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Case Report

# Fatal outcome of disseminated invasive aspergillosis in kidney allograft recipients

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Fungal infections in solid organ transplant recipients are of concern due to the related high mortality and morbidity. *Aspergillus* species are one of the major opportunistic fungal pathogens causing invasive pulmonary infections which rarely involve extrapulmonary organs. The occurrence varies by type of transplantation, with aspergillosis more frequently associated with heart, liver and lung transplantation cases than those involving kidney recipients. Several risk factors have been proposed, with cases occurring early and late after the transplantation. Although pulmonary involvement is the main presentation, invasive extrapulmonary aspergillosis can on rare occasions be observed and is associated with poor prognosis. Herein, we report two cases that presented with extrapulmonary invasive aspergillosis, i.e., one presented with cerebral abscess and the second with soft tissue abscess in the right posterior thigh. While the cerebral abscess was not surgically treated, the soft tissue abscess was surgically drained. When the primary focus was investigated, pulmonary nodulars were found in both cases. Both patients were treated with long-term amphotericin B; however, one patient was lost with functioning graft and the kidney of the second patient failed due to decreased immunosuppression and he died while on maintenance hemodialysis. Invasive extrapulmonary presentation of aspergillosis rarely occurs in kidney transplant recipients and is associated with a high mortality rate.

**Keywords** Abscess, *Aspergillus*, central nervous system, kidney transplantation

## Introduction

Transplant recipients are among the most significant subgroups of immunosuppressed hosts at risk for invasive aspergillosis [1]. Prevalence and outcome of fungal infection in solid organ transplantation (SOT) varies by type of organ transplanted. While kidney recipients are at the lowest risk (ranging from 0.4–5%), liver and heart recipients have moderate risks (with incidence rates ranging from 1–8% and 1–14%, respectively) of acquiring this fungal infection. The highest incidence of aspergillosis is observed among lung transplant recipients (6–16%). The cumulative incidence of aspergillosis at 12 months following SOT was found to be 0.1% after kidney transplantation in a prospective multicenter surveillance program that included 4,110 SOT in 19 centers in the United States [2]. After SOT, mortality at 3 months after diagnosis of aspergillosis ranged from 58–74% for lung transplants to 66.7% for heart and kidney transplants [1,2]. Although the typical presentation of invasive aspergillosis is pulmonary involvement, rare extrapulmonary cases have been demonstrated, such as central nervous

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system (CNS) infection, osteomyelitis, endocarditis and cutaneous infections. While CNS involvement has a high mortality, pulmonary aspergillosis seems to be associated with a lower mortality rate. In this report, we present two fatal cases that presented with invasive extrapulmonary aspergillosis, which is rarely seen in renal transplant recipients.

## Case 1

A 46-year-old man, who had been on hemodialysis for 5 years due to renal amyloidosis secondary to familial Mediterranean fever, underwent cadaveric renal transplantation. He received induction therapy with antithymocyte globulin at the time of transplantation and continued with triple maintenance therapy including prednisone, mycophenolate mofetil (MMF) and cyclosporin A (CsA). Acyclovir, fluconazole and trimethoprim/sulfamethoxazole (TMP-SMZ) were used as prophylaxis. The patient was discharged on the 14th postoperative day with a functioning graft. He was full-matched with the cadaveric donor, his panel reactive antibody was negative, and donor and recipient were positive for cytomegalovirus (CMV) IgG. CMV infection was detected by polymerase chain reaction on the 45th day of kidney transplantation. Intravenous ganciclovir was initiated at 5 mg/kg twice a day for 3 weeks. During the follow-up, there was no acute rejection and his allograft was functioning well (creatinine: 0.8 mg/dl). His prednisone and CsA were decreased gradually to 12 mg and 4 mg/kg/day, respectively, in the third month after transplantation. In the fourth posttransplantation month, the patient developed visual impairment and headache. He was admitted to the hospital and cranial magnetic resonance imaging (MRI) and computerized tomography (CT) scan were performed promptly, which showed a $3 \times 2$ cm occipital lesion, with ring-like contrast enhancement in the left occipital region (Fig. 1). Uveitis and necrotizing retinitis were diagnosed with ophthalmology consultation. While chest X-ray showed no abnormality, high resolution CT of the chest indicated bilateral ground-glass attenuation with small pleural effusions. Conventional amphotericin B at 1 mg/kg/day and two TMP-SMZ 800/160mg tablets twice daily were started empirically on the assumption of invasive fungal infection or nocardiosis. Bronchoscopy was performed and *Aspergillus flavus* was cultured from two bronchoalveolar lavage (BAL) samples. *Aspergillus flavus* was recovered on blood agar, eosine methylene blue agar and Sabouraud agar. On the latter, the colony was at first white and then turned to a yellow color. On microscopic examination, septate hyphae showed dichotomous branching at 45° angles and vesicles were pointing out in all directions. The conventional amphotericin was changed to liposomal amphotericin B at a dose of 5 mg/kg/day. CsA was stopped and MMF was decreased to 500 mg twice a day. On the 45th day of liposomal amphotericin B treatment, follow-up cranial MRI and chest CT scan showed some regression. However, his vision did not resolve and his condition gradually worsened. The patient became unconscious and died in the sixth month of the transplantation with functioning graft.

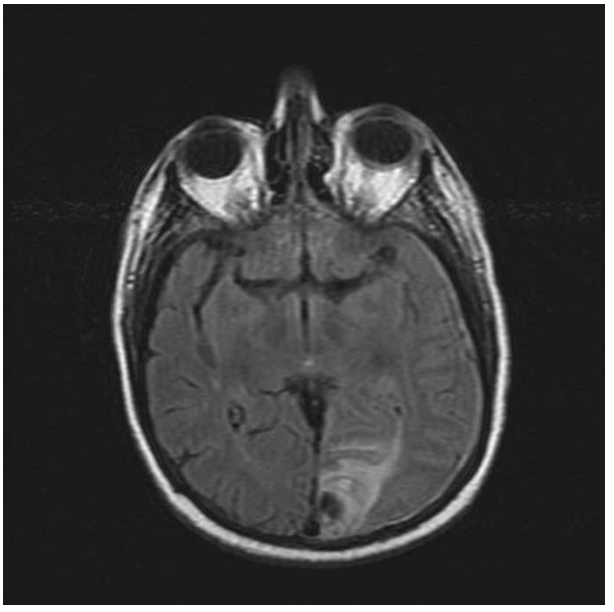


**Fig. 1** Axial FLAIR MR image of a 46-year-old transplant patient showing a necrotic hypointense area surrounded by a hyperintense edema ring in the left occipital lobe.

## Case 2

A 58-year-old man underwent a living-related renal transplantation from his one haplotype- matched sister. Panel reactive antibody was negative. The patient and donor were CMV IgG-positive. He received induction therapy with four doses of daclizumab, and maintenance immunosuppressive treatment included prednisone, MMF and tacrolimus. Acyclovir, fluconazole and TMP-SMZ were started as prophylaxis. Posttransplant diabetes mellitus was diagnosed on the 10th day of transplantation and necessitated insulin treatment. He was discharged with a functioning graft (creatinine: 1.2 mg/dl). On the 50th day of the transplantation, the patient developed fever and severe right posterior thigh pain. The physical examination showed a mass lesion in the posterior of the right thigh. A $15 \times 10$ cm abscess



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was diagnosed on the posterior of the right thigh with MRI and was surgically drained (Fig. 2). *Aspergillus flavus* was cultured from the abscess specimen. Galactomannan antigen test was positive (6.07) in the serum. In order to determine the primary source of *Aspergillus flavus*, chest X-ray and CT scan were performed, which revealed bilateral nodular and cavitary lesions in both lungs. CMV-DNA was found to be positive (137,000 pg/ml). Fluconazole was stopped and liposomal amphotericin B and intravenous gancyclovir were started, both at a dose of 5 mg/kg twice a day. *Aspergillus flavus* was also cultured from sputum, and *Acinetobacter baumannii* was demonstrated from the subsequent sputum culture. Meropenem was added to the therapy for *A. baumannii* infection. CMV-DNA was negative on the posttransplant 78th day. Maintenance immunosuppression was decreased and tacrolimus was stopped. MMF was decreased to 500 mg twice a day with 5 mg/day prednisone. Graft function deteriorated and acute rejection was diagnosed on kidney biopsy. One dose of 500 mg solumedrol was given; however, there was no response and we did not insist on acute rejection treatment. The patient's graft function worsened and he was placed back on hemodialysis during the infection. Three months later while under the anti-fungal treatment, CT of the chest showed a significant progression of nodular consolidation and caspofungin was added to the current therapy. He received 110 days of liposomal amphotericin B and 3 months of liposomal amphotericin plus caspofungin. However, his condition worsened and the patient succumbed at the 7 months after the transplantation.

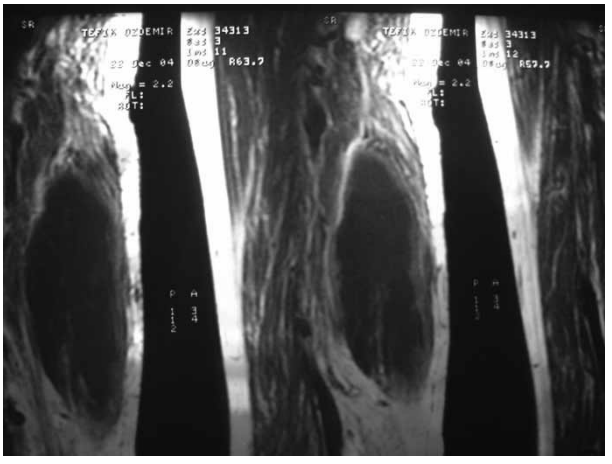


**Fig. 2** Postcontrast T1-weighted fat-saturated coronal image of MR showing a hypointense abscess cavity surrounded by a contrast enhancing rim in the posterior muscle compartment of the thigh involving the semimembranosus, semitendinosus and biceps femoris muscles.

## Discussion

Invasive pulmonary aspergillosis has been recognized as one of the most significant opportunistic fungal infections in organ transplant recipients [4]. While it often involves the lungs, disseminated invasive aspergillosis is very uncommon, and CNS involvement is associated with a very high mortality rate. The infection occurs in the relatively intermediate period after transplantation. However, it can be seen in later period in lung transplant recipients [3,5]. Risk factors for invasive aspergillosis have been defined as use of high-dose steroids, posttransplant diabetes mellitus, antilymphocyte therapy and viral infections, particularly those caused by CMV [2]. Regarding disseminated aspergillosis, there is a paucity of information about the risk factors. It was reported that CMV infections can predispose the allograft recipients to bacterial and fungal infections [6]. Coexistent disseminated invasive aspergillosis involving intraocular, pulmonary, cutaneous tissue and CMV infection was reported previously and CMV seems to favor subsequent bacterial and fungal infections due to more cellular immunosuppression [7–9]. In our cases, risk factors for disseminated invasive aspergillosis were CMV infection and diabetes mellitus in one of the patients. In our patient with diabetes mellitus, disseminated invasive aspergillosis was presented with simultaneous coinfection of CMV within two months after kidney transplantation, while it occurred 2.5 months after CMV infection, that is at the fourth month of transplantation, in the non-diabetic case. It should be considered that tacrolimus causes posttransplant diabetes mellitus more frequently than CsA, therefore, it might be speculated that tacrolimus can be associated with invasive aspergillosis due to its more diabetogenic effect. In our cases, there was no acute rejection and the first patient had anti-thymocyte globulin induction therapy which is a risk factor for aspergillosis. Furthermore, a recent survey of 33,420 renal transplant recipients in the US renal data system documented diabetes, prolonged pretransplant dialysis, acute rejection, and tacrolimus and sirolimus immunosuppression to be risk factors for fungal infections [1,10]. Daclizumab, an interleukin 2 receptor antibody, seems not to be associated with increased infectious complications and it was used as an induction treatment in our second case.

Invasive pulmonary aspergillosis is the most common manifestation of serious *Aspergillus* infection in all hosts [10]. Up to 90% of the organ transplant recipients with invasive aspergillosis have pulmonary involvement and CNS lesions occur in 10–50% of cases. CNS



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aspergillosis presents most frequently as an alteration in mental status, which may be rapidly progressive in onset [6]. Diagnosis of CNS aspergillosis is difficult because the presenting symptoms are nonspecific (e.g., stroke-like symptoms, seizures) and fever may be absent. Cerebrospinal fluid findings usually disclose only minimal abnormalities with slightly elevated protein level [11]. Meningismus occurs rarely. One of our patients had CNS involvement. *Aspergillus* brain abscesses occur most commonly in the cerebral hemispheres, but the cerebellum and brainstem may also be involved [6]. While surgical drainage and local application of amphotericin B is favored by several authors, the mortality seems to remain very high [10–12]. Uveitis and necrotizing retinitis due to *Aspergillus* are rarely reported complications and ocular involvement has always been observed late in the course of the disease, occurring via metastatic fungal intraocular infection [13].

*Aspergillus* spp. have been cultured from sputum in only 8–34% and from BAL fluid in 45–62% of patients with invasive aspergillosis [10,14]. A study involving liver and kidney allograft recipients showed that isolation of two or more colonies or identification of more than one site of infection, particularly if the species were *Aspergillus fumigatus* and *Aspergillus flavus,* was associated with a greater than 70% likelihood of invasive disease. Among organ transplant recipients, the positive predictive value of a respiratory tract culture for *Aspergillus* ranges from 17–72% [2]. After *Aspergillus fumigatus*, *Aspergillus flavus* is the second common cause of invasive aspergillosis and it is the most common cause of superficial infection. Moreover, *Aspergillus flavus* may have higher MICs (minimum inhibitory concentrations) to amphotericin B than *Aspergillus fumigatus* [15]. In our patients, *Aspergillus flavus* was cultured from sputum/BAL and abscess. The appearance of pulmonary infiltrates visualized on chest roentgenogram is nonspecific; high resolution CT has been shown to detect typical signs of invasive aspergillosis and allow earlier diagnosis of infection. Successful management of invasive mycoses depends on early recognition of infection, and arrangement of the level of immunosuppression and antifungal therapy in adjunct with surgery when indicated. Amphotericin B deoxycholate has long been a mainstay of therapy for *Aspergillus* infections. The use of liposomal preparations of amphotericin has been justified by many investigators in transplant recipients with invasive aspergillosis. However, voriconazole is now considered as the first-line treatment of invasive aspergillosis [16]. An echinocandin, caspofungin that inhibits beta 1-3 –D-glucan synthesis has become available. In our cases, we decreased the dose of MMF and stopped calcineurin inhibitors and gave high-dose and long-term amphotericin B. One patient lost his kidney due to acute rejection and both patients died despite anti-fungal treatment [10].

Disseminated invasive aspergillosis has a high mortality rate in kidney recipients and it seems to be associated with CMV infection. Antifungal prophylaxis in organ transplant recipients remains a complex and controversial issue. The types of patients to receive prophylaxis, the antifungal agent, route of administration, and the optimal timing of prophylaxis have not been well-defined. Use of prophylaxis for invasive aspergillosis in liver and lung recipients is justifiable [10]. Due to the high mortality rate, a high degree of suspicion is needed in kidney recipients at high risk, to ensure early diagnosis and appropriate therapy.

***Declaration of interest***: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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