n 2006, research criteria for birdshot chorioretinopathy (BSCR) were published based on the consensus of an international panel.\(^1\) Required characteristics included bilateral involvement, 3 or more peripapillary birdshot lesions inferior or nasal to the optic disc in at least 1 eye, low-grade anterior chamber inflammation, and low-grade vitreous inflammation. Published supportive findings included human leukocyte antigen (HLA)-A29 positivity, retinal vasculitis, and cystoid macular edema. The presence of keratic precipitates; posterior synechiae; or infectious, neoplastic, or other inflammatory diseases that can cause multifocal choroidal lesions excludes the diagnosis, although this is debated.\(^2\)

These criteria have a reported specificity of 100% and sensitivity of 97.5%. The reported positive predictive value is 100% and negative predictive value is 97.6%, although cases that have met inclusion criteria but ultimately proven to have a different diagnosis have since been published.\(^3\) Indocyanine green angiography (ICGA) may permit visualization of subclinical choroidal lesions, thereby allowing earlier diagnosis and improved monitoring of disease activity\(^4,5\) but does not have well-defined use in the 2006 classification scheme. Here we report 3 patients who did not have characteristic choroidal lesions on clinical examination or fluorescein angiography (FA) but were diagnosed as having BSCR based on lesions evident only on ICGA.

Methods

A retrospective case series was performed on 3 patients with mild to moderate vitritis, retinal vasculitis, and HLA-A29-positive status who did not manifest definite birdshot lesions on clinical examination or FA but had hypocyanescent lesions evident on ICGA. The clinical findings of all patients were assessed from January 2007 to December 2014 at 4 academic ophthalmology centers. All patients’ results were positive for human leukocyte antigen–A29. All cases had hypocyanescent lesions visible on ICGA but not detectable on fluorescein angiography.

Results

Case 1

A patient in his 40s with a history of photopsias, floaters, and decreased vision of 2 years’ duration was seen for chronic vitritis with optic disc edema in both eyes. His ocular history was notable for laser in situ keratomileusis in both eyes and retinal tears status postretinopexy in both eyes. He had previously been treated with intermittent oral corticosteroids for his vitritis but always experienced return of symptoms with tapering. Laboratory workup prior to referral included angiotensin-converting enzyme level, lysozyme, Lyme titer, rapid plasma reagin, fluorescent treponemal antibody absorption, chest x-ray posterior-anterior/lateral, and magnetic resonance imaging, the results of which were normal. Because of his recurrent symptoms, the patient sought a second opinion.

Examination was remarkable for visual acuity of 20/20, trace anterior vitreous cell and haze, mild optic disc edema, and chorioretinal scarring in the areas of prior laser in both eyes.
Figure 1. Birdshot Lesions on Indocyanine Green Angiography in Case 1

A Fundus photography

B Fluorescein angiography

C Indocyanine green angiography

No choroidal lesions are visible on fundus photography (A) or fluorescein angiography (B), but lesions are easily discernable on indocyanine green angiography (C). In all panels, the image on the left shows the right eye and the image on the right shows the left eye.

(Figure 1). Fluorescein angiography demonstrated optic disc and retinal vascular leakage in both eyes but no obvious chorioretinal lesions. Indocyanine green angiography revealed multifocal hypocyanescent lesions, which persisted in the late frames of the ICGA. Because of these lesions imaged by ICGA and despite the absence of chorioretinal lesions, a workup for BSCR was performed including HLA typing, the results of which were positive for HLA-A29.

Oral prednisone was initiated at 60 mg/d, with resolution of symptoms. A repeated ICGA showed complete resolution of the choroidal lesions. Cyclosporin A, 75 mg twice daily, was also initiated and oral prednisone was tapered down to 5 mg/d. At 24-month follow-up, the patient’s visual acuity remained 20/20 in both eyes and the patient remains asymptomatic.

Case 2

A woman in her 60s presented with blurred vision, floaters, and flashes in both eyes. Her best-corrected visual acuity was 20/32 OU and examination was remarkable for bilateral mild vitritis and disc hyperemia (Figure 2A). No choroidal lesions were seen on dilated examination or FA (Figure 2B). Fluorescein angiography did reveal bilateral retinal vascular leakage in both eyes along the arcades. Optical coherence tomography confirmed the absence of macular edema. Indocyanine green angiography revealed hypocyanescent lesions particularly in the inferior and nasal periphery (Figure 2C). She was found to be HLA-A29 positive. Rapid plasma reagin, treponemal antibodies, angiotensin-converting enzyme, lysozyme, antineutrophil cytoplasmic antibody, and antinuclear antibody testing results were negative. She was treated with periocular steroid injections and oral antimetabolite therapy, with resolution of her retinal vasculitis and improvement in her symptoms.

Case 3

A woman in her 40s presented with a history of floaters and photopsias in the right eye more than the left for more than 2 years. She had been diagnosed as having BSCR 18 months earlier, was found to be HLA-A29 positive, and had deferred stan-
standard treatment, opting for dietary supplements. Her symptoms subjectively improved. Best-corrected visual acuity was 20/20 OD and 20/15 OS. There was no anterior segment inflammation and trace anterior vitreous cell. Fundus examination findings were unremarkable (Figure 3). Optic nerve leakage and late vascular leakage were present bilaterally on FA. Indocyanine green angiography displayed multifocal hypofluorescence in both eyes. Results from full-field and multifocal electroretinogram were within normal limits in both eyes. The patient was encouraged to begin treatment with chronic immunosuppression but elected close observation instead.

Discussion

Birdshot chorioretinopathy is a rare, bilateral, chronic posterior uveitis that is largely defined by international consensus criteria, although the exact pathogenesis remains poorly understood. A cardinal criterion for diagnosis is the presence of typical birdshot lesions, which tend to be cream-colored irregular indistinct choroidal lesions extending radially from the optic disc. Histopathologic evidence suggests that the primary lesions in BSCR are in the choroid. Our series suggests that these lesions are detectable by ICGA before choroiditis and retinitis are evident clinically and before characteristic macular edema is manifest. These cases may represent patients in whom the disease was caught early and characteristic fundus lesions may develop over time, especially in the absence of treatment. Alternatively, these patients may have a disease similar to BSCR but without fundus lesions. To our knowledge, there are no documented cases of patients with BSCR progressing from ICGA findings without fundus lesions to characteristic fundus lesions. The cases presented highlight the need for a high index of suspicion of birdshot in patients with retinal vasculitis, disc edema, and vitritis even when fundus examination and FA do not suggest choroidal involvement. In these patients, ICGA is essential in confirming the diagnosis.

Birdshot chorioretinopathy is generally defined by characteristics common to most patients, which were originally designed for research purposes, although heterogeneous features may be seen. Some specialists believe that HLA typing is necessary to establish the diagnosis. Although BSCR is strongly associated with the HLA-A*29 gene, a requirement that it must be positive for the diagnosis has been debated because HLA-negative cases have been reported in the literature. Although BSCR has among the highest relative odds of any HLA-associated disease, indiscriminate screening of patients with posterior uveitis for HLA-A29 yields a positive predictive value less than 50%. The
ability to detect birdshot lesions on FA is also variable,10,12, and this series suggests that ICGA may permit detection of spots in instances when they are otherwise not easily seen. Fluorescein angiography may also demonstrate prolonged transit times13,14 but this is not a pathognomonic feature of disease.

This series suggests that ICGA is a more sensitive measure of choroidal activity11,12 than other modalities and may therefore permit earlier detection of disease. This benefits the patient by reducing the need for expensive testing for other conditions, avoiding delay to diagnosis, and expediting appropriate interventions.

Conclusions

Patients with birdshot lesions visible only on ICGA should be monitored closely with serial examinations, visual field testing, 30-Hz multifocal electroretinograms, and optical coherence tomography, and they should be considered for immunosuppression just as any other patient with birdshot. Expansion of research criteria to include the presence of hypofluorescent lesions on ICGA might improve the sensitivity of diagnosis.

REFERENCES