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Belzutifan-induced regression of retinal capillary hemangioblastoma: A case-series

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ABSTRACT

Purpose: To report a series of three patients with von Hippel-Lindau (VHL) disease who demonstrated regression of their retinal hemangioblastomas (RH) using belzutifan in conjunction with photocoagulation therapy.

Observations: Patient 1, a 23-year-old female, presented with multiple RHs in her right eye (OD) that were lasered. Her left eye (OS) revealed a large inferotemporal RH that measured approximately 2.1 mm^2. Systemic belzutifan was administered. Four months after initiation of treatment, the lesion regressed to 1.4 mm^2, but belzutifan was not well-tolerated and was discontinued due to side effects. At the date of belzutifan discontinuation, the lesion measured about 1.1 mm^2. Focal laser photocoagulation was applied. The lesion regressed to around 0.6 mm^2. Two additional laser treatments were applied one month later. On the most recent follow-up, the lesion was completely fibrosed.

Patient 2, a 32-year-old male, presented with one RH OD and two RHs OS. Belzutifan was administered for one month before the patient began experiencing side effects of the medication. Consequently, the dose of belzutifan was decreased. After one month with the lowered dose, laser coagulation was applied to OS. In the most recent follow-up, five months after the initial presentation, the lesions remain less vascularized and reduced in size.

Patient 3, is a 44-year-old male with a large RH OD. Following seven months of belzutifan daily, there was a significant reduction in the RH size.

Conclusions: Belzutifan, a hypoxia-inducible factor inhibitor, is an FDA-approved medication for VHL disease associated with renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors that do not require immediate surgical resection. Because of the high incidence of VHL-associated RHs, adjuvant laser photocoagulation therapy when belzutifan is suspended or withheld can allow for the regression of large lesions. In this case series, we also propose a reproducible and technically simple method to measure RH lesions size, using Optos fundus imaging.

1. Introduction

Von Hippel-Lindau (VHL) disease is an autosomal dominant disease identified by an inactivation of the VHL protein (pVHL).[1] Because an active pVHL acts to ubiquitinate hypoxia-inducible factor, a nonfunctional pVHL has major downstream effects and predisposes the patient to various types of neoplasms due to increased production of vascular endothelial growth factor (VEGF).[2] Retinal and central nervous system hemangioblastomas are the most common tumors described in patients with VHL disease but renal cell carcinomas (RCC), pheochromocytomas, and pancreatic islet cell tumors have also been observed and attributed to the inactivation of pVHL.[3] Various treatment options have been explored for the management of retinal hemangioblastomas (RH), ranging from observation to ablation with cryotherapy, thermal laser, and photodynamic therapy.[4,5] Belzutifan (MK-6482, previously called PT2977) (WELIREG, Merck) is a hypoxia-inducible factor 2-alpha inhibitor recently FDA-approved for managing patients with VHL-associated RCC, central nervous system hemangioblastomas, and

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pancreatic neuroendocrine tumors that do not require immediate surgery.[6]

In this report, we document the regression of multiple RHs in three patients with VHL following treatment with belzutifan. In one patient, adjuvant laser photocoagulation was applied to the regressed RH, leading to a near-complete resolution of the lesion despite discontinuation of belzutifan therapy. We propose a novel method of measuring the surface area of RH lesions, using the green-free pseudocolor images of the Optos imaging system (Optos Sylverstone, Marlborough, MA).

2. Findings

2.1. Case 1

A 23-year-old female patient with VHL disease was started on belzutifan for brain, spinal and pancreatic hemangioblastomas. The patient presented with multiple small peripheral RHs in the right eye, which were lasered, and a left large inferotemporal RH, measuring about 2.1 mm^2 on Optos ultra-widefield green-free image (Fig. 1A–B). Upon initial presentation, visual acuity was 20/20 in OD and 20/25–1 in OS. Systemic treatment with belzutifan, 120 mg daily, was initiated. Four months later, there was marked shrinkage in the size of the left RH with the lesion now measuring approximately 1.4 mm^2 (Fig. 1C–D). Belzutifan was discontinued because the patient developed shortness of breath and anemia. Her hemoglobin level decreased from 13 g/dL to 9.5 g/dL while on the medication, even after decreasing to a minimal dose. After suspending the medication, her anemia completely recovered within two months. The lesion remained stable at about 1.4 mm^2. At this point, focal laser photocoagulation was applied to the left eye lesion. The treatment consisted of the creation of white laser burns around the lesion and over the feeding vessel (577 Pa Laser (Iridex, Mountain View, CA), with a duration of 30 msec, spot size 200 μm, power 200–250 mW, using a 165 pan-funduscopic lens), and blanching of the lesion's vascular network (duration 150–200 msec, spot size 200 μm, power

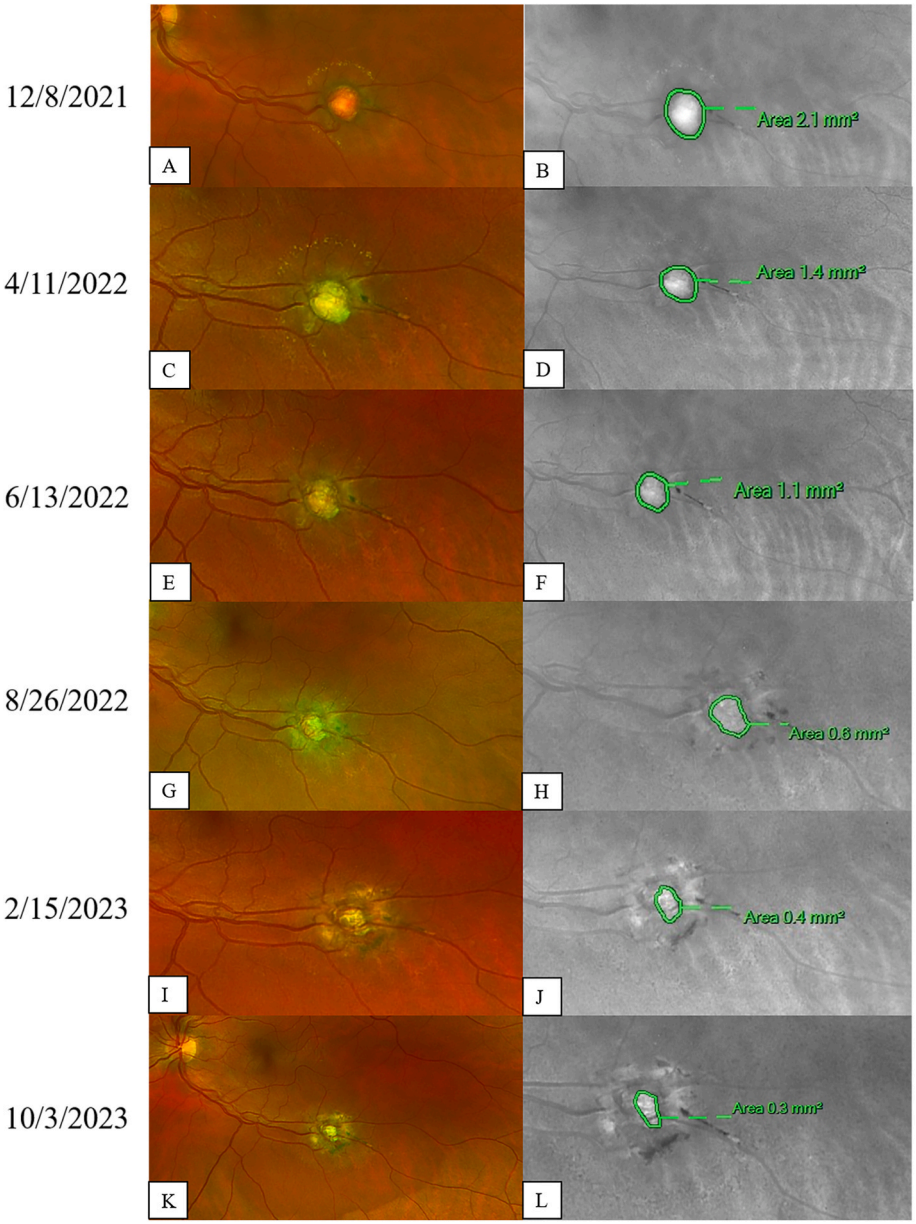

Fig. 1. Fundus photography of the right eye showing left large inferotemporal retinal hemangioblastoma (A) The lesion was markedly reduced in size after initiating belzutifan systemic treatment (C and E). The lesion was lasered and further reduced in size (G and H). Additional laser therapy was administered after I and J. Lesion had almost completely fibrosed (K and L).

150–200 mW). Two months later, the lesion regressed to about 1.1 mm^2 (Fig. 1*E*–F). Two additional laser treatments were applied over the lesion. On the most recent follow-up, 21 months after presentation, the lesion was completely fibrosed (Fig. 1K-L). The visual acuity in her left eye at this time was measured at 20/50–2.

2.2. Case 2

A 32-year-old male patient with VHL disease, who had undergone two previous cerebral hemangioblastoma resections, was started on belzutifan due to multiple spinal and brain hemangioblastomas. He presented with multiple RHs in both eyes. A superior quadrant lesion in the right eye measured about 2.7 mm^2 (Fig. 2A–B). One RH in the temporal quadrant of the left eye was associated with exudative retinal detachment. The left eye lesions measured 5.4 mm^2 and 12.3 mm^2 (Fig. 2C–D). Visual acuity was 20/20–1 in OD and 20/20 in OS. Treatment with belzutifan 120 mg daily was started. Two months after treatment initiation, the lesions in both eyes had decreased in size. Due to anemia and fatigue the dosage of belzutifan was reduced to 80 mg. After a month with a lowered dose, the right eye lesion measured 2.3 mm^2 (Fig. 2*E*–F), and the two lesions in the left eye measured 4.3 mm^2 and 11.4 mm^2 (Fig. 2G–H). One session of focal laser photocoagulation was carried out in the left eye but was poorly tolerated by the patient. On the most recent follow-up, the right eye lesion measured 1.9 mm^2 (Fig. 2I–J). The lesions in the left eye remained less vascularized and reduced in size measuring 4.1 mm^2 and 11.1 mm^2 (Fig. 2K-L). Visual acuity at the most recent follow-up was 20/20–1 in each eye.

2.3. Case 3

A 44-year-old male patient with VHL disease with long-standing vision loss in the right eye from exudative retinal detachment secondary to a large RH, presented for evaluation of blurry vision in the left eye. Visual acuity at this time was no light perception (NLP) OD and 20/20 OS. His past medical history was significant for multiple central nervous system capillary hemangiomas and type II diabetes mellitus. Ultra-widefield fluorescein angiography (FA) highlighted the large RCH in the right eye and a small microaneurysm in the macula in the left eye. The right eye RH measured about 10.3 mm^2 at this time (Fig. 3A–B). Belzutifan 120 mg daily was started for multiple brain and spinal hemangioblastomas. But the dosage had to be reduced to 40 mg daily because the patient developed shortness of breath and anemia. After seven months of belzutifan treatment, there was a significant reduction in the size of the large RH present in the right eye. Although the patient still had NLP OD, the size of the RH was almost halved and measured at about 5.5 mm^2, with a resolution of the serous retinal detachment (Fig. 3C–D). At the most recent follow-up, visual acuity remained NLP OD and 20/20 OS.

3. Discussion

Von Hippel-Lindau disease (familial cerebello-retinal angiomatosis) is a rare autosomal dominant disorder caused by a mutation in the VHL tumor suppressor gene leading to overexpression of VEGF and subsequent angiomatosis.[3,7] It is characterized by the development of neoplasms, the most common of which are retinal and central nervous system hemangioblastomas.[8] Although RH may occur in non-VHL patients, a study by Binderup and colleagues[9] reported that 84% of patients with RH have underlying VHL.[10] Up to 68% of VHL patients develop RHs, and the incidence increases with age.[3] Retinal capillary hemangioblastomas in VHL can be unilateral (42%) or bilateral (58%).[11] A recent study has demonstrated that ultra-widefield FA may detect peripheral RH better than conventional ophthalmoscopy or angiography.[12–14] Several treatment modalities have been attempted to manage RHs including observation, argon laser photocoagulation, cryotherapy, radiotherapy, and ablation during surgery.[4,5] Belzutifan is a novel hypoxia-inducible factor 2-alpha inhibitor recently approved for managing patients with VHL who have associated RCC, central nervous system hemangioblastomas, or pancreatic endocrine tumors.[5,15] In phase II clinical trials, Jonasch and colleagues[16] evaluated the efficacy

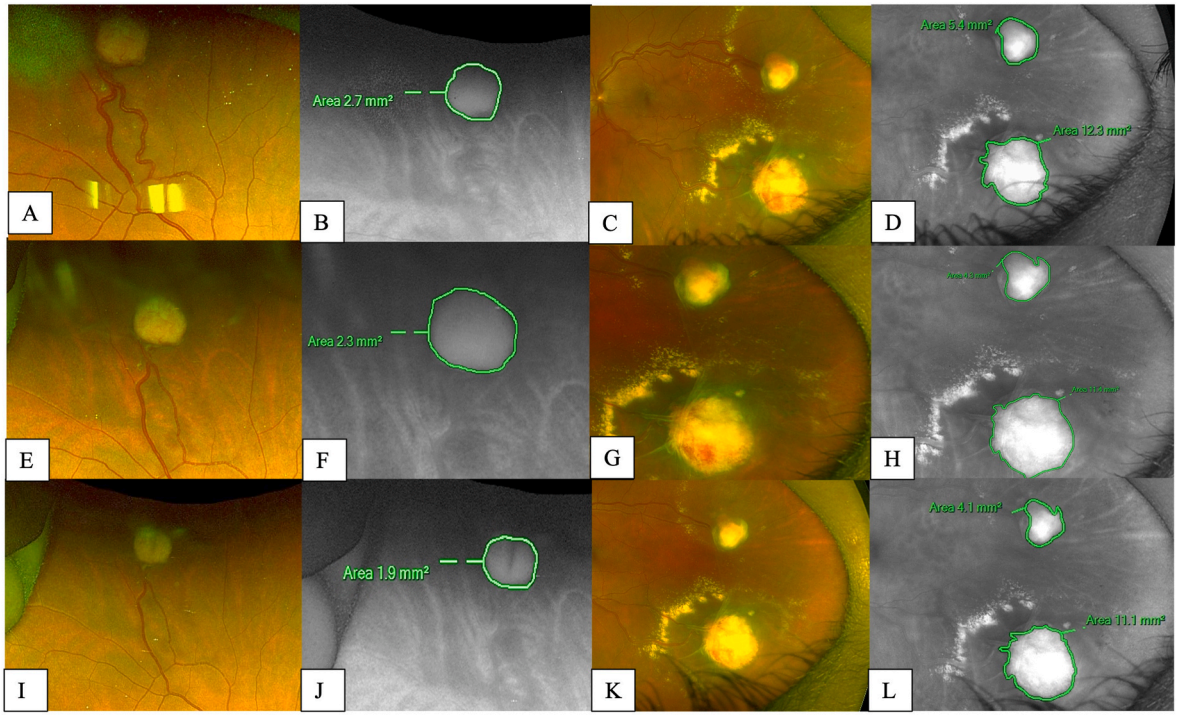

Fig. 2. Fundus photography of the right eye showing a single superior quadrant lesion (A and B) and two lesions present in the left eye (C and D). The lesions were reduced in size after belzutifan systemic treatment prior to laser therapy (E, F, G, and H). The lesions in both eyes reduced in size after initiation of belzutifan systemic treatment and photocoagulation therapy in the left eye (I, J, K, and L).

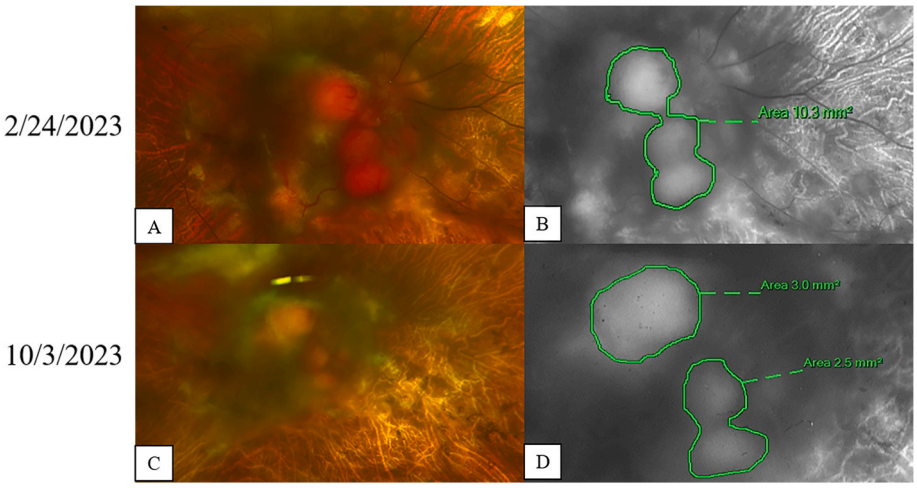

Fig. 3. Fundus photography of the right eye showing large retinal hemangioblastoma with exudative retinal detachment (A and B). After systemic belzutifan therapy, the lesion decreased in size with some resolution of the retinal detachment (C and D).

of belzutifan (120 mg oral dose) in patients with VHL and RCC with a median follow-up of 21.8 months. In their cohort, they demonstrated that 100% of patients (16 eyes of 12 patients) with RH showed improvement in their retinal lesions. Unfortunately, side effects are also common, with 90% of patients developing anemia and 66% experiencing fatigue, ultimately leading to one-third of patients discontinuing treatment.[15]

Our case highlights the efficacy of belzutifan with adjunct photocoagulation therapy in reducing the size, vascularity, and exudation of RHs. For large lesions, initiating systemic treatment may provide advantages before attempting other treatment modalities with higher complication rates, such as cryotherapy and photocoagulation therapy. Additionally, the use of belzutifan for large lesions can allow for RH regression to a size more amenable to laser therapy. Smaller lesions may be more amenable to local therapy (focal laser, photodynamic therapy). Once the lesions show signs of regression, multiple sequential laser treatments can be applied. It is important to mention that some patients may not tolerate the systemic side effects of belzutifan and, thus, may require dose reduction or complete discontinuation.

In our case series, the Optos green-free pseudocolor images were used to measure the RH surface area due to better visualization of lesion borders. As detailed in our figures, the bright solid lesions, which correspond to the vascular component of the tumor, were included in the measurement. On the fundus autofluorescence and pseudocolor frames, scarring, exudation, and serous detachment blurred the edges of the lesion, making reproducible and consistent measurements of the lesions challenging.

One limitation of the present series is the absence of B-scan ultrasonography for lesion measurements. We acknowledge the significance of a carefully performed B-scan in evaluating the three-dimensional size of an RH. Nevertheless, attaining precision in the measurement of intraocular lesions demands the expertise of a skilled operator. Our measurement methodology, albeit unconventional and not factoring in variations in lesion height, is characterized by technical simplicity and reproducibility. Future prospective studies with longer follow-ups are necessary to evaluate the long-term efficacy and safety of belzutifan treatment in managing RHs.

4. Conclusion

Ophthalmologists should be aware of the efficacy of belzutifan as a possible treatment of large RHs associated with VHL disease. In the authors' opinion, local laser therapy should be applied once regression of the lesions is documented.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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CRediT authorship contribution statement

Carson W. Ercanbrack: Writing – original draft, Writing – review & editing. **Abdelrahman M. Elhusseiny:** Writing – original draft, Writing – review & editing. **Riley N. Sanders:** Conceptualization, Writing – original draft. **Erika Santos Horta:** Supervision, Writing – review & editing. **Sami H. Uwaydat:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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