Cryptococcal Infection in Transplant Kidney Manifesting as Chronic Allograft Dysfunction

Abstract

Invasive fungal infections (IFIs) are a significant cause of morbidity in solid organ transplant (SOT) recipients. Common causes among them are *Aspergillus*, *Candida*, and *Cryptococcus*. Antifungal prophylaxis has led to decrease in overall incidence of IFI; however, there is very little decline in the incidence of Cryptococcal infections of SOT recipients because effective prophylaxis is not available against this infectious agent. Spectrum of manifestation of Cryptococcal infection varies in immunocompetent and immunocompromised host with subclinical and self-limiting with lungs being the primary site in immunocompetent and central nervous system as the most common site in an immunocompromised host. Other preferred sites are cutaneous, pulmonary, urinary tract (prostate) and the bone. Herein, we describe a young adult renal transplant recipient male diagnosed as a rare case of biopsy proven Cryptococcal infection in transplant kidney manifesting as chronic allograft dysfunction.

Keywords: *Chronic allograft dysfunction, Cryptococcosis, invasive fungal infections*

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Introduction

Invasive fungal infections (IFIs) are a significant complication in solid organ transplant (SOT) recipients.[1] *Cryptococcus* causes up to 8% of IFIs in SOT recipients and is third in the frequency after *Aspergillus* and *Candida*.[2,3] Improvements in transplantation practices with wider use of antifungal prophylaxis have led to a decrease in the overall incidence of IFI, particularly those due to *Candida* and Aspergillus species.[4,5] However, there is minimal trend toward decline in the incidence of Cryptococcosis in SOT recipients as fluconazole prophylaxis is generally not used in the late post transplant period (after 1 year of transplant) when Cryptococcal infections usually occur. The overall incidence of Cryptococcosis in SOT recipients is 2.8% (range, 0.3%–5%), with mortality rates ranging between 33% and 42%.[2-6] In an immunocompetent host, Cryptococcal infection is subclinical and self-limiting with lungs being the primary site; however, in an immunocompromised host, central nervous system (CNS) is the most common site for Cryptococcal infections, with other preferred sites being cutaneous, pulmonary, urinary tract (prostate) and the bone. In this communication, we describe a rare case of biopsy proven Cryptococcal infection in transplant kidney manifesting as chronic allograft dysfunction.

Case Report

A 31-year-old male, a serving soldier of Indian army, a case of end-stage renal disease since January 2010, due to mesangioproliferative glomerulonephritis, underwent renal transplantation on June 9, 2011, with donor being mother, (human leukocyte antigen –3/6 mismatch, cross-match negative, and panel reactive antibody being <10%). Pretransplant course involved 103 sessions of hemodialysis for 14 months before transplant, blood pressure control requiring three antihypertensive drugs, and supportive therapy for mineral bone disease. Immunosuppression protocol involved induction with basiliximab, steroid pulse on day minus 1 and intraoperatively, with maintenance by triple-drug immunosuppression (tacrolimus, mycophenolate mofetil, and prednisolone). Patient had delayed graft function; graft biopsy revealing acute tubular necrosis with no features to suggest acute rejection, requiring antithymocyte globulin therapy and two sessions of hemodialysis with

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subsequent recovery of renal function with baseline creatinine of 1.4 mg%. He also had new onset diabetes after transplant requiring insulin therapy. He developed Cryptococcal meningitis on February 10, 2014, with cerebrospinal fluid [CSF] analysis showing India ink and Cryptococcal antigen [CRAG] and culture growing *Cryptococcus* requiring cumulative Amphotericin B dose of 4.75 g, followed by maintenance therapy of fluconazole which was continued till CRAG became negative and cultures became sterile. He was asymptomatic till July 2014 with a baseline creatinine of 1.5 mg/dl and was continued on tacrolimus, azathioprine, and prednisolone. However, month later, patient started to have global continuous headache, which was severe in intensity resulting in disturbed sleep, recurrent vomiting, and poor appetite with decreased urine output. Subsequent evaluation did not reveal any signs of meningeal irritation; however, there was mild graft tenderness. Investigations revealed abnormal hematological profile with deranged renal function, with creatinine ranging from 2.8 to 3.2 mg/dl. Urine analysis revealed numerous pus cells; however, cultures were sterile. Graft ultrasonography did not reveal any perigraft collection. Subsequently, graft biopsy was done to ascertain the cause of graft dysfunction, which showed 15 glomeruli with features suggestive of chronic allograft nephropathy. Also noted were numerous round refractile periodic acid–Schiff (PAS) stain positive bodies, suggestive of yeast form of cryptococci, which were confirmed by Grocott stain [Figure 1]. Patient was again initiated on amphotericin B from September 22, 2014. He received cumulative dose of 9.2 g of amphotericin B along with fluconazole. He was continued on immunosuppressants in the form of sirolimus (Tacrolimus was stopped in view of graft dysfunction), azathioprine and prednisolone, insulin, antihypertensives (metoprolol, amlodipine, and indapamide), and supportive therapy. He showed good response to therapy with improvement in symptoms and creatinine levels settling to 2.4 mg/dl. Patients' clinical condition became much better and he is kept on regular follow-up.

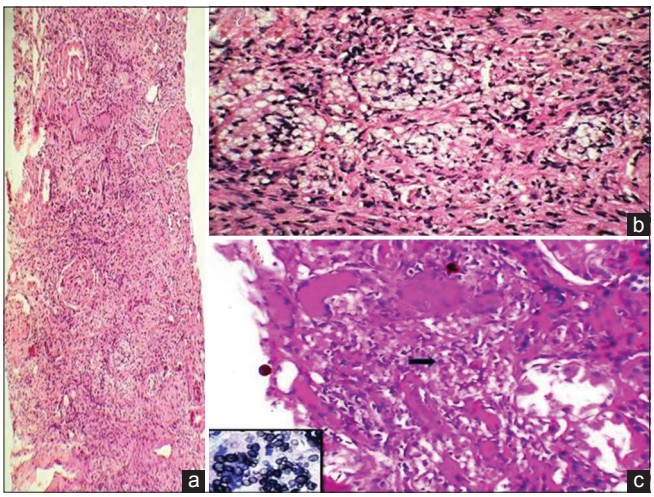

Figure 1: Histopathological examination findings: (a) Photomicrograph (H and E, ×100) renal biopsy showing few sclerosed glomeruli and dense inflammation. (b) Photomicrograph (H and E, ×400) showing numerous, round, refractile fungal yeast form. (c) Photomicrograph (PAS and Grocott, ×400) showing periodic acid–Schiff stain positivity (arrow) and Grocott stain positivity (inset) in the fungal yeast form

Discussion

Cryptococcus neoformans is encapsulated, basidiomycetous yeast that is present in the environment worldwide and has been isolated from a large variety of natural substrates, especially soil contaminated with pigeon droppings.[7] Cryptococcal disease is the third most common IFI after *Candida* and *Aspergillus*, representing 8% of IFI in SOT recipients in transplant-associated infection surveillance network database.[3] Vast majority of cases of cryptococcal disease are considered to be due to reactivation of quiescent or latent infection in immunocompromised state.[8] Indeed, as incidence of *C. neoformans* infection in human immunodeficiency virus (HIV)- infected patients has declined, organ transplant recipients have become the group of immunocompromised patients at highest risk for cryptococcosis. The trends in the incidence of Cryptococcosis in transplant recipients are less well delineated. Fungemia results from lymphohematogenous dissemination from an overt or subclinical pulmonary focus. Since the organism has a preference to invade the CNS, meningitis or meningoencephalitis is often the first clinical evidence of infection. Cryptococcosis in SOT recipients is typically a late occurring infection; the median time to onset is 16–21 months after transplantation.[3,9] The time to onset is earlier in liver and lung transplant recipients than in kidney transplant recipients, possibly due to higher intensity immunosuppression in the former subgroup.[3] The most sensitive and specific approach for diagnosis of Cryptococcal infection is microscopic examination of the aspirate in potassium hydroxide or India ink, revealing encapsulated yeast cells.[10] Additional investigations for precise diagnosis and to rule out systemic dissemination require isolation and identification of organism by culture. Sabouraud glucose agar is optimal for isolation of *Cryptococcus* from sputum, bronchoalveolar lavage, CSF, and urine (preferably after prostatic massage). The latex agglutination and enzyme immunoassay tests for detection of Cryptococcal capsular polysaccharide antigen in serum or CSF are excellent rapid diagnostic tests. Culture for *C. neoformans* is usually positive in 3–7 days and colonies appear as white to cream- colored with a mucoid consistency. In our case, patient presented with gradually deteriorating renal function, which later was confirmed by biopsy due to chronic allograft nephropathy; however, there were numerous round refractile PAS-positive bodies suggestive of yeast form of cryptococci. This finding is later confirmed by Grocott stain [Figure 1c].

Calcineurin inhibitors do not appear to influence the incidence but may affect the extent of cryptococcal disease,[2] while on the other hand; corticosteroids are associated with an increased risk of Cryptococcosis in all non-HIV infected hosts.[11,12] Temperature-dependent inhibition of *Cryptococcus* by Tacrolimus may prevent CNS infection but allow the growth of the fungus at cooler body sites, such as skin, soft tissue, orosteoarticular involvement. Induction treatment in these patients should include a lipid formulation of Amphotericin B, preferably with flucytosine. Patients with severe pulmonary Cryptococcosis may be treated with fluconazole. Our patient was given amphotericin B for 3 weeks, followed by fluconazole. He responded to this therapy adequately, resulting in resolution and symptomatic improvement. Most cases of relapsed documented previously in literature occur in the 1st year of management, supporting the use of suppressive therapy with fluconazole for 6–12 months.

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Conflicts of interest

There are no conflicts of interest.

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