Successful Treatment of Aspergillus Empyema Using Open Window Thoracostomy Salvage Treatment and the Local Administration of an Antifungal Agent

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Abstract

A 76-year-old woman received long-term immunosuppressive treatment for collagen vascular disease-associated interstitial pneumonia. The patient developed a cavitary mass lesion in the right lower lung field, and both nontuberculous mycobacteria and Aspergillus spp. were isolated after bronchial washing. The patient underwent a right lower lobectomy but developed Aspergillus empyema. Empyema due to Aspergillus spp. is a rare and life-threatening condition; however, the standard therapeutic strategies for treating Aspergillus empyema are not clear. We herein report a case of Aspergillus empyema that was successfully treated with a combination therapy which included open-window thoracostomy and the administration of antifungal agents (systemic micafungin and local amphotericin-B).

Key words: nontuberculous mycobacteria, aspergillosis, empyema, open window thoracostomy

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Introduction

Aspergillus species are a ubiquitous fungus and a common pathogen in humans. In Japan Candida spp. and Aspergillus spp. are the predominant causative agents of visceral mycoses in autopsy cases, and Aspergillus spp. accounts for almost 70% of respiratory fungal infections (1). Refractory cases of nontuberculous mycobacteria (NTM) and Aspergillus spp. co-infections have received attention in recent years (2). The types of pulmonary aspergillosis are classified as aspergilloma, invasive pulmonary aspergillosis, chronic pulmonary aspergillosis (CPA), and allergic bronchopulmonary aspergillosis; however, aspergillus empyema is rare (3). Empyema that is complicated with pneumonectomy occurs in 2-16% of cases (4); in general, the common causative pathogens are staphylococci, streptococci, and gram-negative rods (5). Candida spp. is the most common causative pathogen of fungal empyema, followed by Aspergillus spp. (3, 5). Antimicrobial treatment with voriconazole (VRCZ) for chronic necrotizing pulmonary aspergillosis, and itraconazole or VRCZ for chronic cavitary pulmonary aspergillosis, is recommended in the clinical practice guidelines of the Infectious Disease Society of America (IDSA) (6). Micafungin (MCFG) has also been suggested to be effective for the primary treatment of CPA (7); however, a standard therapeutic strategy for Aspergillus empyema is yet to be established. The present paper reports a case of Aspergillus empyema that was successfully treated with a combination therapy that included open window thoracostomy (OWT) and the systemic and local administration of antimicrobial agents.

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Case Report

A 76-year-old woman was diagnosed with systemic sclerosis (SSc) in July 2001. Collagen vascular disease associated interstitial pneumonia developed in November 2004. In September 2009, a chest computed tomography (CT) scan revealed an increase in bilateral lung ground glass opacity, and dyspnea on exertion and dry cough occurred and gradually worsened. The patient received 6 cycles of high-dose cyclophosphamide therapy in November 2009, followed by oral prednisolone (20 mg/day) and mizoribine (150 mg/day) due to the progression of interstitial pneumonia. The patient’s prednisolone dosage was gradually decreased by 2.5 mg every six months to 10 mg/day in March 2012. Two years after the administration of immunosuppressive treatments, a cavitary mass lesion was observed in the right lower lobe. It gradually enlarged and bronchoscopy was performed to diagnose the lesion. Several pathogens, including Mycobacterium avium, M. intracellulare, Aspergillus fumigatus, and A. terreus, were isolated after bronchial washing of the right B6 bronchus. The patient was treated with clarithromycin (800 mg/day), rifampicin (450 mg/day), and ethambutol (750 mg/day) for pulmonary NTM disease in February 2012; however, she developed right hydropneumothorax (Fig. 1A, a). A microbial examination revealed acid-fast staining positivity (equivalent to Gaffky number 8) in the right pleural effusion, and M. avium was isolated. No fungus was cultured at that time. After the right hydropneumothorax proved to be refractory to drainage therapy, a right lower lobectomy was performed in March 2012. We confirmed an air-leak from a cavity in the right lower lobe during surgery. Pathological findings from the cavitary lesion showed caseating granulomas with acid-fast positivity. Despite the performance of lobectomy, the patient developed right empyema with the recurrence of pulmonary fistula which required surgery in June 2012. The surgical treatment included a tissue sealing technique, pleural decortication, and pleurodesis (Fig. 1B, b). Five months after the second surgery, the infiltration of the right middle lobe gradually deteriorated and another fistula developed. The dead space in the right thorax and pleural effusion also increased (Fig. 1C, c). The patient was then admitted to our hospital in November 2012.

On the day of admission, the patient’s vitals were as follows: body temperature, 37.2°C; blood pressure, 87/66 mmHg; heart rate, 78 bpm; respiration rate, 15 breaths/minute. Fine crackles were heard in both lung fields on auscultation; no other appreciable finding were pointed out in the physical examination. The laboratory findings were as follows: WBC, 13,500/μL with 95% neutrophils; erythrocytes, 379×10⁴/μL; Hb, 11.8 g/dL; platelet, 38.8×10⁴/μL; C-reactive protein, 21.99 mg/dL; serum total protein, 8.3 g/dL; albumin, 2.4 g/dL; lactate dehydrogenase, 336 IU/L; aspartate

![Figure 1](https://example.com/figure1.png)

**Figure 1.** The chest radiograph shows consolidation in the mediastinum side of the right lower lung field with diffuse reticular shadows (A). The chest computed tomography (CT) scan reveals a cavity with a thickened wall and right pneumothorax (a). The dead space in the right thoracic cavity persisted (B, b). Pleural effusion increased and the infiltration of the right middle lobe deteriorated eight months after the right lower lobectomy (C, c).
The intraoperative findings from the open window thoracostomy and debridement. The parietal pleura are entirely covered with xanthochromic pus, suggesting fungal proliferation (A, B).

The infiltration of several pathogenic filamentous fungi inside the pleura was confirmed in the HE-stained specimens at 20-fold magnification (A). Y-shaped branching hyphae are confirmed in both the HE-stained specimens (B) and the Grocott’s-stained specimens (C) at 400-fold magnification. HE: hematoxylin and eosin.

aminotransferase, 17 IU/L; alanine aminotransferase, 11 IU/L; blood urea nitrogen, 15 mg/dL; creatinine, 0.49 mg/dL; HbA1c, 7.0%; procalcitonin, 0.178 ng/mL; β-D-glucan, 22.9 pg/mL; *Aspergillus* galactomannan antigen (enzyme-linked immunosorbent assay), 1.0 COI; KL-6, 629 U/mL; SP-D, 30.2 ng/mL; anti-nuclear antibody, 1:320; and antiribonucleoprotein antibody, 96.5 U/mL. The results of an arterial blood gas (O2: 1 L/min) analysis were as follows: pH, 7.433; PaCO2, 40.9 Torr; PaO2, 60.7 Torr; HCO3-, 26.9 mmol/L; base excess, 2.9 mmol/L; and a-ADO2, 38.175 Torr.

*A. fumigatus* and *A. nidulans* were isolated from the right
pleural effusion on the day of admission, and the patient was diagnosed with *Aspergillus* empyema secondary to surgery. No mycobacterial species were isolated at this time. As bacterial pneumonia was also suspected, we initiated empirical antibacterial therapy upon admission. We also performed chest tube drainage; however, the inflammatory reaction remained severe. We then performed an OWT and debridement of the focus in the parietal pleura on admission day 13 (Fig. 2), and performed a pathological examination of the numerous hyphae infiltrating the pleura (Fig. 3). At the same time, we initiated the systemic administration of MCFG (300 mg/day, intravenously). In spite of the continuation of the above therapies, we found (during the replacement of the gauze inside the thoracic cavity) that the membrane covering the lung was thickening, and several ginger patches which were thought to be fungus balls appeared (Fig. 4A, B). A biopsy of the membrane revealed a large amount of filamentous fungi, and *A. fumigatus* was confirmed by a tissue culture. Surgical debridement of the membrane and local antifungal treatment with daily amphotericin-B (AMPH-B)-immersed gauze dressing were carried out in addition to the systemic administration of MCFG. AMPH-B was infused into 50 mL of normal saline at 1 mg on the first day and was increased in a stepwise manner to 5 mg on the third day, 10 mg on the eighth day, and finally 25 mg on the sixteenth day. The membrane and necrotic tissue covering the pleura disappeared after the daily local antifungal treatment and debridement (Fig. 4C).

The systemic and local antifungal treatments were continued for 2 months after surgery, and the general status and inflammatory reactions gradually improved (Fig. 5). The patient was transferred to another hospital on post-OWT day 57. We were able to successfully control the aspergillosis by the systemic administration of antifungals until June 2014 with the localized application of AMPH-B, after patient changed hospital. No fungi were detected in her cultures until she died due to aspiration pneumonia in November 2014.

**Discussion**

The patient in the present case developed a co-infection of NTM and *Aspergillus* spp. We presume that the cavitary

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**Figure 4.** Pleura course after the open window thoracostomy. The xanthochromatic membrane persisted, even after debridement (A: POD4). The membrane covering the lung thickened, and several ginger patches, thought to be fungus balls, appeared (B: POD16). The thoracic cavity showed significant improvement after the initiation of daily local antifungal treatment and the debridement of the membrane covering the parietal pleura (C: POD 44).
mass lesion due to NTM was the likely cause of the hydropneumothorax. *M. avium* was first isolated from the patient’s pleural effusion. Although NTM-induced empyema has rarely been reported (8-10), some cases have been successfully treated with surgical therapy (11). We decided to perform a right lower lobectomy, as it was difficult to administer conservative management using antibiotics and chest tube drainage. We confirmed an air-leak from a cavity in the right lower lobe during surgery and concluded that the hydropneumothorax was mediated by NTM infection since no pathogens other than NTM were detected from the pleural effusion. After initiating oral chemotherapy for NTM and the aforementioned surgery, the patient’s condition stabilized. However, the pneumothorax recurred because of pulmonary fistula and the patient developed *Aspergillus* empyema. The mortality rates after pneumonectomy for a chronic infection range from 1.2-9.5% (12-15). The rate of morbidities, such as empyema or bronchopleural fistula, is suggested to be relatively high (14, 15), and empyema occurs frequently after pneumonectomy, especially in patients with preexisting empyema (16). *Aspergillus* spp. is one of the most common causes of lung fungal infections; however, *Aspergillus* empyema is uncommon. Although bacteria are the main cause of pleural empyema associated with a bronchial stump leak after pneumonectomy (5), *Aspergillus* spp. can facilitate the emergence of *Candida* species in fungal empyema (3, 5). In the present case, the patient developed pulmonary aspergillosis after co-infection with NTM. She was clinically diagnosed with CPA based on the bacteriological and radiological findings which included a BALF culture (obtained from the right B6 bronchus) which was positive for *Aspergillus*, increased infiltration surrounding the bronchial ectasia, and cystic changes of the right middle lobe over the months of treatment. The disease was exacerbated by the patient’s immunosuppressive status and her empyema developed through pulmonary fistula. We presume that the *Aspergillus* empyema developed after pulmonary aspergillosis. We judged that *Aspergillus* was the main disease state of the empyema at this time in view of its detection and the disappearance of NTM in a bacteriological examination. Pulmonary tuberculosis sequelae, lung abscess, lung cysts, bronchiectasis, and lung cancer are respiratory diseases that are known to be associated with CPA. Diabetes, chemotherapy, glucocorticoid therapy, pleural intubation or drainage, and lung resection are also known risk factors (17-19). Lung fragility due to interstitial pneumonia associated with SSC, lung resection due to NTM, and the long-term use of corticosteroids and immunosuppressants may have contributed to the *Aspergillus* infection in the patient of the present case. There is one report of chronic ne-

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**Figure 5.** Clinical course. PSL: prednisolone, CAM: clarithromycin, RFP: rifampicin, EB: ethambutol, MCFG: micafungin, AMPH-B: amphotericin B, WBC: white blood cell counts (closed circles), CRP: C-reactive protein (open circles), AFS: acid-fast stain.
crotizing pulmonary aspergillosis complicated by a cavitary lesion caused by pulmonary MAC disease (20). There are also reports of cases in which aspergillosis developed secondary to SSC or other collagen diseases (21, 22).

Although fungal empyema is a life-threatening infectious disease, which is associated with a high rate of mortality (3, 19), there is no established standard therapy or standardized antifungal treatment for pulmonary aspergillosis. Recently, VRCZ has been recommended for the primary treatment of invasive aspergillosis (6). For patients who are refractory to VRCZ, a change to another drug class using an AMPH-B formulation, an echinocandin, or a combination, may be efficacious (6). It has been suggested that the systemic administration of MCFG and VRCZ can lead to excellent penetration into the pleural fluid (23). In the present case, we chose intravenous MCFG because VRCZ interacts with rifampicin. MCFG is associated with a significantly lower incidence of adverse events than VRCZ (7). Furthermore, there is no difference in the efficacy of the two drugs in the treatment of patients with CPA (7). No appreciable side effects from MCFG occurred in the present case.

In Aspergillus empyema cases, systemic antifungal treatment can facilitate a limited response. There are some reports of Aspergillus empyema being successfully treated with a combination of systemic antifungal therapy and local irrigation of the pleural cavity with AMPH-B (5, 17, 24-28). Additionally, surgical approaches, including drainage, OWT (5, 17, 24-30) and debridement, are performed in some cases. Table summarizes the data of these aforementioned cases. We performed OWT, as we could not manage the patient’s condition with conservative medical treatment. Immediate OWT is a significant predictor of the healing of empyema after partial lung resection (31); thus, it is recommended that OWT be performed rapidly and aggressively (28).

In conclusion, the present paper reports a case of Aspergillus empyema that was successfully treated with OWT and the systemic and local administration of antifungal agents. Although Aspergillus empyema is an intractable disease, the local administration of antifungal agents in the pleural space seems to be effective, along with both surgical approaches and the systemic administration of anti-microbial drugs.

The authors state that they have no Conflict of Interest (COI).

References