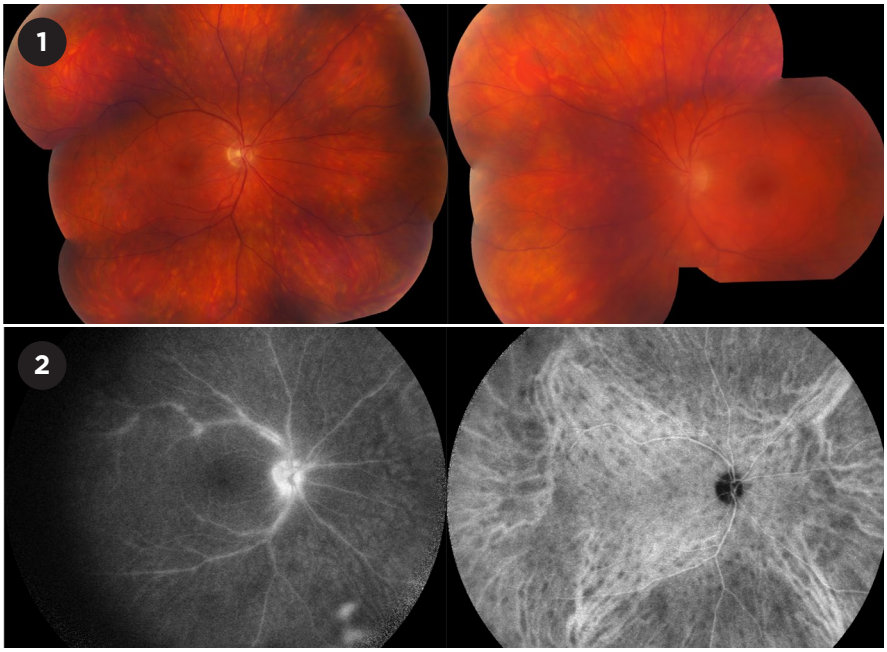
Clinical Follow-Up of Birdshot Chorioretinopathy

Birdshot chorioretinopathy (BSCR) is a bilateral, chronic, posterior uveitis characterized by cream-colored lesions primarily in the posterior pole. It is typically accompanied by vitritis, retinal vasculitis, and cystoid macular edema (CME). BSCR is rare, affecting approximately 8% of patients with posterior uveitis.[1] It has a slight female preponderance and usually manifests in the fourth or fifth decade of life. There is a strong association between BSCR and the HLA-A29 allele.

Ocular symptoms can precede the diagnosis by several years and include shimmering photopsias, floaters, nyctalopia, and blurred vision. However, visual acuity (VA) is often preserved even with end stage disease. Given the chronic nature of BSCR, management usually requires long-term immunosuppression.

Disease monitoring traditionally has been conducted with visual field testing and full-field electroretinography (ERG), but these modalities are cumbersome and detect only the sequelae of intraocular inflammation, making them impractical for real-time disease-management decisions. A beneficial alternative approach to disease monitoring is based on OCT with enhanced depth imaging (OCT-EDI), widefield fundus autofluorescence (FAF), and, if indicated, fluorescein angiography (FA) and indocyanine green angiography (ICGA).



SIGNS. *(1) Classic funduscopic appearance of BSCR: ovoid cream-colored lesions. (2) FA and ICGA (late frame) of the right eye. Note the large-vessel vasculitis (left) and multiple hypocyanescent lesions (right).*

Determining the Diagnosis

A consensus document on BSCR diagnosis was released in 2006.[2] The diagnostic criteria are bilateral disease, low-grade inflammation of the anterior chamber (≤1+ cell), low-grade vitreous inflammation (≤2+ vitreous haze), and at least three peripapillary cream-colored lesions (Fig. 1). It is important to note that these classic lesions may not necessarily be present until the patient has experienced symptoms for several years. Other findings that support the diagnosis include HLA-A29 positivity, retinal vasculitis, and CME. The exclusion criteria are significant keratic precipitates, posterior synechiae, and a diagnosis of any other infectious, inflammatory, or neoplastic condition that can lead to multifocal choroiditis.

Imaging. Several imaging modalities may help to establish the diagnosis. ICGA can depict the birdshot lesions as multiple scattered hypocyanescent spots (Fig. 2). Often, the number of spots detected by ICGA is much greater than that seen clinically. FA may reveal vasculitis of large veins or smaller vessels, which may have a fern-like appearance. OCT also can be used to

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identify characteristics of late-stage BSCR, such as diffuse retinal thinning, a thin choroid, and loss of the ellipsoid zone (EZ) with hyperreflective outer retinal foci.[3]

Monitoring the Disease

The following approach to patient monitoring is recommended.

Signs and symptoms. There is no replacement for a thorough clinical history and exam. Symptoms are key; for example, patients with disease activity often describe shimmering photopsias, which improve or resolve with treatment. VA, however, is not an appropriate indicator for monitoring disease activity, as patients can have end-stage disease with significant retinal atrophy but still maintain good central VA, providing false reassurance to providers. Certainly, a decline in VA warrants investigation and should raise suspicion for CME.

Other indicators of disease activity include vitreous inflammation or clinically apparent retinal vasculitis. Vasculitis of the larger vessels may be seen as subtle venous pinching at the vascular arcades, warranting further investigation with FA. However, in many cases, especially those involving smaller retinal vessels, the vasculitis associated with BSCR is subclinical and identifiable only by FA. Thickness mapping on OCT of the macula can reveal retinal thickening, especially at the vascular arcades, which may clue the clinician to active vasculitis (Fig. 3).[4]

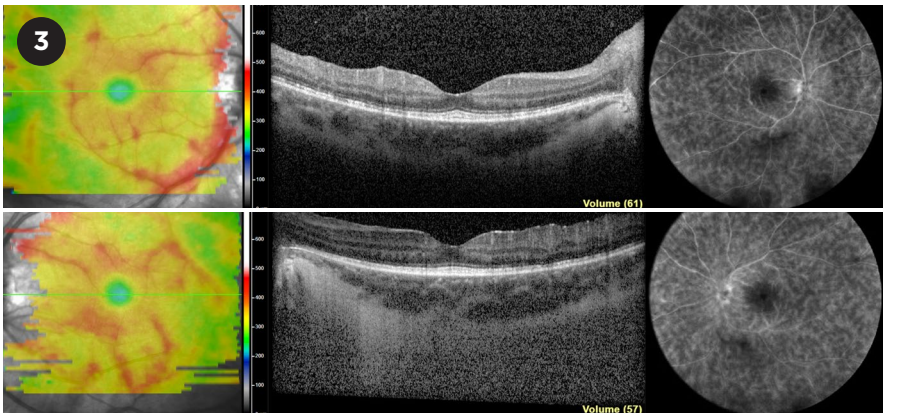
OCT-EDI and FAF. OCT-EDI to evaluate the choroid is invaluable for monitoring disease activity.[5] Choroidal thickness and reflectivity have been extensively studied in BSCR. Compared with age-matched controls, the choroid is thinner in quiescent disease. During active disease, choroidal thickness increases and may be accompanied by a hyporeflective choroid with loss of vascular markings, which may denote inflammatory infiltration (Fig. 4). Hyporeflective foci within the choroid have also been identified as active lesions, but they do not always correlate with the clinically apparent birdshot lesions.

OCT and FAF can be used to identify EZ disruption in BSCR. Acute EZ disruption may occur, and associated diffuse punctiform hyper-autofluorescence (hyper-FAF) may be detected by FAF (Fig. 4).[3,6] Left untreated, EZ disruption may lead to further outer retinal atrophy. If the disruption is extramacular, OCT (nasal to the optic nerve) and widefield FAF can be useful for detecting changes.

FAF can additionally reveal various BSCR patterns.[7] For example, chronic BSCR often includes multiple patterns of hypo-FAF, such as peripapillary, lichenoid, and macular hypo-FAF in the case of resolved CME. These are linked to chronic atrophy of the outer retina and the retinal pigment epithelium.

About ICGA. Although the number and size of lesions on ICGA can decrease with treatment and in some cases may be the main marker of disease activity, this is a relatively difficult marker to routinely follow, and, in many cases, lesions remain despite treatment.[8]

Therefore, OCT-EDI and widefield FAF are the optimal modalities for routine monitoring of disease activity. Additional testing, including ICGA and FA, may be helpful for monitoring responses to changes in therapy and to check the status of characteristics identified by OCT, such as increased retinal thickness.



VASCULITIS. *OCT-EDI and FA of another patient with BSCR shows diffuse fern-pattern vasculitis of the small vessels. The en face OCT thickness map showed thickening (red) of the vasculature in the macula, suggesting active vasculitis, which was confirmed by FA. Although OCT did not show CME, it detected discontinuity and disruption of the EZ.*

Treatment and Prognosis

BSCR generally requires long-term therapy, which may be systemic or local.

Systemic therapy. Long-term immunomodulatory therapy (IMT) is the preferred treatment option for many patients. Although there are no randomized controlled studies of BSCR treatments, ample cohort studies have demonstrated disease control and quiescence with use of IMT. Moreover, this therapy can stabilize the VF and lowers the risk of long-term choroidal thinning.[9]

Many IMT regimens have been used to treat BSCR, including antimetabolites, cyclosporine, anti–tumor necrosis factor (TNF) agents, and interleukin (IL)-2 and IL-6 receptor blockers. The only systemic IMT approved for uveitis treatment is the TNF inhibitor adalimumab. All systemic therapies except for adalimumab are used off label.

Local therapy. Given that BSCR is strictly ocular (not systemic), long-acting steroid implants may be a viable alternative to systemic IMT for patients who have contraindications to IMT or prefer only local treatment.

Long-acting steroid implants include the .59-mg fluocinolone acetonide intravitreal implant (Retisert; Bausch + Lomb), the .19-mg insert (Iluvien; Alimera Sciences), and the .18-mg insert (Yutiq; EyePoint Pharmaceuticals). Retisert has demonstrated high resolution rates for retinal vasculitis and clinical inflammation and has allowed for successful weaning from systemic IMT.[10] However, all patients with Retisert implants will require cataract surgery,

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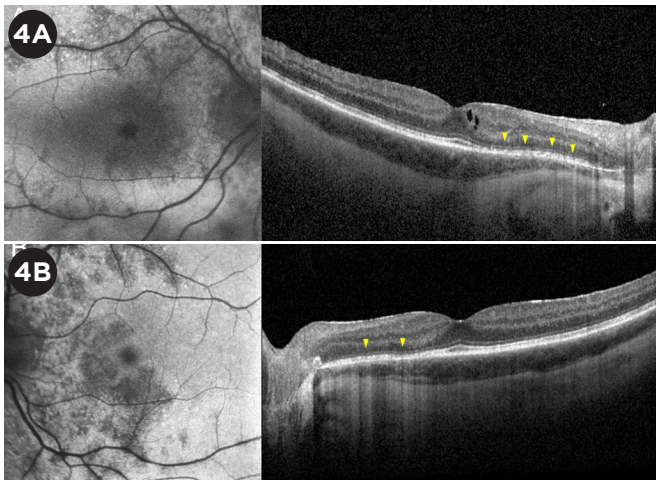
Case Study: BSCR in a 57-Year-Old Woman

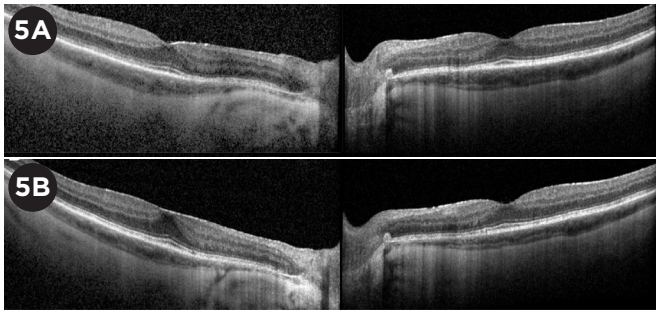
A 57-year-old White woman experienced photopsias and floaters in both eyes in 2017 and underwent vitrectomy in 2019 to address floaters in her left eye. The photopsias and floaters persisted, and BSCR was diagnosed in June 2019. Methotrexate treatment (15 mg/week) was started in November 2020, and the disease was monitored with ERG. In June 2021, the methotrexate dosage was increased to 25 mg/week because ERG detected further deterioration. Despite this, the symptoms continued.

The patient presented to our uveitis service in July 2021. At that time, best-corrected VA was 20/40 in her right eye and 20/20 in her left eye. Noteworthy findings of the clinical exam were mild inflammation of the anterior chamber and 2+ anterior vitreous cell. FA did not show any vasculitis. OCT-EDI demonstrated EZ disruption in the right eye, worse than in the left eye, along with moderate choroidal infiltration and thickening (Fig. 4). Trace CME was found in the right eye via OCT. The patient received an intravitreal dexamethasone implant in her right eye and began treatment with systemic adalimumab. The choroidal infiltration, CME, and EZ disruption improved subsequently (Fig. 5). Final VA was 20/25+2 (right eye) and 20/20 (left eye).

Takeaway messages. There were several clues that this case of BSCR had not been treated adequately. Foremost, the symptoms were persistent, and there was clinical evidence of vitreous cell. Second, there was disruption of the EZ in both eyes and a thickened choroid. Third, CME was noted by OCT. No single symptom or sign guided the treatment. Rather, it was the combination of the patient's symptoms, clinical exam results, and OCT-EDI findings that dictated the need to escalate therapy.



INITIAL VISIT. *FAF and OCT-EDI images of the patient's right eye (4A) and left eye (4B), obtained at the initial consultation. FAF demonstrated areas of peripapillary and scattered hypo-autofluorescence and punctate hyper-autofluorescence. OCT-EDI showed a thickened infiltrated choroid, with patchy areas of outer retinal and EZ disruption (arrowheads denote areas of greatest prominence). CME was apparent in the right eye. VA at this visit was 20/40 in the right eye and 20/20 in the left eye.*



FOLLOW-UP VISIT. *Follow-up OCT-EDI images. (5A) One month after injection of a dexamethasone implant into the right eye, the CME and choroidal infiltration had resolved, and reconstitution of the EZ had begun. (5B) Seven months into adalimumab treatment, there was further evidence of resolution of choroidal infiltration and reconstitution of the EZ, as well as epiretinal membrane formation in the right eye. VA at this visit was 20/25+2 in the right eye and 20/20 in the left eye.*

and many will need glaucoma surgery to control IOP.[10]

The Iluvien implant has been specifically studied in BSCR and has produced good control of retinal vasculitis and CME in patients with this condition. However, many cases have required systemic IMT to resolve choroidal infiltration, indicating that lower-dose implants may not necessarily be sufficient to control the disease.[11] There are currently no studies evaluating the utility of the Yutiq implant in BSCR.

Both Retisert and Yutiq are FDA approved to treat noninfectious intermediate uveitis, posterior uveitis, and panuveitis. Iluvien is not FDA approved to treat any type of uveitis.

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