Case Report

Aspergillus empyema in a patient with hydropneumothorax: Unveiling the exceptional

Sunayana Mukesh Jangla[1], Susan Cherian[2]

From [1]Consultant Clinical Microbiology, [2]Pathologist and Head, Department of Pathology, Bhabha Atomic Research Centre Hospital, Mumbai, Maharashtra, India

ABSTRACT

Pleural aspergillosis is an unusual form of invasive aspergillosis. A 67-year-old female presented with breathlessness, and a catheter inserted on the left side of the chest for draining pleural fluid. The drained pleural fluid was indicative of empyema and showed growth of *Aspergillus flavus.* Treatment with isavuconazole improved her condition. She had history of pleural tuberculosis and developing hydro-pneumothorax in recent past.She was on immunosuppresant for autoimmune disorder. This case highlights risk factors associated with invasive aspergillosis and emphasizes that such an exceptional condition should be considered a differential diagnosis, especially amidst the above medical background. Equally important is to note that newer and better drugs pave the way for efficient patient management.

Key words: Aspergillosis, Empyema, Invasive, Isavuconazole, Pleural fluid

Pleural aspergillosis refers to direct *Aspergillus* infection of the pleura or pleural space [1]. The various presentations of pulmonary aspergillosis are necrotising *Aspergillus* pneumonia, allergic bronchopulmonary aspergillosis, and invasive aspergillosis [2]. It is an uncommon condition that generally occurs secondary to invasive aspergillosis but can occur with or without involvement of the lung. Fungal pleural effusion comprises only 1–5% and is caused by *Aspergillus fumigatus* or *flavus* [1,2]. It usually occurs in immunocompromised patients or those with previous lung pathologies such as infections or surgeries. This condition has a high mortality rate, particularly when invasive pulmonary aspergillosis develops into fungal empyema thoracis [3,4]. Management of this atypical condition is challenging due to the side effects of existing antifungal drugs, identifying and correcting underlying lung pathology, and concurrent lung disease [3,5].

This is one such out-of-the-blue case of invasive aspergillosis presenting as *Aspergillus* empyema in an adult female on immunosuppressive treatment and previous pleural infection. It also accentuates the importance of clinical correlation of microbiological growth.

CASE REPORT

A 67-year-old married female presented with excessive breathlessness and cough with expectoration for 2 days. There was no fever. On examination, a catheter was inserted on the left side of the chest. She had these complaints for a year, but they aggravated intermittently. A year back, she had presented with similar complaints for which she was diagnosed as having left-sided hydropneumothorax along with bilateral lung consolidation on high-resolution computerized tomography (HRCT) scan. For draining it, a left-sided pigtail catheter was inserted. Pleural fluid was drained. GeneXpert of the fluid was positive for *Mycobacterium tuberculosis* complex. She was started on anti-tuberculosis treatment, which she completed. Two months before her current visit, HRCT was repeated, showing a loculated collection with an air-fluid level in the left thoracic cavity. She is a long-standing case of rheumatoid arthritis on methotrexate and hypertension on anti-hypertensives.

On her current visit, Chest X-ray showed the presence of left-sided pleural effusion and left lower zone opacification. Her white blood cell count was 23,590/μL, C-reactive protein (CRP) was 162 mg/dL, and procalcitonin was 3.02 mcg/L. Pleural fluid was drained, which was turbid and of white color (Fig. 1) with a total count of 50,000 cells, of which 98% were polymorphs. Fine needle aspiration cytology (FNAC) of the fluid revealed it to be a purulent exudate. The cell block of the fluid was stained with Grocott-Gomori methenamine silver stain, which showed black thread-like structures with acute angle branching (Fig. 2). Gram stain showed plenty of pus cells. GeneXpert and acid-fast bacilli stain

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Correspondence to: Dr. Sunayana Mukesh Jangla, Department of Pathology, Bhabha Atomic Research Centre (BARC) Hospital, Mumbai, Maharashtra, India. E-mail: sunayanajangla79@gmail.com

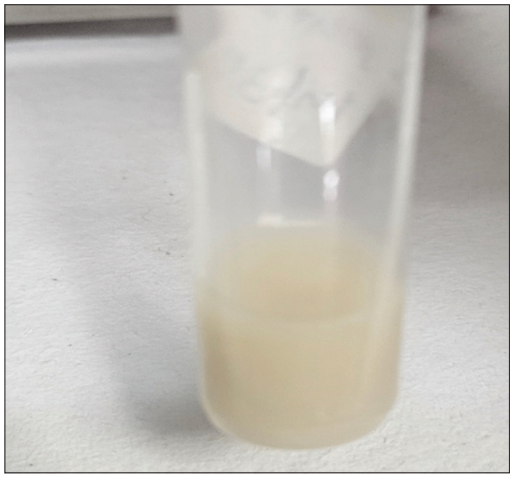

Figure 1: Pleural fluid sample

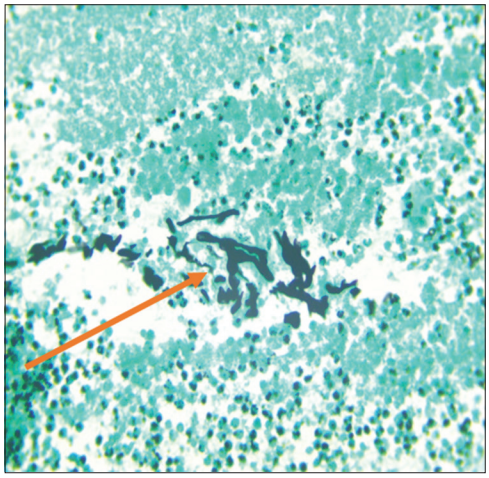

Figure 2: Grocott–Gomori methenamine silver stain of cell block showing black thread-like structures

Figure 3: Growth of fungal mold on chocolate agar and Sabouraud dextrose agar

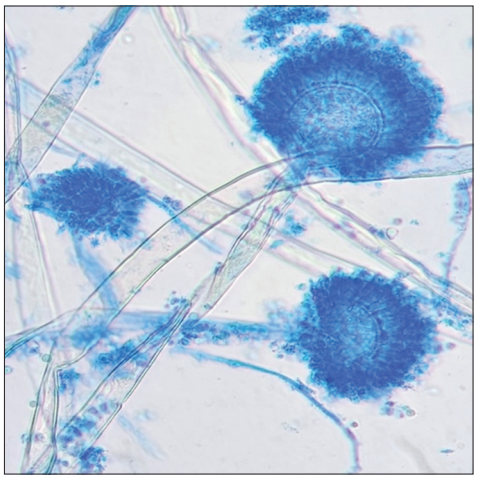

Figure 4: Lactophenol cotton blue mount from growth showing septate hyphae with long conidiophores and phialides covering the entire vesicle (×40)

were negative. Bacterial culture showed growth of white fungal mold with a yellow center on 5% sheep blood agar and chocolate agar at the end of 48 h (Fig. 3). There was no request for fungal culture. However, in the laboratory, the sample was also plated on Sabouraud dextrose agar with and without antibiotics. There was growth of greenish-yellow powdery fungal mold on both media at the end of 24 h (Fig. 3). Lactophenol cotton blue mount of the mold showed septate hyphae with long conidiophores and phialides covering the entire vesicle, and the same was confirmed on slide culture (Fig. 4). It was reported as *Aspergillus flavus*. The fluid was sent for fungal culture in another laboratory, where it showed the same growth.

She was started on oral isavuconazole 200 mg for 15 days. After this, her condition improved, and subsequently, her pleural effusion resolved. The pigtail catheter was removed, and she was discharged. At the end of 3 months, there were no similar complaints.

DISCUSSION

Aspergillosis refers to fungal infections caused by *Aspergillus* species, which include *A. fumigatus*, *Aspergillus niger*, *A. flavus,* and *Aspergillus terreus*. One of the presentations of pulmonary aspergillosis is invasive aspergillosis. Pleural aspergillosis or *Aspergillus* pleurisy is an infrequent condition that usually occurs as a complication of invasive aspergillosis [2]. Most common forms of invasive aspergillosis are rhinosinusitis and pulmonary aspergillosis, whereas chronic aspergillosis and allergic bronchopulmonary aspergillosis occur frequently in patients with underlying respiratory conditions [2]. Organisms causing pleural infection are mainly bacteria and are polymicrobial with diverse bacterial frequencies [6].

Fungal pleural infection is an uncommon condition and constitutes <5% [3]. However, deep fungal infections have increased over the years, with mortality rates being higher, especially in cases of fungal empyema [4,7]. Following *Candida* species, *Aspergillus* spp. are the second most common pathogens causing fungal pleurisy [4,8]. Immune status of the host and route of infection have a considerable role in the development of *Aspergillus* pleurisy. It typically occurs in immunocompromised hosts such as those with hematological malignancy, solid organ transplant, long-term use of anti-bacterial drugs, or those on immunosuppressant therapy. Other important factors that can contribute are hematogenous dissemination from aspergillosis bloodstream infection, active or previous tuberculosis leading to scar tissue development

or formation of bronchopulmonary fistula, the use of thoracic drainage and lung resection, as these add to the risk of *Aspergillus* dissemination from the environment and/or airways into the pleural space [1,2,4,9].

Common routes by which this infection can occur are direct invasion from the lung, adjacent bronchi, and chest wall, or invasion of the pleural cavity from a surgical wound or trauma [4]. Our patient was on immunosuppressant therapy for rheumatoid arthritis. She had developed hydropneumothorax due to past tubercular infection, and for drainage of pleural fluid, a catheter was placed on the left side of the chest. Although she had completed anti-tuberculosis treatment, this condition did not seem to have resolved, as evident on HRCT done a couple of months before her current visit, and the pigtail catheter was still *in situ*. This implied that there was a connection between the lung and the pleura. All these facts make her an ideal host for this infection. Most probably, she must have acquired the organism directly from the lung or while pleural taping. Formation of scar due to treatment and her immunosuppressed status were adjunctive factors.

Management is complex as manifestations are non-specific. Confirmation of diagnosis requires isolating *Aspergillus* species from pleural fluid by microscopic examinations, body fluid cultures, and antifungal sensitivity testing, while radiological diagnosis, such as computerized tomography (CT) scan and X-ray, can be adjunctive. Galactomannan test aids in early diagnosis due to high sensitivity and specificity, and polymerase chain reaction is an important diagnostic modality for confirmation [2,4]. In this case, the pleural fluid was turbid with a significantly high total cell count, indicating acute infection as suggested by the predominant neutrophil count and FNAC. Gram stain also showed plenty of pus cells. Chest X-ray was indicative of left-sided pleural effusion and opacification of the lower zone of the left lung. Other blood investigations, such as CRP, prolactin, and total blood cell count, were also raised, suggestive of infection, affirmative with the presence of empyema. With considerable certainty, her past tuberculosis infection had not healed completely, and the current fungal infection was a super-added entity to the already existing partially treated lung pathology. Being a rare fungal entity, confirmation of fungal pleural infection requires the detection of the fungus by histopathological or cytopathological examination or by culture of the pleural effusion [10]. Furthermore, as per European Organisation for Research and Treatment of Cancer guidelines [11], this is a proven case of *Aspergillus* empyema as the fungus was isolated on two occasions. In this case, the sample was not sent for fungal culture at first. However, the fungus grew on routine bacterial culture media, and since the laboratory had cognizance of this possibility against the given medical background, growth was not disregarded as contamination. This was confirmed when there was the same growth from the sample in another laboratory. Histopathological findings acted as an adjunct to confirm diagnosis.

Due to its uniqueness and underlying pulmonary disease, the ideal treatment for this clinical condition remains yet to be established [1]. Treatment includes administering antifungal therapy and correcting the underlying lung defect. Various options such as amphotericin B and voriconazole are available, with the latter being the drug of choice. However, bearing in mind the immune status of the patient and hepatotoxicity caused by voriconazole, isavuconazole is preferred. It is available as oral and intravenous formulations, has good oral bioavailability, and has fewer drug interactions, making it a reassuring option [2,3,7]. Our patient was treated on similar lines by giving antifungal, and she had already completed anti-tuberculosis treatment.

CONCLUSION

Aspergillus (fungal) empyema is an atypical clinical manifestation of invasive pulmonary aspergillosis that poses a diagnostic dilemma and is hence reported. A high index of clinical suspicion and timely and accurate reports from the laboratory, due to awareness of such a possibility, can go a long way in patient management, especially in such cases with a bad prognosis. It is also essential to bear in mind that clinical correlation of microbiological growth is crucial. Newer treatment options have set the scene for managing such challenging cases.

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