CASE REPORT

COVID-19-associated Pulmonary Cryptococcosis: A Rare Case Presentation

Smita Sharma[1], Gyanendra Agrawal[2], Suryasnata Das[3]

Abstract

Multiple case reports and case series report a surge in opportunistic infections like aspergillosis, mucormycosis, and reactivation of cytomegalovirus infection in coronavirus disease-2019 (COVID-19) patients. We hereby report the first case to the best of our knowledge of pulmonary cryptococcosis in a patient who had successfully recovered from severe COVID-19 illness. The pulmonary cryptococcosis spectrum ranges from asymptomatic infection to frank acute respiratory distress syndrome leading to respiratory failure. Pulmonary cryptococcosis is often underdiagnosed because its clinical presentation, radiographic features, and serologic laboratory investigations are generally inconclusive. The saprophytic colonization of fungus as opposed to invasive disease cannot be assessed from either culture of sputum or currently available serologic tests. Pulmonary cryptococcosis close association with COVID-19 can be further established with reporting of more cases. Hereby, we propose the term CAPC (COVID-19-associated pulmonary cryptococcosis) for such cases.

Keywords: Corticosteroids, COVID-19, Pulmonary cryptococcosis, Uncontrolled diabetes mellitus.

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Introduction

Coronavirus disease-2019 (COVID-19) and its complications have challenged the human race and medical science as never before. The opportunistic infections have increased in immunocompetent COVID-19 patients.[1–3] *Cryptococcus* is encapsulated yeasts also known as Torula histolytica or European blastomycosis. The two main pathogenic cryptococcal species are *Cryptococcus neoformans* and *Cryptococcus gattii* with worldwide distribution. *C. neoformans* is commonly found in the soil and bird droppings (particularly pigeon droppings) whereas *C. gattii* is found in vegetation, such as eucalyptus trees. The portal of entry is usually via inhalation into the respiratory tract which is also a common site of disease. The disease may spread to blood causing cryptococcemia and to central nervous system (CNS) causing meningoencephalitis. Pulmonary cryptococcosis can mimic lung cancer, pulmonary metastases, pulmonary tuberculosis, bacterial pneumonia, and other pulmonary mycoses both clinically and radiologically.[4]

Case Description

A 60-year-old man with a previous history of essential hypertension, poorly controlled diabetes mellitus, and primary hypothyroidism was admitted to our medical facility with chief complaints of fever, intractable dry cough, worsening dyspnea, and headache for 4–5 days. The patient completely recovered from severe COVID-19 illness 2 months back when he required high flow oxygen therapy for about 11 days and was treated with high doses of intravenous corticosteroids, remdesivir, and therapeutic anticoagulation. All relevant blood investigations and high-resolution computed tomography (HRCT) chest were done. HRCT chest showed a focal well-defined air space consolidation in the anterior segment of the right upper lobe (Fig. 1A). CT-guided transthoracic trucut biopsy of the lung lesion was done for definitive diagnosis by an interventional radiologist. Histopathology of the biopsy revealed granulomas with encapsulated rounded yeast forms, morphologically suggestive of cryptococcal infection (Fig. 2). In view of the evidence of invasive mycosis and the presence of hypoxemia, the patient was started on a broad-spectrum antifungal regimen of liposomal amphotericin (5 mg/kg/day). Magnetic resonance imaging of the brain, orbit, and paranasal sinuses was done to look for invasive fungal infections at other sites. Detailed investigations of cerebrospinal fluid (CSF) were also done which ruled out CNS cryptococcosis. Blood and urine culture grew no bacteria or fungus. Later, the biopsy specimen culture grew *C. neoformans* sensitive to amphotericin and fluconazole (Fig. 3). The patient was managed with liposomal amphotericin for 14 days, oxygen therapy, and other supportive treatment. HRCT chest done after 14 days showed resolution of the focal lesion to some extent along with bilateral pleural effusion, more on the right side compared to the left side (Fig. 1B). In view of hypoxemia and respiratory distress, pigtail drainage of right-sided pleural effusion was done. The pleural fluid was exudative with lymphocytic predominance and the cultures were negative for bacteria and fungus. The patient's respiratory symptoms and hypoxemia subsequently improved with the

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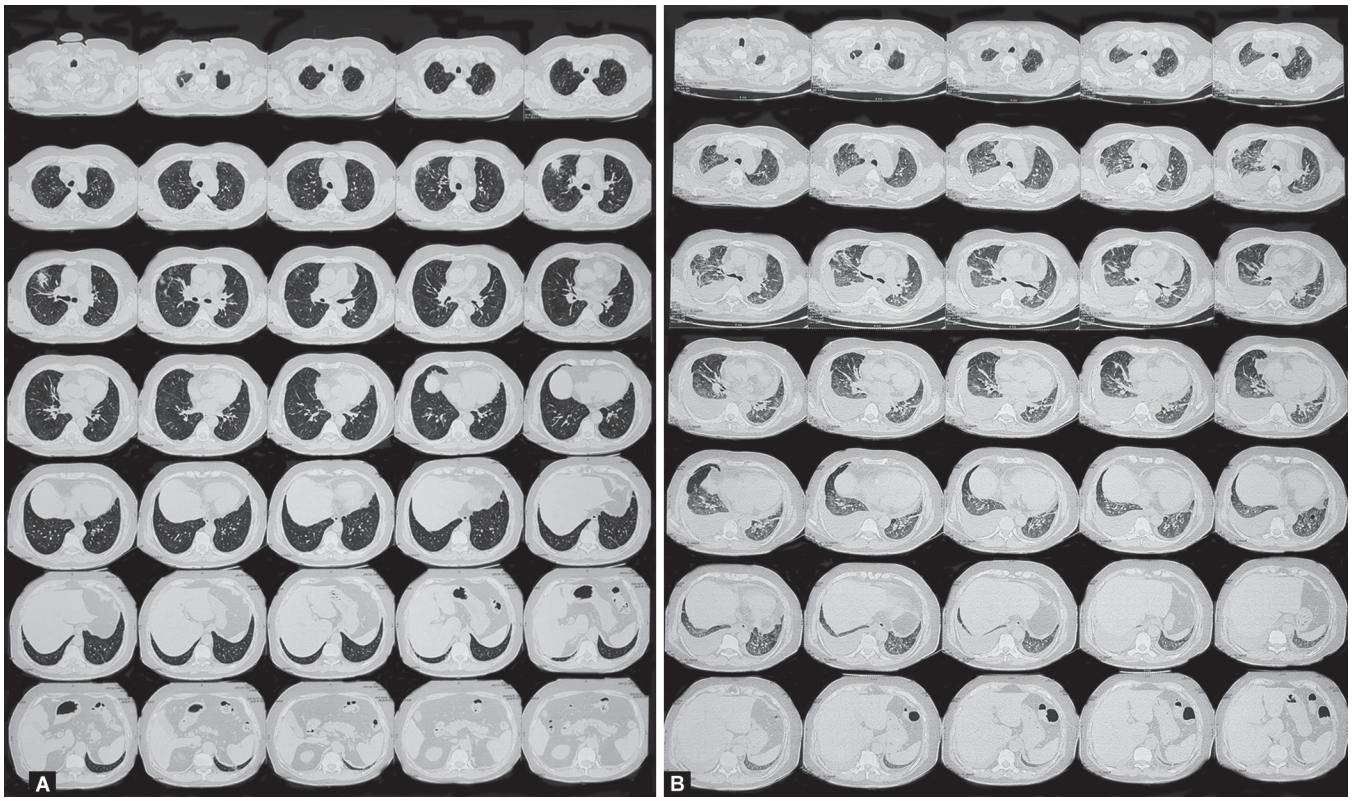
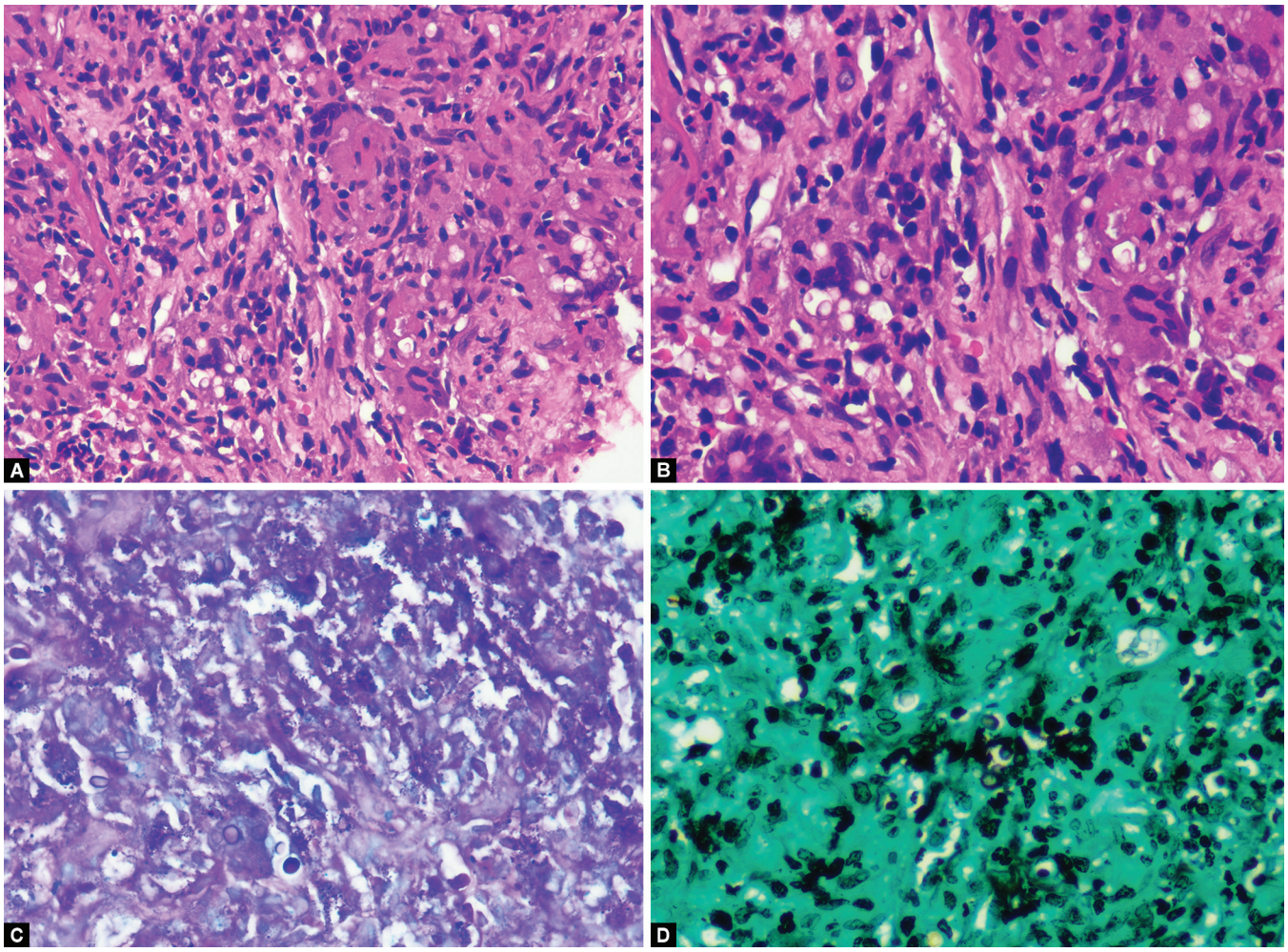


Figs 1A and B: (A) HRCT showing a focal well-defined air space consolidation in the anterior segment of the right upper lobe with surrounding ill-defined ground glassing with interlobular septal thickening; (B) HRCT shows irregular peripheral area of air space consolidation in the anterior segment of the right upper lobe with bilateral pleural effusion (more on the right side compared to the left side)

therapeutic drainage of pleural fluid and diuretics. The patient was discharged normoxemic on the maintenance therapy of oral fluconazole 400 mg per day.

Discussion

The cases of pulmonary cryptococcosis are emerging more rapidly in the immunocompetent hosts nowadays. The main predisposing factors for pulmonary cryptococcosis in immunocompetent hosts are uncontrolled diabetes mellitus, prolonged use of high dose corticosteroids, and use of immunosuppressive drugs, cirrhosis, and malignancy.[4,5] The patient in the present case study is a symptomatic immunocompetent host with risk factors of poorly controlled diabetes and the use of steroids during COVID-19 treatment. The presenting cardinal chest symptoms are cough, worsening dyspnea, chest tightness, and nonspecific symptoms are fever, weight loss, night sweats in adults. Lung tissue biopsies in symptomatic patients by either transthoracic or transbronchial route and histopathological examination along with culture studies are the confirmatory tests for pulmonary cryptococcosis. In the present case study, lung biopsy showed granulomas with encapsulated yeast, morphologically consistent with *Cryptococcus* genus which was later confirmed when the biopsy specimen culture grew *C. neoformans* which was sensitive to amphotericin and fluconazole. The culture of respiratory samples (sputum/brochoalveolar lavage (BAL)) for *Cryptococcus* is neither very sensitive nor specific for invasive infection.[4] Cryptococcal antigen in serum is rarely positive unless the disease is disseminated in pulmonary cryptococcosis. Cryptococcal antigen has not been standardized for respiratory specimens such as sputum, BAL, or even pleural fluid.[4] *Cryptococcus* cell wall has a thick capsule with less (1 → 3)β-D-glycan thereby test is usually negative or only weakly positive.[4] In pulmonary cryptococcosis, usually encountered radiological patterns are: (1) one or more spherical nodules or masses; (2) one or more areas of patchy consolidation; (3) multiple small nodules or irregular shadows. Hilar or mediastinal adenopathy or pleural effusions may accompany any of these patterns.[6] In immunocompetent patients like the present case, the most common presentation is solitary and well-defined nodule or patch of consolidation. Pleural effusions are relatively rare in pulmonary cryptococcosis. CNS involvement needs to be conclusively ruled out by detailed CSF studies and neuroimaging. The management protocol depends on the immune status of the host, the severity of the infection, and the existence of extrapulmonary involvement. This patient was hypoxemic and there was histopathological evidence of invasive mycosis suggestive of cryptococcal infection thereby he was treated with liposomal amphotericin (5 mg/kg per day) for 2 weeks as induction therapy. The consolidation phase of treatment is being given with fluconazole 400 mg (6 mg/kg) per day orally. We plan to give fluconazole for 6–12 months depending upon the clinicoradiological response, as per Infectious Diseases



Figs 2A to D: (A) H&E stained histological section (400 × magnification) shows ill-forming epithelioid granuloma with occasional multinucleated giant cells and surrounded by lymphocytes, histiocytes, and plasma cells; (B) H&E stained histological section (600 × magnification) shows a few pale refractile ovoid fungal spores of *Cryptococcus* species engulfed by giant cells within the granuloma; (C) Periodic acid–Schiff (PAS) stained histological section (600 × magnification) highlights the faint purplish to pinkish stained ovoid fungal spores of *Cryptococcus* species engulfed by giant cells within the granuloma; (D) Grocott-Gomori's methamine silver (GMS) stained histological section (600 × magnification) stains the ovoid fungal spores of *Cryptococcus* species as glassy gray against the dark gray to the black stained inflammatory cell background

Society of America guidelines.[7] The alternatives to fluconazole treatment are itraconazole, voriconazole, or posaconazole.[7] Surgery should be considered for either diagnosis or for persistent radiographic abnormalities and symptoms not responding to antifungal therapy.[7]

Conclusion

This case report and review of literature highlight that risk factors for opportunistic infections like pulmonary cryptococcosis, CAM (COVID-associated mucormycosis), CAPA (COVID-associated pulmonary aspergillosis) in COVID-19 patients are uncontrolled diabetes mellitus, severe COVID-19 illness, severe hypoxemia requiring high flow oxygen or mechanical ventilation, the development of cytokine storms, indiscriminate use of corticosteroids and antimicrobials and the use of immunomodulatory drugs like tocilizumab.[8–11] A high index of suspicion in the post-COVID-19 period can lead to early diagnosis and can change the overall prognosis of the disease. Severe acute respiratory syndrome coronavirus 2 infections in itself can cause immunosuppression by altering T-cell response in several ways.[12–14]

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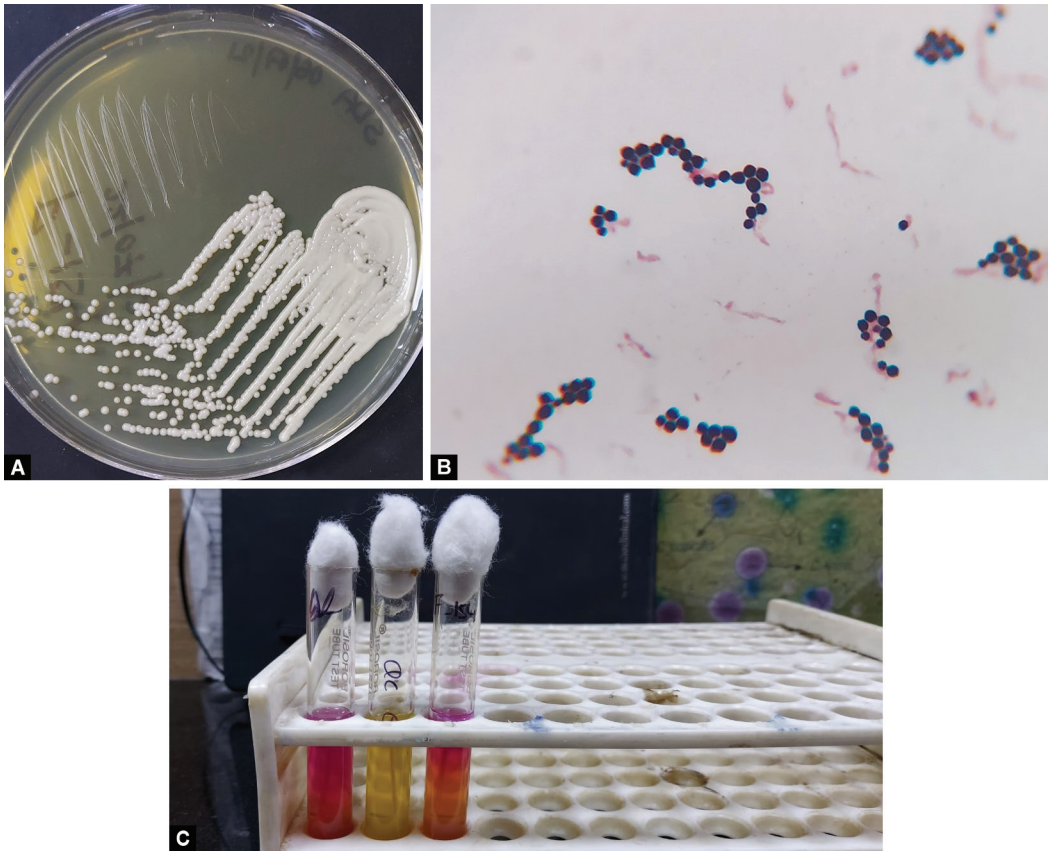

Figs 3A to C: (A) Sabouraud's dextrose agar media plate shows a mucoid creamy white colony of *C. neoformans*; (B) Gram's stain (400 × magnification) on growth from Sabouraud's dextrose agar (SDA) media plate shows gram-positive spherical yeast cells with budding, of *C. neoformans*; (C) Tube 1, positive control for urease test; tube 2, negative control for urease test; tube 3, positive urease test for *C. neoformans* (from left to right)

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