Pleural aspergillosis in a patient with recurrent spontaneous pneumothorax: The challenge of an optimal therapeutic approach

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ABSTRACT

Keywords:
- Recurrent pneumothorax
- Pleural aspergillosis
- Pleural instillation
- Hepatotoxicity
- Isavuconazole

Pleural aspergillosis (PA) is a rare but potentially fatal disease. Most cases are secondary to bronchopleural fistulae or pleural intervention and can occur in the absence of immunosuppression.

We report a case of PA in a young patient after pleurodesis for recurrent pneumothorax. Clinical resolution was achieved with systemic and local antifungal therapy combined with surgical debridement. Hepatotoxicity led to a switch from voriconazole to isavuconazole, with a successful outcome.

1. Introduction

Pleural aspergillosis (PA) is an uncommon manifestation of invasive aspergillosis, and fungal etiology is present in less than 5% of all pleural effusions [1]. Active or previous tuberculosis, bronchopleural fistulae, pleural drainage and lung resection are considered the main predisposing conditions for Aspergillus infection of the pleural space [2,3]. Curiously, classical risk factors for invasive pulmonary aspergillosis, mainly immunosuppression, do not seem necessary for the development of pleural aspergillosis [4].

Due to its rarity, the optimal therapeutic approach is not established. Besides conventional systemic antifungal therapy and thoracic drainage, local pleural instillation of antifungal drugs has been successfully used, especially in patients with persistent pleural fungal infection despite optimized systemic treatment [2,5,6].

The management of side effects related to the antifungal drugs, the failure to identify and surgically correct the primary lung defect or to control the subjacent lung disease are all possible causes of morbidity and potential death in these patients.

We describe the case of a young patient who developed pleural aspergillosis after a thoracic procedure and discuss possible therapeutic options in this context.

2. Case

A 24-year-old male patient was electively admitted for pleurodesis (day 0). He was an active cigarette smoker and had two previous episodes of spontaneous pneumothorax (the first 3 years prior to this hospital admission and the second episode 6 months before), that resolved with thoracic drainage. Diagnostic work-up after the second event included a thoracic CT scan, which identified pulmonary emphysema (predominantly in the right upper lobes) and subpleural blebs (Fig. 1A). However, no immunodeficiency was identified, and he had no respiratory symptoms or pulmonary function test abnormalities.

Surgery was performed to prevent recurrent pneumothorax and consisted of Video Assisted Thoracic Surgery blebectomy and talcage, performed on day 0.

On day +12, the patient developed fever, and empirical vancomycin and cefepime were started considering possible post-operative related respiratory infection. Lack of clinical improvement and persistent fever raised concerns of thoracic empyema. A thoracic CT scan was done at this point and showed a consolidation area in the right upper lung, where the surgical intervention was performed.

A surgical revision was performed on day +14. There was intraoperative confirmation of complete lung suture dehiscence and inspection of the pleural space identified multiple pleuro-parietal adhesions, talc residues and the presence of a thick, yellowish pleural fluid. Intraoperative samples of pleural fluid and tissue were sent to culture. An extensive surgical debridement was made and a thoracic drain was replaced for further drainage.

After a preliminary report of fungal growth, Aspergillus fumigatus was identified on day +17 in mycological culture of pleural fluid and lung tissue samples (no antifungal susceptibility testing was performed as it is not available in our institution); bacterial growth was negative. Antimicrobial therapy was stopped and after 24 hours of amphotericin B (5 mg/kg/day), intravenous voriconazole (VZ) was started (loading...
dose of 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg/day, corresponding to 200 mg/day). By day +18, thoracic drainage was minimal and the drain was removed. Table 1 summarizes the antifungal drugs used and analytical changes over the course of treatment.

Pleural fluid was the only biological fluid where *Aspergillus fumigatus* was isolated. There was no fungal identification in the patient’s bronchoalveolar lavage (myological culture, DNA probes and galactomannan) or blood samples (blood cultures, DNA probes and serum galactomannan). An exhaustive investigation of possible causes of immunodeficiency, that included HIV screening; peripheral blood lymphocyte immunophenotyping; serum immunoglobulin levels; serum C1q and C3c complement fraction levels; anti-nuclear antibodies, anti-neutrophil cytoplasmatic antibodies and neutrophil oxidative burst assay were performed; all results were negative.

Persistent fever and elevated inflammatory markers prompted a new thoracic CT scan on day +23, which identified a hydro-pneumothorax cavity in the right apical lung, in close proximity to the lung resection line (Fig. 1B). A thoracic pigtail drain was introduced in this cavity, with subsequent drainage of a purulent fluid, in which *Aspergillus fumigatus* was once again identified by myological culture.

On day +25, after 8 days of VZ treatment, there was evidence of liver injury, with an elevation of four times the normal range of all liver enzymes. Bilirubin levels and coagulation times were normal (liver injury, with an elevation of four times the normal range of all liver enzymes values available in Table 1.). Hepatotoxicity secondary to VZ was assumed and antifungal therapy was switched to liposomal amphotericin B (LAmB) (5 mg/kg/day, corresponding to 300 mg/day). A request for oral isavuconazole was accomplished by day +113 (200 mg every 8 hours for 2 days and then 200 mg/day).

The patient completed 65 days of isavuconazole treatment, with no gastrointestinal complaints or evidence of hepatic or renal toxicity.

Following 6 months of systemic antifungal treatment and documented radiological resolution of the pneumothorax cavity (Fig. 1C), treatment was stopped.

A year and half later, the patient remains asymptomatic, with no new episodes of spontaneous pneumothorax and with normal pulmonary function tests. He is still regularly observed on the outpatient clinic of the Pneumology department at our hospital center.

### 3. Discussion

Invasive aspergillosis (IA) usually occurs in patients with risk factors for this infection: hematological malignancies, solid tumors, critical illness, HIV/AIDS, allogeneic stem cell transplantation and solid-organ transplantation, especially among patients with prolonged neutropenia. However, IA has also emerged as an important cause of morbidity and mortality in non-neutropenic patients without underlying diseases [7]. Our patient had none of these classical risk factors.

Pleural aspergillosis (PA) is a rare form of IA that is not always associated with pulmonary infection [8]. Immunosuppression does not seem to be an obligatory condition for the development of pleural aspergillosis and several cases describe its occurrence in immunocompetent patients [4,9,10]. Previous lung interventions, such as the use of thoracic drains, lung resection or pleurodesis, as well as scar tissue development secondary to previous lung disease (like, for instance, tuberculosis), seem to play a much more important role [2,6,8,11]. Colonization during these procedures and/or the development of bronchopleural or pleurocutaneous fistulae increase the risk of *Aspergillus* dissemination from the environment and/or airways into the pleural space [12]. Although being an otherwise healthy patient, the two previous thoracic drains due to pneumothorax could have played a role in the pathogenesis of this infection in our patient.

Additionally, it is possible that the pre-existing subpleural blebs and pulmonary emphysema were not innocent bystanders. It has been hypothesized that patients with chronic pulmonary disease have persistent airway inflammation that raises the chance of *Aspergillus* spores being sequestered in the bronchoalveolar tree. This, in turn, could lead to partial obstruction of small bronchioles and induce the formation of blebs with worsening lesions over time [13]. Rare cases of chronic forms of pulmonary aspergillosis, such as allergic bronchopulmonary aspergillosis, have been described as the cause of pleural aspergillosis.

**Fig. 1.** 1A: Thoracic CT scan after the second episode of pneumothorax. Notice the presence of paraseptal emphysema, predominantly in the upper lung, with multiple subpleural blebs. 1B: Thoracic CT scan shows an hydro-pneumothorax chamber with 10 × 10 cm (axial plane) and 7.5 cm (longitudinal plane) in the right upper lung. 1C: Thoracic CT scan after 6 months of therapy. Evidence of complete resolution of the pneumothorax cavity. Maintenance of pulmonary emphysema.
### Table 1

| Occurrence | Voriconazole (VZ) | Liposomal Amphotericin B (LAMB) | Liposomal Amphotericin B (LAMB) | Abstract Isavuconazole |
|------------|------------------|--------------------------------|--------------------------------|------------------------|
| Days since surgery | Day 0 | Day 1 | Day 17 | Day 25 |
| Antifungal treatment (days) | Day 0 | Day 2 | Day 8 | Day 12 |
| Time of systemic hepatotoxicity attributed to VZ (days) | Day 0 | Day 10 | Day 12 | Day 20 |
| Time of pleural aspergillosis (days) | Day 0 | Day 3 | Day 7 | Day 15 |
| Leukocyte count (μL) | 12.80 | 7.85 | 11.01 | 7.39 |
| Albumin (g/L) | 36.8 | 39.8 | 34.7 | 42.0 |
| AST (IU/L) | 25.5 | 27.1 | 21.4 | 28.6 |
| ALT (IU/L) | 18.0 | 16.3 | 12.8 | 14.6 |
| Total bilirubin (μmol/L) | 0.55 | 0.49 | 0.49 | 0.55 |
| Creatinine (mg/dL) | 0.71 | 0.70 | 1.29 | 1.52 |
| CRP (mg/L) | 297.8 | 267.2 | 81.0 | 122.3 |

**Legend:** ALP – Alkaline Phosphatase; ALT – Alanine transaminase; AST – Aspartate transaminase; CRP – C-reactive Protein; GGT – Gamma-Glutamyl transferase; NA – Non-Applicable.

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In conclusion, pleural aspergillosis is a rare occurrence which is usually associated with previous pulmonary interventions. Clinical management is complex and requires effective local control and antifungal therapy. Local instillation of antifungal drugs can be a helpful resource and facilitate pleural sterilization. Careful consideration of the antifungal drugs toxicity profile is needed and in cases of hepatotoxicity, isavuconazole may be a reliable option.
Declaration of competing interest

There are none.

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