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PII: S0002-9394(23)00516-0
DOI: https://doi.org/10.1016/j.ajo.2023.12.010
Reference: AJOPHT 12754

To appear in: *American Journal of Ophthalmology*

Received date: September 21, 2023
Revised date: December 5, 2023
Accepted date: December 10, 2023

Please cite this article as: Celeste Limoli , Laxmi Deepa Raja , Siegfried Karl Wagner , Daniel Ferraz , Matthias Bolz , Stela Vujosevic , Paolo Nucci , Luke Nicholson , Pearse Andrew Keane , Hagar Khalid , Josef Huemer , Exploring Patient Demographics and Presence of Retinal Vascular Disease in Paracentral Acute Middle Maculopathy, *American Journal of Ophthalmology* (2023), doi: https://doi.org/10.1016/j.ajo.2023.12.010

Exploring Patient Demographics and Presence of Retinal Vascular Disease in Paracentral Acute Middle Maculopathy

Running Head / Short title: Patient demographics in paracentral acute middle maculopathy

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Abstract

Purpose: To investigate the sociodemographic profile, the association with retinal vascular diseases (RVD) and systemic comorbidities, and visual outcomes of patients with paracentral acute middle maculopathy (PAMM) in a large, ethnically diverse single-center cohort.

Design: Retrospective cohort study.

Methods: Electronic health record query for all patients presenting with PAMM at Moorfields Eye Hospital, London, was completed. Detailed demographics, clinical and systemic information were collected and analyzed.

Results: A total of 78 eyes of 78 patients with confirmed PAMM were included in the study. 40 patients(51.3%) presented with no RVD, 20 patients(25.6%) with retinal vein occlusion(RVO), 16 patients(20.5%) with retinal artery occlusion(RAO), and two patients(2.6%) with concomitant RAO and RVO. Patients with PAMM+RAO were older than those with RVO(p=0.02) and more likely to have a history of major adverse cardiovascular events(MACE)(p=0.01), with a significantly worse presenting best corrected visual acuity (BCVA)(20/50) compared to patients with RVO (p=0.02) and no RVD (p<0.001). Individuals with isolated PAMM had a significantly higher prevalence of previous MACE (p=0.04) and sickle cell disease (SCD) (p=0.04) compared to those with RVO. At the last follow-up, 64 patients (85.3%) had a good BCVA (>20/32).

Conclusions: The significant association of PAMM with RVD supports the hypothesis of an ischemic etiology. Individuals with isolated PAMM had a higher prevalence of MACE and SCD. Thus, it is important to prompt immediate referral for a comprehensive systemic evaluation. Across the whole cohort, PAMM was associated with good BCVA improvement during follow-up, indicating a good visual prognosis.

Introduction

Paracentral acute middle maculopathy (PAMM) represents the spectral domain optical coherence tomography (SD-OCT) feature of focal or diffuse parafoveal hyper-reflective bands at the level of the inner nuclear layer (INL) in the paracentral region [1–3]. PAMM appears to be a result of acute ischemia or infarction of the middle retina or INL due to transient macular hypoperfusion in the intermediate and deep retinal capillary plexus [4,5]. Subsequently, a permanent thinning of INL develops as a legacy of acute PAMM lesions[6]. PAMM manifests clinically as an acute painless paracentral scotoma, predominantly in individuals with risk factors for retinal ischemia[7]. Given the retinal ischemia and INL thinning, patients with PAMM can suffer from irreversible visual deficits [7], even if central visual acuity prognosis is usually excellent.

Although PAMM can be an isolated SD-OCT finding, current literature depicts a strong association between PAMM and primary retinal vascular diseases (RVD), including central and branch retinal artery or vein occlusions (RAO/RVO), cilio-retinal artery occlusions (CiRAO) [8–12], and various systemic vasculopathic comorbidities, including cardiovascular disease, hypertension, diabetes mellitus (DM), sickle cell disease (SCD), and vasculitis [8,10,11,13–16]. This confers further support that vascular dysfunction plays an important role in the disease process [2,5].

As PAMM is a relatively nascent OCT feature, its epidemiology and prognostic implications are less well established.

The aim of this paper is to investigate the epidemiology, demographics and visual outcomes of patients with PAMM in a large, ethnically diverse single-center cohort. In addition, this study seeks to describe the association with primary RVD and

systemic comorbidities to further elucidate the underlying pathogenesis of these middle retinal lesions.

Methods

This was a retrospective cohort study of all National Health Service patients, aged 18 and over, with a diagnosis of ‘Paracentral Acute Middle Maculopathy’ or ‘PAMM’ attending Moorfields Eye Hospital (MEH). Data was collected between January 2014 and June 2021 inclusive. Institutional review board approval was obtained for a retrospective chart review and the study was performed in accordance with the tenets of Declaration of Helsinki.

We extracted patients who had a provisional diagnosis of PAMM from the MEH Accident and Emergency Department and also those seen in medical retina, neuro-ophthalmology, general ophthalmology and glaucoma clinics. All cases of ‘Paracentral Acute Middle Maculopathy’ or ‘PAMM’ were extracted using structure query language (SQL) within the MEH data warehouse, a locally-held central repository aggregating data from all electronic health record systems used across the Trust. The dataset was manually cleaned to exclude irrelevant entries.

Once eligible patients were identified following data cleaning, clinical and SD-OCT imaging data were assessed for each case. PAMM lesions were defined as hyperreflective parafoveal bands of the INL that evolved into thinning of that retinal layer on SD-OCT in patients with a history of acute-onset paracentral scotoma with or without loss of vision. Presence of PAMM was confirmed by two senior retinal consultants based on clinical details and multimodal imaging including color fundus

photographs (Topcon Medical Systems, Oakland, New Jersey, USA), near-infrared reflectance (NIR) retinal imaging (Spectralis, Heidelberg Engineering, Heidelberg, Germany), fundus autofluorescence (FAF), SD-OCT, OCT-angiography, and fluorescein angiography if available (all, Topcon Medical Systems, Oakland, New Jersey, USA; Spectralis, Heidelberg Engineering, Heidelberg, Germany). Poor quality images that prevented robust analyses were excluded.

Baseline and follow-up best-corrected visual acuities (BCVA), sociodemographic data, clinical variables and systemic comorbidities were manually extracted and analyzed from 'OpenEyes', the electronic medical records system employed at MEH. Previous medical diagnoses as reported in clinical records included hypertension, DM, major adverse cardiovascular events (MACE) [acute myocardial infarction (AMI), stroke, coronary revascularization], SCD, and other medical conditions, such as hypercholesterolemia, migraine, vasculitis, and specified concomitant medication usage. Based on clinical findings on chart review, we classified patients into two main categories: 1) PAMM without RVD (PAMM + no RVD) and 2) PAMM associated with RVD (PAMM + RVD). The PAMM + RVD group was further divided into three sub-categories including, 1) PAMM + RAO, 2) PAMM + RVO and 3) PAMM + combined RAO and RVO.

Statistical analysis

Continuous variables are given as mean ± standard deviation (SD) or median with 25%–75% interquartile range, and categorical variables are presented as percentages.

The Mann-Whitney U test was used to compare groups. In cases of correlated data, Wilcoxon test was selected. Fisher's exact test was used for contingency analysis. P values<0.05 were considered statistically significant. Statistical analysis was performed with SPSS Statistics (IBM corporation, version 28.0.0.0).

Results

A total of 428 patients were drawn from the original SQL search which encompassed PAMM cases as well as irrelevant words which contained the letters 'PAM', so the dataset was manually cleaned to exclude the latter. This reduced the number of actual PAMM patients identified to 138. Subsequently, the images were analyzed in accordance with the grading criteria, and we arrived at a final number of 78 patients with a confirmed diagnosis of PAMM (Figure 1).

An evaluation was conducted of 78 eyes of 78 patients with confirmed diagnosis of PAMM (Figure 1). Forty patients (51.3%) presented without any associated RVD, i.e. an isolated PAMM, whereas 38 patients (48.7%) displayed evidence of concurrent RVD. Of the latter subgroup, 20 (25.6%) were associated with RVO, 16 (20.5%) with RAO, and 2 (2.6%) with concomitant RAO and RVO. The presence and subtypes of RVD are outlined in Table 1 and Figure 2, with the baseline and follow-up FAF and SD-OCT images included.

Median age of the cohort at presentation was 54.5 years old (IQR,69-38 years), and 62.8% were male. Approximately, 37 patients (47.4%) of the cohort were Caucasian, four (5.1%) Afro-Caribbean, five (6.4%) South Asian, 15 (19.2%) identified as other and 17 subjects (21.8%) did not have their ethnicity stated. On initial examination,

Snellen BCVA ranged from 20/20 to hand motion (HM), with a mean BCVA of 20/40 (logarithm of minimal angle of resolution (logMAR) equivalent, 0.31). Most eyes initially presented with good visual acuity, with 53 patients (67.9%) possessing BCVA of 20/32 or better; however, 12 eyes (15.4%) had a BCVA of 20/200 or worse. Baseline information on the onset of vision loss and type of scotoma corresponding to PAMM were not available.

For the entire cohort, mean final BCVA at the most recent examination was 20/35 (range 20/20 to HM, LogMAR equivalent: 0.27). In terms of best corrected visual acuity (BCVA) outcomes, 62 patients (79.5%) demonstrated an improvement in BCVA, 3 patients (3.8%) had no change, and 10 patients (12.8%) experienced worsening of their BCVA. Overall, 64 patients (82%) had a good BCVA (>20/32) at their most recent presentation.

Mean duration of follow-up was 16.2 months (range: 1 to 62.3 median: 15.7), although 7 of the 78 patients were lost to follow-up.

With respect to pre-existing systemic diseases, 35 patients (44.9%) presented with a history of hypertension, ten patients (12.8%) with DM, 13 patients (16.6%) with a previous MACE and nine patients (11.5%) with SCD. Patients' demographics, clinical data and systemic comorbidities are delineated in Table 2, categorized into the whole cohort and also into the 3 separate subgroups.

PAMM patients with no RVD

Forty out of 78 eyes (51.3%) presented with isolated PAMM without any association with RVD (Figure 2, right). Median age of these patients was 55.5 (IQR 68.5–44.5 years) and 24 were male (60%). Baseline BCVA in this subgroup was 20/30 (range

20/20 to HM, logMAR equivalent 0.18) and three individuals (7.5%) had 2/200 or worse at presentation. With regards to pre-existing systemic comorbidities, 21 out of these 40 patients (52.5%) presented with a history of hypertension, eight patients (20%) with previous history of MACE, eight patients (20%) with SCD, seven patients (17.5%) with DM, five patients (12.5%) with hypercholesterolemia and three patients (7.5%) with migraine. Relevant clinical history also included one patient (2.5%) who was pregnant at the time of initial evaluation, one patient (2.5%) who developed PAMM four days after Covid-19 BioNTech vaccination and one case (2.5%) which was associated with amphetamine use. Of note, this subgroup with PAMM and no associated RVD showed a higher prevalence of stroke/MI (p=0.04) and SCD (p=0.04) compared to patients with PAMM in association with RVO (Table 2).

Mean follow-up for these patients with isolated PAMM was 15.5 months (range: 2 to 56.5 months, median: 15.4). Follow-up was not available for five subjects.

Final median BCVA was 20/20 (range 20/20 to HM; logMAR equivalent 0.16), with three patients (7.5%) showing a poor BCVA of 20/200 or worse.

PAMM patients with RVO

Of the 78 eyes with PAMM, 20 (25.6%) displayed evidence of RVO and two (2.6%) had concurrent RVO and RAO at the time of presentation (Figure 2, left). More specifically, we identified 14 patients with PAMM+CRVO, five patients with PAMM+BRVO, two patients with PAMM and concomitant CRVO + CiRAO (Figure 3) (Table 1).

Median age of patients in this subgroup was 47.5 years (IQR 66-32.5 years), there were nine females (40.9%) and 13 males (59.1%), without gender predilection.

Average baseline BCVA was 20/40 (range 20/20 to counting fingers (CF); logMAR equivalent 0.27). In terms of medical comorbidities, six out of 22 patients (27.3%) had a history of hypertension, two patients (9.1%) had DM and four patients (18.2%) reported current use of oral contraceptive pills (OCP). Of note, one patient (4.5%) was diagnosed with PAMM and BRVO following AZD1222 Covid-19 vaccination. Mean follow-up for patients with PAMM and RVO was 17.8 (range: 5.7 to 62.3 months, median: 16); follow-up visits of two patients (9.1%) were not available. Average final BCVA was 20/30 (range 20/20 to CF; logMAR equivalent 0.14) and only one patient (4.5%) presenting with PAMM+CRVO showed a poor visual outcome, remaining at CF at the last examination.

PAMM patients with RAO

16 out of 78 (20.5%) PAMM patients presented with PAMM associated with RAO (Figure 2, middle). Of these patients, ten were diagnosed with CRAO, five with BRAO and one with CiRAO. We also included the two patients who presented with concurrent RVO and RAO in this subgroup (Table 1).

Median age of these patients (13 males [72.2%] and five females [27.8%]) was 68 years (IQR 79.7-47.7 years), which was noted to be significantly older juxtaposed to the subgroup presenting with RVO (p=0.02).

Average baseline BCVA was 20/100 (range 20/20 to HM, logMAR equivalent 0.70). This presenting BCVA was significantly worse when compared to the isolated PAMM subgroup (20/30) (p<0.001) and the PAMM+RVO subgroup (20/40) (p=0.02).

A history of hypertension and hypercholesterolemia were reported in eight (44.4%) and seven patients (38.8%), respectively; five patients (27.8%) had a previous MACE; one patient (5.5%) suffered from SCD and one patient (5.5%) with DM. The

prevalence of MACE was significantly higher in this subgroup compared to the PAMM+RVO subgroup (p=0.01) (Table 2).

Other pertinent medical history included two patients (11.1%) who developed PAMM after uncomplicated cataract surgery in the postoperative period and one (5.5%) patient with systemic lupus erythematosus (LES) and idiopathic thrombocytopenic purpura (ITP).

Mean follow-up for this subgroup was 15.7 months (range: 2 to 52.5, median: 15.7). Final BCVA improved to 20/50 (range 20/20 to HM, logMAR 0.38), however, this did not reach statistical significance (p=0.541, Wilcoxon signed-rank test). This was not significantly worse than the final BCVA recorded in the isolated PAMM group and the PAMM+RVO group.

Discussion

The manifestation of PAMM as an OCT sign is widely acknowledged in the scientific community, with robust associations with RVD and systemic disorders being reported[4,7,14,17]. However, the current state of management options for PAMM is characterized by significant heterogeneity, warranting a deeper investigation into the underlying pathophysiological mechanisms. Thus, it is imperative to identify any potential comorbidities that may be contributing to the manifestation of PAMM for effective therapeutic interventions.

In this paper, we investigated the demographic characteristics of patients with PAMM, and describe the presence of associated RVD and systemic comorbidities. By doing so, we aimed to identify potential areas for targeting management,

ultimately aiding the formation of a robust management pathway for patients with PAMM.

This study identified 78 patients with PAMM from a single tertiary eye center. This is the largest, ethnically diverse reported collection of clinical and demographic data including systemic associations to date. In terms of study participants, there was a relatively even split of patients associated with concomitant RVD (38 patients) to those without (40 patients). Within the RVD cohort, there were approximately equal numbers of RAO (16 patients) and RVO (20 patients) and two patients presented with concomitant CRVO and CRAO.

The median age of presentation of the total patient population was 54.5 years, similar to the median age of patients with no RVD at 55.5 years. The median presenting age of patients with concomitant RVO was younger at 47.5 years and significantly older for patients presenting with RAO at 68 years compared to RVO subgroup (P=0.02). This was in keeping with existing evidence [17, 18]. Our study population was predominantly male (62.8%), which was also consistent with current literature [18]. In the current study, we demonstrated a higher prevalence of PAMM in Caucasian patients, compared to other ethnicities. Establishing demographic and clinical characteristics of patients with PAMM is useful as it may enable us to draw conclusions on their prognostic value.

PAMM can occur as an isolated phenomenon or in association with different retinal vasculopathies in the presence or absence of systemic comorbidities. In our study, we identified 40 patients (51.3%) with isolated PAMM and no associated RVD. Patients in this subgroup harbored similar demographic features to the other

subgroups, but tended to have a higher prevalence of systemic comorbidities. In particular, our study suggests patients with the absence of RVD have a higher prevalence of previous stroke/AMI (p=0.04) and pre-existing SCD (p=0.04) compared to individuals with PAMM+RVO. Associations of SCD and PAMM are well-documented in existing literature with macular vascular changes being reported even in asymptomatic sickle cell patients [4].

Whilst the findings of systemic vasculopathic co-morbidities are supported by current literature, it is interesting to report the absence of RVD in this subgroup of patients. We hypothesize that this may be a result of patients undergoing medical management for their comorbidities. Therefore, it is important to prompt immediate referral for a complete systemic work up identifying these underlying conditions in individuals with PAMM without any known predisposing ocular risk factors.

The second subgroup in our cohort consisted of 20 cases (25.6%) of PAMM that were associated with RVO and two patients (2.6%) with concomitant CRVO and CiRAO.

In accordance with previous studies [14,20,21], we similarly observed that these patients were younger (median age 47.5 years), without significant systemic disease association, and with a higher association of CRVO with CiRAO (2.6%).

Finally, 16 (20.5%) cases of RAO in our series were associated with PAMM. RAO is regarded as another common PAMM etiology [4]. In the first instance, baseline BCVA in PAMM patients with RAO was significantly worse than patients with concomitant RVO (p=0.02) and with no RVD (p<0.001). This result was in keeping with a study based in China, where they also identified poorer baseline BCVA in

PAMM patients with RAO vs. RVO from their dataset of 78 Chinese patients[18]. With regards to clinical risk factors, patients with RAO appeared to have a higher prevalence of stroke/AMI (5 cases, 27.8%) compared to RVO (0 cases) (p=0.01) (Table 2). The findings of this study indicate a positive correlation between the presence of PAMM and notable improvements in visual acuity during follow-up in patients with RAO. Thus, they suggest that patients presenting with both RAO and PAMM may require a more proactive and intensive management approach to optimize outcomes. These results are in line with the study conducted in China by Liang et al [22] who reported that the presence of PAMM was associated with significant visual acuity improvement during follow-up in 52 patients with concomitant RAO.

The study also identified other clinical features or disorders associated with the development of PAMM, including pregnancy, migraine, COVID-19 vaccinations, LES, ITP, medications such as oral contraceptives and amphetamines, and cataract surgery. Any of these disorders, along with the more common RVD, can cause ischemia at the DCP [7,23].

The retrospective design of this study poses some limitations. Data was collected from a single eye center over a seven-year period. Thus, not all medical records were complete and follow-up data was unavailable for seven patients (9%). Additionally, we cannot exclude that cases of PAMM in combination with RVD may have been underestimated potentially due to medical records only documenting diagnoses of RAO or RVO. This selection bias may have impacted our findings related to visual outcomes.

Furthermore, the data did not include the onset and type of scotoma density corresponding to PAMM, which could have provided valuable insights for visual outcomes among various groups.

Despite these limitations, our study is the largest to date characterizing demographic and clinical findings in a multi-ethnic cohort of patients with PAMM. We found that individuals presenting with isolated PAMM had a higher prevalence of cardio- and cerebro-vascular disease and SCD. Therefore, it is important to prompt immediate referral for a comprehensive systemic evaluation. Across the whole cohort, PAMM was associated with good BCVA improvement during follow-up, indicating a potential prognostic value. This study also highlights the significant association of PAMM with RVD given its presence in almost half of the patient cohort, supporting the notion of an ischemic etiology affecting the intermediate and deep capillary plexus underlying this SD-OCT finding.

Acknowledgments and Financial Disclosure

a. Funding/Support: No funding

b. Financial Disclosures: No financial disclosures

c. Drs Celeste Limoli and Laxmi Raja contributed equally as first authors, Drs Hagar Khalid and Josef Huemer contributed equally as last authors

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Figure legends

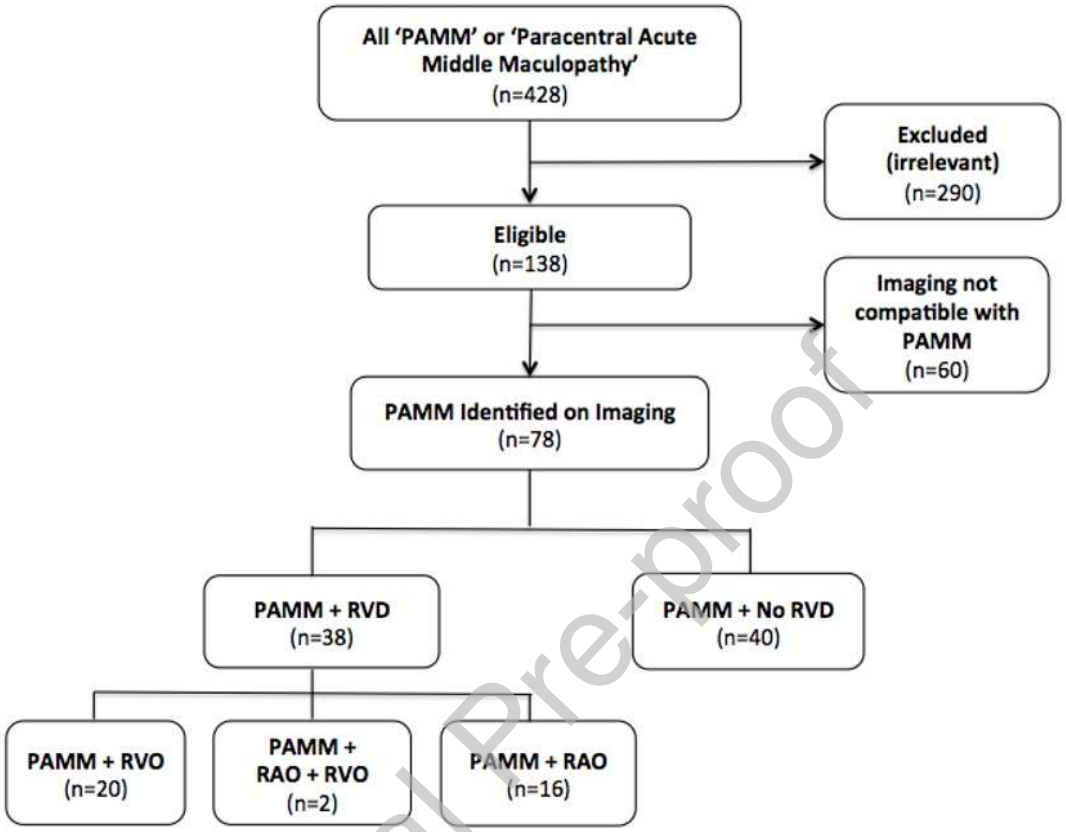

Figure 1: Flow diagram illustrating the eligibility/inclusion criteria and further sub-classification of paracentral acute middle maculopathy with its associated comorbidities.

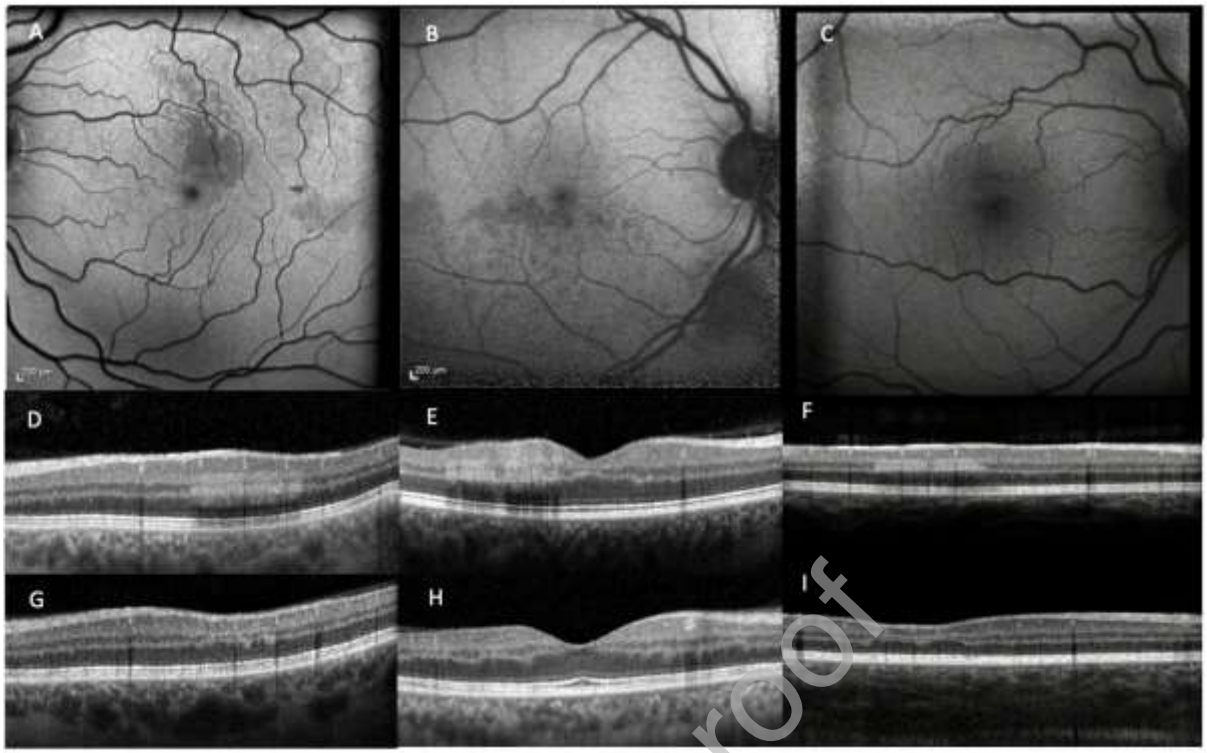

Figure 2. Fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SD-OCT) scans of three cases of paracentral acute middle maculopathy (PAMM) showing the progression of acute PAMM lesions, from inner nuclear layer (INL) hyperreflectivity (D, E, F) to ultimately their INL thinning (G, H, I). These lesions correspond to hypoautofluorescence alterations detected on baseline FAF (A,B,C). In particular, A,D,G show a case of non-ischemic superior BRVO with PAMM; B,E,H a case of PAMM and mild infero-temporal branch RAO; and C,F,I a case of PAMM without any associated retinal vascular disorders.

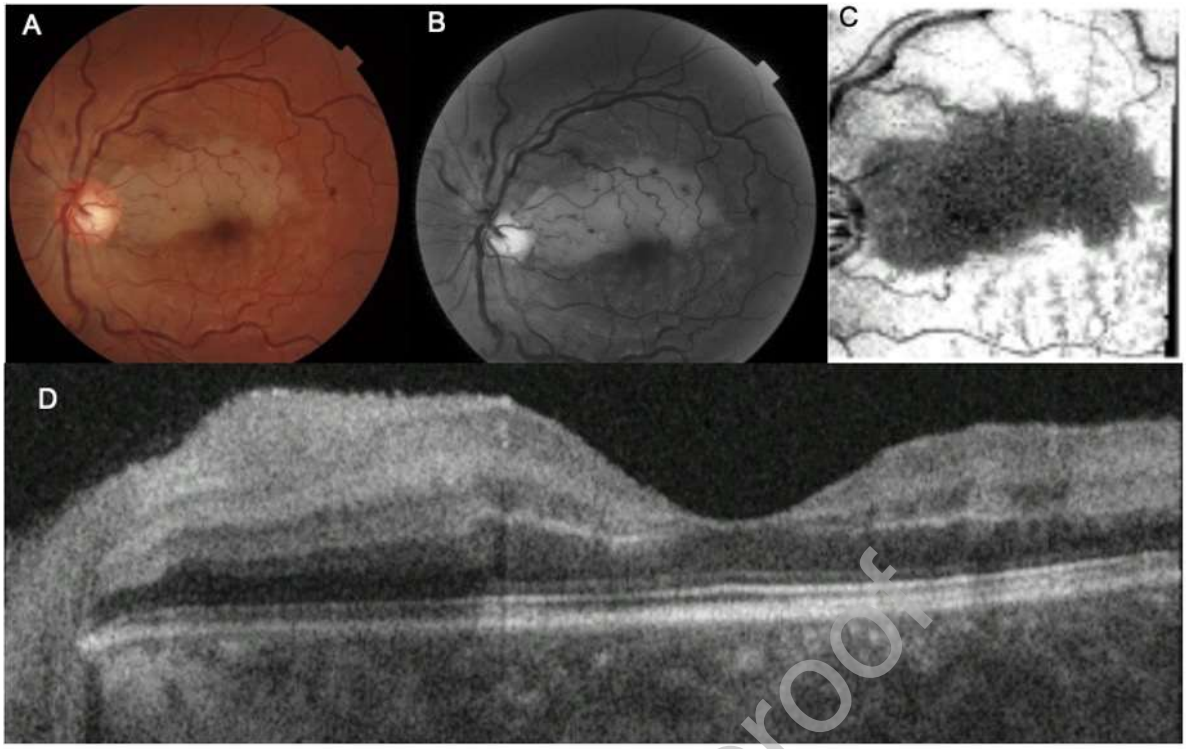

Figure 3. Multimodal imaging of a patient with combined central retinal vein occlusion and cilioretinal artery occlusion in association with paracentral acute middle maculopathy. Color fundus photography (A), infrared image (B), en-face spectral-domain optical coherence tomography (SD-OCT) segmentation of ILM-OS/RPE (C), SD-OCT scan through the fovea (D).

Table 1. Association of RVD in patients presenting with PAMM (*n*=78)		
PAMM + RVD	38 (48.7%)	
	RVO	20 (25.6%)
	- CRVO - BRVO	- 14 - 5
	RAO	16 (20.5%)
	- CRAO - BRAO - CiRAO	- 10 - 5 - 1
	RAO+RVO	2 (2.6%)
	- CRVO+CiRAO	- 2
PAMM and no RVD	40 (51.3%)	

RVD= retinal vascular disease, PAMM= paracentral acute middle maculopathy, RVO= retinal vein occlusion, CRVO= central RVO, BRVO = branch RVO, RAO= retinal artery occlusion, CRAO= central RAO, BRAO= branch RAO, CiRAO= cilioretinal artery occlusion

Table 2. Socio-demographic and clinical characteristics of patients with PAMM

	PAMM patients				*P VALUE*		
	All PAMM (*n*=78)	PAMM+RAO (*n*=18)	PAMM+RVO (*n*=22)	PAMM with no RVD (*n*=40)	PAMM+RAO vs PAMM+RVO	PAMM+RVO vs PAMM with no RVD	PAMM+RAO vs PAMM with no RVD
Age, year, [median (IQR)]	54.5 (69 - 38)	68 (79.7 - 47.7)	47.5 (66 - 32.5)	55.5 (68.5 - 44.5)	0.022*	0.094	0.116
Gender, male, *n* (%)	49 (62.8)	13 (72.2)	13 (59.1)	24 (60)	0.747	1.000	0.772
Ethnicity, n (%)							
Caucasian	37 (47.4)	9 (50)	11 (50)	17 (42.5)			
Afro-Caribbean	4 (5.1)	0	2 (9.1)	2 (5)			
South Asian	5 (6.4)	2 (11.1)	1 (4.5)	2 (5)			
Other	15 (19.2)	2 (11.1)	5 (22.8)	9 (22.5)			
Unknown	17 (21.8)	5 (27.8)	3 (13.6)	10 (25)			
Laterality, left eye, *n* (%)	38 (48.7)	9 (50)	12 (54.5)	18 (45)	1.000	0.573	0.597
Duration of follow-up, months, mean (range)	16.2 (1-62.3)	15.7 (2-52.5)	17.8 (5.7-62.3)	15.5 (2-56.5)	0.772	0.485	0.545
Baseline LogMAR BCVA, mean (range)	0.31 (2.2 – 0)	0.70 (2.2 – 0)	0.27 (1.7 – 0)	0.18 (2.2 – 0)	0.018*	0.308	<0.001*

Final LogMAR BCVA, mean (range)	0.27 (2.2 – 0)	0.38 (2.2 – 0)	0.14 (1.7 – 0)	0.16 (2.2 – 0)	0.161	0.857	0.130
Systemic disorders							
Hypertension, *n* (%)	35 (44.9 %)	8 (44.4%)	6 (27.3)	21 (52.5)	0.327	0.066	0.777
Diabetes Mellitus, *n* (%)	10 (12.8)	1 (5.5%)	2 (9.1)	7 (17.5)	1.000	0.471	0.413
Previous AMI or stroke, *n* (%)	13 (16.6)	5 (27.8%)	0 (0)	8 (20)	0.013*	0.042*	0.516
Sickle Cell Disease, *n* (%)	9 (11.5)	1 (5.5%)	0 (0)	8 (20)	0.45	0.042*	0.249

PAMM= paracentral acute middle maculopathy, RVD= retinal vascular disease, RVO= retinal vein occlusion, RAO= retinal artery occlusion, BCVA= best corrected visual acuity, IQR=interquartile range, LogMAR= Logarithm of the Minimum Angle of Resolution, AMI= acute myocardial infarction.
Asterisk shows a statistically significant difference (p< 05).

Table of Contents Statement

In this retrospective study, the sociodemographic and clinical findings of a multi-ethnic cohort of 78 patients presenting with paracentral acute middle maculopathy (PAMM) were investigated. A strong association of PAMM with retinal vascular disease was found, supporting the hypothesis of an ischemic etiology. A higher prevalence of major adverse cardiovascular events and sickle cell disease in individuals with isolated PAMM was observed. Therefore, an urgent systemic evaluation may be warranted as part of PAMM management.