Cryptococcosis in Renal Transplant Recipients: A Single-Center Experience

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ABSTRACT

Background. In solid organ transplant patients, 8% of invasive fungal infections are attributed to Cryptococcus. The aim of this study was to determine the frequency, risk factors, clinical characteristics, and outcome of kidney transplant recipients (TR) infected with Cryptococcus.

Case Series. Between 2007 and 2014, a total of 500 kidney transplantations were performed at São João Hospital, in Porto, Portugal. Six infections by *C. neoformans* were reported, an incidence of 1.2% (3 disseminated, 2 meningeal, and 1 cutaneous). Patients were 65–72 years of age and 4 of 6 were male, compared with all kidney TR, among whom the mean age was 51.1 years and 60% were male.

Three cases of crytococcosis occurred within the first 6 months after transplantation; 3 patients had cytomegalovirus infection and leukopenia, and 2 patients' immunosuppression had been increased in the last 6 months. Meningitis presented with headache, fever, and acute mental confusion; pulmonary involvement presented with respiratory insufficiency and infiltrative or nodular lung lesions; and cutaneous infections presented as cellulitis or skin abscess. Blood cultures for *C. neoformans* were positive in 3 cases; all of these patients had positive cryptococcal antigen of 1:128 to 1:8192. Five patients received liposomal amphotericin B for 9–21 days, followed by fluconazole. Four patients lost their grafts, and one patients died after a persistent vegetative state due to cryptococcal meningitis.

Conclusions. This small case series led to suspicion of an association between cryptococcosis and older age, renal dysfunction, cytomegalovirus infection, and intensification of immunosuppression after rejection episodes. In our series, cryptococcosis was associated with poor graft outcome.

ALTHOUGH less frequent than bacterial infection, fungal infections in solid-organ transplant recipients (TR) are a major cause of morbidity and mortality. Cryptococcosis is the third most common invasive fungal infection in TR, after infections due to Candida and Aspergillus, and affects about 2.8% of these patients [1]. Among TR, kidney transplant patients have the lowest overall risk of invasive fungal infections, but they remain a vulnerable population because of immunosuppression [1].

Cryptococcus neoformans (*C. neoformans*) is a ubiquitous encapsulated yeast commonly found in soil contaminated by bird feces. It may cause disease when inhaled from environmental sources by immunosuppressed individuals [2]. The central nervous system (CNS) and lungs are the most frequently involved organs [1].

Apart from a few case reports [3,4], not much is known about cryptococcosis among kidney transplant patients in Portugal. We retrospectively analyzed cases of cryptococcosis that occurred in the last 7 years at our Kidney Transplant Unit. We aimed to determine clinical and laboratory features of the infection, time after transplantation, possible risk factors, therapy used, and its effectiveness and clinical outcome.

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METHODS

Between 2007 and 2014, a total of 500 renal transplantations were performed at the Transplant Unit of São João Hospital Center in Porto, Portugal.

Retrospective demographic, clinical, and laboratory data of all patients with cryptococcosis who were followed up at our institution were collected from the hospital electronic and clinical registries. All patients were cadaveric kidney recipients, and one patient was on her second transplant. *C. neoformans* infection was defined as cultures positive for *C. neoformans* in a clinical specimen or positive cryptococcal antigen in the blood or cerebrospinal fluid (CSF) in a patient with suggestive clinical features. We obtained information concerning the underlying diseases, organ dysfunctions, immunosuppressive regimen, calcineurin inhibitor (CNI) dose, lymphocyte count, basal renal function, cytomegalovirus (CMV) infection, antifungal therapy, clinical manifestations, organs involved, and patient and graft outcomes. Disseminated infection was defined as a positive culture from at least 2 different sites or a positive blood culture.

None of the patients was under antifungal prophylaxis except for oral nystatin, which was used in the early posttransplantation period.

The mean age of cryptococcosis TR was compared with the mean age of the other patients who underwent transplantation in the same period, using an independent sample *t* test and considering a *P* value of less than .05 significant.

RESULTS

Six cases were identified, which represents a cryptococcosis incidence of 1.2% among this transplant population (Table 1). Four patients were male and 2 were female, with a mean age of 66.8 ± 1.2 years at the time of infection. This mean age is significantly higher when compared to that of other patients who underwent transplantation during the same period, whose mean age was 51.1 ± 0.62 years ($P = .00$).

Cryptococcosis was diagnosed on average 33 ± 15 months after transplantation, but 3 of the cases occurred within 6 months after transplantation.

All patients were immunosuppressed with a CNI; 3 had cyclosporine and 3 had tacrolimus as their primary immunosuppressive agent, 4 had mycofenolate mofetil (MMF), and all had prednisolone. Patient 1 used anti-thymocyte globulin as induction therapy for her second transplantation. In the 6 months before cryptococcosis, 3 patients had changes in their immunosuppressive regimen. Two of them had their immunosuppression increased after episodes of rejection (patients 2 and 6), and one patient (patient 4) had his immunosuppressive regimen reduced due to lung cancer and chemotherapy. Mean CNI trough levels were within target levels for all patients.

Half of the patients had CMV infection documented by CMV antigenemia assays. The mean leukocyte count at diagnosis was 4.6 ± 1.4 × 10^9/L, and half of the patients had <4.0 × 10^9/L leukocytes.

The mean baseline serum creatinine was 2.45 ± 0.45 mg/dL (35.6 ± 13.0 mL/min/1.73 m^2 of estimated glomerular filtration using the Chronic Kidney Disease Epidemiology Collaboration equation).

All cryptococcosis were caused by *C. neoformans* cultivated in agar Sabouraud, and no antifungal susceptibility test was performed.

Cases included 3 disseminated, 2 meningeal, and 1 cutaneous form. Meningitis presented with headache, acute mental confusion changes, vomiting, and fever, pulmonary involvement with respiratory insufficiency, hemoptysis, and a bronchopneumonic or nodular pattern on thoracic computed tomography, and cutaneous infections such as cellulitis in 1 case of disseminated disease and skin abscess in another case.

Blood cultures for *C. neoformans* were positive in 3 cases and CSF cultures were positive in 2 cryptococcal meningitis cases. All patients had positive serum or CSF cryptococcal antigen with a titer between 1:128 and 1:8192.

Five of the 6 patients received liposomal amphotericin B (AmB) for 9–21 days, followed by fluconazole with renal dose adjustment for 6 weeks to 12 months. Patient 2, who had pulmonary cryptoccocosis, received fluconazole alone.

Four patients lost their grafts during the course of the infection, by prerenal factors due to severe illness, lowering of immunosuppression, or nephrotoxicity of the drugs. One patient had a nephrectomy for suspicion of direct infection of the kidney, which was not confirmed. One patient died as a consequence of the infection, after late detection of *C. neoformans* in the course of his meningitis and prolonged persistent vegetative state.

DISCUSSION

Our retrospective analysis identified 6 cases of cryptococcosis among TR during the last 7 years, an incidence lower than the 2.8% reported by Husain et al in 2001, concerning patients from 3 different continents [5]. However, since then, transplantation practices have changed, including decreased use of OKT3 antibody to treat rejection and increased use of CNI-based immunosuppressive regimens, a possible explanation for our observations [6].

Cryptococcus may occur after primary exposure, usually by inhalation of the organism, or reactivation of a latent infection [7]. It is typically a late-occurring infection [5], although in the present study, half of the patients had the disease within 6 months of transplantation. This early presentation suggests a reactivation of a latent infection, which is known to manifest significantly earlier after transplantation compared to that in patients without evidence of previous contact [7].

Patient 2 developed symptoms after immunosuppression reduction, suggesting a possible immune reconstitution inflammatory syndrome (IRIS). This patient had been diagnosed with lung adenocarcinoma 4 months before, and his MMF was suspended and TAC reduced. IRIS is an inflammatory tissue response in patients whose cellular immunity improves after reduction or cessation of immunosuppressive therapy, and is increasingly being recognized as a mimic of worsening disease or relapse [2].