Long-Term Resolution of Perifoveal Exudative Vascular Anomalous Complex after Intravitreal Injections of Anti-Vascular Endothelial Growth Factor

Nuria Torrell-Belzach\textsuperscript{a}  
Alexandra Miere\textsuperscript{a}  
Eric Souied\textsuperscript{a}  
Salomon Y. Cohen\textsuperscript{a, b}

\textsuperscript{a}Department of Ophthalmology, University of Paris Est-Creteil, Creteil, France; \textsuperscript{b}Centre Ophtalmologique d’Imagerie et de Laser, Paris, France

Keywords
Perifoveal exudative vascular anomalous complex · Capillary aneurysm · Anti-vascular endothelial growth factor

Abstract
Perifoveal exudative vascular anomalous complex (PEVAC) is a perifoveal aneurysmal vascular lesion found in healthy subjects. A 68-year-old woman was diagnosed with a typical unilateral and unifocal PEVAC lesion after extensive multimodal imaging and was treated with three-monthly intravitreal injections of ranibizumab. An immediate and complete resolution of the intraretinal fluid was observed. Visual acuity returned to 20/20 without any recurrence of the exudative signs along the 5 years of follow-up. Therefore, an initial anti-VEGF treatment with three-monthly intravitreal injections may be considered as a first-line treatment in PEVAC lesions and may result in long-term preservation of visual acuity.
Introduction

Perifoveal exudative vascular anomalous complex (PEVAC) is a rare condition of uncertain etiology described for the first time in 2011 by Querques and associates as a perifoveal, unilateral, usually unifocal, and aneurysmal vascular lesion in otherwise healthy subjects [1]. It is usually associated with intraretinal cystic spaces which are the cause of vision loss, and it can also be associated with hemorrhages or hard exudates [2, 3]. Recently, the term PVAC has been proposed to name this entity rather than PEVAC, considering that it can be classified into two different forms: an exudative form (ePVAC) and a non-exudative one. The latter consists of an isolated perifoveal large aneurysmal lesion without signs of exudation (i.e., no evidence of hard exudates and no intraretinal or subretinal fluid) and it can evolve into an ePVAC with time [4].

Patients with this abnormality do not present uncontrolled arterial hypertension, diabetes, or other inflammatory or retinal vascular diseases [5], as they could cause perifoveal retinal vascular abnormalities associated with diabetic or hypertensive retinopathy, retinal vein occlusion, inflammatory diseases, ocular ischemic syndrome, or macular telangiectasia [3]. Nevertheless, it can be diagnosed in patients with well-controlled diabetes and hypertension if no signs of their associated retinopathies are present. Moreover, it can be accompanied by age-related macular degeneration, epiretinal membrane, lamellar hole, and myopic macular degeneration, although all or some of these concomitant findings could be coincidental [6–8]. There are no clear management guidelines considering the few cases reported in the literature. However, it has been described as an entity with incomplete, late, or even no response to anti-VEGF treatment by intravitreal injections [1, 6, 7, 9]. Hence, the purpose of the present case is to report a case of a patient with an ePVAC who presented a complete resolution of the exudation after a limited number of intravitreal injections of anti-VEGF.

Inform consent for publication was obtained from the patient. The Ethical Committee of the Federation France Macula allowed to report the case.

Case Report

A 68-year-old Caucasian woman was referred in May 2017 for visual disturbances in the left eye (LE). She presented a medical history of essential hypertension and hypothyroidism, both well-balanced and treated. The best-corrected visual acuity at presentation was 20/20 in the right eye and 20/25 in the LE with normal intraocular pressure and anterior segment. On fundus examination, an isolated unilateral aneurysmal perifoveal lesion was observed on the LE with an accumulation of small hard exudates inferotemporal to the fovea without any other retinal vascular signs. Spectral-domain optical coherence tomography (OCT) B-scan (Spectralis HRA-OCT Heidelberg Engineering, Heidelberg, Germany) also revealed a cross-sectional view of the aneurysmal round lesion on the LE. It measured 216 μm on largest diameter and presented hyperreflective walls, minimal hard exudates adjacent to it and perifoveal retinal thickening due to intraretinal cystic spaces. We performed an indocyanine green angiography, which highlighted the aneurysmal lesion on the LE. It was well defined from the early phases of the angiography with no leakage in the late phases, and it was connected to an arterial vessel. No other vascular abnormalities were found (Fig. 1).

OCT angiography (OCT-A) (AngioVue RTVue XR Avanti; Optovue, Fremont, CA, USA) was performed in an area of 6 × 6 mm, centered on the fovea on both eyes. The automatic segmentation was manually adjusted by an expert retina specialist to better differentiate the capillary plexus. It revealed the presence of a high blood flow and well-defined round lesion next to the foveal vascular arcade at the deep capillary plexus (DCP) with any signs of neovascularization on the LE (Fig. 1).
No significant abnormalities were found on multimodal imaging on the RE. The patient had no medical history of diabetes, blood dyscrasia, inflammatory diseases, or retinal vascular occlusion. However, she presented essential hypertension medically controlled with no signs of hypertensive retinopathy. Therefore, the diagnosis of PEVAC was considered.

The available options were observation until visual decline, treatment with focal thermal laser photocoagulation, or anti-VEGF intravitreal injections. After discussing potential side-effects and obtaining the consent of the patient, it was decided to perform a treatment of three monthly injections of ranibizumab (0.05 mL/0.5 mg) on the LE, as the lesion was too close to the fovea to consider laser photocoagulation as first-line therapy. A significant improvement was observed at the first follow-up visit 1 month after the third injection. Furthermore, a complete resolution of the macular edema was confirmed in the following month, that is 5 months after presentation, with any other further treatments needed during the 5-year follow-up (Fig. 2).

With time, the lesion has changed into a smaller hyperreflective round appearance on OCT B-scan. Best-corrected visual acuity has been maintained with 20/20 on both eyes.

**Discussion**

Here, we report a patient with a unilateral PEVAC who responded extremely well to three intravitreal injections of ranibizumab, without recurrence of exudation during a 5-year follow-up. The pathogenesis of aneurysmal microangiopathies is generally unknown, although pericytes have a marked role in the formation of microaneurysms related to diabetic retinopathy. It was suggested that their apoptosis could trigger the endothelium to proliferate into microaneurysms. Smid et al. [2] hypothesized that aging is a critical factor in the development of PEVAC lesions, given that an association between microvascular rarefaction and aging has already been established. Thus, Smid et al. [2] proposed that PEVAC could be considered a local microangiopathy emerging associated with aging and/or past or ongoing cardiovascular problems. Indeed, 40% of patients categorized as PEVAC had suffered from a stroke or ischemic attack, and 70% presented controlled hypertension.

The hypothetical mechanism of progressive endothelial cell degeneration proposed by Querques et al. [1] has been used since its first description in 2011 to explain the typical nonresponse to anti-VEGF treatments. Different publications are consistent with this statement, but the number of total injections from patients who received treatment with anti-VEGF intravitreal injections ranged from just one to a total of four [1, 3, 4, 6, 9–11], except for 1 patient treated by Mrejen et al. [7], which showed sustainable resolution of the exudation after 13 anti-VEGF injections, and a patient with PEVAC associated with a lamellar hole who partially responded to 3 injections of ranibizumab with a significant decrease of the edema [8]. In addition, other publications have demonstrated a good response to laser therapy, when the
location of the lesion allowed to perform the photocoagulation [7, 12], and recently one case reported by Tombolini and associates improvement after 1 month of a topical non-steroidal anti-inflammatory drug [13].
However, a spontaneous resolution could be a cofounder when evaluating anti-VEGF intravitreal injection response. Hence, a patient showed spontaneous resolution of intraretinal edema in a case series of 15 patients reported by Sacconi et al. [5, 6] after 11 months. Another case reported by Sacconi in 2020 presented a spontaneous resolution of intraretinal spaces after 6 months, and a patient in the series reported by Kim et al. [9] also resolved macular edema on the follow-up without any treatment. Finally, Verhoekx in 2021 demonstrated that intraretinal cystic spaces can spontaneously regress, as it was observed in 5 out of the 21 patients explored [10]. They also stated that PEVAC lesions can also disappear, as it was observed in 3 of the 21 patients during the follow-up [10]. In the present case, the rapid improvement of visual acuity reported by the patient after the first injection, and the complete resolution of the fluid after 3 injections suggested that the improvement was related to intravitreal injections.

Multimodal imaging is extremely important to well characterize patients with PEVAC. Specifically, OCT-A has a remarkable role in localizing the capillary plexus where the aneurysmal lesion is found, which cannot be distinguished with fluorescein or indocyanine angiography. Thus, the characteristics of the patient together with fundus examination, OCT B-scan, OCT-A, fluorescein, and/or indocyanine angiography avoid misdiagnosis of these lesions as type 1 macular telangiectasia, pseudophakic cystoid macular edema, stage 1 of type 3 neovascularization, or retinal arterial macroaneurysms. Type 1 macular telangiectasia is an idiopathic macular telangiectasia that is usually found in young patients. It consists of multiple capillary, venular, and arteriolar telangiectasia at the SCP and DCP in the juxtafoveal area with marked

---

**Fig. 2.** Evolution of the PEVAC lesion. On the top (a), the OCT at presentation with the largest diameter of the aneurysmal lesion of 216 μm. In the middle (b), 1 month after the third monthly intravitreal injection of ranibizumab, no cystic spaces were seen, and only some exudates around the lesion were present. On the bottom (c), 5 years after the presentation. No cystic spaces nor exudates were observed, and the aneurysmal lesion was more hyperreflective without distinguishing the walls and smaller, with the largest diameter of 89 μm.
exudation. Another important differential diagnosis is a stage-1 type 3 neovascularization, known as “nascent type 3,” as they are a vascular proliferation that can originate at the DCP with no evidence or very minimal fluid, and therefore, it can be difficult to differentiate from non-exudative PVAC. However, with time there is a progression of these neovascular lesions towards the retinal pigment epithelium, which has never been observed in the follow-up of patients diagnosed with PVAC [4, 6].

Finally, the terminology of retinal capillary macroaneurysms has been proposed in 2019 by Spaide and Barquet for large, solitary, and persistent aneurysms greater than 200 μm, which arise from capillaries and which grow over time. In fact, they described 5 cases with similar lesions to those seen in previously described PEVAC lesions. Nevertheless, the definition of retinal capillary macroaneurysms can include a wider spectrum, as they are potentially not limited to the area around the fovea [14].

To our knowledge, this is the first patient diagnosed with unilateral PEVAC with an early and sustainable response to three monthly anti-VEGF intravitreal injections of ranibizumab with a long follow-up period of 5 years. Thus, three-monthly intravitreal injections of anti-VEGF could be considered as the first-line therapy in exudative PEVAC since these lesions are close to the fovea, leaving focal thermal laser photocoagulation as a second line of treatment. However, future research is needed to better elucidate the physiopathological mechanisms and the natural course of this entity, considering its variable response to treatments and the difficulty to predict the evolution of these aneurysmal abnormalities.

**Statement of Ethics**

This study protocol was reviewed and approved by the Ethical Committee of the Federation France Macula, approval number 2022-037. Written informed consent was obtained from the patient for publication of this case report including accompanying images.

**Conflict of Interest Statement**

No conflicting of interest exists for any author related to the study. Financial disclosures not related to the study: S.Y. C. is consultant for Allergan, Bayer, Novartis, and Roche and Thea. E.S. is consultant for Allergan, Bayer, Novartis, Roche, and Teva.

**Funding Sources**

The study was supported in part by CIL-ASSOC, association for research and teaching, Paris, France.

**Author Contributions**

All the authors attest that they meet the current ICMJE criteria for authorship. Nuria Torrell-Belzach and Alexandra Miere: acquisition and writing the draft; Eric Souied: manuscript coordination and critical review of the manuscript; Salomon Y. Cohen: conceptualization, funding acquisition, manuscript coordination, and critical review of the manuscript.
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.

References

1. Querques G, Kühn D, Massamba N, Leveziel N, Querques L, Souied EH. Perifoveal exudative vascular anomalous complex. J Fr Ophtalmol. 2011;34(8):559.e1–e4.
2. Smid LM, Verhoekx JSN, Martinez Ciriano JP, Vermeer KA, Yzer S. Multimodal imaging comparison of perifoveal exudative vascular anomalous complex and resembling lesions. Acta Ophthalmol. 2021;99(5):553–8.
3. Fernández-Vigo JI, Burgos-Blasco B, Dolz-Marcos R, Jiménez-Santos M, López-Guajardo L, Donate-López J. Atypical perifoveal exudative vascular anomalous complex (PEVAC) with multifocal and bilateral presentation. Am J Ophthalmol Case Rep. 2020 Apr 21;18:100717.
4. Sacconi R, Borrelli E, Sassa S, Corradetti G, Freund KB, Yanuzzi LA, et al. Nonexudative perifoveal vascular anomalous complex: the subclinical stage of perifoveal exudative vascular anomalous complex? Am J Ophthalmol. 2020;218:59–67.
5. Sacconi R, Borrelli E, Bandello F, Querques G. Perifoveal exudative vascular anomalous complex in a highly myopic eye. Ther Adv Ophthalmol. 2020;12:25158412094793.
6. Sacconi R, Freund KB, Yanuzzi LA, Dolz-Marco R, Souied E, Capuano V, et al. The expanded spectrum of perifoveal exudative vascular anomalous complex. Am J Ophthalmol. 2017;184:137–46.
7. Mrejen S, Le HM, Nghiem-Buffet S, Tahary S, Quentin G, Cohen SY. Insights into perifoveal exudative vascular anomalous complex. Retina. 2020;40(1):80–6.
8. Siedlecki J, Vountourtipidis E, Vogt D, Wolf A, Priglinger SG, Schumann RG. Lamellar hole-associated epiretinal proliferation presenting with perifoveal exudative vascular anomalous complex. Am J Ophthalmol Case Rep. 2019;14:112–6.
9. Kim JH, Kim JW, Kim CG, Lee DW. Characteristics of perifoveal exudative vascular anomalous complex in Korean patients. Semin Ophthalmol. 2019;34(5):353–8.
10. Verhoekx JSN, Smid LM, Vermeer KA, Martinez Ciriano JP, Yzer S. Anatomical changes on sequential multimodal imaging in perifoveal exudative vascular anomalous complex. Retina. 2021;41(1):162–9.
11. Corvi F, Corradetti G, Juhn A, Sassa S. Long-term follow-up of perifoveal exudative vascular anomalous complex treated with intravitreal injections of anti-vascular endothelial growth factor and thermal laser photocoagulation. Am J Ophthalmol Case Rep. 2020;20:100883.
12. Fu M, Hu P, Zhang G, Huang L, Xu H, Huang J, et al. Case report: a case of perifoveal exudative vascular anomalous complex with a good prognosis. Front Med. 2021;8:757313.
13. Tombolini B, Cavalleri M, Sacconi R, Querques L, Zucchiatti I, Bandello F, et al. Progressive resolution of exudation from perifoveal vascular anomalous complex: a possible role of diclofenac therapy. Am J Ophthalmol Case Rep. 2022;26:101472.
14. Spaide RF, Barquet LA. Retinal Capillary Macroaneurysms. Retina. 2019;39(10):1889–95.