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BRIEF REPORT

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Mucormycosis of the renal allograft: case report and review of the literature

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Abstract Fungal infection is an uncommon complication after renal transplantation. We describe a rare form of mucormycosis in the renal graft. Our method was to review chart data and to perform medline searches. The patient was a 42-year-old man who underwent living-unrelated kidney transplantation in Egypt and returned to Israel on POD 8. Within the ensuing 4 weeks he experienced acute rejection which responded to treatment with steroids. Few days after discharge he was readmitted because of fever and graft dysfunction. An infected large perigraft collection was drained, but the patient became anuric and septic. Kidney biopsy showed infarcted necrotic tissue infiltrated by fungi which grew *Mucor* species. Despite initial improvement following graft nephrectomy and antifungal treatment the patient died of sepsis. Literature review revealed only three additional cases of graft infection due to Mucorales. We conclude that Renal graft infection due to Mucorales is an extremely rare and potentially lethal complication. Living unrelated donation in third world countries might be a possible risk factor. Fungal colonization may occur during transplantation. A high index of suspicion, leading to early diagnosis and initiation of antifungal treatment, in addition to graft nephrectomy, are keys to a more favorable outcome.

Keywords Kidney transplantation · Living donor · Mycophenolate mofetil

Abbreviations *AST* Aspartate aminotransferase · *ALT* Alanine aminotransferase · *CMV* Cytomegalovirus · *CT* Computed tomography · *ESRD* End stage renal disease · *GGT* Gamma glutamine transferase · *HB* Hemoglobin · *HIV* Human immunodeficiency virus · *LDH* Lactic dehydrogenase · *PCR* Polymerase chain reaction · *WBC* White blood cell count

Introduction

Potent antibiotics and antiviral agents, along with new molecular biology diagnostic techniques for detection of viral antigens in blood, have improved our ability to treat bacterial and viral infections after transplantation. Nonetheless, infection is the major cause of death in this patient population [3]. Fungal pathogens, although a rare cause of infection, remain a major diagnostic challenge and are associated with high mortality rate [3]. Indeed, in a recent autopsy study of 102 renal transplant recipients, fungal infection were responsible for 27.5% of infectious deaths [9]. The incidence of fungal infection after renal transplantation is somewhat higher in countries with hot climates [2].

Mucormycosis is usually a rapidly progressive and frequently fatal infection in renal transplant patients [7]. Various manifestations of this infection in renal recipients have been described. The predominant forms of presentation are rhinocerebral, pulmonary, gastroin-

testinal, cutaneous and disseminated. Rarely, mucormycosis develops in the kidney allograft itself. Only three such cases have been previously reported [6, 8, 14]. We describe here another case of a kidney recipient who developed graft mucormycosis, and we review the literature on this rare infectious complication after transplantation.

Case report

A 42-year-old man with ESRD due to glomerulonephritis underwent kidney transplantation in Egypt from a living unrelated donor. His immediate postoperative course was uneventful except for an episode of mild acute rejection, which was diagnosed on biopsy and treated with steroid bolus. The patient returned to Israel on POD 8 and was admitted to another hospital for continuity of care. On admission, he was jaundiced. Laboratory tests revealed elevated bilirubin levels (4.5 mg/dl) and liver enzyme abnormalities (AST, 50 Iu/l; ALT, 335 Iu/l; GGT, 132 Iu/l; LDH, 492 Iu/l) without significantly elevated creatinine levels (1.4 mg/dl). Serum cyclosporine (CyA) level as measured by whole blood RIA was markedly elevated: 1905 ng/ml, (normal, 250–800 ng/ml) and diagnosis of CyA hepatotoxicity was made. The CyA dose was reduced, and liver enzyme abnormalities improved slightly. During the next week, his creatinine levels rose to 2.4 mg/dl. Kidney biopsy findings were compatible with hemolytic uremic syndrome associated with moderate acute rejection. Intravenous pulse steroids were introduced, the CyA dose was further reduced, and fresh frozen plasma was infused, leading to an immediate response with improving renal function and normalization of liver enzyme levels.

The patient was discharged home on posttransplant day 34 but was readmitted a week later because of worsened general condition associated with high fever (38.5 °C) and elevated creatinine level (2.3 mg/dl). On readmission, WBC was 5100/ml, HB 8.9g%, CyA trough level was 527 ng/ml and PCR for CMV was negative. Doppler ultrasonography showed a large perigraft fluid collection (7.5 × 7.2 × 7.5 cm) and edematous renal graft with patent vessels. The collection was drained percutaneously. Cultures of the fluid grew gram-negative bacteria (*Klebsiella oxytoca*) and were negative for fungi. Over the ensuing days, in spite of antibiotic treatment according to culture (i.v. ceftazidine) the patient became anuric and was transferred to our service.

On admission 43 days posttransplant, the patient was afebrile, with some tenderness over the graft and no sign of wound infection. Renal Doppler ultrasonography confirmed the previous findings of an edematous graft with patent renal vessels and a high resistive index (0.9). The patient was started on dialysis. Two days later, his condition suddenly deteriorated; he developed overt sepsis associated with hemodynamic instability and severe metabolic acidosis. Kidney biopsy showed necrotic tissue infiltrated by fungi composed of thick, aseptate hyphae, with wide-angle branching, compatible with Mucorales. Hyphae were detected in the tubules, interstitium, and blood vessels (Fig. 1). A mild inflammatory reaction composed of leukocytes and lymphocytes was also present in the interstitium.

Immunosuppressive therapy was discontinued, amphotericin B at a dose of 1.5 mg/kg was immediately initiated, and graft nephrectomy was performed. Intraoperatively, an edematous, necrotic kidney with some perigraft serotic collection and thrombosed renal vessels was noted. Light microscopy studies of the removed graft revealed extensive infarction and marked infiltration by fungal hyphae, as described above. Cuts from the renal hilum showed

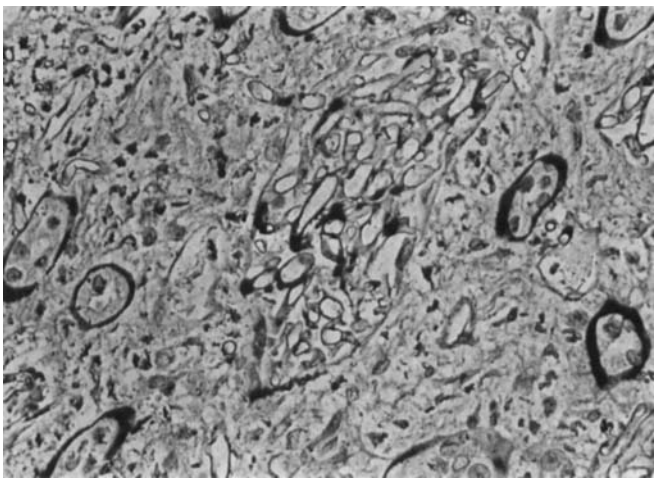

Fig. 1 Fungal hyphae in the interstitium of the renal parenchyma. (Gomori-methinamine silver stain × 190)

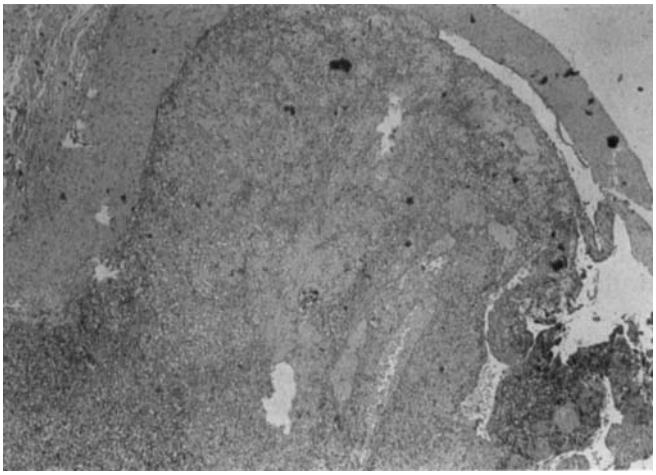

Fig. 2 Hilar artery of the kidney with a thrombus containing fungal hyphae (H and E × 95)

thrombotic vessels with abundant hyphae penetrating the arterial wall (Fig. 2). Culture from the explanted kidney grew *Mucor* species.

Despite an initial remarkable improvement in his condition, the patient developed right hemiplegia and loss of consciousness 24 h after surgery. Brain CT showed a large hemorrhage in the area of the left basal ganglia associated with intraventricular bleeding. There was no evidence of paranasal sinuses involvement with mucormycosis. Two days later, the patient developed gram-negative sepsis, leading to his death. Permission for postmortem examination was denied.

Discussion

Mucormycosis refers to a spectrum of disease presentations caused by fungi of the class *Zygomycetes*, order *Mucorales*. These ubiquitous organisms are common in-

habitants of decaying matter (e.g., moldy bread). The vast majority of mucormycosis infections have been described in patients with systemic- or local conditions that are associated with a severely immunocompromised state (e.g., diabetes mellitus, HIV, malignancies, chemotherapy, burns, etc.) [3]. Transplant recipients are at high risk for opportunistic infections because of chronic immunosuppression, frequent use of broad-spectrum antibiotic therapy, and underlying metabolic disorders such as uremia and hyperglycemia. Mucormycosis has been reported in recipients of kidney, liver, lung, heart, and bone marrow transplants [10, 13].

The overall incidence of invasive fungal infection in renal recipients is low, and ranges between 0–14 % [3], but the course of such infection is very aggressive, causing high morbidity and mortality. Mucormucosis accounts for 1–9 % of all invasive mycoses [13] and is associated with mortality rate as high as 64 % [7]. The fungus enters the body through either the respiratory tract, the digestive tract, or a damaged skin barrier. Augmented immunosuppression to treat rejection, mainly in the form of steroids, as was given to our patient may accelerate the course of mucor infection.

An important characteristic feature of mucor hyphae is their propensity to invade blood vessels and grow through them, causing thrombosis and multiple infarcts and hemorrhages of visceral organs. Usually, these pathologic changes are associated with minimal inflammatory response, because the specific cells are depleted or their function is impaired. Vessel thrombosis by mucor fungi and tissue necrosis are two major hallmarks of mucormycosis. It can be speculated that invasion of blood vessels in our patient may have led to hematogenic dissemination, resulting in cerebral hemorrhage and infarction, but the absence of any signs of fungal infection within the brain or nasal sinuses on CT excluded the possibility of fungal emboli or rhinocerbral fungal coinfection. The final event in our patient was a gram negative sepsis, which is also characteristic of patients with mucormycosis [2].

Mucor infection within the renal graft as occurred in our patient, is a rare complication. We found only three previous reports of similar cases [6, 8] from Kuwait, Saudi Arabia and India [14]. In two cases, like in our patient, the disease was manifested early – on POD 14 [8] and 17 [6], with massive involvement of the transplanted kidney and no evidence of another portal of entry (pulmonary or rhinocerebral). Diagnosis was made by graft biopsy on POD 25 [6] and POD 30 [8]. Graft nephrectomy was performed, and antifungal treatment was initiated immediately after diagnosis. In the third patient, diagnoses was established only after graft nephrectomy at 2.5 months posttransplant, which followed a complicated course of CMV nephritis and acute rejection [14]. One patient died [8] and two survived [6, 14]. Interestingly, as in our patient, in all three cases, fungal infection followed treatment for rejection, and in two cases [8, 14] it was associated with CMV infection representing a net state of immunosuppression.

Mitwalli et al speculate that fungal infection of the graft occurred through the incision during surgery [6]. This possibility, and the importance of the skin as a barrier against fungal invasion, are sustained by other publications. Cases of mucormycosis have been reported after minor skin trauma [11], intramuscular injection [5], and after the use of contaminated commercial elastic dressings [4]. We assume that fungal colonization in our patient occurred during transplantation, because of the early onset of the disease and massive involvement of the renal graft. Graft nephrectomy was performed relatively late and could not save the patient, who died of bacterial coinfection.

Diagnosis of fungal mucormycosis in transplant patients is extremely difficult, due to lack of serologic tests and the difficulty to isolate and grow the organism from infected tissue, blood, and body fluids [1]. Since mucormycosis is a rare disease in transplant recipients, a high index of suspicion is required, which should be followed by an aggressive attempt to obtain tissue for histologic and bacteriologic studies from affected organs. Cytologic preparation from body fluids (sputum, urine, sinuses etc.) have a low yield, as it is difficult to extract fungal elements from the invaded tissues. The hallmark of mucormycosis includes the typical, wide, ribbon-like, hyaline, predominantly aseptate hyphae with wide-angle ($45–90^0$) branching within nodular and necrotic areas of infection. These can be demonstrated using Hematoxylin-Eosin (H&E) staining, however more specific fungal stains (MGS and PAS) are usually more helpful. In the microbiological laboratory, specimens should be plated onto Sabouraud's agar, a fungal selective media. Tissue grinding is not recommended prior to inoculation, since it may lower the chance of fungal recovery from the tissue. Blood cultures are rarely positive [10].

Of note, the incidence of and mortality from fungal infection after kidney transplantation are particularly high in third-world countries with hot climate [8]. Poor hygiene and sanitation, more commonly encountered in these countries, may explain this finding [2].

In our experience at the Rabin Medical Center with 1,450 kidney transplant recipients over 18 years, 5 patients developed rhinocerebral mucormycosis. Four died, and one survived after multiple surgical interventions, including frontal lobectomy (unpublished data).

A high rate of fungal infection has been noted among recipients of renal grafts from living unrelated donors [12]. It is worth noting that all four cases of renal graft mucormycosis, our patient, as well as the three previous case reports, occurred in the same setting of living unrelated donors. In some third-world countries, organs are not uncommonly purchased and harvested under sub-

optimal conditions; this practice may explain such findings and may also serve as an argument against living unrelated kidney transplantation. Nampoory et al. found that 78% of 18 fungal infections, including the case of graft zygomicosis, occurred after living unrelated kidney transplantation [8].

In conclusion, graft mucormycosis is an extremely rare complication of kidney transplantation which occurs predominantly in the setting of living unrelated transplantation performed in third world countries. Augmented immunosuppression, especially with corticosteroids, may further predispose the patients for the infection. A concomitant bacterial infection may substantially complicate the clinical picture. A high index of suspicion, leading to an early diagnosis, may be the key to an early initiation of therapy. Prompt graft nephrectomy and antifungal therapy may result in a more favorable outcome.

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