Retinal Pigment Epithelium Tears Secondary to Age-Related Macular Degeneration

A Simultaneous Confocal Scanning Laser Ophthalmoscopy and Spectral-Domain Optical Coherence Tomography Study

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Objective: To describe the morphology of retinal pigment epithelium (RPE) tears secondary to age-related macular degeneration by using high-resolution, spectral-domain optical coherence tomography (SD-OCT).

Methods: For simultaneous topographic and tomographic in vivo imaging, confocal scanning laser ophthalmoscopy and spectral-domain optical coherence tomography were applied in combination. Retina over the RPE-denuded area was particularly examined for signs of viable photoreceptors.

Results: A total of 26 patients (28 eyes) were included in the study. The mean (SD) age of patients was 78 (8) years (age range, 62-91 years). In cases with recent RPE tears, external limiting membrane, photoreceptor inner and outer segment junction, and nonatrophic outer nuclear layer could be identified in the retina on the RPE-denuded area. Intact external limiting membrane, photoreceptor inner and outer segment junction, and nonatrophic outer nuclear layer could be seen in 1 patient for up to 325 days after the RPE tear. In fibrotic older RPE tears, these structures were atrophic.

Conclusions: In this study, signs for viable photoreceptors could be identified for up to 325 days after an RPE tear using spectral-domain optical coherence tomography. This finding is important to consider in future therapies aimed at rescuing photoreceptors after RPE tears.


Retinal pigment epithelium (RPE) tears are a serious complication that can follow pigment epithelium detachment. Retinal pigment epithelium tears occur spontaneously either after therapy using anti-vascular endothelial growth factors or after any other therapy regarding neovascular age-related macular degeneration (AMD). The RPE tear creates an area where photoreceptors have no RPE support. If the fovea lies within the RPE-denuded area, a marked decrease in visual acuity is observed, often accompanied by eccentric fixation.

In recent years, high-resolution, spectral-domain optical coherence tomography (SD-OCT) has been established as a highly valuable tool in ophthalmology. A total of 40,000 A-scans per second provide high-resolution images, which represent a detailed histological correlate of the retina in vivo. If an eye tracking system is applied, artifacts caused by eye movements can be automatically corrected. Simultaneously, the combined use of confocal scanning laser ophthalmoscope (cSLO) and SD-OCT allow a simultaneous topographic and tomographic examination of the retina.

In this study, we examined the morphology of RPE tears in relation to the RPE-denuded area as seen when using SD-OCT. In particular, we aimed to identify characteristics that may indicate viable photoreceptors.

METHODS

In a cross-sectional study, simultaneous cSLO and SD-OCT images were obtained to examine RPE tears secondary to AMD. In vivo imaging was performed using the Spectralis HRA + OCT device (Heidelberg Engineering, Heidelberg, Germany). This device allows a simultaneous recording of cSLO and high-resolution SD-OCT. Because an eye tracking system is applied, eye movements are corrected automatically, and cSLO and SD-OCT findings can be correlated pixel to pixel. For each patient, imaging using near-infrared fundus reflectance (λ = 830 nm; field of view, 30° × 30°; and image resolution, 768 × 768 pixels) and SD-OCT (λ = 870 nm; acquisition speed, 40,000 A-scans per seconds; scan depth, 1.8 mm; and average images per scan, 15) were...
performed simultaneously. All images were analyzed using the black-and-white and color-spectrum mode.

In all the patients, a detailed ophthalmoscopic examination was performed. The RPE tear was diagnosed using fluorescein angiography; the severity of the RPE tear was assessed according to the grading system developed by Sarraf et al.12 The study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from each patient after explaining the nature and possible risks of the study.

RESULTS

PATIENTS

Twenty-six patients (28 eyes) were included. The mean (SD) age was 78 (8) years (age range, 62-91 years). Sixteen patients were women and 10 were men. The mean (SD) visual acuity at the time of performing OCT scans was 0.88 (0.56) logMAR. A summary of baseline and morphological characteristics is given in the Table.

The relationship between the time at which OCT was performed and the presence or absence of signs of viable photoreceptors is shown in Figure 1. In most cases with recent RPE tears (<365 days old), intact photoreceptor inner and outer segment junction (IS/OS) and external limiting membrane (ELM) could be identified in the retina of the RPE-denuded area. By contrast, in all the cases with older RPE tears (>1 year), no IS/OS or ELM could be found.

NEAR-INFRARED FUNDUS REFLECTANCE

In recent RPE tears, wrinkled pigment epithelium sheath could be seen beside an area of bare choroid (Figure 2). In near-infrared fundus reflectance, this area of retracted pigment epithelium sheath appeared dark, whereas

### Table. Baseline and Morphological Characteristics

<table>
<thead>
<tr>
<th>Patient No./ Age, y</th>
<th>RPE Tear Gradea</th>
<th>Time From Tear to OCT, d</th>
<th>Pretreatment (No. of Intravitreal Injections Received)</th>
<th>VA at OCT Time, logMAR</th>
<th>IS/OS ELM SRF Intraretinal Cysts ONL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/63 2 1899 None</td>
<td></td>
<td></td>
<td>1.30 Obscured owing to intraretinal edema</td>
<td>No No No No</td>
<td>Atrophic</td>
</tr>
<tr>
<td>2/88 3 847 None</td>
<td></td>
<td></td>
<td>2.00 Obscured owing to intraretinal edema</td>
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<td>Obscured owing to intraretinal edema</td>
</tr>
<tr>
<td>3/86 2 717 Bevacizumab (1)</td>
<td></td>
<td>0.35</td>
<td>No No No Yes Yes</td>
<td>Atrophic</td>
<td></td>
</tr>
<tr>
<td>4/74 3 825 Bevacizumab (1)</td>
<td></td>
<td>1.30</td>
<td>No No No Yes Yes</td>
<td>Atrophic</td>
<td></td>
</tr>
<tr>
<td>5/79 3 768 Bevacizumab (3)</td>
<td></td>
<td>1.90</td>
<td>No No No No No</td>
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<td></td>
</tr>
<tr>
<td>6/90 3 882 None</td>
<td></td>
<td></td>
<td>1.95 No No No</td>
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<td></td>
</tr>
<tr>
<td>7/91 2 2562 None</td>
<td></td>
<td></td>
<td>1.90 No No No</td>
<td>Atrophic</td>
<td></td>
</tr>
<tr>
<td>8/77 3 325 Bevacizumab (4)</td>
<td></td>
<td>0.70</td>
<td>Yes Yes Yes Yes</td>
<td>Visible</td>
<td></td>
</tr>
<tr>
<td>9/80 4 &lt;30 Ranibizumab (3)</td>
<td></td>
<td>0.70</td>
<td>No No No No</td>
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<td></td>
</tr>
<tr>
<td>10/76 3 &lt;30 None</td>
<td></td>
<td></td>
<td>1.30 Yes Yes Yes</td>
<td>Visible</td>
<td></td>
</tr>
<tr>
<td>11/73 4 &lt;30 None</td>
<td></td>
<td></td>
<td>0.45 No No No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>12/70 2 &lt;30 None</td>
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<td></td>
<td>0.15 Yes Yes Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>13/72b 3 Unknown None</td>
<td></td>
<td>0.45</td>
<td>No No No No</td>
<td>Atrophic, inhomogeneous</td>
<td></td>
</tr>
<tr>
<td>14/82 1 732 Ranibizumab (3), bevacizumab (1)</td>
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<td>Atrophic, inhomogeneous</td>
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</tr>
<tr>
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<tr>
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<td></td>
<td>0.60</td>
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<td></td>
<td>0.20 Yes Yes Yes</td>
<td>Visible</td>
<td></td>
</tr>
<tr>
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<td>No No No No</td>
<td>Atrophic</td>
<td></td>
</tr>
<tr>
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<td></td>
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<tr>
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<td></td>
<td></td>
<td>1.00 No Yes Yes</td>
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<tr>
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<td></td>
<td>0.40 Yes Yes Yes</td>
<td>Visible</td>
<td></td>
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<tr>
<td>22/62 2 109 None</td>
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<td>Visible</td>
<td></td>
</tr>
<tr>
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<td>1.30</td>
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<td></td>
</tr>
<tr>
<td>24/83 4 Unknown Ranibizumab (1)</td>
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<td>1.30</td>
<td>No No No No</td>
<td>Atrophic</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>1.50</td>
<td>No No Yes Yes</td>
<td>Atrophic</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td>0.50 Yes Yes No</td>
<td>Visible</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ELM, external limiting membrane; IS/OS, photoreceptor inner and outer segment junction; OCT, optical coherence tomography; ONL, outer nuclear layer; RPE, retinal pigment epithelium; SRF, subretinal fluid; VA, visual acuity.

a According to grading system introduced by Sarraf et al.12
b The right eye.
c The left eye.
the RPE-denuded area appeared bright. While the pigment epithelium border could be easily delineated in recent RPE tears, this demarcation was not definite in older RPE tears. The RPE-denuded area in older RPE tears generally appeared more inhomogeneous and consisted of speckled bright and dark areas, indicating extensive fibrosis in this region.

**SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY**

In RPE tears, a dome-shaped retracted pigment epithelium sheath was located beside an area of bare choroid. In SD-OCT, this retracted pigment epithelium sheath was seen as a thick hyperreflective band underneath the retina. The retracted pigment epithelium sheath showed separation from the Bruch membrane layer, as in the case of pigment epithelium detachment (Figure 3).

In recent RPE tears, OCT often showed subretinal fluid on the RPE-denuded area. In some patients, intraretinal cysts could also be seen. A hyperreflective band resembling the ELM could also be identified. This band could be traced up to the RPE border, where it continuously merged with the ELM of the retina still supported by the RPE (Figure 3). On the contrary, the IS/OS could not be easily identified because it was merged into one single band with the Bruch membrane. If subretinal fluid was present, however, one could easily identify the IS/OS (Figure 4). Tracing the IS/OS from the RPE-supported retina at the border of the tear up to the RPE-denuded area helped identify the IS/OS. In this study, we observed intact ELM and IS/OS on the RPE-denuded area in 12 of 28 eyes (+42.9%).

In some cases, the retina over the RPE-denuded area was atrophic, and no ELM could be identified (Figure 5). The atrophic thin outer nuclear layer (ONL) was seen overlying the area of bare choroid. Identifying the ELM was challenging in some cases, but an atrophic retina most often also had an atrophic ONL. Tracing the retina from the border of the RPE tear, one can notice that the ELM continues within the area of RPE-supported retina but then stops at the border of the RPE-denuded area.

Older RPE tears can exhibit subretinal fluid or intraretinal cysts to some extent. In a retina with cysts, it was impossible to clearly identify the ELM band, unlike in recent RPE tears. The ONL and outer plexiform layer were also atrophic to some degree. No continuous or regular ONL and outer plexiform layer could be seen; instead, a layer with inhomogeneous hyporeflective and hyperreflective substances was observed in this region. Over time, a hyperreflective homogeneous mass accumulated under the retina above the Bruch membrane in the RPE-denuded area. This homogeneous mass continued into the RPE layer in the retina still supported by the RPE. In color-spectrum mode, a white hyperreflective band could be observed in the normal RPE layer. This band was not found in the homogeneous mass; however, speckled hyperreflective dots were seen instead (Figure 6). Unlike the pigment epithelium, this hyperreflective mass did not absorb light because there was enhanced choroidal reflectivity underneath it.

**COMMENT**

In this case series, we used simultaneous cSLO and SD-OCT to reveal the morphological characteristics of recent and older RPE tears secondary to exudative AMD. These characteristics are important because they provide evidence for viable photoreceptors after an RPE tear. The findings are important to consider in therapies aimed at rescuing photoreceptors after an RPE tear, such as autologous transplantation of RPE and choroid,13 macular translocation,15 or other future therapies, because replacing the RPE layer after an RPE tear is only beneficial if the overlying retina and especially the photoreceptors are still intact.

The OCT characteristics of RPE tears have been described previously7,13; however, these studies were conducted using time-domain OCT. Therefore, only limited information regarding the retina could be gained owing to the lower resolution of the device. In our study, by contrast, we examined the characteristics of an RPE tear using high-resolution SD-OCT, allowing us to examine the retina in greater detail.

In normal retina, intact IS/OS and ELM are signs of vital and functional photoreceptors in SD-OCT.16,17 Our
colleagues\textsuperscript{13} and we\textsuperscript{18} showed earlier that the retinal stimuli can be regained and photoreceptors are viable for some time after an autologous transplant of pigment epithelium and choroid. It is unknown, however, how long these photoreceptors survive after the RPE tear, before the scarring process outweighs the initial beneficial effects.

We show in this study that SD-OCT is an excellent method for identifying viable photoreceptors. In one patient (patient 8; Figure 1) of our case series, photoreceptors could be identified using SD-OCT for up to 325 days after an RPE tear. In recent RPE tears, the ELM could still be seen for some time in the RPE-denuded area, indicating the viability of photoreceptors. As the ELM continues to the ELM of the nonaffected retina, it is most likely that this layer represents the ELM in the RPE-denuded area.

Figure 3. High-resolution, spectral-domain optical coherence tomography of a recent retinal pigment epithelium tear. Arrowheads indicate the continuous external limiting membrane.

Figure 4. High-resolution, spectral-domain optical coherence tomography of a recent retinal pigment epithelium tear. Arrow indicates the photoreceptor inner and outer segment junction; arrowhead, external limiting membrane.

Figure 5. A. High-resolution, spectral-domain optical coherence tomography of an older retinal pigment epithelium tear. B, Higher magnification of the older retinal pigment epithelium tear (original magnification \(\times 1.5\)). Arrowhead indicates the external limiting membrane that does not exist in the retinal pigment epithelium–denuded area.

Figure 6. High-resolution, spectral-domain optical coherence tomography (black-and-white mode) (A) color mode (B) of an older retinal pigment epithelium (RPE)-tear.
The limitation of this study is the use of only imaging techniques; thus, we were able to show only the anatomical viability of the photoreceptors. The functional viability, however, has yet to be demonstrated using functional tests, such as microperimetry or multifocal electroretinography.

The ELM and the ONL become atrophic over time. This process is accompanied by accumulation of a hyperreflective mass between the retina and the Bruch membrane; the composition of the material is unknown. In the OCT scans, the material appears transparent because light can pass through it. It is likely that the substance isolates the retina from the choroid, thereby compromising the oxygen diffusion to the ONL and photoreceptors. This may also be the reason why the photoreceptor sheaths and the ONL become atrophic over time, while the inner sheaths of the retina remain mostly unaffected.

Some case reports showed that RPE cells can migrate and proliferate from the border of the RPE tear and finally repopulate the RPE-denuded area.10–21 The newly proliferating RPE cells are nonpigmented and do not contain lipofuscin, and are, therefore, difficult to be detected using fundus autofluorescence. On the contrary, our findings show that the retina of the RPE-denuded area becomes atrophic over time, thus rejecting the hypothesis that the hyperreflective mass between the Bruch membrane and retina contains proliferating RPE cells. The composition of this material still remains to be elucidated in histological studies.

Our findings regarding the atrophy of the outer retinal layer are in concordance with observations described by other authors for diseases, such as resolved central serous chorioretinopathy22 or retinal detachment.23 In a murine retinal detachment model, photoreceptors underwent apoptosis, which was first identified at 24 hours and was found to peak by 2 days and to drop to low levels by 7 days after retinal detachment.24 The pathophysiology of photoreceptor degeneration after RPE tears may be similar because subretinal fluid impairs the oxygen diffusion to the outer retinal layer, subsequently leading to outer nuclear layer atrophy.

Nevertheless, RPE tears represent an acute event in most cases. After the acute event, viable photoreceptors can be seen using SD-OCT in the retina of the RPE-denuded area. Visible ELM and nonatrophic ONL are crucial characteristics for recovery therapy of the photoreceptors after RPE tears and can be identified successfully by using SD-OCT.

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REFERENCES