Original Article

Association of Resolved Paracentral Acute Middle Maculopathy Lesions with Diabetic Retinopathy

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Abstract

Purpose: To evaluate the association between paracentral acute middle maculopathy (PAMM) lesions and diabetic retinopathy (DR) using optical coherence tomography angiography (OCTA).

Methods: Thirteen diabetic patients without DR, 13 patients with mild nonproliferative DR (NPDR), 18 patients with moderate-to-severe NPDR, and 20 patients with proliferative DR (PDR) were included in this retrospective study. For each patient, 6 mm × 6 mm macular OCTA scans of both eyes were reviewed for the presence of acute and resolved PAMM lesions.

Results: Among diabetic patients with and without DR, 49 (94.9%) and 7 (53.8%) patients demonstrated small resolved PAMM lesions, respectively. The odds ratio for the presence of resolved PAMM lesions in the eye with DR compared to the eye of diabetic patient without DR was 21.8 ($P < 0.001$, 95% confidence interval 7.0–67.8). In the mild NPDR group, moderate-to-severe NPDR group, and the PDR group, 11 (84.6%), 18 (100.0%), and 20 (100.0%) patients demonstrated resolved PAMM lesions, respectively. There was a statistically significant increasing prevalence of PAMM lesions as the severity of DR increased ($P < 0.001$).

Conclusion: Small resolved PAMM lesions are a common form of ischemic retinal lesions in DR.

Keywords: Diabetic retinopathy, Ischemia, Optical coherence tomography angiography, Paracentral acute middle maculopathy

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Introduction

Progress in optical coherence tomography (OCT) and OCT angiography (OCTA) has enabled a better understanding of the pathophysiology of retinal ischemia. These technologies have revealed a new type of ischemic retinal lesions called paracentral acute middle maculopathy (PAMM).[1,2] Classical PAMM is characterized by localized hyperreflectivity and consequent thinning of the inner nuclear layer.[1-3] PAMM has been described in association with different ocular and systemic conditions, including retinal vein occlusions,[4] Purtscher's retinopathy,[5] sickle-cell disease,[6] hypertension,[7] and cardiovascular disease.[8] Moreover, it has been associated with hypercoagulability,[9] phosphodiesterase-5 inhibitor therapy,[10] cardiopulmonary bypass,[11] aortic aneurysm repair surgery,[12] giant cell arteritis,[13] and other conditions and states. Therefore, PAMM should not be considered a distinct disease but a universal retinal phenomenon associated with vascular events.

Diabetic retinopathy (DR) is a classical vascular disorder of the retina where PAMM may occur. Indeed, PAMM lesions have been identified in eyes with proliferative DR (PDR).[14] However, as the mildest form of retinal ischemia, we could expect the appearance of these lesions in milder stages of DR. Particularly, a specific form of PAMM, small resolved PAMM lesions, has been described in the fellow eye of unilateral retinal vein occlusion patients[4] as well as patients with hypertension[7] and cardiovascular disease.[8]

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In this study, we aimed therefore to evaluate the prevalence of PAMM in diabetic patients with and without DR.

Methods

The study followed the ethical standards stated in the Declaration of Helsinki and was approved by the local ethics committee. All participants signed written informed consent before participating in the study. Patients with type 2 diabetes mellitus with and without DR were included in the study. Exclusion criteria were diabetic macular edema (DME) occupying more than a half of the scan area, center involving DME, advanced PDR, asymmetry in the severity of DR between both eyes, abnormalities of vitreoretinal interface distorting retinal layers, any concurrent retinal disorders, including central retinal vein occlusions, and OCTA scan quality less than Q7.

All participants received OCTA examination with RTVue-XR Avanti (Optovue, Fremont, CA) software version 2017.1.0.150, green (532 nm) scanning laser ophthalmoscopy (F-10 NIDEK, Gamagori, Japan), and color fundus photography (AFC-330 [NIDEK] or Visucam 524 [Carl Zeiss Meditec AG, Jena, Germany]). Based on color fundus photography, the presence or absence of DR was established. The severity of DR was classified as mild nonproliferative DR (NPDR), moderate NPDR, severe NPDR, or PDR. Since the number of severe NPDR eyes was not sufficient for parametric statistical comparison, they were combined with moderate NPDR eyes in the group moderate-to-severe NPDR. OCTA examination included 3-mm and 6-mm OCTA scans centered on the center of the fovea. Two experienced retina specialists (D.S.M. and M.A.B.) reviewed 6-mm OCTA scans for the presence of acute or resolved PAMM lesions. For further analysis, appropriate segmentation lines were inspected and manually corrected where needed.

The resolved PAMM lesions were evaluated using the slab between two segmentation lines of the outer plexiform layer with –9 μm and 0 μm offset where the lesions were defined as small sharply delineated dark areas [Figure 1]. In addition, B-scans were inspected to confirm the presence of the lesions. On B-scans, a resolved PAMM lesion was defined as the area of inner nuclear layer thinning associated with outer plexiform layer disruption/elevation, as has been described previously.[12,13] The presence of at least one lesion on B-scan and *en face* image simultaneously was sufficient for an individual to be considered as having PAMM lesions. Acute PAMM was defined on B-scans as localized hyperreflectivity of the inner nuclear layer.

The vessel density of superficial capillary plexus (SCP) and deep capillary plexus (DCP) for the whole 3 mm × 3 mm OCTA scan was calculated automatically by the OCT device software using standard segmentation settings.

Statistical analysis was performed with MedCalc 18.4.1 (MedCalc Software). The Chi-square test was used to compare the prevalence of the PAMM lesions between eyes without DR and with different stages of DR. The odds ratio was calculated for the presence of resolved PAMM lesions in the eye with DR compared to the eye of diabetic patient without DR. The one-way analysis of variance (ANOVA) was used to compare the foveal avascular zone (FAZ) area, SCP vessel density, and DCP vessel density values between study groups. A logistic regression model was constructed to identify factors associated with the prevalence of resolved PAMM lesions, including age, hypertension, insulin use, and DR severity. $P < 0.05$ was considered statistically significant.

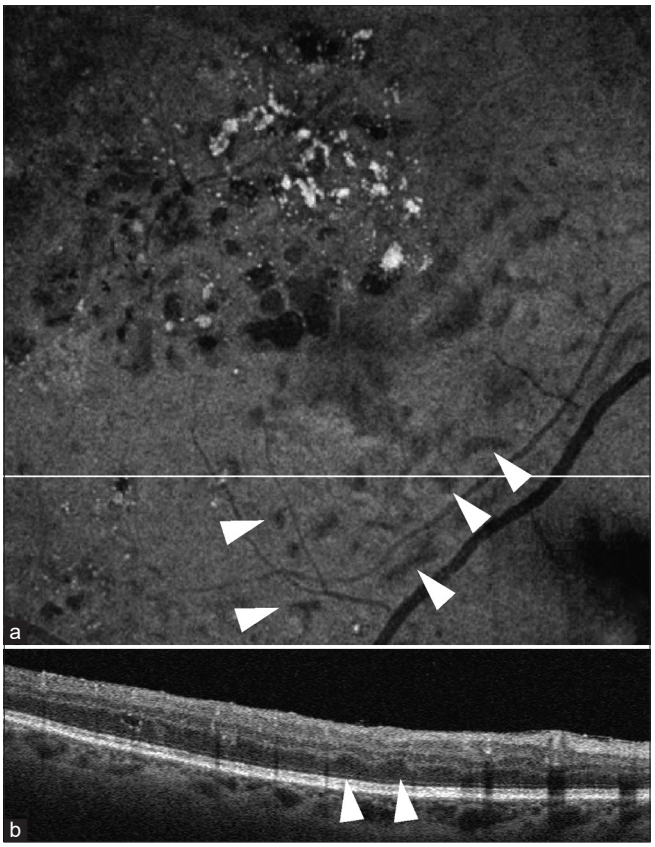

Figure 1: Optical coherence tomography imaging of paracentral acute middle maculopathy lesions in diabetic retinopathy. (a) 6 mm × 6 mm *en face* structural images showing a slab between two segmentation lines of the outer plexiform layer with –9 μm and 0 μm offset. The white line represents the position of B-scans in (b) White arrowheads indicate resolved paracentral acute middle maculopathy (PAMM) lesions. (b) B-scan showing multiple resolved PAMM lesions (white arrowheads)

Results

Sixty-four patients (38 males and 26 females, 58.3 ± 12.7 years) were included in the study [Table 1]. Thirteen (20.3%), 13 (20.3%), 18 (28.1%), and 20 (31.3%) patients had no DR, mild NPDR, moderate-to-severe NPDR, and PDR, respectively. A total of 49 (75.6%) patients had hypertension. The trend toward the increase of the mean age and the prevalence of hypertension between groups was not statistically significant ($P > 0.05$).

Among diabetic patients without DR, 7 (53.8%) patients demonstrated small resolved PAMM lesions: four patients had small resolved PAMM lesions in both eyes and three patients in one eye. Among patients with DR, 49 (94.9%) patients ($P = 0.01$ compared to diabetic patients without DR) demonstrated small resolved PAMM lesions: 47 patients had small resolved PAMM lesions in both eyes and two patients in one eye [Figure 2]. The odds ratio for the presence of resolved PAMM lesions in the eye with DR compared to the eye of diabetic patient without DR was 21.8 ($P < 0.001$, 95% confidence interval 7.0–67.8). No acute PAMM lesions were found among study patients. In patients with mild NPDR, moderate-to-severe NPDR, and PDR 11 (84.6%), 18 (100.0%), and 20 (100.0%) patients, respectively, demonstrated small resolved PAMM lesions [Figure 3]. There was a statistically significant trend toward an increase of the prevalence of resolved PAMM lesions with the progression of DR ($P < 0.001$). However, there was no statistically significant difference in the prevalence of resolved PAMM lesions between patients with mild DR and patients without DR ($P = 0.19$) as well as between patients with PDR and patients with moderate-to-severe NPDR ($P = 0.82$). The logistic regression analysis showed that, in a model which included age, hypertension, insulin use, and DR severity, only DR severity was an independent factor associated with the prevalence of resolved PAMM lesions ($P = 0.025$).

FAZ area in eyes without DR, with mild NPDR, moderate-to-severe NPDR, and PDR was 0.23 ± 0.06 mm^2, 0.27 ± 0.07 mm^2, 0.27 ± 0.11 mm^2, and 0.37 ± 0.21 mm^2 ($P = 0.082$, ANOVA ×4), respectively [Figure 4]. SCP vessel density in eyes without DR, with mild NPDR, moderate-to-severe NPDR, and PDR was 45.8% ± 3.8%, 43.1% ± 2.8%, 41.1% ± 4.6%, and 36.6% ± 3.3% ($P < 0.001$, ANOVA ×4), respectively. DCP vessel density in eyes without DR, with mild NPDR, moderate-to-severe NPDR, and PDR was 53.6% ± 2.1%, 45.8% ± 5.4%, 46.5% ± 4.8%, and 41.8% ± 3.2% ($P < 0.001$, ANOVA ×4), respectively. Among patients without DR and with mild NPDR, a comparison between eyes with and without resolved PAMM lesions showed a statistically significantly lower vessel density in DCP in eyes with resolved PAMM lesions (48.9% ± 5.3% and 55.0% ± 1.9%, respectively, $P = 0.04$). However, only a

Table 1: Demographic and clinical characteristics of study groups

	No DR	Mild NPDR	Moderate-to-severe NPDR	PDR	*P*
Number of participants	13	13	18	20	
Gender (male)	7	9	10	12	0.98*
Age (years)	56.9±15.2	55.4±14.6	55.2±12.8	64.5±8.5	0.19†
Hypertension (%)	46.2	69.2	88.9	90.0	0.7*
Duration of diabetes (years)	8.1±3.6	12.2±8.5	18.6±9.0	21.3±11.7	0.04†
Insulin dependent (%)	38.5	30.7	50.0	55.0	0.54*
HbA1C (%)	6.5±0.7	7.0±1.7	7.8±1.1	7.5±1.0	0.62†

DR: Diabetic retinopathy, PDR: Proliferative DR, NPDR: Non-PDR, HbA1C: Hemoglobin A1C. *: Chi-square test, †: One-way analysis of variance

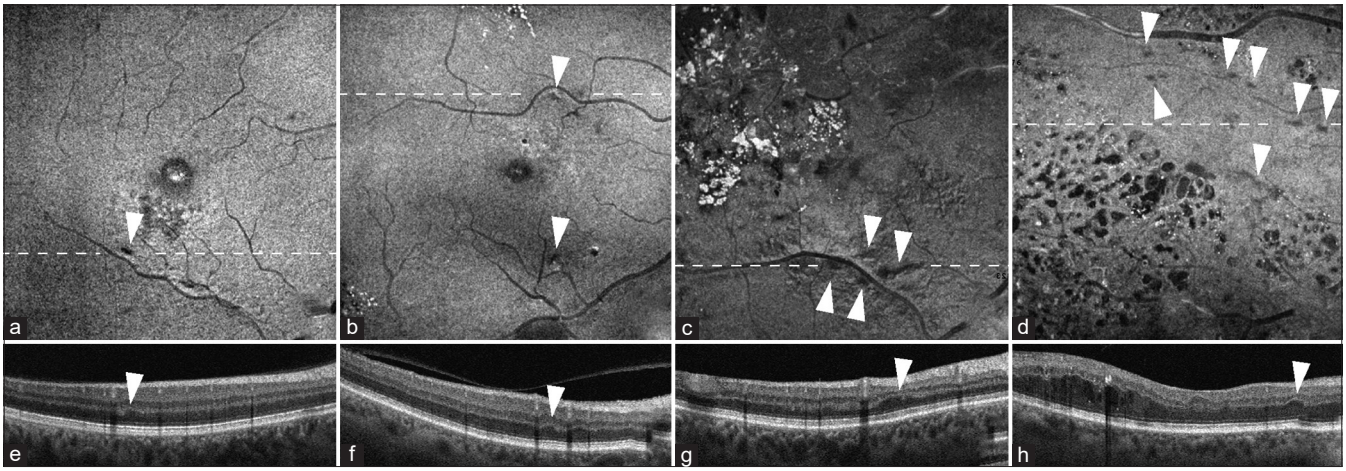

Figure 2: Optical coherence tomography angiography imaging of paracentral acute middle maculopathy lesions in eyes with different stages of diabetic retinopathy (DR). (a) 6 mm × 6 mm *en face* structural image showing resolved paracentral acute middle maculopathy (PAMM) lesions in the eye of diabetic patient without DR. (b) 6 mm × 6 mm *en face* structural image showing resolved PAMM lesions in the eye with mild nonproliferative DR (NPDR). (c) 6 mm × 6 mm *en face* structural image showing resolved PAMM lesions in the eye with moderate-to-severe NPDR. (d) 6 mm × 6 mm *en face* structural image showing resolved PAMM lesions in the eye with proliferative DR (PDR). (e) B-scan through resolved PAMM lesions in the eye of diabetic patient without DR. (f) B-scan through resolved PAMM lesions in the eye of diabetic patient with mild NPDR. (g) B-scan through resolved PAMM lesions in the eye of diabetic patient with moderate-to-severe NPDR. (g) B-scan through resolved PAMM lesions in the eye of diabetic patient with PDR. Dashed lines in (a-d) represent the position of B-scans in (e-h). White arrowheads indicate PAMM lesions

numerical difference was found regarding SCP vessel density (43.9% ± 3.7% and 47.5% ± 1.5% in patients with and without resolved PAMM lesions, respectively, $P = 0.08$).

Discussion

Based on the analysis of structural *en face* images and OCT B-scans, this study shows the high prevalence of small resolved PAMM lesions among patients with diabetes without DR and patients with different stages of DR. PAMM may therefore be considered the earliest and mildest form of ischemic retinal alteration in DR. It may also be used as an early indicator for diabetic retinal damage and the progression of the earliest stages of DR.

Our finding agrees with previous reports showing that small resolved PAMM lesions are the earliest sign of the alteration of retinal microcirculation. Particularly, small resolved PAMM lesions were found in conditions where retinal status had been considered unaltered before the introduction of OCT and OCTA. These lesions were found in mild hypertension without changes in retinal vessel density.[7] Small resolved PAMM lesions, referred to as "retinal ischemic perivascular lesions," were also shown to be associated with coexisting cardiovascular disease (coronary heart disease or stroke).[8] Similarly, these lesions are frequently found in healthy fellow eyes of unilateral retinal vein occlusion patients[4] where their prevalence has been correlated with the status of the choriocapillaris perfusion.[15]

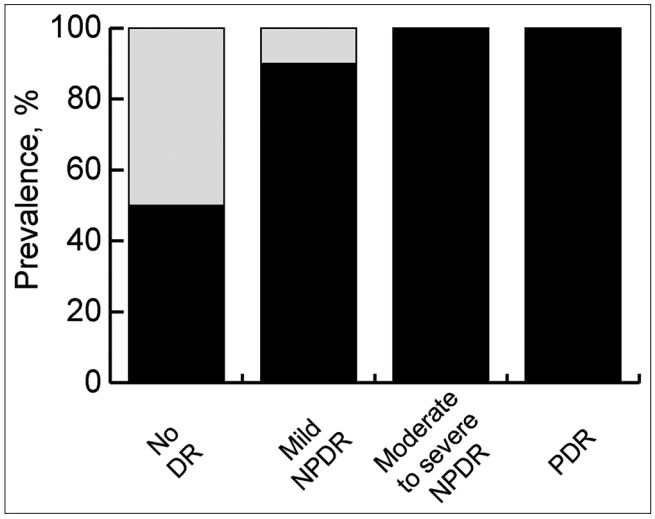

Figure 3: Stacked bar charts showing the prevalence of paracentral acute middle maculopathy lesions among diabetic patients without diabetic retinopathy, and among patients with different stages of diabetic retinopathy. DR: Diabetic retinopathy, NPDR: Nonproliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

PAMM is referred to as ischemic damage of the deep vascular complex appearing as whitening of the inner nuclear layer followed by its thinning. The deep vascular complex lies close to the venous pole of retinal microcirculation and has the lowest level of oxygen saturation. Therefore, even a relatively mild retinal hypoperfusion and slowdown of the blood flow may lead to ischemia in the inner nuclear layer, whereas other parts of retinal microcirculation remain nondamaged. However, it seems that even within the phenomenon of PAMM, there is a spectrum of forms where the most severe cases presented as globular and fern-like patterns,[16] moderate-by arteriolar patterns,[16] and probably the mildest-small perivascular PAMM lesions,[17] which we considered in the current article.

As an important systemic cardiovascular risk factor, diabetes mellitus may be independently linked to the incidence of PAMM. However, its strong association with hypertension required additional attention in interpreting the high prevalence of PAMM lesions among diabetic patients. Indeed, in our study, most patients had hypertension in addition to diabetes. However, the prevalence of small resolved PAMM lesions significantly increases with the progression of DR. In addition, logistic regression analysis indicated that only DR is an independent risk factor for resolved PAMM lesions. This leads us to conclude that diabetes may play a role as an independent risk factor for the occurrence of PAMM lesions.

The change of vessel density with the progression of DR agrees with the prevalence of PAMM lesions. Particularly, vessel density in DCP shows a substantial decrease with the conversion of diabetes without DR to mild NPDR. This seems to agree with the view that PAMM is a form of deep retinal ischemia associated with damage to the DCP. Further, the DCP vessel density demonstrates a decrease as NPDR progresses. These results agree with the report of Ashraf where, in eyes

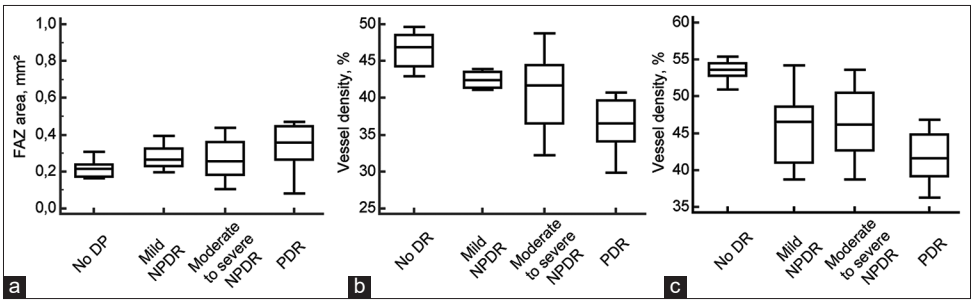

Figure 4: Box-and-whisker plots showing mean foveal avascular zone area (a), vessel density of superficial capillary plexus (b), and vessel density of deep capillary plexus (c) in diabetic patients without diabetic retinopathy (DR), and among patients with different stages of DR. DR: Diabetic retinopathy, FAZ: Foveal avascular zone, NPDR: Nonproliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

with no DR or mild NPDR, the vascular changes were present mostly in the deep vascular complex. In contrast to the deep vascular complex, SCP demonstrated changes across severity levels in more severe DR.[18] We have also compared the vessel density of SCP and DCP between patients with and without PAMM lesions. This analysis was possible only for a combined group of no DR and mild NPDR patients since all patients with advanced DR demonstrated PAMM lesions. This analysis showed the expected lower vessel density in DCP among eyes with PAMM lesions compared to those without.

This study has several limitations. First, the study included only a limited number of severe NPDR eyes, and these eyes were assigned to the moderate-to-severe NPDR group. Therefore, we do not know the exact distribution of the lesions between moderate and severe NPDR. Second, although the prevalence of the PAMM lesions increases with the severity of DR, the quantitative characteristic of the lesions remains unknown. Such data may improve our understanding of the progression of ischemic retinal damage with the deterioration of DR. Third, in this study, we did not analyze other types of diabetic retinal lesions such as ischemic retinal nerve fiber layer defects or cotton wool spots and disorganization of retinal inner layers. We, therefore, do not know the relationship between PAMM and other types of ischemic retinal lesions. The analysis of different ischemic retinal lesions may have a practical application due to its ability to improve the classification of DR through the elucidation of the neurodegenerative component of the DR which play a key role in determining visual impairment.[19] In our study, DR severity was identified as the only independent factor defining the prevalence of the resolved PAMM lesions; however, the role of hypertension as a confounding factor requires further investigation.

In conclusion, this study showed that small resolved PAMM lesions are highly prevalent among diabetic patients with and without DR. However, the presence of DR is an independent risk factor for the appearance of PAMM lesions. The prevalence of resolved PAMM lesions is associated with the severity of DR and the vessel density of the DCP. Resolved PAMM lesions become highly prevalent among patients with advanced stages of NPDR and PDR.

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Conflicts of interest
There are no conflicts of interest.

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