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Perifoveal exudative vascular anomalous complex (PEVAC) resembling lesion in a patient with multiple myeloma

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ABSTRACT

Purpose: To report a case of a perifoveal exudative vascular anomalous complex (PEVAC) resembling lesion in a patient with multiple myeloma.

Observations: A 56-year-old male with multiple myeloma presented with sudden moderate vision loss in the right eye. Best-corrected visual acuity was 20/25 in his right eye. Fundus examination showed a vascular irregularity in the perifoveal region. Fluorescein angiography (FA) revealed an isolated perifoveal aneurysmal lesion with minimal leakage. On optical coherence tomography (OCT) examination, a large oval structure with a hyperreflective wall and exudation was visualised. Three weeks later, spontaneous improvement of the intraretinal fluid was observed on OCT without treatment. However, 3 months later the macular edema recurred. The appearance of the aneurysmal lesion is similar to a PEVAC lesion, which is an isolated well-defined perifoveal intraretinal vascular abnormality presenting on OCT as a round hyperreflective structure with a dark lumen containing variably reflective material and is commonly associated with cystic intraretinal fluid.

Conclusions and Importance: PEVAC was originally described as occurring in healthy patients, but recent observations suggest that it also appears in association with other retinal/choroidal vascular abnormalities or underlying cardiovascular abnormalities. Our case supports this hypothesis by demonstrating a PEVAC resembling lesion in a patient with multiple myeloma.

1. Introduction

Perifoveal retinal vascular abnormalities are usually associated with retinal vascular diseases, such as diabetic retinopathy and retinal vein occlusions, inflammatory diseases, or age-related macular degeneration (retinal angiomatous proliferation (RAP), or type 3 neovascularization). However, these abnormalities may also develop without a known cause. Perifoveal exudative vascular anomalous complex (PEVAC) was initially reported in 2011 by Querques et al. as an isolated intraretinal vascular abnormality that develops in the perifoveal area in otherwise healthy patients, without other retinal or choroidal vascular abnormalities.[1]

PEVAC is an uncommon macular entity, characterized by the presence of a unilateral, isolated, well-defined perifoveal aneurysmal abnormality with rarefaction of the retinal capillaries in the perilesional area but without adjacent capillary aneurysms and/or telangiectasia.[1,2] On optical coherence tomography (OCT) the condition typically presents as a round lesion with a hyperreflective wall surrounding a darker lumen containing variably reflective material.[2] It is commonly associated with cystoid macular edema without any signs of neovascularization. Some patients are asymptomatic without signs of exudation at baseline.[2] Fluorescein angiography (FA) demonstrates the presence of a large aneurysm (as a well-defined hyperfluorescent lesion) with variable leakage and no associated capillary alterations.[2]

Little is known about the pathogenesis, prevalence, natural history, and treatment.[3] It is hypothesized that a PEVAC lesion may be the result of focal and progressive endothelial cell injury in patients without other retinal vascular diseases. This may explain the unresponsiveness of this disorder to anti-VEGF therapy.[2] The recent prospective cross-sectional study by Smid et al.,[4] however, hypothesized that either general cardiovascular issues or local age-related deterioration of the retinal

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vasculature or both are related to the development of a focal PEVAC lesion. Multiple myeloma is a condition that can cause a hyperviscosity-related retinopathy but has not been previously reported to harbor isolated PEVAC lesions.

2. Case report

A 56-year-old man presented to our department complaining of sudden moderate vision loss in his right eye for one day. There was a known medical history of multiple myeloma (type IgA lambda), which was diagnosed in 2008 (12 years ago). At presentation, he was being treated with daratumumab and dexamethasone 20 mg. Other medication used at presentation was acetylsalicylic acid 80 mg a day and acyclovir 800 mg a day. There was no history of diabetes, uncontrolled hypertension, past radiation treatment, or carotid artery occlusion. The last lab result showed an elevated IgA peak, which is a sign of hyperviscosity. The patient had a trauma in his left eye in 1990, but further ocular history was negative.

On ocular evaluation, best corrected visual acuity was 20/25 in his right eye and 20/400 in his left eye (Snellen Eye Chart). Anterior segment examination showed no abnormalities in the right eye. In the left eye there was a known central corneal scar. There were no signs of inflammation in either eye.

Fundus examination showed a vascular irregularity in the perifoveal region of the right eye, appearing as a red dot on binocular funduscopy (which was difficult to visualize on fundus photography). There were no hemorrhages, cotton wool spots or remarkable arteriovenous tortuosity or nicking (Fig. 1). FA revealed an isolated perifoveal aneurysm with mild leakage in the late phase (Fig. 2) and excluded neovascularization. A few peripheral micro-aneurysms were seen in both eyes (Fig. 3). On OCT, the central lesion resembled a PEVAC lesion, presenting as a large oval structure in the inner nuclear en outer plexiform layer with a hyperreflective wall and containing reflective material. Associated exudation appeared as cystic intraretinal changes with the external layers of the retina well preserved (Fig. 4). OCT of the left eye was normal.

After careful discussion with the patient, it was decided not to initiate any treatment (laser photocoagulation or intravitreal injections with anti-VEGF agents). Three weeks later, visual acuity improved to 20/20 and there was a complete resolution of exudation noticed on OCT (Fig. 4). Another 3 months later – after a change of treatment medication from daratumumab to bendamustine – OCT showed a recurrence of the macular edema but without significant visual impact. After 5 months of follow-up, the patient unfortunately died due to complications of multiple myeloma.

3. Discussion

To date, several cases and case series of PEVAC lesions have been reported, and it was recently stated that these lesions may be more prevalent than previously assumed.[3] The disease often displays a stable clinical course, with no significant improvement or worsening in

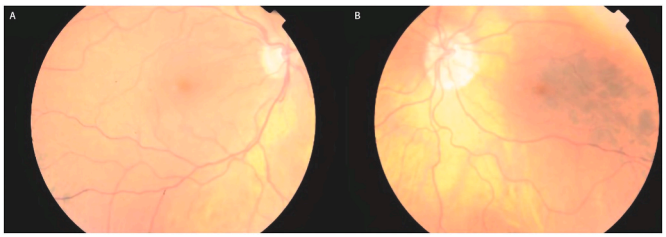

Fig. 1. Fundus photography at presentation.
Fundus photographs of the right (A) and left (B) eye at presentation showed no obvious abnormalities.

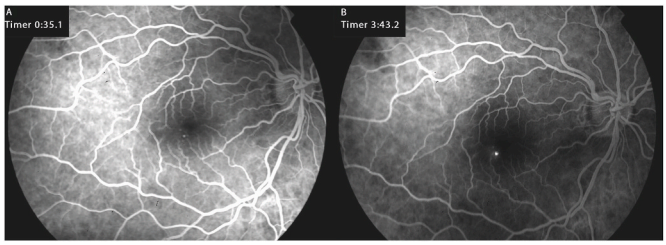

Fig. 2. Fluorescein angiography of the right eye revealed a perifoveal aneurysm with some leakage. (C) early phase (D) late phase.

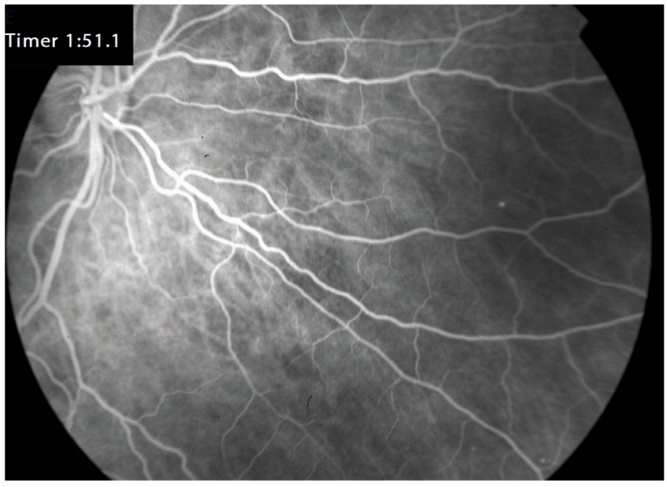

Fig. 3. A peripheral micro-aneurysm of the right eye is shown.

functional and anatomic outcomes during follow-up and is typically resistant to anti-vascular endothelial growth factor (anti-VEGF).[1–5] Thermal laser to the aneurysmal lesion has been described in one case,[5] which led to involution of the lesion and resolution of leakage. However, laser photocoagulation close to the fovea should be considered with caution because of the risk of permanent paracentral scotoma.[3] Spontaneous improvement of the intraretinal cystoid spaces has also been described,[2,3] and Verhoekx et al.[3] even reported complete disappearance of the PEVAC lesion in three patients.

The pathogenesis of PEVAC is not well known. Querques et al.[1] and Sacconi et al.[2] suggested that progressive retinal endothelial cell degeneration may be the triggering, vasogenic cellular mechanism for PEVAC, and this could explain its unresponsiveness to anti-VEGF treatments.

A first case with multifocal and bilateral presentation was described by Fernandez-Vigo et al.[6] They suggest that the possible underlying mechanisms that cause one or multiple aneurysmal dilations in one eye, may be systemic or general, and thus induce PEVAC lesions in both eyes.[6]

Smid et al.[4] compared PEVAC lesions in healthy patients with similar entities (PEVAC resembling lesions) in patients with a history of a retinal vascular disease, such as diabetic retinopathy or retinal vein occlusions. They observed predominantly similar clinical, morphological, and vascular features on multimodal imaging but evident differences in quantity of PEVAC compared with PEVAC resembling lesions, which were more likely to be multifocal. Given these similarities, both PEVAC and PEVAC resembling are considered to be local microangiopathies regardless of their origin. However, as the appearance of PEVAC has no relation to any underlying retinal vascular disease, it can be speculated that a possible cause of the development of this isolated microangiopathy with formation of perifoveal aneurysmal abnormalities might be related to a previous or ongoing general cardiovascular

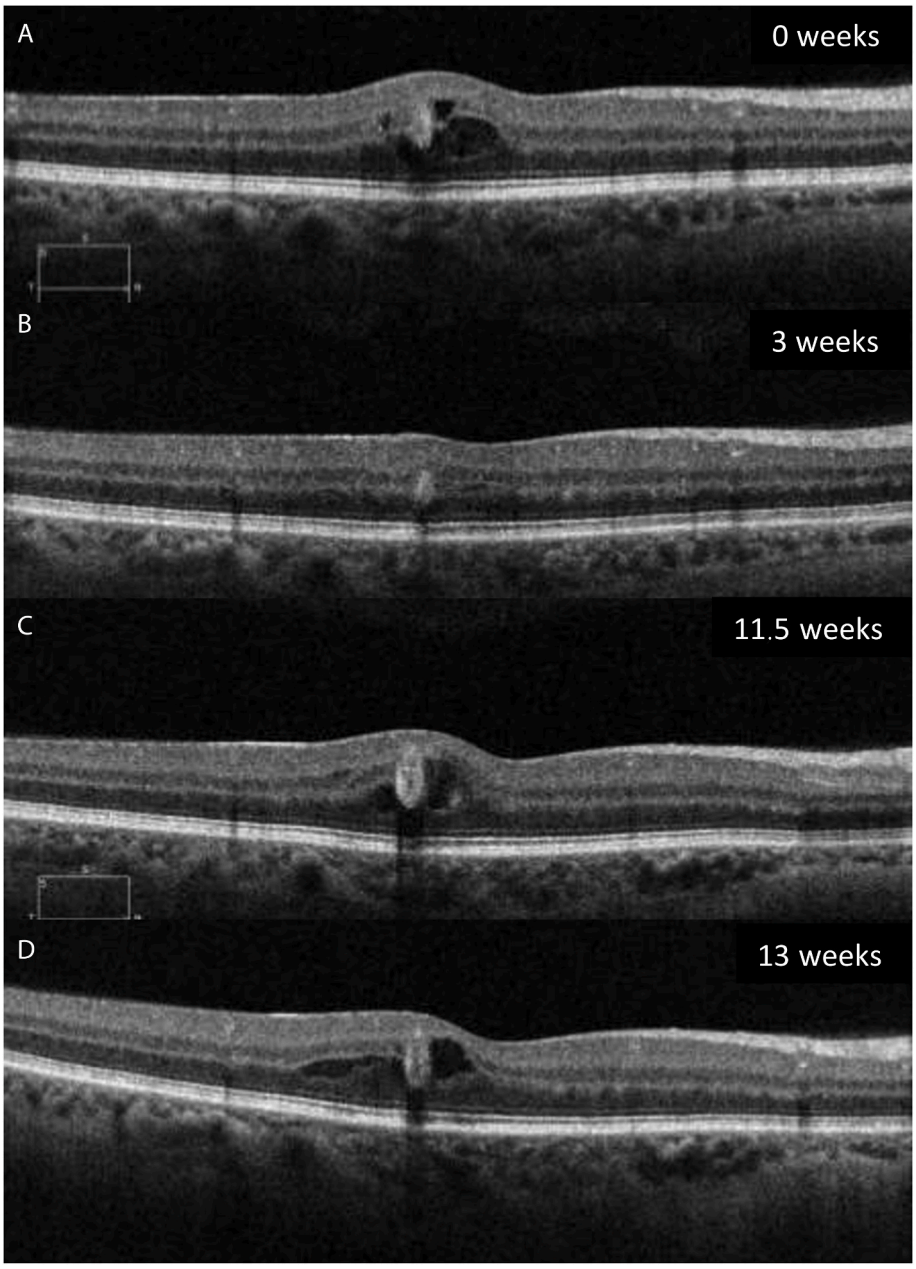

Fig. 4. OCT images during follow-up.
Spectral-domain optical coherence tomography (OCT) image of the right eye shows the typical PEVAC like lesion as an oval structure with hyperreflective wall and exudation. Images at presentation (A), 3 (B), 11.5 (C), and 13 weeks (D) are shown. 3 weeks after presentation there was a resolution of the exudation. Recurrence was noticed at 11.5 weeks.

problem.[3]

This case presents a perifoveal microaneurysm with typical PEVAC features. The unilateral, unifocal lesion presented on FA as a well-defined hyperfluorescent lesion. OCT showed an oval structure, with cystic intraretinal macular edema. The dark aspect of the lumen described in typical PEVAC lesions was less obvious at presentation. In the recurrence after 13 weeks, however, the dark lumen was more apparent and the size of the lesion was rather too large to consider it as an ordinary microaneurysm. Spontaneous fluctuation of the associated intraretinal fluid is also typical for PEVAC. Therefore, we considered this lesion as a PEVAC resembling lesion. The differential diagnosis included type 1 macular telangiectasia (MacTel), an isolated microaneurysm, and neovascular AMD type retinal angiomatous proliferation (RAP). Our case however didn't show dilated, telangiectatic capillaries (typical for MacTel type 1) and had no signs of choroidal neovascularization. Given the PEVAC resembling aspect of the lesion and the known fluctuations in CME, it was decided to withhold treatment and wait for spontaneous improvement.

To our knowledge, this is the first report of a PEVAC resembling lesion in a patient with multiple myeloma (MM). MM is a neoplastic plasma-cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal protein in the blood and urine, and associated organ dysfunction.[7] Common signs and symptoms of MM are bone pain and pathological fractures, anemia, recurrent infections, hypercalcemia, renal failure, and abnormal bleeding. It is associated with the development of cardiovascular complications such as thrombo-embolism, cardiomyopathy, and arrhythmias.[8] Ocular manifestations of multiple myeloma are rare and variable. They range from chorioretinopathy (choroidal infiltrate, choroidal effusion, retinal capillary microaneurysms, hyperviscosity), and

neuro-ophthalmic abnormalities (e.g., extraocular muscle paresis, papilledema) to opportunistic infections of ocular structures.[7] Hyperviscosity-related retinopathy mimics a central retinal vein occlusion retinopathy and is associated with dilated, tortuous veins, sludging of retinal vessels, retinal hemorrhages, or cotton wool spots. Except for some micro-aneurysms in the periphery, there were no typical retinal signs of hyperviscosity, despite a proven elevation of IgA in recent lab results. To date, no PEVAC-like lesions have been described in hyperviscosity-related retinopathy. The spontaneous resolution and recurrence of the cystoid macular edema in our case may reflect the varying results of the treatment of MM and its effect on the generalized microangiopathy and hyperviscosity in our patient.

The systemic medications taken by our patient (bendamustin, acyclovir and acetylsalicylic acid) are not known to cause ocular complications. Daratumumab, a human monoclonal antibody that targets CD38, is an immunotherapeutic agent and can be associated with inflammatory ocular complications.[9] However, in our case, there were no signs of inflammation in either eye. We therefore hypothesize that MM and associated cardiovascular complications contributed to the formation of this PEVAC resembling lesion. This lesion can be interpreted as an atypical presentation of hyperviscosity-related retinopathy.

4. Conclusions

In conclusion, we describe a case of a PEVAC resembling lesion in a patient with multiple myeloma. It is important to recognize these lesions because of the typical unresponsiveness to anti-VEGF treatment. PEVAC is originally described to occur in healthy patients, but more recently, researchers report the occurrence of this lesion in association with other retinal/choroidal vascular abnormalities or underlying cardiovascular abnormalities. Our case supports this hypothesis.

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

Arieke I. Jadnanansing: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization. **Jose P. Martinez Ciriano:** Writing – review & editing. **Jan van Droogenbroeck:** Resources, Writing – review & editing. **Leigh Spielberg:** Writing – review & editing. **Eva Vanhonsebrouck:** Conceptualization, Validation, Writing – original draft, Writing – review & editing, Supervision.

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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