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Coinfection of *Klebsiella pneumoniae* and *Aspergillus* in a patient with chronic obstructive pulmonary disease post cardiac arrest: a case report

Inder Preet Singh Bhatia[1*†], Amulyajit Singh[2†], Jayaraj Hasvi[3†], Amit Rajan[4] and Sri Krishna Venigalla[5]

Abstract

Introduction Chronic obstructive pulmonary disease is a lung condition characterized by chronic respiratory symptoms (breathlessness, cough, and expectoration). In the advanced stages, patients often report to the Accident & Emergency department due to worsening of symptoms. Because of the repeated exposure to corticosteroids during the management of exacerbations, these patients are susceptible to super additional infections. Pulmonary aspergillosis can be divided into three main categories: invasive pulmonary aspergillosis, allergic bronchopulmonary aspergillosis and chronic pulmonary aspergillosis. *Aspergillus* overlap syndrome is defined as the presence of more than one form of *Aspergillus* in a single patient. However, coinfection with Klebsiella and pulmonary aspergillosis overlap syndrome is rare and poses a treatment challenge. As per a pub med search, no such case report has been reported in a case of chronic obstructive pulmonary disease.

Case report We report the case of a 66-year-old male, Punjabi Hindu by ethnicity, who was a reformed smoker with a known case of COPD. He presented with a history of breathlessness (mMRC grade 4) associated with cough with expectoration and wheezing for 15 days and intermittent episodes of hemoptysis for more than 6 months. The examination revealed tachypnea and wheezing throughout the lung fields. He was initially managed with parenteral steroids and frequent nebulization with bronchodilators. On day 5 of hospitalization, the patient experienced worsening of symptoms and cardiac arrest; he was intubated and return of spontaneous circulation was achieved within 5 minutes of cardio pulmonary resuscitation. Tracheal aspirate and culture revealed *Aspergillus fumigatus* and *Klebsiella pneumoniae* respectively. He underwent chest CT, which showed features suggestive of allergic bronchopulmonary aspergillosis and invasive pulmonary aspergillosis. He was found to have elevated β-D-glucan, galactomannan, and aspergillus IgE and IgG. Severe pneumonia and pulmonary *Aspergillus* overlap syndrome were managed with antibiotics, steroids, and antifungals. Over the next 15–20 days, his general condition improved. He was discharged after 45 days of hospitalization and continued on oral corticosteroids, antifungals, and inhaled bronchodilators.

†Inder Preet Singh Bhatia, Amulyajit Singh, and Jayaraj Hasvi have contributed equally to this work.

*Correspondence:
Inder Preet Singh Bhatia
dr.inder0219@gmail.com
Full list of author information is available at the end of the article

Conclusion Coinfection with bacteria and fungi worsens the outcome. Clinicians should be aware of the polymicrobial manifestations and various drug interactions involved. Timely diagnosis aids in better management strategies and improved patient outcomes.

Keywords COPD, *Aspergillus* overlap syndrome, *Klebsiella pneumoniae*, Voriconazole, Corticosteroids

Introduction

Pulmonary aspergillosis can be divided into three main categories: invasive pulmonary aspergillosis (IPA), allergic bronchopulmonary aspergillosis (ABPA), and chronic pulmonary aspergillosis (CPA) [1]. IPA usually occurs in immunocompromised patients with risk factors such as profound neutropenia, prolonged corticosteroid use, and hematopoietic stem cell transplant recipients. However, in recent years, immunocompetent patients have been reported to have IPA [2]. These patients are either critically ill or have underlying lung conditions such as severe COPD. The coexistence of bacterial and fungal infections in preexisting lung conditions has been reported in the past. In this case report, we present a case of acute exacerbation of chronic obstructive pulmonary disease (COPD) with *Aspergillus* overlap syndrome and *Klebsiella pneumoniae*. The coexistence of both of these factors complicated the scenario. This patient suffered cardiac arrest. He was intubated and managed with antibiotics, steroids, and antifungals. He had a good clinical response to the treatment and was discharged after 45 days of hospitalization.

As per pub med search, no such case report has been reported in a case of COPD. Here, we want to highlight the importance of timely diagnosis of these coexisting infectious states, which can guide the formulation of treatment strategies and favorable outcomes.

Case report

A 66-year-old male, farmer by profession, Punjabi Hindu by ethnicity, a reformed smoker with a known case of COPD, presented in September 2023 with a history of fever for 5 days. History of 15-day breathlessness in modified medical research council grade 4, associated with cough and expectoration was there. History of unintentional, unquantified weight loss for 15–20 days. The patient had a history of intermittent episodes of hemoptysis over the last 6 months, which had increased in the last 15 days. He had a past history of multiple hospitalizations for acute exacerbation of COPD, for which he was managed with steroids and had a transient relief in symptoms. No similar family history was there.

On examination, he was found to be dyspneic. His vital signs included a pulse of 110 per minute, a blood pressure of 110/74 mmHg, a respiratory rate of 32 per minute, a SPO_2 of 70% at room air, and a temperature of 98.4 °F. JVP was not raised. Systemic examination revealed decreased breath sounds, wheezing all over the lung fields and crackles over the infra scapular and infra-axillary areas. Investigations revealed a hemoglobin level of 10.5 m/dl, a total leucocyte count of 7300/mm^3, a neutrophil predominance (80%), an absolute eosinophilic count of 1095/mm^3, and a platelet count of 2,46,000/mm^3. The ESR was 66 mm per hour. PBS for microfilaria was negative. Serial sputum samples were negative for acid-fast bacilli, and the Mantoux test was negative. HBsAg, anti-HCV, and anti-HIV antibodies were negative. He was found to be negative for influenza and coronavirus disease 2019 (COVID-19) (rapid antigen test and reverse transcription polymerase chain reaction were negative).

He was initially managed with noninvasive ventilation, parenteral antibiotics (ceftriaxone and azithromycin), parenteral steroids (hydrocortisone 100 mg thrice a day), nebulization with short-acting beta agonists/short-acting muscarinic antagonists/steroids and other conservative measures. He showed no signs of improvement and underwent HRCT (Figs. 1, 2, 3, 4), which showed bronchial wall thickening with cylindrical and cystic bronchiectasis in the lungs bilaterally. Some of the cystic

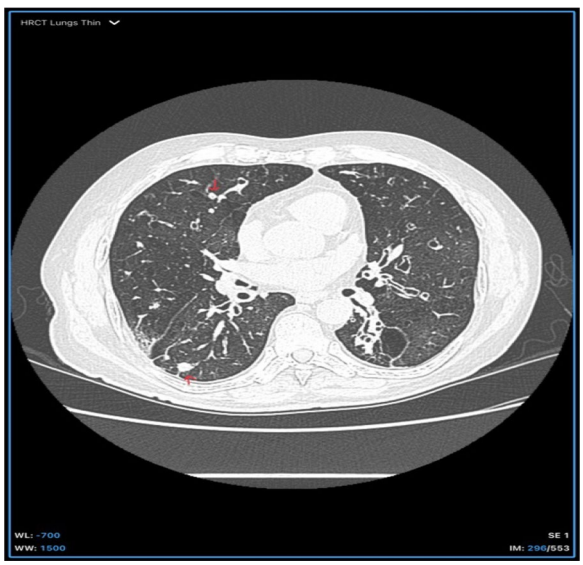

Fig. 1 Red arrows showing variable-sized nodules suggestive of possible airway invasive aspergillosis

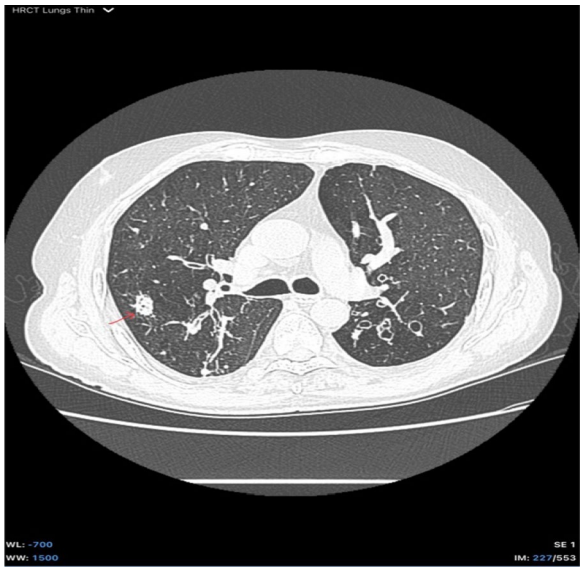

Fig. 2 The red arrow shows consolidation

Fig. 3 Red arrow showing mucoid impaction in the bronchus

bronchiectasis showed air fluid levels and patchy areas of peri-bronchial consolidation in the right upper, middle, and left lower lobes with areas of mucoid impaction in some of the dilated bronchi, features suggestive of ABPA. CT further showed multiple variable-sized nodules scattered in the lungs bilaterally, with some of the nodules exhibiting a tree-in-bud appearance and mosaic attenuation, indicating features pointing toward the IPA. Additionally, CT also showed centrilobular emphysematous changes in the lingula and bilateral lower lobes, likely secondary to prolonged history of smoking.

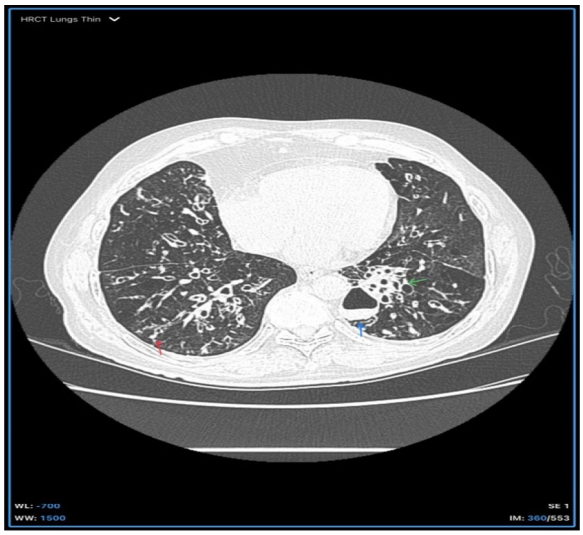

Fig. 4 The red arrow shows the tree in the bud configuration. The green arrow shows bronchiectasis with a thickened bronchial wall. The blue arrow shows cystic bronchiectasis with air fluid levels. Mosaic patterns are also observed

He was continued on steroids and started on caspofungin on day 5 of hospitalization. He continued to experience sinus tachycardia and respiratory distress (respiratory rate of 44 per minute) despite non-invasive ventilation. He suffered cardiac arrest on day 5 of hospitalization. Monitor showed asystole. He was intubated, and return of spontaneous circulation (ROSC) was achieved within 05 min of cardiopulmonary resuscitation (CPR). Electrocardiogram showed no ST segment changes and cardiac enzymes were normal. Arterial blood gases on the day of arrest had respiratory acidosis (pH of 7.24, pCo_2 of 112 mmHg, $HCO3^{-}$ of 43 mmol/l, and lactate of 0.89 mmol/l). Postcardiac arrest, he had hypotension (blood pressure of 70/42 mmHg) and dyselectrolemia (potassium of 3.1 mmol/l) and was managed with adequate fluids (1500 ml of fluid bolus then with maintenance fluid), noradrenaline infusion, and other supportive measures. His antibiotics were upgraded to meropenem (1 g IV every 8 hours), levofloxacin (750 mg IV every 24 hours), and clindamycin (600 mg every 8 hours), and he was continued on corticosteroids and antifungals.

His serum procalcitonin level was 2.0 ng/ml (normal < 0.1 ng/ml). Subsequently, the serum β-D-glucan was 348.9 pg/ml (< 70.0), the serum galactomannan level was 0.52 µg/l (< 0.25), the serum *Aspergillus* IgG level was 45.20 mgA/l (normal < 27.0), the serum *Aspergillus* IgE level was 20.18 kUA/l (normal < 0.35), and the

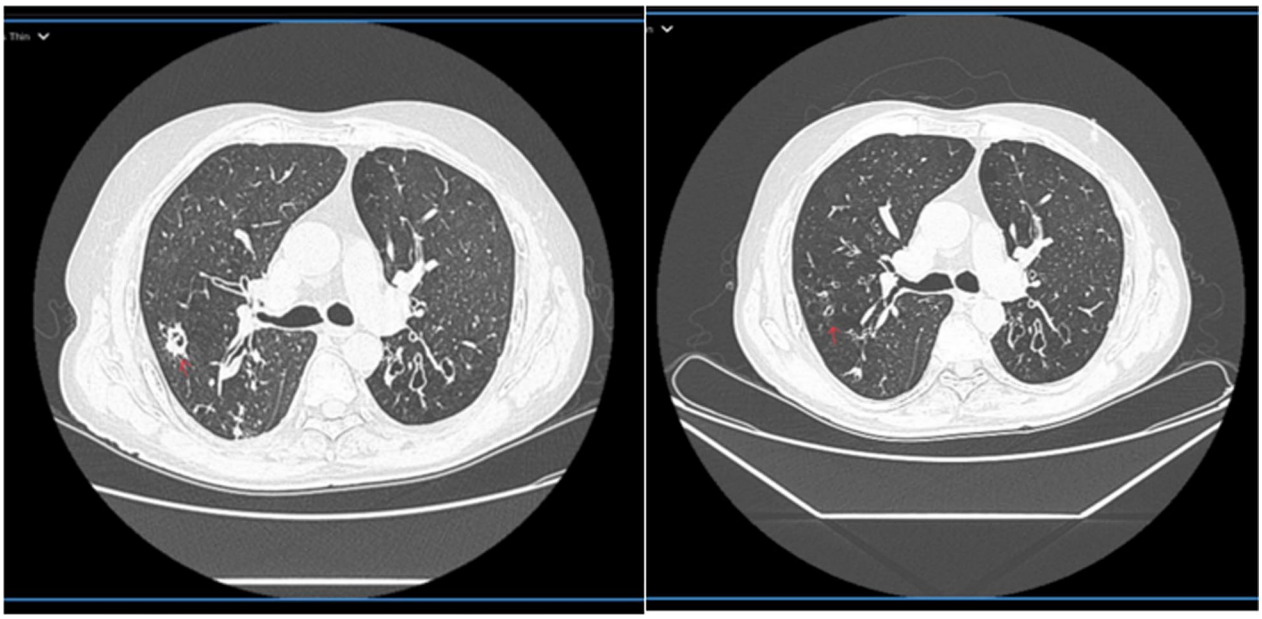

Fig. 5 The red arrow in figure on left side shows a consolidation patch. Figure on right side is follow up CT at 02 months. Red arrow shows resolution of consolidation

total serum IgE level was 1450 IU/ml (normal < 378.0). His sputum culture (initial sample at time of admission) and tracheal culture (taken while patient was intubated) revealed *Klebsiella pneumoniae*. Tracheal aspirate was subjected to lactophenol cotton blue (LPCB) stain and viewed under light microscopy, which revealed *Aspergillus fumigatus* (Fig. 7). His repeat CT chest showed findings similar to those of the previous CT. Based on CT findings, increased serum procalcitonin (PCT), β-D-glucan, galactomannan, *Aspergillus* IgG and IgE, LPCB mount showing *Aspergillus* and sputum and tracheal cultures suggestive of Klebsiella infection, the patient was diagnosed with *Aspergillus* overlap syndrome (ABPA and IPA) and severe pneumonia. He was managed with antifungal agents, corticosteroids and antibiotics. His condition gradually improved. Vasopressors were tapered off on day 8. He was extubated on day 10 of admission. Caspofungin was stopped once the patient became hemodynamically stable, and voriconazole was started. His repeat sputum cultures after 2 weeks of antibiotic treatment with meropenem and levofloxacin showed no growth. The patient was continued on oral corticosteroids (oral prednisolone 30 mg every other day) and voriconazole (200 mg) twice a day and discharged after 45 days of admission. His two-dimensional echocardiography (ejection fraction of 55%, no RWMA, normal LV function, mild TR, no PE/clot/vegetations) prior to discharge was normal. At 1 month post discharge, the patient had significant reduction in hemoptysis, and cough and examination revealed no adventitious sounds. He was continued on oral voriconazole and tapering doses of steroids. He had improvement in breathlessness and was able to walk for 1000–1500 m without breathing difficulty. At 2 months post discharge, he had complete resolution of hemoptysis. Lab investigations at 2 months showed normalization of serum IgE (39.60 IU/ml), *Aspergillus* IgE (less than 0.10 KUA/L) and β-D-glucan levels (0.02 ng/ml). Follow-up chest CT (Figs. 5, 6) showed resolution of consolidation and mucoid impaction. He was continued on voriconazole (200 mg BD) with tapering doses of steroids. Three months after discharge, steroids were discontinued, and voriconazole continued for total of 6 months. Timeline of the events of this case report has been summarized in Fig. 8.

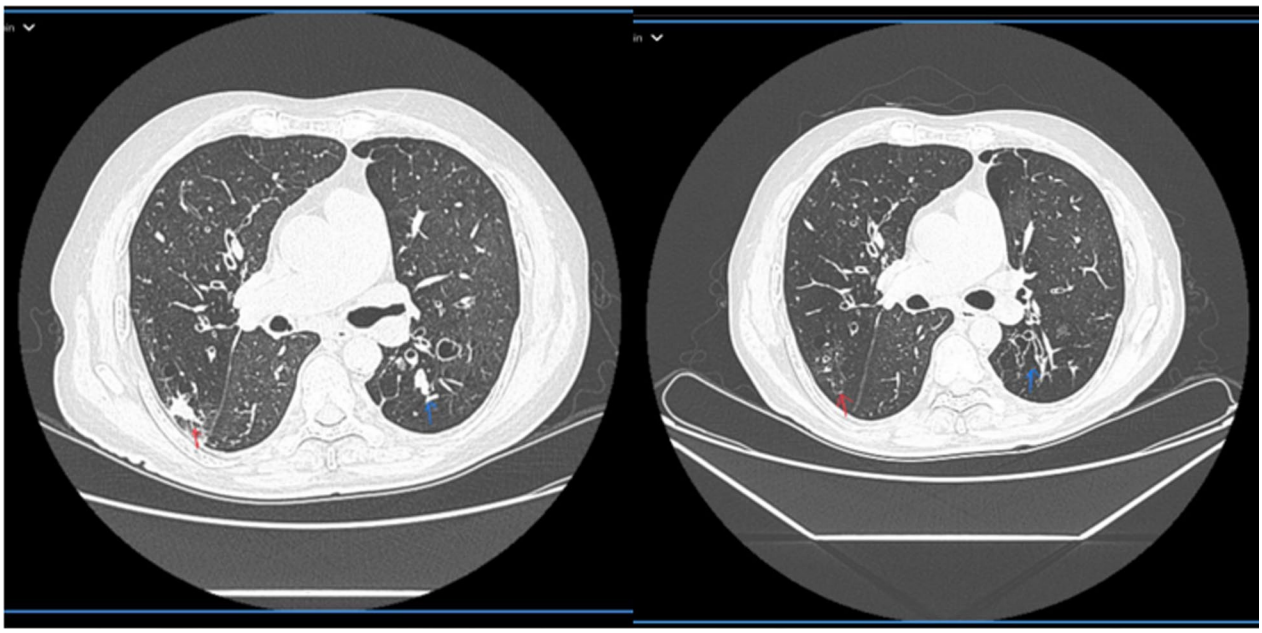

Fig. 6 The red arrow in figure on left side shows a consolidation patch and blue arrow shows mucoid impaction. Figure on right side is a follow up CT and red arrow shows resolution of consolidation & blue arrow shows resolution of mucoid impaction

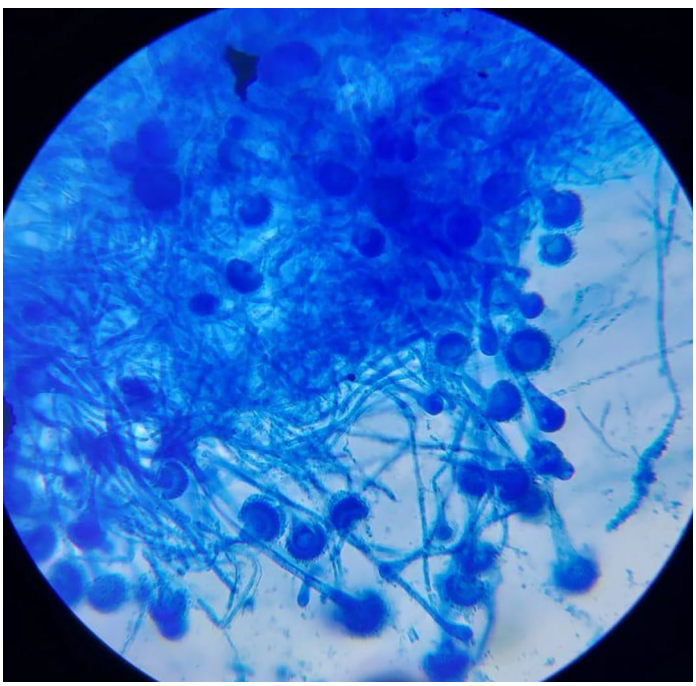

Fig. 7 LPCB mount examined under light microscopy showing septate hyphae with vesicles. Un-branched conidiophore arising from foot cells. Vesicles are covered partially with flask shaped phialides

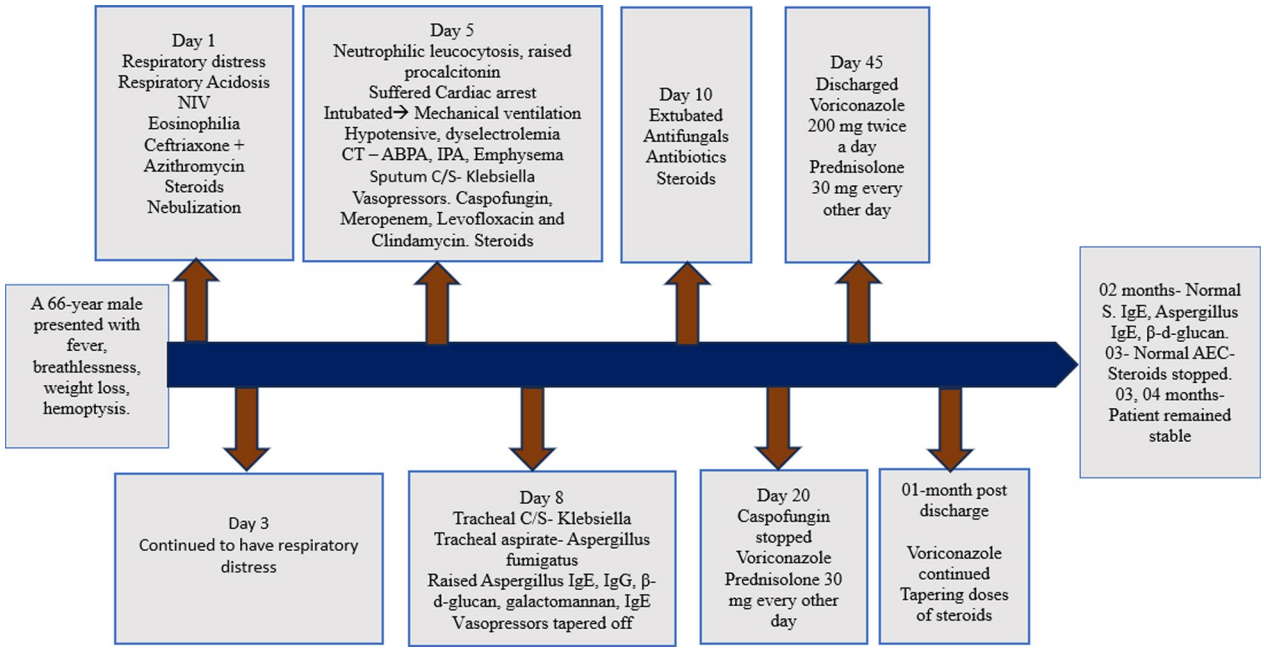

Fig. 8 Timeline of the events

Lab parameter	On admission	Day 5 (Cardiac Arrest)	Day 15	On discharge (day 45)	1 month post discharge	2 months post discharge	3 months post discharge
Hb g/dl	10.5	9.9	9.5	10.2	11.3	12.0	12.8
TLC/ul	7300	23,700	10,300	8200	6900	7200	6200
DLC	N 80%, AEC–1095	N 89%, AEC–1230	N 78, AEC–950	N 65%, AEC–730	N 68%, AEC–630	N 62%, AEC–320	N 61%, AEC–240
Platelets 10^3/ul	2,46,000	2,10,000	2,20,000	1,84,000	2,18,000	1,92,000	2,47,000
Urea/creatinine mg/dl	28/0.9	34/1.0	24/0.8	27/0.9	32/1.0	29/0.8	22/1.0
Na^+/K^+ mEq/L	133/3.7	135/3.1	137/3.8	135/4.2	137/3.9	136/4.4	138/4.2
$Ca^{2+}/Po4^{3-}$ mg/dl	8.9/3.9	8.7/4.1	8.9/3.7	8.8/3.9	8.2/4.0	8.9/3.6	8.6/3.7
Procalcitonin		2.0	< 0.01	< 0.01			
ABG	7.37	7.24	7.37	7.38			
pH	66	112	54	47			
pCo2 mmHg, HCO_3^- mmol/L	33	43	21	23			

Discussion

Aspergillus fumigatus is a thermotolerant fungus that is distributed worldwide. It is ubiquitous in nature. It is also transmitted via an airborne route. Depending upon the immune status of the patient, *Aspergillus* manifests in various forms [1]. The three common manifestations are ABPA, IPA, and CPA. IPA is commonly observed in immunocompromised patients, such as those with profound neutropenia, prolonged exposure to corticosteroids, malignancies, stem cell recipients, and organ transplantations. However, in recent years, immunocompetent patients have been reported to have IPA [2]. These patients are either critically ill or have underlying lung conditions such as severe COPD. Increased susceptibility to IPA in patients with COPD is probably attributed to prolonged corticosteroid exposure [3], permanent changes in the architecture of the lung, and recurrent hospitalization.

CPA is usually detected in immunocompetent or less immunocompromised states. Patients with CPA have a wide spectrum of underlying lung diseases, such as tuberculosis, COPD, sarcoidosis, and pneumothorax [4].

These conditions can be diagnosed with the help of various noninvasive and invasive modalities. Lung biopsy among the invasive and direct microscopy, respiratory sample culture, serum galactomannan, *Aspergillus* antibody, *Aspergillus* polymerase chain reaction (PCR), and chest CT among the noninvasive modalities.

Antifungals such as voriconazole are the first-line therapy for IPA. Echinocandins and amphotericin B are alternative antifungals for aspergillosis.

Our patient had a clinical history of breathlessness in modified medical research council (MMRC-4), associated with cough, expectoration, hemoptysis, and unintentional weight loss. His chest HRCT showed features of ABPA with subtle changes suggestive of IPA [5]. He had significantly increased β-D-glucan, galactomannan, *Aspergillus*, IgE and IgG levels. His tracheal aspirate and culture revealed *Aspergillus fumigatus* and *Klebsiella pneumoniae*, respectively. Based on clinical examination, raised serum IgE, *Aspergillus* IgE, and computed tomography (CT) findings, ABPA was diagnosed. Probable diagnosis of IPA was made based on mycological evidence (LPCB mount showing *Aspergillus fumigatus*, raised serum β-D-glucan, galactomannan), radiological evidence and host factors (COPD, use of corticosteroids on multiple occasions in the past) [6]. Hence, *Aspergillus* overlap syndrome (ABPA and IPA) and severe pneumonia were diagnosed. He was not subjected to lung biopsy, as the patient was hemodynamically unstable in the beginning and post extubation, so he was offered the choice of lung biopsy, but the patient was unwilling for the invasive procedure.

He was initially managed with caspofungin in view of hemodynamic instability and dyselectrolemia post cardiac arrest, as voriconazole is known to cause hypotension, hypokalemia, and arrhythmias [7, 8] in approximately 10% of patients. After 10 days of caspofungin treatment, the patient was switched to oral voriconazole as voriconazole being the first line antifungal for IPA. Among the antibiotics, ceftriaxone was initially used for treatment. However, in view of the poor response to initial antibiotics, he was switched to meropenem and levofloxacin. He had a good clinical response to antibiotics and antifungals and was extubated after 5 days. After 14 days of treatment with meropenem and levofloxacin, his serial sputum cultures showed no growth. Oral voriconazole (200 mg) was continued twice a day along with oral corticosteroids. He was discharged after 45 days of hospitalization. A total of 1, 2, 3, and 6 months after discharge, the patient remained stable and experienced no cough, expectoration and hemoptysis. Presently, patient is on monthly follow up.

Clinicians must consider the possibility of these coinfections and various diagnostic modalities available and must be aware of various drug interactions and adverse effects while managing critically ill patients.

Conclusion

Pulmonary aspergillosis may manifest in different forms depending upon the immune status of the patient. Patients with COPD with a history of repeated exposure to corticosteroids (during management of exacerbation) are susceptible to *Aspergillus*. Coinfection with bacteria complicates the clinical setting and results in worse outcomes than individual infections. However, when diagnosed, this approach can aid in better management strategies and improved outcomes.

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Author contributions
IPSB is the first and corresponding author and has managed the case, conceptualized and analyzed the case report and contributed towards writing original draft and reviewing and editing the manuscript. SA conceptualized the case report and contributed towards describing figures and reviewing and editing the manuscript. JH conceptualized the case report and contributed towards writing original draft and reviewing and editing the manuscript. AR contributed towards reviewing and editing the manuscript. VSK contributed towards reviewing and editing the case report.

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Availability of data and materials
Yes.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Ethics Committee of 167 Military Hospital (file number: IEC/PTK/02/2023). Written informed consent was taken to participate in this study.

Consent for publication
"Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal."

Competing interests
The authors report no conflicts of interest or competing interests related to this study.

Author details
[1]Department of Internal Medicine, Military Hospital, 167 Military Hospital, Dhangu Military Complex, Pathankot 145001, India. [2]Department of Radiodiagnosis, PGI, Jalandhar, India. [3]Department of Internal Medicine, Military Hospital, Bareilly, India. [4]Department of Lab Sciences and Pathology, Military Hospital, Pathankot, India. [5]Department of Anesthesia, Military Hospital, Pathankot, India.

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