Case Report

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Non-Neoformans Pulmonary Cryptococcosis Due to Cryptococcus Laurentii in a Positive SARS-COV-2 Patient

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Running Title Non-Neoformans Pulmonary Cryptococcosis Due to Cryptococcus Laurentii

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ABSTRACT

Non-neoformans Cryptococcus species were formerly considered to be saprophytes and nonpathogenic to humans [1-2]. However, the incidence of Cryptococcus laurentii infections in immunocompromised and immunocompetent patients has been gradually increasing over the last decades [1-2]. During the COVID-19 pandemic, multiple cases of opportunistic bacterial and fungal infections have been reported in patients after a severe SARS-CoV-2 infection. The author reports the first case of opportunistic pulmonary cryptococcosis caused by Cryptococcus laurentii in a severely ill COVID-19 patient who received treatment with Tocilizumab and dexamethasone. This case contributes to the expanding knowledge of emergent secondary infectious complications including opportunistic pathogens after a SARS-COV-2 infection.

Introduction

Pulmonary cryptococcosis is a severe fugal disease of the lung caused by fungi of the Cryptococcus (C.) species [1]. *C. neoformans* constitutes the traditional pathogen of pulmonary cryptococcosis in immunocompromised hosts [1-3]. However, over the last 5 decades, non-neoformans species that were traditionally considered non-pathogenic to the human, such as *Cryptococcus laurentii*, *Cryptococcus albidus*, and *Cryptococcus uniguttulatus,* are now becoming an emerging disease in both immunocompetent and immunocompromised patients [2-13].

C. laurentii is a basidiomycetous encapsulated yeast that is responsible for invasive illnesses (fungemia, pulmonary infections, meningitis), superficial infections (keratitis, onychomycosis, folliculitis decalvans) and musculoskeletal infections (fungal knee arthritis) [2-12]. It is worth noting that invasive

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fungal infections have been increasingly recognized as severe, late sequel and opportunistic infections in patients with COVID-19 disease [14].

Documentation shows that immunosuppressive agents used for severe COVID-19 infections, such as corticosteroids and cytokine blockers (Tocilizumab), increase the risk of cryptococcal opportunistic mycoses specifically those caused by *C. neoformans* [15-21]. The author reports a rare case of pulmonary cryptococcosis caused by a non-neoformans species, *C. Laurentti*, in a patient with COVID-19 disease, constituting the first report in the literature.

Case History

A 63-year-old male with a history of hypertension and obesity was transferred to the hospital with a 12-day history of fever, headache, diarrhea, anosmia, generalized weakness and worsened respiratory distress. On presentation, he was hypoxic with an oxygen saturation (SpO_2) of 85% on nasal cannula at 6 L/min, dyspneic with a respiratory rate of 36 breaths/min, and had a positive SARS-CoV-2 nasopharyngeal swab test. He had a PaO_2/FiO_2 ratio of 35 mmHg (normal value > 300 mmHg) and was diagnosed with severe acute respiratory distress syndrome (ARDS). His white blood cell count (WBC) was found within normal values; however, his lymphocytes were found low at 11% (normal values 25.0% - 45.0%). Due to his increased oxygen requirement, he was admitted to the COVID-19 Intensive Care Unit (ICU) where he was placed on a non-rebreather reservoir mask at 15 L/min. Computed tomography (CT) scan of the chest showed diffuse bilateral ground-glass opacities. Initial D-Dimer levels were elevated at 95,810 ng/mL (normal value ≤ 500 ng/Ml). Therefore, therapeutic anticoagulation with enoxaparin was modified to 80 mg twice daily. He received a 5-day course of Remdesivir (200 mg initially, continued by 100 mg), a single dose of Tocilizumab (800 mg) due to cytokine storm, and had a 10-day tapered course of dexamethasone (6 mg), as part of the COVID-19 management.

Even though he remained critically ill for 10 days, the patient experienced a gradual decrease in oxygen requirement, transitioning from a non-rebreather reservoir mask to a nasal cannula. Although clinically stable, he had to remain on the unit due to persistent elevated D-Dimer levels (14,700 ng/mL). However, on day 16th of admission, he developed a fever along with worsened respiratory distress, and his SpO2 dropped to 89% while on nasal cannula at 6 L/min. D-dimer levels increased to 20,901 ng/mL. An echocardiogram was reported as normal and pulmonary embolism was ruled out. His WBC increased to 24.41 x $10^{3/}$ µL (normal 4.0- 10.0 x $10^{3/}$ µL) and neutrophils increased to 86.7% (normal values 45.0%- 70.0%). Chest X-ray displayed a nodular pattern (Fig. 1). A repeat CT scan of the chest was performed which showed new-onset pulmonary nodules (Fig. 2), small areas of cavitation surrounded by parenchymal infiltrate (Fig. 3) in the left lung, and reverse halo sign in the right lung (Fig. 4).

Since the patient had no red flags suggestive of malignancy and due to the pathological images seen in the lungs along with neutrophilia and leukocytosis, an infectious etiology was suspected. He underwent

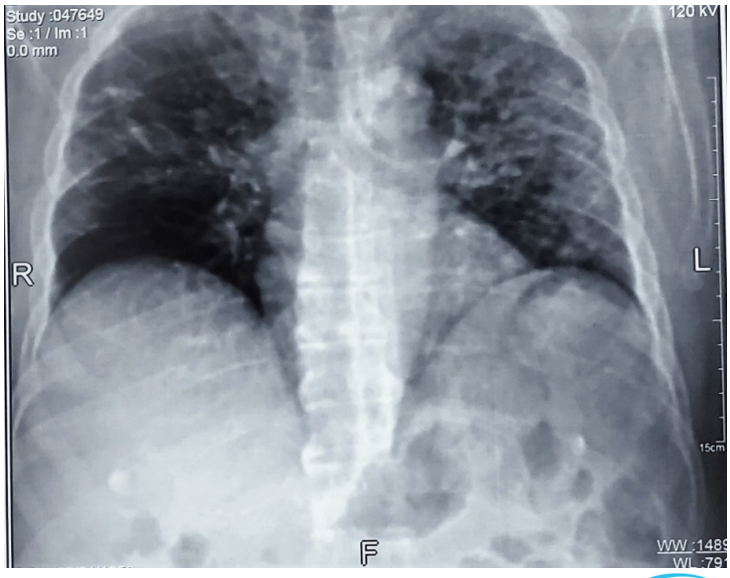

Fig. 1: Chest X-ray showing nodular pattern.

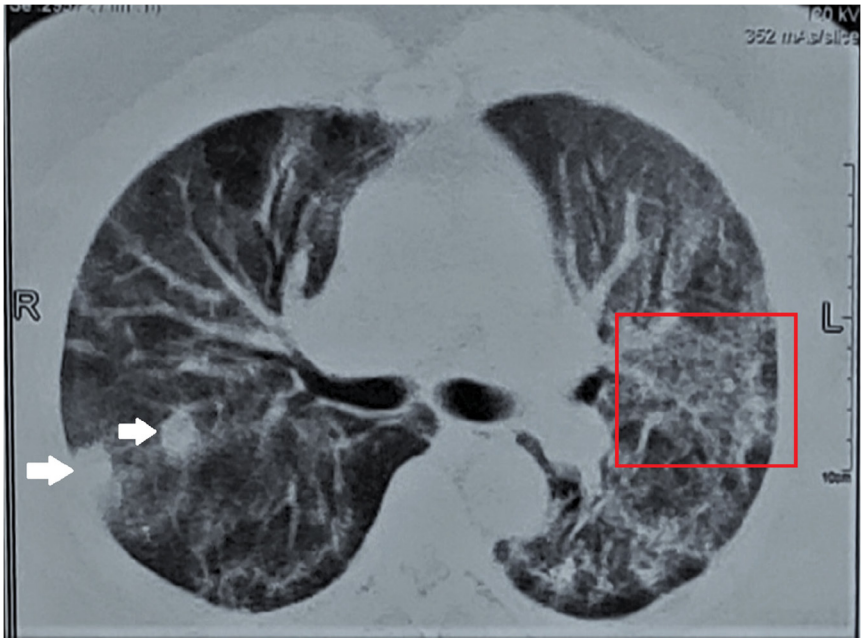

Fig. 2: Axial CT of the chest, in lung window, demonstrating new onset unilateral pulmonary nodules (white arrows): one peripheral nodule attached to the chest wall and one well-defined nodule in the middle aspect of the lung. Bilateral air bronchogram, and old "crazy paving" pattern (red square) present since admission, is also shown.

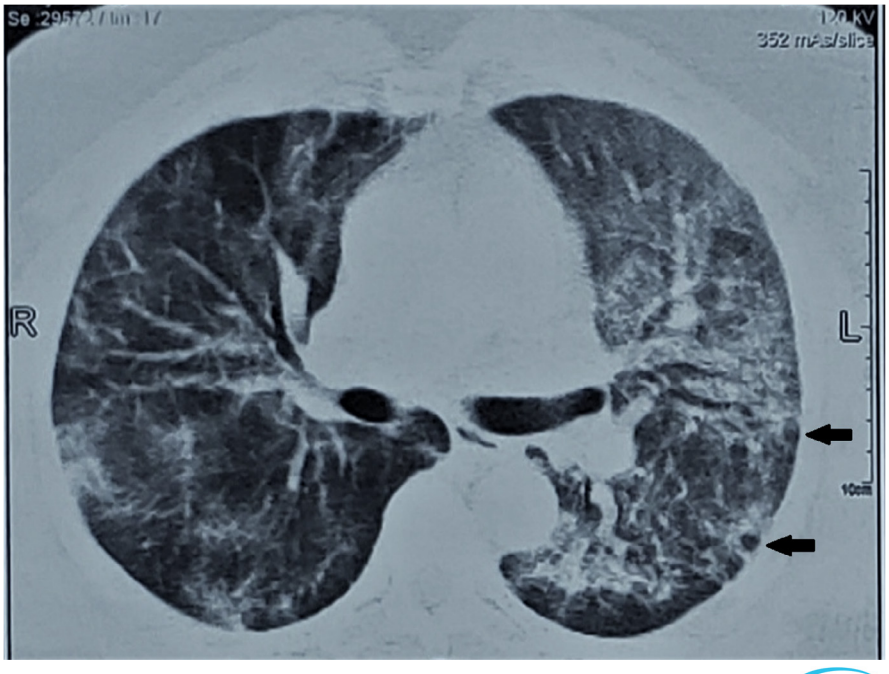

Fig. 3: Axial CT of the chest, in lung window, demonstrating small areas of cavitation (black arrow) surrounded by parenchymal infiltrate in the left lung. Bilateral air bronchogram and patchy bilateral ground glass opacities are also seen.

multiple microbiological investigations including sputum and blood cultures, tuberculin skin test, and blood-borne viruses screening (HIV, Hepatitis C, Hepatitis B). Sputum cultures and bronchoalveolar lavage (BAL) fluid both grew *Cryptococcus laurentii,* and the rest of the tests were negative. Of note, a pigeon infestation was lately seen at the hospital's external areas and crystal windows. The patient was then diagnosed with pulmonary cryptococcosis. Treatment with intravenous (IV)

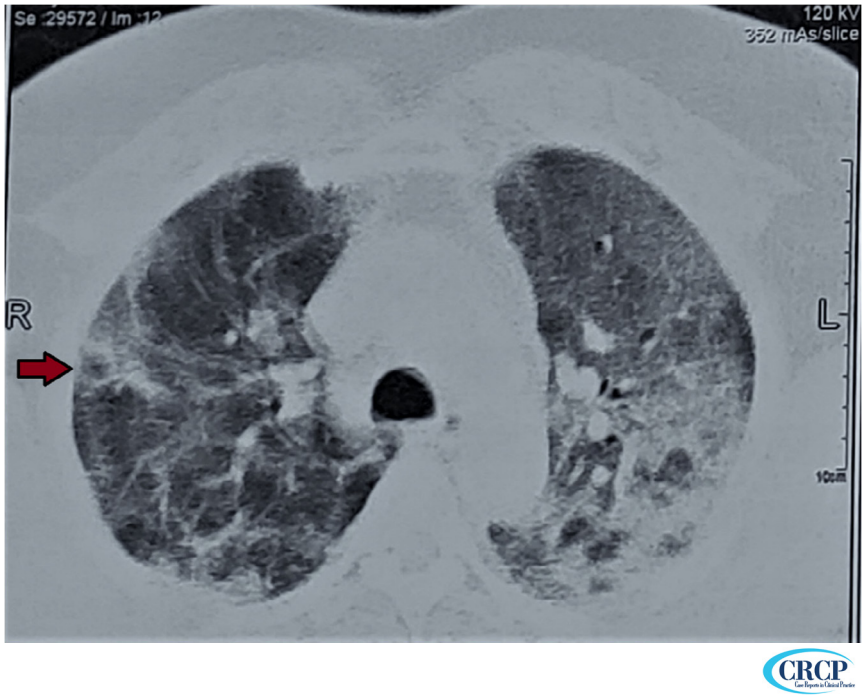

Fig. 4: Axial CT of the chest, in lung window, demonstrating reverse halo sign in the right lung and patchy bilateral ground glass opacities.

fluconazole 400 mg daily was initiated. He completed a 14-day course of IV fluconazole. Respiratory symptoms later resolved and after clinical improvement, he was subsequently discharged home with oral Fluconazole 200 mg daily for 6 months and was ordered follow-ups with the infectious disease department and pulmonology department.

Discussion

The scope of opportunistic mycoses found in both severely ill and immunocompetent patients is expanding [22]. Pulmonary cryptococcosis, an unusual disease before the human immunodeficiency virus (HIV) pandemic, is slowly becoming an important disease to rule out. With the emergence of non-neoformans Cryptococcus species as human pathogens, there is an exponential need to understand the underlying factors that could precipitate these opportunistic infections, especially in the setting of a post-pandemic world with the novel coronavirus disease. The present report is significant in that it potentially describes, to the best of the author's knowledge, the first case of an opportunistic pulmonary mycosis caused by a non-neoformans Cryptococcus species, that showed as a late complication of severe COVID-19 infection in a patient without pre-existing immune-compromising comorbidities on admission.

Non-neoformans species, such as *C. laurentti,* are widely distributed geographically, including the Caribbean [3]. Risk factors for infection with *C. laurentti* include impaired cell-mediated immunity (e.g., HIV, hematologic malignancy, prior steroid or immunosuppressive drug use, or organ transplantation), non-medication-associated neutropenia, and invasive devices [3]. Of note, the patient had a femoral central line which makes him especially susceptible to *C. laurentti* bloodstream infections, however, his blood cultures were clear.

Pulmonary mycoses caused by *C. laurentii* are acquired by inhalation of infectious spores released from droppings of feral pigeons [3, 13]. Interestingly, the Caribbean hospital where the patient was admitted had a recent pigeon infestation which could contribute to the source of the pathogenic spores. Moreover, the isolation of *C. laurentti* from 2 different sources (BAL fluid and sputum), indicated that it was probably the cause of the new pulmonary manifestations seen in the repeat chest CT scan (see Fig. 2-4).

Peripheral lung nodules are the most commonly diagnosed finding on CT scans of immunocompetent patients with proven pulmonary cryptococcosis [1]; whereas immunocompromised patients show a myriad of abnormal CT scan pulmonary findings: single or multiple nodules, segmental consolidation, cavitation, bilateral bronchopneumonia, proximal air bronchogram, halo sign and mass-like lesions [1, 23]. Even though the patient was immunocompetent

upon admission, he exhibited pulmonary CT findings associated with immunocompromised patients with pulmonary cryptococcosis. This raises the concern of whether the pathophysiology and/or therapeutic management of COVID-19 could have played a role in the immune response of the patient towards this opportunistic fungal infection.

Recent studies about COVID-19 disease report how the virus can strike the host immune system by affecting T-cell response by causing lymphopenia, and triggering a reduction in helper T cells and suppressor T cells, CD4+/ CD8+ T cells, B cells, and NK cells. This was more evident in patients with severe COVID-19 cases [24-26]. The patient had a severe COVID-19 infection denoted by a severe ARDS, lymphopenia and markedly elevated inflammation markers, which, inevitably, affected his immune response.

A COVID-19 infection also activates a large number of T lymphocytes and mononuclear macrophages in the host, producing cytokines such as interleukin-6 (IL-6), which causes a cytokine storm and severe inflammation in the lung and other organs [15]. In order to mitigate the cytokine storm effects, 2 large randomized trials recommended the use of an immunosuppressive agent called Tocilizumab, an IL-6 inhibitor, in combination with a 10-day course of dexamethasone in patients exhibiting rapid respiratory decompensation [27-28]. However, despite the lower mortality seen with the use of this pharmacological combination, there have been increasing concerns over a possible risk of late-onset infections, both fungal and bacterial, in COVID-19 patients [17, 29]. Given the fact that the patient received a single dose of Tocilizumab and a 10-day tapered course of dexamethasone, it is conceivable that his susceptibility to a *C. laurentti* infection markedly increased.

Regardless of the baseline immune status of a COVID-19 patient, clinicians should start considering opportunistic pulmonary mycoses, caused by uncommon pathogens such as *C. laurentti*, as the causal pathogens involved in new-onset pulmonary symptoms. In view of the affected host immune response caused by SARS-CoV-2 in severe cases with the subsequent extensive use of corticosteroids plus Tocilizumab, and given this experience, further cases analogous to this one could be expected during this pandemic.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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