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Acute macular neuroretinopathy associated with COVID-19 infection

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ABSTRACT

Purpose: To report a case of bilateral acute macular neuroretinopathy (AMN) associated with a COVID-19 infection.

Observations: A 22-year-old female was referred for evaluation of bilateral scotomas concurrent with a mildly symptomatic COVID-19 infection. Exam showed normal visual acuity, bilateral reddish-brown petaloid retinal lesions which were hyporeflective on near infrared (NIR) optical coherence tomography (OCT), and had associated hypoperfusion of the deep vascular plexus on OCT-angiography (OCT-A) consistent with bilateral AMN. At follow-up, scotomas and retinal findings on near infrared imaging and spectral-domain optical coherence tomography had only slightly improved.

Conclusions: COVID-19 has been documented to be the etiology of a growing number of ocular manifestations including microvascular events. We report a case of bilateral acute macular neuroretinopathy in a patient with a recent diagnosis of COVID-19 infection that had persistent symptoms and findings at six month follow-up.

1. Introduction

COVID-19 (coronavirus disease of 2019) is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first documented in Wuhan, China. This ribonucleic acid (RNA) virus has been known to cause a proinflammatory and hypercoagulable state that leads to multiple systemic complications including respiratory failure, myocardial infarction, deep venous thromboembolism (DVT), and cerebrovascular events with profound morbidity and mortality.[1]

The most commonly documented ocular complication of COVID-19 is conjunctivitis in up to one third of patients.[2] However, there is a growing literature of retinal vascular manifestations potentially related to COVID-19 including isolated cotton wool spots and retinal microhemorrhages,[3] retinal vein occlusions,[4,5] as well as some cases of acute macular neuroretinopathy (AMN) and paracentral middle maculopathy (PAMM).[6,7,8] Many of the reported AMN and PAMM findings associated with COVID-19 have had somewhat atypical presentations and findings including complicated underlying medical histories, advanced age, and atypical retinal findings including hemorrhages or subretinal fluid.

Herein we report the case of a 22-year-old female with symptomatic scotomas and typical fundoscopic and supplementary imaging findings for bilateral AMN associated with an otherwise mild COVID-19 infection.

2. Case report

A 22-year-old female was referred for retina evaluation. The patient had a history of attention deficit disorder for which she took lisdexamfetamine dimesylate 70mg capsule daily. She was also on norgestimate 0.25mg and ethinyl estradiol 35mcg for oral contraception. There was no past ocular history. The patient endorsed subjective sinus headache between the eyes radiating to the right temple and bilateral scotomas she described as a "ring of black dots with a wave in the middle." She was evaluated in the emergency room and was found to have mild lymphopenia (2.75, reference range 3.90–12.70 K/μL), normal comprehensive metabolic panel, trace occult blood on urinalysis, and a positive COVID-19 nasopharyngeal swab. Magnetic resonance venography of the brain was normal without thrombosis. Given no significant systemic findings, the patient and family were reassured and instructed to follow up with ophthalmology on an outpatient basis.

Twenty days after onset of her visual symptoms, the patient presented to the retina service. The patient's headache had resolved but scotomas persisted. Ophthalmic examination revealed uncorrected visual acuity of 20/20 in both eyes and normal intraocular pressure. Anterior segment examination was unremarkable. Posterior segment examination showed multiple subtle reddish-brown petaloid lesions radiating from the fovea in both eyes (Fig. 1A and B) without ocular

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inflammation. Fundus autofluorescence was normal other than hyperfluorescent optic nerve drusen in the left eye. Intravenous fluorescein angiogram (IVFA) showed minimal petaloid hypofluorescence consistent with a filling defect more prominent in the right (Fig. 1C) than left (Fig. 1D) eye, corresponding with fundoscopic findings. Indocyanine green angiography was normal. Near infrared (NIR) imaging demonstrated prominent areas of petaloid hyporeflectivity (Fig. 2A and B) that corresponded to the lesions noted on funduscopic examination and IVFA. Individual spectral domain optical coherence tomography (SD-OCT) B-scans showed disruption of normal retinal banding patterns at the junction of the outer plexiform layer (OPL) and the outer nuclear layer (ONL) as well as attenuated reflectivity of the ellipsoid zone (EZ; Fig. 2C and D). The constellation of these findings correlated with a diagnosis of bilateral acute macular neuroretinopathy (AMN). Observation was recommended given no known treatment has been established for AMN. At five weeks and six months following initial evaluation, the patient's scotomas had slightly improved subjectively. Through six months, retinal findings became slightly less prominent although persistent on exam, NIR (Fig. 3A and B) and SD-OCT imaging (Fig. 3C and D). OCT-angiography (OCT-A) showed hypoperfusion more prominent at the level of the deep vascular complex (Fig. 3E and F) than the superficial vascular complex (3G-H).

3. Discussion

COVID-19 is known to cause a hyperinflammatory and hypercoagulable state, with both a cytokine storm and thrombotic complications of the lungs, spleen, brain, gut, and periphery.[1] Conjunctivitis was the first described ocular finding and those patients with more prominent ocular surface manifestations were found to have more aggressive systemic symptoms.[2] It is now believed that COVID-19 can also directly affect the retina in humans, possibly through direct infection as well as secondarily through its thrombotic and inflammatory systemic effects. In a series of 14 autopsies of patients whom were COVID-19 positive at time of death, three (21%) were found to have COVID-19 RNA in the retina.[9] Therefore, investigations into ophthalmologic complications of COVID-19 in humans is of great interest, especially those complications associated with visual compromise.

Acute macular neuroretinopathy (AMN) is a rare retinal disorder resulting from localized nonperfusion of the deep capillary plexus of the retina with resulting disruption of the OPL, ONL, and EZ and associated temporary or permanent visual changes. Most affected patients are young (mean age 29.5 years old), non-Hispanic Caucasians, and female. The typical subjective complaint is a visual scotoma although decreased visual acuity, subjective blurry vision, floaters and metamorphopsia may occur. Predisposing or possible inciting factors have included

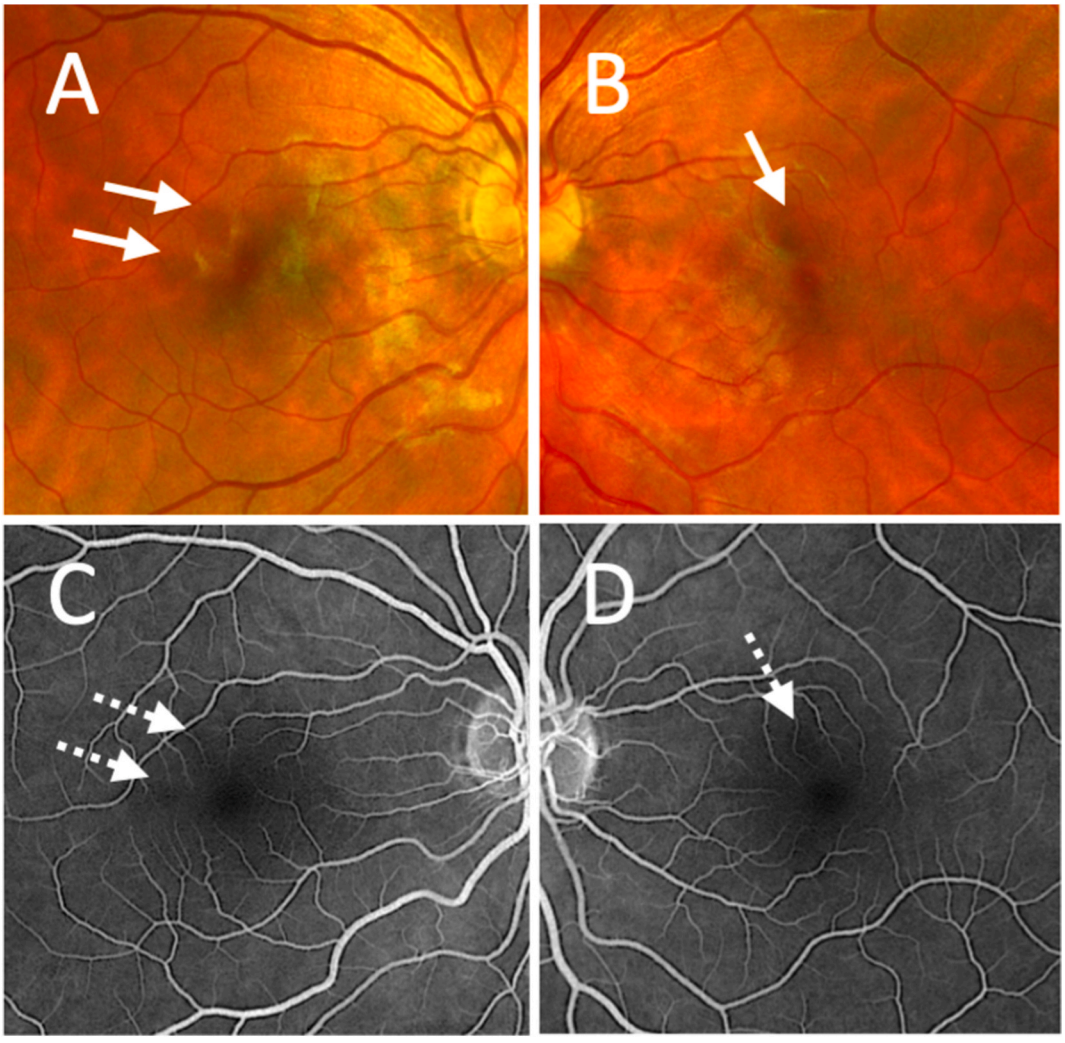

Fig. 1. Fundus photography (A, B) and intravenous fluorescein angiography (C, D) of the right and left eyes, respectively, at presentation. The color fundus photo demonstrates subtle petaloid red-brown lesions (solid white arrow) with their apices at the fovea (A, B). Corresponding areas of hypofluorescence (dotted white arrow) are noted on late phase images of fluorescein angiography of both eyes (C, D). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

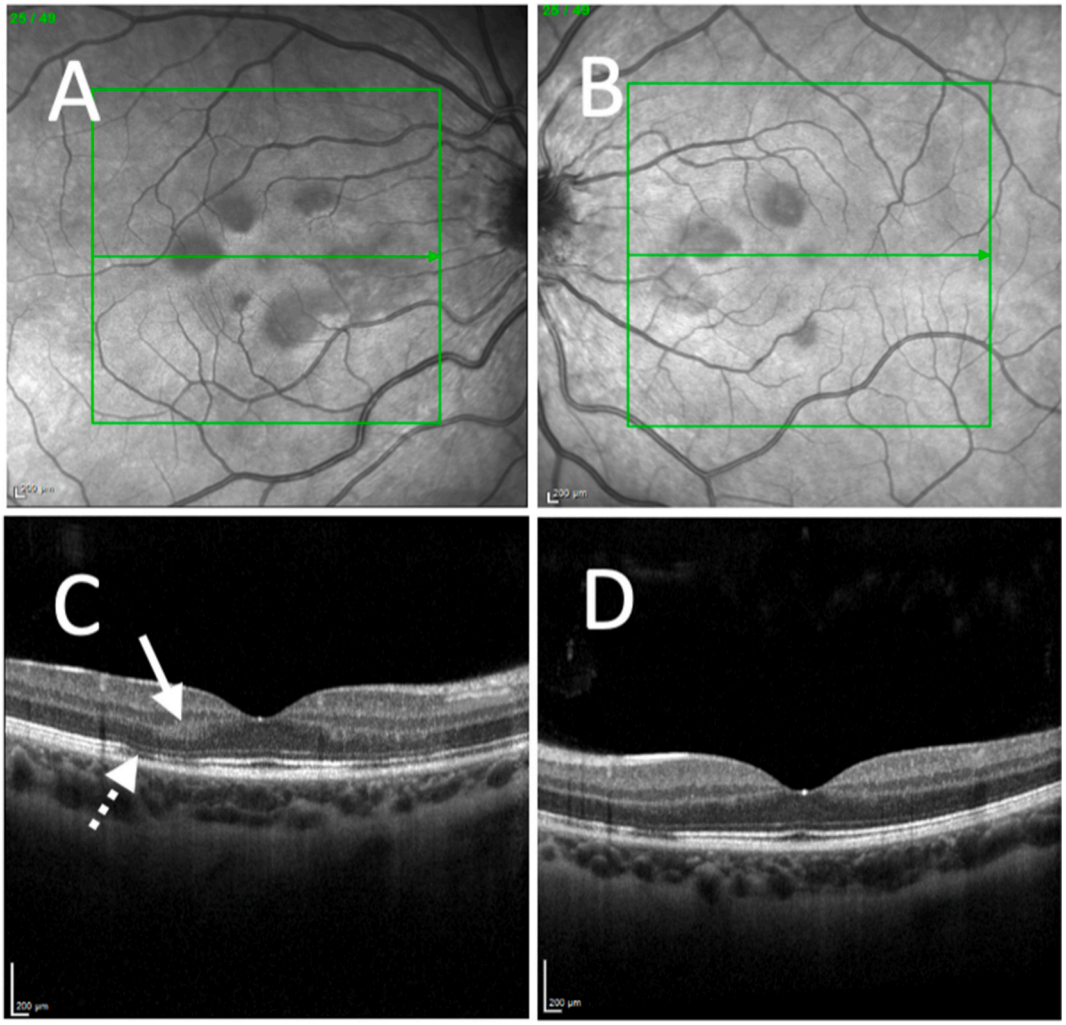

Fig. 2. Near infrared images (A, B) and corresponding spectral domain optical coherence tomogram (SD-OCT) B-scan through the fovea (C, D) of the right and left eyes, respectively, at presentation. The petaloid lesions are well visualized as areas of decreased reflectivity surrounding the fovea on near infrared images (A, B). The SD-OCT scans show disruption at the junction of the outer plexiform layer and the outer nuclear layer (solid white arrow) and associated attenuation of ellipsoid zone reflectivity (dotted white arrow) of the right (C) and left (D) eyes.

nonspecific viral illness or fever (48%), oral contraceptive use (36%), vasoconstrictor and sympathomimetic use (8%), or less common causes such as bodily trauma and systemic shock.[10] One report documented lisdexamphetamine mesylate use as a trigger.[11] On clinical exam of AMN, the most classic findings are reddish-brown or orange petaloid- or wedge-shaped lesions surrounding the fovea which are hyporeflective on NIR imaging and are bilateral in approximately half of patients. Corresponding abnormalities of the OPL, ONL, and EZ are often noted on SD-OCT. IVFA demonstrates abnormalities in only 26% of cases and indocyanine green angiography (ICGA) in 17% of patients, possibly limited by low resolution.[10] On the other hand, OCT-angiography (OCT-A) has been instrumental in visualizing vascular filling defects localized to the deep retinal capillary plexus.[12]

A similar, albeit distinct, pathologic finding termed paracentral acute middle maculopathy (PAMM) was described by Sarraf et al., in 2013. PAMM is thought to result from ischemia of intermediate capillary plexus resulting in a hyperreflective band on OCT at the level of the OPL and INL, which is more superficial than in AMN.[13] PAMM occurs in patients with a mean age of 49–53 years of age, there is no gender predilection, and visual acuity may be slightly worse than in AMN. In addition, the funduscopic findings are deep, smooth gray lesions rather than reddish-brown. Retinal vascular events such as arterial or venous occlusions can involve all three retinal capillary plexuses or cause isolated PAMM lesions, therefore PAMM lesions may sometimes be indicative of a more global retinal ischemic event.[14]

There are a few reported cases of possible AMN and PAMM in the setting of COVID-19, however these have all been confounded by complex underlying medical conditions, less classical NIR images, or concurrent atypical retinal findings such as hemorrhages or subretinal fluid. Gascon et al. described a case of possible combined AMN and PAMM findings in the left eye of a 53-year-old male with COVID19, however the patient also had multiple retinal hemorrhages, Roth spots, and subretinal fluid.[6] Another case of AMN concurrent with COVID-19 infection was reported in a 35-year-old female with a scotoma and typical OCT findings, but the single AMN lesion was adjacent to a retinal hemorrhage. The patient also had other peripapillary hemorrhage and Roth spots in both eyes and had recently started chemotherapy for acute myeloid leukemia, a known risk factor for both retinal hemorrhages and possibly AMN.[7] In the largest documented series of AMN cases of any cause, hemorrhages or macular edema were rare, found in only 3.2% of cases.[10] This may lead one to question whether the aforementioned cases associated with COVID-19 were truly AMN or were due to more generalized ischemic retinal event. Finally, Virgo et al. reported a case of possible PAMM in a 37-year-old pregnant Caucasian female and a 32-year-old Caucasian male following COVID-19 infection, both with scotomas and OCT findings although the lesions were small and singular

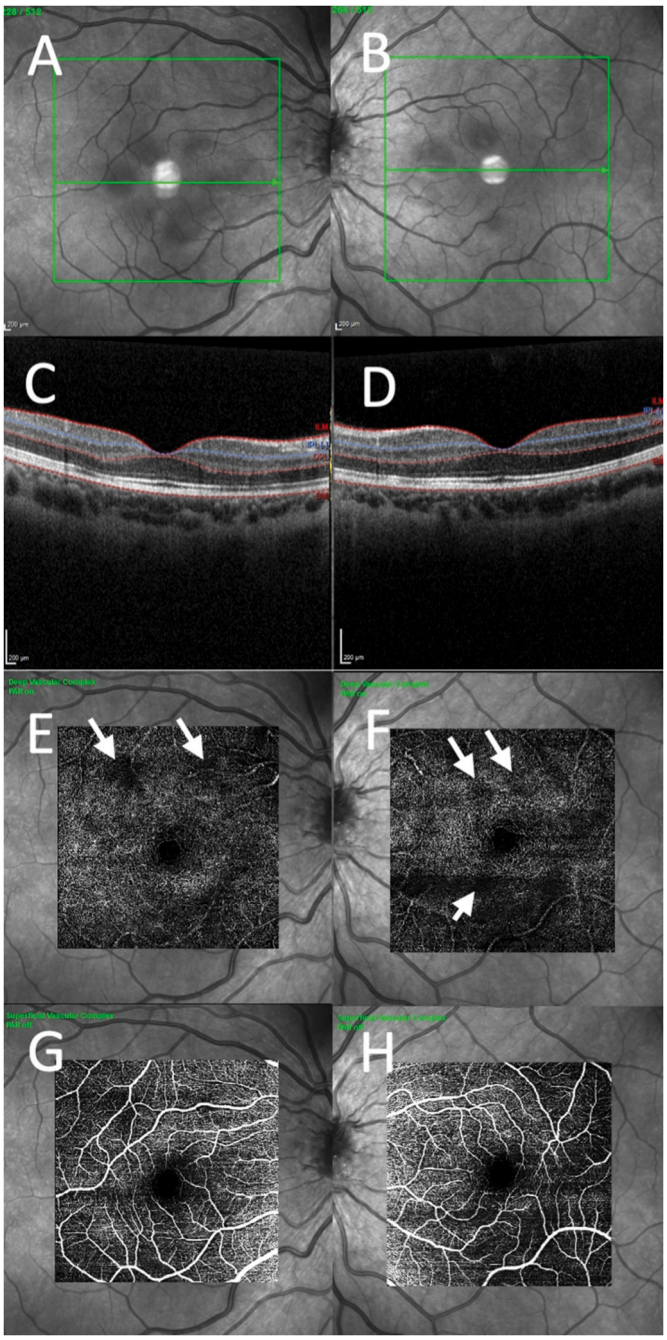

Fig. 3. Near infrared images (A, B) and corresponding spectral domain optical coherence tomogram (SD-OCT) B-scan through the fovea (C, D) of the right and left eyes at six months following presentation show persistence although slight improvement in the appearance of the retinal lesions. OCT-angiography shows much less prominent flow restriction in the superficial vascular complex (E, F) than in the deep vascular complex (G, H) corresponding with lesion seen on OCT (white arrows).

in each case.[8]

The case we report above is a more typical case of AMN in a patient with COVID-19. Our patient is an otherwise healthy, young, non-Hispanic Caucasian female, the most characteristic demographic for AMN. Her symptomatic scotomas and headache were noted to be present at the same time as her positive COVID-19 nasopharyngeal swab, so we believe her COVID-19 infection is likely the triggering etiology of AMN in her case. In addition, our patient's lesions were much more typical on examination and imaging than other reported cases of AMN or PAMM in COVID-19 disease, with reddish-brown petaloid appearance on funduscopy without hemorrhages or macular edema and with typical NIR, OCT, and OCT-A findings. We must concede that our patient did use oral contraceptives as well as lisdexamphetamine mesylate which are both reported risk factors for AMN. We believe that these medications likely augmented the hypercoagulable state caused by her COVID-19 infection, although COVID-19 ultimately was the principal cause for her retinal manifestations given timing of infection and ocular findings. In addition, it may be this combination of hypercoagulability secondary to medication use as well as COVID-19 infection that resulted in the large number of bilateral parafoveal lesions and scotomas in our patient. After observation at five week and six month follow-up, our patient had persistent manifestations from her AMN, albeit slightly improved.

To date, there is no clear treatment for AMN and even more limited data on outcomes of AMN secondary to COVID-19. Whereas intravitreal anti-VEGF injections for retinal vein occlusions (RVOs) may limit vascular nonperfusion and associated macular edema, the microvascular occlusion that occurs in AMN is much smaller in extent compared to an RVO. In a different case with AMN and PAMM lesions related to COVID-19, the small amount of subfoveal fluid resolved on its own within 15 days, lending support to observation for AMN including when associated with COVID-19.[6] In a case of purported bilateral central retinal vein occlusion related to COVID-19, the authors proposed that early initiation of anticoagulation for DVT may have halted and reversed progression of ischemia.[15] Fibrinolytic therapy is considered for COVID-19 related severe acute respiratory distress syndrome (ARDS), but the risk of major hemorrhagic events or hemorrhagic conversion of an unrecognized subacute stroke make this therapy less favorable.[1] Therefore, there is much to be learned about potential interventions to prevent or limit the damage from AMN in COVID-19 cases. In addition, our case should raise the question of whether short term discontinuation of triggering variables such as oral contraceptions or stimulants including caffeine should be considered to prevent further ischemic compromise.

4. Conclusions

Acute macular neuroretinopathy is commonly associated with a flu-like viral illnesses that causes fever as well as multiple conditions that result in a hypercoagulable state. Our case reports adds to the literature that the hypercoagulable state associated with COVID-19 disease may cause retinal vascular complications such as AMN. Although conjunctivitis may be the most common ocular manifestation of COVID-19 disease, we recommend a thorough retinal evaluation including close examination of macular OCT for all patients with visual disturbances that occur surrounding the time of COVID-19 infection.

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

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Patient consent

Written consent to publish the case report was provided by the patient. This report does not contain any personal information that could identify the patient.

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Authorship

All authors attest they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors have no financial or conflicting interests to disclose.

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