


Gastric Mucormycosis in a Liver and Kidney Transplant Recipient: Case Report and Concise Review of Literature

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ABSTRACT

Mucormycosis is an uncommonly encountered fungal infection in solid organ transplantation. The infection is severe and often results in a fatal outcome. The most common presentations are rhino-sino-orbital and pulmonary disease. We describe a rare case of gastric mucormycosis in a patient with a combined liver-kidney transplant affected by glycogen storage disease type Ia.

A 42-year-old female patient presented with gastric pain and melena 26 days after transplantation. Evaluation with upper endoscopy showed two bleeding gastric ulcers. Histological examination of gastric specimens revealed fungal hyphae with evidence of Mucormycetes at subsequent molecular analysis. Immunosuppressive therapy was reduced and antifungal therapy consisting of liposomal amphotericin B and posaconazole was promptly introduced. Gastrointestinal side effects of posaconazole and acute T-cell rejection of renal graft complicated management of the case. A prolonged course of daily injections of amphotericin B together with a slight increase of immunosuppression favored successful treatment of mucormycosis as well as of graft rejection. At 2-year follow-up, the woman was found to have maintained normal renal and liver function. We conclude that judicious personalization of antimicrobial and antirejection therapy should be considered to resolve every life-threatening case of mucormycosis in solid organ transplantation.

MUCORMYCOSIS, previously termed zygomycosis, indicates an uncommon but serious opportunistic infection caused by fungi [1]. The term mucormycosis derives from Mucormycete, a distinctive group of ubiquitous mycetes growing principally on decaying vegetation and organic materials [2]. The most common genera are Rhizopus, Mucor, and Abside [3]. Mucormycetes infect principally immunocompromised subjects with hematologic malignancies [4] and diabetes mellitus [5]. However, several cases have been reported in immunocompetent subjects with multiple trauma [6] or after therapy with deferoxamine [7].

Mucormycosis is a rare complication of solid organ transplantation (SOT) with an incidence of 0.07% at 1 year after transplantation [8,9]. Clinical manifestations can be nonspecific; therefore, diagnosis is often challenging. Sinus-rhinocerebral and lung disease are the most common clinical presentations of mucormycosis [10]. Data regarding treatment are scarce and limited by lack of randomized trials. Generally, therapeutic options rely on few antifungal agents with high toxic profile and with potential for drug interactions with immunosuppressive drugs [11]. Despite appropriate antifungal treatment and aggressive surgical intervention, mortality is particularly high compared to the other common infectious diseases such as candidiasis and aspergillosis; it ranges from 50% to 100% depending on the localization of the disease [12–14].

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We describe a complex case of enteric mucormycosis in a subject affected by inherited metabolic disorder (ie, glycogen storage disease type Ia [GSD Ia]) who underwent combined liver-kidney transplantation for end-stage liver and kidney disease. We report the successful therapeutic strategy of this life-threatening infection that consisted in a delicate and challenging balance between administration of antifungal therapy and reduction of antirejection drugs.

CASE DESCRIPTION

A 42-year-old female patient reported abdominal pain and dark stool after a combined liver-kidney transplantation.

In September 2015, the woman affected by GSD Ia had been admitted for combined liver-kidney transplantation from deceased donator for chronic liver failure with a Model for End-stage Liver Disease score of 20 and end-stage renal disease on hemodialysis. Liver failure occurred as a consequence of the GSD I as confirmed by histological investigation, whereas the same metabolic etiology of renal disease was only presumptive because renal biopsy was never performed. Immunosuppression included intravenous methylprednisolone induction followed by oral tacrolimus, steroids, and mycophenolate mofetil (MMF). Nystatin and valganciclovir were used for oropharyngeal candidiasis and cytomegalovirus (CMV) prophylaxis, respectively. Early postoperative course was complicated by internal bleeding from tissue the surrounding transplanted kidney that was promptly treated by laparoscopic surgery, and by a biopsy-proven acute tubular necrosis (ATN) consequent to hemorrhagic shock. Kidney allograft function improved slowly and the serum creatinine reached a value of 1.5 mg/dL after 3 weeks. On the postoperative day (POD) 26 after transplantation, she was promptly evaluated for upper gastrointestinal bleeding as soon as she reported gastric pain and melena. Physical examination revealed the presence of peristaltic bowel sounds and epigastric tenderness on deep palpation of abdomen; rectal examination confirmed the presence of dark "tarry" feces. Upper gastrointestinal endoscopy showed two ulcers on the posterior wall of the gastric body without signs of active bleeding (Forrest classification III). The proximal and distal ulcer had a diameter of 2 × 2 cm and 3 × 4 cm, respectively; both of them had a grayish base covered by necrotic material, surrounded by hyperemic mucosa. Biopsy specimens of gastric ulcers displayed the presence of several fungal hyphae in a contest of active ulcerative chronic gastritis. Fungi stained with periodic acid-Schiff (Fig 1A) showed a relatively faint and nonuniform staining with Grocott methenamine-silver (Fig 1B). The hyphae, often forming helical twists, have a relatively broad width with very rare septa. Helicobacter pylori and CMV were not detected on biopsy specimens. The morphology and staining characteristics strongly suggested the presence of Mucormycetes. Molecular analysis of gastric tissue using polymerase chain reaction detected Mucormycetes of the genus Rhizopus. Brain and lung computed tomography scans were performed to exclude metastatic spread of infection; both results were negative.

Management of mucormycosis was based on a prompt start of appropriate antifungal therapy and a reversal of underlying predisposing factors for infection, such as immunosuppressive therapy. On POD 42, she started induction antifungal therapy with intravenous liposomal amphotericin B at a dose of 5 mg/kg per day; after 5 days, this drug was switched to oral posaconazole at a dose of 100 mg 3 times a day (target trough level > 2 μg/mL). After steroids and MMF withdrawal, immunosuppressive therapy was maintained with tacrolimus (target trough level of 4 to 7 ng/mL). We planned a prolonged course of antifungal treatment lasting for at least 6 months along with a surveillance endoscopy every 2 months. At POD 50 after transplantation, she was discharged in good general condition without gastrointestinal symptoms. In December 2016, after 1 month from discharge, the woman was again admitted to the hospital with severe gastrointestinal symptoms including vomiting and anorexia that were attributed to side effects of posaconazole administration. Posaconazole withdrawal and restarting of liposomal amphotericin B completely resolved these symptoms. The case was further complicated by CMV reactivation with tissue invasive disease of the oral mucosa that required specific treatment with valganciclovir. At discharge, posaconazole was reintroduced at a reduced dose of 100 mg twice daily with a target trough level of 1 to 2 μg/mL. Nevertheless, gastrointestinal side effects were so debilitating that the drug was definitively stopped and once again she was started on liposomal amphotericin B. After 1 month from her second discharge, renal function deteriorated progressively requiring admission. The serum creatinine level rose from her baseline values of 1.6 mg/dL to 3.2 mg/dL; a trial of normal saline rehydration did not improve renal function. The patient underwent allograft biopsy which was complicated by internal bleeding needing endovascular embolization of the polar inferior artery. Histologic examination showed acute T-cell rejection (Banff classification IA) with ATN. The rejection was treated by adding MMF 500 mg twice daily to tacrolimus; steroids were intentionally excluded from treatment. Recovery of renal

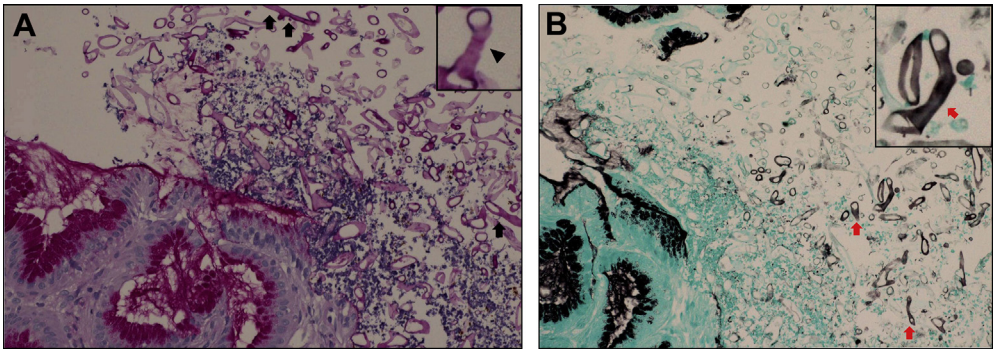

Fig 1. Ulcerative gastritis with fungal forms invasion (*arrows*) with rare septations, broad and irregular width hyphae (10 to 20 μm), staining with **(A)** periodic acid–Schiff (original magnification ×200) and with **(B)** Grocott methenamine silver (original magnification ×200).

functions was partial and her serum creatinine level returned to 2 mg/dL. At discharge, she continued daily intravenous therapy with liposomal amphotericin B as an outpatient. The endoscopic evaluation performed 6 months after the initial presentation showed healing of the previous two ulcers. Histological and molecular analyses were negative for Mucormycetes. Antifungal therapy was stopped after 6 months for successful resolution of infection. Lastly, in view of a progressive increment of blood and urine BK viral load, immunosuppressive therapy was further reduced. The dose of tacrolimus was adjusted to obtain a target trough level of 4 to 7 ng/mL and the dose of MMF was halved (250 mg twice daily). These changes led to a complete resolution of BK virus reactivation over the next 6 months. The woman remained well after 2 years from combined liver-kidney transplantation; she had a stable renal function with a serum creatinine level of 2 mg/dL (estimated glomerular filtration rate of 29 mL/min) and normal liver function tests.

DISCUSSION

After, Candida and Aspergillus spp., Mucormycetes represents an emerging cause of invasive fungal infection [15,16]. Incidence of mucormycosis varies between series: in kidney transplant recipients it is of 0.05% to 1.2% [17–19] and in liver recipients it is 0.4% to 1.61% [20,21]. Clinical presentation is highly heterogeneous, and it can involve a specific organ or be disseminated. In a review of 116 cases in SOT, Almyroudis et al [10] found that rhino-orbital-cerebral was the most common site of fungal infection (31%), followed by lung parenchyma (24.1%) and gastrointestinal tract (11.2%). Regarding gastrointestinal involvement, the stomach is the most prevalent site of infection followed by colon, esophagus, and liver. Gastrointestinal mucormycosis carries a significant morbidity and mortality among transplant recipients because it can lead to bowel perforation and death [4]. Cases of mucormycosis in combined liver-kidney transplantation are rarely reported in the literature [22]; to the best of our knowledge, this is the first case of gastric mucormycosis in a combined liver-kidney transplantation. Gastric mucormycosis frequently presents with epigastric pain, melena, and hematemesis; upper gastrointestinal endoscopy usually shows a solitary or multiple ulcers mimicking a common peptic ulcer [10]. Unfortunately, this clinical presentation is nonspecific and tends to cause diagnostic delay, which in turn increases patient mortality [23]. Diagnosis of mucormycosis remains challenging and is based on direct histologic identification of the characteristic hyphae or on retrieval of the Mucormycetes in culture of specimens obtained from the site of infection [24]. The tests commonly used to detect fungal antigens (ie, β-D-glucan test and Aspergillus galactomannan) are not reliable for diagnosis of mucormycosis [23,25]. In our case, cooperation with a skilled pathologist, who identified the characteristic hyphae from biopsy specimens of gastric ulcers, allowed an early suspicion of mucormycosis. The disease generally develops on average within 6 months from transplantation when high burden of immunosuppression increases the risk of opportunistic infections [10,26]. A prospective, matched case-controlled study revealed that renal failure, diabetes mellitus, and prior use of voriconazole and/or caspofungin were significantly associated with a higher risk of mucormycosis. In addition, liver transplant recipients are more likely to develop a severe, early infection than other types of SOT recipients [27]. In line with the literature, in our case mucormycosis was detected during the second month from transplantation. Although the patient had an unknown predisposition to infections before transplantation, she showed a unique susceptibility to multiple opportunistic pathogens (Mucormycetes, CMV, and polyomavirus BK). Likely factors such as the multiple episodes of bleeding, ATN, and early access in the intensive care unit have contributed to further enhance her immunosuppression. Unlike GSD type Ib, type Ia (the inherited metabolic disorder of our patient) is not generally associated with an impaired immune surveillance [28]. However, a certain degree of neutrophil dysfunction has been documented in some subjects with GSD Ia [29].

Management of Mucormycetes infection is based on the prompt institution of an appropriate antifungal therapy and surgery. Current pharmacotherapeutic options include lipid formulations of amphotericin B or isavuconazole as first-line therapy and posaconazole as salvage therapy [30]. Amphotericin B deoxycholate, which has been the drug of choice against Mucormycetes for more than 50 years, is not currently used due to the high incidence of dose-dependent nephrotoxicity [31]. Availability of less toxic lipid-based formulations of amphotericin B has improved the safety profile of this class of drugs [32,33], and makes them the first-line therapy for several invasive fungal infections including mucormycosis [34,35]. The two triazoles, isavuconazole and posaconazole, are active agents against Mucormycetes and are generally used for maintenance therapy once the clinical stability has been reached [11,36,37]. To date, guidelines on the duration of treatment are lacking; generally, treatment tends to be maintained for as long as necessary to achieve a clinical and radiological resolution of the infection [35].

Surgical debridement of involved tissues has been associated with an improved survival when combined with medical treatment [12–14,38,39]. In SOT recipients, surgery is associated with increased survival rates especially for pulmonary [40] and rhino-orbital-cerebral [41] mucormycosis. However, these studies may have a potential selection bias given that patients who did not undergo surgical treatment likely differed in disease severity, organ involvement, and/or comorbidities from those who did undergo surgery.

In our case, treatment of gastric mucormycosis relied on antifungal therapy and reduction of immunosuppression. Medical therapy was based on amphotericin B and posaconazole, but the latter was prematurely discontinued for its important gastrointestinal side effects. The attempt to continue posaconazole was based principally on its more convenient route of administration (oral versus intravenous), and safer and more economic profile compared to intravenous liposomal amphotericin B. Isavuconazole was not considered because it had not been available in Italy at that time. We

decided to proceed with a conservative treatment avoiding surgery because institution of early therapy controlled the disease and resolved the gastrointestinal symptoms progressively. Moreover, surgical debridement could have exposed the patient to over-immunosuppression from the stress associated with the procedure and the risk of a further postoperative hemorrhage in a subject with bleeding diathesis due to GSD I [42,43].

In SOT recipients, treatment of life-threatening infections may be associated with reduction of immunosuppression to restore host immunological response. We tried to manage this difficult case with withdrawal of steroid and MMF and continued monotherapy with tacrolimus, but an episode of kidney rejection further complicated clinical management of the infection. In view of a high risk of systemic fungal dissemination associated with the treatment of graft rejection [10], we decided to refrain from using conventional therapy with glucocorticoid, commonly used to treat T cell-mediated rejection, as advocated by European guidelines for treatment of mucormycosis [35]. On the other hand, we cautiously potentiated immunosuppressive therapy with MMF that maintained renal function stable over time without threatening the successful treatment of mucormycosis.

In conclusion, this report emphasizes the importance of early diagnosis, effective antifungal therapy, and reduction of immunosuppressive therapy in the successful management of severe cases of mucormycosis in SOT. Furthermore, the judicious personalization of antimicrobial and antirejection therapy should be always considered as an attempt to solve complex and life-threatening infections in the pursuit of the goal of survival after transplantation. Well-designed randomized trials on the treatment of mucormycosis are needed to establish the best treatment of this serious disease and clarify the role of surgery in relation to organ involvement and disease severity.

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