PARACENTRAL ACUTE MIDDLE MACULOPATHY ASSOCIATED WITH PHOSPHODIESTERASE-5 INHIBITOR THERAPY

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Purpose: To present an atypical case of paracentral acute middle maculopathy occurred upon awakening in the morning within hours after phosphodiesterase-5 (PDE-5) inhibitor consumption at bedtime.

Methods: Multimodal retinal imaging findings, including fluorescein angiography, spectral domain optical coherence tomography, optical coherence tomography angiography, and microperimetry of a particular case of paracentral acute middle maculopathy lesion that follow the distribution of the cilioretinal artery.

Results: A 52-year-old healthy man presented with an acute paracentral scotoma in his left eye upon awakening in the morning, after the use of a PDE-5 inhibitor pill the previous night. Spectral domain optical coherence tomography illustrated a hyperreflective band-like lesion at the level of the inner nuclear layer, consistent with a diagnosis of paracentral acute middle maculopathy, along the course of the cilioretinal artery that appeared normally perfused with fluorescein angiography. Optical coherence tomography angiography showed a perfusion deficit and capillary pruning of the retinal deep capillary plexus, with preserved intermediate capillary plexus, that colocalized with the paracentral scotoma confirmed with microperimetry.

Conclusion: To our knowledge, this is the first report of paracentral acute middle maculopathy after the use of PDE-5 inhibitor. Nocturnal arterial hypotension exacerbated by the vasodilatory effect of the PDE-5 inhibitor may have caused transient cilioretinal artery hypo/nonperfusion and insufficiency. Paracentral acute middle maculopathy may represent the earliest form of ischemia in the central macular region, occurring after a milder vascular insult.

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Phosphodiesterase-5 (PDE-5) inhibitors are commonly administered for the treatment of erectile dysfunction and pulmonary arterial hypertension but have been associated with various ocular adverse events, including nonarteritic anterior ischemic optic neuropathy and retinal vascular disorders.[1] Paracentral acute middle maculopathy (PAMM) is defined as a characteristic hyper-reflective band-like lesion at the level of the inner nuclear layer (INL) with spectral domain optical coherence tomography. Paracentral acute middle maculopathy is frequently associated with retinal vascular conditions[2] and is caused by ischemia of the intermediate and/or the deep retinal capillary plexus that flank the INL.[3]

Case Report

A 52-year-old healthy man presented at the emergency department of our Ophthalmology clinic with the acute onset of a paracentral grayish "comma-shaped" scotoma in his left eye upon

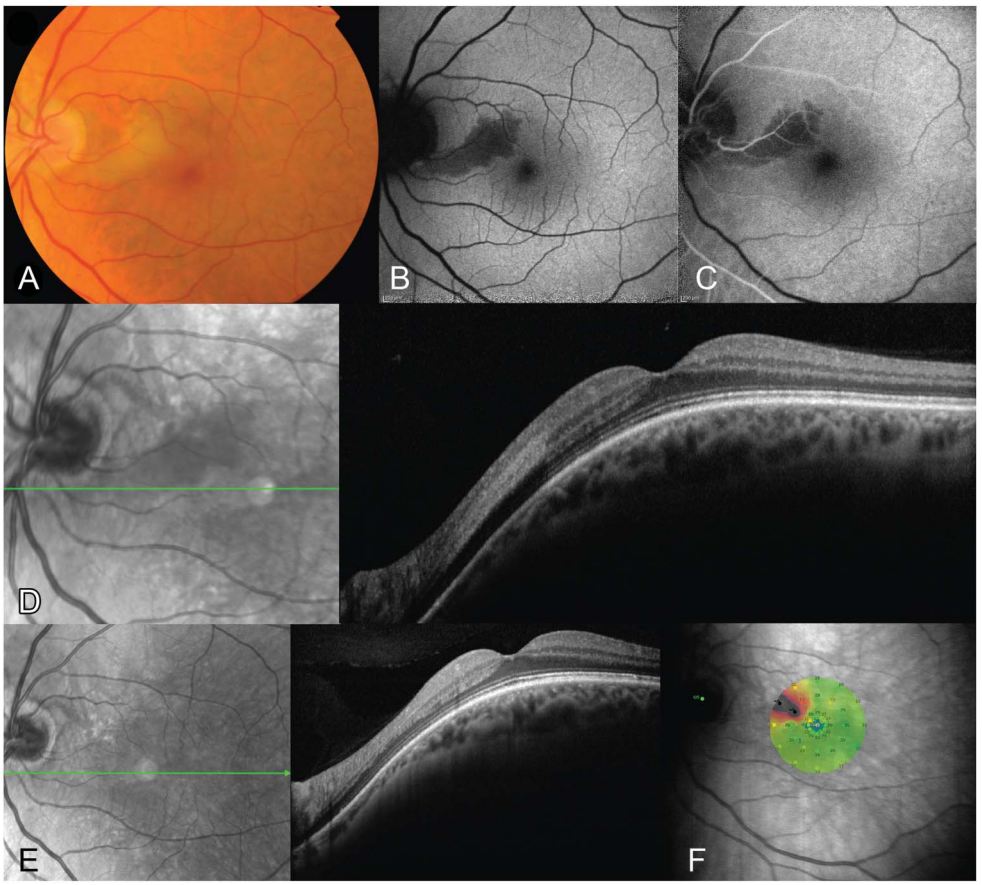

Fig. 1. Multimodal imaging of PAMM along the distribution of the cilioretinal artery in the left eye. **A–B.** Color fundus photography (**A**) illustrates an area of retinal whitening along the course of the cilioretinal artery that is hypoautofluorescent with blue-light fundus autofluorescence (**B**). **C.** Fluorescein angiography demonstrates normal perfusion of the cilioretinal artery with surrounding hypofluorescence due to blockage. **D.** Spectral domain optical coherence tomography displays a dome-shaped macula with a band-like hyperreflectivity at the level of the INL, consistent with PAMM, in the corresponding area supplied by the cilioretinal artery. **E–F.** Four months later, spectral domain optical coherence tomography (**E**) illustrates INL thinning in the same area that colocalizes with the persistent defect at microperimetry (**F**).

awakening in the morning. His medical history was completely noncontributory, except for the use of tadalafil 20 mg the previous night. He reported to have started to use this medication about 2 months ago and used it occasionally about a dozen times before, always at the same dosage. Best-corrected visual acuity was 20/20 in both eyes; anterior segment examination and intraocular pressure were normal in both eyes. Dilated retinal fundus examination of the left eye demonstrated an ill-defined curved area of retinal whitening along the course of the cilioretinal artery that illustrated hypofluorescence with blue-light fundus autofluorescence (Figure 1, A and B).

Fluorescein angiography showed a normally perfused cilioretinal artery (Figure 1C). Spectral domain optical coherence tomography demonstrated a hyperreflective band-like lesion extending from the outer plexiform layer to the inner plexiform layer in the INL (Figure 1D) in the corresponding area of retinal whitening that follows the distribution of the cilioretinal artery, consistent with a diagnosis of PAMM.

At presentation, the patient had normal diastolic and systolic blood pressure values (130/85), and a normal heart rate (72 bpm). He reported to be in good general health with normal blood pressure at previous routine examinations and never had any medical problem before.

Laboratory blood tests including complete blood cell count (hemoglobin, hematocrit, red blood cell count, white blood cell count, and differential, platelet count), triglyceride levels, cholesterol levels (high-density lipoprotein, low-density lipoprotein and total), glucose and glycated hemoglobin, total protein, albumin, creatinine, plasma electrolytes (sodium, potassium, calcium, and magnesium), folate, homocysteine, fibrinogen, C-reactive protein, and erythrocyte sedimentation rate, C3, C4, antinuclear antibody, antineutrophil cytoplasmic antibody, antiphospholipid antibodies were within normal limits. Blood samples were negative for Toxoplasmosis, Bartonella, Borrellia, cytomegalovirus, HSV1-2, varicella zoster virus, hepatitis B virus, hepatitis C virus, HIV, and syphilis (venereal disease research).

In addition, the patient was also referred to the cardiology unit of our hospital to perform a complete cardiologic evaluation, which included resting and stress electrocardiography, echocardiography, 24-hour blood pressure monitoring (Holter), and bilateral carotid artery Doppler ultrasonography. All examinations were within normal limits; the cardiologist excluded underlying cardiovascular risk factors and did not prescribe any treatment to the patient. However, discontinuation of the PDE-5 inhibitor was recommended.

After 1 month, optical coherence tomography angiography (HRA-OCT2; Heidelberg Engineering, Heidelberg, Germany) analysis illustrated normal perfusion of the superficial vascular complex and a perfusion defect in the deep vascular complex that colocalized with the cilioretinal artery distribution. Differential segmentation analysis of the two plexuses constituting the deep

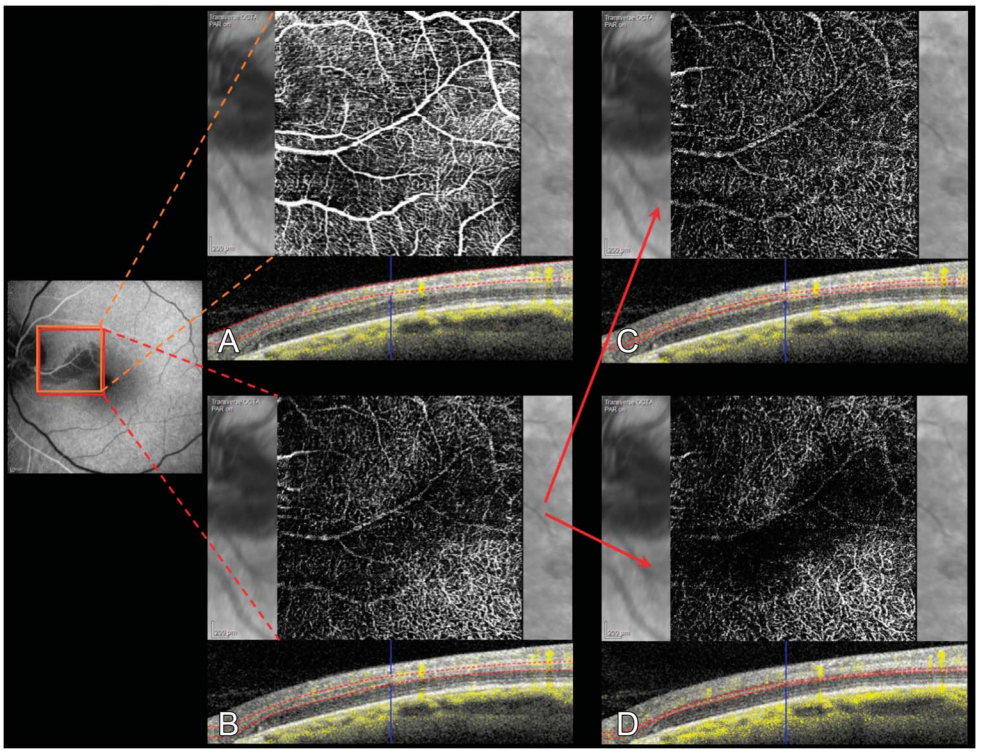

Fig. 2. Optical coherence tomography angiography analysis (with projection artifact removal) through the PAMM lesion, performed 1 month after presentation, based on the segmentation boundaries described by Campbell et al.[4] **A.** Optical coherence tomography angiography segmentation at the level of the superficial vascular complex illustrates normal flow and perfusion. **B.** Optical coherence tomography angiography segmentation at the level of deep vascular complex illustrates a perfusion deficit or flow void. **C–D.** Differential optical coherence tomography angiography analysis of the intermediate and deep retinal capillary plexus, which constitute the deep vascular complex, was performed. A perfusion defect or flow void was confirmed at the level of the deep retinal capillary plexus (**D**), whereas the intermediate retinal capillary plexus was preserved (**C**).

vascular complex, according to the segmentation boundaries described by Campbell et al,[4] demonstrated preserved perfusion of the intermediate retinal capillary plexus and a perfusion deficit (i.e., flow void) and capillary pruning of the deep retinal capillary plexus (Figure 2). Manual adjustments of the segmentation slab failed to identify flow in the deep retinal capillary plexus within the PAMM lesion. Four months later, the spectral domain optical coherence tomography PAMM lesion evolved to inner plexiform layer, INL, and outer plexiform layer thinning, and colocalized with the flow void area at the level of the deep retinal capillary plexus and with the persistent paracentral scotoma still complained by the patient and confirmed stable in serial microperimetry (Figure 1, E and F).

Discussion

The use of PDE-5 inhibitors has been associated with the acute onset of nonarteritic anterior ischemic optic neuropathy because of their vasodilatory effect.[5] Vasodilation may exacerbate nocturnal arterial hypotension that is considered a critical risk factor in the pathogenesis of nonarteritic anterior ischemic optic neuropathy.[5–7] Our patient complained of a paracentral scotoma after awakening in the morning suggesting that tranonperfu/nonperfusion during sleep, probably related to nocturnal arterial hypotension, may have caused the PAMM lesion.

Paracentral acute middle maculopathy has been recently associated with systemic disorders such as migraines, pregnancy, hypovolemia, and dehydration.[2,3] The use of certain oral compounds including amphetamines, vasopressors, caffeine, and contraceptives have also been implicated in the development of PAMM.[2,3] To the best of our knowledge, this is the first report of PAMM associated with the use of PDE-5 inhibitors. The patient's scotoma was noted upon awakening in the morning within hours after tadalafil consumption at bedtime. No other systemic or local risk factors were found.

Fluorescein angiography and optical coherence tomography angiography, within hours of scotoma development, illustrated a normally perfused cilioretinal artery suggestive of a transient hemodynamic block or deficit rather than embolic or thrombotic occlusion. Nocturnal arterial hypotension exacerbated by the vasodilatatory effect of tadalafil may have led to transient cilioretinal artery hypo/nonperfusion and vascular insufficiency. This mechanism is a well-documented association of nonarteritic anterior ischemic optic neuropathy, which is also the result of a ciliary vascular disturbance, albeit at the capillary level.[6,7]

Paracentral acute middle maculopathy may represent the earliest form of ischemia in the central macular region that may progress from the perivenular pole of the INL, and then diffusely through the INL, before ischemia develops in the inner retina.[8,9] Transient cilioretinal artery hypo/nonperfusion, in the absence of a complete occlusion, represents a milder form of vascular insult that only manifests at the level of the deep retinal capillary plexus and the INL,

which may be at greater risk of ischemic injury (vs. the inner retina).

Optical coherence tomography angiography has previously confirmed that PAMM is the result of flow deficits in the deep vascular complex.[10] In this study, it appeared that the deep retinal capillary plexus was the specific cause of ischemic injury with optical coherence tomography angiography analysis, not the intermediate capillary plexus. However, segmentation errors may still represent an important confounding factor in the optical coherence tomography angiography technique, despite recent advances in technology, and therefore, these findings await further validation.

Key words: PAMM, cilioretinal artery, OCT angiography, phospodiesterase-5 inhibitors.

Acknowledgments

The authors thank Dr. Michele Frisone for his helpful technical support.

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