American Journal of Ophthalmology Case Reports 25 (2022) 101394

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

3-D OCT angiographic evidence of Anti-VEGF therapeutic effects on retinal capillary hemangioma

Oscar Otero-Marquez [a], Toco YP. Chui [a,b], Alexander Pinhas [a], Maria V. Castanos Toral [b], Davis B. Zhou [a,b], Justin Migacz [a], Richard B. Rosen [a,b,*]

[a] Ophthalmology, New York Eye and Ear Infirmary of Mount Sinai, New York, NY, USA
[b] Icahn School of Medicine at Mount Sinai, New York, NY, USA

ARTICLE INFO

Keywords:
Retinal capillary hemangioma
Optical coherence tomography angiography
Anti-VEGF
Von Hippel-Lindau disease

ABSTRACT

Purpose: To report the impact of intravitreal anti–vascular endothelial growth factor (VEGF) therapy on a retinal capillary hemangioma (RCH) using clinical OCT angiography (OCT-A) in addition to standard imaging modalities.

Observations: A 25-year-old male patient with Von Hippel-Lindau (VHL) disease presented with a history of bilateral RCH. No view was present in the right eye. Examination of the left eye revealed six peripheral RCH, the smallest of which was temporal to the macula with active exudation. This RCH was thought to be the source of cystoid macular edema (CME) involving the fovea, and therefore, the source of vision decline. 11 injections of 1.25mg of Bevacizumab EA across 14-month was given. Comparison of the pre- and post-treatment OCT-A at the temporal RCH showed a reduction of CME and regression of RCH.

Conclusion: Anti-VEGF therapy appeared to stabilize the visual acuity and produce partial regression of RCH. It offers a safe option when visual acuity is threatened. OCT and OCT-A have the ability to document the impact of antiangiogenic therapy on RCH. 3D renderings of OCT-A offer enhanced sensitivity to recognition of structural and functional changes of RCH which may prove useful for monitoring treatment response.

1. Introduction

Von Hippel-Lindau (VHL) disease is an autosomal-dominant disorder with variable penetrance and expression that is caused by mutations of the VHL gene, a tumor suppressor gene located on the short arm of chromosome 3.[1] Aside from developing retinal capillary hemangiomas (RCHs), the earliest and most common manifestation the disease,[2] individuals with VHL disease also have a high incidence of systemic neoplasms, including renal cell carcinoma, central nervous system hemangiomas and pheochromocytomas.[3]

Despite its non-malignant nature, RCH can produce clinical complications that affect vision such as macular edema, exudative retinal detachment, vitreous hemorrhage and neovascular glaucoma.[4] RCH in VHL usually presents as a unilateral solitary tumor; however, up to one-third of patients may have multiple retinal hemangiomas, and half of the patients may present with bilateral involvement.[5] RCH lesions can grow on the optic nerve head, within the juxtapapillary area, or in the peripheral retina, occurring most commonly at the temporal peripheral retina.[6]

The clinical features of RCH are characteristic and diagnosis can generally be made based upon ophthalmoscopic appearance. The RCH is typically a well circumscribed, round bulging lesion with a red to orange color.[5] Fluorescein angiography (FA), the most used diagnostic test owing to the high degree of vascularity in these tumors, demonstrates early hyperfluorescence with variable late staining and leakage. FA is also helpful in differentiating feeding arterioles from draining venules in cases where ablative treatment is indicated.[7] Shortcomings of FA include its invasive nature, its inability to identify level of retinal involvement; and in some cases, due to profuse leakage, inability to define the precise location of the tumor. Other imaging modalities for the study of these vascular tumors include ultrasonography, optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A). Ultrasonography is helpful in the presence of opaque media, and can be useful in determining overall tumor dimensions, internal reflectivity of the lesion as well as the presence of subretinal fluid.[8] OCT is useful in detecting any RCH-associated subretinal fluid or

* Corresponding author. New York Eye and Ear Infirmary of Mount Sinai, 310 E 14th St, New York, NY, 10003, USA.
E-mail address: rrosen@nyee.edu (R.B. Rosen).

https://doi.org/10.1016/j.ajoc.2022.101394
Received 25 June 2021; Received in revised form 30 January 2022; Accepted 31 January 2022
Available online 7 February 2022
2451-9936/© 2022 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

macular edema and in accurately measuring foveal thickness particularly in cases where treatment response is being assessed.[9]

OCT-A, an emerging technology, has been increasingly used for evaluating retinal vascular diseases. Given its noninvasive nature, its ability to visualize retinal capillary networks at multiple levels, and ability to analyze blood perfusion, OCT-A can be considered an adjunct to traditional imaging methods.[10] However, due to its small field of view and reports of motion artifacts, OCT-A requires repeated imaging and patient cooperation and is often unable to image more peripheral lesions.[11]

In this case report, we demonstrate the effect of antiangiogenic therapy on a RCH temporal to the macula, using multimodal imaging including OCT and OCT-A. Additionally, we show how 3-D reconstruction of OCT-A volumes enhances appreciation of treatment impact.

2. Case report

A 25 year-old monocular male with history of VHL disease and bilateral RCH presented initially with complaint of vision loss in his left eye. The patient had a history of multiple previous retinal surgeries in his right eye since age 13, reportedly due to complications from RCH. On the initial exam, best corrected visual acuity (BCVA) was no light perception (NLP) in his right eye (OD) and 20/40 in his left eye (OS). Intraocular pressure (IOP) OD was 41 mmHg, and OS was 14 mmHg. Anterior segment exam OD revealed an irregular ocular surface with band keratopathy, and anterior and posterior iris synechiae. The lens was opaque and there was no view to the fundus. B-scan ultrasonography revealed a silicone oil-filled vitreous chamber. Anterior segment exam OS was unremarkable. Dilated fundoscopy revealed macular thickening, and six RCH (Fig. 1), the smallest of which was temporal to the macula (Fig. 1, arrow). In the described RCH, two retinal arterioles appeared to feed the lesion, and there was one dilated draining venule (Fig. 2, A1). Arteriovenous connection was not immediately evident due to a robust network of blood vessels within the lesion. FA showed early hyperfluorescence, with staining and leakage during the late phase (Fig. 2, A2 & A3). EDI-OCT scan (Spectralis OCT2, Heidelberg Engineering Inc., Heidelberg, Germany) through the vascular lesion (Fig. 2, A4), showed an isoreflective vascular mass involving multiple retinal layers with surrounding intraretinal cysts. The width of the RCH was 1349 μm. EDI-OCT through the macula (Fig. 3, A1) showed intraretinal cystoid edema, with a central macular thickness of 414 μm. Active fluid exudation from this RCH was thought to be the source of cystoid macular edema (CME) involving the fovea, and therefore, the source of vision impairment.

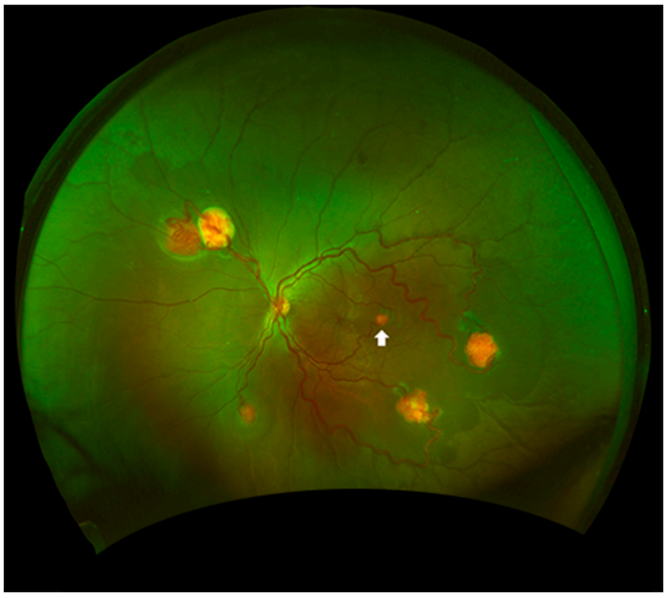

Fig. 1. Wide-field color fundus photo of a 25-year-old male patient with Von Hippel-Lindau disease showing six retinal capillary hemangioblastomas in the left eye. Arrow indicates a retinal capillary hemangioma (RCH) temporal to the macula imaged before and after anti-VEGF treatment with OCT and OCT-A. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Given the patient's monocular status and the size and location of the RCH, ablative therapy was deferred, and treatment with anti-vascular endothelial growth factor (VEGF) injections was pursued, with patient's consent. Intravitreal bevacizumab (Avastin® 1.25 mg in 0.05 cc) was initiated, with 11 subsequent injections across a 14-month time interval. At the last recorded visit, the patient's visual acuity had improved to 20/20. A less congested appearance of the RCH temporal to the macula with some areas of fibrosis was observed (Fig. 2, B1). FA suggested smaller blood vessels network within the lesion and less leakage (Fig. 2, B2 & B3). On the EDI-OCT through the lesion, less CME and surrounding exudation was seen, and the lesion itself appeared smaller, with a width of 1163 μm (Fig. 2, B4). On the EDI-OCT of the macula, the CME was resolved with central macular thickness of 277 μm (Fig. 3, B1).

For a better visualization of the spatial relationship between the retina and its capillary networks, ten sequential 3 × 3 mm scans centered at the RCH temporal to the macula (first location) and fovea (second location) were taken during the first visit and at 14 months follow-up using an OCT-A device (Avanti RTVue-XR; Optovue, Fremont, CA, USA). Image registration and averaging was performed using ImageJ[12] (ImageJ, U.S. National Institute of Health, Bethesda, Maryland, USA). In the RCH temporal to the macula, the regression was noticeable and revealed 3 feeder arterioles which appeared to anastomose within the lesion. (Fig. 2, B5 & B6). OCT-A images centered at the fovea (Fig. 3, A2 and B2) showed consistent vasculature with no apparent capillary dropout but a somewhat larger foveal avascular zone (FAZ) at the last follow-up thought to be due to flattening of the macula with resolution of the CME.

3-D rendered OCT-A volumes of the RCH were generated using MIPAV (Medical Image Processing, Analysis, and Visualization, version 10.0.0; US National Institutes of Health, Bethesda, Maryland, USA). Compared to the initial visit **(Video 1)**, the rendered volume at the RCH temporal to the macula showed a decrease in the size and flow preferentially in the center of the lesion at the last visit. **(Video 2)**. Close observation and periodic follow-ups were recommended to the patient, with continued anti-VEGF injections to maintain the improvement.

3. Discussion

Here we demonstrate the impact of intravitreal bevacizumab on exudation due to VHL-related RCH. Treatment of RCH is based upon tumor size, location, presence of subretinal fluid, traction, and visual acuity. Observation alone is warranted for small-sized lesions, in the absence of exudation, and in cases where visual acuity is not threatened.[13] For larger tumors and those cases where visual acuity is threatened, treatment modalities including laser photocoagulation,[14] cryotherapy,[15] photodynamic therapy,[16] brachytherapy,[17] and various other vitreoretinal procedures[18] including intravitreal anti-VEGF injections[19] have been employed.

VHL pathogenesis is due to the inability of affected cells to degrade hypoxia-inducible factors in the presence of oxygen, resulting in the overproduction of VEGF and other hypoxia-inducible factors.[7] Moreover, a pan-retinal effect has been hypothesized in patients with VHL disease even in the absence of RCH. In a recent study by Lu et al.,[20] a significant increase in vessel density was found in the macula of patients with VHL disease for both superficial capillary plexus and deep capillary plexus on OCT-A, consistent with the pathogenesis of tumor development in VHL. Furthermore, peripheral non-perfusion, capillary telangiectasia and capillary leakage have been reported using ultra-wide field

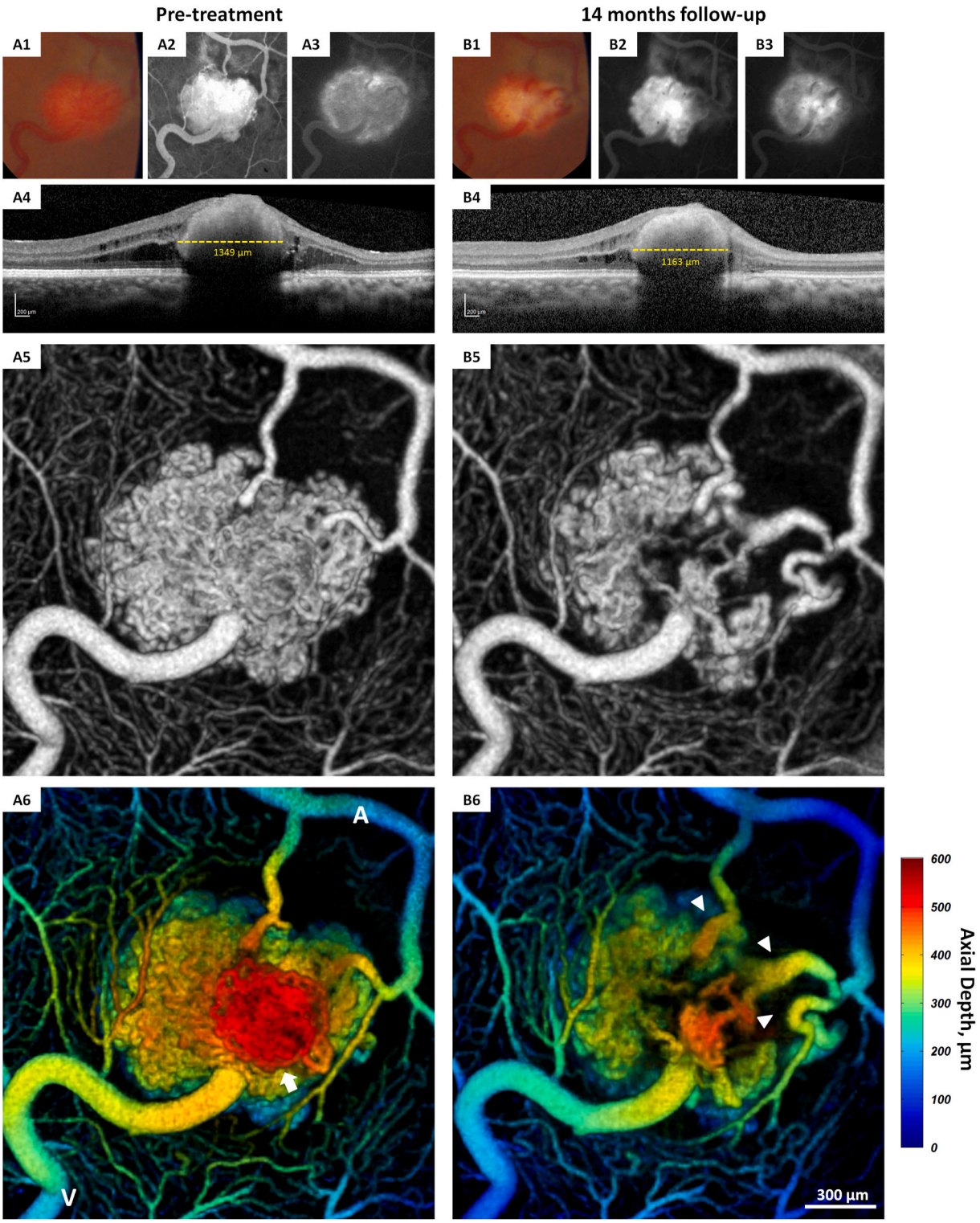

Fig. 2. A) Pre-treatment and B) 14 months follow-up evaluation of the RCH temporal to the macula. A1 & B1) Magnified color fundus photos of the RCH as indicated in Fig. 1. A2 & B2) Early phase fluorescein angiograms. A3 & B3) Late phase fluorescein angiograms. A4 & B4) EDI-OCT scans through the RCH shows regression of the RCH post-treatment. A5 & B5) Maximum intensity projection OCT-A. A6 & B6) Color-coded depth OCT-A. The vascular lesion presented with a robust network of blood vessels and a central elevation (A6, arrow). Two retinal arterioles appeared to enter to the lesion with one large draining venule. Arteriovenous connection was not visible. A = feeder arteriole; V = venule. RCH regression was noticeable post-treatment, revealing three feeder arterioles (B6, arrow heads) which appeared to anastomose within the lesion. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

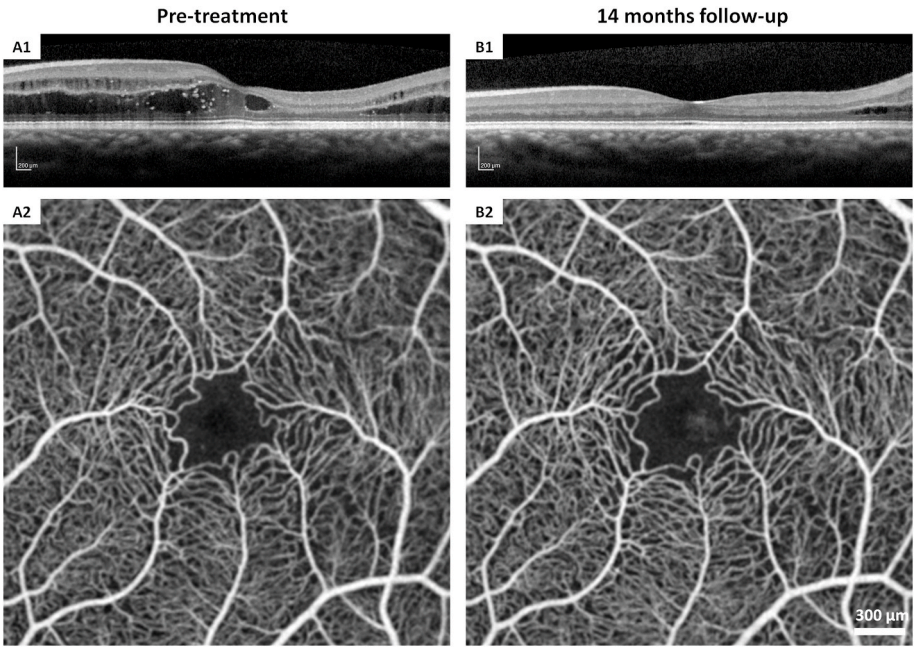

Fig. 3. A) Pre-treatment and B) 14 months follow-up evaluation of the macula. A1 & B1) EDI-OCT scans centered at the fovea shows reduction of cystoid macular edema (CME) post-treatment. A2 & B2) Averaged OCT-A images at the macula shows consistent vasculature with no apparent capillary dropout but a somewhat larger foveal avascular zone (FAZ) at the last follow-up thought to be due to flattening of the macula with resolution of the CME.

FA, indicating stimulation of the vascular bed toward angiogenesis in the presence of hypoxia with consequent VEGF production.[21] To counter these conditions, some highly upregulated molecules, such as VEGF and platelet-derived growth factor (PDGF), have been targeted in systemic[22] and ocular VHL therapies.[19] Reported outcomes of treatment have been mixed, suggesting that the efficacy of anti-angiogenic agents in VHL is less than complete.

Francis et al.[23] reported two cases of treatment-refractory juxtapapillary RCH managed with intra-arterial infusions of bevacizumab administered through the ophthalmic artery, showing a decrease in height (measured by ultrasonography) of the tumors, and showing stability of treatment effect over two years of follow-up. Wackernagel et al.[22] tested systemic bevacizumab in a single patient. Improvement in macular edema and visual acuity was demonstrated; however, new RCHs formed despite the systemic treatment. Dahr et al.[24] tested intravitreal pegaptanib sodium in patients with VHL disease and juxtapapillary or large extrapapillary RCH. While pegaptanib sodium decreased RCH-associated exudation, it did not affect the tumor size. Wong et al.[25] tested intravitreal Ranibizumab in five patients with RCH not amenable or responsive to standard treatments. Mean change in visual acuity was a decrease of 9 (±20) letters, and there was no consistent improvement in RCH exudation or tumor size.

As demonstrated in previous reports, there is a great variability in the response to anti-VEGF treatment. Wang et al.[26] found that this might be conditioned by the regulation of hypoxia-inducible factors (HIF); specifically, upregulation of HIF2α could potentially contribute to the aggressive course of RCH, resulting in the resistance to multiple anti-VEGF injections and other therapies in some patients.

Previously, outcome measures of response to treatment have consisted of visual acuity and lesion appearance on OCT and FA. In this case report, we demonstrated that OCT-A is able to show treatment effects in RCH. Given the proximity of the tumor to the macula and good cooperation of the patient, we were able to obtain high quality OCT and OCT-A images. Changes in OCT features, such as resolution of macular edema and reduction in the tumor exudation served as an early indication of response to therapy, and reduction in the flow and vascular network using OCT-A provided a better appreciation of the response to anti-angiogenic treatment in this vascular tumor.

Prior reports of OCT-A in RCH have shown its utility in identifying lesions close to the posterior pole, particularly on juxtapapillary tumors.[9,11,27] Russel et al.,[27] described the use of OCT-A for the diagnosis and longitudinal management of a patient with exophytic juxtapapillary RCH treated with two injections of anti-VEGF, noticing decreased vascular congestion and macular edema 1–2 weeks after treatment, but with subsided effects after 8 weeks.

In our patient, we observed durable changes after longer follow-up and higher doses of anti-VEFG. This suggests that more frequent or higher dosing of antiangiogenic agents may be capable of inducing long-lasting regression of vascular congestion and macular edema in these lesions.

Additional studies assessing the dose, the quantity of injections, and the route of administration may help elucidate the requirements for antiangiogenic therapies of RCH. Our findings demonstrate the potential contribution of OCT-A to multimodal imaging of treatment outcomes in RCH and other vascular tumors.

4. Conclusion

RCH is a common condition in patients with VHL. Although treatment outcomes of anti-VEGF for RCH are mixed and the standard treatment of small-size lesions has traditionally relied upon ablative therapy, anti-VEGF maintenance offers a safe option when visual acuity is threatened. OCT-A is an imaging modality which may be an effective addition to standard methods for assessing of therapy effectiveness in RCH, if the location of the tumor and cooperation of the patient make it possible. 3D renderings of OCT-A can be used to enhance appreciation of subtle treatment responses for RCH and other vascular pathologies.

Patient consent

Written informed consent was obtained from the patient. This report does not contain any personal information that could lead to the identification of the patient.

Funding

This report was supported by the National Eye Institute of the National Institutes of Health under award number R01EY027301. Additional funding for this research was provided by the New York Eye and Ear Infirmary Foundation Grant, the Marrus Family Foundation, the Challenge Grant award from Research to Prevent Blindness, and the Jorge N. Buxton Microsurgical Foundation.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

OOM: Conceptualization, Investigation, Visualization, Writing – Original Draft. TC: Visualization, Writing – Review & Editing, Supervision, Project administration. AP: Methodology, Writing – Review & Editing. MVC: Methodology, Investigation. DZ: Methodology, Investigation. JM: Data curation, Software. RR: Resources, Writing – Review and editing, Funding acquisition.

Declaration of competing interest

The following authors have no financial disclosures: OOM, TC, AP, MVC, DZ, JM.

RR declares the following interests: OptoVue: Code C (Consultant) & Code P (Patent); Boehringer-Ingelheim: Code C (Consultant); Astellas: Code C; Genentech-Roche: Code C; NanoRetina: Code C; OD-OS: Code C; Opticology: Code I (Personal Financial Interest); Guardion: Code I (Personal Financial Interest); GlaucoHealth: Code I (Personal Financial Interest); Regeneron: Code C (Consultant); Bayer: Code C (Consultant); Teva: Code C (Consultant).

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2022.101394.

References

1. Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science (80)*. 1993;260(5112):1317–1320. https://doi.org/10.1126/science.8493574.
2. Moore AT, Maher ER, Rosen P, Gregor Z, Bird AC. Ophthalmological screening for von hippel-lindau disease. *Eye*. 1991;5(6):723–728. https://doi.org/10.1038/eye.1991.133.
3. Maher ER. Von hippel-lindau disease. *Eur J Cancer*. 1994;30(13):1987–1990. https://doi.org/10.1016/0959-8049(94)00391-H.
4. Niemelä M, Lemeta S, Sainio M, et al. Hemangioblastomas of the retina: impact of von Hippel-Lindau disease. *Investig Ophthalmol Vis Sci*. 2000;41(7):1909–1915. https://pubmed.ncbi.nlm.nih.gov/10845616/. Accessed January 15, 2021.
5. Singh AD, Shields CL, Shields JA. Von hippel-lindau disease. *Surv Ophthalmol*. 2001;46(2):117–142. https://doi.org/10.1016/S0039-6257(01)00245-4.
6. Toy BC, Agrón E, Nigam D, Chew EY, Wong WT. Longitudinal analysis of retinal hemangioblastomatosis and visual function in ocular von hippel-lindau disease. *Ophthalmology*. 2012;119(12):2622–2630. https://doi.org/10.1016/j.ophtha.2012.06.026.
7. Singh A, Turell M. Vascular tumors of the retina and choroid: diagnosis and treatment. *Middle East Afr J Ophthalmol*. 2010;17(3):191. https://doi.org/10.4103/0974-9233.65486.
8. Singh AD, Shields CL, Shields JA. Von hippel-lindau disease. *Surv Ophthalmol*. 2001;46(2):117–142. https://doi.org/10.1016/S0039-6257(01)00245-4.
9. Pierro L, Brambati M, Arrigo A, Gagliardi M, Bandello F. The use of OCT and OCT angiography in detecting an atypical case of retinal capillary hemangioma. *Ophthalmic Surg Lasers Imaging Retin*. 2019;50(3):E81–E83. https://doi.org/10.3928/23258160-20190301-17.
10. Munk MR, Giannakaki-Zimmermann H, Berger L, et al. OCT-angiography: a qualitative and quantitative comparison. *PLoS One*. 2017;12(5). https://doi.org/10.1371/journal.pone.0177059.
11. Sagar P, Rajesh R, Shanmugam M, Konana VK, Mishra D. Comparison of optical coherence tomography angiography and fundus fluorescein angiography features of retinal capillary hemangioblastoma. *Indian J Ophthalmol*. 2018;66(6):872–876. https://doi.org/10.4103/ijo.IJO_1199_17.
12. Rueden CT, Schindelin J, Hiner MC, et al. ImageJ2: ImageJ for the next generation of scientific image data. *BMC Bioinf*. 2017;18(1). https://doi.org/10.1186/s12859-017-1934-z.
13. Singh AD, Nouri M, Shields CL, Shields JA, Perez N. Treatment of retinal capillary hemangioma. *Ophthalmology*. 2002;109(10):1799–1806. https://doi.org/10.1016/S0161-6420(02)01177-6.
14. 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(2):47–58. https://pubmed.ncbi.nlm.nih.gov/10720563/. Accessed January 15, 2021.
15. Shields JA. Response of retinal capillary hemangioma to cryotherapy. *Arch Ophthalmol*. 1993;111(4):551. https://doi.org/10.1001/archopht.1993.01090040143049.
16. Sachdeva R, Dadgostar H, Kaiser PK, Sears JE, Singh AD. Verteporfin photodynamic therapy of six eyes with retinal capillary haemangioma. *Acta Ophthalmol*. 2010;88(8). https://doi.org/10.1111/j.1755-3768.2010.02008.x.
17. Russo V, Stella A, Barone A, Scott IU, Noci ND. Ruthenium-106 brachytherapy and intravitreal bevacizumab for retinal capillary hemangioma. *Int Ophthalmol*. 2012;32(1):71–75. https://doi.org/10.1007/s10792-011-9513-1.
18. Gaudric A, Krivosic V, Duguid G, Massin P, Giraud S, Richard S. Vitreoretinal surgery for severe retinal capillary hemangiomas in von Hippel-Lindau disease. *Ophthalmology*. 2011;118(1):142–149. https://doi.org/10.1016/j.ophtha.2010.04.031.
19. Slim E, Antoun J, Kourie HR, Schakkal A, Cherfan G. Intravitreal bevacizumab for retinal capillary hemangioblastoma: a case series and literature review. *Can J Ophthalmol*. 2014;49(5):450–457. https://doi.org/10.1016/j.jcjo.2014.07.007.
20. Lu Y, Wang JC, Zeng R, et al. Detection of retinal microvascular changes in von Hippel-Lindau disease using optical coherence tomography angiography. *PLoS One*. 2020;15(2). https://doi.org/10.1371/journal.pone.0229213.
21. Kumar P, Ravani R, Agarwal S, Dhanda S, Kumar V. Insights into retinal hemangioblastoma using ultra widefield imaging. *Indian J Ophthalmol*. 2019;67(12):2029–2034. https://doi.org/10.4103/ijo.IJO_802_19.
22. Wackernagel W, Lackner EM, Pilz S, Mayer C, Stepan V. Von Hippel-Lindau disease: treatment of retinal haemangioblastomas by targeted therapy with systemic bevacizumab. *Acta Ophthalmol*. 2010;88(7). https://doi.org/10.1111/j.1755-3768.2009.01611.x.
23. Francis JH, Slakter JS, Abramson DH, Odrich SA, Gobin YP. Treatment of juxtapapillary hemangioblastoma by intra-arterial (ophthalmic artery) chemotherapy with bevacizumab. *Am J Ophthalmol Case Reports*. 2018;11:49–51. https://doi.org/10.1016/j.ajoc.2018.05.007.
24. 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(2):150–158. https://doi.org/10.1097/IAE.0b013e318030a290.
25. Wong WT, Liang KJ, Hammel K, Coleman HR, Chew EY. Intravitreal Ranibizumab therapy for retinal capillary hemangioblastoma related to von Hippel-lindau disease. *Ophthalmology*. 2008;115(11). https://doi.org/10.1016/j.ophtha.2008.04.033.
26. Wang Y, Abu-Asab MS, Shen D, Zhuang Z, Chew EY, Chan CC. Upregulation of hypoxia-inducible factors and autophagy in von Hippel-Lindau-associated retinal hemangioblastoma. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(8):1319–1327. https://doi.org/10.1007/s00417-014-2660-0.
27. Russell JF, Shi Y, Gregori G, Rosenfeld PJ. Longitudinal swept-source OCT angiography of juxtapapillary retinal capillary hemangioblastoma. *Ophthalmol Retin*. 2020;4(9):956–958. https://doi.org/10.1016/j.oret.2020.05.002.