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Case Report

Coincident Acute Macular Neuroretinopathy and Paracentral Acute Middle Maculopathy in COVID-19

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Abstract

An ophthalmology consultation was requested for a 29-year-old woman complaining of visual field defects. The patient had presented to the emergency department with cough and high fever one day earlier. Chest computed tomography demonstrated pneumonia and two severe acute respiratory syndrome coronavirus 2 polymerase chain reaction tests were positive. The patient had undergone renal transplantation 11 years ago due to glomerulonephritis. Best-corrected visual acuity (BCVA) was 20/40 in the right eye and 20/30 in the left eye. Fluorescein angiography showed macular hypoperfusion, and optical coherence tomography (OCT) showed hyperreflectivity in the inner nuclear, outer plexiform, and outer nuclear layers, as well as discontinuity of the ellipsoid zone. Perimetry confirmed bilateral central scotoma. Levels of D-dimer and fibrinogen were 0.86 g/mL and 435.6 g/mL, respectively. The patient was diagnosed as having concurrent acute macular neuroretinopathy and paracentral acute middle maculopathy and was given low-molecular-weight heparin treatment for one month. Her BCVA improved to 20/20 in both eyes, and regression was observed in the retinal findings, hyperreflectivity and ellipsoid zone disruption on OCT, and scotoma in perimetry. Inflammation, thrombosis, and glial involvement may play a role in the pathogenesis of retinal microvascular impairment in COVID-19.

Keywords: COVID-19, retinal ischemia, paracentral acute middle maculopathy, acute macular neuroretinopathy, central scotoma

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Introduction

Acute macular neuropathy (AMN) and paracentral acute middle maculopathy (PAMM) are manifestations of retinal microvascular ischemia. AMN presents with central/paracentral scotoma, photopsia, and mild visual acuity loss. Infections, vasoconstrictor drugs, oral contraceptive drugs, hypotension/shock, preeclampsia, and caffeine consumption are suspected risk factors. Optical coherence tomography (OCT) shows abnormalities in the deep retinal layers especially.[1] During the Coronavirus disease 2019 (COVID-19) pandemic, researchers noticed an upsurge in AMN cases.[2,3] PAMM, a variant of AMN, presents with central/paracentral scotoma and a mild reduction in visual acuity, and is described as related to ischemia of the middle retinal layers. The inner nuclear layer (INL) is a watershed zone and is therefore sensitive to hypoperfusion.[4] OCT shows hyperreflective bands in the INL and outer plexiform layer (OPL). Fluorescein angiography (FA) and OCT angiography (OCTA) can demonstrate ischemia, enlargement of the foveal avascular zone, and capillary drop-out areas. Scotoma can be confirmed with perimetry.

Herein we report a case of bilateral AMN and PAMM findings in a patient with active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient.

Case Report

Our clinic was consulted regarding a 29-year-old woman with bilateral visual field loss. Her description was consistent with a central scotoma. Medical history was negative for ocular diseases. The patient had presented to the emergency department one day earlier with cough and high fever. Chest computed tomography findings were consistent with COVID-19 pneumonia and polymerase chain reaction test for SARS-CoV-2 resulted positive twice. The patient had undergone renal transplantation 11 years earlier because of glomerulonephritis. She was receiving favipiravir (Favira®, Novel, Türkiye), low-molecular-weight heparin (LMWH; (Oksapar®, Koçak, Türkiye) at a prophylactic dose (40 mg once a day), everolimus (Afinitor®, Novartis, Switzerland), tacrolimus (Prograf®,

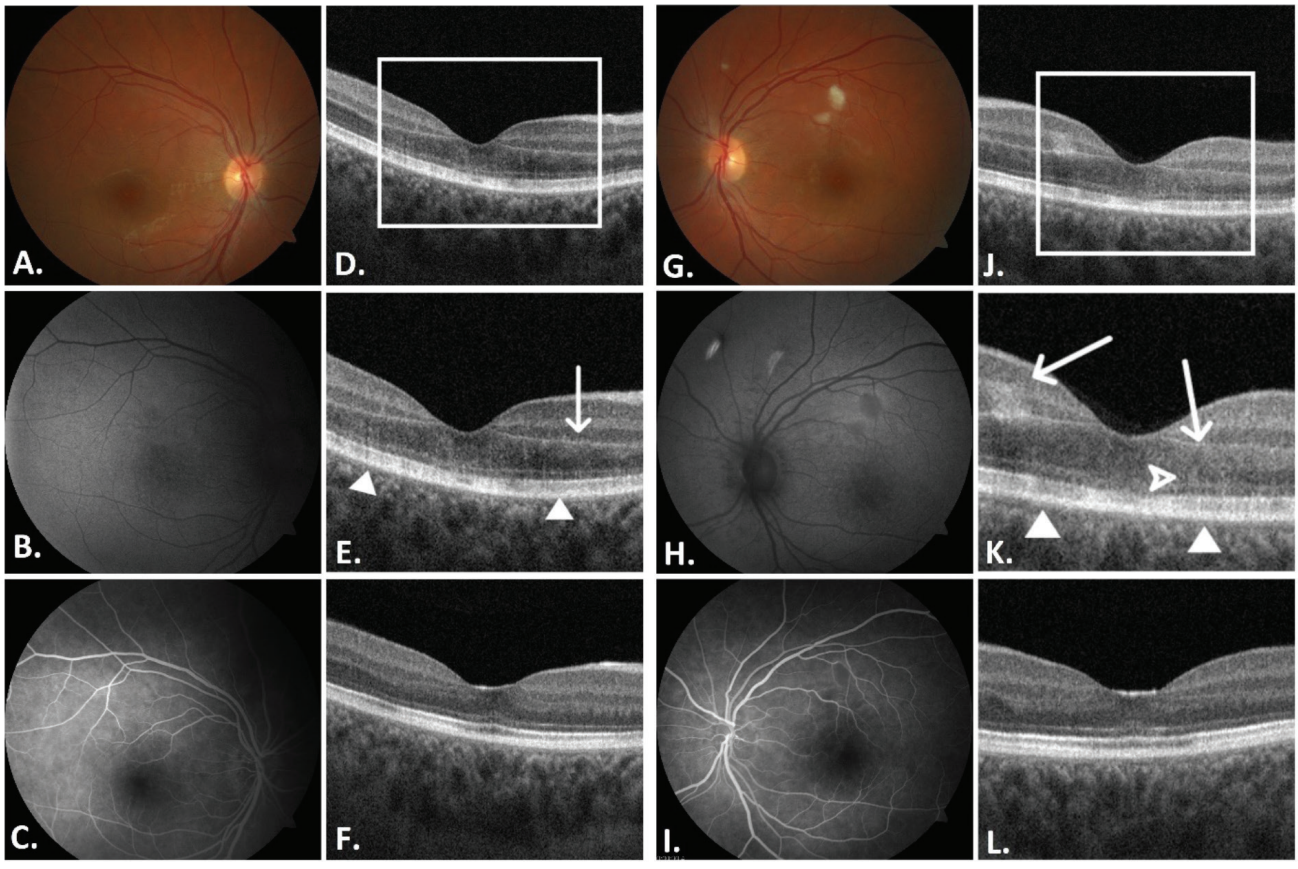

Figure 1. A) Fundus image of the right eye shows subtle retinal whitening. B) Autofluorescence image of the right eye shows a spotted appearance in the superior perifovea. C) Fluorescein angiography of the right eye shows hypoperfusion in the perifovea. D-E) Initial optical coherence tomography (OCT) images of the right eye show hyperreflectivity at the inner nuclear layer (INL) and outer plexiform layer (OPL) junction (white arrow) and disruption of the ellipsoid zone (white arrowheads). F) OCT image of the right eye after 6 months of follow-up. G). Fundus image of the left eye shows cotton wool spots and subtle retinal whitening. H) Autofluorescence image of the left eye shows hypofluorescence at the location of the cotton wool spots and a spotted appearance in the superior perifovea. I) Fluorescein angiography of the left eye shows hypoperfusion in the perifovea. J-K) Initial OCT images of the left eye show hyperreflectivity in the INL and INL-OPL junction (white arrows), disruption of the ellipsoid zone (white arrowheads), and Z-shaped hyperreflectivity in the Henle fiber layer (white empty arrowhead). L) OCT image of the left eye after 6 months of follow-up

Astellas, Ireland), prednisolone (Deltacortril®, Pfizer, Türkiye), valsartan (Diovan®, Novartis, Switzerland), and benidipine (Benipin®, Deva, Türkiye) as systemic treatment at the onset of ocular symptoms. She had no history of oral contraceptive treatment. Best corrected visual acuity was 20/40 in the right eye and 20/30 in the left eye. Biomicroscopy was normal. Intraocular pressure was 15 mmHg in both eyes. Fundoscopy revealed ill-defined patches of subtle retinal whitening in both eyes and cotton wool spots in the left eye (**Figure 1A, 1G**). D-dimer and fibrinogen levels were 0.86 µg/mL and 435.6 µg/mL, respectively. Horizontal OCT (Optovue RTVue XR Avanti; Optovue, Inc, Fremont, CA) scans over the fovea showed hyperreflectivity in the INL and OPL, consistent with PAMM, and discontinuity of the ellipsoid zone and interdigitation zone, which is consistent with AMN (**Figure 1E, 1K**). Z-shaped reflectivity in the Henle fiber layer due to extension of the hyperreflective bands defined by Iovino et al.[5] was observed in the OCT images (**Figure 1K**). FA demonstrated areas of macular hypoperfusion corresponding to the retinal whitening. Perimetry with standard 30-2 program of Humphrey Field Analyzer confirmed bilateral central scotoma. Due to the presence of chronic immunosuppression, further investigations with cranial magnetic resonance imaging and lumbar puncture were conducted by the neurology department but revealed no other pathological findings. The patient was diagnosed with AMN and PAMM. In cooperation with the nephrology and infectious diseases departments, LMWH was increased to treatment dosage (1 mg/kg, twice a day) for one month. A month later, visual acuity increased to 20/20 in both eyes and retinal findings diminished. There was partial regression in the ellipsoid zone disruption on OCT (**Figure 1F, 1L**) and scotoma in perimetry. Her clinical findings were the same at the one-year visit.

Discussion

COVID-19-related vascular complications were found to be associated with D-dimer levels higher than 0.5 µg/mL.[6] COVID-19-related cytokine storm and hyperinflammatory state may contribute to the risk for microvascular alterations.[7]

There are other reports of PAMM or AMN lesions in patients with active or recent SARS-CoV-2 infection. Padhy et al.[8] hypothesized that high D-dimer level was an indicator and risk factor for capillary ischemia. Capuano et al.[3] described an AMN case in a COVID-19 patient with protein S deficiency, which is consistent with the thrombosis hypothesis. Our patient's D-dimer level was 0.86 µg/mL at presentation. Hypotension is a suspected risk factor for AMN.[1] Although valsartan and benidipine are antihypertensive drugs, the patient's medical history was negative for hypotension and she was never hypotensive during the treatment period. In addition, valsartan inhibits vasoconstriction. Ozsaygılı et al.[9] suggested inflammation as a possible mechanism. However, in our patient, microvascular complications occurred while under anti-inflammatory treatment with prednisolone, tacrolimus, and everolimus. Therefore, thrombosis in micro-vessels may better explain the pathogenesis. Gascon et al.[10] stated that post-viral retinal damage may occur through the immune-mediated mechanisms. Given that our patient is immunocompromised, immunological pathways may also play a role in the pathogenesis.

IIovino et al.[5] reported coincident AMN and PAMM in patients with Purtscher retinopathy, retinal vein occlusion, central retinal artery occlusion, and retinal vasculitis. They suggested Müller cell impairment as the shared pathology. Vargas et al.[11] discussed the possibility that glial cell involvement in COVID-19 may be associated with neurological damage. Therefore, our case may represent a form of COVID-19-related Müller cell dysfunction that led to concurrent AMN and PAMM lesions in the same eye.[11]

Our study has some limitations. Firstly, the findings were analyzed retrospectively. The patient's comorbidities and state of chronic immunosuppression can be considered risk factors for ischemia, but the systemic treatment the patient was receiving had no known ischemic ocular complications. Retinal findings in the left eye resembled Purtscher-like retinopathy. However, in Purtscher-like retinopathy we would expect the periarteriolar retina to be spared from whitening.[12] The simultaneous occurrence of AMN and PAMM in the same eye differs from previous reports.

Involvement of the retinal microvasculature in COVID-19 is important because its circulation is an end-artery system. Hence, COVID-19-related retinal microvascular impairment is a potentially vision-threatening clinical manifestation. Further research has to be done to confirm the association between SARS-CoV-2 infection and PAMM/AMN lesions and to elucidate the exact pathogenesis of this involvement.

Ethics

Informed Consent: Oral and written informed consent was obtained from the patient.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y.C., O.K., D.U., Concept: A.Y.C., O.K., D.U., Design: A.Y.C., O.K., D.U., Data Collection or Processing: A.Y.C., O.K.,

Analysis or Interpretation: A.Y.C., O.K., D.U., Literature Search: A.Y.C., O.K., Writing: A.Y.C., O.K., D.U.

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