Intravenous Thrombolysis with Alteplase for Paracentral Acute Middle Maculopathy: a Case Report

Victor F. Bellanda, MD*; Savio Sodre, MD*; Marco S. P. Folgosa, MD*; Ingrid U. Scott, MD, MPH**; Octavio M. Pontes-Neto MD, PhD***; Rodrigo Jorge, MD, PhD*

Background

Paracentral acute middle maculopathy (PAMM) is characterized by a hyperreflective band spanning the inner nuclear layer (INL) observed on optical coherence tomography (OCT).[1] Although its pathophysiology remains unclear, evidence suggests that **PAMM most likely results from hypoxic injury to the middle retinal tissue**.[1] Considering the condition's likely ischemic etiology, thrombolytic therapy may be considered for selected cases, although evidence remains unclear about its benefits.[2]

The randomized clinical trials available to the moment seem to have been underpowered by the inclusion of patients with a period of symptoms beyond the ischemic tolerance of retinal tissue.[2] We here describe the **first reported case of PAMM treated with systemic intravenous thrombolysis**.

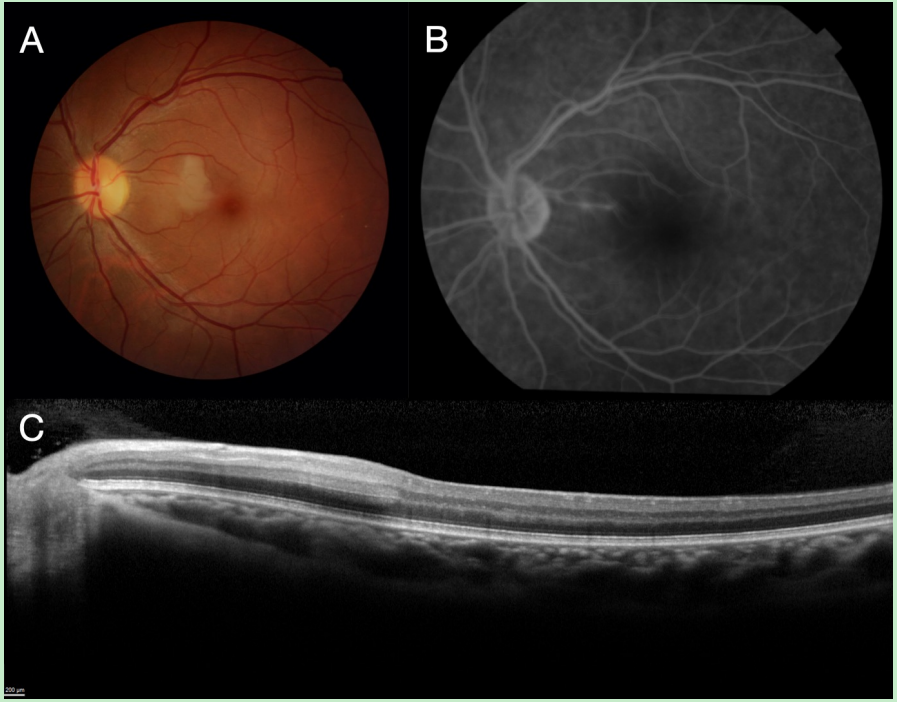
1. Coelho NM, Gaspar T, Ferreira JT, Medeiros MD, Cunha JP. Paracentral acute middle maculopathy-review of the literature. Graefes Arch Clin Exp Ophthalmol. 2020 Jul;258(12):2583-2596.
2. Mac Grory B, Lavin P, Kirshner H, Schrag M. Thrombolytic therapy for acute central retinal artery occlusion. AHA Stroke 2020 Feb; 51(2):687-695.

* *Department of Ophthalmology, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil*
** *Departments of Ophthalmology and Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania, USA*
*** *Department of Neurology, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil*

Report of a Case

A 31-year-old woman presented to the emergency department with a one-hour history of a sudden-onset painless visual scotoma in the left eye. Examination revealed a best-corrected visual acuity (BCVA) of 20/20 (OD) and 20/60 (OS). Fundoscopy revealed a single area of discrete retinal **hypopigmentation in the paracentral macular region** of the OS, near the nasal fovea (Figure A). Fluorescein angiography demonstrated early stages of vascular tortuosity along with progressive perivascular **contrast leakage, extending temporally to the optic nerve** and moving toward the fovea (Figure B). OCT revealed a **hyperreflective band across the INL**, extending to the inner plexiform layer (Figure C). Findings were suggestive of **PAMM**, possibly deriving from an acute ischemic event.

After 4.5 hours from symptom onset and considering the patient's young age and lack of comorbidities, systemic IV thrombolysis with tPA was attempted. A dosage of 0.9 mg/kg of alteplase was infused, 10% administered as a bolus and the remaining 90% as continuous IV infusion for 1 hour.



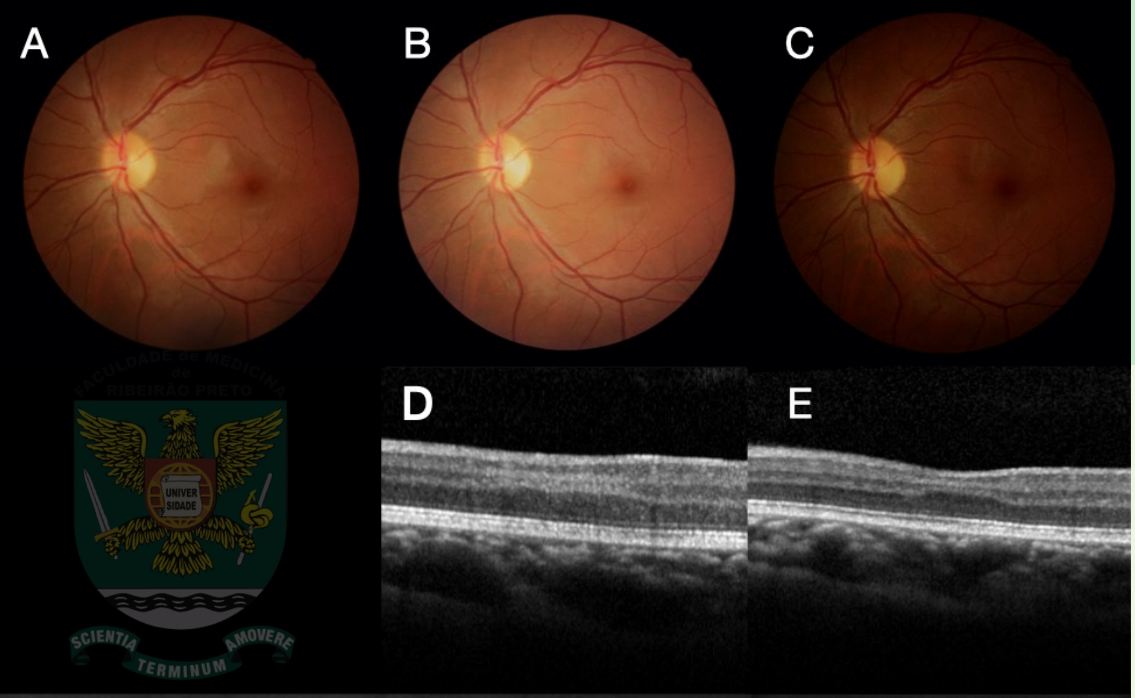
Ten hours later, the patient's scotoma had almost completely disappeared and her BCVA was 20/20 (OS). She was discharged with daily acetylsalicylic acid (100 mg PO). Fundus photographs and OCT images obtained on follow-up revealed a **progressive reduction in retinal whitening and in the hyperreflectivity of the inner retina, respectively**.

Macular integrity assessment (MAIA) microperimetry studies were also obtained one and four weeks after the event. When compared, they demonstrated a **partial increase in sensitivity in the superonasal field, along with substantial improvement in macular integrity indexes (98.5 to 9.1)* and average thresholds (27.0 to 28.9 dB)**. The improvements persisted in a four-month follow-up exam, which showed a prominent increase of sensitivity in the superonasal field, a macular integrity index of 19.8 and an average threshold of 28.8 dB. **After one year, the patient reported the permanence of no more than a pinpoint-sized defect in her visual field.**

Discussion

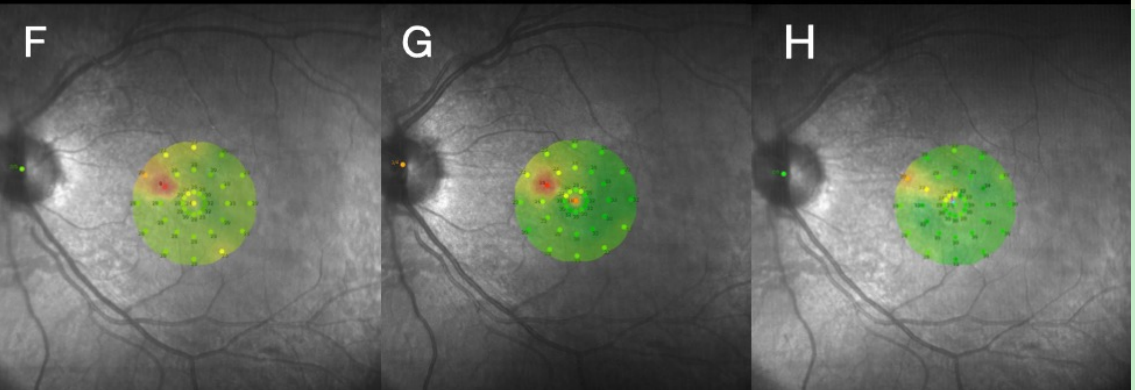
Although the pathophysiological mechanisms of PAMM remain incompletely defined, the advent of OCT angiography allowed the development of studies that point to its relationship with ischemia of the middle layers of the retina; more specifically, the deep and intermediate capillary plexuses.[3,4] These vessels irrigate the outer plexiform and inner nuclear layers, located within a watershed zone where the flow of oxygen provided by retinal and choroidal circulation may be insufficient, making them more susceptible to hypoxia.[1] Given this likely etiology, thrombolytic therapy may be hypothesized as a possible treatment.[2]

The efficacy of thrombolytic therapy for NA-CRAO, which shares similar pathophysiology with ischemic stroke, has not been established through randomized trials.[1,5] Both the European Assessment Group for Lysis in the Eye (EAGLE) randomized clinical trial,[6] which compared outcomes after conservative treatment with those after intra-arterial fibrinolysis, and another clinical trial by Chen et al,[7] which used intravenous tPA, were terminated prematurely due to a compelling rate of adverse events and failed to provide conclusive evidence in support of thrombolytic therapy. The trials, however, recruited participants with symptoms that had set in for up to 20 or 24 hours, far beyond the recommended 4.5 hours for administering tPA in cases of ischemic stroke.[2] Furthermore, experiments with animal models have demonstrated that, after 240 minutes of ischemia, irreversible retinal tissue damage may occur.[2] Thus, the inefficacy in the trials may stem from enrolling patients with excessive time of ischemia for recovery.



Follow up evaluations of the left eye. Color fundus photographs showing progressive **reduction of retinal whitening** one (A), two (B), and fifteen (C) weeks after thrombolytic therapy.

Spectral-domain OCT b-scans demonstrating progressive **reduction of inner retinal hyperreflectivity** two (D) and fifteen (E) weeks after therapy.



Microperimetry pictures demonstrating progressive **improvement of retinal sensitivity** in the nasal paracentral macular region one (F), two (G), and fifteen (H) weeks from baseline.

Recent studies suggest that thrombolysis may be effective for NA-CRAO when performed within 4-6 hours of symptom onset.[8,9] In a German trial, intravenous thrombolysis with tPA resulted in significant improvement in BCVA and reading ability in 20 patients with symptoms lasting 4.5 hours or less, when comparing to the conservative treatment branch of the EAGLE trial.[10]

PAMM's natural history is unclear. Literature suggests it causes INL atrophy and a permanent paracentral scotoma.[1] Visual prognosis may vary based on etiology.[1] Our case showed improved visual acuity and scotoma ten hours after IV tPA infusion. However, improvement can occur spontaneously and tPA carries substantial systemic risks.[1,2] The devastating visual outcomes resulting from retinal ischemic events, however, may counterbalance the risks in this decision. For these reasons, further randomized trials are needed to determine the efficacy and safety of thrombolysis for PAMM and NA-CRAO, when administered within an adequate time frame.

3. Shah A, Rishi P, et al. OCT angiography features of paracentral acute middle maculopathy. Indian J Ophthalmol 2019 Mar;67(3):417-419.

4. Dansingani KK, Inoue M, et al. Optical coherence tomographic angiography shows reduced deep capillary flow in PAMM. Eye (Lond) 2015 Dec;29(12):1620-4.

6. Schumacher M, Schmidt D, et al. Central retinal artery occlusion: Local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial. Ophthalmology. 2010;117:1367–1375 e1361.

7. Chen CS, Lee AW, et al. Efficacy of intravenous tissue-type plasminogen activator in central retinal artery occlusion - report from a randomized, controlled trial. AHA Stroke 2011 Jul; 42:2229–2234.

8. Schrag M, Youn T, et al. Intravenous fibrinolytic therapy in central retinal artery occlusion: a patient-level meta-analysis. JAMA Neurol. 2015; 72:1148–1154.

9. Preterre C, Godeneche G, et al. Management of acute central retinal artery occlusion: Intravenous thrombolysis is feasible and safe. Int J Stroke. 2017 Oct;12(7):720-723.

10. Schultheiss M, Härtig F, et al. Intravenous thrombolysis in acute central retinal artery occlusion - a prospective interventional case series. PLoS One 2018 May 29;13(5):e0198114