En Face Optical Coherence Tomography Imaging of Foveal Dots in Eyes With Posterior Vitreous Detachment or Internal Limiting Membrane Peeling

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PURPOSE. To analyze the morphology of foveal hyperreflective dots (HRD) identified with en face optical coherence tomography (OCT) and evaluate the effects of internal limiting membrane (ILM) peeling and posterior vitreous detachment (PVD) on the number of these lesions.

METHODS. Retrospective cross-sectional study of patients with OCT angiography and en face OCT. Using en face OCT, superficial HRD lying on the foveal floor were measured and quantitated in eyes with ILM peel and in the fellow nonsurgical eyes. Eyes with foveal PVD were also compared to fellow eyes without foveal PVD. High-magnification en face OCT was also performed to better understand the morphology of HRD in the fovea.

RESULTS. Eyes that underwent ILM peel (n = 10) displayed fewer HRD (P = 0.012) compared to control fellow nonoperated eyes. In eyes with foveal PVD, the mean number of HRD was numerically greater, but without statistical significance, compared to the contralateral eye without foveal PVD. High-magnification en face OCT illustrated HRD with irregular shapes and fine cilia-like or dendriform extensions. Average length of HRD was between 15 to 21 μm in all four groups.

CONCLUSIONS. HRD decreased in eyes with ILM peeling by en face OCT compared with fellow nonoperated eyes and exhibited a glial cell-like morphology and size closely resembling the white dot fovea described previously using scanning electron microscopy. HRD may represent processes of activated retinal glia, possibly Muller cells, that traverse defects in the ILM.

Keywords: hyperreflective dots, en face OCT, ILM peel, PVD

In a seminal study using scanning electron microscopy (SEM), Yokotsuka et al. described the white dot fovea comprised of polygonal lesions with ciliary or dendritic-like processes in the central fovea. These findings were attributed to activated glial or Muller cell processes breaking through a thin internal limiting membrane as a result of chronic or increased vitreoretinal traction.

Optical coherence tomography (OCT) has revolutionized our understanding of macular diseases and therapeutic outcomes. The newest spectral-domain and swept-source technologies can generate cross-sectional images of retinal anatomy that approximate histological specimens. Additionally, high-density volumetric OCT scanning has enabled digital reconstruction of retinal layers in the coronal or en face plane, facilitating layer-by-layer analysis of the retina. Several studies combining en face imaging and B-scan OCT have successfully analyzed retinal pathologies of both the inner and outer retinal layers.

Recently, Corradetti et al. described the presence of superficial hyperreflective dots (HRD) on the surface of the fovea in a cohort of normal eyes using en face and B-scan OCT. These dots were quantified using a novel and validated algorithm, and the authors noted a systematic increase in the number of dots in normal eyes according to decade of age, especially over the age of 50. We believe that these HRD may represent the OCT signature of white dot fovea described by Yokotsuka et al. with SEM. As posterior vitreous detachment (PVD) and ILM peeling can mechanically alter the surface of the fovea, we aimed to analyze the effects of these events on the number, number, and area of HRD.
This was a retrospective cross-sectional study of patients imaged with en face OCTA (Optovue, Fremont, CA, USA) at the Stein Eye Institute between 2014 and 2019 and evaluated by one of the authors (D.S.). The OCTA database and electronic health records were queried for patients with diagnosis of epiretinal membrane (ERM), PVD, or macular hole (MH).

Inclusion criteria were OCTA examinations with a quality scan index of ≥7 for both eyes. Eyes with significant inner retinal disease or distortion caused by disorders such as lamellar macular hole, myopic foveoschisis, diabetic macular edema, or atrophy were excluded. Eyes with outer retinal disease causing significant atrophy, such as the advanced (nonneovascular or neovascular) forms of age-related macular degeneration, were also excluded. En face OCT images with significant motion artifact, segmentation errors, or degradation because of media opacity were excluded. For patients with ERM or MH, inclusion criteria were one eye status-post ILM peeling for either idiopathic MH or macular puck and the fellow eye without ILM peeling. For patients with PVD, inclusion criteria were one eye with foveal vitreous detachment (i.e., grade 3 or 4 PVD) and one eye without foveal vitreous detachment (i.e, grade 0, 1, or 2 PVD). Patients were excluded if fellow eyes in either group harbored inner retinal changes that would confound analysis.

### Imaging Protocol and Segmentation

En face OCT images were captured with a spectral-domain OCT machine (RTVue XR Avanti; Optovue, Fremont, CA, USA) and analyzed and segmented on AngioVue software Version 2017.1.0.151 (Optovue). Evaluation for foveal vitreous detachment was performed on the 6 × 6-mm scanning protocol, because recent studies suggest high accuracy using this technique. En face OCT and OCTA images were otherwise analyzed on 3 × 3 scanning protocol only.

A method for isolating the HRD on en face OCT was previously described. The structural en face OCT using the default software “superficial” slab segmentation was isolated and exported. This slab was segmented by default along the superficial vascular complex (SVC). The inner boundary of the slab was positioned 0 μm beneath the ILM, and the outer boundary was positioned 9 μm beneath the inner plexiform layer (IPL). These boundaries corresponded to the foveolar pit where there is an absence of inner layers. This segmentation was chosen to reduce the foveal light reflex with en face OCT, which can mask structural HRD. Any errors in ILM automatic segmentation were manually corrected on a foveal B-scan and propagated to other cross-sections.

Multicolor confocal scanning laser ophthalmoscopy (SLO) images were captured with the Heidelberg Retinal Angiograph 2 Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany). The Heidelberg Retinal Angiograph 2 uses blue (488 nm), green (514 nm), and near-infrared (815 nm) lasers for image registration.

### Quantification of Hyperreflective Dots

Two methods for quantifying HRD have been previously described. Strong statistical correlation between the strategies has been validated. One of the methods, a “threshold reflectivity” method of detecting and quantifying HRD, has been described in detail and was used in this study (see below). The other method involves manually counting dots using our previously developed algorithm of HRD detection and quantification in an effort to better understand the nature of these pathoanatomical findings. We also performed high-magnification en face OCT to better understand the morphology and origin of the dots.

### METHODS

#### Study Cohort

This study was approved by the Institutional Review Board of the University of California–Los Angeles and adhered to the principles of the Declaration of Helsinki. Informed consent was obtained from each patient before en face OCT imaging, because it is not considered a routine clinical tool.

#### Table 1. Comparison of Hyperreflective Dots Between Eyes With PVD and Fellow Eyes Without PVD

|                          | PVD            | No PVD          | P Values |
|--------------------------|----------------|-----------------|----------|
| Mean age (years)         | 66.8 ± 17.4    | 65.7 ± 19.2     |          |
| Male gender (%)          | 1/8 (12.5%)    | 1/8 (12.5%)     |          |
| Right eye (%)            | 7/8 (87.5%)    | 9/8 (100%)      |          |
| FAZ (mm²)                | 0.23 ± 0.141   | 0.24 ± 0.118    | 0.779    |
| PVD                      | 0.23 ± 0.141   | 0.28 ± 0.124    |          |
| No PVD                   | 0.22 ± 0.124   | 0.24 ± 0.132    |          |
| Pseudophakic PVD         | 1/8 (12.5%)    | 2/8 (25%)       | 0.232    |
| PVD                      | 1/8 (12.5%)    | 2/8 (25%)       |          |
| No PVD                   | 1/8 (12.5%)    | 2/8 (25%)       |          |
| Visual acuity (LogMAR)   | 0.24 ± 0.26    | 0.22 ± 0.22     |          |
| PVD                      | 0.25 ± 0.27    | 0.23 ± 0.22     |          |
| No PVD                   | 0.23 ± 0.18    | 0.24 ± 0.20     |          |

Grader 1

- Mean no. of dots: 33.5 ± 47.1
- Range of no. of dots: PVD 3–144, No PVD 0–64
- Mean area of largest dot (μm²): 1600 ± 2280
- Mean dot area (μm²): 236 ± 150

Grader 2

- Mean no. of dots: 38.9 ± 49.8
- Range of no. of dots: PVD 1–151, No PVD 12–69
- Mean area of largest dot (μm²): 1706 ± 2479
- Mean dot area (μm²): 320 ± 303

Mean age of largest dot (μm²): 0.528
Mean dot length (μm): 0.553
Mean no. of dots: 0.612
Mean dot length (μm): 0.635
Mean dot area (μm²): 0.674
Mean no. of dots: 0.889
Mean dot area (μm²): 0.779
Mean dot length (μm): 0.553
Mean no. of dots: 0.612
Mean dot area (μm²): 0.635
Mean dot length (μm): 0.674

This protocol, because recent studies suggest high accuracy using this technique. En face OCT and OCTA images were otherwise analyzed on 3 × 3 scanning protocol only.
the dots on the individual B-scans. Because both methods have been validated and shown to have excellent correlation, the manual counting method was deferred in this study because it cannot measure the foveal area over which the dots are localized. Two non-masked graders (C.P. and A.A.) performed the HRD analysis with the threshold reflectivity method. Briefly, using ImageJ software (1.52; http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA), the 3 × 3-mm en face OCT image was isolated according to the borders of the foveal avascular zone (FAZ), which was determined by manufacturer's default settings, and adjusted so that all parts of this area were within the foveal depression to exclude signal from inner retinal layers. This selection was then binarized and thresholded on the basis of the mean reflectivity of the B-scan ellipsoid zone (EZ). The HRD on the thresholded image could then be counted and the area measured using the ImageJ software. Given the limited resolution of OCT, it was not possible to accurately measure linear dimensions of the HRD. Therefore, to determine diameter, the polygonal dots were assumed to be approximately circular, and the software measured areas were converted to diameters (D) via the equation $D = \sqrt{\frac{4A}{\pi}}$.

The FAZ area may be artificially minified in patients with axial myopia, and the true FAZ is larger after correction with the manufacturer software, particularly in those with axial length >26 mm or spherical equivalent of −6 or less. Axial lengths were not available for the patients in this study. Given that fellow eyes were compared and none exhibited anisometropic amblyopia, the difference in axial lengths between eyes was assumed to be insignificant, and therefore no correction factor was considered.

Since the FAZ in eyes with macular puckers both before and after surgery may be smaller, the number of HRD in these eyes may be artefactually low due to the smaller area in which the HRD are measured. To offset this for the fellow eye, a correction factor of the FAZ area in the ILM peeled eye (FAZILM) divided by the FAZ area in the fellow eye (FAZFEL), multiplied by the number of HRD (HRDFEL) in the fellow eye, was used to calculate the adjusted number of fellow HRD (HRDadj), also denoted by $HRD_{adj} = \frac{FAZ_{ILM}}{FAZ_{FEL}} \times HRD_{FEL}$.

**Statistical Evaluation**

All statistical analyses were performed using either Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, VA, USA) or StataIC 15 (StataCorp LLC, College Station, Texas, USA). Continuous variable data were expressed as mean ± standard deviation when applicable. The Wilcoxon signed-rank test was used to compare HRD data between the groups of study eyes and fellow (control) eyes. Both the Spearman’s rank correlation ($\rho$) and two-way mixed effect intraclass correlation coefficients were calculated to measure the agreement between graders for HRD measurements, with a confidence interval of 95%. A $P$ value < 0.05 was considered statistically significant.

**RESULTS**

Demographic and HRD data from both graders for the PVD cohort are listed in Table 1. In the PVD analysis, eight patients (one male) meeting the above inclusion and exclusion criteria were identified. The average age was 66.8 ± 17.4 years (range, 31 to 87). Seven of eight (87.5%) PVD eyes were right eyes, and of all eyes 3/16 (19%) were pseudophakic at the time of imaging. The average FAZ area was 0.234 ± 0.141 and 0.282 ± 0.124 mm² for the PVD and no PVD eyes, respectively ($P = 0.779$). For
White Dot Fovea Seen With En Face OCT

TABLE 2. Comparison of Hyperreflective Dots Between Eyes With Eyes With ILM Peeling and Fellow Eyes Without ILM Peeling

| ILM peel comparison | P Values |
|---------------------|----------|
| Mean age (years)    | 71.2 ± 12.1 |
| Male gender (%)     | 6/10 (60%) |
| Right eye (%)       | 4/10 (40%) |
| Peel                | 6/10 (60%) |
| No peel             | 0.113 ± 0.085 |
| FAZ (mm²)           | 0.243 ± 0.086 |
| Peel                | 0.012 |
| No peel             | 0.028* |
| Pseudophakic        | 0.463 |
| Mean area of largest dot (μm²) | 949 ± 1074 |
| Peel                | 403 ± 389 |
| No peel             | 272 ± 162 |
| Mean dot area (μm²) | 8.3 ± 7.3 |
| Peel                | 0.07 ± 0.09 |
| No peel             | 21 ± 10 |
| Mean area of largest dot (μm²) | 0.053* |
| Peel                | 19 ± 6 |
| No peel             | 12.1 years (range, 48 to 92) |
| Visual acuity (LogMAR) | 0.2 ± 0.13 |
| Peel                | NA |
| No peel             | 16.7 (range, 1 to 56) |
| Range of number of dots | 162 μm² |
| Peel                | 242 μm² |
| No peel             | 33.5 ± 0.04, 0.84 ± 0.12, and 0.88 ± 0.10, respectively, and the intraclass correlation coefficient (ICC) for the number of HRD was 0.987 ± 0.02. The HRD were an average length of 16 ± 6 μm (range, 6 to 94 μm) in the PVD eyes, and an average length of 15 ± 8 μm (range, 6 to 72 μm) in the no PVD eyes. There was no significant difference in visual acuity between groups, with average LogMAR 0.24 ± 0.26 (Snellen equivalent 20/32) in the PVD group and 0.32 ± 0.22 in no PVD group (Snellen equivalent 20/40) (P = 0.232).

Demographic and HRD data from both graders for the ILM peel cohort are listed in Table 2. Ten patients (six male) meeting the above inclusion and exclusion criteria were identified. The average age was 71.2 ± 12.1 years (range, 48 to 92). Four of 10 (40%) ILM peeled eyes were right eyes, and of all eyes 12 of 20 (19%) were pseudophakic at the time of imaging. Preoperative diagnosis was ERM for six eyes and MH for four eyes. The average FAZ area was 0.113 ± 0.085 and 0.243 ± 0.086 mm² for the ILM peeled and fellow eyes, respectively (P = 0.005). For Grader 1, the average number of HRD was significantly different between groups, at 2.3 ± 3.0, 20.4 ± 16.7 (range, 1 to 56) for the ILM peeled and fellow nonoperated eyes, respectively (P = 0.012) (Fig. 2). After applying the aforementioned FAZ correction factor to the fellow eyes, the average number of HRD was 8.3 ± 7.3, still significantly more than the ILM peeled eyes (P = 0.028). Average dot area was 403 μm² ± 389 μm² and 270 μm² ± 162 μm² for the ILM peeled and fellow eyes, respectively (P = 0.916). Spearman’s rhou between graders for number of HRD, average HRD area, and largest HRD were 0.97 ± 0.03, 0.77 ± 0.14, and 0.59 ± 0.24, respectively, and the intraclass correlation coefficient for the number of HRD was 0.988 ± 0.02. The HRD were an average length of 21 ± 10 μm (range, 6 to 61 μm) in the ILM peeled eyes, and an average of 18 ± 5 μm (range, 6 to 80 μm) in the fellow eyes. There was a significant difference in visual acuity between groups, with average LogMAR 0.2 ± 0.13 (Snellen equivalent 20/32) in the ILM peeled group and 0.07 ± 0.09 (Snellen equivalent 20/25) in fellow eye group (P = 0.031).

Multicolour confocal SLO imaging was available in four patients in the PVD cohort and four patients in the ILM peeled cohort. Qualitatively, the HRD appeared less numerous and bright (Fig. 3) than noted previously with SLO imaging.1,16 The HRD were best identified with either green or blue reflectance but could not be detected with near-infrared. Additionally, the HRD appeared less numerous and less distinct when compared with en face OCT.

Higher-magnification en face OCT imaging was performed in all cases that had at least 10 HRD on counts by both graders. Nineteen of the 36 total eyes displayed at least 10 HRD, and 13 of those 19 displayed HRD demonstrating an irregular polygonal shape with fine ciliary-like or dendritic extensions (Fig. 4).

**DISCUSSION**

Corradetti et al.5 were the first to identify superficial hyper-reflective dots in the central fovea of normal eyes using en face OCT and showed a significant increase according to age. In this study, we attempted to better understand the morphology and origin of these lesions and the effect of PVD and ILM peeling. Although there were no significant differences in the number of HRD in the eyes with foveal...
PVD versus eyes with earlier grades of PVD without foveal detachment, the number of dots was greater in the former group. This study also studied eyes with ILM peeling for macular hole surgery and found that there was a significant reduction in the number of HRD in the eyes with ILM peel versus the fellow nonoperated eyes, even after adjusting for decreased FAZ area. Corradetti et al were not able to determine the exact nature of these HRD and speculated that the lesions could represent Muller cell end-feet versus ILM processes versus vitreous hyalocytes. The greater number of HRD with age in the Corradetti study and the reduced number after ILM peel in this study indicates that vitreous hyalocytes are very unlikely to represent the HRD.

It is still unclear whether the HRD represent acellular material, such as collagen or extracellular matrix, or nucleated cells with processes. However, magnification of the en face OCT images illustrated that the HRD displayed irregular shapes with fine ciliary-like or dendriform extensions along the retinal surface. Yokotsuka et al.\(^1\) in their seminal study, described the white dot fovea. Their landmark SEM illustrations displayed “ciliary-like” extensions associated with the white dots that were remarkably similar to the magnified en face images of the HRD illustrated in our study (Fig. 4). These granules were polygonal, measured between 5 μm and 20 μm in length, were comprised of multiple processes and cilia-like extensions, and were scattered diffusely over the fovea surface, findings that remarkably correspond to the findings in this study and in the study of Corredetti et al.\(^5\) Moreover, in studies of ILM tissue after macular hole\(^17\) or ERM\(^18\) surgery in humans, a population of epi-retinal cells with irregular short processes and hair-like cell extensions was found on SEM, similar to those shown by Yokotsuka et al.\(^1\) Yokotsuka et al.\(^1\) also displayed the white dots clinically with SLO. In this study, we were also able to show that the en face OCT HRD could be identified with SLO, especially with the green channel. It is unclear
FIGURE 3. Montage of a right eye with PVD. SLO images including multicolor (A), green (B), blue (C), and near-infrared (D) demonstrate characteristic HRD most notable on green channel, although they are more prominent with en face OCT (E). Scale bars for A, B, C, D: 500 μm. Scale bar for E: 250 μm.

FIGURE 4. High-magnification en face OCT images with superficial segmentation of three eyes with HRD. (A) A left eye with no PVD from an 87-year-old female. (B) A right eye, fellow eye of ILM-peeled eye from a 73-year-old female. (C) A right eye, fellow eye of ILM-peeled eye, from a 92-year-old female. (D) The scanning electron microscopy image borrowed from Yokotsuka et al.1 (Reprinted from American Journal of Ophthalmology, Volume 123, Yokotsuka et al, White Dot Fovea, Pages 76–83, 1997, with permission from Elsevier). Note the polygonal HRD with fine dendritic or cilia-like extensions that extend from the HRD, suggestive of activated cell processes (red arrows). Scale bar: 250 μm.

why HRD were more visible with the green channel versus the blue channel. This may be due to absorption properties of the HRD or wavelength interactions with macular pigment.19 Therefore it is very likely that the en face OCT HRD described in this study, and in the Corradetti study, represent the white dot fovea described by Yokotsuka et al.1 using SEM. Note that subsequent publications of white dot fovea16,20 illustrated more pathological features suggestive of macular disease and likely do not represent the anatomical landmarks described in the article by Yokotsuka et al.1 and in our studies.

Furthermore, the ILM is known to be especially thin in the fovea21 and around vessels.22 The fovea represents an anatomical location of increased vitreoretinal traction.23 Foos24 originally hypothesized that PVD-induced ILM microbreaks facilitated the extension of glial cells along the
retinal surface. These glia were thought to act as the scaffold for later ERM formation. Similarly, in other areas of increased vitreoretinal traction, such as around the retinal vasculature, activated Muller cells can break through the ILM and grow along the surface of the retina.22,23 Both EM23,24 and immunohistochemical26 studies have demonstrated this population of Muller and glial cells most prominently in areas of ILM thinning. These characteristic cells have been referred to as epivascular glia and exhibit similar glial characteristics of cilia-like or dendritic extensions consistent with the HRD described in this study in the fovea. Our group has recently identified and described epivascular glia, that are most prominent around the major temporal vessels with en face OCT, and these lesions have similar morphological characteristics to the HRD including the cilia-like or dendriform processes.27

The lack of difference of HRD numbers with PVD in this study suggest that the force generated during foveal vitreous separation is insufficient to avulse the HRD, the HRD grow back after PVD, or these HRD integrate at a deeper layer that may be removed during ILM peeling. Spontaneous PVD tends to progress slowly in a stepwise fashion,20 and recent observations suggest that the posterior hyaloid face is formed as a split from the ILM during PVD.20 Chronic vitreoretinal traction preceding PVD may stimulate anterior migration such as occurs around the retinal vasculature. It is possible that HRD therefore may represent glial or Muller cell protrusions through the thin ILM caused by vitreoretinal traction or detachment. Although we did not identify a significant difference in the number of HRD in eyes with foveolar detachment, the number was still greater in this group. Microtrauma to the ILM may induce glial activation, in which cellular processes plug these defects. With larger defects, whole nucleated cells may migrate onto the retinal surface, similar to the process described with lamellar hole epiretinal proliferations.30 With a much larger recruitment of eyes, a significant difference may be elicited.

Limitations of this study include the retrospective nature of the analysis and the small sample size in both groups. The cross-sectional methodology of this study should be validated with longitudinal analysis. During idiopathic MH formation, an inner foveal cap of varying thickness may be avulsed,35 so we are unable to determine whether the loss of HRD results from ILM peeling or MH pathogenesis. However, we found no difference between the number of HRD in ILM peeled eyes with ERM versus MH, although the number for each group was small, and larger groups may show a difference. Outer retinal changes such as age-related macular degeneration in some eyes may have introduced error, but changes were bilateral, symmetric, and with no notable inner retinal effects. The small angles of tilt of the B-scan that introduce artifacts in the Henle fiber layer may affect imaging of the HRD.31 but given the planar configuration of the HRD across the superficial retina, the effect is likely minimal. Comparison of preoperative and postoperative HRD analysis would be ideal, but limitations of available segmentation algorithms on OCT devices prevents accurate preoperative en face segmentation of the superficial layers caused by ERM wrinkling, retinal thickening, or layer disorganization. Additionally, the absence of foveal tissue with macular holes precludes assessment of HRD.

In conclusion, ILM peeled eyes displayed a decreased number of HRD with en face OCT imaging compared with fellow eyes, although additional data is needed to fully evaluate the effect of a PVD. These HRD exhibit a size (15 to 20 um) and morphology with cilia-like extensions closely resembling the white dot fovea described decades ago with scanning electron microscopy,3 and therefore these dots may represent processes of activated glial cells, possibly Muller cells, traversing defects in the ILM. Further imaging and clinicopathological inquiries examining other inner foveal disorders may prove informative in elucidating the structure and function of these dots.

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