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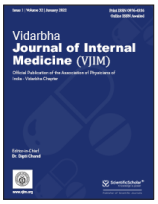

Case Report

Post-COVID Pulmonary Aspergillosis with Pulmonary Thromboembolism and Pulmonary Artery Hypertension Unmasking Prediabetes: A Case Report

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ABSTRACT

Multiple complications during and following COVID-19 infection are being reported worldwide. The most serious and life-threatening are thromboembolism and invasive fungal diseases. We report a post-COVID-19 case with complications of fungal infection of the lungs and pulmonary thromboembolism with pulmonary hypertension and unmasking prediabetes. A 53-year-old male patient presented with complaints of cough, fever, exertional breathlessness for 15 days, chest pain and hoarseness of voice for 7 days. He had a prior history of COVID 10 months earlier and no comorbidities. On further investigation by computed pulmonary tomography angiography, bronchoscopy and other investigations, the patient was found to have pulmonary thromboembolism, pulmonary aspergillosis and pulmonary artery hypertension. He was treated with amphotericin B for 21 days and anticoagulants for 6 months. He had significant clinical and radiological improvement with the resolution of the embolism. The crucial factors for successful care in post-COVID-19 immune-suppressed patients include a high index of suspicion, early use of adequate diagnostic tests helped by antifungal medications, anticoagulants and control of risk factors such as hyperglycaemia.

Keywords: Fungal, PAH, Pulmonary thrombosis, Hyperglycaemia, COVID-19

INTRODUCTION

Multiple complications during and following COVID-19 infection are being reported worldwide. The most serious and life-threatening are thromboembolism and invasive fungal diseases.

COVID-19 associated pulmonary aspergillosis (CAPA), invasive candidiasis and mucormycosis are the three most often documented fungal infections in COVID-19 patients.[1] In the past, it was thought that aspergillosis only occurred in immunosuppressed people. However, patients without immunosuppression who have severe respiratory viral infections, such as influenza or COVID-19, are being reported to have it.[1,2]

CAPA typically occurs in patients with severe COVID-19 (e.g., patients in ICUs, requiring ventilatory support). Due to its non-specific symptoms and the need for a deep lung sample for testing, it can be challenging to identify. It can cause severe morbidity and mortality.[3] A positive culture from a generally sterile place and histological evidence of infection is typically necessary for a conclusive diagnosis of aspergillosis. Radiology, detection of galactomannan antigen, detection of beta-D-glucan and polymerase chain reaction are other diagnostic techniques.[4] Antifungal medications such voriconazole, posaconazole and isavuconazole are used to treat CAPA. When utilising these antifungals in CAPA treatment, therapeutic drug monitoring should be considered.[5]

We report a post-COVID-19 case with complications of fungal infection of the lungs and pulmonary thromboembolism in a patient with no other known risk factors.

CASE REPORT

A 53-year-old labourer presented with complaints of cough with scanty white expectoration, fever and exertional breathlessness for 15 days. He also had chest pain and hoarseness of voice for 7 days.

The patient had no prior medical/surgical comorbidities. He had a history of COVID pneumonia in November 2020, when he was administered symptomatic treatment but did not require hospitalisation. There was no prior history of steroid

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intake. The patient gave a previous history of psychiatric disease, for which he was on medication irregularly. He was a tobacco chewer for 20 years.

On admission, he was thin-built with a body mass index of 16.5kg/m^2. Pulse rate was 138/min, blood pressure was 110/80 mm Hg and oxygen saturation on room air was 99%. Total leukocyte count on admission was 22,400/mm^3, haemoglobin was 8.4 g% and platelet count was 272,000/mm^3. Liver function tests and kidney function tests were within normal limits. The chest radiograph on 18 November 2021 [Figure 1] was suggestive of dense consolidation in the left middle zone and patchy consolidation in the left lower zone. Ultrasonography of the thorax revealed mild left and minimal right pleural effusion. The effusion was haemorrhagic, exudative and lymphocyte predominant, with an adenosine deaminase level of 27 IU/L, a glucose level of 258 mg% and a haematocrit of 17.8%. Sputum and pleural fluid samples were negative for acid–fast bacilli smear and nucleic acid amplification test for tuberculosis (TB). The patient was initiated on parenteral antimicrobial agents (piperacillin-tazobactam, amikacin, metronidazole, clindamycin, fluconazole and meropenem), but there was no clinical improvement. The patient required insulin therapy to control the transient hyperglycaemia, after which it was controlled. High-resolution computed tomography (HRCT) scan of the thorax on 29 November, 2021, revealed multiple bilateral pulmonary cavitatory lesions, more in the left upper lobe and patchy bilateral consolidation, more in the right upper lobe. The HRCT findings were suggestive of pneumonia. On 8 December, 2021, the patient developed left-sided hydropneumothorax, and a chest drain was inserted. The course of hospitalisation was, further, complicated by the development of subcutaneous emphysema as evident on chest radiograph of 26 December 2021 [Figure 1].

Bronchoscopy was done twice on 1 December, 2021 and 31 December, 2021, and bronchial washing samples were sent for investigations for TB, bacteriological profile (gram stain and culture) and cytology for any possible malignant cells. All these investigations yielded negative results. However, the bronchial washing sample for cell block (histopathology) showed inflammatory exudate on proteinaceous background with acute branching hyphae suggestive of fungal infection-aspergillosis [Figure 2].

Bronchial washing galactomannan was negative. With a pulmonary aspergillosis diagnosis, the patient was started on parenteral voriconazole. However, as he developed a life-threatening allergic reaction to voriconazole (fall in saturation with chills and rigors), he was switched to parenteral amphotericin B (0.7 mg/kg) therapy for 21 days. On 19 January, 2022, a CECT scan of the thorax revealed partial thrombosis in lobar arteries of bilateral upper and lower lobes and segmental arteries of the left lower lobes and changes of pulmonary hypertension on the background of an active infective aetiology. Thus, the patient had developed pulmonary thrombosis with pulmonary hypertension. Large loculated left hydropneumothorax with bronchopleural fistula, mild left pleural effusion and multiple fibrotic, cavitatory and fibrobronchiectatic changes in left lung parenchyma and right lower lobe were also visualised on the scan [Figure 3]. The patient was initiated on parenteral anticoagulant therapy (heparin), followed by replacement with oral anticoagulant therapy (dabigatran). After 21 days of receiving injectable amphotericin B, the patient was discharged on tablets of voriconazole and dabigatran for 6 months. He has also advised chest physiotherapy during the post-discharge period. On discharge, he had significant clinical improvement (symptomatic/radiological resolution) with a resolution of left hydropneumothorax as seen on chest radiograph of 14 February 2022 [Figure 1]. His blood sugars (fasting and post-meal) were within normal limits, and his HbA1C was 6.1%. The patient was diagnosed with post-COVID pulmonary aspergillosis with the left hydropneumothorax (drained), pulmonary thromboembolism and pulmonary artery hypertension with prediabetes.

A follow-up computed pulmonary tomography angiography on 3 June, 2022, showed complete resolution of pulmonary thrombosis. It showed dilated pulmonary artery, few nodular and subtle ground glass opacities in the right lung parenchyma and features suggestive of sequelae to old infection. The patient reported significant symptomatic relief.

DISCUSSION

Aspergillosis was once believed only to affect immunosuppressed individuals. However, there are increasing reports of aspergillosis in people with severe respiratory viral

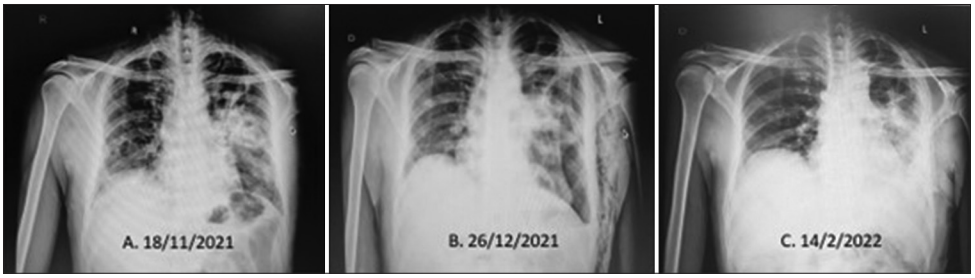

Figure 1: Comparision of chest radiographs (PA view) from three dates (A: 18 November 2021; B: 26 December 2021 and C: 14 February 2022).

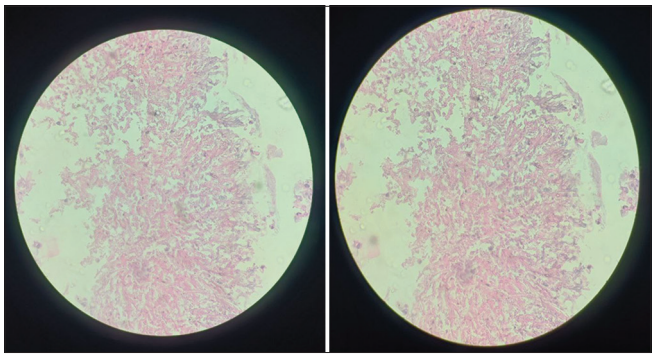

Figure 2: Histological specimen of bronchial washing.

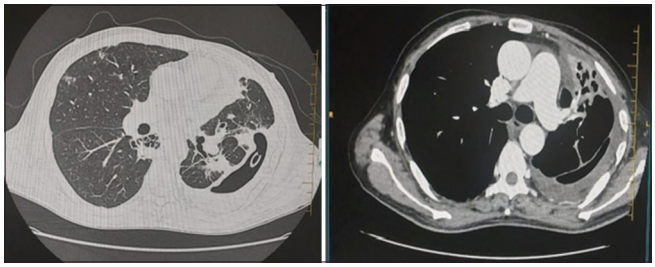

Figure 3: Contrast-enhanced computed tomography scan thorax (19/1/22).

infections such as influenza or COVID-19 but no immunosuppression.[1,2]

According to recent findings, due to immunological changes and the high-dose corticosteroids used to treat severe cases, 7.2% of COVID-19 patients are predisposed to several coinfections and superinfections. This makes the disease more severe and more difficult to diagnose, treat and predict the outcome.[6]

Numerous changes in cell-mediated immunity, including changes in chemotaxis, phagocytosis, cytokine release and reduced natural killer cell activity, occur in diabetes patients with poor glycaemic control, which can predispose the patient to secondary fungal infections. Aspergillus and candida are the two primary fungi responsible for coinfection in COVID-19 patients.

Endothelial damage decreased flow/stasis and hypercoagulable condition are the three main pathways (Virchow's Triad) by which risk factors for thrombosis are usually thought to contribute. A severe COVID-19 infection includes components of all three. The prothrombotic environment associated with COVID may extend well into the post-COVID period.[7]

At least two different but connected pathways in COVID-19 contribute to the disease's propensity for thrombosis. The first one primarily involves large-vessel occlusion, typically brought on by thromboembolism. The second explanation, which is the prevalent one, focuses on microvascular in situ immunological thrombosis due to activation of the innate immune system.[8]

Our patient, however, was not a known diabetic. He had been home quarantined when COVID positive without any hypoxia and received no corticosteroids during this period. Yet on admission, he had transient hyperglycaemia and required glycaemic control. His HbA1C of 6.1% on discharge classifies him with prediabetes.[9] The current episode of pulmonary fungal infection in the post-COVID period probably unmasked the underlying prediabetes.

In addition, our patient also had reduced mobility due to fatigue and breathlessness on exertion, which are risk factors for pulmonary thromboembolism.

Our patient had received two doses of the covishield vaccine (ChAdOx1 nCoV-19 Corona Virus Vaccine [Recombinant]) 1 month before admission. In a multinational prospective study by Bikdeli *et al*. which evaluated the risk of venous thromboembolism (VTE) for 30 days after COVID adenovirus-based vaccine administration, it was reported that VTE following SARS-CoV-2 adenovirus immunisation is accompanied by thrombocytopenia, occurs in unexpected places and is linked to worse clinical outcomes.[10]

A complex interplay of all the above factors leads to the patient of aspergillosis developing lobar pulmonary thromboembolism and pulmonary artery hypertension.

CONCLUSION

In immune-altered post-COVID-19 patients, fatal fungal infections and VTEs have sharply increased. In such circumstances, the clinical presentation and diagnosis are complicated. Successful management of these complications requires a high index of suspicion, early use of appropriate diagnostic methods, proper antifungal agents, and anticoagulants and control of risk factors such as hyperglycaemia.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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