Fatal right-sided endocarditis due to *Aspergillus* in a kidney transplant recipient

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Invasive aspergillosis (IA) is an emerging infectious disease in different groups of immunocompromised patients. In transplant recipients, intensification of immunosuppressive therapy to treat allograft rejection poses a major risk factor for IA. We present the clinical features, diagnostic findings and outcome of a kidney transplant recipient who developed pulmonary aspergillosis complicated by endocarditis of his native tricuspid valve. Despite replacement of the valve and treatment with combined antifungal therapy, the patient died of an acute pulmonary bleeding.

**Keywords** *Aspergillus*, endocarditis, renal transplant

**Introduction**

Invasive aspergillosis (IA) is an emerging disease, not only in haematological patients but also in other groups of immunocompromised individuals [1,2]. In solid organ transplant recipients, the period of highest risk for IA is generally within the first year of transplantation [1]. Intensification of immunosuppressive therapy to treat allograft rejection is a major risk factor [1]. Since diagnosis is difficult and mortality rates are high, there should be a high index of suspicion of IA in these cases. We present a fatal case of invasive pulmonary aspergillosis complicated by *Aspergillus* endocarditis in a kidney transplant recipient.

**Case report**

A 52-year-old man with end-stage renal disease secondary to type I diabetes mellitus, received a combined pancreas-kidney transplantation. The immunosuppressive regimen consisted of induction with the interleukin-2 receptor antagonist basiliximab (30 mg intravenously before transplantation and at day 4), corticosteroids (500 mg methyl-prednisolone intravenously before transplantation, followed by 40 mg daily), oral tacrolimus (initial trough levels aimed at 12–15 μg/l) and oral mycophenolate mofetil (1 g b.i.d.). Eight days postoperatively he received high doses of steroids due to biopsy proven acute antibody mediated rejection type II (Banff’s score: t0/i1/g0/ah0/v0/ci0/ct0/cv0/mm0, C4d positive). At day 21 after transplantation, rabbit anti-T-lymphocyte serum was added since a second biopsy showed similar findings (Banff’s score: t0/i1/g0/ah0/v0/ci0/ct0/cv0/mm0, C4d positive). At day 29, the patient was admitted to the intensive care unit with peritonitis and renal and respiratory failure. Upon admission, he had an elevated temperature and clinical signs of septic shock and peritonitis. He was tachypneic secondary to metabolic acidosis, hypoxic due to bilateral atelectasis and required mechanical ventilation. Laboratory analysis showed a white blood cell count of 3000/mm³ (normal value 4000–10000/mm³), 98% neutrophils, a bicarbonate level of 19.1 mmol/l (normal value 22.0–29.0 mmol/l), a creatinine level of 5.01 mg/dl (normal value 0.70–1.30 mg/dl) and a C-reactive protein (CRP) level of 247.2 mg/l (normal value ≤5.0 mg/l). Abdominal cultures revealed the growth of *Pseudomonas aeruginosa*, *Enterobacter agglomerans* and *Enterococcus* spp. and the patient was treated with piperacillin-tazobactam (4 g t.i.d, 10 days started on day 29). No fungi were cultured from the abdominal fluid. A surgical exploration showed wound dehiscence...
and diffuse peritonitis without perforation along the gastrointestinal tract. Because of wheezing and patchy infiltrates, we performed a bronchoscopy on day 64. This showed signs of tracheobronchial aspergillosis with endobronchial white nodular lesions. Biopsy of these lesions yielded *Aspergillus fumigatus* and galactomannan (GM) detection (Platelia *Aspergillus*; Bio-Rad) in the bronchoalveolar lavage (BAL) fluid was positive (index 6.5) (Fig. 1). GM in serum remained negative (index <0.5). The patient was treated with caspofungin from day 65 to day 192 of his hospital course (70 mg intravenously the first day, followed by 50 mg daily).

With this treatment, signs of peritonitis and respiratory and renal failure gradually improved and bronchoscopy showed an improvement of the endobronchial lesions. On day 90 the patient could be weaned from the ventilation. In order to enable further recovery from the infection, it was decided to stop one of the immunosuppressants, notably mycophenolate mofetil on day 95. The GM in BAL fluid became negative on day 116 and the patient was discharged to the ward on day 127. His hospital course was prolonged because of signs of critical illness neuropathy. He continued to receive caspofungin until day 192, the day of discharge from the hospital, on which caspofungin was replaced by oral voriconazole therapy. Since this treatment resulted in liver function disturbances, the patient was placed on itraconazole capsules, 200 mg daily. At that time, chest X-ray showed no abnormalities, the patient had minor respiratory symptoms and C-reactive protein was within normal limits. Immunosuppression consisted of oral corticosteroids (methyl-prednisolone 6 mg daily) and tacrolimus (trough levels aimed at 8 μg/l). However, five days later, the patient was readmitted to the emergency room because of high fever, hypoxia and hypotension. CT scan showed diffuse pulmonary emboli with pleural-based wedge-shaped lesions (Fig. 2). CRP level was 224.5 mg/l. Blood cultures remained negative and culture of multiple respiratory specimens showed growth of *Enterobacter aerogenes* and *Pseudomonas aeruginosa*. No moulds were found. Meropenem was started because of a presumed bilateral pneumonia. However, on day 203 (6 days after the second admission), GM level in serum was on the rise (index 0.9). A transoesophageal echocardiography was performed on day 211 because of a new cardiac murmur. This showed a large vegetation on the anterior leaflet at the atrial side of the tricuspid valve (maximal size: 3.3 × 1.6 cm). Itraconazole was stopped and caspofungin (70 mg intravenously the first day, followed by
was restarted. Because of rapid deteriorating heart failure, surgery was performed with replacement of the valve on day 213. The affected valve with a large vegetation (2.5 × 2.3 × 1.5 cm) was removed (Fig. 3). Culture of the valve confirmed the diagnosis of *A. fumigatus* endocarditis. Postoperatively, antifungal treatment was broadened with oral voriconazole (400 mg b.i.d. the first day, followed by 200 mg b.i.d.) and aerosolized amphotericin B deoxycholate. Under this treatment, there was a decrease of the infectious parameters and the GM test became negative on day 246. Postoperative course was complicated with difficult weaning, ventilator-associated pneumonia and relapse of renal failure. The patient died on day 274 because of fatal hemoptysis.

Fig. 2 CT scan showing widespread nodules and a wedge-shaped pleural-based infiltrate in the right upper lobe.

Fig. 3 Fungal vegetation on the tricuspid valve.


Discussion

We describe here a rare case of right-sided native valve endocarditis due to *A. fumigatus* in a renal transplant recipient. In this group of patients IA has been reported in 0–4% (mean 0.7%) of affected individuals [3]. This is relatively low compared to other organ transplant recipients.

Fungal endocarditis is a rare condition, with fungi responsible for 1.3–6% of cases of infective endocarditis [4] and yeasts being a more frequent cause than moulds (72% versus 28%). In the latter cases, *A. fumigatus* is the most common etiologic agent. Fungal endocarditis is often characterized by large vegetations and the most common complications are embolic phenomena. The mortality rate among patients with mould endocarditis is 82.1% [4].

Several unusual aspects of this case should be addressed. First, although rare, *Aspergillus* endocarditis can occur in patients without prior cardiac surgery [5]. Nevertheless, the affected valve in this case, although native, was not intact. A previous echocardiogram showed mild insufficiency of the tricuspid valve. It is known that almost any type of structural heart disease (even mild) may predispose to infective endocarditis, especially when the defect results in turbulence of blood flow. Moreover, *Aspergillus* is angioinvasive which facilitates infection of the valves [5,6]. Immunosuppression and uncontrolled diabetes are important risk factors for invasive mold infection. While the former was undoubtedly present in our case, relatively tight diabetes control was reached during the entire hospital stay. Indeed, despite the use of high dose corticosteroids and tacrolimus, glycosylated hemoglobin levels, measured at regular intervals, never exceeded 6.3%. Nevertheless, one cannot rule out the potential influence of the patient’s diabetic state on his clinical history. Gumbo et al. [5] reported 61 patients with *Aspergillus* valve endocarditis without prior cardiac surgery. Nine of these patients were solid organ transplant recipients (4 kidney and 5 liver transplant recipients). The period of highest risk for invasive mold infection is generally within the first year of transplant and intensification of immunosuppressive therapy to treat allograft rejection further increases the risk [1].

Second, the anatomic location of the vegetation is uncommon. In the study of Gumbo et al., the mitral valve was most commonly affected (44%), followed by intramural surface (33%) and aortic valve (23%) involvement [5]. Vegetations on the tricuspid (11%) or pulmonic (3%) valve are rather rare. Mural endocarditis differs from valvular endocarditis by a lower incidence of heart murmurs and embolic events and
occurs most commonly in patients with high levels of immunosuppression [5]. Other risk factors for right-sided endocarditis, such as history of IV drug use or the presence of foreign bodies were not present in our case.

Third, our case demonstrates that in non-neutropenic patients, detection of serum galactomannan is not a sensitive marker for IA, as suggested by Pfeiffer et al. [7] in their meta-analysis on the value of GM in the diagnosis of IA. Husain et al. [8] demonstrated a sensitivity of only 30% in lung transplant recipients. As far as we know, no studies have been published regarding the performance of the GM test in kidney transplant recipients. There have been recent studies reported concerning GM detection in BAL fluid as a diagnostic IA marker in solid organ transplant recipients [9,10]. These investigations indicated that the determination of GM in BAL fluid could be a useful adjunct to conventional tests in diagnosing and following IA among solid organ transplant recipients. However, well-designed prospective studies are needed to validate these findings and to define interpretive criteria. False positive GM results can occur in patients receiving piperacillin/tazobactam [11]. In our case, piperacillin-tazobactam treatment was stopped several weeks before the first GM sample was taken and didn’t influence the result.

Finally, despite prolonged therapy with two antifungals and surgery, the patient’s death due to fatal hemoptysis, emphasises the lethality of this disease. We presume that the patient developed a fatal lung bleeding due to vascular break-through by Aspergillus. However, since no autopsy occured, we can’t confirm this hypothesis.

Voriconazole is considered as first line treatment of invasive aspergillosis. However, due to renal failure and possible interaction with tacrolimus, caspofungin was chosen as the initial therapy. The use of a fungistatic instead of a fungicidal product is one of the factors which could have contributed to the fatal outcome in this case. After discharge from the hospital, the patient was treated with itraconazole capsules. It is known that itraconazole absorption from the capsule formulation has a high degree of variability. Poor absorption of itraconazole might have resulted in a rapid breakthrough of the IA. The use of an oral solution, which combines itraconazole with cyclodextrin, can increase the absorption of itraconazole and its bioavailability. Other possible explanations for the failure of antifungals include the presence of large bulky vegetations, systemic septic emboli, and poor penetration of antifungal agents into the vegetations.

In conclusion, IA is an emerging disease in different groups of immunocompromised patients. Diagnosis in non-neutropenic patients is difficult since detection of serum GM has a low sensitivity. Aspergillus endocarditis is very uncommon and there is limited experience in diagnosis and treatment. However, large vegetations and recurrent emboli in culture-negative cases should alert clinicians to the possibility of fungal endocarditis.

References