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Case report

Migration of an outer retinal element in a healthy child followed by longitudinal multimodal imaging

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ABSTRACT

Purpose: To describe the migration of an outer retinal element using longitudinal multimodal imaging.
Observations: In the retina of a healthy 7-year-old girl, movement of a hyperreflective element of 15 μm extent was seen using optical coherence tomography (OCT), confocal scanning laser ophthalmoscopy (cSLO), and adaptive optics fundus photography (AO). On the OCT B-scan, the element initially appeared at the level of the outer limiting membrane with an umbra reaching the retinal pigment epithelium from where it gradually diminished and disappeared over 33 days. A corresponding disruption of the photoreceptor pattern on AO diminished over 52 days.
Conclusions and importance: This non-invasive observation of an isolated, cell-sized, migrating element in the human retina was made *in vivo* in the absence of confounding retinal disease or similar nearby elements. Based on prior preclinical observations we hypothesize that such a migrating element could be a macrophage. The case provides information about the time-scale and resolution needed for the monitoring of infiltrative processes in the retina.

1. Introduction

Non-invasive retinal imaging techniques have reached cellular resolution,[1,2] but the natural contrast in the retina is limited. Specific cells are therefore difficult to identify on the images, and there are no artificial markers that can be applied *in vivo* to enhance their visualization.[3] Optical coherence tomography (OCT), confocal scanning laser ophthalmoscopy (cSLO), and adaptive optics fundus photography (AO) are supplementary methods that allow non-invasive visualization of the retina with different contrast characteristics and resolutions (OCT 7 μm axial, cSLO 6 μm/pixel lateral, and AO 2 μm lateral).[2,4] OCT primarily shows its ability to reflect infrared light whereas cSLO and AO mainly show both reflection and absorption of infrared and visible light, respectively.[1,2] Thus, different imaging modalities can show different optical characteristics of a given structural element in the retina. This case report presents an incidental, unique observation where an isolated, cell-sized element was seen to move through the retina in a healthy child using these techniques. We introduce the term "longitudinal multimodal imaging" to describe repeated short-term follow-up imaging with multiple modalities for the purpose of detecting and tracking diminutive retinal changes over time.

1.1. Case report

A 7-year old girl in good health underwent a routine eye examination and screening for refractive anomaly. The girl was found to be emmetropic and to have uncorrected visual acuity of 20/20 in both eyes. Slit lamp biomicroscopy of the anterior segment and the fundus was unremarkable. By OCT examination (Spectralis HRA + OCT2, version SP 6.12, Heidelberg Engineering, Heidelberg, Germany) one of multiple, densely spaced B-scans of the upper macula showed an isolated hyperreflective element of 15 μm axial extent at the level of the outer limiting membrane (Fig. 1). On the accompanying infrared cSLO fundus image, this element was correlated with a small isolated hyporeflective (i.e. dark) spot of 30 μm in diameter (Fig. 1). Color fundus photography (TRC-50DX, Topcon Corporation, Tokyo, Japan) showed

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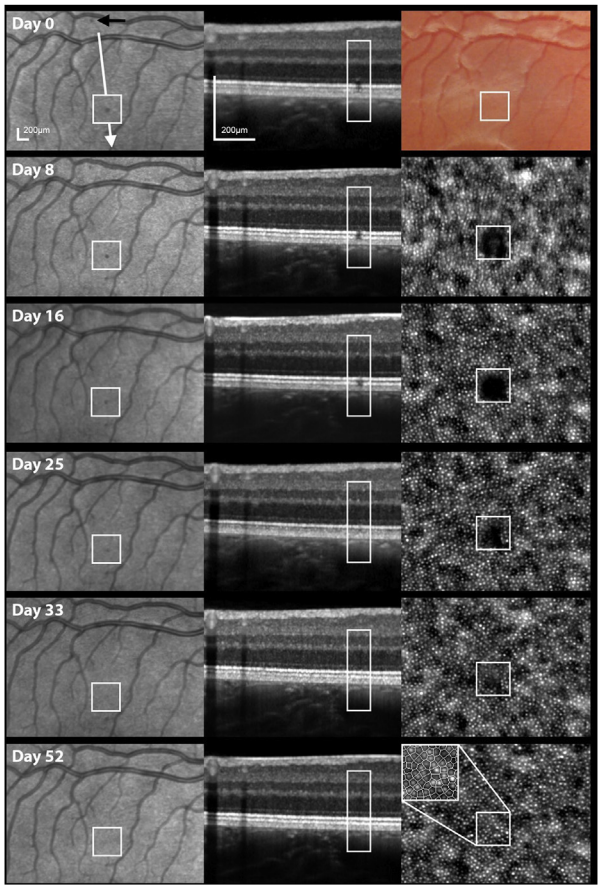

Fig. 1. *Multimodal imaging of a cell-sized element moving through the outer retina.* In the retina of the right eye of a healthy 7-year-old girl, a hyperreflective element was incidentally found in the upper macula on an optical coherence tomography B-scan (OCT, second column, day 0). This element of 15 µm extent was located at the level of the outer limiting membrane with an associated 45 µm umbra (small backshadow). There was a corresponding small dark spot on the infrared confocal scanning laser ophthalmoscopy of the fundus (cSLO, first column, day 0 with white arrow indicating B-scan direction) and a corresponding faint spot on the color fundus photography (third column, first row). On the cSLO image, an additional similar dark spot was found near the upper vessels (black arrow). Longitudinal imaging over 52 days indicated an outward movement of the element on the OCT B-scan as its umbra approached the retinal pigment epithelium at day 8 from where it gradually disappeared from view until day 33. On the cSLO image, the corresponding spot first disappeared completely from view at day 52. Concomitantly on adaptive optics (AO, third column), a corresponding dark spot gradually fainted until day 52 where a normal cone photoreceptor mosaic reappeared (white square, bottom image). . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

this as a faint dark spot without a halo which did not resemble a hemorrhage or pigment. Additional two similar spots were identified in the macula on the cSLO image. One of them were covered by the OCT scan where it had the same characteristics on the B-scan. Because of the unknown nature of these findings, longitudinal examinations of the first mentioned element were made at days 8, 16, 25, 33, and 52 after the initial visit. Follow-up OCT was made as a block of multiple, densely spaced B-scans in high-resolution with an averaging of 70 scans per line. The corresponding photoreceptor area was imaged with *en face* reflectance AO (rtx1, Imagine Eyes, Orsay, France).

At presentation the hyperreflective element on the OCT B-scan was accompanied by an umbra of 45 µm constricted to the myoid, ellipsoid, and outer segment layers[3] whereas the more posterior layers were unaffected (Fig. 1). This limited shadow could be explained by the entry pupil of the OCT device being much larger than the element in the retina. Restitutions of the outer limiting membrane and the ellipsoid zone were seen at days 8 and 16, respectively, when the element was most notable on OCT for its umbra. It remained clearly visible up to day 25 on cSLO and AO despite its gradually diminishing extent on the B-scan (Fig. 1). At day 33 there was no trace of the element on the OCT B-scan while there was still a small spot on cSLO and a slight defect on the AO image. Full restitution of the photoreceptor mosaic was seen on AO at day 52 (Fig. 1 and animation 1). The rate of migration was estimated as 1.2 µm per day by dividing the total length of the element and its umbra, 60 µm, by 52 days.

2. Discussion

The observation of a cell-sized migrating element in the outer retina found incidentally in a healthy child was corroborated by four independent optical techniques of non-invasive investigation. While similar hyperreflective elements have been described in large numbers in retinal disease conditions such as macular edema and choroidal neovascularization,[5,6] the circumstances and low density of elements seen in our subject suggest that we have observed a normal physiological phenomenon.

Preclinical rat studies have found that the retina can be infiltrated by macrophages and microglia in relation to inflammation.[7,8] While the histology techniques applied in these studies do not permit repeated imaging of a cell and its path of migration, they nevertheless found indirect evidence that these cells can move through the retina in the outward direction. The study by Omri et al.[7] furthermore identified pores in the RPE cells that enabled direct migration toward the choroid. Normal rats had an upregulation of these pores after 12 months suggesting that the trafficking of macrophages and microglia has a physiological role during aging.[7] To our knowledge, only one preclinical study has correlated histology with OCT in which a hyperreflective dot in the vitreous seen on a B-scan could be determined to be a macrophage in the light microscope.[9]

Amongst clinical studies, Saito et al. reported the resolution of hyperreflective spots in the outer nuclear layer of the retina over 4 months after a choroidal rupture.[10] It was speculated that these spots could represent inflammatory cells supported by their size and by the number correlating with the inflammatory activity. Compared to our subject, the foci were larger, more hyperreflective and without any umbra. Two other studies used follow-up intervals of approximately one year to detect hyperreflective foci in the inner retina with inward migration.[11,12] This was interpreted as movement of degenerated RPE cells in vitelliform lesions and age-related macular degeneration. Additional proposed sources of granular hyperreflectivity on OCT include hard exudates,[5] RPE organelles containing lipofuscin and melanolipofuscin, melanosomes,[11] lysosomes, and mitochondria.[3] The literature suggests that migrating macrophages may engulf lipids[5] or the listed organelles after they have been shed by the RPE.[13]

This non-invasive observation of an isolated migrating element with the size of a cell was made in a healthy subject in the absence of confounding retinal disease. Based on the preclinical studies, we speculate that such an element could be a macrophage. The case provides information about existence of infiltrative processes in the healthy retina as well as the time-scale and resolution needed for the longitudinal multimodal imaging of these processes *in vivo*.

Patient consent

The patient's legal guardian gave written consent to publication of the case. This case report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors state that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2020.100637.

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