

Case Report

Beyond COVID-19 Paradigm: Devastating Rare Fungal Ocular Complication

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Abstract

Ocular involvement in COVID-19 is rare and often mild. We report a case of severe bilateral ocular candidiasis post-COVID-19 infection. A male, 48 years old, suffered from sudden blurry vision in the right eye (RE). The patient had a history of COVID-19, ICU stay, ventilator use, and a hypercoagulable state. The patient had a history of tocilizumab and steroid use. The initial best corrected visual acuity (BCVA) was 6/30 (RE), with progressive worsening of light perception and 6/6 on the left eye (LE) to 3/60. Examination revealed string-of-pearls and snowball on vitreous, fibrovascular tissue with exudates and subretinal fluid on the macula. Tractional retinal detachment was found in both eyes, and these findings were consistent with fungal endophthalmitis. Culture was taken from a chest lump, and it was positive for *Candida albicans*. The patient was diagnosed with bilateral ocular candidiasis and treated with a 14-day course of intravenous voriconazole and vitrectomy. The final BCVA was hand movement (RE) and 6/45 (LE).

Keywords: endophthalmitis, candidiasis, COVID-19.

**Mengungkap Bahaya Tersembunyi Pasca COVID-19:
Komplikasi Infeksi Jamur di Mata****Abstrak**

Keterlibatan mata di COVID-19 jarang terjadi dan seringkali ringan. Pada kasus ini pasien didiagnosis kandidiasis bilateral di mata pasca-infeksi COVID-19. Seorang laki-laki berusia 48 tahun mengalami penglihatan kabur mendadak di mata kanan (OD). Pasien memiliki riwayat COVID-19, perawatan di intensive care unit (ICU), penggunaan ventilator, dan kondisi hiperkoagulasi. Pasien juga memiliki riwayat penggunaan tocilizumab dan steroid. Tajam penglihatan koreksi terbaik (TPDK) awal OD adalah 6/30 dengan perburukan progresif menjadi persepsi cahaya, serta TPDK awal 6/6 di mata kiri (OS) menjadi 3/60. Pemeriksaan menunjukkan string-of-pearls dan snowball di vitreus, serta jaringan fibrovaskular dengan eksudat dan cairan subretina di makula. Temuan tersebut konsisten dengan endoftalmitis jamur didukung kultur yang diambil dari benjolan di dada yang positif *Candida albicans*. Pasien didiagnosis kandidiasis okular bilateral dan diberikan vorikonazol intravena selama 14 hari serta vitrektomi di kedua mata. TPDK akhir adalah lambaian tangan pada OD dan 6/45 pada OS.

Kata kunci: endoftalmitis, kandidiasis, COVID-19.

Introduction

The novel coronavirus-2, known as SARS-CoV-2, has caused a worldwide pandemic of atypical respiratory disease, coronavirus disease 19 (COVID-19).¹ The disease spreads rapidly, especially in heavily populated areas and areas without proper health measures. The severity of the disease ranges from mild to critical, in which the patient could suffer from acute respiratory distress syndrome (ARDS), shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction, and kidney injury. The host immune response plays a major role in the severity of the disease, which is mainly mediated by T cells.²

Ocular involvement was reported often in patients with complaints such as dry eye or foreign body sensation, redness, tearing, itching, eye pain, and discharge.³ However, ocular involvement in COVID-19 patients is rare and mainly reported to be mild. Recent reports showed possible opportunistic fungal infection post-COVID-19, with risk factors comprising intensive care treatment, steroid use, immunosuppression, and the virus. A report in Italy by Antinori et al⁴ found that three patients suffered from candidemia after administration of tocilizumab, an IL-6 monoclonal receptor blocking agent used for treating cytokine storm in COVID-19 patients. One of them suffered from endophthalmitis caused by *Candida albicans*. Another report by Witting et al⁵ showed invasive pulmonary aspergillosis with positive galactomannan after tocilizumab. Another report in India showed post-COVID-19 candida retinitis in patients who previously received tocilizumab and steroids.⁶ In this case paper, we would like to share a rare case of severe bilateral ocular candidiasis post-COVID-19 infection.

Case Report

A 48-year-old male first came to our ophthalmology clinic due to sudden blurry vision of the right eye (RE), which began approximately three days prior to the visit. The patient complained of floaters but denied any episodes of red eye or pain, but denied any history of hypertension and diabetes. There was a history of critical COVID-19 in which the patient was hospitalized for one month, received care in an intensive care unit (ICU) and was on a ventilator during the care as well as received treatment of favipiravir, tocilizumab, intravenous immunoglobulin (IVIG), heparin, meropenem, and other symptomatic treatments. Two months prior to the complaint, the patient received intensive care and was hospitalised for approximately one month. Previous supportive examination showed marked elevation of erythrocyte sedimentation rate (ESR), fibrinogen level which nearly tripled, and dramatic increase of D-dimer level. The patient also showed elevated fasting blood glucose levels. During the initial visit, the patient's best corrected visual acuity (BCVA) was 6/30 for the right eye (RE) and 6/6 for the left eye (LE). Ophthalmology examination revealed an otherwise normal anterior chamber, although there was a fibrovascular membrane on the optic disc and exudates at macular and perimacular regions on the RE. Ophthalmological examination of RE showed multiple exudates at the perimacular region, but other segments were within normal limits. Optical coherence tomography (OCT) showed subretinal fluid in both eyes (BE). The patient was diagnosed with COVID-19-related retinal vasculopathy of BE and was given oral methylprednisolone three times 16 mg daily steroid. One week later, the visual acuity of RE improved to 6/12 and the OCT result showed decreased subretinal fluid.

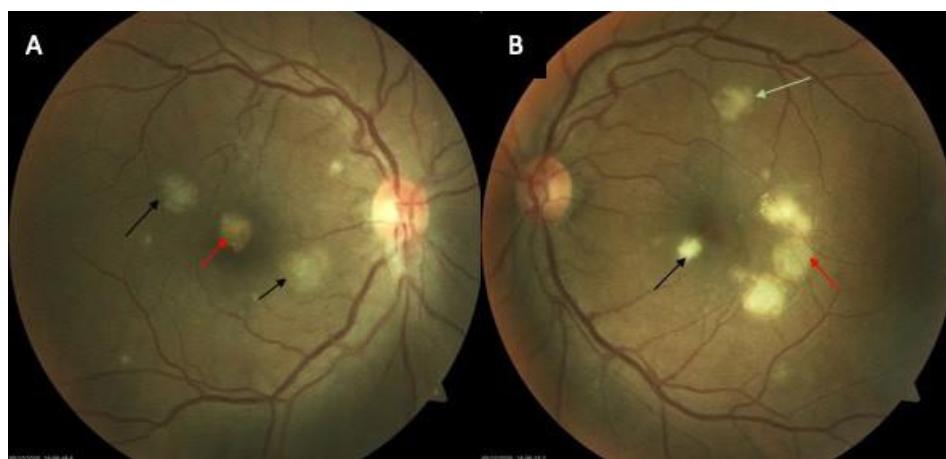


Figure 1. Both Fundus Showed Multiple Exudates (a) RE showed a fibrovascular lesion at the optic nerve (blue arrow) along with exudates right at the macula (red arrow) and perimacular regions (black arrows); (b) LE showed exudates at nasal (black arrow), temporal (red arrow), and superior (green arrow) perimacular regions

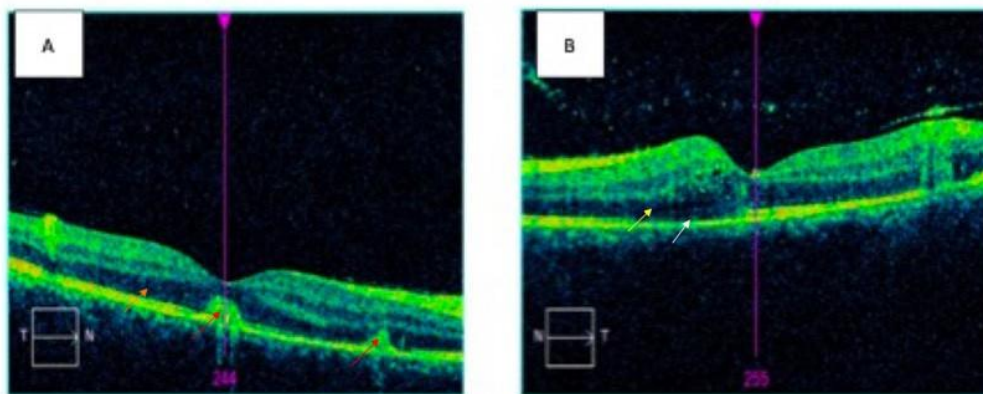


Figure 2. Macular OCT during Initial Visit (a) RE showed subretinal fluid (orange arrow) along with exudates on foveola and macula (red arrows) (b) LE showed mild vitreous opacity along with subretinal fluid (yellow arrow) and segmental disruption of internal segment-outer segment junction (white arrow)

The patient came three months later with significantly worsening blurry vision of RE after he was lost to follow up and took oral steroids on his own accord of the previous dose for two weeks but without improvement. The patient's VA was 1/60 temporal side on RE and 6/7.5 with correction of LE with negative pinhole. Posterior segment evaluation revealed exudative retinal detachment (RD) on the optic nerve with attached peripheral retina, and there was no retinal break on RE and snowball in vitreous LE. The anterior segment of BE was within normal limits. Laboratory results showed a significant increase in fibrinogen (>900 mg/dL) and D-dimer (703.6 μ g/dL). Intravitreal injections of 0.4 mg/0.1 ml dexamethasone and 1.25 mg/0.05 ml bevacizumab for RE were performed.

Two months later, the VA of RE and LE were light perception and three-meter finger counting, respectively. The patient had total RD with proliferative vitreoretinopathy (PVR) on RE and a fluffy yellowish lesion with a haemorrhagic spot on top of the lesion, with a string of pearls and snowball on LE. The patient was diagnosed with suspected ocular candidiasis. Along with this complaint, the patient also had a lump on the left chest that was getting bigger. Thorax computerized tomography scan (CT-scan) showed an irregular mass sized $6.2 \times 3.4 \times 6.5$ cm of the left chest with bone destruction. The thoracic lump was then incised, and culture was positive for *Candida albicans*. Following this, the patient was hospitalized and given a loading dose of 400 mg intravenous voriconazole and an additional 0.1 mg intravitreal injection of voriconazole during vitrectomy.

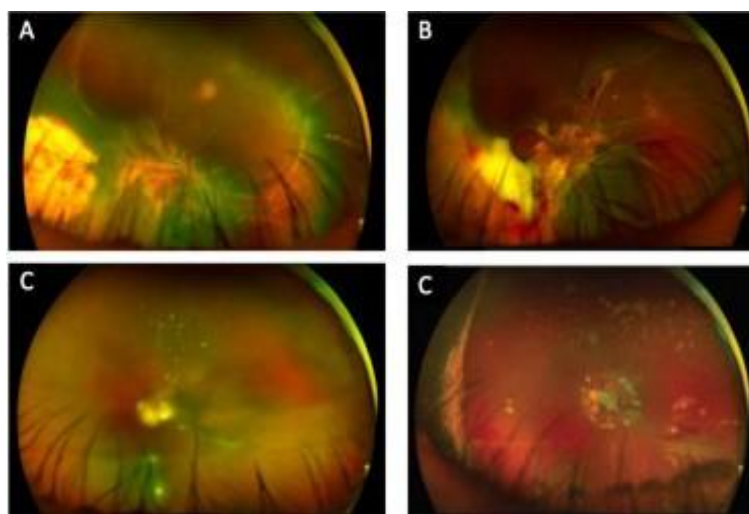


Figure 3. Posterior Findings Pre- and Post-Vitrectomy (a) RE pre-vitrectomy; (b) RE post-vitrectomy; (c) LE pre-vitrectomy; (d) LE post-vitrectomy

During hospitalization, vitrectomy, laser, and biopsy of BE were performed at one-week intervals. Biopsy taken from the vitreous sample showed retinal cells, neutrophils, and lymphocytes. There were no malignant cells, spores or hyphae, or acid-fast bacilli in the Ziehl Neelsen staining. Histopathological examination indicated that there was no specific process. The patient was then discharged and given continued oral voriconazole. The patient's final after six months BCVA was hand movement on RE and 6/45 on LE with complicated cataracts on both eyes and fibrovascular tissue on the retina causing traction surrounding the optic nerve.

Discussion

COVID-19 has taken the world into a pandemic and to date has caused more than three million deaths worldwide.¹ Patients with COVID-19 exhibit increased D-dimer and fibrinogen levels, especially in severe patients with significant endothelial injury.⁷ Endothelial cells express angiotensin-converting enzyme (ACE2), which the virus could adhere to and destroy. As endothelial cells comprise one-third of lung cells, they are also the main building blocks of the vascular system. Hence, damage to these cells could lead to increased microvascular permeability, enabling viral invasion of organ systems.⁷ A meta-analysis showed that COVID-19 patients may have higher retinal microvasculopathy.⁸ The patient presented subretinal fluid and a significant increase in fibrinogen and D-dimer levels, which raised suspicion of COVID-19-related retinal vasculopathy. These findings were consistent with vascular injuries reported in previous studies, so the patient was treated with intravitreal steroid injection. The patient experienced improvement but then was lost to follow-up and came back with a marked deterioration in visual function.

The patient showed multiple risk factors such as a history of COVID-19 infection, prolonged ICU stay, use of tocilizumab, antibiotics, or steroids, and hypercoagulable state. In this case, the exact etiology of the rare ophthalmologic findings is unclear. We suspect that predisposing COVID-19 vasculopathy, along with the patient's immunocompromised state and multiple risk factors of previous COVID-19 history and treatment, contribute to the patient's ocular findings.

The connection between COVID-19 infection and vasculopathy has greatly interested some researchers. The expression of ACE2 receptors within endothelial cells raised concern about its vulnerability to SARS-CoV-2 binding and viral entry,

causing inflammation and vascular injury. Monteil et al⁹ have shown that the SARS-CoV-2 virus can infect engineered human blood vessels. A post-mortem analysis of a renal transplant recipient who had coronary artery disease and arterial hypertension and whose condition deteriorated after a COVID-19 infection revealed viral inclusion structures in endothelial cells.¹⁰ Furthermore, histological analysis found an accumulation of inflammatory cells associated with endothelium in renal, heart, lung, and small bowel tissue.¹⁰ This vasculopathy also infects the retinal microvessels.

A meta-analysis by Teo et al⁸ with a total of 31 studies showed that there was significantly higher odds of retinal microvasculopathy in patients with COVID-19 compared with controls (odds ratio (OR) 8.86; 95% confidence interval (95% CI) 2.54 – 27.53; $p < 0.01$). This study also shows that microvasculopathy caused by COVID-19 infection is clinically visible as reduced vessel density and enlarged foveal avascular zone when viewed using optical coherence tomography angiography (OCTA).⁸ The suspicion of fungal infection arises from the unique posterior segment findings and positive culture for *C. albicans* from chest wall isolate. Therefore, the patient was treated with antifungal but showed slight improvement throughout the disease. Negative isolates were most likely due to the extensive antifungal regimen we had applied prior to testing and the vitreous specimen's low positive predictive value. This finding is also supported by a study that claimed only 38% of vitreous specimens will generate positive culture.¹¹

COVID-19 patients, especially those in severe or critical conditions, have a worse prognosis. Patients are more likely to be admitted to ICU, have a higher secondary infection rate, and are more likely to undergo invasive procedures. A study in Shanghai showed that more than half of COVID-19 patients in their care had secondary infections (57.89%), while those with severe COVID-19 had a higher rate of secondary infections (83.33%, $p < 0.0001$).¹² The causative organisms were likely to be gram-negative bacteria (50%), gram-positive bacteria (26.92%), viruses (11.54%), and fungi (7.69%).¹² A case series by Bilgic et al¹³ showed three patients with endogenous endophthalmitis after recovering from COVID-19 pneumonia. One of the patients in these cases tested positive for SARS-CoV-2 from real-time polymerase chain reaction (RT-PCT) results taken from vitreous

samples, which could suggest a possible role of RT-PCR testing.¹³

Recent reports also showed a possible link between tocilizumab administration and fungal opportunistic infection. Tocilizumab is an interleukin 6 (IL-6) receptor monoclonal blocking agent used in treating COVID-19 patients. High level of IL-6 in COVID-19 patients was shown to be associated with poor prognosis. Previous meta-analysis has shown that COVID-19 patients with complications and mortality showed high levels of IL-6.¹³ However, earlier studies in mice showed that IL-6 deficient mice were more prone to *C. albicans* infection.¹⁴ A meta-analysis study also discovered opportunistic infections of tuberculosis, nontuberculous mycobacteria, invasive forms of candidiasis and other fungal infections in patients given tocilizumab. Hence, the use of tocilizumab in COVID-19 patients should be monitored closely as it may expose them to a higher risk of opportunistic infection.

The term COVID-19 Candidiasis (CAC) is a recently developed concept that poses an additional risk of morbidity and mortality. However, the exact immune response behind this is still yet to be elucidated. *Candida* species have virulence attributes that could attack host cells, especially in an immunosuppressed state, and its colonization is one of the most common findings among patients receiving care in the ICU. Studies on COVID-19 patients worldwide have shown varied epidemiology and target organs of CAC. Risk factors for CAC among ICU patients include the following conditions: diabetes mellitus, renal failure with haemodialysis, abdominal surgery, triple lumen catheters, parenteral nutrition, multiple antibiotics, length of ICU stay >7 days, and prior abdominal infection. Meanwhile, additional risk factors for CAC among COVID-19 patients include the usage of extracorporeal membrane oxygenation (ECMO) and steroids. Steroid therapy suppresses neutrophils, monocytes, and macrophages, increasing the risk of developing candidiasis. Diagnosis of candidemia and other candidiasis requires culture as the gold standard, but even up to 50% of blood cultures may show false negative results.

In this case, ophthalmologic findings are consistent with *Candida* endophthalmitis with hazy vitreous, white lesion at the choroid and retina, tractional RD (TRD), and puff-ball lesion, which indicates vitreal abscesses.¹⁵ A study in Korea on 2014–2017 found that among candidemia patients, 21.5% showed ocular involvement, mostly with chorioretinitis and *Candida* endophthalmitis.¹⁶ This study also showed positive outcomes in nearly 90% of the patients.

However, our patient did not exhibit such a positive outcome. A similar case was reported in India in the near past.⁶ The patient in that study suffered from COVID-19 with similar risk factors such as diabetes mellitus and steroid use. After discharge, the patient showed retinal lesions similar to those found in our patient. The patient was treated with intravitreal voriconazole injection on BE along with fluconazole. He showed clinical improvements regarding visual functions but passed away due to systemic complications.⁶

Conclusion

The patients in this case report showed only moderate improvements despite our best efforts through medical and surgical approaches. Therefore, further research should be conducted into the best management approach in such cases. Monitoring of ocular complications in COVID-19 and post-COVID-19 patients, especially those with risk factors of ICU stay, steroids, and systemic diseases, should be encouraged. Patients should be warned to seek help immediately, and more aggressive approaches should be taken.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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