

# Choroidal Findings in Eyes With Birdshot Chorioretinitis Using Enhanced-Depth Optical Coherence Tomography

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**PURPOSE.** The purposes of this study were to describe choroidal findings observed using optical coherence tomography with enhanced depth imaging (EDI-OCT) in eyes with birdshot chorioretinitis (BSCR) and to test the hypothesis that these findings are related to participant demographics, clinical characteristics, and treatment.

**METHODS.** In a multicenter, cross-sectional study, 172 eyes of 86 individuals with BSCR underwent a standardized clinical evaluation, including defined protocols for EDI-OCT imaging, with macular and peripapillary volume scans. Choroidal findings were compared to demographic information, ophthalmic examination findings, and treatment history, using logistic regression models. EDI-OCT images were evaluated by two independent, masked graders.

**RESULTS.** Median age was 56 years old; 54 participants (62.8%) were female. One or more choroidal lesions (a predefined hyporeflective zone) were identified in 105 eyes (63.6%). Median choroidal thickness was 293  $\mu\text{m}$ . Choroidal lesions were associated with longer disease durations (odds ratio [OR]: 1.08;  $P = 0.03$ ), increased vitreous haze ( $>0.5+$ ; OR: 4.43;  $P = 0.02$ ), presence of macular edema (OR: 3.00;  $P = 0.02$ ), and thick choroids (OR: 3.89;  $P = 0.001$ ). Use of immunomodulatory therapy was associated with lower risk of thin choroids (lower 25th percentile, OR: 0.17;  $P = 0.001$ ) or thick choroids (upper 25th percentile, OR: 0.22;  $P = 0.002$ ). At least some choroidal lesions did not have corresponding, clinically apparent “birdshot lesions” on fundus examination.

**CONCLUSIONS.** Choroidal abnormalities identified by EDI-OCT imaging are common in the macular and peripapillary regions of eyes with BSCR. Choroidal lesions were associated with clinical signs of inflammation, suggesting that they represent foci of disease activity. EDI-OCT may provide useful information about disease mechanisms and response to treatment in future, longitudinal studies of BSCR.

Keywords: birdshot chorioretinitis, EDI-OCT, uveitis

Subretinal, hypopigmented spots are an important feature of birdshot chorioretinitis (BSCR), suggesting involvement of the choroid in disease processes.<sup>1</sup> In the past, the condition was called “vitiliginous chorioretinitis,” on the assumption that the choroid became depigmented in isolated regions.<sup>2</sup> Subsequent studies have led to the general assumption that these “birdshot lesions” are inflammatory in nature and that they are similar to fundus changes caused by sarcoidosis,<sup>3</sup> and limited histopathologic specimens show foci of lymphocytic infiltration.<sup>4,5</sup> Birdshot lesions may not represent the full spectrum of disease features, however. For example, indocyanine green (ICG) angiography may reveal a greater number of hypolucent dark spots than the number of birdshot lesions seen clinically<sup>6–8</sup>; these spots could result from choroidal hypoperfusion, from displacement of vessels by a space-occupying

lesions, or from blockage by the lesions themselves. Monitoring the choroid with ICG angiography can be challenging. For these reasons, alternative techniques for evaluation of anatomic changes in the choroid of eyes with BSCR may be valuable.

Spectral domain optical coherence tomography with enhanced depth imaging (EDI-OCT) may be one such technique. Using EDI-OCT, Mrejen and Spaide<sup>9</sup> demonstrated hyporeflective zones in the choroid of eyes with BSCR. Keane et al.<sup>10</sup> subsequently reported choroidal depigmentation and hyperreflective foci in the choroid and speculated that these findings were most likely inflammatory in nature. Other choroidal findings by EDI-OCT included thinning of the Sattler layer, generalized choroidal thinning, focal depigmentation, and presence of a suprachoroidal space.<sup>10,11</sup> The clinical relevance of these findings remains poorly understood. To expand our

understanding of these choroidal findings, we performed a large, prospective, cross-sectional, multicenter study of people with BSCR, using EDI-OCT. We sought to provide a detailed description of choroidal findings and to identify associations between choroidal findings and other features of the disease.

## METHODS

### Study Population

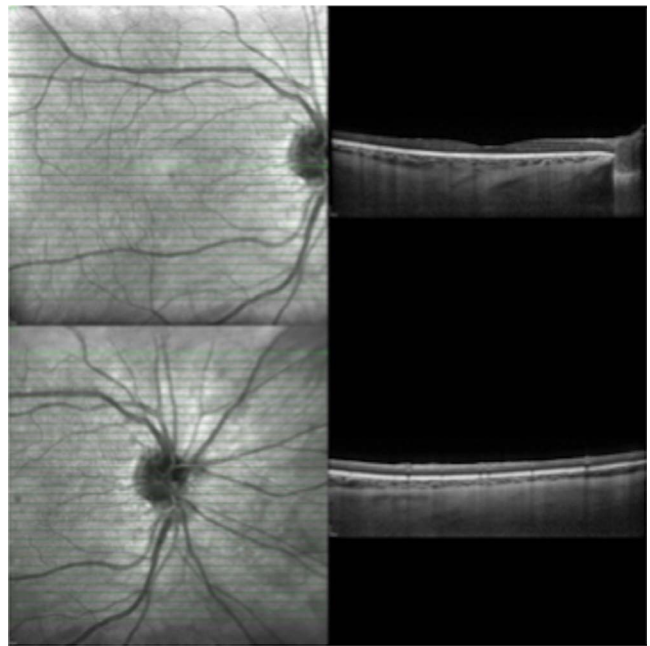
We recruited patients with BSCR from University of California Los Angeles, Johns Hopkins University, Northwestern University, University of Utah, and Duke University. All study participants met criteria for the diagnosis of BSCR, established by an international group of investigators.<sup>12</sup> Individuals with high myopia or hyperopia (spherical equivalent more than 6 diopters [D]), age-related macular degeneration, or diabetic retinopathy were excluded, as these ocular conditions have been associated with choroidal abnormalities on EDI-OCT.<sup>13–15</sup> Individuals with media opacities that precluded imaging were also excluded. The study was approved by the institutional review boards at each clinical site, and written informed consent was obtained from each study participant. The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

All study participants underwent a standardized set of imaging studies, visual function tests, and clinical examinations on a single day, as described below.

### Clinical Evaluations

Data collected from each participant included demographic information (age, sex); medical history; ophthalmic history (duration of visual symptoms attributable to BSCR, interval since diagnosis of BSCR, surgeries [glaucoma, vitreoretinal], or complications of BSCR, including optic disc edema, cystoid macular edema [CME], choroidal neovascularization, or retinal vasculitis); and any past or current treatment for BSCR (topical, regional, or systemic medications, such as oral and intravenous corticosteroids, dexamethasone implant [Ozurdex; Allergan, Inc., Irvine, CA, USA], fluocinolone acetonide implant [Retisert; Bausch and Lomb, Rochester, NY, USA], immunomodulatory agents [methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, infliximab, adalimumab], glaucoma medications, or anti-VEGF agents).

A questionnaire was administered at the study visit to determine the presence or absence of eight prospectively defined visual symptoms in each eye (blurry vision, floaters, nyctalopia, abnormal contrast sensitivity, abnormal color vision, vibrating vision, metamorphopsia, and decreased peripheral vision).<sup>16</sup> Four measurements of visual function were determined. Best-corrected visual acuity (BCVA) was assessed using Early Treatment of Diabetic Retinopathy Study charts, with manifest refraction. Color vision was assessed with the Lanthony desaturated 15-hue color test.<sup>17</sup> Color confusion index (C-index), as described by Vingrys and King-Smith,<sup>18</sup> was determined for each eye by entering participant responses into a Web-based application (<http://www.torok.info/colorvision/d15.htm>; in the public domain). The minimum possible score for C-index is 0.96, with higher C-index values indicating poorer color vision; a C-index value of 1.78 or higher is considered abnormal. Contrast sensitivity (CS) was measured using Pelli-Robson charts.<sup>19,20</sup> The log of the CS (logCS) measurement was calculated and used for analyses. LogCS values <1.5 were considered abnormal, as previously described.<sup>21</sup> Automated perimetry was performed using the 24-2 threshold program of the Humphrey field analyzer (Carl Zeiss



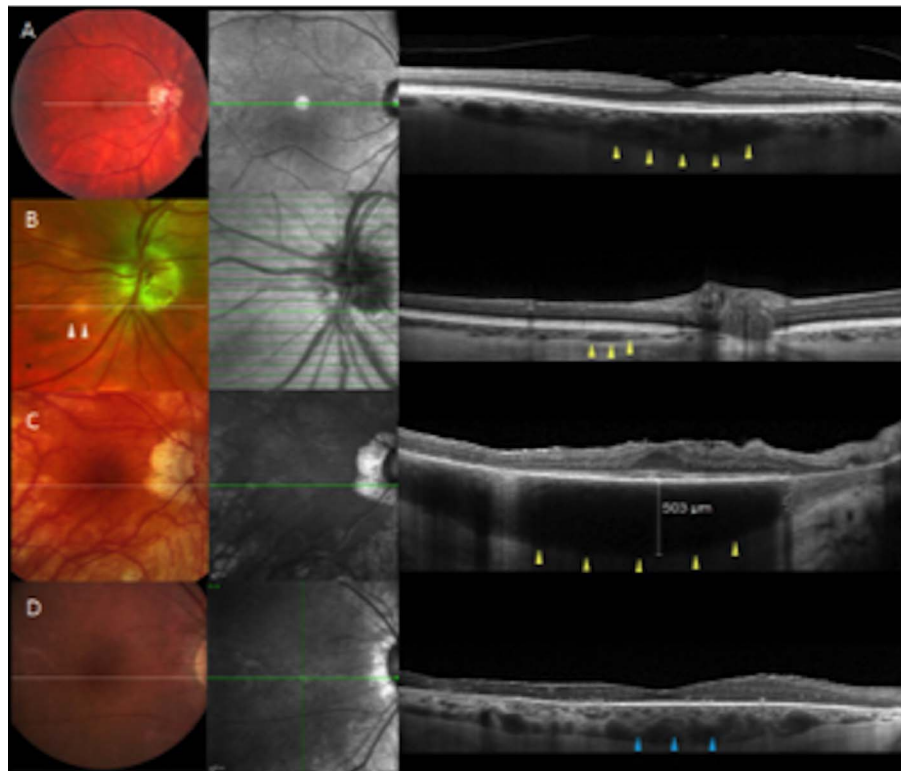
**FIGURE 1.** The OCT imaging protocol included volume scans of the macular region (centered on the fovea, *top row*) and the peripapillary region (centered on the optic disc, *bottom row*). As shown to the *left* of each OCT scan, the near-infrared image illustrates the size of the volume scans according to the predefined protocol. Corresponding fundus images were also obtained (not shown).

Meditec, Dublin, CA, USA). Humphrey visual field mean deviation (HVF-MD) scores were used in analyses; values of  $-3.0$  decibels (dB) or less were considered abnormal.<sup>22,23</sup>

Ophthalmologic examinations included IOP determination by applanation tonometry; assessment of anterior chamber cells by slit-lamp biomicroscopy (categorized according to SUN Working Group recommendations<sup>24</sup>); quantification of vitreous inflammatory reactions (as described by Nussenblatt and associates<sup>25</sup>); dilated indirect ophthalmoscopy (noting the presence or absence of optic nerve abnormalities; CME, choroidal neovascularization, or retinal vasculitis). For study purposes, active disease was defined as a vitreous haze score of  $\geq 0.5+$ . Presence of CME was confirmed with OCT.

### Image Acquisition Protocol and Image Analysis

The Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) was used at each site to acquire macular and peripapillary volume scans (Fig. 1). The macular volume scan was centered on the fovea. The peripapillary volume scan was centered on the optic disc, allowing additional assessment of the area superior, nasal, and inferior to the disc. Both the macular and peripapillary scans were performed using defined settings (EDI mode, high resolution,  $25^\circ \times 30^\circ$  size, 31 horizontal scans, a minimal automatic real time (ART) setting of 16). Spectralis software associated with the device ( $1:1 \mu\text{m}$ ) was used to determine thickness measurements. Additionally, horizontal and vertical single scans through the fovea were obtained using composite scans (including EDI and non-EDI techniques, high resolution,  $30^\circ$  size, ART 100). A scan of the peripapillary retinal nerve fiber layer was acquired with ART 30. Autofluorescence was acquired using the Spectralis system set at  $55^\circ$  with ART 30; a macular scan and an optic disc-centered autofluorescence image were included. Fundus images were obtained using either a Zeiss or a Topcon fundus



**FIGURE 2.** Four cases of birdshot chorioretinitis that illustrate relationships between OCT images (shown with the associated infrared image for each) and the corresponding fundus appearance, which may or may not reveal clinically apparent “birdshot lesions.” (Top row) OCT reveals a large hyporeflective choroidal lesion (*yellow arrowheads*) without a corresponding clinical lesion in the fundus photograph (A). (Second row) OCT shows a small, hyporeflective lesion in the inner choroid, just below the retinal pigment epithelium; the segmentation plane colocalizes at the position of a typical birdshot lesion on the fundus photograph (B, *white arrowheads*). There is a notable absence of choroidal vascular markings. (Third row) OCT shows a large diffuse area of hyporeflectivity in an area of marked choroidal thickening (*yellow arrowheads*), without a corresponding clinically apparent lesion on the fundus photograph (C). This area of hyporeflectivity appears to represent a choroidal mass, possibly an infiltrate, that is blocking signal penetration. Note the presence of juxtapapillary retinal pigment epithelial atrophy, which allows increased transmission in the sclera and hyperreflectivity, despite the presence of a probable choroidal lesion, identified by thickening and loss of the normal choroidal vascular markings. (Fourth row) OCT shows hyporeflective areas associated with physiologic choroidal vessels (*blue arrowheads*) but no choroidal lesions as seen in the other scans.

camera set at 50° and included a macular and an optic disc-centered image.

Two authors (C.B., R.F.S.) masked to clinical data graded the presence of choroidal abnormalities (choroidal lesions, suprachoroidal space) and measured subfoveal choroidal thickness. For the purposes of this study, a choroidal “lesion” was defined by the following characteristics: (1) present external to the Bruch membrane and internal to the choroidal scleral border; (2) a region of homogenous hyporeflectivity; (3) obscuration of vascular borders within the region of the lesion; (4) lack of a hyperreflective outer boundary, as would be seen with a vessel; (5) potential association with regional choroidal thickening; (6) minimal shadowing; and (7) presence in multiple adjacent scans. Figure 2 shows examples of choroidal lesions. Lesion type was defined by its size, for example, a focal lesion was  $\leq 1500 \mu\text{m}$  in both the horizontal and the vertical meridians, and a diffuse lesion was  $>1500 \mu\text{m}$  in either meridian. Reader confidence in assessing the presence or absence of a choroidal lesion was defined by the following scale: grade 1, possible; grade 2, probable; grade 3, definite. A macular lesion was defined as the presence of a focal or diffuse choroidal lesion within a circle 6 mm in diameter, as determined by device-associated software, and centered on the fovea. A suprachoroidal space was thought to be present if a hyporeflective band with the following characteristics was present between the outer border of the large choroidal vessels

and the homogeneously increased reflectance of the sclera was seen: extension across multiple adjacent scans and diameters of at least 3.5 mm in both the horizontal and the vertical meridians. Both of the observers measured the subfoveal choroidal thickness from the outer border of the hyperreflective line corresponding to the retinal pigment epithelium to the inner border of the sclera. If there was a difference of more than 15% between the two observers for a particular measurement, the difference was arbitrated through open adjudication. The mean of the measurements of both of the observers was used for statistical analysis.

### Analyses and Statistical Techniques

Choroidal characteristics and thickness were quantified, and relationships between various characteristics were investigated. Macular and peripapillary scans were considered together in analyses because their areas partially overlap and individual lesions can cross the borders from one scan to the other. We also analyzed the macular area separately, because of its unique association with disease complications (e.g., CME) and its role in the visual changes commonly seen in people with BSCR, such as reduced contrast sensitivity and abnormal color vision. Because choroidal thickness represents a spectrum with thinner choroids potentially reflecting choroidal atrophy and thicker choroids potentially reflecting choroidal inflammation, we sought to evaluate the lower 25th percentile (“thin



choroid”) and the upper 25th percentile (“thick choroid”) as possible disease states relative to the IQR of choroidal thickness in our patient population, which we utilized as the reference or “normal” state. We also present the combined data (thin plus thick) as simply “abnormal choroidal thickness.”

Choroidal findings were compared to demographics, disease duration, clinical disease activity, findings on fundus photographs, and treatment history. Percentages were calculated for categorical variables. Means  $\pm$  SD and medians with interquartile range (IQR) values were calculated for continuous variables. The associations between choroidal findings and clinical data were evaluated using logistic regression and odds ratios (ORs). Both the crude and adjusted ORs were calculated using logistic regression models that incorporated generalized estimating equations to account for any correlation between eyes of an individual patient.<sup>26</sup> For the outcome of choroidal thickness, in which values on both the low and high ends of the range could represent a disease state, crude and adjusted multilevel logistic regression models (e.g., “mlogit”) with robust variance were used, with the middle range of choroidal thickness (e.g., “normal thickness”) serving as the reference. *P* values for all analyses were nominal, with a value of  $\leq 0.05$  considered statistically significant. All statistical analyses were performed with Intercooled Stata SE version 12.0 software (StataCorp LP, College Station, TX, USA).

Details about visual function and analyses involving retinal images and fundus autofluorescence (FAF) will be published in subsequent reports.

## RESULTS

Eighty-six patients were included in the study (172 involved eyes). Demographic and clinical data are summarized in Table 1. Median age was 56 years old (IQR: 51–64 years old), and 54 participants (62.8%) were female. Each of 83 participants tested had the HLA-A29 gene. Median duration of disease was 5.0 years (IQR: 1.9–9.1 years). Disease was considered active in 50 eyes (29.1%); few eyes had a vitreous haze score of 2+ or greater (1.2%). CME was present in 38 eyes (22.1%) at the study visit, whereas 58 eyes (33.7%) had a history of CME. Previous retinal vasculitis was reported for 85 eyes (49.4%). Only six eyes (3.5%) had a history of choroidal neovascularization. Median BCVA was 0.1 logMAR (Snellen equivalent: 20/25). Median logCS was 1.5 (IQR: 1.35–1.65), and 51 eyes (34.7%) had abnormal CS. Median C-index was 2.4, and 69.3% of eyes had abnormal color vision test results. Median HVF-MD was  $-3.5$  dB (IQR:  $-9.4$  to  $-1.8$  dB), and 54.9% of eyes had an abnormal HVF-MD. Of 74 eyes with 20/20 vision or better, 54.2% had abnormal color vision, 23.3% had abnormal HVF-MD, and 10.0% had abnormal CS.

Choroidal findings are shown in Table 2. Seven eyes of 5 participants were excluded from qualitative analysis of choroidal findings because scans were not acquired according to protocol. For the remaining 165 eyes that were evaluated, 6 eyes (3.6%) of 5 participants had a focal lesion (mean confidence level: 2.91) and 103 eyes (62.4%) of 56 participants showed a diffuse choroidal lesion (mean confidence level: 2.61). No lesions were found in 60 eyes (36.4%; mean confidence level: 2.71). Macular lesions were present in 97 eyes (58.8%) of 56 participants, and a suprachoroidal space was observed in 45 eyes (27.3%) of 27 participants. Three eyes of 2 participants were excluded from choroidal thickness analysis because scans were not obtained according to protocol. For the remaining 169 eyes, the median choroidal thickness was 293  $\mu$ m (IQR: 205–362  $\mu$ m). Abnormal visual field was statistically related to the

presence of thin choroid (OR: 3.10; *P* = 0.02), and there were weak associations between abnormal visual field and the presence of any choroidal lesion (OR: 1.96; *P* = 0.06) and suprachoroidal space (OR: 0.49; *P* = 0.07), but these relationships did not reach statistical significance. There were no statistical associations between other measurements of visual function (abnormal BCVA, abnormal CS, abnormal color vision) and any of the following choroidal findings: any choroidal lesion, suprachoroidal space, thin or thick choroid (all *P* > 0.10).

There was a weak association between active disease and presence of choroidal lesions. Among 50 eyes identified clinically as having active disease, 38 (76%) had choroidal lesions; among the remaining 122 eyes, 74 (60.7%; *P* = 0.055, chi-squared test) had choroidal lesions. Table 3 shows further associations between choroidal findings and selected demographic and clinical characteristics. Table 4 summarizes correlations between various choroidal findings. Thinner choroids tended to be in older participants, and thicker choroids were associated with increased hyperopia. A longer disease duration was associated with any type of choroidal lesion (OR: 1.08; *P* = 0.03) and with thin choroids (OR: 1.10; *P* = 0.01). Vitreous haze  $\geq 0.5+$  (clinically active disease) was associated with any type of choroidal lesion (OR: 4.43; *P* = 0.02), with macular choroidal lesions (OR: 3.82; *P* = 0.03), and with both thin (OR: 3.08; *P* = 0.03) and thick (OR: 2.75; *P* = 0.03) choroids but not with the presence of a suprachoroidal space (OR: 0.95; *P* = 0.92). Macular edema was a risk factor for thick choroids (OR: 5.47; *P* = 0.02), presence of any choroidal lesions (OR: 3.00; *P* = 0.02), and macular lesions (OR: 3.65; *P* = 0.05). Interestingly, macular edema appeared to be associated with the absence of a suprachoroidal space (OR: 0.22; *P* = 0.02). The presence of any choroidal lesion and of macular lesions were strongly associated with thick choroids (OR: 3.89; *P* = 0.001 and OR: 4.56; *P* < 0.001, respectively) and with absence of a suprachoroidal space (OR: 0.43; *P* = 0.02 and OR: 0.39; *P* = 0.01, respectively). Presence of a suprachoroidal space was associated with having a normal choroidal thickness, defined as being within 1 SD of the mean (OR: 3.19; *P* = 0.03). Relationships between choroidal findings and signs of intraocular inflammation remained essentially the same after adjustment for age, duration of disease, current immunomodulatory therapy, and current corticosteroid use in multivariate analyses (Table 3).

Participants treated with immunomodulatory therapy had a lower risk of abnormal choroidal thickness (OR: 0.21; *P* = 0.001), both for thin choroids (OR: 0.17; *P* = 0.001) and for thick choroids (OR: 0.22; *P* = 0.002). Also, use of oral corticosteroid therapy appeared to lower risk of abnormal choroidal thickness (OR: 0.55; *P* = 0.04), particularly in eyes with thick choroids (OR: 0.53; *P* = 0.04). In a multivariate analysis controlling for age, duration of disease, refractive error, presence of cataract, presence of vitreous haze  $\geq 0.5+$ , and visual function (presence of abnormal BCVA, logCS, C-index, and HVF-MD), treatment with oral corticosteroids and with immunomodulatory therapy remained significantly associated with a lower risk of thickened choroid (OR: 0.40; *P* = 0.03 and OR: 0.12; *P* = 0.007, respectively). Immunomodulatory therapy, but not oral corticosteroids, was associated with a decreased risk of thin choroids after controlling for the same potential confounders (OR: 0.31; *P* = 0.05).

## DISCUSSION

The choroid is thought to be an important site of disease in people with BSCR,<sup>12</sup> which stimulated us to study choroidal features with EDI-OCT imaging. Using volume scans, we were

**TABLE 1.** Demographic and Clinical Data for Study Participants With Birdshot Chorioretinitis

Characteristic	Result
<b>Patient-specific</b>	
Total study population	86 participants
<b>Age, y</b>	
Mean ± SD	57.3 ± 9.5
Median (IQR)	56 (51–64)
Females (%)	54 (62.8%)
<b>Treatment history, n (%)*</b>	
Never treated	4 (2.3%)
<b>Systemic corticosteroid treatment</b>	
Current	26 (30.2%)
Ever	77 (89.5%)
Only corticosteroids, never immunomodulatory therapy	8 (4.7%)
<b>Immunomodulatory therapy</b>	
Current	60 (69.8%)
Ever	74 (86.0%)
<b>Time since onset of BSCR-related symptoms</b>	
Mean ± SD	7.8 ± 5.4 y
Median (IQR)	7.1 y (3.2 to 11.1 y)
<b>Time since diagnosis of BSCR</b>	
Mean ± SD	6.3 ± 5.1 y
Median (IQR)	5.0 y (1.9 to 9.1 y)
<b>Ocular symptoms in participants, n (%)</b>	
Blurry vision	50 (58.1%)
Floaters	60 (69.8%)
Nyctalopia	39 (45.4%)
Abnormal contrast	24 (27.9%)
Abnormal color	40 (46.5%)
Vibrating vision	24 (27.9%)
Metamorphopsia	14 (16.3%)
Decreased peripheral vision	29 (33.7%)
<b>Eye-specific</b>	
Total study population	172 eyes
<b>Local treatment history, n (%)</b>	
Never	97 (56.4%)
<b>Periocular corticosteroid injection</b>	
Intravitreal triamcinolone	15 (8.7%)
Intravitreal dexamethasone implant	17 (9.9%)
Intravitreal fluocinolone acetonide implant	22 (12.8%)
Intravitreal anti-VEGF injection	5 (2.9%)
Subconjunctival sirolimus injection	2 (1.2%)
<b>Previous surgery, n (%)</b>	
Glaucoma surgery	25 (14.5%)
Vitrectomy	6 (3.5%)
IOP Median (IQR <sup>†</sup> , n = 170 <sup>‡</sup> )	14 mm Hg (12 to 16 mm Hg)
<b>Lens status, n (%)</b>	
Pseudophakia	53 (30.1%)
Clear lens	39 (22.7%)
Cataract (≥0.5+)	80 (46.5%)
<b>Vitreous haze<sup>§</sup>, n (%)</b>	
None	122 (70.9%)
0.5+	42 (24.4%)
1+	6 (3.5%)
2+	2 (1.2%)

**TABLE 1.** Continued

Characteristic	Result
<b>Vitreous cells, n (%)</b>	
None	64 (37.2%)
< 1+	86 (50%)
1+	16 (9.3%)
2+	6 (3.5%)
<b>Posterior findings, n (%)</b>	
Pale disc/optic nerve atrophy	34 (19.8%)
Glaucomatous disc	12 (7.0%)
Cystoid macular edema	38 (22.1%)
Previous optic disc swelling	45 (26.2%)
Previous cystoid macular edema	58 (33.7%)
Previous choroidal neovascularization	6 (3.5%)
Previous retinal vasculitis	85 (49.4%)
<b>Refractive error (D)  , n = 148<sup>‡</sup></b>	
Median (IQR)	−0.5 (−1.5 to 0.25)
Range	−5.0 to +4.3
<b>BCVA (logMAR<sup>#</sup>, n = 172<sup>‡</sup>)</b>	
Median (IQR)	0.1 (0 to 0.3)
Mean ± SD	0.19 ± 0.32
<b>≤ 20/25 Snellen equivalent (n eyes [%])</b>	
	98 (57.0%)
<b>≤ 20/50 Snellen equivalent (n eyes [%])</b>	
	30 (17.4%)
<b>≤ 20/200 Snellen equivalent (n eyes [%])</b>	
	8 (4.7%)
<b>Contrast sensitivity (logCS,** n = 147<sup>‡</sup>)</b>	
Median (IQR)	1.5 (1.35 to 1.65)
Abnormal (n eyes [%])	51 (34.7%)
<b>Color vision (C-index,†† n = 101<sup>‡</sup>)</b>	
Median (IQR)	2.4 (1.6 to 3.1)
Abnormal (n eyes [%])	70 (69.3%)
<b>Visual field mean deviation (dB,‡‡ n = 144<sup>‡</sup>)</b>	
Median (IQR)	−3.5 (−9.4 to −1.8)
Abnormal (n eyes [%])	79 (54.9%)

BCVA, best-corrected visual acuity; BSCR, birdshot chorioretinopathy; IOP, intraocular pressure; IQR, interquartile range; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation; VEGF, vascular endothelial growth factor.

\* Systemic medications included oral corticosteroids (current 30.2%, ever 89.5%), intravenous corticosteroids (current 0%, ever 4.7%), methotrexate (current 7%, ever 24.4%), mycophenolate mofetil (current 57%, ever 75.6%), cyclosporine (current 18.6%, ever 38.4%), tacrolimus (current 2.3%, ever 3.5%), azathioprine (current 2.3%, ever 3.5%), daclizumab (current 0%, ever 1.2%), infliximab (current 3.5%, ever 5.8%), and adalimumab (current 7.0%, ever 10.5%).

† IOP-lowering medications were being administered to 23 eyes (13.5%).

‡ Number of eyes tested, if different than 172.

§ As defined by Nussenblatt et al.<sup>25</sup>

|| Refraction spherical equivalent before development of cataract.

# As determined by ETDRS technique; converted to Snellen equivalent.

\*\* Pelli-Robson test; abnormal logCS defined as <1.5.<sup>20,21</sup>

†† Lanthony D15 color test.<sup>18</sup> Abnormal C-index defined as ≥1.78.<sup>17</sup>

‡‡ Humphrey visual field; abnormal MD defined as <−3 dB.

able to evaluate structural variations in an area between the major vascular arcades and extending nasal to the optic disc. Because most birdshot lesions appear to radiate out from the optic disc, the peripapillary area is important for such an evaluation. Our study shows that choroidal abnormalities are common among a large cohort of people with BSCR. Distinct

**TABLE 2.** Choroidal Findings and Choroidal Thickness in Eyes of Study Participants With Birdshot Chorioretinitis

Findings	No. of Patients (%) <sup>*</sup>	No. of Eyes (%) <sup>*</sup>
Presence of focal lesion†	5 (6.0%)	6 (3.6%)
Presence of diffuse lesion‡	56 (66.7%)	103 (62.4%)
No lesion§	34 (40.5%)	60 (36.4%)
Presence of macular lesion	56 (66.7%)	97 (58.8%)
Presence of suprachoroidal space	27 (31.4%)	45 (27.3%)
Choroidal thickness, $\mu\text{m}$		
Median (IQR)	-	293 (205-362)
Range	-	65-617

IQR = interquartile range.

<sup>\*</sup> Excluded from analyses of choroidal findings were 7 eyes of 5 participants because of incomplete scans or insufficient scan quality; excluded from choroidal thickness measurement were 3 eyes of 2 participants due to insufficient scan quality.

† Focal lesion size  $\leq 1500 \mu\text{m}$ ; mean confidence level 2.91.

‡ Diffuse lesion size  $> 1500 \mu\text{m}$ ; mean confidence level 2.61.

§ Neither diffuse nor focal lesion; mean confidence level 2.71.

|| Focal or diffuse lesion within a circle 6 mm in diameter centered on the geometric center of the fovea.

areas of hyporeflectivity not well characterized in previous studies were present in over 60% of eyes. Most of these lesions were larger than  $1500 \mu\text{m}$  in diameter (“diffuse”) but not well demarcated. These lesions were related to longer durations of disease and may be affected by systemic corticosteroids and immunomodulatory therapy.

We hypothesize that these diffuse lesions represent infiltration of inflammatory cells. This idea is appealing, given the association of lesions with thicker choroids, disease activity, and treatment. There have been two published reports that describe histopathologic findings associated with BSCR;

each study was a single case report of eyes from HLA A29-positive individuals with BSCR.<sup>4,5</sup> In one case, multiple foci of predominantly lymphocytic infiltrates were located at various levels of the choroid.<sup>4</sup> Occasionally, lymphocytes were occupying the full choroidal thickness and abutting choroidal vascular channels. Rare plasma cells were seen, and a few foci contained epithelioid cells. The retinal pigment epithelium did not appear to be involved in the underlying choroidal process. In the other case, nongranulomatous nodular lymphocytic infiltrates were found in the choroid and ciliary body.<sup>5</sup> These infiltrates contained T cells, B cells, and only scattered histiocytes. Our EDI-OCT findings are consistent with these histopathological studies, in that diffuse choroidal infiltration could account for thickening with hyporeflectivity, but additional study will be necessary to confirm the assumption that the lesions represent foci of inflammatory cells.

When inflammation occurs in the deep choroid, infiltrates will follow along and surround the larger choroidal vessels. The deep choroidal vessels radiate outward toward the vortex veins, which could suggest a reason for the radiating pattern of birdshot lesions seen by ophthalmoscopy. We did not, however, find a consistent relationship between the lesions seen on EDI-OCT imaging and clinical birdshot lesions, as shown in Figure 2. The nature of any relationship between these lesions, if it does exist, should be studied in a systematic manner, using colocalization software to compare clinical and EDI-OCT findings. In seeking a statistical relationship, investigators will need to consider the fact that birdshot lesions extend beyond the topographic areas covered in our study.

A regular distribution of hypolucent dark dots is the most characteristic sign of choroidal involvement in eyes with BSCR on ICG angiography.<sup>6-8,27</sup> Relationships between these changes and the lesions seen on EDI-OCT are not known. Interpretation of ICG angiograms may be challenging, and serial monitoring of patients with BSCR using ICG angiography

**TABLE 3.** Risk Factors for Choroidal Characteristics Among Study Participants With Birdshot Chorioretinitis

Characteristic	Any Choroidal Lesion		Macular Lesion		Suprachoroidal Space		Thin Choroid		Thick Choroid		Any Abnormal Choroidal Thickness	
	OR	P Value <sup>*</sup>	OR	P Value <sup>*</sup>	OR	P Value <sup>*</sup>	OR	P Value <sup>*</sup>	OR	P Value <sup>*</sup>	OR	P Value <sup>*</sup>
Host, disease, and treatment factors												
Age (per y)	1.01	0.71	0.98	0.32	1.01	0.62	1.06	0.01	0.96	0.06	1.00	0.94
Disease duration† (per y)	1.08	0.03	1.04	0.18	0.95	0.15	1.10	0.01	1.00	0.94	1.03	0.31
Sex (male vs. female)	0.83	0.58	0.90	0.75	0.62	0.17	1.06	0.90	1.24	0.56	1.17	0.64
Refractive error (per +1.0 D)	0.94	0.55	0.92	0.41	1.23	0.08	0.96	0.74	1.36	0.01	1.20	0.09
Current on IMT (yes vs. no)	0.68	0.20	0.66	0.24	1.38	0.41	0.17	0.001	0.22	0.002	0.21	0.001
Current systemic corticosteroids (yes vs. no)	0.99	0.97	1.05	0.84	0.75	0.32	0.63	0.19	0.53	0.04	0.55	0.04
Intraocular inflammation factors												
Vitreous haze ( $\geq 0.5+$ vs. none)												
Univariate analysis	4.43	0.02	3.82	0.03	0.95	0.92	3.08	0.03	2.75	0.03	2.96	0.01
Multivariate analysis	5.33	0.02	4.79	0.02	1.09	0.88	2.89	0.25	7.52	0.02	5.96	0.03
Macular edema (presence vs. absence)												
Univariate analysis	3.00	0.02	3.65	0.05	0.22	0.02	1.13	0.85	5.47	0.02	2.33	0.08
Multivariate analysis	3.17	0.02	2.41	0.05	0.23	0.04	1.27	0.72	3.60	0.02	2.55	0.06
Retinal vasculitis (presence vs. absence)												
Univariate analysis	1.28	0.46	0.93	0.82	1.03	0.94	1.23	0.63	1.23	0.57	1.17	0.64
Multivariate analysis	1.04	0.91	0.80	0.50	0.91	0.80	0.88	0.78	1.43	0.37	1.08	0.84

IMT, immunomodulatory treatment; OR, odds ratio.

<sup>\*</sup> Univariate logistic regression models for comparisons involving host, disease, and treatment factors; univariate and multivariate logistic regression models for comparisons involving intraocular inflammation factors. Multivariate comparisons adjusted for age, duration of disease, current immunomodulatory therapy, and current corticosteroid use.

† Duration calculated from onset of symptoms.

TABLE 4. Interrelationships Between Choroidal Measurements in Study Participants With Birdshot Chorioretinitis

Choroidal Findings*	Any Choroidal Lesion		Macular Lesion		Suprachoroidal Space		Thin Choroid†		Thick Choroid‡		Abnormal Choroidal Thickness§	
	OR	P Value	OR	P Value	OR	P Value	OR	P Value	OR	P Value	OR	P Value
Any choroidal lesion			NA	NA	0.43	0.02	0.58	0.20	3.89	0.001	1.41	0.32
Macular lesion	NA	NA			0.39	0.01	0.60	0.24	4.56	<0.001	1.57	0.19
Suprachoroidal space	0.43	0.02	0.39	0.01			0.31	0.03	0.65	0.26	0.52	0.08
Thin choroid†	0.58	0.20	0.60	0.24	0.31	0.03						
Thick choroid‡	3.89	0.001	4.56	<0.001	0.65	0.26						

NA, not applicable; OR, odds ratio.

\* Categories for all comparisons were presence versus absence.

† Presence of thin choroid represents the lower quartile of choroidal thickness.

‡ Presence of thick choroid represents the upper quartile of choroidal thickness.

§ Either thin or thick choroid.

may not be as practical as EDI-OCT, because it is an invasive technique. Studies should be undertaken to determine whether EDI-OCT provides the same or different information than ICG angiography, which may influence its use as a tool for monitoring disease.

Generally, choroidal thickness is highly variable and is affected by age, sex, refraction, axial length, diurnal changes, and other systemic factors. The relationship between choroidal thickness and features of BSCR should therefore be interpreted with caution.<sup>13,28,29</sup> Even so, our measurements did reveal several relationships between choroidal thickness and other factors. Eyes with submacular lesions had thicker choroids. Thin choroids were significantly associated with longer disease duration, suggesting the possibility of disease-related choroidal atrophy. Systemic immunomodulatory and corticosteroid therapies were both associated with a lower risk of abnormal choroidal thickness, suggesting a treatment benefit; however, the effect of these drugs alone on choroidal thickness is not known. The influence of treatment on choroidal features should be assessed further in longitudinal studies. If it is demonstrated that drugs decrease an abnormally thick choroid or prevent progression to an abnormally thin choroid, while also preserving vision, EDI-OCT imaging of the choroid may provide an objective surrogate marker for treatment benefit. Mrejen and Spaide<sup>9</sup> described near-complete resolution of a choroidal hyporeflective zone in a patient with BSCR after 6 months of local corticosteroid therapy and oral mycophenolate mofetil.

In other prior studies of BSCR, Keane et al.<sup>10</sup> found choroidal thinning, discrete hyperreflective foci, focal depigmentation, and presence of a suprachoroidal hyporeflective space on EDI-OCT scans from 12 individuals. The authors had the impression that birdshot lesions on fundus photographs were focal areas of “choroidal depigmentation” suggested by increased scleral reflectivity on the OCT images. They also speculated that fluid in the suprachoroidal space may be indicative of ongoing choroidal inflammatory activity.<sup>10</sup> Birnbaum et al.<sup>11</sup> reported that a few of their 14 patients showed “suprachoroidal fluid.” Based on our definitions for our study, 27.3% of eyes had a suprachoroidal space, and the finding was related to the patient’s refractive error and to absence of CME or macular lesions; thus, results do not provide evidence that the suprachoroidal space is an activity marker for BSCR. The suprachoroidal space has previously been reported in up to 44.6% of healthy eyes.<sup>30</sup> The relevance of this choroidal finding will also best be determined in longitudinal studies.

We found only limited relationships between choroidal findings and measurements of visual function. The observed relationship between thin choroid and visual field suggests an influence of the choroid on vision, but both of these

abnormalities may simply reflect disease duration (Table 3). Although the choroid is thought to play an important role in disease pathogenesis, its relationship to vision will be mediated through its effect on the retina and on intraocular inflammation. The nature of these relationships will be explored in a future paper that focuses on OCT findings of the retina. An important issue will be the extent to which choroidal changes influence other factors that may impact vision, such as retinal vascular inflammation, CME, and vitreous inflammatory reactions.<sup>16,31-35</sup> In that paper, we will be able to perform multivariate analyses that seek to identify the direct and indirect relationships of choroidal findings, retinal pigment epithelium findings, and retinal findings with vision, while also accounting for potential confounders related to demographics and treatment on each type of OCT finding.

In our study, eyes with choroidal macular lesions on OCT-EDI had a greater likelihood of CME and higher vitreous haze levels, which provides support for the concept that OCT-EDI may be helpful in monitoring the activity of BSCR. The relationships between choroidal findings and previous or current retinal vasculitis were not strong, however, suggesting other, independent influences on the retinal vasculopathy of BSCR.

There are limitations to this study. As with any cross-sectional analysis, we could not establish temporal or causal relationships between EDI-OCT characteristics and other, clinical findings. Data were collected from different sites, using different equipment, but images were acquired with a well-defined, standardized protocol, and only a few imaging data were excluded from the analyses. BSCR is thought to affect a wide area of the retina, and our study only investigated a portion of the posterior pole. Imaging areas outside the major vascular arcades might have shown different results. Relationships between choroidal thickening and treatment could have been confounded by therapeutic indication, such that more severely affected cases or those with long-standing disease were more likely to be treated; however, we would have expected these biases to lessen any protective effect that we observed, which was not the case. If patients were treated until their vision improved or stabilized, this treatment strategy could have influenced associations observed between treatment and choroidal thickness. Almost all participants had undergone some treatment for BSCR before presenting to our institutions; we therefore could not adjust for this variable. Because our institutions are all tertiary referral centers, study participants may not be representative of all individuals with BSCR.

There are no standard criteria for “active” disease in eyes with BSCR; it is common to consider the presence of vitreous inflammatory reactions as a sign of activity. For purposes of this



study, we chose vitreous haze as a measurement of inflammation rather than vitreous cells, which can remain adherent to strands within the vitreous humor for prolonged periods, even after response to treatment. Using this criterion, only 50 eyes met our study definition for active disease. The fact that choroidal lesions were statistically associated with signs of intraocular inflammation and the fact that they could be identified in eyes without vitreous haze suggests that further investigation of choroidal lesions by EDI-OCT in longitudinal studies may help to refine the definition of active disease.

In summary, our EDI-OCT study demonstrates the presence of lesions with characteristic hyporeflectivity in the choroids of a substantial proportion of eyes with BSCR. Furthermore, these lesions do not necessarily correspond to the typical, hypopigmented birdshot lesions observed clinically, which underscores the potential importance of imaging the choroid with EDI-OCT for a more complete picture of the disease. These lesions likely represent inflammatory reactions, as they are related to other signs of inflammation in the eye. The evolution of choroidal findings and their temporal relationships to other features of disease should be evaluated further in longitudinal studies. Such investigations may reveal EDI-OCT to be a more precise tool for monitoring disease activity and the effect of treatment than clinical examination. They may also provide additional insight into disease pathogenesis.

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