American Journal of Ophthalmology Case Reports 35 (2024) 102001

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Bilateral acute macular neuroretinopathy associated with COVID-19 infection presenting with central scotoma

Shivani Sinha *, Vidya Bhusan Kumar, Abhishek Anand, Bibhuti Prassan Sinha

Regional Institute of Ophthalmology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

ARTICLE INFO

Keywords:
COVID-19
Acute macular neuroretinopathy
HFA 10-2
Central scotoma
Red free
Near infrared imaging

ABSTRACT

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

Observation: A 26-year-old female presented with a chief complaint of bilateral central scotomas for the last seven days. She had a history of fever over the past ten days, and RT-PCR test for COVID-19 was positive on the second day of fever. She had been vaccinated against COVID-19 eight months prior. Her best corrected visual acuity was 6/6 in both eyes on the Snellen chart. Dilated fundus evaluation revealed subtle bilateral perifoveal grey macular lesions. Optical coherence tomography (OCT) demonstrated focal hyperreflectivity at the level of the outer nuclear and plexiform layer consistent with bilateral AMN. Near-infrared reflectance (NIR) and red-free (RF) imaging showed large, confluent hyporeflective lesions in the right eye and discrete petaloid lesions with apices pointing toward the fovea in the left eye. OCT angiography (OCTA) revealed decreased flow signal at the level of the deep capillary plexus (DCP) and choriocapillaris (CC) in both eyes. Automated visual field testing (Humprey Field Analyzer (HFA) 24-2) revealed bilateral central scotoma with depression of adjacent points. After two weeks, the patient had depressed visual fields on HFA 10-2. At two months of final follow-up, OCT macula, NIR and RF images revealed resolving AMN lesions in both eyes. OCTA showed an increase in perfusion at the level of the DCP. There was a decrease in scotoma density on HFA 10-2, suggestive of resolving AMN.

Conclusion and importance: AMN with central scotoma as presenting feature of COVID-19 is rare. Fundus findings may be very subtle in AMN, but NIR and RF imaging delineate the lesions well. OCT, NIR imaging, OCTA and HFA 10-2 can be used to assess the clinical course of AMN.

1. Introduction

COVID-19 has been associated with a myriad of retinal manifestations. Retinal microhemorrhages, cotton wool spots, and central retinal vein and artery occlusion have been reported.[1–6] AMN and PAMM have been reported in patients with COVID-19.[7–14]

AMN is most frequently associated with non-specific illness in approximately half of reported cases.[15] The lesions of AMN are macular and reddish brown wedge-shaped, the apices of which are directed toward the fovea.[15] It usually presents with mild vision loss, paracentral scotomas and photopsia.[15] Central scotoma has been less commonly reported in AMN.[16–18] The most sensitive imaging modality to detect AMN is near-infrared imaging (NIR) with OCT. NIR may be especially useful when clinical examination and color fundus photography fail to detect lesions of AMN.[15]

We report the case of a 26-year-old female with symptomatic central scotomas and imaging findings consistent with bilateral AMN associated with mild COVID-19 infection.

2. Case report

A 26-year-old female presented with a seven-day history of bilateral central scotomas. She had a history of fever ten days prior and was evaluated for COVID-19 infection. She had been vaccinated against COVID-19 eight months previously. The RT-PCR test for COVID-19 was positive on the second day of fever. Her best corrected visual acuity was 6/6 in both eyes. Pelli-Robson contrast sensitivity and color vision were within normal limits. The blood investigations were as follows: total leukocyte count: 8700 per microliter, erythrocyte sedimentation rate: 13 mm/hr, D-dimer: 0.41 μg/mL, prothrombin time 13.1 seconds, and international normalized ratio 1.03. Dilated fundus evaluation revealed subtle bilateral perifoveal grey macular lesions (Fig. 1a and b). NIR

* Corresponding author. Regional Institute of Ophthalmology, Indira Gandhi Institute of Medical Sciences, Patna, 800014, Bihar, India.
E-mail address: shivanisinha64@gmail.com (S. Sinha).

https://doi.org/10.1016/j.ajoc.2024.102001
Received 1 February 2023; Received in revised form 23 October 2023; Accepted 22 January 2024
Available online 11 February 2024

(Fig. 1c and d) and red-free (RF) (Fig. 1e and f) images showed large, confluent, hyporeflective, well-delineated lesions in the right eye and discrete petaloid lesions in the left eye. The apices of these macular lesions pointed toward the fovea. Optical coherence tomography (OCT) demonstrated focal hyperreflectivity at the level of the outer nuclear and plexiform layers consistent with bilateral AMN (Fig. 2a and b). There was decreased parafoveal reflectivity of the external limiting membrane (ELM) and ellipsoid zone (EZ) on OCT. Automated visual field testing (Humphrey Field Analyzer (HFA) 24-2) revealed bilateral central scotoma with depression of adjacent points (Fig. 2c and d). OCT angiography (OCTA) revealed decreased flow signal at the level of the deep capillary plexus (DCP) in both eyes (Fig. 3). There was rarefaction of choriocapillaris (CC) in the subfoveal region bilaterally (Fig. 3).

The patient was followed up after two weeks. As the patient still complained of central scotoma, HFA 10-2 was done which confirmed central scotoma. OCT demonstrated resolving AMN. NIR imaging revealed a decrease in the size of the macular lesions bilaterally (Fig. 4). OCTA showed an overall increase in perfusion at the level of DCP and CC. At two months of final follow-up, on the OCT macula, there was a decrease in hyperreflectivity of OPL and ONL at the level of AMN lesions with a recovery of reflectivity of parafoveal ELM and EZ (Fig. 5) in both eyes. NIR and RF images showed a decrease in the size of the confluent and petaloid lesions in the right and left eyes respectively. OCTA showed an increase in perfusion at the level of DCP. In the right eye, vascular density in DCP increased in the superior, nasal and temporal quadrants, while it remained stable in the inferior quadrant as well as within the 1

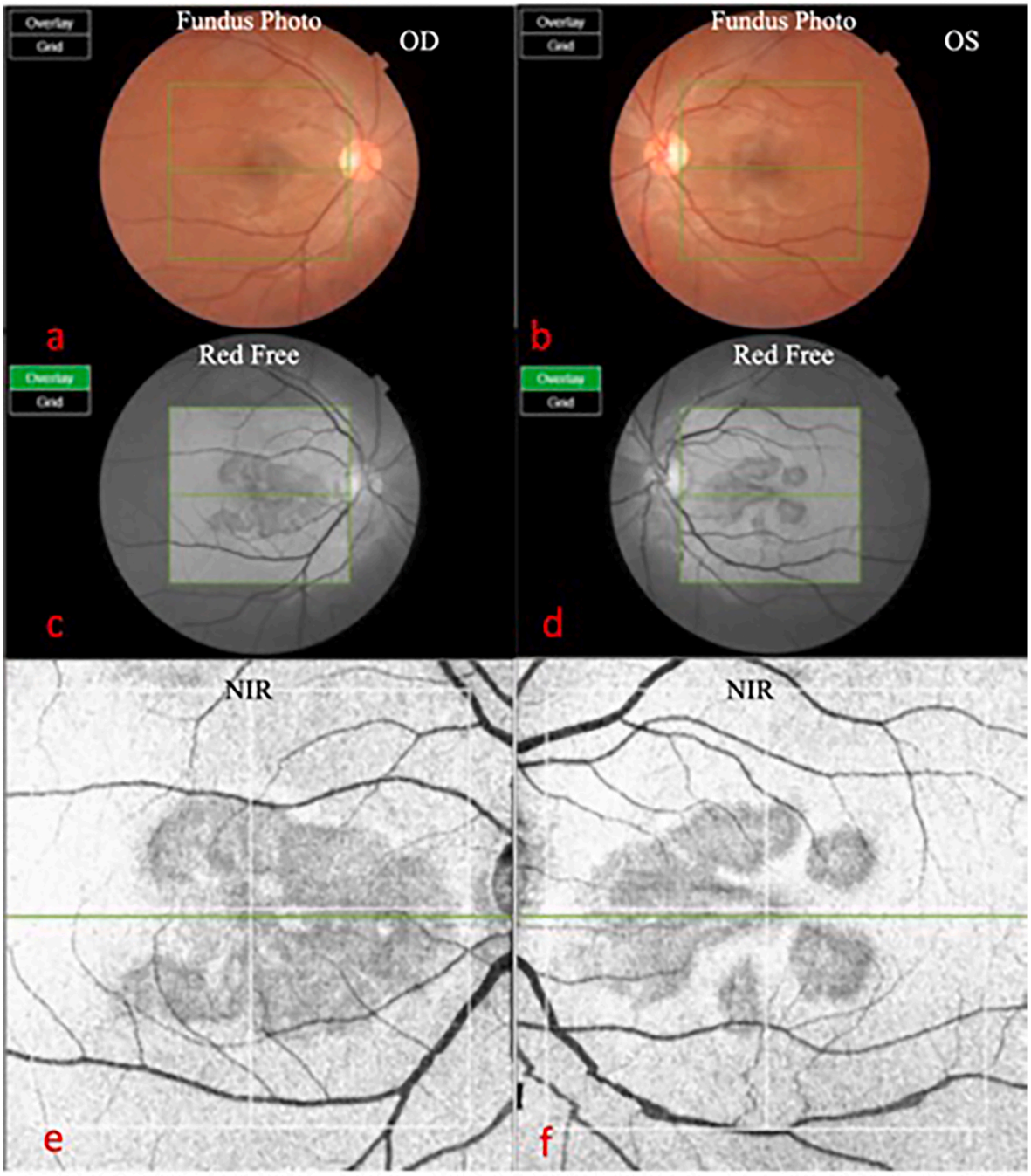

Fig. 1. Fundus photo of both eyes showing mild perifoveal greying. Red-free images and near-infrared images (NIR) show confluent hypo-reflective lesions at the macula in the right eye (c, e) and well delineated hypo-reflective lesions with apices pointing toward the fovea (d, f).

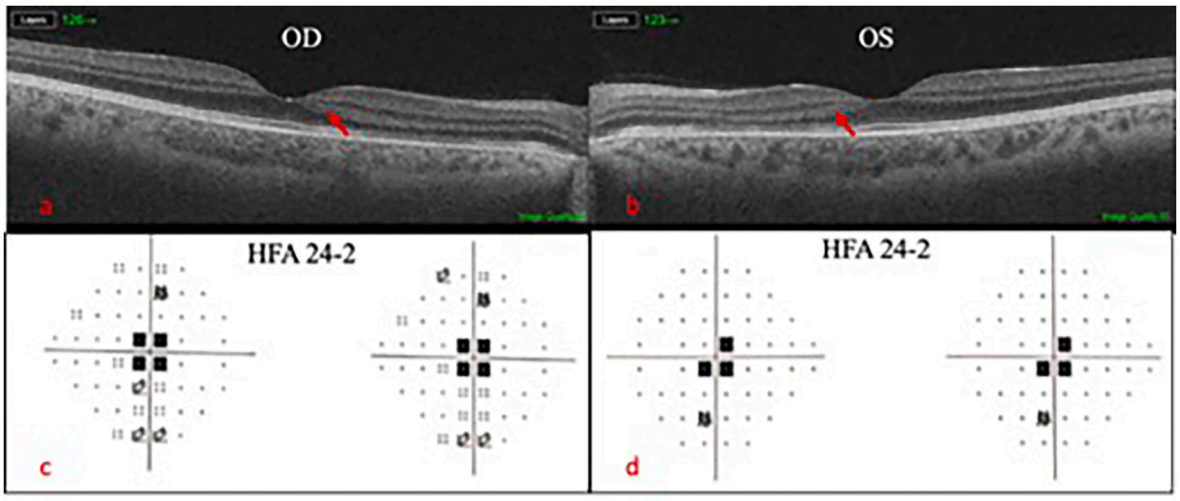

Fig. 2. OCT macula shows increased hyperreflectivity of the outer plexiform layer, depicted by the arrow. The total and pattern deviation plots on Humprey Field Analyzer (HFA) 24-2 depict central scotoma in both eyes.

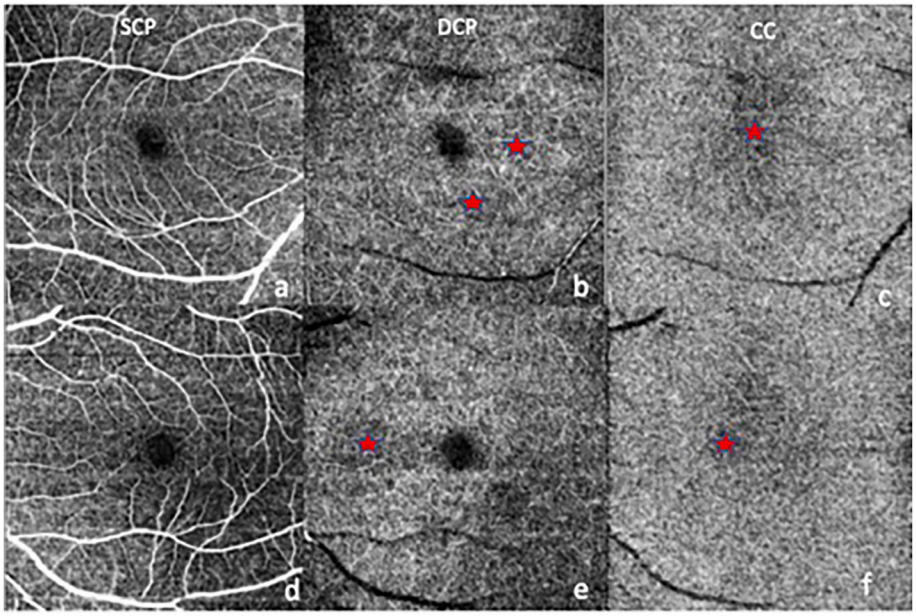

Fig. 3. Superficial capillary plexus shows no vascular voids in both eyes. The deep capillary plexus and choriocapillaris show vascular voids depicted by the star.

mm ETDRS grid centered on the macula. The vascular density of the left eye increased in the 1 mm area, nasal, temporal and inferior quadrants while remaining comparable in the superior quadrant. The density of the scotoma on HFA 10-2 decreased but never recovered fully (Fig. 6).

3. Discussion

In this report, we describe an unusual presentation of central scotoma in AMN and show how multimodal imaging can assist the clinician to diagnose and monitor the disease process. AMN has been found to be most frequently associated with non-specific respiratory or influenza-like illness in approximately half of the cases.[15] AMN has also been associated with COVID-19.[7–14] Our patient noticed the onset of central scotoma after three days of onset of fever secondary to documented COVID-19 infection.

The characteristic fundus abnormality of AMN is one or more wedge-shaped, well-delineated lesions pointing toward the fovea.[15] The clinically observed lesions are reddish brown or orange in color in more than half of the cases. In a small number of patients there were no clinically identifiable lesions, while NIR imaging revealed retinal defects.[15] In our case there were subtle perifoveal grey macular lesions. NIR imaging revealed large, confluent hyporeflective well-delineated lesions in the right eye and discrete petaloid lesions in the left eye. NIR imaging and SD-OCT may be abnormal even in the presence of normal clinical examination and color fundus photography.[15] Even RF imaging helps us delineate the lesions well, due to less scatter and excellent contrast. It can also be considered as a primary screening tool due to its wider availability.

The majority of eyes with AMN have been reported to have one or more paracentral scotomas.[15] In a recent case series all patients with AMN with concurrent COVID-19 infection had paracentral scotoma.[19] Central scotoma has been reported in only four patients of AMN following COVID-19 infection.[20,21] Our patient described her scotoma as being central, which was further documented on HFA 24-2 and 10-2, an unusual presentation in a case of AMN. Subsequent follow-up HFA 10-2 confirmed central depression and depressed visual fields. The recovery

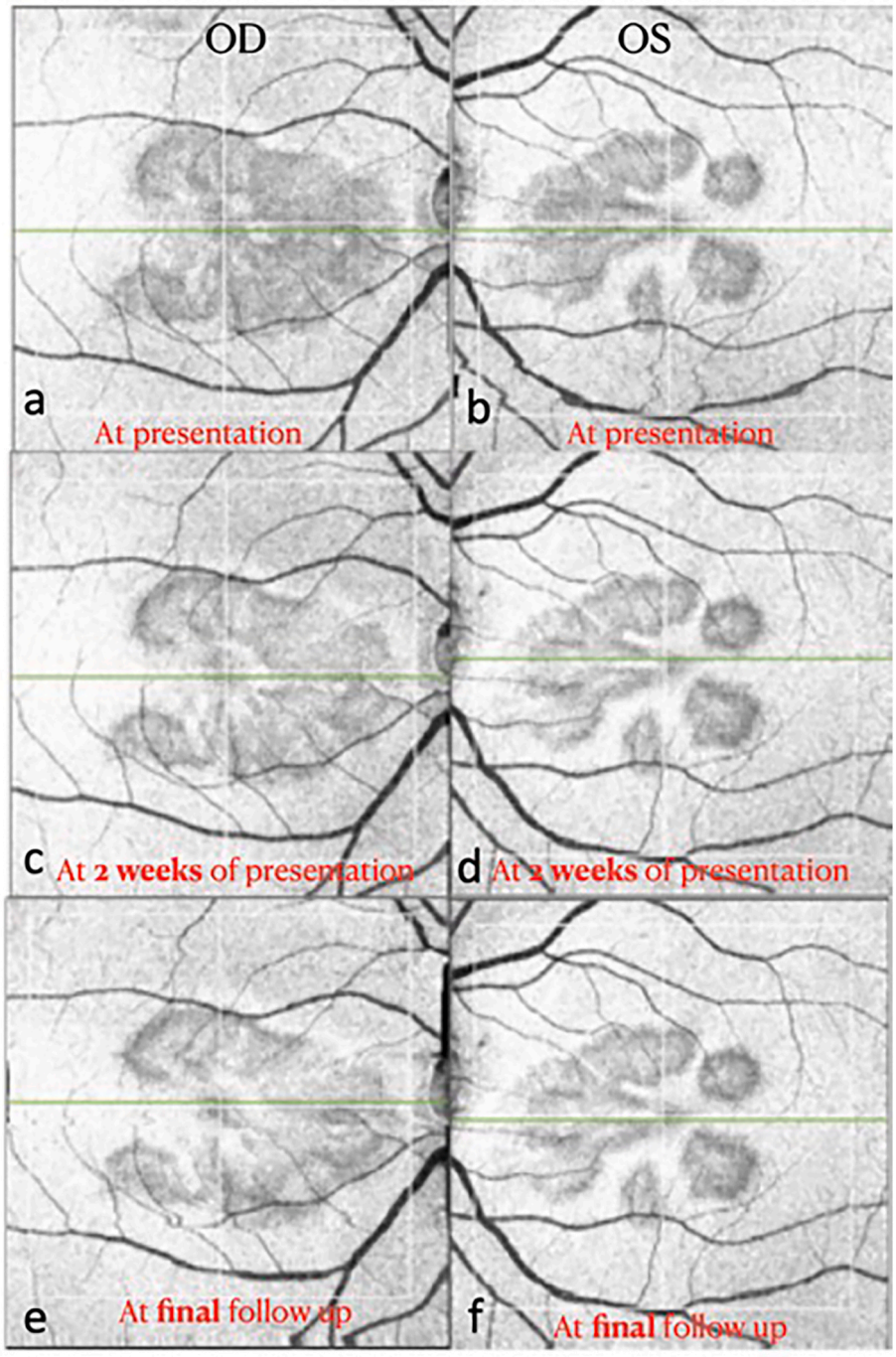

Fig. 4. Sequential follow-up of the patient on NIR shows a decrease in hypo-reflectivity of the lesions, thereby indicating resolution of the AMN lesion.

of visual fields has not been documented on serial follow-up in any of the cases reported. In our patient the density of scotoma decreased on follow-up, but complete recovery was not observed. Previous studies have reported the persistence of scotoma in more than half of the cases.[15]

OCT often demonstrates hyper-reflectivity of the ONL and OPL. OCT findings in AMN with COVID-19 have also demonstrated similar changes in outer retinal structure as well as foveal thinning.[8,10,13,19] In our case the patient had hyperreflectivity of OPL and ONL. There was a decrease in hyperreflectivity of the parafoveal ELM and EZ adjacent to the AMN lesion. During the subsequent final follow-up at two months there was a decrease in reflectivity but not complete resolution. Similarly, we observed an increase in reflectivity of ELM and EZ on subsequent follow-up.

Vascular events involving DCP have been implicated in the pathogenesis of AMN.[15,22] OCTA in this patient showed rarefaction of the capillary plexus in DCP and CC, suggesting decreased perfusion in the area of AMN lesions, while SCP did not show any alteration in vascular perfusion. In the subsequent follow-ups, the vascular voids decreased, indicating partial restoration of the perfusion at the level of DCP and CC. Earlier reports also have shown a decreased vascular flow signal in DCP and CC in AMN.[12,19,23–25]

During the height of the COVID-19 pandemic the diagnosis of AMN increased from 0.66 per 100,000 visits in 2019 to 8.97 per 100,000 visits.[20] Also, there was an increased number of published case reports and series associating COVID-19 to AMN.

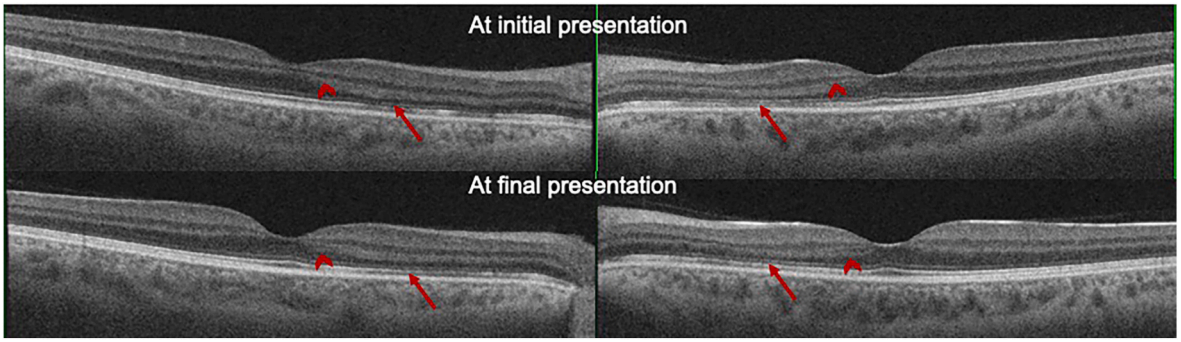

Fig. 5. There is a recovery in the rarefaction of the external limiting membrane and ellipsoid zone (depicted by arrow) with a decrease in hyperreflectivity of the outer plexiform layer (depicted by arrowhead).

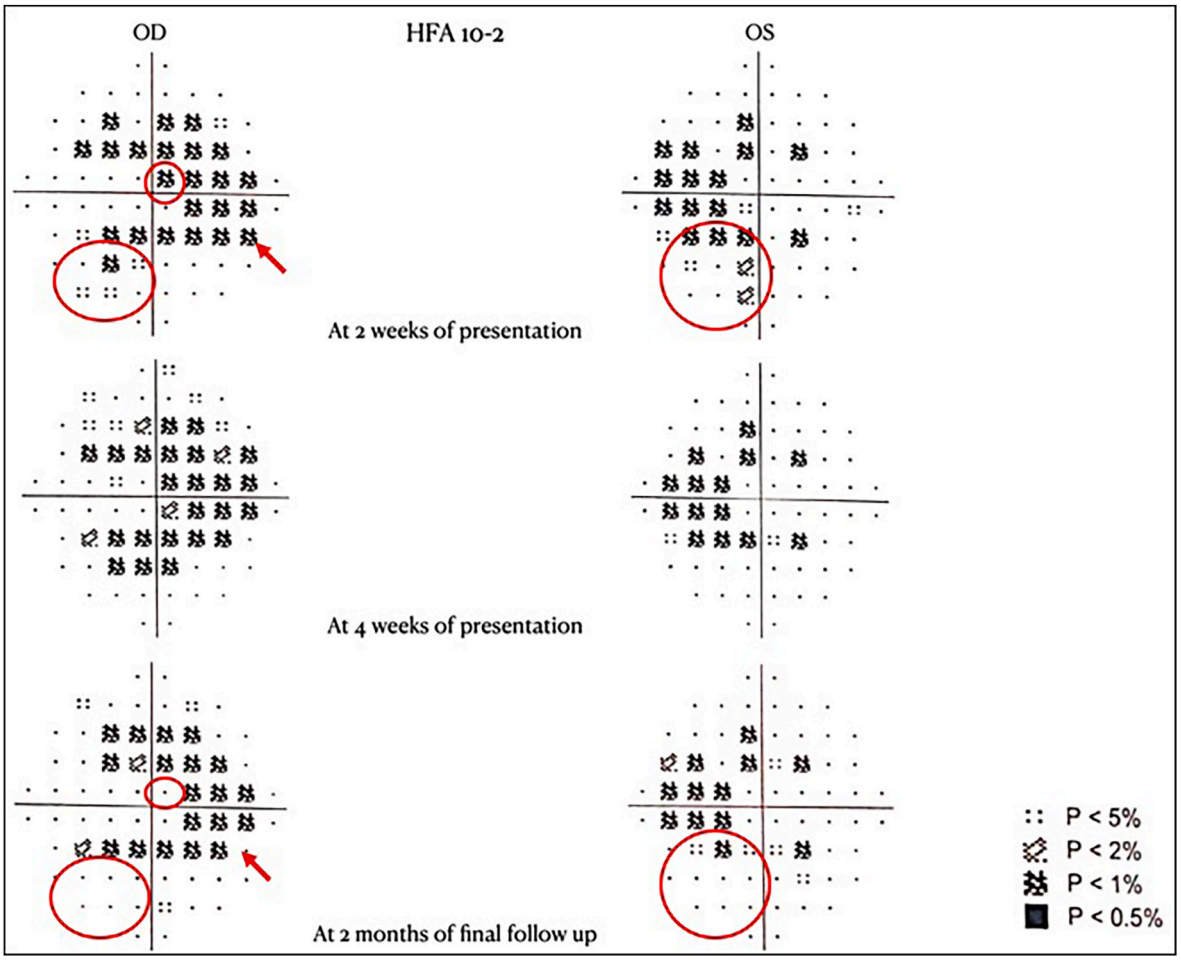

Fig. 6. Sequential HFA 10-2 of both eyes shows a decrease in density of the scotoma, as depicted by arrows and circles.

Retina and choroid have the highest vascularization per unit area in our body. Hence, the effects of inflammation and ischemia due to systemic disease can be observed locally in these tissues. COVID-19 is known to be associated with microangiopathy, which can cause impaired blood flow in the retina and choroid.[26] The exact mechanism by which SARS-CoV-2 affects retinal and choroidal vasculature is not completely understood. Angiotensin-converting enzyme 2 receptor is expressed on some of the cells in retina and choroid.[27] It is known that SARS-CoV-2 enters human cells using ACE 2 receptors. SARS-CoV-2 has been postulated to cause both direct cytopathic damage and indirect damage as it results in intense inflammation and hypercoagulable state.[27] So, the retinal vascular system may be altered by a myriad of events including thromboembolism, hypercoagulability, hypoxia, and endothelial dysfunction.[28] Reduced vessel density has been reported in patients with COVID-19.[29] A decrease in choroidal blood flow may be due to inflammation and edema.[30]

The outer retinal layers and fovea are supplied by choroidal circulation. The choroidal vascular insult can result in subfoveal and outer retinal layer changes and hence can lead to central involvement. In our case, we hypothesize that, as our patient had mild COVID-19, the resulting inflammation or inflammatory response may have led to altered vascular perfusion in the DCP and CC. Although these changes were not severe enough to cause structural alterations in the subfoveal retinal layers, they resulted in subclinical changes leading to central

scotoma. As there were no evident structural changes in subfoveal retinal layers, the vision was preserved throughout.

4. Conclusions

COVID-19 has been documented to have multiple ocular manifestations including microvascular events. AMN has been associated with COVID-19. Central scotoma, although rare, can be the presenting complaint in AMN. Multimodal imaging especially NIR and RF can help delineate AMN lesions in an apparently normal-looking fundus. Further imaging and HFA 10-2 can help monitor the course of the disease.

Patient consent

Written consent has been obtained from the patient to publish this case report.

Funding

No funding or grant support.

Authorship

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

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors have no conflict of interest.

Acknowledgement

None.

References

1. D'Aloisio R, Nasillo V, Gironi M, Mastropasqua R. Bilateral macular hemorrhage in a patient with COVID-19. *Am J Ophthalmol Case Rep*. 2020 Dec;20, 100958. https://doi.org/10.1016/j.ajoc.2020.100958. Epub 2020 Oct 9. PMID: 33073058; PMCID: PMC7546668.
2. Pereira LA, Soares LC, Nascimento PA, et al. Retinal findings in hospitalised patients with severe COVID-19. *Br J Ophthalmol*. 2022 Jan;106(1):102–105. https://doi.org/10.1136/bjophthalmol-2020-317576. Epub 2020 Oct 16.PMID: 33067361.
3. Invernizzi A, Torre A, Parrulli S, et al. Retinal findings in patients with COVID-19: results from the SERPICO-19 study. *EClin Med*. 2020 Oct;27, 100550. https://doi.org/10.1016/j.eclinm.2020.100550. Epub 2020 Sep 20. PMID: 32984785; PMCID: PMC7502280.
4. Ju Sheth, Narayanan R, Goyal J, Goyal V. Retinal vein occlusion in COVID-19: a novel entity. *Indian J Ophthalmol*. 2020 Oct;68(10):2291–2293. https://doi.org/10.4103/ijo.IJO_2380_20. PMID: 32971697; PMCID: PMC7727974.
5. Raval N, Djougarian A, Lin J. Central retinal vein occlusion in the setting of COVID-19 infection. *J Ophthalmic Inflamm Infect*. 2021 Apr 2;11(1):10. https://doi.org/10.1186/s12348-021-00241-7. PMID: 33796944; PMCID: PMC8016503.
6. Montesel A, Bucolo C, Mouvet V, Moret E, Eandi CM. Case report: central retinal artery occlusion in a COVID-19 patient. *Front Pharmacol*. 2020 Dec 23;11, 588384. https://doi.org/10.3389/fphar.2020.588384. PMID: 33424598; PMCID: PMC7785811.
7. Masjedi M, Pourazizi M, Hosseini NS. Acute macular neuroretinopathy as a manifestation of coronavirus disease 2019: a case report. *Clin Case Rep*. 2021;9(10), e04976. https://doi.org/10.1002/ccr3.4976. . Accessed October 17, 2021.
8. Virgo J, Mohamed M. Paracentral acute middle maculopathy and acute macular neuroretinopathy following SARS-CoV-2 infection. *Eye (Lond)*. 2020;34(12):2352–2353. https://doi.org/10.1038/s41433-020-1069-8.
9. Gascon P, Briantais A, Bertrand E, et al. Covid-19-Associated retinopathy: a case report. *Ocul Immunol Inflamm*. 2020;28(8):1293–1297. https://doi.org/10.1080/09273948.2020.1825751.
10. Aidar MN, Gomes TM, de Almeida MZH, de Andrade EP, Serracarbassa PD. Low visual acuity due to acute macular neuroretinopathy associated with COVID-19: a case report. *Am J Case Rep*. 2021;22, e931169. https://doi.org/10.12659/AJCR.931169. . Accessed April 30, 2021.
11. Preti RC, Zacharias LC, Cunha LP, Monteiro MLR. Acute macular neuroretinopathy as the presenting manifestation of covid-19 infection. *Retin Cases Brief Rep*. 2022;16(1):12–15. https://doi.org/10.1097/ICB.0000000000001050.
12. Giacuzzo C, Eandi CM, Kawasaki A. Bilateral acute macular neuroretinopathy following COVID-19 infection. *Acta Ophthalmol*. 2022;100(2):e611–e612. https://doi.org/10.1111/aos.14913.
13. Zamani G, Ataei Azimi S, Aminizadeh A, et al. Acute macular neuroretinopathy in a patient with acute myeloid leukemia and deceased by COVID-19: a case report. *J Ophthalmic Inflamm Infect*. 2021;10(1):39. https://doi.org/10.1186/s12348-020-00231-1. . Accessed January 8, 2021.
14. Macé T, Pipelart V. Acute macular neuroretinopathy and SARS-CoV-2 infection: case report. *J Fr Ophtalmol*. 2021;44(9):e519–e521. https://doi.org/10.1016/j.jfo.2021.07.004.
15. Bhavsar KV, Lin S, Rahimy E, et al. Acute macular neuroretinopathy: a comprehensive review of the literature. *Surv Ophthalmol*. 2016;61(5):538–565. https://doi.org/10.1016/j.survophthal.2016.03.003.
16. Gelman R, Chen R, Blonska A, Barile G, Sparrow JR. Fundus autofluorescence imaging in a patient with rapidly developing scotoma. *Retin Cases Brief Rep*. 2012;6(4):345–348. https://doi.org/10.1097/ICB.0b013e318260af5d.
17. Radwan LM, Bou Ghanem GO, Daye GN, Ghazi NG. Acute macular neuroretinopathy associated with intravitreal anti-VEGF injection: a case report. *Am J Ophthalmol Case Rep*. 2022;28, 101687. https://doi.org/10.1016/j.ajoc.2022.101687. . Accessed August 18, 2022.
18. Makino S, Tampo H. Acute macular neuroretinopathy in a 15-year-old boy: optical coherence tomography and visual acuity findings. *Case Rep Ophthalmol*. 2014;5(1):11–15. https://doi.org/10.1159/000358166. . Accessed January 8, 2014.
19. Dinh RH, Tsui E, Wieder MS, et al. Acute macular neuroretinopathy and coronavirus disease. *Ophthalmol Retina*. 2019;2022. https://doi.org/10.1016/j.oret.2022.09.005. S2468-6530(22)00481-X . Accessed October 8, 2022.
20. Azar G, Bonnin S, Vasseur V, et al. Did the COVID-19 pandemic increase the incidence of acute macular neuroretinopathy? *J Clin Med*. 2021;10(21):5038. https://doi.org/10.3390/jcm10215038. . Accessed October 28, 2021.
21. Yılmaz Çebi A, Kılıçarslan O, Uçar D. Coincident acute macular neuroretinopathy and paracentral acute middle maculopathy in COVID-19. *Turk J Ophthalmol*. 2023;53(2):120–123. https://doi.org/10.4274/tjo.galenos.2022.55156.
22. Cabral D, Ramtohul P, Zatreanu L, et al. Deep capillary plexus features in acute macular neuroretinopathy: novel insights based on the anatomy of henle fiber layer. *Invest Ophthalmol Vis Sci*. 2022;63(13):4. https://doi.org/10.1167/iovs.63.13.4.
23. Ramtohul P, Comet A, Denis DL. Optical coherence tomography angiography recovery pattern of acute macular neuroretinopathy. *JAMA Ophthalmol*. 2020;138(2):221–223. https://doi.org/10.1001/jamaophthalmol.2019.5066.
24. Thanos A, Faia LJ, Yonekawa Y, Randhawa S. Optical coherence tomographic angiography in acute macular neuroretinopathy. *JAMA Ophthalmol*. 2016;134(11):1310–1314. https://doi.org/10.1001/jamaophthalmol.2016.3513.
25. El Matri K, Werda S, Chebil A, et al. Acute macular outer retinopathy as a presumed manifestation of COVID-19. *J Fr Ophtalmol*. 2021;44(8):1274–1277. https://doi.org/10.1016/j.jfo.2021.06.002.
26. Turker IC, Dogan CU, Guven D, Kutucu OK, Gul C. Optical coherence tomography angiography findings in patients with COVID-19. *Can J Ophthalmol*. 2021;56(2):83–87. https://doi.org/10.1016/j.jcjo.2020.12.021.
27. Guemes-Villahoz N, Burgos-Blasco B, Vidal-Villegas B, et al. Reduced macular vessel density in COVID-19 patients with and without associated thrombotic events using optical coherence tomography angiography. *Graefes Arch Clin Exp Ophthalmol*. 2021;7:1-7.
28. Wang S, Wang J, Hu J, Wang N. Retinal microvascular impairment in COVID-19 patients: a meta-analysis. *Immun Inflamm Dis*. 2022 Jun;10(6):e619. https://doi.org/10.1002/iid3.619. PMID: 35634955; PMCID: PMC9091999.
29. Teo KY, Invernizzi A, Staurenghi G, Cheung CMG. COVID-19-Related retinal microvasculopathy - a review of current evidence. *Am J Ophthalmol*. 2022 Mar;235:98–110. https://doi.org/10.1016/j.ajo.2021.09.019. Epub 2021 Sep 26. PMID: 34587494; PMCID: PMC8465265.
30. Erdem S, Karahan M, Ava S, et al. Evaluation of choroidal thickness in patients who have recovered from COVID-19. *Int Ophthalmol*. 2022;42:841–846.