Medical Case Reports Journal

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Pulmonary Cavitation Due to Mixed Fungal Infections in Moderate to Severe COVID-19 Survivors: Case Series

Arjun Kumar[1], Rahul Gupta[1], Suyash Singh Rathore[1], Ayushi Sahu[2], Akhlesh[1], Manju Bala[1]and Avishek Layek[1]*

[1]Department of Pulmonary, Sleep and Critical Care Medicine, All India Institute of Medical Sciences Rishikesh, Uttarakhand, India
[2]Department of Anesthesiology, All India Institute of Medical Sciences Rishikesh, Uttarakhand, India

Article info

Received 30 July 2021
Revised 26 August 2021
Available Online 05 Sept 2021

*Corresponding author: Dr. Arjun Kumar, Senior Resident, Department of Pulmonary, Sleep and Critical Care Medicine, All India Institute of Medical Sciences Rishikesh, Uttarakhand, India.

Abstract

Recently several post corona viral infection disease-19 (COVID-19) complications have been reported. The recent emergence of the pulmonary cavities due to multiple etiology have been seen in COVID-19 disease. However, associated fungal superinfection such as aspergillosis, mucormycosis and candidiasis especially among critically ill patients, treated with steroids are one of the common causes of morbidity and mortality in post COVID-19 survivors. Here we presented the case series of three patients with mixed pulmonary fungal infections who were cured COVID-19 infection.

Keywords: COVID-19; Fungal infections; Cavitation; Mucor mycosis; Aspergillosis

Introduction

The coronavirus disease 2019 (COVID-19) is a viral pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In India alone up to 9000 cases of invasive mucormycosis popularly known as black fungal infection in post COVID-19 patients being reported in various studies and numbers are continuously rising [1-3]. Both Mucormycosis and Aspergillosis are rare fungal infections, mainly affecting immunocompromised human hosts and despite surgical debridement and antifungal therapy, both of these are life-threatening fungal infections with mortality rates over 50% [4,5]. Rhizopus arrhizus and Aspergillus fumigatus are responsible for up to 70% of all cases of mucormycosis and invasive pulmonary aspergillosis in adults [4,6]. The diagnosis of proven invasive aspergillosis is made by the combination of host status and imaging and mycological findings of combined microscopic, culture and biopsy showing angioinvasion [7]. The optimal treatment of aspergillosis and mucormycosis are administration of voriconazole or isavuconazole and liposomal amphotericin B respectively [5,8]. We report the first case series of three patients with mixed up pulmonary fungal infections in patients who recovered from the initial phase of COVID-19 infection.

Case 1

A 42-year-old male was presented to the emergency department (ED) with increased respiratory distress, cough with yellow expectations and high-grade fever for one week. The patient was alert and responding well to commands, and he had history COVID-19 pneumonia one month back with 40 % of chest involvement on CT-scan and was managed successfully and discharged to home. He was diagnosed diabetes mellitus one month back. He conscious oriented, heart rate of 110 beats per minute, respiratory rate of 26 breaths per minute, oxygen saturation of 92% on room air, and blood pressure of 110/ 72 mmHg. On examination, he was ill, and tachypnoea and rest of

systematic examinations were unremarkable. Initial routine laboratory studies revealed a white blood cell count of 17× 103 cells/um3, HgA1c of 7.9% and renal and liver function tests were normal. Nasopharyngeal swab polymerase chain reaction (PCR) test was twice negative for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). A portable chest radiograph (CXR) showed patchy left upper zone cavities with sarunding infiltrates. Computed tomography (CT) with pulmonary angiograms for the chest was done in view of suspected associated pulmonary embolism revealed left upper lobe multiple cavities with post Covid-19 sequelae changes (Figure 1A).

His sputum examination was negative for tuberculosis but found to be positive for Klebsiella pneumoniae sensitive to piperacillin and tazobactam and potassium hydroxide (KOH) mount showed a budding yeast cell with pseudo hyphae. The patient was treated with intravenous (IV) piperacillin and tazobactam 4.5 g 6 hourly and Oral tablet azithromycin 500 mg once daily along with IV subcutaneous human insulin for glycemic control. However, patients continue to develop high grade fever with chills daily and all fever work up including dengue, malaria, blood, urine culture were negative. Patient underwent fiberoptic bronchoscopy (FOB) for further investigation and bronco alveolar lavage was taken from left upper bronchial segments and which was came to be positive for Pseudomonas aeruginosa sensitive to vancomycin and KOH mount microscopy showed hyaline septate hyphae and characteristic conidial heads of the BAL specimen. The Aspergillus galactomannan assays of serum (4.2), and of the BAL fluid (2.6) were positive. On 5-day he was admitted to the ICU due to increased respiratory distress and oxygen requirement and for closer respiratory monitoring and IV vancomycin 1250 mg every 8 hours and IV voriconazole 200 mg 12 hourly were initiated along with oxygen and other supportive therapy. On day 8th, his respiratory status deteriorated further and not able to tolerate non-invasive ventilation (NIV) and was intubated due to hypoxic respiratory failure. On day 10, the patient continued to have fevers and decreased urine output and required vasopressor support with norepinephrine along with crystalloid therapy. On day +14, the BAL culture grew fungus which was suggestive of Aspergillus species.

Bedside ultrasound guided percutaneous biopsy from left upper lobe lesion was done and sample sent for culture and histology in view of no clinical and radiological worsening on repeat chest CT scan (Figure 1B) on day 16. His KOH mount microscopy showed pauciseptate broad hyphae suggesting Mucor mycosis hence antifungal treatment was changed to IV L-AmB 400 mg daily for suspected pulmonary Mucor mycosis and an additional specimen was sent for identification. Unfortunately, the patient died on day 29 and day 26, *Rhizopus arrhizus* was identified on lung biopsy culture susceptibility tests were performed.

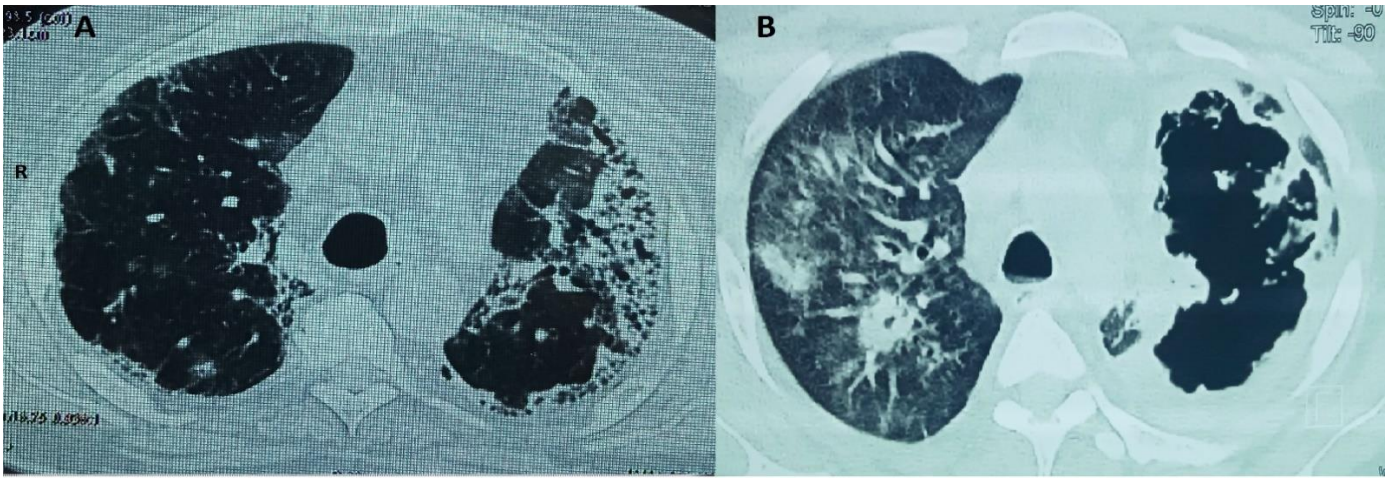

Figure 1: Axial CT scan for the chest (A) showing left upper lobe multiple cavities with post Covid-19 sequelae changes. (B) Radiological worsening on repeat chest CT scan was seen on day 16 of admission.

Case 2

A 50-year-old female presented to ED with dyspnea, dry cough, fever with rigor for 15 days of duration. She was treated for COVID-19 two weeks before this complaint, with 30% of chest involvement on computed tomography scan (CT-scan). She was diagnosed with a case of diabetes mellitus 2 years ago and underwent cholecystectomy for gallstones 1 year back. Nasopharyngeal swab polymerase chain reaction (PCR) test was negative for SARS-CoV-2. She denied any past history of tuberculosis and prolonged immunosuppressive treatment. On examination the patient was conscious oriented, pale with increased respiratory rate (24/min) rest vitals were unremarkable. Her oxygen saturation was 84% on room air.

Baseline complete blood count (CBC) were normal except anemia (Hemoglobin 8.1 g/dl) and high white blood cells (14 × 106 cells/cm2), HbA1c 7.4%. Her chest X-Ray showed ill-defined round cavity lesions involving the right upper zone. CT scan showed right upper lobe consolidation with cavitary lesions (Figure 2A). As the patient was unable to expectorate sputum FOB was done for further diagnostic evaluation and bronchoscopy findings were normal. Her BAL fluid KOH microscopy revealed features suggesting pulmonary aspergillosis and rest of the microscopy and molecular tests for tuberculosis were negative. Patient was not afforded for serum and BAL beta galactomannan and beta D glucagon tests.

On Day 3 her oxygen requirement increased to 8 litre/min from 2 litres of nasal prongs, and the patient was administered broad spectrum antifungal (IV voriconazole 200 mg 12 hourly) and antibiotics (IV Ceftriaxone 1 g 12 hourly) along with supportive therapy without clinical response. Due to further patient deterioration and decreasing oxygen saturation and persistent fever the patient was started on prophylactic low molecular weight heparin (LMWH) and pulmonary CT angiography was performed which came to be negative for any pulmonary embolism, but her chest cavity increased, and well-defined cavity developed as compared to previous chest CT (Figure 2B). Meanwhile her blood cultures showed growth of Candida albicans and she was started on caspofungin along with other therapy. She gradually showed clinical improvement and she completed the one-month course of anti-fungal treatment and her repeat blood cultures on 14th day was sterile and her repeat BAL fluid analysis was negative for any fungal and bacterial infections. She was discharged home and she has been on regular follow up with uneventful courses until now.

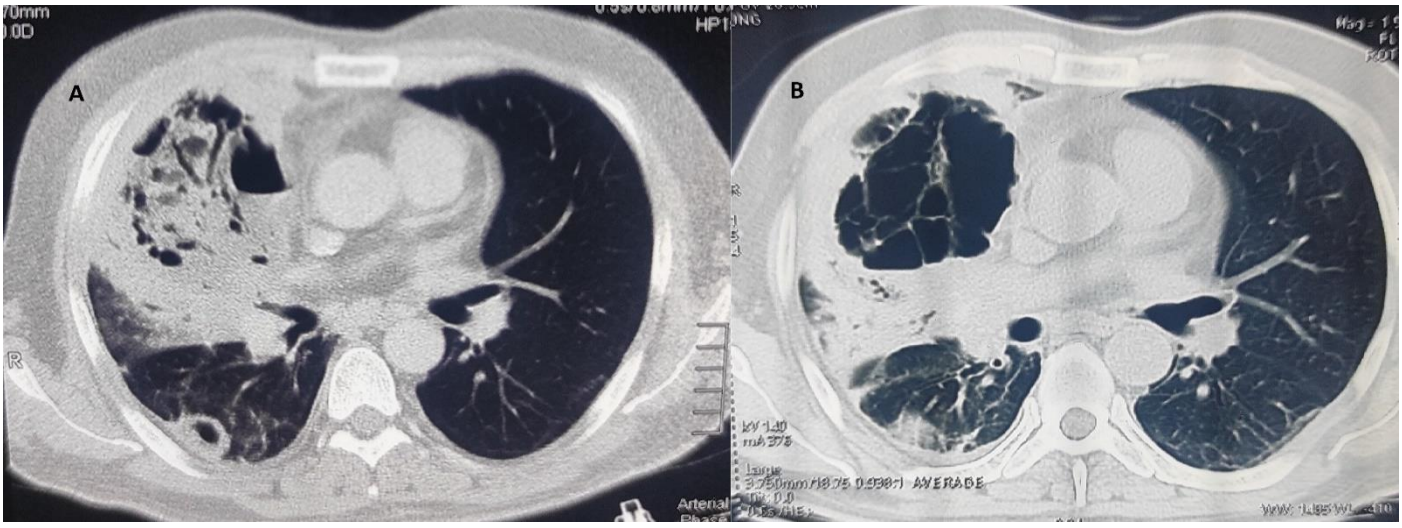

Figure 2: Axial chest CT scan shows (A) dense consolidation with cavity forming lesion involving the right upper lobe. (B) Repeat chest CT on day 12 showed increased chest cavity size and well-defined cavity developed as compared to previous chest CT.

Case 3

A 68-year-old male admitted with complaints of increased shortness of breath, left chest pain and blood-tinged sputum expectations for the past 14 days. He was recently treated for COVID-19 infection at an outside hospital with 12 days of oral corticosteroid and other symptomatic medication. He denied any other significant past medical history. He was recently diagnosed with type 2 diabetes mellitus. He is a chronic smoker and occasionally takes alcohol for the past 30 years. On chest auscultation the left infra scapular region air entry was diminished, and rest of systemic examination was normal. Her vitals showed tachycardia, tachypnoea and oxygen saturation of 84% on room air. Routine blood investigation was normal except raised WBC counts and fasting blood sugar levels. His chest radiograph showed left lower zone dense opacity. Contrast computed tomography (CECT) of thorax revealed the left lower lobe thick-walled cavity shown in the (Figure 3A). His sputum for bacterial, fungal, tuberculosis staining, and culture were negative and BAL fluid from the affected bronchial segment sent for further infective analysis. The KOH mount microscopy revealed septate hyphae suggesting aspergillosis and fungal culture was negative. Serum and BALF beta galactomannan and beta D glucan were normal. BALF was negative for mycobacterium tuberculosis and other bacterial organisms. The patient was started on IV voriconazole 200mg twice daily along with empirical antibiotics (IV piperacillin and tazobactam) along with oxygen therapy and other supportive treatment. In view of localized lung cavity, cardiovascular surgical opinion was sought for lobectomy, but patient refused for the same; hence patient was advised for close follow up to the outpatient department after 2 weeks of antifungal therapy or anytime if hemoptysis occurs. Patient showed clinical improvement after 10 days of antifungal therapy and was discharged home after explaining possible symptoms/ complications related to disease and advised for routine follow up. Patient again admitted with increased respiratory distress on day 14th of discharge in ED where he was intubated in view of severe type 1 respiratory failure. Chest CT showed worsening of pulmonary lesion with cavity formation along with area of consolidation surrounding ground glass opacity (reverse Halo sign) in left lower zone shown in figure 3B. CT guided percutaneous biopsy from left lower lobe lesion was performed which revealed mucormycosis on tissue culture and KOH mount microscopy. But the patient died on day 2 of possible readmission due to pulmonary embolism and or severe respiratory failure though we are not able to speculate the exact cause of death in this patient.

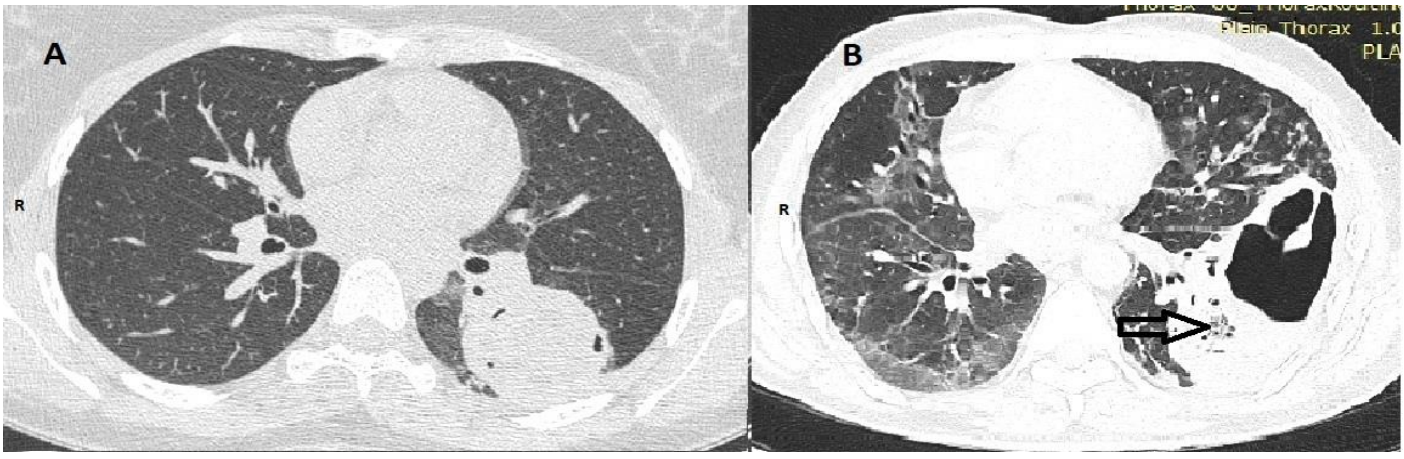

Figure 3: Axial CT scan of chest shows (A) left lower lobe thick-walled cavity (B) Chest CT showed worsening of pulmonary lesion with cavity formation along with area of consolidation surrounding ground glass opacity suggestive of reverse Halo sign (arrow) in left lower zone shown in figure 3B.

Discussion

Coronavirus belongs to the order Nidovirales, family Coronaviridae and subfamily Coronavirinae which is further divided into alpha, beta, gamma and delta coronaviruses based on phylogenetic clustering [9]. The COVID-19 patient commonly presents with fever, dry cough, fatigue and shortness of breath. However,

patients with moderate to severe COVID-19 pneumonia with multiple comorbidities can further develop fatal outcomes. Severe acute respiratory distress syndrome (ARDS), pulmonary fibrosis, pneumomediastinum, pneumothorax are common complications of severe COVID-19 pneumonia [10]. However, out of those who survived the initial phase COVID-19 pneumonia can present subsequently with pulmonary complications including thromboembolism, secondary bacterial and fungal pneumonia with lung cavitation's on chest CT image. Recently a retrospective study reported incidence chest cavitation in 1.7 % (12/689) of post total admitted patients of COVID-19 and 11% (12/110) of severe COVID-19 patients developed lung cavitation and 11% of those admitted to intensive care (ICU), 5 of 12 had solitary cavities with size ranging between 30-100 min diameter, all patients received tocilizumab and steroid during treatment, 6 out of 12 patients died and rest discharged home [11]. The risk factors for fungal infections include uncontrolled diabetes mellitus (50-70%), prolonged immunosuppressive therapy, steroid overuse, malignancy, chronic lung diseases, post solid organ transplants recipient and other possible causes are non-sterile practice in health care providers during patient care might be associated with cross infections between patients [12-15].

Only medication that has shown some benefit in the treatment of COVID-19 in clinical trials are corticosteroid and oxygen. Hence, overuse of high dose corticosteroid might be possible predisposing factor for invasive fungal infections due to reduced immunity in patients with severe COVID-19 pneumonia [16]. Most recent studies of COVID-19 fungal infections reported the development of fungal infections are usually after two weeks of the development of COVID-19 infection related symptoms [17]. All the cases in our study also were mostly presented after two to three weeks of symptom onset, suggesting late presentations of fungal superinfection. Serological assay such as beta Galactomannan can further add to diagnostic work up to early detection of inversive (angioinvasion beyond the airways) fungal infection especially invasive aspergillosis [18,19]. In our 1st case serum galactomannan was raised suggesting invasive aspergillosis. All of our cases showed pulmonary cavitation's on chest imaging and for further etiological work up we underwent chest CT scans so that early treatment can be initiated to prevent further fatal outcomes, but we lost two out of three patients due to rapid progression of disease. Hence, follow up chest imaging is important in post COVID-19 patients with persistent fever and respiratory symptoms. Most of the patients of COVID-19 pneumonia presents with dry cough and sputum examination for fungal infection usually does not reveal the invasive fungal organism due to high rate of upper airway fungal colonization [20]. Hence, we should go for upfront BAL whenever there is strong suspicion of invasive fungal infection with much delaying to early confirmation and identification exact organism causing fungal infections so that early treatment can be initiated to prevent morbidity and mortality associated with invasive fungal infections. Most of the invasive fungal pneumonia can be managed with selective antifungal therapy. Due to multiple comorbidities, antifungal resistance, limited treatment options, along with prolonged immune suppression in critically ill patients' management of fungal pneumonia is challenging [21].

In our two cases, though patients were started on antifungal therapy, but both the patient eventually scummed suggesting possibility of antifungal drug resistance along with other secondary bacterial infections might have changed the course of disease. Overall mortality rate of invasive fungal infection is 40% which may increase up to 80% in Mucor mycosis patients [22]. However, last resort is lobectomy whenever possible if single lobe is infected with other healthy lung parenchyma. In the current cases also 2 out of three patients died suggesting poor outcomes of disease. Hence, we have to work on prevention of COVID-19 disease probably mass vaccination is the answer to prevent current pandemic. Currently more than 16 vaccines are approved in different countries and new trials are also ongoing for making safe, effective vaccine [22].

In conclusion, pulmonary fungal infections are a serious complication of COVID-19 patients warranting high index of suspension and early diagnosis and treatment with appropriate antifungal therapy is key to prevent morbidity and mortality associated with it.

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This manuscript was peer-reviewed
Mode of Review: Single-blinded
Academic Editor: Dr. M.A. Jahangir