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Birdshot chorioretinopathy in an HLA-A29 positive Asian patient

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ABSTRACT

Purpose: To present a case of birdshot chorioretinopathy (BCR) in a Chinese patient with HLA-A29 positivity.
Observations: A 45-year-old Chinese female presented at a tertiary Ophthalmology Clinic with complaints of frequent headaches as well as blurred vision, photophobia, and pressure in the left eye (OS). The patient had a significant ocular history of left orbital cavernous hemangioma status post lateral orbitotomy and resection. Uncorrected visual acuity was 20/20 in the right eye (OD) and 20/40 in OS (pinhole 20/30). Funduscopic examination demonstrated optic disc edema, left eye worse than right eye, and vascular tortuosity in both eyes (OU). Late phase fluorescein angiography (FA) showed extensive perivascular and optic disc leakage and peripheral capillary leakage in OU. Laboratory evaluations were positive for human leukocyte antigen-A29 (HLA-A29). The patient was started on 40 mg prednisone daily; mycophenolate mofetil 500 mg twice daily was subsequently added.
At the 3-month consultation visit to the Uveitis Clinic, dilated funduscopic examination revealed 1+ vitreous cells and improved optic disc edema in OU. FA showed improved vascular and optic disc leakage in OS but worsened leakage in OD. At this point, indocyanine green angiography (ICGA) was ordered which revealed hypocyanescent lesions throughout the choroid that were centered on the optic disc, supporting and confirming the diagnosis of BCR.
Conclusions and Importance: The index patient is the first reported case of BCR in an HLA-A29 positive Asian patient.

1. Introduction

Birdshot chorioretinopathy (BCR) is a rare form of chronic bilateral posterior uveitis with an incidence of 0.1–0.6 cases per 100,000 individuals.[1] BCR accounts for approximately 0.6–15% of cases seen at uveitis centers.[2] In a study examining pooled data of over 500 patients with BCR, the authors indicated that the average age at presentation was 53 years old (15–79 years) and 54.1% were female.[3]

BCR is strongly associated with the human leukocyte antigen serotype HLA-A29 and is most prevalent in Caucasians.[1] Although the association of BCR with HLA-A29 is among the strongest in all known HLA-associated diseases, the diagnosis of BCR cannot be made based solely on the presence of HLA-A29 positivity; rather, it requires the clinical finding of chorioretinal lesions seen on clinical examination and/or ICGA. BCR has not been described or reported among patients of Asian ethnicity. The index report describes a case of BCR in a Chinese patient with HLA-A29 positivity. To our knowledge, this is the first report of BCR in an HLA-A29 positive Asian patient.

2. Case report

A 45-year-old Asian female born to two native Chinese and raised in China presented with complaints of frequent headaches, blurred vision, photophobia, and pressure in the left eye (OS) that began one month prior to presentation. Genetic testing showed that 99.9% of the patient's ancestral heritage is Chinese and Southeast Asian (https://www.23andme.com). The patient had a history of left orbital cavernous hemangioma status post left lateral orbitotomy and resection 6 years prior to presentation. She had no other significant ocular history except for a previously diagnosed posterior vitreous detachment in OS.

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Upon examination, the patient's uncorrected visual acuity (VA) was 20/20 in the right eye (OD) and 20/40 in OS, which improved to 20/30 with pinhole. Intraocular pressure (IOP) was 18 and 12 mmHg in OD and OS, respectively. Slit-lamp examination (SLE) of the anterior segment was unrevealing in both eyes (OU). Fundus examination showed optic disc edema which was worse in the left eye than the right, and vascular tortuosity in OU (Fig. 1). A few poorly-defined cream-colored lesions were visible inferonasal to the optic disc in OD (Fig. 1). Extensive laboratory evaluation was ordered to assess for infectious and inflammatory markers. The patient was sent to the Emergency Department for magnetic resonance imaging of the brain and orbit with and without contrast which showed no evidence of a mass lesion or vascular process.

At 7-day follow-up, uncorrected VA was 20/20 in OD and 20/40 (pinhole 20/30) in OS. Laboratory evaluations were all negative, including syphilis treponemal and QuantiFERON tests, except for HLA-A29 positivity. The patient had normal blood levels of angiotensin-converting enzyme and lysozyme, providing evidence against sarcoidosis as a possible etiology. A chest x-ray revealed no granulomas. Fluorescein angiography (FA) imaging showed late phase optic nerve, perivascular, and temporal retina leakage in OD and late phase optic nerve, perivascular, and diffuse retinal leakage in OS (Fig. 2). Prednisone was started at 40 mg once daily.

At 18-day follow-up, uncorrected VA was 20/20 and 20/25 in OD and OS, respectively. Dilated fundus examination revealed 1+ vitreous cell in OU and findings previously noted, including optic disc edema left eye worse than right and vascular tortuosity in OU. FA in OU showed improved but persistent leakage (Fig. 3). Given the improvement on FA, prednisone dose was tapered and mycophenolate mofetil was started at 500 mg twice daily by the referring ophthalmologist. The patient was also referred to the Uveitis Service.

At the initial consultation in the Uveitis Clinic, best-corrected visual acuity (BCVA) was 20/20 in OU. FA showed worsening optic disc and vascular leakage in OD but improvement in OS. At this point, based on the clinical suspicion and laboratory results, even though there were very subtle finding of chorioretinal lesions on funduscopic examination, indocyanine green angiography (ICGA) was performed which revealed diffuse hypocyanescent punctate spots throughout the choroid (Fig. 4). The subtle cream-colored lesions identified on fundus examination appear to correspond to hypocyanescent spots on ICG (Fig. 1). The diagnosis of BCR was therefore confirmed. To control the inflammation better, mycophenolate mofetil was increased to 1000 mg twice daily and prednisone dose was increased to 40 mg daily.

3. Discussion

We have described a case of a 45-year-old HLA-A29 positive, Chinese female diagnosed with BCR. BCR is most prevalent in Caucasians, and to the best of our knowledge, no case of BCR has ever been reported in an HLA-A29 positive patient of Asian ancestry.[1,4]

The differential diagnosis for posterior uveitis in similar age groups includes infectious etiologies, such as tuberculosis and syphilis, autoimmune etiologies, including sarcoidosis and white dot syndromes, and masquerade etiologies, such as lymphoma. Laboratory and imaging results, including HLA-A29 positivity and hypocyanescent choroidal lesions on ICGA are consistent with BCR. Based on this clinical scenario, we propose that the index patient is the first reported HLA-A29 positive Asian patient with a diagnosis of BCR.[4]

BCR associated inflammation is usually limited to the posterior segment of the eye.[1] The fundus typically reveals whitish, yellow chorioretinal lesions ranging in diameter from 500 to 1500 μm.[1] They tend to be localized around the optic nerve and posterior pole and spread outwards towards the periphery.[1] As the disease progresses, these lesions become increasingly atrophic.[1] These lesions are not always evident on fundus examination.[5] Because of these characteristic small, whitish-yellow chorioretinal lesions that resemble birdshot ammunition scatter, the disease was dubbed "birdshot" chorioretinopathy.[6]

It is possible that our patient is in an early stage of the disease and has yet to develop more evident whitish-yellow chorioretinal lesions typically seen in BCR. Reddy et al.[7] suggest that ICGA lesions seen in BCR are present before choroiditis and retinitis manifest clinically. Godel et al.[5] noted that the characteristic whitish-yellow fundus lesions may not be present on fundus examination in the early stages of the disease and may only begin to manifest up to eight years after onset of symptoms. Knezevic et al.[8] describe an HLA-A29-positive African American patient who did not have fundus lesions visible on clinical exam but had hypocyanescent lesions on ICGA. Given other features of the clinical course, the authors diagnosed the patient with BCR.[8] Based on The Classification Criteria for Birdshot Chorioretinitis set in place by the Standard of Uveitis Nomenclature Group, diagnostic criteria for BCR can be satisfied by having multifocal hypocyanescent spots on ICGA without characteristic "birdshot" spots on ophthalmoscopy in addition to HLA-A29 positivity.[9]

BCR is a disease that disproportionately affects non-Hispanic Caucasians.[1] There are few documented cases of BCR in other racial groups. There have been two incidences of BCR documented in Hispanic patients.[10,11] In addition, two incidences have been documented in African American patients[8,12,13] In a case study by Saito et al.[14] from 2002, the authors reported that there were 10 documented cases of BCR in Japan. Interestingly, all patients included in that study were HLA-A29 negative.[14] To the best of our knowledge, the index patient may be the first HLA-A29 positive Asian patient with a diagnosis of BCR.

Approximately 95.7% of patients with BCR are HLA-A29 positive.[15]

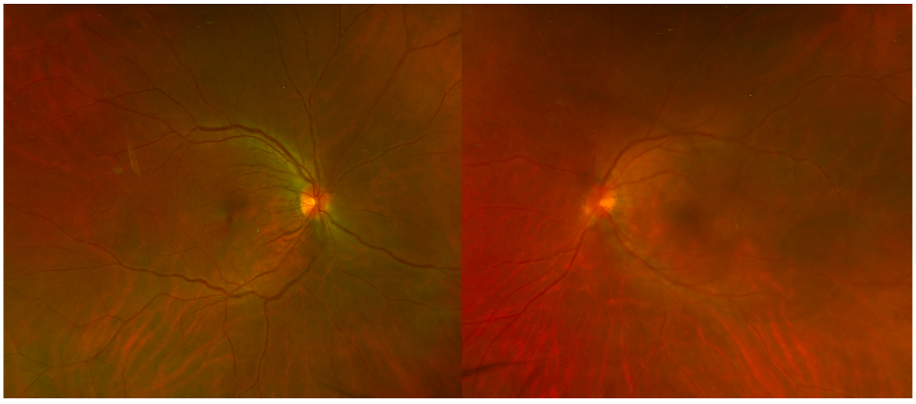

Fig. 1. Color fundus photographs of both eyes at the first visit showing edematous discs that are slightly hyperemic, and venous tortuosity. Poorly-defined cream-colored lesions can be seen inferonasal to the optic disc in the right eye. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

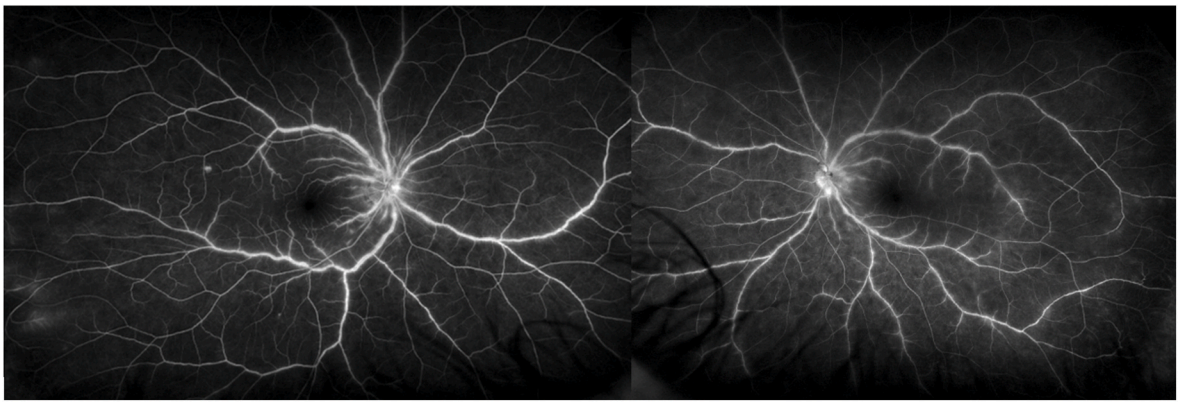

Fig. 2. Left, late phase fluorescein angiography (FA) of the right eye at 7-day follow up showing optic disc, perivascular, and peripheral retina leakage, and staining of a lesion superotemporal to the macula. Right, late phase fluorescein angiography (FA) of the left eye at 7-day follow up showing optic disc, perivascular, and diffuse retinal leakage.

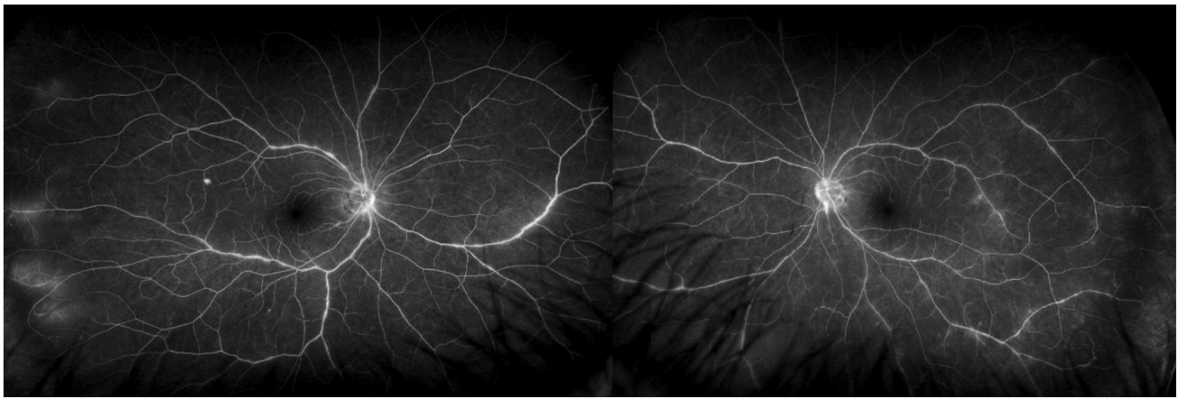

Fig. 3. Late phase fluorescein angiography of both eyes at the 18-day follow-up visit showing improved but persistent optic nerve, perivascular, and retinal leakage.

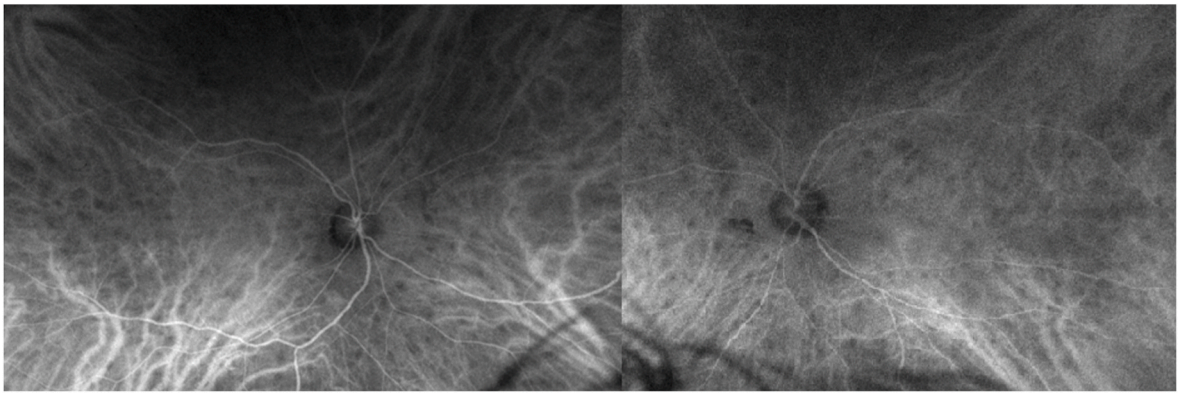

Fig. 4. Indocyanine green angiography of both eyes at the 3-month follow up visit showing diffuse hypocyanescent spots.

This substantial relationship implies that HLA-A29 plays a role in the etiology of BCR. HLA-A29*2902 and HLA-A29*2901 are the two most common genetic variants associated with BCR.[16] HLA-A29*2902, the subtype most commonly associated with BCR, is present in Caucasians at 4.3% and Asians at 0.42%.[16] Minos et al.[1] notes that this may help to explain why BCR is most commonly seen in Caucasians versus Asian populations. This finding, however, does not offer an explanation as to why BCR is less prevalent in African-American and Hispanic populations compared to Caucasians.[1] The presence of HLA-A29*2902 in African-Americans and Hispanics, respectively, is 3.57% and 4.91%.[16]

Given the relatively common prevalence of the HLA-A29 allele, the presence of the gene alone cannot be the sole cause attributing to BCR development.[15] Certain environmental factors have been suggested to play a role in BCR development in patients who are predisposed due to presence of the HLA-A29 allele.[15] Antigens such as the retinal S-antigen and interphotoreceptor retinoid-binding protein may have a role in BCR pathogenesis.[17,18] In a genome-wide association study, the authors discovered polymorphisms near the endoplasmic reticulum aminopeptidase 2 (ERAP2) gene at 5q15 that predispose patients to BCR.[19] It is still largely unknown why BCR is most prevalent among Caucasians and additional studies are needed to elucidate the pathogenesis of this disease.

We are describing the index patient to demonstrate that, despite the fact that BCR is uncommon in non-Caucasians, it is not impossible.

4. Conclusions

Birdshot chorioretinopathy is a chronic bilateral posterior uveitis that affects a significantly higher proportion of non-Hispanic Caucasians. We describe the first case of an HLA-A29 positive Asian patient with BCR.

Patient consent

Written consent from the patient to publish this report was obtained.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

The following authors have no financial disclosures: JR, HG, AA, PO, VB, DVD, QDN, CO.

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