An Early Warning Eye Finding In The Diagnosis of Hereditary Thrombophilia: Paracentral Acute Middle Maculopathy

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ABSTRACT

Paracentral acute middle maculopathy (PAMM) is an optical coherence tomography (OCT) finding secondary to retinal ischemia. In this presentation, we describe the diagnosis of hereditary thrombophilia caused by multiple gene mutation, based on the PAMM finding on OCT, in a patient with no known disease who presented with unilateral scotoma. Hematological evaluation has an important role in young PAMM cases without systemic and ocular disease. Patients with thrombophilic mutations may be first recognized with ocular symptoms by ophthalmologists. It may be life-saving to reveal the risks of patients such as cardiovascular disease and thromboembolism at an early age.

Keywords: Hereditary thrombophilia, Paracentral acute middle maculopathy, Optic coherence tomography, Retinal ischemia.

INTRODUCTION AND AIM

Paracentral acute middle maculopathy (PAMM) is a optical coherence tomography (OCT) finding which was first defined as hyper-reflective band in inner nuclear layer by Sarraf et al. in 2013.[1] Initially, PAMM was considered as a subtype of acute macular neuropathy, it was understood that PAMM is a distinct finding by advance of spectral-domain OCT and optical coherence tomography angiography (OCTA).[2,3] Although there are ongoing studies on its mechanism, it is known that PAMM is due to ischemia resulting from hypoxia of middle retinal layers.[4]

In the literature, association of PAMM with many systemic and ocular diseases have been reported. Rahimy et al. reported PAMM lesion in 25 of 484 patients with non-ischemic central retinal vein occlusion.[5] The association of PAMM with cilioretinal artery occlusion, hypertensive retinopathy and diabetic retinopathy have been reported.[6-7] Again, it was also reported that it may also be associated with inflammatory chorioretinopathies where ocular ischemia is seen, ocular diseases such as congenital glaucoma or foveal hypoplasia and intraocular and extra-ocular surgeries.[8-9] In addition, PAMM is also associated with systemic (e.g. intracranial hypertension, meningitis, dyslipidemia) and viral diseases.[10, 11]

The term thrombophilia is used for conditions where predisposition to thrombosis is increased in hemostatic mechanisms; thus, risk for thromboembolism is increased.[12] Many hereditary and acquired factor have been defined, which cause thrombophilia. Hereditary thrombophilia is defined as increased predisposition to venous thromboembolism genetically. [12]

In this care report, we discussed diagnosis of hereditary thrombophilia based on findings of retinal venous stasis accompanying to PAMM in a young male with no known disease who presented with unilateral scotoma. Here, it is emphasized that OCT, which plays great role in the ophthalmology practice, is also valuable in the early diagnosis of systemic diseases such as thrombophilia that may be associated with fatal complications.

CASE REPORT

A 30-years old male patient with no known systemic or

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ocular disease presented with blurred vision and scotoma in the right eye. In the ophthalmological examination, visual acuity was 20/20 and intraocular pressure was 16 mmHg in both eyes. Anterior segment findings were normal and optic nerve were also normal in both eyes; however, there was increased tortuosity in retinal veins. There was marked dilatation in the right superior temporal vein; slight paleness macula and splinter hemorrhage inferior to optic disc (Figure 1a). On fundus fluorescein angiography (FFA), it was seen that there was no pathology other than hypo-fluorescence due to hemorrhagic blockade in the right (Figure 1b). On OCT imaging of right eye, hyper-reflective band appearance, which is characteristic for PAMM, was observed at the inner nuclear layer in the sections corresponding to pale areas on macula (Figure 2). OCT imaging of left eye was normal. Due to findings of retinal venous stasis accompanying to PAMM in the right eye, the patient was consulted with infectious diseases, rheumatology and hematology for evaluation of underlying etiology. Systemic blood pressure, complete blood count, acute phase reactants (erythrocyte sedimentation rate, C-reactive protein), prothrombin time, fibrinogen level and lipid profile (serum triglyceride, low-density lipoprotein [LDL] and high-density lipoprotein [HDL] levels) were

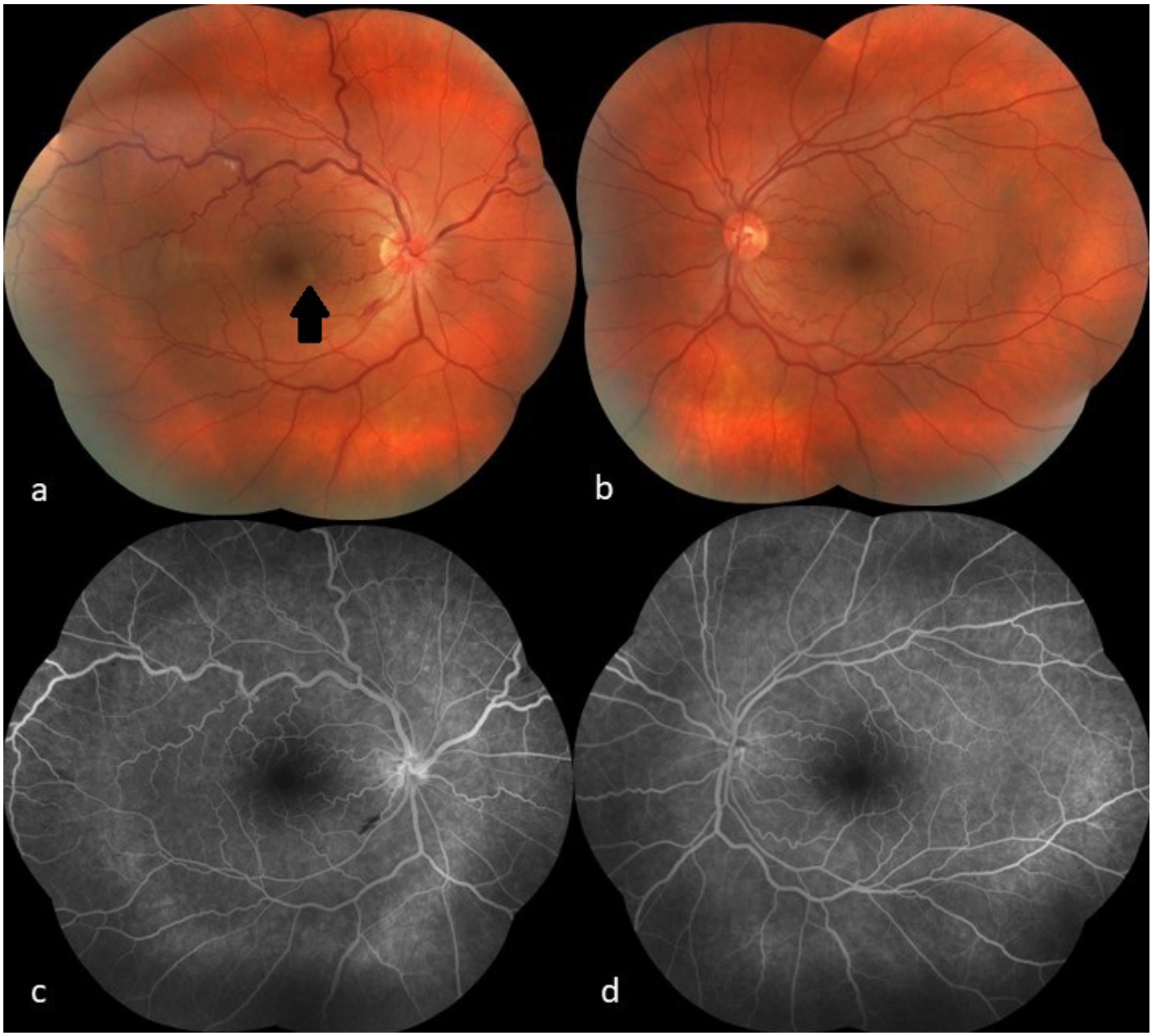

Figure 1: a) *Color fundus image; increased tortuosity and dilatation in superior temporal retinal vein, paleness in macular (arrow), splinter hemorrhage inferior to optic disc in the right eye;* **b)** *no pathological finding other than mildly increased tortuosity in retinal veins in left eye;* **c)** *Fundus fluorescein angiography: no abnormal finding other than hypo-fluorescent image due to blockade of hemorrhage in the right eye;* **d)** *normal fluorescein angiography in the left eye.*

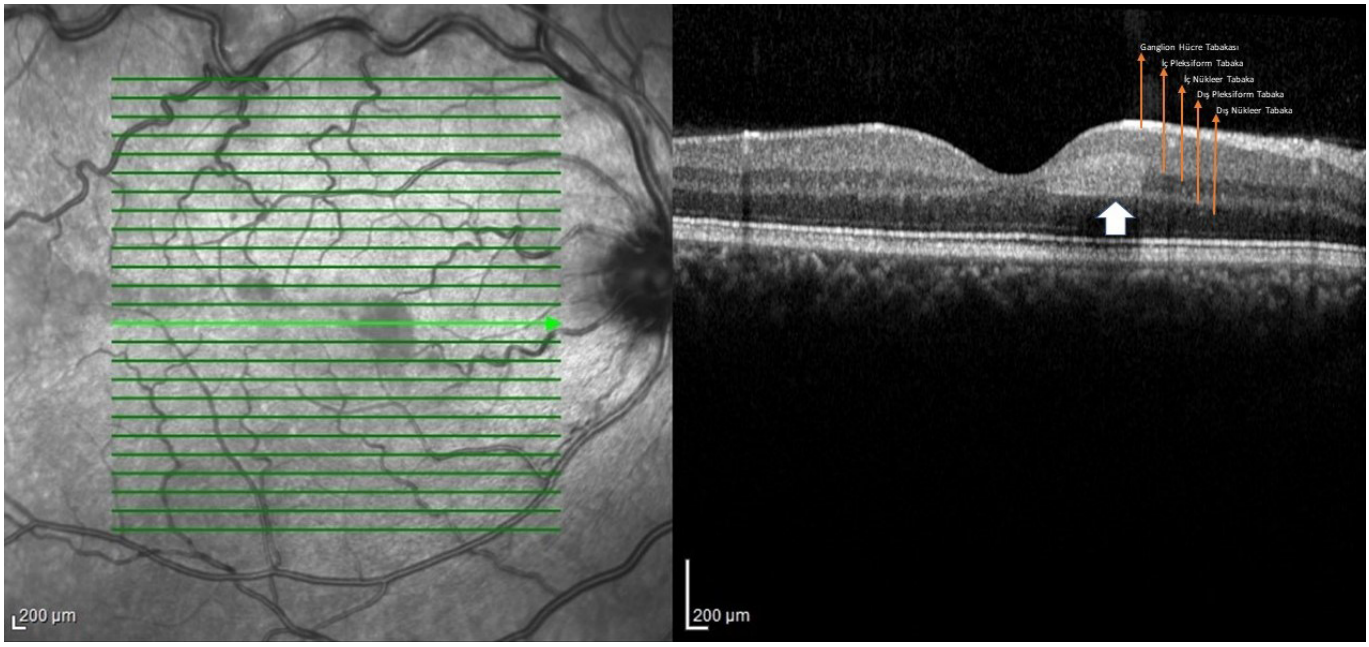

Figure 2: *Hyper-reflective band appearance at inner nuclear layer (arrow) compatible to PAMM on right eye OCT imaging.*

normal. The patient underwent genetic testing for hereditary thrombophilia, which revealed multiple mutations (Factor V Leiden heterozygous mutant, Plasminogen Activator Inhibitor-1 [PAI-1] 4G/4G homozygous mutant, Methylene Tetrahydrofolate Reductase [MTHFR] [A1298C] homozygous mutant). Oral acetyl salicylic acid (100 mg once daily) was prescribed to the patient.

In the control visit on day 45, visual acuity was 20/20 and anterior segment examination was normal. In the fundus examination, preretinal hemorrhage was observed in the periphery while venous tortuosity was decreased and macular reflection was normal (Figure 3a). Derangement was seen at middle retinal layers secondary to PAMM lesion on OCT (Figure 3b). In the control visit on month 3, it was seen that preretinal hemorrhage was regressed. The patient is still attending control visits.

DISCUSSION

Paracentral acute middle maculopathy (PAMM) is an OCT finding secondary to retinal ischemia. In OCTA studies, ischemia was observed in middle and deep vascular structure of retina in PAMM cases.[13] Retinal blood supply has two components as choroidal and retinal circulation. Inner layers are supplied by retinal arteries while outer layers are supplied by choroidal circulation. Outer plexiform and inner nuclear layer comprise a margin between two components of circulation and are supplied by both.[13] Thus, the border is highly vulnerable to ischemia. The ischemia in this borderline appears as hyper-reflective band on OCT imaging.[13] Later, PAMM lesions can lead sequel as thinning of inner nuclear layer. The patients may experience permanent scotoma due to these lesions.[14] In patients with finding of PAMM, potential inflammatory, vascular and infectious diseases should be evaluated for differential diagnosis.[3] As seen in our patient, in case of venous stasis accompanying to PAMM, a potential hyper-coagulability state must be kept in mind, particularly in young patients with no known systemic or ocular disease. In the differential diagnosis, previous COVID-19 disease and anti-phospholipid syndrome should be considered.[15] In a publication by Arf et al., anti-phospholipid syndrome was diagnosed in a patients presented with ischemia of deep retinal capillary and findings of increased hyper-reflectivity in inner plexiform layer on OCT. [16] In the definitive and differential diagnosis of PAMM cases, a comprehensive ocular examination, OCT, FFA, computerized visual field testing and OCTA can be used.

Factor V is one of the major proteins in the common pathway in the coagulation system. In carriers of heterozygous Factor V Leiden mutation, lifetime risk for venous thromboembolism is increased by 5-10 folds while it reaches up to 80 folds in cases with homozygous mutation.[17] Plasminogen activator inhibitor-1 (PAI-1) is the primary inhibitor of plasminogen activator in the plasma. The serum levels of PAI-1 is associated to genetic factors and higher serum levels contribute development of hypo-fibrinolytic by increasing thrombotic predisposition.[17] In a study by Onalan et al., it was reported that individuals with PAI 4G/4G mutation are at higher risk for myocardial

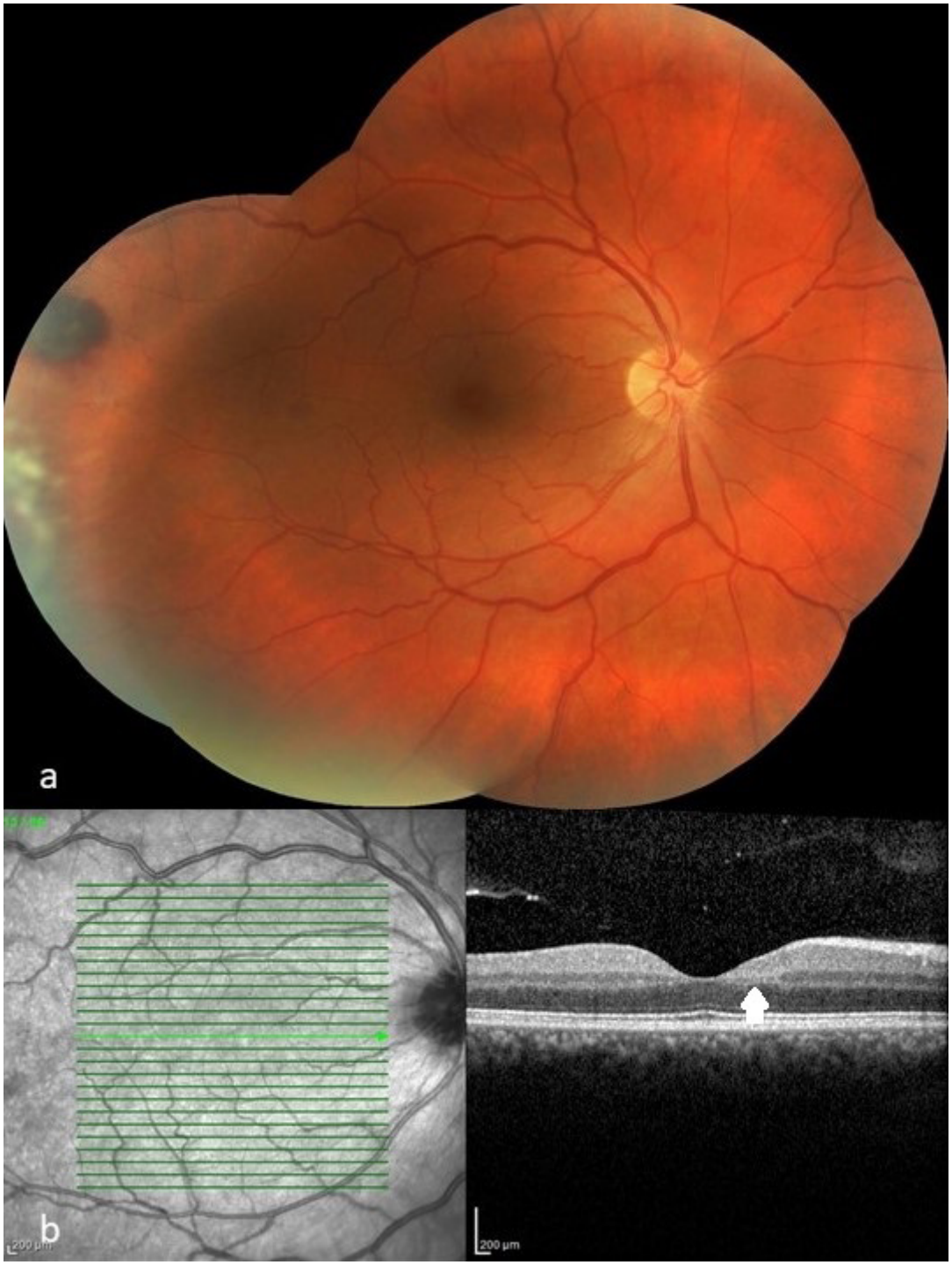

Figure 3: a) *Color fundus image of right eye: preretinal hemorrhage in temporal peripheral region;* **b)** *OCT image in the same eye: derangement (arrow) in inner nuclear layer due to PAMM lesion.*

infarction at early ages.[18] Methylenetetrahydrofolate reductase is an enzyme involved in the metabolism of homocystein and play role in conversion of homocystein into methionine.[5] There are two mutations as MTHFR C677T and MTHFR A129C. Although it is known that MTHFR C677T homozygous mutation increased risk for cardiovascular disease and preeclampsia, it was reported that heterozygous C677T/A1298C and A1298C homozygous mutations did not increase thromboembolism risk markedly.[19] In case of hyper-coagulopathy, retinal hemorrhage (subretinal, subhyaloid and/or intraretinal), venous dilatation and increased tortuosity can be observed. In our case, there was no history of venous thromboembolism and the patient presented with ocular symptoms alone. It was found that thromboembolism risk was markedly higher than normal population due to

heterozygous Factor V Leiden and homozygous PAI-1 mutations detected and thromboprophylaxis was initiated rapidly.

In conclusion, individual with hereditary thrombophilia mutations can first recognized with ocular symptoms at early age by ophthalmologists. Although it can be recognized at younger ages by recurrent abortions in female patients, diagnosis may be delayed in male patients. Particularly, hyper-coagulopathy states should be considered in young, asymptomatic patients with association of PAMM and retinal venous stasis. In such patients, early diagnosis and initiation of thromboprophylaxis as soon as possible are helpful in preventing serious complications such as cardiovascular diseases, thromboembolism and preeclampsia. In addition to ocular examination, it is important to evaluate these patients regarding systemic risks and consult relevant departments.

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