macula demonstrates prototypical features, including a pink or orange color, nodular appearance, dilated and tortuous feeding and draining blood vessels, and exudation involving both perilesional retina and the macula. Note the scant lipid at the border of subretinal fluid surrounding the tumor, and the prolific lipid present in the macula. **B.** An early frame of the fluorescein angiogram shows hyperfluorescence of the tumor body, which progressed to leakage in late frames (not shown). Note the blocking of fluorescence by macular lipid and the absence of macular microvascular abnormalities.





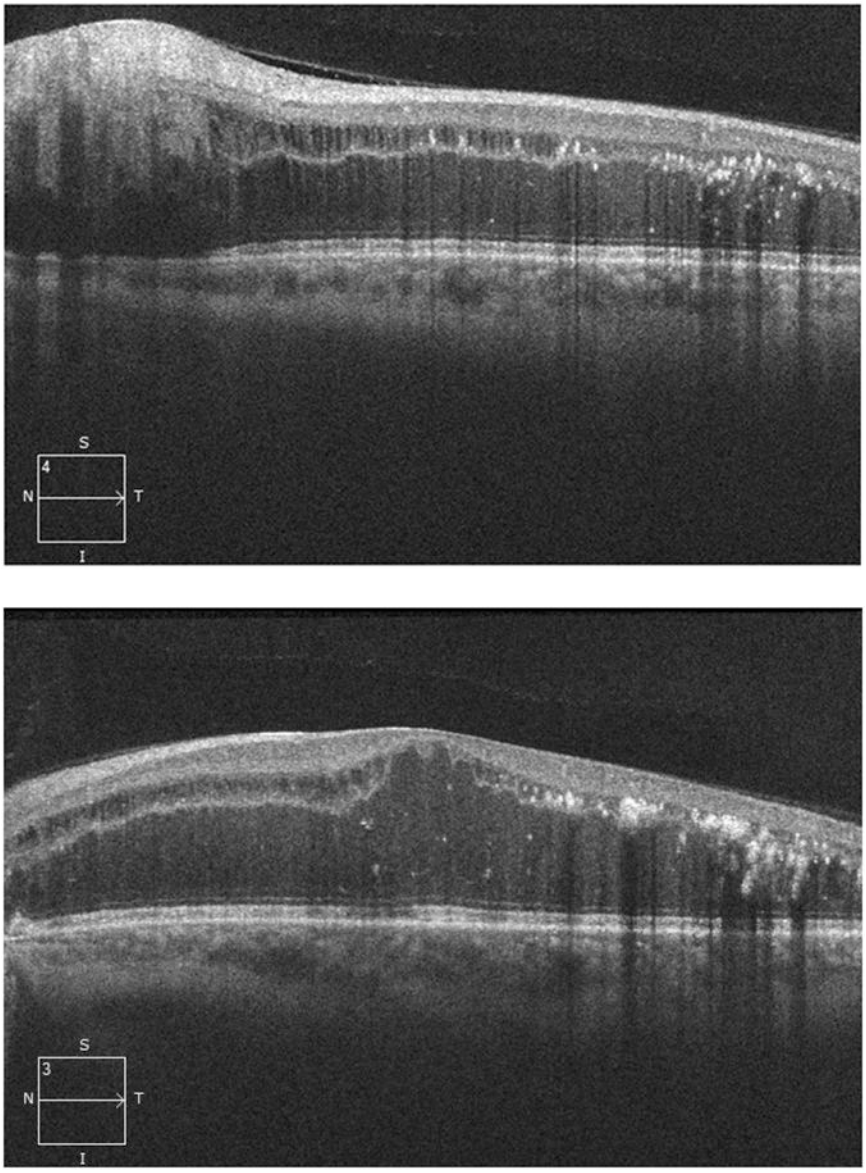


Figure 3. Juxtapapillary retinal hemangioblastoma with exudation.

A. A subtle whitening and focal thickening of the retina adjacent to the inferotemporal rim of the optic disc are the only features visible on ophthalmoscopy indicating the presence of a juxtapapillary retinal hemangioblastoma responsible for severe macular exudation. **B.** An early frame of the fluorescein angiogram shows hyperfluorescence of the tumor body, which progressed to leakage in late frames (not shown). **C.** A horizontal SD-OCT line scan through the tumor body illustrates the degree of retinal thickening and the location of the lesion in the inner retina, with shadowing of more external structures. **D.** A horizontal SD-OCT line scan through the central macula shows diffuse, severe intraretinal cystic macular edema.

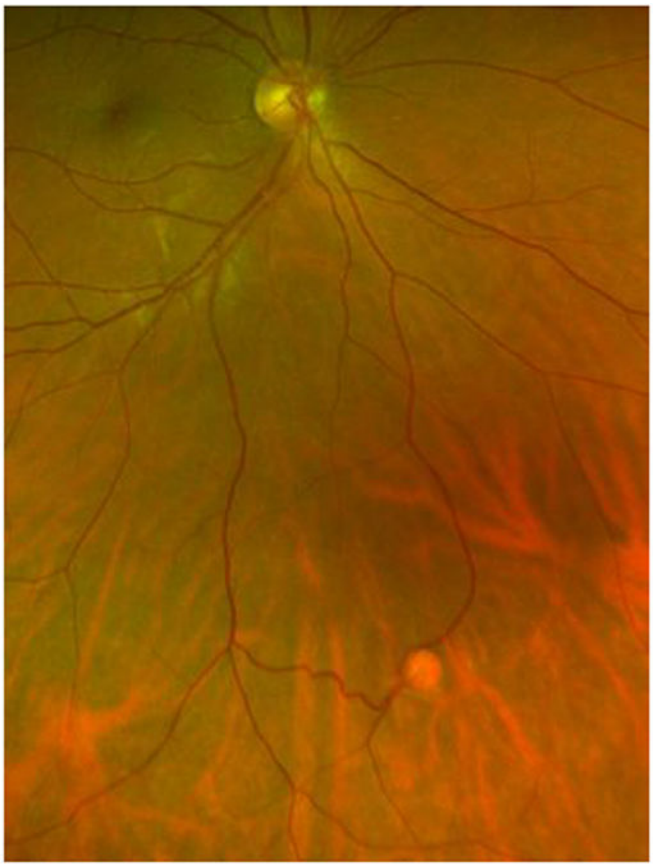
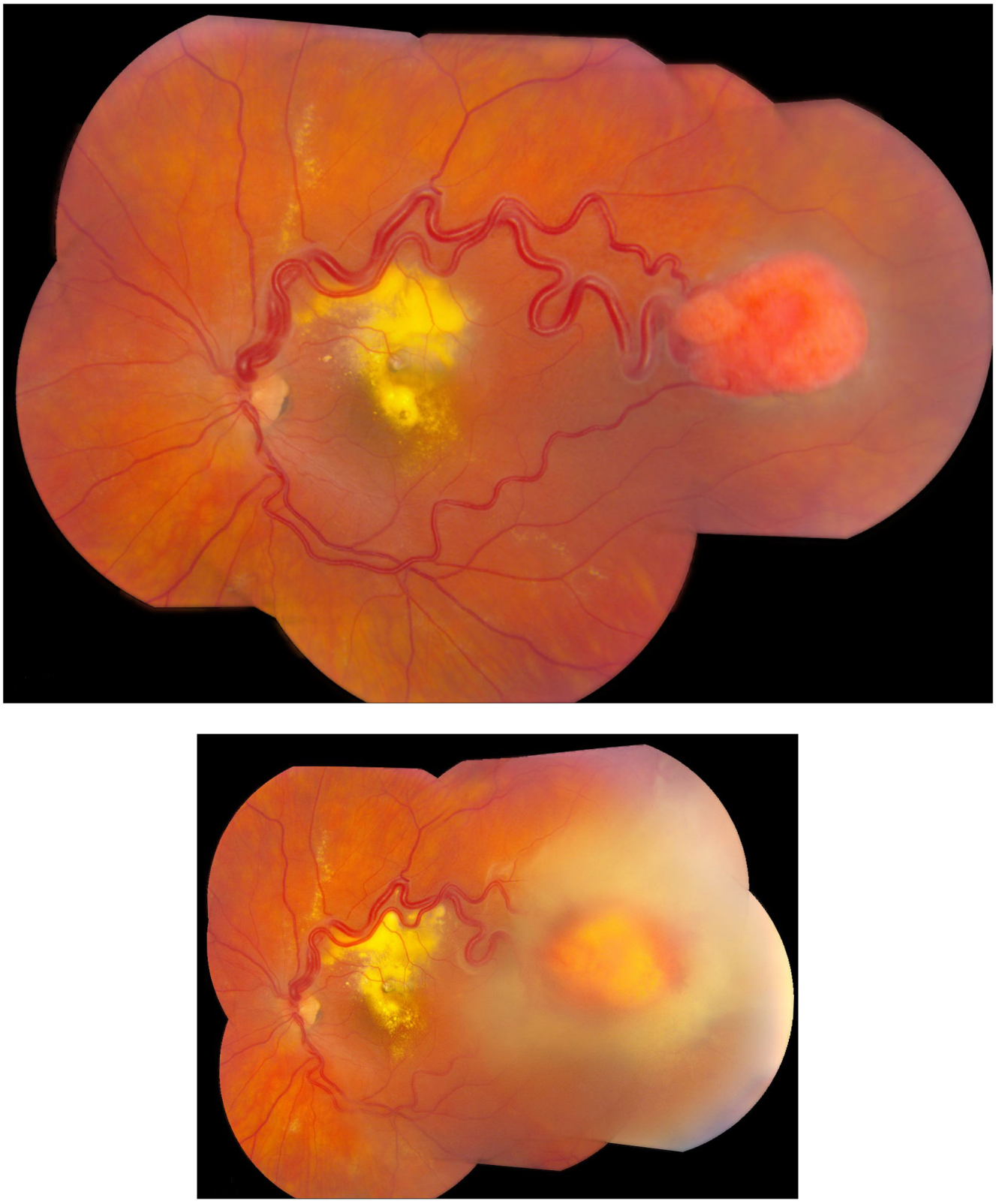


Figure 4. Thermal laser photocoagulation for ablation of an extrapapillary retinal hemangioblastoma.

A. A solitary retinal hemangioblastoma approximately 0.75 mm in diameter is visible in the inferior periphery. Note the dilated feeding and draining vessels. There is no exudation from the lesion. **B.** A chorioretinal scar is present at the site of the prior tumor one year following thermal laser photocoagulation. Note normalization of the former feeding and draining vessels. Such scars are observed for any recurrent tumor growth.



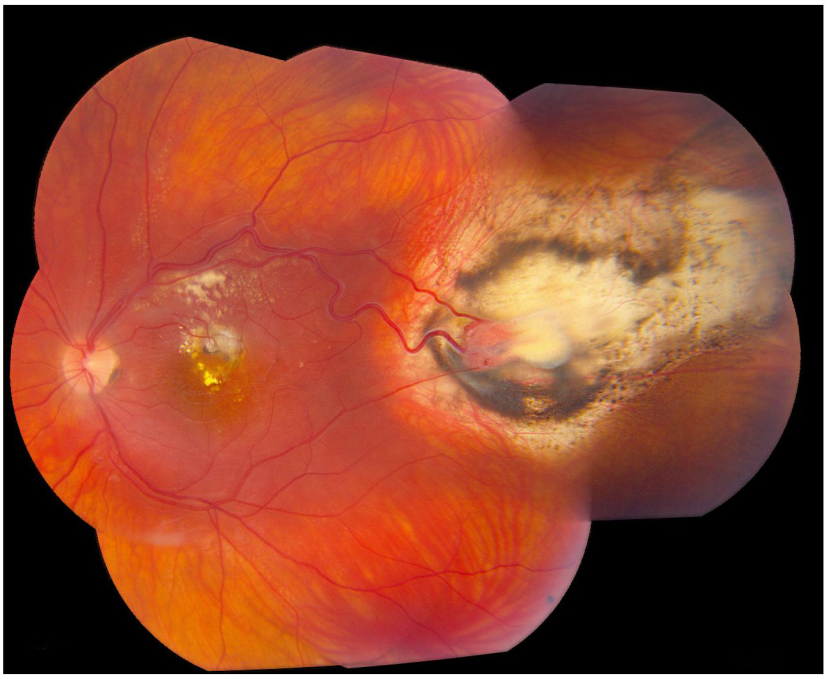
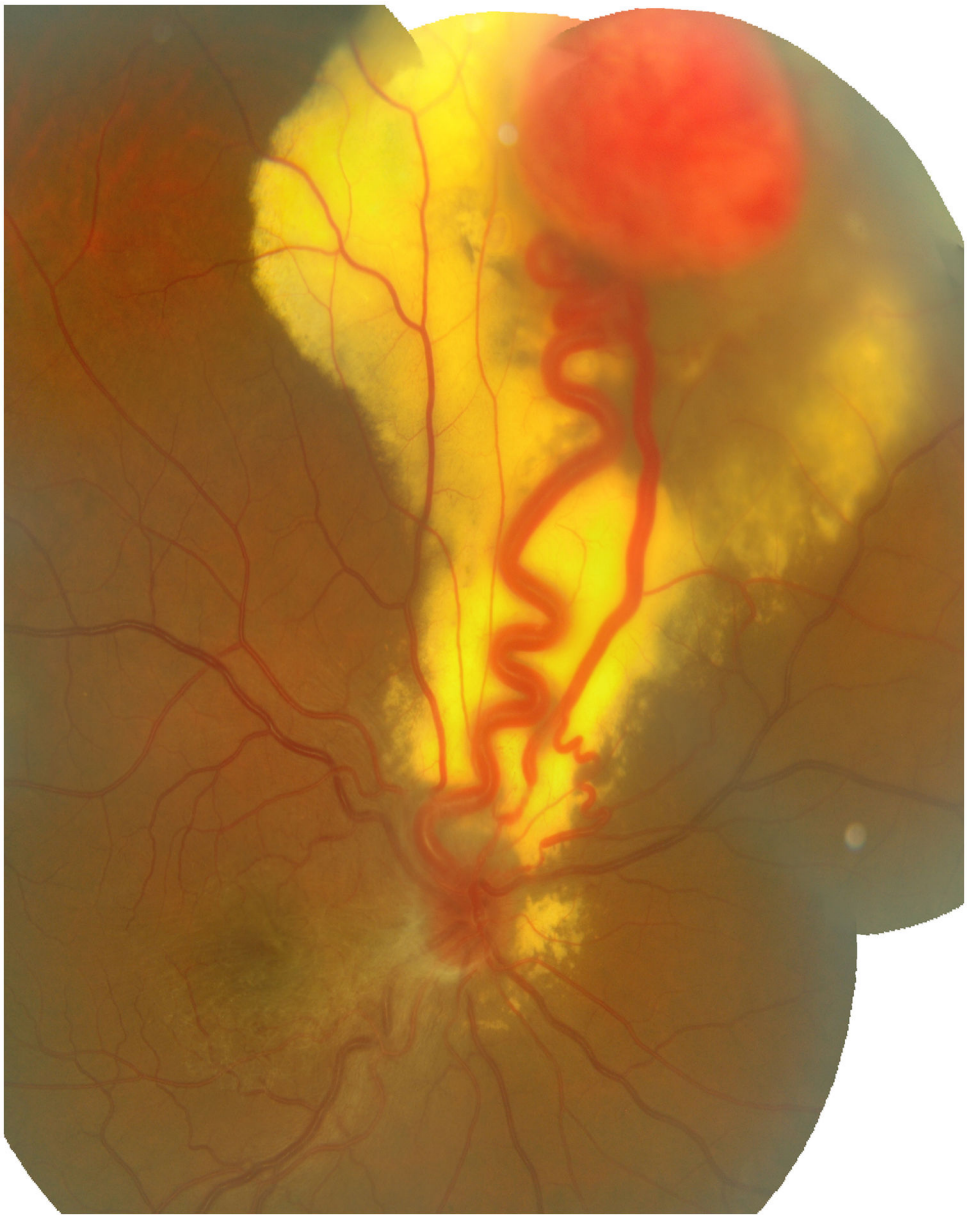


Figure 5. Trans-scleral cryotherapy for ablation of an extrapapillary retinal hemangioblastoma.
A. A solitary retinal hemangioblastoma approximately 4.5 mm in diameter is present superotemporal to the macula. Cystic macular edema and intra- and subretinal lipid are present, and visual acuity is 20/160. Note the focus of white subretinal fibrosis in the parafovea superotemporal to the fovea, where lipid organization has induced subretinal neovascularization. **B.** One day after double freeze-thaw trans-scleral cryotherapy, performed in the operating room with conjunctival incision and administration of intravenous corticosteroids, the tumor is surrounded by pre- and subretinal proteinaceous exudates. An exudative retinal detachment extends into the temporal macula, but is most prominent inferior to the tumor. Visual acuity remains 20/160. **C.** Five months after cryotherapy, the tumor is significantly smaller and its temporal aspect appears fibrotic. Feeding/draining vessels are much less dilated and tortuous. Macular edema and lipid have improved. Serial ranibizumab injections have been given to treat macular subretinal neovascularization. Visual acuity is 20/125. The pink-red color of the nasal aspect of the tumor is concerning for viability, and further treatment (thermal laser photocoagulation) is planned.



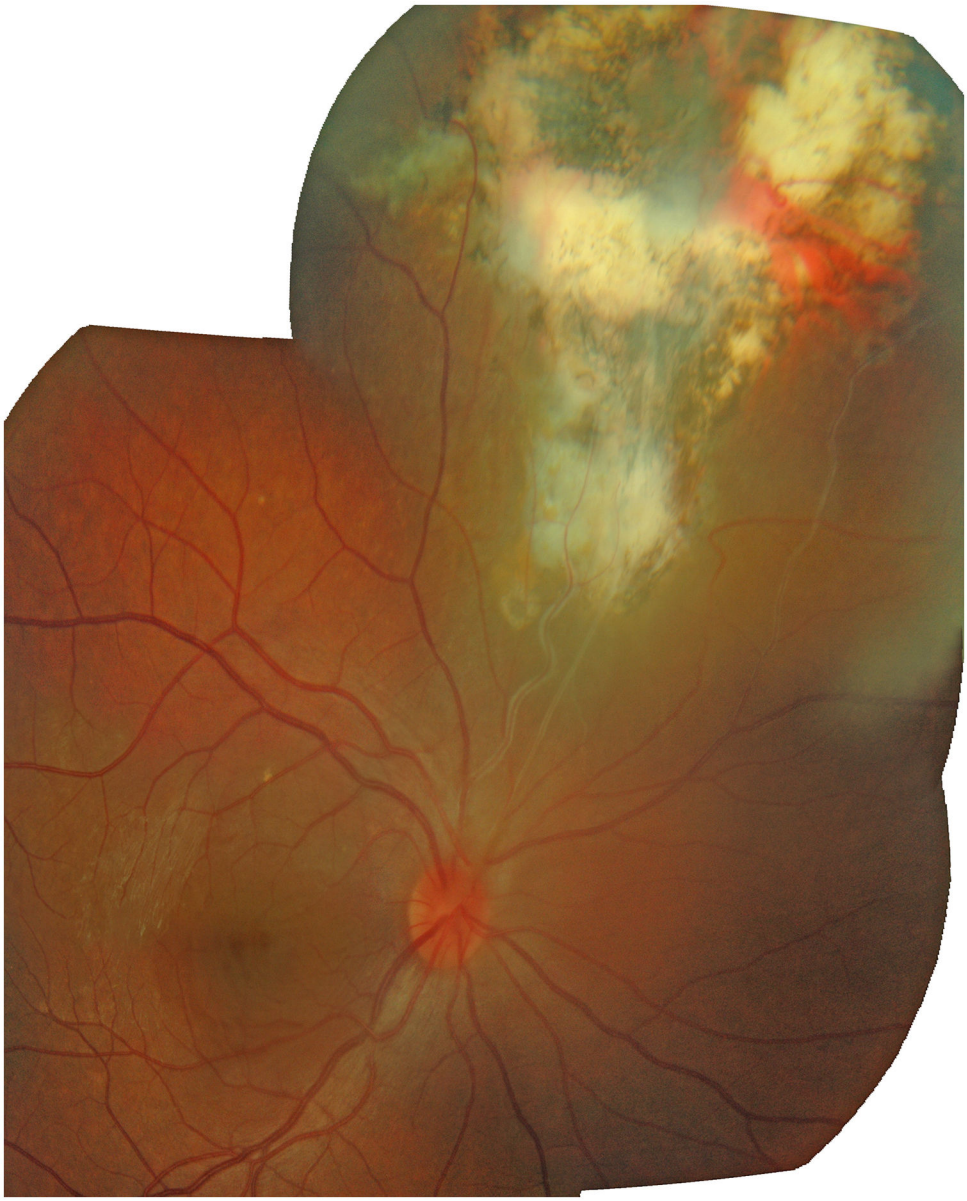


Figure 6. Surgical excision of an extrapapillary retinal hemangioblastoma.

A. A large retinal hemangioblastoma approximately 6 mm in diameter is present in the superonasal periphery, surrounded by exudation. A macular epiretinal membrane is present. **B.** Five years after vitrectomy with tumor excision and epiretinal membrane peeling, a scar without any vestige of the retinal hemangioblastoma is present at the site of retinectomy, exudation has completely resolved, and the feeding/draining vessels are reduced to ghost vessels.