Purpose: COVID-19 infection is being increasingly identified as a risk factor for the development of ocular infections, especially endogenous endophthalmitis. Current studies primarily report cases among survivors, and the overall prevalence, especially amongst patients admitted with active sepsis is unknown. We report on the fundus and systemic findings of inpatients who were being treated for post-COVID-19 systemic secondary infections in a tertiary intensive care unit. Methods: Retrospective observational study based on chart review. Results: A total of 24 patients were identified. These included 21 (87.5%) males and 3 (12.5%) females with ages ranging from 33 to 72 years (mean 54.1 years). Pre-existing risk factors included type 2 diabetes mellitus, systemic hypertension, chronic kidney disease, multiple myeloma, and patients on long-term corticosteroid/immunosuppressive treatment. Nine patients (37.5%) died and 15 (62.5%) survived. Of a total of 48 eyes, observed fundus lesions included endogenous endophthalmitis (4 eyes of 2 patients, 8.3%), preretinal hemorrhages (4 eyes of 2 patients, 8.3%), optic disc pallor (2 eyes of 1 patient, 4.1%), moderate non-proliferative diabetic retinopathy (4 eyes of 2 patients, 8.3%), Roth spots (2 eyes of 1 patient, 4.1%), and 2 eyes of 1 patient (4.1%) with evidence of previous pan-retinal photocoagulation. Conclusion: Two patients had evidence of endogenous endophthalmitis. These findings suggest that the actual incidence of ocular lesions, especially infections is higher than that reported. Fundus examination should form a part of the management protocol for patients being treated for post-COVID-19 systemic infections.

Key words: COVID-19, endogenous endophthalmitis, fundus

COVID-19 is a global pandemic caused by the novel coronavirus 2 (SARS-CoV-2) with an estimated 410 million cases worldwide as of February 14, 2022. India has been severely affected with as many as 42 million cases to date. Current case fatality rates currently vary from 0.28% to 2.36% with significant associated morbidity. Commonly described complications include pneumonia, acute respiratory distress syndrome, acute hepatic injury, myocardial injury including dysrhythmias and myocarditis, prothrombotic states, and secondary infections.

Bloodstream infections may occur primarily, usually as a result of intravascular devices, or secondary to systemic infections. These may lead to the development of infectious retinitis/endogenous endophthalmitis if the blood–retinal barrier is breached. Recently, several groups of authors have described several such small case series in survivors of COVID-19. Shroff et al. described the clinical findings of five patients with endogenous endophthalmitis, whereas Agarwal et al. reported on the findings of six patients. All these patients presented to ophthalmologists in an outpatient setting. The overall prevalence of fundus lesions, especially of an infectious etiology, amongst admitted patients in an intensive care setting, is unknown.

We report on the fundus and systemic findings of post-COVID-19 patients who were being treated for systemic secondary infections in a tertiary intensive care unit.

Methods

With Institutional Review Board (IRB) approval, we conducted a retrospective observational study based on a chart review. We examined patients in a tertiary medical intensive care unit in Mumbai, India, from August 2020 until February 2022 with an admitting diagnosis of post-COVID-19 sepsis. We used the current definition of sepsis as organ dysfunction that occurs due to faulty host response to infection to help identify these patients.

These patients had initially been admitted, with an Reverse Transcriptase polymerase chain reaction (RT-PCR) confirmed diagnosis of COVID-19, in the COVID-19 ward/ intensive care unit (ICU) and were subsequently transferred to a non-COVID-19 ICU following a negative RT-PCR or were readmitted to the ICU following a clinical diagnosis of post-COVID-19 sepsis.
All patients underwent a clinical and systemic evaluation. At the discretion of the admitting physician, patients underwent complete and differential blood counts, C-reactive protein (CRP), procalcitonin (PCT), renal and liver function tests, blood glucose estimations, blood cultures from peripheral sites for aerobic/anaerobic/fungal organisms, additional cultures from the trachea, broncho-alveolar lavage (BAL), sputum, urine, etc., as needed and systemic imaging including chest X-rays/computed tomography (CT) scans (brain, chest, abdomen, pelvis), magnetic resonance imaging (MRI) scans or whole-body positron emission tomography (PET)/CT scans.

As per a standard protocol and at the request of the admitting physician, we performed a bedside fundus evaluation. Following consent and dilatation, we used a standard 20 Dioptre lens and an indirect ophthalmoscope to evaluate these patients. For patients with detectable fundus lesions, we used a handheld fundus camera (Zeiss VisuScout 100, Carl Zeiss Meditec, Dublin CA) to perform bedside fundus photography.

**Results**

A total of 24 patients were identified. These included 21 (87.5%) males and 3 (12.5%) females with ages ranging from 33 to 72 years (mean 54.1 years). Pre-existing risk factors included type 2 diabetes mellitus (11 patients, 45.8%), systemic hypertension (7 patients, 29.1%), chronic kidney disease (5 patients, 20.8%), multiple myeloma (1 patient, 4.1%), and patients on long-term corticosteroid/immunosuppressive treatment (4 patients, 16.6%); for hypersensitivity pneumonitis (1 patient, 4.1%), neumomyelitis optica (1 patient, 4.1%) and post renal transplant (2 patients, 8.3%). Nine patients (37.5%) died and 15 (62.5%) survived.

Patients underwent a variety of treatment regimes in their initial illness. These included corticosteroid therapy (14 patients, 58.3%), broad-spectrum antibiotics (8 patients, 33.3%), remdesivir (12 patients, 50%), convalescent plasma (1 patient, 4.1%), and favipiravir (3 patients, 12.5%) either as a monotherapy or as part of multidrug therapy. All these patients had previously required admission with a diagnosis that ranged from mild pneumonia to acute respiratory distress syndrome (ARDS) with multi-organ failure and required the use of supplemental oxygen either by use of a non-invasive modality or mechanical ventilation.

The duration for transfer to a non-COVID-19 ICU or readmission varied from 5 to 45 days (mean 15.8 days).

Baseline investigations revealed normal hemoglobin values (11.2 gm/dL); mildly elevated white cell counts (13,233.4 cells/mm$^3$), and normal platelet counts (165,400 cells/mm$^3$). Relevant imaging included patchy ground-glass opacities/consolidation/cavitary disease suggestive of chest infection associated with post-COVID-19 sequelae in 20 patients (83.3%), which were potentially the source of the infection, normal chest findings (with/without increased broncho-vascular markings) in 4 patients (16.6%).

Blood cultures were positive in 13 of 24 (54.1%) patients. Other significant sites that yielded positive cultures included nasal swabs (1 patient, 4.1%), tracheal secretions (3 patients, 12.5%), urine cultures (1 patient, 4.1%), and sinus debridement cultures (1 patient, 4.1%). Pathogenic isolates included Candida species (7 patients, 29.1%), Aspergillus species (4 patients, 16.6%), Cytomegalovirus (2 patients, 8.2%), Pseudomonas aeruginosa (1 patient, 4.1%), Acinetobacter baumannii (2 patient, 8.2%), Enterococcus faecium (1 patient, 4.1%), Enterococcus faecalis (1 patient, 4.1%), Enterobacter cloacae (1 patient, 4.1%), Escherichia coli (1 patient, 4.1%), no pathogen identified (4 patients, 16.6%), whereas 1 patient (4.1%) did not undergo blood culture studies. The source of infection was assumed to be the lungs in the majority of cases with a secondary bloodstream infection.

Of a total of 48 eyes, observed fundus lesions included creamy white areas of retinitis with grade 3 vitritis consistent with endogenous endophthalmitis (4 eyes of 2 patients, 8.3%), preretal hemorrhages (4 eyes of 2 patients, 8.3%), optic disc pallor (2 eyes of 1 patient, 4.1%), moderate non-proliferative diabetic retinopathy (4 eyes of 2 patients, 8.3%). Roth spots (2 eyes of 1 patient, 4.1%) and 2 eyes of 1 patient (4.1%) with evidence of previous pan-retinal photocoagulation.

Two of 24 (8.3%) patients had evidence of endogenous endophthalmitis. The first patient was a 49-year-old male patient with pre-existing type 2 diabetes mellitus and chronic kidney disease who developed disseminated candidiasis and subsequently bilateral retinitis with hemorrhages. [Figs. 1-5]. Candida tropicalis was identified in blood cultures but he died before any ocular therapeutic measures could be undertaken. The second patient was a 60-year-old male who developed hemophagocytic lymphohistiocytosis (HLH) following a COVID-19 infection. The diagnosis of HLH was suggested by the clinical appearance of splenomegaly, pancytopenia (hemoglobin values 6.8 gm/dL; leucocyte count 5300/mm$^3$; platelet count 7700/mm$^3$), and hyperferritinemia. He subsequently developed invasive aspergillosis as confirmed by a positive serum galactomannan test. Bilateral endogenous endophthalmitis was detected but the patient died soon after and thus no treatment was possible.

**Discussion**

Several large cohorts have assessed the proportion of patients with secondary infections associated with severe COVID-19 infection to range from 6% to 15% and isolates include both bacteria and fungi.\(^7\) Common fungal infections reported include aspergillosis, candidiasis, cryptococcosis, and mucormycosis. Several potential causes exist for the development of these secondary bacterial and fungal infections. These include

1. Hypoxia that may occur as a result of inflammation-induced capillary damage with subsequent abnormalities of tissue oxygenation. Several fungal pathogens have evolved adaptations that may permit survival within hypoxic environments.
2. Hyperglycemia either due to diabetes or corticosteroid-induced
3. Other potential causes including viral infection-induced dysregulated T cells, high serum ferritin levels, need for prolonged hospitalization, and intravascular catheterization.\(^9\)

COVID-19 infection appears to be a new risk factor for the development of endogenous endophthalmitis possibly due to hematogenous dissemination from systemic infections. Shroff et al.\(^8\) described the findings of seven eyes of five cases who had been admitted for severe COVID-19 infection and had received systemic corticosteroid steroid treatment for a period ranging from 18 to 80 days. These patients presented on an average 6 days after discharge. Microbiological analysis revealed Candida sp. in four eyes and Aspergillus sp. in one eye. All blood cultures of these patients were negative, suggesting
a transient blood stream seeding or the effects of prolonged antibiotic therapy. No details are available of any systemic imaging/investigations.

Agarwal et al. described a case series of six patients who presented up to 90 days after COVID-19 infection. The majority had received intravenous corticosteroid treatment. Isolates included two cases of fungal infection (Candida and Bipolaris species), two cases of Staphylococcus infection and two patients were culture negative.

The largest series from India has analyzed 33 eyes of 24 patients. Patients had received broad-spectrum antibiotics and in the majority of cases, corticosteroids during their admission. Of the 19 eyes that underwent vitrectomy, 14 were positive for isolates either via culture, PCR or microscopy. Of these, 11 were fungi. In 11 of 21 patients, they were able to isolate the systemic focus that included positive blood cultures for Candida spp, Streptococcus pneumoniae, Escherichia coli, Aspergillus spp., and Mucor spp.

All these reports have generally described patients who were treated for endogenous endophthalmitis post-discharge, thus precluding an accurate estimate of ocular involvement in all secondary infections irrespective of the final outcome. Mild cases with minimal or no symptoms may resolve with the administered antifungal therapy and no ophthalmological consultation might be sought or severely ill/unconscious patients may die. In either case, an accurate estimate would not be reported.

In a review of 31 case series of endogenous endophthalmitis before the COVID-19 pandemic, the authors report that endogenous endophthalmitis accounted for between 2 and 8% of all reported endophthalmitis cases. However, data regarding the prevalence of retinal lesions especially endogenous endophthalmitis in a cohort of patients with systemic sepsis in the pre-COVID-19 era are limited. In a prospective study, Bouza et al. studied 202 patients with bacteremia (> 1 positive blood culture), 101 patients with systemic inflammatory response syndrome (SIRS) but with negative blood cultures, and 90 control patients. Ocular lesions were seen in 28 eyes of 24 patients (12%) of the bacteremic patients. These included cotton wool spots, hemorrhages, Roth’s spots, and 3 eyes of 2 patients (0.9%) with choroiditis. These included a 76-year-old male with unilateral chorioretinitis with Staphylococcus aureus bloodstream infection and a 48-year-old male, seropositive for HIV infection, with Cryptococcus neoformans infection.

Similarly, Rodriguez-Arriban et al. studied 77 patients with disseminated bloodstream (bacterial and candidal) infection in an intensive care unit. Common findings included cotton wool spots, hemorrhages, and Roth’s spots in 15 patients (19%). No chorioretinal lesion or vitritis was seen in any patient. The authors also assessed the prevalence of retinal lesions in 180 patients with candidemia and could find such lesions in 27 patients (15%). These were largely retinal hemorrhages or cotton wool spots. Two patients had (1%) had white lesions with vitritis consistent with endogenous endophthalmitis and 5 (2.7%) had chorioretinitis without vitritis.

This limited study was to assess the ocular findings in visually asymptomatic patients admitted with documented secondary infections following COVID-19 infections. The cohort we describe was primarily composed of middle-aged males with a high prevalence of diabetes mellitus, previous immunosuppressive treatment, or broad-spectrum antibiotic treatment, or had chronic health conditions. We were able to detect ocular lesions in the form of bilateral endogenous endophthalmitis in two patients as part of a disseminated fungemia and bilateral preretinal hemorrhages in one patient who had a positive PCR blood test for cytomegalovirus (CMV) and associated with thrombocytopenia in the other patient.

These findings suggest that the actual incidence of ocular lesions especially endogenous infections following COVID-19 infections is higher than that reported currently, which primarily consists of survivors of the pandemic. Additionally, the prevalence of endogenous endophthalmitis in post COVID-19 sepsis appears to be higher than that reported in earlier series without prior COVID-19 infection, but a small cohort suggests a need for a larger sample size to confirm this. The presence of endogenous endophthalmitis was associated with a poor prognosis for survival possibly due to severe immunosuppression and consequently more profound bacteremia or may simply reflect higher mortality in patients with COVID-19-associated sepsis versus those without sepsis (61.2% vs. 15.2%).

Figure 1: Bed-side fundus photograph of the right eye (case 7) showing fungal retinitis, hemorrhages with a grade 3 vitritis

Figure 2: Bed-side fundus photograph of the left eye (case 7) showing fungal retinitis, hemorrhages with a grade 3 vitritis
Funduscopy is non-invasive, fast, accurate, and may offer valuable clues to the diagnosis of bacteremias/fungemias, often days earlier than blood cultures, imaging studies, or another invasive testing. Early diagnosis may also allow early prompt bedside treatment with intravitreal antibiotics/antifungals thus reducing subsequent ocular morbidity.

Flaws in our study include a limited number of patients and a potential referral bias as patients were referred at the discretion of the admitting physician. A larger study would be needed to assess whether detection of ocular lesions, especially infectious retinitis, would be an accurate marker to predict outcomes in the form of longer hospitalization durations or mortality.

**Conclusion**

Fundus examination should form a part of the management protocol for patients being treated for post-COVID-19 systemic infections.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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