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MACULOPATHY DIAGNOSED WITH HIGH-RESOLUTION FOURIER-DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN EYES WITH PREVIOUSLY UNEXPLAINED VISUAL LOSS

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Abstract

Purpose—To describe maculopathy diagnosed with high-resolution Fourier-domain optical coherence tomography among eyes with previously unexplained visual loss.

Methods—Nine eyes from six patients with previously unexplained vision loss based on funduscopy, fluorescein angiography, and Stratus optical coherence tomography and 32 eyes from 25 asymptomatic age-matched control subjects were imaged with a Fourier-domain optical coherence tomography instrument with axial resolution of 4 μm to 4.5 μm and transverse resolution of 10 μm to 15 μm.

Results—Among eyes with unexplained vision loss, visual acuity ranged from 20/20 to 20/80 and central scotoma was noted in all eyes by microperimetry or Amsler grid. Fourier-domain optical coherence tomography showed abnormality in the foveal photoreceptor (PR) layer in six eyes from four subjects (67%). These abnormalities include focal loss of the PR layer with microcystoid changes in the macula (n = 2), focal discontinuity of the PR layer (n = 3), and focal elevation and blurring of the PR layer associated with a mild epiretinal membrane (n = 1). Among age-matched control eyes, no foveal PR abnormality was seen.

Conclusion—Fourier-domain optical coherence tomography detected subtle changes in the foveal PR layer in some eyes with vision loss and central scotoma unexplained with routine clinical diagnostic tests.

Keywords

Fourier-domain optical coherence tomography; high-resolution optical coherence tomography; macular microhole; tamoxifen; maculopathy; toxic maculopathy; unexplained vision loss

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Optical coherence tomography (OCT) was introduced to ophthalmologists in 1995 as a diagnostic tool capable of in vivo imaging of a cross-section of the retina.[1] The commercially available Stratus OCT (OCT-3, Carl Zeiss, Meditec, Inc., Dublin, CA) is routinely used to diagnose macular holes and cysts and to quantitate macular thickening among subjects treated for macular edema or choroidal neovascularization. [2,3] The main limitation of the Stratus OCT is that the data are acquired slowly as a result of

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implementation in the time domain. The resulting relatively long data acquisition time (0.5 to 1.0 B-scans/s, 400 A-scans/s) limits the ability to sample the retina completely because only a limited number of A- and B-scans can be acquired.[4] Stratus OCT uses only six radial B-scans to create a macular thickness map. Thus, the entire macula is not imaged, and small macular lesions may be visualized incorrectly or missed when using this imaging modality.[4]

Fourier-domain, or spectral-domain, OCT (Fd-OCT) is an alternative imaging modality developed recently.[4] This method of data acquisition reduces the image data acquisition time by a factor of 20 to 40 while maintaining high axial resolution. The rapid data acquisition allows serial B-scans of the macula such that the entire macula can be imaged in high resolution with minimal motion artifact. This technology has been shown to improve visualization of the entire macular lesion and to provide more information on anatomic structural changes in the retina that may be missed with conventional time-domain OCT.[4]

In this report, we used a high-resolution Fd-OCT instrument developed at our institution to image the maculae of subjects with previously unexplained vision loss based on funduscopy, fluorescein angiography, and Stratus OCT. These eyes were compared with eyes from age-matched control subjects.

Materials and Methods

This study is a prospective observational case series of all subjects seen in the Retina Service at the University of California Davis Medical Center between February 2005 and March 2008 with previously unexplained vision loss who agreed to participate in this study. Each subject was diagnosed with unexplained vision loss based on dilated funduscopy, fluorescein angiography, and Stratus OCT imaging. For the control, subjects older than 40 years of age with a normal examination in the imaged eye were enrolled. Written informed consent was obtained from each subject before imaging with Fd-OCT, and the study was performed according to a protocol approved by the Office of Human Research Protection at the University of California Davis Medical Center.

A high-resolution Fd-OCT system constructed and developed in the Vision Science and Advanced Retinal Imaging Laboratory at our institution was used.[4] The instrument uses a superluminescent diode as a light source, model D855 (855 nm at 75 mm bandwidth; Superlum Diodes Ltd., Moscow, Russia) and creates images with an axial resolution of 4 μm to 4.5 μm and calculated transverse resolution between 10 μm and 15 μm. A raster series of 100 B-scans (1000 A-scans/frame, nine frames/s) imaged over a 6 mm × 6 mm × 2-mm volume of retina (lateral × lateral × depth) centered over the macula was obtained. Serial consecutive B-scan images, laterally separated by 60 μm, were registered using custom software to minimize fine axial motion artifacts.

Results

Nine eyes from six subjects with unexplained vision loss were imaged using Fd-OCT. The demographic information and clinical data at presentation are summarized in Table 1. Table 1 also summarizes the Stratus and Fd-OCT findings. None of the eyes had an afferent papillary defect, but a small central scotoma was detected by Amsler grid and/or microperimetry (Nidek, MP-1, Nidek, Inc., Fremont, CA) in all eyes. Six eyes from four subjects with maculopathy on Fd-OCT are described in detail subsequently. Case 1 has been previously presented as a case report and described briefly in this report.[5] Figure 1 is a previously published figure of a normal macula with retinal layers labeled for orientation.[6]

Case 1

A 67-year-old woman presented with progressive blurring of vision in her right eye for 3 months and the left eye for 3 years. She was on tamoxifen for 4.5 years for breast cancer. Visual acuity was 20/30 in the right eye and 20/80 in the left eye. Funduscopy, fluorescein angiography, and multifocal electroretinography were normal. Stratus OCT showed trace cystoid changes in the fovea with probable disruption of the outer retina near the fovea that was poorly visualized in both eyes (Figure 2, A–B). Microperimetry showed a small central scotoma in both eyes. Fourier-domain OCT showed scattered microcystoid changes in the macula of both eyes from inner nuclear layer to the photoreceptor (PR) layer with focal patches of loss of PR extending to the fovea of both eyes (Figure 2, C–D). Tamoxifen was discontinued. Visual acuity and OCT remained unchanged after 1 year.

Case 2

A 60-year-old woman presented with a central scotoma in left eye, which was first noted 3 years earlier. She was diagnosed with unexplained vision loss previously. On presentation, visual acuity was 20/20 in the right eye and 20/25 – 2 in the left eye. On Amsler grid testing, she noted a small central scotoma involving the central 16 squares. Funduscopy and fluorescein angiography were unremarkable. Stratus OCT showed a mild macular epiretinal membrane (ERM) with mild blunting of the foveal depression in the left eye (Figure 3, A). Fourier-domain OCT showed a subtle foveal detachment associated with a mild ERM (Figure 3, B). The PR inner segment– outer segment junction around and over the detachment showed blurring and distortion. One year later, examination, symptoms, and OCT were unchanged.

Case 3

A 65-year-old woman presented with a new complaint of a gray spot in her vision of the left eye for 3 months. She had a history of vitreomacular traction syndrome in the right eye, leading to a lamellar hole. On presentation, visual acuity was 20/20 in the right eye and 20/40 in the left eye. On Amsler grid, she noted a new small central scotoma in the left eye involving the central 16 squares. Dilated funduscopy showed an inner lamellar hole in the right eye, which was unchanged and unremarkable macula in the left eye. Fluorescein angiography was unremarkable. Stratus OCT in the left eye showed perifoveal vitreous detachment with vitreous adherence to the fovea and possible irregularity of the foveal PR layer (Figure 4, A). Fourier-domain OCT showed focal discontinuity of the foveal PR layer with blurring of the adjacent inner segment– outer segment function in the left eye (Figure 4, B). Visual acuity improved to 20/25 – 2 in the left eye 8 months later and scotoma resolved spontaneously. Fourier-domain OCT showed vitreous detachment from the macula with resolution of foveal PR discontinuity (Figure 4, C).

Case 4

A 60-year-old woman presented with a 2-week history of a central blur in the right eye and a 2-year history of a similar central blur in the left eye. She had no history of trauma or sun gazing. On presentation, visual acuity was 20/20 in both eyes, but a small central scotoma was noted both eyes, the size of the fixation spot on the Amsler grid. Funduscopy and fluorescein angiography were unremarkable. Stratus OCT was unremarkable with vitreomacular separation in both eyes (Figure 4, D). Fourier-domain OCT showed subtle subfoveal discontinuity of the PR layer (inner segment–outer segment junction) extending to the outer limiting membrane of both eyes (Figure 4, E).

Among the nine eyes from six subjects imaged with Fd-OCT for unexplained vision loss, subtle abnormalities in the foveal PR layer was diagnosed in six eyes (67%), which

correlated with the central scotoma noted by the subjects (Table 1). Among three eyes from two subjects with unexplained vision loss in which no maculopathy was noted on Fd-OCT, Case 6 was diagnosed subsequently with a hypercoagulable state secondary to antiphospholipid antibodies and Case 5 refused further workup.

To determine whether these foveal changes are unique to symptomatic eyes, 32 eyes from agematched asymptomatic subjects were imaged using Fd-OCT. All eyes had a normal-appearing fovea on Fd-OCT. A mild ERM was noted in five eyes without associated morphologic changes in the macula. Two eyes were noted with a small focal extrafoveal thickening of Bruch's membrane suggestive of a druse. One eye was noted with an extrafoveal focal disruption of the retinal pigment epithelium layer.

Discussion

In this report, we used a Fd-OCT instrument developed at our institution to visualize subtle maculopathy among subjects previously diagnosed with unexplained vision loss based on routine diagnostic testing, including Stratus OCT. Among nine eyes from six subjects with unexplained vision loss and central scotoma noted on Amsler grid or perimetry, abnormalities in the foveal PR layer could be seen using Fd-OCT in 67% of the eyes. Our Fd-OCT instrument has axial image resolution of 4 μm to 4.5 μm and transverse image resolution of 10 μm to 15 μm. It also obtains serial fine B-scan cuts of the entire macula, each separated by 60 μm. Both these features allowed detection of subtle changes in the foveal PR layer that were not well visualized using Stratus OCT.

Previous studies using Fd-OCT have shown that improved image resolution allows for improved visualization of intraretinal abnormalities, including changes in the PR layer.[4,5] This was noted in our study also. Stratus OCT showed microcystoid changes in Case 1 and a mild ERM in Case 2, but these changes would not be expected to cause central scotoma. Although subtle irregularities in the PR layer could not be ruled out on magnification of some Stratus OCT images, the foveal PR abnormalities could be clearly visualized on Fd-OCT.

The size and location of the foveal PR layer abnormalities visualized using Fd-OCT in all six eyes seem to correlate with the central scotoma noted on Amsler grid or microperimetry (Table 1). These abnormalities included focal loss of PR in two eyes, a subtle foveal detachment with foveal PR layer blurring in one eye, and focal subfoveal discontinuity of the PR layer in three eyes. None of these changes were noted in the age-matched asymptomatic eyes. The size of the lesion on Fd-OCT was equal to or somewhat smaller than that predicted by the scotoma size (Table 1), suggesting that abnormality may extend beyond that noted on Fd-OCT in some eyes. In Case 3, the spontaneous resolution of the foveal PR abnormality was associated with resolution of the central scotoma and improvement in vision.

Cases 5 and 6 had normal-appearing macula on Fd-OCT. Although it is possible that these eyes had maculopathy that could not be detected with Fd-OCT, it is also likely that they had other causes of unexplained vision loss such as an occult retinal vascular occlusion, optic neuropathy, or functional vision loss.

Among the eyes with maculopathy diagnosed by Fd-OCT, the etiology is likely to be varied. The microcystoid changes with focal loss of PR in both eyes of Case 1 are likely the result of tamoxifen because similar changes were noted using Stratus OCT in subjects diagnosed with tamoxifen maculopathy on funduscopy.[5,7] The foveal discontinuity of the PR layer noted in Cases 3 and 4 has been described with OCT among eyes diagnosed with a macular microhole clinically.[4,8] In Case 3, the central scotoma and Fd-OCT abnormalities resolved

spontaneously after vitreous detachment from the macula, suggesting that this PR abnormality may result from vitreomacular traction. Finally, Case 2 had a subtle foveal detachment associated with a mild macular ERM. Although foveal detachment associated with macular thickening has been described previously using OCT in eyes with vision loss from ERM,[9] the central scotoma noted by our subject is atypical for ERM and more likely explained by the foveal detachment and adjacent PR layer distortion seen on Fd-OCT. Fine PR layer striae associated with vision loss from ERM was recently visualized using adaptive optics, suggesting that subtle PR layer changes may contribute to vision loss associated with ERM.[10]

In summary, this pilot study showed that Fd-OCT can diagnose subtle PR layer changes in some eyes with unexplained vision loss. The improved visualization of the retinal layers and a more complete scan of the entire macula using this technology allow detection of macular changes that may be missed with routine diagnostic testing. Although the Fd-OCT instrument used in this study has an axial resolution that is slightly higher than that obtainable with commercial Fd-OCT units now available, the PR abnormalities noted in our study should be discernible with these commercial units. Thus, future larger studies using commercial Fd-OCT are possible and may provide further insight into understanding the pathogenesis of maculopathies that may present as unexplained vision loss.

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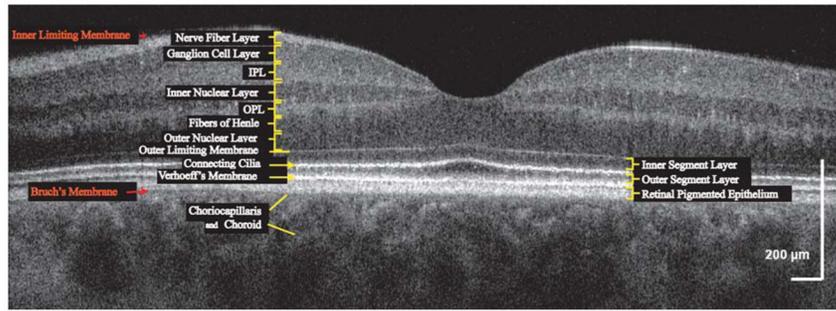
Fig. 1.
High-resolution Fd-OCT imaging of normal retina showing the various retinal layers.6 IPL, internal plexiform layer; OPL, outer plexiform layer.
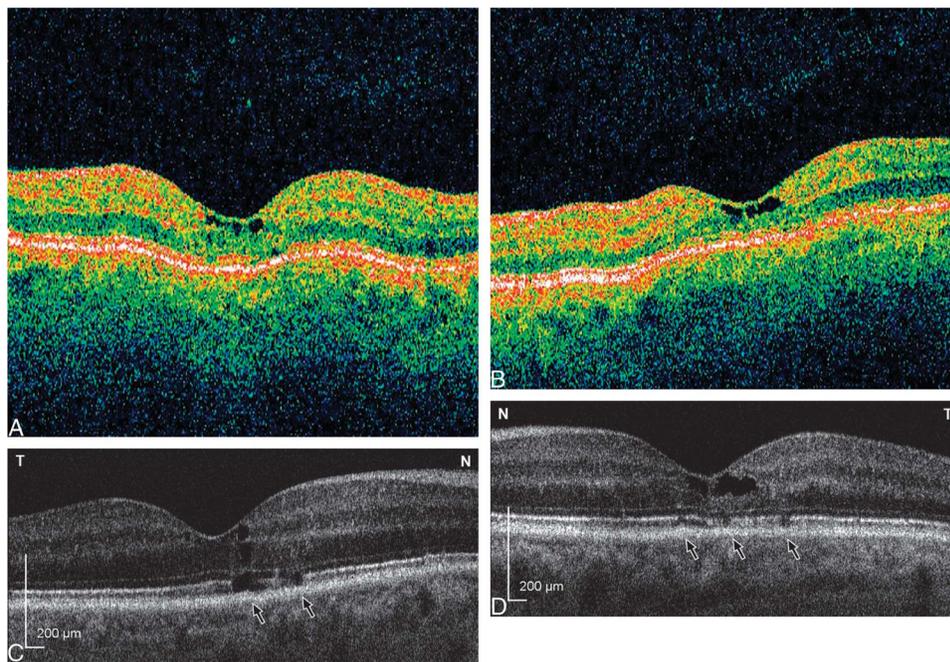
Fig. 2.
Optical coherence tomographic imaging of the macula of both eyes of Case 1 showing microcystoid maculopathy associated with tamoxifen use of over 4 years. Axially magnified (×2) Stratus OCT images of the right (**A**) and left (**B**) macula show microcystoid changes in the fovea with probable irregularity in the photoreceptor (PR) or retinal pigment layer that is poorly visualized. High-resolution Fd-OCT images of the right (**C**) and left (**D**) macula show the microcystoid changes more clearly. In addition, distinct patches of loss of the inner segment–outer segment junction of the PR layer are seen scattered throughout the macula and involving the fovea in both eyes (arrow). N, nasal; T, temporal.
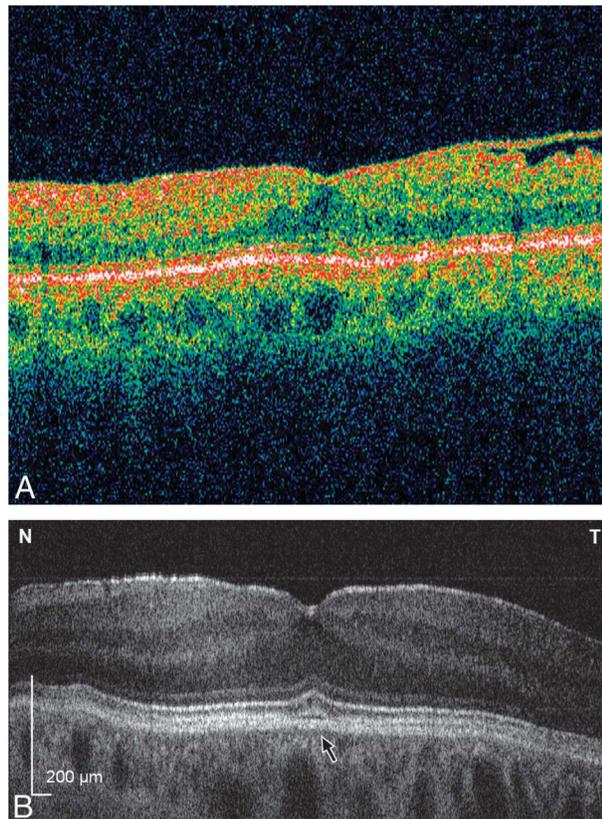
Fig. 3.
Optical coherence tomographic imaging of the macula of the left eye of Case 2 showing subtle foveal detachment imaged using high-resolution Fd-OCT. **A**, Axially magnified (×2) Stratus OCT radial line scan showing a mild macular epiretinal membrane with blunting of the foveal depression. **B**, Horizontal Fd-OCT B-scan shows a subtle foveal detachment with distortion and blurring of the inner segment–outer segment junction of the PR layer adjacent to the detachment (arrow). In this horizontal view, the mild epiretinal membrane is diffusely adherent to the underlying retina and blunting of the foveal depression is also noted. N, nasal; T, temporal.
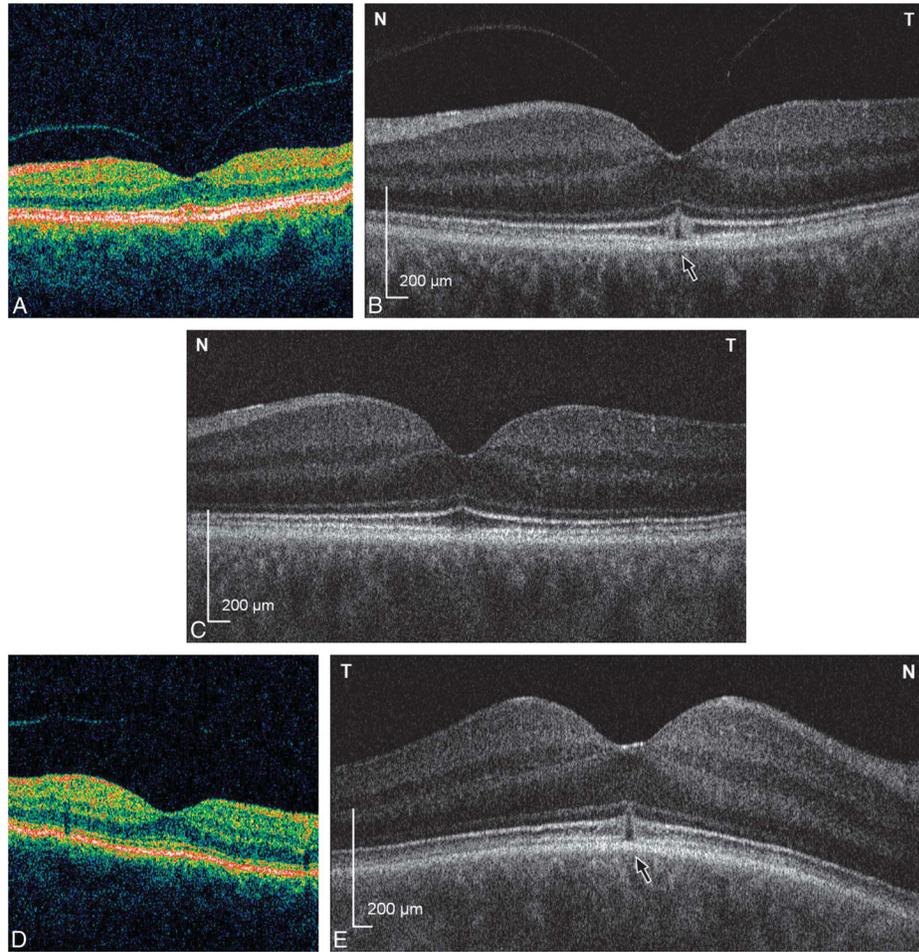
Fig. 4.
Optical coherence tomographic imaging of the macula of Cases 3 and 4 showing discontinuity of the subfoveal PR layer on high-resolution Fd-OCT. **A**, Axially magnified (×2) Stratus OCT image of the left macula in Case 3 shows perifoveal vitreous detachment with vitreous adherence to the fovea and possible irregularity of the foveal PR layer. **B**, Fd-OCT image of the left macula in Case 3 clearly shows focal subfoveal discontinuity of the inner segment–outer segment junction of the PR layer with adjacent blurring and distortion of this layer (arrow). **C**, Fd-OCT image of the left macula in Case 3, 8 months later, shows vitreous detachment from the macula with resolution of the foveal PR abnormality concurrent with improvement in vision and resolution of the central scotoma. **D**, Axially magnified (×2) Stratus OCT image of the right macula in Case 4 is unremarkable. **E**, Fd-OCT image of the right macula in Case 4 shows subfoveal discontinuity of the inner segment–outer segment junction of the PR layer that appears to extend to the outer limiting membrane (arrow). N, nasal; T, temporal.

Table 1

Summary of Stratus and Fd-OCT Findings and Clinical Information on All Subjects Imaged With Unexplained Vision Loss

Case No.	Age (yr)	Gender	OD/OS	Symptoms and Duration	VA	Stratus OCT Findings	Fd-OCT Findings	Size of Foveal IS/OS Junction Abnormality on Fd-OCT	Predicted Size of Lesion Based on Size of Scotoma*	Diagnosis Based on Fd-OCT
1	67	Female	OD	Vision loss ×3 mo	20/30[†]	Microcystoid foveal changes with ? foveal PR irregularity	Microcystoid changes with subfoveal and extrafoveal patches of PR loss	800 μm	1.5 mm	Tamoxifen maculopathy
			OS	Vision loss ×3 yrs	20/80[†]	Same as OD	Same as OD	800 μm	1.5 mm	Same as OD
2	60	Female	OS	Central blur ×3 yrs	20/25[‡]	Mild ERM	Mild ERM with foveal detachment and adjacent blurring of IS/OS junction	400 μm	1 mm	Foveal detachment resulting from ERM
3	65	Female	OS	Central blur ×3 mo	20/40[‡]	Vitreous adherence to fovea with ? foveal PR irregularity	Subfoveal discontinuity of PR layer with adjacent blurring of IS/OS junction	350 μm	1 mm	Microhole
4	60	Female	OD	Central blur ×2 wk	20/20[‡]	Normal	Subfoveal discontinuity of PR layer	150 μm	150 μm	Microhole
			OS	Central blur ×2 yr	20/20[‡]	Normal	Same as OD	150 μm	150 μm	Microhole
5	63	Male	OD	Central blur ×6 mo	20/70[†]	Normal	Normal	None	500 μm	Unknown
			OS	Central blur ×6 mo	20/70[†]	Normal	Normal	None	500 μm	Unknown
6	47	Female	OD	Central blur ×3 mo	20/60[†]	Normal	Normal	None	1 mm	Unknown

*
Calculated size of defect based on size of scotoma on Amsler grid and/or microperimetry.

[†]
Central scotoma detected by microperimetry.

[‡]
Central scotoma detected by Amsler grid.

OD, right eye; OS, left eye; VA, visual acuity; IS/OS, inner segment–outer segment of photoreceptor; PR, photoreceptor.