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## Documentation of Intraretinal Retinal Pigment Epithelium Migration via High Speed Ultrahigh Resolution Optical Coherence Tomography

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### Abstract

**PURPOSE**—To describe the features of intraretinal retinal pigment epithelium (RPE) migration documented on a prototype spectral domain high speed, ultrahigh resolution optical coherence tomography (OCT) device in a group of patients with early to intermediate dry age-related macular degeneration (AMD). To correlate intraretinal RPE migration on OCT to RPE pigment clumping on fundus photographs.

**DESIGN**—Retrospective, non-comparative, non-interventional case series.

**PARTICIPANTS**—Fifty-five eyes of 44 patients seen at the New England Eye Center between December 2007 and June 2008 with early to intermediate dry AMD.

**METHODS**—3D OCT scan sets from all patients were analyzed for presence of intraretinal RPE migration, defined as small discreet hyper-reflective and highly-backscattering lesions within the neurosensory retina. Fundus photographs were also analyzed to determine the presence of RPE pigment clumping, defined as black-colored, often spiculated areas of pigment clumping within the macula. OCT en face images were correlated with fundus photographs to demonstrate correspondence of intraretinal RPE migration on OCT and RPE clumping on fundus photo.

**MAIN OUTCOME MEASURES**—Drusen, Dry AMD, intraretinal RPE migration, RPE pigment clumping.

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#### Disclosures

The sponsors had no role in the design or conduct of this research. Authors with financial/conflicting interests are listed after references.

**RESULTS**—54.5% of eyes (61.4% of patients) demonstrated intraretinal RPE migration on OCT scans. 56.4% of the fundus photographs demonstrated RPE pigment clumping. All eyes with intraretinal RPE migration on OCT had corresponding RPE pigment clumping on fundus photographs. RPE pigment migrated most frequently into the outer nuclear layer (66.7% of eyes) and less frequently into more anterior retinal layers. Intraretinal RPE migration mainly occurred above areas of drusen (73.3% of eyes).

**CONCLUSIONS**—The appearance of intraretinal RPE migration on OCT is a common occurrence in early to intermediate dry AMD, occurring in 54.5% of eyes or 61.4% of patients. The area of intraretinal RPE migration on OCT always correlated to areas of pigment clumping on fundus photography. Conversely, all but one eye with RPE pigment clumping on fundus photography also had areas of intraretinal RPE migration on OCT. The high incidence of intraretinal RPE migration observed above areas of drusen suggests that drusen may play physical and catalytic roles in facilitating intraretinal RPE migration in dry AMD patients.

## Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in patients over 65 years of age in industrialized nations.<sup>1-3</sup> Early on in the dry form of the disease, extracellular material forms deposits under and within Bruchs' membrane; these deposits are known as drusen.<sup>4</sup> This condition may progress to the development of abnormal choroidal vessels below or within the retina, which often leak and cause accumulation of fluid and distortion of vision (known as neovascular AMD)<sup>5</sup>, or may progress to geographic atrophy with widespread atrophy of the retina and retinal pigment epithelium (RPE) layers.<sup>6</sup>

Optical coherence tomography (OCT) is a device designed to perform non-invasive “virtual biopsy” of biological tissues.<sup>7</sup> Time domain OCT technology was the first to become commercially available. The current standard time domain Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA) has a scanning speed of 4,000 A-scans/second and an axial resolution of 10  $\mu\text{m}$ . Spectral domain OCT became commercially available in 2006, and has allowed for even higher scan speeds of ~25,000 to 50,000 A-scans/second and axial resolutions of ~3-5  $\mu\text{m}$ . Improved scanning speed decreases instances of fixation drift and motion artifacts and allows for the acquisition of dense scan sets, thus resulting in a more accurate depiction of the retina. Higher axial resolution allows for better delineation of pathologies than previously possible with time domain detection.<sup>8</sup> Our group utilizes a prototype ultrahigh resolution spectral domain OCT system in the eye clinic. This machine is capable of axial resolution of ~3 $\mu\text{m}$  and scanning speeds of 25,000 a-scans/second.

Three previous reports have documented the presence of small hyper-reflective lesions within the retina in patients with dry AMD utilizing spectral domain OCT, which had not been previously reported using time domain detection.<sup>9-11</sup> The authors from these studies speculated that the lesions observed were of retinal pigment epithelium (RPE) origin and demonstrated intraretinal RPE migration. However, intraretinal RPE migration as visualized on OCT is still ill-defined. In addition, to our knowledge, previous studies correlating intraretinal RPE migration with color fundus photography have not been conducted. The purpose of this study is to utilize our prototype high-speed ultrahigh resolution OCT instrument to better define the entity of intraretinal RPE migration in patients with dry AMD, and to verify that these lesions actually correlate to areas of RPE pigment clumping observed on color fundus photography.

## Methods

### Subjects and OCT Scan Protocol

A retrospective spectral domain OCT scan review was conducted for dry AMD patients seen at the New England Eye Center retina service between December 2007 and June 2008. Charts of all patients with a diagnosis of age-related macular degeneration who were imaged with our prototype OCT instrument during that time period were reviewed. Patients were included in the study if they had dry age-related macular degeneration and both ultrahigh-resolution OCT images as well and color fundus photographs available for comparison. Patients were excluded from the study if OCT scans, funduscopy, fundus photography, and/or fluorescein angiography revealed evidence of neovascular disease or geographic atrophy, or if the patient had co-existing macular pathology (such as diabetic retinopathy).

The OCT device utilized was a prototype high speed, ultrahigh resolution OCT with a scan speed of 25,000 A-scans/second and an axial resolution of 3  $\mu\text{m}$ . Imaging was performed using our 3D scan protocol consisting of 180 evenly spaced horizontal B-scans, each made up of 512 A-scans, acquired in ~4 seconds within a 6 mm  $\times$  6 mm region centered at the fovea (as previously reported).<sup>12</sup> As a reference, an “OCT Fundus image” was generated via summation of axial data points from all B-scans in the scan set. A white horizontal line through the fundus image could then be used to delineate where an individual OCT B-scan was taken in relation to the fundus. This study was approved by the Tufts Medical Center Institutional Review Board and was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki.

### OCT Image Analysis and Correlation with Color Fundus Photography

For each patient, all 180 frames in the OCT scan set were analyzed for evidence of intraretinal RPE migration. Intraretinal RPE migration was identified as well-defined hyper-reflective and highly backscattering lesions within the neurosensory retina, which were often discreet, but sometimes seen attached to areas of elevated RPE overlying drusen (Figure 1A). In patients where OCT B-scans demonstrated intraretinal RPE migration, the OCT B-scans as well as the en face “fundus image” were exported as JPEG images into Adobe Photoshop (version CS4, Adobe Systems, Inc., San Jose, CA, USA) for registration with the color fundus photographs. The en face OCT fundus image was resized and moved so that the retinal vessel tracings best matched and overlapped those from the color fundus photograph (Figure 1C, D). Individual OCT B-scan images were indicated on the OCT fundus image with a white line, therefore pathologies observed on OCT B-scans could be correlated to pathologies observed on the color fundus photograph utilizing this method.

Color fundus photographs from each patient included in this study were then analyzed for any signs of RPE clumping, regardless of whether or not intraretinal RPE migration was observed on OCT scans. RPE clumping was visualized as black-colored, often spiculated lesions within the macula. The presence or absence of observable RPE pigment on color fundus photograph was determined and recorded (Figure 1B).

## Results

Of the 44 patients recruited, 19 were male and 25 were female. The average age of the patients was  $70 \pm 10$  year old. 42 patients were Caucasian and 2 patients were Asian. Average age of patients with intraretinal RPE migration documented on OCT in at least one eye was  $73 \pm 8$  years old, while the average age in those without intraretinal RPE migration was  $67 \pm 13$  year old; this difference was not statistically significant ( $p= 0.09$ ). Average right eye visual acuity for all patients was 20/37 and 20/28 for the left. Average right eye visual acuity for patients with intraretinal RPE migration documented on OCT was 20/42

and 20/31 for those without documented intraretinal RPE migration ( $p= 0.25$ ). Average visual acuity for the left eye in patients with documented intraretinal RPE migration on OCT was 20/33, and for those without intraretinal RPE migration was 20/34 ( $p= 0.86$ ).

Fifty-five eyes from 44 patients with dry AMD were imaged using the prototype high speed, ultrahigh resolution OCT from December 2007 to June 2008. Intraretinal RPE migration, defined as well-defined hyper-reflective and highly backscattering lesions within the neurosensory retina— were always found overlying areas of RPE disturbance (defined as either RPE thickening or irregularity), either over drusen or areas where the RPE layer appeared more focally irregular. Due to the highly backscattering nature of RPE pigment on OCT, the migrated pigment “clump” created a shadowing effect in tissues directly posterior to the clump.

54.5% of eyes (30 out of 55 eyes) or 61.4% of patients (27 out of 44 patients) analyzed revealed evidence of intraretinal RPE migration documented on at least one OCT scan. All areas of intraretinal RPE migration on OCT corresponded to areas of RPE pigment clumping on color fundus photographs. Color fundus images from all 55 eyes were also examined separately to detect the presence of RPE pigment clumping, which was found in 56.4% (31/55) of eyes. Out of the color fundus images with visible RPE pigment, all but one eye (96.8%, or 30/31 eyes) also had corresponding intraretinal RPE migration on OCT scans, while 1/31 eyes (3.2%) with RPE clumping visible on color photographs had no obvious areas of intraretinal RPE migration on OCT. Summary of findings are presented in Table 1.

The localization of intraretinal RPE migration into the retina was also recorded for all OCT scans. Of the 30 eyes with intraretinal RPE migration on OCT (out of the total of 55 eyes examined), the majority of them demonstrated pigment migration to the outer nuclear layer (66.7% or 20/30). 13.3% (4/30) of the eyes had intraretinal RPE migration up to the outer plexiform layer. A minority of eyes demonstrated intraretinal RPE migration into the inner retina: 13.3% (4/30) of the eyes contained intraretinal RPE migration into the inner nuclear layer and 6.7% (2/30) into the inner plexiform layer.

In most patients, areas of RPE pigment migration were located anterior to areas of drusen, which were visible on OCT as small elevations of the RPE layer from Bruchs’ membrane (Figure 1A). The majority of intraretinal RPE migration observed (73.3% or 22/30 eyes) fell into this category. However, in a minority of patients, the areas of intraretinal RPE migration were not associated with areas of drusen (Figure 2A). The following are two illustrative cases describing intraretinal RPE migration associated with and without underlying drusen.

### Case 1

An 81-year-old Caucasian female with a history of dry AMD in her right eye and neovascular AMD in her left eye presented to our clinic for evaluation of AMD. Fundus examination revealed multiple drusen in her right eye, and RPE clumping centrally (Figure 1B). High speed, ultrahigh resolution OCT images revealed a discreet round hyper-reflective lesion within the outer nuclear layer, overlying an area of drusen (Figure 1A). Vessel tracing was used to register the OCT en face image with the color fundus photograph (Figure 1C). After registration of the OCT B-scan to the fundus photograph, it was evident that the hyperreflective lesion on OCT corresponded to an area of RPE pigment clumping on fundus photograph (Figure 1D; blue arrow).

### Case 2

An 84 year-old Caucasian female with a history of dry AMD in her right eye and neovascular AMD in her left eye presented to our eye clinic for evaluation of AMD. Fundus examination of her right eye revealed multiple drusen with areas of RPE clumping nasally

(Figure 2B). High speed ultrahigh resolution OCT scan revealed a discreet round hyper-reflective lesion in the outer nuclear layer, not associated with drusen (Figure 2A). The lesion is highly scattering of OCT signal, and a shadow is created posterior to the lesion. Vessel tracing was used to register the OCT en face image with the color fundus photograph (Figure 2C). After registration of the OCT B-scan to the fundus photograph, it was again evident that the hyperreflective lesion on OCT corresponded to an area of RPE pigment clumping on fundus photograph (Figure 2D; blue arrow).

## Discussion

The RPE is a single cell layer posterior to the neurosensory retina. It plays an important role in maintaining the health of the photoreceptors by phagocytosis of photoreceptor outer segments, visual pigment regeneration, and transport of fluid between choroid and the retina. The RPE is also a reactive tissue, and its responses to various stimuli include proliferation, hypertrophy, change in pigmentation, and migration. Intraretinal RPE migration into the neurosensory retina has been well described on histopathology in lesions of congenital hypertrophy of the RPE, reactive hyperplasia of the RPE, and in “bone spicule” formation in retinitis pigmentosa and other pan-retinal degenerations.<sup>13</sup> However, intraretinal RPE pigment migration in dry AMD has not yet been well described.

The present study documents visualization of intraretinal RPE migration using a prototype high speed ultrahigh resolution OCT device. Overall, a high incidence of intraretinal RPE migration was observed in patients with dry AMD (61.4% of patients or 54.5% of eyes). In addition, all eyes with documented intraretinal RPE migration on OCT had corresponding areas of RPE clumping on color fundus photographs. Our and other groups have previously demonstrated the presence of hyper-reflectivity present in the retina above the RPE and speculated that these lesions represented intraretinal RPE migration.<sup>9-11</sup> Schuman et al found that 40% of eyes with dry AMD demonstrated the presence of intraretinal RPE migration utilizing a 4.5  $\mu\text{m}$  prototype spectral domain OCT.<sup>9</sup> This number was close to our calculated prevalence of 54.5% using a 3  $\mu\text{m}$  prototype spectral domain OCT.

31 eyes demonstrated intraretinal RPE pigment clumping on color fundus photography, while 96.8% or 30 out of 31 of these eyes examined contained intraretinal RPE migration on OCT. In the lone case where this mismatch occurred, irregular clumping of the RPE causing elevation of the retinal contour was observed at the region where pigment was documented on fundus photography (Figure 3). It is possible that RPE clumping observed in this case may not actually be due to intraretinal RPE migration, but rather RPE hyperplasia under the retina.

Areas of intraretinal RPE pigment migration on OCT were located directly above drusen in the majority of the eyes analyzed (73.3%). Reviewing consecutive frames in these cases revealed a linear growth of RPE emanating from the RPE layer above the drusen (Figure 4B) which then “bud” off from the RPE layer and into the inner retina (Figure 4 C, D) in subsequent frames. The high prevalence of intraretinal RPE migration occurring in association with areas of drusen suggests that drusen may play a role in stimulating intraretinal migration of RPE pigment.

It is widely known that RPE cells have the ability to migrate towards various inflammatory mediators like TNF- $\alpha$ .<sup>14-16</sup> However, under normal conditions they do not migrate due to the lack of a chemical signal and their attachment to Bruch’s membrane via various integrins.<sup>17</sup> Drusen are round accumulations made up of extracellular debris, lipids, and lipofuscin found between the RPE and Bruch’s membrane. It is possible that the presence of drusenoid material may weaken the attachment of RPE to Bruch’s membrane, potentiating

its motility. Several studies have confirmed the presence of inflammatory mediators present in drusen.<sup>18</sup> These mediators could lead to an inflammatory reaction, causing cells in the surrounding environment to secrete various chemokines (like MCP-1) and cytokines (ie. IL-1, TNF- $\alpha$ ). *In vitro* studies have confirmed the chemotactic nature of these cytokines and chemokines on RPE cells.<sup>19-21</sup> It is not entirely clear why in a minority of the cases RPE pigment was observed above areas of RPE without drusen beneath it. Thus, although it appears that presence of drusen aids in pigment migration, it is not an absolute requirement. It is possible that chemotactic factors may be secreted from the accumulation of drusenoid material adjacent to regions of where intraretinal RPE migration may occur. The presence of these factors in the surrounding milieu then predisposes the adjacent RPE to undergo intraretinal migration. However, this is purely hypothesis generating, and thus required further studies for validation.

Given that the smallest sized intraretinal RPE migration observed in this study was 40  $\mu$ m in length from RPE to extension into the neurosensory retina (while the axial resolution of the standard resolution OCT is 10  $\mu$ m), standard resolution OCT should be able to observe the majority of the lesions. However, the enhanced resolution allows for reduction in speckle, and subsequently better depiction of the lesion as well as the associated underlying RPE disturbances. In addition, the high speed of the prototype OCT used in this study (spectral vs time domain OCT) allows for high density scanning, and thus wider and denser coverage of the macula. Also, the high number of data points offered by high-speed OCT scanning allows for the creation of accurate enface images, which may be used to correlate OCT to fundus photography.

## Limitations

The current investigation defined RPE pigment clumping on color fundus photographs as black-colored specks of pigment clumping. Pigment clumping on color fundus photography may occasionally be mistaken for RPE pigment hypertrophy or choroidal hyperpigmentation, therefore care has to be taken not to confuse these other entities with RPE pigment clumping.<sup>22</sup>

A high rate of intraretinal RPE migration was observed in this study. While it was similar to the 40% seen on OCT as presented by Schuman, et al, it was considerably higher than the 20.3% of patients with “hyperpigmentation” as presented in AREDS report 17.<sup>9, 23</sup> The higher rates of intraretinal RPE migration and RPE pigment clumping in this study may be due to smaller sample size of this study or enhanced resolution or speed of the prototype OCT device used in this study. However, the principal conclusion remains, that pigment clumping may be visualized using spectral domain OCT.

This study utilized untracked SD OCT scans, and thus exact registration of OCT scans to fundus photographs was not consistently possible. Scans with large amounts of motion artifacts due to poor fixation were not included in this study since it was not possible to register the fundus photograph to the OCT scan. Thus, this may be a source of bias in this study.

The smallest size foci which fit the definition of intraretinal RPE migration (defined as well-defined hyper-reflective and highly backscattering lesions within the neurosensory retina) in this study was 40  $\mu$ m in the smallest diameter. It is possible that smaller foci of RPE migration were also present in the retina, but not easily detectable due to limitations in transverse resolution of OCT technology without the use of adaptive optics. Their exclusion may also in part contribute to the high correlation observed between pigment clumping on fundus photographs and RPE migration seen on OCT scans.

This study used a “one or none” system for assessing whether an image contains RPE clumping on fundus photos or RPE migration on OCT. In other words, the high rate of agreement in this study does not necessarily mean that all areas of RPE hyperpigmentation were visualized as RPE migration on OCT. Instead, the high rate of agreement means that almost all patients with RPE clumping on fundus photos have corresponding RPE migration visualized on OCT. The use of this “one or none” system may have contributed to the high correlation observed between OCT scans and fundus photography.

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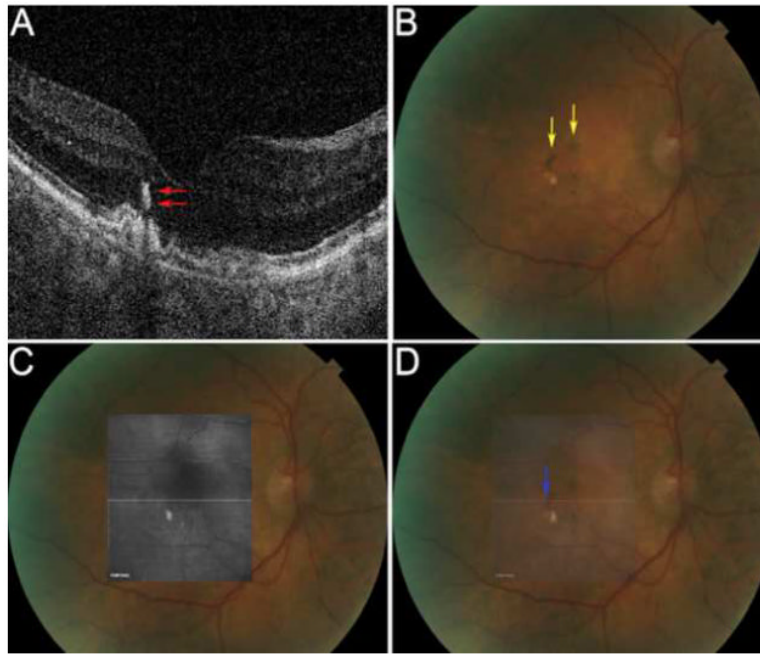
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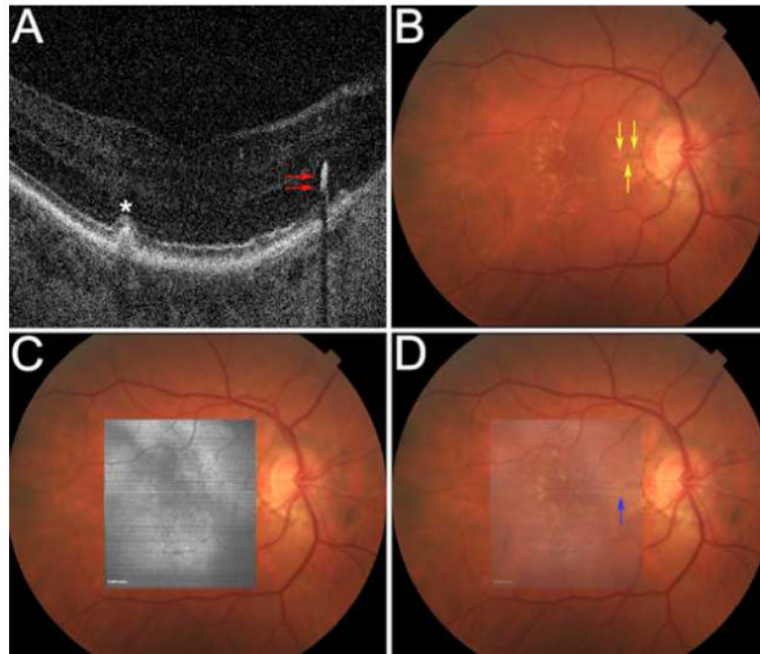
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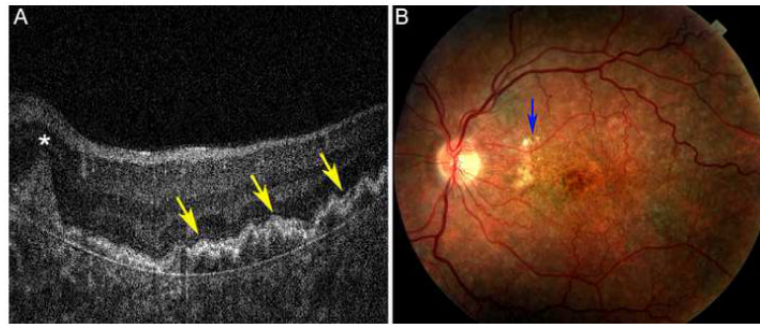




**Figure 1.**  
 Example of intraretinal retinal pigment epithelium (RPE) migration, type 1:  
 (A) Prototype high speed, ultrahigh resolution optical coherence tomography (OCT) scan of intraretinal RPE migration. Rod-shaped hyper-reflectance was seen detached from the RPE directly above a drusen extending into the outer nuclear layer (red arrows);  
 (B) Color fundus photograph showing multiple drusen and jet-black RPE pigment centrally (yellow arrows);  
 (C) OCT en face image with a line corresponding to the scan in (A) overlaid on the color fundus photograph and resized for vessel tracing;  
 (D) Transparency of the OCT en face image was brought up showing the location of the intraretinal RPE migration on the OCT en face image (white line) corresponding to RPE pigment clumping on color fundus photograph (blue arrow).



**Figure 2.**  
 Example of intraretinal retinal pigment epithelium (RPE) migration, type 2:  
 (A) Prototype high speed, ultrahigh resolution optical coherence tomography (OCT) scan of intraretinal RPE migration. Rod-shaped hyper-reflectance extending into the outer nuclear layer was seen above the RPE but not at an area of drusen (red arrows). Asterisk demonstrated a drusen;  
 (B) Color fundus photograph of drusen centrally and jet-black RPE pigment close to the optic disc (yellow arrows);  
 (C) OCT en face image with a line corresponding to the scan in (A) overlaid on the color fundus photograph and resized for vessel tracing;  
 (D) Transparency of the OCT en face image was brought up showing the location of the intraretinal RPE migration on the OCT en face (white line) corresponding to RPE pigment clumping on color fundus photograph (blue arrow).

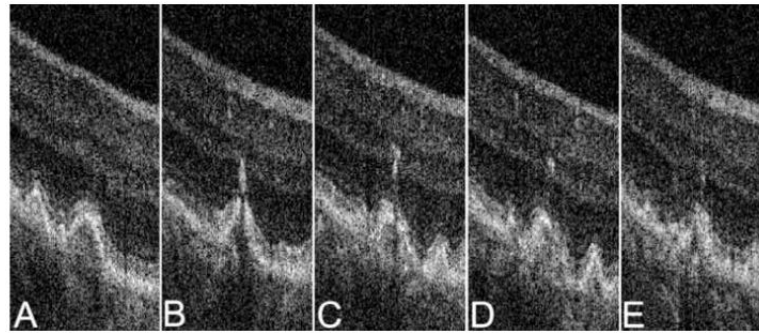


**Figure 3.**

Retinal pigment epithelium (RPE) clumping on fundus in absence of migration on optical coherence tomography (OCT):

(A) Elevation of RPE layer (yellow arrows) visualized at the location of RPE clumping on the fundus image. Area of RPE clumping is also observed (asterisk).

(B) Fundus image with an area of RPE pigment clumping (blue arrow).



**Figure 4.**

Intraretinal retinal pigment epithelium (RPE) morphology:

(A) Prototype high speed, ultrahigh resolution optical coherence tomography (OCT) scan of a patient with intraretinal RPE migration taken from a dataset with 180 consecutive scans. Two drusen were seen below the RPE but no intraretinal RPE migration was observed;

(B) Scan further inferior from the previous scan (A). Rod-shaped hyper-reflectance was observed connected to RPE;

(C) Scan following (B) inferiorly. Rod shaped hyper-reflectance seen over drusen but now detached from the RPE into the outer nuclear, outer plexiform and inner nuclear layers;

(D) Scan further inferior to (C). Spherical-shaped hyper-reflectance seen over drusen located to the inner nuclear layer;

(E) Scan inferior to (D). Faint spherical-shaped hyper-reflectance seen in outer nuclear and outer plexiform.

**Table 1**

Characteristics of intraretinal retinal pigment epithelium (RPE) migration

| Characteristic   | Percent of Cases (N) |
|--|----------------------|
| Intraretinal RPE Migration, per patient                    | 61.4% (27/44)        |
| Intraretinal RPE Migration, per eye                        | 54.5% (30/55)        |
| RPE pigment on fundus, per eye                             | 56.4% (31/55)        |
| Intraretinal RPE migration above drusen                    | 73.3% (22/30)        |
| Migration up to ONL  | 66.7% (20/30)        |
| Migration up to OPL  | 13.3% (4/30)         |
| Migration up to INL  | 13.3% (4/30)         |
| Migration up to IPL  | 6.7% (2/30)          |
| Pigment present on fundus without OCT RPE migration        | 3.2% (1/31)          |
| Intraretinal RPE migration correlated to pigment on fundus | 100.0% (30/30)       |

Note: 44 patients, 55 eyes. ONL= outer nuclear layer, OPL= outer plexiform layer, INL= inner nuclear layer, IPL= inner plexiform layer, OCT= optical coherence tomography, RPE= retinal pigment epithelium.