An Uncommon Cause of Refractory Pleural Effusion

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Dear Editor,

Pleural effusion is a frequently encountered clinical problem with a broad differential diagnosis encompassing infectious, malignant, cardiac, hepatic, and inflammatory etiologies. In countries such as India, tuberculosis remains a leading cause of exudative pleural effusion, while malignancy is another major consideration in elderly patients.[1] However, fungal infections involving the pleural space are exceedingly uncommon and often remain unrecognized because of their nonspecific clinical presentation and the low diagnostic yield of routine pleural fluid investigations. We report a rare case of pulmonary aspergillosis presenting as recurrent hemorrhagic pleural effusion, highlighting the importance of considering fungal etiologies when common causes have been excluded.

A 70-year-old male with multiple comorbidities, including chronic liver disease, type 2 diabetes mellitus, hypertension, hypothyroidism, and a history of right nephroureterectomy for renal transitional cell carcinoma 4 years earlier, presented with progressive dyspnea and left-sided chest discomfort. He also had a recent history of recurrent hematuria secondary to left nephrolithiasis requiring percutaneous nephrolithotomy and double-J stent placement. Clinical examination revealed reduced breath sounds and dullness to percussion over the left hemithorax. Chest radiography and computed tomography demonstrated a moderate-to-large left-sided pleural effusion with underlying lung collapse. An intercostal drainage tube was inserted, yielding hemorrhagic pleural fluid (Fig. 1).

Initial pleural fluid analysis was inconclusive. The fluid was hemorrhagic with elevated protein levels and mixed cellularity. Importantly, microbiological investigations, including acid-fast bacilli staining and GeneXpert MTB/RIF testing, were negative. Cytological examination did not reveal malignant cells, and aerobic cultures were sterile. Despite adequate drainage, the pleural effusion persisted, prompting further evaluation.

Given the absence of a definitive diagnosis, bronchoscopy with bronchoalveolar lavage (BAL) was performed. Although routine stains, bacterial cultures, and GeneXpert testing of BAL samples were negative, the BAL galactomannan index was markedly elevated at 4.5. Furthermore, fungal culture subsequently grew *Aspergillus* species after 1 week of incubation (Fig. 2). These findings established the diagnosis of pulmonary aspergillosis with pleural involvement. The patient was treated with intravenous amphotericin B followed by oral voriconazole. Clinical symptoms gradually improved, and follow-up imaging demonstrated near-complete resolution of the pleural effusion after completion of antifungal therapy.

Pleural aspergillosis is a rare manifestation of *Aspergillus* infection.[1,2] Unlike invasive pulmonary aspergillosis, which primarily affects severely immunocompromised hosts, pleural involvement generally occurs secondary to thoracic surgery, bronchopleural fistula, empyema, or contiguous spread from underlying pulmonary disease. The largest contemporary review by Zhang et al.[3] evaluated 13 cases of pleural aspergillosis and found that most patients had a history of thoracic intervention or bronchopleural fistula, with mortality remaining substantial despite treatment. Our patient had no previous thoracic surgery or fistula, making the presentation particularly unusual.

Several isolated case reports have described atypical manifestations of pleural aspergillosis. Chang et al.[4] reported a case of *Aspergillus* pleural empyema in a patient with bronchiectasis, while Kant et al.[5] described pyopneumothorax caused by *Aspergillus* infection. Other reports have documented pleural-based aspergillosis mimicking malignant disease (Table 1). In contrast, our patient presented primarily with recurrent hemorrhagic pleural effusion, a clinical picture that strongly suggested tuberculosis or malignancy rather than fungal infection. Consequently, the diagnosis was considerably delayed.

The diagnostic challenge in pleural aspergillosis arises largely because pleural fluid studies are frequently nondiagnostic. Isolation of *Aspergillus* species from pleural fluid is uncommon, and culture sensitivity is generally poor. As demonstrated in the present case, BAL galactomannan testing combined with fungal culture can provide critical diagnostic information when pleural investigations fail to identify an etiology. Galactomannan, a polysaccharide component of the *Aspergillus* cell wall, has become an important biomarker for invasive aspergillosis and may be particularly useful in patients with unexplained pleural disease and radiological evidence of pulmonary involvement. The elevated BAL galactomannan index and positive fungal culture in our patient were instrumental in establishing the diagnosis.

Management of pleural aspergillosis remains challenging because of the rarity of the condition and the absence of standardized treatment protocols. Current therapeutic strategies generally involve a combination of pleural drainage, systemic antifungal therapy, and, in selected cases, surgical intervention. Voriconazole is widely regarded as the first-line treatment for invasive aspergillosis owing to its favorable efficacy profile, while amphotericin B remains an important option in severe disease. In our patient, a combination of initial amphotericin B followed by prolonged voriconazole therapy resulted in complete symptomatic improvement and radiological resolution, thereby avoiding the need for surgical management.

This case underscores several important clinical lessons. First, fungal infections should be considered in patients with persistent or recurrent pleural effusion when conventional investigations fail to establish a diagnosis. Second, the absence

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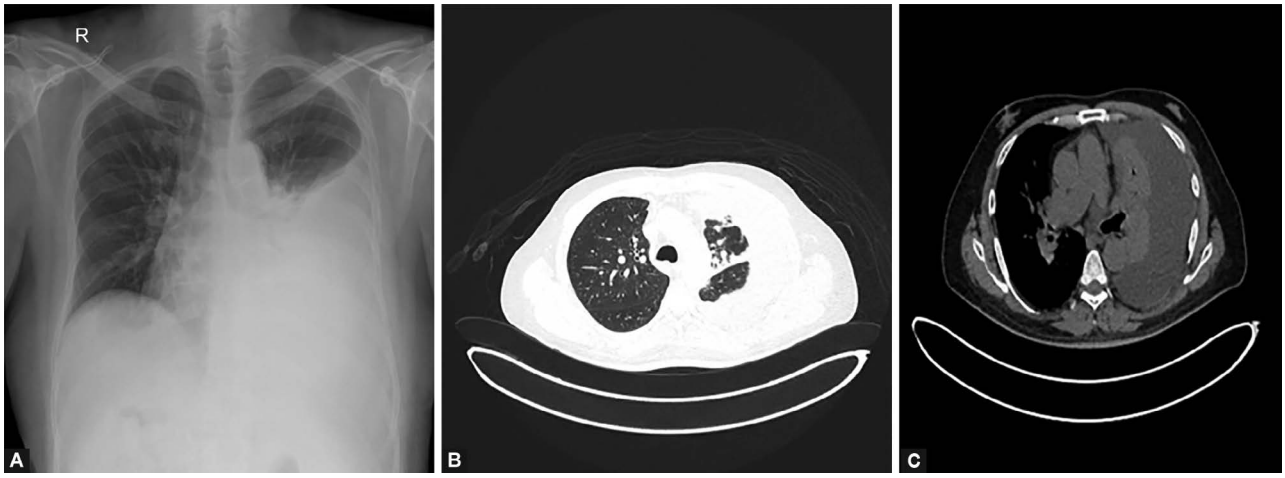
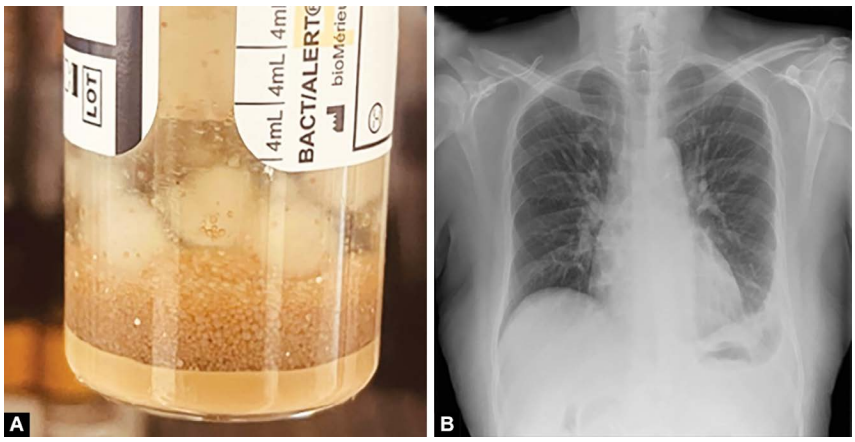
Table 1: Summary of cases of pleural aspergillosis in literature and their Outcomes

Study	*Age/sex*	*Site*	*Complaints at presentation*	*Presentation*	*Diagnosis Method*	*Treatment*	*Outcome*
Zhang et al.[3] (Case series)	Median age—65 years with 90% male patients	Not mentioned	Not mentioned	Mainly postsurgical, pleural *Aspergillus*	Pleural culture/ biopsy	Systemic ± topical antifungals	9 recovered; poor with fistula
Chang et al.[4]	70/male	Right	Shortness of breath, fatigue, and generalized weakness for 10 days.	Smoker with bronchiectatic changes, empyema	Pleural culture/ GalM	VATS + IV voriconazole	Mortality
Zhang et al.[9]	31/ Male	Right	Not mentioned	Recurrent Pneumothorax	Biopsy/culture	Lobectomy and loop ligation of the blebs and Itraconazole for 9 months	Recovery
Kant et al[5]	32/male	Right	Fever, dry cough, right-sided chest pain and progressive breathlessness (2 months)	Pyopneumothorax, tube thoracostomy	Thoracoscopic pleural biopsy & culture	Voriconazole for 6 months and thoracotomy	Recovery
O'Connor et al.[6]	27/male	Bilateral	Not mentioned	Pleural effusion in ABPA	Clinical + labs	Steroids	Resolved
Goel et al.[7]	57/male	Right	Fever, dry cough and chest pain	Pleural-based homogeneous shadow with Pleural effusion	Thoracoscopic pleural biopsy and culture	Thoracotomy and voriconazole	Recovered
Jing et al.[8] (Case series)	Mean age 58.5 years/50% male	Bilateral/left	Chest pain, cough, yellow pus sputum, dyspnea, fever, chest congestion, hemoptysis	Pleural effusion with thickening	Pleural fluid Biochemistry, cytology, culture, NGS, and BALF	Antifungals and thoracoscopic surgery	75% recovered



Figs 1A to C: (A) Chest radiograph showing a large left-sided pleural effusion with mass effect causing a slight midline shift of the mediastinal structures; (B and C) axial CT images of the thorax in parenchymal and mediastinal windows showing moderate-to-large left-sided pleural effusion with underlying lung collapse



Figs 2A and B: (A) Macroscopic appearance of pleural fluid culture showing extensive growth of *Aspergillus fumigatus* with fluffy whitish-gray colonies; (B) follow-up chest radiograph 3 months after catheter removal and continuation of antifungal therapy showing near-complete resolution of the effusion with minimal residual pleural effusion and thickening at the left costophrenic angle

of classic risk factors such as thoracic surgery or bronchopleural fistula does not exclude pleural aspergillosis. Finally, BAL galactomannan testing and fungal cultures can significantly enhance diagnostic yield and should be considered early in the evaluation of unexplained pleural effusions, particularly in individuals with underlying immunocompromising conditions or chronic systemic illnesses.

In conclusion, pulmonary aspergillosis may rarely present as refractory pleural effusion and mimic more common conditions such as tuberculosis or malignancy. A high index of suspicion, combined with appropriate fungal investigations, is essential for timely diagnosis and initiation of antifungal therapy. Recognition of this uncommon presentation can facilitate

earlier treatment and improve clinical outcomes.

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Conflict of Interest

None.

Authors' Contribution

PS, RSB, and DG contributed equally to the study concept, drafting, and writing of the manuscript.

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