Bilateral juxtapapillary choroidal neovascularization secondary to Birdshot chorioretinopathy – case report

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March 4, 2021

Abstract

Central vision loss, photopsia, floaters and macular edema in a highly myopic patient can easily be misrelated to high myopia complications. However, in atypical cases, detailed examination along with a thorough diagnostic is required to establish the right diagnosis, which is often beyond the limits of the condition originally considered.

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ABSTRACT

Central vision loss, photopsia, floaters and macular edema in a highly myopic patient can easily be misrelated to high myopia complications. However, in atypical cases, detailed examination along with a thorough diagnostic is required to establish the right diagnosis, which is often beyond the limits of the condition originally considered.

INTRODUCTION

Birdshot chorioretinopathy (BCR) is a rare, chronic, bilateral, posterior inflammatory disease involving the retina and the choroid. It is an uncommon type of idiopathic bilateral posterior uveitis that is typically seen in Caucasians in their 5th and 6th decade of life, with slight female predominance (54.1%) [1-3]. The earliest report of this disorder was in 1949 by Franceschaetti and Babel as candle wax spot chorioretinopathy ("la choriorétinite en tâche de bougie") [4]. Ryan and Maumenee relabeled it as Birdshot retinochoroidopathy in 1980[5]. It is responsible for 6%–8% of cases of posterior uveitis [2, 6-8]. The condition has a distinct clinical phenotype consisting of discrete anterior uveitis, moderate vitritis and/or vitreous debris, retinal vasculitis, and multiple characteristic, hypopigmented, cream-colored, irregularly shaped choroidal lesions, radiating from the optic disc to the equator. The typical birdshot lesions may take as long as 8 years to appear after onset of early symptoms [9]. The lesions, initially, seem to be located in the choroidal stroma. The ERG pattern, an electronegative b wave, suggests that the initial dysfunction is located in the inner neural retinal layers [1-2, 6-7]. In later stages the lesions take on a more atrophic appearance and enlarge, involving the outer retina, retinal pigment epithelium (RPE), and become irreversible, meaning that therapy is unlikely to be of any benefit[10].

Cystoid macular edema (CME), leading to macular atrophy and permanent vision loss is the main complication observed, affecting around 50% of cases. Epiretinal membranes occur in nearly 10% of cases. Choroidal neovascularization, or CNV, represents a rare complication and has been reported in 6% of cases. It usually develops at the margin of areas of RPE damage, juxtafoveally or subfoveally, and can also appear as juxtapapillary. Neovascularization of the retina, peripapillary or peripherally, has also been observed. Other complications include central retinal vein occlusion, recurrent vitreous hemorrhage, subretinal neovascular membranes, progressive choroidal atrophy, and optic disc atrophy [9-12].

In the early stages, patients mostly complain of symptoms that indicate involvement of the peripheral retina, despite often having good best corrected distance visual acuity until late in the disease[13]. Clinical signs are subtle, insidious, mostly with no pain and redness [14]. Decline in central vision appears due to development of long term complications (egg. CME, epiretinal membranes, CNV, progressive choroidal atrophy, vitreous opacity, cataract, optic disc atrophy) [9].

Generally, it is considered to be an isolated ocular disorder, despite a few reports in the literature describing its possible association with systemic illnesses, including essential hypertension, cerebrovascular accidents, hearing loss and cutaneous immune-mediated conditions such as vitiligo and psoriasis [10, 12, 15]. The majority of patients develop chronic disease with progressive retinal dysfunction, although a smaller proportion have limited occurrence of the disease with spontaneous remission of their intraocular inflammation[16]. It is an autoimmune condition but its pathogenesis, however, remains unclear, and this has contributed to a lack of optimal treatment protocol.

In this case report a middle-aged woman presented with bilateral juxtapapillary CNV and profound central vision loss due to long standing advanced BCR.

CASE PRESENTATION

2.1 Case history/examination and investigations

A 55-year-old female, presenting painless, unspecific central vision loss, complaining of blurry vision, floaters and photopsia, visited our hospital in April 2007. She was previously treated for one year and diagnosed with high myopia-related CNV. She occasionally noticed photopsia and floaters many years before the decline in central vision occurred, and she was told it was due to high myopia. She had a medical history with no other comorbidities. At the time she came to see us, her best-corrected visual acuity (BCVA) was 0.6 OD and 0.3 (eccentric) OS and her manifest refraction was -9.50 diopters OD and -8.50 diopters OS. Snellen visual acuity testing, slit lamp examination, spectral domain optical coherence tomography (SD OCT), fluorescein angiography (FA), fundus autofluorescence (AF), electroretinogram and electrooculogram were performed and were rechecked. There was a trace of cells in the anterior segment with other findings presenting as normal on biomicroscopy. Ophthalmoscopy findings revealed mild anterior vitritis, juxtapapillary CNV with macular edema, a patterned distribution of yellowish-white round to oval choroidal inflammatory lesions radiating

from the optic disc to the equator, with mild atrophy and fibrosis, and signs of retinal vasculitis in both eyes. SD OCT presented predominantly macular edema and right eye macular fibrosis (Figure 1A and B). FA confirmed the presence and demonstrated the location of juxtapapillary CNV leakage with retinal hemorrhage and typical BCR inflammatory lesions in both eyes (Figure 1C and D). Electroretinography findings showed serious pathological findings with no rod and very few cone responses. Clinical and diagnostic findings of diffuse inflammatory retinochoroidopathy led us to perform HLA testing. The HLA-A29-positive haplotype finally helped us to confirm the diagnosis of BCR. In a case like this, an inexperienced ophthalmologist could very easily miss the correct diagnosis given the subtle anterior segment clinical signs without conjunctival redness, by confusing the signs of mild vitritis with vitreous opacities due to high myopia, by not recognizing changes in the peripheral retina, especially in earlier stages of the disease, as well as by concluding that macular edema is a consequence of myopic CNV.

2.2 Treatment, outcome and follow-up

After establishing the diagnosis, she was treated with courses of anti-VEGF and corticosteroids intravitreally, combined with oral immunosuppressive therapy (IMT) in defined doses. A total of 25 intravitreal injections were applied, 21 of 1,25 mg bevacizumab, of which 13 applications in OD, and 9 in OS, and 4 intravitreal injections of 8 mg triamcinolone acetonide, 3 in OD, 1 in OS combined with 12.5 mg methotrexate (MTX) weekly orally. One year after therapy initiation, remission of inflammation was established as well as CNV attenuation together with complete macular edema regression.

During a two-year period, from 2009 to 2011, she discontinued recommended systemic therapy, which resulted in exacerbation of inflammation, but with no signs of CNV reactivation or newly formed CNV. Again, MTX was given to her orally and she reached stabile remission. In 2015, due to stabile disease control, our decision was to discontinue IMT therapy. Unfortunately, two years later signs of ocular inflammation recurred and since 2017, she has constantly been on cyclosporine A (CsA) therapy at doses between 2.5 and 5 mg/kg/day orally. In the meantime, she developed cataract in both eyes and underwent cataract surgery.

Her last visit was in December 2020. Her best best-corrected visual acuity with intraocular lenses was 0.1 OD (eccentric) and 0.6 OS with manifest refraction -0.50 diopters OD and -1,50 diopters OS. Biomicroscopy showed few cells in the anterior segment. Ophthalmoscopy findings revealed no signs of vitritis or vasculitis. Pronounced disseminated retinal atrophy and fibrotic lesions affecting the right eye macular region were dominating, with inactive fibrotic juxtapapillary CNV membranes left on both eyes, with no signs of macular edema. Left eye macula findings were within the normal limits (Figure 2).

DISCUSSION

A patient suffering from an uncommon condition with even more uncommon complications often poses a diagnostic and therapeutic challenge. Our patient was presented with central vision loss due to CNV development in severe long standing BCR. Firstly, she was misdiagnosed with high myopic complications that led to misguidance for years before a correct diagnosis was established and adequate treatment was begun. Her ocular findings (mild anterior uveitis, vitritis, vasculitis, and chorioretinal inflammatory lesions) made us suspect of a specific form of posterior uveitis. BCR, together with acute posterior multifocal placoid pigment epitheliopathy, multiple evanescent white dot syndrome, multifocal choroiditis with panuveitis, punctate inner choroidopathy, and acute zonal occult outer retinopathy, belongs to a group of white dot syndromes with overlapping clinical features, which posed an additional diagnostic problem. After performing abovementioned diagnostic procedures, with the patient having typical ophthalmoscopy features, diagnostic criteria and HLA-A29 testing, the correct diagnosis was finally reached, reinforced by HLA-A29-positive haplotype. At the time the correct diagnosis was made, diagnostic findings already showed advanced retinal dysfunction. BCR typically requires aggressive therapy to prevent loss of vision. According to literature, treatment protocols widely differ, without any established therapeutic protocol guidelines. The mainstay of treatment is steroid-sparing immunomodulatory therapy (IMT), e.g. MTX, mycophenolate mofetil, T-cell transduction/calcineurin inhibitors (e.g. CsA), intravenous immunoglobulin, and other biologic therapies, each of which may be used alone or in combination with other agents [17]. In our case, systemic MTX monotherapy

combined with intravitreal anti-VEGF and triamcinolone acetonide therapy led to CNV attenuation and macular edema regression followed by suppression of intraocular inflammation that showed exacerbation after systemic therapy discontinuation. Recommencement of systemic MTX, followed by CsA monotherapy achieved remission of inflammation, suggesting that low dose immunosuppressive (MTX or CsA) monotherapy may achieve long-term inflammation control. According to literature, low dose MTX has also been shown to be more effective in improving visual acuity in birdshot patients compared to untreated patients and corticosteroid-based treatment regimens [18]. In this case, the applied therapy led to CNV regression, preservation of the central vision and diminishing of intraocular inflammation. However, widespread progressive retinal changes developed despite long lasting sufficient therapy, presenting the refractory progressive nature of the disease.

CONCLUSION

This is an overview of the case of a patient presenting long-standing BCR complicated with resistant macular edema and juxtapapillary CNV that seemed to be successfully treated with immunosuppressive and combined intravitreal anti-VEGF and corticosteroid therapy, especially in terms of CNV attenuation, macular edema resolution, preservation of the central vision, and minimization of the intraocular inflammation. However, progression of typical widespread choroidal and retinal changes such as in this case tends to be resistant to therapy and mostly irreversible. This potentially eye-threatening condition requires careful examination in order to establish a proper diagnosis as soon as possible, as well as early initiation of appropriate therapy and monitoring. Also, it requires more future investigations with more patients and longer follow-ups to resolve ethological dilemmas and to reach agreement on the best therapy protocol. Low frequency of the disease makes it difficult to investigate in one place and requires cooperation and harmonization of multiple medical centers.

ACKNOWLEDGMENT

Conflict of Interest:" The authors state that they have no financial conflict of interest."

Funding: "This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors."

Financial Disclosure: "No author has a financial or proprietary interest in any material or method mentioned."

Informed Patient Consent: "Written informed consent was obtained from the participant in order to publicize this case report and accompanying images."

AUTHOR CONTRIBUTIONS

Sania Vidas Pauk: conceived and drafted the paper. Nenad Vukojević: guided the patient's diagnostic and treatment protocols and he also reviewed and revised the paper for important intellectual contributions. Sonja Jandroković: revised the paper for important intellectual contributions. Miro Kalauz: consulted the treatment and contributed in drafting. Martina Tomić: reviewed and revised the paper for important intellectual contributions. Sanja Masnec: consulted the treatment and contributed to drafting. Ivan Škegro: contributed to drafting and revision. Danijela Mrazovac Zimak: revised the paper for important intellectual contributions.

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FIGURE LEGENDS

Fig 1 a) right eye and b) left eye first visit OCT presented predominantly macular edema and discreet macular fibrosis, c) right eye and d) left eye first visit fluorescein angiography confirmed the presence and demonstrated the location of juxtapapillary CNV, retinal hemorrhage, and patterned choroidal lesions related to birdshot chorioretinopathy.

OCT – optical coherence tomography, CNV- choroidal neovascularization

Fig 2 a) right eye last visit OCT presented complete macular edema resolution with macular fibrosis, b) left eye macula OCT findings were within the normal limits, c) right eye and d) left eye last visit fotofundus and e) right eye and f) left eye fundus autofluorescence presented attenuated juxtapapillary CNV, with inactive fibrotic juxtapapillary membranes, and disseminated retinal fibrosis and atrophic lesions.

OCT - optical coherence tomography, CNV- choroidal neovascularization.