Mucormycosis of the Transplanted Kidney With Renal Papillary Necrosis

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Abstract
The occurrence of renal allograft mucormycosis is uncommon, but its association with renal papillary necrosis has not been reported. We describe such an association in a patient who survived on peritoneal dialysis after nephrectomy and antifungal therapy.

Key words: Renal mucormycosis, Transplantation, Medullary necrosis

Introduction
Mucormycosis, or “zygomycosis,” is a fungal infection that is increasingly encountered in renal transplant recipients.1 The presentation is usually in rhino-sino-orbital/cerebral, pulmonary, gastrointestinal, or disseminated form.2 Renal allograft mucormycosis has been described in isolated case reports,3-5 but its association with renal papillary necrosis has not been reported, even though renal papillary necrosis is known to occur in fungal infections of the native kidney,6,7 as well as transplanted kidney.8,9 We report one such case and review the literature.

Case Report
A 59-year-old man, previously diagnosed with chronic glomerulonephritis and end-stage renal disease was admitted to our hospital with complaints of fever and dysuria 2 weeks after undergoing a live-unrelated renal transplant at a private center. Immunosuppression consisted of cyclosporine (8 mg/kg), azathioprine (1.5 mg/kg), and prednisolone (0.5 mg/kg). He also had received induction with basiliximab (20 mg on days 1 and 4). His postoperative serum creatinine level 1 week after transplant was 97.2 mmol/L (1.1 mg/dL).

On evaluation at our hospital, the patient showed evidence of graft dysfunction. His serum creatinine level was 176.8 mmol/L (2 mg/dL), and his hemoglobin was 140 g/L, his total leukocyte count was 13 400 mm3; he had 78% polymorphonuclear leukocytes, and a platelet count of 300 100 mm3. The results of his serum electrolyte and liver function tests were normal. The results of his blood glucose tests were within normal limits (fasting 4.88 mmol/L (88 mg/dL), and postprandial glucose was 7.7 mmol/L (140 mg/dL). Results were negative for hepatitis B surface antigen, and antibodies to hepatitis C virus and human immunodeficiency virus. Cytomegalovirus antigen (pp65) was positive.

The patient was given intravenous ganciclovir therapy for 3 weeks. Blood cultures obtained from the patient showed no growth. An examination of his urine revealed gross leukocytes, and a culture grew Pseudomonas aeruginosa, for which he was given intravenous piperacillin and amikacin. An ultrasound of the graft showed a focal, hyperechoic area in the midpolar region. Despite treatment with the antibiotics, the patient’s urine continued to grow Pseudomonas, and a bulge appeared at graft site. An contrast-enhanced computerized tomography scan of abdomen was performed, revealing multiple, hypodense areas within the graft kidney and multiloculated collection suggestive of abscesses in the perigraft area. Pus was aspirated and when cultured, it revealed Pseudomonas. Fungal cultures of pus and urine did not show any growth.

Subsequently, the patient underwent surgical evacuation of the abscess. Intraoperatively, the upper pole of the graft was seen to be necrotic, and multiple...
biopsies were obtained from the graft. Histopathological examination revealed extensive areas of necrosis, mixed inflammatory infiltrates, giant cell reaction, and fungal profiles suggestive of mucor (Figure 1). Subsequently, the patient’s graft dysfunction became worse (serum creatinine 265.2 mmol/L [3.0 mg/dL]), and his coagulation profile became abnormal, and he had evidence of fibrin degradation products in the blood suggestive of disseminated intravascular coagulation.

An intravenous infusion of amphotericin B deoxycholate was begun at a dosage of 1 mg/kg/d. Cyclosporine and azathioprine were withdrawn. Prednisolone dosage was decreased to 10 mg/d. The patient then underwent a graft nephrectomy, and was placed on maintenance hemodialysis. A nephrectomy specimen confirmed the biopsy findings, with extensive areas of tissue infarction and necrosis, with dense inflammatory infiltrates and fungal profiles of mucor (Figure 2). A large area of papillary necrosis also was seen on graft histology (Figure 3). A radiograph of the chest, and computed tomography scan of the head and abdomen, and radiographs of the paranasal sinuses showed no evidence of zygomycosis at these sites. The patient received a dosage of 3 g of amphotericin B deoxycholate during his 8-week stay in the hospital. Afterwards, his fever became normal, and his coagulation parameters normalized. He was discharged and advised to have regular hemodialysis sessions 3 times per week. After 6 months of maintenance hemodialysis, the patient opted for continuous ambulatory peritoneal dialysis, which he continued until the time of this writing (3 years follow-up).

**Discussion**

Mucormycosis is caused by the fungi class Zygomycetes, order Mucorales, and the most-common pathogenetic species responsible for infection in transplant recipients are the Rhizopus oryzae, Mucor circinelloides, and Absidia corymbifera. Species of 3 more genera, Rhizomucor, Apophysomyces, and Cunninghamella, although less common, also have been documented to be pathogenic to human beings. Mucormycosis is associated with diabetes mellitus, malignancy, deferoxamine therapy, and...
immunocompromised states like solid-organ transplant. Renal transplant recipients have been reported to develop this infection often in developing countries, especially in those persons who undergo live-unrelated “commercial” transplant.

Occurrence of mucormycosis in renal transplant is related to many factors including heightened immunosuppression in the initial posttransplant period with induction protocols and antirejection therapy like pulse steroids, antilymphocyte antibodies, and interleukin-2 receptor antagonists, intraoperative or postoperative surgical complications, “transmission” from infected donors, and the presence of immunomodulating viruses such as cytomegalovirus and hepatitis C. Involvement of the renal allograft may occur in disseminated diseases, with isolated graft involvement. Being angioinvasive, the Mucorales invade the blood vessels, causing vascular thrombosis and associated ischemic necrosis of the kidney. Fungal hyphae may invade the glomeruli, the tubules, and the parenchyma, aside from the renal vessels. The cortical and modularly necrosis results in irreversible kidney damage and renal failure. Clinical presentation of these patients includes pain and tenderness over the graft site, fever, a progressive decline in renal function, leukocytosis, hematuria, enlarged kidney on ultrasonography with typical radiologic features on contrast-enhanced computerized tomography.

Renal papillary involvement may sometimes be seen in transplant patients owing to acute rejection, with fungal infections of the renal allograft including renal candidiasis, aspergillosis, cryptococcosis, or histoplasmosis. The association of renal papillary necrosis with renal allograft mucormycosis as seen in our patient is unusual. This may be because of total necrosis of the renal parenchyma in this condition, without recognition of the papillary tissue in the renal histology or urinalysis of these patients.

Although renal histology, with demonstration of broad aseptate hyphae, branching at right angles, at irregular intervals, is the standard criterion for diagnosing renal mucormycosis and associated renal papillary necrosis, the latter condition may be recognized by imaging as well. The findings include the presence of a curvilinear, or ringlike, calcification of up to 5 to 6 mm in diameter (indicating a calcified sloughed tissue) on a plain radiograph, the “ring” sign in retrograde or antegrade pyelography, or preferably, ultrasonography and multiphasic computerized tomography.

Managing renal allograft mucormycosis includes nephrectomy, withdrawal of immunosuppression, and administering antifungal therapy, primarily amphotericin B deoxycholate or its lipid formulations. More recently, posaconazole also has been used both as a “step-down” therapy given after initial amphotericin administration, and as a “salvage” therapy in patients resistant to amphotericin. Our patient survived because of a timely decision to do the nephrectomy and administer an adequate dosage of amphotericin B deoxycholate.

The occurrence of cytomegalovirus infection, with invasive fungal infections, also has been documented in the general population, as well as in transplant recipients. Apart from the direct effects of invasive disease, cytomegalovirus produces immunomodulatory effects, resulting in further immunosuppression and an increased risk of other opportunistic infections after transplant.

We conclude that renal allograft mucormycosis is a serious condition requiring early suspicion and recognition of the condition, and its aggressive management with surgery and antifungal medication.

References