INTRODUCTION

Birdshot chorioretinitis is a rare bilateral intraocular inflammatory condition that is most often seen in white populations. Birdshot chorioretinitis is linked to the presence of the HLA-A29 tissue histocompatibility antigen, but has no known systemic association.1-4 One classic sign of birdshot chorioretinitis is oval, depigmented “birdshot” lesions, located primarily in the nasal peripapillary choroid but also beyond the vascular arcades up to the midperiphery.1,2 The presence of these lesions signifies disease evolution of at least sev-
eral months, if not longer. Early-stage birdshot chorioretinitis (when “birdshot” lesions are not yet present) can only be diagnosed or confirmed using indocyanine green angiography, which reveals evenly distributed occult choroidal hypofluorescent dark dots.\(^5,6\)

In most chorioretinal inflammatory diseases, the inflammatory process takes place in one structure (such as the choroid in Vogt–Koyanagi–Harada disease or the retina in toxoplasmosis) and secondarily extends to neighboring structures (the retina and the choroid, respectively). The pathogenesis of inflammation is unique in birdshot chorioretinitis because it occurs independently but simultaneously in the choroid and the retina.\(^7\) Retinal involvement is characterized by an exudative vasculopathy that involves both small capillaries and large retinal vessels, leads to retinal atrophy in the late phase of birdshot chorioretinitis, and is the origin of functional deleterious damage.\(^3,7\) The presenting complaints of patients are usually floaters, decreased visual acuity, and dimness of vision; however, central vision can remain excellent in the absence of macular edema and this is not a good functional parameter to monitor disease evolution. Visual field changes more appropriately identify activity of the disease and functional damage.\(^8,9\) Optical coherence tomography (OCT) analysis of retinal profiles might be a useful tool to monitor birdshot chorioretinitis progression at the retinal level. Some authors have already reported the presence of retinal atrophy visualized by OCT in late-stage birdshot chorioretinitis.\(^10,11\) The aim of this study was to follow the retinal profiles in early, intermediate, and late birdshot chorioretinitis over years of evolution.

**PATIENTS AND METHODS**

Charts of patients seen in the uveitis clinic at the Centre for Ophthalmic Specialised Care, Lausanne, Switzerland, between 1995 and 2011 were reviewed. Patients with the diagnosis of birdshot chorioretinitis were identified and their cases were studied retrospectively. For posterior uveitis with functional impairment, it is standard care in our practice to perform dual indocyanine green angiography and fluorescein angiography. Early diagnosis of birdshot chorioretinitis was set in the presence of retinal vasculitis on fluorescein angiography and hypofluorescent dark dots on indocyanine green angiography and a positive HLA-A29 antigen. All patients underwent the complete routine work-up applied to patients with posterior uveitis. All patients with birdshot chorioretinitis had at least two inflammation suppressive treatments, including systemic corticosteroids (90%), immunosuppressive therapies, and/or biologic therapies. For comparison, this study also included 14 healthy volunteers, in whom 28 eyes were examined. The study was performed in accordance with the ethical standards devised in the 1964 Declaration of Helsinki.

Twenty-eight eyes in 14 patients with birdshot chorioretinitis were divided into three groups according to the duration of birdshot chorioretinitis: early untreated (< 1 year; \(n = 6\) eyes), intermediate (1 to 6 years, including only treated patients; \(n = 10\) eyes), and late (> 6 years; \(n = 12\) eyes).

Fluorescein angiography and indocyanine green angiography were performed using a standard protocol described previously.\(^1,2\) Briefly, fluorescein angiography and indocyanine green angiography were usually performed simultaneously. A Topcon 50 IA camera (Tokyo, Japan) coupled to an ImageNet (Topcon) digital imaging system was used to acquire images.

For all participants, OCT was performed using OTI-Spectral OCT/SLO (OTI Inc., Toronto, Canada). The G1 program of the OCTOPUS 900 (Octopus 900, G Standard; Haag-Streit International, Bern, Switzerland) was used for visual field assessment. OCT measurements were analyzed retrospectively in patients with early, intermediate, and late birdshot chorioretinitis, as well as in healthy volunteers. OCT images were evaluated and retinal thickness was calculated in the horizontal plane in the central macula (foveola), nasal and temporal parafovea (0.5 mm from the foveola), nasal and temporal mid-periphery (1.5 mm from the foveola), and nasal and temporal periphery of the macula (2.5 mm from the foveola). The percentage of cystoid macular edema and presence of epiretinal membranes were also noted.

**RESULTS**

Of 1,268 new patients seen at the uveitis clinic at the Centre for Ophthalmic Specialised Care from 1995 to 2011, 24 patients (1.8%; 18 women and 6 men) were diagnosed as having birdshot chorioretinitis. Of these, 14 patients (28 eyes) had sufficient data to be included in the study. Of the patients with birdshot chorioretinitis included in the study, 10 were women and 4 were men. The mean patient age at birdshot chorioretinitis onset was 46.1 ± 7.4 years and mean diagnostic delay was 13.9 ± 11 months. Mean follow-
up was 109.5 ± 52.7 months. The histocompatibility antigen HLA-A29 was positive in all patients (100%). The mean age of the age-matched control group (n = 14 volunteers) was 44.3 ± 8 years, which was not significantly different from the disease group.

Among patients with birdshot chorioretinitis, mean best-corrected visual acuity at presentation was 0.84 ± 3.4 in the right eye and 0.74 ± 3.8 in the left eye. At the last follow-up visit, the mean best-corrected visual acuity was 0.87 ± 0.12 in the right eye and 0.88 ± 0.12 in the left eye (P = not significant in the right and left eyes).

Visual field defects in patients with birdshot chorioretinitis were found in all eyes (100%) and had been present since early disease. The mean defects at presentation were 5.8 ± 3.8 dB in the early disease group, 7.1 ± 5.5 dB in the intermediate disease group, and 8.7 ± 7.7 dB in the late-stage disease group. Despite treatment, severe visual field defects were found in 10 of 28 eyes (36%). Among these, tubular visual field impairment with a visual acuity of 1.0 was noted in 4 of 28 eyes (16%).

Retinal thickness in the early birdshot chorioretinitis group was consistently elevated in comparison with a group of healthy controls (Table 1): foveola (332.5 ± 110.3 vs 268.3 ± 0.7 µm; P < .075), parafoveal nasal area (437.5 ± 83.0 vs 370 ± 21.7; P < .016), parafoveal temporal area (395.0 ± 62.4 vs 346.7 ± 25.0 µm; P < .03), nasal mid-periphery (415 ± 54.5 vs 379.2 ± 23.9 µm; P < .001), nasal periphery (422.5 ± 96.7 vs 340.8 ± 23.9 µm; P < .01), and temporal periphery (345 ± 17.3 vs 292.5 ± 12.2 µm; P < .001). In only 3 of 7 measured locations, the difference was not statistically significant due to the small number of eyes in the early disease group. Thickening of the retina (Figure 1A) was the result of diffuse retinal leaky vasculopathy, which was clearly depicted by fluorescein angiography (Figure 1B) and by an OCT cut over large retinal vessels.

In the intermediate phase of birdshot chorioretinitis, mean retinal thickness was reduced compared with the early disease group and was comparable to the control values (Figure 2). However, thickness varied from one location to another, showing areas of atrophy and concomitant areas of still thickened and edematous retina (Figure 2).

In late-stage birdshot chorioretinitis, retinal thickness was significantly thinned compared with early disease in all measured locations: foveola (259.3 ± 40 vs 332.5 ± 110 µm; P < .046), parafoveal nasal area (324.3 ± 43.8 vs 340.8 ± 23.9 µm; P < .001), parafo-
veal temporal area (310.7 ± 42.9 vs 395.0 ± 62.4 µm; \( P < .0001 \)), nasal mid-periphery (338.6 ± 32.8 vs 415 ± 54.5 µm; \( P < .002 \)), temporal mid-periphery (320 ± 38.2 vs 380 ± 23.1 µm; \( P < .0001 \)), nasal periphery (301.4 ± 26.8 vs 422.5 ± 96.7 µm; \( P < .0004 \)), and temporal periphery (268.6 ± 40.0 vs 345 ± 17.3 µm; \( P < .002 \)). Retinal atrophy on OCT (Figure 3A) corresponded in some extreme cases to pseudo retinitis pigmentosa (Figure 3B). Retinal thickness in patients with late-stage birdshot chorioretinitis was also significantly less than that of normal controls in all locations except for the macula, where retinal thickness was comparable to normal controls (Table 1).

Figure 4 graphically depicts the mean values of retinal thickness in eyes affected by early, intermediate, and late birdshot chorioretinitis.

In addition, OCT revealed epiretinal membrane development in 92% (11 of 12) of late disease cases. These membranes were usually thin and had no significant effects on central visual function. Cystoid macular edema was present in 3 of 6 eyes in the early disease group, 4 of 10 eyes in the intermediate disease group, and 2 of 12 eyes in the late-stage disease group.

**DISCUSSION**

Birdshot chorioretinitis is a bilateral, intraocular, inflammatory condition characterized by the simulta-
neous and independent involvement of the retina and the choroid. Previous studies demonstrated that choroidal inflammatory involvement was far less deleterious than retinal involvement, and therapy was rapidly successful in treating choroidal lesions thanks to precise follow-up of the choroidal compartment using indocyanine green angiography. However, several authors showed that the retinal structure was more resistant to therapy and was progressively damaged by inflammation despite therapy, with functional consequences mainly to visual fields. Therefore, clinicians should focus on follow-up and the evolution of retinal disease in patients with birdshot chorioretinitis. OCT has become available as a precise morphological tool to investigate the retina. It is non-invasive, easy to perform, and easily repeatable.

The current study demonstrates that the retina goes through different stages: in early disease, when only occult indocyanine green angiography but no “birdshot” lesions are present, the retina is thickened and exudative;
at an intermediate stage, the mean thickness appears to be returning to normal numerical values; at the late stage, retinal thinning/atrophy is noted and accompanied by a high rate of epiretinal membrane. Except for the group of patients with early untreated disease, all eyes were being treated with at least two systemic inflammation suppressive treatments. Choroidal disease followed by indocyanine green angiography responded well and promptly to treatment, with resolution of hypofluorescent dark dots (data not shown). In contrast to good choroidal response to therapy, retinal disease was less responsive and OCT allowed a more detailed understanding of retinal evolution in birdshot chorioretinitis.

Detailed data analysis revealed that in patients with early disease, the retina was thickened throughout the macula, including the foveola and peripheral macula, although not all measurement points showed a statistically significant difference to measurements in healthy volunteers due to small numbers in the early disease group. The thickened retina was the result of diffuse retinal vascular leakage, as was clearly observed on corresponding fluorescein angiography frames, mainly causing diffuse retinal edema and sometimes cystoid macular edema. In early disease, exudation of retinal vessels was such that during fluorescein angiography the dye gradually permeated into the tissue, thus leading to a lack of proper filling of large vessels and a pseudo arteriovenous circulatory delay, as already described previously in the literature.

In the intermediate phase of birdshot chorioretinitis, thickness diminished globally compared with the early stage; this change can be explained by reduced exudation as a result of therapy. Intermediate OCT scans were morphologically inhomogeneous, revealing areas of normalized thickness concomitant with areas of thinned atrophic retina and areas still thickened by retinal edema. The uneven retinal thickness indicated an uneven response of different retinal sectors to inflammation suppressive treatment, which could be correlated to irregular degrees of exudation in different sectors on fluorescein angiography. As a result of this uneven thickness of the retina, the mean thickness in this stage apparently returned to almost normal values.

In late disease, the retina showed not only reduced thickness but also atrophy; measurements were significantly thinner compared with early disease and were also reduced compared with healthy control retinas. The only measurement point that was not significantly reduced when compared with healthy retinas was the central macula (foveola), although it was significantly less thick than in early disease, indicating that, after some edema during early birdshot chorioretinitis, the central macula remains preserved in treated patients until the late stage of the disease. Measurement of the central macula is therefore not a reliable follow-up parameter to determine disease severity or disease progression. This result is in accordance with our previous findings, which indicate that cystoid macular edema was not as predominant in birdshot chorioretinitis as might be expected considering the severe and diffuse exudation found on fluorescein angiography. The lower-than-expected incidence of cystoid macular edema is probably due to the fact that the foveola gets its blood supply from the choroidal circulation, whereas the surrounding retina depends on retinal circulation for its inner layers. As documented by indocyanine green angiography, choroidal disease was under control in all of our patients, which likely contributed to foveolar preservation.

However, the retinal thickness was profoundly thinned in late disease in the extrafoveal macula, and functional repercussions on visual fields were clearly documented. In more than 15% of eyes, this condition reached the state of tubular visual field with full central vision. In some patients, the extent of thinning on OCT was pronounced and corresponded to extreme retinal atrophy, resembling pseudo retinitis pigmentosa on fundus examination.

The proportion of epiretinal membranes was high; epiretinal membranes were present in 9 of 10 eyes with late-stage birdshot chorioretinitis. However, all of these epiretinal membranes were thin and they rarely had severe functional consequences on central visual acuity.

As indicated earlier, the proportion of foveal cystoid macular edema found in our study population was disproportionately low when the highly exudative character of birdshot chorioretinitis throughout the retina is considered, and in comparison with published findings in the literature. Therefore, central vision remained good until the late stage of the disease.

Compared with a previously published study on the same topic, our study diverged regarding methodology and results. Birch et al. elegantly showed the layers affected by atrophy in chronically evolving disease. Another report also highlights a case of end-stage birdshot chorioretinitis in which causes and consequences of lesions were difficult to evaluate. Our study represents a longitudinal OCT follow-up of the retina from early
disease (diagnosed on the basis of fluorescein angiography findings and confirmed by indocyanine green angiography findings even before typical birdshot lesions were visible on fundus examination) to late disease. In our study, central vision and foveolar thickness were correlated and well conserved, whereas the rest of the macula was thinned and atrophic. Preservation of foveolar thickness, and therefore good central visual acuity in our sample population compared with other series, also reflects divergent therapeutic attitudes among countries and centers. One side considers birdshot chorioretinitis to be a severe disease requiring aggressive therapy from the beginning if there is functional impairment (and this is our attitude). By contrast, many articles published have presented birdshot chorioretinitis as a benign disease and have supported limited therapeutic intervention for decades, explaining deleterious evolution in many published series. 

Our study demonstrates that OCT represents a useful additional tool with which to follow retinal inflammation in patients with birdshot chorioretinitis. Our findings show that aggressive therapy can preserve the fovea but not the extrafoveal macula. In early disease, management of birdshot chorioretinitis relies on indocyanine green angiography to detect choroidal inflammation (allowing early diagnosis and the following of choroidal disease until it is under control) and fluorescein angiography to assess retinal inflammation. The protracted course of retinal disease must be subsequently followed by repeat fluorescein angiography, which provides panoramic information on retinal inflammation. Therefore, fluorescein angiography will never be entirely replaced by OCT. However, OCT allows clinicians to monitor retinal disease more frequently, and therefore more precisely, because it is easily performed. More precise monitoring will help to fine-tune therapeutic intervention and optimize management, and will also allow clinicians to reduce the frequency and use of fluorescein angiography, if not completely replace it.

REFERENCES