**Abstract**

Coronavirus disease 2019 (COVID-19) Ocular manifestations have a thousand faces and yet each ocular presentation has a unique course, treatment and prognosis. We present a rare case of post-COVID-19 bilateral Aspergillosis endogenous endophthalmitis (EE) with aggressive manifestation at first but an appropriate treatment response. A 54-year-old man presented with bilateral decreased vision four weeks after post-COVID-19 hospitalization. Initially, he was diagnosed with noninfectious uveitis and treated with topical and systemic prednisolone for one week. Subsequently, he was treated with systemic voriconazole after a positive vitreous sample polymerase chain reaction (PCR) result for Aspergillus fumigatus. This case demonstrated the effectiveness of systemic antifungal treatment without surgical intervention in post-COVID-19 bilateral Aspergillosis EE.

**Introduction**

The coronavirus pandemic has recently challenged the medical system. Various ocular manifestations of coronavirus infection have been reported.

[1] One of the disastrous ocular manifestations detected in these patients is endophthalmitis.

[2] There have been previous case series of patients with COVID-19 pneumonia having bacterial endogenous endophthalmitis (EE) originating from the throat, kidneys, and teeth as a source of infection, and even the COVID-19 virus had been isolated from the vitreous sample.

[3] Regarding fungal EE, Candida species are reported as the most common pathogen, although there are two reports with a specific diagnosis of Aspergillus. The present case report on bilateral Aspergillosis EE is novel in disease course and recovery.

**Case report presentation**

A 54-year-old man presented with both eyes blurred vision two days before visiting an ophthalmologist. He had a history of COVID-19-related pneumonia with approximately 30% lung involvement, confirmed by polymerase chain reaction (PCR), which led to eight days of hospitalization. He received intravenous dexamethasone (8 mg/day) and Ceftriaxone 1gr every 12 hours for seven days during admission. There was no airway intubation or intensive care unit (ICU) admission. The patient had a history of first dose COVID-vaccination with COViран Barekat (Barkat Pharmaceutical Group) vaccine [6] three weeks before hospitalization. He could not receive the next dose of his vaccine due to subsequent health problems. He did not have any other previous systemic disease.

His ocular symptoms developed four weeks after post-COVID-19 hospitalization. At presentation, the Snellen best-corrected distance visual acuity (BCVA) of the right and left eyes was 20/200 and finger counts (FC) 4 m, respectively. He was diagnosed with noninfectious uveitis by his primary ophthalmologist and received systemic prednisolone (25mgr /day) with topical
steroids and cycloplegic drops. Due to a lack of recovery, he was referred to our clinic after one week. On examination, the BCVA of the right and left eyes were CF 6m and CF 1 m, respectively. Anterior segment slit lamp exam was unremarkable; however, vitreous cell (+2 in both eyes) was detected. Fundoscopy in the right eye showed extensive confluent yellowish intraretinal and subretinal collections in the inferior arcade involving the macula. In the left eye, the same lesion with surrounding sub-retinal cream-coloured fluid was seen in the post pole, which involved the fovea. Lesions appeared to expand in size five days later. Both eyes’ macular optical coherence tomography (OCT) revealed intraretinal and subretinal hyper-reflective materials with mild intraretinal and subretinal fluid (SRF), which disrupted macular structure. Fundus fluorescein angiography of the right eye and left eye displayed early hyper fluorescence due to vascular leakage around the lesions.

Clinically suspicious of EE, systemic workup was performed, including obtaining blood and urine culture, vasculitis laboratory tests, purified protein derivative (PPD) skin test, trans-esophageal echocardiography, and repeating spiral chest CT, and no systemic source of infection was detected. Because of highly suspicious fungal chorioretinitis, vitreous sampling for smear, culture and PCR for herpes viruses, Mycobacterium, Candida, and Aspergillus species was obtained, then oral voriconazole (200 mg/bid) and systemic antibiotic (ciprofloxacin 500mg/bid) was started. Although the culture from vitreous aspiration failed to yield any organism, Real-time PCR analysis detected the
### Table 1: Demographic details, ocular and microbiological results, treatment aspects, and consequences in Aspergillosis endogenous endophthalmitis in post-COVID-19 patients have been reported to date.

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>Case 1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>Case 2&lt;sup&gt;nd&lt;/sup&gt;</th>
<th>Case 3&lt;sup&gt;rd&lt;/sup&gt;</th>
<th>Case 4&lt;sup&gt;th&lt;/sup&gt;</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>51</td>
<td>46</td>
<td>62</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Male</th>
<th>Male</th>
<th>Male</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Illness</td>
<td>HTN*</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of hospitalization</th>
<th>8 days</th>
<th>9 days</th>
<th>10 days</th>
<th>8 days</th>
<th>8 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

THE INTERVAL between discharge and onset of symptoms:
- Case 1: 4 weeks
- Case 2: 1 day
- Case 3: 4 days
- Case 4: 31 days
- Case 6: 21 days

<table>
<thead>
<tr>
<th>Treatment for COVID (CORTICOSTEROID)</th>
<th>Dexamethasone IV and oral Methylprednisolone IV *7 days, oral prednisolone in tapering doses</th>
<th>Dexamethasone IV <em>10 days, oral prednisolone</em>9 days</th>
<th>Dexamethasone IV *8 days, oral Prednisolone *15 days</th>
<th>Dexamethasone IV *7 days, oral Prednisolone *14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other COVID treatment</td>
<td>Not Mentioned</td>
<td>Immunoglobulins *15 doses</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Vaccination status:
- Case 1: Not Mentioned
- Case 2: Not received
- Case 3: Not received
- Case 4: Not received

Systemic workup:
- Case 1: Negative
- Case 2: Presumed lung Aspergillosis.
- Case 3: Negative
- Case 4: Negative

Eye Presenting Visual Acuity:
- OS: OD<sup>†</sup> CFCF<sup>‡‡</sup> HM<sup>††</sup> |
- OD: OS<sup>‡</sup> CFCF<sup>‡‡</sup> LP<sup>***</sup> |

Posterior segment finding:
- Vitreous exudates, granuloma nasally and at posterior pole.

Total Retinal detachment.

Condensed vitreous exudates, yellowish subretinal infiltrate with interspersed hemorrhage involving the entire posterior pole.

Condensed vitreous exudates, pseudo hypopyon retinal infiltrates with interspersed temporal hemorrhage at posterior pole extending beyond the inferior arcade.

Condensed vitreous exudates, retinal abscess of about 1 DD<sup>†††</sup> no involving fovea.

Condensed vitreous exudate the inferior and temporal to the fovea, and a bulky subretinal abscess beneath the fovea covering with area suspected of retinal necrosis and localized vitritis in front of the lesion.

OD: retinal abscess in the same area as the previous eye but with a smaller size. Localized vitritis.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Aspergillus sp.</th>
<th>Aspergillus niger</th>
<th>Aspergillus niger</th>
<th>Aspergillus fumigatus</th>
<th>Aspergillus fumigatus</th>
</tr>
</thead>
</table>

Visual Outcome:
- Case 1: 20/1200 HM
- Case 2: 20/400 CFCF
- Case 3: 20/400 CFCF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Re-Vitrectomy +Lensectomy+ IVV&lt;sup&gt;†††&lt;/sup&gt;+SOI</th>
<th>PPV+SOI</th>
<th>IVV+PPV+SOI</th>
<th>Oral Voriconazole 200mg BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism</td>
<td>Aspergillus niger</td>
<td>Aspergillus fumigatus</td>
<td>Aspergillus niger</td>
<td>Aspergillus fumigatus</td>
</tr>
</tbody>
</table>

HTN* hypertension, DM† Diabetes Mellitus, OD‡ Right eye, OS**Left eye, HM††hand motion, CFCF‡‡counting finger close to face, PL*** Perception of light, DD†††disc diameter, IVV<sup>†††</sup>intravitreal Voriconazole, SOI****silicone oil injection, PPV††††pars plana vitrectomy


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Aspergillus Fumigatus while negative for Candida, HSV-1, HSV-2, CMV, VZV, and Mycobacterium genome. By diagnosis of confirmed Aspergillus EE, oral voriconazole was continued. After three weeks, vitreous inflammation, the subretinal lesions’ size, and SRF reduced significantly. The patient's vision gradually enhanced in both eyes. After eight weeks, in the follow-up, BCVA was 20/32 in the right and 20/40 in the left eye. Fundus photography and OCT showed improved lesions [figure 4A-B]. Informed consent was obtained from the patient to report this case.

Discussion

The presented case is the first bilateral confirmed Aspergillus EE in a COVID-19-recovered patient who responded to the antifungal treatment without surgical intervention. There are various treatment protocols for Aspergillus EE, and systemic voriconazole is a critical drug. [7] It is suggested to begin systemic antifungal drugs in clinically presumed cases until the results of PCR or vitreous aspiration culture reveal the definitive diagnosis. [8] Surgical procedures such as multiple intravitreal injections of antifungal drugs and pars plana vitrectomy with or without silicone injection have been reported as valuable ways to manage fungal EE. [2,3] It is necessary to consider the positive history of COVID-19 recent infection, corticosteroid use and the existence of posterior pole necrotizing chorioretinal lesion for considering the clinical suspicion of fungal EE. Most of the Aspergillus EE patients are initially misdiagnosed as noninfectious uveitis by their primary ophthalmologists and treated Inadvertent with local or systemic steroids or immunomodulators. This scenario was happening for our patient and recently reported cases. [4,5] Also, all recent reports regarding post-COVID-19 recovery Fungal EE indicate no systemic focus of infection and negative blood and urine culture in these patients; therefore, misdiagnosis of noninfectious uveitis is expected. [3,5] A majority of vitrectomies in all fungal species EE had initial negative tap because the vitreous involvement with filamentous fungi is rare, and initial positive smear is uncommon. [9] Sowmya P et al. showed that the PCR reported for fungal genomes verified a 100% microbial detection rate and can be regarded as a gold standard. [10]

The following chart briefly reviews the recent report of the five patients with confirmed Aspergillus-associated EE in COVID-19-related pneumonia and their characteristic retinal signs. [Table 1] Once comparing clinical details and characteristics of the present case with previous reports, there are some crucial differences. This patient only received systemic voriconazole and did not require a pars plana vitrectomy or intravitreal antifungal injection for treatment; However, baseline BCVA was better than in other cases; therefore, the poor presenting vision may be related to poor visual outcome. [11] The visual outcome and healing process were significantly restored compared to other previous fungal EE cases. [4,5] The lower percentage of lung involvement and milder Covid-19 disease course compared to the previous case reports may play the role in this difference. In this case, since the vaccine course was not completed, the effect of a single dose could not be accurately determined.

Conclusion

The purpose of presenting this case is to draw attention to considering fungal pathogens cause EE in patients following COVID-19. In addition to demonstrating differences in the course of illness, progression, and even treatment compared to previously reported cases. This article highlights the need for an in-depth examination of the fundus of patients who have ocular symptoms after COVID-19 and takes fungal pathogens into account.

Declarations

Ethics approval and consent to participate

The patient consented to publish his data and pictures without mentioning his name.

Availability of data and material Data is available as needed

Conflict of Interest: None of the authors has a conflict of interest.

Author contribution: All authors fulfil the ICJME authorship criteria

Financial support and sponsorship: Nil.

References

8. Agarwal A. Commentary: Fungal endophthalmitis–Newer insights


