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Challenges in Diagnosing and Treating Cryptococcal Meningitis in Renal Transplant Recipients: A Case Series

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Abstract

Aims: Cryptococcal meningitis (CM) remains a significant complication in renal transplant (RT) recipients due to their immuno compromised status. This case series describes three RT patients who developed CM, highlighting the clinical presentations, diagnostic challenges, and management strategies.

Case Presentation: The first case involved a 51-year-old male with chronic kidney disease and hypertension (HTN) who presented with fever, headache and generalized weakness. He was diagnosed with CM based on cerebrospinal fluid (CSF) analysis and treated with liposomal amphotericin B (AMB) and Fluconazole, resulting in symptomatic improvement. The second case was a 32-year-old male with a history of chronic graft dysfunction and antibody-mediated rejection. He presented with altered sensorium and was found to have CM. Despite appropriate antifungal treatment and immunosuppressive adjustments, the patient experienced neurological deterioration and ultimately succumbed to complications. The third case involved a 52-year-old male with diabetes and HTN who presented with headache and giddiness. He was diagnosed with CM and treated with liposomal AMB and Fluconazole. Although he initially showed improvement, persistent graft dysfunction required further adjustments in his treatment regimen.

Discussion: These cases underscore the importance of early diagnosis and tailored management of CM in RT recipients. Close monitoring of renal function and careful adjustment of immunosuppressive therapy are crucial to improving patient outcomes.

Conclusion: This case series provides valuable insights for clinicians managing similar patients, emphasizing the need for vigilance and prompt intervention in this vulnerable population.

Keywords: Cryptococcal meningitis, Renal transplant recipients, Opportunistic infections, Antifungal therapy, Immunosuppression

Introduction

Renal transplant (RT) patients are at significant risk for both common and opportunistic infections, which can lead to considerable morbidity and mortality [1]. These infections are categorized into community-acquired infections, such as respiratory and enteric infections, and opportunistic infections, which include reactivation of prior infections, nosocomial infections and zoonotic sources. Zoonotic infections, which are transmitted

between animals and humans, pose a growing concern in the transplant population [1].

Cryptococcus neoformans and Histoplasma capsulatum are the most common bird-related infections in RT patients [2]. The central nervous system (CNS) is the primary site of clinical infection by C. neoformans, often presenting as subacute meningoencephalitis. Symptoms typically include headache, altered mental status, lethargy, fever, stiff neck, nausea and vomiting. However, RT recipients may exhibit minimal or nonspecific symptoms at presentation [2].

Early detection of cryptococcal meningitis (CM) in RT recipients is feasible through serum cryptococcal antigen testing. Definitive diagnosis is achieved through lumbar puncture, revealing lymphocytic pleocytosis, hyperproteinorachia and hypoglycorrhachia [3]. India ink staining and cryptococcal antigen testing are critical for diagnosis, with the antigen test showing high sensitivity in both cerebrospinal fluid (CSF) and serum [3]. Neuroimaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI), are used to assess the extent of CNS involvement. CT scans may reveal meningeal enhancement, nodules, cerebral edema, or hydrocephalus, although these findings are not pathognomonic for cryptococcal meningitis [4]. MRI is more sensitive for detecting multiple enhancing nodules within the brain parenchyma, meninges, basal ganglia, and midbrain [5].

Management of CM in RT recipients involve induction therapy with liposomal amphotericin B (AMB) and Flucytosine or Fluconazole, followed by consolidation and maintenance therapy with Fluconazole [6]. Close monitoring of renal function during treatment is crucial due to the nephrotoxicity associated with liposomal AMB, as well as potential drug-drug interactions between Fluconazole and calcineurin inhibitors. Recent studies have found that the risk of nephrotoxicity in RT patients taking AMB is significantly increased when the cumulative dose of 5000 mg is exceeded [7]. Lipid formulations of AMB are preferred due to their lower incidence of adverse effects [8].

Our case series aims to highlight the clinical features, diagnostic challenges and management strategies for CM in RT recipients, emphasizing the importance of early diagnosis and tailored treatment to improve patient outcomes. This case series is unique as it highlights the diverse clinical presentations of cryptococcal meningitis in renal transplant recipients, ranging from subacute symptoms to severe neurological deterioration. Additionally, it underscores the challenges of balancing effective antifungal therapy with the management of immunosuppression and graft function, offering valuable insights for clinicians treating similar high-risk patients.

Case Presentation

Case 1

A 51-year-old male, known to have hypertension (HTN) and CKD, had been living with a renal transplant for 10 years, managed with maintenance immunosuppressants. He presented with complaints of fever, severe headache and generalized weakness. His clinical history revealed exposure to pigeon droppings near his residence. His baseline graft function was stable. Upon admission, he was febrile, but his vital parameters were normal. Both general and systemic examinations revealed no abnormalities and there was no nuchal rigidity or skin rashes.

Laboratory investigations showed normal blood counts and all infective causes were ruled out. Blood and urine cultures were sterile. Imaging studies, including a chest X-ray and high-resolution computed tomography (HRCT), indicated an infective pathology in the left upper lobe. Magnetic resonance imaging (MRI) of the

brain revealed prominent cortical sulci and cerebrospinal fluid (CSF) spaces. CSF analysis showed a cell count of 60 cells/mL, with 30% neutrophils and 70% lymphocytes, glucose level less than 20 mg/dL and protein level of 187 mg/dL. CSF culture was sterile, Mycobacterium tuberculosis polymerase chain reaction was negative, adenosine deaminase was 19 units/L, Venereal Disease Research Laboratory (VDRL) test was non-reactive and both malignant cytology and India ink staining were negative. However, cryptococcal antigen was positive. Bronchoalveolar lavage (BAL) fluid analysis was normal.

A diagnosis of cryptococcal meningitis was made. The patient was started on intravenous (IV) liposomal Amphotericin B (AMB) 200 mg once daily for 14 days and IV Fluconazole 800 mg once daily. Adequate hydration was maintained throughout the treatment. Within three days of initiating therapy, the patient showed symptomatic improvement. His immunosuppressant regimen was adjusted, with a reduction in the dose of Mycophenolate mofetil (MMF). His graft function and urine output remained stable.

After two weeks of treatment, a repeat CSF analysis showed improving cell counts and a lower cryptococcal antigen titer of 1:32. The patient was discharged with oral Fluconazole 800 mg, as consolidation therapy. On follow-up, he continues to do well with stable graft function.

Case 2

A 32-year-old male with a history of HTN, chronic kidney disease (CKD) and a renal transplant recipient for six years presented with sudden onset of altered sensorium, irritability and altered behavior. He had a history of chronic graft dysfunction and biopsy-proven antibody-mediated rejection, for which he had been treated with pulse steroids. There was no history of fever, skin rashes or gastrointestinal symptoms.

On examination, he was confused and disoriented, though his vital parameters were stable. General and systemic examinations were unremarkable. MRI of the brain indicated hydrocephalus and a possible infection. Electroencephalography (EEG) suggested diffuse encephalopathy. CSF analysis revealed a cell count of 20 cells/mL, with 35% neutrophils and 65% lymphocytes, glucose level of 20 mg/dL, adenosine deaminase level of 21 units/L, protein level within normal limits and negative results for the VDRL test and malignant cytology. The CSF culture was sterile, but the cryptococcal antigen test was positive.

He was diagnosed with cryptococcal meningitis and treated with IV liposomal AMB 200 mg once daily for 14 days and oral Fluconazole 800 mg once daily. His immunosuppressive regimen was optimized by discontinuing MMF. He showed symptomatic improvement within a few days and was discharged on oral Fluconazole 400 mg daily.

Despite this, he had frequent hospitalizations due to worsening graft function. During his last admission, he presented with a headache, left-sided weakness and altered sensorium. MRI of the brain revealed an intracranial bleed. Hemodialysis was planned, along with further optimization of his immunosuppressive drugs. Unfortunately, his condition continued to deteriorate, and he ultimately succumbed to his illness.

Case 3

A 52-year-old male, with a history of post-renal transplant status for two years, diabetes, and HTN, presented with a complaint of headache and giddiness for 15 days. His native kidney disease was autosomal dominant polycystic kidney disease and he had undergone a left nephrectomy. He was on maintenance

immunosuppression with normal graft function. He also reported chest discomfort, vomiting and weight loss. Further history revealed exposure to pigeon droppings near his residence. There was no history of fever, cough or altered sensorium.

MRI of the brain showed normal findings. Due to persistent headache, CSF analysis was performed, revealing a cell count of 8 cells/mL, with 10% neutrophils and 90% lymphocytes, glucose level of 57 mg/dL, protein level of 57 mg/dL and negative malignant cytology. The culture grew Cryptococcus and the cryptococcal antigen test was positive. He was diagnosed with cryptococcal meningitis and started on IV liposomal AMB 200 mg and oral Fluconazole 1200 mg once daily.

During treatment, his serum creatinine increased to 1.8 mg/dL and serum Tacrolimus level was 8.8 ng/mL. AMB and immunosuppressant drugs were adjusted due to the possibility of drug-induced acute graft dysfunction. After 14 days of therapy, liposomal AMB was stopped, and his headache partially resolved. During hospitalization, he was also treated for a urinary tract infection. Ultrasound Doppler of the graft was within normal limits. A repeat CSF analysis after two weeks was still positive for Cryptococcus (India ink, cryptococcal antigen and fungal culture).

He was restarted on liposomal AMB 200 mg and Fluconazole 800 mg. The dose of MMF was reduced and Fluconazole was changed to oral Flucytosine on day 8. Due to persistent graft dysfunction, a graft biopsy was performed, revealing acute patchy tubular necrosis. After four weeks of induction therapy, repeat CSF analysis was positive for India ink and cryptococcal antigen, but the fungal culture was sterile. The patient showed symptomatic improvement. MMF was discontinued and he was continued on oral Fluconazole 800 mg once daily for consolidation therapy. Summary of diagnostic and clinical findings of these three cases is presented in Table 1.

Table 1: Summary of diagnostic and clinical findings in renal transplant recipients with cryptococcal meningitis

Variable	**Case 1**	**Case 2**	**Case 3**
Age	51 years	32 years	52 years
Time post-transplant at admission	10 years	6 years	2 years
Symptom duration before Diagnosis	10 days	5 days	20 days
Immunosuppressive therapy	MMF/TAC/ PRED	MMF/TAC/ PRED	MMF/TAC /PRED
CSF cell count (cells/mL)	60	20	8
Leukocytes	30%	35%	10%
Glucose (mg/dL)	<20	20	57
Proteins (mg/dL)	187	Nil	57
Initial empirical anti-infective therapy	Ceftriaxone (1g/12 hour)	Ceftriaxone (1g/12 hour)	None
Initial immunosuppressive therapy adjustment	MMF & TAC dose was reduced, Prednisolone dose was increased	MMF stopped, TAC continued on same dose, Prednisolone dose was increased	MMF dose was decreased initially then stopped, TAC- dose was reduced, Prednisolone dose was

			increased
Cryptococcal antigen test (CSF)	Positive (3 days after admission)	Positive (3 days after admission)	Positive (1 week after admission)
Antifungal therapy	Liposomal AMB 200 mg once daily IV, Fluconazole 800 mg once daily IV	Liposomal AMB 200 mg once daily IV, Fluconazole 800 mg once daily IV	Liposomal AMB 200 mg once daily IV, Fluconazole 1200mg once daily IV, Flucytosine 2500 mg once daily

MMF - Mycophenolate mofetil. TAC – Tacrolimus; PRED - Prednisolone; CSF – Cerebrospinal fluid; AMB – Amphotericin B; IV – intravenous

Discussion

We reported three cases of CM in RT recipients to emphasize the significance of timely diagnosis and effective management of this life-threatening condition. The importance of documenting these cases lies in providing a reference for clinicians encountering similar scenarios, aiding in early recognition and appropriate treatment to improve patient outcomes.

Infection with Cryptococcus neoformans in solid organ transplant recipients typically occurs in the late post-transplantation period, more than six months after transplantation [2]. The susceptibility to opportunistic infections in these patients largely depends on the overall state of immunosuppression [9]. Glucocorticoids facilitate infection with C. neoformans by diminishing cell-mediated immunity [10,11]. Induction therapy with basiliximab is associated with a low incidence (0.4%) of CM [12]. Conversely, patients treated with tacrolimus are less prone to cerebral involvement, likely due to its antifungal properties and ability to cross the blood-brain barrier [13].

Clinical signs of CM are non-specific, necessitating lumbar puncture for definitive diagnosis. This procedure typically reveals elevated opening pressure, lymphocytic pleocytosis, hyperproteinorachia, and hypoglycorrhachia. India ink examination is positive in most cases (38-93%), with confirmation obtained via culture. Cryptococcal antigen is the most sensitive test for the diagnosis of CNS infection both in the CSF (up to 100% sensitivity) and in the serum (above 85% sensitivity) [3].

There are no pathognomonic CT or MRI images for CM. CT scans may appear normal or show meningeal enhancement, nodules (cryptococcomas), cerebral edema or hydrocephalus [4]. In highly immuno compromised patients, cryptococcosis often demonstrates minimal enhancement on head CT. MRI scans are more sensitive, detecting multiple enhancing nodules within the brain parenchyma, meninges, basal ganglia and midbrain [5].

Current guidelines for managing disseminated cryptococcosis recommend induction therapy with liposomal AMB plus Flucytosine (or Fluconazole as an alternative), followed by Fluconazole in the consolidation and maintenance phases [14]. Evaluating the use of AMB in renal transplant patients is crucial due to the increased risk of nephrotoxicity when the cumulative dose exceeds 5000 mg [15]. Lipid formulations of AMB are associated with a lower incidence of adverse effects [16].

Of the three cases presented, two patients are doing well with stable graft function. However, the second patient deteriorated neurologically a few months after the initial presentation and was diagnosed with an intracranial bleed. Despite plans for renal replacement therapy and further reductions in immunosuppressive therapy due to worsening graft function, the patient could not be revived and succumbed to the illness.

Conclusion

Cryptococcal meningitis remains a significant threat to renal transplant recipients, especially in the late post-transplant period. Early diagnosis through vigilant monitoring and prompt lumbar puncture, followed by appropriate antifungal therapy and careful management of immunosuppressive medications, is crucial for improving patient outcomes. Our case series highlights the necessity for increased awareness and tailored treatment strategies in this vulnerable population to mitigate complications and improve survival.

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