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Aspergillus fumigatus endocarditis of the mitral valve in a heart transplant recipient: a case report

Florent Morio[a,b,*], Michèle Treilhaud[c], Didier Lepelletier[d], Patrice Le Pape[a,b], Jean-Claude Rigal[e], Laurent Delile[e], Jean-Philippe Robert[a], Ousama Al Habash[c], Michel Miegeville[a,b], Françoise Gay-Andrieu[a,b]

[a]*Laboratoire de Parasitologie-Mycologie, CHU de Nantes, 44093 Nantes Cedex 1, France*
[b]*Département de Parasitologie et de Mycologie Médicale, Université de Nantes, Nantes Atlantique Universités, EA1155-IICiMED, Faculté de Pharmacie, 44035 Nantes Cedex 1, France*
[c]*Unité de Transplantation Thoracique, CHU de Nantes, 44093 Nantes Cedex 1, France*
[d]*Laboratoire de Bactériologie-Hygiène, CHU de Nantes, 44093 Nantes Cedex 1, France*
[e]*Service d'Anesthésie et de Réanimation Chirurgicale, CHU de Nantes, 44093 Nantes Cedex 1, France*

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Abstract

Aspergillus endocarditis is a rare event after heart transplantation. We report a case of *Aspergillus fumigatus* endocarditis after orthotopic heart transplantation. The patient was treated with a combination of voriconazole and caspofungin without valve replacement and survived for 168 days after the diagnosis. Previously reported cases are reviewed.

Keywords: Aspergillus endocarditis; Heart transplantation; Galactomannan antigen

1. Case report

A 53-year-old man with hypertrophic cardiomyopathy and cardiac insufficiency (New York Heart Association, NYHA IV) was referred to our hospital for orthotopic heart transplantation. A long-term cyclosporin regimen (140 mg/day) was started the day after the operation. The immunosuppressive therapy was completed on day 5 by a 38-day course of mycophenolate mofetil (1.5 g/day) and polyclonal antithymocyte globulins for 6 days (cumulative dose of 575 mg). The early postoperative period was complicated by Gram-negative bacteremia and *Staphylococcus aureus* bronchitis, leading to the initiation of broad-spectrum antibiotherapy.

On the 38th postoperative day, just after antibiotic treatment had been stopped, the patient developed bacterial endophthalmitis (fungal cultures were not performed) and impaired consciousness. Cerebral tomodensitometry and magnetic resonance imaging revealed multiple infectious cerebral abscesses, suggesting an embolic process. Transthoracic echocardiography performed on day 40 revealed no cardiac vegetations. Without any obvious microbial etiology for the cerebral abscesses, several laboratory investigations were carried out, leading to the detection of serum galactomannan at an index of 1.189 (Platelia® *Aspergillus*; Bio-Rad, Marnes La Coquette, France), followed by the isolation of *Aspergillus fumigatus* from a respiratory tract specimen. The patient was considered to have probable invasive aspergillosis (IA), and combination antifungal therapy with voriconazole (400 mg/day) and caspofungin (70 mg/day loading dose followed by 50 mg/day) was started on day 46.

On the 51st postoperative day, the patient developed a massive pericardial effusion with cardiac tamponade, requiring immediate surgery. Control transesophageal echocardiography performed at the end of the operation revealed

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* Corresponding author. Laboratoire de Parasitologie-Mycologie, CHU de Nantes, Hôtel Dieu, 9 quai Moncousu, 44093 Nantes cedex 1, France. Tel.: +33-2-40-08-40-79; fax: +33-2-40-08-42-49.
E-mail address: florent.morio@chu-nantes.fr (F. Morio).

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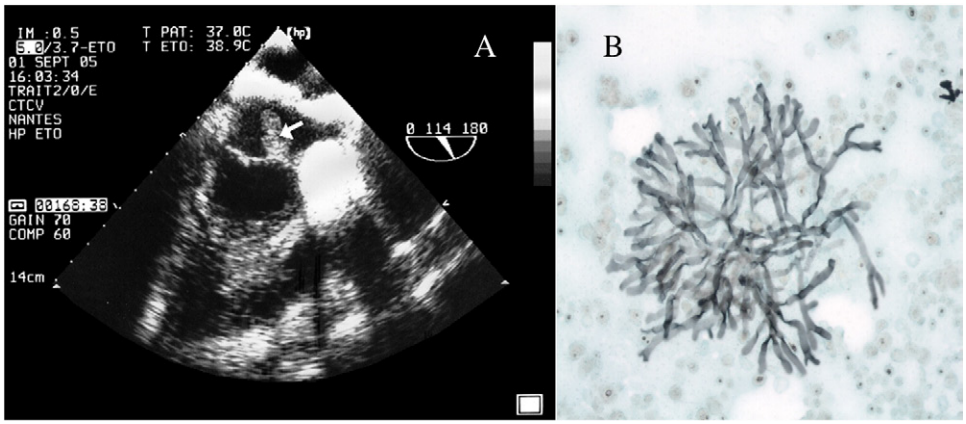

Fig. 1. (A) Transesophageal echocardiogram showing the large vegetation on the mitral valve (white arrow). (B) Microscopic examination of the mitral valve biopsy showing several hyphae typical of a hyaline septated filamentous fungi (Gomori–Grocott staining, ×400).

a large mass on the mitral valve (Fig. 1A). A 2-cm friable vegetation was excised, but valve replacement was not technically feasible because of excessive tissue fragility. Microscopic examination of pericardial fluid and mitral valve biopsies revealed a large amount of branched septate hyphae (Fig. 1B), and cultures yielded *A. fumigatus*. Considering the rapid evolution under combination antifungal therapy and the impossibility of replacing the valve as bad prognostic markers, it was decided to complete antifungal therapy with liposomal amphotericin B (3 mg/kg/day) while awaiting MIC determinations according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) standardized methodology. The isolate displayed low MICs for caspofungin, voriconazole, itraconazole, and liposomal amphotericin B (0.25 μg/mL for each). The antifungal regimen based on voriconazole and caspofungin was therefore pursued as long-term therapy. Voriconazole drug monitoring was performed regularly. Galactomannan tests were positive on day 61 (index 2.459) but decreased over the following weeks, suggesting a good response (0.539 and 0.494 on days 80 and 147, respectively). However, despite intense supportive care, the patient remained in multiorgan failure and experienced recurrent Gram-negative bacterial pneumonia. Galactomannan increased again on day 156 (index 1.091), and *A. fumigatus* was recovered from a lung fibroscopy on day 187, suggesting a poor outcome. In light of these results, without any signs of improvement and with the occurrence of intractable neurologic deterioration, the medical staff decided to withdraw life-sustaining treatment. The patient died on the 220th postoperative day.

2. Discussion

Laboratory diagnosis of *Aspergillus* endocarditis remains a challenge; diagnosis is usually based on positive fungal cultures from cardiac specimens because blood cultures are usually negative. This characteristic is supported by our data. Indeed, despite the large number of blood cultures performed in our patient during hospitalization ($n = 15$), all were negative for fungi. Monitoring of galactomannan is not yet recommended for the diagnosis of IA in solid-organ transplant recipients despite promising results from 2 studies in liver and lung transplant recipients (Husain et al., 2004; Kwak et al., 2004; Wheat and Walsh, 2008). Interestingly, it has recently been shown that the recovery of *A. fumigatus* from respiratory

Table 1
Clinical features of previously published cases of *Aspergillus* endocarditis after heart transplantation

Case no.	Age/sex	Time to IE diagnosis	Organism	Site	Surgical treatment	Antifungal therapy	Survival after the diagnosis	Reference
1	63/M	Unknown	*A. fumigatus*	MV	Yes	AMB	16 days	O'Donnell et al. (1995)
2	64/M	6 months	*A. fumigatus*	AV	Yes	ABLC followed by ITR	Alive after a follow up of 18 months	Keating et al. (1996)
3	65/M	6.5 months	*A. fumigatus*	MV	No[a]	AMB	7 days	Rueter et al. (2002)
4	63/M	7.4 months	*A. fumigatus*	MV	Unknown	Unknown	1 month	Sherman-Weber et al. (2004)
5	36/M	4.3 months	*A. fumigatus*	MV, possible TV	Unknown	Unknown	4.5 months	Sherman-Weber et al. (2004)
6	58/M	8.5 months	*A. fumigatus*	MV	Unknown	Unknown	3.4 months	Sherman-Weber et al. (2004)

MV = mitral valve; AV = aortic valve; TV = tricuspid valve; AMB = amphotericin B; ABLC = amphotericin B lipid complex; ITR = itraconazole.
[a] Diagnosis of *Aspergillus* valve endocarditis was made on autopsy.

specimens from heart transplant recipients can be highly predictive of IA (Muñoz et al., 2003). Here, our patient was considered to have probable IA, and treatment was started after the isolation of *A. fumigatus* from a respiratory tract specimen and a positive galactomannan test several days before the diagnosis was proven by biopsy (De Pauw et al., 2008). In agreement with a previous study showing that immunosuppressed patients with IA can develop antibodies against *Aspergillus* spp., antibodies were detected retrospectively in our patient by immunoelectrophoresis (Paragon®; Beckman, Gagny, France) at the time of the 1st positive galactomannan test and by hemagglutination on day 61 (Aspergillose®; Fumouze, Clichy, France) (Herbrecht et al., 2002). The usefulness of the galactomannan antigen and anti-*Aspergillus* antibodies tests as early markers of IA in heart transplant recipients warrants further investigation.

Aspergillus endocarditis has a poor prognosis, requiring surgical valve replacement and aggressive antifungal therapy (Ellis et al., 2001; Singh and Paterson, 2005). These infections usually occur in patients with prosthetic heart valves, and only a few cases have been described after heart transplantation (Keating et al., 1996; O'Donnell et al., 1995; Rueter et al., 2002; Sherman-Weber et al., 2004). Despite antifungal therapy, the prognosis remains poor, with only 1 reported case of survival, death occurring from 1 week to 4.5 months after the diagnosis (Table 1). Most cases have involved the mitral valve, but valve replacement was performed in only 2 cases. Until recently, there were no guidelines about the choice of antifungal therapy for *Aspergillus* endocarditis (Walsh et al., 2008). Data from 2 clinical trials reported that voriconazole in combination with caspofungin could improve the outcome of patients with IA (Marr et al., 2004; Singh et al., 2006). Here, the occurrence of multiple septic emboli in the brain and the impossibility of replacing the valve led us to start salvage therapy based on a combination of voriconazole and caspofungin. Despite this, a recurrence of aspergillosis was observed and death occurred 168 days after the diagnosis. We assume that the choice of this combination therapy, started several days before the diagnosis, could explain, at least in part, this long survival. Immunosuppressive therapy with cyclosporin probably played a significant role in the outcome.

This report raises the question of the contamination source. Although a pulmonary portal of entry of *Aspergillus* cannot be excluded, the huge number of *Aspergillus* hyphae seen in cardiac specimens in contrast to respiratory specimens suggests that the infection probably started in the graft. However, fungal culture of the transplant preservation fluid was negative, and no valve disease was seen on physical examination of the graft. Routine epidemiological investigations (controls of the ultra-clean ventilation system and routine environmental controls of air and surfaces) performed in the operating theater the month before the transplantation as well as the same controls performed again, immediately after the diagnosis, were unremarkable. One hypothesis is that the donor could have been subclinically infected with *A. fumigatus*. To the best of our knowledge, no *Aspergillus* infection was noticed from the 2 other patients receiving grafts from this donor.

This report suggests that the serum galactomannan assay used in neutropenic patients could also be useful for the early diagnosis of IA in solid-organ transplant recipients. The efficacy of new antifungal agents and combination therapy remain to be evaluated in this setting.

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