Retinal Capillary Hemangioma Leading to a Diagnosis of von Hippel-Lindau Disease in a Patient with Retinopathy of Prematurity

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Abstract
Von Hippel-Lindau (VHL) disease is a rare inherited cancer syndrome that results in the development of tumor formation in multiple systems. In the eye, retinal capillary hemangioma (RCH) can lead to severe vision loss. Retinopathy of prematurity (ROP) is likewise a rare disease in which abnormal retinal vasculature develops in premature infants. Hallmarks of this disease include temporal dragging of the macula and retinal vessels. Here, we describe a 36-year-old myopic woman with a known history of ROP who presented with a vitreous hemorrhage in the right eye. As the vitreous hemorrhage cleared, she was found to have not only a retinal tear but also a juxtapapillary RCH that lead to a diagnosis of VHL disease in the patient, her mother, and her aunt. This is the first reported case of an individual with concomitant ROP and RCH from VHL. Her vision was remarkably well preserved over 25 years of follow-up despite having a moderate-sized laser scar temporal to the disc from treating the juxtapapillary RCH, likely due to the temporal macular dragging from her underlying ROP. This case highlights the importance of being aware that rare diagnoses can co-exist, and one must be aware of the protean manifestations of VHL.
**Introduction**

Von Hippel-Lindau (VHL) disease is a rare autosomal dominant condition caused by germline mutations in the \textit{VHL} gene located on chromosome 3 and results in tumor formation in multiple organs including the adrenal glands, central nervous system, kidney, and eye [1]. Loss of properly functioning VHL protein results in an inability to properly degrade proangiogenic factors and results in the formation of vascular tumors. In the eye, patients develop retinal capillary hemangiomas (RCH) which can be treated with various modalities including cryotherapy, thermal laser, photodynamic therapy, intravitreal injections, radiation (external beam or brachytherapy), and vitrectomy surgery [1–4]. However, patients can still experience severe vision loss as sequelae particularly in the setting of juxtapapillary angiomas which are difficult to treat without causing damage to the optic nerve [1].

Retinopathy of prematurity (ROP) is a retinal vascular disorder unrelated to VHL and can also result in blindness. ROP occurs in premature infants in the setting of abnormal levels of oxygen at various stages of development [5], which leads to abnormal development of the retinal vasculature. Patients can experience a spectrum of disease which can result in anywhere from no to severe vision loss, depending upon the degree of disease and timing of treatment [5]. Clinical findings can include temporal dragging of the retinal vessels and macula, peripheral ridges between avascular and vascularized tissues, retinal detachment, and long-term sequelae such as high myopia, amblyopia, and strabismus [6].

Here, we describe a case of an individual with known ROP who was later found to have VHL based upon an ophthalmic exam. Remarkably, this patient’s foveal dragging from her underlying ROP prevented severe vision loss from treatment of a juxtapapillary RCH. This is the first known reported case of an individual with both VHL-associated RCH and ROP.

**Case Description**

A 36-year-old woman presented with a complaint of decreased vision in the right eye. She had a known history of myopia and ROP with temporal dragging of the fovea and an inactive temporal fibrovascular ridge in both eyes. She had a reported history of amblyopia in her left eye and had no prior history of ocular laser or surgery in either eye. Visual acuity was hand motion in the right eye and 20/100 in the left eye. She was found to have a dense vitreous hemorrhage with concern for a retinal tear as the cause for the hemorrhage, but no break was seen clinically or on echography. The right eye and was carefully observed. Over several days, the vitreous hemorrhage cleared, and she was found to have a posterior retinal tear in the right eye that was treated with cryotherapy.

As the vitreous hemorrhage in the right eye continued to clear, it was noted that there was juxtapapillary subretinal fluid. Indocyanine green angiography demonstrated the presence of a juxtapapillary optic disc angioma in addition to an angioma along the inferotemporal arcade (Fig. 1). Two probable peripheral angiomas were also identified in the left eye at this time. Laser was applied to supplement the cryotherapy surrounding the retinal tear in the right eye, and the peripheral angiomas in both eyes were treated with yellow laser (577 nm). The decision was made to observe the juxtapapillary angioma in the right eye as the subretinal fluid spared the fovea which was dragged temporally.

Her visual acuity in the right eye returned to 20/30 after the vitreous hemorrhage cleared. Upon review of her medical history, she reported having undergone resection of a tumor of the ureter at the age of 9 years. Pathology results from this procedure were obtained, and it was determined that the lesion was a pheochromocytoma. Molecular studies for VHL were
performed, and she was found to have a Tyr98His mutation in the VHL gene, confirming the diagnosis of VHL disease. She underwent systemic evaluation for other VHL-associated tumors, and there was no evidence of central nervous system tumors or renal-cell carcinoma. Her mother underwent ophthalmic screening as a result of her diagnosis and was also found to have VHL disease. Her maternal aunt was also found to have a pheochromocytoma which led to a diagnosis of VHL.

One year later, the exudation in the right eye increased, and her visual acuity declined to 20/50. We reviewed management options with her, including external beam radiation, photodynamic therapy, and transpupillary thermotherapy laser. She elected to defer radiation, and the optic-disc angioma was treated with diode 810-nm red laser. Treatment was performed with the goal of heating the tumor from the base toward the apex, with an attempt to spare treatment to the inner retina and vessels supplying blood to the fovea. This meant the treatment did not close all the vasculature within the tumor, as is often the goal for laser ablation of RCH. Over the next 11 months, she had two supplemental laser treatments to the juxtapapillary angioma, with stabilization of her visual acuity at 20/50 in the right eye (shown in Fig. 2).

Over the next 25 years, she developed 31 new angiomas in both eyes, managed with thermal laser ablation. She had two mild reactivations of the optic disc angioma in the right eye over 25 years, which were treated lightly with transpupillary thermotherapy (five total treatments to the juxtapapillary angioma). She has maintained 20/80 vision in the right eye and 20/40 vision in her left eye at the time of her last follow-up at age 62 years after undergoing cataract extraction in both eyes. Images from her most recent follow-up visits at age 61 years (Fig. 3) and age 62 years (Fig. 4) showed a stable exam without active tumors. She continues to undergo surveillance for other VHL-associated tumors.

**Discussion**

This is the first known reported case of an individual with both ROP and RCH from VHL. This case highlights the importance of obtaining a detailed history and performing a meticulous ocular examination as this patient had two unrelated, rare diagnoses which complicated the clinical picture. In particular, it is important for the clinician to be aware of diseases such as VHL that have risk for additional tumors not only in the individual but also in family
Fig. 2. Color fundus photographs 16 years after presentation. In the right eye, the fovea is dragged temporally, and there is chorioretinal atrophy at the site of the treated juxtapapillary angioma. There are numerous laser scars temporally at the site of the treated retinal tear and peripheral retinal angiomas. a There is an active-appearing angioma in the inferior mid-periphery (white arrow). In the left eye, the vessels and fovea are dragged temporally. b There is extensive peripapillary atrophy and atrophy at the sites of the previously treated peripheral angiomas.

Fig. 3. Pseudo-color wide-field fundus photographs (age: 61 years). a There is chorioretinal atrophy at the sites of previously treated retinal angiomas and the retinal tear in the right eye. b Mid-phase fluorescein angiography of the right eye shows staining of some of the larger, previously treated angiomas within laser scars but no untreated angiomas. c There is chorioretinal atrophy at the sites of previously treated angiomas in the left eye. d Late-phase fluorescein angiography of the left eye shows staining of some of the treated angiomas within the laser scars of previously treated angiomas but no active angiomas.
members as in this case where the patient's diagnosis led to examination and diagnosis of VHL in the patient's mother and aunt. This is similar to work by Kuhlman et al. [7] who found an incidental diagnosis of VHL in a patient who presented with both lung cancer and hepatocellular carcinoma. RCH is often the first presenting sign of a diagnosis of VHL, and one must be aware of the systemic implications [8].

This patient's juxtapapillary angioma in the right eye extended 4 mm temporal to the optic disc. In a normal emmetropic eye, the foveal center is located about 3.4 mm temporal to the disc, so this lesion would have been in a subfoveal location. Fortuitously for this patient, her fovea was dragged temporally due to her ROP and was not directly damaged by the laser treatment. Juxtapapillary RCH is particularly difficult to treat without causing severe vision loss due to their proximity to the optic nerve [1]. Modalities such as photodynamic therapy, transpupillary thermotherapy, intravitreal vascular endothelial and growth factor inhibitors, and steroid injection have all been attempted, but patients often still lose significant vision due to damage to the optic nerve sustained at the time of treatment [1–4, 9]. The nonablative laser treatment method used to manage the juxtapapillary angioma allowed for sparing of the vessels and nerve fiber layer to the fovea with maintenance of useful central vision, but likely led to the two tumor reactivations, and the need for close monitoring.

Fig. 4. OCT (age: 62 years). a Infrared image of the macula of the right eye shows atrophy at the sites of previously treated angiomas. b OCT of the macula of the right eye shows temporal dragging of the fovea which is spared from atrophy in the area of prior laser treatment temporal to the optic disc. c Infrared image of the macula of the left eye shows temporal dragging of the macula and atrophy at the site of a previously treated angioma. d OCT of the macula of the left eye shows temporal dragging of the fovea and retinal thickening from an epiretinal membrane. OCT, optical coherence tomography.
The timing of angioma development in this patient’s case is also interesting given her underlying ROP. One could postulate that she may have been more likely to develop RCH at a younger age, given the abnormal oxygen tension present as an infant. Both ROP and VHL increase levels of HIF1-alpha and result in aberrant VEGF expression [10, 11]. VHL requires a “two-hit” loss of the VHL gene, and it is possible that as an infant, the loss of the second allele had not yet occurred. This patient is of a more typical age of presentation given the RCH in her 30s [12]. Based upon this individual case, the presence of ROP does not appear to result in development of RCH at a younger age.

Conclusion

Though uncommon, patients can present with multiple rare diagnoses. Patients with ROP can also harbor other genetic mutations and disease entities such as VHL. It is important for the clinician to be aware of the multiple manifestations of VHL disease, take a thorough history, and perform a careful physical examination in patients with RCH.

Statement of Ethics

This project adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This case was reviewed by the institutional review board at the University of Iowa, and it was deemed that institutional review board approval was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Drafting of the manuscript, data acquisition, analysis, and interpretation: Elaine Binkley, Culver Boldt, Connie Hinz, and Lola Lozano; critical review of the manuscript and approval of the final manuscript: Elaine Binkley, Culver Boldt, Connie Hinz, Lola Lozano, and Budd Tucker.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.
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