The ROYAL COLLEGE of OPHTHALMOLOGISTS

BRIEF COMMUNICATION

Soft drusen accumulation within a full-thickness macular hole: new insights into the mechanisms of lipid cycling pathways in age-related macular degeneration

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INTRODUCTION

A long-standing hypothesis in age-related macular degeneration (AMD) is that accumulated Bruch's membrane debris originated as photoreceptor outer segment membranes that were phagocytosed and processed by the retinal pigment epithelium (RPE) [1]. New concepts based on direct assay of human tissues and experimental studies suggest a dual origin of Bruch's membrane lipid constituents, with the fatty acids largely derived from diet [2]. Using serial retinal imaging over a 7-year follow-up, we report an unusual case of progressive soft drusen accumulation and remodelling occurring without overlying photoreceptors within a chronic full-thickness macular hole. We discuss the potential implications for the current understanding of lipids contributing to Bruch's membrane lipoprotein deposition.

CASE DESCRIPTION

A woman in her 80s was followed in our institution for exudative neovascular AMD in her right eye (OD) and a large, chronic, full-thickness macular hole in her left eye (OS) after an unsuccessful vitrectomy. Past medical history was relevant for hypertension. Best-corrected visual acuity was 20/100 OD and counting fingers OS. The anterior segments were unremarkable except for bilateral pseudophakia. Serial colour fundus photographs over 7 years documented progressive soft drusen accumulation within the full-thickness macular hole OS (Fig. 1). Serial tracked optical coherence tomography demonstrated drusen growth and coalescence within the hole where photoreceptors were absent (Fig. 2).

DISCUSSION

In aging and AMD, Bruch's membrane undergoes cross-linking, thickening, calcification and lipidization [2]. Soft drusen and basal linear deposits (BLinD) on histology are primarily composed of apolipoproteins B and E-containing lipoproteins secreted by the RPE in a physiologic lipid-recycling system [2]. Evidence that plasma lipoproteins are the major fatty acid sources to Bruch's membrane lipids derived from high-performance liquid chromatography assays showing that all lipid classes in Bruch's membrane are largely dominated by the fatty acid linoleate (implicating dietary sources) with little docosahexaenoate (implicating outer segment membranes) [3]. Therefore, soft drusen and BLinD have been conceptualized as sharing mechanisms with an atherosclerotic progression, which also initiates with lipoproteins, of hepatic and intestinal origin [2].

Our case provided a rare opportunity to observe in vivo clinical findings directly supporting these experimental findings. We show that soft drusen may accumulate in the sub-RPE space even in the absence of overlying photoreceptors. This gives credence to the concept that lipid-recycling pathways of RPE-secreted lipoproteins are predominantly driven by diet [2]. This also supports experimental studies showing sub-RPE deposition of drusen components without exposure to photoreceptor outer segments by highly differentiated and well-polarized RPE cells in culture [4, 5].

Xanthophyll carotenoid pigments, of dietary origin, are concentrated in the fovea, as are soft drusen [2]. The RPE expresses receptors to take up plasma high-density and low-density lipoproteins carrying these pigments for transfer to the retina [2]. Our proposed model suggests that the RPE re-packages and releases the unneeded lipids in its own linoleate-rich lipoproteins to the circulation [2]. These may accumulate as the choriocapillaris fails [2].

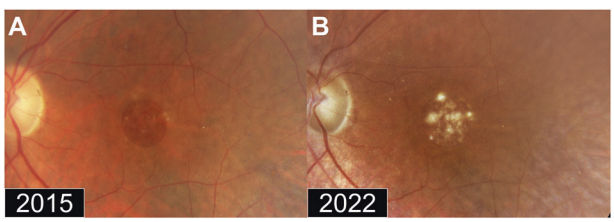

Fig. 1 Fundus photographs of the full-thickness macular hole OS. **A** Colour photograph performed at baseline showing a full-thickness macular hole with minimal drusen accumulation within the macular hole area. **B** Confocal colour photograph performed 7 years later showing marked increase in drusen deposition within the macular hole area.

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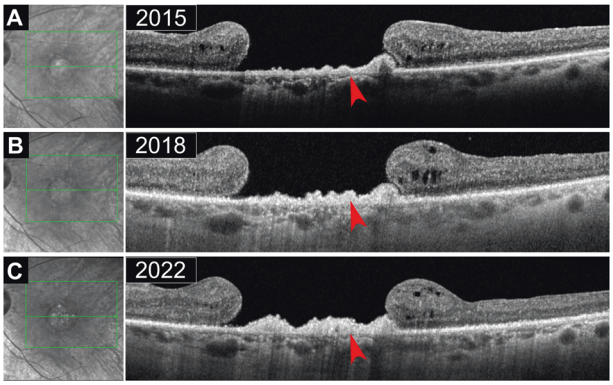

Fig. 2 Longitudinal tracked optical coherence tomography (OCT) B-scans of a full-thickness macular hole OS. A Macular OCT B-scan performed at baseline showing discrete sub-retinal pigment epithelium (RPE) deposits (*red arrowhead*) within the macular hole area. The green line in the near-infrared reflectance image indicates the position of the OCT B-scan. Follow-up tracked macular OCT scans performed 3 years later (**B**) and 7 years later (**C**) show progressive drusen growth and coalescence into larger sub-RPE deposits (*red arrowheads*) within the macular hole area. The green lines in the near-infrared reflectance image indicate the position of the OCT B-scans.

In summary, using serial imaging over a long-term follow-up, we demonstrated continuous sub-RPE deposit accumulation in the absence of photoreceptors, which further suggests that diet rather than outer segment phagocytosis is the principal driver of RPE lipoprotein secretion into Bruch's membrane.

REFERENCES

1. Hogan MJ. Role of the retinal pigment epithelium in macular disease. Trans Am Acad Ophthalmol Otolaryngol. 1972;76:64–80.
2. Curcio CA. Soft drusen in age-related macular degeneration: biology and targeting via the oil spill strategies. Investig Ophthalmol Vis Sci. 2018;59:AMD160–AMD181. https://doi.org/10.1167/iovs.18-24882.
3. Wang L, Li CM, Rudolf M, Belyaeva OV, Chung BH, Messinger JD, et al. Lipoprotein particles of intraocular origin in human Bruch membrane: an unusual lipid profile. Investig Ophthalmol Vis Sci. 2009;50:870–7. https://doi.org/10.1167/iovs.08-2376.
4. Johnson LV, Forest DL, Banna CD, Radeke CM, Maloney MA, Hu J, et al. Cell culture model that mimics drusen formation and triggers complement activation associated with age-related macular degeneration. Proc Natl Acad Sci USA. 2011;108:18277–82. https://doi.org/10.1073/pnas.1109703108.
5. Pilgrim MG, Lengyel I, Lanzirotti A, Newville M, Fearn S, Emri E, et al. Subretinal pigment epithelial deposition of drusen components including hydroxyapatite in a primary cell culture model. Investig Ophthalmol Vis Sci. 2017;58:708–19. https://doi.org/10.1167/iovs.16-21060.

AUTHOR CONTRIBUTIONS

Data collection: KBF, JMK, and DC. Data interpretation: PR, DC, JMK, CAC, and KBF. Manuscript drafting: PR and DC. Critical revision of the manuscript: CAC and KBF. Final approval of the manuscript: all authors.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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