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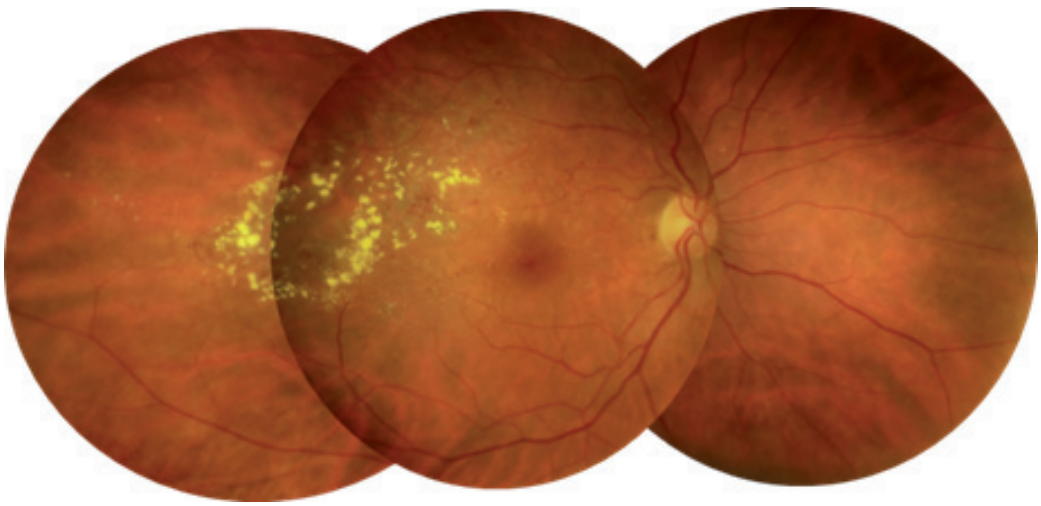
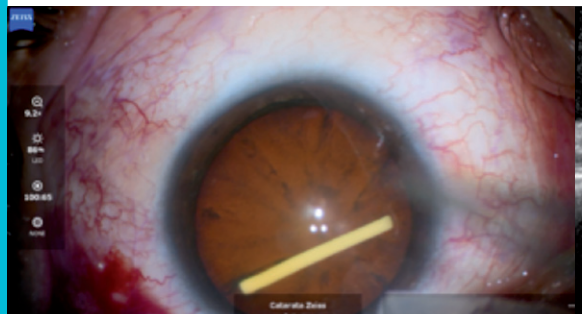
Suplemento Edema Macular

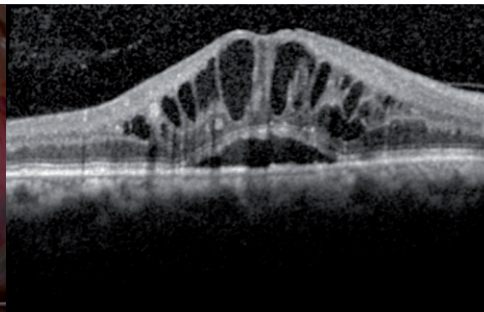
Casos Clínicos

Edema Macular Diabético

Oclusões Venosas Retinianas







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EDITORIAL

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Macular Edema in Diabetes and Retinal Vein Occlusion

Edema Macular na Diabetes e na Oclusão Venosa Retiniana

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Macular edema is a frequent complication of both diabetic retinopathy and retinal vein occlusion (RVO), two common conditions that affect millions of people worldwide. Understanding the pathophysiology, impact, and treatment options for macular edema is critical to improving patient outcomes and quality of life.

Intravitreal anti-VEGF, steroid implants, and, to a lesser extent, laser photocoagulation are the mainstay of treatment for macular edema secondary to the aforementioned conditions. Surgical procedures may also be useful in selected cases.

Case reports have a great advantage in that they involve real patients in real settings, providing day-to-day scenarios and solutions. In our selection, we tried to include not only rare and unusual cases, but also examples of more standard cases that challenge our therapeutic approach.

We would like to thank everyone who contributed to this supplement, and we hope you'll find it useful in your clinical practice.

O edema macular é uma complicação comum tanto da retinopatia diabética como da oclusão da veia da retina (OVR), duas doenças prevalentes que afetam milhões de pessoas em todo o mundo. Compreender a fisiopatologia, o impacto e as opções de tratamento do edema macular é fundamental para melhorar os resultados e a qualidade de vida dos doentes.

Os anti-VEGFs intravítreos, os implantes de corticosteróides e, em menor grau, a fotocoagulação LASER são a base do tratamento do edema macular secundário às doenças supracitadas. Os procedimentos cirúrgicos também podem ser úteis em casos selecionados.

Os casos clínicos têm a grande vantagem de envolverem doentes reais em contextos reais, fornecendo cenários que encontramos na nossa prática clínica diária, bem como fornecerem as soluções encontradas por quem reporta os casos. Na nossa seleção, tentámos incluir não só casos raros e invulgares, mas também exemplos de casos mais rotineiros, mas que desafiam a nossa abordagem terapêutica.

Antes de terminarmos, gostaríamos de agradecer a todos os que contribuíram para a elaboração deste suplemento e esperamos que o mesmo seja útil para a prática clínica de quem o ler.

RESPONSABILIDADES ÉTICAS

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Paracentral Acute Middle Maculopathy in the Setting of Retinal Vein Occlusion: A Case Report

Maculopatia Média Aguda Paracentral no Contexto de Oclusão Venosa da Retina: Um Caso Clínico

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ABSTRACT

Paracentral acute middle maculopathy (PAMM) is a tomographic finding observed in retinal occlusive vascular disorders of various aetiologies. While an association between PAMM and retinal vein occlusion (RVO) has been established, there are limited reports to date on its occurrence in younger patients. We present the case of a 57-year-old female with a history of migraine who experienced sudden visual loss in the left eye. Multimodal imaging, including retinography, optical coherence tomography (OCT), OCT-angiography (OCT-A) and fluorescein angiography (FA) revealed PAMM with impending central retinal vein occlusion (CRVO). Initially, a watchful-waiting strategy was adopted, with complete regression of lesions. However, 3-years after the initial presentation, the patient's visual loss worsened abruptly, and a new CRVO with macular edema was diagnosed. The patient was managed with intravitreal injections of aflibercept. To this date, macular edema is gradually resolving, and visual acuity slowly improving. In cases of atypical CRVO presentation in younger patients, we emphasize the importance of performing a comprehensive diagnostic work-up to exclude any associated predisposing factors such as systemic vasculopathies.

KEYWORDS: Macula Lutea/pathology; Retinal Vein Occlusion; Tomography, Optical Coherence.

RESUMO

A maculopatia média aguda paracentral (PAMM) é um achado tomográfico encontrado em doenças vasculares oclusivas da retina de diversas etiologias. Apesar da associação descrita entre a PAMM e oclusões venosas da retina, até à presente data, existem poucos casos descritos da sua coocorrência em doentes de idades mais jovens. No presente manuscrito, apresentamos o caso de uma mulher, de 57 anos, com antecedentes pessoais de enxaqueca, que recorreu ao Serviço de Urgência (SU) por uma perda súbita da acuidade visual do olho esquerdo. A imagiologia multimodal, incluindo retinografia, tomografia de coerência óptica (OCT), angio-OCT e angiografia fluoresceínica (AF), revelou uma PAMM com oclusão da veia central da retina (OVCR) iminente. Inicialmente, foi adotada uma estratégia de vigilância ativa, havendo regressão completa das lesões descritas. Três

anos após a apresentação inicial, a doente voltou a recorrer ao SU por novo agravamento da acuidade visual, tendo sido diagnosticada uma nova OVCR com edema macular. A doente foi tratada com injeções intravítreas de aflibercept. Até à presente data, o edema macular encontra-se em resolução e com melhoria gradual da acuidade visual. Perante casos atípicos de OCVR em pacientes de idades jovens, torna-se fulcral a realização de um estudo etiológico abrangente para exclusão de fatores predisponentes associados, nomeadamente vasculopatias sistémicas.

PALAVRAS-CHAVE: Macula Lutea/patologia; Oclusão da Veia da Retina; Tomografia de Coerência Óptica.

INTRODUCTION

Paracentral acute middle maculopathy (PAMM) was first identified by Sarraf *et al* in 2013.[1] It is characterized by hyperreflective band-like lesions in the inner nuclear layer and outer plexiform layer on spectral domain optical coherence tomography (SD-OCT).[2,3] Currently, PAMM is considered a manifestation of focal ischemia of the deep retinal circulation that may indicate the presence of an underlying retinal vascular disorder or systemic vasculopathy.[4] It has been reported to occur in approximately 5% of the patients presenting with central retinal vein occlusion (CRVO).[5] In this case report, we present the natural course and multimodal imaging of a case of PAMM secondary to non-ischemic RVO. Written informed consent was obtained from the patient to publish this case report, including its accompanying images.

CASE REPORT

A 57-year-old female presented to the emergency department with sudden painless vision loss in the left eye (LE). The patient had a medical history of fibromyalgia, depression, and migraine, for which she was taking topiramate, amitriptyline, fluoxetine, and tramadol. Past ocular history was unremarkable. Best corrected visual acuity (BCVA) was 20/25 in the right eye (RE) and 20/100 in the LE. Anterior segment examination was unremarkable in both eyes. Dilated fundus examination of the RE was innocent. The fundus of the LE revealed slight venous tortuosity and dilation, widespread intraretinal hemorrhages in all four quadrants, and whitening of the inferior macular area (Fig. 1A). SD-OCT scans of the LE showed hyperreflective band lesions at the level of the inner plexiform layer (IPL) and outer plexiform layer (OPL) (Fig. 1B). Fluorescein angiography (FA) of the LE revealed delayed vascular filling and leakage of the optic nerve head and retinal veins (Fig. 1C). En-face OCT showed hyperreflective areas in the deep retinal layers with a perivascular fern-like pattern (Fig. 2A). OCT angiography (OCT-A) showed scattered no-flow areas in the macular region, mainly at the level of the deep retinal plexus (Fig. 2B). No abnormalities were detected on SD-OCT scans, FA or OCT-A of the RE. Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), thrombophilic screening, metabolic panel and serologies were innocent.

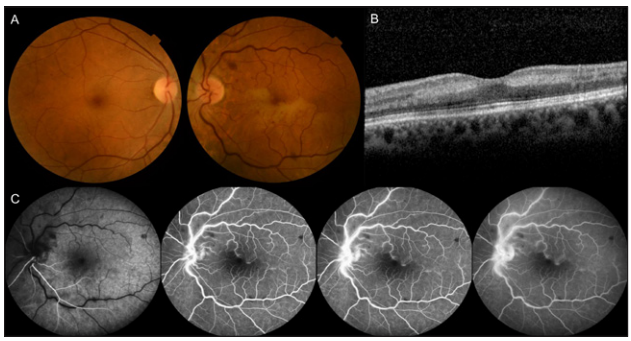

Figure 1. A) Retinography: RE unremarkable, LE with venous tortuosity and dilation, posterior pole intraretinal haemorrhages and whitening of the inferior macular area. B) LE OCT showing hyperreflective band lesions at the level of IPL-OPL. C) LE FA with delayed vascular filling and leakage of the optic nerve head and retinal veins.

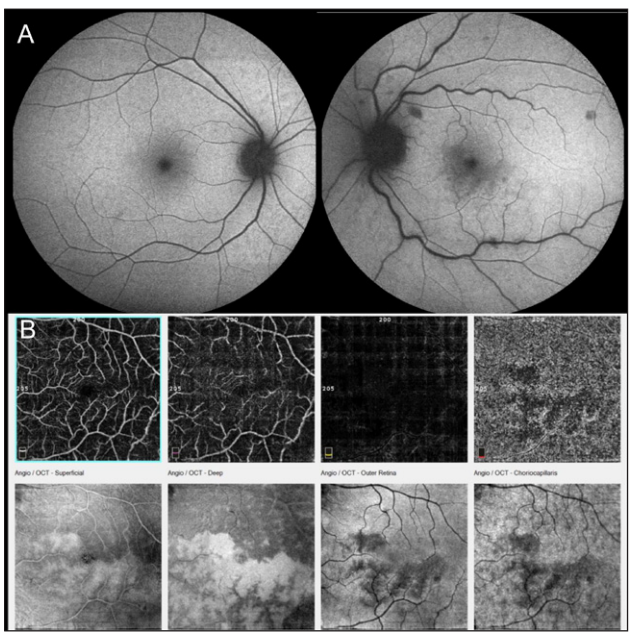

Figure 2. A) En face OCT: RE unremarkable, LE showing hyperreflective areas in the deep retinal layers and a perivascular fern-like pattern. B) LE OCT-A with macular scattered no-flow areas, mainly at the level of the deep retinal plexus.

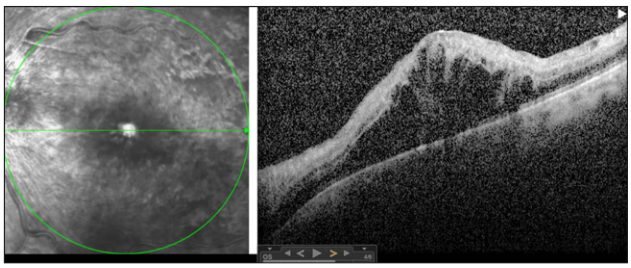

Figure 3. LE SD-OCT with cystoid macular edema and subfoveal fluid.

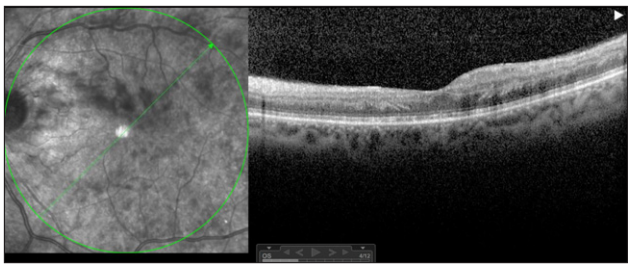

Figure 4. LE SD-OCT showed residual macular edema with atrophy of the inner retina layers.

DIFFERENTIAL DIAGNOSIS

The diagnosis of PAMM was strongly suspected given the history of acute onset of visual loss with no other ocular symptoms and abnormal bands of hyperreflectivity observed on SD-OCT as markers of deep retinal ischemia. On fundoscopic examination, PAMM lesions appear as subtle whitish parafoveal lesions with a smooth contour deeper within the retina. Although FA has been the gold standard for assessing retinal ischemia, it cannot detect flow in the deep capillary plexus.[5] OCT-A, on the other hand, provides detailed, high-resolution images of retinal vasculature segmented by layer, including the deeper retinal circulation. In PAMM, OCT-A typically shows a reduced vascular density, capillary perfusion, and vessel diameter of the deep capillary plexus.[6]

The patient´s fundoscopy, however, was also relevant for widespread intraretinal hemorrhages and mild vein tortuosity. Additionally, FA indicated a delayed filling of retinal veins, suggestive of an impending CRVO. While the fundoscopic appearance of RVO is typically distinctive, FA can provide valuable assistance in doubtful cases.[7] In non-ischemic occlusions, standard FA typically shows leakage from damaged veins and around the optic disk, without avascular zones in the posterior pole.[7] Previous studies have reported the occurrence of PAMM in 5.2% of patients with non-ischemic CRVO.[6,8]

OUTCOME AND FOLLOW-UP

The diagnosis of PAMM with impending CRVO was assumed, and the patient was discharged with a watchful-waiting approach, and scheduled for outpatient follow-ups in retina appointments. At the two-year follow-up, LE BCVA had improved to 20/63, and fundoscopic examination showed vessels with a normal course and calibre and clearance of all macular hemorrhages. SD-OCT confirmed further normalization of hyperreflective bands at the level of the OPL-IPL.

Three years after the initial presentation, the patient returned to the emergency department with complaints of sudden, new-onset visual loss in the LE. BCVA was reduced to hand motion, and fundoscopy revealed new, widespread, dot-blot and flame-shaped hemorrhages throughout all four quadrants and marked tortuosity and dilation of the central retinal vein. RE examination was again unremarkable. SD-OCT revealed cystoid macular edema with subfoveal fluid (Fig. 3). The patient underwent treatment with intravitreal aflibercept in a treat-and-extend regimen, starting with an initial loading phase of three doses given one month apart. Following the second intravitreal injection, LE BCVA had improved to 20/400, the macular edema had resolved, but areas of atrophy of inner retinal layers persisted.

At four-year follow-up, SD-OCT still showed residual macular edema with atrophy of the inner retina layers (Fig. 4). The patient currently maintains a regimen of bi-monthly intravitreal aflibercept injections in the LE.

DISCUSSION

In cases of CRVO with sudden visual loss and absent macular edema, clinicians should remain vigilant for any hyperreflective lesions in the middle retinal layers on OCT, which may indicate the presence of PAMM.[5] The sudden occlusion of the central retinal vein significantly increases intraluminal pressure throughout the entire retinal capillary network, resulting in ischemia of vulnerable vascular regions such as the watershed zoned of the OPL and INL.[9]

The typical PAMM pattern identified on en face OCT in CRVO patients is a fern-like pattern, attributable to the dense capillary distribution in perivenular areas.[9] Recognizing this pattern of PAMM is clinically significant and can assist in diagnosing non-ischemic CRVO, particularly in cases with minimal retinal hemorrhages and venous dilation, like our case.[9]

Identification of perivenular PAMM can also provide insights into the causes of vision impairment in CRVO and offer prognostic clues.[9] This pattern has been linked to better visual outcomes and less severe retinal ischemia, while diffuse globular PAMM patterns correlate with poorer visual results.[10] It also suggests ischemia resulting from arteriolar insufficiency in the deep capillary plexus, leading to damage at the level of OPL/INL.[9] This is supported by the observed thinning of the INL on subsequent imaging, explaining the persistent paracentral scotomas in patients with PAMM complicating non-ischemic CRVO.[9] The natural course of visual recovery in patients with PAMM and CRVO varies, with the extent of deep capillary plexus dropout on OCT-A potentially reflecting the degree of visual impairment.

The finding of PAMM on OCT demands a thorough investigation of the underlying cause. PAMM is not an isolated entity and has an intimate association with vascular diseases.[11] In our case, we were unable to determine the definitive cause of PAMM and accompanying CRVO. However, her history of migraine might have played a role in this ischemic event. Studies have shown that migraine can induce structural changes in the retinal microvasculature and increase susceptibility to retinal ischemia.[12,13] Despite the good recovery from the initial episode and a negative systemic work-up, the patient experienced a new and more severe event in the same eye years later. This highlights the importance of long–term follow-up for atypical CRVO cases in younger patients.

QUESTIONS

1. How does this case contribute to the therapeutic approach and decision-making for patients with retinal vein occlusion?

    a. In atypical CRVO cases in relatively young patients, clinicians should remain attentive to OCT findings that may suggest an underlying etiology. PAMM, in particular, has an intimate association with vasculopathies and its identification demands a thorough systemic work-up.

2. What are the implications for the functional prognosis in these patients, and would you recommend any additional diagnostic tests in subsequent evaluations to better document visual deficits, given that many of these patients achieve good visual acuity recovery?

    a. Fluorescein angiography has long been the gold standard exam for assessing retinal ischemia. However, it cannot detect flow in the deep capillary plexus. In patients with atypical CRVO, such as those with suggestive PAMM on OCT, OCT-A offers high-resolution images of retinal layers, including deeper circulations. Particularly, the pattern of PAMM was shown to be correlated with the severity of retinal ischemia and to have implications on the visual prognosis.

3. In these cases, is any prophylactic measure, particularly regarding thrombosis prevention, indicated?

    a. In patients with RVO without apparent systemic factors, particularly those under 45 years old, thrombophilic screening is recommended. In patients with RVO and high cardiovascular risk, it is currently recommended to consider long-term aspirin administration for the prophylaxis of further cardiovascular events.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

IF: Writing, literature research, and editing of the manuscript.

NG, CF, JF: Review and supervision of the manuscript.

All authors approved the final version to be published.

IF: Redação, pesquisa bibliográfica e edição do manuscrito.

NG, CF, JF: Revisão e supervisão do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Patient Consent: Consent for publication was obtained.

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Combined Central Retinal Vein and Cilioretinal Artery Occlusion in a 16-Year-Old Adolescent Girl: A Case Report

Oclusão Combinada da Veia Central da Retina e da Artéria Ciliorretiniana numa Adolescente de 16 Anos: Relato de um Caso

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ABSTRACT

We report an unusual case of a 16-year-old adolescent who was diagnosed with unilateral central retinal vein occlusion combined with cilioretinal artery occlusion, with a 3-year follow-up. Investigation showed atherosclerotic disease in the carotid axis. Repeated emergency pill contraception pill usage might have also contributed to the pathogenesis. She was treated with ranibizumab intravitreal injections in a "treat & extend" protocol, over 11 months. The response was excellent, with no recurrence of macular edema to date, 2 years after the last injection, and a final best-corrected visual acuity of 20/25.

KEYWORDS: Adolescent; Ciliary Arteries; Contraceptives, Oral; Macular Edema; Retinal Vein Occlusion.

RESUMO

Apresentamos um caso clínico pouco comum de uma adolescente de 16 anos diagnosticada com oclusão da veia central da retina combinada com oclusão da artéria ciliorretiniana, com 3 anos de seguimento. A investigação revelou doença aterosclerótica nos eixos carotídeos. A toma repetida da pílula anticoncepcional de emergência poderá, também, ter contribuído para a patogénese. A doente foi submetida a tratamento com injecções intravítreas de ranibizumab, com um protocolo de "treat & extend", durante um período de 11 meses. Manteve-se sem recorrência do edema macular até à data, 2 anos após a última injeção, com uma acuidade visual final de 20/25.

PALAVRAS-CHAVE: Adolescente; Artérias Ciliares; Contraceptivos Orais; Edema Macular; Oclusão da Veia da Retina.

INTRODUCTION

Central retinal vein occlusion (CRVO) combined with cilioretinal artery occlusion (CLRAO) is rare and less common than either occlusion alone.[1] Retinal vein occlusion is the second most frequent retinal vascular disease worldwide.[2] However, it is uncommon under 60 years of age, with an estimated prevalence of 0.7%.[3] CRVO comprises 20% of all RVO cases.[2] On the other hand, CLRA comprises only 5% of all retinal artery occlusions.[4]

We report an unusual case of a 16-year-old adolescent who was diagnosed with unilateral CRVO combined with CLRAO, with a 3-year follow-up.

CASE REPORT

A 16-year-old Caucasian adolescent girl attended the Emergency Department reporting sudden and painless vision blurriness with multiple scotomas in the left eye (LE). The symptoms had started 3 hours ago while she was at home.

She had been medicated in the past with rosuvastatin for hypercholesterolemia. She denied any past ocular history.

On clinical examination, her visual acuity was 20/20 in the right eye (RE) and 20/20 in the LE. Pupils were isocoric and isoreactive, with no rapid afferent pupillary defect. Biomicroscopy was unremarkable in both eyes. On Goldmann applanation tonometry, intraocular pressure (IOP) was 18 mmHg bilaterally.

Fundus examination was unremarkable in the right eye (Fig. 1, A). The left eye fundoscopy showed dilated and tortuous retinal veins in the four quadrantes and occasional retinal hemorrhages, suggestive of an impending CRVO (Fig. 1, B). Spectral domain ocular coherence tomography (SD-OCT) was performed and showed no changes in the RE. The LE SD-OCT showed hyperreflectivity of the inner two-thirds of the retina nasally to the fovea, suggestive of CLRAO, with no intra or subretinal fluid (Fig. 1, D). Fundus fluorescein angiography (FFA) was unremarkable in the right eye. In the LE FFA (Fig. 1, E-H), there was delayed filling of the cilioretinal artery and delayed arteriovenous (AV) transit time, with focal hypofluorescence corresponding to the retinal hemorrhages. Vascular leakage and ischemia were absent. The clinical and imaging findings were therefore consistent with LE CRVO combined with CLRAO.

Upon further questioning, the patient reported to have taken the emergency contraceptive pill twice in the last month. Although she was initially unable to recall the brand name, she informed us on a later consultation that she recalled having taken ulipristal acetate. She denied recent illness or fever, vaccinations, night sweats, weight loss, joint pain, shortness of breath, mouth or genital ulcers, skin changes, genitourinary symptoms or gastrointestinal symptoms.

The patient was assessed by our Pediatrics Service. Blood pressure was 118/59 mmHg. Body mass index was in the overweight range (28 kg/m^2). Physical examination was otherwise normal. She was also referred to the Family Planning clinic and was started on progestative oral contraceptive.

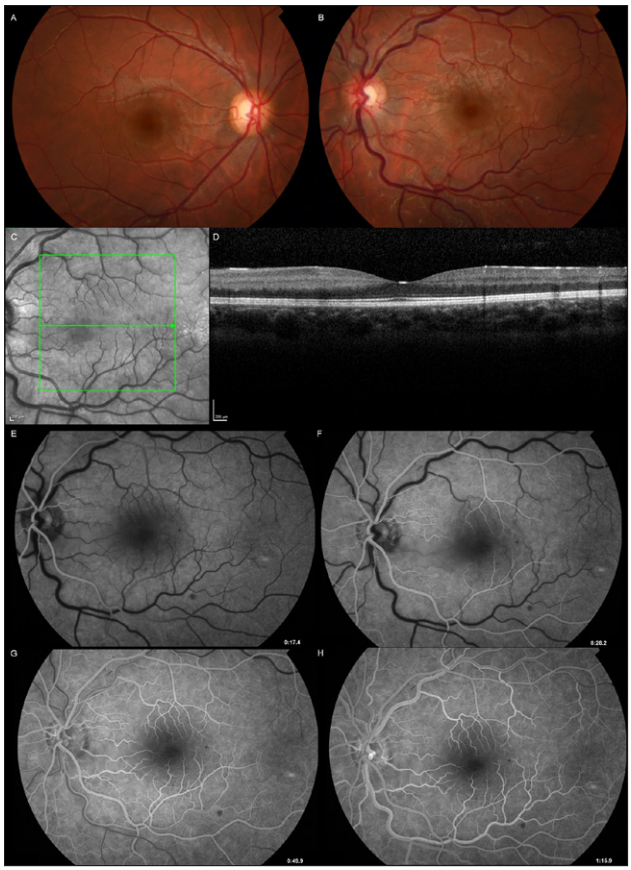

Figure 1. Patient's imaging on presentation. Color fundus photo of the right eye did not show any changes (A). The left eye (LE) colour fundus photo was suggestive of an impending central retinal vein occlusion, with dilated and tortuous retinal veins in the four quadrants and occasional retinal hemorrhages in the posterior pole (B). Macular spectral domain ocular coherence tomography (SD-OCT) (D) depicted hyperreflectivity of the inner two-thirds of the retina nasally to the fovea, suggestive of cilioretinal artery occlusion, with no intra or subretinal fluid. Fundus fluorescein angiography of the LE (E-H) showed delayed filling of the cilioretinal artery and delayed arteriovenous transit time, with focal hypofluorescence corresponding to the retinal hemorrhages. Vascular leakage and ischemia were absent. C: infrared imaging of the corresponding SD-OCT b-scan. Angiographic times in minutes and seconds are depicted in the right lower corner of each frame.

Bloods tests results were all within normal limits, namely full blood count, fasting glucose, lipid profile, erythrocyte sedimentation rate (ESR), C-reactive protein, antiphospholipid syndrome antibodies, prothrombotic defects (C protein, S protein, antithrombin III, factor V Leiden), homocysteine, serum angiotensin-converting enzyme, human immunodeficiency test, venereal disease research laboratory test, *Treponema pallidum* hemagglutination assay, serum protein electrophoresis, antinuclear antibodies and antineutrophil cytoplasmic antibodies.

Electrocardiogram was unremarkable. No changes were detected on brain and orbits magnetic resonance angiography. Carotid Doppler ultrasound showed a mild atheromatous infiltration on both carotid axis, without sig-

nificant morphologic or hemodynamic changes. On Doppler echocardiography, a patent foramen ovale was found. This finding was discussed with Pediatric Cardiology and closure was not found to be indicated.

Two weeks later, BCVA in the LE was 20/25. Fundus examination of the LE showed a full-blown CRVO (Fig. 2, A). Nasally to the fovea, macular SD-OCT showed more demarcated hyperreflectivity areas of the inner two-thirds of the retina (Fig. 2 – B). Temporally to the fovea, it was possible to observe new hyperreflectivity bands in the inner nuclear layer, consistent with paracentral acute middle maculopathy (PAMM). Repeated FFA in the LE showed delayed AV transit, retinal veins staining in the later frames, several hypofluorescent areas corresponding to the retinal hemorrhages and optic disc staining (Fig. 2, C-H). Vascular leakage and retinal ischemia were absent (Fig. 2, C-H). We decided to observe the patient closely.

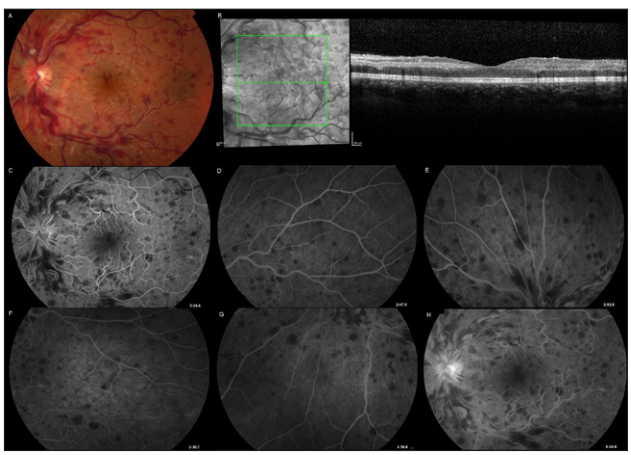

Figure 2. Patient's imaging two weeks after presentation. Color fundus photo of the left eye (LE) (A) showed a full-blown central retinal vein occlusion, with marked four quadrants retinal veins dilation and tortuosity, widespread superficial and dot and blot retinal hemorrhages, occasional cotton wool spots and blurred optic disc margins. Nasally to the fovea, macular spectral domain ocular coherence tomography showed more demarcated hyperreflectivity areas of the inner two-thirds of the retina (B). Temporally to the fovea, it was possible to observe new hyperreflectivity bands in the inner nuclear layer, consistent with paracentral acute middle maculopathy (B). Repeated FFA in the LE showed delayed AV transit, retinal veins staining in the later frames, several hypofluorescent areas corresponding to the retinal hemorrhages and optic disc staining (C-H). Vascular leakage and retinal ischemia were absent (C-H). C: infrared imaging of the corresponding SD-OCT b-scan. Angiographic times in minutes and seconds are depicted in the right lower corner of each frame.

Three days later, LE BCVA had decreased to 20/40. Macular SD-OCT showed macular edema, with macular thickening and new juxtafoveal and superonasal intraretinal fluid (Fig. 3). We decided to start treatment with ranibizumab 0.5 mg intravitreal injections. After a loading dose of three injections, LE BCVA improved to 20/25, the retinal hemorrhages improved and macular edema resolved. The patient entered a "treat & extend" regimen. She had a total of 7 IVT ranibizumab over 11 months, with a final BCVA of 20/25 in the LE and no recurrence of the macular edema.

Two years after the last injection, LE BCVA remains stable.

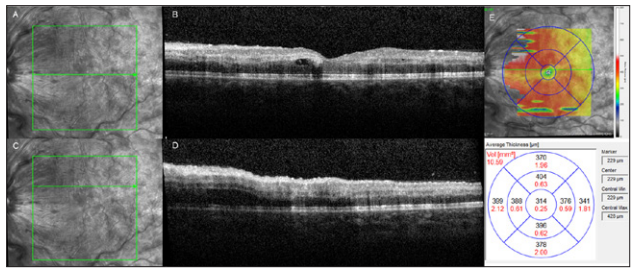

Figure 3. Patient's imaging 17 days after presentation. Macular spectral domain ocular coherence tomography (SD-OCT) showed macular edema, with new juxtafoveal (B) and superonasal (D) intraretinal fluid and macular thickening on macular thickness ETDRS subfield analysis map (E). A and C: infrared imaging of the corresponding SD-OCT b-scan.

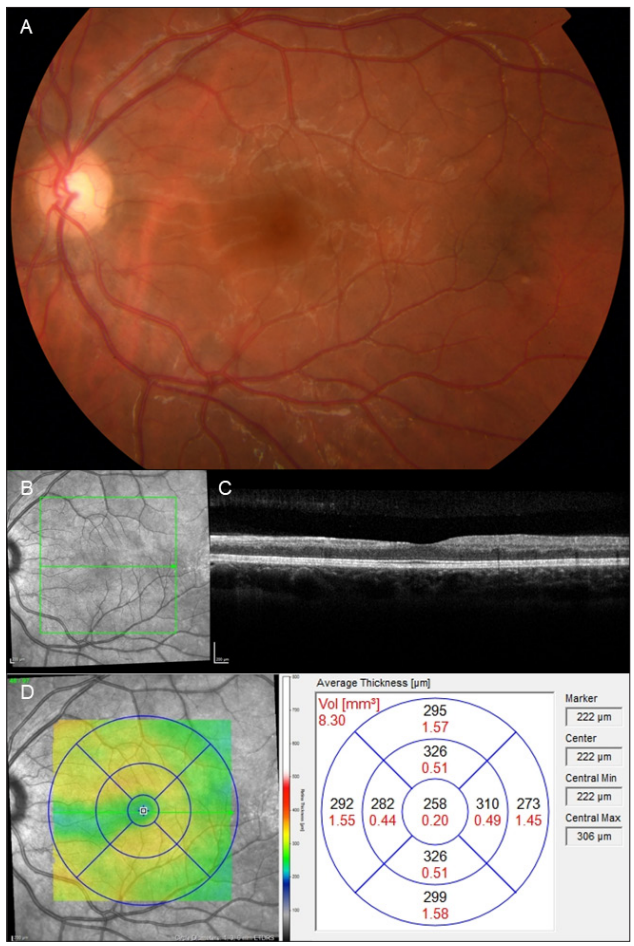

Figure 4. Patient's imaging three years after presentation. Color fundus photo of the left eye (LE) shows normal calibre and configuration of the retinal veins, with no macular edema, no retinal hemorrhages, no new vessels at the disc or elsewhere and no optic disc pallor (A). Macular spectral domain ocular coherence tomography (SD-OCT) shows no intra or subretinal fluid (C), with thinning of the inner two thirds of the retina in the papilomacular bundle, corresponding to the cilioretinal artery perfusion area, which was previously occluded. The thinning is also appreciated on macular thickness ETDRS subfield analysis map (D). Temporally to the fovea, the INL is thinned, corresponding to the previous PAMM lesions' location (C). B: infrared imaging of the corresponding SD-OCT b-scan.

LE fundus examination shows normal calibre and configuration of the retinal veins, with no macular edema, no retinal

hemorrhages, no new vessels at the disc or elsewhere and no optic disc pallor (Fig. 4, A). Macular SD-OCT shows no intra or subretinal fluid. There is thinning of the inner two-thirds of the retina in the papilomacular bundle, corresponding to the cilioretinal artery perfusion area, which was previously occluded (Fig. 4 – B-D). Temporally to the fovea, the INL is thinned, corresponding to the previous PAMM lesions' location (Fig. 4 – B-D).

DISCUSSION

CRVO is secondary to central retinal vein thrombosis, more commonly due to central retinal artery atherosclerosis, which compresses the central retinal vein at the *lamina cribosa*.[5] Patients with CRVO of any age should be assessed regarding cardiovascular risk factors, namely blood pressure, full blood count, glucose levels and HbA1C and ESR.[6] ESR should also be requested to screen for vasculitis and hematologic conditions such as multiple myeloma.[6] Other etiology and risk factors for CRVO include hypercoagulability/ hyperviscosity states, vasculitis, glaucoma and, rarely, retrobulbar external compression.[6] In young patients with CRVO these risk factors should be considered and blood tests requested as indicated.[6] Nevertheless, in most cases of RVO in young patients, the cause is unclear.[6]

In our patient, atherosclerotic disease seemed to have played a role, as her Doppler carotid ultrasound showed atheromatous infiltration on both carotid axis at the young age of 16. Her blood tests were otherwise within normal limits.

Oral contraceptive pills with estrogen increase the risk of cardiovascular and venous thromboembolism, pulmonary embolism and stroke.[7] A previous study has shown a 2-fold increase in the retinal vascular lesions risk and oral contraception.[8] However, this study was published in 1998, when higher doses of estrogen were used.[7] Our patient reported to have taken the emergency contraceptive pill ulipristal acetate twice in the month prior to the clinical presentation. Ulipristal acetate is a progesterone receptor modulator analogue[9] and has not been shown to increase venous thromboembolism risk.[10] Nevertheless, as the patient was initially unable to recall the pill brand, we wonder if she might have taken different contraceptive pills at different occasions and if one or more of them contained estrogen.

Our patient presented with CRVO combined with CLRA. Different theories have been proposed for this association. The most widely accepted is the hemodynamic block theory.[11,12] The prevalence of cilioretinal artery in the general population ranges from 6.9% to 49.5%.[4] Differently from the central retinal artery system, the cilioretinal artery does not have an autoregulation mechanism. In CRVO, an increase in the retinal capillary plexus is transmitted in a retrograde manner to the cilioretinal artery system, whose perfusion is suppressed. This causes a hemodynamic transitory blockage of the cilioretinal artery, whereas embolic sources do not play a role.[11,12] Although the patient was found to have a patent *foramen ovale*, this was therefore not felt to be the cause of her CLRAO combined with CRVO. Additionally, patent *foramen ovale* are common in the general population, with a prevalence of around 25%.[13]

Macular edema is the main cause of visual impairment in CRVO.[6] RVO tends to be more benign in younger patients, with a higher rate of spontaneous regression and lower need for macular edema treatment with anti-vascular endothelial growth factor (VEGF).[3,14] However, our patient progressed from impending to full-blown CRVO. Macular edema was not initially present and was detected more than 2 weeks after presentation. Clinical trials results[15–18] and established experience with ranibizumab in RVO allowed us to initiate treatment with confidence, as soon as mild macular edema was detected, with rapid resolution. This enabled an excellent preservation of the macular structure and function in a young patient with a long-life expectancy. The initial loading dose was followed by a "treat & extend regimen", with a total of seven injections, with no recurrence of macular edema. She was able to stop injections eleven months later. Her vision remains at 20/25 at 3 years of follow-up since presentation.

QUESTIONS

What makes this case different and original?

We present a case of a combined central retinal vein and cilioretinal artery occlusion in a 16-year-old teenage girl. Both pathologies are rare in this age group and the combination of the two is even rarer. We also think the images are very illustrative and have a strong didactic component.

Did you reach any conclusions about the etiology?

The patient was thoroughly investigated according to current guidelines. The examination revealed atherosclerotic pathology of the carotid axes, even though she was only 16 years old. This teenager also reported taking an emergency oral contraceptive (ulipristal acetate) twice in the month before her clinical presentation. This drug is a progesterone receptor modulator analog and, unlike estrogen contraceptives, has not been reported to increase the risk of thrombosis. However, the brand name of the drug was only recalled by the patient on a later occasion. Hence we wondered if she had taken an estrogen contraceptive at some point.

What treatment was given and what was the outcome?

Mild macular edema was noted about 2.5 weeks after presentation. We decided to start treatment with intravitreal ranibizumab - a loading dose followed by a treatment and extended protocol. This is another interesting aspect of this case. The clinical trials and accumulated experience with anti-VEGF allowed us to start treatment with confidence in still mild macular edema and with excellent results. The patient received 7 injections over 11 months. We present a follow-up of more than 2 years after the last injection, with no recurrence of edema to date.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

FGR and SH: Conceptualization, Data Collection and Analysis.

HS and ML Data Collection, Analysis and Critical Revision.
FR: Manuscript Writing.
All authors approved the final version to be published.

FGR e SH: Conceptualização, recolha e análise de dados.
HS e ML: Recolha de dados, análise e revisão crítica.
FR: Redação do Manuscrito.
Todos os autores aprovaram a versão final a ser publicada.

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Widefield Optical Coherent Tomography Angiography for Classification of Central Retinal Vein Occlusion

Angiografia por Tomografia de Coerência Óptica de Campo Alargado na Classificação de Oclusão da Veia Central da Retina

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ABSTRACT

Our purpose is to report a case of central retinal vein occlusion (CRVO) with clinical findings suggestive of ischemic disease where widefield optical coherence tomography angiography (OCTA) allowed for the accurate diagnosis of non-ischemic CRVO with subsequent appropriate management.

Clinical examination and imaging were conducted. Treatment consisted of intravitreal injections of anti-VEGF for macular edema following a treat-and-extend protocol. Visual acuity testing and proper imaging were conducted throughout treatment.

Intravitreal injections of anti-VEGF were successful in controlling macular edema. Non-perfusion at the superior macula and disorganization of the outer retinal bands at the fovea persisted. No other areas of nonperfusion were identified. Right eye best corrected visual acuity remained 20/400 after treatment.

Although poor visual acuity, significant macular and optic nerve edema, and extensive hemorrhage on ophthalmoscopy are consistent with ischemic cases of central retinal vein occlusion, non-ischemic cases may also present similarly. Widefield OCTA allows for an accurate evaluation of retinal nonperfusion, making it possible to distinguish ischemic from non-ischemic CRVO quickly and non-invasively.

KEYWORDS: Fluorescein Angiography; Macular Edema; Retinal Vein Occlusion/classification; Retinal Vein Occlusion/diagnostic imaging; Tomography, Optical Coherence.

RESUMO

Reportar o caso de uma oclusão da veia central da retina (OVCR) com achados clínicos sugestivos de doença isquémica, onde a angiografia por tomografia de coerência óptica (OCTA) de campo alargado permitiu o diagnóstico adequado de OVCR não isquémica.

O tratamento foi feito com recurso a injeções intravítreas de anti-VEGF dirigidas ao edema macular, segundo o protocolo *treat-and-extend*. As avaliações clínica e imagiológica foram realizadas ao longo do tratamento.

As injeções intravítreas de anti-VEGF foram eficazes no controlo do edema macular. Apesar da ausência de outros defeitos de perfusão, verificou-se a persistência de uma área não perfundida na mácula superior e da desorganização das camadas externas da retina ao nível da fóvea. A melhor acuidade visual corrigida manteve-se 20/400 após o tratamento.

Ainda que a baixa acuidade visual, o edema macular significativo, o edema do disco óptico, e as numerosas hemorragias na oftalmoscopia sejam achados sugestivos de OVCR isquémicas, casos não isquémicos também se podem manifestar de forma semelhante. O OCTA de campo alargado, ao avaliar adequadamente a extensão da área não perfundida, permite distinguir de forma rápida e não invasiva as formas isquémicas e não isquémicas da doença.

PALAVRAS-CHAVE: Angiografia com Fluoresceína; Edema Macular; Oclusão da Veia da Retina/classificação; Oclusão da Veia da Retina/diagnóstico; Tomografia de Coerência Óptica.

INTRODUCTION

Central retinal vein occlusion (CRVO) is a common cause of retinal vascular disease and vision loss. There are two very different clinical entities in CRVO, namely ischemic and non-ischemic.[1] Ischemic CRVO is a severe blinding disease with a high risk of ocular neovascularization, a low chance of improvement in visual acuity and a poor visual outcome. In contrast, non-ischemic CRVO is comparatively benign, with vision loss essentially due to macular edema and no risk of ocular neovascularization.[2] It is therefore essential in daily clinical practice to determine which type of CRVO one is dealing with.

Ischemic CRVO has been associated with low visual acuity (<20/200 Snellen equivalent), the presence of a relative afferent pupillary defect (RAPD), extensive optic disk/macular edema and hemorrhage on ophthalmoscopy, extensive capillary obliteration on fluorescein fundus angiography (> 10 optic disk areas) and subnormal b-wave amplitude on electroretinography.[2] However, in the early stages of CRVO, fluorescein angiography does not provide reliable information about capillary non-perfusion due to various limitations, and ERG is not routinely available. Therefore, the detection of ischemic CRVO and its treatment is usually based on the evaluation of VA, pupillary response, and fundus examination.

We observed a patient with severe vision loss and fundus changes consistent with ischemic CRVO. Widefield OCTA revealed capillary obliteration in the macula and preserved peripheral perfusion, leading to reclassification as non-ischemic CRVO, which is important for clinical decision-making and management. The following report will discuss the role of OCTA in the classification and management of acute CRVO.

CASE REPORT

A male in his 50s presented to the clinic with a history of sudden visual loss in his right eye two months prior. Past medical history was unremarkable. His best corrected visual acuity was 20/400 in the right eye (OD) and 20/20 in the left eye (OS). Intraocular pressure was within normal range and anterior segment examination was normal.

Dilated ocular fundus examination and color fundus photography of the right eye revealed generalized retinal vein dilatation and tortuosity, extensive dot and blot hemorrhages that extended from the optic disk head to all four quadrants of the retina and macular edema (Fig. 1A). OCT angiography showed vascular tortuosity, telangiectasia and a superior parafoveal area of nonperfusion (Fig. 1B). Cross-sectional optical coherence tomography (OCT) showed intraretinal fluid (IRF) within the neurosensory retina and hyperreflectivity and disorganization of the outer retinal bands at the fovea (Fig. 1C). A diagnosis of non-ischemic central retinal vein occlusion with macular edema was made.

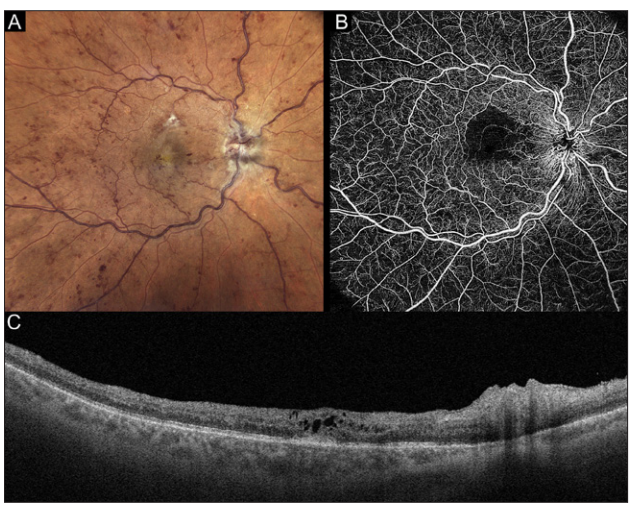

Figure 1. (A) Color fundus photography shows generalized retinal vein dilatation and tortuosity, extensive dot and blot hemorrhages, cotton wool spots and edema of the central macula and optic nerve head. (B) Widefield optical coherence tomography (OCT) angiography shows capillary non-perfusion at the superior macula and absence of significant capillary drop-out at the peripheral retina. (C) Cross-sectional OCT spanning the foveal shows revealing intraretinal fluid and hyperreflective material with disorganization of the outer retinal bands at the foveal bouquet.

Treatment with scatter laser photocoagulation was not advised. Macular edema was managed with regular intravitreal injections of anti-VEGF that followed treat-and-extend protocol. During follow-up, intra-retinal fluid subsided, though disorganization of the outer retinal bands at the central macula in OCT persisted, indicating irreversible photoreceptor damage (Fig. 2). Although visual acuity remained 20/400, the patient noticed a significant visual field improvement and found this very important for his daily activities.

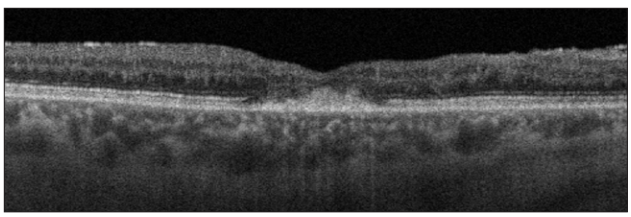

Figure 2. Optical coherence tomography performed while regular treatment with anti-vascular endothelial growth factor shows that there is no intra-retinal fluid, while the disorganization of the outer retinal bands at the central foveal bouquet persists.

DISCUSSION

At the time of diagnosis of a CRVO, the distinction between ischemic and non-ischemic disease is of critical importance, as their management and visual prognosis strongly differ.

The Central Vein Occlusion Study (CVOS) group defined ischemic CRVO as the presence of more than 10 disk areas of retinal nonperfusion documented by fluorescein angiography. Poor visual acuity (usually <20/200), relative afferent pupillary defect (RAPD), significant visual field defects, optic disk/macular edema, extensive hemorrhage and cotton-wool spots on ophthalmoscopy and the presence of severe venous tortuosity and dilation also support this diagnosis.[2,3]

Fluorescein angiography provides valuable information on the status of the retinal capillary bed including the presence of hyperpermeability or nonperfusion. Associated features include late leakage in the macular area and late staining of the main posterior veins.[4] Nevertheless, due to the extensive hemorrhage, fluorescein angiography does not provide reliable information at time of diagnosis, which makes clinical assessment an extremely relevant tool for the distinction between ischemic and non-inchemic CRVO.

The capillary non-perfusion and subsequent retinal hypoxia seen in cases of ischemic CRVO lead to the release of vascular endothelial growth factor (VEGF), responsible for the development of ocular neovascularization. In fact, *rubeosis iridis* develops in about 50% of the cases, imposing the risk of permanently increased intraocular pressure and the consequent development of neovascular glaucoma. Complications associated with ischemic CRVO may justify treatment with scatter laser photocoagulation in order to prevent neovascularization, a treatment modality that may be necessary but that also imposes significant risks, such as decreased peripheral vision, color vision and nyctalopia.

Hence, the decision of pursuing laser treatment must be well reasoned. Nowadays, the availability of widefield OCT angiography strengthens clinical assessment and can be decisive in cases where clinical findings do not align with the degree of ischemia, as seen in this case.

In the case we present, poor visual acuity was found to be caused by macular edema and macular ischemia. What could have been mistakenly interpreted as a case of ischemic CRVO, was clarified by OCT angiography. This imaging modality was done at the time of diagnosis and allowed for a correct interpretation of the actual cause of low visual acuity, leading to the reclassification as non-ischemic CRVO.

OCT revealed the presence of macular edema, one of the causes of low baseline visual acuity in CRVO. Macular edema results from the capillary hyperpermeability secondary to venous obstruction and can occur both in ischemic and non-ischemic types of CRVO. Both persistent and recurrent macular edema in CRVO are associated with worse visual outcomes compared to patients with persistently dry maculas.[5,6]

In cases of non-ischemic CRVO with macular edema, some degree of VA improvement is expected after resolution of central macular edema. In our case, the use of OCT angiography allowed for the detection of a superior macular area of nonperfusion. The location of nonperfused retina can explain the poor visual acuity even after resolution of central macular edema. The presence and consistent extent of foveal outer retinal band disorganization may also be a contributing factor for the absence of visual function improvement after macular edema resolution.

The diagnosis of ischemic CRVO is, by this definition, based on FA. However, OCT angiography has proven to be a valid and useful tool in these cases. OCT-A macular findings, namely enlargement of foveal avascular zone area and decreased perfusion density (PD) in the superficial and deep capillary plexus significantly correlate with the ischemic index (ISI) measured on ultra-widefield (UWF) fluorescein angiography. The extent of microvascular changes also correlate with best-corrected visual acuity in eyes with CRVO. Hence, OCT angiography can aid in the diagnosis and determination of non-perfusion extent, it can help in assessing the need for additional UWF FA, and support visual acuity prognosis.[7,8]

This case supports the idea that vision loss after central retinal venous occlusion is not solely dependent on the extent of macular nonperfusion. Hence, not all cases of CRVO with poor baseline visual acuity should be interpreted as ischemic cases of CRVO. It highlights the importance of OCT angiography as a noninvasive method that can detail retinal perfusion and allow for the correct diagnosis of ischemia profile and extent, guaranteeing a correct management and treatment choice.

Q&A

Which are the main OCT angiography findings in cases of CRVO?

Microvascular changes both in the superficial and deep capillary networks, including a decrease in foveal and

parafoveal vascular densities, capillary engorgement and formation of telangiectasias, vascular tortuosity, microaneurysms, disruption of the foveal perivascular plexus, and formation of collateral vessels. Appearance of areas of non-perfusion, similar to our case, has also been described.

Which factors might influence final visual acuity in cases of CRVO?

A group of biomarkers has been identified as potential prognostic factors that predict a better final BCVA, namely: younger age, male gender, absence of smoking, good baseline BCVA, shorter duration of symptoms (<3 months), intact external limiting membrane, absence of ellipsoid zone disruption and fewer hyperreflective foci. Regarding OCT angiography parameters, enlargement of the macular non-perfusion area in the superficial and deep plexus directly correlates with poorer final BCVA. Baseline central macular thickness does not predict visual outcomes, as long as an adequate treatment plan is implemented.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

IM; MB and DC: Conceptualization, data collection, analysis, writing, critical revision and approval.

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Central Retinal Vein Occlusion Secondary to Antiphospholipid Syndrome: Case Report

Oclusão da Veia Central da Retina Secundária a Síndrome Antifosfolipídico: Relato de Caso

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ABSTRACT

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by hypercoagulability, defined by the presence of venous and/or arterial thromboembolism in association with antiphospholipid antibodies (aPL). The frequency of APS in patients with retinal vein occlusion (RVO) was estimated at 13.2%

A 46-year-old male patient presented with sudden, painless, vision loss of the left eye (LE). Dilated, tortuous retinal veins, retinal hemorrhages and cotton-wool spots, distributed along the four quadrants, were observed on LE fundoscopy. The patient was diagnosed with central RVO (CRVO) complicated by macular edema. Thrombophilia screening revealed positive beta-2 glycoprotein and anti-cardiolipin antibodies.

Younger patients with RVO in whom no common risk factors have been identified may be screened for thrombophilia including APS.

KEYWORDS: Antiphospholipid Syndrome/complications; Macular Edema; Retinal Vein Occlusion/etiology.

RESUMO

A síndrome antifosfolipídica (SAF) é uma doença autoimune caracterizada por hipercoagulabilidade, definida pela presença de tromboembolismo venoso e/ou arterial

em associação com anticorpos antifosfolípidos (aPL). A frequência de SAF em doentes com oclusão venosa da retina (OVR) foi estimada em 13,2%.

Doente do sexo masculino, de 46 anos, apresentou perda súbita e indolor da visão do olho esquerdo (OE). Veias retinianas dilatadas e tortuosas, hemorragias retinianas e manchas algodonosas, distribuídas pelos quatro quadrantes, foram observados na fundoscopia do OE. O doente foi diagnosticado com OVR central (OVCR) complicada por edema macular. O rastreio de trombofilia revelou anticorpos positivos contra a beta-2 glicoproteína e anticardiolipina.

Os doentes mais jovens com OVR em que não tenham sido identificados os fatores de risco comuns podem ser rastreados para a trombofilia, incluindo APS.

PALAVRAS-CHAVE: Edema Macular; Oclusão da Veia Retiniana/etiologia; Síndrome Antifosfolipídica/complicações.

INTRODUCTION

Besides age and major cardiovascular risk factors, in particular hypertension, a hypercoagulable state has been found to play a pathogenic role in patients with retinal vein occlusion (RVO). A high prevalence of coagulation disorders was found in younger (<45 years) RVO patients, those with a family history of thromboembolism and/or without cardiovascular risk factors.[1]

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial, venous, or microvascular thrombosis, pregnancy morbidity, or nonthrombotic manifestations in patients with persistent antiphospholipid antibodies (aPL).[2] The frequency of APS in patients with RVO was estimated at 13.2%, through screening of aPL.[3] These antibodies were found to be more prevalent in RVO patients than in healthy controls.[4] Likewise, the frequency of ocular vaso-occlusive disorders in patients with APS ranges from 0.5% to 8%, with the majority affecting the retinal vasculature.[5]

We report a case of APS where the primary manifestation was central retinal vein occlusion (CRVO).

CASE REPORT

A 46-year-old male patient presented to the emergency room complaining of sudden, painless, vision loss of the left eye (LE). He had a past medical history of acute coronary stroke two years ago and positive cardiovascular risk factors, such as hypertension, dyslipidemia and previous smoking habits.

The clinical exam revealed a visual acuity (VA) of 10/10 in the right eye (RE) and 4/10 in the LE, with no relative afferent pupillary defect. RE fundoscopy was normal. Optic disc edema and dilated, tortuous retinal veins, superficial and deep retinal hemorrhages and cotton-wool spots, distributed along the four quadrants, were observed on LE fundoscopy (Fig. 1). Optical coherence tomography (OCT) at presentation confirmed LE macular edema, with 707 µm of central retinal thickness (CRT) (Fig. 2). A clinical diagnosis of LE CRVO complicated with macular edema was established.

Besides identifying the aforementioned risk factors in the patient history, systemic investigation was pursued with complete blood count (red blood cells 5.2x10^9/L, hemoglobin 15.5 g/dL, white blood cells 5.1x10^9/L and platelets 250x10^9/L), erythrocyte sedimentation rate 24 mm/hr, C-reactive protein 0.21 mg/L, fasting blood glucose test 80 mg/dL and glycated hemoglobin (A1C) 5.6%. Thrombophilia screening was added, considering the relatively young patient age. Lupus anticoagulant (LA) test was negative. Beta-2 glycoprotein (aβ2GPI) IgM antibody was positive (35.8 U/mL), with negative IgG. Anti-cardiolipin (aCL) antibody was also positive (50.7 U/mL).

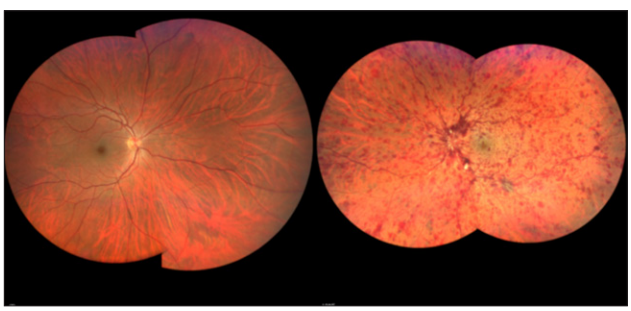

Figure 1. Retinography at presentation (RE and LE, respectively).

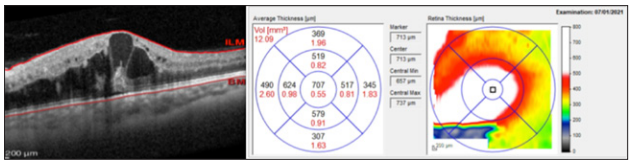

Figure 2. LE macular OCT at presentation.

The ocular investigation was complemented by fluorescein angiography (FA), which showed mask effect on the areas of hemorrhage, prolonged arteriovenous transit time, late staining along vessel walls and late optic disc and macular leakage in a petaloid pattern (Fig. 3). Notably, there was an absence of extensive capillary dropout, confirming the diagnosis of non-ischemic CRVO.

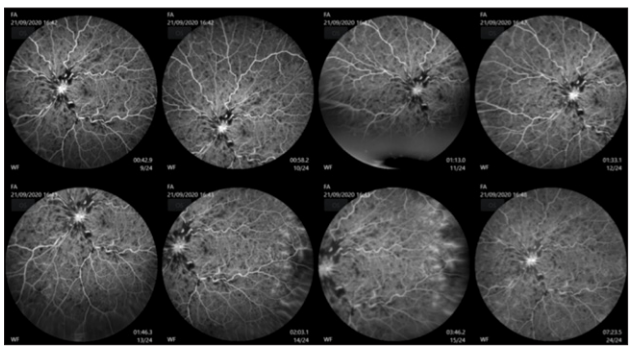

Figure 3. LE FA at presentation.

Regarding systemic treatment, the patient was referred to Cardiology and Rheumatology. Apart from addressing cardiovascular risk factors, anticoagulation was started for APS, using acetylsalicylic acid (150 mg/day) as a bridge to warfarin (target international normalized ratio 2-3).

Three monthly LE intravitreous aflibercept injections were proposed for the treatment of CRVO-associated macular edema. The follow-up schedule was decided at 6-week intervals after the last injection. At the second visit, VA was 2/10, with persistent macular edema (407 µm CRT) on OCT, so more 3 monthly aflibercept injections were suggested. At the third visit, VA improved to 6/10 with reabsorption of macular edema, only remaining 2 perifoveal cysts (307 µm CRT). A new treatment cycle of 3 monthly aflibercept injections was started. At the fourth visit, a 10/10 visual acuity was achieved, with complete resolution of macular edema (301 µm CRT). A total of 9 monthly intravitreous aflibercept injections were employed during the first year (Fig. 4).

FA was repeated 3 months after the diagnosis, to minimize the limitation of the extensive hemorrhages (Fig. 5).

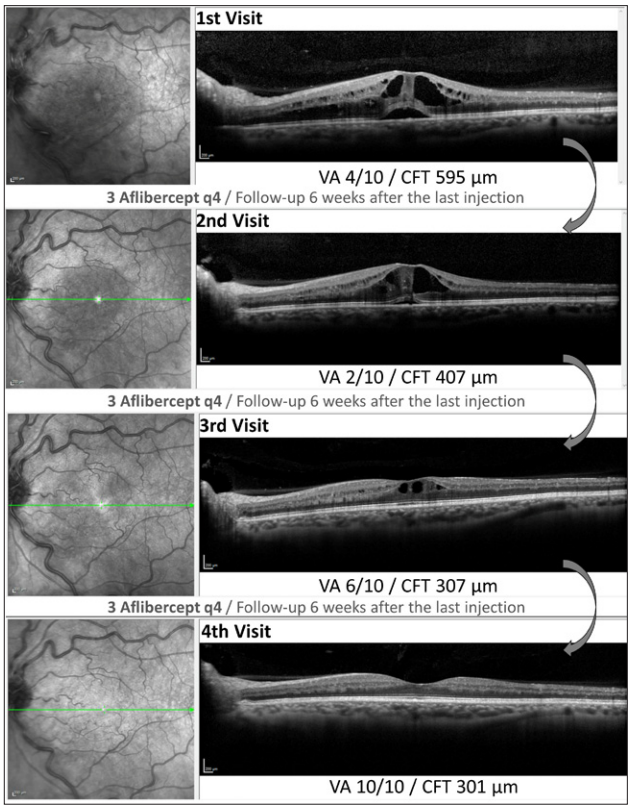

Figure 4. LE OCT during follow-up for macular edema treatment.

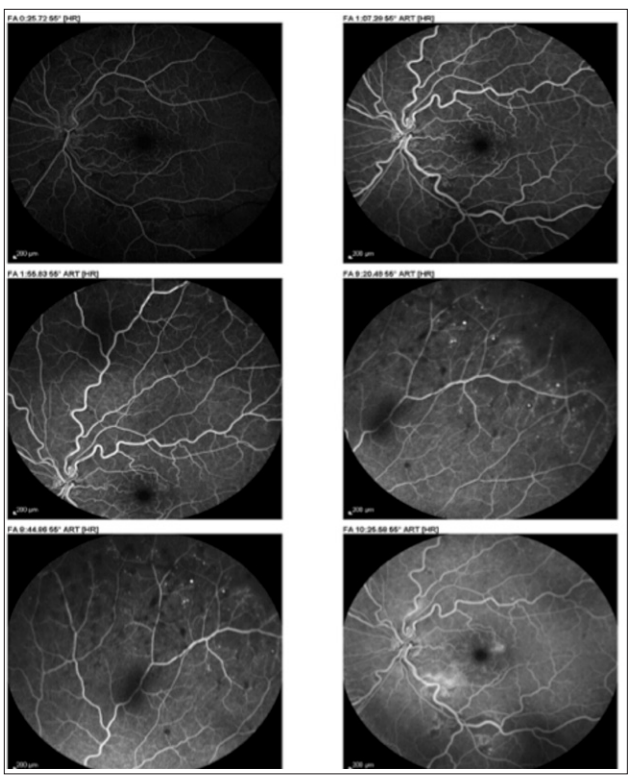

Figure 5. LE FA at 3 months follow-up.

Retinal capillary nonperfusion greater than 10-disc areas were identified in the temporal and superior quadrants, now comprising an ischemic CRVO. Targeted scattered photocoagulation was performed in those areas (Fig. 6).

During follow-up, the intraocular pressure remained within normal values and no neovascularization of the iris and/or angle was observed.

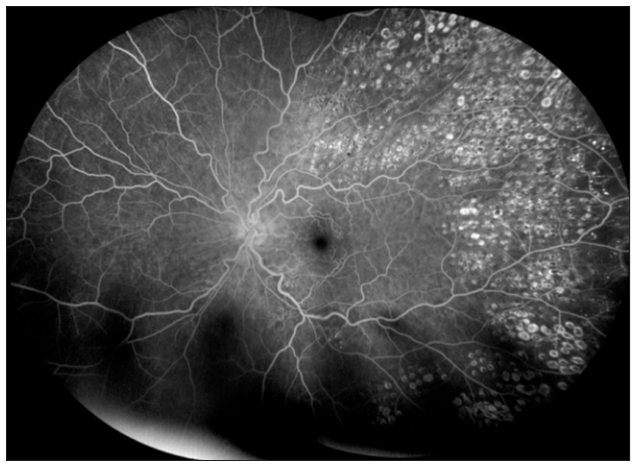

Figure 6. LE FA after prophylatic laser photocoagulation.

DISCUSSION

Blood coagulation and hyperviscosity disorders are known causes of RVO in younger patients, as stated in the guidelines for the management of RVO by the European Society of Retina Specialists.[6] They recommend that younger patients with RVO in whom no common risk factors have been identified may be screened for thrombophilia including APS, despite a weak association. It was that screening that provided the underlying diagnosis of APS in our patient.

RVO is included in the macrovascular clinical criteria that can be used to diagnose APS.[2] In our case, CRVO was the clinical criteria used to establish this diagnosis. A diagnosis of score 11 APS was made according to the 2023 American College of Rheumatology/European Alliance of Associations for Rheumatology APS classification criteria (3 points - macrovascular venous thromboembolism [CRVO]; 4 points – macrovascular arterial thrombosis [coronary stroke]; 4 points – moderately positive aβ2GPI and aCL).[2] Anticoagulation was necessary for systemic disease control.

Regarding the association between aPL and RVO, a meta-analysis found that aβ2GPI and aCL antibodies were significantly associated with the risk of RVO, rather than LA.[7] According to the literature, these were the antibodies found in our CRVO patient.

Aflibercept has proven to be effective in the treatment of macular edema secondary to CRVO, in the landmark trials COPERNICUS and GALILEO.[8] Accordingly, we chose a pro re nata treatment regimen, that resulted in the same

median 9 injections in the first year, less 406 µm of CRT and maximum VA.

Sequential OCT performed to monitor treatment response confirmed the absence of hyperreflective foci on the outer plexiform layer and the integrity of the ellipsoid zone/photoreceptor layers. These are considered positive biomarkers for VA prognosis after therapy, which may explain the total restitution VA in our case, regardless of an initial VA <5/10.

In the CVOS, approximately one-third of eyes with nonischemic CRVO underwent conversion to an ischemic perfusion status over 3 years, half of them in the first 4 months.[9] These intervals may be extended in the setting of antiangiogenic treatment for macular edema. For that reason, it is important to maintain monthly visits in the first 3 months and bi-monthly visits during the first year, checking intraocular pressure, iris and/or angle neovascularization. Those parameters remained normal in our follow-up.

Photocoagulation is recommended only after iris neovascularization has developed based on CVOS, requiring a weekly or biweekly follow-up of patients with extensive capillary non-perfusion.[9] Because of the close surveillance burden, the European guidelines advocate that prophylactic laser photocoagulation should be considered in patients with extensive retinal ischemia.[6] That was our option for this patient whose repeat FA confirmed a conversion to an ischemic CRVO at 3 months follow-up.

QUESTIONS

Under what circumstances should a secondary cause be considered for RVO?

Older age and hypertension are the main systemic risk factors for RVO. Younger patients with RVO in whom no cardiovascular risk factors have been identified may be screened for thrombophilia including APS. At the very least, they should be referred to an Internal Medicine specialist to exclude other uncommon predispositions.

Does the finding of APS in RVO change ocular management?

Regarding ophthalmology, if the cardiovascular history is not significant (exclude myocardial infarction and stroke in the last 3 months), anti-VEGF therapy can still be used as first-line therapy for associated macular edema. Above all, the diagnosis of APS in a RVO changes the patient's systemic management, because anticoagulation should be considered to prevent further thromboembolic events. Again, collaboration with Internal Medicine, Cardiology and/or Rheumatology is fundamental.

What is the current role of FA in the management of RVO?

Nowadays, OCT is the preferred exam to diagnose macular edema in RVO. In the past, FA was used to detect and quantify leakage from retinal vessels, highlighting areas of macular edema. Assessment of peripheral retinal perfusion, particularly the diagnosis of ischemic RVO and guiding areas of photocoagulation, is the fundamental role of FA in RVO, at least while wide-field OCT angiography is still not available in clinical practice.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

MM, AC, HU e FV: Revisão bibliográfica, recolha de dados, redação e revisão. Todos os autores aprovaram a versão final a ser publicada.

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Central Retinal Vein Occlusion Associated with Lupus Anticoagulant: A Case Report

Oclusão da Veia Central da Retina Associada ao Anticoagulante Lúpico: Relato de Caso

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ABSTRACT

Retinal vein occlusions (RVO) are the second most frequent cause of retinal vascular blindness worldwide and the main risk factors are RVO in the fellow eye, older age, arterial hypertension, and diabetes mellitus. Although investigation of hypercoagulability states is usually only indicated in patients under the age of 50, we present the case of a 65-year-old patient with a second RVO episode in 4 years, just three weeks after COVID-19 infection. Systemic investigation detected positive lupus anticoagulant (LAC) and in this report we discuss the possible induction of LAC by the SARS-CoV-2 virus and its possible causative role for RVO.

KEYWORDS: COVID-19/complications; Lupus Coagulation Inhibitor; Macular Edema/etiology; Retinal Vein Occlusion/etiology.

RESUMO

As oclusões venosas da retina (OVR) são a segunda maior causa de cegueira de causa vascular a nível mundial. Os principais fatores de risco são idade avançada, hipertensão arterial, diabetes *mellitus* e história de OVR no olho adelfo e uma investigação sistémica de fatores de hipercoagulabilidade está indicada em doentes jovens (< 50 anos). Apresentamos um caso de um homem de 65 anos que se apresentou com um segundo episódio de OVR 4 anos após o primeiro, e apenas 3 semanas após uma infeção COVID-19. A investigação sistémica revelou anticoagulante lúpico (ACL) positivo. Discutiremos a possível indução do ACL pelo vírus SARS-CoV-2 e ainda a possível relação de causalidade entre o ACL e OVR.

PALAVRAS-CHAVE: COVID-19/complicações; Edema Macular/etiologia; Inibidor de Coagulação do Lúpus; Oclusão da Veia Retiniana/etiologia.

INTRODUCTION

Retinal vein occlusions (RVO) are the second most frequent cause of retinal vascular blindness worldwide, just behind diabetic retinopathy.[1] These can be divided into central retinal vein occlusions (CRVO) when they occur up to the level of the optic disc, hemiretinal vein occlusions (HRVO) when occurring at the first major venous bifurcations, and branch retinal vein occlusions (BRVO) when occurring distally. Distal RVOs have a greater incidence rate than those that are more proximal.[2,3] Well-established risk factors for RVO include older age and atherosclerotic risk factors (ARF) such as arterial hypertension, and diabetes mellitus, although the strongest predicting factor for RVO is a RVO in the contralateral eye.[2] In younger patients however, these factors may play a smaller role and many authors advocate for an extensive investigation of inflammatory or hypercoagulability states in patients with RVO under the age of 50.[4–6] These additional causes of RVO in young patients include hyperhomocystenemia, factor V Leiden mutation, prothrombin gene mutations, anti-phospholipid antibodies (APLA) and Behçet's disease.[5,7]

Here we will describe the case of a patient with two RVO episodes, including a CRVO one month after being diagnosed with COVID-19 infection. A positive APLA, in this case lupus anticoagulant (LAC), was detected. LAC's possible causative role and relation to COVID-19 infection will be discussed.

CASE REPORT

We describe the case of a 65-year-old male who presented to the emergency department with complaints of a sudden decrease in visual acuity in his left eye (LE) earlier that day. He reported no other ocular or systemic symptoms but had been diagnosed with COVID-19 three weeks earlier. The patient had a history of dyslipidaemia and depression, medicated with pravastatin 40 mg, sertraline 100 mg and acetylsalicylic acid (ASA) 100 mg. Ocular history was relevant for superior temporal (ST) BRVO in his right eye (RE) 4 years earlier, for which he had already received 15 intravitreal injections (IVI) of aflibercept on a treat and extend (T&E) scheme, currently undergoing IVI every 9 weeks (q9w), with good anatomical and functional results. No etiological investigation had been conducted at the time of the STBRVO due to the patient's age and risk factors.

On presentation best corrected visual acuity (BCVA) for the RE was 83 letters ETDRS and for the LE 9 letters ETDRS. The anterior segment of the LE was unremarkable but fundoscopy revealed mild vascular tortuosity and diffuse intraretinal flame hemorrhages in all quadrants. Pupil reflexes were normal. A diagnosis of CRVO was presumed. At diagnosis, the fluorescein angiography did not show significant ischaemic areas and thus this CRVO was classified as non-ischaemic (Fig. 1).

A systemic work-up was carried out after referring the patient to internal medicine. This was positive only for

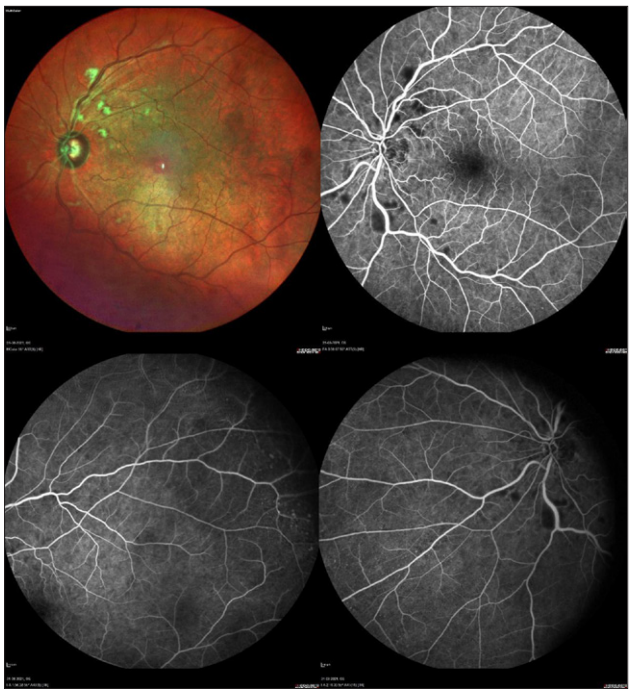

Figure 1. Multicolor and fluorescein angiography of the LE after the diagnosis of CRVO. No significant areas of ischemia can be identified.

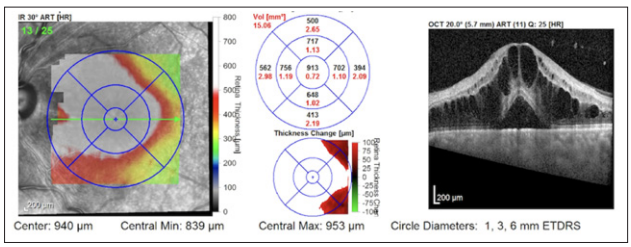

Figure 2. Macular SD-OCT 2 weeks after the LE CRVO episode, showing significant CME with intraretinal and subretinal fluid, and a central macular thickness of 913 µm.

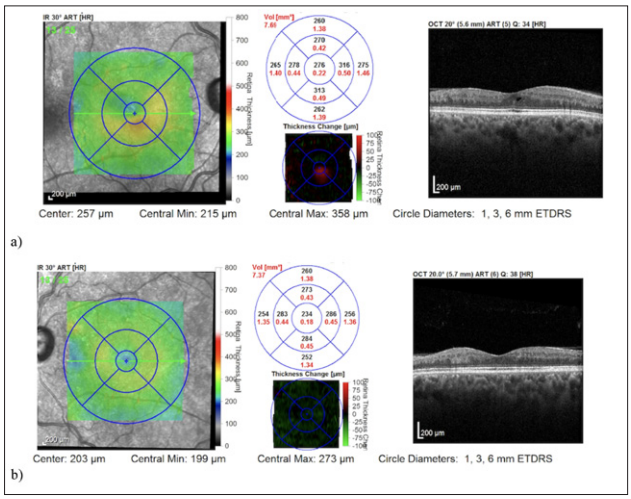

Figure 3. Macular SD-OCT of the RE (a) and LE (b) at the last follow-up, showing the absence of CME on a q9w aflibercept IVI treatment plan. Only a small intraretinal cyst can be seen in the RE.

LAC. Complete blood count, prothrombin time, activated partial thromboplastin time and homocystenemia were normal. HbA1c was 6.6%, antinuclear antibodies were negative, as were the remaining APLA, and there were no other systemic signs of rheumatologic disease.

At 2 weeks of follow-up the patient presented with significant cystoid macular edema (CME) (Fig. 2). Loading dose of 3 IVI of aflibercept q4w was started, with good anatomic results. Both eyes are currently on a q9w aflibercept IVI T&E scheme and RE and LE BCVA are 78 and 51 ETDRS letters respectively (Fig. 3). The patient still maintains active outpatient follow-up with internal medicine.

Informed consent was obtained from the patient for this report and associated figures.

DISCUSSION

RVO are an important cause of vascular blindness and the main risk factors are RVO in the fellow eye, older age, arterial hypertension, and diabetes mellitus.[1–3,6] In patients under the age of 50 a work-up for hypercoagulability states is usually indicated.[4,5] We present the case of a patient with a history of RE BRVO at the age of 61 and LE CRVO at the age of 65. At the time of the first RVO diagnosis the patient's age and history of ARF (dyslipidemia only) dictated that no systemic investigation was carried out. Statistically this patient had a 10% risk of developing any type of RVO in his RE in the following 3 years.[1] Despite this, when the patient presented with a CRVO 4 years later, a systemic work-up was requested through an internal medicine referral. This was mainly due to two factors: the first was that only dyslipidemia was present as a risk factor, and it is not considered to be a major risk factor as the other ARF previously mentioned.[8] Furthermore, the probable link between dyslipidemia and RVO has only recently been established by Zheng *et al*.[9] Secondly, various case reports describe CRVO after recent COVID-19 infections,[10,11] which this patient was diagnosed with one month prior to presenting with CRVO.

In this patient a positive LAC was detected. It is known that SARS-CoV-2 infection can induce the production of LAC in the acute phase, although no definite related systemic thrombotic events have been reported.[12] Cuadros *et al*[13] reported a case of CRVO presumably associated with a positive LAC that had been transiently induced by SARS-CoV-2 infection and we hypothesize that this may be a similar case, although we do not have a negative LAC prior to infection to confirm this hypothesis. It must also be said that although APLA have been clearly associated with RVO, this association is strongest with anti-cardiolipin antibody, and LAC was not correlated with RVO in a statistically significant manner in a recent review by Wei *et al*.[7] Several cases of SARS-CoV-2-associated RVO have also been described, with no relation to LAC.[13]

This case highlights the need for a high degree of suspicion for the need for systemic investigation even when the etiology of RVO can be attributed to age and ARF. Satisfactory anatomical and functional results were achieved with aflibercept IVI regiments and the detection of LAC after the second episode of RVO has led to follow-up by internal medicine, which can reduce the risk of future systemic complications and improve overall outcomes.

QUESTIONS AND ANSWERS

Q1: Why did you think this case was special?

A1: This is a case where a high degree of suspicion was required and a low threshold for systemic investigation was applied. A case of a second episode of RVO within a few years of the first in a not so young patient would be statistically expected. However, the team felt that the patient's low cardiovascular risk factors and recent medical history were suspicious.

Q2: Is the link between lupus anticoagulants and RVO definite?

A2: Although antiphospholipid antibodies in general have been associated with RVO, the evidence for the association between lupus anticoagulant and RVO specifically is inconclusive, to say the least. However, we believe that the case reports documenting this are indicative of this possible cause and effect relationship.

Q3: What is known about the duration of these lupus anticoagulant antibodies induced by COVID-19 infection?

A3: Reports suggest that they may circulate for one to two months. However, we have no data on this specifically in our patient. Also, we do not have a negative result for lupus anticoagulants prior to COVID-19 infection, so we suggested regular follow-up with internal medicine.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

MS: Manuscript Writing, Conceptualization and Data Collection and Analysis.

JMP: Conceptualization and Data Collection and Analysis.

JPC: Conceptualization.

BD and TV: Manuscript Writing, Data Collection and Analysis.

All authors approved the final version to be published.

MS: Escrita do Manuscrito, Conceptualização e Recolha e Análise de Dados.

JMP: Conceptualização e Recolha e Análise de Dados.

JPC: Conceptualização.

BD e TV: Redação do Manuscrito, Coleta e Análise de Dados.

Todos os autores aprovaram a versão final a ser publicada.

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Branch Retinal Vein Occlusion: Case Report

Oclusão de Ramo da Veia Central da Retina: Caso Clínico

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ABSTRACT

Branch retinal vein occlusion is the most common retinal venous occlusive disorder. It can develop macular edema and retinal neovascularization with subsequent visual compromise. The author presents a case report of a superior temporal branch retinal vein occlusion with macular edema treated with anti-VEGF and steroid injections and laser photocoagulation with 8 years of follow-up.

A 58-year-old female patient with hypertension and dyslipidemia was sent to our ophthalmology department due to painless progressive vision loss in her right eye. After fundus examination and macular optical coherence tomography (OCT), a diagnosis of macular edema secondary to superior temporal branch retinal vein occlusion was made. The patient started treatment with intravitreal anti-VEGF (1.25 mg bevacizumab) injections in a modified treat and extend (mTaE) regimen. Due to persistent macular edema, it was decided to switch to 2.0 mg aflibercept and combine it with concomitant dexamethasone intravitreal injections (Ozurdex®) and, later, focal laser photocoagulation. Ultra-wide field imaging was used throughout follow-up. Afterward, due to good anatomical and functional response, the patient was only monitored on a PRN (pro re nata) regimen up to the end of the follow-up period of 8 years.

This case report is a real-life example of the application of a therapeutic protocol involving the use of anti-VEGF drugs, a dexamethasone implant and laser photocoagulation for branch retinal vein occlusion treatment. Ultra-widefield imaging was useful in the identification of complications and so must be considered in the careful monitoring of these patients.

KEYWORDS: Dexamethasone; Laser Coagulation; Macular Edema; Retinal Vein Occlusion; Vascular Endothelial Growth Factors.

RESUMO

A oclusão de ramo da veia central da retina é a oclusão venosa retiniana mais comum. Esta pode complicar-se com edema macular e neovascularização da retina com subsequente comprometimento visual. O autor apresenta um caso clínico de uma oclusão de ramo temporal superior da veia central da retina com edema macular com 8 anos de seguimento tratada com injeções de anti-VEGF e de corticosteroides e fotocoagulação laser.

Uma doente de 58 anos, do sexo feminino, com hipertensão e dislipidemia foi enviada ao nosso serviço de oftalmologia por perda progressiva e indolor da visão no olho direito. Após avaliação

fundoscópica e realização de tomografia de coerência ótica (OCT) macular foi feito o diagnóstico de edema macular secundário a oclusão de ramo temporal superior da veia central da retina. A doente iniciou o tratamento com injeções intravítreas de anti-VEGF (1,25 mg de bevacizumab) num regime de treat and extend modificado (mTaE). Devido à persistência do edema macular, foi decidido mudar o anti-VEGF para 2,0 mg de aflibercept e combiná-lo com injecções intravítreas concomitantes de dexametasona (Ozurdex®) e, posteriormente, fotocoagulação laser. Ao longo do seguimento recorreu-se à avaliação fundoscópica por imagens de campo ultra-amplo. Posteriormente, devido à boa resposta anatómica e funcional, o doente foi apenas monitorizado num regime PRN (pro re nata) até ao final do período de seguimento de 8 anos.

Este caso clínico é um exemplo real da aplicação de um protocolo terapêutico que envolve a utilização de fármacos anti-VEGF, um implante de dexametasona e fotocoagulação laser para tratamento de uma oclusão de ramo da veia central da retina.

PALAVRAS-CHAVE: Dexametasona; Edema Macular; Fatores de Crescimento do Endotélio Vascular; Fotocoagulação a Laser; Oclusão da Veia Retiniana.

INTRODUCTION

A 58-year-old female patient was referred to our Ophthalmology Department with reduced visual acuity in her right eye for the last six months secondary to a superior temporal branch retinal vein occlusion. She took medications for arterial hypertension and dyslipidemia. Her best corrected visual acuity was 55 letters. The fundus exam showed macular oedema, telangiectatic vessels, microaneurysms and minimal retinal hemorrhages in the superior temporal macula of her right eye. She was diagnosed a superior temporal "macular" branch retinal vein occlusion.

The optical coherence tomography (OCT) showed intraretinal cysts, but preservation of the integrity of the external layers of the fovea (Fig. 1).

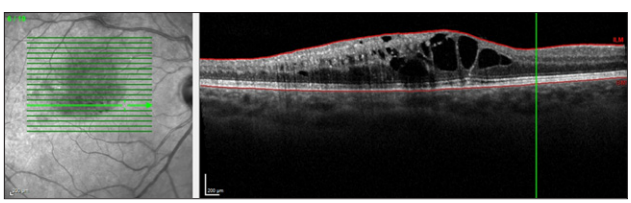

Figure 1. OCT image at presentation.

It was decided to implement the Department's BRVO treatment protocol with three monthly intravitreal injections (IVI) of 1.25 mg bevacizumab (off-label) and evaluation 4 weeks after the 3rd injection.

At the second visit, the patient did not show any visual improvement, maintaining 55 letters of BCVA. She noticed, however, a visual improvement after the first Intravitreal Injection, that subsided days after the second intravitreal injection. Fundus examination showed increased number of retinal haemorrhages and cotton-wool exudates suggesting a recurrent vein occlusion.

The OCT showed only partial reduction of the macular edema, so it was decided to maintain treatment interval at q4 (Fig. 2).

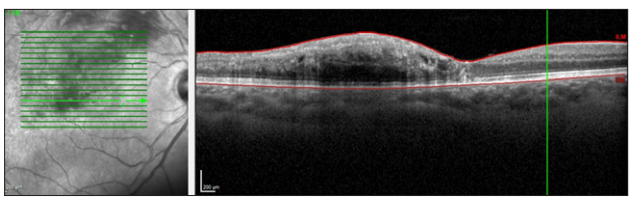

Figure 2. OCT at the second visit, 4 weeks after the third intravitreal injection of bevacizumab.

At the third visit, 4 weeks after the sixth intravitreal injection, BCVA was 50 letters and there was persistence of macular edema. It was then decided to switch to aflibercept 2.0 mg IVI (Fig. 3).

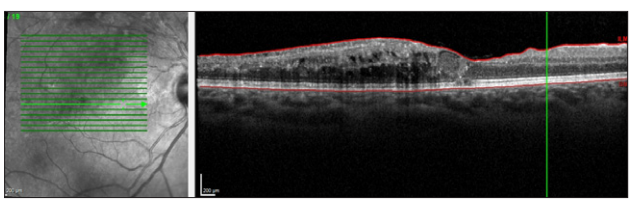

Figure 3. OCT image showing persistence of macular edema despite monthly treatment with bevacizumab.

Eight weeks after two consecutive series of three aflibercept IVI: 3 IVI 2q4 (AFB) and 3 IVI 2q8 (AFB) there were some visual gains (BCVA: 60 letters), but there was persistence of macular edema (Figs. 4 and 5). It was decided to combine aflibercept treatment with a dexamethasone implant (Ozurdex®) intravitreal injection. The treatment was well tolerated, and intraocular pressure remained normal.

Continued combination therapy with dexamethasone implant and intravitreal aflibercept 2.0 mg led to the formation of cataract and subsequent compromise of BCVA to 20 letters (Fig. 6).

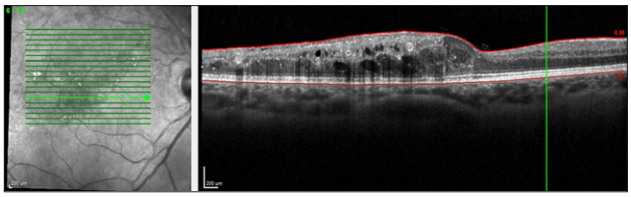

Figure 4. OCT image 15 months after the first treatment with intravitreal anti-VEGFs. Persistence of macular edema led to combination treatment with a dexamethasone implant (Ozurdex®) intravitreal injection.

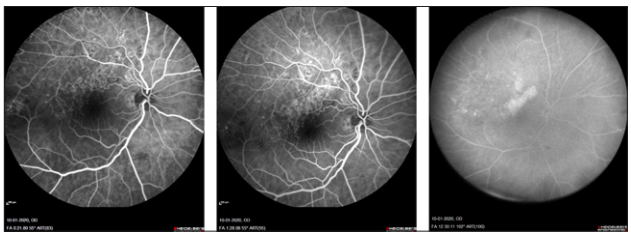

Figure 5. Fluorescein angiography showed telangiectatic vessels, microaneurysms and leakage.

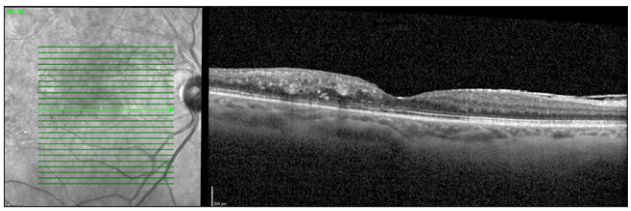

Figure 6. OCT image showing good anatomical response, but dense cataract: decision to do cataract surgery and dexamethasone implant.

After uneventful cataract surgery, BCVA improved to 70 letters, despite maintenance of intraretinal cysts affecting mainly the inner retina (Figs. 7 and 8).

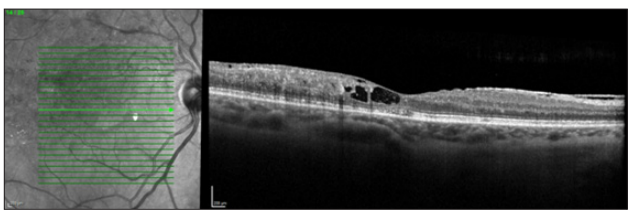

Figure 7. OCT scan with intraretinal cysts.

Due to COVID-19 pandemic there were some missed visits and treatments and BCVA dropped to 60 letters.

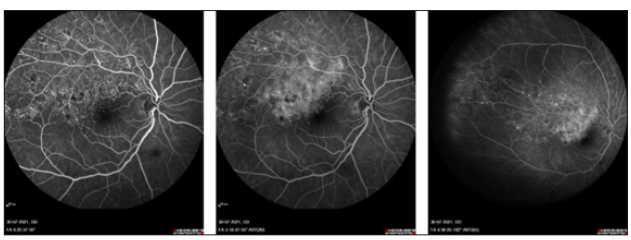

Figure 8. Fluorescein angiography showed increased macular edema and peripheral ischemia, but no new vessels were identified.

Worsening of the macular edema led to the decision to perform focal laser photocoagulation (Fig. 9).

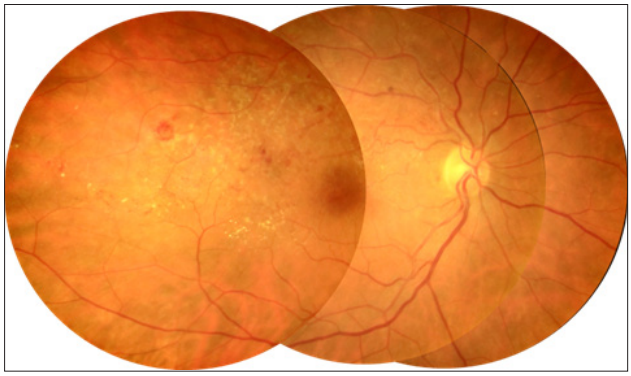

Figure 9. Mosaic fundus color photography one month after focal laser photocoagulation.

After focal laser photocoagulation and continuation of the combination treatment with 2.0 mg aflibercept and dexamethasone implant (Ozurdex®) IVI, there was improvement of BCVA to 70 letters and reduction of the macular edema (Fig. 10).

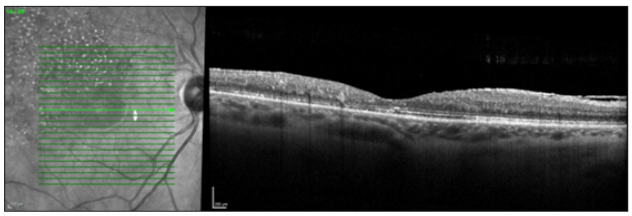

Figure 10. OCT scan shows dry macula after focal laser photocoagulation, intravitreal anti-VEGF and dexamethasone implant.

After three consecutive dexamethasone implant q16 the macula remained with no fluid. Pro re nata regimen was then established and the patient was evaluated every three months for one year.

Nine months after the last dexamethasone implant (Ozurdex®) IVI, the macula was still dry, but a ring of hard exudates was noticed temporal to the macula (Fig. 11).

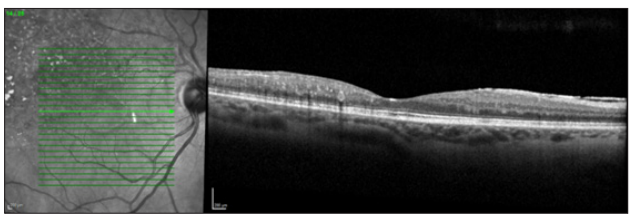

Figure 11. OCT scan shows no fluid in the macula nine months after the last dexamethasone implant (Ozurdex®) intravitreal injection, but some hard exudates are visible in the temporal part of the macula.

Fourteen months after the last dexamethasone implant (Ozurdex®) intravitreal injection, the macula was still dry, but some hard exudates were evident in the temporal part of the macula (Figs. 12 and 13).

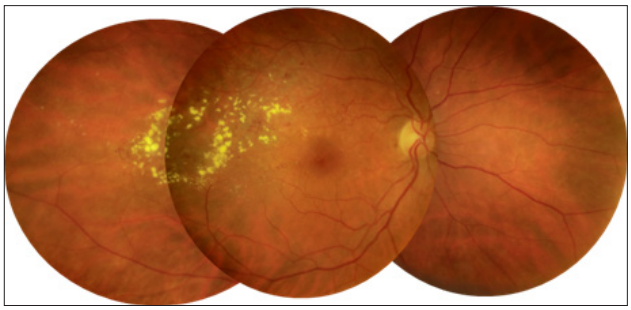

Figure 12. Mosaic color fundus photography shows a ring of hard exudates in the temporal part of the macula.

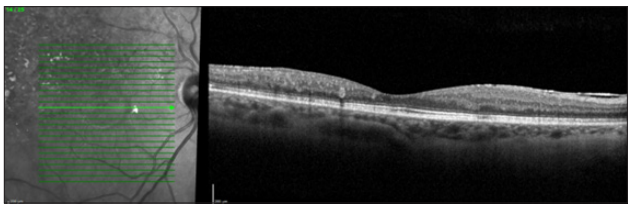

Figure 13. OCT scan shows absence of macular fluid fourteen months after dexamethasone implant (Ozurdex®) intravitreal injection.

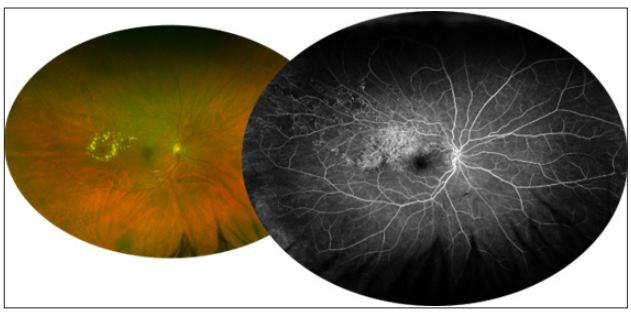

Figure 14. Optos ultra widefield imaging allows detailed visualization of the peripheral retina. In the present case, it is possible to identify an area of a peripheral nonperfused retina.

Focal laser photocoagulation was aimed at the leaking vessels related to the ring of hard exudates, but not to the nonperfused areas of the peripheral retina. Subsequent appointments showed reduction of the hard exudates and absence of macular edema. At the time of the final visit, BCVA was 70 letters.

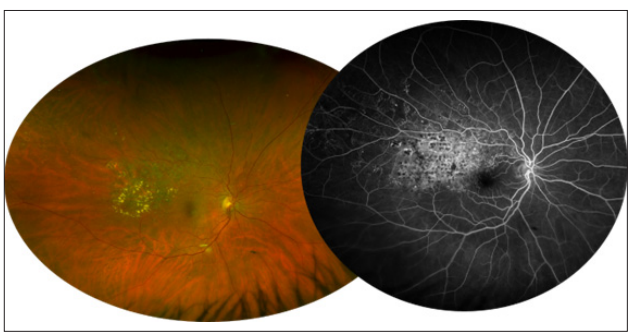

Figure 15. Optos fundus pseudocolor and fluorescein angiography show the reduction in size of the hard exudates 4 months after laser photocoagulation.

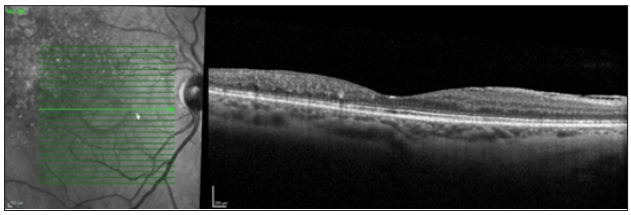

Figure 16. OCT scan shows absence of macular edema twenty months after the last dexamethasone implant (Ozurdex®) intravitreal injection.

DISCUSSION

BRVO is a common retinal vascular disorder. Macular edema and retinal neovascularization are common complications of this entity. Laser photocoagulation and anti-VEGF and dexamethasone implant (Ozurdex®) IVI are approved for the treatment of macular edema secondary to BRVO. TaE is a popular treatment regimen, but due to the need of increased number of monitoring visits, and the for the sake of limited appointment availability, our preference goes to a modified TaE regimen, which only advocates visit every three IVI. Nevertheless, it is very important to carefully monitor these patients under treatment for early identification of recurrent macular edema and for excluding significant areas of retinal nonperfusion in the peripheral retina. Indeed, retinal nonperfusion is an important risk factor not only for retinal neovascularization and subsequent vitreous hemorrhage (neovascular glaucoma in BRVO is a very rare complication in contrast to central retinal vein occlusion), but also for macular edema, with subsequent visual acuity compromise. So, ultra-widefield imaging is a very important tool to consider when monitoring these patients because peripheral lesions and areas of nonperfusion are inaccessible to conventional 35º or 50º imaging techniques even resorting to montage of individual images like the ETDRS (Early Treatment Diabetic Retinopathy Study) seven-field protocol.

This case report stresses the importance of careful monitoring and shows the efficacy of the treatment of the macular edema secondary to BRVO with anti-VEGF intravitreal injection, dexamethasone implant intravitreal injection and focal laser photocoagulation in a real-life setting.

QUESTIONS AND ANSWERS

Why did you choose this case?

This is a typical case of a patient with BRVO in a real-life setting treated with anti-VEGF, steroids and laser photocoagulation. However, there are some peculiarities that I would like to stress. Firstly, it has a long follow-up (8 years). Secondly, it is a late referral case. Patients with macular edema secondary to BRVO should be treated promptly. Nevertheless, a late referral should not contraindicate treatment. Indeed, this case shows that patients with BRVO who present with long-standing macular edema may still benefit from delayed treatment. Thirdly, the

patient lived very far away from the hospital facilities and was caring for a relative making optimisation of monitoring and treatment mandatory. The implementation of our modified treat-and-extend protocol with anti-VEGF and later a steroid implant allowed extended monitoring and treatment intervals with effective visual gains. Finally, this case shows that ultra-widefield imaging and targeted laser photocoagulation can be very useful in identifying ischaemic and exudative lesions.

Your department has a specific treatment protocol for retina vein occlusions including branch retinal vein occlusion. it provides for the use of modified treat and extend. Can you explain it?

Modified treat and extend (mTaE) is based on the original TaE, but it further extends the monitorization. In TaE, visits are done at every single treatment. In mTaE, visits are done only after three injections. We acknowledge that the latter may, in some cases, overtreat patients, but the reduction of the number of visits without jeopardising the functional outcome is a huge benefit.

Later the patient developed a ring of hard exudates in the temporal part of the macula and a significant nonperfusion area in the peripheral retina. Still, you did not laser the nonperfused retina, but only the leaking vessels related to the ring of hard exudates. What was the rationale for your decision?

Nonperfused retina may cause macular edema and retinal neovascularization with subsequent compromise of the visual acuity. The bigger the area of nonperfusion in relation to the total area of the retina (Ischemic Index), the bigger the risk of the mentioned complications. But not all nonperfused retinas are equally dangerous. Indeed, in addition to the extent of the area of nonperfused retina, the location and the type of nonperfusion are also factors to be considered. So, a non-perfused retina which is more posteriorly located and surrounded by leaking vessels entails an increased risk of complications. Of course, we must not forget that laser photocoagulation also carries some risks, namely epiretinal membrane formation. So, the benefit for the use of laser photocoagulation needs to be carefully weighed. In this case, we only lasered the leaking vessels related to the circinate ring of exudates, because the area of nonperfusion was very peripheral and relatively limited, making monitoring a viable option.

RESPONSABILIDADES ÉTICAS

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Branch Retinal Vein Occlusion in a Patient with Sarcoidosis: A Case Report

Oclusão Venosa de Ramo da Retina num Doente com Sarcoidose: Relato de Caso Clínico

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ABSTRACT

Sarcoidosis is a multisystemic granulomatous disease that commonly presents with ocular manifestations, chief among them anterior uveitis. However, more rarely, posterior involvement occurs, which can happen in the absence of anterior segment findings. Venous occlusion is a relatively rare presentation of ocular sarcoidosis, but one that must be kept in mind.

We report the case of a young patient presenting with unilateral branch retinal vein occlusion, in which, following an atypical evolution with intravitreal anti-VEGF therapy, a careful history taking revealed a previous diagnosis of sarcoidosis. Only after the start of adequate therapy (systemic corticosteroids) was rapid improvement achieved. This illustrates the importance of adequate history taking in all patients presenting with retinal venous occlusion, and the special need for exclusion of secondary infectious/inflammatory causes in patients presenting with atypical factors, namely age < 50 years.

KEYWORDS: Macular Edema; Retinal Vein Occlusion; Sarcoidosis/complications.

RESUMO

A sarcoidose é uma doença granulomatosa multissistémica que cursa frequentemente com manifestações oculares, primariamente uveíte anterior. Mais raramente, pode ocorrer envolvimento do segmento posterior, que se pode verificar na ausência de alterações do segmento anterior. A oclusão venosa é uma manifestação pouco frequente da sarcoidose ocular, mas que não deve ser esquecida.

Apresentamos o caso de um doente jovem com oclusão venosa de ramo unilateral, que sob terapêutica anti-VEGF intravítrea demonstrou uma evolução atípica. Uma revisão cuidada da história clínica veio a revelar um diagnóstico prévio de sarcoidose, não inicialmente reportado, e só após o início de corticoterapia sistémica se observou uma rápida e franca melhoria clínica.

Este caso sublinha a importância de uma história clínica detalhada em todos os pacientes com oclusão venosa retiniana, sobretudo em casos com características atípicas, como idade inferior a 50 anos, em que a exclusão de causas infeciosas ou inflamatórias secundárias deve ser uma prioridade.

PALAVRAS-CHAVE: Edema Macular; Oclusão da Veia da Retina; Sarcoidose/complicações.

INTRODUCTION

Sarcoidosis is an idiopathic systemic disease that is characterized by noncaseating granulomas, with no histologic evidence of infection or foreign body. Pulmonary manifestations are most common (90%), and the major cause of morbidity, but ocular involvement also frequently occurs, having been reported in up to 60% of patients with systemic sarcoidosis, and is the complaint leading to diagnosis in 10%-20% of patients.[1,2]

Anterior uveitis is the most common ocular manifestation, occurring in two-thirds of ocular sarcoidosis (OS) patients, and accounting for up to 10% of all cases of uveitis. Intermediate and posterior uveitis can also be found less frequently, occurring in less than 20% of patients with OS, although it may be a more common presentation in leucodermic patients.[1-4] Occlusive retinal vascular disease may occur in this context, especially branch retinal vein occlusion, but also less commonly central retinal vein occlusion. This may lead to neovascularization and vitreous hemorrhage if untreated.

Although sarcoidosis has a worldwide distribution, affecting all ethnic groups, it is most common in Northern Europe, primarily Sweden and Denmark, but also in Afro-descendants. A slight female preponderance is noted as well. Onset is more common in young to middle-aged adults (20-50 years), but it is also recognized as a common cause of uveitis in patients aged 60 or older. Indeed, Caucasian patients present more often with late-onset sarcoidosis, and seem more likely to have uveitis, whilst being less likely to have asymptomatic chest radiograph alterations.[4]

CASE REPORT

We performed a retrospective case report by reviewing clinical notes, optical coherence tomography (OCT), retinography and angiography images. A statement of informed consent was obtained from the patient for the publication of the case report and associated images.

We report the case of a Portuguese man in his forties that presented to the emergency department with sudden painless loss of vision in his right eye (RE). He was pseudophakic RE after a cataract had developed following a prolonged course of topical steroids due to viral keratitis, during which he had also developed glaucoma RE. He also had severe dry eye syndrome for which he was using topical cyclosporine. His only systemic medication was hydroxychloroquine for apparently nonspecific cutaneous lesions.

On presentation, he had a best corrected visual acuity (BCVA) RE of 20/40. RE examination revealed normal intraocular pressure (12 mmHg) and no new anterior chamber alterations. Fundus examination revealed retinal hemorrhages and vessel tortuosity compatible with an inferotemporal branch retinal vein occlusion. Left eye examination was unremarkable. There was also associated cystoid macular edema (CME), confirmed on OCT (Fig. 1).

Faced with this apparently obvious diagnosis, prompt intravitreal ranibizumab was administered. However, no improvement was noted. On the contrary, OCT revealed worsening CME after intravitreal treatment, and an inferior serous retinal detachment had developed (Figs. 2 and 3). Fluorescein angiogram was performed and revealed changes compatible with a branch retinal vessel occlusion with no changes in the left eye (Figs. 4 and 5).

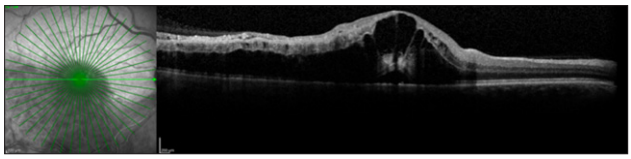

Figure 1. Optical coherence tomography at presentation.

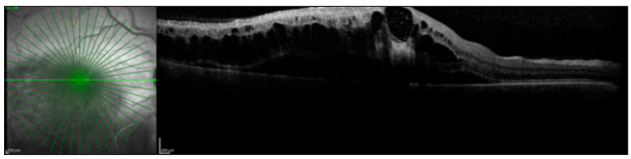

Figure 2. Optical coherence tomography one month after ranibizumab injection.

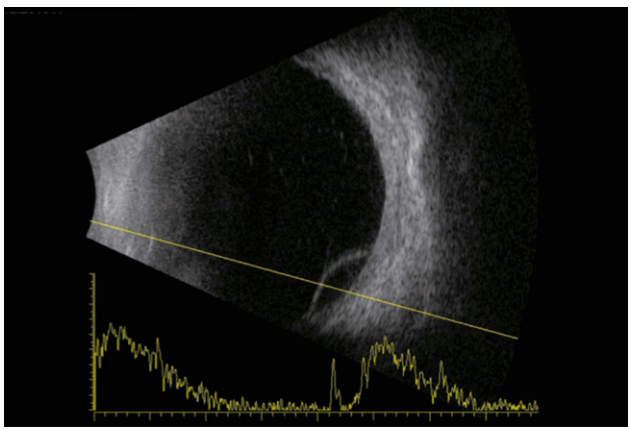

Figure 3. Ocular ultrasound of the right eye revealing an inferior serous detachment.

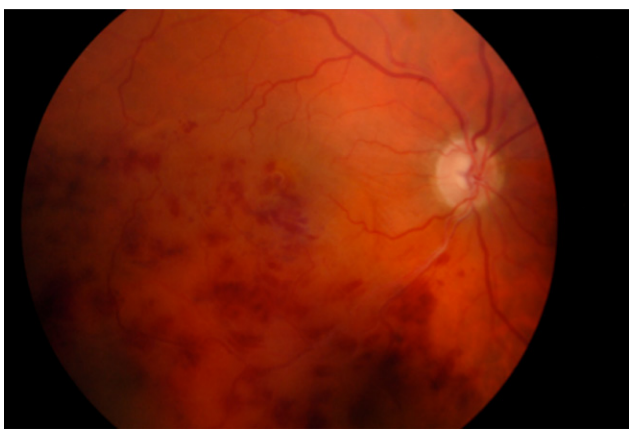

Figure 4. Fundus photograph of right eye at the time of the fluorescein angiogram showing infero-temporal venous tortuosity associated with hemorrhages.

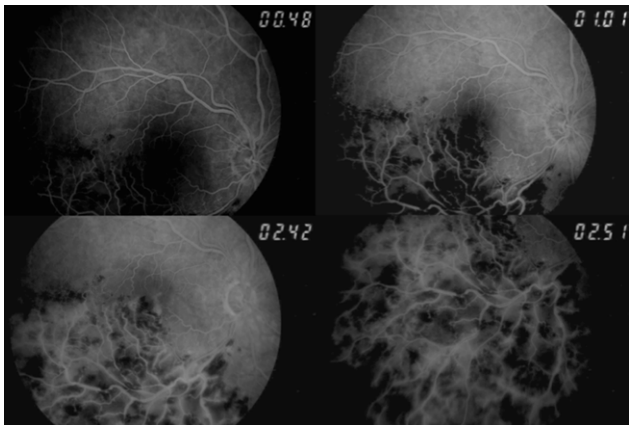

Figure 5. Fluorescein angiogram of the right eye showing diffuse venous leakage in the infero temporal sector associated with masking from the hemorrhages.

Given his age and atypical response to intravitreal anti-VEGF, other diagnosis were considered, namely vasculitis, either infectious, viral, spirochetal or tuberculous, or autoimmune, as well as other masquerade syndromes. He was therefore directed to the Uveitis department for further study.

Blood work revealed normal blood count, normal erythrocyte sedimentation rate, slightly elevated C reactive protein, no alterations in protein electrophoresis or thyroid, renal, or liver function. Titers were negative for antinuclear antibodies (ANA), anti dsDNA, or HBV, HCV, HIV or syphilis testing. Interferon gamma release assay (IGRA) was also requested, and was negative. He was HLA B27 negative. Lupic anticoagulant was weakly positive, but no other alterations were found on thrombophilia testing. An elevated angiotensin converting enzyme (ACE) level (81.2 UI) was found, with normal calcium and lysozyme levels.

A complete history was finally taken, and the patient, when asked, revealed recent evaluation in internal medicine for persistent respiratory symptoms. Indeed, it was uncovered that he had already done a chest computed tomography (CT) that revealed symmetric bilateral hilar lymphadenopathy (BHL) with irregular nodular thickening, followed by a bronchoscopy and bronchoalveolar lavage (BAL). BAL revealed an elevated total cell count with a lymphocyte predominance and a normal amount of eosinophils and neutrophils. Endobronchial biopsy revealed noncaseating granulomas compatible with a diagnosis of sarcoidosis. Skin alterations had also already been biopsied and similarly showed alterations suggestive of sarcoidosis.

Subsequently, having thus established the diagnosis of OS, systemic steroids were promptly started, in a dosage of 1 mg/kg/day prednisone equivalent, followed by gradual tapering to a low dose of long-term corticosteroids. Three monthly 2 mg aflibercept intravitreal injections were also administered, followed by laser photocoagulation of ischemic areas.

Rapid improvement was achieved after starting systemic steroids, with a rapid structural resolution of CME at 3 months of therapy (Fig. 6) and marked functional improvement, with BCVA at 3 months of steroids having improved

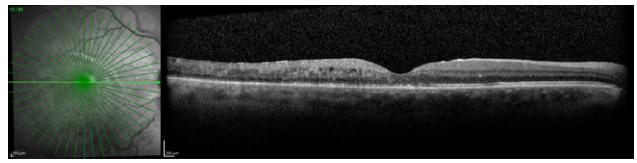

Figure 6. Optical coherence tomography 3 months after start of systemic corticosteroids and monthly aflibercept

to 20/32, and also noting gradual improvement of retinal hemorrhages. Tapering of systemic steroids was possible, with no reoccurring CME or vasculitis after stopping them.

DISCUSSION

While ocular involvement is common in patients with systemic sarcoidosis, posterior segment involvement occurs in less than 20% of patients with OS. Occlusive retinal vein disease may occur in this context, most commonly branch retinal vein occlusion, arising either as an occlusive vasculitis, or more rarely due to compression by a choroidal granuloma.[5]

The clinical presentation, if there is macular involvement, is that of a painless drop in visual acuity, such as described by our patient. On fundus examination, segmental perivenous exudates can be seen, and the thrombosed vein appears a torturous and dilated vessel. Fluorescein angiography confirms venous occlusion whilst detecting potential complications, such as areas of ischemia and the presence of new vessels. All these findings, apart from the neovascularization, were found in our patient.

The IWOS criteria, which have recently been revised, base the diagnosis of OS on the presence of indicative ocular alterations, with suggestive systemic investigation, while ruling out other causes of granulomatous uveitis. They consider definitive OS diagnosis if it is supported by biopsy with compatible uveitis findings; presumed OS if not supported by biopsy but with BHL present, with two intraocular signs; and probable OS even in the absence of BHL but when there are three intraocular signs and two suggestive systemic investigations.[6]

Among these systemic investigations are a negative tuberculin test/IGRA, an elevated ACE, elevated serum lysozyme, an elevated CD4/CD8 ratio in BAL fluid, lymphopenia, suggestive parenchymal lung changes, or a positive positron emission tomography/scintigraphy.[6]

Among intraocular clinical signs of OS are mutton-fat keratic precipitates, iris nodules (Koeppe or Busacca) or trabecular meshwork nodules (Berlin), snowballs/string of pearls vitreous opacities, multiple chorioretinal peripheral lesions, nodular and/or segmental periphlebitis, macroaneurysm in an inflamed eye, optic disc granulomas, solitary choroidal nodule, and also bilaterality of these findings (assessed by ophthalmological examination including ocular imaging showing subclinical inflammation).[6]

This patient, having posterior uveitis and a histological diagnosis, falls under the definitive diagnosis, but he also

had several systemic suggestive findings, besides de BHL, namely the ACE level, negative IGRA, and suggestive parenchymal nodularity.

Systemic corticosteroid therapy, usually in high doses of 1 mg/kg/day prednisone with progressive tapering, is needed at the start of treatment in severe cases (such as in optic neuropathy, CME with BCVA <20/200, or occlusive retinal vasculitis with retinal ischemia), as well as recalcitrant cases or when active systemic disease is present. Other immunosuppressive treatments may be used in different cases of cortico-resistant or cortico-dependent disease, providing control of the disease while minimizing the risks of long-term steroids.

In cases of branch retinal vein occlusion, laser photocoagulation may be indicated when there is significant retinal ischemia, persistent macular edema, or neovascularization, and anti-VEGF is recommended in the presence of macular edema or retinal ischemia.[3,4,7,8]

It is worth noting that these cases of sarcoid uveitis, namely with posterior segment involvement and CME, have typically worse visual prognosis. Other suggested negative prognostic factors are advanced age, black phototype, female gender, underlying chronic systemic disease, multifocal choroiditis, persistent ocular inflammation, and glaucoma.[4]

In this case, the atypical presentation in regards to age should have elicited particular care in history taking. Indeed, although retinal vein occlusion can occur in young patients, with an estimated global prevalence of 0.26% in people age 30–39 years and of 0.44% in people age 40–49 years, it is more commonly associated with risk factors other than hypertension, which is the major risk factor in older patients.[7,9]

Therefore, even though a thorough history taking, arterial pressure measuring and basic blood work with blood count, ERS, lipid panel and HbA1c is recommended in all patients presenting with a venous retinal occlusion; we must remember that in young patients (and in bilateral presentation) further investigation is recommended, namely: factor V Leiden, anti-cardiolipin, lupic anticoagulant, C protein, S protein, antithrombin III and homocysteine, ANA, antineutrophil cytoplasm antibodies, and anti-dsDNA antibodies, and ACE dosing.[7]

When there is clinical suspicion of sarcoidosis, a chest x-ray is still the single best screening test, as it will be altered at some point in 90% of patients in which sarcoidosis is diagnosed, most commonly showing BHL.[1,2] However, these abnormalities do not always persist throughout the disease, and may therefore not be present at the time of workup. As such, high-resolution chest CT may be of interest in patients with normal chest x-ray but for whom a high clinical index of suspicion remains.[3]

CONCLUSION

This case illustrates that retinal vein occlusion can occur in a patient as a complication of sarcoidosis even without iridocyclitis, and thus that a complete history taking is crucial even when faced with an apparently obvious diagnosis of branch retinal vein occlusion, especially when there are atypical factors. Indeed, in young patients with retinal occlusion, an exclusion of secondary causes, namely infectious/inflammatory ones, is mandatory, not only through careful history taking but also blood work. It also illustrates that in these patients with systemic diseases multidisciplinary collaboration is essential for optimal management.

QUESTIONS

How does age change the management in patients with venous occlusion?

n young patients with retinal occlusion an exclusion of secondary causes, namely infectious/inflammatory ones, is mandatory. In patients younger than 55 years old the most common risk factors for venous occlusion in the elderly are not as prevalent and other causes are more likely to be a factor for this disease.

What is the importance of taking a thorough clinical history in patients with venous occlusion?

As this clinical case shows, performing a thorough patient review is of the utmost importance in these patients. Although frequently overlooked, asking for other systemic complaints and reviewing the medical history can lead us to an infrequent secondary cause to a common disease such as retinal venous occlusion.

How important is the collaboration with other medical specialties in these patients?

These patients frequently have other symptoms of the disease, that might have been overlooked or underestimated. It is also common for these patients to need immunosuppression to control ocular inflammation or inflammatory changes elsewhere and thus a multidisciplinary approach is mandatory.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

RF and ID: Conceptualization.

RA: Conceptualization, data collection, analysis and manuscript writing.

JC: Data collection, analysis and manuscript writing.

All authors approved the final version to be published.

RF e ID: Conceptualização.

RA: Conceptualização, recolha de dados, análise e redação do manuscrito.

JC: Recolha de dados, análise e redação do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

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OCT Biomarkers: Driving DME Decision Making

Biomarcadores de OCT: Indicadores de Decisão Terapêutica no EMD

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ABSTRACT

The case report describes a patient with treatment-naïve diabetic macular edema (DME) who was treated according to the guidelines with anti-VEGF as the first-line treatment and was switched to steroid treatment early on, based on OCT biomarkers, despite having good response criteria. The patient underwent six intravitreal injections of ranibizumab, with a reduction in central subfield thickness (CST) of more than 20% and an improvement of 20 letters in visual acuity, which are considered criteria for a good response. However, because he had biomarkers indicating a superior response to steroids, which subsequently deteriorated following anti-VEGF injections, he was treated with a short-acting steroid, resulting in a clear improvement. This case report suggests that the decision-making process for DME treatment options should include evidence-based guidelines, imaging biomarkers, and treatment burden as drivers.

KEYWORDS: Biomarkers; Diabetic Retinopathy; Macular Edema; Tomography, Optical Coherence.

RESUMO

O presente caso descreve um doente com edema macular diabético (EMD) sem tratamento prévio, que foi tratado, de acordo com as orientações, com anti-VEGF como tratamento de primeira linha e que, fez uma substituição precoce para tratamento com esteróides, com base em biomarcadores de OCT, apesar de ter bons critérios de resposta. O doente foi submetido a seis injecções intravítreas de ranibizumab, com uma redução da espessura do central (CST) superior a 20% e uma melhoria de 20 letras na acuidade visual, que são considerados critérios de boa resposta. No entanto, como tinha na visita inicial, biomarcadores que indicavam uma resposta superior aos esteróides, que posteriormente se deterioraram após as injecções de anti-VEGF, foi tratado com um esteroide de curta duração, resultando numa clara melhoria. Este caso clínico sugere que o processo de decisão sobre as opções de tratamento do EMD deve incluir orientações baseadas na evidência, biomarcadores de imagem e o "burden" de tratamento como factores determinantes.

PALAVRAS-CHAVE: Biomarcadores; Edema Macular; Retinopatia Diabética; Tomografia de Coerência Ótica diabético.

INTRODUCTION

Diabetes mellitus is a global health concern. According to the International Diabetes Foundation (IDF), the prevalence of diabetes has been on the rise, with an estimated 537 million individuals aged 20 to 79 years old affected in 2021. By 2045, IDF projections indicate that one in eight adults, or approximately 783 million individuals, will be living with diabetes, representing a 46% increase.[1] Individuals with diabetes are at an increased risk of developing complications, with the most prevalent being kidney failure, cardiovascular pathology, and vision loss. In fact, one-third of individuals with diabetes will experience vision loss due to the disease. Macular edema is the primary cause of vision loss in diabetic patients.[2] A published systematic review revealed that the pooled prevalence of DME was 5.47% (95% CI: 3.66%-7.62%) overall, 5.81% (95% CI: The prevalence of DME was found to range from 0.07% to 18.51% in low-to-middle-income countries, and from 5.14% to 7.15% in high-income countries.[3] The authors propose that, given the global prevalence of diabetes, there is a clear need to inform medical professionals and educate individuals diagnosed with diabetes about the importance of detecting DME early through optical coherence tomography (OCT).[3] The initial definition of diabetic macular edema based on fundus photography was subsequently superseded with the advent of OCT. This technology has made it possible to identify, classify, guide, and follow up the treatment of diabetic macular edema with greater accuracy. The current guidelines for the treatment of diabetic macular edema are still largely based on the measurement of edema thickness using optical coherence tomography (OCT). Nevertheless, several functional OCT biomarkers have already been identified, with the ESASO classification arguably representing the most detailed.[4] Despite the growing body of evidence, there is still no consensus on the prognostic value of biomarkers of better response to treatment with anti-VEGF or corticosteroids. The identification of OCT biomarkers of best response to treatment with anti-VEGF or corticosteroids could potentially alter the decision-making processes underlying current treatment guidelines for diabetic macular edema. A case report is presented of a patient with diabetic macular edema whose treatment decision was based entirely on OCT biomarkers, resulting in an early switch from anti-VEGF to steroid therapy.

CASE REPORT

A 74-year-old man presented to our ophthalmology department for the first time, reporting a progressive decline in his visual acuity. He had been diagnosed with type 2 diabetes one year prior yet had not sought medical attention or undergone any diagnostic procedures for over a decade prior to the diagnosis. He had no other significant medical history. Upon initial examination, the patient exhibited a best-corrected visual acuity (BCVA) of 20/40 in the right eye (RE) and 20/50 in the left eye (LE), with bilateral cataracts. He subsequently underwent cataract surgery on both eyes. One year after cataract surgery, the patient was referred to the diabetic retina clinic. At that time, his BCVA was 20/40 in the right eye and 20/50 in the left eye. Additionally, he exhibited moderate non-proliferative diabetic retinopathy and macular edema in both eyes (380 micron RE, 539-micron LE) with a mild vitreous-retinal traction (VRT) on the right eye. (Fig. 1). The patient underwent fluorescein angiography and

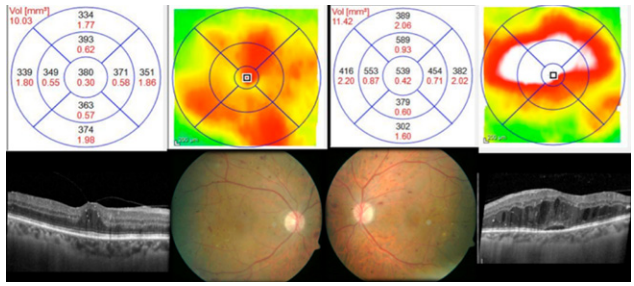

Figure 1. Baseline OCT and CFP of RE (left) and LE (right). On RE: diffuse foci of ME with VRT and few HRF. Moderate NPDR with small hemorrhages and HE. On LE: diffuse ME with central involvement, large cysts, some with hyperreflective content, few HRF, NSD. NPDR with small hemorrhages and HE.

OCT- optical coherence tomography, CFP- color fundus photography, RE- right eye, LE- left eye, ME- macular edema, VRT- vitreoretinal traction, HRF- hyperreflective foci, NPDR- nonproliferative diabetic retinopathy, HE- hard exudates, NSD- neurosensory detachment.

a loading dose of three-monthly injections of ranibizumab (RBZ). Fluorescein angiography demonstrated late macular exudation, significant peripheral microangiopathy, and the absence of peripheral ischemia in both eyes (Fig. 2). Fol-

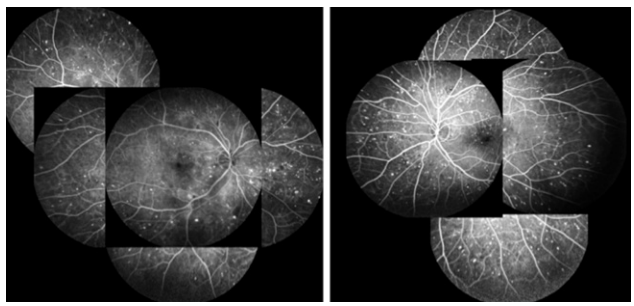

Figure 2. Fluorescein angiography: Both eyes - Late macular exudation, significant peripheral microangiopathy, without peripheral ischemia.

OCT- optical coherence tomography, RBZ- ranibizumab, RE- right eye, LE- left eye, ME- macular edema, VRT- vitreoretinal traction, HRF- hyperreflective foci, NSD- neurosensory detachment, CST- central subfield thickness.

lowing the administration of the loading dose, visual acuity improved to 20/25 in the right eye and 20/40 in the left eye, with a slight reduction in central subfield thickness (CST) on the left eye (Fig. 3). Given the evidence of a functional and anatomical response, the patient underwent three additional monthly intravitreal injections of ranibizumab. Following the sixth dose of RBZ, there was a marked improvement in visual acuity (20/25 RE, 20/20 LE) and CST in the left eye (374

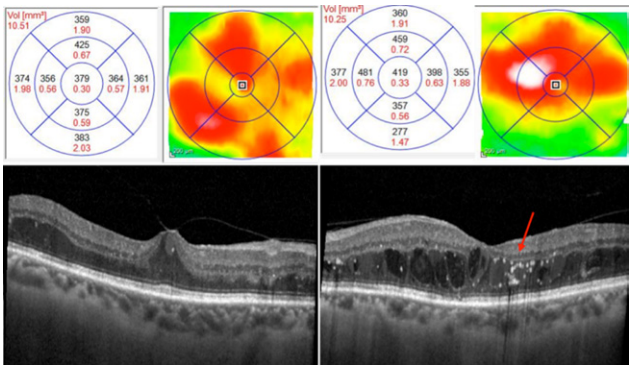

Figure 3. OCT after 3 loading doses of RBZ on RE (left) and LE (right). On RE: slight increase of cysts on the diffuse foci of ME, persistence of VRT and few HRF. On LE: decrease in CST of diffuse ME with central involvement, large cysts, some with hyperreflective content, increase in the number of HRF (red arrow), resolution of NSD.

OCT- optical coherence tomography, CFP- color fundus photography, RE- right eye, LE- left eye, ME- macular edema, VRT- vitreoretinal traction, HRF- hyperreflective foci, NPDR- nonproliferative diabetic retinopathy, HE- hard exudates, NSD- neurosensory detachment.

micron RE, 331-micron LE) (Fig. 4). The OCT and retinography images were analyzed from the baseline to the sixth injection. At baseline, the OCT biomarkers were as follows: RE: Foci of extra-foveal macular edema, small cysts, VRT, few hyperreflective foci (HRF), very small hard exudates (HE); LE: Diffuse macular edema center involving, large cysts with hyperreflective content, few HRF, small HE, and

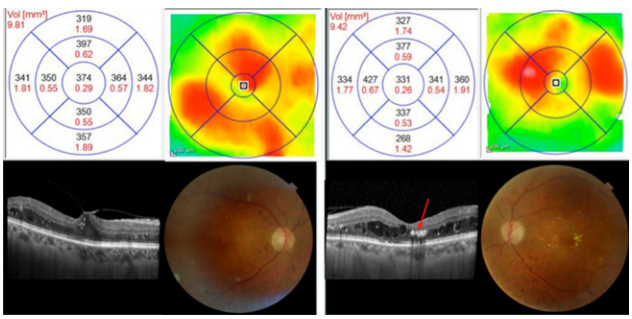

Figure 4. OCT and CFP after the 6th injection of RBZ on RE (left) and LE (right). On RE: slight improvement of diffuse foci of ME with persistence of VRT and a slight increase in HRF number. Moderate NPDR with small hemorrhages, small HE. On LE: great decrease in CST, médium-sized cysts, confluence of HRF in a HE plaque near the fovea (red arrow). Moderate NPDR with small hemorrhages and increased HE.

neurosensorial detachment (NSD). Following the sixth RBZ injection (Fig. 4), no significant alterations were observed in the RE, although a slight increase in the VRT was noted. In contrast, on the left eye, there was a significant reduction in the central subfield thickness (CST), accompanied by a decrease in cyst size and the hyperreflective content within them. Furthermore, NSD resolution was observed, although there was an increase in the HRF, which coalesced into HE plaque near the fovea. Although the response to treatment in the left eye met the criteria for a good response, as defined by the guidelines, with a reduction in CST of more than

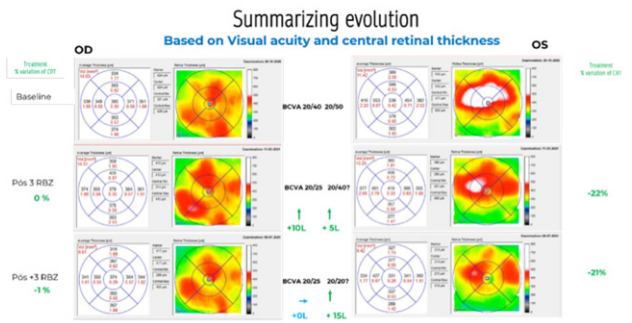

Figure 5. Progression based on visual acuity and central subfield thickness from baseline to after the 6th anti-VEGF injection.

20% and an improvement in visual acuity of 20 letters, the worsening of some imaging biomarkers commonly related to inflammation led to the decision to switch to intravitreal injection of a short-acting steroid (Figs. 5 and 6). The patient was administered an intravitreal injection of a short-acting steroid in both eyes. Three months later, the best-corrected visual acuity (BCVA) was 20/25 in the right eye (RE) and 20/20 in the left eye (LE). The central subfield thickness (CST) exhibited a slight improvement in the right eye (RE) due to a reduction in the vitreous retinal traction (VRT), while the

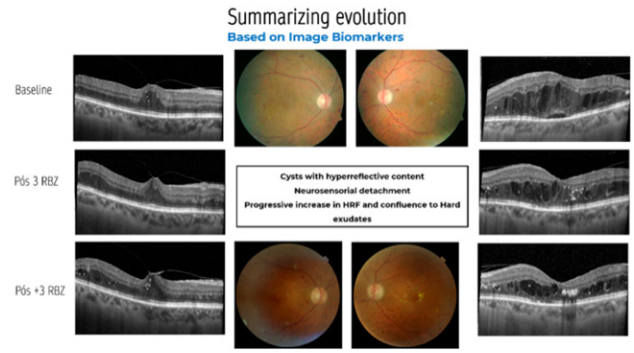

Figure 6. Progression based on image biomarkers from baseline to after the 6th anti-VEGF injection.

OCT- optical coherence tomography; CFP- color fundus photography; RE- right eye; LE- left eye; ME- macular edema; VRT- vitreoretinal traction; HRF- hyperreflective foci; DR- diabetic retinopathy; HE- hard exudates, CST- central subfield thickness.

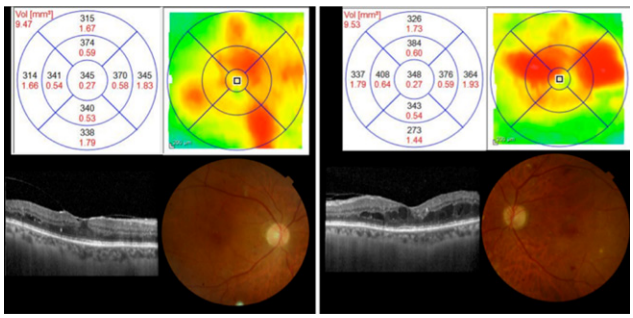

Figure 7. OCT and CFP 3 month after the short acting steroid injection on RE (left) and LE (right). On RE: slight improvement of CST due to a reduction in the VRT, and reduction in the extrafoveal ME and the HRF. On LE: CST remained similar, complete resolution of the HE and reduction of the number of HRF. On both eyes a slight improvement on the DR level with a reduction in the number of hemorrhages observed in the retina.

CST remained similar in the left eye (LE). A reduction in the extrafoveal cystoid macular edema was observed in the right eye. The HE was completely resolved in the LE, and the HRF exhibited a reduction in both eyes. A reduction in the number of hemorrhages observed in the retina was noted (Fig. 7).

DISCUSSION

This clinical case describes how, despite the improvement in the standard parameters of the guidelines, namely CST and visual acuity, with anti-VEGF therapy, other biomarkers in the OCT suggestive of an inflammatory association worsened, leading to the decision to switch early to a steroid, with marked improvement of the anatomic features on OCT, and an extent of the treatment interval. The current recommendations for the treatment of diabetic macular edema, as outlined in the EURETINA guidelines, indicate that treatment should commence with monthly injections of anti-VEGF, with steroids serving as a second-line option or for specific cases.[5] However, diabetic maculopathy has a complex and multifactorial etiology that involves processes of altered permeability, which are highly dependent on VEGF. However, there is a whole cascade of inflammation that contributes to the cellular and neuronal dysfunctions of damage in DME.[6] This may help to explain why the results of anti-VEGF treatments are not always satisfactory. It is often assumed that steroids are the most effective treatment for chronic edema. However, in real-world scenarios, as evidenced by our case report, newly diagnosed diabetic macular edema may not correspond to recent diabetic edema or retinopathy. The identification of biomarkers on OCT for which a correlation with higher levels of inflammatory cytokines has already been demonstrated could lead to a more targeted treatment with the choice of steroid earlier or even as first line, which would change the paradigm of the current guidelines.[7–9] It is also important to note that one of the major problems of treatment with anti-VEGF is the burden of frequent injections. By identifying patients early on who may have a better response to steroids, the number of injections needed to treat DME can be reduced. Although this report demonstrates a clear response to an early switch in treatment based on biomarkers, it is limited by the fact that it is a single case study. In order to be validated, further evidence from a significant sample size is required.

CONCLUSION

In conclusion, the decision-making process for DME treatment options should include evidence-based guidelines, imaging biomarkers, and treatment burden as drivers.

An early decision to treat and switch may result in more effective disease control and a reduction in the associated burden.

FOCAL POINTS FROM THIS REPORT:

This clinical case may raise some questions:

Q1: Anti-VEGF treatment was started. Given the good response to corticosteroids, would it have been beneficial to start corticosteroid treatment immediately?

A1: This is probably an example of a case where corticosteroids could have been used as first line treatment. The guidelines where anti-VEGF is the first line of treatment were followed. However, in real life, as in this example, treatment-naive macular edema may not always represent new diabetic eye disease.

Several clinical factors, such as uncertainty about the true date of onset of diabetes in a patient who was not very compliant with medical follow-up, previous bilateral cataract surgery, and some imaging biomarkers, such as neurosensory detachment, large cysts with hyperreflective content, and some HRF, were already present in the first observation as drivers for the therapeutic decision to use steroids.

Q2: The response to treatment with anti-VEGF met the criteria for a good responder. Should anti-VEGF not have been continued?

A2: The criteria defined for a good responder are limited to visual acuity and central retinal thickness. This can be limiting, as other parameters of severity or risk of disease progression have to be taken into account. In this case, a worsening of the hyperreflective foci was accompanied by the development of hard exudates in close proximity to the fovea, a phenomenon that can be attributed to the rapid resolution of the cystoid macular edema, which was accompanied by the presence of biomarkers of inflammation from the outset. It is also crucial to consider additional parameters, such as the state of perfusion, the level of retinopathy, as well as macular edema not involving the central region. The aforementioned guidelines serve as a framework for clinical decision-making, but the optimal treatment plan for a given patient is one that integrates the available clinical and imaging information to provide a comprehensive and individualized approach.

Q3: What are the advantages of the approach in this clinical case?

A3: The decision to make an early switch to steroids was based on imaging biomarkers, which allowed for a more rapid resolution of macular edema, an improvement in biomarkers, an improvement in the level of diabetic retinopathy, and an extension of the treatment interval. These outcomes have clear clinical and burden benefits.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

LD: Conceptualization, data collection, analysis, manuscript writing and reviewing.

MR and RS: Reviewing.
All authors approved the final version to be published.

LD: Conceptualização, recolha de dados, análise, redação e revisão do manuscrito.
MR e RS: Revisão.
Todos os autores aprovaram a versão final a ser publicada.

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Targeted Retinal Photocoagulation to Peripheral Retinal Ischemia for Recurrent Diabetic Macular Edema: A Case Report

Fotocoagulação Eletiva de Áreas de Isquemia Retiniana Periférica no Tratamento do Edema Macular Diabético Recorrente: Um Caso Clínico

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ABSTRACT

We report a case of recurrent diabetic macular edema (DME) associated with peripheral retinal ischemia, which subsided only after adjunctive targeted retinal photocoagulation (TRP).

A 32-year-old man presented with painless persistent vision loss OS and progressive visual acuity decrease OD for months despite intravitreal anti-vascular endothelial growth factor (anti-VEGF). He had been diagnosed with diabetes mellitus type 1 and developed non-proliferative diabetic retinopathy (NPDR) and DME bilaterally. Clinical examination revealed severe NPDR OD and vitreous hemorrhage OS. After vitrectomy was performed in the left eye, treatment with bilateral anti-VEGF injections was initiated following a treat and extend strategy. Only after completion of TRP was it possible to extend beyond 8 weeks.

Despite the latest evidence suggesting that photocoagulation of ischemic peripheral retina does not reduce the number of intravitreal injections in DMO, this report emphasizes that TRP may be an effective treatment strategy in recurrent DME cases.

KEYWORDS: Diabetic Retinopathy; Intravitreal Injections; Ischemia; Laser Coagulation; Macular Edema.

RESUMO

Descrevemos um caso de edema macular diabético (EMD) recorrente associado a isquemia retiniana periférica e tratado com fotocoagulação retiniana adjuvante.

Trata-se de um doente do sexo masculino com 32 anos diagnosticado com diabetes *mellitus* tipo 1, retinopatia diabética não proliferativa e EMD bilateralmente. Apresentava perda de acuidade visual persistente e indolor à esquerda, bem como diminuição progressiva da acuidade visual à direita com meses de evolução apesar do tratamento com injeções intravítreas de anti-fator de crescimento vascular endotelial (anti-VEGF). À observação confirmou-se a presença de retinopatia diabética não proliferativa grave à direita e hemovítreo à esquerda. Após realização de vitrectomia à esquerda, iniciou-se tratamento bilateral com injeções intravítreas de anti-VEGF

em regime treat-and-extend. Somente após completar fotocoagulação eletiva de áreas de isquemia retiniana periférica, foi possível aumentar os intervalos de tratamento acima de 8 semanas.

Apesar de estudos recentes demonstrarem que a fotocoagulação retiniana não reduz o número de injeções intravítreas no tratamento do EMD, este caso clínico evidencia que a fotocoagulação eletiva de áreas de isquemia retiniana periférica poderá ser eficaz no tratamento de casos recorrentes.

PALAVRAS-CHAVE: Coagulação a Laser; Edema Macular; Injecções Intravítreas; Isquemia; Retinopatia Diabética.

INTRODUCTION

Diabetic macular edema (DME) is the most frequent cause of vision loss in patients with diabetes.[1-3] According to a meta-analysis, 10.2% of individuals with diabetes had diabetic retinopathy, and 6.81% had DME.[2]

The development of DME is intricately linked to ischemic changes, retinal microangiopathy, and inflammation.[2] Retinal hypoxia and inflammation triggers the overproduction of vascular endothelial growth factor (VEGF) and other vasoactive cytokines, resulting in a compromised blood-retinal barrier and increased retinal vessel permeability, which ultimately contributes to DME.[3,4]

Previous studies have established a correlation between the degree of peripheral retinal ischemia and the presence and responsiveness of DME.[3,5] Moreover, ultra-widefield fluorescein angiography (UWFA) enables a better detection of peripheral retinal ischemia, which may have direct implications in the diagnosis, follow-up and treatment such as targeted peripheral photocoagulation (TRP).[3]

In the management of DME, long-term suppression of VEGF using intravitreal injection of anti-VEGF agents reduces DME and improves visual acuity. However, there is a high rate of recurrence, and frequent injections are required to prevent vision loss.[2,4]

Several clinical trials have explored the role of targeted retinal photocoagulation (TRP) in areas of capillary nonperfusion guided by UWFA to prevent the development of DME. Despite the initial evidence implying that TRP could decrease treatment burden, two recent randomized controlled trials (RCT) concluded that there was no evidence that a combination therapy with anti-VEGF and TRP improved visual outcomes or reduced treatment burden.[1,2,4,6]

We present a case of recurrent DME associated with peripheral retinal ischemia, highlighting the challenges in managing such cases and the potential role of laser photocoagulation in improving outcomes.

CASE REPORT

A 32-year-old man with a history of poorly controlled type 1 diabetes mellitus and chronic kidney disease presented with painless persistent vision loss in his left eye (OS) and progressive visual acuity decrease in his right eye (OD) for several months despite receiving intravitreal anti-VEGF therapy. He had been diagnosed with non-proliferative diabetic retinopathy (NPDR) and DME bilaterally. Best corrected visual acuity (BCVA) was 20/32 OD and hand motion OS. Intraocular pressure (IOP) was 12 mmHg OD and 14 mmHg OS. Clinical examination revealed severe NPDR OD (Fig. 1),

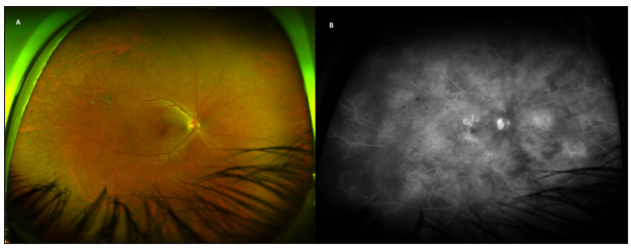

Figure 1. (A) Ultra-widefield fundus photograph OD with severe NPDR; (B) Ultra-widefield fluorescein angiography OD with extensive areas of capillary non-perfusion in the four quadrants and macular edema.

and rubeosis iridis with vitreous hemorrhage OS. Fluorescein angiography (FA) demonstrated retinal leakage from multiple microaneurysms within the macular region, alongside areas of capillary non-perfusion spanning all four quadrants (Fig. 1). Optical coherence tomography (OCT) imaging confirmed the presence of DME (Fig. 2).

Following vitrectomy with fibrovascular proliferation peeling and endolaser in the left eye, bilateral anti-VEGF

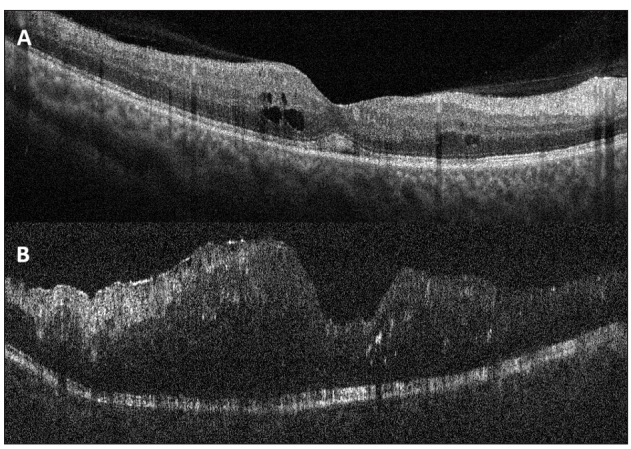

Figure 2. (A) OCT OD showing EMD with intraretinal cysts and subretinal fluid; (B) OCT OS with EMD.

injections were administered using a treat-and-extend strategy. Despite receiving a total of 16 aflibercept injections over a span of 2 years, the patient's DME persisted, and treatment intervals could not be extended beyond 8 weeks. Considering the significant areas of peripheral retinal ischemia demonstrated by FA, the presence of severe NPDR and poor glycemic control, targeted laser photocoagulation in the ischemic areas was initiated.

After completion of laser treatment, there was a remarkable reduction in macular edema, allowing for extension of treatment intervals beyond 8 weeks without recurrence of edema. At the last follow-up visit, BCVA had improved to 20/25 OD and 20/64 OS, with bilateral intraocular pressures of 16 mmHg. Rubeosis iridis was absent in both eyes. OCT showed residual perifoveal cystoid spaces OD and no edema OS (Fig. 3). OCT-angiography revealed extensive areas of capillary non-perfusion bilaterally (Fig. 4).

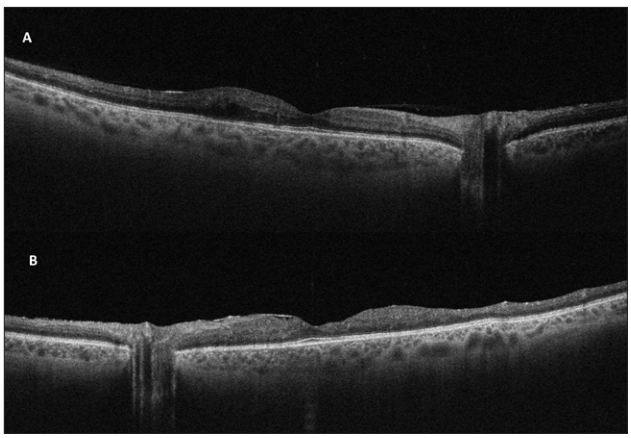

Figure 3. (A) OCT OD showing residual temporal parafoveal intraretinal cysts; (B) OCT OS without signs of EMD.

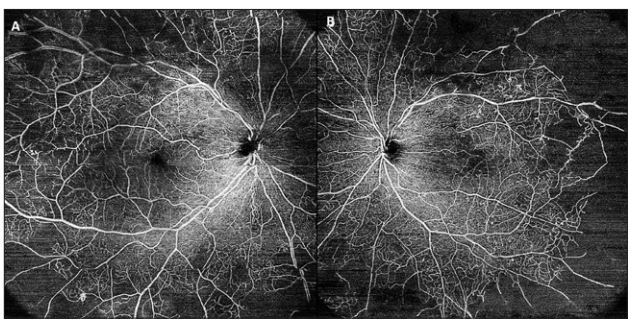

Figure 4. (A) OCT angiography OD revealing areas of capillary non-perfusion; (B) OCT angiography OS revealing areas of capillary non-perfusion.

DISCUSSION

The management of recurrent DME under anti-VEGF therapy poses a significant clinical challenge. Although intravitreal injections effectively treat DME, they fail to target the ischemic areas and the hypoxic drive triggering VEGF production. Relying solely on intravitreal anti-VEGF injections imposes a long-term and burdensome treatment approach on patients.[1]

Several clinical trials were conducted in recent years based on the hypothesis that TRP would reduce VEGF production in ischemic retinal areas, subsequently decreasing the burden of intravitreal injections in DME treatment.[2]

Takamura *et al* conducted a 6-month RCT comparing DME treatment with bevacizumab versus TRP plus bevacizumab. They found that the addition of TRP in areas of capillary non-perfusion was more effective in maintaining a reduced central retinal thickness in patients with DME.[6] Similarly, in our case, the adjunctive use of laser photocoagulation targeting peripheral retinal ischemia led to a significant improvement in macular edema and allowed for extension of treatment intervals.

On the other hand, Brown *et al* demonstrated in a 3-year RCT that there was no evidence that TRP combined with ranibizumab improved visual outcomes or reduced treatment burden compared to ranibizumab alone.[4] Additionally, Cornish *et al* conducted a RCT comparing aflibercept monotherapy against TRP associated with aflibercept for treating DME over a 24-months period.[1] Despite its low completion rate, they concluded that the addition of targeted retinal laser photocoagulation to areas of retinal ischemia did not reduce treatment burden of DME compared with intravitreal aflibercept treatment alone.[1]

This case report highlights the potential efficacy of laser photocoagulation as an adjunctive therapy in select cases of recurrent DME associated with peripheral retinal ischemia. Furthermore, it emphasizes the importance of a multifaceted approach tailored to individual patient characteristics and disease phenotypes in optimizing treatment outcomes.

In conclusion, while anti-VEGF therapy remains the cornerstone in the management of DME, clinicians should consider the role of adjunctive treatments such as laser photocoagulation, particularly in cases refractory to anti-VEGF therapy. Further studies are warranted to elucidate the optimal treatment strategies for recurrent DME with peripheral retinal ischemia.

QUESTIONS

To what extent did this case change your treatment approach in patients with recurrent DME?

This case demonstrated that in select cases TRP for peripheral retinal ischemia may help achieve a better control of recurrent DME after anti-VEGF injections. In such cases, we should pay attention to ischemic areas in the peripheral retinal, striving for a patient-tailored treatment approach.

What additional imaging modalities would you recommend in similar cases?

Ultra-widefield fluorescein angiography plays a crucial role in identifying areas of peripheral retinal ischemia associated with the pathogenesis of DME. These peripheral areas may otherwise go unnoticed in standard 7-field imaging.

What other benefits does TRP have in the management of DR?

Besides contributing to a better control of DME in cases associated with peripheral retinal ischemia, TRP may also be considered earlier in severe NPDR to prevent progression towards proliferative DR in patients with poor compliance or uncontrolled diabetes mellitus, for example.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

All authors contributed equally and approved the final version to be published.

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Managing Severe Proliferative Diabetic Retinopathy and Macular Edema in the Postpartum Period: A Case Report

Tratamento da Retinopatia Diabética Proliferativa Grave e do Edema Macular no Período Pós-Parto: Relato de Caso

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ABSTRACT

The incidence of diabetic retinopathy (DR) is increasing and diabetes mellitus type 2 (T2DM) accounts for most cases. However, diabetes mellitus type 1 (T1DM) is associated with more severe ocular complications, and it is estimated that 80% of patients will develop DR after 15 years of disease. Pregnancy can hasten DR progression, with worst prognosis in T1DM patients. In this case report, we illustrate a severe case of proliferative DR and macular edema in a T1DM patient during postpartum period, managed successfully with anti-VEGF intravitreal injections and PRP.

KEYWORDS: Diabetes Mellitus, Type 2; Diabetic Retinopathy; Macular Edema; Pregnancy.

RESUMO

A retinopatia diabética (RD) tem uma incidência crescente, principalmente atribuível a diabetes *mellitus* (DM) tipo 2. No entanto, a DM tipo 1 está associada a complicações oculares mais severas e estima-se que 80% dos doentes irão desenvolver RD após 15 anos de doença. O período da gravidez pode contribuir para a progressão de RD, com pior prognóstico nas doentes com DM tipo 1. Neste caso clínico tencionamos ilustrar um caso de RD proliferativa severo com edema macular numa doente no período pós-parto, com DM tipo 1, que foi tratada com sucesso com injeções intravítreas de anti-VEGF e fotocoagulação panretiniana.

PALAVRAS-CHAVE: Diabetes Mellitus, Tipo 2; Edema Macular; Gravidez; Retinopatia Diabética

INTRODUCTION

Although type 2 diabetes mellitus (T2DM) accounts for 90% to 95% of the diabetic population, type 1 diabetes mellitus (T1DM) presents a higher risk of severe ocular complications. Up to 80% of T1DM patients have diabetic retinopathy (DR) after 15 years of disease and proliferative diabetic retinopathy (PDR) is present in about 67% of these patients who have had diabetes for 35 years.[1]

When appropriate glycemic control is not established, pregnancy can hasten retinopathy progression, resulting in a particularly aggressive form of the disease.[2] Prevalence of DR in early pregnancy in T2DM has been reported as 14% while in T1DM ranges between 34% and 72%, associated with a worst prognosis.[3-5] In this report, we present a severe case of PDR and macular edema in a postpartum woman with T1DM.

CASE REPORT

Patient information: A 28-year-old postpartum woman presented to the ophthalmology emergency department with complaints of bilateral blurred vision over the last 3 months. She was diagnosed with T1DM at the age of four years old. Over the subsequent years, she maintained inadequate glycemic control and hemoglobin A1c (HbA1c) ranged between 10% and 12%. She had an eight years history of arterial hypertension fand a previous pregnancy complicated with pre-eclampsia five years before.

Clinical findings: At presentation the best corrected visual acuity (BCVA) was 0.3/1.0 on the right eye (RE) and 0.2/1.0 on the left eye (LE) using Snellen's acuity chart, with an intraocular pressure of 18 mmHg in both eyes. Anterior segment observation was unremarkable. Fundus examination revealed multiple scattered retinal hemorrhages, hard and soft exudates, and presence of retinal neovascularization elsewhere (NVE), surrounded by concentric lipid exudation in both eyes (Fig. 1).

Fluorescein angiography (FA) showed severe ischemia with macular involvement and widespread NVE leaking into the vitreous. Additionally, optical coherence tomography (OCT) imaging displayed macular edema in both eyes (Fig. 2).

Therapeutic intervention: The patient was assigned to combined therapy with 3 monthly anti-vascular endothelial growth factor (anti-VEGF) bevacizumab 1.25 mg/0.05 mL intravitreal injections and panretinal photocoagulation (PRP). After treatment completion, BCVA improved to 0.4/1.0 on both eyes, despite retinal structural changes present in OCT imaging (Fig. 3). During follow-up, the patient was also evaluated with routine FAs and due to the severity and persistence of ischemia a top-up PRP was required.

After 9 months of follow-up the VA of the LE started decreasing due to the progression of a posterior subcapsular cataract. The patient underwent phacoemulsification with intraocular lens implantation and the uncorrected VA improved to 1.0 on the LE.

After 18 months of follow-up a small tuft-shaped neovascular lesion appeared on the posterior pole of the RE and the patient was given 3 monthly anti-VEGF bevaci-

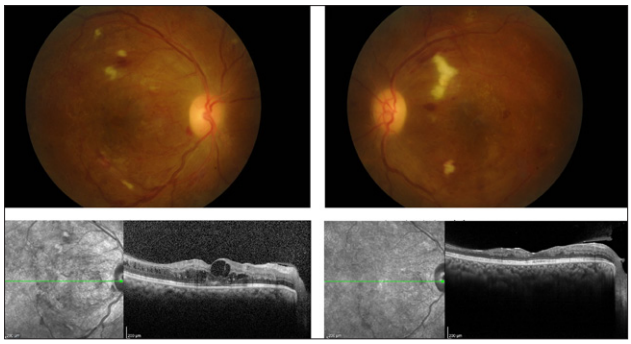

Figure 1. Fundus examination disclosing multiple scattered retinal hemorrhages, hard and soft exudates, lipid exudation and presence of retinal neovascularization in both eyes. OCT imaging displaying macular edema in both eyes.

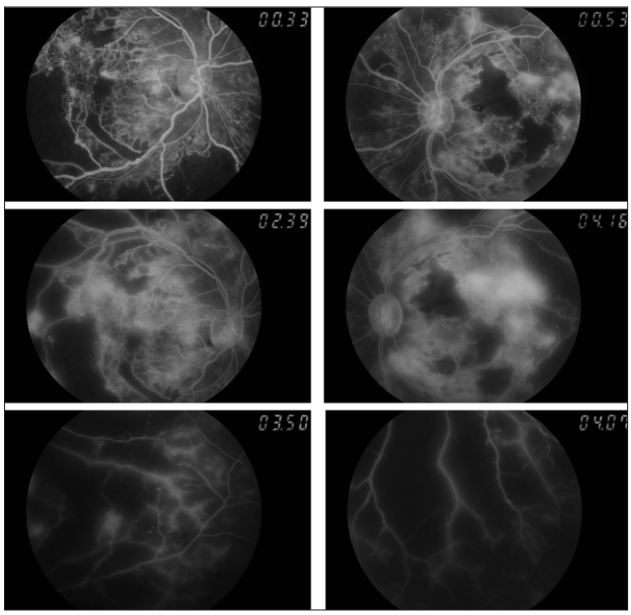

Figure 2. FA images showing severe ischemia with macular involvement and widespread NVE leaking into the vitreous.

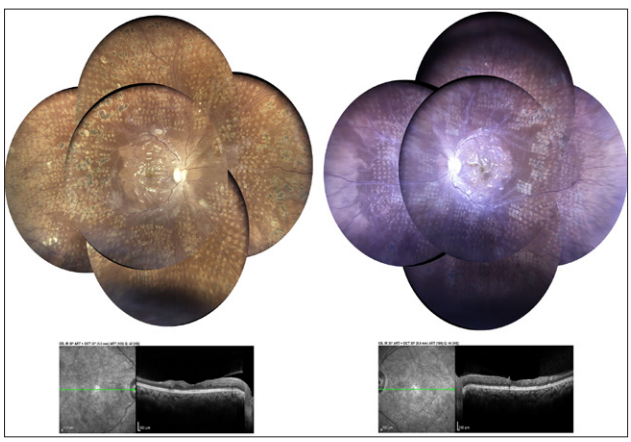

Figure 3. OCT presenting retinal structural changes after combined therapy with PRP and anti-VEGF.

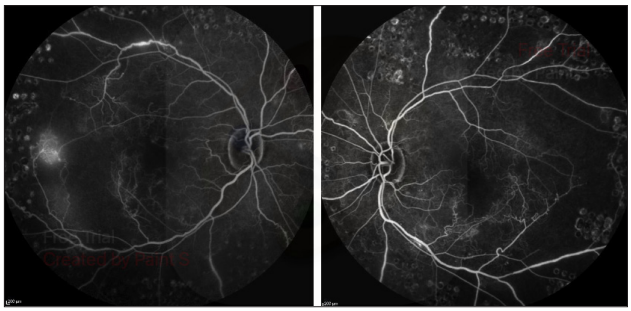

Figure 4. FA with evidence of a small tuft-shaped neovascular lesion at 18 months of follow-up.

zumab 1.25 mg/0.05 mL intravitreal injections and resolution of the lesion was observed (Fig. 4).

On the 24th month of follow-up the FA shows no sign of retinal neovascularization.

DISCUSSION

The effect of pregnancy in DR depends largely on the status of the patients' DR at the start of the pregnancy.[2] Prepartum ophthalmological examination and PRP in PDR would be the optimal management for a patient with previous PDR.[2] There are several known risk factors for DR progression during pregnancy such as duration of diabetes, metabolic control, baseline severity of DR and presence of other cardiovascular diseases such as arterial hypertension.[5]

According to the American Academy of Ophthalmology, International Council of Ophthalmologists and the Royal College of Ophthalmologists, DR examination in pregnant women should occur before conception, in the first trimester soon after conception, at 28 weeks gestational age if the first examination was normal and at 16 to 20 weeks if any DR at initial visit.[6-8] Use of anti-VEGF is controversial during pregnancy due to risk of teratogenicity and should be avoided. However, laser treatment is considered safe and is advised to prevent vision loss during pregnancy.[5-8] Additionally intravitreal treatment with corticosteroid implants may be a safe modality for managing severe diabetic macular edema.[9]

A recent meta-analysis on patients with severe PDR indicated that combined therapy of PRP with anti-VEGF attenuates the central macular thickness and decreases the risk of progression and future vitrectomy.[3]

In our case, the patient presented late to the Ophthalmology department. However, combined therapy was successful in improving BCVA and retinal ischemia signs. Also, our case enhances the importance of glycemic control before and during pregnancy, especially in women with previously diagnosed DR, since it can trigger its progression.

QUESTIONS

What are the main challenges in managing diabetic retinopathy (DR) during pregnancy?

As exemplified in this case, pregnancy is a risk factor for the progression of DR, especially in women with type 1 diabetes mellitus (T1DM), who have poor metabolic control and prolonged disease duration. The mechanism underlying the progression of DR during pregnancy is multifactorial. Preconception care is essential to reduce the possibility of complications for both the mother and the developing fetus. On the other hand, the follow-up of young patients with chronic diseases is more complex as these individuals often have other systemic comorbidities and present a greater risk of non-adherence to medical follow-up.

What were the main challenges in approaching proliferative diabetic retinopathy (PDR) in this case?

Although the main treatment for PDR remains panphotocoagulation (PRP), the role of anti-VEGF has become increasingly important, with Protocol S demonstrating a lower rate of vitrectomy in patients treated with anti-VEGF compared to a PRP group.

The combined approach seems to provide the best visual results and good control of these patients, having achieved a good visual result in this challenging case.

It is, therefore, essential to carry out ophthalmological follow-up before and during pregnancy in patients with T1DM. What is the current protocol?

At our institution, we establish a follow-up plan, after the first appointment, which should be carried out as early as possible during pregnancy.

If the pregnant woman does not present DR, she will be re-evaluated at 28 weeks (in 3-6 months). If she shows signs of DR, she will be re-evaluated at 16-20 weeks, with frequency depending on the severity (mild 3-6 m, moderate 1-3 m, severe 1-2 m). Cases of PDR are monitored for at least 6 months after birth.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

PS, MSG: Writing, literature research and editing of the manuscript.

BB: Review and supervision of the manuscript.

All authors approved the final version to be published.

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BB: Revisão e supervisão do manuscrito.

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Diabetic Macular Edema Management and Coexisting Heart Disease: Case Report

Tratamento do Edema Macular Diabético e Doença Cardíaca Coexistente: Relato de Caso

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ABSTRACT

The risk of cardiovascular disease (CVD) is greater in diabetic retinopathy (DR) patients, particularly in diabetic macular edema (DME) and proliferative DR (PDR). Anti-vascular endothelial growth factor (VEGF) agents are contraindicated in CVD.

A 39-year-old male patient followed at the DR department developed moderate DR with DME. Treatment was started with an intravitreal dexamethasone implant (DEXi), to which the DME was responsive but dependent. A total of 6 injections were performed before a rare complication occurred. The DEXi was inadvertently injected into the lens, promptly resolved by early cataract surgery. A switch to fluocinolone acetonide intravitreal implant (Fac) restituted VA and resolved DME.

Corticosteroid intravitreal injections should be employed as first-line treatment for DME in the coexistence of strong CVD.

KEYWORDS: Cardiovascular Diseases; Diabetic Retinopathy; Glucocorticoids/therapeutic use; Macular Edema.

RESUMO

O risco de doença cardiovascular (DCV) é maior nos doentes com retinopatia diabética (RD), particularmente no edema macular diabético (EMD) e na RD proliferativa (RDP). Os agentes anti-fator de crescimento endotelial vascular (VEGF) estão contra-indicados na DCV. Um doente do sexo masculino, de 39 anos, seguido no departamento de RD, desenvolveu RD moderada com EMD. O tratamento foi iniciado com um implante intravítreo de dexametasona (DEXi), ao qual o EMD respondeu mas tornou-se dependente. Foi efectuado um total de 6 injecções intravítreas antes de ocorrer uma complicação rara. O DEXi foi inadvertidamente injetado no cristalino, o que foi prontamente resolvido por uma cirurgia de cataratas. A mudança para o implante intravítreo de acetonido de fluocinolona (Fac) restabeleceu a AV e resolveu o EMD. As injecções intravítreas de corticosteróides devem ser utilizadas como tratamento de primeira linha para o EMD na coexistência de DCV forte.

PALAVRAS-CHAVE: Doenças Cardiovasculares; Edema Macular; Glucocorticóides/uso terapêutico; Retinopatia Diabética.

INTRODUCTION

The relative risk of cardiovascular disease (CVD) is greater in diabetic retinopathy (DR) patients with the incidence of CVD in DR estimated at 44.64 per 10 000 person-months.[1] In particular, patients with diabetic macular edema (DME) and proliferative DR (PDR) are more likely to have incident CVD and fatal CVD compared with those without DME or PDR.[2]

While anti-vascular endothelial growth factor (VEGF) agents are mostly chosen as a first-line treatment, a history of myocardial infarction or cardiovascular accident in the preceding 6 months limits their use.[3] As such, there is an important role for corticosteroids in the treatment algorithm for DME in this population.

We report a case of DME in a young patient with a strong CVD history who was successfully treated with intravitreal corticosteroid therapy.

CASE REPORT

A 39-year-old male patient presented for routine DR screening, denying any visual complaints. He had type 1 diabetes for 15 years, with glycated hemoglobin (HbA1C) at 7%, under insulin therapy. He had a past medical history of an acute coronary stroke 6 months preceding his appointment. Regarding ocular history, he had right eye (RE) refractive amblyopia.

On the ophthalmological exam, visual acuity (VA) was 0.5/10 in the RE and 10/10 in the left eye (LE). Only microaneurysms were visible at fundoscopy, so he was diagnosed with mild DR without DME. Routine optical coherence tomography (OCT) performed at presentation confirmed normal macular architecture without intraretinal cysts or subretinal fluid (central retinal thickness [CRT] 272 µm RE and 259 µm LE) (Fig. 1). He was advised to optimize control of blood glucose levels, arterial tension and lipid profile, while maintaining a balanced diet and active lifestyle.

One year later, he maintained the aforementioned VA but retinal hemorrhages were also observed in the fundus, and LE OCT revealed small perifoveal intraretinal cysts (CRT 256 µm; European School for Advanced Studies in Ophthalmology [ESASO] T0, C1, E0, D0, H0, F0, V2). A diagnosis of moderate DR with very early focal DME was made (Fig. 2).

A follow-up was scheduled 6 months later with fluorescein angiography (FA). LE visual acuity dropped to 8/10. The fundus maintained a similar appearance, while the LE OCT showed a large intraretinal foveal cyst (CRT 359 µm; ESASO T2, C3, E0, D0, H0, F0, V2 – advanced DME). FA revealed hyperfluorescent dispersed microaneurysms, intraretinal hemorrhages with a mask effect and peripheral capillary non-perfusion in both eyes (Fig. 3). Early panphotocoagulation guided by FA was performed over those ischemic areas.

Six months later, visual acuity was 0.5/10 in the RE and 7/10 in the LE. At LE fundoscopy a diffuse macular edema was observed with significant retinal thickening on OCT (CRT 735 µm; ESASO T2, C3, E1, D0, H1, F1, V2 – advanced DME) (Fig. 2). The assistant Cardiologist was consulted regarding the possibility of starting anti-VEGF treatment, which was denied due to the history of 2 additional acute coronary syndromes over the last one and a half years. The patient was proposed for an intravitreal dexamethasone implant (DEXi).

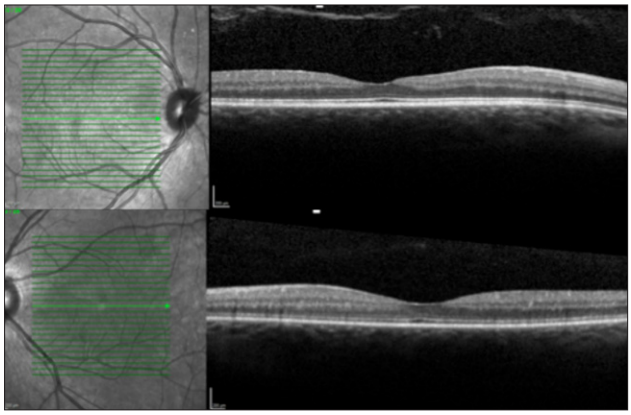

Figure 1. OCT at presentation (RE and LE, respectively).

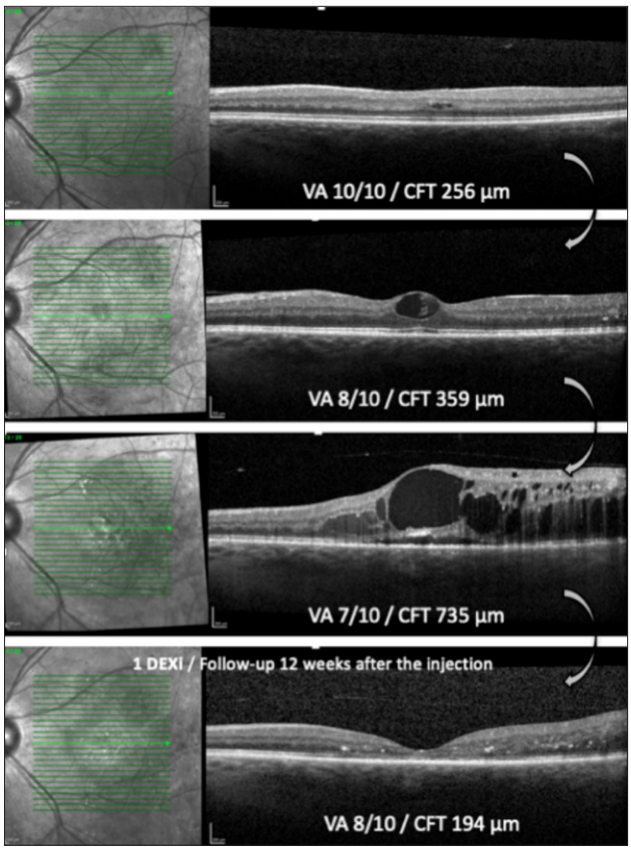

Figure 2. LE OCT during follow-up for DME treatment.

Three months after DEXi injection, LE visual acuity improved to 8/10 with a total resolution of DME confirmed by OCT (CRT 194 µm; ESASO T0, C0, E1, D0, H1, F0, V2) (Fig. 2). A treat and extend regimen were initiated with follow-up intervals of 12 to 16 weeks. A favorable response was obtained with all the next 5 DEXi, however treatment

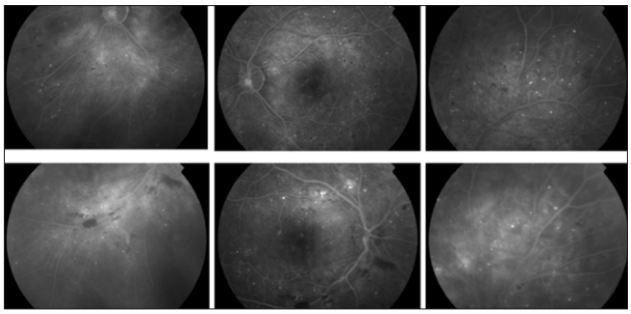

Figure 3. FA at 1.5 years follow-up (RE superior and LE inferior).

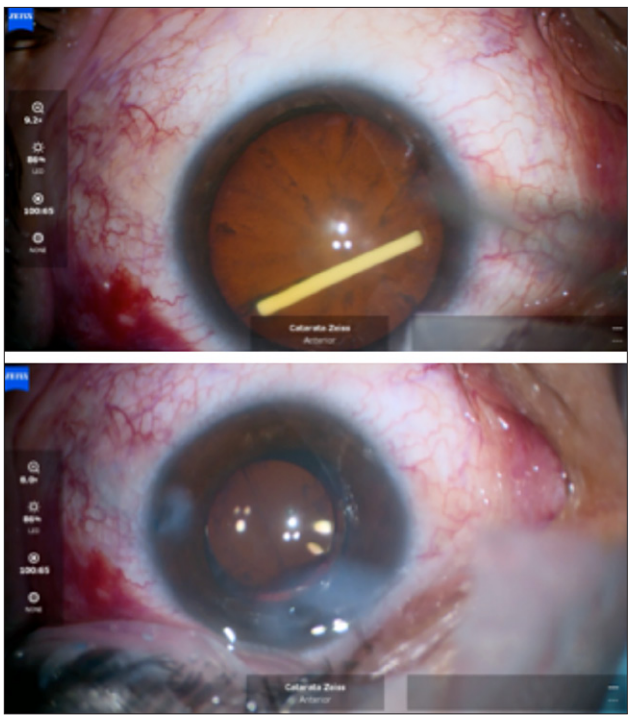

Figure 4. LE DEXi inadvertently injected into the lens, during and after cataract surgery.

intervals could not be extended further than 16 weeks. During this period, intraocular pressure (IOP) was normal, and no peripapillary retinal nerve fiber layer (RNFL) defects or visually significant cataract developed.

At the sixth injection, the DEXi was inadvertently injected into the lens (Fig. 4). The patient underwent early cataract surgery, implant removal and intraocular lens (IOL) implantation. LE visual acuity dropped to 5/10 and significant worsening of macular edema (CRT 772 µm; ESASO T2, C3, E1, D0, H1, F0, V2 – advanced DME). Treatment was proposed with fluocinolone acetonide intravitreal implant (Fac).

One month after Fac injection, LE VA had improved to 7/10 and DME was regressing (CRT 567 µm), with resolution 3 months after Fac injection (CRT 209 µm; ESASO T0, C1, E1, D0, H1, F0, V2) (Fig. 5). IOP remained within normal values during treatment.

Throughout follow-up, RE was monitored with clinical examinations, OCT and FA. VA was stable at 0.5/10 (refractive amblyopia), IOP was normal, and OCT showed no diabetic maculopathy with CRT between 266-302 µm, which

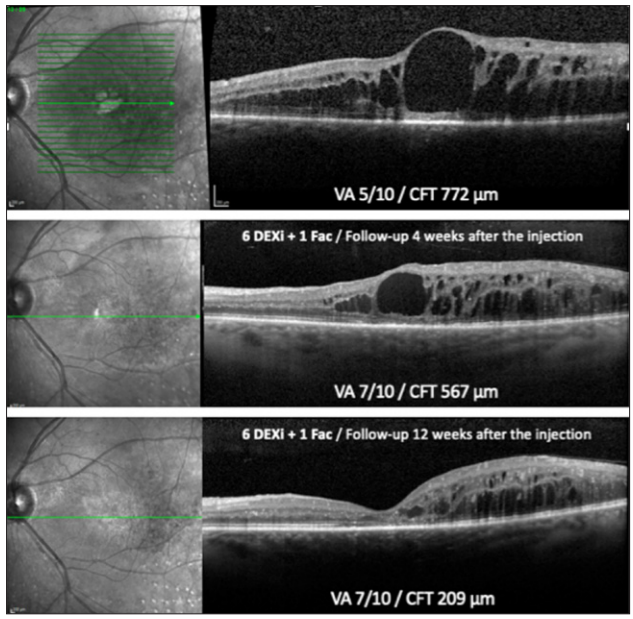

Figure 5. LE OCT during follow-up after Fac implantation for DME.

did not require ocular treatment.

DISCUSSION

According to the Portuguese DR guidelines, the use of corticosteroids as a first-line therapy in DME should be considered in patients with severe cardiovascular risk and/or a history of myocardial infarction or stroke in the preceding 3 months.[3]

Also, when there is a significant inflammatory component, it should be considered earlier, for example, advanced maculopathy by the ESASO classification or OCT biomarkers of exsudation and inflammation (large cysts, hyperreflective foci and subretinal central fluid).[3]

In our case, the patient fulfilled all of the criteria mentioned above, showcasing both a cardiovascular and an inflammatory profile.

The most frequent adverse effects associated with intravitreal corticosteroids are the development of cataracts and increased intraocular pressure.

Regarding cataract-related adverse events, the foundation MEAD and FAME trials report an incidence of 67.9% (DEXi 0.7 mg) *vs* 20.4% (sham) and 81.7% (Fac 0.2 µg) *vs* 50% (sham), respectively.[4,5] Importantly, the visual benefit of the corticosteroid implant after cataract surgery was similar to that of subjects who were pseudophakic at baseline.

The accidental injection of a DEXi into the crystalline lens is a rare, unexpected complication, reported in about a dozen cases in the literature.[6] Most of them detail cataract progression in days to 11 months, with authors opting for both early or delayed cataract surgery, according to the opacification development and the remaining therapeutic effect of the implant. In our case, the implant was promptly extracted and substituted for a Fac injection, to protect the only functional eye of the patient.

The decision to switch to Fac was based on the pseudophakic status, a serious complication with DEXi and a responsive, but steroid-dependent chronic DME (intervals between DEXi injections <16 weeks).

IOP and OCT peripapillary RNFL defects should be monitored during intravitreal corticosteroid treatment. In the MEAD and FAME trials, 41.5% and 38.4% of treated patients required medical hypotensive therapy and 0.3% and 4.8% incisional surgery, respectively.[4,5] Fortunately, that was not the case for our patient, whose IOP remained normal.

QUESTIONS

What is the importance of a thorough clinical history in selecting the appropriate therapy for DME?

Despite the recent advances in multimodal imaging, a good clinical history is still crucial in ophthalmology. Specifically, cardiovascular history should be inquired in detail. Severe cardiovascular risk factors and/or a history of myocardial infarction or stroke in the preceding 3 months preclude antiangiogenic use.

Why is anti-VEFG intravitreal therapy contraindicated in the setting of CVD?

The use of systemic anti-VEGF in oncology may increase the risk of serious cardiovascular, venous thromboembolic and hemorrhagic adverse events. When administered intravitreally, even at low doses, a small systemic exposure can be observed. This exposure is highest with bevacizumab. However, the findings of recent meta-analysis suggest that intravitreal anti-VEGF drugs are not associated with an increase in major cardiovascular events.

What should be the first-line choice of therapy for DME in the CVD group?

Intravitreal corticosteroids are considered first-line therapy in this subgroup of patients. Their safety profile is mainly related to ocular adverse events, such as an increase in IOP and cataract formation, which should be monitored carefully during follow-up.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

MM, AC, HU e FV: Revisão bibliográfica, recolha de dados, redação e revisão. Todos os autores aprovaram a versão final a ser publicada.

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Long-Term Follow-Up of a Patient with Bilateral Chronic Diabetic Macular Edema

Seguimento a Longo-Prazo de Doente com Edema Macular Diabético Bilateral Crónico

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ABSTRACT

This case report describes the course of a patient with bilateral diabetic macular edema over 9 years of follow-up. The patient was first treated with intravitreal anti-VEGF, but no significant functional and anatomic improvements were observed. The treatment strategy was later switched to intravitreal steroids, first intravitreal triamcinolone acetonide, and later fluocinolone acetonide implant in both eyes. A complete, sustained anatomical response was observed. Ocular hypertension was later observed in both eyes, which was first managed with glaucoma topical treatment, and later with selective laser trabeculoplasty. The disease course diverged between eyes in the final months of follow-up. The right eye presented a severe, rapid progression to terminal glaucoma, and an Ahmed glaucoma valve was implanted. The left eye underwent pars plana vitrectomy due to epiretinal membrane development.

KEYWORDS: Diabetic Retinopathy/drug therapy; Diabetic Retinopathy/therapy; Macular Edema/ drug therapy; Macular Edema/therapy.

RESUMO

Este caso clínico descreve a evolução de uma doente com edema macular diabético bilateral ao longo de 9 anos de seguimento. A doente foi inicialmente tratada com agentes anti-VEGF intravítreos, contudo sem melhoria funcional ou anatómica significativa. A estratégia de tratamento foi posteriormente alterada para corticosteroides intravítreos, inicialmente acetonido de triamcinolona, seguido de implante de acetonido de fluocinolona nos dois olhos. Observou-se uma resposta anatómica completa e sustentada ao longo do tempo. Subsequentemente, desenvolveu-se hipertensão ocular em ambos os olhos, inicialmente controlada com tratamento antihipertensor tópico, e mais tarde com recurso a trabeculoplastia laser seletiva. O curso clínico entre os dois olhos divergiu nos últimos meses de seguimento. O olho direito apresentou uma progressão rápida e severa para glaucoma terminal, tendo sido implantada uma válvula de Ahmed. O olho esquerdo foi submetido a vitrectomia via pars plana devido ao desenvolvimento de membrana epirretiniana.

PALAVRAS-CHAVE: Edema Macular/tratamento; Edema Macular/tratamento farmacológico; Retinopatia Diabética/tratamento; Retinopatia Diabética/tratamento farmacológico.

INTRODUCTION

Laser photocoagulation, intravitreal anti-vascular endothelial growth factors (anti-VEGF) injections, intravitreal corticosteroid injections and long-acting implants, and pars plana vitrectomy (PPV) are currently available for the treatment of diabetic macular edema (DME).[1]

The standard of care for DME treatment was macular laser before the advent of intravitreal therapy.[2] Nowadays, relative indications include laser application especially to the vasogenic subform of DME, in areas of focally grouped microaneurysms and leaking capillaries.[1] Anti-VEGF agents are currently considered the first-line therapy. However, not all patients respond adequately to anti-VEGF therapy, so a prompt switch to other available therapies is needed in some cases.[3] Intravitreal corticosteroids are preferred in patients with an insufficient response to anti-VEGF agents, with contraindications to their use, or who have a significant inflammatory component.[4–6] Ocular hypertension (OHT) and cataractogenesis are the main side effects of treatment with intravitreal corticosteroids.[7] PPV is indicated in the presence of vitreomacular traction.[8]

This case report describes the course of a patient with bilateral DME over 9 years of follow-up, her clinical evolution, and the challenges inherent to the treatment of chronic DME. All diagnostic and therapeutic procedures took place at the Ophthalmology Department of Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Portugal. The authors believe that this case report has important educational value since it describes nearly all available treatment strategies for DME, from laser to intravitreal injections of different agents and surgical treatment. It not only gives an example of when to apply such strategies, but also explores the management of associated complications. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

CASE REPORT

A 63-year-old female was followed since February 2015 for bilateral diabetic macular edema.

Her past medical history included type 2 diabetes mellitus since 1997 (insulin-dependent since 2002), arterial hypertension, dyslipidemia, and morbid obesity. Her past ophthalmological history included moderate-severe nonproliferative diabetic retinopathy and panretinal photocoagulation in both eyes.

At her initial visit (February 2015), the best corrected visual acuity (BCVA) was 20/40 in her right eye (RE), and 20/63 in her left eye (LE). Intraocular pressure (IOP) was 17 mmHg in her RE and 16 mmHg in her LE. The anterior segment was unremarkable, except for bilateral developing cataracts. Fundoscopy revealed severe nonproliferative diabetic retinopathy and clinically significant macular edema in both eyes (Fig. 1). The optical coherence tomography (OCT) confirmed bilateral macular edema with intraretinal

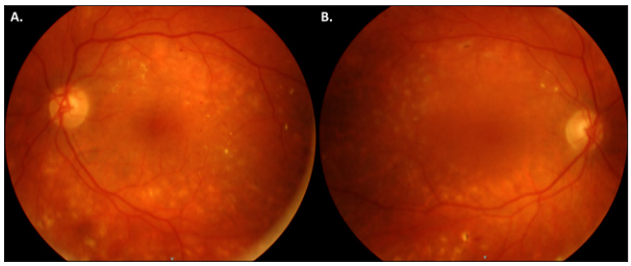

Figure 1. Initial retinography of the right eye (A) and the left eye (B) showing severe nonproliferative diabetic retinopathy with clinically significant macular edema in both eyes.

cysts, subretinal fluid and hyperreflective foci (Figs. 2A-a and 2B-a). The patient was initially proposed for monthly intravitreal injections of bevacizumab 1.25 mg/0.05 mL in both eyes.

To facilitate the analysis of treatment results and events, the authors chose to describe the clinical evolution of each eye separately.

Regarding the RE, there were no significant improvements in BCVA and central macular thickness (CMT) after a total of 6 intravitreal injections of bevacizumab 1.25 mg/0.05 mL and 2 sessions of panretinal photocoagulation (PRP) (Figs. 2A-b and 3A). For this reason, the treatment strategy was switched to intravitreal corticosteroid injections. The patient was treated with intravitreal triamcinolone acetonide (IVTA) 4 mg/0.1 mL injections and focal laser. The patient was unresponsive to the first injection (Fig. 2A-c) but presented a partial anatomical response after the second one (Fig. 2A-d). CMT improvement did not translate in proportional visual improvement due to cataract progression (Figs. 2A-e and 3A). The patient was submitted to phacoemulsification with concurrent IVTA injection (June 2018), which resulted in excellent anatomical and functional responses (Fig. 2A-f). However, recurrent macular edema was soon observed, and the same trend was maintained after one more IVTA injection (Figs. 2A-g to 2A-i). The patient was then proposed for treatment with a long-acting 0.19 mg fluocinolone acetonide (FAc) intravitreal implant (April 2019). A complete, sustained anatomical response was achieved (Figs. 2A-j to 2A-l and Fig. 3A). Functional results were limited due to the presence of retinal atrophy and the development of terminal glaucoma. OHT was first noticed between months 4 and 9 following the FAc intravitreal implant, with no identifiable glaucomatous structural damage at that time (Fig. 4A). Initially, OHT was controlled with glaucoma medical treatment: with two drugs at first, and later with three. Selective laser trabeculoplasty (SLT) was performed at month 18 (October 2020) in an attempt to reduce the number of glaucoma topical treatments given the patient's intolerance to brimonidine. There was a significant, sustained response to the SLT treatment, and the IOP remained well-controlled under two drugs for several months. BCVA progressively decreased over time, as a severe, rapid progression of glaucomatous neuropathy to a terminal stage occurred. (Figs. 3A and 4A). The patient eventually confessed she had bad compliance with the eye-

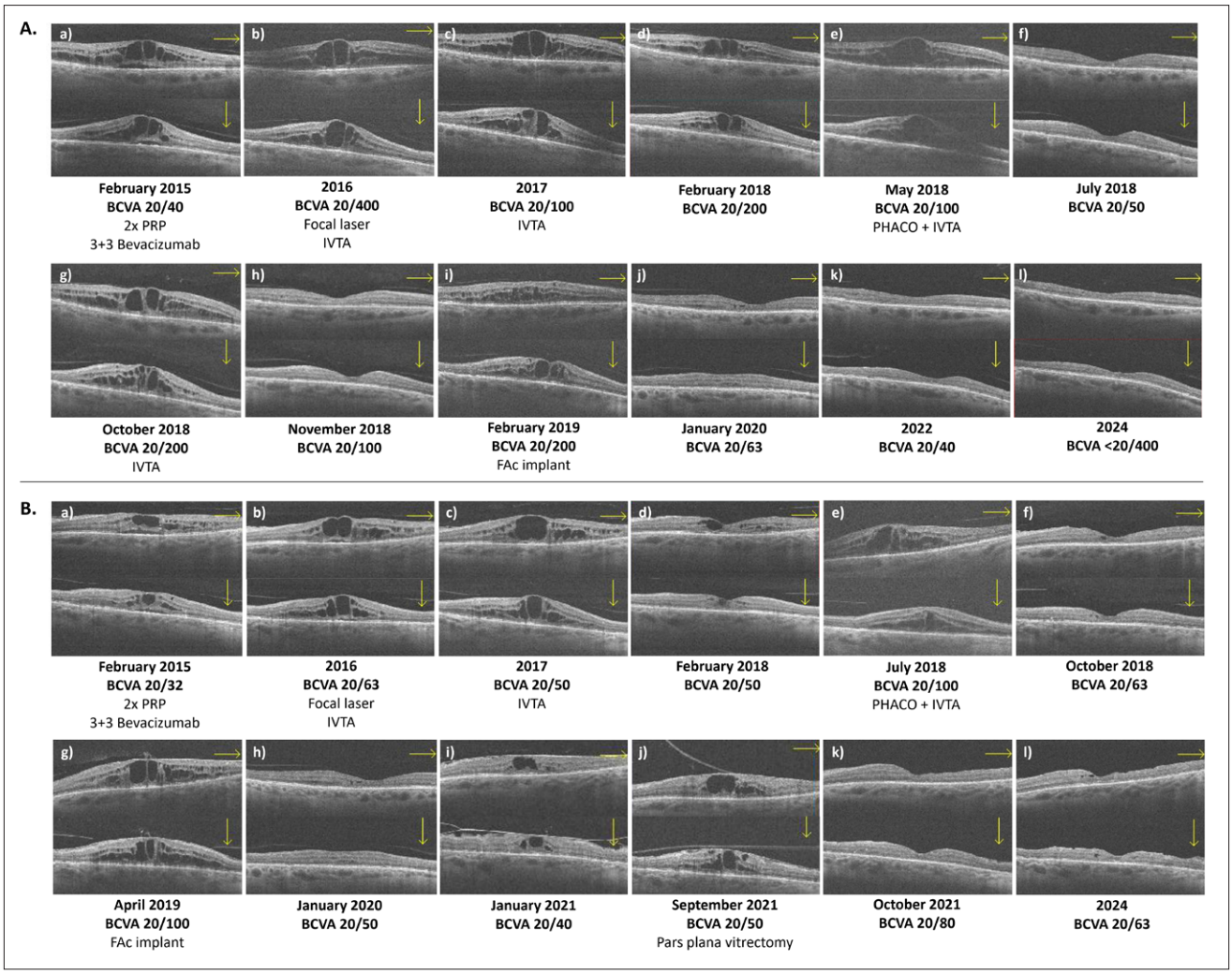

Figure 2. Spectral-domain optical coherence tomography successive images (linear horizontal and vertical transfoveolar scans) of the right eye (A) and the left eye (B). Date, best corrected visual acuity (BCVA) in Snellen equivalent and proposed treatments are presented below each scan. FAc, fluocinolone acetonide; IVTA, intravitreal triamcinolone acetonide; PHACO, phacoemulsification; PRP, panretinal photocoagulation.

drops regimen between consultations. An Ahmed glaucoma valve was then implanted in November 2023. The IOP remained controlled under hypotensive topical treatment until the end of the follow-up period, although with a final BCVA of <20/400.

Interestingly, the LE presented a similar response to the adelphic eye regarding intravitreal pharmacotherapy. There were poor functional and anatomical responses to the anti-VEGF treatment (Fig. 2B-b) and the first IVTA injection with adjuvant laser treatment (Fig. 2B-c). Subsequently, a good anatomical response was seen after the second IVTA injection (Fig. 2B-d). Phacoemulsification with concurrent IVTA injection was performed in September 2018 after the patient showed visual deterioration secondary to cataract progression (Figs. 2B-e and 3B). Both CMT and BCVA improved (Fig. 2B-f), but there was an early recurrence of macular edema (Fig. 2B-g). A sustained response was only achieved after treatment with FAc implant in May 2019 (Figs. 2B-h and 3B). Later over time, a progressive increase in CMT and a progressive decrease in BCVA were observed, reflecting the development of an epiretinal membrane (Figs. 2B-i, 2B-j and 3B). The patient underwent PPV with epiretinal membrane and internal limiting membrane peeling, IVTA injection, and sulfur hexafluoride (SF6) gas tamponade in September 2021. Macular edema resolved and there was a sustained maintenance of both CMT and BCVA, after surgery (Figs. 2B-k and 2B-l). Glaucoma medical treatment was initiated 8 months after FAc implantation due to OHT, with two drugs at first, and later with triple therapy (Fig. 4B). SLT was performed at month 17 (October 2020) given the patient's intolerance to brimonidine. At the end of the follow-up, latanoprost was added, considering the development of terminal glaucoma in the adelphic eye. There was no evidence of glaucomatous structural damage until the end of the follow-up and the final BCVA was 20/63.

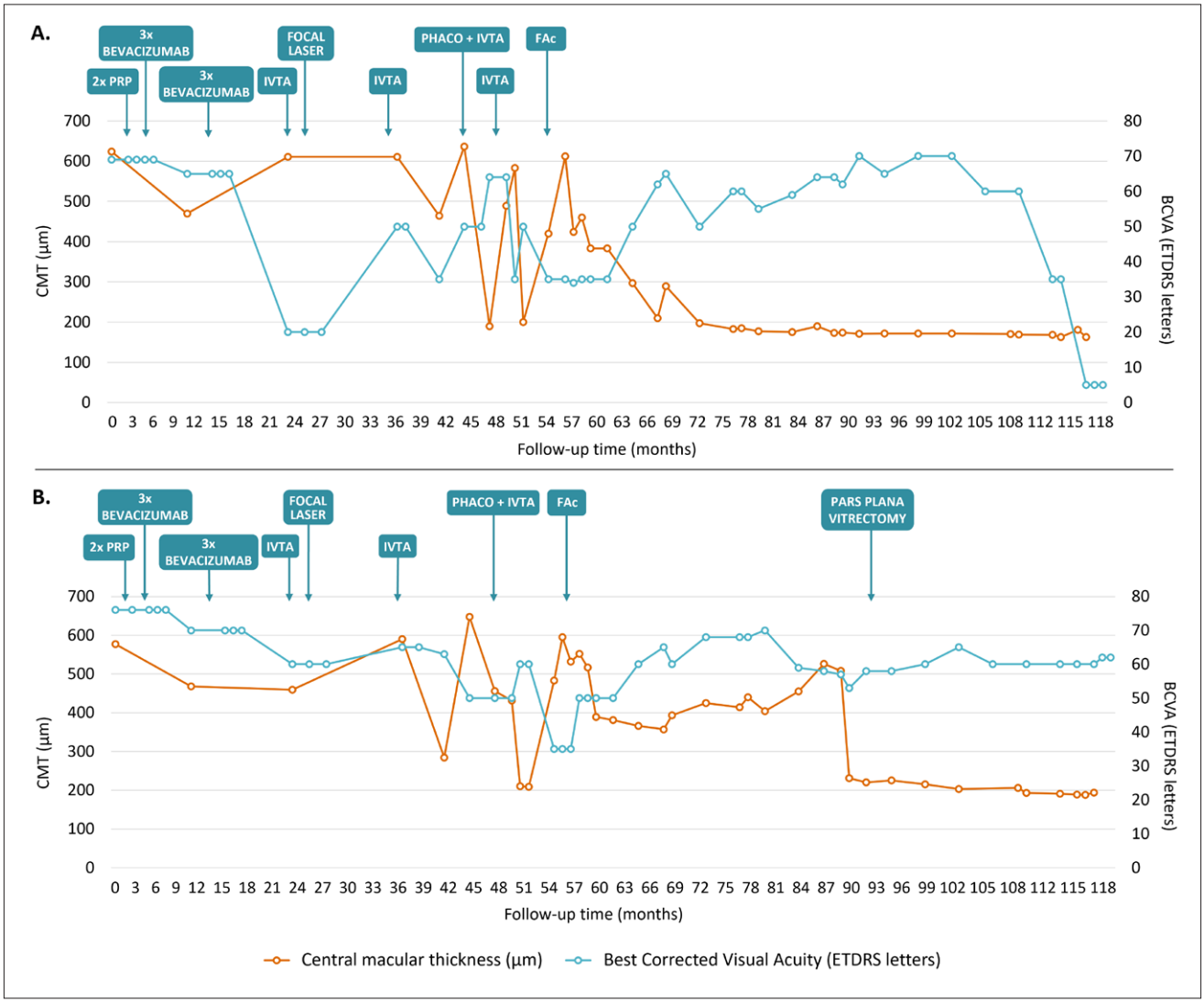

Figure 3. Central macular thickness (CMT; µm) and best corrected visual acuity (BCVA; converted to Early Treatment of Diabetic Retinopathy Study [ETDRS] letters for graph representation) through time in the right eye (A) and the left eye (B). Labels with arrows show treatment strategies performed according to the timeline. FAc, fluocinolone acetonide implant; IVTA, intravitreal triamcinolone acetonide; PHACO, phacoemulsification; PRP, panretinal photocoagulation.

DISCUSSION

This is a case report of bilateral DME with a long follow-up period. It shows that the relationship between functional and anatomical improvements is not always proportional and depends on many variables. It illustrates the complete therapeutic escalation and therapeutic options available for the treatment of DME: intravitreal injections of anti-VEGF agents as first-line strategy, adjuvant laser treatment, therapeutic switch to intravitreal corticosteroids when there was no satisfying response to those, first with short-acting corticosteroids and then prolonged-release devices, as well as PPV in the presence of a tractional component of DME.

DME pathophysiology involves blood-retinal barrier breakdown and increased permeability from blood vessels due to the loss of supportive cells, cell dysfunction, and inflammatory changes.[9] Signaling molecules involved in microangiopathy include VEGF, insulin-like growth factor-1, platelet-derived growth factor, and angiopoietin. VEGF plays a crucial role in the breakdown of the blood-retinal barrier, which led to the use of anti-VEGF agents as first-line treatment in DME.[10] Corticosteroids provide an alternative therapeutic strategy by blocking leukotriene and prostaglandin synthesis via glucocorticoid receptors and subsequently acting on the arachidonic acid pathway. Corticosteroids also inhibit and interfere with other pro-inflammatory molecules, such as VEGF-alpha, interleukin-6, and intercellular adhesion molecule-1, and increase vasoconstriction by nitric oxide inhibition.[9] Anti-VEGF agents can be highly effective in the early phase of DME.[4] As the disease progresses to chronic stages, inflammatory mediators may play a more important role than VEGF. Thus, corticosteroids are expected to be more efficient in chronic forms of DME, although this theory lacks further evidence.[8]

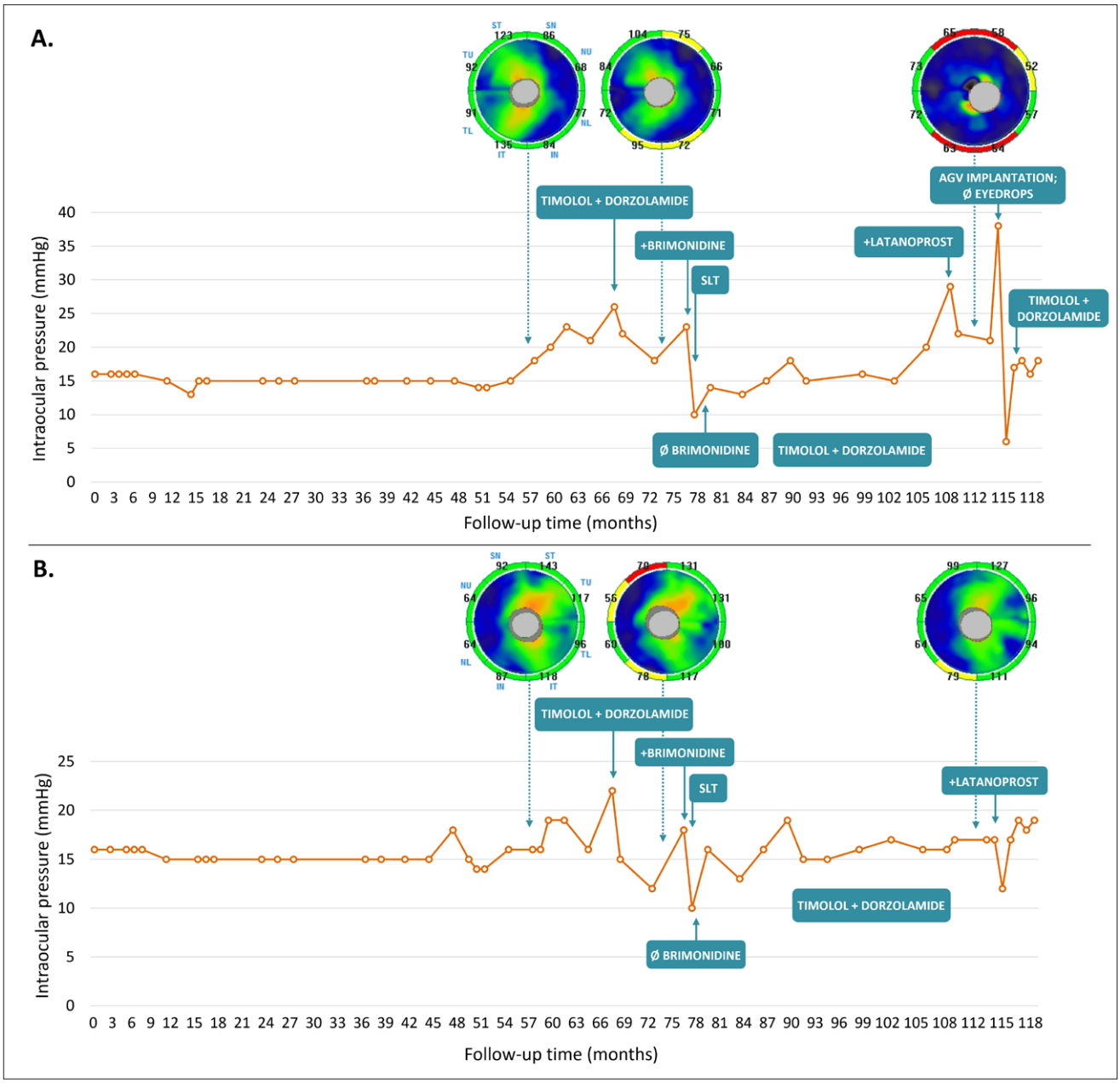

Figure 4. Intraocular pressure through time in the right eye (A) and the left eye (B). Labels with arrows show treatment strategies according to the timeline, including eyedrops, laser treatment and surgical treatment. Graphs from optical coherence tomography retinal nerve fiber layer analysis at month 57, 74 and 112, respectively, are also presented. AGV, Ahmed glaucoma valve; SLT, selective laser trabeculoplasty.

The presence of inflammatory retinal biomarkers such as disorganization of retinal inner layers, subretinal fluid, hyperreflective retinal foci, and hard exudates, have been proposed to identify DME cases with a prominent inflammatory component. Intravitreal corticosteroids can also be better suited in such cases.[3,8] Some of these biomarkers were also found in the current case report, and a good response was observed after intravitreal steroids.

In diabetic retinopathy, PPV improves oxygen delivery to the retina and removes inflammatory mediators of DME, including VEGF, from the retina. Vitreomacular traction is a relevant factor in the development and persistence of DME. The presence of anterior–posterior traction (anomalous posterior vitreous detachment) in eyes with DME may be an indication that PPV is required. PPV is more controversial when only tangential traction (epiretinal membrane) is present, but it can be considered when the response to anti-VEGF or corticosteroids is incomplete. There is no consensus regarding the advantages of PPV when there is no evidence of traction.[8]

This case report also demonstrates that treatments are

not free from risks and adverse effects, such as the well-known risks of OHT secondary to intravitreal corticosteroids and cataract development and progression.

In the present case, cataract progression was managed with phacoemulsification and concurrent IVTA injection. Cataract surgery increases the risk of developing edema or worsening the preexisting edema due to postsurgical inflammation that is increased by preexisting diabetic retinopathy.[11] Perioperative anti-inflammatory eyedrops lower the risk of new-onset DME after cataract surgery. In patients with preexisting DME, if the cataract is not interfering with the patients' activity of daily living or the fundus visualization for disease monitoring, it is preferable to defer cataract surgery until DME is controlled. If not possible, subtenon injection of triamcinolone acetonide or intravitreal injection of corticosteroids and anti-VEGF agents should be administered perioperatively for the prevention of DME worsening in patients undergoing cataract surgery.[12]

This case report also illustrates OHT management through a wide range of antihypertensive therapeutic options: glaucoma eyedrops, laser (SLT), and surgical treatment (AGV implantation). Interestingly, a rapid progression of glaucomatous neuropathy to a terminal stage was observed in the RE, even after the end of the FAc implant's period of action. This highlights the importance of maintaining a regular long-term follow-up of DME patients, especially when treated with intravitreal steroids, including frequent IOP and optic nerve head evaluation.

3 QUESTIONS TO THE AUTHORS

1) What are the most original facts about this case report?

The long-term follow-up, the use of mostly all available treatment strategies for DME, and the comparison of the disease's course between both eyes.

2) Which therapeutic strategy do you prefer?

Anti-VEGF agents are currently considered the first-line therapy, but the treatment strategy should be adapted for each patient. Intravitreal steroids are also an important alternative when there is no satisfying response to anti-VEGF, in chronic DME cases, and cases with a prominent inflammatory component.

3) What are the key messages of this case report?

DME is a complex, challenging disease. Several therapeutic options are currently available, from intravitreal agents to surgical treatment. Clinicians should be aware of the commonest lateral effects of such therapeutic strategies and their management.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

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CT: Data collection and analysis, review of the article's scientific content.

All authors approved the final version to be published.

ARV: Recolha e análise de dados, redação do manuscrito.
CT: Recolha e análise de dados, revisão do conteúdo científico do artigo.

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Diabetic Macular Edema: A Case Report Regarding the Importance of Treatment Escalation

Edema Macular Diabético: Um Relato de Caso sobre a Importância do Escalonamento do Tratamento

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ABSTRACT

We describe the multimodal management of a patient with diabetic retinopathy (DR) and diabetic macular edema (DME) refractory to anti-vascular endothelial growth factor (VEGF) therapy, who underwent treatment escalation to sustained-release steroid implant therapy.

A 59-year-old woman presented with visual loss in the right and left eye due to DME. Best corrected visual acuity (BCVA) was 52 letters (ETDRS letter scale) in the right eye (OD) and 72 letters in the left eye (OS). Fundus examination and spectral domain optical coherence tomography (SD-OCT) revealed DME with a macular thickness of 715 µm OD and 369 µm OS, and an ischemic peripheral retina. Pan-photocoagulation, macular laser photocoagulation and three intravitreal anti-VEGF injections with bevacizumab at 4-week intervals were performed. Nonetheless, the patient had persistent DME in both eyes, requiring triamcinolone acetonide intravitreal injections with marked clinical and structural improvement. Three months after the steroid injection, DME recurred, and a dexamethasone intravitreal sustained-release implant (Ozurdex®) was injected in both eyes. Despite treatment with Ozurdex®, the patient had significant DME recurrence within 16 weeks and the decision was made to inject an intravitreal fluocinolone acetonide implant (Iluvien®). Following this implant, the patient had excellent clinical and structural improvements.

KEYWORDS: Diabetic Retinopathy; Macular Edema; Vascular Endothelial Growth Factors.

RESUMO

Caso clínico sobre a abordagem multimodal de um doente com retinopatia diabética (RD) e edema macular diabético (EMD), refratário ao tratamento com anti-fator de crescimento endotelial vascular (anti-VEGF), com necessidade de escalada terapêutica para implantes de libertação prolongada de corticoides.

Uma mulher de 59 anos com RD apresentava diminuição da acuidade visual no olho direito e esquerdo. A acuidade visual no olho direito era de 52 letras (escala de letras ETDRS) e 72 letras no olho esquerdo (OE). A fundoscopia e a tomografia de coerência óptica (OCT) demonstravam EMD com uma espessura macular de 715 µm no OD e 369 µm no OE, além de isquemia na retina periférica. Foi realizada pan-fotocoagulação, fotocoagulação com laser macular e três injeções intravítreas de anti-VEGF com bevacizumab em intervalos de 4 em 4 semanas. No entanto, a doente mantinha EMD persistente em ambos os olhos, com necessidade de injecções intravítreas

de acetato de triancinolona com uma melhoria clínica e estrutural acentuada. Três meses após a injeção de triancinolona, houve reaparecimento de EMD pelo que foi injetado bilateralmente um implante intravítreo de libertação prolongada de dexametasona (Ozurdex®). Apesar do tratamento com Ozurdex®, a doente teve recorrência significativa do EMD em 16 semanas e optou-se pela injeção de um implante intravítreo de acetato de fluocinolona (Iluvien®). Após este implante, a doente manteve excelentes melhorias clínicas e estruturais.

PALAVRAS-CHAVE: Edema Macular; Fator de Crescimento do Endotélio Vascular; Retinopatia Diabética.

INTRODUCTION

Diabetic retinopathy is a major cause of vision loss among working-age individuals, driven by retinal vascular hyperpermeability, hypoperfusion, and neovascularization. Diabetic macular edema (DME) emerges as a clinical condition resulting in severe visual impairment. Over the past decade, the traditional approaches of laser photocoagulation and surgical interventions for treating diabetic retinopathy (DR) have shifted to intravitreal administration of anti-vascular endothelial growth factor (VEGF) and corticosteroids. Nowadays, multiple long-term corticosteroid delivery implants are available.

CASE REPORT

A 59-year-old woman, diagnosed with diabetes mellitus 13 years earlier, with an HbA1c of 8.%, was referred to our Ophthalmology Department for progressive vision loss. On examination, her best corrected visual acuity (BCVA) was 52 letters (ETDRS letter scale) in the right eye (OD) and 72 letters in the left eye (OS) with an intraocular pressure (IOP) of 12 mmHg in both eyes (OU). Biomicroscopy was unremarkable bilaterally. Fundus examination and spectral domain optical coherence tomography (SD-OCT) revealed bilateral macular edema with a thickness of 715 µm OD and 369 µm OS (Fig. 1 a,b). Fluorescein angiography revealed an ischemic peripheral retina OS, thus non-proliferative DR in the OD and proliferative DR in the OS with DME was diagnosed.

Pan-photocoagulation associated with macular laser photocoagulation and three intravitreal anti-VEGF injections with bevacizumab at four-week intervals were performed bilaterally. After this treatment, the patient had decreased but persistent DME OU, but BCVA decreased to 42 letters OD and 68 letters OS.

Due to resistance to treatment with anti-VEGF injections, the patient received a triamcinolone acetonide intravitreal injection in each eye, resulting in significant structural improvement along with BCVA improvement (58 letters OD and 72 letters OS) (Fig. 2 a,b). IOP increased to 22 mmHg bilaterally, and the patient initiated a combination of brimonidine and timolol eyedrops twice daily.

Three months after the corticosteroid injection, DME recurred, decreasing BCVA to 35 letters OD and 48 letters OS.

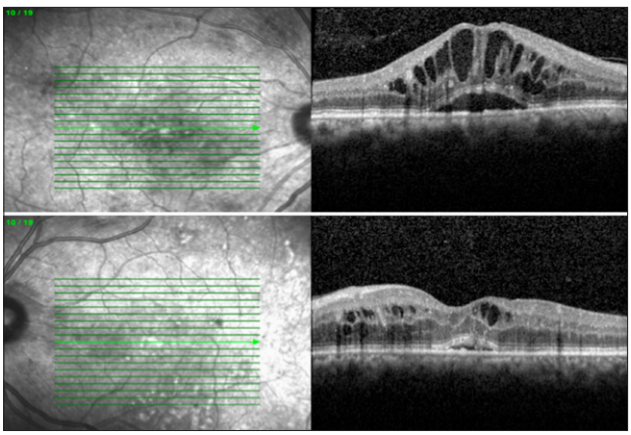

Figure 1. a) Right eye - macular edema with a thickness of 715 µm, b) Left eye – macular edema with a thickness of 369 µm.

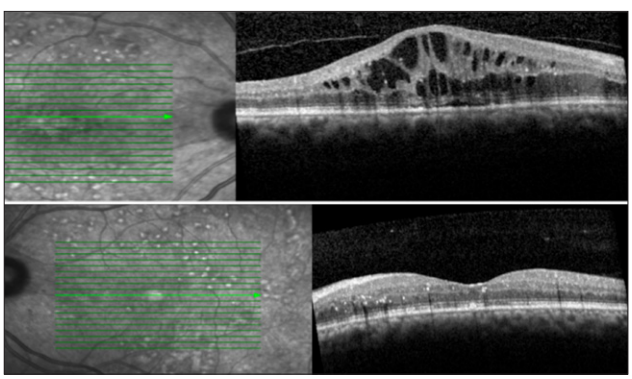

Figure 2. a) Right eye and b) Left eye – macular edema improvement after triamcinolone acetonide intravitreal injection.

Given the refractory response to anti-VEGF and excellent response to the intravitreal corticosteroid injection, a dexamethasone intravitreal implant (Ozurdex®) was inserted in both eyes (Fig. 3 a,b).

One month after treatment with Ozurdex®, the right eye did not show a good clinical response, with BCVA decreasing to 25 letters, but a reduced macular thickness was recorded. The decline in BCVA was attributed to a likely corticosteroid-induced cataract. On the other hand, BCVA OS improved to 68 letters. Uncomplicated phacoemulsification

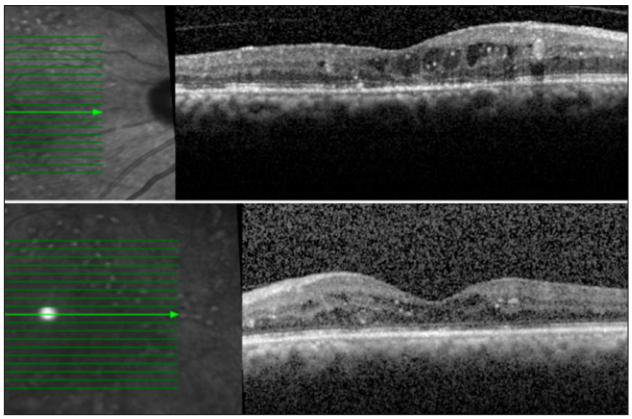

Figure 3. a) Right eye and b) Left eye – excellent structural improvement to intravitreal corticosteroid injection, a dexamethasone intravitreal implant (Ozurdex®).

surgery with intraocular lens placement was performed OU. Treatment with Ozurdex® was repeated in each eye, approximately 16 weeks after the last implant, to treat DME recurrence.

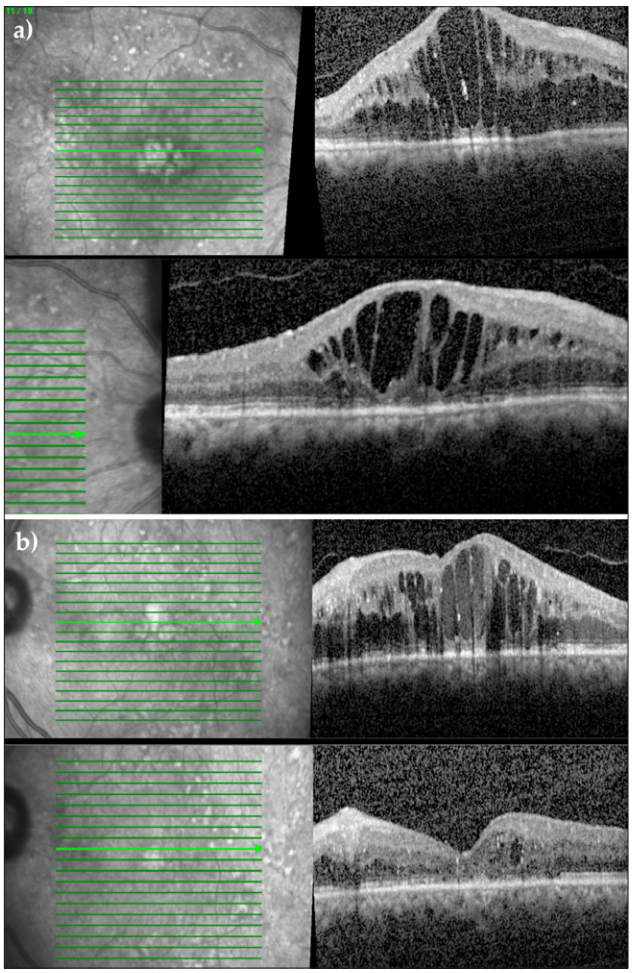

Figure 4. a) Right eye and b) Left eye – before and after intravitreal fluocinolone acetonide implant (Iluvien®) injection structural outcome.

Four months after the last Ozurdex® implant, retinal thickness increased to 638 µm OD and 467 µm OS. As a result, treatment was escalated with intravitreal fluocinolone acetonide implant (Iluvien®) injection, resulting in excellent clinical and structural outcomes. BCVA increased to 40 letters OD and 35 letters OS (Fig. 4 a,b).

For the following 10-year follow-up period, the patient-maintained treatment with aflibercept injections, in a treat-and-extend protocol, with anatomical benefits and maintained functional gains (Fig. 5 a,b).

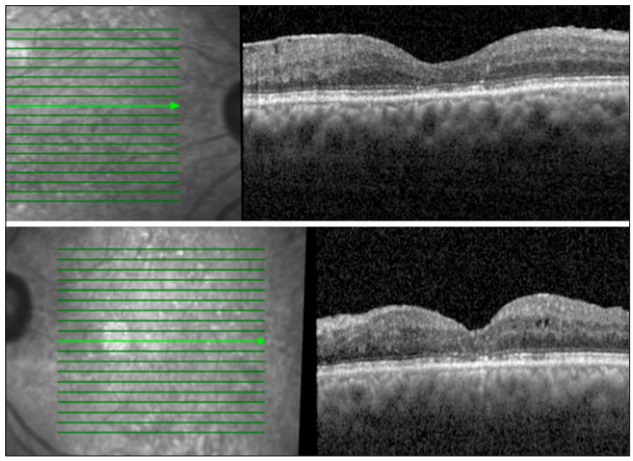

Figure 5. a) Right eye and b) Left eye – 10-year follow-up outcome.

DISCUSSION

DME is a significant cause of visual impairment in patients with DR, especially when refractory to standard first line treatments such as anti-VEGF therapy. This case underscores the challenges and complexities involved in managing DME, particularly in patients exhibiting resistance to conventional therapies.

In this case, initial management of DME involved pan-photocoagulation, macular laser photocoagulation, and intravitreal anti-VEGF therapy with bevacizumab, which is consistent with standard treatment protocols for DME.

Clinical trials have consistently shown the benefits of anti-VEGF treatments for DME. The DRCR.net Protocol I study was a pivotal phase 3 trial that demonstrated the superiority of intravitreal anti-VEGF therapy over laser treatment for center-involved DME. Further supporting these findings, the RISE and RIDE phase 3 trials demonstrated that ranibizumab significantly improved vision, reduced the risk of further vision loss, and improved macular edema in DME patients compared to sham injections, with low complication rates. Similarly, the VIVID and VISTA trials confirmed the efficacy of aflibercept, showing substantial visual acuity gains with an initial phase of five monthly injections followed by monthly or bimonthly therapy over 3 years.[1-5]

However, the persistence of DME despite these interventions prompted the need for an alternative therapeutic strategy.

The subsequent administration of intravitreal triamcinolone led to significant clinical and structural improve-

ments, suggesting a favourable response to corticosteroid therapy. However, the recurrence of DME three months post-injection indicated the temporary nature of this treatment and the necessity for a more sustained approach.

Corticosteroids are generally used as second-line agents for DME because of the inferiority in visual outcomes and higher adverse effects with continued use, such as cataract formation and rising intraocular pressure.

The introduction of the dexamethasone intravitreal implant (Ozurdex®) provided another step in therapy escalation. While the left eye responded well to treatment, the right eye did not exhibit the same degree of improvement, partially due to cataract formation, a known complication of intravitreal corticosteroids. Cataract surgery was necessary to improve visual acuity.

Despite the initial benefits observed with Ozurdex®, the recurrence of DME urged further treatment escalation. The decision to use an intravitreal fluocinolone acetonide (Iluvien®) proved to be an important step for sustained DME resolution. Iluvien® has been shown to provide extended control of DME with a reduction in the frequency of injections required. Following the Iluvien® implantation, the patient experienced stable visual acuity and maintained macular edema reduction, demonstrating the efficacy of this long-term treatment option.

Corticosteroids can be beneficial for some patients with DME. Studies on sustained-release steroid implants, such as dexamethasone and fluocinolone acetonide, have shown visual acuity improvements of 3 or more lines in DME-affected eyes. For patients who have already undergone cataract surgery, steroid treatment may be a viable alternative to anti-VEGF therapy. The DRCR.net Protocol I trial found that visual acuity in pseudophakic eyes treated with steroids was comparable to those treated with anti-VEGF and superior to laser-treated eyes.[6-9]

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

AGC: Conception and design of the work; data acquisition, analysis, interpretation and writing.

AMF, IC: Data acquisition, analysis and interpretation.

RL, MF, SP, AC: Critical review of the manuscript.

All authors approved the final version to be published.

AGC: Conceção e desenho do trabalho; aquisição de dados, análise, interpretação e redação.

AMF, IC: Aquisição, análise e interpretação dos dados.

RL, MF, SP, AC: Revisão crítica do manuscrito. Todos os autores aprovaram a versão final a ser publicada.

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Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

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