Aspergillus Fumigatus Spondylodiskitis in Renal Transplant Patient: Voriconazole Experience

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Abstract

The incidence of invasive *aspergillosis* has increased after solid organ transplant. However, *aspergillus* osteomyelitis in vertebrae is rare. We report a case of *aspergillus* spondylodiskitis after pulmonary aspergillosis in a renal transplant recipient. He was treated by antifungal therapy and surgical intervention. The transplantist should be alert for a diagnosis of *aspergillus* spondylodiskitis in recipients who developed back pain after aspergillosis infection in other sites.

Key words: Aspergillus fumigatus, *Spondylodiskitis, Renal transplant, Voriconazole, Immunosuppression*

Introduction

Aspergillus infections, especially invasive pulmonary aspergillosis, particularly that involving the central nervous system, are accompanied by the highest mortality rate.[1] Aspergillosis is the second most-common opportunistic fungal infection after kidney transplant. Aspergillosis usually causes pulmonary, paranasal sinus, and cerebral infections,[2] but it also affects bone, joint, and the urinary tract.[3, 4] Vertebral osteomyelitis is associated with significant morbidity because delays in diagnosis can lead to disabling complications. A rare cause of osteomyelitis of the spine is aspergillosis involving either the vertebral body or the intervertebral disk.[5] Herein, we report a case of thoracic and lumbar spondylodiskitis caused by *Aspergillus fumigatus* after pulmonary *aspergillus* and tuberculosis infections.

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Case Report

A 46-year-old man was on chronic hemodialysis program for 2 years because of end-stage renal disease owing to hypertension. His personal history was significant for pulmonary tuberculosis and impaired glucose tolerance. He underwent a renal transplant from a living donor on September 4, 2008. His initial immunosuppressive regimen consisted of basiliximab, cyclosporine, mycophenolate mofetil, and prednisolone. During the early postoperative period, he had hypertension and hyperglycemia, which improved with medical treatment. Posttransplantation, isoniazid prophylaxis (300 mg/d) was started. A urinary infection of *Pseudomonas aeruginosa* was treated with ceftazidime and ciprofloxacin. He was discharged with a serum creatinine of 150.2 μmol/L (1.7 mg/dL) after 3 weeks. On 50th day after transplant, he presented with malaise, anorexia, sweating, and increased serum creatinine (176.8 μmol/L = 2.8 mg/dL).

Results of scintigraphic and ultrasonographic appearances of the allograft were normal. At that moment, his *cytomegalovirus* DNA was 28 114 copy/mL, and ganciclovir treatment was started at 5 mg/kg. On the fifth day of hospitalization, a thoracic computed tomography scan revealed ground-glass appearance and 2 cavitary lesions in the superior segment of lower lobe, and the lateral segment of middle lobe in the right lung. Hyphae were seen on direct sputum examination. His sputum culture grew *Aspergillus fumigatus* and *Pseudomonas aeruginosa*. Caspofungin treatment was administered for 65 days (70 mg on first day, then 50 mg/d). *Aspergillus fumigatus* was isolated in his

bronchoalveolar lavage cultures. Galactomannan antigen test and acido-resistant bacilli were positive in this sample. Also, the culture indicated growth of *Mycobacterium spp*. Furthermore, the patient had a urinary tract infection caused by *Pseudomonas aeruginosa*; ceftazidime was added to his treatment.

Antituberculous treatment consisting of isoniazid, rifampicin, pyrazinamide, ofloxacin, and ethambutol was initiated with renal dosage adjustment. Ofloxacin was chosen as the fifth drug in the first-line tuberculous therapy owing to the presence of previous tuberculosis infection history and the probability of multidrug resistance to tuberculosis in this setting. On follow-up, cavitary lesions were distinctly reduced in his lung. His immunosuppressives were only cyclosporine (400 mg/d) and prednisolone (20 mg/d) during this period.

On December 5, 2008, he complained of back pain aggravated at night that could not be relieved by rest, exercise, or different analgesics. An appearance of suspected compression fracture of T8 vertebra on thoracic radiograph was detected. The results of a lumbar radiograph revealed normal findings. On December 18, 2008, thoracic magnetic resonance imaging showed uncertain degeneration of T7-T8 vertebrae. On January 5, 2009, caspofungin was discontinued. On January 12, 2009, bone scintigraphy showed an increased tracer uptake at the corpus of T8 vertebra. Spondylodiskitis was determined based on thoracic magnetic resonance imaging (Figure 1).

In February 2009, the patient was hospitalized for severe back pain. A biopsy of his bone revealed an acute, nonspecific infection (suppurative spondylodiskitis). Although ceftazidime and ciprofloxacin treatment was instituted for spondylodiskitis, the back pain continued, and there was progression of the lesion on thoracic magnetic resonance imaging. Therefore, anterior corpus resection of T8-T9 vertebrae and diskectomy of T7-T8, T8-T9, and T9-T10 vertebrae was performed, and the abscess was drained on February 25, 2009. The material from the operation was compatible with granulomatous spondylodiskitis, and the results of a culture of this material yielded *Aspergillus fumigatus*. Voriconazole was started at dose of 200 mg/d.

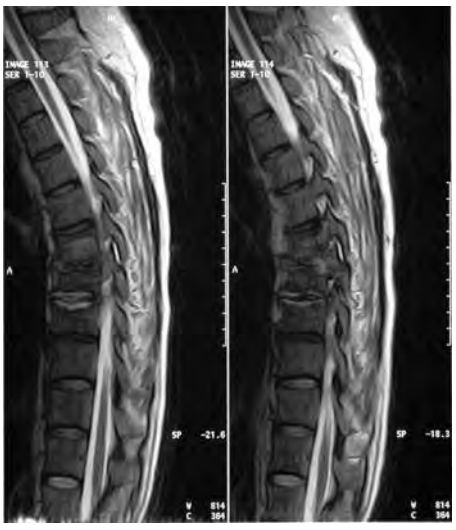

Figure 1. Thoracic spondylodiskitis.

A urinary tract infection caused by *Enterococcus faecium* also was detected and treated with teicoplanin (400 mg/d). At this time, antituberculosis treatment was tripled, with discontinuing rifampicin, and thoracic computed tomography findings consisting of only sequela changes. The patient's complaints ceased after these treatments. Azathioprine (50 mg/d) was added to immunosuppressive treatment. But he complained a new low back pain.

A lumbar magnetic resonance image revealed a new spondylodiskitis focus at L2-L3 vertebrae. Bone scintigraphy also disclosed spondylodiskitis at L2-L3 vertebrae and postoperative changes at T8-T10 vertebrae. On April 24, 2009, the culture obtained with scopy-guided intervertebral disk puncture remained negative for fungi. On May 5, 2009, the results of his diffusion cranial magnetic resonance were normal (which was performed because of a complaint of severe headache). Despite antifungal treatment, his pain persisted.

Before the operation for lumbar spondylodiskitis, a diffuse maculopapular drug reaction developed on his skin. Oral voriconazole treatment was discontinued after 107 days. Intravenous immunoglobulin (30 g/d) was administered for 3 days. While relieving maculopapular eruptions, zona zoster was added to the present clinical situation and was treated with valacyclovir at dosage of 2 g/d. A diskectomy was performed for L2-L3 lesions, and results of a pathologic specimen were chronic, nonspecific inflammation and callus tissue. Then amoxicillin-clavulanic acid and ciprofloxacin treatment was administered for 6 months. Immunosuppressive treatment now consisted of cyclosporine 175 mg/d, azathioprine 50 mg/d, and prednisolone 10 mg/d. There were no acido-resistant

bacilli in the new sputum samples, and only sequela changes were present in the new thoracic computed tomography. Antituberculosis treatment that consisted of ofloxacin and isoniazid was completed after 18 months. The patient remained well with no complaints after this treatment, with a serum creatinine value of 167.9 μmol/L (1.9 mg/dL).

Discussion

Vertebrae are the most common site of *Aspergillus* infection in bone.[5] Few cases of *Aspergillus* vertebral osteomyelitis after heart, liver, kidney, or multivisceral transplants have been reported.[5-11] Risk factors for invasive aspergillosis after transplant include renal failure, immunosuppression, high doses of steroids, neutropenia, defective phagocytes, bacterial and *cytomegalovirus* infections, use of antibiotics, presence of vascular complications, allograft rejection, diabetes, malignancy, parenteral nutrition, and dialysis.[12, 13] Our patient was predisposed to *Aspergillus* by a combination of multiple infections and use of various immunosuppressives and broad-spectrum antibiotics.

Back or neck pain without diagnostic characteristics is the initial complaint of vertebral osteomyelitis, which is noted in all transplanted patients. It usually begins insidiously, and progressively worsens over several weeks or months, as in our case. Some patients may present with fever, neurologic deficits, and other nonspecific complaints.[14] Vertebral osteomyelitis is usually first suspected based on clinical features and abnormal imaging findings, and is then usually confirmed by aspiration of the infected intervertebral disk space or vertebral bone. The definitive diagnosis requires demonstration of characteristic, acute branching, broad, septate hyphae in biopsy materials, and a culture showing *Aspergillus*.

The characteristics of patients with *Aspergillus* spondylodiskitis after renal transplant in the 3 published case reports and our present case are shown in Table 1. The median time of the infection was 8 weeks to 3 years. The most frequently isolated type was *Aspergillus fumigatus* (75%). All patients presented radiologic evidence of lumbar osteomyelitis and diskitis, which is the primary location of *Aspergillus* osteomyelitis in vertebra. Our case had both thoracic and possible lumbar

Table 1. The characteristics of renal transplant recipients with Aspergillus spondylodiskitis

Ref No.	Organ	Age, sex	Cause	Time	Initiation treatment	Comorbidities and risk factors	Symptoms and findings	Location	Diagnosis tool	Antifungal treatment	Outcome
9	Simultaneous pancreas and kidney	46, M	Diabetes mellitus	12 mo	Thymoglobulin, P, TAC, MMF	Severe GI bleed, bladder leak, multiple hospitalization due to arterial insufficiency, inferior vena cava thrombosis, recurrent UTI, graft loss, neutropenia	Progressive low back pain, daily fever, tenderness in the paravertebral lumbar region	L2-L3	Direct smear and culture of computed tomography-guided biopsy	Amphotericin B, discektomy, flucytosine, caspofungin	Complete cure
10	Kidney	59, F	NA	36 mo	TAC-Based treatment	Chronic transplant glomerulopathy, *CMV* retinitis, intestinal tuberculosis	Lower extremity paresthesias and weakness, then fever, paraparesis, paraspinal abscess	L2-L4	Culture of computed tomography-guided drainage	Amphotericin B	Died owing to fungal sepsis and septic shock
11	Multivisceral and kidney	25, M	Recurrent nephrolithiasis	8 wk	TAC, P, Thymoglobulin, infliximab, then methyl-P, MMF	Fungal pneumonia, nontissue-invasive *CMV* infection, acute cellular kidney rejection	Recurrent pain in the lower back and limited mobilization	L2-L3	Direct smear and culture of surgical material	Voriconazole, caspofungin, liposomal amphotericin B, surgery	Complete cure
*	Kidney	46, M	Hypertension	5 mo	Basiliximab, cyclosporine, MMF, P	Recurrent UTI, *CMV* infection, fungal pneumonia, pulmonary tuberculosis	Back pain	T8-9, L2-L3?	Culture of surgical material	Caspofungin, voriconazole, surgery	Complete cure

Abbreviations: CMV, *cytomegalovirus;* F, female; GI, gastrointestinal; M, male; mo, month; MMF, mycophenolate mofetil; NA, not available; P, prednisolone; TAC, tacrolimus; UTI, urinary tractus infection; wk, week

* Present case

involvement. A recipient with paraspinal abscess died of fungal sepsis because antifungal treatment was started too late because tuberculous spondylitis was initially considered.[10] Indeed, we did not exclude tuberculosis bone disease at first owing to the presence of pulmonary tuberculosis. *Aspergillus* spondylitis is often misdiagnosed as tuberculosis spondylitis, especially in its early stages. The morbidity and mortality rates among patients with *aspergillus* spondylitis continue to be high, underlying the importance of an early diagnosis. Tuberculosis responds better to drug therapy, in contrast to invasive aspergillosis.[10]

Bone infections in patients with invasive aspergillosis often require prolonged medical therapy.[15] Penetration of amphotericin B into bone tissues is poor. Itraconazole has been used to treat a limited number of cases of bone aspergillosis, although the unpredictable bioavailability of the oral capsules and the emergence of resistant strains may limit the effectiveness of this drug. Flucytosine and rifampicin do not have good intrinsic *aspergillus* activity.[16] Cortet and associates[17] reported that itraconazole alone or in combination with flucytosine or amphotericin B was an effective therapy in 9 patients with *aspergillus* spondylodiskitis (including 3 heart transplant patients) without the need for surgical debridement after a mean of 22 weeks of treatment. Caspofungin penetration into bone tissue is likely to be poor. In our case, the poor penetration might explain the development of *aspergillus* spondylodiskitis despite caspofungin treatment. It should not be used as monotherapy; instead, it may play a part in combination therapy with an agent with good bone penetration such as flucytosine, rifampicin, and possibly posaconazole or ravuconazole.[16] A combination of amphotericin B, caspofungin, and surgical intervention was used to treat a kidney-pancreas transplant recipient with spondylodiskitis successfully.[9] Voriconazole that has excellent tissue penetration is effective as first-line and salvage therapy of invasive aspergillosis in patients who were experiencing treatment failure or did not tolerate other antifungals.[15, 16] Mouas and associates[15] found that 11 patients with satisfactory responses received a median duration of voriconazole treatment of 180 days when compared with just 14 days for 9 patients with unsatisfactory responses. In their series, 1 liver transplant recipient had a partial response, while the therapy failed in a heart transplant patient. However, voriconazole therapy was safety and efficiency for spondylodiskitis in heart transplant recipients of Wéclawiak and associates.[7] Surgical intervention can rapidly reduce fungal load, remove necrotic material and abscesses increasing drug penetration, and prevent mass effects of the infection such as paralysis.[16]

We successfully treated the pulmonary aspergillosis with caspofungin. However, the pathogen could possibly reach the spine by hematogenous spread from the respiratory tract. After the diagnosis of thoracic spondylitis, we administered voriconazole treatment. The therapy was maintained more than 3 months. At the end of this period, he experienced serious cutaneous lesions associated with multiple drug use including voriconazole. But, new foci of spondylodiskitis in the lumbar region developed during the course of the therapy. Antifungal, antituberculous, and nonspecific treatments were completed. He underwent the lumbar operation late owing to medical complications. The pathologic specimen revealed chronic nonspecific findings. The second infection could possibly be due to direct inoculation of *aspergillus* or nonspecific pathogen from thoracic spinal surgery. In conclusion, these patients can be successfully treated with surgical intervention and voriconazole therapy.

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