Cytokine Storm in COVID 19 Culminating in Candida Endocarditis

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Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had made its demonic debut on the world stage in December 2019 and has been sweeping across the globe since then.1 This new kid on the block soon also joined the cluster of risk factors, leading to fungal infections. Cases of mucormycosis, colloquially called “black fungus,” (COVID-19 associated mucormycosis [CAM]), had escalated in India, and the focus then shifted to Candida, the so-called “white fungus.” The dysregulated immune system in COVID-19, along with the immunosuppressants used to treat it, may give rise to fatal secondary infections. We present a patient who had a stormy, prolonged course following COVID-19, with multiple bacterial and viral infections, subsequently culminating in fungal endocarditis with Candida tropicalis.

Keywords

COVID-19, Candida, fungal infections

Introduction

Despite global containment measures, cases of Coronavirus disease 2019 (COVID-19) continue to mount around the world.1 The immunosuppression caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the treatment of this disease predisposed the patients to secondary bacterial and fungal infections. Although COVID-19 associated pulmonary aspergillosis and COVID-19 associated mucormycosis have been the focus of research, COVID-19 associated candidiasis, which is underreported, may too be fatal.2 COVID-19 associated candidiasis occurs in critical COVID-19 patients, because of both COVID-19 related factors and non-COVID-19 related risk factors. We report a case of COVID-19 associated Candida infective endocarditis (CIE) in a female patient who had a very stormy course.

Case Report

A 53-year-old hypertensive and diabetic female, recently diagnosed with chronic kidney disease, presented with fever and breathlessness of 4 days duration. She had 3 recent admissions for fluid overload at another hospital. Her SARS-CoV-2 RTPCR had been negative on all 3 occasions and HRCT thorax had shown no features of COVID-19. At our institute, the patient’s HRCT thorax was suggestive of COVID-19 with a severity score of 13/25 with RTPCR for SARS-CoV-2 being positive. She was tachypneic, febrile, hemodynamically stable, and had decreased air entry in the right lung base. Her oxygen saturation on room air was 92% and her PaO2/FiO2 ratio was 245. Pallor and edema feet were present and jugular venous pressure (JVP) was marginally raised. All the inflammatory markers were raised, with a C reactive protein (CRP) of 92 mg/L, Se ferritin 2400 mgm/L, Se lactate dehydrogenase (LDH) 1200 units/L, D-dimer 1500 mcg/mL (FEU).

Her WBC was 15,400/cmm, Hb 7.4 gm%, platelet count 1,86,000/cmm, blood sugar (BS) 180 mg/dL, SGOT 42 IU/L, SGPT 86 IU/L, and Se creatinine 6.3 mg%. NTproBNP was 3600 pg/mL and HbA1C was 7.8. Electrocardiogram and echocardiography were within normal limits. She was treated for fluid overload and COVID-19 as per our institutional protocol, which included injection Remdesivir, intravenous methylprednisolone, anticoagulation, and was initiated on hemodialysis. She required 4 L to 6 L of oxygen by nasal prongs, for 15 days. In view of fever, raised counts, and raised procalcitonin (1.5 ng/mL), broad spectrum antibiotics were added in renal corrected doses. However, there was no obvious focus of infection after diligent investigations and appropriate cultures. After 45 days of admission, when she stabilized and turned RTPCR negative...
twice, she was shifted from the ICU to the non-COVID-19 ward. Around day 60 of admission, she developed copious diarrhea and was diagnosed to have *Clostridioides difficile* diarrhea (glutamate dehydrogenase and toxin A positive) with pseudomembranous colitis on colonoscopy, which was treated with oral vancomycin and intravenous metronidazole. A few days later, she developed vesicular lesions on the left buttock, extending till the left knee (Figure 1). Intravenous acyclovir in renal corrected doses was started for herpes zoster. Shortly thereafter, she developed an episode of catheter associated urinary tract infection with multidrug resistant (MDR) *E. coli* which required colistin with double dose meropenem (as per sensitivity).

After 15 days, a repeat 2D echo was done in view of persistent fever and hypotension. An echogenic mass of size 28 mm × 19 mm (vegetation) was seen in the right atrium, which seemed to be attached to the catheter tip and extended up to the tricuspid valve orifice (Figure 2). The catheter tip grew *Candida tropicalis*, which was identified using the conventional method, on chrome agar and corn meal agar. This was because our laboratory did not have the automated system (Vitek 2) at that time.

2 sets of blood cultures, sent with strict aseptic precautions, showed no growth. She was started on intravenous liposomal amphotericin B along with intravenous fluconazole but succumbed on the next day, after almost a 3-month hospital stay.

**Discussion**

A notable proportion of COVID-19 critically ill patients require ICU admission and mechanical ventilation, which in turn predisposed them to nosocomial bacterial and fungal infections. Invasive yeast infections were increasingly recognized as a complication of severe COVID-19. In contrast to mucormycosis, which may be seen in asymptomatic and mild COVID-19, invasive pulmonary aspergillosis, which is a late complication in critical COVID-19 and invasive candidiasis were also seen mainly in critical COVID-19 patients needing ICU care, in the presence of other host factors. Although *Aspergillus fumigatus* has gained focus as an important cause of fungal super-infections among critically ill COVID-19 patients (COVID-19 associated pulmonary aspergillosis), the incidence of candidiasis has not been adequately studied in the COVID-19 scenario. The risk factors for COVID-19 associated candidiasis include “common risk factors” predisposing ICU patients to invasive candidiasis such as diabetes mellitus, renal failure requiring hemodialysis, abdominal surgery, triple lumen catheters, parenteral nutrition, receipt of multiple antibiotics, length of ICU stay >7 days, prior abdominal infections, and “COVID-19 specific risk factors” such as the use of corticosteroids and tocilizumab, and the hyperglycemic effect of SARS-CoV-2 in patients who are not known diabetics. In addition, patients with sepsis or septic shock, commonly observed in severe COVID-19 patients in the ICU, may develop a leaky gut that facilitates *Candida* translocation from the gastrointestinal tract (GI) tract into systemic circulation. The new landscape of candidemia reveals an increasing incidence of nonalbicans *Candida* species, with intrinsic resistance to antifungals and/or with a propensity to rapidly acquire antifungal resistance. CIE is a rare disease with a high mortality rate accounting for only 1% to 2% of all cases. It is 1 of the most serious manifestations of candidiasis. Fungal endocarditis most commonly involves the left side of heart (combined aortic and mitral, 70%). Tricuspid valve endocarditis occurs in 5% to 10% of cases with infective endocarditis (IE). Risk factors include prosthetic valve implantation, cardiac implantation devices, and injection drug use. Blood cultures are positive only in 50% of the cases and nonculture-based tests have to

![Figure 1. Left Leg with Vesicles Up to the Thigh s/o Herpes Zoster.](image)

![Figure 2. An Echogenic Mass of Size 28 mm × 19 mm in the Right Atrium, Attached to the Catheter Tip and Extending Up to the Tricuspid Valve Orifice s/o a Vegetation.](image)
be utilized for the diagnosis. Candidal infections in COVID-19 have been reported from all over the globe, but possibly a few reports of Candida endocarditis in COVID-19 have been reported. CIE is associated with a high mortality rate that is not impacted by the choice of antifungal therapy or by the adjunctive surgical intervention. Currently, the IDSA and ESCMID recommend either an amphotericin B-based regimen or an echinocandin-based regimen, both of these in combination with adjunctive surgical therapy if possible.

Our patient had a particularly stormy course post COVID-19. She unfortunately had multiple viral, bacterial, and fungal infections sequentially namely moderate COVID-19, Clostridioides difficile diarrhea with pseudomembranous colitis, herpes zoster, UTI with MDR E. coli, culminating in probable Candida tropicalis catheter related blood stream infection leading to endocarditis. She had all the classical risk factors for developing candidemia namely multiple comorbidities (HT, DM, CKD on MHD), prolonged and multiple hospital stay, prolonged ICU stay (1.5 months), multiple indwelling catheters, COVID-19, steroid use, bacterial, and viral superinfections, receipt of multiple broad-spectrum antibiotics. However, there was no history of azole use and she had not received tocilizumab.

Conclusions

Fungal coinfections and their impact on COVID-19 patients are still understudied. Understanding the burden of COVID-19 patients with secondary infections and their etiologic agents is paramount for the optimal management of COVID-19 patients. Routine antifungal prophylaxis in critically ill COVID-19 patients is a debatable issue. While aspergillosis and mucormycosis have gained attention in the COVID-19 era, Candidal infections in the critically ill COVID-19 patients may be much more common and deserve to be studied in large trials.

Consent

The consent of the patient’s kin has been obtained for publishing this case report.

Author Contribution

Dr Mala V. Kaneria has diagnosed and managed the patient, conceptualized and drafted the article and written the article. Dr Abhijeet Budhe has helped with the obtaining the figures and in drafting the article. Dr Prasenjit Lade has contributed in drafting the article. Dr Tejas Poyekar had contributed in drafting the article.

Declaration of Conflicting Interests

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