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Non-Neoformans Cryptococcal Infections in the Post-Coronavirus Disease-19 (COVID-19) Era: Are We Ready to Face the Emerging Challenge?

Umayra Fatima[1] Hina Ahmed[2] Gautam Singh[2] K.Y. Giri[3] Md. Sania Azmi[4] Archana Meenakshi[5] Suresh Babu Jandrajupalli[6] Swarnalatha Chandolu[6] Abhishek Singh Nayyar[7]

[1] Department of Dentistry, Princess Esra Hospital, Deccan College of Medical Sciences, Hyderabad, Telangana, India
[2] Department of Conservative Dental Sciences, Ibn Sina National College for Medical Studies, Jeddah, Kingdom of Saudi Arabia
[3] Department of Oral and Maxillofacial Surgery, Drs Sudha and Nageswara Rao Siddhartha Institute of Dental Sciences, Gannavaram, Andhra Pradesh, India
[4] Department of Oral and Maxillofacial Pathology, Care Dental College, Guntur, Andhra Pradesh, India
[5] Department of Periodontology, Ragas Dental College and Hospital, Chennai, Tamil Nadu, India
[6] Division of Periodontology, Department of Preventive Dental Sciences, College of Dentistry, University of Ha'il, Ha'il, Kingdom of Saudi Arabia
[7] Department of Oral Medicine and Radiology, Saraswati Dhanwantari Dental College and Hospital and Post-graduate Research Institute, Parbhani, Maharashtra, India

Address for correspondence Abhishek Singh Nayyar, MDS, Department of Oral Medicine and Radiology, Saraswati Dhanwantari Dental College and Hospital and Post-graduate Research Institute, Parbhani, Maharashtra 431401, India (e-mail: singhabhishekndls@gmail.com).

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Abstract

Coronaviruses are a large group of viruses that infect animals as well as humans, while it is also suggested that, rarely, coronaviruses that infect animals can evolve and infect humans. Current evidence suggests that severe acute respiratory syndrome (SARS) coronavirus-2 leads to coronavirus disease-19 (COVID-19), the respiratory illness responsible for COVID-19 pandemic, while it has a zoonotic origin, closely related to the bat-origin SARS-like coronavirus. Also, as per the current knowledge, the disease may induce significant and persistent lymphopenia which in turn may increase the risk for various opportunistic infections. *Cryptococcus laurentii* is one such rare, but serious fungal infection which has been reported in post-COVID-19 disease and is a rising cause of concern since it can turn out to be fatal. The infection is caused by a non-neoformans rare human pathogen. The present case report describes the case of a 45-years old male patient who reported to the Outpatient Department (OPD) for a routine dental complaint with a grossly destructed tooth in left lower back tooth region due to extensive carious involvement, while, simultaneously, presenting with fever since 5 days in the post-COVID-19 phase, and was later diagnosed as being positive for *C. laurentii* infection on urine culture sensitivity test.

Keywords

- coronaviruses
- non-neoformans cryptococcal infections
- *Cryptococcus laurentii*
- coronavirus disease-19

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Introduction

Coronaviruses are a large group of viruses that infect humans and animals. Rarely, coronaviruses that infect animals can evolve and infect humans and then spread in between them such as the one seen in case of Middle East respiratory syndrome and severe acute respiratory syndrome (SARS). Current available evidence for coronavirus disease-19 (COVID-19) suggests that the causative virus SARS coronavirus-2 (SARS-CoV-2), a strain of coronavirus that causes COVID-19, the respiratory illness responsible for the COVID-19 pandemic, has a zoonotic origin, closely related to the bat-origin SARS-like coronavirus.[1–4] First identified in the city of Wuhan, Hubei, China, the World Health Organization designated the outbreak as a public health emergency of international concern from January 30, 2020, till May 5, 2023.[5–7] As per the current knowledge, COVID-19 may induce significant and persistent lymphopenia (reflecting as decreased cluster of differentiation-4 and -8 [CD4 and CD8 cells] which in turn may increase the risk for various opportunistic infections including a plethora of bacterial, viral, and fungal infections).[8,9] In similar context, pulmonary cryptococcosis is a severe form of fungal disease seen, particularly, in case of immunocompromised hosts, with *Cryptococcus neoformans* constituting the main causative pathogen. There is a change observed, however, in the recent trends over the last few decades wherein non-neoformans species such as *Cryptococcus laurentii*, *Cryptococcus albidus*, and *Cryptococcus uniguttulatus* have increasingly been linked with the severe form of disease in immunocompromised as well as immunocompetent hosts.[10–12] The exact association between cryptococcosis and COVID-19 is unclear, though, the use of steroids and immunomodulators in COVID-19 patients is being assumed to lead to the reactivation of Cryptococcus spores which are otherwise present in the host, and which remain dormant for prolonged periods of time until the host gets immunocompromised, when they express as life-threatening opportunistic infections that may turn out to be fatal.[13–15] The present case report describes the case of a 45-years old male patient who reported to the Outpatient Department (OPD) for a routine dental complaint along with fever since 5 days in the post-COVID-19 recovery phase, and was later diagnosed as being positive for *C. laurentii* infection on urine culture sensitivity test.

Case Report

The present case report describes the case of a 45-years old male patient who reported to the Outpatient Department (OPD) for a routine dental complaint with a grossly destructed tooth in left lower back tooth region due to extensive carious involvement, while, simultaneously, presenting with fever along with loose stools and burning sensation during *micturition* since 5 days in the post-COVID-19 recovery phase. The patient was a reverse transcription-polymerase chain reaction (RT-PCR) test COVID-19 positive and was admitted to the hospital, and subsequently discharged in an asymptomatic and RT-PCR negative state during his first admission to the hospital. On elicitation of history and confirmation with the records of the patient, the patient was kept on intravenous remdesivir (RDV) for three consecutive days along with symptomatic treatment provided in the form of acetaminophen in conjunction with guaifenesin, pseudoephedrine, and dextromethorphan to relieve fever and congestion on a need basis along with plenty of fluids as an inpatient during his hospital stay. Furthermore, the patient was found to be a known diabetic since 10 years and was on medication with his diabetic status being under control. On physical examination, the patient was febrile, while chest auscultation revealed bilateral crepitations and rhonchi, following which the patient was advised necessary investigations including a chest X-ray (CXR) and routine hematological investigations which revealed hemoglobin (Hb) as 10.6 g/dL of blood with the total leukocyte count

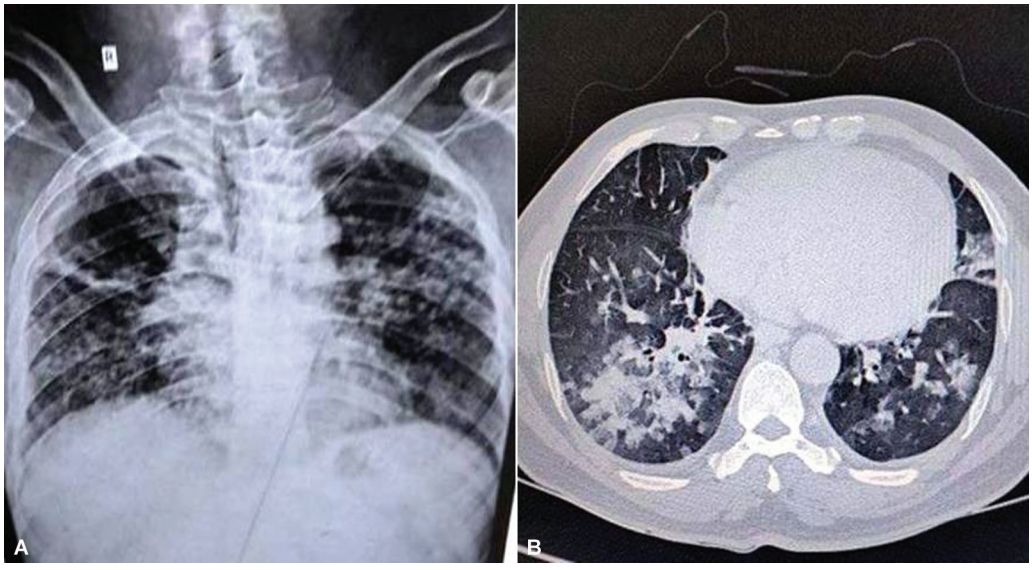

Fig. 1 (A, B) Chest X-ray (CXR) and high-resolution computed tomography (HRCT) of the patient indicating post-coronavirus disease (COVID) fibrotic changes with lung involvement.

being 20,000 cells/μL, platelet count being 3,66,000 cells/μL, and glycated Hb level being 8.9% when the patient reported for the second time with post-COVID-19 symptoms including fever and malaise. Also, normal urine microscopic examination of the patient revealed pus cells in the counts of 30 cells/μL, while proteins in the range of ± 15 mg/dL. Kidney and liver function tests of the patient, though, were found to be within normal range, while the patient was found to be malaria parasite, dengue antigen and antibody, and Widal negative, with the viral markers being nonreactive. The characteristic CXR findings of the patient included bilateral peripheral and basal multifocal airspace opacities with consolidation (►**Fig. 1A**), while high-resolution computed tomography (CT) of the patient indicated typical consolidation and mosaic pattern of attenuation in relation to the right lower lobe and ground glass attenuation with scattered consolidations in relation to the left lower lobe and lingular segment of the left upper lobe (►**Fig. 1B**) suggestive of post-COVID fibrotic changes with lung involvement. The patient was later advised urine culture sensitivity test done at the Department of Pathology, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India, wherein the patient was diagnosed positive for *C. laurentii* infection. The patient was immediately put on intravenous Amphotericin B (AMB) (0.5 mg/kg/day) along with oral fluconazole (FLZ) (400 mg/day) for 3 weeks when the patient showed uneventful recovery, and was discharged after 3 weeks of treatment.

Discussion

Severe COVID-19 is associated with an increase in the proinflammatory markers such as interleukin-1 and -6 (IL-1 and IL-6), and tumor necrosis factor-alpha, and lesser CD4 interferon-gamma (IFN-gamma) expression with fewer CD4 and CD8 cells which increase susceptibility to various bacterial and fungal infections.[16,17] Initially, it was debated whether a person taking immunosuppressants such as corticosteroids and monoclonal antibodies will be at higher risk for COVID-19 and associated complications or, whether the immunosuppressive state, itself, would lead to a more severe COVID-19. Immunosuppressants are currently being continued, though, unless the patients are at an uncontrollably high risk of severe COVID-19 or are on high-dose corticosteroid therapy. It is also noted that the laboratory findings of 85% of COVID-19 patients showed lymphopenia.[18–20] This means that patients with severe COVID-19 have markedly lower absolute number of T lymphocytes, CD4 + T cells, and CD8 + T cells, and since lymphocytes play a major role in maintaining immune homeostasis, patients with COVID-19 are highly susceptible to numerous deep fungal infections as well as various other opportunistic infections including mucormycosis, other fungal diseases such as candidiasis, SARS-CoV-2-associated pulmonary aspergillosis, *Pneumocystis jiroveci*, formerly known as *Pneumocystis carinii*-associated pneumonia, and a plethora of cryptococcal infections in the post-COVID-19 phase.[21] In similar context, among the 19 species of the genus Cryptococcus, *C. neoformans* is the most common pathogen associated with human infections, however, infection due to non-neoformans species like *Cryptococcus luteolus* and *C. albidus* have also been reported. Furthermore, disseminated *C. neoformans* infection is a serious infection that has been seen in immunocompromised patients in the post-COVID-19 disease phase.[22–24]

Currently, more and more Cryptococcus species are being identified as causative human pathogens, while no standard or validated treatment is defined for these organisms due to paucity of the literature in this regard. In similar context, the case reported by Khatib et al[25] highlights the significance of an early suspicion of *C. neoformans* and other opportunistic infections in immunocompromised patients considering that patients with *C. neoformans* infection have a high risk of mortality which warrants the use of corticosteroids and immunomodulatory drugs in critically ill patients with COVID-19. In the present scenario, however, the use of immunosuppressive therapy has been declared justified in patients with opportunistic infections like *C. neoformans* infection which can lead to rapid sepsis increasing the risk of mortality in the affected patients.[26]

Again, recent trends have indicated the increasing possibility for *C. laurentii* infection in post-COVID-19 disease, which is another similar opportunistic infection caused by a non-neoformans Cryptococcus, *C. laurentii*. *C. laurentii* is considered to be a rare human pathogen which was earlier considered a saprophyte, but now being perceived as a rare but serious fungal infection. Infections caused by this encapsulated, basidiomycetous, yeast-like fungus have been increasingly documented, especially in immunocompromised patients in the post-COVID-19 disease which may lead to invasive illnesses including fungemia, pulmonary infections, and meningitis, and can turn out to be fatal.[27–29]

Till date, around 12 cases of *C. laurentii* fungemia have been reported worldwide and most of the cases reported were diagnosed in cancer patients. All the patients recovered after treatment except for one who died due to the underlying disease. AMB has been considered as the most successful drug and the first line of treatment to treat *C. laurentii* fungemia. Again, besides fungemia, *C. laurentii* reportedly leads to severe peritonitis and acute lung infection apart from cutaneous and severe ocular involvement.[30–33] The significant imaging findings in the infected patients include single or multiple nodules to segmental consolidation, cavitation, bilateral bronchopneumonia, and mass-like lesions as discovered on chest radiography and CT scans.[34] In this pretext, for asymptomatic patients and patients with mild-to-moderate pulmonary infections, the United States Centers for Disease Control and Prevention (CDC) recommended FLZ as the choice of drug for treatment, while for patients with severe and acute pulmonary infections or infections in the central nervous system involving the brain and spinal cord, the CDC recommended initial treatment with AMB in combination with flucytosine, also, known as 5-fluorocytosine, while the affected patients are then switched to FLZ for an extended period of time until the infection subsides. Some patients may even require surgery for removal of the fungal growths known as cryptococcomas.[35,36] As we have limited data related to the *C. laurentii*

infections in post-COVID-19 disease, further comments on the disease entity related to this fungal infection need acquisition of more data on this.

In similar context, Sen et al[37] conducted a retrospective study on six COVID-19 patients who developed rhino-orbital mucormycosis and were managed at a tertiary ophthalmic center. All patients reported in the study were male patients with a mean age of 60.5 ± 12 years and type 2 diabetics, while all except one patient was on systemic steroids for COVID-19. The researchers reported a mean duration of 15.6 ± 9.6 days between diagnosis of COVID-19 and development of symptoms indicative of mucormycosis. Furthermore, all patients had undergone endoscopic sinus debridement, while two patients required orbital exenteration. To add, all six patients were alive till the last follow-up in the study. The researchers emphasized high index of suspicion, along with an early diagnosis and appropriate management for achieving high patient survival.

Similarly, Kanwar et al[38] also reported a fatal case of a 56-year-old male patient who was hospitalized for COVID-19. The patient had a preexisting end-stage renal disease and was on hemodialysis, and eventually, developed mucormycosis during the hospital stay. Patient had a positive SARS-CoV-2 RT-PCR, though was asymptomatic until only after 4 days when he was hospitalized for fatigue and shortness of breath. Upon admission, blood cultures were found negative for bacterial and fungal microorganisms. The patient was started with methylprednisolone, tocilizumab (TCZ), and single dose of convalescent plasma therapy following which the patient was discharged after 7 days of treatment. The patient reported again with generalized fatigue, shortness of breath, and hemoptysis after 5 days of discharge when he was started on empiric antibiotic therapy including intravenous vancomycin and piperacillin-tazobactam combination for suspected pneumonia. The CXR of the patient revealed increasing airspace density in both lungs with pleural effusion, while on day 3, repeat sputum examination revealed filamentous fungus following which empiric treatment of liposomal AMB was started. Despite persistent drainage of pleural effusion over the next few days, however, repeat chest CT did not show signs of improvement, and on repeat sample analysis, Rhizopus azygosporus was diagnosed, and despite all efforts, patient developed cardiac arrest and died on the 17th day of hospitalization. The researchers, then, recommended that severe COVID-19 should be considered as a potential risk factor for invasive fungal infections, particularly in patients who receive immunosuppressive therapy including high-dose corticosteroids and IL-6 inhibitors (TCZ) during treatment. Furthermore, because there are no noninvasive tests available for invasive fungal infections, researchers believe cases of mucormycosis may actually be higher in numbers than what numbers are getting reported.

On similar lines, Moorthy et al[39] conducted a multicentric retrospective study on 18 patients with diabetes mellitus (DM) with positive SARS-CoV-2 infection wherein 15 out of 18 patients had uncontrolled DM, and all had received high-dose corticosteroids for COVID-19. The researchers observed that 12 out of 18 patients had complained of loss of vision following which 7 patients underwent orbital exenteration. Surprisingly, the study revealed that 16 out of 18 patients under observation were found positive for mucormycosis, while 1 patient each was diagnosed with aspergillosis and mixed fungal infection. Six of these patients died eventually, while 11 patients survived and 1 patient was lost to follow-up. The researchers, therefore, confirmed significantly higher incidence of fungal infections ($p = 0.03$) among diabetic patients, and suspected a strong association between immunosuppression related to steroid administration and incidence of such infections.

Karimi-Galougahi et al[40] also reported a case of a 61-year-old female patient with no past medical history who was hospitalized for COVID-19 for a period of 2 weeks. During her hospital stay, the patient received RDV, IFN-alpha, and systemic steroids for treatment, though intubation and mechanical ventilation were not indicated. The patient reportedly developed right hemifacial pain with no other sinonasal symptoms, hemifacial numbness, decreased visual acuity, and chemosis, 1 week after her discharge which prompted her second hospitalization. Noncontrast CT of paranasal sinuses, magnetic resonance imaging, and diagnostic sinonasal endoscopy of the patient confirmed the case to be an invasive fungal infection of mucormycosis. In this case, though the patient was healthy, researchers indicated that steroid-induced immunosuppression in the patient in addition to the immune dysregulation secondary to COVID-19 had led the patient to end up having invasive mucormycosis.

Several other rhino-orbital mucormycosis cases have been reported in patients in the post-COVID-19 period. Waizel-Haiat et al[41] also reported a case of a 24-year-old female patient who tested positive for COVID-19 and was brought to the emergency department wherein she complained of left midfacial pain 6 days prior to the hospital admission which had worsened to left lid edema and maxillary hypoesthesia since 2 days. The patient was started with oral amoxicillin-clavulanate combination, though when it did not provide relief, rhinoscopy was completed with contrast-enhanced CT of head and chest, revealing an invasive fungal infection. The patient eventually developed multiple other complications of COVID-19 including metabolic acidosis combined with pulmonary insult and acute kidney injury due to disseminated intravascular coagulopathy, leading to death of the patient due to multiple organ failures, probably due to septic shock. The researchers concluded that this patient had immunosuppressive state secondary to diabetic ketoacidosis making her susceptible to COVID-19-related complications in the form of mucormycosis. Her late diagnosis and delay in treatment further contributed to this unfortunate outcome.

Recently, a multicentric, observational cohort study registered with ClinicalTrials.gov, NCT04368221, and conducted at 18 French intensive care units at Rennes University Hospital in France to assess the prevalence, risk factors, and mortality associated with invasive fungal infections in mechanically ventilated patients with COVID-19, also concluded that with the high prevalence of invasive pulmonary aspergillosis and candidemia, and an increased risk of mortality with the patients ending up in life-threatening

complications in the form of acute respiratory distress syndrome, there is a need for active surveillance of fungal pathogens in patients with severe COVID-19.[42]

Conclusion

COVID-19 presents with a spectrum of disease manifestations ranging from being asymptomatic to mild, nonspecific flu-like symptoms to severe and acute lung involvement, pneumonia and sepsis, and multiple organ failures. In addition, secondary opportunistic infections due to frequent use of steroids for the management of patients have proven to be the major independent risk factors for the reported adverse COVID-19 outcomes. Also, concerns for the secondary complications of COVID-19 have further increased due to the use of various broad-spectrum antimicrobial agents with concomitant fear of increased antimicrobial resistance. The present case report describes the case of a 45-year-old male patient who presented with fever since 5 days in the post-COVID-19 phase and was later diagnosed as being positive for *C. laurentii* infection on urine culture sensitivity test. The case reported in the present case study intends to raise awareness for the need of a vigilant and active surveillance and appropriate treatment of such opportunistic infections which have presented with high mortality rates. It is also essential to assess the predisposing risk factors, type of infection, its invasiveness, and associated morbidity and mortality risks to provide an appropriate individualized treatment. Further studies and additional investigations are highly warranted to understand the exact role and status of opportunistic infections in COVID-19 patients that may assist in a strategic diagnosis and management of such infections which might turn out to be fatal.

Authors' Contributions

All authors contributed significantly to this work across multiple areas. They were involved in developing the concepts, designing the structure of the case report format, as well as in defining the intellectual content. Each contributed to the literature search, as well as in the acquisition and analysis of patient-related data. The manuscript was prepared with contributions from all authors, who also played key roles in editing and reviewing the final draft. Finally, all authors share responsibility as guarantors, ensuring the accuracy and integrity of the work.

Conflict of Interest

None declared.

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