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Paracentral acute middle maculopathy in a patient with Myelin Oligodendrocyte glycoprotein antibody associated optic neuritis

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ABSTRACT

Purpose: There is insufficient literature reporting the concurrent occurrence of retinal ischemic lesions with optic neuritis. In this case report, we present a distinctive instance of Optic Neuritis with a positive Myelin Oligodendrocyte glycoprotein (MOG) antibody, accompanied by retinal ischemia manifesting as paracentral acute middle maculopathy (PAMM) lesions.

Observations: Our patient is a 25-year-old female who tested positive for MOG antibodies and exhibited retinal PAMM lesions without any apparent underlying ischemic cause. She received intravenous pulse steroid therapy, and her symptoms and signs completely resolved one month later.

Conclusion: PAMM can serve as an initial manifestation of Myelin Oligodendrocyte glycoprotein Antibody Associated Disease (MOGAD). This case has the potential to contribute to the existing literature, facilitating a deeper exploration of the pathophysiology of retinal ischemia in MOG associated optic neuritis.

1. Introduction

Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease (MOGAD) is a relatively recently described etiology of optic neuritis, which can manifest as either a monophasic disease or have a relapsing course. It often presents alongside other central nervous system demyelinating conditions, such as transverse myelitis and acute disseminated encephalomyelitis.[1] Retinal involvement in MOGAD is infrequent. Reported retinal findings in MOGAD include serous retinal detachment, premacular hemorrhage, acute macular neuro-retinopathy (AMN), and a neuro-retinitis pattern.[2–5] Paracentral acute middle maculopathy (PAMM), an AMN type 1, is characterized by hyper-reflective lesions in the inner nuclear layer and outer plexiform layer of the retina on optical coherence tomography (OCT), indicating retinal ischemia affecting the superficial capillary plexus.[6] Sarraf et al. described this variant of the disease and differentiated it from the traditionally described AMN (Type 2), which presents as hyper-reflective lesions in the outer nuclear layer on optical coherence tomography.[6,7] Deshchamps et al. reported an association between acute optic neuritis and AMN type 2, with an increased prevalence of AMN observed in MOGAD patients compared to other forms of optic neuritis.[3] However, our literature search revealed only one case report that showcases the presence of PAMM in a middle-aged female with bilateral MOG-associated optic neuritis.[8] This case report highlights a unique occurrence of PAMM in a patient with unilateral MOGAD.

2. Case report

A 24-year-old female presented to our hospital's emergency department, reporting a sudden, painless blurring of vision in her left eye that she had noticed for the past two days. She had previously sought medical advice elsewhere and was subsequently referred to our hospital with a diagnosis of left-eye optic neuritis. Notably, she did not experience concomitant complaints of headache, pain upon ocular movements, other neurological symptoms, or similar issues in her right eye. Her medical history included multiple episodes of transient visual obscurations in the last month, each episode lasting about 5–10 seconds and resolving spontaneously. Her visual acuity at a distance measured 20/20 in her right eye and 20/40 in her left eye, which improved to 20/20 when tested with a pinhole. She also failed a color vision test in her left eye. A swinging flashlight test revealed a relative afferent pupillary defct in her left eye. Her ocular motility and slit lamp examination findings were unremarkable. Dilated examination of the right eye's fundus showed no abnormalities, while the left eye exhibited a healthy

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optic nerve head. As a result, the diagnosis was retrobulbar optic neuritis in the left eye, and an order was placed for Magnetic Resonance Imaging (MRI) of the brain and orbits with contrast.

On the following day, her left eye's vision remained unchanged. A detailed fundus examination revealed a healthy optic disc in both eyes. However, in the left eye, distinct perivascular hypopigmented patches were observed temporally to the fovea in the posterior pole (Fig. 1A). The retinal vessels appeared normal, maintaining an arteriovenous ratio of 2:3.

On the same day, she underwent several diagnostic tests, including visual field testing using the Humphrey Visual Field Analyzer 3 (Carl Zeiss, USA), optical coherence tomography (OCT) performed with the Spectralis OCT (Heidelberg Engineering, Dossenheim, Germany) and Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA). Additionally, fundus autofluorescence (FAF) imaging was conducted using cSLO, Heidelberg Retina Angiograph 2 (HRA2; Heidelberg Engineering, Dossenheim, Germany), and fundus fluorescein angiography (FFA) was performed with the Heidelberg HRA2 system (Heidelberg Engineering, Inc., Vista, CA).

Her visual field analysis of the left eye indicated depressed points in the periphery without a central scotoma. The foveal threshold was lower (27 dB) compared to the right eye (33 dB) (Fig. 1G). Fundus Autofluorescence imaging revealed multiple perivascular hypoautofluorescent lesions at the macula in the left eye (Fig. 1B) and a normal autofluorescence pattern in the right eye. Spectral domain OCT of the left eye revealed hyper-reflective lesions in the inner nuclear layer and outer plexiform layer, suggestive of PAMM lesions (AMN, type 1) (Fig. 1C). Her FFA did not show any perivascular leakage; however, there was delayed central retinal artery filling (19 seconds) (see Fig. 1D, E, 1F). T1-weighted magnetic resonance (MR) imaging of the orbit with gadolinium contrast revealed enhancement of the left optic nerve sheath at the orbital apex, indicative of left eye optic nerve perineuritis (Fig. 2). No demyelinating or ischemic lesions were found in the brain and brainstem.

The presence of PAMM lesion on OCT indicates ischemia in the superficial capillary plexus of the retina and the poor color vision and presence of afferent pupillary defect in the left eye along with the MRI findings indicate optic neuritis. This dual presentation of retinal ischemia alongside optic nerve perineuritis posed a challenging situation, prompting us to conduct a comprehensive investigation. We aimed to explore potential biomarkers for ischemia such as complete blood profile, inflammatory markers, connective tissue disease profile, prothrombotic profile, and conducted enzyme-linked immunosorbent assays (ELISA) for HIV and Treponema pallidum haemagglutinin assay for syphilis and biomarkers for atypical optic neuritis, including serum Aquaporin-4 antibodies and serum Myelin Oligodendrocyte Glycoprotein (MOG) antibodies.

Her blood reports (Table 1), which included a complete blood count profile, erythrocyte sedimentation rate, C-reactive protein, prothrombotic profile, human immunodeficiency virus, and syphilis serology, all returned normal results. Additionally, her connective tissue disease profile, Serum angiotensin-converting enzyme (Serum ACE) levels, and a contrast-enhanced computed tomography of the chest were all unremarkable. The only positive finding in her serology was the presence of anti-MOG antibodies.

Furthermore, we recommended that she consult a physician and undergo a 2D Echocardiogram, electrocardiography, and carotid Doppler, all of which yielded results within the normal range.

With all serology reports being negative, except for testing positive for anti-MOG antibodies, the patient was initiated on intravenous methylprednisolone (IVMP) at a dosage of 1 g per day for five days. This was followed by a tapering regimen of oral steroids, in addition to calcium supplements.

Remarkably, she experienced significant improvement in her symptoms and achieved a visual acuity of 20/30 after completing the five doses of IVMP. During the one-month follow-up, her visual acuity had further improved to 20/25. Both fundus examination (Fig. 3A) and FAF imaging (Fig. 3B) revealed no hypopigmented areas, and her OCT scan showed the absence of PAMM lesions in her left eye (Fig. 3C) and resolved peripheral depressed points on Humphrey Visual fields (Fig. 3D).

3. Discussion

While retinal abnormalities are frequently observed in cases of infectious or inflammatory optic neuritis, such as syphilitic optic neuritis

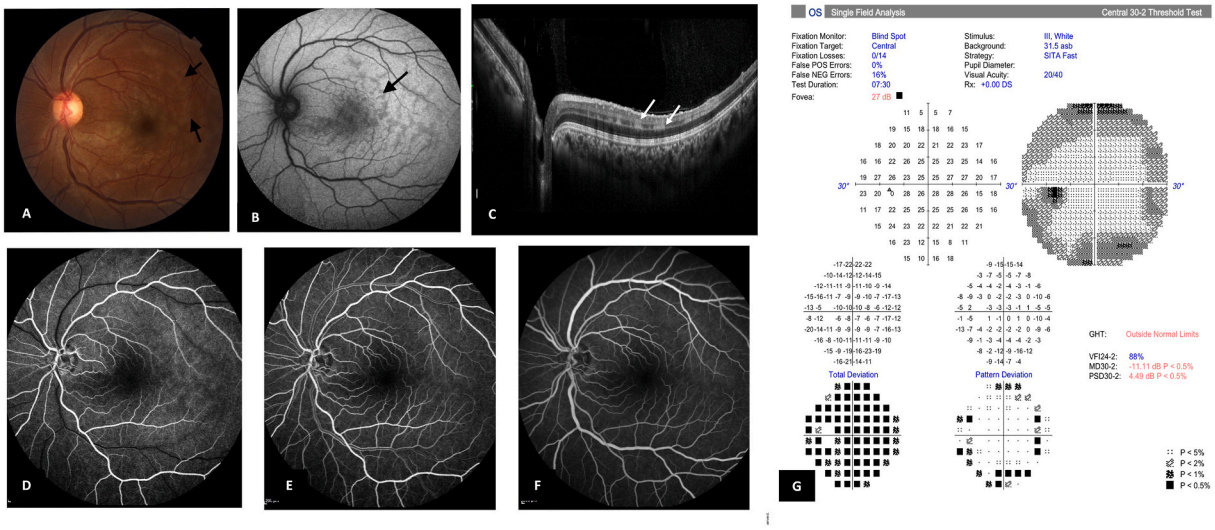

Fig. 1. (A) Color fundus photograph of the left eye showing perivascaular hypopigmented patches within the posterior pole (black arrows) (B) Fundus autofluorescence showing hypoautofluorescent lesions (black arrows) corresponding with the hypopigmented patches on the color fundus pictures. (C) Spectral domain optical coherence tomography (SD-OCT) line scan passing through the paramacular region of the left eye showing hyperreflectivity in the inner nuclear and outer plexiform layer suggestive of paracentral acute middle maculopathy (white arrows). (D,E,F) Fundus Flourescein Angiography of the left eye in Arterial phase(D), Arteriovenous phase(E), and Venous phase(F) demonstrating no leakage at the corresponding lesions seen on color fundus pictures. (G) 30-2 Humphrey visual field analysis of the left eye of the first visit showing multiple depressed points in the periphery on the grayscale map corroborating on the pattern deviation and pattern deviation probability plots.

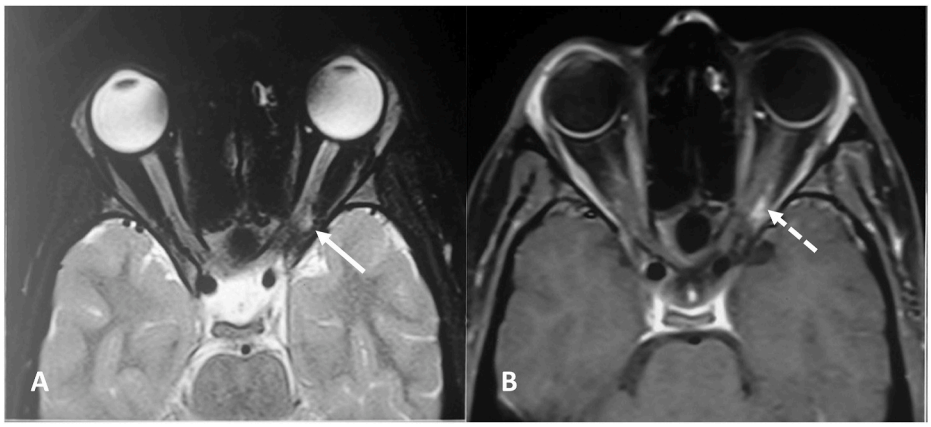

Fig. 2. Magnetic Resonance Imaging (A) Axial T2 weighted image weighted image showing thickening of left optic nerve sheath at the apex (white arrow). (B) Axial T1 weighted post contrast fat suppressed image showing perineural sheath enhancement at the orbital apex (dashed arrows).

Table 1
The values of individual serology test in our patient with normal physiologic range.

Investigations	Value	Physiologic range
Haemoglobin	10.4	12–15 g/dl
Red Blood Cell count	4.4	4–5.2 mill/cumm
White Blood Cell count	3.9	3.5–9 th/cumm
Random Blood Sugar	91	<160 mg/dl
Bleeding time	2.5 min	
Clotting time	4.3 min	
Blood urea	14	10–40 mg/dl
Serum Creatinine	0.5	0.5–1 mg/dl
Acetly Cholinesterase (ACE)	18.5	12–68 IU/L
Estradiol (E2)	83.91	26.6-382 pg/ml
Erythrocyte sedimentation rate (ESR)	20	<20 mm/hr
C Reactive Protein (CRP)	1.1	<6 mg/L
Prothrombin Time (PT)	15	11–15 s
ActiFated Partial Thromboplastin Clotting Time	40	22–37 s
International Normalized Ratio (INR)	1.2	
Human Immunodeficiency Virus 1&2 Antibody	0.39	<0.9
Treponema pallidum Haemagglutination Assay	Negative	
Anti Neutrophil Antibody (ANA)	0.59	<0.90
C-Anti Neutrophilic Cytoplasmic Antibody (C-ANCA)	7.10	<20 Units
P-Anti Neutrophilic Cytoplasmic Antibody (P-ANCA)	8.50	<20 Units
Anti Phospholipid Antibody	4.30	<12 U/mL

or neurosarcoidosis, these findings are less common in demyelinating optic neuritis. Instead, accelerated thinning of the inner retinal layer has been documented, both in optic neuritis associated with multiple sclerosis (MS) and MOGAD.[9,10] The number of reports detailing retinal ischemic lesions alongside optic neuritis becomes even scarcer, with only a single case series documenting an association with AMN type 2 and a solitary case report demonstrating PAMM, or AMN Type 1, in the context of MOGAD.[3,8] AMN type 2 typically involves the outer retinal layers and is characterized by reddish-brown wedge-shaped retinal lesions. In the case series conducted by Deschamps et al. out of 114 patients with optic neuritis, AMN type 2 was observed in six patients, and of those, three were diagnosed with MOGAD.[3] None of the patients exhibited PAMM lesions. It's worth noting that although PAMM was initially described as AMN Type 1, it is now recognized as a distinct entity, characterized by the presence of hyper-reflective bands in the outer plexiform layer and inner nuclear layer (OPL/INL).[11] The OPL and the INL are particularly vulnerable to ischemic damage because they are situated in the watershed zone where oxygen is supplied by both the choroidal and retinal circulation.[12] Furthermore, due to the high oxygen consumption by horizontal cells, the middle retina is prone to ischemic damage.[13] The presence of PAMM lesion on OCT indicates ischemia in the superficial capillary plexus of the retina. There are numerous potential causes for PAMM, including dyslipidemia, anemia, migraine disorder, carotid artery disease, excessive caffeine consumption, and drug-induced PAMM triggered by Phosphodiesterase-5 inhibitors such as Sumatriptan. Additionally, neuro-ophthalmological disorders like idiopathic intracranial hypertension, meningitis, and leptomeningeal tumor infiltration have also been implicated as contributing factors.[12] The incidence of PAMM in retinal vascular diseases is well-documented and easily understandable, given the pathogenesis.[14–16]

However, PAMM has also been reported in various ocular conditions, including inflammatory chorioretinopathies, congenital glaucoma, foveal hypoplasia, and even following intraocular procedures such as phacoemulsification and pars plana vitrectomy for tractional retinal detachment, as well as vitreous hemorrhage. In the latter cases, the suspected cause appears to be hypoperfusion resulting from periocular pre-operative anesthesia.[17–21]

The available literature discussing the incidence of PAMM in cases of optic neuritis is quite limited. In their case series, Deschamps et al. put forward a hypothesis suggesting a connection between optic neuritis and AMN Type 2, with 50% of their patients being attributed to MOGAD as the underlying cause.[3] In a recent case report by Fernandez et al. they documented a case that closely resembled ours.[8] However, their patient was a 5-year-old female with a severe presentation, exhibiting bilateral optic neuritis and her symptoms rapidly progressed to complete blindness within a mere ten-day period. A possible explanation for this difference could be the severity of MOGAD, with our patient displaying relatively better visual acuity and experiencing primarily peripheral vision loss, as indicated by the good pinhole visual acuity and confirmed through visual field analysis. A striking similarity, nonetheless, was observed during the one-month follow-up after intravenous methylprednisolone therapy, as both patients achieved significant visual improvement. The hyper-reflective PAMM lesions on the OCT diminished, mirroring the outcomes in our case. A similar battery of tests to identify the ischemic etiology was performed, but unfortunately, they failed to provide any conclusive results.

In our patient, we inquired about a history of contraceptive use and medications for migraine disorder, both of which are known vasculopathic risk factors for PAMM, and ruled them out. Although the history of transient visual obscurations suggests an ischemic etiology, we conducted a carotid Doppler and a 2D ECHO, both of which yielded normal results in our case. Given the absence of an ischemic cause, it is reasonable to consider that perineuritic inflammatory edema associated with MOGAD might have led to mechanical compression and diminished blood flow in the superficial retinal capillary plexuses, resulting in the development of PAMM lesions. A similar hypothesis was proposed by both Deschamps et al. and Fernandez et al. who also documented

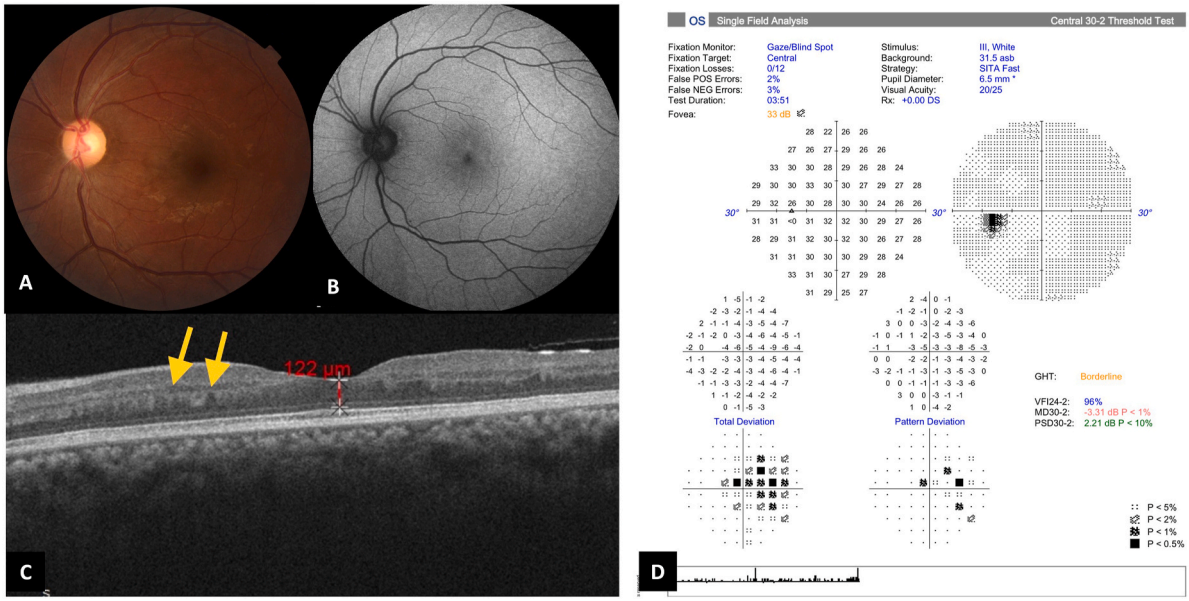

Fig. 3. (A) Color fundus photograph of the left eye at the last hospital visit showing resolution of hypopigmented patches. (B) Fundus autofluorescence showing completely resolved hypoautofluorescent lesions. (C) Spectral domain optical coherence tomography line scan passing through the paramacular region of the left eye showing reduction of hyperreflective lesions (yellow arrows). (D) 30-2 Humphrey visual field analysis of the left eye of the last visit showing normal gray scale plot and scattered depressed points with a single central depressed point on pattern deviation plot, there are no depressed points in the periphery.

inflammatory edema secondary to optic neuritis as a possible cause.[3,8] Feucht et al. conducted a study where they found that individuals who had experienced early stages of multiple sclerosis (MS) or clinically isolated syndrome (CIS) and had a prior episode of acute optic neuritis (AON) exhibited a reduction in the density of blood vessels within both the superficial and deep layers of the retina, as observed through retinal optical coherence tomography angiography (OCT-A).[22] This decrease in vessel density could potentially be attributed to a direct inflammatory response affecting the retinal vasculature during the acute phase of optic neuritis. Optic neuritis is occasionally associated with inflammation around the peripheral retinal vessels, a condition known as periphlebitis. In some cases, this inflammation can progress to occlusive vasculitis, resulting in impaired blood flow. The authors suggest that the retinal manifestations observed in acute macular neuroretinopathy could be a consequence of this process extending to the posterior pole.[22]

In essence, the findings suggest a potential link between the inflammatory events seen in optic neuritis and subsequent vascular alterations within the retina, shedding light on the pathophysiological mechanisms underlying acute macular neuro-retinopathy (type 1or type 2) development in individuals with a history of optic neuritis. PAMM leads to long-term and permanent thinning of the inner nuclear layer (INL). However, a more extended follow-up period will be necessary to observe and document the same in our patient.

4. Conclusion

The lack of any specific etiology for PAMM suggests that MOGAD may be the underlying cause. Although there is limited literature on ischemic retinal lesions in MOGAD, further investigation of this association can provide insights into the pathophysiology of the disease.

Patient consent

Consent to publish this care report has been obtained from the patient in writing in accordance with the Elsevier patient consent policy.

Institutional review board

An ethical clearance was obtained from the Institutional review board (LEC-BHR-R-01-24-1168) for the current report.

Authorship

All authors attest that they meet the 4 current ICMJE criteria for Authorship.

Declaration of figures' authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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CRediT authorship contribution statement

Aniruddh Heroor: Writing – review & editing, Writing – original draft, Methodology, Data curation. **Mudit Tyagi:** Writing – review & editing, Validation, Supervision, Methodology. **Ramesh Kekunnaya:** Writing – review & editing, Validation, Supervision, Methodology. **Goura Chattannavar:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors have no conflict of interest.

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