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Case Report: Cryptococcal Infection in Renal Transplant Patient

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Abstract

A significant portion of all invasive fungal infections in solid organ transplants are due to cryptococcus. It can be a debilitating infection and affects the quality of life in transplant patients. We report a case of a 57-year-old male patient with recent kidney transplant, who presented with cryptococcal meningitis, after exposure to birds during a trip to Mexico 1 week ago. In addition to a two-day history of generalized weakness, dizziness, intermittent fever, and lightheadedness, the patient presented with on and off headaches, increased sinus pressure, neck stiffness, clogged ear sensation, confusion, and night sweats. The patient was initially treated empirically with fluconazole. Lumber punctuation showed elevated opening pressure, increased WBC, with neutrophil predominance. Cryptococcal antigen tests were positive in both serum and cerebrospinal fluid sources. After confirmation from CSF analysis, he was administered liposomal amphotericin B and flucytosine. Patient's symptoms rapidly improved. Due to his immunocompromised state, the patient will require lifelong fluconazole maintenance therapy. Even though kidney transplant recipients have a positive outcome in terms of longevity, they are at increased risk of post-transplant infection, such as zoonotic infections. Therefore, in any recent kidney transplant patient with meningitis symptoms, cryptococcal meningitis should always be considered. We report the appropriate criteria, procedures, and tests that allow for a cryptococcal meningitis diagnosis in immunocompromised patients.

Keywords

Cryptococcal Meningitis, Renal Transplant, Case Report, Zoonotic Infection, Meningitis

Introduction

While renal transplant can improve the quality of life for those suffering with end stage renal disease on dialysis, transplant patients are at risk to catch common and opportunistic infections which can lead to significant morbidity and mortality [1]. Infections can be categorized as common (community acquired respiratory, enteric infections) and opportunistic infections. Opportunistic infections in an immunocompromised patient include reactivation of prior infections, nosocomial infections, and zoonotic sources. In 2022, we must consider COVID-19 infection as well.

Many viral infections after renal transplantation result from reactivation of "latent" viral infection in the host or from the graft. When a virus will reactivate is dependent on the nature of the virus itself, the tissue infected, and the host immune response. Some latent viruses are metabolically inactive, whereas others are

constantly replicating at low levels determined by the effectiveness of the host's immune response. Cytomegalovirus (CMV) is the most common opportunistic pathogen seen in transplant recipients. However, renal transplant patients are at a lower risk for CMV infections compared to other organ transplant recipients because of the lower burden of latent virus in the renal allograft [2]. Urinary tract infections (UTIs) are the most common cause of nosocomial infections in renal transplant patients, followed by surgical site infections, pneumonia, and catheter-related bloodstream infections. Risk factors for UTIs include recipient of kidney from a deceased donor, substitution of the initial immunosuppressive regimen, duration of urinary bladder catheterization, and length of hospitalization before the infection [3].

Zoonotic infections, those that are transmitted and shared between animals and humans, represent a problem of rising importance in the transplant population. These infections come from a wide and diverse range of pathogens and modes of transmission. Human activities as well as climate and landscape changes significantly impact transmission and distribution of zoonoses [4]. In comparison to immunocompetent hosts, immunocompromised state renal transplant patients are an inevitable additional risk for the infection and unfavorable outcomes caused by atypical presentation, more frequent presence of disseminated/advanced disease, and prolonged treatment. Common zoonotic infections in transplant patients include West Nile virus, Chagas disease and toxoplasmosis [4]. Additionally, pathogens in the soil, such as aspergillus or nocardia species, *C. neoformans* in birds, and respiratory viruses with subsequent bacterial or fungal superinfection lead to major infection after transplantation [5]. Patients are impacted by bird-related infections commonly by inhaling dust containing feathers, secretions, and droppings from infected birds. Avian infections, not limited to immunocompromised or renal transplant patients, include: chlamydiosis, salmonellosis, avian influenza, eastern equine encephalitis (EEE), and avian tuberculosis [6]. Cryptococcus neoformans and histoplasmosis are the most common bird-related infections found in renal transplant patients [7].

Although *C. neoformans* enters the body through the lungs, the central nervous system (CNS) is the main site of evident clinical infection, presenting as a subacute meningoencephalitis. Patients commonly present with headache, altered mental status, lethargy, fever, stiff neck, nausea, and vomiting. Kidney transplant patients may have minimal or nonspecific symptoms at presentation. A differential diagnosis for *C. neoformans* meningitis in a kidney transplant patient is based on other infective causes of intracranial mass lesions such as histoplasma capsulatum infection, pyogenic, nocardial or aspergillus abscess, mycobacterium tuberculosis infection, lymphomas, lymphocytic meningitis, meningeal metastases, and hemorrhages [8]. In this study, we report a case of a 57-year-old, immunosuppressed due to a renal transplant, male who presented with *C. neoformans* meningitis infection.

Case Description

A 57-year-old Latino man was admitted for a two-day history of generalized weakness, dizziness, fever, and lightheadedness. He had an intermittent fever, on and off headaches, increased sinus pressure, neck stiffness, clogged ear sensation, confusion, and night sweats for 2 days. Past medical history significant for end stage renal disease, due to complications of diabetes and hypertension, status post deceased donor renal transplant in September 2020, obesity with BMI of 34, hypertension, diabetes type 2. In February 2022, the patient had just returned from a month-long trip to Guanajuato, Mexico. He stayed in a house with many birds during the trip. He contracted COVID-19 with mild symptoms while abroad and fully recovered. Patients received three doses of Pfizer-BioNTech (COMIRNATY) vaccine with the last dose given on 9/2021. On review of symptoms, the patient had fatigue, generalized weakness, subjective fever, dizziness, lightheadedness, mild confusion, night sweat, headache, stiff neck, photophobia, and decreased sensitivity to sound. He had no swollen lymph nodes, change in vision, shortness of breath, cough, chest pain, palpitation, abdominal pain, or nausea and coming. Also, there was no numbness/tingling in fingers or toes. At time of presentation, the patient's medication included prednisone 5 mg daily, mycophenolate mofetil

(CellCept) 250 mg twice a day, and tacrolimus (Prograf) 1 mg twice a day.

Patient's vitals on presentation were stable and afebrile; blood pressure 122/50, pulse 74, respiratory rate of 18, with 97% oxygen saturation on room air, temperature of 98. The patient did not appear to be in distress on the exam. His lungs were clear, and heart sounded regular. On physical examination, there was no palmar rash, no nuchal rigidity, respiratory distress, guarding of abdomen, rash/lesions, or gross deficits.

Upon labs, the patient's white blood cell count was normal at 8,700 WBCs per microliter. Hemoglobin was slightly low at 9.4 g/dl. Patient was hyponatremic at 126 mEq/L (normal 136-145 mEq/L), hypochloremic at 93 mEq/L (normal 95-105 mEq/L, and random blood sugar at 211 mg/dL (normal < 140 mg/dL). The imaging that was done on the patient included a brain CT and chest X-ray, both of which were unremarkable (**Fig-1** and **Fig-2**).

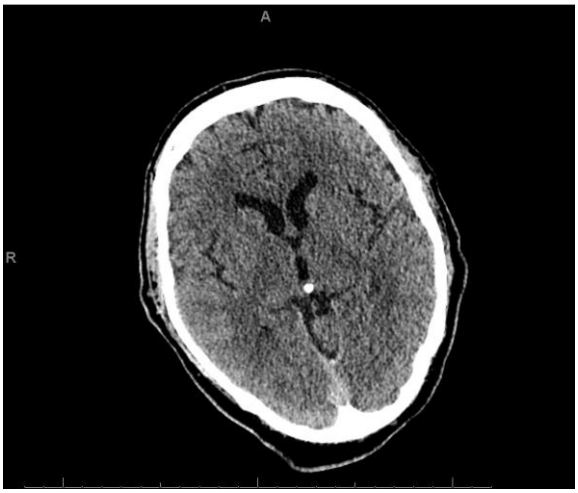

Fig-1: CT head, taken on 2/20/22, was unremarkable.

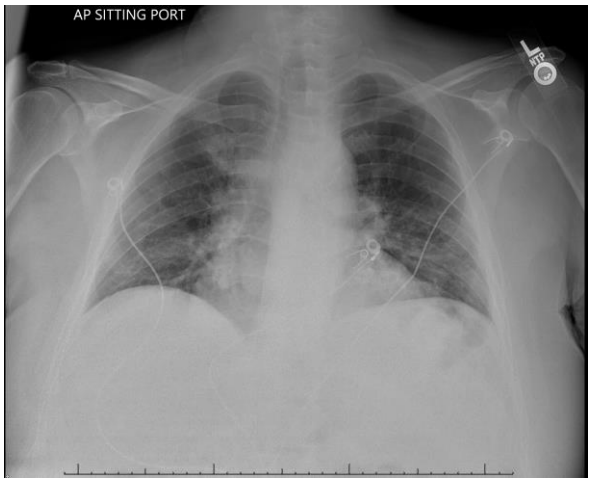

Fig-2: Chest X ray, taken on 2/19/22, was unremarkable; showed no signs of pneumonia (cryptococcal pneumonia).

The patient's cerebrospinal fluid (CSF) analyses were: opening pressure of 35 cmH_2O (normal < 20) and closing pressure of 25 cmH_2O. Shown in **Table-1**, there was a WBC of 122/uL (normal 0-5/uL), RBC of 1/uL (normal 0-5/uL), protein of 186/uL (normal 15-45/uL), and glucose of 74/uL (normal 40-70/uL), which were all elevated in this patient. His blood cultures drawn on admission showed yeast growing in one of two bottles and therefore he was diagnosed with fungemia, suspected meningitis, sepsis. Also as shown in **Table-1**, both serum and CSF cryptococcal antigen tests were positive (1:280). The human immunodeficiency virus (HIV) screen is negative.

Table-1: CSF Analysis

	Value	Reference Range
WBCs	122/uL	0-5/uL
	PMN 76%	
	Lymphocytes 21%	
	Monocytes 3%	
RBCs	1/uL	0-5/uL
Protein	186/uL	15-45/uL
Glucose	74/uL	40-70/uL
Other	Cryptococcus sp AG, titer, EIA: Positive for Cryptococcal Antigen: 1:1280	

He was treated initially with fluconazole. After confirmation of cryptococcal infection, he was switched to liposomal amphotericin B once a day (350 mg, IV at 125 mL/hr) and flucytosine every six hours (1500mg), which significantly alleviated his headache and other associated symptoms. Additionally, the patient was hydrated to minimize potential infectious and drug-induced nephrotoxicity. Patient was discharged home with life-long fluconazole maintenance therapy on day 19. He felt much better compared to the day he came to the hospital. His headache is almost resolved, he has no fever, chills, night sweats, and his appetite is improved.

Discussion

Kidney transplantations are associated with

improvements in a patient's mortality and quality of life, especially in comparison to life-long dialysis therapy. However, the associated follow-up medical management of the kidney transplant recipients can be challenging. Due to chronic immunosuppressive therapy that transplant patients are on, they often face diagnostic and treatment challenges because of potential drug interactions, drug toxicities, malignancies and importantly, opportunistic infections.

Cryptococcosis is the third most common invasive fungal infection in solid organ transplant recipients [9]. *C. neoformans* is found in soil, decaying wood, and bird droppings. The most common mode of transmission is through inhalation of fungal spores in the environment, and we suspect this is how our patient became infected. None of the clinical signs of cryptococcal meningitis are specific, and definitive diagnosis is made by the lumbar puncture which usually shows elevated opening pressure, elevated lymphocytes and protein and decreased glucose levels. An India ink stain is positive, and confirmation is obtained from culture. However, the cryptococcal antigen is the most sensitive diagnostic test [10]. This patient's diagnosis was based on the elevated serum and CSF cryptococcal antigens.

No pathognomonic CT or MRI image exists for cryptococcal meningitis [11]. CT scans may be normal or reveal meningeal enhancement, single or multiple nodules (cryptococcomas), cerebral edema, or hydrocephalus [11]. This patient's CT scan was unremarkable, eliminating a malignant pathology such as a CNS lymphoma, as well as other CNS infections: CNS toxoplasmosis, CNS tuberculosis, and pyogenic abscesses. Furthermore, if the patient had meningoencephalitis, significant swelling and "soap bubbles" would be seen in the gray matter of the brain on CT. Importantly, in patients notably immunocompromised, cryptococcosis demonstrates little enhancement on CT of the head [12]. MRI scans are more sensitive for detection of multiple enhancing nodules within the brain parenchyma, meninges, basal ganglia, and midbrain [12]. Specifically, for a CNS meningitis infection in immunocompromised patients, an MRI shows dilated perivascular spaces and basal ganglia pseudocysts [12].

CSF opening pressure is elevated to >25cm H_2o in 60–80% of patients with cryptococcal CNS infection [13]. Our patient's opening pressure was 35 cmH_2O (normal: 20-25 cmH_2O). The differential diagnosis for elevated CSF opening pressure include CSF leaks, cerebral venous thrombosis, and idiopathic intracranial hypertension (IIH) [13].

Amphotericin B has many toxic side effects and can be detrimental to renal tissue. Consideration must be taken with evaluating a renal transplant patient for the use of amphotericin. Concern of allograft loss with amphotericin B is real. Recent studies have found that the risk of nephrotoxicity in renal transplant patients taking amphotericin B is significantly increased when the cumulative dose of 5,000 mg is exceeded [14]. In addition, a lipid formulation of amphotericin B may be associated with lower incidence of adverse effects [15]. Recommended liposomal amphotericin B dosage is 3-5 mg/kg IV per day. The flucytosine can be given orally with a dose of 100 mg/kg/day, divided into four separate doses. The dosage will need to be adjusted for reduced renal clearance. After the initial therapy, it is recommended for patients to take fluconazole (200 mg orally daily) as part of maintenance therapy for up to one-year post-infection. Furthermore, immunocompromised patients may require long duration of suppressive therapy.

Our patient was treated with fluconazole based on symptoms but after confirmed diagnosis of cryptococcal meningitis post-CSF values, he was switched to intravenous liposomal amphotericin B and oral flucytosine. The administration of these therapies led to rapid improvement in his headache and other symptoms. He continued the amphotericin B plus flucytosine therapy for two weeks. Given the associated nephrotoxicity of amphotericin B, the patient was adequately hydrated, and electrolyte levels were monitored closely. The patient was discharged on lifelong fluconazole maintenance because of his highly immunosuppressed state.

Conclusion

Immunocompromised patients are recommended to

avoid potential zoonotic exposure. Importantly, cryptococcal meningitis is an integral part of the differential diagnosis for transplant patients with neurological impairment. Early diagnosis and treatment of cryptococcal meningitis is essential for a good recovery.

Informed Consent

All patient identifiers are removed and not used in the preparation of this report. Written informed consent was obtained from the patient for publication of details of his medical case and accompanying images without any patient identifier.

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