Case Report

Pulmonary Fungal Infections in Diabetic Postcoronavirus Disease 2019 Patients - A Report of Three Cases

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Abstract

This article aims to present the spectrum of pulmonary fungal infections observed in postcoronavirus disease 2019 (COVID-19) diabetic patients. In this case series, three post-COVID-19 diabetic patients with poor glycemic control were diagnosed with pulmonary mucormycosis, invasive candidiasis, and pulmonary aspergillosis, respectively. The patients were subjected to clinical, radiological evaluation, including bronchoscopy. The etiologic agents were isolated in these cases and identified by biopsy and subsequent histopathological confirmation. A high index of suspicion, early use of appropriate diagnostic methods aided with suitable antifungal agents, and control of risk factors such as diabetes mellitus are the main factors governing the successful management of fungal infections in post-COVID-19 immune-suppressed patients, presenting with worsening respiratory symptoms.

Keywords: Bronchoalveolar lavage, coronavirus disease 2019, coronavirus disease 2019-associated pulmonary aspergillosis, diabetes mellitus, invasive candidiasis, mucormycosis

Introduction

Coronavirus disease 2019 (COVID-19) primarily affects the lungs causing pneumonia, but many other organ systems including cardiovascular, nervous, digestive, and immune systems can be affected. As per the recent reports, about 7.2% of COVID-19 patients get predisposed to several coinfections and superinfections, owing to the immune alterations and the high-dose corticosteroids used to treat severe cases, adding to the disease severity and difficulty in the diagnosis, treatment, and prognosis.[1]

In diabetic patients with poor glycemic control, several alterations occur in cell-mediated immunity, such as in chemotaxis, phagocytosis, cytokine secretion, and reduced activity of natural killer cells, paving the way for secondary fungal infections. The main fungal pathogens responsible for coinfection in people with COVID-19 are *Aspergillus* and *Candida*.

Pulmonary mucormycosis is a rare and severe, invasive fungal infection. It occurs mostly in immunocompromised patients, especially in uncontrolled diabetes mellitus or hematological malignancies, neutropenic patients as well as patients with elevated serum iron levels and in previously healthy subjects with open wound contamination.[2] Pulmonary mucormycosis is the second most common presentation of *Mucor* in diabetic patients after rhinocerebral form. Such cases undergo rapid clinical progression and are difficult to diagnose early, and there is lack of effective treatment.[3]

Wider usages of antibiotics, steroids, and the insult by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection cause the commensal *Candida* to invade internal organs. The hematogenous spread of *Candida* is responsible for the pulmonary infection. The various predisposing factors include immunosuppression, neutropenia, sepsis, prolonged antibiotics, and total parenteral nutrition.[4] Invasive candidiasis is associated with high mortality rates of 15%–25%.[5] Thus, a high index of suspicion is required in post-COVID-19 patients with comorbidities and worsening symptoms.

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There has been a recent rise in COVID-19-associated pulmonary aspergillosis (CAPA) in predisposed patients with weak immune responses. Invasive aspergillosis is a well-described complication, reported in severe viral pneumonias.[6] The diagnosis in these patients is often difficult, owing to the nonspecific symptoms and the requirement of invasive testing. Pulmonary aspergillosis in post-COVID-19 cases is a serious complication. It may not respond well to the medical management, making pulmonary resection the last and effective option for disease control.

The aim of this case series is to reflect the secondary pulmonary fungal infections occurring in post-COVID-19 patients with uncontrolled diabetes, as well as to demonstrate the importance of early diagnostic interventions for achieving better outcomes in such cases.

Case Reports

Case 1

A 57-year-old diabetic female came with chief complaints of dry cough, fever, and chest pain for 10 days. Chest pain was dull aching, aggravated on coughing and deep inspiration. She had recovered from COVID-19 4 weeks ago. She was on oral hypoglycemic agents for the last 10 years.

On examination, she was alert, conscious, with pulse rate 84/min, blood pressure 130/84 mmHg, respiratory rate 18/min, temperature 99.6°F, and oxygen saturation 97% on room air. On auscultation, crepitations were present in the left infraclavicular region.

On laboratory evaluation, hemoglobin was 10.9 g/dL, total leukocyte count (TLC) 14,890/mm^3, and glycosylated hemoglobin 9.1%. Liver and renal function tests were within normal limits. Sputum for acid-fast bacilli (AFB), Gram staining, and culture sensitivity was negative. Sputum for fungus revealed the growth of *Rhizopus*.

On chest X-ray, an inhomogeneous opacity was noted in the left upper and middle zone. Contrast-enhanced computed tomography (CECT) scan of the chest was performed, which showed areas of interseptal thickening and ground-glass haze, giving crazy-paving appearance. Areas of airspace consolidation with few atelectatic bands were present in the left upper lobe [Figure 1].

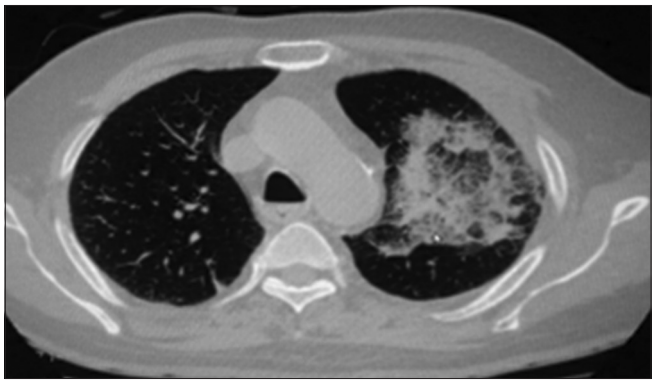

Figure 1: Contrast-enhanced computed tomography chest showed areas of interstitial septal thickening with ground-glass haze and air space consolidation. Few atelectatic bands seen in the left upper lobe

With the worsening of the symptoms, the patient was subjected to flexible bronchoscopy and subsequent biopsy. Bronchoscopy revealed a normal endobronchial examination, but the gross specimen from transbronchial biopsies obtained from the left upper lobe revealed several black tissue fragments. Histopathological analysis of left upper lobe bronchoalveolar lavage (BAL) and transbronchial biopsies revealed aseptate fungal hyphae with right-angled, irregular branching pattern, morphologically suggestive of *Mucor* [Figure 2]. Cultures were positive for a *Rhizopus* species. She was then initiated on intravenous (IV) amphotericin B 0.7 mg/kg once daily dose.

On the 10th day, she developed headache, facial pain, and chemosis in the right eye. On examination, right eye swelling and restricted ocular movements, along with nasal crusting and obstruction on the right side, were noted. X-ray of the paranasal sinus revealed haziness in the right maxillary sinus. Noncontrast computed tomography of the paranasal sinuses showed circumferential mucosal thickening with interspersed hyperdensities in the right maxillary sinus. KOH mount and culture of the nasopharyngeal swab scraping demonstrated the *Rhizopus*, broad aseptate fungal hyphae.

The treatment was started on empirical broad-spectrum antifungal therapy using high-dose liposomal amphotericin B 5 mg/kg/day for 21 days, with posaconazole 300 mg per day added as a combination therapy. Ten days after the treatment initiation, she was referred for surgical debridement. She recovered with minimal residual deformity.

Case 2

A 60-year-old male presented with complaints of breathlessness, fever, and progressively worsening cough for 20 days. He was

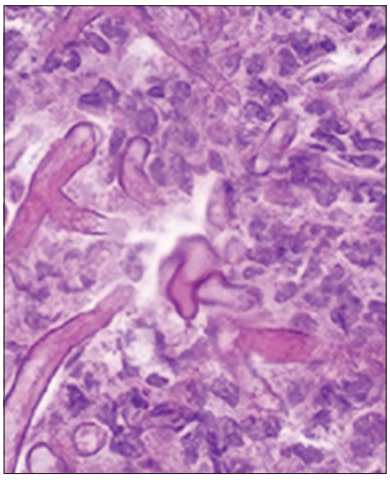

Figure 2: Microscopic evaluation of the tissue specimen showed filamentous nonseptate branching fungal hyphae suggestive of mucormycosis (H and E staining, magnification ×40)

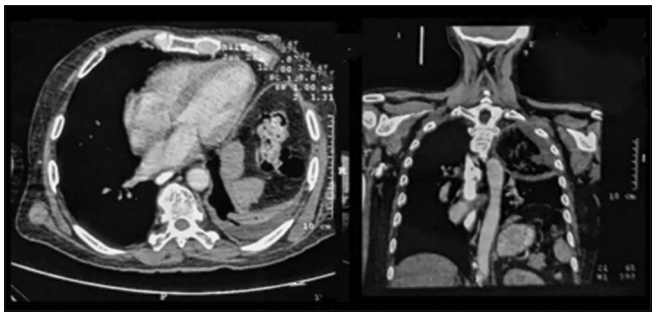

Figure 3: Contrast-enhanced computed tomography chest showing areas of consolidation with cavitation and surrounding ground-glass opacities along with inter- and intralobular septal thickening with crazy-paving appearance in the left upper lobe

a known case of type 2 diabetes mellitus for the past 25 years, with poor glycemic control. There was no previous history of tuberculosis. He recovered from COVID-19 pneumonia about 4 weeks before the onset of these complaints.

On examination, he was pale and febrile 101.2°F with 95% oxygen saturation on room air. There were basilar crackles on the left side of the chest on auscultation. Heart sounds were normal. Maxillofacial, nasal, and ocular examinations were normal.

The initial laboratory evaluation results were hemoglobin 8.9 g/dl, TLC 13,900/mm^3, and glycosylated hemoglobin 11.2%. Renal and liver function tests were within normal limits. Mantoux test was nonreactive. Sputum examination for AFB was negative. Sputum sample sent for CBNAAT testing did not detect *Mycobacterium tuberculosis*. Subsequent samples of sputum and blood were sent for culture, which revealed the growth of *Candida* spp.

On CECT chest, consolidation was present along with cavitation, surrounding ground-glass opacities (GGO) and thickening of inter- and intralobular septa in the left upper lobe, and focal invasion of the left subclavian artery [Figure 3].

Flexible bronchoscopy with BAL was performed next, which revealed whitish exudates, in the form of diffuse white plaques, in the sites starting from the vocal cords and covering the bronchial systems. Culture of the tissue obtained during the transbronchial biopsy of the left upper lobe revealed the growth of *Candida zeylanoides* [Figure 4].

He was started on IV fluconazole therapy 400 mg per day. After 4 weeks of therapy, a sufficient clinical response was observed. Subsequent blood cultures, performed after 6 weeks of fluconazole therapy, tested negative for fungus. The patient was followed up on regular intervals.

Case 3

A 44-year-old male presented with chief complaints of shortness of breath, hemoptysis, cough, and fever of 3-week duration. He recovered from COVID-19 pneumonia about 4 weeks before the onset of these complaints. He was a known

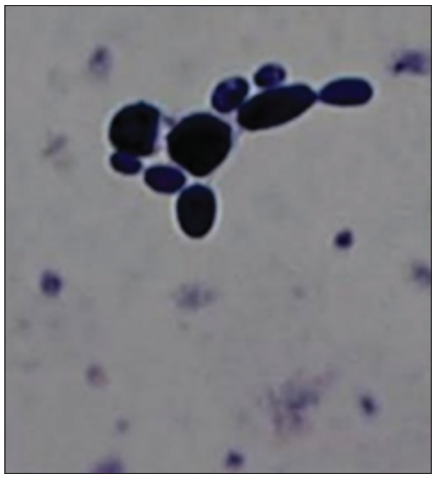

Figure 4: Gram stain of bronchoalveolar lavage showing budding yeast cells, suggestive of *Candida* spp. (Gram stain, ×100)

case of type 2 DM for 2 years, with a history of irregular intake of oral hypoglycemic agents.

He was alert, conscious, and cooperative. He was pale and had a heart rate of 86/min, blood pressure of 109/72 mmHg, respiratory rate of 16/min, temperature of 98.2°F, and oxygen saturation of 94% on room air. On auscultation, decreased air entry in bilateral upper zones was noted. Nasal and ocular examinations were normal.

On investigations, hemoglobin was 9.2 g/dl, TLC 15,800/mm^3, erythrocyte sedimentation rate 48 mm/h, and glycosylated hemoglobin 12.8%. Sputum samples sent for AFB testing were negative. Sputum examination for fungus, Gram stain, and culture sensitivity was negative. Mantoux test was nonreactive.

Chest X-ray showed bilateral areas of cavitation in the upper and lower zones. An X-ray of the paranasal sinus was performed, which revealed normal findings. CECT chest revealed multifocal areas of cavitation involving bilateral upper and lower lobes, along with fungal balls in bilateral upper lobe cavities, showing air-crescent sign [Figure 5].

He underwent flexible bronchoscopy with subsequent transbronchial biopsy and BAL analysis. Video bronchoscopy showed no abnormalities in the tracheobronchial tree, and further tests of BAL were negative. Bronchial tissue biopsy obtained from the right upper lobe showed inflammatory signs and microscopic examination of the histopathological specimen revealed dichotomous branching hyphae with frequent septation, confirming the presence of *Aspergillus* spp. on PAS stain [Figure 6].

He was started on broad-spectrum antifungal therapy (IV voriconazole 6 mg/kg bd followed by 4 mg/kg bd). During the 14-day hospital stay, the patient improved clinically and maintained stable vital signs. Two weeks after discharge, the patient deteriorated, presented with persistent hemoptysis, was referred for surgical intervention, and improved significantly thereafter.

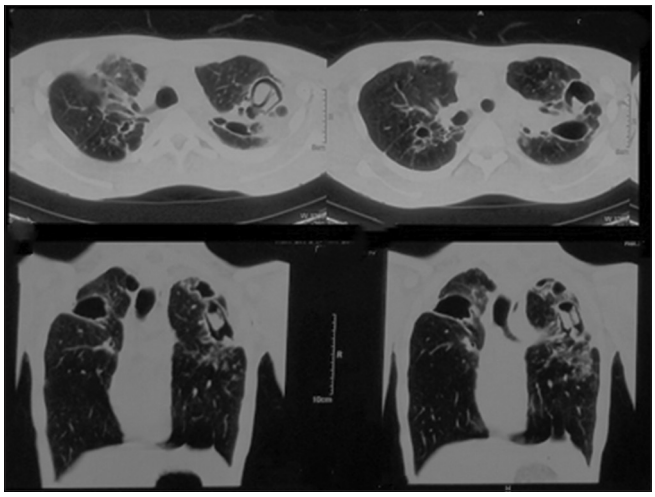

Figure 5: Contrast-enhanced computed tomography chest showing multifocal areas of cavitation involving bilateral upper and lower lobes of the lung with fungal balls seen in bilateral upper lobe cavities showing air-crescent sign

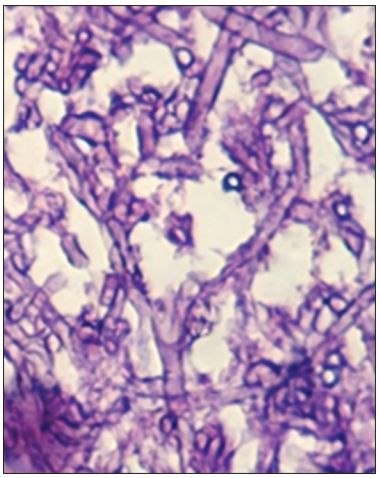

Figure 6: Microscopy illustrates typical dichotomous branching hyphae with frequent septation characteristic of *Aspergillus* (PAS stain, ×100 objective)

Discussion

COVID-19 is a very infectious disease, most prevalent in young adult and middle age group, with individuals having history of diabetes being more prone to contract the disease.[7] The acute clinical presentation of COVID-19 disease is mostly clear now. It is also known now that the disease may have sequelae affecting various systems.[8] Many opportunistic bacterial and fungal infections are seen in association with SARS-CoV-2. As per the study by Intra *et al*., among the COVID-19 patients, those who were admitted to intensive care unit have a higher probability (57% cases) of acquiring a secondary fungal or bacterial infection.[9] The increasing frequency of these infections has been attributed to host factors such as poorly controlled diabetes, use of corticosteroids in severe COVID-19 pneumonia, and anti-interleukin 6 therapy (tocilizumab) in hospitalized patients.[8]

Pulmonary mucormycosis is a life-threatening infection. The key causative agents for mucormycosis in humans include *Rhizopus*, *Absidia,* and *Cunninghamella*. *Rhizopus* species are the most common causative organisms. Sinuses, brain, and lungs are the frequently infected sites. Pulmonary mucormycosis may also invade mediastinum, pericardium, and the chest wall. The focal point in accelerating mucormycosis is uncontrolled blood sugar levels.[10] COVID-19-associated significant and sustained lymphopenia compromises the immune system. The major risk factors for invasive mucormycosis include long-term neutropenia, immune-altered state as in diabetes mellitus, stem cell or organ transplantation, IV drug use, malnutrition, and severe skin damages.[11] These patients usually present with nonspecific symptoms, such as dyspnea, chest pain, and fever. The radiological features in such cases are mostly nonspecific. Thus, diagnosis requires clinical suspicion and histopathological examination. The mainstay of treatment is amphotericin B, along with surgical resection of the involved areas of the lung and treatment of the underlying disease.

Wide usage of steroids, along with the insult by SARS-CoV-2 infection, can result in commensal *Candida* to become invasive candidiasis. *Candida* pneumonia is rare and occurs after hematologic spread from other body sites, such as the skin, gastrointestinal tract, and genitourinary tract. There are three histologic forms of pulmonary candidiasis: embolic, disseminated, and bronchopulmonary. For reliable diagnosis of bronchopulmonary and disseminated *Candida* infection, BAL, cultures along with morphologic and cytologic analyses, in conjunction with histopathology (the gold standard) are to be performed. Delay in the therapy initiation adds on to the increased mortality and morbidity.

Aspergillosis, caused by *Aspergillus fumigatus,* is a common fungal infection that causes secondary pulmonary infection in patients who are severely immunocompromised.[12] As per the recent studies, aspergillosis occurs in about 20%–30% of severely ill COVID-19 patients, owing to the association between COVID-19 and pulmonary fungal infections. This is denoted as CAPA.[13] The risk factors for CAPA include diabetes, immunosuppressive drugs, previous exposure to anti-interleukin-6 treatment, and corticosteroids.[14] When the immunity is impaired, harmless inhabitation of the airways by *Aspergillus* can occur. In cases of CAPA, the diagnosis is challenging since serum *Aspergillus* galactomannan enzyme immunoassay is usually negative, limiting the reliability of serum-based diagnosis. On imaging, the lung invasion varies from early inflammation of airways to airway necrosis and cavitary lesions.[15] CAPA management is challenging and controversial, owing to antifungal resistance characteristics, limiting possible medical treatment options.[16] Some studies suggest that the early use of antifungals may improve clinical outcomes.[15]

In COVID-19 patients, these opportunistic fungal infections can significantly increase mortality and morbidity, thus requiring prevention and early management.

Conclusion

There has been a sharp rise in incidence of life-threatening mycotic infections in immune-altered post-COVID-19 patients. The clinical presentation and diagnosis in such cases is complex. A high index of suspicion is required since the patient survival is dependent on an early diagnosis. Early detection, appropriate antifungal agents, and management of risk factors are important for management of these life-threatening mycotic infections in post-COVID-19 patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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