REVIEW ARTICLE

Paracentral Acute Middle Maculopathy: A Review

Amro Alhazimi[1]*

ABSTRACT

Paracentral acute middle maculopathy (PAMM) is identified by the occurrence of an inner nuclear layer (INL) hyperreflective band on optical coherence tomography (OCT), which was subsequently accompanied by INL atrophy. A multitude of systemic diseases and vasculopathy risk factors have been linked to PAMM. PAMM, which has been associated with infection with Coronavirus disease 2019(COVID 19), may indicate post-infectious complications. By influencing vascular endothelial cells, COVID-19 infection can induce an inflammatory and procoagulatory state, resulting in vascular thromboembolic complications, although the precise mechanisms underlying these complications remain unknown. Thus, the present review explores and discusses about paracentral acute middle maculopathy, its diagnosis and treatment and adds a note on its implications after the outbreak of COVID 19.

Keywords

Paracentral Acute Middle Maculopathy, PAMM, optical coherence tomography angiography, COVID 19

INTRODUCTION

The central macula contains the retinal capillary system, which is a stratified vascular structure consisting of deep as well as superficial capillary plexuses. The intermediate and deep plexuses (IDP) comprise inner and outer surfaces, respectively, of INL[1,2.] Ischemia of the superficial capillary plexus, detected via fluorescein angiography, may present as a cottonwool spot. Nevertheless, fluorescein angiography is insufficient in its ability to depict IDP. Prior to introduction of spectral-domain optical coherence tomography (SD-OCT), abnormalities in the middle retinal plexuses, which are situated in deeper regions, were not easily discernible [3].

In 2013, Sarraf et al. introduced the term "paracentral acute middle maculopathy"(PAMM), which is distinguished by a hyper-reflective band-like lesion in the INL. Prominent OCT findings revealing PAMM co-localizes precisely with IDP, resulting in permanent INL thinning [3,4]. Subsequent occurrence of INL thinning that corresponds to initial lesion of acute middle maculopathy (AMM) in paracentral region suggesting IDP ischemia could be the main cause [5].

Initially, its classified as subtype of acute macular

Correspondence:
Dr Amro Alhazimi, Department of Ophthalmology, College of Medicine, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh, Saudi Arabia; E-mail : ayalhazimi@imamu.edu.sa

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neuroretinopathy (AMN), where lesions manifest above outer plexiform layers (OPL). Nonetheless, at present, PAMM is recognised as an independent entity distinct from AMN5. There is mounting evidence to suggesting it must be classified as a clinical manifestation associated with ischemia of the deep retinal circulation rather than a distinct retinal disorder. Ischemia of the IDP distributed through INL is thought to be the aetiology of PAMM [4-6].

A abrupt onset paracentral scotoma, hyperreflective bands, parafoveal greyish-white lesions etc localised to middle layers of the retina, specifically OPL and inner plexiform layer (IPL), with or without decreased vision, constitute a typical presentation on SD-OCT. Due to ischemia of IDP, distinctive lesions develop [7,8]. There may be an association between this condition and systemic microvascular diseases [9]. Thus, the present paper discusses about paracentral acute middle maculopathy, its diagnosis and treatment and adds a note on its implications after COVID-19 outbreak.

Pathophysiology

It is generally agreed upon that the major cause of PAMM is sublethal ischemia hypoxia of the middle retinal tissue. This is despite the fact that the particular mechanism that underlies PAMM is still clouded [10]. The vessels of the deep capillary plexus (DCP) and the intermediate capillary plexus (ICP) have been seen to change in the region where the choroidal and retinal circulations both feed oxygen to INL and OPL, which are seen in watershed zone[11-13]. As the oxygen supply starts to drop, the oxygen tension is highest in the vicinity of the choroid and superficial retinal layers. This makes this region more susceptible to ischemia than other areas of the eye. It is possible that middle retina is more susceptible to ischemia-related damage because of high oxygen demand of the horizontal cells [14]. There is a possibility that the ICP is the first site of PAMM pathogenesis, with additional downstream DCP changes taking place later. Hence, there have been suggestions that changes in PAMM could potentially serve as an indicator of a middle retinal hypo oxygenation condition, which originates in the inner retina and manifests initially at the level of distal capillary circulation (ICP and DCP) [15]. Although DCP receives blood supply from the SCP by vertical anastomoses that connect the two plexuses, the SCP's involvement in PAMM is intermittent and only occurs when there is ICP/DCP hypoperfusion as SCP obtains blood supply from the ICP. In circumstances in which the ischemia was not as severe, such as when vascular flow was maintained or perfusion was rapidly repaired, the reperfusion injury may be critical to the destruction of the INL. The process of reperfusion leads to an increase in the formation of reactive oxygen species, leakage, neurotoxicity caused by nitric oxide, and inflammation from extravascular spaces [16]. Transient hypoperfusion of the DCP that is an instant restoration of microcirculation can lead to prolonged abnormalities in PAMM as well as reperfusion injury. This can happen when the microcirculation is promptly restored[17]. In individuals who have been diagnosed with foveal hypoplasia (FH), a unique form of paracentral acute middle maculopathy known as central acute middle maculopathy (CAMM) has been discovered. CAMM displays characteristics that are comparable to PAMM, initially appearing as acute changes in the IN [18]. Following that, CAMM enters a stage known as the chronic stage, which is characterised by degenerative changes occurring in both the inner and the outer layers of the retina. There is documented disruption in the vascular patterns of both the deep and superficial retinal layers in individuals who have FH. This may suggest that there is a correlation between the severity of the condition and the disarray in the vascular patterns [19,20]. There is no sign of the foveal avascular zone(FAZ), and the SCP and DCP meet in the middle of the fovea. This is an abnormality. Because of the changes that have been brought up, there has been a reorganisation of the oxygen supply that has been given to the photoreceptors, which has led to an increased percentage of oxygen being supplied by the retinal circulation. In the event that ischemia affects the single foveal vascular layer, the changes that have been described have the potential to put at risk the integrity of the outer retinal layers [19-21]. In this particular setting, depletion of central Muller cells that might occur as a result of ischemia events may also play a part in the loss of photoreceptors. PAMM lesions, regardless of the underlying aetiology, lead to the atrophy of the INL, which causes scotomata, which are the most common symptom that patients present as their major complaint.

Diagnostic Evaluation

Clinically, PAMM can be unilateral or bilateral, with one or more paracentral scotomata that usually appear suddenly. Patients may report having difficulties in focusing or having blurry vision in the centre. There

is no gender preference and a 49–53 average age range is usually seen in PAMM presentation9. In order to diagnose PAMM, various imaging modalities are utilised such as en face OCT, SD-OCT, Swept-source OCT (SS-OCT), optical coherence tomography angiography (OCTA), fluorescein angiography, indocyanine green angiography, infrared reflectance imaging, Blue light fundus autofluorescence, Electrophysiology and microperimetry. SD-OCT, SS-OCT, and CT-A are frequently utilized [22]. Haskes C employed SD-OCT on a PAMM lesion in a 2017 case report, showing irregularity in the central retina while the lesion's slight hypofluorescence was revealed by fluorescein angiography. The patient's persistent scotoma maintained even after the retinal injury resolved, making it easier for SD-OCT to monitor changes in the retina [23]. Shah et al. highlighted the results of OCT angiography (OCTA) in their discussion of 2 cases of PAMM in Indian participants employing multimodal imaging. The first example is a female middle-aged patient who has a paracentral scotoma and SS-OCT results that point to "chronic" PAMM. The second patient showed signs of abrupt visual loss, several creamy white lesions indicative of "acute" PAMM, and imaging characteristics indicative of potential venular blockage [24]. In a 2018 case report, Yaman A employed fundoscopic investigation in a PAMM case, which indicated mild alterations in the temporal fovea of right eye's retinal pigment epithelium. Fundoscopic examination of the left eye found normal results [25].

Associations with other diseases

PAMM was observed to emerge in several systemic conditions, encompassing neurological disorders such as meningitis, idiopathic intracranial hypertension and leptomeningeal tumors9. The occurrence of carotid arterial disease was seen in conjunction with PAMM, encompassing internal carotid artery dissection and high-flow carotid-cavernous fistulas. PAMM have been associated with several vascular procedures, including endovascular coil embolization, cardiopulmonary bypass and aortic aneurysm repair, Documented cases of iatrogenic embolic events resulting in PAMM subsequent to septoplasty procedures including the intraoperative administration of triamcinolone acetonide have been studied [25-28]. In a recent 2023 report, Mishra et al presented two cases of PAMM with ischemic cardiomyopathy [29]. In a study by Burnasheva et al. (2019), researchers examined alterations in retinal microcirculation as well as occurrence of chronic PAMM lesions among individuals with mild hypertension. The findings indicated a high prevalence of chronic PAMM lesions in a sample of 44 hypertensive patients. Moreover, it was suggested that these lesions may serve as the initial indicators of retinal microcirculation changes in individuals with mild hypertension, preceding the manifestation of alterations in OCT angiography parameters [30].

Cerebrovascular illness, periocular anaesthesia that raises orbital pressure and narrows the central retinal artery's flow, and elevated intraocular pressure in early postoperative phases are also suggested as contributory causes [31]. A 70-year-old Caucasian woman with a history of coronary artery disease, multiple prior strokes, hypertension and peripheral vascular disease was the subject of a case study published in 2020 by Kelly H et al [32]. Chen X and Scott RA reported two cases of PAMM that were linked to pregnancy. They used OCT-A to demonstrate the outer retinal capillary plexus's flow attenuation, which further supported the diagnosis of PAMM in pregnancy [33].

Multiple retinal vascular diseases have been linked to PAMM, providing additional evidence where vascular dysfunction is crucial factor in PAMM. A correlation between PAMM and retinal artery or venous occlusions (RVO), including cilioretinal arterial occlusion, has been demonstrated in multiple papers [34]. A 2020 study by Maltsev DS compared the eyes of healthy individuals and patients with unilateral RVO to determine the prevalence of resolved PAMM lesions in fellow eyes. The findings revealed that patients with unilateral RVO have a significantly higher incidence of resolved PAMM lesions, which are defined as INL thinning accompanied by OPL elevation. Resolved PAMM lesions might be correlated with RVO [35].

In recent times, PAMM has been linked to a range of retinal vascular disorders, like non-proliferative diabetic retinopathy, central retinal vein occlusion (CRAO), and RVO. These findings provide additional evidence in favour of the potential ischemic origin of the SD OCT result. Several ocular conditions, including congenital glaucoma, inflammatory chorioretinopathies, and FH have been linked to PAMM [36]. Patients with juvenile dermatomyositis have been reported to have PAMM, which is most likely the result of vasculitic occlusive retinopathy [37].

Additionally, both intraocular and extraocular

ophthalmic procedures have been linked to PAMM. Macular hypoperfusion may be caused by the periocular anaesthesia administered during external ocular surgery [38]. Chen et al. assessed the range of retinal disorders in which isolated ischemia of PAMM, ICP, and DCP can form. A broad spectrum of retinal vascular diseases that are best identified with SDOCT analysis shows that PAMM developed and may represent ischemia of the ICP and DCP, the researchers concluded. These lesions are crucial in determining the cause of unexplained vision loss as they frequently lead to permanent thinning of INL [39]. Long-term retinal alterations in PAMM led to INL thinning, excavation of the inner retinal surface, abnormal vasculature and ONL thickening, particularly in IDP, according to a 5-year follow-up study by Nakamura et al. A focal SRD can occur four years after the commencement of the condition; it is a rare complication [40]. The prognosis for PAMM cannot be ascertained as its natural course is still undetermined. However, the degree of ischemia injury and the aetiology of PAMM, along with any coexisting ocular illnesses, are associated with variable visual outcomes. Since there is currently no known cure for PAMM, care should focus on addressing its underlying cause [9].

PAMM and COVID 19

There are many publications detailing ophthalmological manifestations that have been linked to the COVID-19 outbreak. Although they typically manifest in the eye within 15 days of onset of symptoms, it may be the first site of COVID19 infection in 2.26% of cases [41]. The initial indication or symptom may consist of ocular surface disorders, like conjunctivitis, its incidence is indicative of the condition's severity. Episcleritis and keratitis were also frequently observed. Retinal microhaemorrhages and cotton wool patches have also been documented [42]. Multiple cases emphasising the same have been noted. One such case by Turedi N et al in 2022, described a case of PAMM in COVID positive patient who within 15 days of COVID19 diagnosis, reported vision loss in his right eye. CRAO was detected on fundoscopic examination. Consistent with PAMM, OCT analysis revealed elevated diffuse reflectance and INL thickening [43]. Two patients who tested positive for COVID-19 and developed ocular symptoms within two to four weeks of their diagnosis were detailed in another report. An area of intense reflection was observed in both the inner and OPL, accompanied by a reduction in volume within the inner nuclear layer. OCT revealed a correlation between the alterations in infrared reflectance and the location of the scotoma in the other patient. AMN was confirmed by the observation of a focal region of slight hyperreflective change in OPL and interdigitation zone disruption. These characteristics aligned with PAMM [44]. A similar case was discussed by Gameiro Filho AR et al in 2023 [45]. A greater number of cases, nevertheless, is necessary to ascertain whether a genuine association exists.

PAMM and COVID 19 Vaccinations

Diverse new technologies were utilised to expedite the development of highly effective vaccines in response to the COVID-19 pandemic, which occurred at an unprecedented rate. Two mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna, Cambridge, MA, USA) and one vector COVID-19 vaccine (AstraZeneca, Frederick, MD, USA) are the most frequently used approved vaccines. PAMM has been documented in a number of COVID-19 cases, including those that had received the vaccine. A recent report from 2023 described a patient who developed PAMM symptoms 3 days after getting Pfizer-BioNTech vaccine [46]. Valenzuela et al. presented an additional case involving Pfizer-BioNTech COVID-19 vaccine. They described a 20-year-old female who developed photopsia and scotomata in both eyes 48 hours after getting her second dose of the vaccine. OCT findings confirmed that she had AMN [47]. Ishibashi K et al., Dehghani A, Mentes et al., and others reported similar occurrences in 2022–2023 [48–50]. Pichi et al. reported PAMM and AMN following Sinopharm COVID-19 vaccinations (Shanghai, China), 5 days post Sinopharm BIBP COVID-19 vaccine, which is an inactivated COVID-19 vaccine. A case of PAMM was also documented in an Abu Dhabi patient undergoing vaccination [51]. Vinzamuri et al. documented an instance of PAMM in a 35-year-old male in India, 30 days subsequent to administration of the second dose of the recombinant "Covishield" vaccine [52].

Although the precise mechanisms through which COVID-19 vaccinations induce PAMM/AMN are still unknown, molecular mimicry and antibody-mediated hypersensitivity reactions involving antigen-specific cells are among the most frequently postulated mechanisms. Furthermore, after confirmed COVID-19 infections, CRAO, PAMM, and AMN have been reported. Vascular endothelial cells can be adversely affected by COVID-19 infections, resulting in a procoagulatory and inflammatory state that can

potentially give rise to vascular thromboembolic complications [53]. The presence of significant overlap in the occurrence of retinal adverse events following COVID-19 vaccinations and infections implies that the immune response to COVID-19 might play a role in the development of these complications [54]. More research in this area must be performed and taken into consideration.

Conclusion

Diagnosed as hyper-reflective bands in the intermediate layers of the retina only following the advent of optical coherence tomography, PAMM is a relatively recent discovery in the literature. Although the disorder can potentially be idiopathic, lesions are known to present as direct ischemia reflections of multiple potential risk factors, such COVID-19 infection, vasoconstrictor use, microvascular diseases, and retinal vascular diseases. When a patient's visual abnormalities cannot be diagnosed just by clinical examination, retinal imaging becomes crucial. The related conditions determine the prognosis for PAMM. While idiopathic patients typically have satisfactory outcomes, some PAMM cases may experience significant visual loss. Therefore, if PAMM is detected, particularly in the acute phase, it necessitates a thorough history and the prompt exclusion of significant underlying ocular and systemic etiologies.

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Conflict of Interest

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Data Availability

Not applicable

Authors' Contribution

Dr Amro Alhazimi has conceptualized the study, literature search, manuscript preparation and review.

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