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

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ABSTRACT

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

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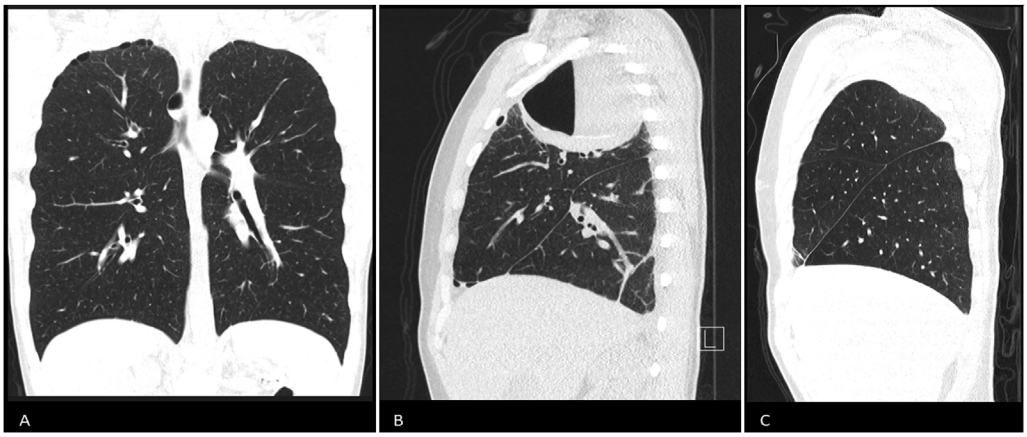

Fig. 1. 1A: Thoracic CT scan after the second episode of pneumothorax. Notice the presence of parasseptal emphysema, predominantly in the upper lung, with multiple subpleural blebs. **1B:** Thoracic CT scan shows an hydropneumothorax chamber with 10 × 10 cm (axial plane) and 7,5 cm (longitudinal plane) 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.

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 (mycological 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 hydropneumothorax 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 mycological 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 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).

Following this change, there was no recurrence of fever, serum inflammatory markers decreased, and liver enzymes slowly returned to normal. However, after more than 30 days of systemic antifungal therapy, there was persistent high-volume purulent thoracic drainage. By day +38, *Aspergillus fumigatus* was again identified in the pleural fluid's mycological culture. The Cardiothoracic Surgery and Infectious Diseases teams agreed on starting pleural instillation of conventional amphotericin B by the thoracic drain [5 mL (mL) of the drug in 70 mL of 5% glucose solution]. Five days later the patient developed fever with simultaneous rise of C-reactive protein. This led to the interruption of conventional amphotericin B instillation and removal of the thoracic drain, as there was concern that the fever could be secondary to local administration of the drug. Actually, a diagnosis of acute pyelonephritis with acute renal failure was made a few days later. This was further complicated by nosocomial pneumonia, requiring a 14 days treatment course with piperacillin/tazobactam and linezolid.

Pulmonary tuberculosis and aspergillosis were screened in every opportunity. All tests were persistently negative. There was also no evidence of a bronchopleural fistula.

A new attempt to switch from LAmB to (oral) VZ (with a loading dose of 400 mg every 12 hours for 2 doses and then 200 mg every 12 hours) was made on day +55. This was again complicated by hepatotoxicity and required stepping back to LAmB (5 mg/kg/day, corresponding to 300 mg/day). A request for oral isavuconazole was made at this point. The patient was discharged at day +73 and kept outpatient therapy with LAmB. A switch to 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

Table 1
Antifungal treatment: sequence, duration and associated toxicities.

Antifungal drugs	Voriconazole (VZ)	Liposomal Amphotericin B (LAmB)			Voriconazole (VZ)		Liposomal Amphotericin B (LAmB)		Isavuconazole			
Occurrence	Evidence of pleural infection by *Aspergillus fumigatus*.	Hepatotoxicity. Switch from VZ to LAmB	–	–	Attempted switch to oral VZ.	–	Hepatotoxicity attributed to VZ.	–	Switch to an oral regimen.	Interruption of isavuconazole. End of treatment.	–
Days since surgery	Day +17	Day +25			Day +57		Day +68		Day +113	Day +178	Day +424
Time of systemic antifungal treatment (days)	Day 0	Day +8	Day +20	Day +36	Day +40	Day +50	Day +51	Day +67	Day +96	Day +133	Day +161	NA
Time of specific drug (days)	Day 0	Day 0	Day +12	Day +28	Day 0	Day +10	Day 0	Day +16	Day 0	Day +37	Day +65	NA
Leukocyte count (μ/L)	12.80	7.85	11.01	7.39	5.71	4.17	–	5.57	6.15	4.72	6.13	6.42
Albumin (g/L)	52.5	25.5	36.8	34.7	–	42.0	–	41.7	39.8	47.2	42.6	46.9
AST (IU/L)	22	171	17	19	13	65	–	36	34	21	24	24
ALT (IU/L)	25	207	23	34	18	93	–	63	41	23	36	24
ALP (IU/L)	–	654	286	146	128	165	–	144	108	98	85	105
GGT (IU/L)	–	639	286	116	102	217	–	94	47	44	29	30
Total bilirubin (μmol/L)	–	0.66	0.55	0.49	0.56	0.47	–	0.25	0.17	0.35	–	0.56
Creatinine (mg/dL)	0.71	0.70	1.29	1.52	27.1	0.95	–	0.90	15.7	1.03	0.83	0.84
CRP (mg/L)	297.8	247.2	81	122.3	1.52	9.7	–	16.3	1.00	6.5	8.2	14.0

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

[14] and therefore should be excluded in the presence of PA.

Early recognition of fungus as the causing agent and combination of early antifungal therapy with pleural drainage are consensual measures in order to achieve clinical resolution [9,15]. Screening for bronchopleural or pleurocutaneous fistulae and correcting the identified defects is mandatory if complete resolution is intended.

Regarding the choice for the optimal systemic antifungal regimen, there are a few options. Consideration of institutional access variability to more recent antifungal drugs (as isavuconazole) and experience in managing potential side effects related to therapy should be taken into account when making a decision.

Systemic amphotericin B (conventional and liposomal) has been frequently used, either alone or in combination with an echinocandin [2,3,6,11], especially in the initial stages of infection, in seriously ill patients and/or in cases of disseminated infection. However, voriconazole (VZ) should always be the first option, particularly because it has activity against all *Aspergillus* species, excellent bioavailability, possible therapeutic drug monitoring and good penetration in the pleural space [5]. However, susceptibility testing is of growing importance considering the increasing rate of azole resistance of *Aspergillus fumigatus*, especially in the absence of clinical response [16]. Regarding itraconazole, there was one case report in which it was used with good clinical response [13]. Isavuconazole was approved in 2015 for the treatment of IA. The availability of intravenous and oral formulations, good oral bioavailability and reduced drug-to-drug interactions makes it a promising therapeutic option.

In our clinical case, voriconazole's induced hepatotoxicity precluded its use and meant that alternative options (ideally oral drugs) had to be considered. When considering the hepatotoxicity potential of oral antifungal drugs, a relative frequency of 2–11% and < 5% for posaconazole and isavuconazole, respectively, have been described [17]. With our patient, the decision was to privilege the antifungal drug option with the least hepatotoxic profile.

Pleural instillation with antifungal drugs, in combination with systemic treatment or as an exclusive therapeutic approach have been described, both in children and adults [2,6,11,12,18,19]. The mechanism of action is not established, but sclerosis of the infected pleural space probably explains the clinical results (rather than direct antifungal activity) [11].

Pleural instillation with antifungal drugs is usually well tolerated, with a few patients reporting mild cough during administration. Rare complications of percutaneous administration of therapy into the pleural space include pneumothorax, percutaneous emphysema and hemoptysis [20]. Considering the benefits and potential complications, pleural antifungal instillation should be pondered in cases of persistent pleural fungal infection and protracted clinical course.

Treatment duration is dependent on clinical evolution, ability to provide adequate surgical control and management of treatment associated toxicities. Systemic antifungal treatment duration is highly variable, ranging from 2 to 13 months in previously referenced case reports.

Reported mortality for this infection is high; however, it seems to be more driven by the fragility and complexity of the majority of these patients, rather than by the fungal infection itself [2]. Nonetheless, prolonged systemic antifungal treatment is essential for cure.

In our case report, a 6-month period of systemic antifungal treatment was established considering there was clinical stability, radiological improvement and no need for new surgical procedures. Clinical and microbiological cure was achieved.

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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