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

G. Alfano[a,*], F. Fontana[a], D. Francesca[a], G. Assirati[b], P. Magistri[b], G. Tarantino[b], R. Ballarin[b], G. Rossi[c], E. Franceschini[d], M. Codeluppi[d], G. Guaraldi[d], C. Mussini[d], F. Di Benedetto[b], and G. Cappelli[a]

[a]Nephrology Dialysis and Transplant Unit, University of Modena and Reggio Emilia, AOU Policlinico of Modena, Modena, Italy; [b]Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University of Modena and Reggio Emilia, AOU Policlinico of Modena, Modena, Italy; [c]Pathology Unit, Azienda USL Valle d'Aosta, Aosta, Italy; and the [d]Infectious Diseases Clinic University of Modena and Reggio Emilia School of Medicine, Department of Medicine and Medical specialities, AOU Policlinico of Modena. Modena, Italy

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 further 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. After 2-year follow-up examination, the woman was found to have maintained normal renal and liver function tests. 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

*Address correspondence to Gaetano Alfano, MD, University Hospital of Modena, Via del Pozzo, 71, 41124, Modena, Italy. E-mail: alfano.gaetano.md@gmail.com

230 Park Avenue, New York, NY 10169

0041-1345/18
https://doi.org/10.1016/j.transproceed.2017.11.036

100% depending on the localization of the disease [12–14].

Despite aggressive surgical intervention and intensive antifungal treatment, mortality of mucormycosis is high; it ranges from 50% to 100% depending on the disease form [3,5,6].

We describe a complex case of enteric mucormycosis in a subject affected by inherited metabolic disorder (ie, glycogen storage disease type Ia [GSD I]) 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 who had been affected by GSD I 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 level reached a value of 1.5 mg/dL in 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; 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

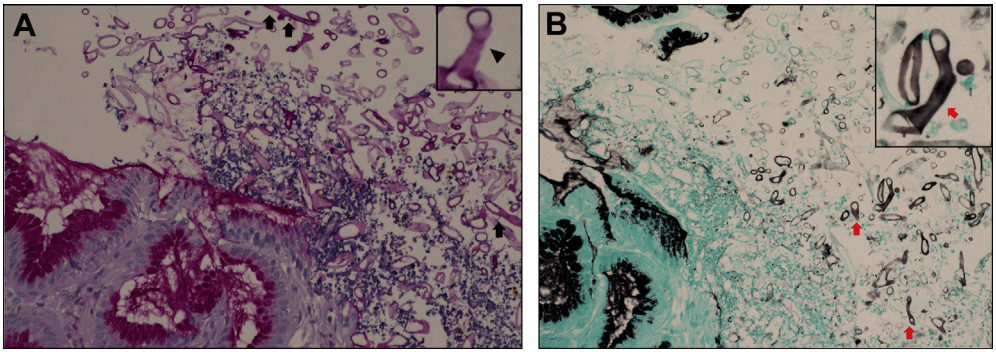

Fig 1. Ulcerative gastritis with fungal forms invasion (*arrows*) with rare septations, broad and irregular width hyphae (10 to 20 μm), staining with **(A)** periodic acid–Schiff (original magnification ×200) and with **(B)** Grocott methenamine silver (original magnification ×200).