Characteristics of Diabetic Capillary Nonperfusion in Macular and Extramacular White Spots on Optical Coherence Tomography Angiography

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PURPOSE. To compare the characteristics of macular and extramacular white spots on wide-field swept-source optical coherence tomography angiography (SS-OCTA) and optical coherence tomography (OCT) images in diabetic retinopathy (DR).

METHODS. We retrospectively reviewed 107 eyes of 64 patients with DR, of whom nominal 12 × 12 mm SS-OCTA images centered on the optic disc and ultrawide field photographs were acquired. White spots on fundus photographs corresponded to hyperreflective lesions in the superficial en-face OCT images, and the characteristics of these white spots were investigated. We compared such OCT findings with the vertical and horizontal extents of nonperfused areas (NPAs) on OCT images.

RESULTS. We observed 136 white spots and corresponding hyperreflective lesions in 49 eyes. The hyperreflective lesions in the extramacular areas had greater areas (P < 0.001) and more frequently spanned from the nerve fiber layer to the outer plexiform layer (P < 0.001), while those in the macula were superficial. All of macular hyperreflective lesions were accompanied with nerve fiber layer defects, whereas only 18 (15.4%) of 117 extramacular lesions had them (P < 0.001). Comparative studies showed that most extramacular hyperreflective lesions corresponded to the NPAs in the whole layers on OCTA images, compared to the lamellar NPAs of the superficial layer in most of the macular lesions (P < 0.001). The NPAs extended to the peripheral side more frequently in the extramacular hyperreflective lesions compared with macular lesions (P < 0.001).

CONCLUSIONS. This study proposed that most of the extramacular white spots may be discriminated from macular spots with respect to diabetic NPAs on OCTA images.

Keywords: diabetic retinopathy, optical coherence tomography angiography, nonperfused area, cotton-wool spot

Diabetic retinopathy (DR) often leads to severe visual loss in working ages worldwide.1 Diabetes promotes microangiopathy mediated via several mechanisms, for example, pathological activation of biochemical pathways and secretion of growth factors and cytokines.2 In particular, transient or persistent capillary nonperfusion leads to retinal hypoxia and concomitant VEGF expression.3 Resultant angiogenic responses and vascular hyperpermeability play a pivotal role in proliferative DR (PDR) and diabetic macular edema (DME), respectively.4,5 The structure and function in retinal parenchyma are impaired within the nonperfused areas (NPAs) on fluorescein angiography (FA) in DR.6–9

Whitish lesions are often observed in extramacular areas of diabetic retinas, although the OCT and OCTA characteristics are not fully elucidated. FA images demonstrated focal ischemia in typical cotton-wool spots; however, whether this fundus finding can predict PDR development is controversial.10–12 Microinfarction in the inner retinal layers leads to the disturbance of axoplasmic flow, and deposits of axonal cargoes correspond to histological cytoid bodies and clinical whitish swelling in cotton-wool spots.13,14 In circulatory disorders, for example, retinal artery occlusion (RAO) and paracentral acute middle maculopathy (PAMM), the retinal parenchyma becomes cloudy.15,16 These ischemic and whitish lesions correspond to hyperreflective masses in retinal parenchyma on structural optical coherence tomography (OCT) images16–19; however, the OCT characteristics in the macular and extramacular lesions remains to be investigated. In addition, the clinical differences on other imaging modalities should be fully elucidated.

Three-dimensional images of OCT angiography (OCTA) enable us to evaluate the NPAs in the superficial and deep capillary plexuses layers individually.20–22 Histological and OCTA studies reveal that the deep capillary plexuses appear to form a seamless network beneath arterioles and venules in the macula.23–25 We speculated that the macula is perfused by several overlapping arterioles mediated via deep capillaries as collateral vessels.26 By contrast, the extramacular areas are segmented by large arterioles as the boundaries of retinal perfusion and may be nourished by one or two large arterioles. A recent publication revealed that the probability of the NPAs is associated with the retinal areas segmented by large arterioles and may depend on the overlap of the retinal perfusion in severe nonproliferative DR (NPDR) and PDR.24 We therefore
hypothesize that ischemic processes are different between the macular and extramacular white lesions in DR.

In this study, we investigated white spots, which corresponded to hyperreflective lesions on the en-face swept-source (SS)-OCT images in the superficial layer, and compared the OCT and OCTA findings of these lesions in the macular and extramacular regions in DR.

**METHODS**

**Patients**

In this retrospective study, we investigated consecutive cases with DR, of whom both wide-field SS-OCTA images and ultrawide field scanning laser ophthalmoscope (SLO) images of sufficient quality (signal strength index of 8 or more) were acquired. The exclusion criteria were the presence of any other chorioretinal disease; significant segmentation error at the vitreoretinal interface; optic nerve diseases, including glaucoma and ischemic optic neuropathy; previous photocoagulation in the extramacular areas, for example, panretinal photocoagulation; any previous treatment of DME; cataract surgery within 3 months or any intraocular surgery other than cataract extraction; or the axial length <22 and >26 mm. All research and measurements adhered to the tenets of the Declaration of Helsinki. The Kyoto University Graduate School and Faculty of Medicine Ethics Committee approved the study protocol (protocol number R0565-1), and all participants provided written informed consent.

**Pseudocolor SLO Image**

After a comprehensive ophthalmic examination, ultrawide field fundus images (approximate 200-degree retinal fields) were obtained using ultrawide field SLO (Optos200Tx, Optos PLC, Dunfermline, Scotland). After export as TIFF files, the fundus images with actual pixel resolution were opened with image processing software (Adobe Photoshop, Adobe Systems, Inc., San Jose, CA, USA) and evaluated on a diagnostic monitor (FlexScan SX2762W, EIZO Co., Ishikawa, Japan) using default parameter settings as described previously (Fig. 1a). Typical cotton-wool spots appear to be polymorphic and are accompanied with fluffy margins in the proximal and distal sides. We observed additional whitish lesions of various shapes without the fluffy margins (Fig. 2a). We therefore defined these fundus lesions as “white spots” after discrimination from small white dots and yellowish deposits, for example, hard exudates and drusen.55

We measured the central subfield (CSF) thickness using spectral-domain (SD)-OCT images (Spectralis, Heidelberg Engi-
neering, Heidelberg, Germany) as described previously.56,57 Briefly, three-dimensional images were obtained using the raster scan mode, and the manufacturer’s software was used to calculate the mean retinal thickness within the central 1 mm.

**SS-OCT and OCTA Images**

Axial length was measured using partial coherence interferometry (IOLMaster, Carl Zeiss Meditec, Inc., Dublin, CA, USA). SS-OCTA images within the nominal 12 × 12 mm square centered on the optic disc were acquired using Plex Elite 9000 (Carl Zeiss Meditec, Inc.) because hyperreflective spots or cotton-wool spots are delineated mainly around the optic disc.58 This imaging device, which operates at 100,000 A-scans/s and is equipped with a SS tunable laser with center wavelength between 1040 and 1060 nm, delineates motion contrast signals using optical microangiography (OMAG) algorithm.59 Sequential B-scans were obtained at a fixed position, followed by the calculation of variations in both intensity and phase information. Side-by-side B-scans allowed for the construction of three-dimensional OCTA images. The nominal 12 × 12 mm square was acquired with 500 × 500 A-scans and digitally converted to a 1024 × 1024 pixel array for further analyses.

We compared the characteristics of hyperreflective lesions between the macular and extramacular areas (Figs. 2, 3). We first defined hyperreflective lesions and evaluated their qualitative findings on structural OCT images that were simultaneously obtained. We created en-face structural OCT images in the superficial layer (from the inner limiting membrane [ILM] to the inner plexiform layer [IPL]) determined by the default setting of the manufacturer’s software. We defined swollen and hyperreflective spots in the superficial retinal layers on the en-face and B-scan OCT images as “hyperreflective lesions” (Figs. 2i–p). We measured the areas on superficial en-face images using the “Freehand selection” tool of ImageJ (NIH, Bethesda, MD, USA). Briefly, we manually traced the edge of each hyperreflective lesion. Then, pixels were quantified and converted to millimeters squared after the lateral length was corrected for axial length.40 The hyperreflective lesions resided from the nerve fiber layer (NFL) to various retinal layers, and we determined whether such lesions reached the outer plexiform layer (OPL). The arcuate hyporeflective bands proximal or distal to white spots on superficial en-face OCT images and corresponding dark bands on the pseudocolor SLO image were defined as the “NFL defect (NFLD)” as described previously (Fig. 4i, arrowheads).41,42

We manually evaluated the capillary perfusion status on en-face OCTA images. We therefore created en-face OCTA images in the deep layer (from the IPL to 110 μm above the retinal
FIGURE 2. Capillary nonperfusion in white spots and corresponding hyperreflective lesions within the macular and extramacular areas in a 68-year-old man with severe NPDR. (a–h) Raw images of 12 × 12 mm rectangles centered on the optic disc. White spots, including typical cotton-wool spots, on pseudocolor SLO images (a) correspond to hyperreflective spots in the superficial layer on OCT images (b). The OCTA images of the entire retinal layers (c) and the merged images (d) reveal the NPAs in the hyperreflective lesions. Arrowheads indicate arteriolar arcades spanning from the superficial to deep layers. (g, h) The macular or extramacular areas determined by arteriolar arcades were indicated in the OCTA images of the whole retinal layers. (i–l) The magnified images of the rectangles in the merged image (d). The extramacular hyperreflective lesions (arrows) are accompanied with NPAs in all layers that extend to the peripheral side. (m–p) The localized and lamellar NPA correspond to a hyperreflective lesion in the macula (arrows). B-scan images along the green arrows indicate that the extramacular hyperreflective lesions span from the NFL to the OPL (l), whereas the macular lesions were delineated mainly in the NFL (p). Scale bar: 2 mm.
FIGURE 3. The extramacular white spots in the progressive NPAs to the proximal side in a 47-year-old man with severe NPDR. (a–h) Raw images of 12 × 12 mm rectangles centered on the optic disc. Pseudocolor SLO, structural OCT, OCTA, and merged images at baseline (a–d) and 4 months (e–h). The magnified images of the rectangle in the merged images (d, h) at baseline (i) and 4 months (j) indicate that the NPAs progressed to the proximal (arrows) and distal (arrowheads) sides. (j) The white spots and corresponding hyperreflective lesions coincide with NPA progression to the proximal side (arrows) in the extramacular areas. Asterisk indicates hyperreflective lesions. Scale bar: 2 mm.
pigment epithelium (RPE)) and whole retinal layers (from the ILM to 70 μm above the RPE) according to the default setting of the manufacturer’s software. We determined the “NPAs in all layers” on the whole retinal en-face OCTA images (Fig. 4j). In addition, we compared the en-face OCTA images in the superficial layer and whole retinal layers and defined the capillary nonperfusion in the superficial layer alone as the “lamellar NPAs” (Fig. 4i). The NPAs in all layers were often delineated in the extramacular hyperreflective lesions and their distal areas (Fig. 5j). Such OCTA findings were defined as the “NPAs extending to the peripheral side” on the whole retinal en-face OCTA images.

Considering the perfusion boundary, we divided the macular and extramacular areas according to the large arterioles. Briefly, OCTA images delineated that large arterioles encompass the superficial and deep capillary layers.

Figure 4. OCT angiographic characteristics of a typical cotton-wool spot within the macular areas in a 47-year-old man with severe NPDR. (a–h) Raw images of 12 × 12 mm rectangles centering on the optic disc. Pseudocolor SLO image (a), structural OCT image in the superficial layer (b), and OCTA images in each layer (e–g). (f) The merged images of the superficial OCT image and OCTA images in each layer demonstrate that white spots and corresponding hyperreflective lesions were accompanied with the NPAs. (i, j) The magnified images of black rectangles presented in d. (i) A typical cotton-wool spot (arrows) in the macula is accompanied with lamellar and superficial NPAs and theNFLD (arrowheads). (j) A white spot (arrows) in the extramacular areas includes NPAs in all layers but not the accessory NFLD. Scale bar: 2 mm.
Diabetic NPAs in Extramacular White Spots on OCT

RESULTS

Characteristics of Hyperreflective Lesions in the Superficial Retinal Layers

We retrospectively reviewed 107 eyes of 64 patients with DR, and their characteristics are presented in Table 1. One or more white spots (κ coefficient = 1.000) on pseudocolor SLO images and corresponding hyperreflective lesions, which appeared to be swollen in the superficial en-face and B-scan OCT images, were delineated in 21 (29.6%) of 71 eyes with moderate NPDR, 20 (90.9%) of 22 with severe NPDR, and 8 (66.7%) of 12 with PDR. The signal strength index was 8 in 81 eyes or 9 in 26 eyes. We determined the macular and extramacular areas using arteriolar arcades (Figs. 2g, 2h), and the distance between the fovea to arteriolar arcades was 3.98 mm (3.74–4.18).

We then compared the morphologic OCT features of 136 hyperreflective lesions between the macular and extramacular areas (κ coefficient = 1.000) in only 49 eyes. Their shapes appeared to vary in the macular and extramacular areas (Figs. 2–4). The extramacular hyperreflective lesions exhibited greater areas (ICC = 0.988) and reached the OPL (κ coefficient = 0.893) more frequently compared with macular lesions (P < 0.001 and P = 0.002; Table 2). Thirty-seven (27.2%) of all 136 hyperreflective lesions were accompanied withNFLD (κ coefficient = 0.944), and such accessory findings were depicted more frequently in the macular areas compared with extramacular areas (P < 0.001; Table 3).

We further investigated the capillary nonperfusion in hyperreflective lesions (κ coefficient = 0.912) and often observed the superficial NPAs in hyperreflective lesions, some of which were accompanied with the deep NPAs (Figs. 4i, 4j). Seventeen (89.5%) of 19 hyperreflective lesions on OCT images had the NPAs in the superficial layer on corresponding OCTA images in the macular areas, whereas only 10 extramacular lesions (8.5%) were accompanied with lamellar NPAs (Table 3; Fig. 4). The NPAs in all layers were delineated in most (91.5%) of extramacular hyperreflective lesions (Fig. 4j), although complete NPAs were in only two macular lesions (10.5%). In addition, 78 (66.7%) of extramacular hyperreflective lesions were accompanied with NPAs extending to the peripheral side (κ coefficient = 1.000; Fig. 3j) compared with only one lesion with extensive NPAs in the macular areas (5.3%; P < 0.001).

The areas of hyperreflective lesions with the NPAs in all layers were greater compared with those with lamellar NPAs (P < 0.001; Table 2). Seventy-nine (72.5%) of 109 hyperreflective lesions with complete NPAs were accompanied with NPAs extending to the peripheral side; however, lesions with lamellar NPAs did not have extensive NPAs (P < 0.001; Table 2). Most lesions (85.2%) with lamellar NPAs were accompanied withNFLD, although only 14 (12.8%) of 109 lesions with the NPAs in all layers had accessoryNFLD (P < 0.001; Table 2). In addition, hyperreflective lesions with extensive NPAs com-

Statistical Analysis

Two retinal specialists evaluated all qualitative and quantitative parameters in a masked fashion. The average areas of such lesions were applied for further analyses. Any disagreement regarding qualitative parameters was discussed until consensus was achieved. To assess the interevaluator agreements, we calculated intraclass correlation coefficients (ICCs) or κ coefficients for quantitative or qualitative parameters. The results are expressed as the median (interquartile range [IQR]). Significant differences in the sampling distributions were determined using Fisher’s exact test. Mann-Whitney U test was employed for the comparisons of nonparametric parameters. P < 0.05 was considered significant.

TABLE 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes/patients</td>
<td>107/64</td>
</tr>
<tr>
<td>Age, median (IQR), yr</td>
<td>70 (61–73)</td>
</tr>
<tr>
<td>Sex</td>
<td>Men 43, Women 21</td>
</tr>
<tr>
<td>Hemoglobin A1c, median (IQR), %</td>
<td>7.5 (7.0–8.5)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>Absent: 12, Present: 52</td>
</tr>
<tr>
<td>LogMAR VA, median (IQR)</td>
<td>−0.079 (−0.079 to 0.071)</td>
</tr>
<tr>
<td>Lens status</td>
<td>Phakia: 40 eyes, Pseudophakia: 67 eyes</td>
</tr>
<tr>
<td>DR severity</td>
<td>Mild NPDR: 2 eyes, Moderate NPDR: 71 eyes, Severe NPDR: 22 eyes, PDR: 12 eyes</td>
</tr>
<tr>
<td>CSF thickness, median (IQR), μm</td>
<td>501 (266–352)</td>
</tr>
<tr>
<td>The distance between the fovea to arteriolar arcades (mm)</td>
<td>3.98 (3.74–4.18)</td>
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Histological publications documented a periartrial capillary-free zone along the large arterioles, indicating that retinal capillaries rarely cross these arterioles. We therefore hypothesized that larger arterioles correspond to the perfusion boundaries and defined the areas inside and outside the arteriolar arcades as the “macular areas” and “extramacular areas”, respectively, with respect to capillary perfusion (Figs. 2g, 2h). We then compared the OCT and OCTA findings of hyperreflective lesions between the macular and extramacular areas.

We also measured the distance between the fovea to the arteriolar arcades in the superior, superonasal, inferonasal, and inferior subfields using “straight line” tool of ImageJ. We converted pixels to lengths (millimeters), followed by the correction for axial length.

Statistical Analysis

Two retinal specialists evaluated all qualitative and quantitative parameters in a masked fashion. The average areas of such lesions were applied for further analyses. Any disagreement regarding qualitative parameters was discussed until consensus was achieved. To assess the interevaluator agreements, we calculated intraclass correlation coefficients (ICCs) or κ coefficients for quantitative or qualitative parameters. The results are expressed as the median (interquartile range [IQR]). Significant differences in the sampling distributions were determined using Fisher’s exact test. Mann-Whitney U test was employed for the comparisons of nonparametric parameters. P < 0.05 was considered significant.

TABLE 2. Relationship Between Lamellar Capillary Nonperfusion and OCT Findings in 136 White Spots

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lamellar NPA (n = 27)</th>
<th>NPA in All Layers (n = 109)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area on en-face OCT images, mm²</td>
<td>0.12 (0.07–0.23)</td>
<td>0.30 (0.20–0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depth reaching to the OPL, yes/no</td>
<td>7/20</td>
<td>76/33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Accessory NFLD, present/absent</td>
<td>23/4</td>
<td>14/95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NPA extending to the peripheral side on OCTA images, present/absent</td>
<td>0/27</td>
<td>79/50</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
prised greater areas \((P = 0.010)\) and were accompanied with NFLD less frequently \((P < 0.001)\) compared with those without extensive NPAs (Table 4).

**Association Between Hyperreflective Lesions and DR Severity**

Quantitative evaluation demonstrated that eyes with mild/moderate NPDR, severe NPDR, and PDR had 0(0–1), 3(2–5), and 1(0–2) hyperreflective lesions, respectively, and the number of hyperreflective lesions was greater in eyes with severe NPDR compared with eyes with mild/moderate NPDR or PDR \((P < 0.001\) or \(P = 0.034\), respectively).

**DISCUSSION**

It was widely accepted that cotton-wool spots at fundus examination correspond to fluorescein angiographic focal NPAs and histological cytoid bodies due to the acute or subacute circulation disturbances in NFL.\(^{13,14}\) In this study, white spots on fundus photographs corresponded to hyperreflective lesions on structure OCT images. Three-dimensional OCT angiographic analyses revealed that extramacular or macular hyperreflective lesions were accompanied with NPAs in all layers or lamellar NPAs in the superficial layer, respectively. In addition, some of these lesions spanned from the NFL to the OPL and others were limited to the NFL on retinal sectional OCT images. Interestingly, most hyperreflective lesions in the extramacular areas were located from the NFL to the OPL and were often accompanied with vertically and horizontally extensive NPAs. In contrast, such lesions in the macular areas included lamellar and localized NPAs and were often limited to the NFL. In vivo three-dimensional analyses of OCT and OCTA findings suggest that most extramacular hyperreflective lesions are novel OCT findings that are discriminated from histologically reported cotton-wool spots.

Cotton-wool spots and whitish opacification in RAO corresponded to histological cytoid bodies and cloudy swelling due to degenerative changes.\(^{15,14,44}\) In RAO, cellular hypoxia or malnutrition impair ion or water pumps in the plasma membrane, and the retinal parenchyma subsequently becomes turbid and swollen.\(^{15}\) Most extramacular white spots appeared as cotton-wool spots on fundus photographs in this study. However, most of extramacular hyperreflective lesions spanned from the NFL to the OPL and had the NPAs in all retinal capillary layers. In RAO, the reflectivity was increased from the NFL to the OPL on structural OCT images.\(^{19}\) With respect to capillary nonperfusion, the extramacular hyperreflective lesions might be similar to acute or subacute NPAs in all retinal layers in RAO. In contrast, most of macular hyperreflective lesions were delineated in the NFL and corresponded to the NPAs in the superficial layer. We therefore speculated that macular lesions are mostly cotton-wool spots, which are limited to the NFL due to the circulatory disturbance in the superficial layer.\(^{13,14}\)

Extramacular hyperreflective lesions exhibited vertically and horizontally extensive NPAs, whereas the lamellar NPAs were localized in the macular lesions. These differences might be dependent on the overlapping perfusion.\(^{34}\) The macular areas were nourished in an overlapping fashion by several arterioles via a seamless deep capillary network.\(^{30,31}\) In contrast, only one or two arterioles perfuse the superficial and deep capillaries in the extramacular areas.\(^{34}\) We therefore hypothesized that the overlap of perfusing arterioles may allow the remodeling of blood flow around the NPAs and reduce the likelihood of NPA progression in the macula. In the extramacular areas, the oriented blood flow in the artery-capillary-vein unit might not permit the rescue of perfusion. In addition, the seamless deep plexus might prevent the progression from the superficial to the deep capillary nonperfusion in the macula, whereas minimal NPAs can progress in both the superficial and deep layers simultaneously in the extramacular areas.

Extramacular hyperreflective lesions were often accompanied with NPAs extending to the peripheral side rather than the deep side. This finding suggests that hyperreflective lesions develop when NPAs progress toward the optic disc (Fig. 3). We hypothesized that the capillary nonperfusion propagates to the proximal and distal sides of the oriented artery-capillary-vein unit in the extramacular areas after minimal NPAs develop at random. Acute or subacute circulatory disturbance may lead to hyperreflective lesions, as shown in RAO\(^{15}\); however, chronic nonperfusion induces neuroglial degeneration.\(^9\) In the distal or downstream side of the NPAs, the mild and gradual decrease in perfusion pressure may result in chronic degeneration of neuroglial tissues.\(^9\) In contrast, the proximal or upstream side of the NPAs may be completely nourished by the high perfusion pressure, and the progression of capillary nonperfusion may lead to the acute or subacute malnutrition of neuroglial tissues and subsequent cloudy swelling.\(^{44,45}\) Resultantly, hyperreflective lesions develop in the proximal side rather than the distal side. Another possibility may be that ischemic changes or hyperreflective lesions are more definite

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**Table 3. Characteristics of 136 White Spots in the Macular or Extramacular Areas in 49 Eyes**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Macular Areas ((n = 19))</th>
<th>Extramacular Areas ((n = 117))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area on en-face OCT images, mm(^2)</td>
<td>0.11 (0.07–0.27)</td>
<td>0.29 (0.19–0.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depth reaching to the OPL, yes/no</td>
<td>5/14</td>
<td>78/39</td>
<td>0.002</td>
</tr>
<tr>
<td>Accessory NFLD, present/absent</td>
<td>19/0</td>
<td>18/99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perfusion status on OCTA images, lamellar NPA/NPA in all layers</td>
<td>17/2</td>
<td>10/107</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NPA extending to the peripheral side on OCTA images, present/absent</td>
<td>1/18</td>
<td>78/39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Table 4. Association of Extensive Capillary Nonperfusion With Other OCT Findings**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NPAs Extending to the Peripheral Side</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area on en-face OCT images, mm(^2)</td>
<td>Present ((n = 79))</td>
<td>Absent ((n = 57))</td>
</tr>
<tr>
<td>Depth reaching to the OPL, yes/no</td>
<td>0.32 (0.21–0.58)</td>
<td>0.22 (0.11–0.39)</td>
</tr>
<tr>
<td>Accessory NFLD, present/absent</td>
<td>51/28</td>
<td>32/25</td>
</tr>
<tr>
<td>NPA extending to the peripheral side on OCTA images, present/absent</td>
<td>8/71</td>
<td>29/28</td>
</tr>
</tbody>
</table>
in the thick retinas, which are nourished by retinal vessels rather than choroidal vessels.

The number of hyperreflective lesions was greater in eyes with severe NPDR compared with those with mild/moderate NPDR. This finding may be consistent with the association between these lesions and NPDR to some extent. Eyes with PDR had fewer lesions compared with severe NPDR. We hypothesized that hyperreflective lesions develop during NPA progression and disappear due to the degenerative processes. Further longitudinal studies should reveal the processes of synchronized degeneration of the neurovascular unit and the clinical relevance to predict the development of neovascularization.42,46

There are several limitations to this retrospective study with a small population. We just characterized the structural changes in neurovascular components, and further study should elucidate the structural-functional relationship. We defined the areas without flow signals on OCTA images as the NPAs in this study. The absence of flow signals may mean the NPAs or the fixed interscan time of this OCTA device may depict the blood flow with a limited velocity alone.23 Further multimodal imaging including FA would contribute to a better understanding of capillary nonperfusion. Poor images in the peripheral areas influence the quality of image acquisition. Advances in fundus imaging should allow wider OCTA images to delineate the hyperreflective lesions in more peripheral areas. Incorrect image processing might occasionally occur due to the specific methods used to remove the projection artifacts or the segmentation errors caused by lesions at the vitreoretinal interface and intraretinal lesions in DME.47,48

The parameters were manually assessed. Both eyes were included in 43 cases, which correspond to the “within subjects” factor.49 The inclusion of these factors in the data analyses might affect the accuracy of data evaluation and analyses. Future prospective and large-scale studies should be planned to confirm the generalizability to other populations and other OCTA devices and to develop automatic methods to evaluate these lesions.

In conclusion, for the first time, we documented the characteristics of the extramacular white spots and corresponding hyperreflective lesions in DR, which may be discriminated from typical cotton-wool spots, on SS-OCTA images. Given that these lesions were associated with the pathogenesis of NPAs, future studies should elucidate their clinical relevance in DR severity or predictions of PDR development.

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References


