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Case Report

Atypical COVID-19-Related Acute Macular Neuroretinopathy with Progression Resulting in Severe Vision Loss

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Keywords
COVID-19-induced acute macular neuroretinopathy · Atypical acute macular neuroretinopathy · Visual acuity loss

Abstract
Introduction: We review the clinical course of a patient with decreased vision in the setting of COVID-19 infection consistent with an atypical presentation of acute macular neuroretinopathy (AMN). ***Case Presentation:*** A 56-year-old Caucasian woman developed a scotoma in the right eye 3 days after COVID-19 diagnosis and in her left eye on day 5. Baseline exam showed significantly reduced visual acuity bilaterally best corrected visual acuity of 20/60 in the right eye and 20/40 in the left eye from a patient-reported baseline of 20/20 in each eye. Examination of the fundus was remarkable for small flame-shaped hemorrhages in the superior arcade of both eyes. Near-infrared reflectance imaging revealed a singular wedge-shaped lesion in each eye close to the fovea and spectral domain-optical coherence tomography confirmed disruption of the photoreceptor layer and ellipsoid zones. Our leading diagnosis given the presentation was COVID-19-associated AMN. Given no evidence of a clear treatment, observation was selected. Three weeks later, visual acuity deteriorated further to 20/100 OD and 20/80 OS, with persistence of the wedge-shaped lesions. At 3-month follow-up, fundus photographs remained unremarkable; however, visual acuity had dropped further to 20/300 bilaterally, with persistence of the scotomata and outer retinal layer disruptions. 6 months later, treatment with a dexamethasone implant improved vision to 20/125 OD and 20/150 OS. ***Conclusion:*** Among COVID-19-induced AMN, our case is remarkable for the severe progression of visual impairment over 3 months of follow-up and improvement with a

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dexamethasone implant. Furthermore, absence of classical AMN lesions on fundus photography raises the question whether COVID-induced AMN may lead to a clinically distinct, potentially more severe picture than AMN arising from previously identified causes.

Introduction

Acute macular neuroretinopathy (AMN) is a rare condition characterized by the sudden onset of paracentral scotomata corresponding to clinically evident lesions. These were originally described as intraretinal, reddish-brown, wedge-shaped petaloid lesions, the apices of which tend to point toward the fovea [1]. While the causes are multifactorial, the most common association is nonspecific flu-like illness or fever; and many recently published case reports have described AMN arising consequent to COVID-19 infection or vaccination [2]. COVID-19 targets the endothelium via the ACE2 receptor expressed in several body organs including the retinal endothelial cells [3]. Loss of ACE2 activity due to viral invasion is known to lead to increased angiotensin II levels causing vasoconstriction that creates a pro-thrombotic environment by increasing platelet and leukocyte adhesion [4]. OCT angiography has shown reduced deep capillary plexus (DCP) flow signals in AMN [5]. DCP ischemia at the photoreceptor axons in the outer plexiform layer ultimately compromises their function, resulting in outer nuclear layer thinning [5]. Analysis of risk factors for AMN further supports a common underlying vascular pathogenesis [2]. Herein we report the presentation of AMN following COVID-19 infection.

Case Report

A 56-year-old Caucasian woman presented with bilateral scotomata which appeared 3 and 5 days after COVID-19 diagnosis in the right and left eye respectively. Her past medical history was significant for Graves' disease treated with thyroid radioactive iodine therapy, hyperlipidemia, and migraines. There was no past ocular history. Drug history was limited to levothyroxine and pantoprazole as well as self-reported medical use of cannabis, with no allergies, recent travel, or occupational exposures.

The patient was hospitalized on day 5 following development of bilateral scotomata and cloudy vision, and a magnetic resonance venography scan was performed which showed a right transverse sinus thrombosis. Urgent treatment with IV heparin was initiated in response, only to be discontinued a day later after further FLAIR imaging revealed the thrombosis to be of chronic nature. The ophthalmology examination on day 6 showed reduced best corrected visual acuity bilaterally (20/60 in the right eye and 20/40 in the left eye from a baseline of "normal vision" as reported by patient). Examination on day 6 revealed small flame-shaped hemorrhages in the superior arcades of both eyes (shown in Fig. 1). This finding was further corroborated by fluorescein angiography which showed blocked background fluorescence corresponding to the area of flame hemorrhages (shown in Fig. 2). Near-infrared reflectance imaging revealed a singular wedge-shaped parafoveal zone of hyporeflectivity in each eye (shown in Fig. 3). Spectral domain-optical coherence tomography of these zones showed them to be consistent with disruption of the photoreceptor layer and ellipsoid zones bilaterally. Static and dynamic visual fields were concentrically reduced and revealed the

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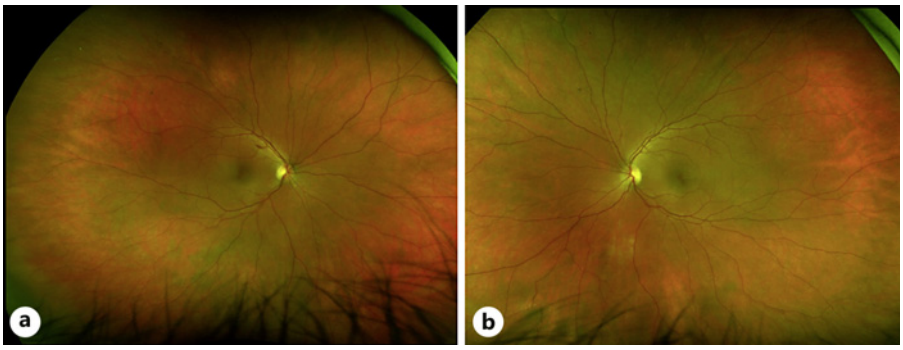

Fig. 1. Wide-angle color fundus photography of right eye (**a**) and left eye (**b**). Yellow arrows point toward location of small, flame-shaped hemorrhages bilaterally.

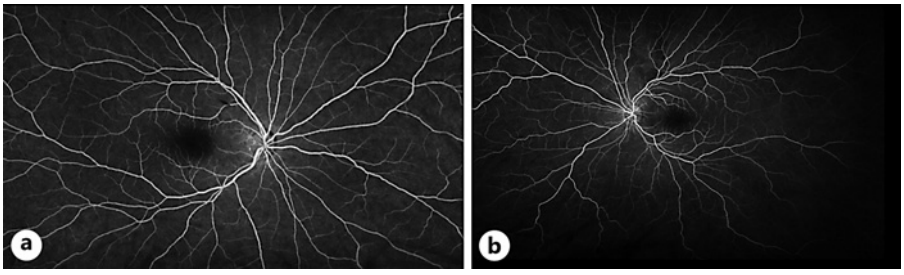

Fig. 2. Intravenous fluorescein angiography of right eye (**a**) and left eye (**b**) shows hypofluorescence in both eyes corresponding to the areas of hemorrhage.

scotomata as reported by the patient. Our leading diagnosis given the patient's examination and imaging findings was AMN; however, further testing was performed to rule out any other systemic causes. Infectious and autoimmune evaluation was negative (Table 1).

Evaluation included PT, PTT, protein C activity, fibrinogen, factor V Leiden, antithrombin 3, and antiphospholipid antibody panel, which was unremarkable except for an elevated PTT time. An MRI scan with contrast of the brain showed no abnormal signals involving the optic nerves and no acute intracranial processes, while a CT venogram of the head revealed diffusely small calibers of the right transverse sinus and jugular vein with a nonocclusive filling defect at the right jugular bulb extending into the proximal internal jugular vein consistent with chronic venous thrombosis.

On follow-up 3 weeks later, the visual acuity deteriorated to 20/100 in the right eye and 20/80 in the left eye. The wedge-shaped lesions were persistent bilaterally on near-infrared imaging and OCT (shown in Fig. 3). Given no evidence of a clear treatment for this condition, the decision was made to observe and follow-up in 3 months. An electroretinogram was also carried out at the time of follow-up which was consistent with normal outer retina function in each eye, and there was lack of evidence suggesting an inherited retinal disease, such as retinitis pigmentosa or cone dystrophy. Anti-recoverin test was negative, showing a lack of evidence for cancer-associated retinopathy.

The patient's visual acuity had further deteriorated to 20/300 after 3 months in the right eye and 20/300 in the left eye. Fundus photography was normal. Spectral domain-optical coherence tomography showed persistence of the disruptions in the photoreceptor layer and ellipsoid zones of each eye (Fig. 3). Indocyanine green did not show any abnormal areas of hyper- or hypofluorescence.

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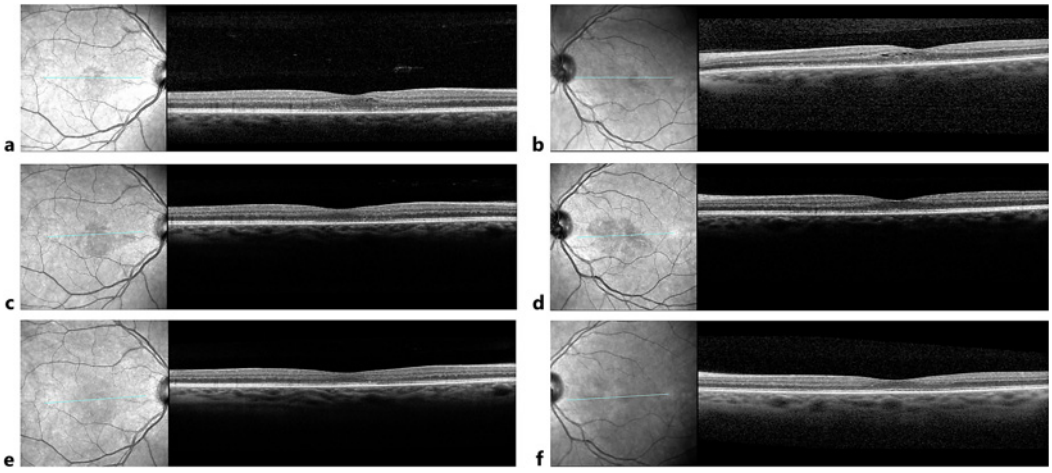

Fig. 3. Near-infrared reflectance imaging with SD-OCT at presentation to ophthalmology in the right eye (**a**) and the left eye (**b**), compared to 3 weeks later in the right eye (**c**) and left eye (**d**), and 3 months later in the left eye (**e**) and right eye (**f**). All images (**a–f**) show persistence of a wedge-shaped hyporeflectivity on near-infrared reflectance imaging. There is also a corresponding defect in the photoreceptor layer and ellipsoid zones in both eyes as shown by SD-OCT. SD-OCT, spetral domain-optical coherence tomography.

Table 1. Results of CSF analysis

CSF (cerebrospinal fluid) cell count	Normal
Appearance of CSF	Clear
Color of CSF	No color
White blood count, CSF	1
Red blood count, CSF	2.14
Other cell absolute, CSF	0.0
Glucose, CSF	62
Total protein, CSF	24.4

OCTA, taken 1 month later, showed no flow abnormalities in the DCP and choriocapillaris. Given concern for an autoimmune etiology and the patient's hesitation for systemic steroids, the decision was made to inject the patient with a dexamethasone implant (Ozurdex, AbbVie Inc., North Chicago, IL, USA) in both eyes. 6 months later, a significant visual improvement to 20/125 OD and 20/150 OS was noted with reduction in central subfield thickness on structural OCT.

Discussion

Our patient's presentation of bilateral paracentral scotomata with wedge-shaped hyporeflectivity and disruption of the photoreceptor layers and ellipsoid zone was indicative of AMN [5]. These lesions have typically been attributed to ischemia of the DCP; yet OCT angiography, taken 1 month later, showed no disruption in flow signals from the DCP or CC. However, this finding does not preclude AMN, as OCTA may be limited in its resolution of deeper retinal layers due to signal disruptions from more superficial retinal layers, introducing projection artifacts [6]. Additionally, reperfusion of affected zones may lead to regression of flow voids over time [6].

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Furthermore, AMN has an autoimmune etiology consistent with the patient's prior history of Graves' disease making her predisposed to autoimmune conditions [5]. Although there are only very few case reports describing thrombotic complications in patients with Graves' disease and concomitant APL antibodies, Graves' disease is thought to induce a procoagulant state through multiple mechanisms, including increased clotting factor levels [7]. Onset of ocular symptoms 3 days after COVID-19 diagnosis in our patient points toward COVID-19 as the most likely etiology; yet vascular sequelae of Graves' disease could be considered a potential predisposing factor. Also, the patient was diagnosed with untreated hyperlipidemia, which has also been shown to shift total hemostatic balance toward hypercoagulability [8].

The presence of flame-shaped hemorrhages may further reflect COVID-19-induced dysregulation of the retinal microenvironment, as COVID-19 infection is currently thought to be associated with an 8.86-fold increased prevalence of retinal microvasculopathy, including flame hemorrhages [9].

This case is remarkable for multiple reasons. Prior to the COVID-19 pandemic, only 8% of patients reported to have AMN in the literature were in the age group of 51–60 years [2], and the mean age of onset was 29.5 years [2]. Yet a recent case series on COVID-19 illness-related cases of AMN found that patients in this cohort were on average 45.9 years old [10], much closer to the age of our patient, which was 56 years. Nevertheless, visual acuity at presentation is generally reported to be good in AMN patients with relatively good preservation of vision. This contrasts with our patient who had vision loss that deteriorated to 20/300 OU over 3 months. It is worth noting that there is great heterogeneity with regards to the timing of final follow-up in this literature review. Additionally, visual acuity in this patient recovered remarkably in both eyes, to 20/125 OD and 20/150 OS, respectively, following insertion of dexamethasone implants highlighting the benefits of systemic immunosuppression. The dexamethasone implant works by inhibiting phospholipase A2 and thereby inflammatory cell migration and onset of an inflammatory reaction. Since the publication of this literature review, a few other COVID-19-related case reports have described very poor visual acuity in association with AMN, with partial rescue of visual acuity following treatment with oral corticosteroids or methotrexate [11–13].

Additionally, there was a striking lack of clinically identifiable lesions on color fundus photography in both eyes and retinal defects became apparent only on near-infrared reflectance imaging. This contrasts with the more typical presentation of AMN where fundus lesions are noted and decreased vision is of mild degree [1, 12, 13]. These differences suggest that perhaps the presentation of AMN is different in the context of COVID-19 [12, 13].

Conclusion

In summary, the case highlights the different presentation of AMN in the setting of COVID-19. The age of our patient was older than that typical for patients who have AMN. The patient had a worse presenting vision than would be expected in patients with AMN. Finally, our case shows highlights the importance to consider AMN in patients with COVID-19 even in those who do not have any lesions on color fundus photography.

Whether atypical presentations of AMN, or AMN presentations of greater severity, might be more prevalent in the cohort in COVID-19-related cases will remain to be seen with the publication of more case reports on COVID-19-related AMN. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000542802).

Statement of Ethics

For sole reporting of cases, ethical approval was not required in accordance with local/national guidelines. Written informed consent was obtained from our patient for publication of their relevant medical data and any accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

E.M.W., Dr. L.T., and Professor Dr. J.F.A. wrote the manuscript. Dr. L.T. and Professor Dr. J.F.A. contributed to explanations and project supervision.

Data Availability Statement

The data that support the findings of this study are not publicly available since they contain information that could compromise the privacy of research participants but are available from Professor Fernando Arevalo (J.F.A.) upon reasonable request.

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