Unique presentations of aspergillosis endogenous endophthalmitis in two hospitalized patients with severe COVID-19

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We present two ICU-hospitalized patients with coronavirus disease-19 (COVID-19) presenting with endogenous endophthalmitis in one eye and variable manifestations of chorioretinitis in the fellow eye. Two diabetic patients (57 and 62 years old) showed anterior uveitis and yellowish-white subretinal infiltrations. The fellow eye of one patient showed patches of choroiditis, while the other showed full retinal thickness infiltrations. A workup yielded high serum titers of galactomannan, diagnostic of aspergillosis. The widespread use of high doses of corticosteroids in the management of COVID-19 may predispose to various secondary fungal opportunistic infections and may manifest in different forms of chorioretinal infiltration.

Key words: Aspergillosis, COVID-19, endophthalmitis, fungal, galactomannan, uveitis

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), a novel single-stranded RNA virus responsible for coronavirus disease 2019 (COVID-19), was reported as a global pandemic by the World Health Organization (WHO) in early 2020.[1] Since then, it has quickly been demonstrated that the systemic impact of the viral infection has surpassed respiratory system affection to various other morbidities, including cardiovascular and gastrointestinal disorders, as well as hematological and neurological abnormalities.[2] In this article, we present two patients with previous intensive care unit (ICU) admission for respiratory complications related to COVID-19 displaying endogenous endophthalmitis and chorioretinal infiltration in the fellow eyes.

Case Reports

Case 1

A 57-year-old diabetic female patient, previously admitted to the ICU for COVID-19 a month prior, presented with right acute painless diminution of vision. On admission, her HbA1c was 7.9. During her ICU stay, the patient has been kept on continuous positive airway pressure (CPAP) for declining oxygen saturation levels. She was managed with intravenous dexamethasone 6 mg daily for 5 days for pulmonary changes related to COVID-19. After 10 days of admission, her condition began to stabilize, and she was discharged.

Ophthalmological examination revealed a best-corrected visual acuity (BCVA) of 20/125 in the right eye and 20/25 in the left eye. Pupillary light reflex examination showed bilateral brisk responses with no signs of afferent pupillary defect. Intraocular pressure was recorded as 13 mm Hg in the right eye and 14 mm Hg in the left eye. Anterior segment examination was unremarkable in the left eye; however, the right eye showed granulomatous anterior uveitis and mutton fat keratic precipitates.

Dilated fundus examination of the right eye revealed vitreous haze with a temporal juxtafoveal subretinal grayish lesion extending under the fovea. The left eye showed subtle grayish spots along the superotemporal arcade.

Fluorescein angiography (FA) of the right eye demonstrated juxtafoveal hyperfluorescence with cystoid macular leakage, while optical coherence tomography angiography (OCT) revealed a hyperreflective dome-shaped lesion infiltrating all retinal layers temporal to the fovea with intraretinal and subretinal fluid. The dots seen in the left eye showed early hyperfluorescence on FA and appeared on OCT as deposits underneath the retinal pigmentary epithelium (RPE) [Fig. 1]. Unfortunately, no true-color photography was obtained.

Case 2

A 62-year-old diabetic male patient, previously admitted to the ICU for COVID-19 2 months prior, presented with a history of left acute painless diminution of vision. On admission, his HbA1c was 8.3. During his ICU stay, his condition showed signs of deterioration brought on by a developing cytokine storm for which he was managed with mega doses of intravenous methylprednisolone 1 g daily for 3 days and Remdesivir, and he eventually recovered.

Ophthalmological examination revealed a BCVA of 20/20 in the right eye and 20/125 in the left eye. Pupillary light reflex examination showed bilateral brisk responses with no signs of afferent pupillary defect. Intraocular pressure was recorded as 12 mm Hg in the right eye and 11 mm Hg in the left eye. Anterior segment examination was unremarkable for the right eye; however, the left eye showed a rim of hypopyon occupying the lower third of the anterior chamber.

Dilated fundus examination of the right eye revealed multiple tiny whitish circular lesions within the temporal arcades. The

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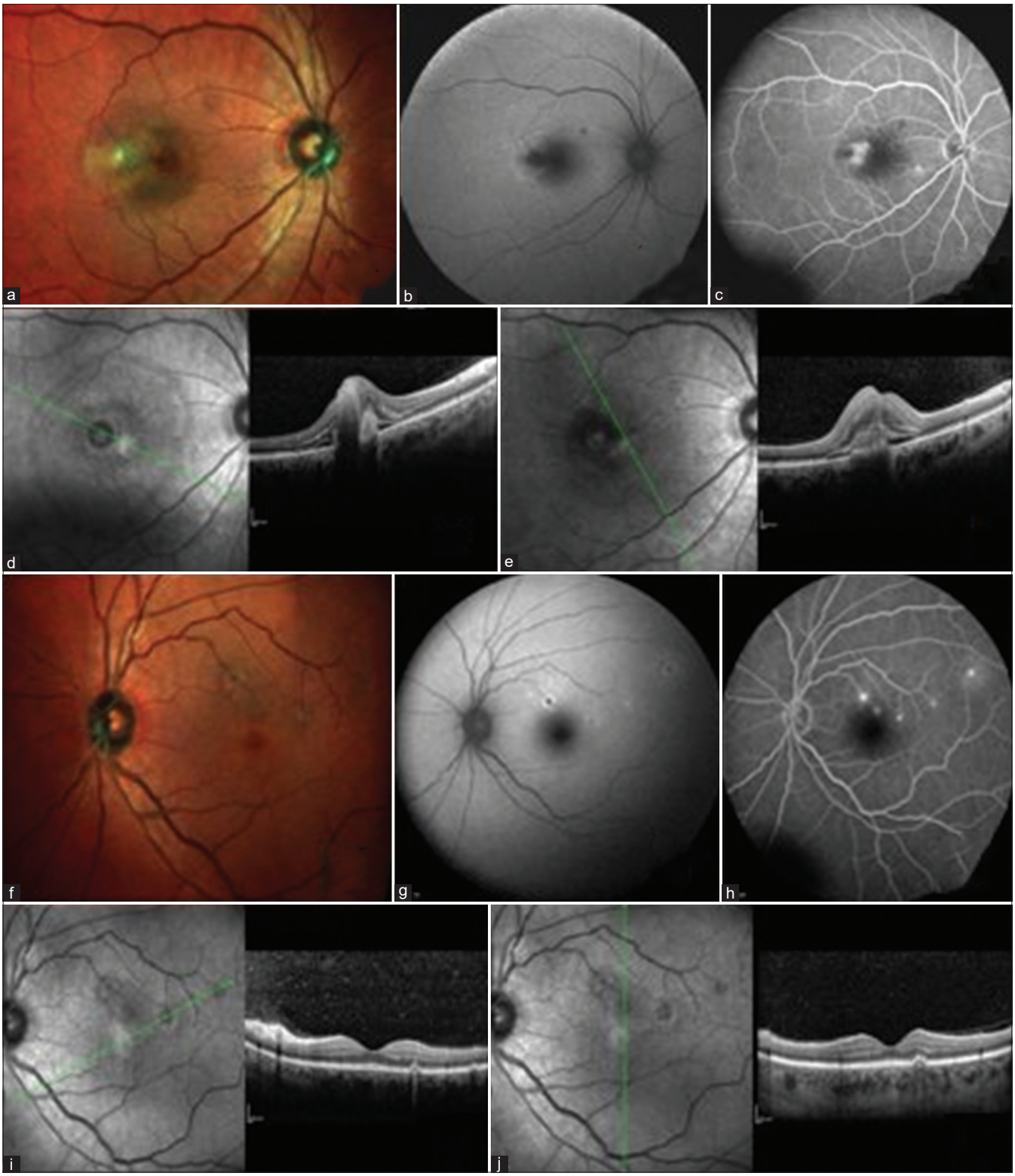

Figure 1: Aspergillosis endophthalmitis in case 1. (a) Multicolor image of the right eye shows a juxtafoveal subretinal lesion with retinal infiltration. (b) Blue autofluorescence (BAF) reveals mixed hyper and hypoautofluorescence. (c) FA demonstrates juxtafoveal hyperfluorescence, increasing in intensity in late frames (5 min) due to late staining. (d) OCT reveals infiltration of all retinal layers with subretinal fluid and choroidal thickening. (e) OCT demonstrates a subfoveal infiltrative lesion. (f) Multicolor image of the left eye shows gray lesions along the temporal arcades. (g and h) BAF and FA show hypoautofluorescent spots and hyperautofluorescent halos with hyperfluorescence on FA. (i and j) OCT shows multifocal choroiditis with deposits under the retinal pigmentary epithelium (RPE)

Figure 2: Aspergillosis endophthalmitis in case 2. (a) Multicolor image of the right eye shows gray lesions between the temporal arcades. (b) BAF shows hypo and hyperautofluorescent spots. (c) FA reveals early hyperfluorescence with late increased intensity. (d) OCT shows vitreous cells with a normal choroid. (e) OCT angiography reveals avascular spots of full retinal thickness hyperreflectivity and loss of retinal layers differentiation (Yellow box). (f) Multicolor image of the left eye shows vitreous haze, a hot disc, and subfoveal infiltrative lesions across the arcades. (g) BAF shows mid-peripheral hypo and hyperautofluorescent. (h) FA shows late hyperfluorescence and staining of the vessel walls suggesting phlebitis. (i and j) OCT reveals intraretinal and subretinal infiltrative lesions denoting retinitis

left eye showed vitreous haze, with a large yellowish-white subretinal infiltration across the superotemporal arcade, and a smaller patch just inferotemporal to the fovea. The macula appeared elevated with subfoveal infiltration.

The whitish lesions in both eyes demonstrated early hyperfluorescence on FA. On OCT, they corresponded to full retinal thickness infiltration. The left eye revealed hypofluorescent lesions at the superotemporal arcade

and inferotemporal aspect of the fovea caused by blocked choroidal fluorescence, and inferotemporal occlusive phlebitis. OCT showed subretinal fluid and hyperreflective subretinal infiltration inferotemporal to the fovea and across the superotemporal arcade with hyperreflectivity and loss of differentiation of the overlying retinal layers denoting retinitis [Fig. 2].

Both cases presented with varying pictures of retinochoroiditis in a setting of prior ICU admission for COVID-19. Differential diagnoses of these cases include multifocal choroiditis and uveitis, choroidal neovascularization, tuberculosis, syphilis, hematological malignancies, and endogenous endophthalmitis. Based on their prior medical history and bilaterality of the condition, a preliminary diagnosis of endogenous endophthalmitis secondary to a presumed opportunistic infection was determined. The patients were offered vitreous taps; however, both declined these being invasive interventions. An infectious disease workup included IgG and IgM TORCH screening (Toxoplasmosis, Rubella, Cytomegalovirus & Herpes Simplex 1&2), Quantiferon gold TB testing, and Fluorescence Treponema Antibody (FTA-Abs) syphilis testing, as well as a blood culture and serum antibody titers for various bacterial and fungal organisms. An immunological assay was also ordered, including a complete blood count with differential (CBC), quantitative C-reactive protein (CRP), anti-nuclear antibodies (ANA), and quantitative anti-phospholipid antibodies.

Both cases yielded high titers of galactomannan antigen of 0.5 and 0.7, diagnostic of invasive aspergillosis.[3] In addition to topical prednisolone acetate 1%, the patients were also managed with 200 mg of oral voriconazole, to which preliminary favorable responses were observed, including resolution of anterior chamber reaction and amelioration of vitreous haze. Although galactomannan antigen may yield false-positive results in some cases, the favorable responses to voriconazole confirm the fungal nature of the disease. Both patients have been followed up for a period of 9 months with a stable course showing a BCVA of 20/40 and 20/80, respectively.

Discussion

Severe cases of COVID-19 are widely treated with broad-spectrum antibiotics, immunosuppressives, and high doses of corticosteroids. Serological testing of these patients also revealed higher pro-inflammatory cytokine levels and fewer CD_4 and CD_8 cells.[4] These factors render patients, particularly diabetics, vulnerable to multiple opportunistic infections, especially those caused by fungal organisms.[5]

A few reports have documented various forms of intraocular inflammation complicating cases with COVID-19. Bettach *et al*.[6] described a case with bilateral acute anterior uveitis, while Quintana-Castanedo *et al*.[7] demonstrated concurrent retinal vasculitis and chilblains in a child, both presenting with serological evidence of COVID-19 infections and no other underlying infectious etiologies. Interestingly, other reports were able to identify pulmonary Aspergillosis as an increasingly common secondary opportunistic infection complicating patients with COVID-19 pneumonia.[8,9] In light of the above, diabetic and immunocompromised patients with fungemia secondary to pulmonary infections are at risk of developing blood-borne endogenous endophthalmitis.

In our set of patients, aspergillosis endophthalmitis manifested in uniquely different pictures of chorioretinitis. Although both cases demonstrated dense subretinal granulomatous infiltrations, the fellow eyes were not identical. Case 1 showed multifocal spots of choroiditis with sub-RPE deposits and intact overlying retinal tissue, whereas case 2 showed full retinal thickness infiltrations with normal underlying choroidal architecture and thickness.

The reason behind this discrepancy is unclear. Histopathological reports have suggested a predilection of Aspergillosis to sub-RPE and choroidal invasion, likely due to a protective mechanism brought on by RPE-generated anti-oxidants.[10] Extrapolating on these findings, it is possible that the full retinal thickness infiltrations seen in case 2 may represent an inflammatory cellular infiltration rather than fungal invasion.

Conclusion

In conclusion, our case reports suggest it is likely that the era of COVID-19-related widespread use of substantial doses of corticosteroids may widen the scope of presentations of endogenous Aspergillosis endopthalmitis, which should be considered in all settings of post-COVID-19 ocular inflammation, especially in diabetic patients.[10]

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Conflicts of interest

There are no conflicts of interest.

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