

Cavitary lung lesion 6 years after renal transplantation

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Abstract

The differential diagnoses of a cavitary lung lesion in renal transplant recipients would include infection, malignancy and less commonly inflammatory diseases. Bacterial infection, Tuberculosis, Nocardiosis, fungal infections like Aspergillosis and Cryptococcosis need to be considered in these patients. Pulmonary cryptococcosis usually presents 16-21 mo after transplantation, more frequently in patients who have a high level of cumulative immunosuppression. Here we discuss an interesting patient who never received any induction/anti-rejection therapy but developed both BK virus nephropathy as well as severe pulmonary Cryptococcal infection after remaining stable for 6 years after transplantation. This case highlights the risk of serious opportunistic infections even in apparently low immunologic risk transplant recipients many years after transplantation.

Key words: Lung cavity; Immunosuppression; Renal transplantation

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Core tip: Here we discuss an interesting patient who never received any induction/anti-rejection therapy but developed both BK virus nephropathy as well as severe pulmonary Cryptococcal infection after remaining stable for 6 years after transplantation. This case highlights the risk of serious opportunistic infections even in apparently low immunologic risk transplant recipients many years after transplantation.

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INTRODUCTION

Fungal infections causing cavitory lung lesions usually manifest in transplant recipients who have received a high level of cumulative immunosuppression. We describe an unusual case, where a low risk transplant recipient who had been stable for 6 years developed severe pulmonary Cryptococcal disease and BK virus nephropathy.

CASE REPORT

A 40-year-old Indian man was admitted with low grade fever and dry cough for one month. He had end stage renal disease due to unclassified primary disease and had a live related renal transplantation with his sister as the donor in 2009. He was detected hepatitis B surface antigen (HBsAg) positive before transplantation and has been on Tenofovir since then. He received no induction and was initially maintained on Tacrolimus, Mycophenolate Mofetil (MMF) and Steroids. After a year, MMF was changed to Azathioprine due to financial constraints. He received Trimethoprim-Sulfamethoxazole for 6 mo after transplantation but no primary prophylaxis for Cytomegalovirus (CMV), Tuberculosis (TB) or fungal infection. His postoperative course was uneventful and he maintained serum creatinine of 1.1-1.2 mg/dL. He is a non smoker.

Clinically, the patient was febrile, hemodynamically stable and hypoxemic (SPO₂ 92% on room air) requiring oxygen by mask. Investigations revealed pancytopenia (Hb 7.4 g/dL, total leucocyte count -3400/cu mm, platelet count -87000/cu mm) and high serum creatinine (2.5 mg%). Azathioprine was stopped. Tacrolimus trough level was 3.7 ng/mL. Urinalysis was unremarkable. Graft biopsy showed BK virus (BKV) nephropathy and serum BKV plasma load was more than 10⁴ copies/mL.

He was started empirically on broad spectrum antibiotics. Blood and urine cultures and quantitative CMV PCR assay were non-contributory. A non-contrast CT thorax showed bilateral, multiple, diffuse centrilobular and peribronchovascular cavitating nodules coalescing to form areas of consolidation with a larger cavity in apico posterior segment of upper lobe of left lung (Figure 1). Bronchoscopy with bronchoalveolar lavage (BAL) fluid cultures was unrevealing. Serum Cryptococcal antigen was negative. Serum and BAL fluid galactomannan were negative.

Since patient continued to be febrile, computed

tomography guided biopsy of the cavitory lesion in the left lung was done and the histopathology (Figure 2) showed Cryptococcal infection. He was treated with liposomal Amphotericin for 6 wk and given Fluconazole prophylaxis. Flucytosine was not available at that time. Patient showed clinical as well as radiologic improvement and was discharged on oral fluconazole. His pulmonary infection has subsequently recurred and now he is being treated with a combination of Amphotericin and Flucytosine.

DISCUSSION

A renal transplant recipient may present with a cavitory lung lesion due to infection, malignancy (post-transplant lymphoproliferative disorder) or inflammatory disease, though infections are the predominant causative factor^[1-3]. TB is the commonest cause of cavitory lung lesions in endemic areas like India and patients may receive empiric anti-TB therapy if the index of suspicion for rarer infections is not high and investigations are non-contributory. Aspergillosis (either angioinvasive or chronic necrotizing form) is the most common fungal infection associated with cavitation. Other causes are Nocardiosis, Cryptococcosis, Actinomycosis and rarely Legionella pneumophila. In a sick patient, the possibility of septic emboli has to be kept in mind^[1,2].

Cryptococcosis is the third most common fungal infection seen in transplant recipients^[4,5]. It typically occurs late with median time to onset being 16 to 21 mo after renal transplantation. However our patient presented very late - 6 years after transplantation. So besides TB and fungal infection, post-transplant lymphoproliferative disease was an important differential diagnosis considered. All factors which increased the cumulative immunosuppression in patients increase the risk of disseminated Cryptococcal disease. Presence of chronic liver disease and use of steroids, T cell depleting antibodies and Alemtuzumab are specifically associated with increased risk of Cryptococcosis. Calcineurin inhibitor based regimens are believed to be protective, being associated more commonly with Cryptococcosis limited to lungs with less likelihood of dissemination^[5,6].

Our patient is HBsAg positive. But he had not received induction, had no history of rejection requiring pulse steroid therapy and has not been on MMF for 5 years. Though the apparent dose of immunosuppressive drugs given seems to be low, his cumulative immunosuppression level is definitely high as is suggested by the onset of late BKV associated nephropathy.

Cryptococcal infection commonly presents with neurologic disease (meningitis) or pneumonia. But it may also involve the skin and soft tissue, bones, joints and other organs like the liver and the kidney. Isolated pulmonary disease is uncommon seen in only 33% of the patients. Serum Cryptococcal antigen has 90% sensitivity in disseminated disease but may be

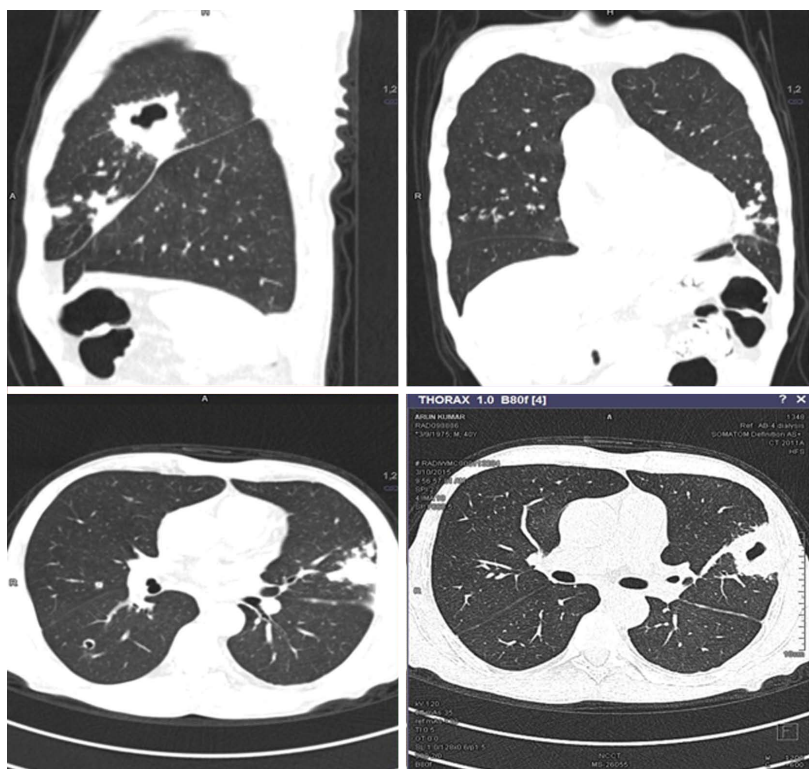


Figure 1 Multiple diffuse bilateral centrilobular and peribronchovascular cavitating nodules coalescing to form areas of consolidation with larger cavity in apico posterior segment of upper lobe of left lung.

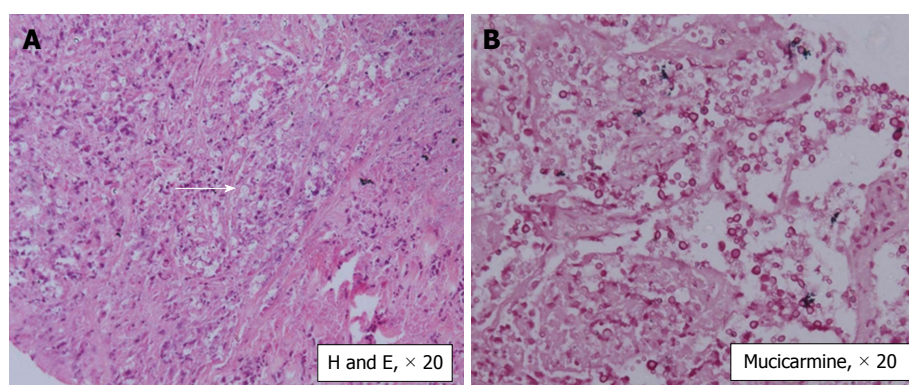


Figure 2 The histopathology showed cryptococcal infection. Histopathology of the lung lesion shows: A: Large area of necrosis with numerous capsulated yeast forms of fungi (arrow) morphologically resembling *Cryptococcus*; B: Special histochemical stain (Mucicarmine) highlights its polysaccharide capsule.

negative in immunosuppressed patients especially with isolated pulmonary disease^[5] as seen in our patient. The final diagnosis is by tissue biopsy and/or culture. The organism can be recognized by its oval shape, and narrow-based budding on histopathology. With the use of mucicarmine staining, the *Cryptococcal* capsule will stain rose to burgundy in color and help differentiate *Cryptococcus neoformans* from other yeasts, especially *Blastomyces dermatitidis* and *Histoplasma capsulatum*^[5].

Choice of antifungal therapy depends on the severity and extent of the disease. In patients with severe pulmonary infection, neurological involvement and disseminated disease, combination of liposomal Amphotericin with Flucytosine for 2 wk followed by Fluconazole for

12 mo is recommended. If Flucytosine is not available, which was the case initially in our patient, Amphotericin should be given for a minimum of 4-6 wk^[5].

Cryptococcal infection has an overall mortality of 14% in solid organ transplant recipients^[6]. Early diagnosis and initiation of treatment is the key to survival. A high index of suspicion and step-wise approach to diagnosis including a lung biopsy is required as the duration of therapy differs significantly from other fungal infections.

COMMENTS

Case characteristics

A 40-year-old male renal transplant recipient presented with low grade fever

and dry cough for one month.

Clinical diagnosis

A febrile patient with respiratory symptoms.

Differential diagnosis

Chest infection-bacterial/Tuberculosis/fungal.

Laboratory diagnosis

Pancytopenia with high serum creatinine.

Imaging diagnosis

Non contrast computed tomography scan of chest showed bilateral, multiple, diffuse centrilobular and peribronchovascular cavitating nodules coalescing to form areas of consolidation with a larger cavity in apico posterior segment of upper lobe of left lung.

Pathological diagnosis

Biopsy from the lung lesion showed Cryptococcal infection and graft kidney biopsy showed BK virus associated nephropathy.

Treatment

He was treated with liposomal Amphotericin and Flucytosine.

Related reports

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Term explanation

Cryptococcal infection is the third most common fungal infection seen in transplant recipients. It commonly presents with neurologic disease (meningitis) or pneumonia, but may also involve the skin and soft tissue, bones, joints and

other organs like the liver and the kidney.

Experiences and lessons

Tissue biopsy or culture is required to diagnose isolated pulmonary cryptococcosis. Early diagnosis and initiation of treatment is essential for survival.

Peer-review

The case discusses an important issue in patients with kidney transplantation.

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