

Ocular Candidiasis Following COVID-19 Hospitalization: A Case Report

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Abstract

Purpose: Coronavirus Disease 2019 (COVID-19) is a complex infectious pathology characterized by systemic inflammation. Monoclonal antibodies are being currently being tested to reduce inflammation, but their long-term effects are unknown. The purpose of this report is to give an insight on late manifestations of the disease, including unusual ocular involvement. **Patients:** We describe a case of an immunocompetent 57 years old man, presenting with a decreased visual acuity after COVID-19-related pneumonia and ARDS. He underwent mechanical ventilation and received Tocilizumab. After recovery from respiratory failure and seroconversion, SARS-CoV-2 was persistently not detected on nasopharyngeal swab, but inflammatory markers and interleukin-6 were persistently elevated. Several haemocultures confirmed *Candida albicans*. The ophthalmologic examination detected a unilateral (left eye) chorioretinitis. Intravenous voriconazole was administered with complete resolution of both clinical and ophthalmoscopic findings. **Conclusion:** This is a case report on COVID-19 respiratory distress and haematogenous candida spp. spread leading to unilateral chorioretinitis. Candidiasis is likely more common than what is reported during and after critical illness. Furthermore, anti-inflammatory targeted-therapy such as Tocilizumab, may interfere on long-term immune response. For this reason, coinfections should be carefully investigated, and ophthalmologic examination should be performed in presence of candidemia.

Keywords: Ocular candidiasis; Covid-19; Haematogenous

Introduction

COVID-19 can lead to Acute Respiratory Distress Syndrome (ARDS) and early Intensive Care Unit (ICU) admission. The disease has a very variable presentation and progression. According to data from Wuhan in China, an estimated 14% of cases experience a severe illness, and 5% of cases progress to a critical disease requiring treatment in ICU. ^[1] The case fatality rate decreased from a 7%-9% worldwide during the first wave to a 2%-5% reported during 2021. ^[2]

During the first wave pandemic in China, Chen et al. suggested that COVID-19 patients are at higher risk of co-infections of bacteria and fungi. ^[3]

Most likely, critical illness is associated with an increased susceptibility to bacterial and fungal infections because of the pro-inflammatory status characterized by over expression of interleukins. ^[4]

Candida species can cause hospital infections. Higher incidence in ICU has been reported in Europe with alarming morbidity and mortality. ^[5] At the same time, some authors mentioned that the prevalence of pulmonary microbial co-infections is modest among COVID-19 patients upon admission to ICU, with fungemia accounting for only 15%. ^[6]

Nevertheless, during the current COVID-19 pandemic, many patients are undergoing prolonged hospitalization, mechanical ventilation and total parenteral nutrition. Patients are mostly receiving long term therapy with antibiotics, antivirals,

immunosuppressants and systemic steroids. For this reason, candidemia and its complications are probably more frequent than what is reported.

Ocular candidiasis is remarkably rare in immunocompetent patients. However, it is a potentially severe complication and can cause visual impairment or visual field defects. Prompt diagnosis and treatment are essential to preserve vision. ^[7]

Case Report

A 57-year-old man was admitted to ICU (Cotugno hospital, Naples, Italy) due to fever, dyspnea and acute respiratory failure. The patient had neither relevant respiratory medical history nor ophthalmologic but he reported systemic hypertension.

RT-PCR on nasopharyngeal swab detected SARS CoV-2. A High-Resolution Computed Tomography (HRCT) scan showed diffuse bilateral ground glass opacities [Figure 1]. The laboratory testing showed elevated serum C-reactive protein 13 mg/dL (n.r.<1.0). Ferritin was 1496.0 ng/dL (n.r. 10-450). Procalcitonin was 0.27 ng/mL (n.r.<0.05). Complete blood count showed pancytopenia, with WBC $3.65 \times 10^3/uL$ (neutrophils 80%,

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lymphocyte 16%). Glucose was 153 mg/dL. Serum immune globulins level were within normal ranges (IgG 964 mg/dL; IgM 98 mg/dL; IgA 321 mg/dL). Hemocultures, urinculture, rectal and nasal swab were performed at admission, in order to detect any other microbe, virus, or fungus. All samples were negative. Blood test ruled out HIV infection. Sporadic yeast colonies were isolated from tracheobronchial secretions.

A distinctive pattern of immune response was detected at baseline. Interleuchin-2 Receptor (IL-2R) was 1392 IU (n.r. 223-710) and Interleuchin-6 (IL-6) was 78.6 pg/mL (n.r. 0-5).

An empiric antibiotic therapy with ceftriaxone and azithromycin

was initiated. Antivirals, hydroxychloroquine and tocilizumab were administered, as well as total parenteral nutrition. At day 16 from admission, the patient was extubated and transferred to Sub-intensive care unit where he received helmet CPAP.

At day 18 the RT-PCR was negative for SARS CoV-2. The HRCT showed a significant resolution of interstitial pneumonia [Figure 2]. Unfortunately, C-reactive protein and ferritin were persistently elevated and cultures were repeated. At day 28 from admission, *Klebsiella pneumoniae* and *Candida albicans* were isolated from 2 serial hemocultures. Urinculture was negative instead. At this point, IL-2R was 450 IU and IL-6 was 1002 pg/mL.

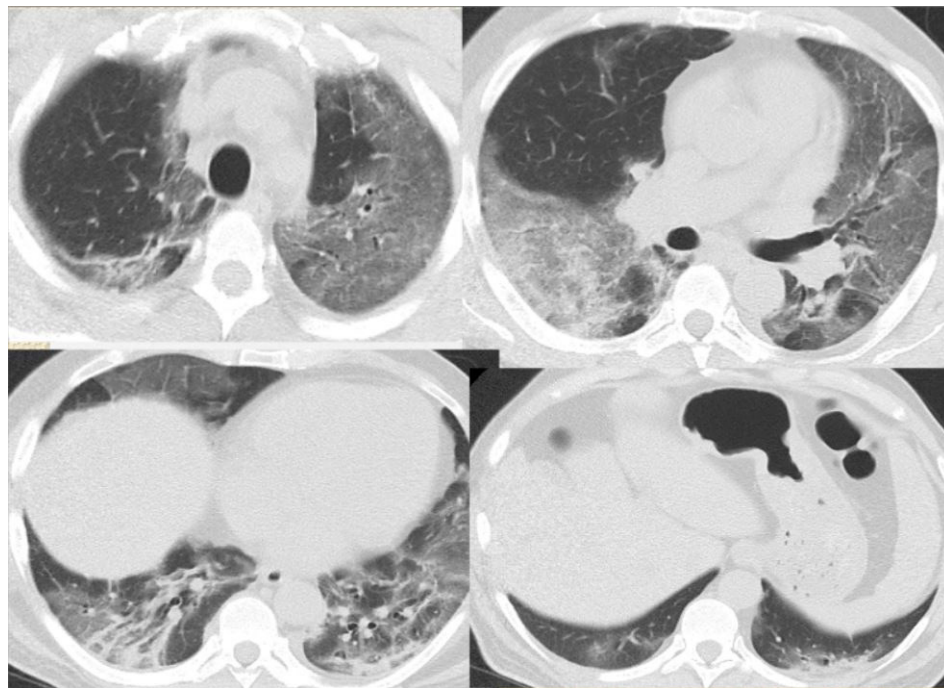


Figure 1: HRCT at baseline.

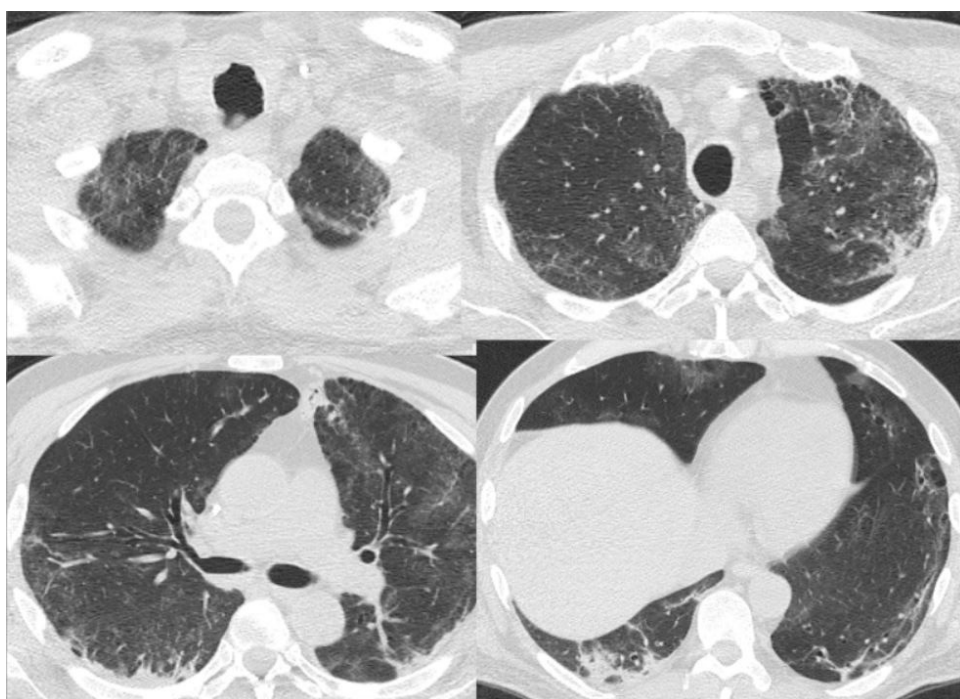


Figure 2: HRCT follow up at week 3.



Figure 3: Posterior pole photo of the left eye showing yellow fluffy lesion involving fovea, and microhemorrhage at the superior retinal arcade.

Therefore, therapy was shifted to meropenem and intravenous fluconazole based on antibiogram. Three days after the patient started to refer visual impairment. An ophthalmoscopic examination was performed as recommended in case of fungaemia.^[8] The vitreous was clear in both eyes. Funduscopy revealed retinal infiltrates in the left eye [Figure 3].

Eight days after fluconazole initiation, both visual symptoms and blood stream *Candida albicans* persisted. According to multidisciplinary team discussion antifungal was switched to intravenous voriconazole administered for 6 weeks. Blood culture did not show any fungal growth eight days after voriconazole initiation. Symptoms and ocular lesions completely regressed at respectively 15 and 40 days after voriconazole initiation.

Discussion

Despite clinical and radiological improvement, our patient had atypical but severe ocular complications. Although all *Candida* spp. can disseminate, *Candida albicans* infection is mostly associated with ocular candidiasis.^[9] According to this study, a mouse model was proposed showing that inflammatory mediators and ocular infiltration of neutrophils and monocyte were significantly higher during *Candida albicans* infection compared to any other species. Typically, ocular concentrations of IL-6, CXCL1/KC, CXCL2/MIP-2, and CCL2/MCP-1 were higher following exposure to *Candida albicans*.

COVID-19 can be very tricky in its presentation. It is likely characterized by hyper inflammation and impaired immunity.^[10] Similarly to our patient, increased cytokine levels (IL-6, IL-10 and TNF- α) and lymphopenia were associated with severe COVID-19.^[11] This condition can predispose to opportunistic infection and dissemination to other organs. Furthermore, we have very few data on long-term effects of anti-inflammatory targeted-therapy such as Tocilizumab; further investigations are required to assess the trend of IL-6 expression and infectious

diseases susceptibility in subjects who received a one-shot dose of the drug, compared to chronic use in rheumatoid arthritis.

Unfortunately, most patients show no symptoms of ocular involvement. But also, no certain predictors of ocular candidiasis were identified. Therefore, all patients with candidemia should undergo ophthalmologic examination.^[12]

This report remarks that a co-operation between pulmonologists, infectivologist and ophthalmologists is absolutely indispensable in case of fungaemia.

Conclusion

This is a case report on COVID-19 respiratory distress and haematogenous candida spp. spread leading to unilateral chorioretinitis. Candidiasis is likely more common than what is reported during and after critical illness. Furthermore, anti-inflammatory targeted-therapy such as Tocilizumab, may interfere on long-term immune response. For this reason, coinfections should be carefully investigated, and ophthalmologic examination should be performed in presence of candidemia.

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Consent for Publication

The patient provided written consent.

Competing Interests

The authors declare that they have no competing interests

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