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Case report

HLA-A29 negative Birdshot-like chorioretinopathy associated with common variable immunodeficiency

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ABSTRACT

Purpose: To report the longest ophthalmic follow-up and the associated ocular complications of HLA-A29 negative Birdshot-like chorioretinopathy (BLCR) associated with common variable immunodeficiency (CVID).

Observations: A 22-year-old man known for CVID presented with a 3-month history of decreased visual acuity OS. Funduscopy revealed significant cystoid macular edema OS, as well as optic disk edema and chorioretinal infiltrates without signs of vitritis OU. No infectious, inflammatory or neoplastic etiologies were identified. He subsequently received one dose of intravitreal triamcinolone OS which completely resolved the macular edema. The optic nerve edema persisted despite the addition of intravenous immunoglobulin. His visual acuity was 20/20 OU at the 24th follow-up month.

Conclusion: and importance: To our knowledge, this is the third case of HLA-A29 negative BLCR associated with CVID. It is the first case with long-term follow-up providing, in consequence, the best understanding of the natural history and possible complications of this rare disease. Aggressive systemic treatment, in collaboration with an immunologist, is generally needed to control the ophthalmic complications.

1. Introduction

Common Variable Immunodeficiency (CVID) is a primary immunodeficiency leading to defects in B-cell differentiation and a subsequent decrease in antibody-producing plasma cells along with hypogammaglobulinemia. Patients with this disorder typically present with recurrent sino-pulmonary bacterial infections as well as increased risk for autoimmune disease.[1–3] In North America, CVID is the most common primary immunodeficiency and the most severe form of antibody deficiency affecting both children and adults.[4] The etiology of CVID remains unclear.

Birdshot chorioretinopathy (BCR) is a rare autoimmune chorioretinal disease manifesting as bilateral posterior uveitis with typical white-creamy hypopigmented choroidal lesions. Its pathogenesis remains poorly understood despite its strong association with the HLA-A29 haplotype, suggesting a possible pathophysiological role for T-cells. Clinically, most patients with BCR present with blurred vision, floaters, nyctalopia and a typical fundus appearance.[5,6]

A literature review detected nine cases of CVID that manifested with unique ocular findings during the course of disease. Among these, HLA-A29 negative Birdshot-like chorioretinopathy (BLCR) was reported in only two cases.[7–12] In this work, we report a unique case of chorioretinitis presenting with creamy chorioretinal infiltrates with a scattering mimicking that of BCR (hence, the “birdshot-like” naming) in a patient with CVID. To our knowledge, we report the third case of HLA-A29 negative BLCR associated with CVID, and we document, for the first time, its natural history over a 2-year follow-up period.

2. Case report

A 22-year-old man was referred to our clinic after reporting a 3-month history of decreased vision in his left eye. His past medical history was relevant for CVID and psoriasis. The CVID was diagnosed by the allergy and immunology services after presenting with recurrent sino-pulmonary infections and frequent otitis media in his childhood. At that time, a diagnosis of CVID was made based on marked hypogammaglobulinemia (IgG and IgA). The patient was subsequently treated with subcutaneous immunoglobulins.

The patient, who was known for −7.5 D of myopia OU, did not report any significant past ocular history. His visual acuity (VA) at presentation was 20/30 OD and 20/60 OS. Pupil reaction to light was normal. His intraocular pressures were 12 mmHg OU. The anterior segment examination was also within normal limits and demonstrated no cellular reaction. Fundoscopy revealed bilateral nasal chorioretinal creamy infiltrates as well as bilateral optic nerve edema more pronounced in the left eye (Fig. 1A and B). Fluorescein angiography (FA)

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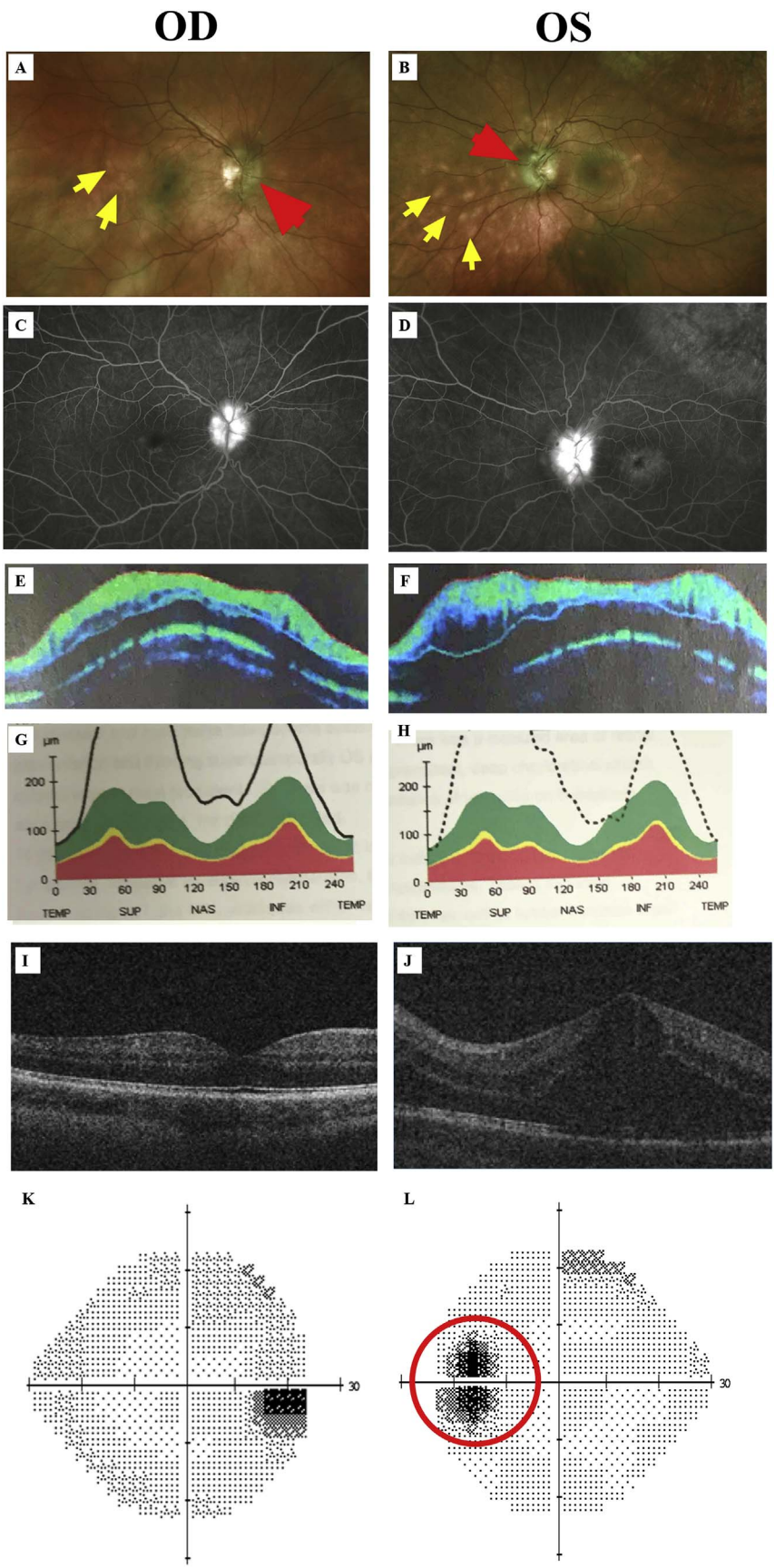

Fig. 1. Initial presentation: 22-year-old man with HLA-A29 negative Birdshot-like chorioretinopathy associated with common variable immunodeficiency. A & B. Fundus photo of OD and OS, respectively, showing optic nerve edema (red arrow) and yellow creamy chorioretinal infiltrates (yellow arrows). **C & D.** Mid phase fluorescein angiography (FA) showing diffuse optic nerve hyperfluorescence OD and diffuse optic nerve hyperfluorescence as well as central foveal leakage in a petalloid pattern OS, respectively. **E & F.** Optic nerve optical coherence tomography (OCT) showing significant optic nerve elevation due to edema OD and OS, respectively. **G & H.** Retinal nerve fiber layer (RNFL) thickness graph showing increased thickness due to edema in OD and OS, respectively. **I & J.** Macular OCT showing normal retinal architecture OD and significant cystoid macular edema (CME) OS, respectively. **K & L.** Humphrey visual field (30-2 SITA) showing no abnormalities OD and enlarged blind spot (red circle) OS, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

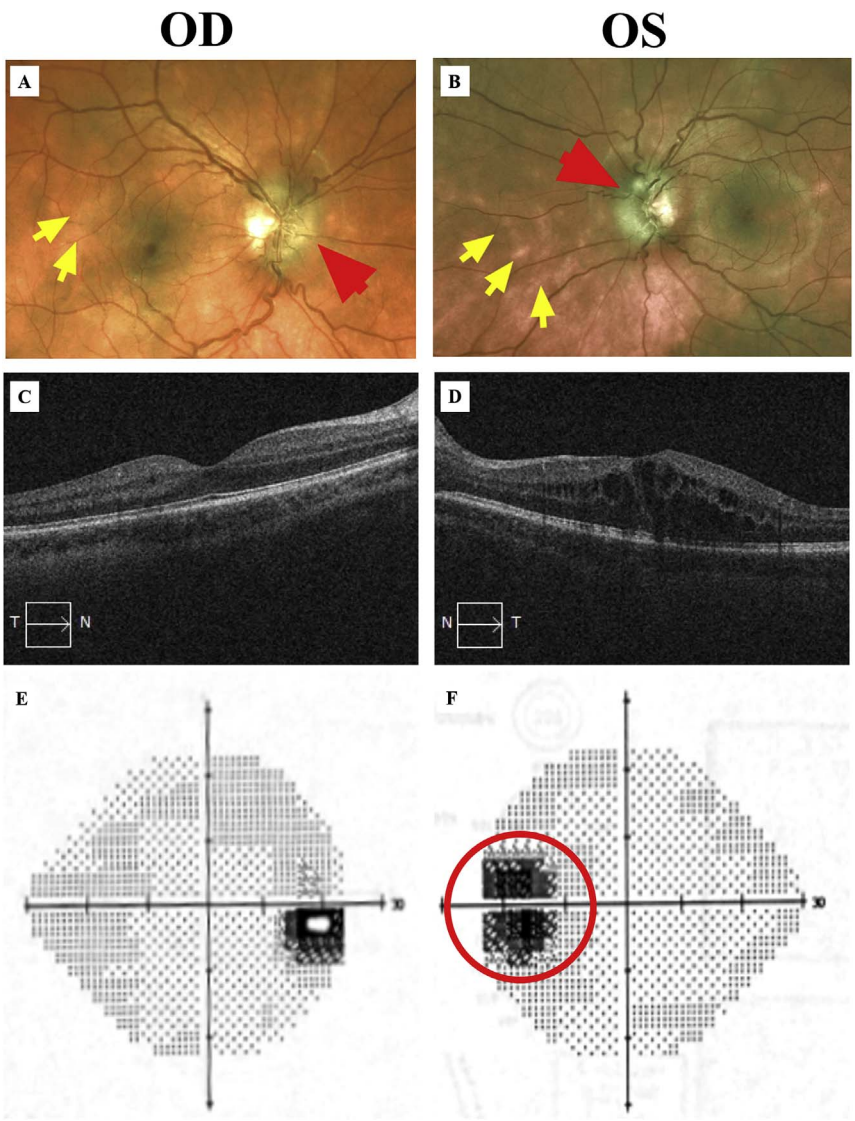

Fig. 2. 6-months follow-up: 22-year-old man with HLA-A29 negative Birdshot-like chorioretinopathy associated with common variable immunodeficiency. A & B. Fundus photo of OD and OS, respectively, showing persistent optic nerve edema (red arrow) and yellow creamy chorioretinal infiltrates (yellow arrows). **C & D.** Macular OCT showing subtle small cysts foveally and perifoveally OD and improving but persistent CME OS, respectively. **E & F.** Humphrey visual field (30-2 SITA) showing no abnormalities OD and a denser enlarged blind spot compared to that seen at presentation (red circle) OS, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

revealed bilateral optic nerve hyperfluorescence (Fig. 1C and D). The optic nerve edema OU was documented on OCT (Fig. 2E and F) and the corresponding retinal nerve fiber layer TSNIT profile was typical for RNFL edema (Fig. 2G and H).[13] Indocyanine green (ICG) angiography revealed hypofluorescent choroidal lesions in the juxtapapillary region, again most pronounced in the left eye. There were no signs of vitritis on both clinical exam and B-scan ultrasonography. Macular optical coherence tomography (OCT) was normal OD (Fig. 1I) but showed significant cystoid macular edema (CME) OS (Fig. 1J). While the 30-2 Humphrey visual field was normal OD (Fig. 1K), it showed an enlarged blind spot OS (Fig. 1L). It is important to emphasize that the patient's myopic tilted disc could contribute to this visual field abnormality. However, in the context of an inflammatory papillitis confirmed on fundus exam, OCT and FA, the enlarged blind spot is likely attributed to the underlying inflammatory pathology rather than to the anatomical myopic variant. Electroretinograms were remarkable for diminished amplitudes most severe in the left eye (data not shown).

An extensive work was performed to rule out major infectious, neoplastic and inflammatory etiologies. A computed tomography (CT) scan of the brain without intravenous contrast was performed and was normal. Subsequently, a magnetic resonance imaging (MRI) study of the brain without gadolinium was done and was also unremarkable. A lumbar puncture showed normal opening pressure of 20 mmH_2O. The cerebrospinal fluid analysis was negative for infectious processes. Furthermore, no evidence of infectious or secondary autoimmune processes were detected on blood work up. Human leukocyte antigen-typing was negative for HLA-A29.

The patient's ocular symptoms were likely associated with the autoimmune and inflammatory components of his disease. As such, the management options were carefully reviewed with the patient and included periocular and intraocular steroid injections along with systemic immunomodulation therapy. Despite the variable responses to corticosteroid treatments in the literature, we believed that the treatment of the ocular manifestation was indicated.[14] Other treatment options included high-dose IVIG. The patient ultimately declined all treatment options based on the risk-benefit profile of latter.

There were no changes in the patient's clinical exam at the second month of follow-up. As observation continued, by the 6-month follow-up visit, the VA in the left eye improved from 20/60 to 20/40. The previously noted bilateral chorioretinal infiltrates and optic nerve edema remained stable (Fig. 2A and B). The macular OCT was showed new small cysts foveally and perifoveally OD (Fig. 2C). The previously noted CME on OCT OS slightly improved and the central foveal thickness decreased from 570 μm to 412 μm (Fig. 2D). 30-2 Humphrey visual fields showed a denser and persistent enlarged blind spot OS (Fig. 2F). Despite the mild changes in the patient's ocular presentation, he still

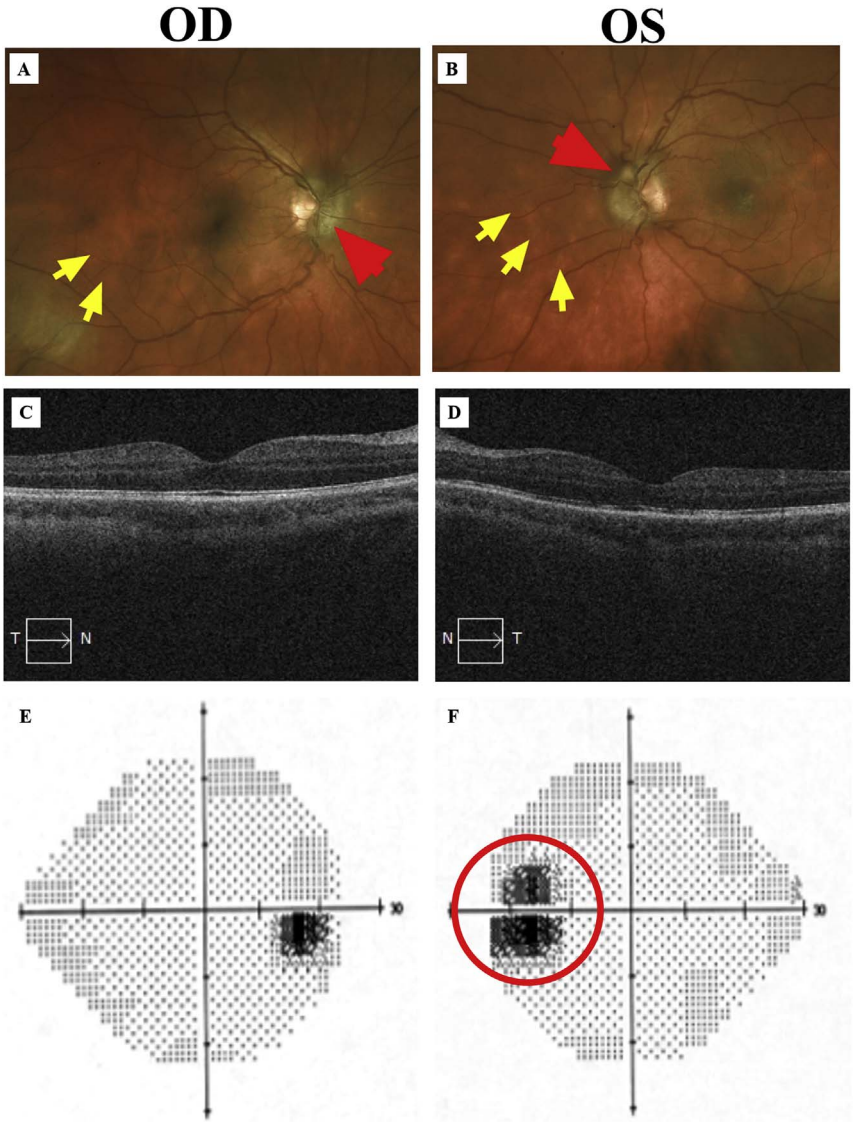

Fig. 3. 15-months follow-up, 3 months post intravitreal injection of triamcinolone: 22-year-old man with HLA-A29 negative Birdshot-like chorioretinopathy associated with common variable immunodeficiency. **A & B.** Fundus photo of OD and OS, respectively, showing persistent optic nerve edema (red arrow) and yellow creamy chorioretinal infiltrates (yellow arrows). **C & D.** Macular OCT showing normal retinal architecture OD and resolved CME and re-establishment of normal retinal architecture OS, respectively. **E.** Humphrey visual field (30-2 SITA) showing no abnormalities OD and a persistently enlarged blind (red circle) OS, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

declined all treatment.

At the 12-month follow up, the previously described bilateral chorioretinal infiltrates and optic nerve edema were unchanged. CME persisted in the left eye with a corresponding VA of 20/50. At that time the patient agreed to an intravitreal injection of triamcinolone 2mg (IVK). Three months following the IVK injection, the patient's left eye improved to 20/20 and the previously reported CME completely resolved (Fig. 3D). There was, however, no change in the previously noted chorioretinal lesions (Fig. 3A and B) and the enlarged blind spot OS persisted (Fig. 3F).

Twenty months after the initial presentation, the patient reported severe unremitting headaches. No changes were noted in his ophthalmologic clinical exam. CVID is not typically associated with neurologic symptoms and there are no standardized treatment protocols for such a CVID-associated clinical presentation. A decision was made by the treating immunologist and the patient to start a trial of IVIG therapy given the lack of clear etiology for his headaches and the unsuccessful control of the symptoms with pain relievers. The patient was evaluated 4-months post IVIG treatment (i.e. two years after the initial presentation) and found to have a VA of 20/20 OU. While the creamy chorioretinal lesions were still unchanged OU there was the suggestion of less optic nerve head edema OS on fundus examination (Fig. 4A and B). The macular OCT scans continued to show an absence of CME OU (Fig. 4C and D). The 30-2 Humphrey visual field was normal OD and showed an improving but persistently enlarged blind spot OS (Fig. 4E and F). The patient reported that his headaches resolved following the IVIG treatment.

3. Discussion

CVID is the most common primary immunodeficiency syndrome in humans. Despite not being fully understood, the pathophysiology of CVID is related to an abnormal activation of T-cell lymphocytes, which are important for B-cell induction. This leads to defects in B-cell differentiation and lymphocytosis stemming from a continuous state of T-lymphocyte activation.[2] Interestingly, CVID can be classified into two main phenotypes: those with only a history of infections and those who additionally have associated inflammatory and/or autoimmune conditions. The latter subset of patients is the most difficult to treat and control given the high likelihood of morbidity and mortality associated with immune suppressive treatments. The largest longitudinal studies on CVID showed that 70% of patients suffered from inflammatory manifestations.[15,16] The most prevalent of these conditions is progressive lung diseases (28%).[16] Additionally, about 10% of patients develop a sarcoid-like syndrome with non-caseating granuloma deposition.[3]

CVID-associated ocular involvement is very rare and is thought to be related to CD4 + T-cell infiltrative lymphocytosis. So far, nine cases

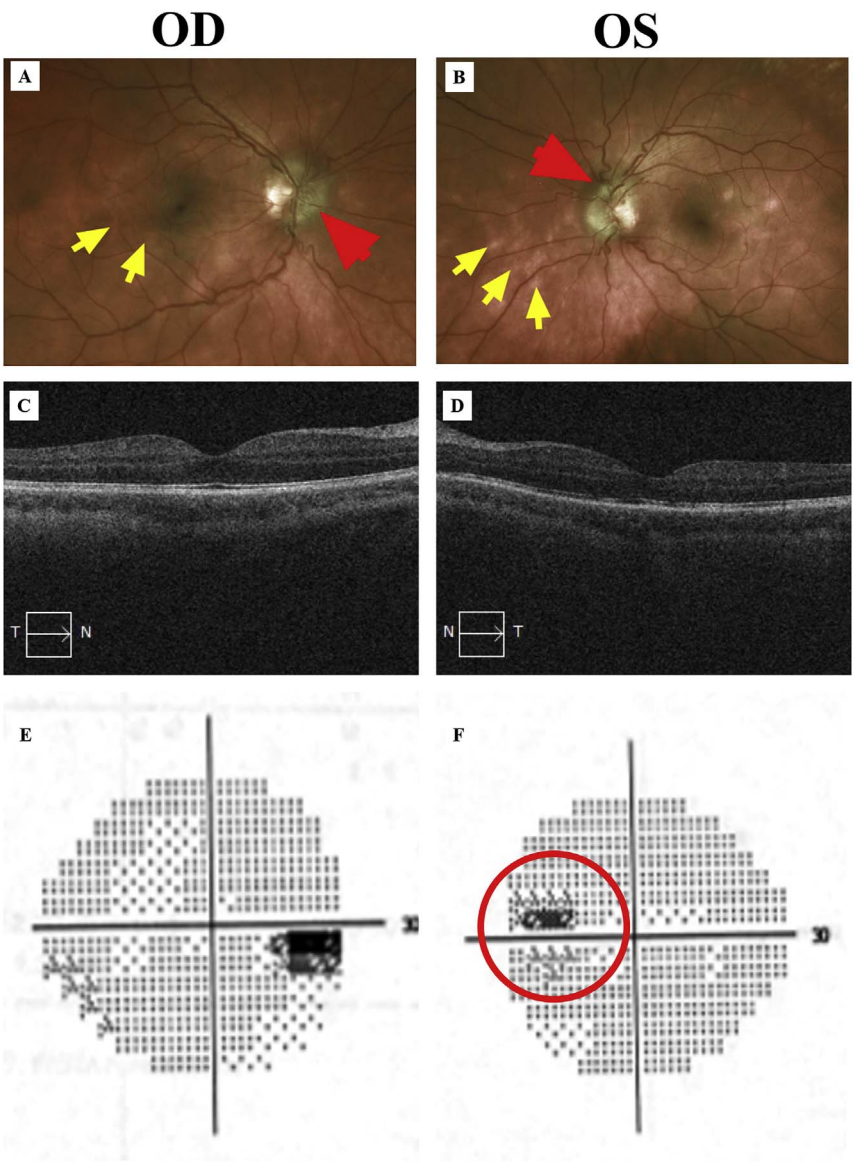

Fig. 4. 24-months follow-up, on 4 months of IV immunoglobulin treatment: 22-year-old patient with HLA-A29 Birdshot-like chorioretinopathy associated with common variable immunodeficiency. **A & B.** Fundus photo of OD and OS, respectively, showing persistent optic nerve edema (red arrow) and yellow creamy chorioretinal infiltrates (yellow arrows). **C & D.** Macular OCT showing normal retinal architecture OD and OS, respectively. **E.** OD Humphrey visual field (30-2 SITA) showing no major abnormalities (pattern standard deviation did not differ significantly from previous: 4.30 dB at 6 months vs. 4.15 dB at 24 months). **F.** OS Humphrey visual field (30-2 SITA) showing a reduced and less dense blind spot (red circle). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

have been reported in the literature (Table 1). van Meurs et al. described three cases of retinal vasculitis in patients with CVID.[11] In all three cases, optic nerve and macular edema were reported bilaterally with no chorioretinal infiltrates present (Table 1). The first case, which was complicated by retinal vasculitis and choroidal neovascularization (CNV), was treated with peribulbar steroid injections that possibly helped to preserve the visual acuity over 10 years despite persistent macular and optic nerve edema. In the second and third cases, which were also complicated by CNV, both systemic prednisone and cyclosporine were not sufficient to preserve functional vision.[11]

Cohen et al. reported a case of CVID-associated bilateral granulomatous uveitis and optic nerve edema characterized by multifocal areas of choroidal pallor and anterior chamber cells (Table 1). There was no evidence of vitritis or retinal vascular changes. Topical steroids were effective in preserving the patient's visual acuity.[8] Kashani et al. described a case of CVID-associated bilateral choroidal granulomas in an asymptomatic 27-year-old man.[7] Multiple pale choroidal lesions were noted on examination without any signs of inflammation in both the anterior and posterior segments. The patient was successfully managed with oral prednisolone. Gray et al. reported a case of CVID in a 55-year-old man who presented with decreased VA OD with CME and vitritis as well as creamy chorioretinal infiltrates.[12]

Birdshot chorioretinopathy (BCR) is a very rare cause of autoimmune uveitis with an incidence of 0.2–1.7 cases per 100,000[6]. Its etiology remains unknown but there is a very strong association with the HLA-A29 haplotype. Affected patients typically complain of blurry vision, floaters and nyctalopia. Fundus exam is relevant for multiple, cream-colored depigmented choroidal lesions with a preferential scattering in the peripapillary region. These lesions, which can fluctuate in number and size over time, classically give the “Birdshot” fundus appearance responsible for the name of the condition. BCR is typically bilateral and typically has some degree of vitritis.[6]

In 2012, de Maeyer et al. gave the name of “Birdshot-like chorioretinopathy” (BLCR) after reporting a similar scattering of creamy depigmented choroidal lesions that were preferentially located in the peripapillary region of a 17-year-old woman with known CVID and HLA-A29 negative haplotype.[9] Despite a fundus appearance mimicking BCR, the absence of the HLA-A29 haplotype in the context of CVID makes this chorioretinopathy a birdshot-like chorioretinopathy: hence the name BLCR. The patient was on hydroxychloroquine for lymphoid interstitial pneumonia and presented with creamy chorioretinal infiltrates concentrated in the posterior pole and juxtapapillary region along with optic nerve edema OU and a spontaneously resolving serous retinal detachment OS. The patient was also noted to have bilateral S-shaped superior

Table 1
Summary of previously reported cases of Birdshot-like chorioretinopathy associated with common variable immunodeficiency.

Authors	CVID	Ocular Findings at Presentation								Treatment
		Visual acuity	HLA-A29	Vitritis	Optic nerve edema	FA leak along major retinal arcades	Macular edema	Chorioretinal infiltrates	Others	
van Meurs et al., 2000[9]	✓	OD: 20/40 OS 20/20	Not mentioned	✓	✓ OU	Not mentioned	✓ OU	×	Vasculitis, CNV	Peribulbar steroid injections
	✓	OD: 5/200 OS: 20/100	Not mentioned	×	✓ OU	Not mentioned	✓ OU	×	Vasculitis, CNV	PO steroid, cyclosporin
	✓	OU: 20/200	Not mentioned	✓	✓ OU	Not mentioned	✓ OU	×	Vasculitis	PO/IV steroid, cyclosporin
Gray et al., 2003[7]	✓	OD: 20/60 OS: 20/20	Not mentioned	OD	Not mentioned	Not mentioned	✓ OD	✓ OD	OD anterior chamber cells	Orbital floor injection depomedrone, Topical steroid
Cohen et al. 2005[10]	✓	OD: 20/20 OS: 20/30	Not mentioned	×	✓ OU	Not mentioned	×	✓ OS	OU granulomatous uveitis with mutton-fat keratic precipitates and anterior chamber cells	Topical steroid
Kashani et al. 2005[11]	✓	Not mentioned	Not mentioned	×	×	Not mentioned	×	✓ OU	None	PO steroid
de Maeyer et al. 2012[12] *BLCR case#1*	✓	20/20 OU	×	×	✓ OU	✓ OU	OS Serous retinal detachment	✓ OU	None	IVIG, systemic corticosteroids, PO hydroxychloroquine
Oh et al. 2014[2] *BLCR case#2*	✓	OD: 20/15 OS: 20/300	×	×	✓ OU	✓ OU	✓ OU Serous retinal detachment	✓ OU	None	IVIG, SCIG, IVK, PDT
Our case ***BLCR case#3***	✓	OD: 20/30 OS: 20/60	×	×	✓ OU	✓ OU	✓ OU (OS > OD)	✓ OU (OS > OD)	Enlarged blind spots OU (OS > OD)	IVK, IVIG

✓: indicates presence of a given condition. ×: indicates absence of a given condition.
Abbreviations: CVID, Common variable immunodeficiency; BLCR, Birdshot-like chorioretinopathy; FA, fluorescein angiography; PO, per os; IV, intravenous; IVIG, intravenous immunoglobulins; SCIG, subcutaneous immunoglobulins; IVK, intravitreal triamcinolone; PDT, photodynamic therapy.

eyelid swelling. The patient was treated with systemic steroids, IVIG and continued oral hydroxychloroquine.

Oh et al. reported a similar case with characteristic patchy, cream-colored hypopigmentation of the choroid in keeping with HLA-A29 negative BLCR in a patient with CVID. Despite treatment, which included systemic IVIG, intravitreal steroids and photodynamic therapy to treat a serous retinal detachment, the vision did not improve. The patient died from systemic complications of CVID shortly thereafter.[1]

It is worth mentioning that it is unusual for typical HLA-A29 + BCR to present with severe and persistent optic nerve edema as the one described in our case. Interestingly, the other two case of BLCR also reported noticeable optic nerve edema. Additionally, in all three cases of BLCR reported so far, there is no retinal vascular leakage of the main arcade vessels on FA. This is as opposed to classic BCR, which displays significant leakage. Perhaps, the severity and persistence of the optic nerve edema as well as the absence of major arcade leakage on FA can be considered useful characteristics to differentiate BCR from BLCR (birdshot-like).

In summary, ocular manifestations of CVID are indeed rare. Case descriptions are not uniform and follow a spectrum of pathology with chorioretinal infiltrates being a common finding. To our knowledge, this is the third case of documented HLA-A29 negative BLCR associated with CVID. It is, however, the first case with a two-year follow-up documenting both functional and anatomical changes pre- and post-treatment. Treatment for BLCR associated with CVID can include topical, local and systemic options. Despite improvement in the macular edema OS following one dose of intravitreal triamcinolone, local treatment has limited efficacy as it does not treat the underlying presumed immunological cause. Lifelong antibody replacement therapy with human serum immunoglobulins, whether intravenous, intramuscular or subcutaneous, is needed in patients with CVID. It is not yet known whether systemic treatment with immunoglobulins alters the classic fundus appearance of BLCR and/or modify the risk of recurrent ocular complications. However, based on previous reports (Table 1), it seems that most HLA-A29 negative BLCR patients, who were treated with local corticosteroids and systemic immunoglobulins, were able to preserve their visual acuity.

Patients with CVID are predisposed to a variety of autoimmune illnesses. The eye is another organ that can reflect the activity of CVID. Based on our report and those previously reported, we recommend that all CVID patients undergo baseline and periodic ophthalmic exams in order to detect and treat complications of this systemic disease.

Patient consent

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

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Conflict of interest

RGC and FA have no financial disclosures. We have the following financial and/or commercial disclosures to disclose:

- D. E. Lederer is a consultant for Alcon, Bayer, Janssen, Novartis and Zeiss.

Authorship

Each of the authors has contributed equally to prepare, edit and approved this manuscript. All authors attest that they meet the current ICMJE criteria for Authorship.

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