Birdshot Chorioretinopathy

7

Taylor W. Starnes, Pooja Bhat, and Ann-Marie Lobo

Introduction

Birdshot chorioretinopathy (BSCR) is a rare, bilateral, posterior uveitis with a chronic course. BSCR has a very strong association with HLA-A29, with approximately 96% of patients testing positive (Shah et al. 2005). The first report of BSCR has been credited to Franceschetti and Babel in 1949, who described a patient with multiple hypopigmented choroidal lesions as having "chorioretinopathy with candle wax spots" (Franceschetti and Babel 1949). Ryan and Maumenee coined the name "birdshot retinochoroidopathy" in their 1980 case series of 13 patients. The clinical findings in their patients included creamy chorioretinal lesions, macular edema, disc edema, and vitreous debris with minimal anterior segment inflammation (Ryan and Maumenee 1980). In 1981, Gass further characterized the syndrome, but chose the name "vitiliginous chorioretinitis," due to the similarity of the fundus findings in the skin of patients with vitiligo. This description of BSCR also recognized the development of nyctalopia, dyschromatopsia, and electroretinographic abnormalities as the disease progressed (Gass 1981). Consensus criteria for the definition of BSCR have been developed (Table 7.1), which closely resemble the clinical findings noted in these early studies (Levinson et al. 2004). Since the first comprehensive descriptions in the early 1980s, many advances have been made in our understanding of the genetics, pathogenesis, and treatment of BSCR. This chapter summarizes our current understanding of BSCR, with a focus on the role of fundus examination and chorioretinal imaging techniques to diagnose BSCR, assess disease activity, and monitor progression.

Table 7.1 Birdshot chorioretinopathy diagnostic criteria (adapted from Levinson et al. (2004))

Birdshot chorioretinopathy diagnostic criteria	
Required characteristics	• Bilateral disease
	• Three or more peripapillary birdshot lesions in one eye
	• No or minimal anterior segment inflammation
	• Low-grade vitreous haze
Supportive findings	• HLA-A29 positivity
	• Retinal vasculitis
	• Cystoid macular edema
Exclusion criteria	• Keratic precipitates
	• Posterior synechiae
	• Presence of other infectious, inflammatory, or neoplastic disease causing choroidal lesions

Epidemiology and Demographics

Although there have been no large studies to determine the prevalence of BSCR in the general population, it is certainly a rare disease. In the United States and Europe, BSCR comprises 0.5–1.5% of the cases seen in uveitis practices and 6.0–7.9% of posterior uveitis cases. By extrapolating from the overall prevalence of uveitis in the general population (38–115 cases/100,000 persons), Minos and colleagues arrived at an estimated prevalence of 0.2–1.7 cases/100,000 persons (Vadot et al. 1984; Gritz and Wong 2004; Minos et al. 2016). They further postulated that the true prevalence is at the lower end of the range because the referral centers conducting the studies likely have an overrepresentation of rare uveitis syndromes (Minos et al. 2016).

The onset of BSCR occurs most commonly in middle age. In a comprehensive review of 52 published studies, Shah and colleagues determined that 53 years (standard deviation ±9.4 years) was the mean age of onset (Shah et al. 2005). Although it is rare in childhood, cases have been reported in the teenage years (Pivetti-Pezzi 1996). Most of the larger case series report a slight female predominance.

T. W. Starnes · P. Bhat · A.-M. Lobo (✉)
Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, IL, USA
e-mail: alobo2@uic.edu

H. G. Yu (ed.), *Inflammatory and Infectious Ocular Disorders*, Retina Atlas, https://doi.org/10.1007/978-981-13-8546-9_7

There are also substantial differences in prevalence by race, with Caucasian patients representing nearly all of the reported cases of BSCR (Shah et al. 2005). However, individual cases of BSCR have been reported in black and Hispanic patients, and a case series of patients has been reported in Japan (Saito et al. 2002; Baddar and Goldstein 2016; Knezevic et al. 2016). No cases have been reported from South Asia. Although some of the racial predilection may be due to HLA-A29 prevalence by race, this alone cannot completely explain the difference, as is discussed in the next section.

Genetics and Pathophysiology

Approximately 96% of BSCR patients are HLA-A29 positive, which is the strongest known association of an HLA allele with any disease. The association is so strong that other diagnoses should be considered if a patient is HLA-A29 negative (Brézin et al. 2011). However, the exact role of HLA-A29 in the pathogenesis remains unclear. Some of the controversy over the role of HLA-A29 comes from its racial distribution. The two main subtypes of the HLA-A29 allele, HLA-A∗29:01 and HLA-A∗29:02, have both been associated with BSCR. However, the vast majority of reported HLA-A29-positive BSCR patients have the HLA-A∗29:02 allele (Levinson et al. 2004; Brézin et al. 2011). The frequency of HLA-A∗29:02 in the United States is greatest in the Caucasian population at 4.34% and lowest in Asians at 0.1%. However, the frequency in African-Americans and Hispanics is 3.57% and 4.20%, respectively. Although the low frequency of HLA-A29 in Asians may be a protective factor, the frequency in Hispanics and African-Americans is similar overall to Caucasians. Unknown protective factors present in Hispanics and African-Americans, or unknown risk factors in Caucasians, are likely to explain the difference in BSCR prevalence despite similar HLA-A29 frequencies (Brézin et al. 2011).

Mice engineered to express a human HLA-A29 transgene derived from a patient affected by BSCR spontaneously develop a posterior uveitis similar to BSCR, providing the best evidence of a direct role for HLA-A29 in BSCR pathogenesis (Szpak et al. 2001). HLA-A29 codes for a major histocompatibility complex class 1 (MHC-I) protein, whose function is to present antigens to CD8 T cells. A recent genome-wide association study has also linked endoplasmic reticulum aminopeptidase 2 (ERAP2) with BSCR. ERAP2 is an enzyme that processes antigens for presentation by MHC-I molecules, which raises the interesting hypothesis that ERAP2 antigen processing in conjunction with HLA-A29 presentation may be sequential steps in the development of autoimmunity in BSCR patients (Kuiper et al. 2014b). Although more than 100 endogenous HLA-A29 ligands have been identified, none have been directly linked with BSCR (Boisgerault et al. 1996).

Consistent with the strong HLA-A29 association, T cells also appear to play an important role in BSCR pathogenesis. Histopathologic studies of enucleated BSCR eyes demonstrate choroidal lesions in which T cells predominate (Pulido et al. 2012). Vitreous samples from BSCR eyes are rich in T cells that react to retinal and choroidal extracts, and aqueous samples are rich in interleukin-17 (IL-17), a T-cell cytokine (Kuiper et al. 2011; 2014a).

Clinical Findings

Symptoms

Patients with BSCR often present with complaints of decreased vision while maintaining good central acuity on formal testing. In many cases, the mild symptoms in the early stages of disease can lead to a delay in diagnosis. In their comprehensive review, Shah and colleagues found the following visual complaints among a group of symptomatic BSCR patients: blurry vision (88%), floaters (43%), nyctalopia (18%), and dyschromatopsia (9%). At the time of initial presentation, 62% of patients had visual acuity better than 20/40 in both eyes and 76% had acuity better than 20/40 in at least one eye. Even among the small subset of patients with 20/20 acuity in both eyes, the vast majority complained of blurriness or floaters (Shah et al. 2005). Formal testing of color vision demonstrates defects in the majority of patients, most commonly in the blue-yellow axis (Gasch et al. 1999). The course of BSCR has been described as chronic and insidious, with gradual decline in visual function, although recent studies have found that long-term stability can be achieved with chronic immunosuppression (Shah et al. 2005; Tomkins-Netzer et al. 2014). Pain, photophobia, and conjunctival injection are atypical and suggest another underlying etiology of the posterior segment findings (Shah et al. 2005; Minos et al. 2016).

Clinical Signs and Exam Findings

Anterior examination generally demonstrates a quiet anterior chamber, although low-grade cell may be present. Flare, keratic precipitates, and posterior synechiae are not typically seen.

The diagnosis of BSCR is made primarily on the basis of the fundus examination, and the most recent diagnostic criteria, defined in 2006, are summarized in Table 7.1. Early in the disease course, there may be no apparent fundus abnormalities, as development of chorioretinal lesions often lags

behind symptom onset by several years (Godel et al. 1989). The classic finding in BSCR is birdshot lesions, which are creamy, ovoid choroidal lesions that are one eighth to one half disc diameter in size (Fig. 7.1). Birdshot lesions are often oriented with their long axis perpendicular to the disc and appear to radiate toward the periphery (Priem and Oosterhuis 1988). Lesions are typically concentrated near the optic disc and in the inferior and nasal quadrants (Fig. 7.1a). With time, the lesions may coalesce to form linear patterns or to create the appearance of peripapillary atrophy (Fig. 7.1b, c) (Ryan and Maumenee 1980; Gass 1981; Priem and Oosterhuis 1988). Eventually, the lesions may develop hyperpigmentation or become well-demarcated areas of atrophy. Other common findings are cystoid macular edema and epiretinal membranes. Retinal and choroidal neovascularization have also been reported (Priem and Oosterhuis 1988).

Examination of the vitreous frequently demonstrates anterior vitreous cells and vitreous haze. Snowballs and snowbanks are typically absent in BSCR patients. Retinal vasculitis is present with active disease and most commonly presents with phlebitis, which is characterized by venous beading and irregular venous caliber. With time, the arterioles become attenuated. Vessel sheathing is uncommon but may be present (Ryan and Maumenee 1980; Priem and Oosterhuis 1988). Examination of the optic disc may demonstrate edema, or in late stages, pallor (Priem and Oosterhuis 1988). Although the fundus exam is key to making the diagnosis of BSCR, additional imaging modalities are useful in confirming the diagnosis in uncertain cases and for monitoring disease activity.

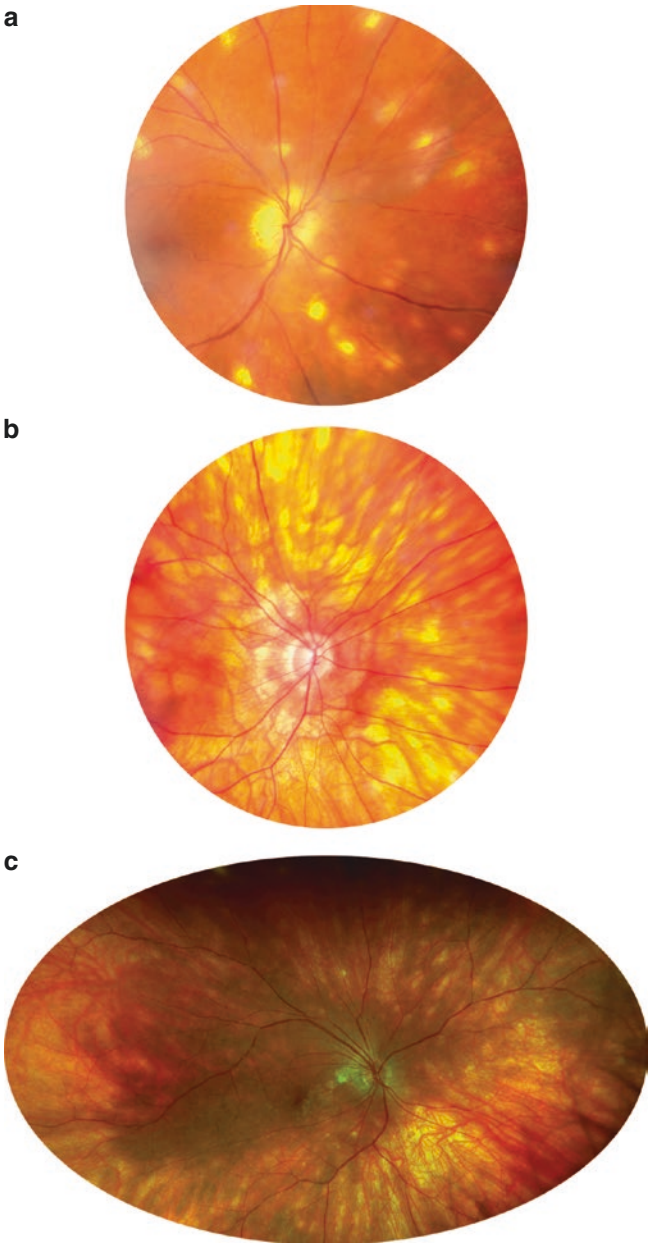

Fig. 7.1 (**a**) Fundus photograph of a 62-year-old female taken 6 years after her initial diagnosis with BSCR demonstrates discrete, round to ovoid birdshot lesions concentrated inferonasally to the disc. Also note attenuation of the arterioles and the irregular venous caliber. (**b**) Fundus photograph of a 53-year-old female taken 6 years after her initial diagnosis. The birdshot lesions appear as more elongated or linear areas of hypopigmentation. The patient also has a large area of peripapillary atrophy, which can result from coalesced birdshot lesions near the optic disc. (**c**) Optos 200Tx image from a 72-year-old female taken approximately 3 years after the onset of her symptoms. Her lesions are concentrated nasally and appear to radiate from the optic disc. Some lesions coalesce into linear areas of hypopigmentation

Imaging

Fluorescein Angiography (FA)

Fluorescein angiography is a very versatile technique for diagnosing and monitoring BSCR, as it facilitates evaluation of most of the affected structures. BSCR patients frequently develop macular edema, which often has a petalloid appearance on FA. The retinal vasculitis, characterized by vascular leakage, arteriole attenuation, and irregular venous caliber, is also best evaluated by FA, since it may be subtle or undetectable on clinical exam. The optic disc may also demonstrate hyperfluorescence or leakage (Fig. 7.2). Although it is uncommon, choroidal neovascularization may occur in BSCR and is readily detected by FA (Priem and Oosterhuis 1988; Howe et al. 1997).

Detection of the birdshot lesions is often easier on clinical exam than by FA, since the lesions demonstrate subtle and variable staining patterns. In early phases of the angiogram, the birdshot lesions may demonstrate hyper- or hypofluorescence (Fig. 7.3a, b). In late phases, the lesions usually demonstrate mild to moderate hyperfluorescence (Gass 1981; Priem and Oosterhuis 1988).

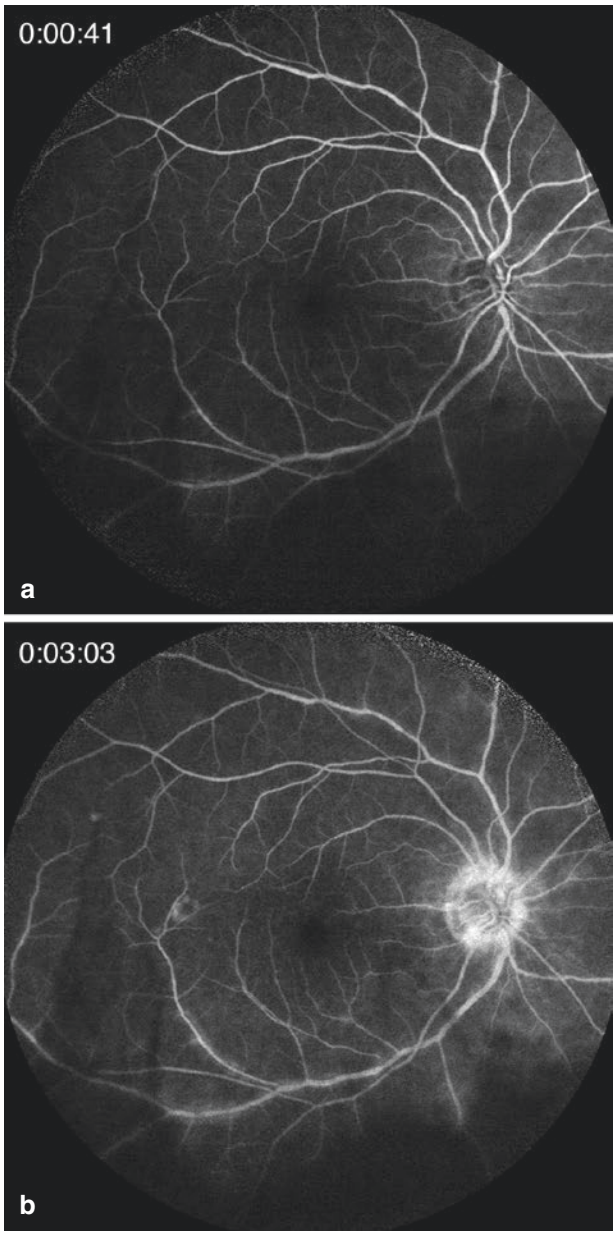

Fig. 7.2 Representative fluorescein angiogram images from a patient with active disease. (**a**) Venous beading and irregular caliber seen along the superotemporal arcades in early venous phase. (**b**) In this mid phase image, there is extensive vascular leakage, mostly from the veins. Disc leakage is also seen. No birdshot lesions are seen in these images

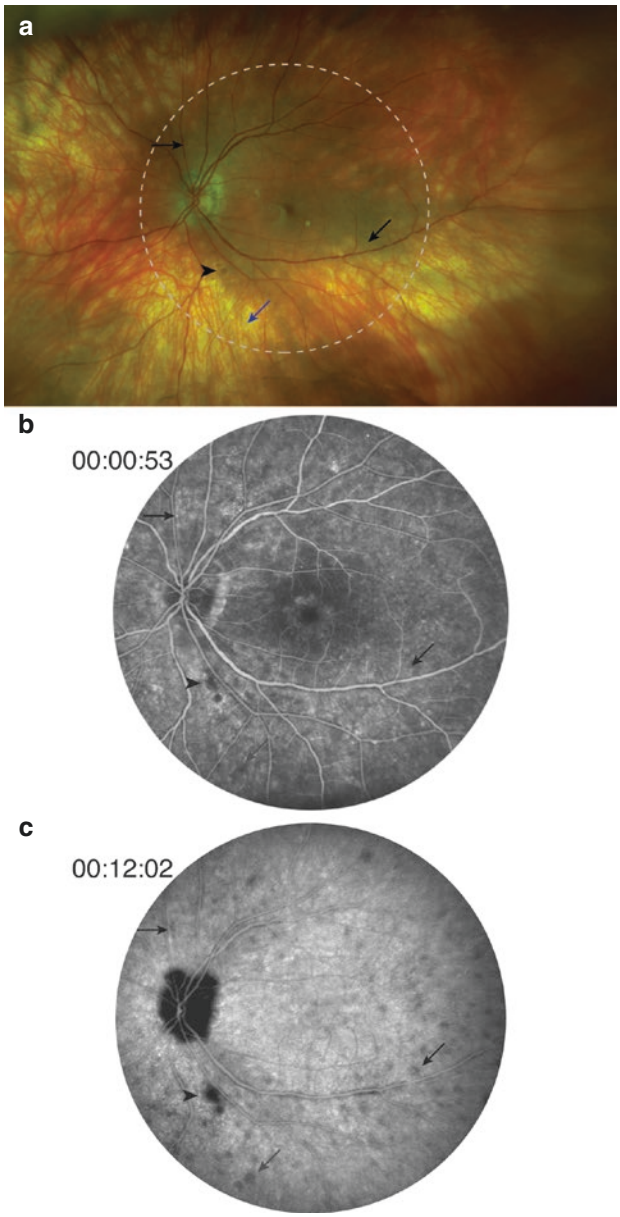

Fig. 7.3 (**a**) Optos 200Tx image demonstrating subtle, hypopigmented birdshot lesions that are apparent in both the nasal and temporal periphery. Gray circle indicates the approximate area imaged in (**b**) and (**c**). (**b**) Venous phase fluorescein angiogram image with extensive venous beading. (**c**) Late phase indocyanine green angiogram image. Black arrows denote birdshot lesions with a subtle hypopigmented appearance on the Optos image, subtle hyperfluorescence on fluorescein angiography, and hypocyanescence on ICG. Blue arrows indicate a lesion with hypofluorescence on FA. Many of the lesions seen on the Optos and ICG images are isofluorescent or not readily apparent on FA. The black arrowheads indicate a retinal hemorrhage with associated blockage on the FA and ICG images

Indocyanine Green (ICG) Angiography

ICG angiography can facilitate the evaluation of birdshot lesions, since the lesions are often more apparent on ICG than they are on clinical exam. Early stage lesions are typically round, hypocyanescent, and located near large choroidal vessels. They are more apparent in the intermediate and late phase ICG images (Figs. 7.3c and 7.4) (Fardeau et al. 1999). Two hypotheses proposed for the hypocyanescent appearance are blockage by the lymphocytic infiltrates and choroidal non-perfusion in the area of the lesions (Howe et al. 1997). Lesions that are mature or atrophic have an isocyanescent appearance. In active or progressive disease, the lesions will become larger or numerous, whereas the lesions can shrink or disappear entirely during remission (Fig. 7.5). In active disease, the ICG angiogram may show late diffuse hypercyanescence or indistinct choroidal vessels (Fardeau et al. 1999).

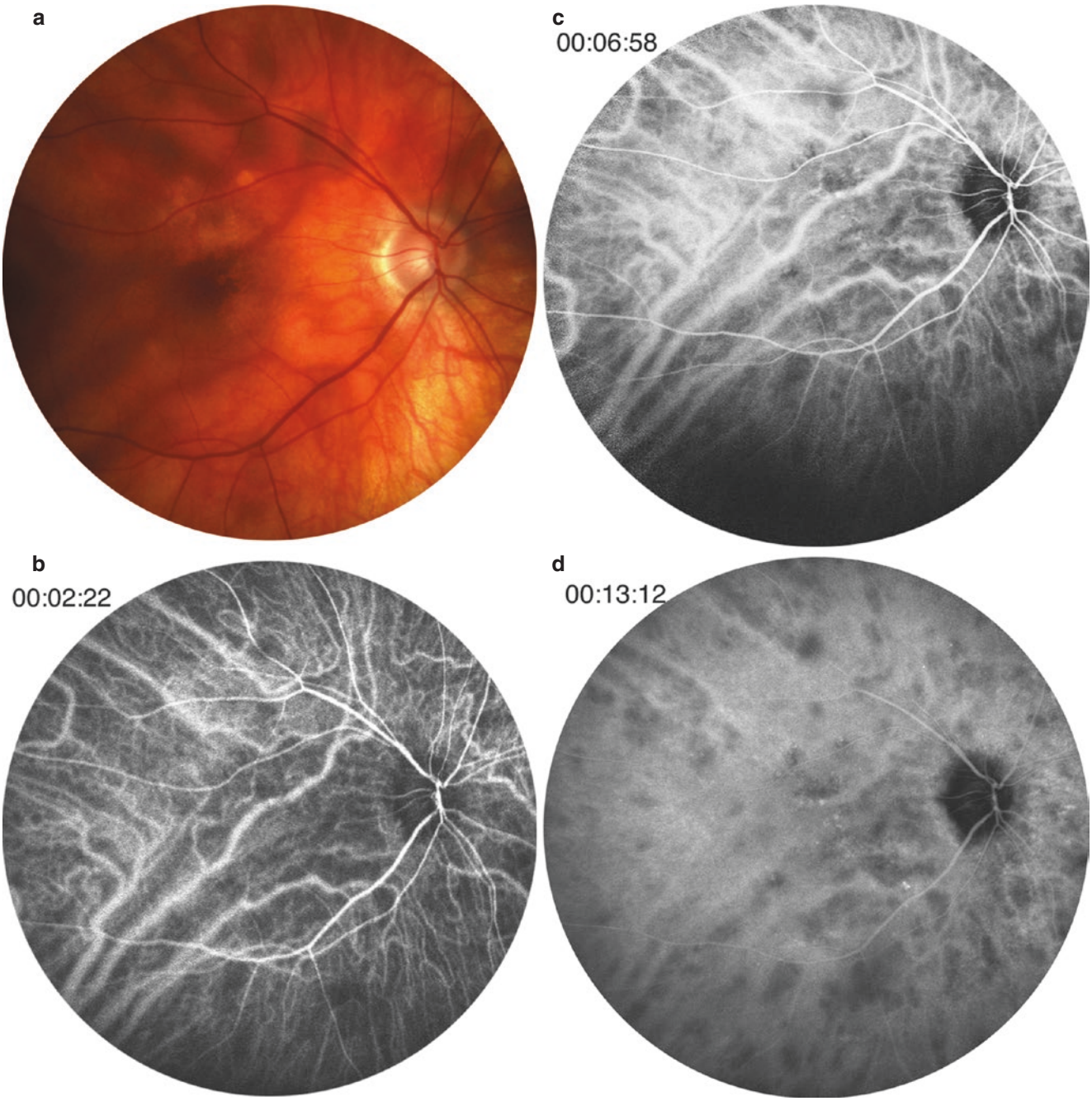

Fig. 7.4 (**a**) Color fundus photo of a patient with subtle birdshot lesions. (**b**) Early, (**c**) middle, and (**d**) late phase ICG images from the same eye. The birdshot lesions are not apparent on the early phase image. Subtle areas of hypocyanescence are seen in the mid phase image, but many distinct lesions are present in the late phase image

Fundus Autofluorescence (FAF)

Retinal pigment epithelium changes in BSCR can be followed with FAF. Birdshot lesions may demonstrate hypoautofluorescence, especially as they become more atrophic. In patients with lightly pigmented fundi, FAF can be useful to localize the lesions. Hypoautofluorescence may develop along the retinal vasculature (Giuliari et al. 2009).

Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCT-A)

There are several well-defined OCT abnormalities in BSCR. Cystoid macular edema is common in BSCR, and OCT is an excellent tool for monitoring the response to treatment (Fig. 7.6a). Ellipsoid zone disruption is common, even

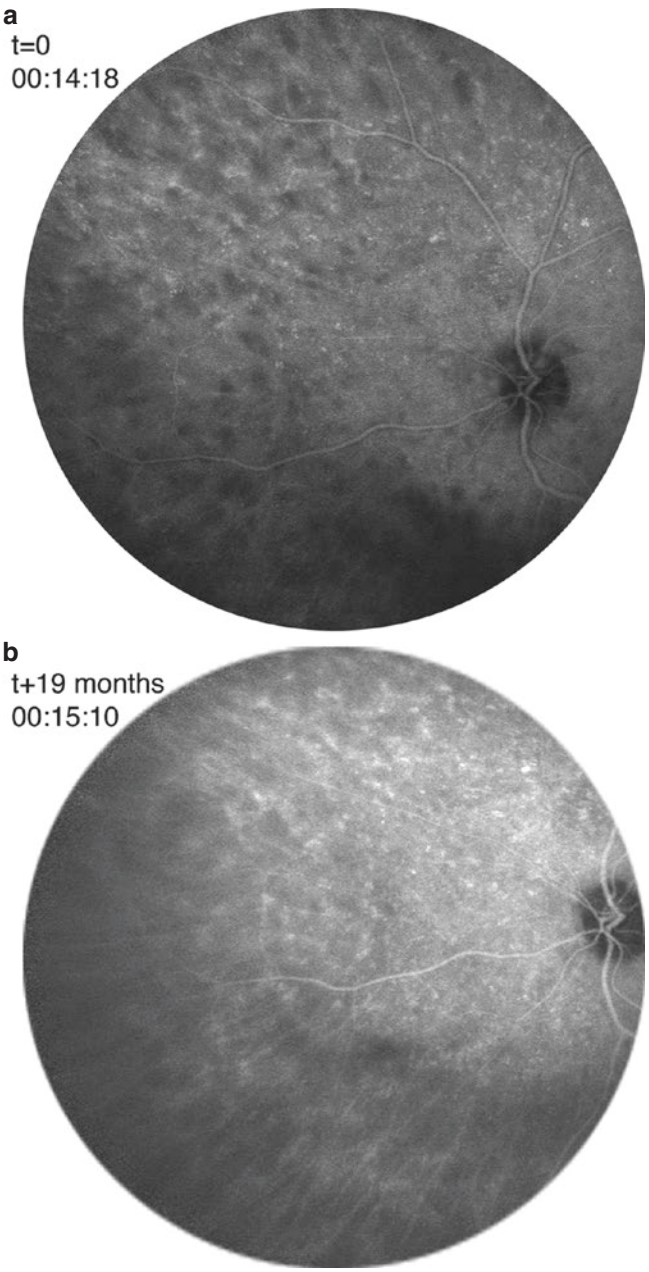

Fig. 7.5 Resolution of birdshot lesions. (**a**) Late phase ICG image at initial presentation of a patient reporting photopsias and floaters for 3 months, which demonstrates many hypocyanescent birdshot lesions. The patient also had marked phlebitis at this time (Fig. 7.2). Treatment with mycophenolate mofetil and prednisone was initiated, but inflammation worsened whenever the steroids were tapered necessitating a switch to infliximab with improvement in vasculitis (not shown) and haze. (**b**) ICG image of the same eye 19 months after the initial presentation and 6 months after initiation of infliximab demonstrating a marked decrease in birdshot lesions

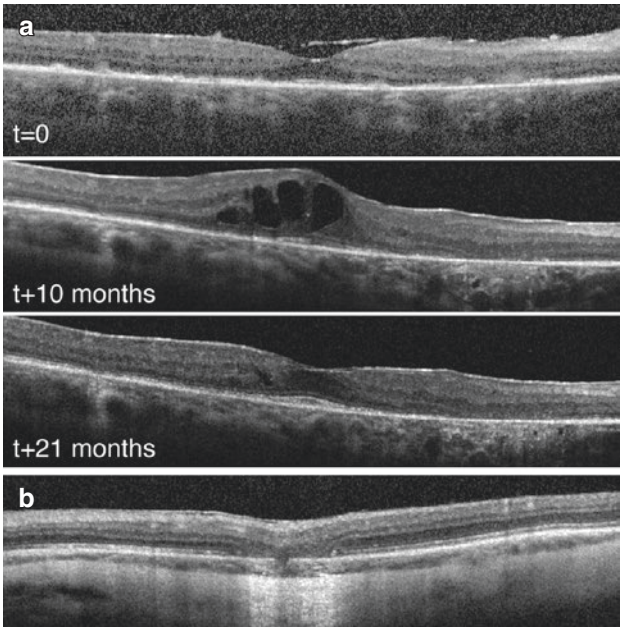

Fig. 7.6 (**a**) Series of OCT images from the same patient. The top ($t = 0$) image was taken at the time of initial presentation. The patient complained of floaters and decreased vision for 2 weeks prior to this evaluation. The OCT demonstrates an epiretinal membrane and ellipsoid disruption. She started on oral prednisone and mycophenolate mofetil. The patient developed cystoid macular edema (t + 10 months) that eventually improved and stabilized (t + 21 months) with an intravitreal dexamethasone implant (Ozurdex). (**b**) OCT image of the left eye of a 61-year-old patient, taken 14 years after the initial diagnosis. This image is superior to the fovea and demonstrates focal atrophic scarring with otherwise well-preserved retinal architecture. There is choroidal thinning and a mild epiretinal membrane

in patients with inactive disease. Epiretinal membranes and areas of retinal atrophy can also be assessed with OCT (Fig. 7.6). A few studies of enhanced depth imaging have found choroidal abnormalities, but they are not yet well-established disease markers. Boni and colleagues found hyporeflective choroidal lesions in many patients, which correlated with disease duration and the presence of vitreous haze. Some, but not all, birdshot lesions noted on color photography were associated with choroidal lesions on OCT (Böni et al. 2016). Birnbaum and colleagues found that the presence of suprachoroidal fluid correlated with the presence of vasculitis and vitreous haze and suggested its potential use in monitoring disease activity (Birnbaum et al. 2014). Only a few small studies regarding the OCTA findings in BSCR have been published. The largest study to date analyzed 37 BSCR eyes and found decreased capillary density without a change in the size of the foveal avascular zone (Fig. 7.7) (Roberts et al. 2018). Another report found increased intercapillary space, telangiectasias, and capillary loops (de Carlo et al. 2015).

Functional Testing

In addition to imaging, other modalities used to monitor BSCR progression include visual field testing and electroretinogram (ERG). Visual field testing has been used to monitor

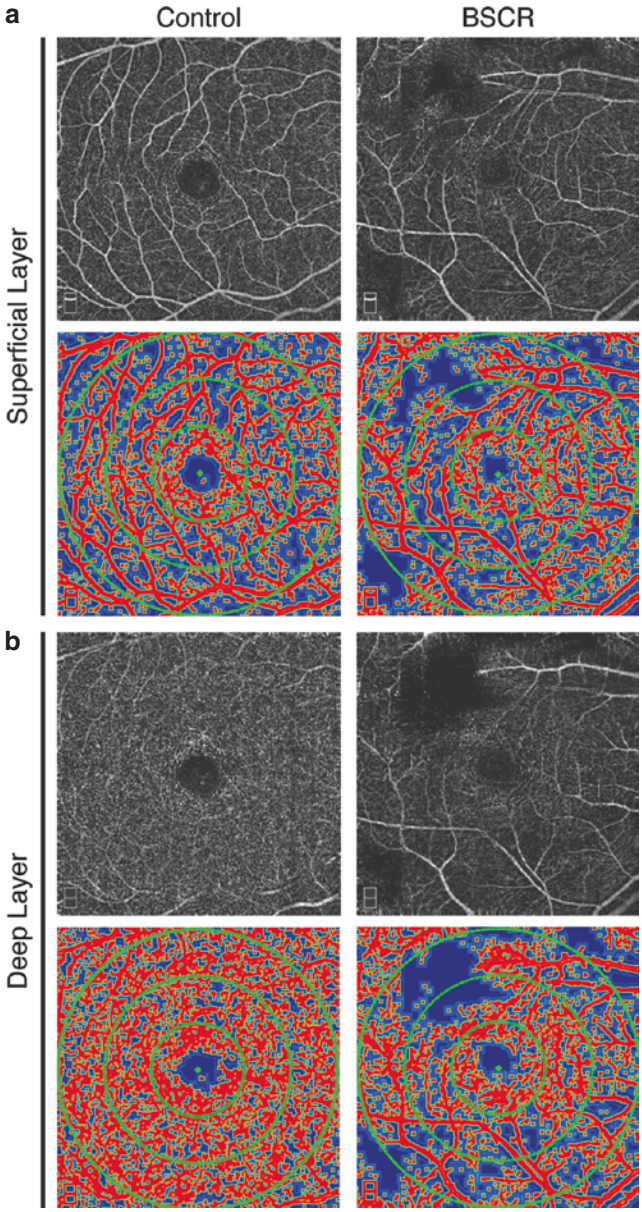

Fig. 7.7 Optical coherence tomography angiography images were acquired from a healthy control and a BSCR patient using an Optovue Angiovue (Fremont, CA). Images of the (**a**) superficial and (**b**) deep capillary layers are shown. An algorithm used to measure vessel density was used to generate the false color images below, which show capillary density in red. This BSCR patient has decreased superficial and deep capillary density

BSCR progression and response to treatment. Patients who are treated with immunosuppressive medications have improvements in their visual fields (Thorne et al. 2008; Shao et al. 2014). Electroretinography (ERG) is also a well-established modality to monitor progression in BSCR. In full-field ERG, the prolongation of the 30 Hz flicker implicit time is the most sensitive measure of damage by BSCR, and it can improve with treatment (Holder et al. 2005). In a small retrospective study, an abnormal 30 Hz flicker prior to tapering systemic immunosuppression correlated with recurrence of inflammation during the subsequent year (Zacks et al. 2002). Depression of both the photopic and scotopic b-wave amplitudes has been reported across many studies (Tzekov and Madow 2015).

Treatment

Many agents have been used to treat BSCR, but there are no randomized controlled trials to definitively prove the efficacy of these treatments. Oral corticosteroids are the most commonly used treatment. While oral corticosteroids have demonstrated efficacy in controlling the acute inflammation in BSCR, they do not appear to adequately control chronic inflammation with about one third of eyes experiencing a decline in vision with oral corticosteroids over long follow-up periods (Shah et al. 2005). Many authors have advocated for the early introduction of steroid sparing immunosuppressive therapy to limit steroid side effects and to better preserve visual function (Kiss et al. 2005; Becker et al. 2005; Menezo and Taylor 2014; Knecht et al. 2014).

Cyclosporin A has been used as a first-line option because it targets T cells, which appear to play a central role in BSCR pathogenesis. Other groups have demonstrated success using antimetabolite agents, such as mycophenolate mofetil, azathioprine, and methotrexate (Kiss et al. 2005; Goldberg et al. 2014; Doycheva et al. 2015). Monotherapy has been successful with all of these agents, although combination with corticosteroids or other steroid-sparing agents is necessary in many cases (Goldberg et al. 2014; Doycheva et al. 2015). Biologic agents have been used successfully to treat BSCR, and the TNF-α inhibitors are the most widely studied among this group. In a retrospective case series of 22 patients who had failed other immunosuppressive strategies, 93% of patients treated with infliximab achieved remission after 1 year of treatment (Artornsombudh et al. 2013). Other biologics, such as adalimumab, have been used to treat BSCR, but they have only been reported as small case series (Menezo and Taylor 2014; Shao et al. 2014).

Local corticosteroid therapy has also been used to manage BSCR. Periocular triamcinolone and intravitreal triamcinolone have both demonstrated efficacy in treating posterior uveitis (Menezo and Taylor 2014). Corticosteroid implants, including the dexamethasone implant (Ozurdex, Allergan) and fluocinolone acetonide implant (Retisert, Bausch and Lomb), are effective in treating noninfectious posterior uveitis, and they have been employed to treat BSCR (Lowder et al. 2011; Burkholder et al. 2013; Menezo and Taylor 2014). The corticosteroid implant has demonstrated good control of inflammation in BSCR, but it was associated with high rates of cataract and glaucoma that required additional surgical interventions (Burkholder et al. 2013).

References

Artornsombudh P, Gevorgyan O, Payal A, et al. Infliximab treatment of patients with birdshot retinochoroidopathy. Ophthalmology. 2013;120:588–92.

Baddar D, Goldstein DA. HLA-A 29-positive birdshot chorioretinopathy in a Hispanic patient. Ocul Immunol Inflamm. 2016;24:110–2.

Becker MD, Wertheim MS, Smith JR, Rosenbaum JT. Long-term follow-up of patients with birdshot retinochoroidopathy treated with systemic immunosuppression. Ocul Immunol Inflamm. 2005;13:289–93.

Birnbaum AD, Fawzi AA, Rademaker A, Goldstein DA. Correlation between clinical signs and optical coherence tomography with enhanced depth imaging findings in patients with birdshot chorioretinopathy. JAMA Ophthalmol. 2014;132:929–35.

Boisgerault F, Khalil I, Tieng V, et al. Definition of the HLA-A29 peptide ligand motif allows prediction of potential T-cell epitopes from the retinal soluble antigen, a candidate autoantigen in birdshot retinopathy. Proc Natl Acad Sci U S A. 1996;93:3466–70.

Böni C, Thorne JE, Spaide RF, et al. Choroidal findings in eyes with birdshot chorioretinitis using enhanced-depth optical coherence tomography. Invest Ophthalmol Vis Sci. 2016;57:OCT591–9.

Brézin AP, Monnet D, Cohen JHM, Levinson RD. HLA-A29 and birdshot chorioretinopathy. Ocul Immunol Inflamm. 2011;19:397–400.

Burkholder BM, Wang J, Dunn JP, et al. Postoperative outcomes after fluocinolone acetonide implant surgery in patients with birdshot chorioretinitis and other types of posterior and panuveitis. Retina. 2013;33:1684–93.

de Carlo TE, Bonini Filho MA, Adhi M, Duker JS. Retinal and choroidal vasculature in birdshot chorioretinopathy analyzed using spectral domain optical coherence tomography angiography. Retina. 2015;35:2392–9.

Doycheva D, Jägle H, Zierhut M, et al. Mycophenolic acid in the treatment of birdshot chorioretinopathy: long-term follow-up. Br J Ophthalmol. 2015;99:87–91.

Fardeau C, Herbort CP, Kullmann N, et al. Indocyanine green angiography in birdshot chorioretinopathy. Ophthalmology. 1999;106:1928–34.

Franceschetti A, Babel J. [Chorioretinitis with "candle spots," a manifestation of Besnier-Boeck disease]. Ophthalmologica. 1949;118:701–710.

Gasch AT, Smith JA, Whitcup SM. Birdshot retinochoroidopathy. Br J Ophthalmol. 1999;83:241–9.

Gass JD. Vitiliginous chorioretinitis. Arch Ophthalmol. 1981;99:1778–87.

Giuliari G, Hinkle DM, Foster CS. The spectrum of fundus autofluorescence findings in birdshot chorioretinopathy. J Ophthalmol. 2009;2009:567693.

Godel V, Baruch E, Lazar M. Late development of chorioretinal lesions in birdshot retinochoroidopathy. Ann Ophthalmol. 1989;21:49–52.

Goldberg NR, Lyu T, Moshier E, et al. Success with single-agent immunosuppression for multifocal choroidopathies. Am J Ophthalmol. 2014;158:1310–7.

Gritz DC, Wong IG. Incidence and prevalence of uveitis in northern California; the northern California epidemiology of uveitis study. Ophthalmology. 2004;111:491–500; discussion 500

Holder GE, Robson AG, Pavesio C, Graham EM. Electrophysiological characterisation and monitoring in the management of birdshot chorioretinopathy. Br J Ophthalmol. 2005;89:709–18.

Howe LJ, Stanford MR, Graham EM, Marshall J. Choroidal abnormalities in birdshot chorioretinopathy: an indocyanine green angiography study. Eye. 1997;11(Pt 4):554–9.

Kiss S, Ahmed M, Letko E, Foster CS. Long-term follow-up of patients with birdshot retinochoroidopathy treated with corticosteroid-sparing systemic immunomodulatory therapy. Ophthalmology. 2005;112:1066–71.

Knecht PB, Papadia M, Herbort CP. Early and sustained treatment modifies the phenotype of birdshot retinochoroiditis. Int Ophthalmol. 2014;34:563–74.

Knezevic A, Munk MR, Pappas F, et al. HLA-A29-positive birdshot chorioretinopathy in an African American patient. Retin Cases Brief Rep. 2016;10:201–4.

Kuiper JJW, Mutis T, de Jager W, et al. Intraocular interleukin-17 and proinflammatory cytokines in HLA-A29-associated birdshot chorioretinopathy. Am J Ophthalmol. 2011;152:177–182.e1.

Kuiper JJW, Rothova A, Schellekens PAW, et al. Detection of choroid- and retina-antigen reactive CD8(+) and CD4(+) T lymphocytes in the vitreous fluid of patients with birdshot chorioretinopathy. Hum Immunol. 2014a;75:570–7.

Kuiper JJW, Van Setten J, Ripke S, et al. A genome-wide association study identifies a functional ERAP2 haplotype associated with birdshot chorioretinopathy. Hum Mol Genet. 2014b;23:6081–7.

Levinson RD, Rajalingam R, Park MS, et al. Human leukocyte antigen A29 subtypes associated with birdshot retinochoroidopathy. Am J Ophthalmol. 2004;138:631–4.

Lowder C, Belfort R, Lightman S, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. Arch Ophthalmol. 2011;129:545–53.

Menezo V, Taylor SR. Birdshot uveitis: current and emerging treatment options. Clin Ophthalmol. 2014;8:73–81.

Minos E, Barry RJ, Southworth S, et al. Birdshot chorioretinopathy: current knowledge and new concepts in pathophysiology, diagnosis, monitoring and treatment. Orphanet J Rare Dis. 2016;11:61.

Pivetti-Pezzi P. Uveitis in children. Eur J Ophthalmol. 1996;6:293–8.

Priem HA, Oosterhuis JA. Birdshot chorioretinopathy: clinical characteristics and evolution. Br J Ophthalmol. 1988;72:646–59.

Pulido JS, Canal I, Salomão D, et al. Histological findings of birdshot chorioretinopathy in an eye with ciliochoroidal melanoma. Eye. 2012;26:862–5.

Roberts PK, Nesper PL, Goldstein DA, Fawzi AA. Retinal capillary density in patients with birdshot chorioretinopathy. Retina. 2018;38(2):387–94.

Ryan SJ, Maumenee AE. Birdshot retinochoroidopathy. Am J Ophthalmol. 1980;89:31–45.

Saito W, Yamamoto S, Mitamura Y, Takeuchi S. [Birdshot chorioretinopathy—a case report and a case study in Japanese patients]. Nippon Ganka Gakkai Zasshi. 2002;106:229–235.

Shah KH, Levinson RD, Yu F, et al. Birdshot chorioretinopathy. Surv Ophthalmol. 2005;50:519–41.

Shao EH, Menezo V, Taylor SRJ. Birdshot chorioretinopathy. Curr Opin Ophthalmol. 2014;25:488–94.

Szpak Y, Vieville JC, Tabary T, et al. Spontaneous retinopathy in HLA-A29 transgenic mice. Proc Natl Acad Sci U S A. 2001;98:2572–6.

Thorne JE, Jabs DA, Kedhar SR, et al. Loss of visual field among patients with birdshot chorioretinopathy. Am J Ophthalmol. 2008;145:23–8.

Tomkins-Netzer O, Talat L, Bar A, et al. Long-term clinical outcome and causes of vision loss in patients with uveitis. Ophthalmology. 2014;121:2387–92.

Tzekov R, Madow B. Visual electrodiagnostic testing in birdshot chorioretinopathy. J Ophthalmol. 2015;2015:680215.

Vadot E, Barth E, Billet P. Epidemiology of uveitis-preliminary results of a prospective study in Savoy. In: Saari K, editor. Uveitis update. Amsterdam: Elsevier; 1984. p. 13–6.

Zacks DN, Samson CM, Loewenstein J, Foster CS. Electroretinograms as an indicator of disease activity in birdshot retinochoroidopathy. Graefes Arch Clin Exp Ophthalmol. 2002;240:601–7.