Objective: To characterize foveal atrophy in a heterogeneous group of patients with uveitis using clinical findings and high-definition (HD) optical coherence tomography (OCT).

Design: Cross-sectional, retrospective case series.

Results: The HD-OCT scans of 140 patients seen in a tertiary referral center were reviewed and 23 patients (33 eyes) with foveal atrophy were identified. All of the patients with foveal atrophy were diagnosed with intermediate uveitis, posterior uveitis, or panuveitis. The status of the photoreceptor layer as visualized with HD-OCT was associated with significant differences in mean visual acuity (P < .001). Clinical findings associated with foveal atrophy included atrophy of the retinal pigment epithelium and choroid (30 eyes [91%]), macular ischemia (13 eyes [39%]), cystoid macular edema (5 eyes [15%]), choroidal neovascularization (4 eyes [12%]), retinal detachment involving the macula (2 eyes [6%]), and serum antiretinal antibodies (2 eyes [6%]).

Conclusions: Foveal atrophy can be a complication of intraocular inflammation in a variety of uveitic syndromes. The cause of foveal atrophy is multifactorial and may include dysfunction and atrophy of the retinal pigment epithelium and choroid, cystoid macular edema, macular ischemia secondary to occlusive retinal vasculitis, choroidal neovascularization, retinal detachment, and possibly antibody-mediated damage directed against photoreceptors. Careful observation of the photoreceptor layer using HD-OCT may help to identify patients who are at risk for visual loss secondary to foveal atrophy.


The sequelae of intraocular inflammation are responsible for a significant amount of visual morbidity associated with uveitis. Macular pathological findings secondary to intraocular inflammatory disease include choroidal neovascularization (CNV), epiretinal membrane, macular hole, and cystoid macular edema (CME). Cross-sectional studies have demonstrated that CME is a significant cause of visual impairment in the uveitic population. Any type of uveitis can be complicated by CME; however, CME is more common with intermediate uveitis, posterior uveitis, and panuveitis. Macular edema has been described as a common cause of visual loss in specific uveitic syndromes including birdshot chorioretinopathy (BCR), Behçet’s disease, sarcoid uveitis, and intermediate uveitis. The pathogenic mechanisms underlying uveitic CME are multifactorial and involve disruption of the inner blood-retina barrier secondary to inflammation and vitreous traction, choroidal inflammation, and retinal pigment epithelial (RPE) dysfunction.

The clinical features and disease associations of uveitic CME have been extensively discussed in the literature. However, discussion of uveitic macular atrophy has been more limited. One retrospective series described macular atrophy as a predominant cause of compromised vision in patients with BCR. A relationship between loss of the photoreceptor layer and decreased visual acuity has previously been shown in BCR using Stratus time-domain optical coherence tomography (OCT) (Carl Zeiss Meditec, Inc, Dublin, California). Although macular atrophy with photoreceptor degeneration has been described as a significant cause of vision loss in patients with BCR, the contribution of this entity to visual morbidity in other uveitic syndromes has not been well characterized.

Optical coherence tomography is an objective and reliable test for diagnosing maculopathy and has been used to describe macular pathological findings in uveitis. The use of high-definition (HD) OCT using spectral (Fourier)–domain technology in the diagnosis and management of macular disease has become increasingly prevalent. A recent article has demonstrated that spectral-domain imaging using the Cirrus HD-OCT (Carl Zeiss Meditec, Inc) provides superior
imaging of macular pathological findings in uveitic eyes compared with the Stratus OCT. The higher resolution of HD-OCT may be especially important in helping to define specific retinal structures such as the photoreceptor layer. Photoreceptor atrophy and disorganization of retinal layers have been described in a case of BCR using HD-OCT. However, to our knowledge, an HD-OCT description of retinal morphology in patients with uveitic disease other than BCR has not been reported to date. The purposes of this study were to further characterize foveal atrophy in the setting of various uveitic syndromes seen at a tertiary referral center and to delineate the role of various pathological processes such as RPE damage, vascular disease, and photoreceptor degeneration in the development of uveitic foveal atrophy. To evaluate these questions, we retrospectively reviewed and categorized the clinical and Cirrus HD-OCT findings in a cohort of patients with uveitic foveal atrophy.

### METHODS

This study was performed with informed patient consent and conducted under a protocol approved by the local institutional review board in accordance with the ethical standards stated in the 1964 Declaration of Helsinki. All of the HD-OCT scans that were performed using Cirrus HD-OCT during a 6-month period (July 1, 2007, to December 30, 2007) at the National Eye Institute Uveitis Clinic were reviewed. Scans obtained using the 512 × 128 scan pattern from a total of 140 patients were analyzed. This protocol scans a 6 × 6-mm area on the retina with 128 horizontal lines, each consisting of 512 A-scans per line (total of 65,536 sampled points) within a scan time of 2.4 seconds. Using the 3-dimensional topographical macular map output, the center of the fovea was determined using the crosshair function of the Cirrus HD-OCT. Following this, the center point foveal thickness was determined using the caliper function of the software program included with the Cirrus HD-OCT. The measurement of center point foveal thickness using this technique is not dependent on patient fixation; hence, the potential for erroneous measurements in eyes with eccentric fixation was avoided. As normal values for foveal thickness using Cirrus HD-OCT have not been established yet, we defined foveal atrophy based on our own experience with Cirrus HD-OCT scans in healthy and diseased eyes. Foveal atrophy was defined as a center point foveal thickness less than 150 μm, normal foveal thickness was defined as 150 to 250 μm, and CME was defined as a macular thickness greater than 250 μm with the presence of intraretinal cysts. To determine the integrity of the photoreceptor layer, we examined the inner segment/outer segment junction (IS/OS junction) using the horizontal 5-line raster scan pattern, which performs 4096 A-scans per line. The photoreceptor layer was assessed by visualization of the IS/OS junction, which appears as a highly reflective line in the outer retina, adjacent and inner to the highly reflective line that demarcates the RPE layer. The status of the IS/OS junction was categorized as intact, partially intact, or absent based on a previously described grading system. Furthermore, the presence of the normal hyporeflective space between the IS/OS junction and the RPE line, which represents the photoreceptor outer segments, was noted.

The records, fundus photographs, and fluorescein angiograms of all of the patients who were identified as having foveal atrophy based on Cirrus HD-OCT were reviewed. All of the patients had these ancillary tests performed. Macular findings seen on fundus photographs and fluorescein angiograms as well as corrected visual acuities obtained using Early Treatment of Diabetic Retinopathy Study charts at the time of Cirrus HD-OCT scanning were documented. The status of the RPE and choroid was assessed based on color photographs and fluorescein angiograms. Severe disease of the RPE and choroid was defined as the presence of atrophy or fibrosis of the RPE and choroid with visualization of the underlying choroid or sclera. Mild to moderate pigmentary disease was defined as RPE mottling, hyperplasia, or granularity. Angiographic macular ischemia was defined as closure of parafoveal capillaries identified by an enlarged and/or irregular foveal avascular zone or diffusely diminished macular perfusion. A history of prior CME, CNV, retinal vasculitis, and/or retinal detachment (RD) involving the macula was also noted. One patient had been screened for serum antiretinal antibodies using previously described methods.

The relationship between center point foveal thickness and visual acuity in eyes with macular atrophy was determined using Pearson correlation. The mean visual acuity of all of the eyes with an intact, partially intact, or absent IS/OS junction was calculated and then compared using analysis of variance with Newman-Keuls posttest. All of the statistical analyses were 2-tailed, and statistical significance was determined at α = .05. Analyses were performed using GraphPad Prism version 4.0 software (GraphPad Software Inc, San Diego, California).

### RESULTS

We identified a total of 140 patients who had Cirrus HD-OCT scans performed during a 6-month period at the National Eye Institute Uveitis Clinic. A total of 23 patients were identified as having foveal atrophy based on our criteria. A summary of the uveitic diagnoses of our cohort of patients with uveitic foveal atrophy is shown in Table 1. Aside from uveitis, no patients had any other disease that could contribute to foveal atrophy such as diabetic retinopathy, age-related macular degeneration, or central serous chorioretinopathy. There were a total of 12 men and 11 women, with a median age of 43 years (range, 17-70 years). The median duration of follow-up was 52 months (range, 1-195 months). It should be noted that because many of the patients in our cohort had the diagnosis of uveitis before being referred to our clinic, the duration of disease activity in many of these patients is longer than the duration of follow-up at our clinic. Among our cohort, 33 eyes had foveal atrophy, 1 had CME, 6 had normal macular thickness, and 6 could not be assessed owing to the presence of significant

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients, No. (%)</th>
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<tr>
<td>Behçet’s disease</td>
<td>3 (13)</td>
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<tr>
<td>Serpiginous choroidopathy</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Sympathetic ophthalia</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Birdshot chorioretinopathy</td>
<td>2 (9)</td>
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<tr>
<td>Idiopathic granulomatous panuveitis</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Vogt-Koyanagi-Harada syndrome</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Lupus vasculitis</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Sarcoid panuveitis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Acute retinal necrosis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Idiopathic intermediate uveitis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Idiopathic retinal vasculitis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Multifocal choroiditis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Punctate inner choroidopathy</td>
<td>1 (4)</td>
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media opacities or prostheses. All of the prostheses were for enucleated globes. A detailed description of the patient cohort with clinical findings is shown in Table 2.

The mean visual acuity of eyes with foveal atrophy was 20/150 (range, 20/20-20/800). All of the patients with foveal atrophy were diagnosed with intermediate uveitis, posterior uveitis, or panuveitis according to established criteria.17 We did not find a significant association between cen-
ter point foveal thickness and visual acuity (P = .99) in eyes with foveal atrophy. However, the visual acuities of all of the eyes with an intact, partially intact, or absent IS/OS junction as visualized in HD-OCT were significantly different from each other (P < .001). All of the pairwise comparisons between these groups were also significantly different (P < .001) (Figure 1). In all of the eyes with foveal atrophy, we observed a complete or partial loss of the normal hyporeflective space between the IS/OS junction and the RPE line, suggestive of photoreceptor outer segment shortening. Figure 2 shows a representative HD-OCT scan of a normal macula and Figure 3 shows representative HD-OCT scans from eyes with foveal atrophy and varying degrees of IS/OS junction atrophy. The prevalence of posterior segment sequelae of intraocular inflammation, either present or prior, in eyes with foveal atrophy is summarized in Table 3.

Defects at the level at the RPE and choroid were observed in 30 of 33 eyes (91%). The primary clinical and angiographic abnormalities seen in patients with serpiginous choroidopathy (patients 2, 3, and 4), Vogt-Koyanagi-Harada disease (patients 12 and 13), and sarcoid granulomatous panuveitis (patient 17) were defects at the level of the RPE and choroid. These patients did not have current or prior evidence of CME, CNV, macular ischemia, or RD. Among these patients, all of the eyes with severe disease at the level of the RPE and choroid had an absent IS/OS junction on HD-OCT imaging. Eyes with mild to moderate RPE and choroid disease had a preserved or partially preserved IS/OS junction. Furthermore, in 1 case (patient 2), a clear delineation could be seen between an intact IS/OS junction overlying a healthy-appearing RPE and choroid and an absent IS/OS junction overlying an atrophic RPE and choroid (Figure 4).

Based on angiographic criteria, we identified a total of 13 of 33 eyes (39%) in our series with evidence of macular ischemia. The diagnoses in these cases were as follows: idiopathic intermediate uveitis (1 eye [8%]), Behcet’s disease (4 eyes [31%]), idiopathic granulomatous panuveitis (3 eyes [23%]), sympathetic ophthalmia (1 eye [8%]), lupus chorioretinopathy (2 eyes [15%]), and idiopathic retinal vasculitis (2 eyes [15%]). The majority of these eyes (11 eyes [85%]) had active or resolved retinal vasculitis. In 2 eyes without a history of active or resolved retinal vasculitis, the presence of serum antiretinal antibodies had previously been demonstrated using immunohistochemical staining techniques (data not shown). In 2 of 4 eyes (50%) with active vasculitis, fluorescein angiography demonstrated macular ischemia with evidence of active vasculitis of the parafoveal vasculature (Figure 5). A review of records demonstrated that 3 of 6 eyes (50%) with resolved vasculitis previously had a similar pattern of parafoveal vasculitis.

Of 33 eyes with foveal atrophy, 5 had a history of prior CME, 4 (12%) had a history of CNV, and 2 (6%) had a history of RD involving the macula. Cystoid macular edema was seen in eyes with idiopathic intermediate uveitis, BCR, and Behcet’s disease. Choroidal neovascularization was a complication in eyes with BCR, sympathetic ophthalmia, multifocal choroiditis, and punctate inner choroidopathy. A history of RD involving the macula was noted in eyes with acute retinal necrosis and sympathetic ophthalmia.

**COMMENT**

In this article, we describe clinical features and associations of foveal atrophy in a heterogeneous group of pa-
tients with uveitis. Patients in our cohort were diagnosed with a variety of uveitic syndromes that could be classified as intermediate uveitis, posterior uveitis, or panuveitis. We found that visual acuity was related to the status of the IS/OS junction as seen on HD-OCT imaging. The visual outcome of uveitic CME has been shown to depend on anatomical location, with uveitic entities affecting the posterior segment (intermediate uveitis, posterior uveitis, and panuveitis) having a poorer visual prognosis. This suggests that posterior segment inflammation may be associated with other sequelae such as foveal atrophy that portend a poor visual outcome. This theory is supported by our observation of foveal atrophy in patients with intermediate uveitis, posterior uveitis, and panuveitis. Numerous manifestations of posterior segment inflammation including dysfunction and atrophy of the RPE and choroid, CME, CNV, macular ischemia secondary to vasculitis, RD involving the macula, and retinal autoimmunity could conceivably be involved in the development of foveal atrophy.

We observed HD-OCT evidence of marked photoreceptor degeneration in eyes with severe atrophy of the RPE and choroid in which no other posterior segment sequelae of intraocular inflammation could be identified. In the remaining majority of cases of foveal atrophy, we observed RPE pigmented change suggestive of damage to this cellular layer. The photoreceptor layer, along with other components of the outer retina, relies heavily on the RPE and choroid for nutrient and oxygen support. Dysfunction of the RPE and choroid mediated by various inflammatory factors likely represents a contributing factor in the development of uveitic foveal atrophy.

Macular ischemia was observed in a large percentage of eyes with evidence of foveal atrophy and photoreceptor degeneration on HD-OCT. Most of these eyes had evi-

Table 3. Prevalence of Present or Prior Uveitic Sequelae in Eyes With Macular Atrophy

<table>
<thead>
<tr>
<th>Abnormal Findings</th>
<th>Eyes, No. (%)</th>
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<tr>
<td>Retinal pigment epithelium and choroid defects</td>
<td>30 (91)</td>
</tr>
<tr>
<td>Macular ischemia</td>
<td>13 (39)</td>
</tr>
<tr>
<td>Cystoid macular edema</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Choroidal neovascularization</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Antiretinal antibodies</td>
<td>2 (6)</td>
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</table>

Figure 3. Representative high-definition optical coherence tomographic images demonstrating varying degrees of macular atrophy. The right eye (A) and left eye (B) of patient 20 had an intact photoreceptor layer, while the photoreceptor outer segments appeared attenuated. The right eye of patient 17 (C) and the left eye of patient 1 (D) had a partially intact photoreceptor layer. The left eye of patient 11 (E) and the right eye of patient 5 (F) had an absent photoreceptor layer. White arrows indicate hyperreflective line corresponding to the photoreceptor layer; blue arrows, hyperreflective line corresponding to the retinal pigment epithelium; and VA, visual acuity. The images represent horizontal line scans through the center of the fovea.
idence of active or prior retinal vasculitis, and in some of these cases we observed vasculitic changes within the parafoveal vasculature. Macular ischemia secondary to occlusive parafoveal vasculitis has previously been described in cases of Behcet’s disease, sarcoidosis, and idiopathic retinal vasculitis. We observed macular ischemia in eyes with these syndromes as well as in eyes with idiopathic intermediate uveitis, idiopathic granulomatous panuveitis, sympathetic ophthalmia, and lupus vasculitis. Furthermore, we observed angiographic evidence of active occlusive parafoveal vasculitis in eyes with idiopathic intermediate uveitis, Behcet’s disease, and lupus vasculitis. Retinal vasculitis in uveitis typically involves vessels of larger caliber, but our observations along with those of other investigators suggest that the foveal vasculature is susceptible to vasculitis as well. Furthermore, our finding of macular thinning and photoreceptor degeneration in this group of patients demonstrates that macular ischemia secondary to parafoveal occlusive retinal vasculitis is an important cause of foveal atrophy in patients with uveitis.

Cystoid macular edema may represent another pathogenic factor in uveitic foveal atrophy. A significant percentage of eyes in our series had a history of CME. The visual morbidity of uveitic CME has been well established. Photoreceptor dysfunction has been observed in eyes with macular edema secondary to diabetes and uveitis. Nitric oxide has been shown to contribute to breakdown of the blood-retina barrier in diabetic macular edema, and aqueous levels of nitric oxide are elevated in patients with uveitis. Nitric oxide–mediated oxidative stress and apoptotic death of photoreceptors have been demonstrated in animal models of uveitis. Although the role of uveitic CME in the development of foveal atrophy remains to be fully elucidated, it is possible that inflammatory mediators (eg, nitric oxide) in uveitic CME are involved in the induction of apoptotic photoreceptor death and in the pathogenesis of foveal atrophy.

A small percentage of eyes with foveal atrophy in our series had a history of CNV, which is a known but rare complication of posterior uveitis and panuveitis. Choroidal neovascularization has been reported in numerous uveitic entities including multifocal choroiditis, BCR, sympathetic ophthalmia, serpiginous choroidopathy, Behcet’s disease, and punctate inner choroidopathy. Choroidal neovascular membranes can be classified into 3 growth patterns: subretinal, sub-RPE, or combined. The sequelae of CNV include exudation, hemorrhage, and fibrosis. Photoreceptor degeneration could conceivably oc-
cur directly as a result of the growth of CNV in the subretinal space or secondary to RPE dysfunction induced by a sub-RPE choroidal neovascular complex.

The presence of uveitis has been associated with RD in specific uveitis entities such as Vogt-Koyanagi-Harada disease and acute retinal necrosis. Retinal detachment occurs more frequently in patients with panuveitis than in those with other anatomical locations of uveitis. Retinal detachment involving the macula was a rare complication in our cohort and was observed in eyes with posterior uveitis or panuveitis. Photoreceptor apoptosis has been observed in patients following primary and recurrent RD. Apoptotic death of photoreceptors following RD involving the macula may contribute to the development of foveal atrophy in some patients with uveitis.

The serum of one of our patients was found to contain antiretinal antibodies using immunohistochemical techniques. Previous experiments have demonstrated immunohistochemical labeling of photoreceptors by antiretinal antibodies from the serum of patients with Vogt-Koyanagi-Harada disease, Behçet’s disease, and sympathetic ophthalmia. Interestingly, we observed cases of foveal atrophy in patients with all of these diagnoses. Antiretinal antibodies have been shown to induce apoptotic death of photoreceptors in vivo. The pathogenic role of antiretinal antibodies in uveitis remains to be fully established, but our observations suggest that this form of humoral autoimmunity may play a role in the development of uveitic foveal atrophy.

In summary, uveitic foveal atrophy may be a complication of intermediate uveitis, posterior uveitis, or panuveitis. Macular thinning and, more importantly, photoreceptor degeneration are serious sequelae of this process. Several etiologic factors may contribute to the evolution of foveal atrophy in the setting of uveitis. Inflammatory damage to the RPE and choroid can cause dysfunction and atrophy of these tissues, leading to hypoxia and nutritional deprivation of the macula. Longstanding CME may also contribute to the development of foveal atrophy via toxic inflammatory mediators. Occlusive parafoveal retinal vasculitis can lead to foveal ischemia and

Figure 5. Macular ischemia associated with macular atrophy. Arteriovenous (A and C) and late venous (B and D) phases of fluorescein angiograms of the left eye of patient 1 (A and B) and the left eye of patient 9 (C and D) demonstrated active vasculitis at the border of the fovea with an irregular foveal avascular zone.
infarction in some cases. Complications such as CNV and RD can also result in photoreceptor death. Finally, antiretinal antibodies may induce apoptotic death of retinal elements including photoreceptors. Pathogenic risk factors for uveitic foveal atrophy can be identified using clinical examination, and ancillary testing such as HD-OCT can help identify atrophy of the IS/OS junction. Careful attention to these factors is important in identifying patients who may be at risk for developing foveal atrophy or those who have already started to show signs of photoreceptor degeneration. Monitoring the progression of potential conditions that could predispose individuals to future foveal atrophy may be important in prompting early and aggressive therapy to avoid this vision-threatening complication. Furthermore, the status of the IS/OS junction may serve as an important outcome measure in clinical trials in uveitis.

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