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Fatal invasive aspergillosis caused by *Aspergillus niger* after bilateral lung transplantation

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ABSTRACT

Aspergillus niger is usually considered to be a low virulence fungus, not commonly reported to cause invasive infections. Invasive pulmonary aspergillosis due to *Aspergillus niger* was diagnosed in a 43-year-old woman following bilateral lung transplantation. Intravenous voriconazole failed to control progression of the disease. Despite salvage therapy with a combination of voriconazole and caspofungin for 23 days, the patient developed massive hemoptysis leading to death. The authors report the clinical features and treatment of this case.

1. Introduction

Invasive aspergillosis is a common complication after lung transplantation (LT) and is associated with high morbidity and mortality rates [1,2]. Most cases of invasive aspergillosis are caused by *Aspergillus fumigatus*. *Aspergillus niger* is usually considered to be a low virulence fungus. We report a case of fatal invasive pulmonary aspergillosis caused by *Aspergillus niger* in a 43-year-old woman after LT.

2. Case report

A 43-year-old woman with α1-antitrypsin deficiency emphysema underwent bilateral LT. Sputum analysis performed prior to transplantation did not reveal any evidence of bacterial or fungal colonization. Surgery was performed according to the usual procedure [3]. According to our standard protocol, perioperative antibacterial prophylaxis by cefamandole was administered at induction of anesthesia, and continued for 48 h. No antifungal prophylaxis was administered to the patient. Immunosuppressive therapy was based on a combination of prednisolone, mycophenolate mofetil and tacrolimus. Cytomegalovirus prophylaxis with ganciclovir was administered, due to lung donor and recipient positive serologies.

Multiple infectious complications occurred after the surgical procedure. Two days after LT, *Candida albicans* was isolated from a respiratory sample. Ischemic bronchitis and a small zone of bronchial necrosis were discovered on fiberoptic bronchoscopy at Day-6 and fluconazole (400 mg per day, IV route) was initiated according to our standard practice. On the same day, bacterial pneumonia was diagnosed, associated with multiple organ dysfunction syndrome, with hemodynamic failure, acute respiratory distress syndrome, and anuric acute renal failure, requiring continuous hemofiltration. Empiric antimicrobial therapy by cefepime was initiated and was deescalated to cefotaxime after identification of *Klebsiella pneumoniae*, for a total duration of 7 days. Pneumothorax was diagnosed on chest X-ray on Day-9. Chest CT scan performed on Day-14 confirmed the persistence of right anterior pneumothorax despite percutaneous pleural drainage and demonstrated the presence of a right posterior bronchial anastomosis fistula, and the presence of numerous bilateral cystic lesions in a large zone of consolidation of the right lower lobe (Fig. 1). Serum galactomannan assay, performed on Day-16, was negative. On the same day, *Pseudomonas aeruginosa* bacterial pneumonia was diagnosed, and treated by ceftazidime and amikacin for a total duration of 10 days.

On Day-18, *Aspergillus niger* was cultured from bronchial aspirate, in combination with *Candida albicans*. The presence of *Aspergillus niger* was confirmed in BAL performed on Day-22, associated with a high galactomannan concentration in BAL (cutoff optical density (OD) index = 4.55; Platelia™ *Aspergillus* EIA, BioRad, Marnes la Coquette, France). Voriconazole (800 mg (13 mg/kg) on the first day, then 400 mg daily (6 mg/kg) intravenously) was initiated on Day-21. Despite voriconazole therapy, *A.niger* cultures were obtained on repeated BAL samples. A

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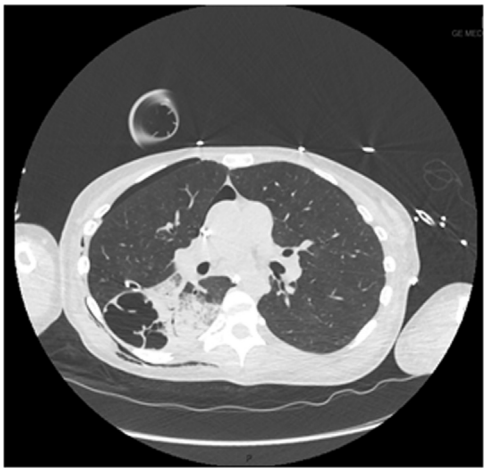

Fig. 1. Chest CT scan performed on Day-14.

progressive extension of images was noted on chest CT scan, involving the right upper lobe on Day-21 (Fig. 2). Due to progression of the lung lesions, caspofungin (70 mg on the first day, and then 50 mg daily) was introduced on Day-23, in combination with voriconazole, as salvage therapy. However, subsequent BAL samples remained positive for *A. niger*. Susceptibility to voriconazole was confirmed by susceptibility testing on Day-22 (voriconazole MIC 0.19 mg/L; micafungin MIC 0.004 mg/L), and Day-38 (caspofungin MIC 0.004 mg/L). Serum and BAL galactomannan concentrations were monitored (Table 1). Serum voriconazole concentrations were also assayed by isocratic high-performance liquid chromatography with ultraviolet detection (255 nm) [4], with concentrations ranging between 0.9 and 1.2 mg/L (Table 2). The daily dose of voriconazole was increased to 500 mg per day on Day-34 (8 mg/kg/day), because of low serum concentrations. On Day-45, whole-body CT scan ruled out any extrapulmonary sites of invasive aspergillosis.

The patient experienced hemoptysis on Day-37. Despite several interventional vascular radiology procedures designed to ensure occlusion of multiples pseudoaneurysms between Day-37 and Day-46, hemoptysis persisted. A recurrence of hemoptysis on Day-46 was complicated by hypoxic cardiac arrest. Arteriography revealed two pseudoaneurysms that were treated by occlusion. On the same day, massive hemoptysis led to refractory cardiorespiratory arrest and to the patient's death.

3. Discussion

Invasive fungal infections (IFI) are common complication after LT, responsible for high mortality and morbidity rates [1,2]. *Aspergillus* species are responsible for 44% of all fungal infections after LT [5]. Several forms of infections have been described, including tracheobronchitis, anastomosis infection, pulmonary invasive aspergillosis, and disseminated aspergillosis. A great majority of these complications are caused by *A. fumigatus* [6]. *Aspergillus niger* is usually considered to be a low virulence fungus, and is not commonly reported to cause invasive infections. Its low virulence is explained by various physiological characteristics. The large size of *A. niger* conidia and the presence of strong interspore bridges make penetration into the lower respiratory tract more difficult [7]. The ideal temperature for growth is around 30 °C, making germination difficult at human body temperature [8]. The pathogenicity of *A. niger* is also limited by its acidophilic nature [9]. These characteristics explain why *A. niger* invasive infection only occurs in a context of severe immunosuppression. Only a few case reports of *A. niger* invasive infections have been published: a few cases of pulmonary aspergillosis [10,11], two cases of tracheobronchitis [7,12], and one case of peritonitis in a patient on peritoneal dialysis

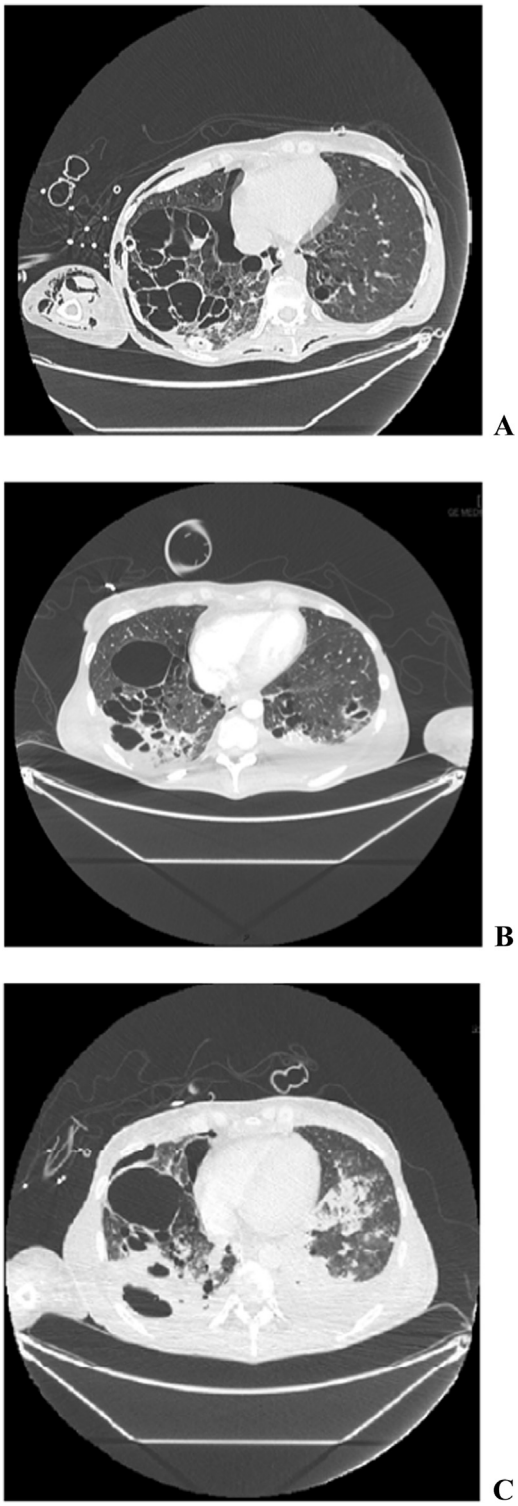

Fig. 2. Evolution of pulmonary images (chest CT scan performed on Day-21 (Panel A), Day-29 (Panel B), Day-45 (Panel C)).

[13]. Among 194 documented cases of invasive aspergillosis in a cohort of patients with hematologic diseases over a 10-year period, only eight cases (4%) were due to *Aspergillus niger* [14].

An unusual feature of the present case report is the development of invasive aspergillosis during the early postoperative period. Invasive aspergillosis usually occurs later, a median of 271 days after lung transplantation [2]. This early onset could be explained by the absence of systematic antifungal prophylaxis in our center. Antifungal prophy-

Table 1
Serum and BAL galactomannan levels expressed in cutoff optical density (OD) index.

Day after LT	BAL galactomannan	Serum galactomannan
Day 16		0
Day 22	4.55	
Day 23		1.89
Day 31		2.08
Day 36		3.17
Day 38	5.68	

Table 2
Serum voriconazole concentrations.

	Serum voriconazole concentrations (mg/L)
Day 25	**0.9**
Day 35	**1.2**
Day 44	**0.9**

laxis policies are heterogeneous worldwide, as no published guidelines were available until recently. In a previous study, a universal antifungal prophylaxis was used in 59% of LT centers after LT [15]. However, an earlier study performed in a non-cystic fibrosis population suggested that the incidence of invasive fungal infections was not increased in the absence of universal antifungal prophylaxis [2]. Our patient presented several risk factors for invasive aspergillosis: postoperative complications, recurrent bacterial infections or hemofiltration are usual risk factors for early invasive aspergillosis [1]. It is also noteworthy that this patient had no previous Aspergillus colonization prior to transplantation and did not present any CMV infection or acute rejection, while these conditions are commonly recognized to be risk factors for invasive aspergillosis. No other case was observed over the same period of time in our center.

Interestingly, despite voriconazole antifungal therapy for 25 days, and salvage therapy by a combination of voriconazole and caspofungin for an additional 23 days, *A. niger* persisted in all BAL samples, despite its susceptibility to voriconazole and caspofungin confirmed by two tests. This unsuccessful outcome can be explained by several factors. Firstly, invasive aspergillosis is a severe complication after lung transplantation, responsible for high mortality rate, estimated to be about 55% [2]. Secondly, the modalities of our treatment may need to be reviewed. Since the study by Herbrecht et al. [16], voriconazole has become the first-line treatment for invasive aspergillosis, with successful outcome in 53% of patients. Caspofungin has been proposed as second-line treatment when conventional treatment is not tolerated, or in the case of refractory aspergillosis [17], leading to a favorable response in 40% of cases. Several non-randomized clinical trials have suggested the benefit of various combination therapies for invasive aspergillosis, especially caused by *A. niger* [18]. According to the Infectious Disease Society of America (IDSA) guidelines, combination therapy may be used as salvage therapy, but is not recommended as first-line treatment [19]. Finally, amphotericin-B could have been proposed, but renal replacement therapy is a major limitation to the use of this drug.

In this case, serum voriconazole assays revealed low serum levels, which could partly explain the unsuccessful outcome. Monitoring of serum voriconazole levels remains controversial, as marked variability of serum voriconazole concentrations has been reported in healthy hosts, due to variable host CYP450 enzyme activities. In a retrospective review [20], a pharmacokinetic-pharmacodynamic breakpoint was observed around 2.05 μg/mL. When the serum voriconazole concentration was below this breakpoint, 44% of patients experienced disease progression [20]. Finally, adjuvant treatments are also useful in invasive aspergillosis. In this case, the dosage of immunosuppressive therapy was reduced from Day-40 until the patient's death, as recommended by IDSA guidelines [19]. Surgical resections can also be useful when lesions are contiguous to great vessels or pericardium, when a single cavitary lesion is responsible for hemoptysis, or when infection involves the chest wall [19]. In the present case, surgical resection was not possible due to the presence of large, bilateral pulmonary lesions.

This case illustrates the value of serum and BAL galactomannan assays for diagnosis and evaluation of the efficacy of treatment, even in the case of *Aspergillus niger* infection. Galactommanan assay is not recommended by IDSA for screening in SOT recipients, however, as illustrated by this case, it could be useful to confirm the pathogenic role of *Aspergillus* spp. isolated from non-sterile samples and to confirm invasive aspergillosis in the presence of positive serum galactomannan.

We report an unusual case of early *A. niger* invasive aspergillosis after lung transplantation. Despite salvage combination therapy by voriconazole and caspofungin, and reduction of immunosuppressive therapy, invasive aspergillosis caused massive hemoptysis leading to the patient's death.

Conflict of interest

The author declares no conflicts of interests regarding publication of this paper.

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