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Case Report

A Case of Disseminated Cryptococcus Post-Kidney Transplant

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Abstract

Cryptococcosis is a common invasive fungal infection in solid organ transplant recipients (SOTR) that can be challenging to manage. We discuss a case of disseminated cryptococcosis in a transplant recipient. A 26-year-old woman with a history of ESRD from C1q nephropathy, living-related kidney transplant in early 2012, and allograft nephrectomy in 2015, received a deceased donor kidney transplant (DDKT). Induction after the first transplant was anti-thymocyte globulin (ATG) and maintenance immunosuppression (IS) included tacrolimus (TAC), mycophenolate (MMF), and prednisone. In December 2014, she developed nephrotic range proteinuria due to recurrent FSGS failing plasmapheresis and Intravenous immunoglobulin leading to advanced chronic kidney disease and dialysis dependence. MMF was held due to Cytomegalovirus (CMV) DNAemia. In January 2015, she developed bilateral, painful leg ulcers. Skin biopsy, spinal fluid analysis, and culture were positive for *Cryptococcus neoformans.* She was treated with liposomal Amphotericin B (LAB) for 3 weeks and 5 doses of flucytosine (5FC) followed by maintenance oral fluconazole with recurrence requiring resumption of LAB and 5FC. The patient underwent a transplant nephrectomy in May 2015 following which IS, LAB, and 5FC were discontinued and maintenance fluconazole initiated. In 2018, another skin biopsy revealed a recurrence. Maintenance antifungal was switched to

itraconazole based on fungal isolate minimum inhibitory concentration (MIC) leading to remission that persisted through subsequent DDKT in August 2022. Induction IS was ATG and maintenance included TAC, MMF, and prednisone. The post-transplant course was complicated by delayed graft function requiring dialysis for about three weeks, followed by renal recovery. She continues maintenance of itraconazole under the supervision of a transplant infectious disease specialist and *cryptococca*l disease remains in remission. IS reduction or complete withdrawal is important in managing disseminated cryptococcosis in SOTR. Management of disseminated disease may require an extended course of LAB, 5FC, and maintenance azole based on MIC.

Keywords
Transplant; *cryptococcus;* immunosuppression

1. Introduction

Cryptococcosis is an invasive fungal infection that can be challenging to manage in solid organ transplant (SOT) recipients (SOTR). It is typically a late-occurring infection with the median time to onset from 16 months to 21 months post-transplant [1]. The symptomatic cryptococcal disease predominantly affects immunocompromised hosts. Although rare cases of transmission through donor organs have been described [2], they should be considered when *Cryptococcus* is diagnosed within thirty days post-SOT. About 53%–72% of cases of cryptococcal disease among SOTR are disseminated [3]. In 1 report involving 111 patients, about 61% of the SOTR had disseminated disease, 54% had pulmonary disease, and 8.1% had skin, soft-tissue, or osteoarticular involvement [4]. *Cryptococcus gattii* species is the most common responsible organism in the immunocompetent, whereas *Cryptococcus neoformans* is more common in immunocompromised patients [5]. It has been suggested that renal transplant recipients may be further predisposed to rapid clinical progression of cryptococcosis due to the impaired production of tumor necrosis factor, interleukin 12 (IL-12), interleukin 18 (IL-18), and other cytokines in uremia [6].

Cryptococcus neoformans is usually acquired through inhalation to the lungs and can then disseminate to other sites including the central nervous system (CNS), bone, and skin [7-9]. Pulmonary and CNS cryptococcal disease are the most common sites reported for patients with disseminated cryptococcosis [3, 7]. The disseminated disease rarely presents with skin involvement [9]. There is evidence however, that primary cutaneous cryptococcosis (PCC) can occur as a distinct entity [10] and it has been suggested that PCC may serve as a portal of entry for secondary disseminated cryptococcosis [3, 11, 12]. We report a rare case of performing a deceased donor kidney transplant in a patient with a known history of disseminated dermal and CNS cryptococcal disease and prior failed transplant. We describe the management of disseminated disease in an immunosuppressed patient and highlight other challenges transplant physicians could face while evaluating such patients for re-transplantation.

2. Materials and Methods

We discuss a case of deceased donor kidney transplantation (DDKT) in a patient with a history of failed kidney transplant (KT), and disseminated cryptococcal disease including dermatologic involvement, highlighting challenges with immunosuppression (IS) management and prophylaxis.

Informed consent was obtained from the patient to acquire details of the case for publication.

3. Results (Case Report)

A 26-year-old woman with a history of ESRD from C1q nephropathy-related FSGS, failed living-related kidney transplant (2012-2015), underwent a DDKT in August 2022. Kidney donation for the first transplant was from the patient's mother with HLA mismatch 1A, 1B, and 1DR. IS Induction was with ATG and maintenance included tacrolimus (TAC), mycophenolate mofetil (MMF), and prednisone. The calculated panel reactive antibody (cPRA) score before DDKT was 99%.

About two years after the first transplant, around November 2014, the patient developed Cytomegalovirus (CMV) DNAemia, followed by recurrent FSGS leading to dialysis dependence. The course was further complicated by Epstein-Barr Virus (EBV) DNAemia and *Pneumocystis* pneumonia leading to discontinuation of MMF and retention of TAC and prednisone as maintenance IS. Around January 2015, she presented to an outside hospital with a ten-day history of painful, blistering, bilateral leg lesions (Figure S1) and headache. Wound cultures were positive for yeast, later identified as *cryptococcus neoformans* on biopsy. Serum analysis revealed the presence of cryptococcus antigen titer 1:3 and upon lumbar puncture, cerebral spinal fluid (CSF) analysis revealed cryptococcus antigen titer 1:23, later confirmed as *Cryptococcus neoformans* on culture. She completed a three-week course of liposomal amphotericin B (LAB) along with five days of oral flucytosine (5FC). TAC and prednisone were continued. LAB was stopped after about 5 weeks of treatment in February 2015, when two CSF samples were negative for *Cryptococcus* and culture. She was transitioned to oral fluconazole at 800 mg daily and 5FC three times a week dosed after dialysis. Within days, the patient developed a fever with a headache. Skin lesions worsened (Figure S2) and CSF analysis again revealed Cryptococcal antigen titer 1:10. Fluconazole and 5FC were discontinued. LAB was resumed. To assist with the management of disseminated cryptococcal disease, in the setting of dialysis dependence, she underwent a transplant nephrectomy around May 2015, following which TAC and prednisone were discontinued. She was maintained on LAB until two weeks post nephrectomy after which she was transitioned to daily oral fluconazole and 5FC three times a week leading to clinical remission.

Notably, in December 2014 the patient developed an acute kidney injury with proteinuria. Allograft biopsy showed recurrence of FSGS (mild interstitial inflammation and tubular injury, no C4D deposition, no other evidence of rejection, and negative BK staining), but a denovo donor-specific antibody to DQ8 was discovered. She received four sessions of plasmapheresis followed by intravenous immunoglobulin. The patient however failed treatment and progressed to advanced CKD requiring chronic dialysis.

In the summer of 2018, she had a recurrence of bilateral lower and upper extremities skin lesions along with headaches. She had reported adherence to 5FC and fluconazole. A repeat spinal tap had revealed a recurrence of meningitis. It is unclear whether she received another course of LAB but the maintenance antifungal was switched to itraconazole based on susceptibility data from 2015. *Cryptococcus* isolates had high MICs to fluconazole and low MICs to itraconazole, which could

explain treatment failure. The patient responded well to Itraconazole maintenance leading to clinical resolution of the disease along with negative CSF and skin Cryptococcal antigen and culture. Her local infectious disease specialist maintained her on itraconazole until six months before the second KT.

Donor characteristics for the second transplant included donation after circulatory death, kidney donor profile index of 62%, cold ischemia time of 11 hours and 38 minutes, warm ischemia time of 28 minutes, HLA mismatch at 2A, 2B, and 1DR loci. Induction was with ATG at a total dose of 3 mg/kg. The postoperative course was complicated by delayed graft function (DGF) requiring dialysis on the first postoperative day (POD). Transplant infectious disease resumed itraconazole prophylaxis on POD two. She underwent a renal allograft biopsy on POD ten, with findings of focal neutrophilic interstitial infiltrate along with ischemic ATN. She was treated with antibiotics for *Proteus* bacteriuria. Her allograft function improved, leading to hemodialysis discontinuation on POD twenty. She has been maintained on itraconazole prophylaxis given her previous history of cryptococcal disease with a target trough level of 1-2 mcg/mL. There has been no evidence of FSGS recurrence to date. Her creatinine is stable at 1.7 mg/dl with a protein: creatinine ratio of 0.1 mg/mg. She is currently on triple therapy IS regimen with tacrolimus (12-hour trough goal, 6-8 ng/mL), mycophenolate 750 mg twice a day, and prednisone 5 mg daily.

4. Discussion

Opportunistic infection by *Cryptococcus neoformans*, in SOTR, can occur as early as two to six months after transplantation. Clinical symptoms of cryptococcal infections in SOTR can be vague and nonspecific. Patients with meningitis can present with prolonged headaches, altered mental status, and fever or malaise [1]. Pulmonary cryptococcosis can present with a syndrome ranging from asymptomatic infection to severe pneumonia with respiratory failure [1]. Dermal cryptococcosis is a rare form that should be considered in the differential diagnosis of lesions resembling cellulitis, panniculitis, or molluscum contagiousum [5] because the clinical presentation of these lesions can mimic other cutaneous conditions [1, 5].

An important risk factor for *Cryptococcus* infection is IS with corticosteroids [3]. The daily dose that confers this increased risk among SOTR is unknown. Additionally, T-cell depleting agents such as anti-thymocyte globulin (ATG) and alemtuzumab often used in SOTR have been associated with an increase in the risk of *Cryptococcus* infection due to profound lymphocyte depletion of CD4+ T cells [3]. Calcineurin inhibitors (CNI) do not appear to influence the incidence but may alter manifestations and outcomes of the disease as patients receiving a CNI-based regimen had lower odds of a disseminated disease likely due to activity against fungal homologs of calcineurin [4].

The diagnosis of cryptococcosis is made by demonstration of the yeast at the site of infection. Pulmonary cryptococcosis is diagnosed by the detection of yeast in bronchoalveolar lavage or lung tissue biopsy specimens. *Cryptococcus* in the prostate and kidney can present as yeast in the urine and a biopsy with a culture of these tissues will confirm the diagnosis. Cryptococcal skin involvement can be diagnosed by microscopy, a culture of secretions, histopathology, or detection of cryptococcal antigen by polymerase chain reaction (PCR) [5]. It may be difficult to diagnose on hematoxylin and eosin staining, though Periodic acid-Schiff, methenamine silver, and India ink stains allow for identification.

Guidelines developed by the Infectious Disease Society of America (IDSA) recommend amphotericin B used in conjunction with flucytosine as primary induction therapy for disseminated cryptococcosis followed by fluconazole for consolidation and maintenance therapy [13]. The routine use of antifungal susceptibility testing for cryptococcal infection is not recommended, however, in patients with recurrent cryptococcal disease, antifungal susceptibility testing for fluconazole at a minimum is warranted. It is also recommended that overall immunosuppression is reduced gradually as it is proposed that abrupt withdrawal of immunosuppression could lead to a T helper (Th)1 pro-inflammatory state thereby increasing the risk of immune reconstitution inflammatory syndrome (IRIS) or organ rejection [13, 14].

It has been shown in vitro that TAC suppresses the growth of *Cryptococcus neoformans* at 37 degrees Celsius but not at 24 degrees Celsius suggesting that temperature-dependent inhibition of cryptococcal replication may help reduce CNS infection while allowing the growth of fungus in the more peripheral cooler sites such as skin. This exemplifies the importance of suspecting peripheral sites for cryptococcal infection in immunosuppressed patients and supports using calcineurin inhibitors as the preferred choice of immunosuppression in circumstances of cryptococcal infection whereby ongoing immunosuppression is required [15, 16].

Knowledge of probable risk factors for cryptococcal infection could help decide immunosuppressive regimens in patients undergoing transplantation. This included our decision to utilize a relatively low-dose ATG (at 3mg/kg) for induction during the second kidney transplant. It also reinforced our choice to continue to use tacrolimus for maintenance immunosuppression due to the risk mitigation properties of CNI in cryptococcal infections. The judicious decision that the patient be maintained on a corticosteroid-containing regimen was reached based on the transplant center's protocol for a second KT with a cPRA of 99%. Additionally, previous fungal susceptibility testing guided us to utilize itraconazole as post-transplant fungal prophylaxis.

5. Conclusions

The updated guidelines from the Infectious Diseases Community of Practice for the American Society of Transplantation now include a discussion of *Cryptococcus* in SOTR [1]. Clinical onset is often insidious, and clinicians need to be vigilant about its possibility in transplant recipients presenting with headaches, fevers, and mental status changes with or without skin lesions. This is particularly true for SOTR who received induction with T-cell depleting antibodies such as ATG and alemtuzumab which often lead to profound lymphocyte depletion of CD4+ T cells, as well as those on maintenance corticosteroids [1, 3, 6]. The cryptococcal antigen assays are the preferred tests for the diagnosis of cryptococcus in the serum and CSF. Dermatologic lesions require a biopsy to demonstrate the yeast. Amphotericin with flucytosine is often used as induction pharmacotherapy for meningitis and disseminated infection followed by fluconazole as consolidation therapy; however, susceptibility testing should be entertained particularly in those with relapse on prophylactic therapy. IS reduction is an important part of the management of disseminated cryptococcosis in solid organ transplant recipients. Re-transplantation could be considered and seems safe, in patients with clinical and serologic remission of disease after completion of induction and maintenance antifungals. The wait time from disease remission to transplantation however remains unclear.

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Author Contributions

Amer Belal MD contributed to the literature review, write-up of the first draft of the case report, and final revisions of this manuscript. Shawna Lord APRN contributed to the literature review for the write-up of the case report and reviewed this manuscript. Rohan V. Mehta MD contributed to the literature review, write-up of the case report, and final revisions of this manuscript. Alfonso Santos MD contributed to the literature review, write-up of the case report, and final revisions of this manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

Additional Materials

The following additional materials are uploaded to the page of this paper.

1. Figure S1: Patient photo of dermal cryptococcus in January 2015.
2. Figure S2: Patient photo of dermal cryptococcus in late February 2015.

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