Case Series: Paracentral Acute Middle Maculopathy as a Sign of Severe Systemic Vasculopathy

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Abstract
Paracentral acute middle maculopathy represents deep capillary ischemia that can cause acute symptoms of scotoma. This case series describes two cases of symptomatic paracentral acute middle maculopathy that reflect the more severe spectrum of associated etiologies. Case 1: A 65-year-old male with recent history of hypertensive encephalopathy presented with sudden onset central visual disturbance described as amorphic in shape. Dilated fundus exam revealed severe hypertensive retinopathy with paracentral acute middle maculopathy. The patient died one year after the initial discovery of the retinal lesions. Case 2: A 87-year-old male presented with paracentral vision loss in one eye for three days. Clinical examination revealed multiple Hollenhorst plaques and paracentral acute middle maculopathy at presentation, and a subsequent branch retinal artery occlusion two days later. The patient was found to have 76% left carotid artery stenosis with numerous brain infarcts. The detection of paracentral acute middle maculopathy indicates an investigation through ocular and systemic risk factors to determine an attributable etiology. The search for possible etiologies should be tailored to the particular patient, based on age, associated ocular findings, systemic history, and symptomatic versus incidental presentation. The presence of symptomatic paracentral acute middle maculopathy, particularly in at-risk vasculopathic patients, should be addressed urgently as it may be an indicator of an underlying severe systemic disease process.

Introduction
Paracentral acute middle maculopathy (PAMMM) was first described in 2013 by Sarraf et al. as parafoveal focal or diffuse hyper-reflective lesions localized to the middle inner nuclear layer with spectral-domain optical coherence tomographic (SD-OCT) imaging. The middle retinal layers are supplied by the intermediate and deep retinal capillary plexuses, and acute lesions in this area suggest ischemia of the capillary systems. Paracentral acute middle maculopathy has since been associated with the use of vasoconstrictors, systemic vasculopathy, retinal vascular diseases, or idiopathic cause. The range of retinal vascular etiologies include diabetic retinopathy, hypertensive retinopathy, sickle cell retinopathy, and retinal vascular occlusions. Thus, management of most acute presentations primarily focuses on a detailed search for causative factors. This case series presents symptomatic paracentral acute middle maculopathy occurring in at-risk vasculopathic patients, which reflect the more severe spectrum of the novel finding and its impact on management for patients with existing vasculopathy. No identifiable health information was reported in the case reports.

Case 1
A 65-year-old Caucasian male presented with a chief complaint of a daily visual disturbance in his left eye that began two weeks ago. The visual disturbance was described as an amorphic shape that changed colors and shapes, located in the central field, slightly left of fixation. The visual disturbance was noticed 70% of the time throughout the day and was more noticeable today and when looking at white walls. Significantly, the patient had a medical history of chronically uncontrolled hypertension due to poor medication adherence. One month prior to the eye exam, the patient was admitted to the emergency department due to a hypertensive emergency. With a blood pressure reading of 250/150 mmHg in addition to an episode of slow responses, confusion, head tilting, and unusual bot-like movements, the patient was diagnosed with hypertensive encephalopathy. After resolution of the encephalopathy and improvement in hypertensive control with treatment, the patient was then discharged to the nursing home to be managed closely by an interdisciplinary team. The patient’s Snellen acuities were 20/20 in the right and left eye. Frequency-doubling technology C-20-5 test revealed no defects in the right eye and shallow repeatable superior temporal central defects in the left eye. Dilated examination findings were significant for bilateral vein nicking, arterial attenuation, few scattered cotton wool spots, macular exudates, and multiple flame hemorrhages and a subtle, small, hazy hypopigmented area nasal to the fovea in the left eye (Figures 1 and 2). SD-OCT scans of the macula revealed a patch of hyper-reflectivity at the outer plexiform layer and inner nuclear layer nasal to the fovea in the left eye (Figure 3A). Further ischemia, such as from a branch retinal artery occlusion, was ruled out with fluorescein angiography (Figures 4 and 5). At the

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Patient’s two-month follow-up, the patient reported intermittent and infrequent dark spots in vision in the left eye, but overall reduction in visual disturbances. An updated SD-OCT scan of the macula showed middle retinal thinning corresponding to the location of previously active lesion (Figure 3B). The patient was diagnosed with severe hypertensive retinopathy OU with paracentral acute middle maculopathy OS associated with severe hypertension. Because PAMM is a self-limiting finding, management involved notifying the primary care provider of the acute visual disturbance as well as its likely systemic etiology. In this case, the patient was already closely observed for severe hypertension by an interdisciplinary team. The patient subsequently died 6 months after the initial discovery of maculopathy.

Figure 1 and 2. Fundus photos of severe hypertensive retinopathy, including arterial attenuation, vein nicking, few scattered cotton wool spots, macular exudates, and multiple flame hemorrhages right eye (Figure 1) and left eye (Figure 2). Left eye is significant for a small grey-white area inferior nasal to the fovea (blue arrow).

Figure 3A and 3B. Heidelberg SD-OCT macular scan of acute maculopathy involving the inner plexiform and inner nuclear layers left eye (A) and subsequent atrophy two months later (B). The near infrared image portrays the PAMM lesion as dark or hypo-reflective (yellow arrow).

Figure 4. Late phase fluorescein angiogram at 5 minutes demonstrating scattered areas of hypo-fluorescence from overlying cotton wool spots, but an otherwise normally perfused retina right eye.

Figure 5. Late phase fluorescein angiogram at 2 minutes demonstrating a subtle area of nonperfusion inferior nasal to fovea (red) left eye.
Case 2
A 87-year-old Caucasian male presented with vision loss in the left eye for three days. He reported a large central spot, light “grey-blue” in color noticed upon waking three days ago. Significant medical history consisted of benign hypertension, stage 3 chronic kidney disease, cerebral infarction, and hyperlipidemia. Entering Snellen visual acuities were 20/20 in the right eye and 20/60 in the left eye. Fundus exam revealed three subtle paramacular patches of hypopigmentation in the left eye. A SD-OCT scan showed edema of outer plexiform and inner nuclear layers nasal parafoveally a smaller patch temporal parafoveally (Figure 6). Two days after initial presentation of multiple areas of paracentral acute middle maculopathy, the patient reported with no changes in visual symptoms. On the follow-up dilated fundus exam of the left eye, the patient was noted to have three arterial emboli: one at the disc and two along inferior arcades (Figure 7). The macula was remarkable for multiple paracentral acute middle maculopathy lesions parafoveally and an evolving superior branch retinal artery occlusion of the left eye. The patient was referred to the emergency department immediately for a stroke work-up. A carotid ultrasound was ordered to evaluate the level of stenosis, as well as a magnetic resonance imaging brain scan to search for other cerebral emboli. The patient’s same-day magnetic resonance imaging of the brain revealed multiple newly discovered cerebral infarcts, while the carotid ultrasound showed 76% left carotid artery stenosis.

Discussion
First discovered by Sarraf et al. in 2013, paracentral acute middle maculopathy (PAMM) was descriptively termed for the parafoveal location of the gray-white lesion, the acute onset of scotoma, and the localization to the middle inner retinal layers on SD-OCT.1 The presence of PAMM serves as a sign of ischemia as opposed to a disease in itself, somewhat analogous to a cotton wool spot within the inner retinal layers. PAMM is relatively new in literature, discovered only with the advent of high-resolution imaging. In the original study by Sarraf et al., the average age of onset was 59 years with a predilection for males.1 Because of the rarity of the retinal finding, reported in only small case studies, the prevalence rates are unknown. Paracentral acute middle maculopathy was originally believed to be a novel superficial variant of acute middle neuroretinopathy (AMN). AMN lesions differ in that they develop deeper, specifically at the junction of the outer plexiform layer and outer nuclear layer, and can be associated with disruption of the ellipsoid zone. PAMM and AMN are now recognized as independent entities due to the differences in pathophysiology as AMN is thought to primarily develop from ischemia to the inner choroid. Demographic disparity also exists: patients with PAMM lesions typically present in males later in life at 59 years old, whereas patients with AMN lesions present most commonly in females at 33 years of age.3

Patients with paracentral acute middle maculopathy can be asymptomatic or present with symptoms of sudden onset single or multiple paracentral scotomas accompanied with mildly decreased visual acuity.1 Funduscopic examination often reveals subtle, parafoveal lesions that are gray-white in color, though some cases lack visible fundus abnormalities.1 Subtle or absent retinal appearance has caused a shift towards more sophisticated imaging to diagnose PAMM. With SD-OCT, thickened hyper-reflective bands in the middle retina are characteristic for the condition.1 OCT angiography with en face projection can obtain high-resolution scans of the microvasculature in PAMM, specifically flow void in the deep capillary plexus and sparing of the superficial capillary plexus.4,5 Although fluorescein angiography is the gold standard for detecting ischemia and should hypothetically allow for visualization of capillary dropout from PAMM, its resolution is insufficient for detecting isolated loss of the deep capillary plexus, likely due to normal flow of the overlying superficial capillary plexus.2
The presentation of PAMM is hypothesized to represent intraretinal ischemia of the intermediate and deep retinal capillary plexuses within the inner nuclear layer.\textsuperscript{1} This retinal vasculopathic etiology is supported by Nemiroff et al. in a study analyzing patients with PAMM using OCT angiography.\textsuperscript{5} During the subsequent stages of PAMM, the study found that the superficial capillary plexus in that area had minimally attenuated perfusion in affected eyes, while the deep capillary plexus was significantly attenuated on OCT angiography.\textsuperscript{6} The mean vessel density of the deep capillary plexus in normal eyes was significantly higher than that of eye with PAMM lesions, further supporting the ischemic pathogenesis of the condition.\textsuperscript{6}

In addition, some evidence revealed that the choriocapillaris may also be hypoperfused along with the deep capillary plexus in PAMM lesions.\textsuperscript{7} Retinal changes 2.5-5 years after acute PAMM lesions include excavation of the inner retinal surface, inner nuclear layer thinning, and presence of abnormal vasculature in the deep capillary plexus.\textsuperscript{8}

The etiology of PAMM has not been clearly elucidated as causative factors range from the use of vasoconstrictors, such as caffeine, amphetamines, epinephrine, and oral contraceptives, to microvascular diseases, including hypertension, diabetes, and sickle cell disease.\textsuperscript{9,10,11} PAMM has also appeared with embolic retinal occlusive diseases, such as Purtcher’s retinopathy, retinal arterial occlusions, and retinal vein occlusions.\textsuperscript{12,13} In a series of 484 patients with central retinal vein occlusions, paracentral acute middle maculopathy was observed in 5.2% of patients.\textsuperscript{14} Migraines, orbital trauma, severe hypovolemia, post-H1N1 vaccine, upper respiratory infection, retinal vasculitis, giant cell arteritis, and birdshot retinopathy have all been reported in association with PAMM as well.\textsuperscript{3,15,16,17} PAMM may also develop idio pathically in young and healthy individuals.\textsuperscript{18} Newest reports have shown evidence of resolved PAMM in patients previously infected with the novel coronavirus disease (SARS-CoV-2).\textsuperscript{19,20,21} Despite the wide range of possible risk factors, PAMM is a sign of retinal capillary plexus ischemia that may herald the presence of a secondary underlying condition.

There is no ocular treatment for PAMM at this time. Permanent inner nuclear layer thinning at the area of the retinal lesion is expected with subsequent ischemia.\textsuperscript{8} The scotoma may improve but generally persist.\textsuperscript{8} Management of PAMM is targeted toward identification and treatment of related ocular and systemic risk factors. The search for possible etiologies should be tailored to the particular patient, based on age, associated ocular findings, systemic history, and symptomatic versus incidental presentation. An incidental OCT finding suggestive of chronic PAMM in a patient with established risk factors requires a less urgent management plan than that of an acute, symptomatic presentation. Unless the retinal vascular etiology and underlying diagnosis is apparent, as in hypertensive retinopathy or retinal vascular occlusions, the detection of PAMM in the acute phase indicates an exhaustive search for extrinsic risk factors. Timely screening of more serious systemic risk factors, including stroke, carotid artery disease, sickle cell disease, hypertension, diabetes, and giant cell arteritis, is critical. Patients diagnosed with PAMM should also be questioned about vasopressor exposure, especially if the patient has minimal existing vasculopathic risk factors.\textsuperscript{9} An idiopathic etiology should only be established if all other risk factors have been excluded.\textsuperscript{18} PAMM lesions with associated paracentral scotomas may drive a patient towards initial eye examination and be the cause of a newly discovered entity. Therefore, a symptomatic presentation of PAMM should always be treated with significance, first ruling out severe and life-threatening ocular and systemic causative risk factors, then modifying the investigation for the specific patient.

**Conclusion**

Paracentral acute middle maculopathy is a relatively new finding in literature, diagnosed only during the era of optical coherence tomography as hyper-reflective bands in the middle layers of the retina. At this time, lesions are known to present as direct ischemic reflections of a number of possible risk factors, including vasoconstrictor use, microvascular diseases, retinal vascular diseases, as well as the novel COVID-19 infection, but the condition can also exist as idiopathic in nature. This case series represents the more severe spectrum of paracentral acute middle maculopathy etiologies. Thus, the presence of paracentral acute middle maculopathy, notably in the acute phase, warrants a detailed history and timely exclusion of serious underlying ocular and systemic etiologies.

**References**