

中文題目：侵襲性肺麴菌病：土麴菌感染病例分享及文獻回顧

英文題目：Invasive pulmonary aspergillosis: A case caused by *Aspergillus terreus* and literature review

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**Introduction:** Invasive aspergillosis is an infection caused by the ubiquitous saprophytic fungus, *Aspergillus* species, that accounts for the majority of invasive fungal infections in the immunocompromised population. Common risk factors include preexisting pulmonary diseases, hematopoietic stem cell transplantation, prolonged neutropenia, solid organ transplantation, and critical illnesses. The most common causative pathogens include *A. fumigatus* species complex, *A. flavus* species complex, and *A. terreus* species complex. Here, we present a case of invasive pulmonary aspergillosis caused by *A. terreus* that was treated by isavuconazole, the newest triazole.

**Case presentation:** A 48-year-old man with right upper lung adenocarcinoma recently started his third cycle of taxotere seven days ago was admitted with low-grade fever, dyspnea, and neutropenia. Antibiotic therapy with piperacillin/tazobactam was initiated for neutropenic fever, but was later shifted to imipenem/cilastatin and levofloxacin due to progressing pneumonia. Chest computed tomography (CT) on day 6 of hospitalization revealed a right upper lung cavitory lesion in a background pattern of bilateral ground glass opacification. The initial *Aspergillus* galactomannan (GM) antigen levels was not elevated. Sulfamethoxazole/trimethoprim was prescribed under the suspicion of *Pneumocystis jirovecii* pneumonia (PJP), while steroids was added for suspected taxotere-induced pneumonitis of the left lungs. Endotracheal intubation was performed on Day 11, followed by shock. The patient was transferred to the Medical Intensive Care Unit for further care.

At the Medical Intensive Care Unit, unstable respiratory pattern with worsening bilateral lung pneumonia had continually been noted. Treatment regimen for PJP was then changed to clindamycin and caspofungin for suspected resistant PJP. Bronchoscopy on Day 19 revealed the presence of whitish plaques at the orifice of right upper bronchus and right middle bronchus with occlusion of the right upper bronchus. The bronchoalveolar lavage (BAL) gram staining clearly showed the presence of conidiophores under direct microscopy. Empirical voriconazole was thus initiated. The tissue culture later confirmed the growth of *Candida albicans* and *Aspergillus terreus*. Both the serum GM test (index = 20) on Day 17 and the bronchoscopy pathology supported the nature of invasive aspergillosis. Infectious Diseases was re-consulted and antifungal treatment was shifted to isavuconazole (since D21). Follow-up bronchoscopy (Day 25) showed improving invasive aspergillosis and pulmonary candidiasis of the right bronchus. However, clinical deterioration ensued.

Follow-up survey showed worsening inflammatory profiles with rapidly progressing bilateral lung pneumonia. Emergent bronchoscopy (on Day 28) noted increased sputum production within the right lower bronchi. Under the impression of progressing ventilator-associated pneumonia, empirical antibiotic was shifted to the combination regimen of tigecycline, doripenem, and colistin (both inhaled and intravenous dosings). Both blood and endotracheal aspirate cultures returned with the growth of *Acinetobacter baumannii*. Clinical improvement was only noted briefly. Progressing right lower lung pneumonia was noted again since Day 37, followed by shock. Bronchoscopy on Day 38 revealed large amounts of pus-like sputum within the right lower and middle bronchi. Chest computed tomography on Day 40 reported pneumonia/abscess of the right lung with invasion into the other right lung and mediastinum. Based on the blood and bronchoalveolar lavage culture results (*Serratia marcescens*), his antibiotic regimen was readjusted to imipenem/cilastatin (since Day 40) and colistin (inhaled and intravenous). Lower BAL galactomannan test levels (35, 79, 324 Index, respectively on Days 19, 28, 38) continued to rise. His clinical conditions continued to deteriorate. The patient expired on Day 49 of hospitalization.

**Discussion:** Definite treatment in the early stages of invasive pulmonary aspergillosis is critical for treatment response. But early diagnosis of the disease has been clinically challenging. Our present case was able to diagnose invasive pulmonary fungal infection from the initial bronchoscopy via direct microscopy of the BAL. Voriconazole and isavuconazole were used consecutively for treatment. Isavuconazole was approved by the Taiwan Food and Drug Administration in January 2020 for invasive aspergillosis and mucormycosis. The phase 3 randomized double-blind non-inferiority trial, SECURE trial, showed non-inferiority of isavuconazole to voriconazole. Other studies had shown significantly less adverse events in patients treated with isavuconazole as compared with those treated by other azoles.

**Conclusion:** *A. terreus* infection is associated with a poor clinical outcome with the well-known innate tolerance/resistance to the polyene antifungal amphotericin B. At present, limited reports are available for invasive aspergillosis treated by isavuconazole.