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Atypical acute fovealitis in COVID-19 context

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ABSTRACT

Purpose: To describe the clinical and multimodal imaging findings, including optical coherence tomography (OCT), and OCT angiography (OCTA) in a case presenting with acute fovealitis after COVID-19 infection, and its differential diagnosis.

Observations: A 39-year-old man presenting with acute central metamorphopsia in his right eye (OD) right after positive test for COVID-19 underwent comprehensive ophthalmic examination, including best corrected visual acuity (BCVA), color fundus (CF) examination, optical coherence tomography (OCT), OCT angiography (OCTA), fundus autofluorescence (FAF) and fluorescein angiography (FA). Baseline BCVA was 20/40 in his OD and fundus examination showed small inferior juxtafoveal hemorrhages with no other vascular abnormalities or peripheral changes. The OCT B-scans revealed a central focal defect of the ellipsoid and interdigitation zones associated with foveal and perifoveal columnar hyperreflectivities involving the photoreceptor layers, the external limiting membrane and outer nuclear layer up to the outer plexiform layer with preservation of the retinal pigment epithelium-Bruch's membrane complex. Both FAF and FA images were unremarkable. Over three months follow-up, the findings progressively resolved, and BCVA improved to 20/20.

Conclusions and importance: The presence of hyperreflective material at the fovea in association with adjacent hemorrhages, the absence of alterations of the retinal pigment epithelium in OCT, OCTA, FAF and FA suggested the diagnosis of acute fovealitis in COVID-19 context. The presence of these findings highlights the importance of detailed ophthalmic evaluation in symptomatic patients with COVID-19 positive test.

1. Introduction

Coronavirus disease 2019 (COVID-19) known since December 2019, has plunged the world into a huge health crisis due to its rapid expansion because of its contagiousness and significant lethality, mainly due to respiratory complications.[1–3]

COVID-19 patients can present with variable ophthalmological manifestations. Transmission through infected ocular tissue or fluid has been a controversy. It is hypothesized that the nasolacrimal system can act as a conduit for viruses to travel from the upper respiratory tract to the eye. Some authors suggest that ocular involvement only occur when COVID-19 disease is systemic, while others think that they may be incipient findings of this disease.[1] However, more studies are still needed to try to eliminate the controversies around the causal relationship of COVID-19 and the different ophthalmological manifestations. Conditions of the ocular surface, such as follicular conjunctivitis, have been the most reported finding. In addition, cases of retinal vasculitis have been documented due to its ability to generate an exaggerated inflammatory response and damage to the vascular microcirculation, becoming a more serious ocular problem.[2] Moreover, optical coherence tomography angiography (OCTA) images in patients recovered from COVID-19 showed decreased vessel density in the superficial and deep capillary plexus, and choriocapillaris flow deficits at follow-up.[4]

Ledesma-Gil and Spaide used the term acute fovealitis to describe acute alterations in the outer retinal layers in the absence of retinal pigment epithelium (RPE) involvement, accompanied by hyperreflective foveal material that extended from the outer nuclear layer to the inner limiting membrane. They also highlighted its unknown etiopathogenesis and good prognosis with resolution of the lesions and recovery of visual acuity with no pigmentary changes.[5]

We present a detailed multimodal imaging analysis in a case showing

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unilateral foveal acute abnormalities in the context of COVID-19 infection, resembling acute fovealitis and we discuss the differential diagnosis.

2. Case report

A 39-year-old man presented with a history of 1-month of central metamorphopsia in his right eye (OD). The visual decline started in association with general malaise, cough and low-grade fever. Due to the progression of symptoms, he was referred to the hospital for a PCR test for COVID-19, which tested positive. He presented a seizure in the context of high fever. A brain and lung CT scan were performed and reported as normal. No additional significant alterations were observed in blood and urine tests. After an admission of approximately 12 hours, the patient was discharged with anticonvulsant treatment. The neurological examination a week after was reported as normal. No antiplatelet or anticoagulant treatment was required.

Ocular history was otherwise unremarkable. He also denied any use of recreational drugs and previous trauma or exposure to laser light and sun gazing. At baseline, his best-corrected visual acuity (BCVA) was 20/40 in his OD and 20/20 in his left eye (OS). Intraocular pressure and anterior segment examination were unremarkable. Posterior segment examination showed a clear vitreous with no cells. Dilated fundus examination of the OD revealed small inferior juxtafoveal hemorrhages in the absence of other vascular abnormalities or peripheral changes (Fig. 1). Posterior segment examination in his OS was unremarkable.

Optical coherence tomography (OCT) B-scans revealed a central focal defect involving the ellipsoid zone (EZ) and the interdigitation zone (IZ) associated with columnar hyperreflectivities in the foveal area involving the photoreceptor layers, the external limiting membrane, outer nuclear layer up to the outer plexiform layer with preservation of the RPE-Bruch's membrane (RPE-BM) complex (Fig. 1 E, F). The subfoveal choroidal thickness was 121 μm (μm). The largest diameter of disruption of the EZ in the foveola was 433 μm, and the maximum height of the hyperreflective material from the RPE-BM complex towards the inner layers was 185 μm. No abnormalities were detected in the superficial vascular plexus, intermediate or deep capillary plexi or choriocapillaris using OCTA (Fig. 2). Fundus autofluorescence (FAF) demonstrated small hypoautofluorescent lesions inferior to the fovea corresponding to areas of hemorrhage with no additional abnormalities (Fig. 1 C, c.1). Fluorescein angiography (FA) did not show additional alterations (Fig. 3).

A week after, BCVA in his OD improved to 20/25 without treatment. OCT B-scans progressively showed a regression of central focal defect involving the ellipsoid and interdigitation zone and of the columnar hyperreflective material in the central foveal area. After 3 months, the defects in OCT B-scans were almost resolved completely and no

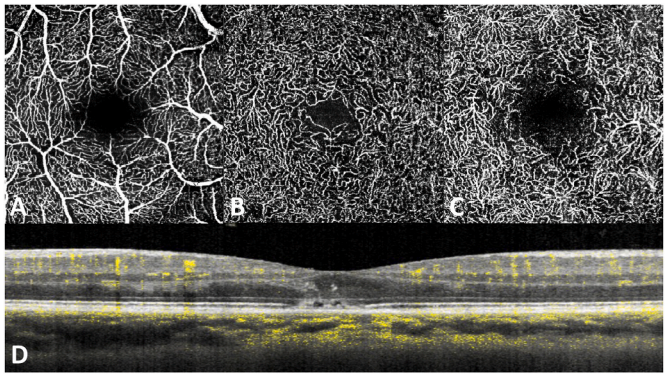

Fig. 2. Optical coherence tomography angiography *en face* images show no abnormal findings in the (**A**) superficial vascular plexus, (**B**) intermediate capillary plexus or (C) deep capillary plexus. (**D**).The cross-sectional B-Scan with flow signal overlay shows no significant abnormalities other than the structural changes previously described.

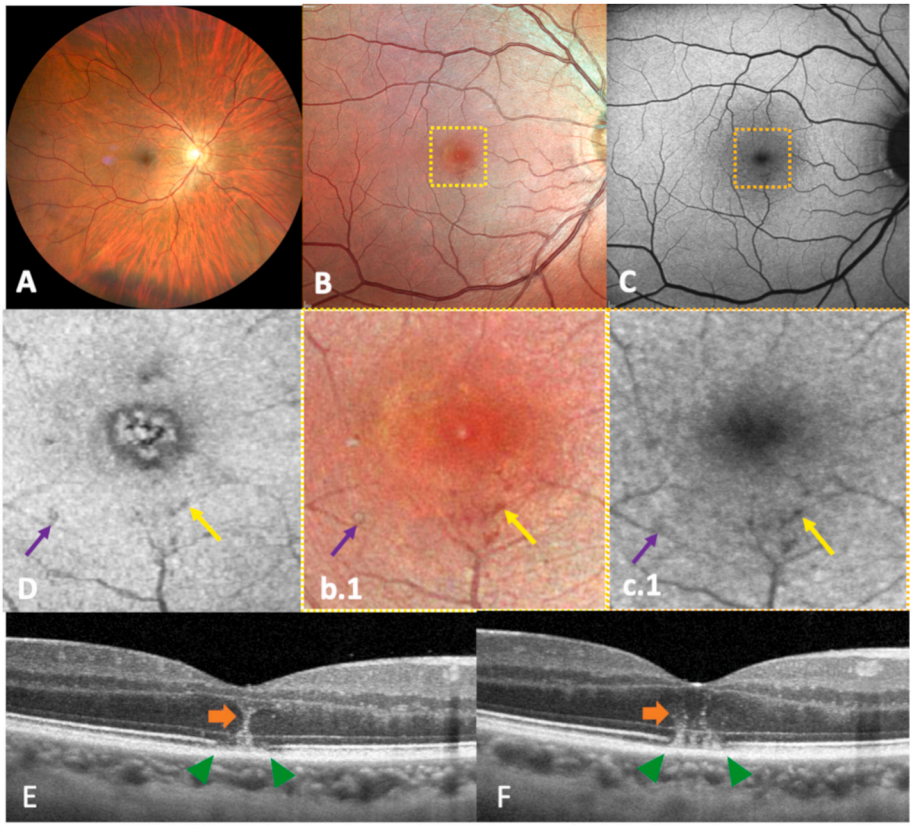

Fig. 1. Presentation of a 39-year-old man with a history of 1-month of central metamorphopsia in his right eye in COVID-19 context. **A)** Color wide-field fundus image showing small inferior juxtafoveal hemorrhages in the absence of other vascular abnormalities or peripheral changes. **B, b.1)** Multicolor reflectance clearly shows the inferior juxtafoveal hemorrhages (yellow arrows). **(C, c.1)** Fundus autofluorescence hypoautofluorescent dots corresponded to the areas of hemorrhage. (**D**). *En face* optical coherence tomography (OCT) showed these same areas as hyporeflective focal round dots resembling microaneurysms (purple arrow) with no B-scan correlation. **E, F)** B-scan OCT shows a central focal defect involving the ellipsoid and interdigitation zone, with preservation of the retinal pigment epithelium-Bruch's membrane complex (green asterisks), associated with columnar hyperreflective material (orange arrow) in the central foveal area involving the photoreceptor layers, the external limiting membrane, outer nuclear layer up to the outer plexiform layer. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

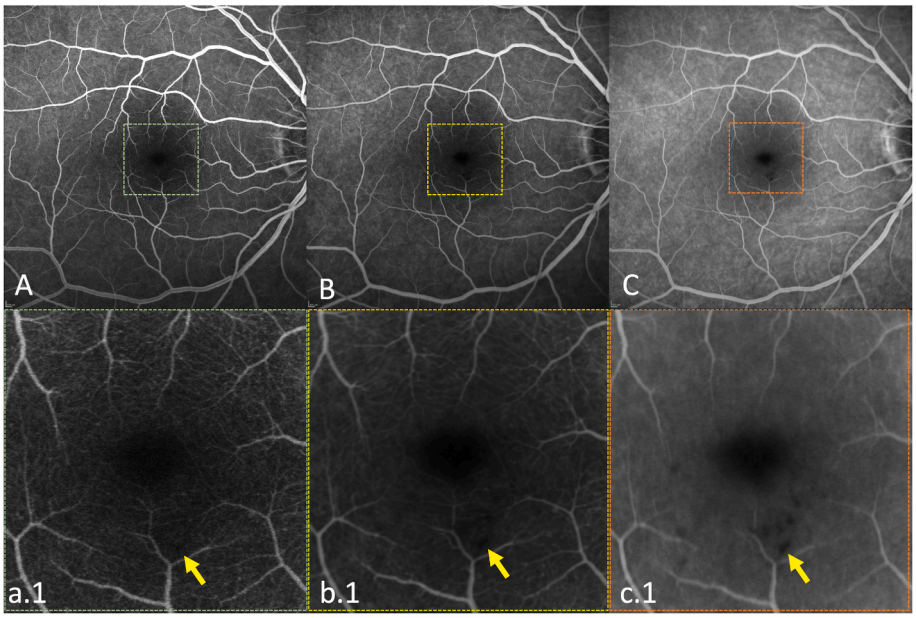

Fig. 3. Fluorescein angiography images at **(A, a.1)** 00:31, **(B, b.1)** 1:26 and **(C, c.1)** 6:10 minutes demonstrate normal filling with absence of hot disk and no remarkable vascular alterations. The hypofluorescent dots (yellow arrows) correspond to the hemorrhages seen on fundus examination and become more evident in late phases. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

hemorrhages were detected on fundus examination. BCVA was 20/20 in his OD and 20/20 in his OS, with a reported normal vision (Fig. 4).

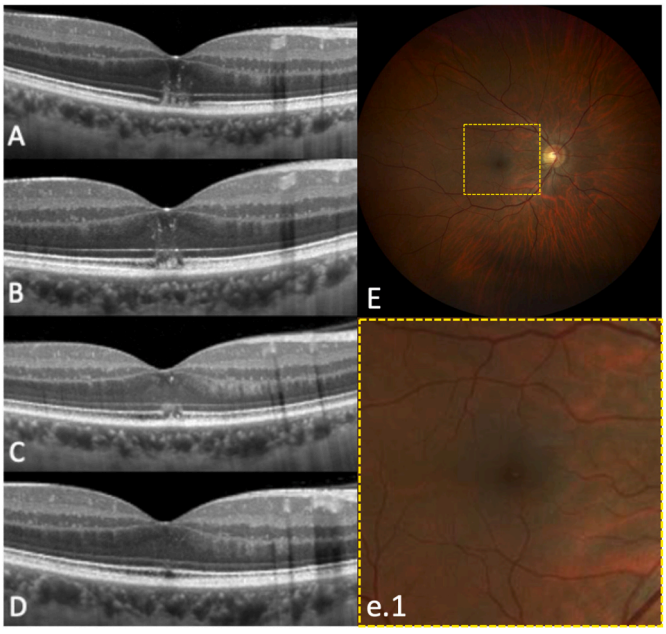

Fig. 4. B-scan optical coherence tomography image through the follow-up at A. 1-week, B. 2-weeks, C. 1-month and D. 3-months follow-up shows a progressive regression of the central focal defect involving the ellipsoid and interdigitation zones and fading of the columnar hyperreflective material in the central foveal area in his right eye. D. Almost complete restoration of the outer retinal bans is observed. with improvement of visual acuity to 20/20. E. Color fundus examination at 3-month follow-up shows resolution of the hemorrhages, magnification of the macular area is provided (e.1.) for detail evaluation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

Our case presented with acute foveal hyperreflective material in association with disruption of the outer retinal layers and small juxtafoveal hemorrhages, with fully preservation of the RPE-BM complex. The present case was presumably due to COVID-19 since the patient tested positive for COVID-19 in the presence of malaise and fever at baseline. Based on the multimodal imaging findings and the progressive recovery with preservation of the RPE, our final diagnosis was acute fovealitis in the context of COVID-19.

Cases of foveal abnormalities in the context of viral infection have been widely described. Coxsackie virus infection may express acute idiopathic maculopathy, which is associated with acute central vision loss, exudative detachment of the neurosensory retina, pigment epithelial hyperplastic changes and surrounding atrophy that resembles a “bull’s eye” appearance. It can also manifest as multifocal retinitis, characterized by multiple posterior segment lesions that gradually resolve without leaving significant changes of outer retinal layers. Dengue fever has been also associated with diffuse retinal thickening, cystoid macular edema and fovealitis, which is characterized by an area of thickening and high reflectivity at the subfoveal outer retina layer. Another classical post-viral manifestation is acute retinal pigment epitheliitis (ARPE). This rare self-limited macular disorder affects healthy young adults. Initially, the fovea may have a yellow-white appearance, but over time, there is pigment stippling surrounded by hypopigmented halo-like zones.[5] The characteristic OCT feature is a dome-shaped hyperreflective lesion at the photoreceptor outer segment layer disrupting the EZ and IZ towards the external limiting membrane. The outer nuclear layer and Henle’s layer could show hyperreflective plumes that do not extend above the internal limiting membrane (ILM), different to which occurs in acute fovealitis. A hyporreflective gap in the interdigitation zone could also be observed. Foveal pigment stippling could be visible on ophthalmoscopy.[5] The fundus autofluorescence may show an increased autofluorescence in the foveal center and in the areas corresponding to the hypopigmented white dots.[6] The FA could show hyperfluorescence at the fovea due to window defects. Our case, showed preservation of the RPE-BM complex with no visible pigmentary changes throughout the follow-up, thus ARPE was not considered as a primary diagnosis, although the photoreceptor changes were similar to previous

reported atypical cases.[7] In early stages ARPE affects the neurosensory retina and the RPE-Bruch's membrane complex may be intact,[7] cockade-like appearance on *en face* OCT image of the IS/OS junction has been described, but was not observed in our case, also, there was an absence of hyperreflective punctate lesions on *en face* OCT image of the outer nuclear layer. Nevertheless, atypical ARPE could not be definitely ruled out as a diagnostic possibility for this case.

In 2020, Ledesma-Gil and Spaide[5] reported a case with acute alterations in the outer retinal layers (IZ, EZ and ELM) accompanied by hyperreflective foveal material that extended from the outer nuclear layer to the inner limiting membrane. They highlighted its good prognosis with resolution of the lesions and recovery of visual acuity with no pigmentary changes. Based on the multimodal imaging findings, RPE was not affected and the authors hypothesized that a transient inflammation affecting only the foveolar cellular components, cones and Müller cells, was present.[5] They used the term acute fovealitis to describe this case, with unknown etiopathogenesis. Moraes et al.[8] subsequently published a series of four patients with similar characteristics.[8] The authors also noted that the subfoveal choroidal thickness did not significantly changed between the acute and recovery phases in acute fovealitis, suggesting a lack of choroidal inflammation. Our case presented with preservation of the RPE-BM complex, central focal defect of the outer retinal layers, columnar hyperreflectivities in the fovea. No changes in subfoveal choroidal thickness were observed and subsequent resolution of the lesions and recovery of visual acuity with no pigmentary changes was achieved, as seen in the cases described by Ledesma-Gil[5] and Moraes.[8] However, our case presented juxtafoveal hemorrhages with no prominent vascular abnormalities on FA or OCTA images, and the hyperreflective material did not reach the ILM.

In our case, the presence of foveal acute hyperreflective lesions with disruption of the outer retinal layers led us to include other retinal and chorioretinal diseases in the differential diagnosis such as idiopathic multifocal choroiditis (MFC), or multiple evanescent white dot syndrome (MEWDS). Additionally, solar or laser-induced maculopathies and some drugs could also lead to hyperreflectivity and outer retinal abnormalities.

Idiopathic MFC presents with multiple inflammatory lesions involving the retina and choroid mainly affecting young myopic women.[9] Initial lesions could be seen as gray or yellowish lesions corresponding with focal hyperreflective sub-RPE material on OCT with a variable degree of focal or diffuse outer retinal disruption. This focal hyperreflective lesions may lead to chorioretinal scars with a variable degree of pigmentation and persistent outer retinal disruption. Underlying choroidal thickening can also be present. Recently, long standing foveal hyperreflectivities have been described in the context of MFC, showing a mottled hyperautofluorescence. Our case presented with hyperreflective material in the foveal area, that progressively fade away in weeks, however, no additional inflammatory lesions or abnormalities in the RPE were detected and no pigmentary changes were seen, thus MFC was ruled out.

MEWDS is a self-limited inflammatory retinal disease, similar to ARPE, that typically affects young adults. The orange foveal granularity observed may resemble the foveal pigment stippling in ARPE. However, MEWDS tends to be widespread, and resolved completely within several weeks of their onset.[9] On OCT, dome-shaped hyperreflective lesions in the subretinal space and multifocal or diffuse attenuation and disruption of the hyperreflective band at the ellipsoid zone are observed. Initially, FAF shows areas of hyperautofluorescence that correspond with the white dots and pinpoint areas of decreased autofluorescence around the disc and in the macula corresponding to small brownish lesions visible on ophthalmoscopy. FA shows punctate hyperfluorescence in a wreath-like configuration. In our case, presentation was unilateral, but limited to the fovea. Also, both FAF and FA were unremarkable only showing the small juxtafoveal hemorrhages, with no other alterations, thus MEWDS was also ruled out.

Solar radiation can cause a disruption of the outer segments-to-RPE interdigitation.[10] Fundus examination shows an absent foveal reflex and a granular appearance of the fovea. In OCT, solar maculopathy includes focal defects in the hyperreflective layers corresponding to the EZ, the IZ, and the RPE. These defects in outer retinal layers are surrounded normally by an hyperreflective ring in en face OCT. An involvement of all retinal layers in the fovea with hyperreflective area have also been described. The FAF shows small hypoautofluorescence spots in the fovea, which may be attributed to focal depletion of lipofuscin pigments in the photoreceptor layer, with later recovery if the light is not very intense or the damage is not maintained. FA examination is normal. Laser-induced maculopathy shows a similar pattern, but can present with extensive alterations like retinal hemorrhages or full thickness macular holes when repeated exposure is present or in cases of high-energy laser power. Our patient denied any abnormal exposure to sun or laser. Additionally, no pigmentary changes were observed, thus these causes were ruled out. Other conditions that may have similar features, such as Poppers maculopathy, were also ruled out, due to the absence of consumption and the unilateral presentation.

We present a case of acute fovealitis with the atypical association of juxtafoveal hemorrhages, presumably caused by COVID -19 infection. Despite the incessant study of COVID and its ophthalmological consequences, the evidence in this area is still scarce and uncertain. Therefore, on numerous occasions COVID has been suggested as a causal agent only as an exclusion diagnosis. The microcirculatory damage in COVID patients is a complement-mediated thrombotic microangiopathy.[2] As angiotensin-converting enzyme-2 (ACE-2) receptors are expressed in ocular structures like the choroid or the RPE, COVID-19 is able to target vascular pericytes expressing ACE-2.[1] This infection could lead to a complement-mediated endothelial cell dysfunction, microvascular damage, and thus, ocular circulation involvement. COVID-19 coagulopathy may predispose to a spectrum of thromboembolic events, like central retinal vein occlusion, central retinal artery occlusion, acute macular neuroretinopathy or paracentral acute middle maculopathy.[3] It has been recently described the presence of deposits of hyperreflective material at the level of the ganglion cell and inner plexiform layers caused specifically by COVID. These deposits are most striking in the papillomacular bundle and occur in both eyes simultaneously. The OCTA images and ganglion cell complex analysis are unremarkable in these cases. In addition, it could present with cotton wool spots and microbleeds along the retinal arcades. Visual acuity in these patients is normally preserved.[11] However, further research may disclose a possible COVID-19 implication in retinal vascular pathology.

4. Conclusion

In conclusion, we present a case showing hyperreflective material involving the outer retinal layers but not reaching the ILM and juxtafoveal hemorrhages in the context of a COVID-19 infection, and we hypothesize that these findings belong to the clinical spectrum of acute fovealitis. The diagnosis was made after exclusion of other retinal diseases, and the association with COVID-19 virus was only stated as possible. Further studies with large population data are warranted in order to clarify ocular associations with COVID-19 infection, however proving the relationship is always challenging.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

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

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