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Macular edema in Wyburn-Mason syndrome: Resolution with anti-VEGF intravitreal injections. Case report and review of the literature

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ABSTRACT

Purpose: Macular edema is an infrequent complication of retinal arteriovenous malformations. We present the management of unilateral macular edema with Bevacizumab 1.25mg/0.05mL and Aflibercept 2mg/0.05mL in a 16-year-old child with Wyburn-Mason syndrome.

Observations: The patient developed macular edema after 15 years of unremarkable ophthalmological follow-up. After a one-month observation period, a first intravitreal injection of Bevacizumab 1.25mg/0.05mL, the treatment most frequently described in the literature, was found to be insufficient to reduce the macular edema. After the switch to Aflibercept 2.0mg/0.05mL, a significant reduction in macular edema was observed after three monthly intravitreal injections. This effect was prolonged over the 15-month observation follow-up.

Conclusions and importance: Aflibercept 2mg/0.05mL may be a safe and effective option to manage macular edema complications in retinal arteriovenous malformations.

1. Introduction

Wyburn-Mason syndrome is a rare, non-hereditary congenital neuro-oculocutaneous syndrome responsible for arteriovenous malformations (AVMs) of the midbrain, visual pathways, and facial nevi.

These congenital lesions are hamartomas and are not progressive.[1] However, disruption of haemodynamic flow has been shown to be responsible for a progressive worsening of lesions.[2]

The ocular expression of AVMs, also called *racemose angiomatosis* or *racemose hemangioma*, can affect the iris, the retinal periphery or be adjacent to the optic nerve head. Archer et al.[3] classified retinal AVMs into three groups: group I with an abnormal capillary plexus between arteries and veins, group II with distinctive artery and vein but without capillary plexus, and group III without distinction between artery and vein. The finding of a retinal AVM in a patient warrants a cerebral evaluation, as coexisting intracranial AVMs in patients with retinal AVMs is approximately 30 %.[4]

Although most of the retinal AVMs remain asymptomatic, 19 % of cases are described to present complications including retinal vein occlusion (9 % of cases), hemorrhages (6.5 % of cases) and macular edema (1.8 % of cases).[5]

Macular edema in AVMs presents as an uncommon complication of a rare disease, and there is currently no consensus on its management. With this case, we share our experience of treating macular edema in a grade III AVMs with intravitreal injections of Bevacizumab 1.25mg/0.05mL and Aflibercept 2mg/0.05mL (Eylea, Regeneron Pharmaceuticals).

2. Case report

A 15-year-old patient under our care since 2009 presented with a complaint of progressive vision loss in the right eye (RE) during his bi-annual follow-up visit in August 2022.

The patient was under regular monitoring for a known Wyburn-Mason syndrome with ipsilateral AVMs affecting the right cerebral, mandibular, facial, orbital, and ocular regions (Fig. 1). His systemic history includes left hemiplegia following a right thalamic hemorrhage and embolization 14 years ago and right superior homonymous quadrantanopia following embolization of 3 aneurysms of the left choroidal artery 13 years ago. He has been treated for 5 years with carbamazepine for epilepsy. The patient's condition remained stable for many years, without any systemic complication, a preserved visual function with visual acuity (VA) at 20/20 and an unchanged right superior homonymous quadrantanopia. His vital parameters and basic biological results

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have been within normal limits for many years.

In August 2022, the VA of the RE declined to 20/40. The VA of the left eye (LE) remained at 20/20. Slit lamp examination revealed no abnormalities in the anterior segment of either eye.

The posterior segment of the RE appeared to be consistent with the previous examinations: dilated and tortuous vessels characteristic of racemose hemangioma in every 4 quadrants of the fundus (Fig. 1). Macular-OCT examination unveiled a macular edema on the RE, with the posterior vitreous not detached. We considered the edema significant as it involved the central 500 μm of the macula. Fluorescein angiography demonstrated the retinal AVMs as being a grade III,[3] with no evidence of leakage or neovascularization (Fig. 2). The posterior segment of the LE was unremarkable.

Initially, we decided to follow the natural history of the macular edema for one month and wait for a possible spontaneous resolution. As we did not observe any improvement (Fig. 3), considering the subjective and objective decrease of VA and the young age of the patient, we decided to treat our patient *pro re nata* (PRN) for macular edema. Our criterion for re-injection was defined as the persistence of edema in the central 500 μm of the macula. We began treatment with the administration of an intravitreal injection (IVI) of Bevacizumab 1.25 mg/0.05mL in September 2022 (IVI1).

At 4 weeks follow-up, VA of the RE improved to 20/25 with a subtle reduction in macular thickness (Fig. 3). In the absence of a significant reduction in edema in the central 500 μm of the macula and with the desire to limit off-label drug injections in a child suffering from associated cerebral vascular malformations, we decided to switch to Aflibercept 2mg/0.05mL for the second IVI (IVI2).

At 4 weeks follow-up, a persistent macular edema justified a third IVI of a second dose of Aflibercept 2mg/0.05mL (IVI3) and then a fourth IVI of a third dose of Aflibercept 2mg/0.05mL (IVI4) with a 4 weeks interval. The patient experienced a subjective improvement in VA after each injection, and the macular edema dramatically responded on the OCT after the third IVI of Aflibercept 2mg/0.05mL (IVI3).

Indeed, in November 2022, the central macular edema had disappeared, allowing recovery of 20/20 VA. (Fig. 3). The infero-macular location of residual retinal edema outside the central 500 μm and the visual recovery prompted discontinuation of the IVIs and observation.

In April 2024, after 15 months of follow-up, no recurrence of central macular edema was observed, and visual acuity remained preserved at 20/20.

3. Discussion

The mechanism by which AVMs cause macular edema is not fully understood. In Wyburn-Mason syndrome, the abnormal embryological development of the vascular tissue prevents the differentiation of the vessels into arteries and veins and the development of capillary beds. The direct connection between artery and vein leads to an abnormally high pressure in this primitive vascular tissue[1] and to retinal ischemia due to the bypassing of capillaries in the area of the AVMs.[6,7] Although these congenital lesions are hamartomas and therefore not progressive,[1] it has been shown that disruption of haemodynamic flow is responsible for a progressive worsening of the lesions.[2]

The excessive transmural pressure on a more fragile vessel can lead to vascular decompensation and leakage. In addition, the excessive venous pressure downstream of the malformation can cause reflux into the adjacent veins with subsequent leakage of the normal capillaries adjacent to the malformation.[1,8,9]

The local tissue hypoxia around the malformation is the driver of local VEGF production. VEGF-A, amongst the other isomers of VEGF, is recognized as a key mediator of vascular permeability through its

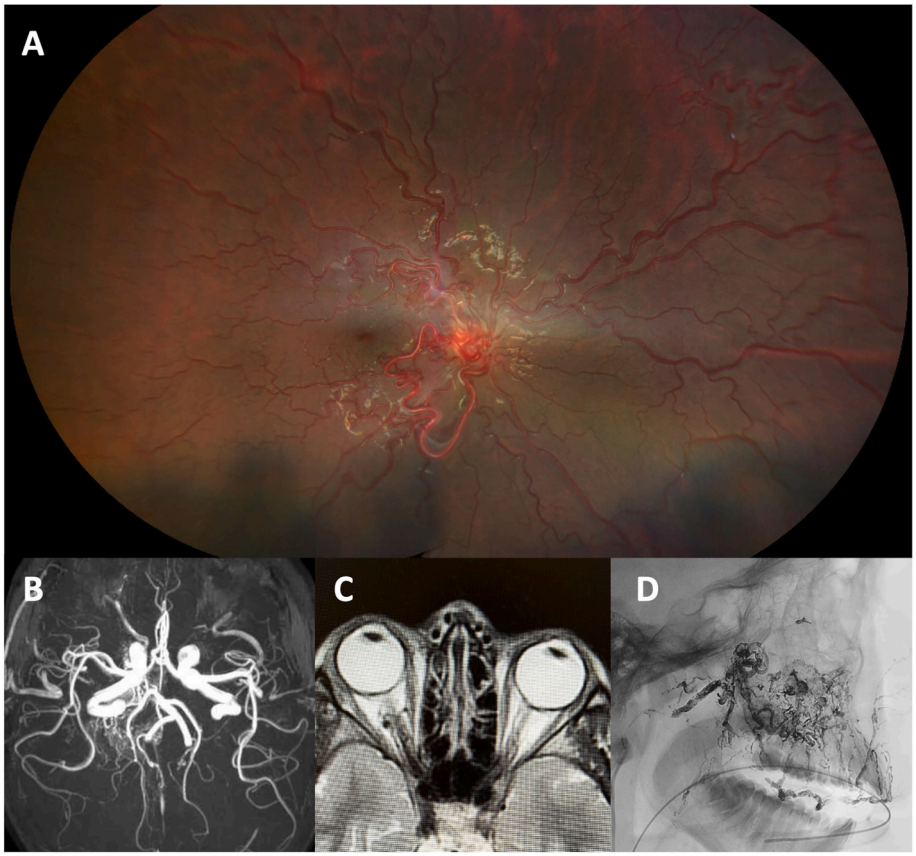

Fig. 1. Wyburn-Mason syndrome with ipsilateral right arteriovenous malformations of the patient. A. Fundus photography: Racemose hemangioma RE. B. Angio-MRI: Right mesencephalic and right sylvian AVMs. C. MRI: Right orbital AVMs. D. Right facial and maxillary AVMs.

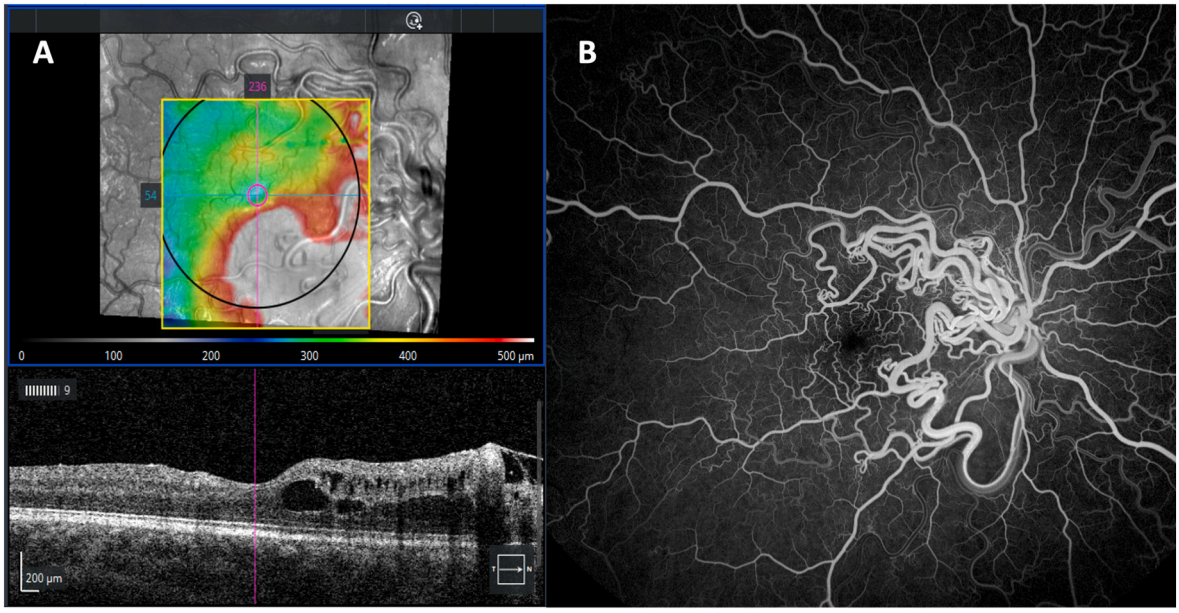

Fig. 2. Multimodal imaging of the posterior pole of the RE at presentation in 08.2022. A. Macular-OCT demonstrating a macular edema. B. Fluorescein angiography highlighting the direct AV communication in early phases.

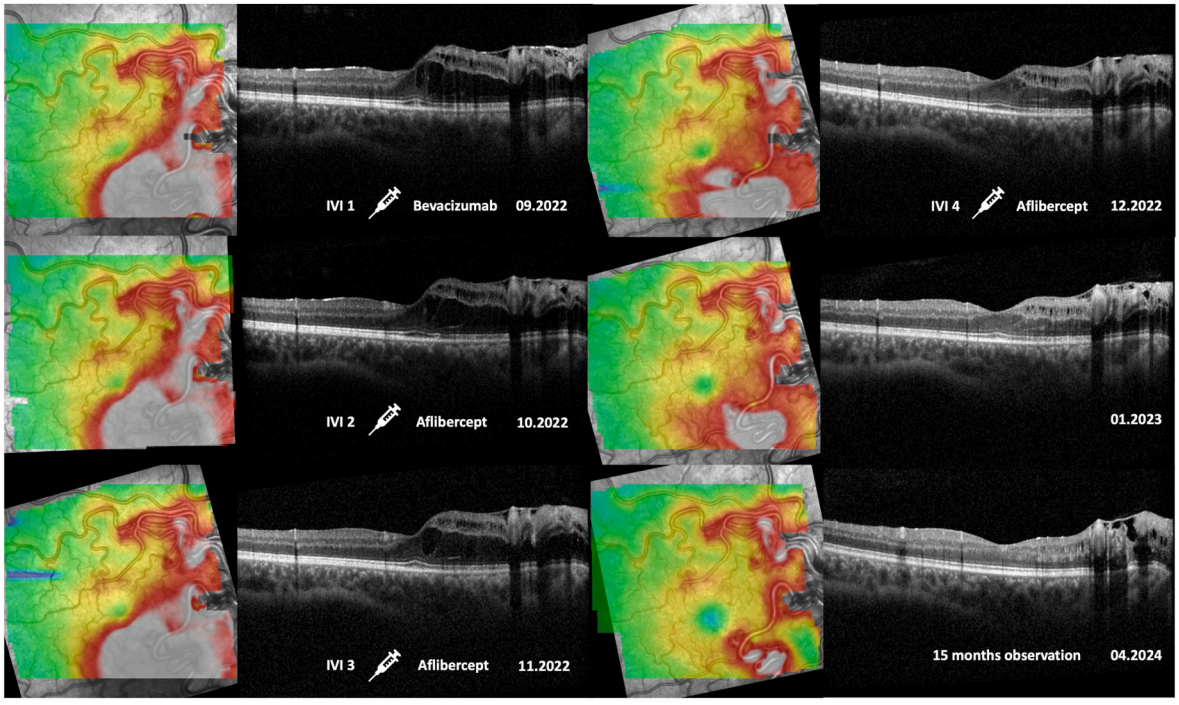

Fig. 3. Macular-OCT aspect at the time of administration of each IVI, at the follow-up 1 month and 15 months after the fourth IVI.

receptor VEGFR2,[10] disrupting the mechanisms of the blood-retinal barrier, which is composed of vascular endothelial cells and retinal pigment epithelial cells.[11]

Currently, there is no consensus on the management of macular edema in racemose retinal hemangioma. Less than 200 cases of racemose hemangioma have been reported in the literature, and we found 9 case reports describing the management of retinal edema. Two cases of extra-macular retinal edema resolved spontaneously on observation.[12,13] Four case reports demonstrated the efficacy of treatment with Bevacizumab 1.25mg/0.05mL in the treatment of macular edema in grade I and II AVMs, either in 1 [9,14] or 3 IVIs regimen.[15,16] In one case report, resolution of cystoid macular edema was observed following a posterior subtenon injection (PST) of triamcinolone 20mg.[17] Another case demonstrated resolution of edema with PST triamcinolone after initial worsening of a cystoid macular edema under Bevacizumab IVI.[6] Additionally, one case showed a favorable response to two laser photocoagulation sessions targeting a limited area of leakage.[8]

We initially decided to wait for a period of one month to assess the kinetics of the macular edema and monitor for possible spontaneous resolution. In the absence of spontaneous improvement and based on the results of the four previous cases on IVIs of Bevacizumab,[9,14–16] we decided to initiate our patient with an off-label Bevacizumab IVI of

1.25mg/0.05m. Although not approved by the Food and Drug Administration (FDA) for any ocular indication, bevacizumab is commonly used in ophthalmology for the treatment of macular edema. Less expensive than other anti-VEGF agents, it is generally preferred when the treatment indications do not meet health insurance reimbursement criteria. We decided to carry out a *pro re nata* (PRN) treatment with the aim of limiting the number of injections in a child with multiple vascular malformations. In addition to ocular safety considerations, there are systemic safety considerations to be considered when injecting anti-VEGF. The VEGF is involved in many physiological processes and the systemic use of anti-VEGF therapies in solid tumors has highlighted the risks of thromboembolic events, myocardial infarction, thrombosis, hypertension, gastrointestinal perforation and renal disease.[18] As all anti-VEGF agents administered intravitreally have been shown to have a systemic passage, there are safety considerations to be had in relation to them.[19] However, the RISE and RIDE[20] or VISTA and VIVID[21] studies showed no significant difference in terms of death, stroke or myocardial infarction in diabetic patients.

The subsequent switch to Aflibercept 2mg/0.05mL was carried out following the poor initial anatomical response to the first injection, with the aim of limiting the number of off-label drug injections in a child suffering from associated cerebral vascular malformations. This drug is approved by the FDA for numerous ocular indications and is used off-label in this particular ocular indication. However, no difference in safety profile has been demonstrated between Bevacizumab and Aflibercept in terms of myocardial infarction, acute cerebrovascular disease, major bleeding or any cause of hospitalization in routine clinical practice.[22]

The mechanism by which anti-VEGF reduces macular edema in the case of vascular malformation is not thoroughly understood. The blockage of this growth factor could restore balance in cases of vascular decompensation by reducing vascular permeability,[23] reducing vasodilation,[24] reducing the activity of matrix metalloproteinase in endothelial cells[25] and reducing dysplastic vessels.[8,26] The prolonged effect of anti-VEGF treatment over one year could be linked to long-term vascular stabilization and the re-establishment of local homeostasis achieved through a short course of treatment.[6,7]

However, close monitoring is essential, as this treatment only treats the consequences of hemodynamic disturbances, which may lead to further vascular decompensation at a later date.

In addition to the ischemic component, the mechanical component of transudate edema is likely, given the Starling forces present in these malformations. It may therefore be worth exploring in the future the benefits of subtreshold laser treatment to restore homeostasis by stimulating pigment epithelial cells to improve the resorption of the edema.[27]

4. Conclusion

Aflibercept 2mg/0.05mL appears to be a safe and effective treatment of macular edema complications in grade III retinal AVMs, here in the case of a Wyburn-Mason syndrome.

CRediT authorship contribution statement

Nathan Hupin: Writing – review & editing, Writing – original draft, Project administration. **Thomas Cahill:** Investigation, Conceptualization. **Antonella Boschi:** Validation, Supervision. **Alexandra Kozyreff:** Visualization, Validation, Supervision, Resources, Investigation.

Patient consent

The patient and patient's legal guardian consented orally to publication of the case.

Acknowledgments and disclosures

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

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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