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Resolution of epiretinal membrane after anti-VEGF and photodynamic therapy of retinal hemangioblastoma

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ABSTRACT

Purpose: To describe the clinical and multimodal imaging features in a case of resolution of pre-macular fibrosis after photodynamic therapy (PDT) of retinal hemangioblastoma (RH) not related to von-Hippel-Lindau (VHL).
Observations: A 25-year-old man presenting with blurred vision and central metamorphopsia in his left eye (LE) due to macular epiretinal membrane secondary to a peripheral RH. The patient had a comprehensive ophthalmic examination, including best corrected visual acuity (BCVA), wide-field fundus photography and autofluorescence (FAF), wide-field optical coherence tomography (OCT) and OCT angiography (OCTA), fluorescein angiography (FA) and indocyanine green angiography (ICGA) and ocular ultrasound. Baseline BCVA was 20/200 in his LE, and it improved to 20/40 nineteen months after anti-VEGF and photodynamic therapy were performed. The treatment led to a progressive shrinkage of the tumor and associated intraretinal exudation, and to a progressive resolution of the epiretinal membrane.
Conclusions and importance: Treatments performed on the peripheral retina may result in changes at the level of the vitreo-retinal interface in the macular region. In our patient, after an intravitreal anti-VEGF associated with PDT, a posterior vitreous detachment (PVD) was induced resulting in auto-peeling of the macular epiretinal membrane secondary to a peripheral RH. An accurate assessment of the macular area by OCT is highly recommended in the first days following treatments.

1. Introduction

Retinal hemangioblastoma (RH) is a benign retinal vascular tumor that usually appear as a round-shaped, orange-red mass, and may be observed isolated or in the context of von Hippel–Lindau disease (VHL).[1–3]

RH can sometimes result in visual deterioration due to its location or complications, such as macular extension of intraretinal or subretinal fluid, exudation, presence of an epiretinal membrane or vitreoretinal traction, vitreous hemorrhage, and the presence of serous or tractional retinal detachment.[2,3]

Numerous treatment modalities have been employed for managing RH and its complications, such as observation, laser photocoagulation, cryotherapy, transpupillary thermotherapy, brachytherapy, proton beam radiotherapy, photodynamic therapy (PDT) and vitreoretinal surgery, with variable results depending on the tumor characteristics.[1,2]

In the literature, cases of peripheral RHs treated with PDT have been reported, showing tumor regression and good retinal anatomical and functional results, and with few complications.[2–4]

We present a case of unilateral peripheral RH associated with epiretinal membrane in which the treatment of the peripheral tumor by anti-VEGF and PDT led to auto-peeling of the macular epiretinal membrane.

2. Case report

A 25-year-old man presented to the ocular oncology service of Luigi Sacco Hospital (Milan, Italy) with an history of blurred vision and central metamorphopsia in his left eye (LE). Ocular history was otherwise unremarkable; no systemic diseases or previous trauma were reported.

At baseline, his best-corrected visual acuity (BCVA) was 20/20 in his right eye (RE) and 20/200 in his LE. Intraocular pressure and anterior segment examination were within normal limits. Posterior segment examination in his RE was unremarkable.

Dilated fundus examination of the LE revealed a macular epiretinal membrane and a circumscribed amelanotic reddish retinal mass with

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prominent feeder and draining vessels in the inferior retinal periphery surrounded by hard exudates (Fig. 1A).

Dynamic Fluorescein angiography (FA) showed the lesion as a vascularized retinal mass hyperfluorescent in early and late imaging frames with well-defined feeder and draining vessels. (Fig. 1D).

Optical coherence tomography (OCT) scan of macular region revealed an epiretinal membrane pulling the macular area, generating a loss of foveal morphology, a significant disorganization of the retinal inner and outer layers; also, some cystic spaces and hyperreflective dots in outer retinal layers could be detected (Fig. 2C).

According to the above mentioned clinical and multi-modal imaging findings, a diagnosis of RH was made. Its association with von Hippel-Lindau disease (VHL) was investigated by a VHL specialist, which performed a complete systemic evaluation and the genetic test. No evidence of other supportive features or gene testing was found for VHL.

Photodynamic therapy (PDT) using the full-fluence protocol (50 J/cm2 and 83 seconds duration) was performed on the tumor a week after an intravitreal injection of anti-vascular endothelial growth factor (VEGF) (aflibercept). One month later, in the color fundus photography and near-infrared retinography, a release of the epiretinal membrane from the macula and its persistence anchorage in the neuroretinal ring (Fig. 2D–F) was observed.

Two years after the PDT, due to an increase of intra and subretinal exudation nearby the RH (Fig. 1B) and macular edema (Fig. 2I), a focal laser on both the feeder and draining vessels preceded by an anti-VEGF injection was performed.

At last visit, one year after focal laser, BCVA improved to 20/40 with no residual metamorphopsias. OCT scans confirmed an improved retinal and foveal anatomy with no traces of macular edema (Fig. 2L). The remains of the epiretinal membrane persisted anchored to the neuroretinal ring (Fig. 2J; 2K). The exudative response of RH was almost reabsorbed (Fig. 1C), and FA detected an attenuation of the tumor hyperfluorescence (Fig. 1F).

3. Discussion

Retinal hemangioblastoma (RH) (or retinal capillary hemangioma) is a benign vascular tumor occurring either as an isolated mass or as a component of the von Hippel–Lindau (VHL) disease, with variable course.[1,3,4] Recent studies documented VHL disease as the primary cause of RH in 84 % of cases.[5]

RH can be found in any region of the retina, from juxtapapillary area to peripheral retina.[4,6] Extrapapillary RHs usually start as a small reddish intraretinal lesion, and with increasing size, may display distinctive features such as increasing nodularity, feeding and draining blood vessels that become progressively dilated and tortuous, and exudative retinopathy, as in our case.[4,5]

On OCT, RH typically appears as a hyperreflective inner retinal mass that can displace outer retinal layers. Dynamic Fluorescein angiography (FA) is instrumental in detecting RH in early stages. Typically, RHs display early and late hyperfluorescence on FA. In bigger tumors, a rapid filling of the feeding artery and a rapid exit through the draining vein may be noticed.[5]

Differential diagnosis for small-sized RH includes micro and macroaneurysms or punctate intraretinal hemorrhages. Bigger lesions may be confused with retinal vasoproliferative tumors (VPT).[4] However, VPT usually manifests as a yellow-red retinal mass often located in the inferior periphery, with normal or slightly dilated retinal feeding artery and vein, unlike RH which they are more dilated and tortuous and characterized by typical FA filling.[5,7]

Although some of these lesions grow slowly, most progress and can cause intraretinal accumulation of hard exudates in the peritumoral area, macular edema, or preretinal glial proliferation with development of areas of traction on the retina.[1,3,6,8] Small, isolated, non-complicated tumor can be observed, but most of them need treatment.[1,3] Spontaneous regression or inactivity has been described in a minority of cases.[3,4]

Treatment options include observation, laser photocoagulation, cryotherapy, photodynamic therapy (PDT), radiotherapy

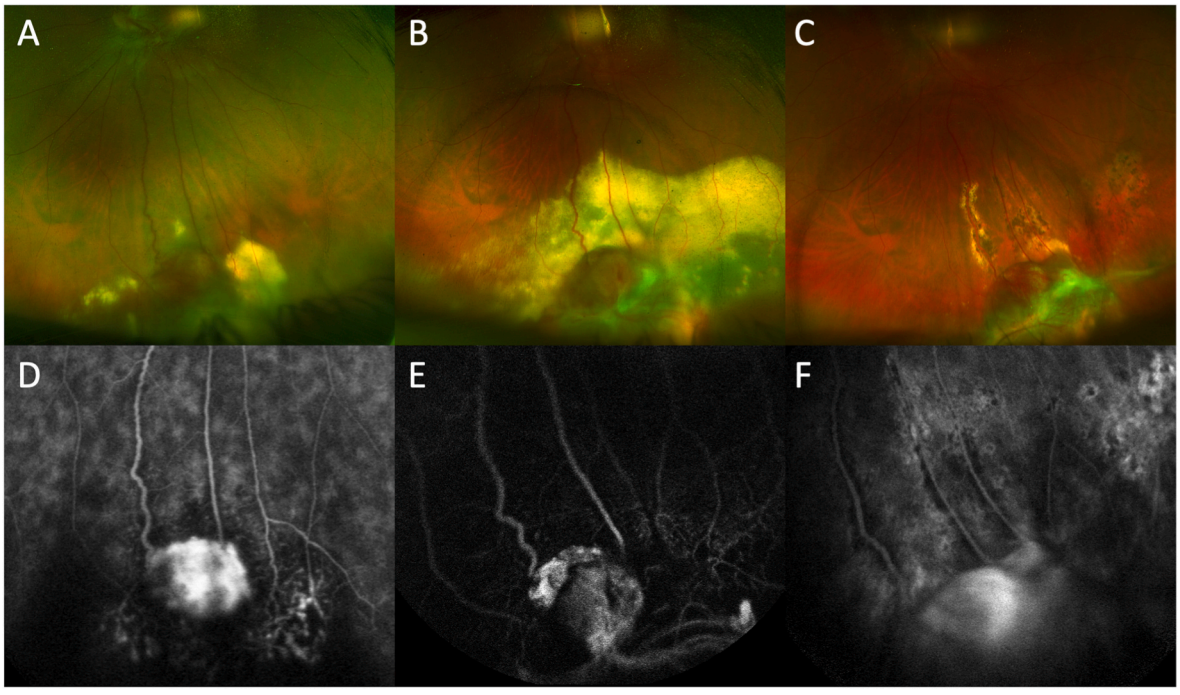

Fig. 1. Evolution of the retinal hemangioblastoma following photodynamic therapy (PDT).
Wide field color fundus photography (A–C) and Fluorescein Angiography (FA) (lower row) at baseline (A, D), one year after PDT (B, E) and last follow up examination, three years after PDT (C, F). At last visit, most of the exudative response has been reabsorbed, as well as an attenuation of the tumor hyperfluorescence in FA can be noticed.

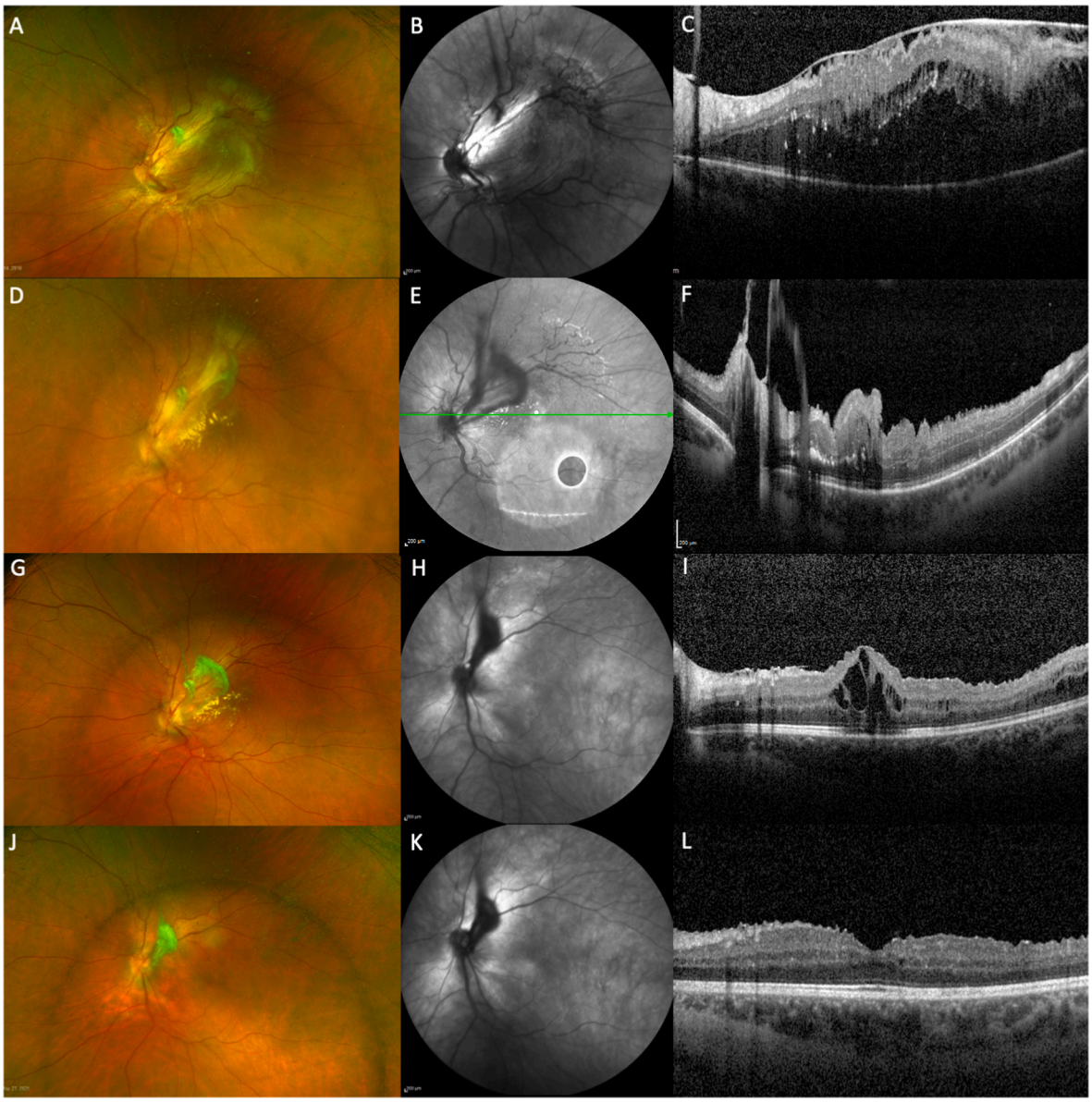

Fig. 2. Evolution of epiretinal membrane secondary to retinal hemangioblastoma (RH). Wide field color fundus photography (A, D, G, J), near-infrared retinography (B, E, H, K) and Optical Coherence Tomography (OCT) (C, F, I, L)
(A-C) At baseline examination, epiretinal membrane generating significant thickening of the retina and full-thickness distortion can be noticed; abundant hyper-reflective points and cystoid spaces due to the epiretinal membrane can also be noticed.
(D–F) One month after the anti-VEGF injection and photodynamic therapy (PDT), a release of the epiretinal membrane from the macula can be observed with residual anchorage in the neuroretinal ring. Also, significant improvement of retinal anatomy occurs as displayed on OCT (F).
(G–I) Anti-VEGF injection and focal laser on the feeder and draining vessels of the RH are performed at two years since PDT treatment due to a recurrence. Macular edema is evident on OCT b-scan (I) at this time-point.
(J–L) One year after focal laser, the epiretinal membrane persists anchored to the neuroretinal ring and the macula has almost recovered the normal foveal morphology. Also, a gradual restoration of the vascular arcades profile can be observed on both color fundus photography (J) and near-infrared retinography (K).

(brachytherapy, external beam radiotherapy, and proton beam radiotherapy), transpupillary thermotherapy, and vitreoretinal surgery.[8] Treatment choice depends on visual acuity, tumor size and location, and presence of complications, such subretinal fluid or epiretinal fibrosis.[1,5]

Small, isolated, non-complicated tumor can be observed, but most of them need treatment.[1,3] If lesions are small (<2 mm) or medium (2–4.5 mm) in size, laser photocoagulation, cryotherapy or PDT can be applied.[1,5] Laser photocoagulation is particularly effective for small tumors located outside the macula and peripapillary zone, and consists to treat directly the tumor, the feeding vessels (targeting the artery to reduce the influx of the blood to the tumor), or both.[1] Cryotherapy is employed usually for medium-sized tumors located anteriorly or in the presence of moderate subretinal fluid.[1] However, cryotherapy has been related with possible severe exudative response leading to vitreous hemorrhage, proliferative vitreoretinopathy, or vision loss.[3] In large (>4.5 mm) tumors brachytherapy, external beam radiotherapy or proton beam radiotherapy have been successfully employed whereas there is no consensus on tumor endoresection.[1,4,5]

PDT using verteporfin is a non-thermal procedure that destroys the tumor by occluding its vasculature with minimal residual effects to the surrounding structures. In particular, the verteporfin is activated by light energy from a specific laser. After the activation, the photosensitizer becomes toxic leading to an angio-occlusive effect on tumor vessels. It is an effective alternative treatment for both small and medium-

size tumors in the post-equatorial retina, especially for juxta-papillary lesions.[1,3] Nevertheless, PDT can be performed also on peripheral lesions by using appropriate laser contact lenses. Since VEGF levels can increase following PDT, an intravitreal injection of anti-VEGF agent may be considered before the laser as for our patient.[2,3,9]

Epiretinal membrane or vitreoretinal tractions spontaneous release is rare (3–6%); it is more commonly described in women, and myopes.[8,10,11] Previous reports observed this phenomenon following laser photocoagulation and cryotherapy.[11] In our case, we observed a peeling of the macular epiretinal membrane after anti-VEGF and photodynamic therapy, without the need of surgical intervention. The PDT causes an acute phototoxic reaction in the tumor, and the heat and mild inflammation caused by the treatment could accelerated the development of a posterior vitreous detachment (PVD), leading to ERM peeling. Moreover, also the intravitreal injection itself may induce a PDV, especially in older patients.[12] Despite this, the low prevalence of PVD in young patients receiving intravitreal injections is more leaning towards the role of the PDT in facilitate the induction of PVD, especially in a case in which the presence of a low-grade inflammation in the setting of a RH can also result in earlier completion of a PVD.

This is an interesting case of macular epiretinal membrane resolution after a single intravitreal anti-VEGF associated with PDT in RH; however, a larger series of PDT-treated RH with secondary ERM would be necessary to elucidate the impact of both intravitreal injections and peripheral laser treatments on the vitreoretinal interface.[8]

4. Conclusion

In this manuscript, we reported a case of peripheral RH treated with anti-VEGF and PDT followed by a resolution of the associated macular epiretinal membrane. Good anatomic and functional results were observed at last visit.

Treatment of peripheral tumors by means of PDT, lasers or cryotherapy may led to PVD and possibly affect the macular anatomy. The intravitreal injection of anti-VEGF could also induce a partial PVD and the effect could be added to that of the PDT. For these reasons, an accurate assessment of the macular area by OCT is highly warranted in these patients in the first days following treatments.

Patient Consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

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

CRediT authorship contribution statement

Javier Munoz-Solano: Writing – original draft, Data curation. **Chiara Preziosa:** Writing – review & editing, Data curation, Conceptualization. **Giovanni Staurenghi:** Validation, Investigation, Conceptualization. **Marco Pellegrini:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization.

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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