Disseminated candidiasis 18 years after renal transplantation

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ABSTRACT

Although mucocutaneous candidiasis is a common infection in renal transplant recipients, disseminated candidiasis is rare. Candida pnemonia causing miliary mottling on X-ray chest with the central nervous system involvement is still rarer. We report an unusual case with disseminated candidiasis that presented 18 years after renal transplantation and improved on conventional antifungal therapy; the relevant literature is reviewed.

Key words: Amphotericin B, disseminated candidiasis, immunosuppressive therapy, Military mottling on chest skiagram

Introduction

Renal transplantation is the preferred mode of renal replacement therapy for thousands of patients worldwide with end-stage renal disease. But they have a substantial risk for post-transplant infections, of which invasive fungal infections (IFIs) are among the most serious ones. The incidence of IFI due to Candida has been increasing over the years.[1,2] Commonly reported IFIs among organ transplant recipients are invasive candidiasis[2] and majority of these occur within the first 3 months after transplantation.[2,3] The term disseminated candidiasis is used when multiple organ infections occur; blood cultures are negative in up to 40-60% of patients with disseminated candidiasis. We report an unusual case of disseminated candidiasis in a renal transplant recipient occurring 18 years after transplantation.

Case Report

A 47-year-old male was admitted in our hospital for the first time with history of fever and cough with expectoration for about 3 weeks; he had loss of appetite and weight loss of 8 kg in 2 months. He underwent live-related donor renal transplantation in December 1993 with his mother as the kidney donor; the native kidney disease was chronic glomerulonephritis. He had a stable normal graft function till September 2010. His initial immunosuppression was with cyclosporine, azathioprine, and prednisolone, which was modified to cyclosporine (3 mg/kg/day), mycophenolate mofetil (30 mg/kg/day), and prednisolone (15 mg/day) 5 years back. Since 2 years he was self-titrating the medications and was also on irregular follow-up with the transplant unit. He was on cyclosporine 75 mg twice a day (BID), mycophenolate mofetil 1 g BID, and prednisolone 15 mg once a day (OD) when he first visited us. On examination he was conscious oriented, febrile (100°F) with blood pressure of 170/90 mm Hg, skin and oral cavity were normal. He had no edema and had a urine output of 2000 ml per day. Systemic examination including optic fundi was normal. Investigations showed normal hemogram, blood urea 62 mg/dl, serum creatinine 2.58 mg/dl, SGOT 46 IU/l, SGPT 117 IU/l, normal serum electrolytes, and C-reactive protein (CRP) 126.36 mg/l; urine examination showed 1+ proteinuria with no sediments on microscopy. Ultrasonogram abdomen and Doppler study showed normal renal allograft. Blood, urine, and sputum culture showed no growth. Transesophageal echocardiography was normal (there were no vegetations); upper Gastrointestinal (GI) endoscopy was normal. X-ray chest showed bilateral miliary mottling in the upper, middle, and lower zones [Figure 1a]. A high resolution computed tomography of the thorax showed miliary mottling involving all the lobes of lung uniformly [Figure 1b]. Sputum did not reveal any acid fast bacilli on Ziehl Neelsen stain and Acid-fast bacilli (AFB) culture. cytomegalovirus (CMV) serology and Polymerase chain

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reaction (PCR) for cytomegalovirus (in blood) were negative.

Fiber-optic bronchoscopy showed normal trache-obronchial tree with no endobronchial lesions. Broncho-alveolar lavage, brush scrapings from the bronchial wall, and transbronchial lung biopsy were taken. A lung biopsy showed macrophages laden with tiny multiple ovoid cells with a perinuclear hallow on H and E stain [Figure 2a]; Gomori's methenamine stain highlights these ovoid bodies in brown color [Figure 2b]. Ziehl-Neelsen stain for acid fast bacilli was negative. These features were suggestive of a yeast infection.

Culture of broncho-alveolar lavage (BAL) and lung tissue on Sabouraud's dextrose agar grew white to cream colored, round, smooth, glabrous to waxy surfaced yeast-like colonies at 37°C and 25°C [Figure 2c]. Lactophenol cotton blue mount and Gram stain of the colonies showed budding yeast cells. The isolate was germ tube positive and slide cultures on corn meal agar showed blastoconodia, pseudohyphae, and terminal chlamydospores [Figure 2d] which were suggestive of *Candida albicans*. The isolate was also tested using a semi-automated identification system ID 32C/mini analytic profile index (API) (antibiotic fungus is a micromethod for yeast susceptibility testing from Biomerieux, France) which confirmed the identification as *Candida albicans*. The isolate was susceptible to amphotericin B, flucytosine, itraconazole, fluconazole, and voriaconazole using the ATB FUNGUS 2/mini API system (Biomerieux, France). Cultures of BAL and lung tissue for mycobacterium were negative.

After admission the patient developed altered sensorium. There was no focal neurological deficit. MRI brain was suggestive of multiple micro-infarcts in bilateral corona radiata and the periventricular region with few infarcts showing a rim of hemorrhage around [Figure 1c and d].

With microbiological evidence of *Candida albicans* in lung tissue, with clinical and radiologic features suggestive of pulmonary and central nervous system (CNS) involvement, a diagnosis of disseminated candidiasis was made in this renal allograft recipient who was on a good dose of immunosuppressants. The patient was started on intravenous amphotericin B and oral flucytosine; mycophenolate mofetil was reduced to 500 mg twice a day, prednisolone to 7.5 mg daily, and cyclosporine was stopped. He was given amphotericin B-deoxycholate (AmB-d) 1 mg/kg intravenous daily and flucytosine as 25 mg/kg four times daily (dose was adjusted as per the estimated glomerular filtration rate) for 6 weeks. The patient showed marked improvement, his sensorium became normal, his serum creatinine

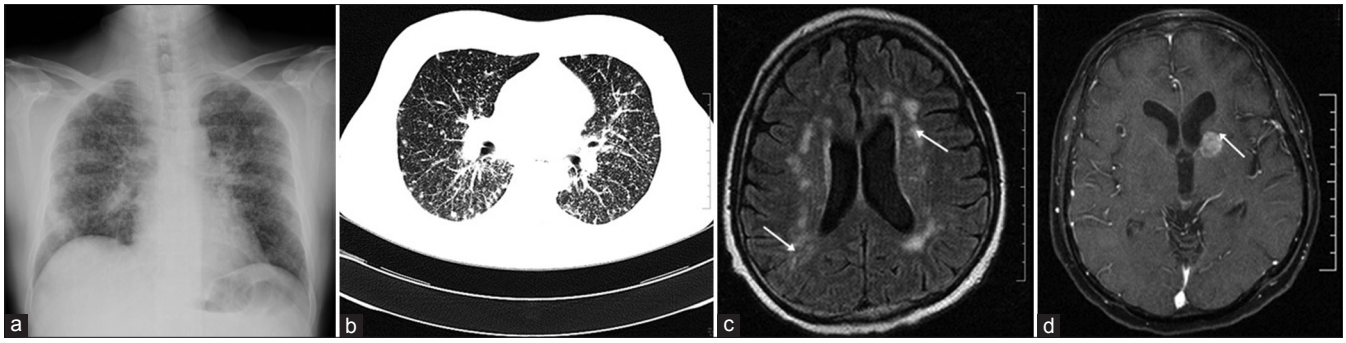

Figure 1: (a) X-ray chest (posterior-anterior view) showing bilateral miliary mottling. (b) HRCT of the chest showing bilateral miliary nodules with no lymph nodes or calcification. (c) MRI brain: T2 flare images show hyperintense lesions in the bilateral corona radiata region and in periventricular white matter (white arrows). (d) MRI brain showing cerebral infarct with a thin rim of hemorrhage anterolaterally (white arrow)

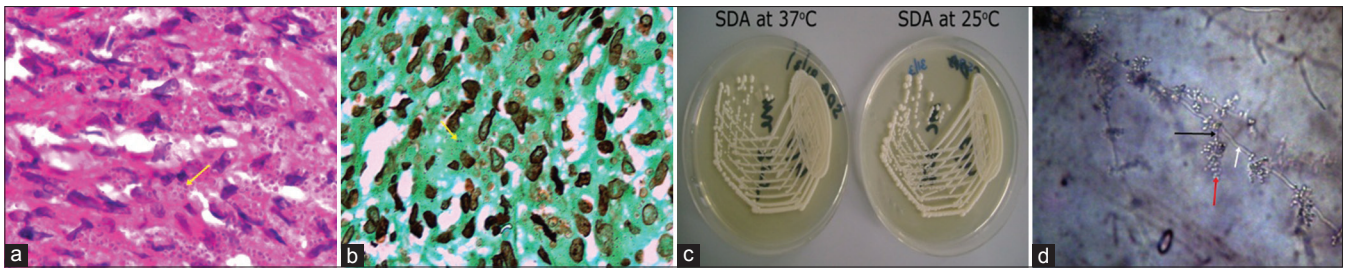

Figure 2: (a) Transbronchial lung biopsy: H and E stain (×40) showing macrophages laden with tiny multiple ovoid cells (yellow arrow). (b) Transbronchial lung biopsy: GMS stain (×100) highlights these ovoid bodies as brown (yellow arrow). (c) Lung tissue culture: SDA agar showing creamish yeast like colonies at 37 and 25° C. (d) Lung tissue culture: Growth on corn meal agar showing pseudohyphae, blastoconidia, and chlamydospores (arrows white, black, and red)

improved to 1.6 mg/dl, fever responded, serum CRP became normal, liver enzymes improved, and the radiologic features resolved on X-ray chest at the end of 6 weeks. He was advised to take fluconazole for a period of 6 weeks.

Discussion

Infections complicate the course of 50-75% of renal transplant recipients in tropical countries with mortality ranging from 20% to 60%.[4] IFIs are seen in 0.87% of patients undergoing renal transplantation.[5] The incidence is more with cyclosporine-based regimens.[4] The most common cause of IFIs is candidiasis (53%). Median time to onset of candidiasis was 103 days after transplantation.[2] Candidiasis is the most common systemic fungal infection encountered among renal transplant recipients in India and it accounts for 55% of all IFIs.[6] Most of the candida infections occur in the first 3 months after transplantation.[1] Candida constitutes 7-9% of all mucocutaneous fungal infections in tropical countries. The term disseminated candidiasis is used when multiple organs are infected with the fungus as a result of blood stream spread; a tissue biopsy helps to identify the organism. Blood cultures are helpful but yield positive results in only 50-60% of cases of disseminated infection.[7] Risk factors associated with invasive or systemic candidiasis include granulocytopenia, broad spectrum antibiotic therapy, solid-organ transplantation (liver, kidney), hematologic malignancies, urinary catheters, and intravascular access devices, corticosteroids, and immunosuppressive medications.[8] This infection is most common in liver transplants followed by pancreas, kidney, and other organs.[2]

The incidence of pulmonary mycosis among kidney recipients was 2.1% in a study from China.[9] Sputum culture is not diagnostic because of the possibility of contamination with pharyngeal secretion where this organism resides usually. The lung biopsy is mandatory to definitively establish the diagnosis of respiratory tract candidiasis.[6] Our patient had respiratory symptoms and had miliary mottling on radiographs of the chest; transbronchial lung tissue culture was confirmatory of *Candida albicans* and culture for *Mycobacterium tuberculosis* was negative at 6 weeks after incubation.

CNS infections with candida in adults can occur as a manifestation of disseminated candidiasis, as a complication of a neurosurgical procedure (especially after shunt surgery), or as an isolated chronic infection.[10] The two primary forms of infection are exogenous infection and endogenous infection. The exogenous infection results from post-operative infection, trauma, lumbar puncture, or shunt placement. The endogenous infection results from hematogenous dissemination and thus involves the brain parenchyma and is associated with multiple small abscesses. The spectrum of this disease includes meningitis, granulomatous vasculitis, diffuse cerebritis with microabscesses, and mycotic aneurysms. CSF culture yield was poor (only 31%) and required a large amount of CSF sample, whereas development of diagnostic tests based on protease detection was of limited value as different species of candida secreted antigenically distinct proteases.[11] Our patient had fever and alteration of higher mental function with worsening sensorium, and MRI brain showed lesions suggestive of multiple infarcts and hemorrhage. We had a lung biopsy with candida pneumonitis and neurological manifestations responded well to antifungal therapy. Given the poor yield of CSF culture in diagnosing CNS candidiasis, we did not do a CSF analysis in our patient.

Recent IDSA (Infectious Diseases Society of America) guidelines for disseminated candidiasis involving CNS recommends lipid formulations of amphotericin B (LFAmB) at a dosage of 3-5 mg/kg daily, with flucytosine at a dosage of 25 mg/kg four times daily with dose adjustment, for renal dysfunction, for the initial several weeks of treatment and is continued until all signs and symptoms, and radiologic abnormalities have resolved; then fluconazole at a dosage of 400-800 mg (6-12 mg/kg) daily is recommended as step-down therapy after the patient responds to initial treatment with LFAmB and flucytosine 7. Recommendations favor LFAmB over AmB-d because of lower nephrotoxity and the higher levels attained in the brain in a rabbit model of candida meningoencephalitis. The combination of AmB and flucytosine is useful because of the *in vitro* synergism noted with the combination and the excellent CSF concentrations achieved by flucytosine. The length of therapy with AmB alone or in combination with flucytosine has not been defined, but several weeks of therapy before transition to treatment with an azole may be required[10] (after the patient has shown clinical and CSF improvement). We used AmB-d with flucytosine and the patient responded well to this conventional treatment.

Mortality of invasive fungal infections in renal transplant recipients has been reported to be around 65%.[4] Our patient has shown good response after treatment for 6 weeks; the optimal duration of treatment for invasive candidiasis in renal transplant recipient with CNS and lung involvement is not known.[10] This patient was advised to continue fluconazole 6 weeks more.

The degree of immunosuppression correlates with chances of occurrence of fungal infection; this patient was on a high dose of immunosuppressant (due to irregular follow-up and self-titration), which predisposed him to this infection. This is a rare case of disseminated candidiasis involving both lungs and CNS in a renal transplant recipient occurring 18 years after transplantation, with unusual features like miliary mottling on X-ray chest, multiple infarction, and hemorrhage on MRI brain; a detailed histopathologic and microbiological workup helped us to confirm the diagnosis; he responded well to conventional amphotericin B and flucytosine, along with reduction in dose of immunosuppressive drugs.

Conclusion

Disseminated candidiasis can occur even in long-term survivors after renal transplantation. The presence of candida in tissue biopsy (lung biopsy) is a definitive method of diagnosis of invasive fungal infection and treatment with a combination of antifungal agents is useful. Though with best of the available treatment, mortality in disseminated candidiasis remains high, we would be able to save some patients with an early and timely diagnosis, and a proper aggressive treatment. This case report also highlights the need for regular follow-up and down gradation of immunosuppressants with increasing duration after transplantation.

References

1. Silveira FP, Husain S. Fungal infections in solid organ transplantation. Med Mycol 2007;45:305-20.
2. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, *et al*. Invasive fungal infections among organ transplant recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis 2010;50:1101-11.
3. van Hal SJ, Marriott DJ, Chen SC, Nguyen Q, Sorrell TC, Ellis DH, *et al*. Candidemia following solid organ transplantation in the era of antifungal prophylaxis: The Australian experience. Transpl Infect Dis 2009;11:122-7.
4. Jha V, Chugh S, Kirpal S. Chugh. Infections in dialysis and transplant patients in tropical countries. Kidney Int 2000;57:S85-93.
5. Einollahi B, Lessan-Pezeshki M, Pourfarziani V, Nemati E, Nafar M, Pour-Reza-Gholi F, *et al*. Invasive fungal infections following renal transplantation: A review of 2410 recipients. Ann Transplant 2008;13:55-8.
6. Gupta RK. Opportunistic infections in renal allograft recipients. Transplant Proc 2007;39:731-3.
7. Alexander BD, Pfaller MA. Contemporary tools for the diagnosis and management of invasive mycoses. Clin Infect Dis 2006;43:S15-27.
8. Pappas PG. Invasive candidiasis. Infect Dis Clin North Am 2006;20:485-506.
9. Chen G, Zhang Z, Gu J, Qiu J, Wang C, Kung R, *et al*. Incidence and risk factors for pulmonary mycosis in kidney transplantation. Transplant Proc 2010;42:4094-8.
10. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, *et al*. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;48:503-35.
11. Shankar SK, Mahadevan A, Sundaram C, Sarkar C, Chacko G, Lanjewar DN, *et al*. Pathobiology of fungal infections of the central nervous system with special reference to the Indian scenario. Neurol India 2007;55:198-215.

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