Case Report

# Paracentral acute middle maculopathy progressing to central retinal artery occlusion following coronavirus disease vaccination: a multimodal imaging report

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**ABSTRACT**

**Background:** Coronavirus disease (COVID-19) vaccines can cause adverse ocular effects, including vascular insults, acute macular neuroretinopathy, paracentral acute middle maculopathy (PAMM), ophthalmic vein thrombosis, Graves' disease, arteritic anterior ischemic optic neuropathy (A-AION), and nonarteritic AION. Here, we report a case of unilateral PAMM progressing to central retinal artery occlusion (CRAO) after COVID-19 vaccination, identified using multimodal imaging.

**Case Presentation:** A 24-year-old healthy man presented with unilateral progressive blurring of vision in the right eye. He had a recent history of fever without rashes 2 weeks after coronavirus disease vaccination (COVISHIELD™). He was diagnosed with PAMM in the right eye at a local hospital and treated with a tapering dose of oral steroids. At presentation, he showed progressive blurring of vision in the right eye and the best-corrected distance visual acuity (BCDVA) was 20/60. The anterior segment was normal. Fundus examination revealed a pale optic disc with arteriolar attenuation. CRAO was diagnosed based on the right eye findings. The patient underwent multimodal imaging, including wide-field fundus photography using optos® (optos Carfornia®, optos Inc., Dunfermline, United Kingdom), multicolor imaging with Spectralis™ (Heidelberg Retinal Angiograph; Heidelberg Engineering, Inc., Dossenheim, Germany), fundus fluorescence angiography (Heidelberg Retinal Angiograph; Heidelberg Engineering, Inc., Dossenheim, Germany), and optical coherence tomography angiography (ANGIOVUE, OPTOVUE, Inc., Fremont, CA, USA) using the split-spectrum amplitude-decorrelation angiography algorithm. The condition progressed from PAMM to CRAO during the oral steroid treatment course. At the 2-month follow-up, the right eye BCDVA had improved to 20/50, with fundus findings remaining the same as at the previous visit.

**Conclusions:** This was the first report of a young patient with PAMM presenting with focal vascular occlusion that evolved to global occlusion in the form of CRAO in the absence of systemic vascular risk factors and with a normal coagulation profile. This case suggests that arterial occlusion may exert a temporary effect secondary to COVISHIELD™ vaccination. Randomized controlled trials and case – control studies on the role of vaccination in precipitating thromboembolic events in healthy individuals would provide insight into the causation.

**KEYWORDS**

COVID-19 vaccine AstraZeneca, covishield, paracentral acute middle maculopathy, PAMM, central retinal artery occlusion, imaging, multimodal, hybrid imaging

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## INTRODUCTION

Ocular adverse effects of coronavirus disease (COVID-19) vaccination include episcleritis, scleritis, denovo and recurrent anterior uveitis, central serous chorioretinopathy, Vogt-Koyanagi-Harada disease, multifocal choroiditis, ophthalmic vein thrombosis, Graves' disease, arteritic anterior ischemic optic neuropathy, nonarteritic anterior ischaemic optic neuropathy, cranial nerve palsies (facial or abducens nerve palsies), acute zonal occult outer retinopathy, herpes zoster ophthalmicus, acute retinal necrosis following re-activation of the varicella-zoster virus, and multiple evanescent white dot syndrome [1-10]. Retinal vascular insults following COVID-19 vaccination include acute macular neuroretinopathy (AMN) and paracentral acute middle maculopathy (PAMM) [2,11-15].

On spectral-domain optical coherence tomography (SD-OCT), PAMM manifests as hyperreflective band-like lesions involving the outer plexiform layer (OPL)/inner nuclear layer (INL) junction, resulting in permanent INL thinning [16]. AMN is identified by intraretinal, reddish-brown, wedge-like lesions, the apices of which tend to point toward the foveal hyperreflective plaque between the OPL and the outer nuclear layer (ONL), with disruption of the ellipsoid/interdigitation zone. Vascular pathologies associated with PAMM and AMN include post-viral illness, vasoconstriction, trauma, hypovolemic shock, thrombocytopenia, anemia, and hyperviscosity [17, 18]. The diagnosis is based on patient history and OCT changes [16-18].

PAMM and AMN have been reported with severe acute respiratory disease coronavirus syndrome (SARS-CoV-2) infection and may be post-infection complications [7, 19]. Here, we report a case of unilateral PAMM, which progressed to central retinal artery occlusion (CRAO), after COVID-19 vaccination, identified using multimodal imaging.

## CASE PRESENTATION

A 24-year-old Indian man, with no systemic comorbidities, presented with a history of fever without rashes on August 8, 2021, and blurring of vision in the right eye (OD) 2 days later. He had been presented with viral fever and admitted to a local hospital for 8 days. Two weeks before the onset of fever, he had been vaccinated with the first dose of the COVID-19 vaccine COVISHIELD™ (Oxford–AstraZeneca COVID-19 vaccine, manufactured by the Serum Institute of India, Pune, India).

The reverse transcription polymerase chain reaction was negative for SARS-CoV-2. The patient consulted a local eye hospital on August 16, 2021, and was diagnosed with PAMM in the OCT image of the right eye that revealed a hyperreflective band in the middle INL, suggestive of PAMM (Figure 1, provided by the patient). The patient was started on oral prednisolone 60 mg (Wysolone®, Pfizer Ltd.) at a local hospital; the dose was tapered by 10 mg every week and then stopped. At presentation, he had completed the course of oral steroids 3 days before. He reported no relevant medical or family history.

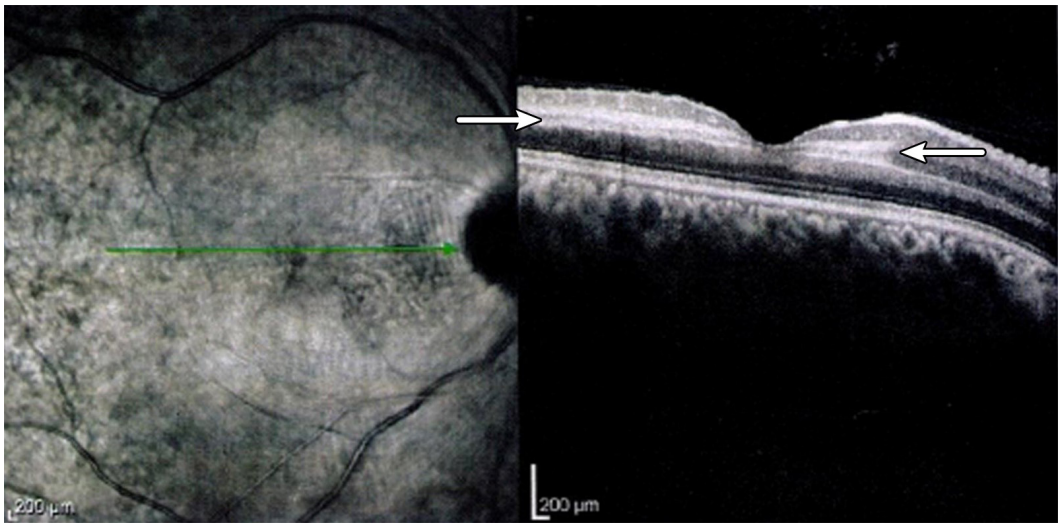


**Figure 1. The optical coherence tomography image of the right eye taken when the patient consulted a local eye hospital (this image provided by the patient) shows hyperreflective bands in the middle layer of the retina (white arrows) with a normal inner retinal layer.**

On ocular examination, the Snellen chart (auto chart projector CP 670; Nidek Co., Ltd., Gamagori, Japan) showed a best-corrected distance visual acuity (BCDVA) of 20/60 OD and 20/20 in the left eye (OS). The intraocular pressure measured using the Goldmann applanation tonometer (Haag Streit AG, Koeniz, Switzerland) was normal in both eyes. Slit-lamp biomicroscopic examination (Topcon Corporation, Tokyo, Japan) of both eyes was normal, with no relative afferent pupillary defect in the right eye. Fundus examination of the right eye using binocular indirect ophthalmoscopy (Keeler Instruments, Inc., PA, USA) and a + 20-diopter ancillary lens (VOLK Optical Inc., Mentor, OH, USA) revealed a pale optic disc with arteriolar attenuation and barrage laser scars in the inferotemporal periphery for multiple retinal holes in both eyes. The optic disc in the OS was within normal limits. Wide-field fundus photography of the right eye performed using optos® (optos Carfornia®, optos Inc., Dunfermline, United Kingdom) showed pale discs and attenuated arteries (Figure 2A).

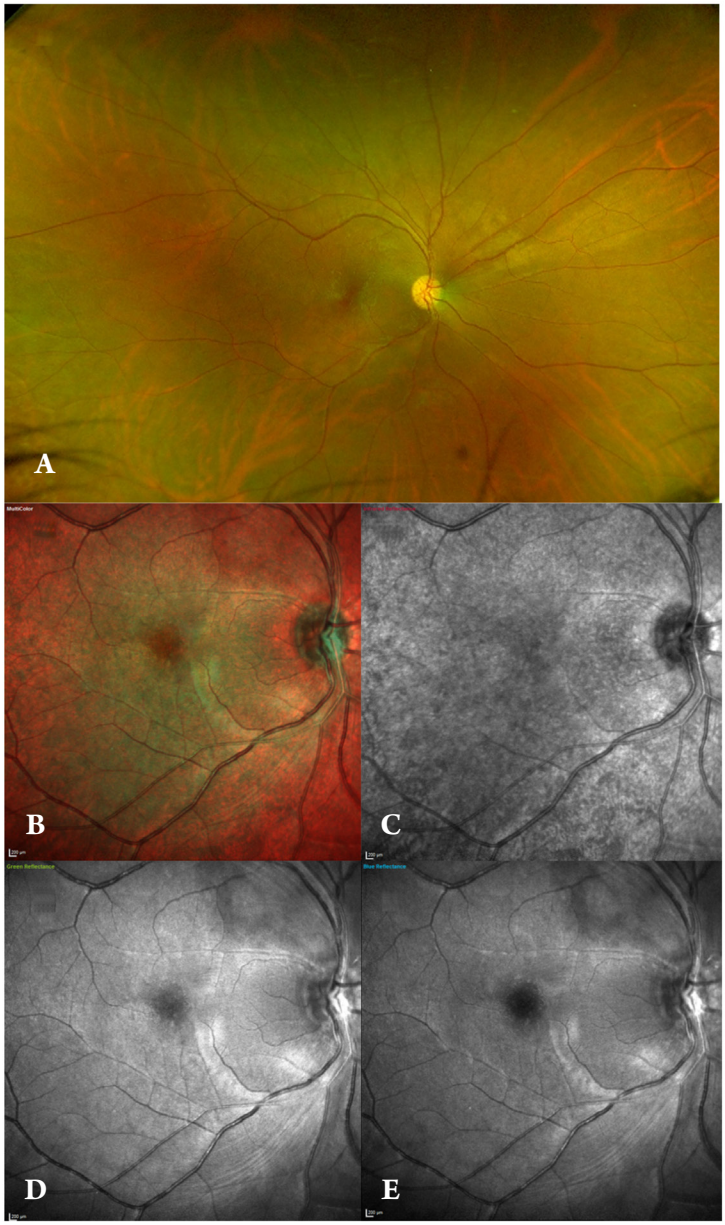


**Figure 2. (A) The widefield fundus photograph of the right eye with optos™ (optos Carfornia®, optos Inc., Dunfermline, United Kingdom) shows pale disc and attenuated arteries. (B-E) Multicolor imaging with Spectralis™ (Heidelberg Retinal Angiograph; Heidelberg Engineering, Inc., Dossenheim, Germany) was performed. The pseudo image (B) shows a bright orange foveal area surrounded by the greenish hue of the posterior pole. The infrared image shows (C) hyporeflective areas at the posterior pole with a stippled-reflective foveal center. (D) The green reflectance shows a dense white area of hyperreflectance at the posterior pole with a normal hyporeflective foveal center, which is less apparent in blue reflectance (E), indicating a deeper pathology.**

Multicolor imaging performed with Spectralis™ (Heidelberg Retinal Angiograph; Heidelberg Engineering, Inc., Dossenheim, Germany). The pseudo-image (Figure 2B) showed a bright orange foveal area surrounded by a greenish hue of the posterior pole. Infrared imaging (Figure 2C) revealed hyporeflectance areas at the posterior pole with a stippled reflective foveal center.

Green reflectance (Figure 2D) showed a dense white area of hyperreflectance at the posterior pole with a normal hyporeflective foveal center, which was less apparent on blue reflectance (Figure 2E), indicating a deeper pathology.

SD-OCT (Heidelberg Retinal SD-OCT; Heidelberg Engineering, Inc., Dossenheim, Germany; Figure 3A, B) of the right eye revealed retinal thinning with disorganization of the retinal layers, sparing the maculopapillary bundle. SD-OCT results of the left eye were within the normal limits.

Fundus fluorescence angiography (Heidelberg Retinal Angiograph; Heidelberg Engineering, Inc., Dossenheim, Germany; Figure 3C-G) showed an arm retinal time of 29 s (normal range: 11 – 18 s). The right eye showed delayed filling of the veins, multiple hypofluorescence areas in the superior macula, and staining of the laser scar inferiorly (Figure 3C-G), and the left eye showed staining of laser scars inferiorly, superiorly, and nasally.

Optical coherence tomography angiography (OCTA; ANGIOVUE, OPTOVUE, Inc., Fremont, CA, USA) using the split-spectrum amplitude decorrelation angiography algorithm to quantify the vasculature structure, foveal avascular zone (FAZ), and superficial and deep retinal vascular plexus (SCP and DCP, respectively) densities was performed by a single trained operator.

Figure 3H-K shows OCTA images of the right eye sequentially from the SCP, enlarged FAZ (black area; Figure 3H), DCP pruning, terminal bulbar dilatation of vessels with enlarged FAZ (Figure 3I), outer retinal projection artifacts (Figure 3J), and choriocapillaris (Figure 3K).

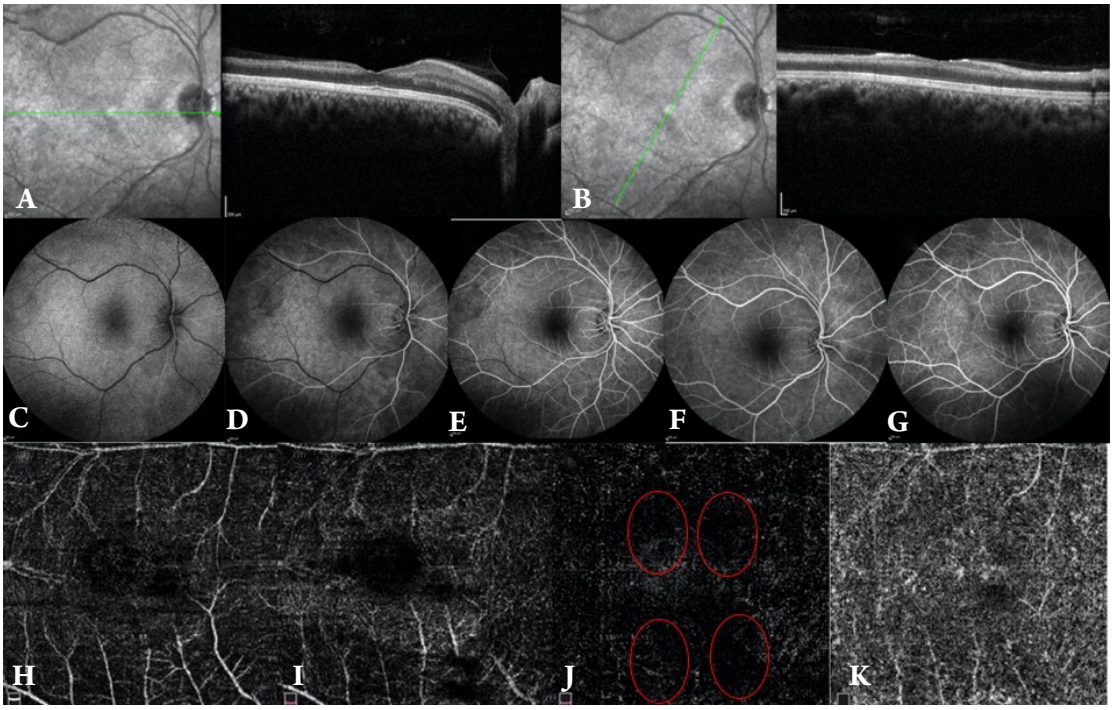


**Figure 3. (A, B) The spectral-domain optical coherence tomography (Heidelberg Retinal SD-OCT; Heidelberg Engineering, Inc., Dossenheim, Germany) scan of the right eye shows retinal thinning with disorganization of the retinal layers sparing the maculopapillary bundle. (C-G) The fundus fluorescence angiography (Heidelberg Retinal Angiograph; Heidelberg Engineering, Inc., Dossenheim, Germany) scan shows an arm retinal time of 29 s (normal: 11 – 18 s). The right eye shows delayed filling of the veins, multiple hypofluoroscence in the superior macula, and staining of the laser scar inferiorly. (H-K) The optical coherence tomography angiography (ANGIOVUE, OPTOVUE, Inc., Fremont, CA, USA) scans of the right eye sequentially shows the (H) superficial capillary plexus, enlarged foveal avascular zone (black area), (I) deep capillary plexus, pruning and terminal bulbar dilatations of vessels with an enlarged foveal avascular zone, (J) outer retina projection artifacts (red ovals), and (K) choriocapillaries.**

Investigations at our center showed a random blood sugar level of 79 (reference range: 90 – 130) mg/dL. The lipid profile, complete blood count, erythrocyte sedimentation rate (ESR), prothrombin time, activated partial thromboplastin time, D-dimer, serum ferritin, lactate dehydrogenase, fibrinogen, serum vitamin D, and urine microscopy were normal. The C-reactive protein (CRP) was negative. Human immunodeficiency viruses 1 and 2 (J. Mitra and Co., New Delhi, India), hepatitis B surface antigen (OSCAR Medicare, New Delhi, India), anti-hepatitis virus C antibody (OSCAR Medicare, New Delhi, India), dengue immunoglobulin (Ig) M/NS 1 antigen/IgG (Sd Biosensor Healthcare Pvt. Ltd., Biosensor Healthcare, Gurugram, Haryana, India), chikungunya IgM/IgG (CTK Biotech, Poway, California, USA), *Treponema pallidum* hemagglutination test (Bio-Rad Clinical Diagnostics, Marnes-la-Coquette, France), and WIDAL antigen set (ARKRAY Healthcare Pvt. Ltd., Kyoto, Japan) for *Salmonella Typhi* O and H antigens and *Salmonella paratyphi* A and B antigens were non-reactive.

Antigens *Proteus vulgaris* OX2, *P. vulgaris* OX19, and *P. mirabilis* OXK were obtained from CROMATEST (LINEAR CHEMICALS, S.L.U., Joaquim Costa, Barcelona, SPAIN). The Weil Felix test was performed using a standard protocol with a doubling dilution of 1:20 to 1:160 for initial screening, followed by further dilution (from 1:20 to 1:1280) to achieve the final titer [20, 21]. The Weil Felix test for the OX-19 antigen was weakly positive at a 1:80 dilution and negative for the OXK and OX2 antigens.

Anti-SARS-CoV-2 IgG antibodies (COVID Kavach-Anti-SARS CoV2 IgG Antibody Detection ELISA, M/s Cadila Healthcare Limited, Ahmedabad) were non-reactive. The Mantoux test was negative, and the chest radiograph was normal. All tests ruled out inflammatory causes of vascular occlusion. The peripheral blood smear was normal, and thrombophilia screening was negative.

At the 2-month follow-up, the BCDVA had improved to 20/50 OD, with fundus findings remaining the same as those at the previous visit.

This case report is part of a study approved by the Narayana Nethralaya Ethics Committee (Ethics Committee approval reference number: C/2020/09/09 [virtual]). All tenets of the Declaration of Helsinki were adhered to while recruiting the patient for this study. Written informed consent was obtained for participation and publication of the study data.

## DISCUSSION

Our patient developed fever 2 weeks after the first dose of COVID-19 vaccination and developed progressively worsening blurring of vision in the right eye. The patient was initially treated with oral steroids for PAMM at a local hospital. The condition progressed from PAMM to CRAO during the oral steroid treatment course. At the 2-month follow-up, the right eye BCDVA had improved to 20/50, with fundus findings remaining the same as at the previous visit. The Weil Felix test performed at presentation showed OX19 antigen positivity with negative OXK and OX2 results, indicating a past infection with Indian tick typhus. However, all other laboratory tests were unremarkable.

COVID-19 vaccination with adenovirus vector-based vaccines can be associated with thromboembolic events [22-27] and possibly with systemic inflammation and platelet and endothelial dysfunctions [27, 28]. In the present patient, the retinal vascular occlusion could not be attributed to vaccination or rickettsial infections due to study design. Further studies on the role of vaccination in precipitating this complication in healthy individuals would provide insight into the causation. The Weil Felix test showing antibodies against the OX19 antigen could be false-positive, particularly at the 1:80 dilution [21]. Therefore, clinical correlation is required.

COVID-19 vaccination may be associated with sight-threatening ocular thrombotic conditions that respond to a combination of anti-inflammatory and anticoagulant therapies. A 34- year-old Caucasian man was diagnosed with combined CRAO and vein occlusion with ischemic optic neuropathy and treated with a combination of aflibercept, steroidal and nonsteroidal medications, acetazolamide, antiplatelet agents (aspirin and pentoxifylline), and an anticoagulant (apixaban) [29].

The present patient was initially diagnosed with PAMM in the right eye and treated with oral steroids. Oral prednisolone induces a procoagulant state in healthy individuals, suggesting that corticosteroid treatment may increase the thromboembolic risk in patients with inflammatory diseases [30]. We postulate that the present patient's condition progressed from PAMM to CRAO during the oral steroid treatment course. Hypercoagulable markers, such as the D-dimer, serum ferritin, and lactate dehydrogenase, were normal at the time of presentation.

Pichi et al. [2], in their series of seven patients who developed transient ocular complications 5.2 days after Sinopharm-inactivated COVID-19 vaccine administration, supported an association with the ocular findings but cautioned that a causal relationship could not be established from their study design. Two patients in their series [2] developed PAMM/AMN. One patient had a history of central serous chorioretinopathy and presented

with a profound loss of central vision 1 week after receiving the inactivated COVID-19 vaccine. SD-OCT showed hyperreflectivity of the OPL, Henle fiber layer, and ONL with attenuation of photoreceptors compatible with AMN. The patient did not receive any treatment, and at the 2-month follow-up, the SD-OCT findings had resolved. Another patient in their series [2] developed acute paracentral scotoma following the Sinopharm vaccine administration. Swept-source OCT showed opacification of the inner layers, which they suggested could be PAMM or secondary to an intraretinal hemorrhage. An initial SD-OCT image of the right eye of the present patient revealed a hyperreflective band in the middle INL, suggestive of PAMM. On our examination, the right eye SD-OCT image revealed retinal thinning with disorganization of the retinal layers, sparing the maculopapillary bundle.

Vinzamuri et al. [11] published a report highlighting SARS-CoV-2 vaccination as a possible cause for bilateral PAMM and AMN in the form of a rare adverse effect. Sanjay et al. [12] suggested that AMN and PAMM are possibly related to vascular occlusion and fundus fluorescein angiography or OCTA could add value to SD-OCT findings.

Ishibashi et al. [14] reported that four patients presented with visual field defects associated with branch retinal artery occlusion, AMN, and PAMM after receiving the Pfizer–BioNTech COVID-19 vaccine.

Susac syndrome after SARS-CoV-2 infection and subsequent vaccination, presenting with meningitis and retinal microembolization in the form of PAMM, was reported in a woman in her 50s. The eye fundus examination and OCT findings were consistent with PAMM. D-dimer levels and ESR were elevated [15]. Dehgani et al. [13] reported a 38-year-old patient with no predisposing systemic history who was developed PAMM following the Sinopharm vaccine and debated whether or not it was a mere coincidence or was related to causation.

Regarding PAMM and COVID-19, several case reports have also mentioned the possibility of PAMM occurring after COVID-19 infection [19, 31-40].

Ozsaygili et al. [32], reported in a 26-year-old woman patient an isolated ciliary retinal artery occlusion (CILRAO) and PAMM that were presumed to be associated with COVID-19 (polymerase chain reaction-proven) without severe respiratory distress. They postulated that CILRAO and PAMM are associated with inflammatory and procoagulant conditions caused by SARS-CoV-2 infection [32]. CRAO with PAMM occurred in a 54-year-old man with no relevant medical history and a normal coagulation profile [33]. Gascon et al. [34] reported a 53-year-old man with unilateral PAMM and AMN who was positive for SARS-CoV-2 and postulated that thrombotic complications in the retina could be because of infection. Jonathan et al. [35] reported a case of PAMM in a 47-year-old man with a history of COVID-19 2 months before. Subsequently, the patient developed temporal headache and jaw claudication, and giant cell arteritis was investigated. ESR, CRP, and temporal artery biopsy performed 2 weeks after the initiation of steroids were normal. They suggested that their patient could be the first to potentially be implicated with COVID-19 in both small- and large-vessel vasculitis in an ophthalmic setting [35].

PAMM can present as a discrete monocular painless paracentral scotoma and be associated with a combination of retinal artery/vein occlusions/ciliary artery occlusions as described below. It can also be an initial presentation that evolves into major occlusion, as illustrated in the present patient and a previous case series [41].

PAMM can progress from perivenular to more severe central retinal vein occlusion (CRVO), or from incomplete to complete CRAO [7]. A periventricular PAMM is the only sign of retinal vascular occlusion [42].

Riazi-Esfahani et al. [42] described the multimodal findings of PAMM. They noted that most patients in their series had signs of retinal vascular disease, such as cilioretinal artery or branch retinal artery obstruction, nonischemic CRVO, or a combination of these vascular disorders.

Concerning OCTA and en face OCT, Bakhoum et al. [41], in their series of patients presenting with PAMM and secondary retinal vascular occlusion, showed that the analysis of en face OCT segmentation of the INL identified distinct patterns of PAMM correlating with the severity of ischemia and not with the type of occlusion. They noted that a perivenular fern-like PAMM pattern was associated with better visual outcomes. This pattern was noted to sequentially progress in two cases to a diffuse globular PAMM pattern in the INL or a pattern of ischemia involving both the middle and inner retinal layers, with commensurate vision loss. Globular patterns of PAMM or ischemia involving both the middle and inner retinal layers are correlated with poor visual outcomes [41].

Riazi-Esfahani et al. [42] described PAMM patterns on en face OCT, which included arterial, globular, and fern-like changes at the DCP level. En face OCT can precisely delineate the margins of PAMM. In their series, OCTA showed decreased vascular density in the DCP [42]. Likewise, the present patient's OCTA images of the right eye showed DCP pruning.

OCTA findings in a case of PAMM associated with CRAO in an elderly man showed pruning, attenuation, and low flow of the DCP in the affected eye [43]. The present patient showed pruning of the DCP on OCTA. FAZ was increased at the SCP and DCP levels in en-face scans of the right eye in the present patient, showing an increase in bright areas surrounding the fovea, delineating the area of occlusion (sectoral globular pattern) on 3-mm OCTA scans of the DCP, indicating a greater area of involvement. Furthermore, the INL was thin.

Pichi et al. [44] postulated that isolated CILRAO and CILRAO secondary to CRVO result from hypoperfusion or insufficiency rather than occlusion of the cilioretinal artery and are associated with PAMM or selective infarction of the INL. If giant cell arteritis is associated with CILRAO, complete occlusion of the cilioretinal artery produces ischemia involving both the middle and inner retinal layers, which is associated with worse visual outcomes [44].

This case report illustrates the progression of focal PAMM to global vascular occlusion, possibly following the administration of oral steroids. A single case report may not validate our hypothesis regarding the procoagulant effect of steroids, and whether or not CRAO occurs as a natural course of disease progression should be proven. What was known is that PAMM can be associated with different retinal vascular occlusions. It can occur following COVID-19 vaccination. What this report adds is that unilateral PAMM occlusion can progress to CRAO after COVID-19 vaccination. Randomized controlled trials and case–control studies on the role of vaccination in precipitating thromboembolic events in healthy individuals can provide insight into the causation.

## CONCLUSIONS

We report, for the first time, a young patient with PAMM presenting with focal vascular occlusion that progressed to global occlusion in the form of CRAO and had a normal coagulation profile. The relationship with COVID-19 vaccination was a temporal event with no causality. The present patient had no systemic vascular risk factors associated with retinal vascular events.

## ETHICAL DECLARATIONS

**Ethical approval**: This case report is part of a study approved by the Narayana Nethralaya Ethics Committee (Ethics Committee approval reference number: C/2020/09/09 [virtual]). All tenets of the Declaration of Helsinki were adhered to while recruiting the patient for this study. Written informed consent was obtained for participation and publication of the study data.

**Conflict of interests:** None

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**None.**

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