Clinicopathological Correlation of Outer Retinal Tubulation in Age-Related Macular Degeneration

Outer retinal tubulation (ORT) on spectral-domain optical coherence tomography (SD-OCT) is a hyporeflective area surrounded by a hyperreflective band in the outer nuclear layer. It comprises interconnected tubes containing degenerate photoreceptors, almost exclusively cones, and Müller cells. In longitudinal studies, ORTs are dynamically involving structures that may portend a poor visual outcome. We present clinical and postmortem imaging and histological findings of ORT in a patient with advanced age-related macular degeneration. We test our hypothesis that the reflective border includes translocated mitochondria within degenerating inner segments (ISs) and the external limiting membrane (ELM).

Methods | A woman in her mid-90s presented with bilateral vitelliform lesions. Two years later, the vitelliform lesion in her right eye began shrinking, with complete absence 3 years after presentation. On her last examination, 4 years after presentation, she had central geographic atrophy (GA) bilaterally, with ORT in her right eye noted on SD-OCT. She died of stomach cancer 8 months after the last examination.

Eyes were recovered by eye bank personnel 8 hours 55 minutes after death, opened anteriorly with an encircling cut at the limbus, and preserved by immersion into 10% neutral buffered formalin. Following overnight shipping, formalin was replaced with buffered 1% paraformaldehyde and 2.5% glutaraldehyde. Eye tracking software (Spectrals; Heidelberg Engineering) was used to align in vivo and ex vivo B-scans from preserved globes. Tissue was postfixed with osmium tannic acid paraphenylenediamine. Macula-wide, 0.8-μm-thick sections at locations matching SD-OCT B-scans were stained with toluidine blue and imaged as described. Sections at silver-gold thickness were viewed by transmission electron microscopy.

Results | An ORT found in the inferior macula by clinical SD-OCT was also visible by ex vivo SD-OCT and histological analysis (Figure 1). Comparison of in vivo (Figure 1A and B) and ex vivo (Figure 1C and D) SD-OCT reveals edema due to the interval between death and preservation. The ORT is nasal to the temporal border of GA formed by the collapsed central vitelliform lesion (Figure 1E). The ORT luminal wall contains cone photoreceptors, with ISs and without outer segments (ie, at the mature phase). Transmission electron microscopy reveals translocated mitochondria internal to the ELM (Figure 2A and B). At a level superior to that in Figure 1E, a glancing section through the ORT reveals cone cell bodies (Figure 2C). A section at a level inferior to Figure 1E shows that the ORT opens up to and is continuous with the GA border (Figure 2D).
Discussion  |  To our knowledge, this is the first clinicopathologic correlation of SD-OCT and histological analysis from the same patient with age-related macular degeneration. By histological analysis and transmission electron microscopy, the reflective border of ORT can be accounted for by a combination of the ELM and IS mitochondria that are translocated to the same level as the ELM by shrinkage of the IS, supporting the proposal that mitochondria are independent reflectivity sources in SD-OCT. This mature-phase ORT lacked outer segments but was still visible, indicating that photoreceptors do not require outer segments to contribute reflectivity to SD-OCT. In healthy eyes, hyperreflective band 2 aligns with IS ellipsoids, which are mitochondria rich, implicating these organelles as reflectivity sources. Mitochondria may also contribute to reflectivity in synaptic layers and basolateral retinal pigment epithelium, where they are also abundant.

Histological analysis demonstrates the microscopic continuity of the ELM at the ORT with the ELM at the GA border. By en face OCT, curvilinear ORT can be seen to line the inner border of atrophy. A defining feature of ORT is a free edge to scroll. A connection of ORT to nonatrophic areas could conduct trophic support to persisting photoreceptors via luminal fluid and trapped cells, as postulated.

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Figure 2. Histological Analysis and Ultrastructure of Outer Retinal Tubulation

A-D, Green arrowheads indicate external limiting membrane.
A, Transmission electron microscopy of outer retinal tubulation. The section outlined by the box is shown at higher magnification in B. B, Higher-magnification transmission electron microscopy shows cones with short inner segments and ovoid mitochondria (red arrowheads) translocated internally to the external limiting membrane. The section outlined by the box is shown at higher magnification in the inset. C, Histological analysis (toluidine blue) shows that a cone nuclei cluster (orange arrowheads) composes an outer retinal tubulation sidewall. BLamD, basal laminar deposit; BrM, Bruch membrane; ONL, outer nuclear layer; and RPE, retinal pigment epithelium. D, Histological analysis (toluidine blue) shows that outer retinal tubulation opens to the geographic atrophy border. IS indicates inner segment.

Presumed Primary Papillary Sebaceous Carcinoma of the Palpebral Conjunctiva

Sebaceous carcinoma can arise in the meibomian glands of the eyelids and in the sebaceous glands of the eyelashes. Origin from the conjunctival epithelium is controversial in contrast to the sebaceous glands. We describe a de novo palpebral sebaceous carcinoma that did not display involvement of the tarsal meibomian glands.

Report of a Case | A woman in her late 50s developed a left upper eyelid mass over 10 months (Figure 1A). There was no history of chronic blepharoconjunctivitis. On eversion of the eyelid, a pedunculated yellow mass with papillary fronds was seen. Neither eyelash loss nor marginal ulceration was observed. The tumor (Figure 1B) was removed with 2 mm of surrounding normal tissue. An inferior portion of the tarsus near the eyelid margin was separately excised. No map biopsies were performed owing to the uninflamed appearance of the palpebral conjunctiva. The tumor has not recurred 6 months later.

Microscopically, the tumor exhibited exophytic papillae (Figure 1C and D) and microinvasion at its base (Figure 1E). Intraepithelial tumor did not extend to the margins of excision (Figure 1F). Many tumor cells displayed cytoplasmic vacuoles (Figure 2A) with scattered pleomorphic and multinucleated forms (Figure 2B). The small piece of tissue between the inferior border of the tumor and the eyelid margin was tumor free (Figure 2C). Immunostaining revealed adipophilin positivity (Figure 2D) as well as androgen receptor nuclear positivity (Figure 2E). The Ki-67 proliferation index was 50% (Figure 2F).

Discussion | Because the embryonic conjunctival epithelium is the source of the hairs and sebaceous glands of the car-

Figure 1. Conjunctival Sebaceous Carcinoma

A, Interpalpebral papillary lesion. B, Pedunculated base. C, Flattened surface (black arrowheads) and papillary fronds (blue arrowheads). ST indicates stroma (hematoxylin-eosin, original magnification ×10). D, Elongated fronds (arrowheads) (hematoxylin-eosin, original magnification ×12.5). E, Microinvasive tumor (T) into stroma (ST) and up to tarsus (arrowhead) (hematoxylin-eosin, original magnification ×50). F, Short extension of carcinoma in situ (arrowhead). TA indicates tarsus (hematoxylin-eosin, original magnification ×100).