Objective: To describe tubular structures found in the outer retina seen in a variety of retinal disorders.

Methods: Sixty-nine eyes of 63 patients were examined with spectral-domain optical coherence tomography. Optical coherence tomography C-scans were correlated with their corresponding B-scans. The prevalence, number, size, and shape of the tubular structures were determined.

Results: Branching tubules were identified in the outer retina of 54 patients with age-related macular degeneration and in 9 patients with other diagnoses. The tubules appeared as round or ovoid hyporeflective spaces with hyperreflective borders on the B-scans, measuring 40 to 140 µm high and 40 to 2260 µm wide. Morphologic features ranged from single straight or branching tubules to complex cavitary networks, usually overlying areas of pigment epithelial alteration or subretinal fibrosis. The tubules generally remained stable over time. In a retinal practice specializing in advanced age-related macular degeneration, these structures were identified in 60 of 248 patients (24.2%) seen during a 3-month period.

Conclusions: Degenerating photoreceptors may become arranged in a circular or ovoid fashion during a process we propose to term outer retinal tubulation. These changes are apparently common in advanced diseases affecting the outer retina and retinal pigment epithelium. This observation has practical implications because these findings can be misinterpreted as intraretinal or subretinal fluid, possibly prompting unnecessary interventions.

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With advances in retinal imaging, in particular the advent of spectral-domain optical coherence tomography (SD-OCT), our ability to image retinal microarchitecture in vivo has reached an unprecedented, near histologic level. Refinements in SD-OCT technology, such as the combination of eye tracking with averaging of multiple B-scans, provide even more precise delineation of retinal detail. New interpretation algorithms, including the ability to compute curved C-scan images, allow for en face visualization of the individual layers of the posterior segment, including those of the retina and choroid. Curved C-scans may be set to conform to contours of the internal limiting membrane, the retinal pigment epithelium (RPE), or a spherical approximation to the RPE surface called the RPE fit. If the structures of interest are located in the outer retina as, for example, in cystoid macular edema (CME), it is preferred to base the C-scan on the internal limiting membrane. If the structure is located in the outer retina, the C-scan may be based on RPE or the RPE fit. These views enable a better appreciation of the topographic relationships of intraretinal structures in a manner that cannot be readily observed through conventional B-scan sections alone.

Through these enhanced imaging modalities, we have detected a peculiar outer retinal morphologic change occurring in a variety of advanced degenerative retinal disorders. We have termed this finding outer retinal tubulation (ORT). These branching tubular structures are located in the outer nuclear layer of the retina and appear as round or ovoid hyporeflective spaces with hyperreflective borders on conventional B-Scan OCT sections; they were first detected in patients with neovascular age-related macular degeneration (AMD). Because these tubules can simulate the appearance of CME and subretinal fluid on single B-scan sections, their recognition may help to prevent unnecessary interventions.
We propose that ORT represents a rearrangement of the photoreceptor layer in response to retinal injury in a variety of retinal diseases. To our knowledge, this unusual outer retinal finding has not previously been identified in a clinical setting.

**METHODS**

We used 3 different SD-OCT devices (Cirrus HD-OCT [Carl Zeiss Meditec, Dublin, California], Heidelberg retinal angiography with OCT [Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany], and Topcon 3D OCT-1000 [Topcon Medical Systems, Paramus, New Jersey]) and 1 time-domain OCT (Stratus OCT; Carl Zeiss Meditec) to image the retina of patients with a variety of advanced retinal diseases seen in a group retina practice in New York, New York. The C-scans (obtained with Cirrus HD-OCT) were superimposed on fundus images captured with confocal scanning laser ophthalmoscopy and were correlated with the conventional B-scan OCT images.

Data from all patients in whom ORT was identified during a 3-month period (August 1 through October 31, 2008) were retrospectively entered into a database. For 1 patient, we included a more recent follow-up from January 20, 2009 (eFigure 1B; http://www.archophthalmol.com). We analyzed features of the ORT structures, including the size, shape, location in the fundus, change over time, and response to anti-vascular endothelial growth factor (anti-VEGF) treatment. The height and width of the ORT structures were measured with the calipers provided with the device manufacturer’s image analysis software. Patient characteristics, including age, sex, visual acuity, and ocular comorbidities, were recorded. The prevalence of ORT in patients examined in the practice of a physician specializing in AMD (K.B.F.) was estimated by dividing the number of patients with ORT by the total number of patients examined during the study period.

One patient underwent microperimetry with scanning laser ophthalmoscopy (Spectral OCT/SLO; Ophthalmic Technologies Inc, Toronto, Ontario, Canada) to investigate whether there was preservation of visual function overlying the ORT structure.

**RESULTS**

The recognition of ORT as distinct from CME or subretinal fluid was achieved through an analysis of the higher-resolution modes of the SD-OCT devices (eFigure 2). Unlike CME, which ORT resembles on individual B-scan sections, ORT was detected exclusively in the outer nuclear layer as round or ovoid structures with a hyperreflective border (Figure 1).

Overall, the size, shape, and configuration of the tubular structures and the occasional cavitary network were quite variable, but some patterns emerged. We measured the height of ORT structures with the calipers provided by the Heidelberg retinal angiography and high-definition OCT image analysis software to range from 40 to 140 µm, whereas the width on horizontal OCT B-scan sections ranged from 40 to 2260 µm. Curved OCT C-scan images provided a better recognition of the more complex tubular and branching nature of this peculiar abnormality than could be appreciated with conventional B-scan images (see Figures 1, 2, and 3). The distribution of the lesions in the macula appeared to relate to specific aspects of the associated disease entity. These disorders all shared similar features, the most frequent being secondary choroidal neovascularization (CNV) or RPE atrophy. With SD-OCT, the ORT structures were typically noted in areas where there was considerable disruption of outer retinal architecture with relative preservation of the photoreceptor layer (preserved inner and outer segment [IS/OS] junction), often overlying RPE damage or subretinal fibrosis (Figures 1 and 2 and eFigures 1, 2, 3, and 4). In eyes undergoing treatment with intravitreal anti-VEGF agents, ORT was typically found in areas where, before treatment, there had been substantial intraretinal fluid. In eyes without CNV, ORT was detected at the junction between areas of intact (preserved IS/OS junction) and absent (loss of IS/OS junction) photoreceptors (Figure 3 and eFigure 5).

During the 3-month study period, ORT was identified in 69 eyes of 63 patients, representing 60 of 248 patients (24.2%) seen by a single member (K.B.F.) of a tertiary retinal practice with a primary focus on AMD. The median age of patients was 80 (range, 27-92) years. Twenty-seven patients (43%) were female. Sixty-two patients were white and 1 was Asian. Fifty-two patients (53 eyes) had neovascular AMD; 2 patients (3 eyes) had CNV associated with pseudoxanthoma elasticum; 1 patient (1 eye) had multifocal choroiditis and panuveitis with CNV; 2 patients (3 eyes) had geographic atrophy; 2 patients (2 eyes) had central serous chorioretinopathy; 1 patient (2 eyes) had Bietti crystalline dystrophy; 1 patient (1 eye) had a tissue inhibitor of metalloproteinase-3 negative pattern dystrophy; 1 patient (2 eyes) had a retinal degeneration phenotypically consistent with a mitochondrial A3243G mutation; and 1 patient (2 eyes) had choroideremia. Snellen visual acuity ranged widely from 3/400 to 20/20, with a median acuity of 20/200. Thirteen eyes had visual acuities of 20/40 or better. Thirteen eyes had visual acuities of 20/50 to 20/150, and 43 eyes were legally blind (20/200 or worse).

One patient underwent microperimetry with scanning laser ophthalmoscopy (Spectral OCT/SLO), which seemed to demonstrate limited preservation of visual function over a small portion of the tubular structure (eFigure 4). This finding suggests that some of the photoreceptors within ORT may still function; however, in other patients tested, poor fixation precluded meaningful perimetric evaluations.

In most of the cases, ORT remained stable over time, even in patients receiving ongoing treatment with intravitreal anti-VEGF injections (eFigure 1A and B). Occasionally, the height of the tubules and tubule diameter decreased temporarily after intravitreal anti-VEGF injection (eFigure 1C).

**REPORT OF CASES**

**Case 1**

A 69-year-old man received 2 treatments of verteporfin photodynamic therapy for neovascular AMD. Two years after photodynamic therapy, he received 2 intravitreal injections of bevacizumab. During the following 2 years, he received 4 injections of intravitreal ranibizumab. Vi-
Visual acuity was 20/200 at the time the SD-OCT B-scan showed 2 different types of hyporeflective circular structures. Round spaces, predominantly in the inner nuclear layer, were consistent with typical CME presumably secondary to leakage from underlying CNV. Additional round and ovoid structures were found exclusively in the outer nuclear layer, presumably representing surviving photoreceptors arranged in tubular structures. Unlike CME,
the tubular structures had a distinct hyperreflective border and contained hyperreflective material within their lumen (Figure 1A and B).

Case 2

An 81-year-old woman with long-standing neovascular AMD in her right eye was seen for a routine examination. Visual acuity was 5/400 related to subretinal fibrosis, pigment hyperplasia, and RPE atrophy. There was no clinical evidence of active exudation. The SD-OCT images showed multiple round and ovoid structures with hyperreflective borders visible on multiple B-scan sections. With curved OCT C-scan imaging on the high-definition OCT, it was apparent that these structures formed an interconnected network of branching tubules (ORT) of varying cross-sectional shapes and calibers. Fluorescein angiography and indocyanine green angiography demonstrated that the ORT structures did not represent vascular structures because there was no apparent correlation between the tubular network and the retinal or choroidal vascular distribution (Figure 1E).

Case 3

A 78-year-old woman with neovascular AMD in her left eye received intravitreal ranibizumab injections at intervals of every 7 to 8 weeks for 33 months. Visual acuity was 20/200. With SD-OCT imaging, B-scan sections revealed a cavitary space in the outer nuclear layer (Figure 2B), simulating the appearance of subretinal fluid. On other adjacent OCT B-scan sections, this structure appeared to bifurcate, forming 2 ovoid tubular structures (Figure 2C) that tapered into smaller tubules (Figure 2D) in an area of greater photoreceptor loss. Unlike CME, these ORT structures contained hyperreflective material (eFigure 5).

Cases 4-7

Cases 4 to 7 are examples of ORT in other atrophic disorders.

A 52-year-old man with Bietti crystalline dystrophy (case 4) had visual acuities of 20/50 OD and 20/60 OS at the initial examination (Figure 3A). Bilateral crystalline deposits were scattered throughout the posterior fundus. Overlaid curved SD-OCT C-scan and corresponding SD-OCT B-scan sections demonstrated multiple short, nonbranching tubules, located predominantly at the junction between the atrophic and preserved photoreceptors in the left eye (Figure 3B). Identical findings were noted in the right eye.

A 67-year-old woman with bilateral retinal degeneration phenotypically consistent with a mitochondrial A3243G mutation (case 5) had visual acuities of 20/40 OD and 20/25 OS at initial examination. Autofluorescence imaging of the left eye (Figure 3C and D) demonstrated focal fundus hyperautofluorescence coinciding with ORT originating at the junction between the preserved and absent RPE and the photoreceptor layer (IS/OS junction on SD-OCT). Identical findings were noted in the right eye.

A 77-year-old woman with geographic atrophy secondary to AMD in both eyes (case 6) had visual acuities of 20/200 OD and 20/40 OS (Figure 3E). Overlaid curved SD-OCT C-scans demonstrated ORT structures at the...
Figure 3. Outer retinal tubulation (ORT) in retinal disorders without choroidal neovascularization. At the top of the figure are images of the left eye of a 52-year-old man with Bietti crystalline dystrophy and a visual acuity of 20/60 (case 4). A, A color fundus photograph shows crystalline deposits scattered throughout the posterior pole. B, Overlaid curved C-scan and corresponding spectral-domain optical coherence tomography (SD-OCT) B-scan section demonstrate multiple short, nonbranching tubules, predominantly at the junction between areas of lost and preserved retinal pigment epithelium (RPE) and photoreceptors (yellow circles). C, Autofluorescence imaging of the left eye of a 67-year-old woman with a bilateral unclassified retinal degeneration (case 5). D, Higher magnification of the boxed section in C (red arrow) with the corresponding SD-OCT B-scan (white rectangle) shows ORT in atrophic areas containing hyperautofluorescent material (green arrow). E and F, A color fundus photograph and the overlaid curved SD-OCT C-scan, respectively, of the left eye of a 77-year-old woman with geographic atrophy due to age-related macular degeneration (case 6) demonstrate ORT structures (dashed white line) at the junction between preserved and absent RPE and the photoreceptor layer (inner and outer segment junction on SD-OCT). Visual acuity was 20/40 OS. G, A color fundus photograph of the right eye of a 27-year-old man with choroideremia (case 7). Visual acuity was 20/25 OD. H, The corresponding SD-OCT B-scan (white line in G) shows ORT at the margin between preserved and absent RPE and the photoreceptor layer.
juncture between the preserved and absent RPE and the photoreceptor layer (Figure 3F). Identical findings were noted in the left eye.

A 7-year-old man with choroideremia (case 7) had visual acuities of 20/25 OD (Figure 3G) and 20/30 OS at the initial examination. At the margin between the areas of preserved and atrophic RPE, SD-OCT B-scan sections showed multiple short, branching tubules (Figure 3H). Identical findings were noted in the left eye.

Cases 8-11

Cases 8 to 11 are examples of ORT in non-AMD entities such as CNV or subretinal fibrosis.

A 39-year-old woman (case 8) had fundus changes in her left eye at the initial examination due to chronic central serous chorioretinopathy related to long-term use of oral corticosteroids for idiopathic thrombocytopenic purpura (eFigure 3A). Visual acuity was 20/20. The fundus examination results showed widespread pigment epithelial alterations, including areas of fibrous metaplasia. The SD-OCT B-scan sections overlying 1 of these fibrotic areas revealed multiple distinct tubular structures confined to the outer nuclear layer.

A 38-year-old woman (case 9) had a history of multifocal choroiditis and panuveitis with secondary CNV in her left eye. She had received oral corticosteroids and a single treatment with verteporfin photodynamic therapy 2 years before the initial examination, with no further inflammatory or neovascular recurrences. Visual acuity was 20/25. The SD-OCT B-scan overlying the superior edge of a chorioretinal scar revealed a single straight ORT structure within an area of absent IS/OS junction (eFigure 3B).

A 60-year-old woman (case 10) had a history of CNV in her right eye secondary to pseudoxanthoma elasticum and angiod streaks. She had previously undergone thermal laser treatment followed by verteporfin photodynamic therapy in combination with intravitreal triamcinolone acetonide (eFigure 3C). Visual acuity was 20/200. On SD-OCT B-scan imaging, multiple distinct tubular structures were detected overlying the inferior edge of the fibrotic macular lesion. As with many of the other cases, the ORT structures occurred in a zone between regions of lost and intact photoreceptor layer (IS/OS junction).

A 53-year-old man with a tissue inhibitor of metalloproteinase-3 pattern dystrophy complicated by secondary CNV in his left eye (case 11) was previously treated with 2 intravitreal injections of bevacizumab (eFigure 3D). Visual acuity was 20/200. Multiple SD-OCT B-scan sections revealed 2 vertically orientated tubular structures in the outer retina that did not communicate.

Case 12

A 73-year-old woman with neovascular AMD had received 18 intravitreal injections of ranibizumab in her right eye at intervals of approximately every 7 weeks. Visual acuity was 20/100. The patient underwent microperimetry with scanning laser ophthalmoscopy (Spectral OCT/SLO). Overlays of the curved SD-OCT C-scan data onto the microperimetry analysis suggested that some of the photoreceptors within ORT remained functional (eFigure 4).

COMMENT

We observed ORT in 69 eyes of 63 patients with a variety of retinal diseases. Many of the eyes had neovascular AMD and were undergoing treatment with intravitreal injections of ranibizumab or bevacizumab. Outer retinal tubulation was also observed in patients with CNV secondary to causes other than AMD and in atrophic disorders without CNV or subretinal fibrosis. Although the height of the tubules (40-140 µm) was limited by their location within the outer nuclear layer of the retina, the width and distribution of ORT throughout the macular region varied widely.

We believe that degenerating photoreceptors become arranged in a tubular fashion during a process we propose to term outer retinal tubulation. It is possible that other adjacent cells such as RPE and glial elements may also contribute to the tubular structures. Although the underlying pathogenesis of these changes is not known, they seem to represent a common final pathway in a variety of retinal degenerative conditions because ORT was observed in numerous distinct disease entities. A potential first step in the process may be sublethal injury to the photoreceptors, maybe through loss of the interdigitation of the outer segments with the RPE or through degeneration of the RPE itself. After this injury, or concurrently, there may be disruption of tight junctions and other points of attachment to neighboring neural elements with outward folding of the photoreceptor layer until opposite sides of this fold establish contact and form new lateral connections through tight junctions, thus reconstituting the IS/OS junction and forming a tubular structure. When ORT develops in eyes with CNV after treatment with antiangiogenic agents, we believe that, before treatment, intraretinal and subretinal exudation damages the photoreceptor layer causing focal loss of cells, disruption of tight junctions with neighboring cells, and loss of the interdigitation with the RPE. With resolution of fluid after treatment, the remaining cells reestablish lateral connections in the process of tubulation we described. This process is illustrated in the schematic in Figure 2E. The distribution of the resulting ORT structures in these eyes conforms to the antecedent exudative changes.

In all eyes examined, the ORT networks were entirely confined to the outer nuclear layer, although in some cases there were portions of the network that appeared to communicate with the subretinal space. Unlike the cystic spaces in macular edema, which are mostly found in the inner nuclear layer, the ORT structures were surrounded by a hyperreflective border, which we hypothesize to be composed of the connecting cilia (IS/OS junction) of the photoreceptor cells and possibly other glial cells (case 1 in Figure 1). Furthermore, unlike the cysts of CME, the lumina of ORT typically contain varying amounts of hyperreflective material likely representing malformed and degenerating photoreceptor outer seg-
ments with an appearance similar to other photoreceptor degenerations such as a cone dystrophy (case 5 in Figure 3D and eFigure 5).

We noticed that these tubules typically occur in areas of normal retinal thickness near areas of more healthy photoreceptor layer (intact IS/OS junction). We did not observe these structures in patients with complete photoreceptor loss such as end-stage retinitis pigmentosa.

Perhaps ORT represents a misguided reparative attempt, in which new lateral connections occur between the circularly arranged photoreceptors and their processes, a “circling of the wagons” phenomenon. This peculiar retinal phenotype is seen not only congenitally in retinal dysplasia but also in mouse models of Pax6 overexpression and in models of retinal transplantation. The phenotype can also be acquired, as seen in rats in which protein prenylation was inhibited by intravitreal statin injection and in patients with retinitis pigmentosa.

With low-resolution OCT imaging, ORT may be easily mistaken for intraretinal or subretinal fluid. Recognizing ORT’s hyperreflective boundary may help to identify this entity (Figure 1 and eFigure 2). Unlike the cysts in CME, which are arranged in a petaloid fashion, the distribution of ORT is fairly random over the macula. Unlike subretinal fluid, ORT often forms branching arrays related to the localization of the underlying abnormality. Finally, ORT was detected in diseases affecting the outer retina such as AMD and outer retinal degenerations but was not detected in conditions associated with typical CME such as diabetic macular edema or retinal venous occlusive disease.

In most of the cases, ORT remained stable over time, even in patients receiving ongoing treatment with intravitreal anti-VEGF injections (eFigure 1A and B), and we observed only minimal change in the size and shape of the tubular structures after treatment. A transient decrease in retinal elevation and tube diameter in a single patient 5 weeks after intravitreal injection of ranibizumab returned to the pretreatment status 10 weeks after each injection. In this case, the temporary collapse of the ORT structures was not associated with visual improvement. We hypothesize that, in the occasional ORT structure that communicates with the subretinal space, such as this particular case, fluid leakage from underlying CNV may fill the tubular network. Treatment with an intravitreal anti-VEGF could then transiently collapse the ORT structures by reducing the leakage of fluid into the tubular network.

We believe that the recognition of ORT is of clinical importance, particularly in disorders associated with CNV such as neovascular AMD. Outer retinal tubulation appears to represent a morphologic change, and its presence may not be indicative of active leakage from underlying pathologic new vessels. The presence of ORT could be misinterpreted by practitioners following OCT-guided treatment regimens such as “treat and extend” or the strategy described in the Plavix Reduction of New Thrombus Occurrence trial in which the presence of subretinal fluid or cystic change within the retina represents an indication for retreatment. Clinicians relying on printouts of the OCT data are less likely to recognize ORT, which typically requires dynamic viewing of multiple adjacent B-scan sections to be fully appreciated. The higher resolutions of the latest-generation SD-OCT devices are helpful in identifying the features of ORT, including the characteristic hyperreflective border, the location entirely within the outer nuclear layer, and the frequent presence of hyperreflective material with the tubular structures themselves.

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