Pulmonary Mucormycosis in a Patient with Decompensated Cirrhosis of the Liver Successfully Treated with Oral Posaconazole- A Case Report

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Data availability statement

The data that support the findings of this case report is available from the corresponding author upon reasonable request.

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Ethical approval: Written informed consent was obtained from the patient. The purpose of this case report was completely explained to the patient and were assured that their information would be kept confidential by the researcher.

Consent: Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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Author's contribution

Noor Alam Ansari: Conceptualization, data curation, investigations, writing-original draft,

Susanta Kumar Paul: Conceptualization, data curation, investigations, writing-original draft, writing-review & editing

Shamim Ahmed: Conceptualization, visualization, writing-review & editing

Rajashish Chakrabortty: Conceptualization, Software, writing- review & editing

Mohammed Atiqur Rahman: Project administration. Supervision

ABSTRACT

Our patient was known case of decompensated CLD and DM and presented with cavitary lung lesions. A CT-guided biopsy followed by histopathology confirmed the diagnosis of pulmonary mucormycosis. We started oral posaconazole due to financial constrained. The patient improved significantly without any notable side effects and survived beyond the treatment.

1 | INTRODUCTION

Mucormycosis is a rare opportunistic fungal infection compared to Candida and Aspergillus species and is caused by Mucorales fungi of the Zygomycetes class.[1] Immunocompromised conditions like Diabetes mellitus, systemic corticosteroid therapy, neutropenia, hematologic malignancies, stem cell transplant, and immunocompromised state are the predisposing conditions for mucormycosis.[2,3] Though rhino-cerebral is the most common presentation however pulmonary mucormycosis is not rare. Pulmonary mucormycosis results from the inhalation of sporangiospores or by hematogenous or lymphatic spread.[4] Patients with pulmonary mucormycosis usually present with non-specific symptoms such as cough, breathlessness, chest pain, and fever. Though early diagnosis is needed to prevent life-threatening complications however clinical diagnosis is difficult.

Pulmonary mucormycosis is rare in patients with liver cirrhosis. There are only 19 reported cases of mucormycosis associated with cirrhosis mainly by HBV and HCV. However, liposomal amphotericin B is the treatment of choice, and only one report of rhino-cerebral mucormycosis with cirrhosis was treated effectively

with oral posaconazole.[5] All of the patients died during the treatment. Our case might be the first case of pulmonary mucormycosis in a patient with decompensated cirrhosis of the liver treated effectively with oral posaconazole without any side effects and the patient survives beyond treatment.

Keywords: Decompensated, Posaconazole, Pulmonary Mucormycosis, Treatment

2 | CLINICAL PRESENTATION

A 66-year-old male smoker (10 pack/ year), known diabetic, and recently diagnosed case of decompensated cirrhosis of the liver was admitted to the Department of Respiratory Medicine of BSSMU with fever, cough, and shortness of breath for 2 weeks. There was no history of chest pain, skin rash, bony tenderness, epistaxis, hemoptysis, or weight loss.

The patient denied any history of steroid intake or contact with smear positive pulmonary tuberculosis patient. Physical examination revealed the patient was anemic, non-icteric, generalized clubbing without hypertrophic pulmonary osteoarthropathy, multiple spider naevi over the chest, and cervical lymphadenopathy were present. However, vitals were within the normal limit. Respiratory system examination had normal findings, and abdominal examination revealed ascites and small testes without any organomegaly.

Laboratory investigation showed hemoglobin 9.9 g/dl, total WBC count 3500 cells/cumm, and platelet 1 lakh/cumm. Biochemical investigation revealed serum creatinine 0.93 mg/dl, CRP 12.89 mg/dl, RBS 11.7 mmol/L, HbA1c 9.0 %, Bilirubin 1.4 mg/dl, Albumin 26 gm/dl. Serum electrolytes and liver function tests were normal. Ultrasonography of the whole abdomen showed chronic parenchymal liver disease with splenomegaly with features suggestive of portal hypertension, and mild ascites (600ml). Upper GIT endoscopy showed- Grade III esophageal varices with severe portal hypertensive gastropathy.

Chest X-ray showed- left-sided cavitary lesion and right-sided consolidation with basal pleural effusion [**Figure 1**]. Sputum microbiological investigation for gram staining revealed - a moderate number of gram-positive cocci arranged in clusters and short chains with a moderate number of pus cells. Culture and sensitivity reports showed profuse growth of Klebsiella spp. and fungal stain showed budding yeast cells with pseudo-hyphae. Sputum for AFB, Gene X-pert MTB/RIF, and malignant cells were negative. HRCT of the chest showed a bilateral upper lobe cavitary lesion with a right-sided minimal pleural reaction suggestive of abscess [**Figure 2**] .

According to the culture and sensitivity, the patient was put on intravenous ceftriaxone 2gm twice daily and tab itraconazole 400 mg/day for 14 days respectively without any response. Ascitic fluid aspiration was also performed which showed lymphocytic (90%) predominant exudative (protein 13.08 g/dL, albumin 5.38 g/dL) ascitic fluid with normal ADA (6.51 U/L). ascitic fluid AFB and Gene X-pert MTB/RIF were also negative. For further evaluation, fine needle aspiration cytology (FNAC) from the left cervical lymph node was performed that revealed- discrete and non-caseating epithelioid granulomata containing foreign body type as well as Langhans type giant cells, focal hyalinization of the stroma present, finding consistent with non-granulomatous lymphadenitis.

For further evaluation, a CT-guided biopsy from the left cavitary lung lesion was done. Microscopic examination of the biopsy specimen revealed an area of infarction with surrounding fibrofatty tissue containing broad non-septate hyphae with right-angled branching [**Figure 3**] and positive for GMS staining [**Figure 4**] compatible with mucormycosis. Gene X-pert MTB/RIF and culture for MTB of the biopsy tissue were negative.

After confirmation of a diagnosis of pulmonary mucormycosis, the patient was counseled about the treatment protocol. The patient was financially constrained to bear the expense of Liposomal amphotericin B therefore we started tablet posaconazole (Xpos) 300mg twice daily on Day 1 followed by 300mg daily for 3 months. Consultations from the hepatologist and endocrinologist were obtained regarding the optimal management of chronic liver disease (CLD) and diabetes mellitus and managed accordingly. After one month of follow up patient symptoms amended with nearly the complete resolution of the chest X-ray finding[**Figure 5**]

without any documentation of side effects. During the end of three months of treatment, the patient was asymptomatic with complete resolution of chest x-ray findings

[Figure 6].

3 | DISCUSSION

Mucormycosis represents a group of infections caused by the fungi belonging to the order Mucorales and family Mucoraceae.[1,6] Pulmonary mucormycosis accounts for ˜25% of cases of mucormycosis with more than 50% mortality.[2] The most frequent mode of infection is through inhalation of pervasive spores into the bronchioles and alveoli, which typically results in the rapid development of pneumonia or endobronchial disease. Risk factors for mucormycosis include diabetes mellitus (DM), systemic corticosteroid medication, neutropenia, hematologic malignancies, stem cell transplant, and other immunocompromised statuses. Among the risk factors, DM is the most common predisposing factor. Our patient was diabetic however his glucose level was well controlled with subcutaneous insulin.

In comparison to bacterial infections, fungal infections in people with cirrhosis are still relatively rare. In cirrhotic patients, infections caused by Candida, Cryptococcus, Aspergillus, and Coccidioidomycosis have all been documented.[7] Only a few instances of invasive mucormycosis in these patients have been documented.[8,9] Neutropenia and thrombocytopenia are frequently present in cirrhotic individuals and may act as risk factors for fungus infections.

The presentation of pulmonary Mucormycosis might be acute, subacute, or chronic. Patients with pulmonary mucormycosis commonly present with fever, cough, dyspnea, and chest pain. Hemoptysis occurs due to vascular invasion which is usually fatal. Pancoast syndrome, progressive subcutaneous emphysema, bronchial perforation, chronic mediastinitis, or Horner's syndrome are rare presentations of pulmonary Mucormycosis.[10-14]

The radiological evidence of pulmonary mucormycosis is mostly non-specific. An abnormal chest x-ray is found in more than 80% of patients.[15] Radiological presentations include infiltrates, consolidation, cavitation, single or multiple nodules or masses, air crescent sign, halo sign, reversed halo sign, lymphadenopathy, pleural effusion, pulmonary artery pseudoaneurysms, and bronchopleural fistula. Cavitations are found in as many as 40% of patients, but air crescent sign is uncommon. The right lung is more commonly involved than the left, and there is a predilection for the involvement of the upper lobes, although the reason for this remains unknown.[16,17]

Our patient presented with a fever, cough, and breathlessness for 2 weeks. On examination, cervical lymphadenopathy was present with features suggestive of CLD. Systemic respiratory system examination was normal and chest X-ray and HRCT scan of chest findings were suggestive of the cavitary lesion. Though sputum for Gram staining showed Klebsiella spp. and fungal stain showed budding yeast cells with pseudohyphae. The patient was treated with injectable ceftriaxone and oral itraconazole for 2 weeks according to the C/S without any significant improvement.

The gold standard for the diagnosis of pulmonary mucormycosis is the demonstration of characteristic hyphae (broad, non-septate, ribbon-like hyphae, with right-angled branching) and histopathologic changes (vascular invasion with tissue necrosis and neutrophilic infiltration of the tissue) in a biopsy specimen.[18] As our patient, the intravenous antibiotics and oral antifungal treatment were ineffective, then cervical lymph node FNAC was performed that showed non-caseating granuloma. So, for further evaluation, a CT-guided biopsy from a left-sided cavitary lesion was performed to confirm the diagnosis. Histopathological specimens of lung tissue showed features suggestive of Mucormycosis.

Pulmonary mucormycosis is associated with bacterial pneumonia in 30% of cases, which can delay the diagnosis of the fungal infection.[19] The sensitivity of microscopic examination of sputum and sputum culture is low, and the false positive rate is high. Our patient's sputum examination showed Klebsiella growth and we treated the patient according to the culture and sensitivity without any significant improvement. Polyenes (Amphotericin B and Liposomal amphotericin B) are the first-line agents for the treatment of mucormycosis,

and Liposomal amphotericin B is the choice of treatment as it improves the response rates and survival compared to amphotericin B.

In the present case, oral posaconazole was used rather than polyenes due to financial constrain. Posaconazole is metabolized mainly by the liver through glucuronidation, and it elevates liver function tests by approximately 1–5 %. No dose adjustment is necessary in patients with hepatic impairment.[4] Our patient received itraconazole for a short bridging period of 20 days without significant improvement and then finally posaconazole was started with a strict follow-up. During follow up patient improved clinically and radiologically without any documented side effects during the 3 months of treatment with posaconazole.

There are approximately 18 case reports of mucormycosis with decompensated CLD. Among them HCV in 8 patients; HBV in 2; autoimmune hepatitis in 2; alcoholic liver disease in 4; and unknown etiology 2.[20] None of them had lymph node involvement. This may be the first reported case of pulmonary mucormycosis with CLD with cervical lymph node involvement. The etiology of CLD of our patient was non-B non-C (NBNC).

The principal limitation of our report is that we did not obtain definitive culture confirmation of Mucorales from the biopsy material. However, the culture yield rate for this organism is relatively low, and as it can be falsely negative in up to 50% of mucormycosis cases. The low culture yield rate may be the result of the deleterious effects of tissue grinding, interactions with other organisms, and/or less-than-optimal culture temperature.[21] Different molecular methods are used for the confirmation of mucormycosis diagnosis. Among them, PCR of Mucorales can be performed on tissue biopsy and blood samples. They can confirm diagnosis earlier than the conventional mycological method. Although serum PCR sensitivity is lower than in tissue, it is highly specific.[22] We couldn't perform PCR on tissue or blood samples due to a lack of facilities.

4 | CONCLUSION

This case report demonstrates the association between liver cirrhosis and mucormycosis and shows that with close monitoring of liver function, the infection can be safely and effectively treated with oral posaconazole. Early diagnosis by imaging and histopathology and adequate treatment constitute the best approach to the eradication of mucormycosis.

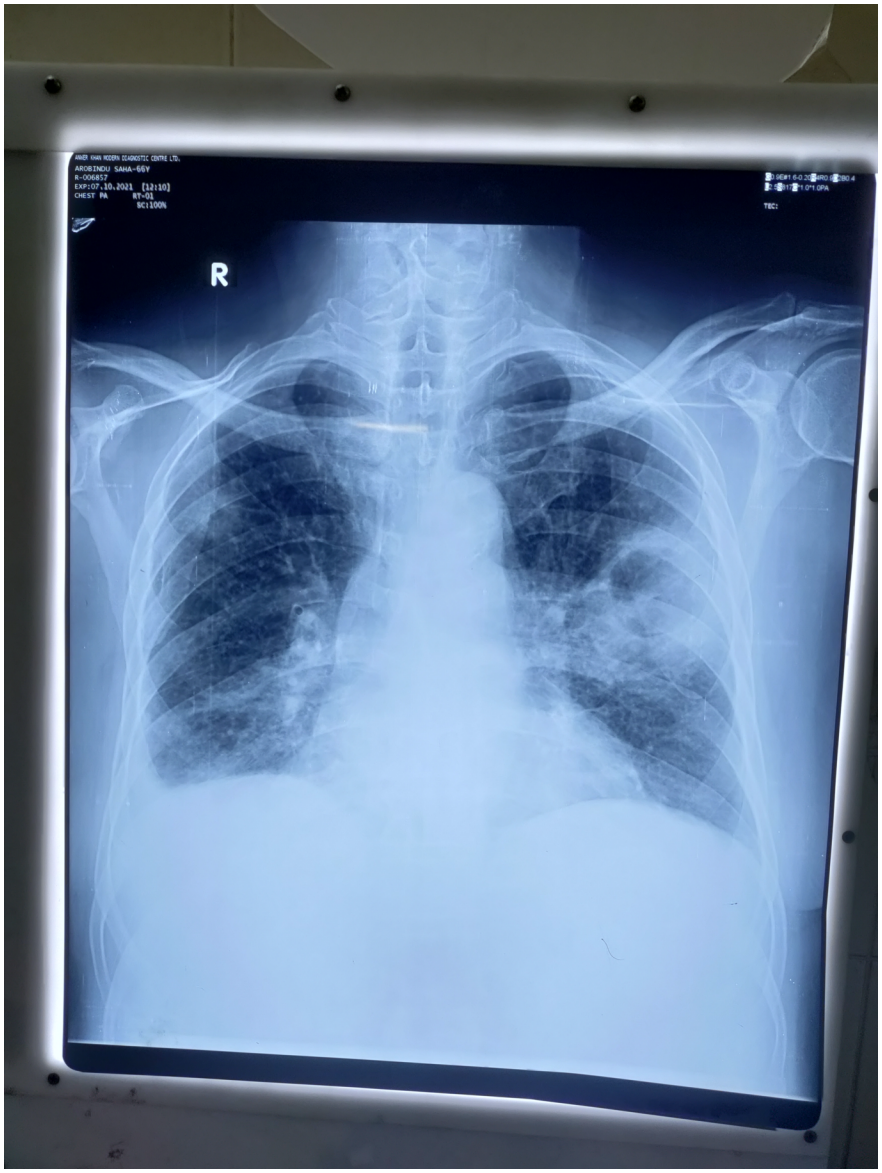

Figure 1: Chest x-ray at the time of hospitalization showing a left-sided cavitary lesion and right-sided consolidation with basal pleural effusion

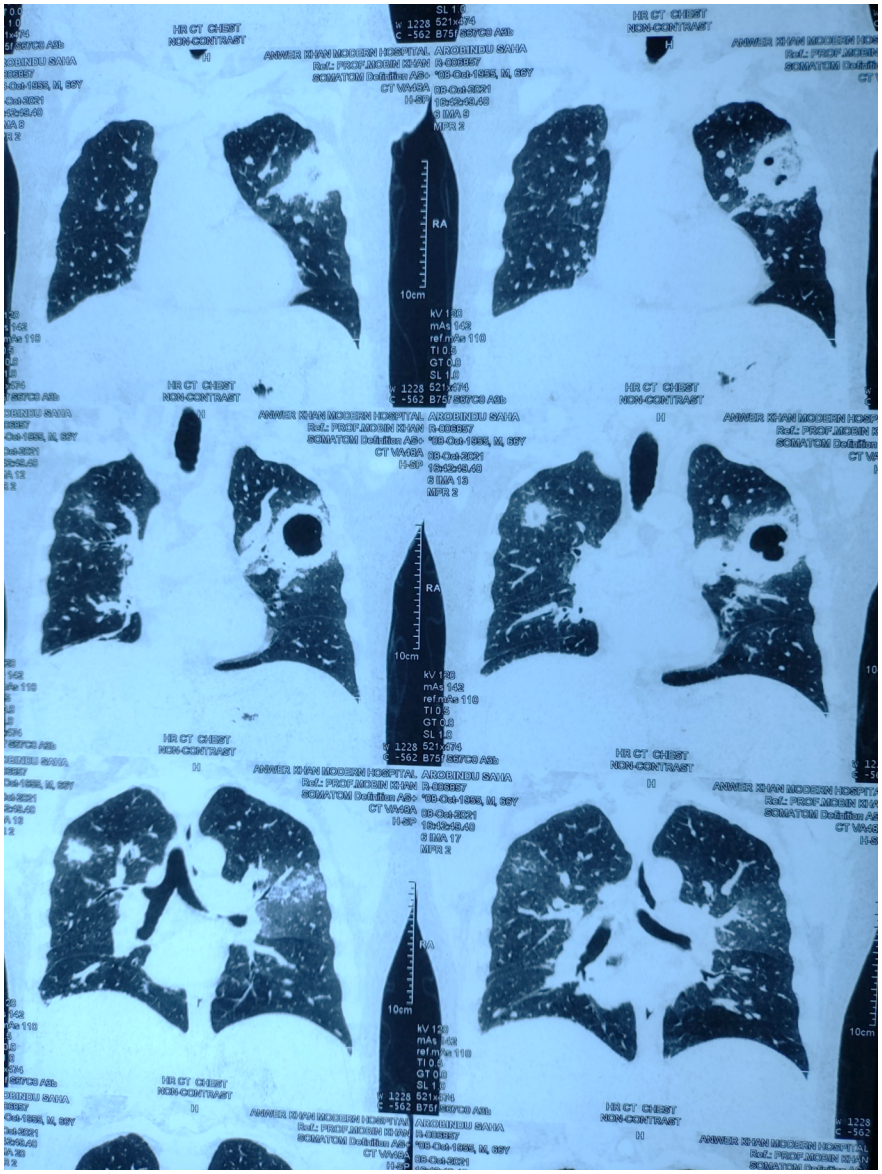

Figure 2: Chest computed tomography scan (coronal view) showing left-sided cavitary mass lesion and right-side focal consolidation with pleural reaction

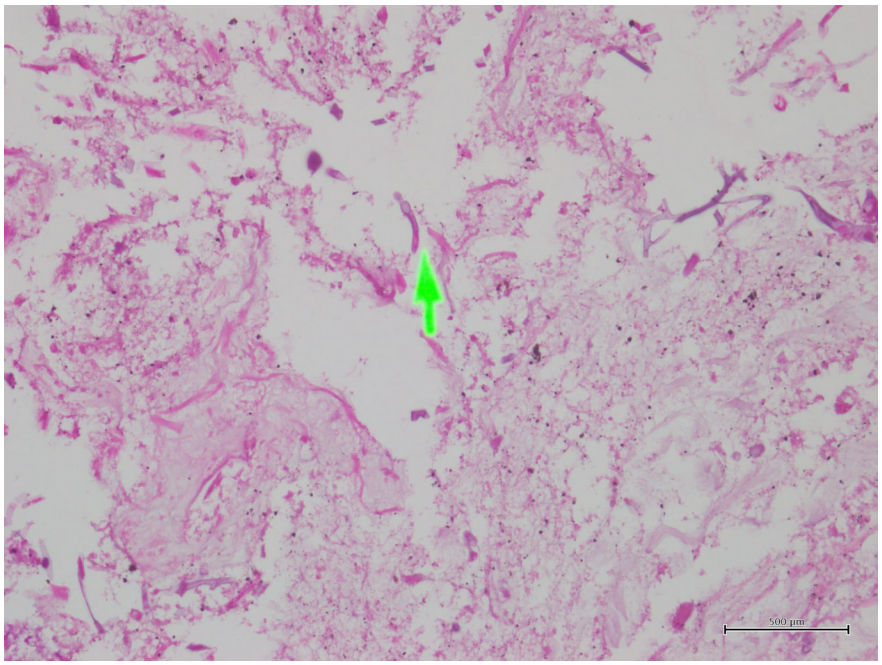

Figure 3: Lung biopsy specimen showing broad, non-septate hyphae with right-angled branching (hematoxylin and eosin staining)

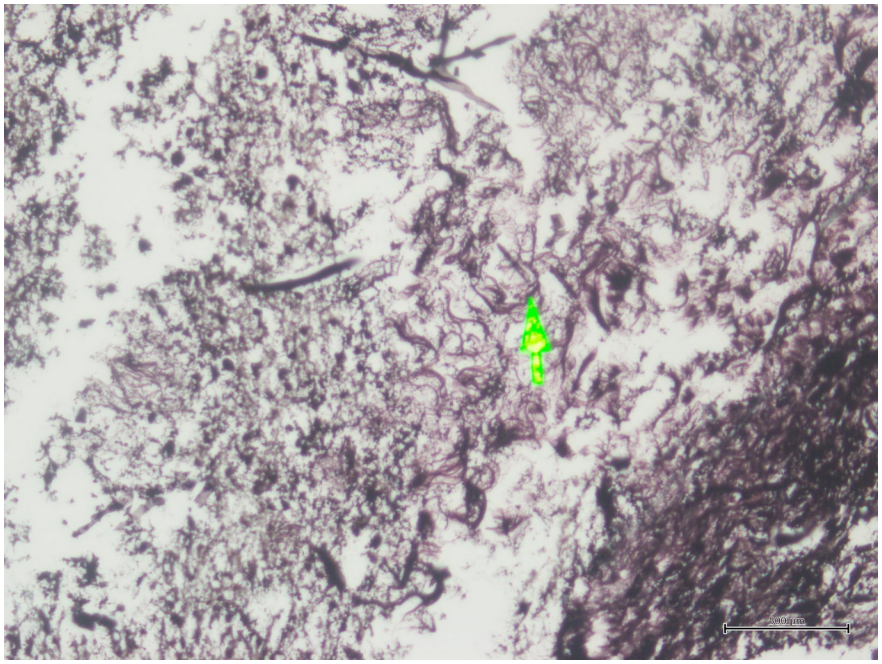

Figure 4: Broad non-septate fungal hyphae with right-angled branching (Gomori's methenamine silver staining)

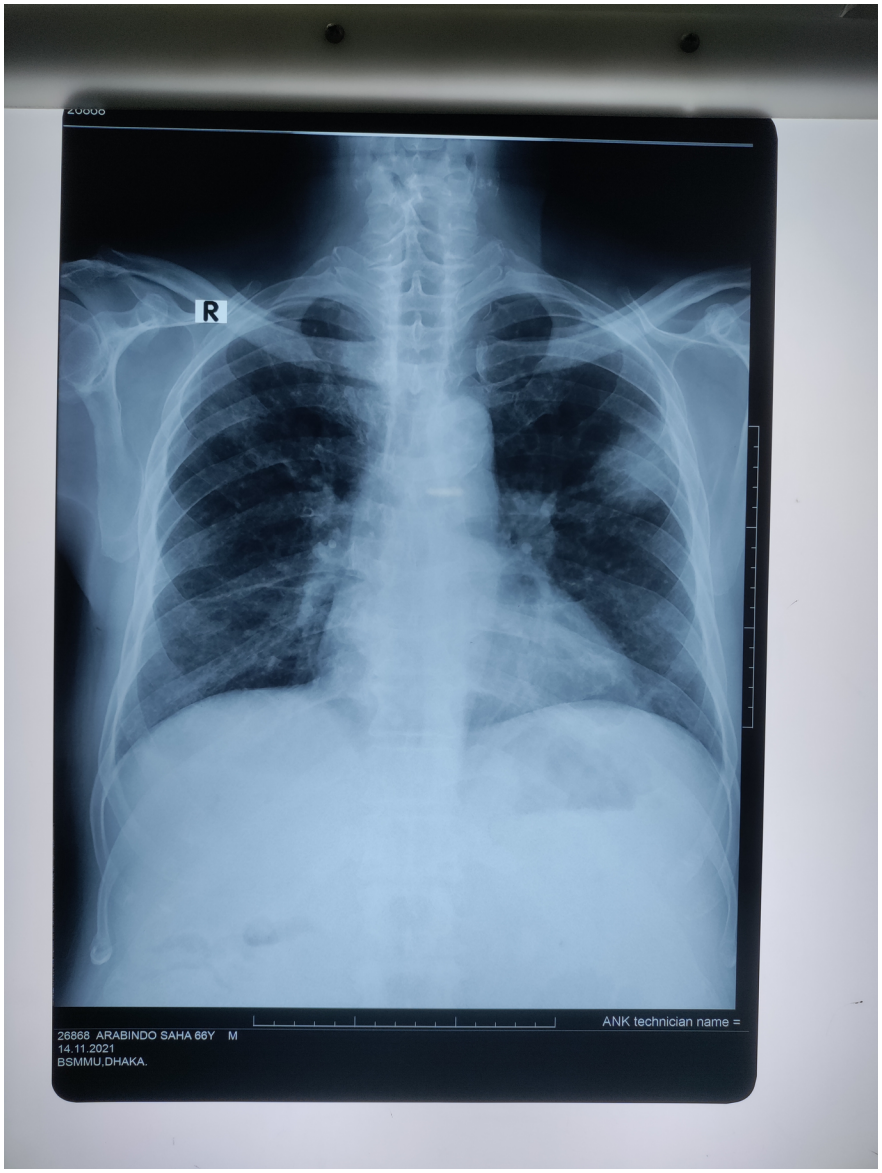

Figure 5: chest x-ray after one month of treatment with oral posaconazole showing near complete resolution of lung lesions

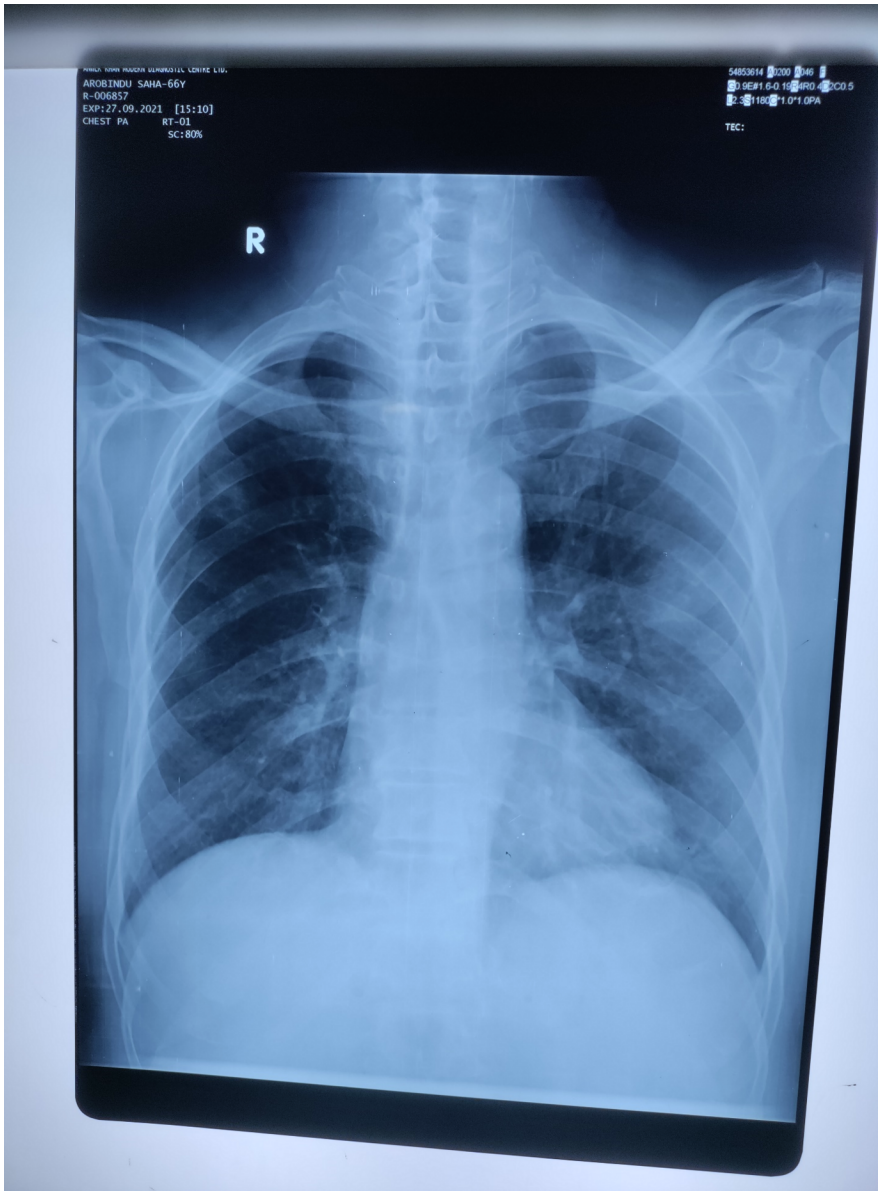

Figure 6: Chest X-ray P/A view after three months of treatment showed complete resolution of lung lesions