Coexisting Cutaneous Aspergillosis and Pulmonary Tuberculosis in a Renal Transplant Recipient

Chi Yuen Cheung,1 Tak Chiu Wu,2 Yiu Han Chan,1 King Chung Lee,3 Hoi Wong Chan,1 Ka Foon Chau,1 Chun Sang Li1

We report a 70-year-old renal transplant recipient with endophthalmitis and cutaneous aspergillosis who presented with painful red eyes and skin nodules. The presenting symptoms subsided gradually after voriconazole therapy. However, he developed fever with progressive pulmonary infiltrates. He was subsequently diagnosed to have coexisting pulmonary tuberculosis. This case illustrates that co-infection should always be borne in mind in immunocompromised patients, especially when the patient’s clinical condition fails to respond favorably to initial treatment. [Hong Kong J Nephrol 2008;10(2):74–7]

Key words: aspergillosis, endophthalmitis, pulmonary tuberculosis, renal transplant

INTRODUCTION

Infections are one of the leading causes of morbidity and mortality among renal transplant recipients. In these patients, Aspergillus is a common cause of systemic fungal disease, with an incidence ranging from 0.4% to 2.4%, and a high mortality of 56–100% [1,2]. We describe a case of cutaneous aspergillosis that presented with subcutaneous nodules coexisting with endophthalmitis and pulmonary tuberculosis in a renal transplant recipient.

CASE REPORT

A 70-year-old Chinese man with long-standing hypertension and end-stage renal failure due to unknown cause was initiated on regular hemodialysis twice weekly since 2002. He underwent cadaveric renal transplantation in mainland China in December 2006. After the transplantation, he received triple therapy including prednisolone, tacrolimus and mycophenolate mofetil (MMF) as the maintenance immunosuppressive regimen. There was no history of induction therapy. He was discharged from hospital with a serum creatinine level of 197 μmol/L.

He developed fever and pancytopenia when he came back to our center for follow-up in January 2007. Blood test revealed the following: hemoglobin 6.8 g/dL; white blood cell (WBC) count 2.8 × 10^9/L; platelet count 111 × 10^9/L; serum creatinine concentration 126 μmol/L; cytomegalovirus (CMV) pp65 antigen 1 positive cell per 2 × 10^5 cells. He was treated with valganciclovir 450 mg daily for 3 weeks in view of the possibility of CMV disease. The tacrolimus trough level was 12.2 μg/L. The dosage of tacrolimus was reduced and MMF was switched to azathioprine in view of the possibility of bone marrow suppression due to MMF. Bone marrow aspiration was planned but not done because the fever subsided with normalization of complete blood count after treatment. The CMV pp65 antigen test was repeated and the result was negative.
In May 2007 (6 months after transplant), he complained of a painful and red left eye. There was also blurring of vision. He was diagnosed to have left endophthalmitis by our ophthalmologist, and was admitted to hospital for further management. There was no fever on presentation. Laboratory investigations revealed the following: hemoglobin 10.4 g/dL; WBC count $4.5 \times 10^9/L$; platelet count $262 \times 10^9/L$; sodium concentration 136 mmol/L; potassium concentration 5.1 mmol/L; serum creatinine concentration 115 μmol/L; C-reactive protein 75.6 mg/L; CMV pp65 antigen was negative. Tacrolimus level was within the therapeutic range. Left eye vitreous tapping was done. Bacterial culture, fungal culture and polymerase chain reaction assay for CMV of vitreous fluid were all negative.

At the same time, the patient was noted to have two subcutaneous skin nodules measuring 1.5 cm in diameter, one on the right flank and the other on the right thigh. Both nodules were present for 2 weeks and there was no history of skin injury. Excisional biopsies of the skin nodules were done. The histology of both skin nodules showed fungal infection favoring aspergillosis (Figure 1). Tissue fungal culture grew *Aspergillus fumigatus*. Blood for galactomannan was negative and blood for (1,3)-β-D-glucan titer was > 500 pg/mL. He was treated for disseminated aspergillosis. Voriconazole 200 mg twice daily was started. The dosage of tacrolimus was further reduced in view of the presence of fungal infection and drug interaction with voriconazole. The tacrolimus level was closely monitored. Computed tomography (CT) scan of the brain was unremarkable and echocardiography revealed no features of infective endocarditis. Although the redness and pain of the left eye resolved, visual acuity remained light perception only.

One week later, he complained of persistent fever despite a course of cefoperazone/sulbactam (sulperazone). There was no cough, sputum or shortness of breath. There was also no dysuria or diarrhea. His ocular condition remained static. No more skin nodules were noted. Laboratory investigations revealed the following: hemoglobin 10.9 g/dL; WBC count $2.3 \times 10^9/L$; neutrophil count $1.2 \times 10^9/L$; lymphocyte count $0.9 \times 10^9/L$; platelet count $262 \times 10^9/L$; C-reactive protein 56.9 mg/L. Liver and renal function tests were normal, CMV pp65 antigen was negative, and blood and urine culture were negative. Chest X-ray revealed mild pulmonary infiltrate over hilar regions. Abdominal ultrasound showed no significant abnormality. CT scan of the thorax showed multifocal and bilateral small pulmonary nodules with an oval soft tissue nodule at the right mediastinum adjacent to the ascending aorta that looked likely to be adenopathy (Figure 2). Fine needle aspiration of the lung nodules revealed reactive changes with necrosis only. The bacterial culture, fungal culture and acid-fast bacilli (AFB) culture of the aspirate were all negative.

Figure 1. High power view of the fungal organisms in biopsy of the skin nodule: regularly straight septated hyphae, branching at acute angle or occasional right angle, ovoid spore-like structures mingle with the hyphae (hematoxylin & eosin).

Figure 2. Computed tomography scan of the thorax shows multifocal and bilateral small pulmonary nodules.
AFB staining of sputum was subsequently positive (4+) and he was diagnosed to have co-infection of pulmonary tuberculosis with aspergillosis. Anti-tuberculosis therapy including isoniazid, ethambutol, pyrazinamide, morxifloxacin and vitamin B6 was started. Sputum AFB culture confirmed the presence of Mycobacterium tuberculosis. His fever responded to the antituberculosis therapy and he was discharged with voriconazole and antituberculosis medication. His renal function remained stable on discharge. At the 6-month follow-up, his chest X-ray was clear and there was no evidence of aspergillosis recurrence.

DISCUSSION

Cutaneous involvement is a rare manifestation of aspergillosis. Cutaneous infection is reported in only 5% of documented Aspergillus infections, and can be primary or secondary [3]. Primary cutaneous aspergillosis occurs as a result of direct inoculation of the fungus into breaks in the skin and commonly involves sites of skin injury [4,5]. On the other hand, the secondary form is rare. It develops as a result of hematogenous or contagious spread from an underlying infected organ [4]. Most of the infections are caused by Aspergillus fumigatus [5], as in our patient.

Endophthalmitis is also an unusual infection in renal transplant recipients [6]. In our patient, the exact causative organism of the endophthalmitis could not be confirmed because of the negative culture results and the absence of histology. However, the coexisting cutaneous aspergillosis with resolution of ocular inflammation after the administration of antifungal agent suggests that Aspergillus fumigatus was the causative agent of endophthalmitis in our patient. The incidence of Aspergillus endophthalmitis is not known, but a recent study identified 89 cases over the last 50 years, with 23% occurring in solid organ transplants [7]. The prognosis of Aspergillus endophthalmitis in renal transplant patients is poor as the organisms might already have disseminated to other sites, and recovery of vision is unlikely due to extensive retinal necrosis and choroidal damage [8].

Our patient received potent immunosuppressive agents including corticosteroids, tacrolimus and MMF, which rendered him vulnerable to opportunistic infections. Recent studies show that use of MMF is associated with a higher incidence of infections including CMV and Aspergillus [9]. CMV infection itself has been suggested to predispose to aspergillosis in transplant recipients [10]. Furthermore, corticosteroids are known to inhibit macrophage and neutrophil function, which are the most important cells in the host defense against Aspergillus [11]. Amphotericin B, itraconazole and voriconazole are the major therapeutic options for disseminated aspergillosis [4,12]. While amphotericin B has been the standard therapy for systemic aspergillosis, it has recently been shown that voriconazole leads to better responses, improved survival and fewer side effects compared with amphotericin B [12]. Both amphotericin B and itraconazole have poor intraocular penetration [13,14]. On the other hand, voriconazole has been shown to have good concentration in aqueous humor [15] and has fungicidal action against Aspergillus fumigatus. Our patient was put on voriconazole because we suspected that he had Aspergillus endophthalmitis to start with, and his ocular inflammation responded well to voriconazole therapy. The duration of voriconazole therapy depends on whether the patient is in an immunocompromised state. As long as our patient is on immunosuppressive agents, voriconazole will be continued.

Pulmonary involvement is a common presentation in disseminated aspergillosis. However, as in our patient, not all pulmonary nodules in a patient with disseminated aspergillosis are due to Aspergillus fumigatus. Although one-man one-disease is the general rule, immunocompromised patients may have several co-infections. We should try hard to rule out other coexisting pulmonary infections, such as bacterial pneumonia, CMV pneumonitis or mycobacterial infection. Mycobacterial infection is a particularly important consideration in endemic areas. Microbiologic or histologic diagnosis of pulmonary lesions should be obtained in all transplant recipients. When all the findings are negative, bronchoscopy might be helpful to make correct diagnosis for prompt and appropriate therapy. In our patient, the occurrence of persistent fever and abnormal pulmonary infiltrates despite voriconazole suggested that other opportunistic infections were present. Pulmonary tuberculosis was finally diagnosed by sputum results. The symptoms and abnormal radiologic features resolved after antituberculosis therapy. The duration of the antituberculosis therapy was at least 1 year.

As infections are one of the leading causes of morbidity and mortality among immunocompromised patients, early diagnosis and prompt treatment are important. Immunocompromised patients might have atypical presentation of common infections, such as cutaneous or ocular aspergillosis. The possibility of co-infection should always be borne in mind, especially when the patient’s clinical condition fails to respond favorably to initial treatment.

REFERENCES

Aspergillosis in a renal transplant patient