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Case Report

Vitreoretinal Surgery and Panretinal Photocoagulation in a Patient with Multiple Large Retinal Capillary Hemangiomas (von Hippel-Lindau Disease): A Novel Approach

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Keywords
Retinal capillary hemangioma · Von Hippel-Lindau disease · Laser photocoagulation · Vitreoretinal surgery

Abstract
The authors present a novel surgical approach for the treatment of retinal capillary hemangiomas (RCHs) secondary to von Hippel-Lindau (VHL) disease. This is a case report of a 23-year-old male patient with VHL that presented with multiple large RCHs and a thick epiretinal membrane (ERM) in his left eye, with best-corrected visual acuity (BCVA) of 20/80. This condition was surgically addressed with 23-gauge pars plana vitrectomy, ERM and internal limiting membrane peeling, and panretinal photocoagulation. Three monthly intravitreal injections of bevacizumab were administered after surgery. In a 14-month follow-up period, hemangiomas have regressed after laser therapy, macular anatomy has improved, retina remained completely attached, and there has been no development of new tumors or proliferative vitreoretinopathy. The patient achieved a BCVA of 20/40 in the treated eye. Panretinal photocoagulation

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combined with pars plana vitrectomy may be useful to reduce development of new capillary hemangiomas and reduce overall occurrence of complications in patients with VHL disease. Postoperative intravitreal injections of bevacizumab may have a role in this positive outcome.

Introduction

Retinal capillary hemangiomas (RCHs) are retinal vascular tumors that may appear sporadically or as a component of von Hippel-Lindau (VHL) disease [1]. VHL disease is an autosomal-dominant, multi-organ, familial neoplastic disorder caused by aberrations of the tumor suppressor *VHL* gene. This gene, landmark of VHL disease, is located on chromosome 3p35 and encodes the pVHL protein. One proposed mechanism of tumorigenesis involves the regulatory effect pVHL has on hypoxia-inducible factors (HIF). Under normal conditions, pVHL ubiquitinates HIF for degradation, but a lack of pVHL, such as in VHL disease or hypoxia, leads to stabilization of HIF and increased expression of tumorigenic molecules, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor peptide (PDGF), and transforming growth factor-α (TGF-α) [2].

Diagnosis of VHL disease is often based on clinical criteria. Patients with a positive family history must present a central nervous system (CNS) hemangioma, RCH, pheochromocytoma, or clear cell renal carcinoma to meet the criteria. Those with no relevant family history must have 2 or more RCHs, 2 or more CNS hemangiomas, or either an RCH or CNS hemangioma associated with the previously related visceral tumors to be diagnosed with the disease [3].

RCHs are multiple in about one-third of patients, and approximately half the cases have bilateral involvement. Patients are typically diagnosed in the second or third decades of life, with a mean age of 25 years [4], and they typically notice progressive worsening of vision which may be associated with photopsia and metamorphopsia. Nevertheless, many patients remain asymptomatic, and hemangiomas are only detected on a routine examination or on screening evaluation because of a family history of VHL disease [5].

Treatment can be challenging for several reasons, such as presence of multiple bilateral tumors and also potential for the growth of new tumors. Small lesions (up to 4.5 mm, but preferentially 1.5 mm or smaller in size) can be treated with laser photocoagulation [6]. Peripheral and larger lesions can be treated with cryotherapy [7]. A few successful results with photodynamic therapy [8] and brachytherapy [9] have also been reported. Regarding intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs [10], effects were limited to transitory improvement in macular edema with no effects on lesion size.

Finally, surgery should be considered in cases with multiple large hemangiomas, exudative and/or tractional retinal detachment, proliferative vitreoretinopathy, vitreous hemorrhage, or when associated with thick epiretinal membranes [11], but long-term outcomes are somehow limited.

This case report was written in accordance with the CARE guidelines [12].

Case Report

A 23-year-old male patient was referred to the Ocular Oncology Service of the Paulista School of Medicine (Federal University of São Paulo) in August 2016, because of a positive family history for VHL disease. His older brother and his niece, who were already patients in

our clinic, had retinal and CNS hemangiomas. His brother had undergone multiple neurosurgical procedures, and both brother and niece had developed aggressive forms of disease. Despite treatment with laser and cryotherapy, his niece lost vision in one eye.

The patient initially had no visual complaints, had no other comorbidities, did not use medications, and denied any prior ophthalmological treatment. In the first exam (August 2016), he reported best-corrected visual acuity (BCVA) of 20/20 in both eyes and had no anterior segment abnormalities. Intraocular pressure (IOP) was 12 mm Hg in the right eye and 13 mm Hg in the left eye. Ocular fundus was absolutely normal in the right eye. However, in the left eye, he had multiple confluent RCHs in the superior mid-peripheral retina, measuring approximately 1 disc diameter each. Tumors were well delimited, retina was attached, and the posterior pole was preserved. Therefore, we decided to observe this patient every 4 months.

The patient remained stable until June 2018, when he started to complain of visual loss and metamorphopsia in the left eye. His BCVA remained 20/20 in the right eye but decreased to 20/80 in the left eye. Anterior biomicroscopy remained unchanged, and IOP was 14 mm Hg in each eye. In the fundus, we observed development of new tumors in the superior and inferior periphery of the left eye, growth of preexisting lesions, and perilesional exudation threatening the posterior pole (Fig. 1a). With the aid of fluorescein angiography, RCHs could be precisely located (Fig. 1b), and optical coherence tomography (OCT) (Fig. 1c, d) showed a thick epiretinal membrane in the macular region with intraretinal cysts and retinal architecture distortion.

In August 2018, 23-gauge pars plana vitrectomy was performed in the left eye. After extensive vitrectomy and posterior hyaloid detachment with the aid of intravitreal triamcinolone, brilliant blue G dye was injected into the vitreous cavity for chromovitrectomy. Epiretinal membrane and internal limiting membrane were peeled, and preretinal membranes covering the angiomatous masses were carefully dissected. Panretinal photocoagulation (300 mW, 300 ms, 1,200 shots) was performed up to the far periphery, sparing the posterior pole. RCHs were also locally treated (100 mW, continuous duration) until they were whitish in appearance, when possible. In the end, balanced saline solution was left in the vitreous cavity, and sclerotomies were sutured.

Three days after surgery, the patient developed a transvitreal fibrinoid reaction in the left eye (Fig. 2a). He had no ocular pain or hypopyon but presented ocular hypotonia (IOP was 6 mm Hg), dense vitreous bands, and serous retinal detachment involving the macular region and retinal folds (Fig. 2b, c). In addition to usual postoperative gatifloxacin and steroid drops, we injected bevacizumab (1.25 mg/0.05 mL) into the vitreous cavity. Injections were repeated monthly for 3 months.

Transvitreal fibrinoid reaction gradually improved and, after a 14-month follow-up, BCVA improved in the left eye, reaching 20/40 in April 2019. Incipient nuclear and posterior subcapsular cataract had developed, and IOP was 11 mm Hg in the operated eye. As can be seen in wide-field retinography (Fig. 3a), the retina is attached, exudation is reduced, and RCHs are stable (Fig. 3b). There was no formation of proliferative vitreoretinopathy or development of new tumors. OCT (Fig. 3c, d) showed improvement of intraretinal cysts and relative reorganization of inner retinal layers.

Discussion/Conclusion

Most interventions focus on shrinking or removing the tumors present in VHL disease, but no gold standard treatment has been established and results are extremely variable. Lesions may be too numerous or large to treat, new tumors may grow in spite of the therapy, and there is risk of proliferative vitreoretinopathy and retinal detachment.

One retrospective study [13] suggests a relationship between prior treatment of RCH and the occurrence of posterior pole and peripheral fibrovascular proliferation, but the authors could not determine that it was causative. Further prospective studies are required to see if current treatments may increase the risk of developing fibrovascular proliferation in VHL patients.

Several surgical techniques have been proposed [11]. They include, besides vitrectomy in all cases, the addition of intense endolaser photocoagulation of the RCH, intraoperative cryotherapy, or resection of RCH masses with the aid of retinectomy. Nevertheless, complications, such as RCH reproliferation, massive intraoperative bleeding, and neovascular glaucoma, have arisen. Transretinal feeder vessel ligature [14] was also performed in a single case, but revascularization occurred because of the opening of vessels adjacent to the tumor.

Special consideration has been given to the role of VEGF in the disease, and its production may not only be limited to the tumoral lesions themselves, but to the adjacent retina as well [15]. In addition to VEGF, other HIF-induced molecules that are involved in VHL disease also secrete a number of cytokines and growth factors, such as PDGF and TGF. Many of these factors are also related to angiogenesis. These factors may promote the proliferation of vessels within the tumefactions in the eye and the production of various systemic tumors in other tissues with VHL disease. Therefore, anti-VEGF therapy alone will not be efficient or sufficient to treat all VHL disease-associated lesions in the eye [16]. A recent study has detected diffuse vascular leakage from retinal venules around and away from RCHs in patients with VHL disease, in the late phases of fluorescein angiography, but the clinical and prognostic importance of this finding is still uncertain [17].

Furthermore, peripheral retinal nonperfusion can be associated with RCHs and could be more common with larger, more peripheral tumors in younger patients with VHL disease. Eyes with RCH-associated peripheral nonperfusion could be more likely to develop neovascularization and lose visual acuity [18].

Curiously, none of the previously reported surgical techniques have incorporated the addition of panretinal photocoagulation to the strategy. The inclusion of this step in all cases may reduce intraocular levels of VEGF and other angiogenic factors, contributing to better long-term results. Nonetheless, side effects of extensive laser therapy should be considered. Peripheral visual field restriction, nyctalopia, and even severe inflammatory reaction may occur, and these consequences should be discussed with the patients.

Our patient has had a good evolution so far, with gradual BCVA improvement, stability of RCH lesions and no need of further intravitreal injections. After a 14-month follow-up, the retina remains attached, and by now, there has been no development of new tumors. However, prospective studies with a larger number of patients and longer follow-up periods are essential to confirm our theory.

Statement of Ethics

The authors have no ethical conflicts to disclose. Written informed consent was obtained from the patient.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Sturzeneker wrote and reviewed the manuscript and assisted during surgery. Dr. Maia is head of the Retina Service and reviewed the manuscript. Dr. Morales is head of the Ocular Oncology Service and reviewed the manuscript. Dr. Belfort reviewed the manuscript. All authors read, edited, and approved the case report.

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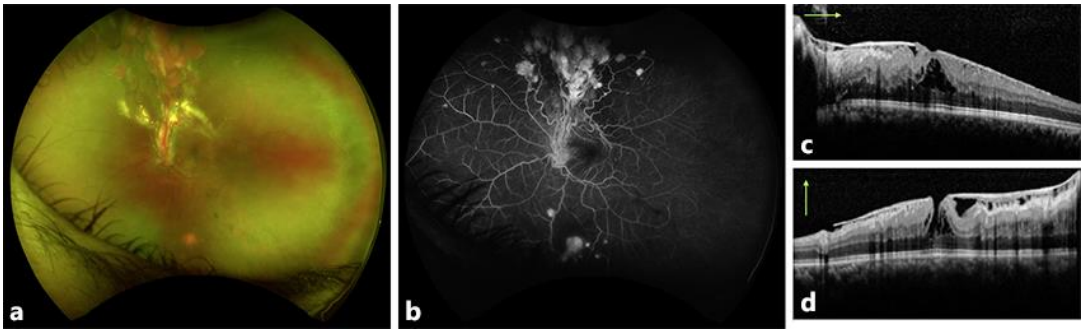

Fig. 1. Wide-field retinography (**a**) and fluorescein angiography (**b**) in the left eye of a 23-year-old male patient with multiple superior and inferior retinal capillary hemangiomas, secondary to von Hippel-Lindau disease. Horizontal (**c**) and vertical (**d**) spectral-domain optical coherence tomography cuts in the macular region demonstrated a thick epiretinal membrane with intraretinal cysts and retinal distortion. These pictures were obtained preoperatively, and his best-corrected visual acuity was 20/80.

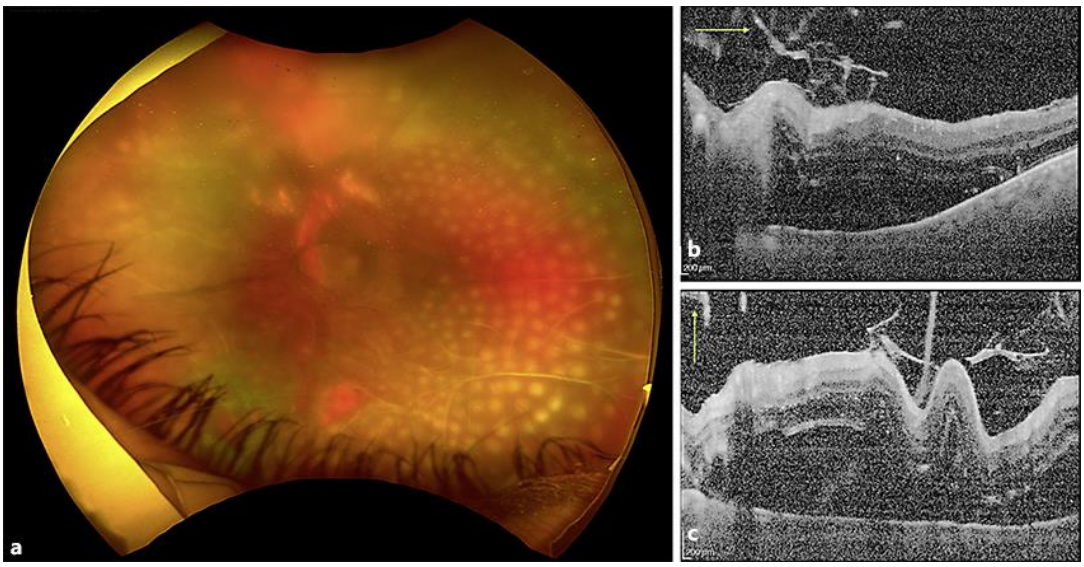

Fig. 2. Three days after vitreoretinal surgery, the patient developed a transvitreal fibrinoid reaction in his left eye, as shown in wide-field retinography (**a**). Spectral-domain optical coherence tomography showed macular neurosensory detachment, retinal folds, and dense vitreous bands, as shown in horizontal (**b**) and vertical (**c**) cuts. The patient was treated with topical steroid and gatifloxacin drops, combined with monthly intravitreal bevacizumab injections, during 3 months.

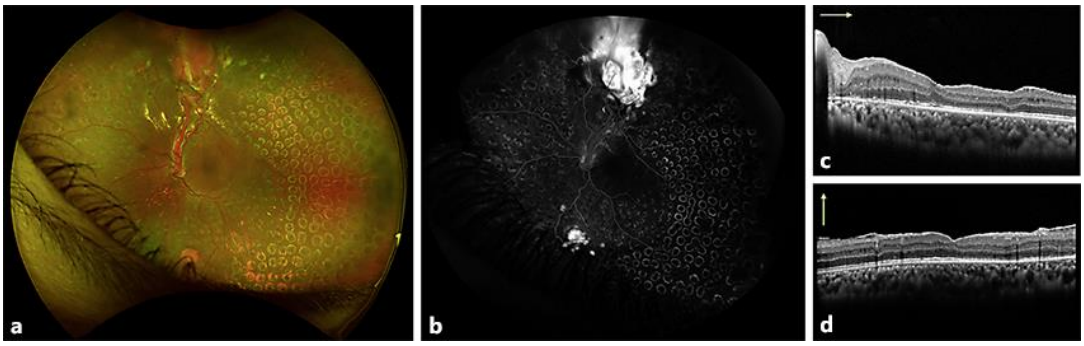

Fig. 3. Wide-field retinography (**a**) and fluorescein angiography (**b**) obtained 14 months after vitreoretinal surgery. Retina was entirely attached, superior and inferior capillary hemangiomas were stable, and superior exudation was decreased. Horizontal (**c**) and vertical (**d**) spectral-domain optical coherence tomography cuts in the macular region demonstrated improvement of intraretinal cysts, reorganization of the internal retina, and mild retinal distortion – achieving a best-corrected visual acuity of 20/40.