Delayed post-pneumonectomy empyema necessitans caused by *Aspergillus flavus*: An unusual report

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**Abstract**
Post-pneumonectomy empyema (PPE), with or without bronchopleural fistula, is a challenging and serious entity with significant mortality and morbidity. PPE is usually caused by bacteria such as staphylococci, streptococci and also gram-negative rods. Among fungal pathogens, *Aspergillus* species is a very rare cause of this entity. Herein, we describe an unusual case of delayed post-pneumonectomy empyema necessitans caused by *Aspergillus flavus* in a 65-year-old man with favourable clinical outcome by combined surgical and antifungal therapy.

**KEYWORDS**
abscess, *Aspergillus*, empyema, fungal infections, lung cancer, pneumonectomy

**INTRODUCTION**
Post-pneumonectomy empyema (PPE), with or without bronchopleural fistula (BPF), is a challenging, serious and uncommon complication responsible for significant mortality and morbidity. The incidence of PPE with or without BPF is reported between 0.8% and 15%.1,2 It can occur at any time after pneumonectomy, including years later.3 The risk factors consist of general factors including diabetes, sepsis, corticosteroid therapy and local factors including pre-existent empyema, right pneumonectomy and preoperative local radiotherapy.4,5 Pleural empyema is mainly caused by bacteria. Early PPE is mostly associated with poly-microbial cultures, including gram-negative bacteria. By contrast, delayed PPE is mostly mono-microbial with gram-positive bacteria.6 PPE caused by *Aspergillus* species is very rare and mainly affect the immunocompromised hosts. Herein, we report a case of delayed post-pneumonectomy empyema necessitans caused by *Aspergillus flavus* with favourable clinical outcome by combined surgical and antifungal therapy.

**CASE REPORT**
In September 2021, a 65-year-old man presented to the emergency department with a 20-day history of cough and skin erythema with purulent and foul-smelling discharge from the previous thoracotomy site. In April 2019, he underwent right pneumonectomy for lung squamous cell carcinoma in combination with chemotherapy. At admission, the patient was haemodynamically stable and afebrile. Physical examination was unremarkable except for erythema of the right chest wall with cutaneous fistula and purulent discharge. The complete blood count showed a leucocyte count of 11,800 cells/μl, a haemoglobin level of 10 g/dl and a platelet count of 336,000 platelets/μl. Renal function tests and liver enzymes were...
within normal ranges. The pleural fluid analysis was as following: white blood cells: many, Polymorphonuclear leukocytes (PMN): 99%, glucose: 13 mg/dl, protein: 4 g/dl, lactate dehydrogenase: >15,000 IU/L. Empiric treatment with piperacillin-tazobactam (4.5 g every 6 h) and vancomycin (1 g every 12 h) was initiated. According to the right empyema necessitans, the patient underwent drainage of the pleural space immediately. In the operating room, at the site of the previous thoracotomy incision, in the anterior fifth axillary space, incision was made, and about 500 cc of thick and foul-smelling purulent discharge was drained from the area between the skin and the thoracic wall. Then, by entering the right hemithorax cavity, about 2 L of thick pus came out and chest tube was inserted. The purulent discharge and chest wall tissue resection were evaluated for histopathology, smear and culture (Figures 1–3).

Gross pathological examination showed the specimen consisted of one membranous tan-yellow elastic tissue fragment measuring 10 × 5 cm in area and 0.3 cm in thickness. Histopathological examination revealed necrohyalinization with invasion of hyaline septated fungal hyphae (haematoxylin and eosin stain 10 × 20 magnification) with invasion of hyaline septated fungal hyphae (haematoxylin and eosin stain 10 × 20 magnification). Hence, piperacillin-tazobactam and vancomycin were discontinued and intravenous voriconazole 6 mg/kg every 12 h.
for day 1 and 4 mg/kg every 12 h for the following was initiated. Seven days later, Eloesser flap, an open window thoracostomy procedure, was performed successfully which allowed passive drainage of the purulent discharge. This procedure allowed sufficient access to the pleural space, effective packing, serial dressing changes and also debridement, until the cavity became sterile (Figure 5). Due to high inflammation, the bronchial fistula was not manipulated and toilet bronchoscopy was performed at the end. After 10 days, the patient was discharged with favourable clinical outcome and the therapy switched to oral voriconazole.

**DISCUSSION**

PPE is classified into three types including PPE associated with BPF, PPE without BPF or PPE of haematogenous origin. PPE associated with BPF is the most common and serious type that is usually caused by bacteria such as staphylococci, streptococci and also gram-negative rods. Among fungal aetiologies, *Candida* spp. have been more frequently reported than *Aspergillus* species and the latter is a very rare cause of this entity. The incidence of BPF after pneumonectomy is greater than that after lobectomy. Some authors use a 3-week period to distinguish the acute phase from the chronic phase PPE.

When infected pleural fluid dissects the parietal pleura and invades the subpleural tissues, empyema necessitans occurs. Invasion into the surrounding soft tissue of the chest wall leads to subcutaneous abscess formation, which can extend to the trachea, oesophagus and diaphragm. In severe cases, discharge may be externalized. The most likely pathogen for empyema necessitans is *Mycobacterium tuberculosis*, and less commonly are *Nocardia*, *Actinomyces* and *Aspergillus* species.

There are some reports on the spontaneous empyema necessitans caused by *Aspergillus* species and, on the other hand, there are very few cases of post-pneumonectomy *Aspergillus* pleural empyema necessitans.

Lee et al. reported a 58-year-old woman who presented with painful skin rash on the right thorax and three fistulas communicating with the pleural space. Pleural culture showed *Aspergillus fumigatus* and also chest wall biopsy revealed numerous fungal hyphae. The diagnosis of spontaneous empyema necessitans was made and the patient treated with necrotic tissue debridement and antifungal agents. Chen et al. reported a 60-year-old woman who presented with fever, chest wall pain and mild dyspnoea with an abscess formation in area of low density in the chest wall on CT scan of the chest. The resected specimens revealed abundant hyphae of *Aspergillus* species. The patient was treated with itraconazole and surgical debridement.

Bonatti et al. reported four cases of post-pneumonectomy *Aspergillus* pleural empyema. Two patients had lung cancer, one had Hodgkin’s disease and one of the patient acquired aspergillosis by thoracic trauma. The risk factors reported for these patients were poly-chemotherapy, cachexia, locally recurrent, pleural carcinomas and radiation. In all of the four patients, empyema was treated with surgery in combination of voriconazole and caspofungin.

Lampo et al. described a case of an immunocompetent 54-year-old woman, who developed *Aspergillus* pleural empyema invading the thoracic wall and subcutaneous tissues after completion pneumonectomy for aspergilloma. Local and systemic amphotericin therapy for 8 weeks was continued but according to the persistent infection, an open window thoracostomy was performed and the patient was on itraconazole for 6 months with favourable outcome.
Our patient had a history of right pneumonectomy for lung cancer 2 years before his current admission. He was hospitalized because of cough and purulent discharge from the right side of chest wall and the diagnosis of post-pneumonectomy Aspergillus flavus empyema necessitans was made. Another point about our patient is that the last chemotherapy for lung cancer was 2 years ago. The patient was not neutropenic at the time of admission and also had no evidence of other immunodeficiency status.

Management in the late phase of PPE includes sterilization of the pleural space, closure of the BPF and chest wall closure. This closure can only be performed when the pleural cavity has been cleared of Aspergillus. The presented case underwent drainage of the pleural space initially and treated with voriconazole and surgical debridement, and then Eloesser flap procedure was performed with favourable clinical outcome.

In conclusion, PPE with BPF can be caused by Aspergillus species in some patients. A surgical approach combined with antifungal therapy can enable successful treatment of this serious complication.

CONFLICT OF INTEREST
None declared.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

ETHICS STATEMENT
The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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