Projection-Resolved OCT Angiography of Microvascular Changes in Paracentral Acute Middle Maculopathy and Acute Macular Neuroretinopathy

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Purpose. To identify the microvascular changes associated with paracentral acute middle maculopathy (PAMM) and acute macular neuroretinopathy (AMN) and to improve our understanding of the relevant involvement of the three retinal capillary plexuses using projection-resolved optical coherence tomography angiography (PR-OCTA).

Methods. This was a retrospective study of 18 eyes with AMN or PAMM imaged with OCTA. We used cross-sectional PR-OCTA to localize reduced flow signal to the superficial (SCP), middle (MCP), or deep capillary plexus (DCP) or choriocapillaris that corresponded to inner retinal PAMM or outer retinal AMN lesions on OCT.

Results. Five eyes with AMN showed outer retinal disruption on OCT associated with reduced DCP flow signal. All three eyes with AMN and follow-up had recovery of DCP flow. Thirteen eyes with PAMM showed middle retinal disruption on OCT associated with reduced flow signal in both the MCP and DCP. Of these, five also had reduced flow signal in the SCP. All 10 eyes with PAMM and follow-up showed variable recovery of flow signal in one or more plexuses. PAMM reperfusion was primarily arterial in nature. Three eyes with PAMM and no evidence of MCP reperfusion experienced severe thinning of the inner nuclear layer (INL), while seven eyes with robust MCP flow signal recovery showed relative preservation of INL thickness.

Conclusions. Using PR-OCTA, we found that AMN was associated with reduced DCP flow signal, while PAMM was associated with reduced MCP and DCP flow signal and occasionally the SCP. The MCP appears to be important in sustaining INL thickness in these eyes.

Keywords: paracentral acute middle maculopathy, acute macular neuroretinopathy, OCT, projection-resolved optical coherence tomography angiography, OCTA, PAMM, AMN

Paracentral acute middle maculopathy (PAMM) and acute macular neuroretinopathy (AMN) are two clinical entities that present with characteristic, hyporeflective paracentral lesions on infrared imaging (IR) with corresponding scotomas in vision.1,2 Despite the similarities on en face IR, these entities can be distinguished using spectral-domain optical coherence tomography (SD-OCT). AMN, originally described by Bos and Deutman3 and further characterized by Fawzi et al.,4 presents with hyperreflectivity in the outer plexiform layer (OPL) and outer nuclear layer (ONL) on SD-OCT.1,2,5 Over time, ONL reflectivity recovers and lesion progresses to disruption of the inner segment/outer segment (IS/OS) and OS/retinal pigment epithelium (OS/RPE) junctions with chronic thinning of the ONL. Hansen and colleagues6 found that the outer retinal involvement in the later stages of AMN correspond to either reduced cone density or reduced cone wave-guiding on adaptive optics scanning laser ophthalmoscopy. In contrast, PAMM lesions, originally characterized by Sarraf et al.,7 present with hyperreflectivity of the inner plexiform (IPL) and inner nuclear layer (INL), and progress to INL thinning without outer retinal involvement.7 The underlying and precipitating pathologies associated with these lesions vary widely, but they generally share a vascular origin.8–10 OCT angiography (OCTA) studies have shown that both PAMM and AMN lesions are associated with capillary vascular occlusions.9 However, the primary capillary plexus affected in these entities remains an area of great controversy, and the possibilities include the superficial (SCP), middle (MCP), and deep capillary plexuses (DCP) of the retina, as well as the choriocapillaris. PAMM has been associated with reduced blood flow of the SCP and DCP;12 MCP alone,7 or MCP and DCP.13,9–11 Similarly, AMN has been associated with occlusion of the DCP12 or choriocapillaris.13,14 The two major confounding factors in all these studies are projection artifacts cast from superficial blood vessels onto the deeper layers, and artifactual OCT signal attenuation underneath INL/ONL hyperreflective lesions. These issues are further complicated by accentuation of flow projection artifacts within OCT hyperreflective lesions.15

In order to better delineate the capillary plexuses and to overcome these challenges, we used a version of projection-
resolved (PR)-OCTA, an algorithm developed by Zhang et al.,\textsuperscript{16} which reduces the projection artifacts while preserving the continuity of the middle and deep capillaries.\textsuperscript{12,17} The goal of our study was to employ PR-OCTA to elucidate the capillary plexus/es involved in AMN and PAMM. In a subcohort of eyes that underwent repeat OCTA imaging during follow-up, we also explored the potential correlations between capillary reperfusion on OCTA and structural integrity of the relevant retinal layers on OCT in PAMM and AMN.

**METHODS**

This was a retrospective analysis of patients diagnosed with AMN or PAMM recruited in the Department of Ophthalmology at Northwestern University in Chicago, Illinois, and the Department of Ophthalmology at the Mayo Clinic in Rochester, Minnesota, between October 2015 and September 2017. This study was approved by the Institutional Review Board of Northwestern University and Mayo Clinic, followed the tenets of the Declaration of Helsinki, and was performed in accordance with the Health Insurance Portability and Accountability Act regulations.

Inclusion in this study required a diagnosis of PAMM or AMN, based on clinical examination and multimodal imaging findings, including a characteristic wedge-shaped lesion seen on IR. PAMM diagnosis required the presence of either hyperreflectivity at the INL/OPL junction, or INL thinning on SD-OCT. AMN diagnosis required either hyperreflectivity at the OPL/ONL junction, or ONL thinning with subtle photoreceptor attenuation on SD-OCT. We included all cases of AMN and PAMM regardless of underlying diagnosis. We excluded patients with a history of retinal surgery.

All patients underwent a complete ophthalmologic examination, including best-corrected visual acuity (BCVA; Snellen charts), slit-lamp biomicroscopy, indirect fundus ophthalmoscopy, and retinal imaging. IR and SD-OCT were performed using Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany). OCTA examinations were performed using the RTVue-XR Avanti OCTA system (Optovue, Inc., Fremont, CA, USA) with split-spectrum amplitude-decorrelation angiography (SSADA) software.\textsuperscript{18,19} This device has a center wavelength of 840 nm with a full width at half-maximum bandwidth of 45 nm, and an A-scan rate of 70,000 scans per second. Two consecutive B-scans (M-B frames), each containing 304 A-scans, were captured at each sampling location to form a three-dimensional OCTA data cube of 304 B-scans. OCTA was performed in all patients with a scanning area of 3 × 3 mm² centered on the fovea or the lesion (parafocal), using IR images as a guide. In this study, we included only eyes with a signal strength index score above 50 and minimal to no motion artifact.

We applied a projection-resolved (PR-OCTA) algorithm in postprocessing to reduce projection artifacts from superficial vessels projected onto the deeper capillary layers and to reduce projection artifacts within hyperreflective lesions. We implemented a version of the PR-OCTA algorithm developed by Zhang et al.\textsuperscript{12,16,17} These authors noted that projection tail artifacts in OCTA have lower decorrelation values compared to real vessels.\textsuperscript{17,20} Taking advantage of this observation, the algorithm searches each A-scan for successive, high-valued peaks, which correspond to real vessels. Only the OCTA decorrelation values at the peak positions are kept, while the remaining pixels in each A-scan are set to zero, resulting in the removal of projection artifacts.

After applying PR-OCTA, cross-sectional B-scans of the retina with flow overlay were closely evaluated for flow signal at each of the plexuses (SCP, MCP, DCP, and choriocapillaris). Flow signal from the ILM to the superficial portion of the IPL was considered SCP. Flow from the deep portion of IPL to the superficial portion of INL was considered MCP, and flow from the deep portion of INL to the OPL was considered DCP, as previously described.\textsuperscript{18-21} Flow signal immediately below the retinal pigment epithelium (RPE) was considered choriocapillaris.\textsuperscript{22} A single grader (S.C.) examined the cross-sectional PR-OCTA for capillary nonperfusion, defined as absence or reduction of flow signals in the anatomic locations of the capillary plexuses described above. To improve the reliability of our assessment, confirmation of capillary nonperfusion required consistently absent flow signal at the relevant plexus in three adjacent B-scans.

For 13 eyes that had follow-up OCTA, a single grader (S.C.) examined the affected capillary plexuses for evidence of capillary reperfusion, defined as appearance of flow signal at the follow-up visits in capillary segments where flow was absent at baseline. Follow-up B-scans were also assessed for the integrity of the retinal layers at presentation of follow-up. In eyes with reperfusion, another grader (P.L.N.) traced the newly reperfused blood vessels back to their main arteriolar or venular source using a combination of cross-sectional and en face OCTA, as well as IR and color fundus images.

**RESULTS**

Of a total of 22 eyes of 21 subjects imaged for this study, 4 eyes were excluded due to signal strength index (SSI) below 50 or significant artifacts on OCTA images, leaving 18 eyes of 18 subjects for analysis (Table). Of those 18 eyes, 13 had follow-up imaging. Five eyes were diagnosed with AMN and 13 eyes were diagnosed with PAMM (Table). Patient ages ranged from 22 to 83 years (mean 47.5 ± 17.7 years; median 47). Three patients had a history of migraines and/or headaches, two patients had a history of hypertension, and one patient had a history of diabetes. At baseline, mean BCVA was 20/25 Snellen equivalent (Table).

In all five eyes with AMN, hyperreflectivity and/or thinning of the ONL was observed on SD-OCT. All five eyes had reduced DCP flow signal, along with normal SCP, MCP, and choriocapillaris flow signal in the area of the lesion (Figs. 1, 2). All three eyes with follow-up imaging showed partial recovery of DCP capillary flow signal, along with variable ONL thinning and IS/OS and/or OS/RPE disruption (Table; Fig. 2). We were unable to track the type of blood vessels (arteriole or venule) associated with reperfusion in AMN lesions, due to inadequate resolution of OCTA at the deeper capillaries (n = 3).

In eyes with PAMM, IPL hyperreflectivity was observed on SD-OCT in all eyes imaged during acute PAMM (7 of 13 eyes). Thinning of the INL was present in all eyes with PAMM either at baseline or during follow-up SD-OCT (13 of 13 eyes). All 13 eyes with PAMM had reduced MCP and DCP flow signal in the area of the lesion (Figs. 3–7). We found that the PR-OCTA algorithm was more effective at eliminating the projection artifacts associated with hyperreflective lesions than the commercial software projection artifact removal (PAR; Optovue, Inc.) algorithm (Fig. 3). Five of 13 eyes had reduced flow signal at all three capillary plexuses (SCP, MCP, and DCP) (Figs. 6, 7), of which 4 eyes had additional findings of thinning of the ganglion cell complex (GCC). Of the 10 eyes with follow-up studies in PAMM, 7 had partial recovery of MCP and DCP capillary flow signal (Figs. 4, 5, 7; Table). The remaining three eyes had partial recovery of flow signal at the level of the SCP only (Figs. 6, 7). In general, lesions with more profound reperfusion of the MCP had less severe INL thinning on OCT (Fig. 7).
## Table: Demographics and Ocular Findings in Patients with Paracentral Acute Middle Maculopathy (PAMM) and Acute Macular Neuroretinopathy (AMN)

| Case No. | Age/Sex | Diagnosis | Principal Complaint | Systemic Disease | Eye Disease | Eye BCVA | Baseline OCT | Reduced Capillary Flow Signal | Follow-Up Appointment | Follow-Up BCVA | Follow-Up OCT | Recovering Capillary Flow Signal |
|----------|---------|-----------|---------------------|------------------|------------|----------|-------------|--------------------------|---------------------|---------------|--------------|-------------------------------|
| 1        | 47/F    | AMN       | Black spot in vision OS for 3 mo | None | None | OS 20/20 | Thin ONL, IS/OS disruption | DCP | None | N/A | N/A | N/A |
| 2        | 33/F    | AMN       | Blind spot OU in center of vision for 5 d | Migraines | None | OD 20/20 | Hyperreflective ONL | DCP | 1 wk | 20/20 | Thin ONL, IS/OS disruption | DCP |
| 3        | 32/F    | AMN       | Constant OS temporal scotoma for 2 wk | History of floaters | None | OS 20/20 | Hyperreflective ONL, IS/OS disruption | DCP | 8 wk | 20/20 | Thin ONL, IS/OS disruption | DCP |
| 4        | 59/F    | AMN       | Central scotoma OD | Hairy cell lymphoma | Gatactars; dry eye syndrome | OD 20/50 – 2 | Hyperreflective and thin ONL | DCP | None | N/A | N/A | N/A |
| 5        | 49/F    | AMN       | Motor vehicle accident 3 d prior; vision loss | mild HTN | None | OS 20/25 – 2 | Hyperreflective ONL, IS/OS disruption | DCP | 4 wk | 20/20 OU | Thin ONL, IS/OS disruption | DCP |
| 6        | 36/M    | PAMM      | Cloudy vision OD, morning headache, same day | Excessive of alcohol and caffeine intake | History of LASIK OU for high myopia | OD CF at 3’ | Hyperreflective INL | MCP and DCP | 6 wk; 14 wk | 20/15 – 2 | Some INL thinning, Hyperreflective INL | MCP and DCP |
| 7        | 22/F    | PAMM      | OD inferior blurred vision and new floaters; central gray dots for 2 d | Headaches | History of LASIK OU for high myopia | OD 20/20 | Hyperreflective INL | MCP and DCP | 3 d; 4 wk | 20/20 | Some INL thinning, hyperreflective INL | MCP and DCP |
| 8        | 32/F    | PAMM      | OD flashes and floaters with headache for 1 d; distorted central vision | Migraines; headaches | History of floaters | OD 20/20 | Thin INL | MCP and DCP | 8 wk | 20/20 | Thin INL | MCP and DCP |
| 9        | 47/F    | PAMM      | Off-center scotomas OD | Type 2 DM | History of LASIK OU for high myopia; BRAO OD | OD 20/20 | Hyperreflective and thin INL | SCP and MCP and DCP | 16 wk | 20/40 | Some INL thinning, thin GCC | SCP and MCP and DCP |
| 10       | 57/F    | PAMM      | 2 wk of cloudy and darker vision | Type 2 DM; hyperlipidemia; HTN | Moderate NPDR; DME | OD 20/25 | Hyperreflective INL | MCP and DCP | 8 wk; 16 wk | 20/25 + 1 | Hyperreflective and thin INL | MCP and DCP |
| 11       | 47/F    | PAMM      | Referred visit | Type 2 DM; breast cancer; chronic renal disease; stage III | HTN retinopathy; vascular attenuation; arteriolar narrowing | OD 20/25 – 1 | Thin INL | MCP and DCP | None | N/A | N/A | N/A | N/A |

**Microvascular Changes in PAMM and AMN**

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| Case No. | Age/Sex | Diagnosis | Principal Complaint | Systemic Disease | Eye Disease | Baseline BCVA | Baseline OCT | Reduced Capillary Flow Signal | Follow-Up Appointment | Follow-Up BCVA | Follow-Up OCT | Recovering Capillary Flow Signal |
|----------|---------|-----------|---------------------|------------------|-------------|---------------|--------------|-----------------------------|---------------------|--------------|-------------|--------------------------------|
| 12       | 74/F    | PAMM      | Wavy lines on Amsler grid OD | Colon cancer, cecal adenocarcinoma stage I endometrial cancer | OD | 20/25 −3 | Hyperreflective and thin INL | MCP and DCP | 16 wk | 20/25 −2 | Some INL thinning | MCP and DCP |
| 13       | 83/F    | PAMM      | Blurry, cloudy vision OS for 2 mo | Atherosclerosis/ hypercholesterolemia; HTN | OS | 20/25 | Thin INL | SCP and MCP and DCP | 16 wk | 20/40 +1 | Thin INL, thin GCC | SCP |
| 14       | 58/M    | PAMM      | Superior scotoma OS after workout 2 wk prior | Inflammatory arthritis; carotid Doppler with early, <60%, blockage | OS | 20/20 | Hyperreflective INL | SCP and MCP and DCP | 4 wk | 20/20 | Thin INL | SCP |
| 15       | 30/F    | PAMM      | New gray-appearing floater OS for 2 wk | None; pregnancy, 26 wk | None | 20/20 −1 | Hyperreflective INL | SCP and MCP and DCP | 12 wk | 20/20 −2 (pinhole)/20/60 −2 | Hyperreflective and thin INL, thin GCC | SCP |
| 16       | 78/F    | PAMM      | Purple spot in vision, 1 y prior | Prediabetic; HTN | OS | 20/20 | Thin INL | MCP and DCP | None | N/A | N/A | N/A |
| 17       | 36/F    | PAMM      | Seeing occasional floaters | Lupus | OS | 20/25 | Thin INL | MCP and DCP | None | N/A | N/A | N/A |
| 18       | 35/F    | PAMM      | Blurry vision 1 mo prior | Type 2 DM | OD | 20/20 −3 | Hyperreflective INL | SCP and MCP and DCP | 24 wk | 20/20 −2 | Some INL thinning, thin GCC | MCP and DCP |

If duration of complaint is not stated in Principle Complaint column, duration was unknown. BRVO, branch retinal vein occlusion; BRAO, branch retinal artery occlusion; DM, diabetes mellitus; DME, diabetic macular edema; HTN, hypertension; N/A, not applicable; NPDR, nonproliferative diabetic retinopathy; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; PCIOL, posterior chamber intraocular lens; PVD, posterior vitreous detachment.
Of the 10 eyes with PAMM and follow-up studies, reperfused capillaries could be traced to arterioles in 3 eyes (Figs. 5, 6). In one of these eyes, we traced the reperfused capillaries to both venules and arterioles. Figure 5 shows an example of robust reperfusion of the MCP with largely intact INL on follow-up. Figure 6 shows an example of PAMM with reduced flow signal in all three plexuses. During follow-up, reperfusion was limited to the SCP, with thinning of the INL as well as the GCC. We were unable to identify the type of vessel associated with reperfusion in the other eyes due to the limited resolution of the OCTA device (n = 7).

Four representative cases of AMN and PAMM are described in detail below, and all cases are summarized in the Table.

Case 1
A 47-year-old woman presented with a several-month symptom of a “spot with a slight ripple effect in her left eye.” SD-OCT imaging revealed focal disruption at the IS/OS and OS/RPE junctions nasally, suggesting the diagnosis of AMN. Visual acuity was 20/20 in both eyes. PR-OCTA revealed reduced DCP flow signal throughout the lesion, but preservation of the SCP, MCP, and choriocapillaris (Fig. 1F, circles).

Case 2
A 33-year-old woman presented with an acute onset of central scotomas in her right eye. Visual acuity was 20/20 in both eyes. Anterior segment and dilated examinations were unremarkable except for the central scotomas. SD-OCT imaging revealed a hyperreflective band in the OPL/ONL junction, consistent with AMN. PR-OCTA imaging revealed reduced DCP flow signal surrounding this hyperreflective band with preservation of the SCP, MCP, and choriocapillaris (Fig. 2B, yellow circle). SD-OCT imaging 1 week later revealed resolution of the hyperreflective band at the ONL, along with decreased reflectivity of the IS/OS and OS/RPE. PR-OCTA imaging revealed recovery of the DCP flow signal in the area of the lesion (Fig. 2D, green circles).
Case 6

A 36-year-old male presented with cloudy vision in his right eye that started in the morning with complaint of headache. The patient had a history of alcoholism, excessive caffeine use, hypertension (134 systolic/85 diastolic), and myopic LASIK. The patient was diagnosed with central retinal vein occlusion in his right eye. Visual acuity in the right eye was 20/20. SD-OCT revealed a hyperreflective band at the INL, consistent with central retinal vein occlusion.

**Figure 3.** Projection-resolved optical coherence tomography angiography (PR-OCTA) of paracentral acute middle maculopathy (PAMM). Case 6: 36-year-old man presented with acute scotoma noticed after strenuous exercise. On examination, faint grayish lesions were seen in the macula that followed the distribution of tortuous venules as well as one small hemorrhage. (A) Infrared reflectance (IR) of healthy left eye with arrows showing location of B-scans. (B) Spectral-domain optical coherence tomography (SD-OCT) of the healthy fovea. (C) PR-OCTA of three consecutive scans of the foveal region with red flow overlay shows healthy distribution of flow signals in three capillary plexuses. (D) OCTA with projection artifact removal (PAR) of same three scans shows similar flow signal with more projection tailing. (E) IR showing characteristic PAMM lesions following venules in the parafovea. (F) SD-OCT reveals hyperreflectivity of inner nuclear layer (INL) (circle). (G) PR-OCTA of three consecutive B-scans with red flow overlay at presentation shows reduced flow signal in the middle (MCP) and deep capillary plexuses (DCP) corresponding to PAMM lesions (circles). The superficial (SCP) appears normal and the choriocapillaris cannot be assessed due to signal attenuation from the hyperreflective INL lesion. (H) OCTA with PAR of same three scans shows increased projection artifact in hyperreflective INL lesion.

**Figure 4.** Recovery of middle (MCP) and deep capillary plexus (DCP) flow signal in paracentral acute middle maculopathy (PAMM). Case 7: 22-year-old woman presented with 24-hour history of acute scotoma and flashing lights. On examination, faint grayish-white lesions were seen in the superior macula, adjacent to the tortuous retinal venules. On follow-up, there was gradual decrease in tortuosity and lesion intensity over time. (A) Infrared reflectance (IR) showing characteristic PAMM lesions following superior macular venules (yellow circles) and location of B-scans (arrows). (B) Projection-resolved optical coherence tomography angiography (PR-OCTA) of three consecutive scans of the PAMM lesion with red flow overlay. PR-OCTA reveals hyperreflectivity of the inner nuclear layer (INL) with reduced flow signal of the MCP and DCP (yellow circles). (C) IR image at 3-day follow-up. (D) PR-OCTA of the same location shows less hyperreflectivity of the INL and partial recovery of flow signal in the MCP and DCP (yellow circles). (E) IR image at 1-month follow-up shows attenuation of the PAMM lesions. (F) PR-OCTA of the same location shows further decreased INL hyperreflectivity and more prominent recovery of the MCP and DCP flow signals within the lesions (green circles).
with PAMM. PR-OCTA revealed reduced MCP and DCP flow signal with relative preservation of DCP flow signal in the areas immediately surrounding the lesion (Fig. 3G). The hyperreflectivity of the INL (top of PAMM lesion) accentuated the projection artifacts from the SCP, which were incompletely eliminated in this region. The choriocapillaris could not be evaluated due to signal attenuation underlying the hyperreflective PAMM lesion.

**Case 7**

A 22-year-old woman with a history of LASIK for high myopia presented with a complaint of right eye inferior half blurred vision and some flashing lights. Visual acuity was 20/20 in both eyes. SD-OCT revealed multiple parafoveal hyperreflective bands at the INL, suggesting PAMM. PR-OCTA revealed reduced MCP and DCP flow signal, but preservation of the SCP (Fig. 4B). Choriocapillaris flow signal could not be accurately assessed due to signal attenuation underlying acute PAMM (Fig. 4B). Follow-up 3 days later revealed similar hyperreflective bands at the INL on SD-OCT and reduced DCP flow signal on PR-OCTA (Fig. 4D). Interestingly, at this point there was some MCP flow signal recovery in middle of the lesion (Fig. 4D). Follow-up 1 month later revealed further resolution of the hyperreflective bands at the INL on SD-OCT (Fig. 4F). PR-OCTA revealed further recovery of the MCP and DCP flow signal (Fig. 4F).

**FIGURE 5.** Retinal arteriolar to capillary flow signal recovery in the middle capillary plexus (MCP) in paracentral acute middle maculopathy (PAMM). Case 6: On examination, we identified faint grayish lesions and a single small intraretinal hemorrhage. Over the following 6 weeks, there was gradual fading of the whitish lesions and hemorrhage. (A) Projection-resolved optical coherence tomography angiography (PR-OCTA) through PAMM lesion with red flow overlay. PR-OCTA shows hyperreflectivity of the inner nuclear layer (INL) and reduced flow signal in the MCP (yellow circle). (B) PR-OCTA of the same location at 6-week follow-up shows increased flow signal in MCP in location of PAMM lesion (green circle). The hyperreflectivity of the INL is reduced and the thickness of the INL is retained. (C) En face OCTA segmented at the MCP. (D) En face OCTA segmented at the MCP at 6 weeks shows increased flow corresponding to the location on cross section (green circle). (E) En face OCTA segmented at the SCP. (F) En face OCTA segmented at the SCP at 6 weeks shows the connection between MCP vessels with restored flow signal and the retinal arteriole (arrow). (G) 3 × 3 mm² en face OCTA of the SCP at 6-week follow-up with location of enlarged inset shown in (C–F) (green box). (H) Color fundus photo with location of OCTA scan (green box), where we can trace the capillary to feeding arteriole and to the retinal artery (arrows).

**FIGURE 6.** Retinal arteriolar flow signal recovery at the superficial capillary plexus (SCP) in paracentral acute middle maculopathy (PAMM). Case 15: On examination, a grayish wedge-shaped lesion was seen superior to the fovea, which was attenuated at 3 months. (A) Projection-resolved optical coherence tomography angiography (PR-OCTA) through PAMM lesion with red flow signal overlay. PR-OCTA shows hyperreflectivity of the inner nuclear layer (INL) corresponding to reduced flow signal in the SCP middle (MCP) and deep capillary plexuses (DCP) (yellow circle). (B) PR-OCTA of the same location at 3-month follow-up shows increased red flow in the superficial capillary plexus (SCP) (green circle). The MCP and/or DCP are only slightly restored and the GCC and INL are thinner. It is not possible to distinguish with any certainty whether the increased flow signal below the inner plexiform layer is from the MCP, DCP, or both because of INL thinning. (C) En face OCTA segmented at the SCP at baseline. (D) En face OCTA of the SCP at 3 months shows increased flow signal corresponding to the location on cross section (green circle) and illustrating connection between the retinal arteriole (arrow) and capillaries with flow signal recovery. (E) 3 × 3 mm² en face OCTA of the SCP at 3 months with location of enlarged inset shown in (C, D) (green box). (F) Infrared reflectance image with location of OCTA scan (green box), tracing the relevant branch arteriole to a larger second-order retinal arteriole (arrows).
**DISCUSSION**

Using PR-OCTA, we found that PAMM lesions were associated with reduced MCP and DCP flow signals, with additional reduced flow signal in the SCP in some eyes. In eyes with PAMM and severe INL thinning on follow-up, we observed a relative paucity of reperfusion at the MCP. In these eyes, persistent ischemia at the MCP could explain the subsequent INL thinning seen in PAMM. In contrast, AMN lesions in our study were associated with reduced DCP flow signals, confirming isolated focal DCP ischemia at the photoreceptor axons in the OPL as the trigger for AMN pathology, ultimately compromising the entire photoreceptor unit with long-term OPL thinning. It is noteworthy that all AMN and PAMM lesions in our longitudinal dataset had evidence of variable recovery of capillary flow signal at the different capillary levels (Table; Figs. 2, 4–7).

The vascular pathology in PAMM/AMN remains an area of great debate. Fawzi et al. noted the earliest lesion in AMN at the level of the OPL, and suggested ischemic insult to the capillary network (DCP) located at the outer border of the INL. This initial OPL lesion is followed by disruption of the IS/OS and OS/RPE along with appearance of the hyperreflectivity on IR. With time, these eyes develop ONL thinning, presumably as ischemic photoreceptor cell bodies atrophy. In contrast, several groups have suggested choriocapillaris nonperfusion in AMN. Notably, however, these studies used large OCTA scans (6 × 6 mm²), which have limited scan density with limited resolution for smaller capillaries, especially those in the DCP. Furthermore, the representative OCTA B-scans in the study by Lee et al. did not reveal distinctive lack of choriocapillaris flow in the area of the AMN lesions compared to adjacent retina. These studies relied largely on en face images of the choriocapillaris, and did not account for attenuation of OCT signal from hyperreflectivity in the overlying retina (Fig. 8). Hyperreflectivity in the inner retina from PAMM or AMN attenuates the OCT (and OCTA) signal, which appears as nonspecific hyperreflectivity on en face OCT (and OCTA) at the level of the RPE and choriocapillaris. Therefore, signal attenuation could largely explain the apparent choriocapillaris flow voids in these aforementioned studies. Furthermore, the use of en face OCTA to identify the affected plexus in PAMM or AMN can be unreliable, since segmentation and projection artifacts are generally exacerbated because of focal thinning and hyperreflective lesions, respectively. In contrast, the use of cross-sectional PR-OCTA in our study greatly overcomes these potential errors.

Using cross-sectional B-scans analyzed by PR-OCTA, our data show clear evidence of DCP nonperfusion, which correlates precisely with the AMN lesion, while the choriocapillaris was either normal or could not be assessed due to shadowing from overlying hyperreflective lesions (Figs. 1, 2). In areas immediately adjacent to the AMN lesion, the DCP was preserved, implying focal DCP flow signal attenuation in AMN lesions. In eyes with follow-up imaging, we found robust recovery of DCP flow signal in areas of the original AMN lesion (within 6 weeks), which suggests a rather transient vaso-occlusive event. This reperfusion could also explain the lack of flow abnormalities detected at the DCP when imaging AMN during recovery (Fig. 2).

Sarraf et al. in 2013 first characterized PAMM as hyperreflective lesions at the IPL/INL junction and suggested that this location of the hyperreflectivity corresponded with occlusion of the SCP. Since then, Sridhar et al. have suggested nonperfusion of both the SCP and DCP in PAMM with subsequent long-term pruning of the deeper capillary plexuses. In contrast, Chen et al. suggested that PAMM was associated with ischemia of the MCP and DCP. Using PR-OCTA, our data show a wide range of abnormalities in PAMM. The consistent evidence of reduction of MCP and DCP flow signal corresponding precisely to the PAMM lesions in all affected eyes suggests that the pathogenesis of PAMM and location of...
pathology start at the MCP with secondary downstream changes in the DCP (Figs. 3–5). Interestingly, we found additionally reduced SCP flow signal in five of these eyes, among which four of the five eyes had subsequent thinning of the GCC (Fig. 6). More specifically, eyes in which reperfusion did not occur at the MCP showed more severe INL thinning (Figs. 6, 7), while eyes with more robust MCP reperfusion showed relative preservation of INL thickness (Figs. 4, 5, 7).

This study was limited by a relatively small sample size, explainable by the imposed stringent image quality criteria. Another limitation is lack of OCTA imaging at the onset of AMN or PAMM in 7/18 eyes, precluding the assessment of perfusion status in these eyes at its worst. Also, only 13/18 eyes had follow-up imaging to facilitate studies of reperfusion. Future prospective studies with larger cohorts and standardized follow-up intervals could be important to further explore these questions in greater detail.

In conclusion, using PR-OCTA, we found that PAMM lesions were associated with reduced flow signal in both the MCP and DCP, with occasional involvement of the SCP. AMN was associated with reduced flow signal limited to the DCP. We found that eyes experienced a wide range of reperfusion at the different plexuses. In PAMM, we could trace the reperfused capillaries to arteriolar origin, with more robust reperfusion of the MCP appearing to mitigate INL thinning. Similarly, during AMN recovery, as the lesion transitions from hyperreflectivity to ONL thinning, we found partial recovery of flow signal at the DCP. Our findings illustrate the complexity of ischemic macular pathology, the role of reperfusion, and the importance of projection artifact removal and cross-sectional OCTA to facilitate accurate analysis of flow at the macular capillaries.

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FIGURE 8. Hyperreflectivity of paracentral acute middle maculopathy (PAMM) lesion attenuates underlying optical coherence tomography (OCT) signal and decorrelation signal at the level of the choroid. Case 7: On examination, grayish lesions were seen following tortuous retinal venules. (A) En face OCT angiography (OCTA) at the level of choriocapillaris with location of B-scan (yellow line) and cross-sectional OCTA below with flow signal overlay in red and segmentation boundaries (red lines). The area of reduced choriocapillaris flow (hypo-intense) on en face OCTA is located below areas of hyperreflectivity of the inner nuclear layer (INL), which is seen on cross-sectional OCTA as reduction of red flow signal underlying these areas. (B) En face structural OCT segmented at the level of the retinal pigment epithelium (RPE) with cross-sectional OCT showing segmentation boundaries (red lines). The areas of attenuated decorrelation signal in (A) correspond to areas of OCT signal attenuation in (B), which are located under the hyperreflective lesions of the INL.
References

1. Chen X, Rahimy E, Sergott RC, et al. Spectrum of retinal vascular diseases associated with paracentral acute middle maculopathy. *Am J Ophthalmol*. 2015;160:26–34.e1.

2. Sridhar J, Shahlaee A, Rahimy E, et al. Optical coherence tomography angiography and en face optical coherence tomography features of paracentral acute middle maculopathy. *Am J Ophthalmol*. 2015;160:1259–1268.e2.

3. Bos PJ, Deutman AF. Acute macular neuroretinopathy. *Am J Ophthalmol*. 1975;80:573–584.

4. Fawzi AA, Pappuru RR, Sarraf D, et al. Acute macular neuroretinopathy: long-term insights revealed by multimodal imaging. *Retina*. 2012;32:1500–1513.

5. Nemiroff J, Kuehlewein L, Rahimy E, et al. Assessing deep retinal capillary ischemia in paracentral acute middle maculopathy by optical coherence tomography angiography. *Am J Ophthalmol*. 2016;162:121–132.e1.

6. Hansen SO, Cooper RF, Dubra A, Carroll J, Weinberg DV. Selective cone photoreceptor injury in acute macular neuroretinopathy. *Retina*. 2013;33:1650–1658.

7. Sarraf D, Rahimy E, Fawzi AA, et al. Paracentral acute middle maculopathy: a new variant of acute macular neuroretinopathy associated with retinal capillary ischemia. *JAMA Ophthalmol*. 2013;131:1275–1287.

8. Bhavsar KV, Lin S, Rahimy E, et al. Acute macular neuroretinopathy: a comprehensive review of the literature. *Surv Ophthalmol*. 2016;61:538–565.

9. Casalino G, Williams M, McAvoy C, Bandello F, Chakravartthy U. Optical coherence tomography angiography in paracentral acute middle maculopathy secondary to central retinal vein occlusion. *Eye (Lond)*. 2016;30:888–893.

10. Sridhar J, Shahlaee A, Shieh W-S, Rahimy E. Paracentral acute middle maculopathy associated with retinal artery occlusion after cosmetic filler injection. *Retin Cases Brief Rep*. 2017;11: S216–S218.

11. Khan MA, Rahimy E, Shahlaee A, Hsu J, Ho AC. En face optical coherence tomography imaging of deep capillary plexus abnormalities in paracentral acute middle maculopathy. *Ophthalmic Surg Lasers Imaging Retina*. 2015;46:972–975.

12. Liu JC, Nesper PL, Fawzi AA, Gill MK. Acute macular neuroretinopathy associated with influenza vaccination with decreased flow at the deep capillary plexus on OCT angiography. *Am J Ophthalmal Case Rep*. 2018;10:96–100.

13. Thanos A, Faia LJ, Yonekawa Y, Randhawa S. Optical coherence tomographic angiography in acute macular neuroretinopathy. *JAMA Ophthalmol*. 2016;134:1310–1314.

14. Lee SY, Cheng JL, Gehrs KM, et al. Choroidal features of acute macular neuroretinopathy via optical coherence tomography angiography and correlation with serial multimodal imaging. *JAMA Ophthalmol*. 2017;135:1177–1183.

15. Ashraf M, Goldstein D, Fawzi A. Optical coherence tomography angiography: potential artifacts in acute macular neuroretinopathy. *JAMA Ophthalmol*. 2017;135:675–676.

16. Zhang M, Hwang TS, Campbell JP, et al. Projection-resolved optical coherence tomographic angiography. *Biomed Opt Express*. 2016;7:816–828.

17. Onishi AC, Ashraf M, Soetikno BT, Fawzi AA. Multi-level ischemia in disorganization of the retinal inner layers on projection-resolved optical coherence tomography angiography [published online ahead of print April 10, 2018] *Retina*. doi:10.1097/IAE.0000000000002179.

18. Campbell J, Zhang M, Hwang T, et al. Detailed vascular anatomy of the human retina by projection-resolved optical coherence tomography angiography. *Sci Rep*. 2017;7:42201.

19. Hwang TS, Zhang M, Bhavsar K, et al. Visualization of 3 distinct retinal plexuses by projection-resolved optical coherence tomography angiography in diabetic retinopathy. *JAMA Ophthalmol*. 2016;134:1411–1419.

20. Zhang M, Hwang TS, Dongye C, Wilson DJ, Huang D, Jia Y. Automated quantification of nonperfusion in three retinal plexuses using projection-resolved optical coherence tomography angiography in diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2016;57:5101–5106.

21. Chan G, Balaratnasingam C, Paula KY, et al. Quantitative morphometry of perifoveal capillary networks in the human retina. *Invest Ophthalmol Vis Sci*. 2012;53:5502–5514.

22. Choi W, Mohler KJ, Potsaid B, et al. Choriocapillaris and choroidal microvasculature imaging with ultrahigh speed OCT angiography. *PLoS One*. 2013;8:e81499.