Case Report

Successful Treatment of Invasive Mucormycosis in Orthotopic Liver Transplant Population

Taryn A. Eubank,1 Constance M. Mobley,2,3,4 Mozghon Moaddab,1 Mark J. Hobeika,2,3,4,5 Melissa O’Neal,1 William L. Musick,1 Joseph S. Galati,3,4,7 Sudha Kodali,3,4,5,7,8 Akshay Shetty,3,4,5,7,9 David W. Victor III,3,4,5,7,9 Ashish Saharia,2,3,4 R. Mark Ghobrial,2,3,4,5 and Kevin A. Grimes4,5,6,8

1Department of Pharmacy, Houston Methodist Hospital, Houston, TX, USA
2Department of Surgery, Houston Methodist Hospital, Houston, TX, USA
3JC Walter Jr Transplant Center, Houston Methodist Hospital, Houston, TX, USA
4Sherrie and Alan Conover Center for Liver Disease & Transplantation, Houston, TX, USA
5Weill Cornell College of Medicine, New York, NY, USA
6Department of Medicine, Houston Methodist Hospital, Houston, TX, USA
7Department of Hepatology, Houston Methodist Hospital, Houston, TX, USA
8Division of Infectious Diseases, Houston Methodist Hospital, Houston, TX, USA
9Houston Methodist Research Institute, Houston, TX, USA

Correspondence should be addressed to Taryn A. Eubank; teubank@harding.edu

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Mucormycosis is caused by ubiquitous fungi and encompasses a variety of different opportunistic syndromes in humans that disproportionately affect immunocompromised patients. Mortality has been documented to range between 50 and 100%; however, location of infection greatly dictates likelihood of survival. Treatment of mucormycosis involves aggressive surgical intervention and combination therapy of antifungal agents. In solid organ transplant recipients, immunosuppressive agents used to prevent rejection of the transplanted organ pose additional obstacles in the treatment of invasive fungal infections. We report on 3 high models for end-stage liver disease (MELD-Na) score orthotopic liver transplant (OLT) recipients who all were diagnosed with Rhizopus spp. infections with positive, 1-year outcomes after aggressive, individualized treatment.

1. Introduction

Mucormycosis represents a group of filamentous fungi that belong to the order Mucorales which causes life-threatening infections. Immunocompromised hosts, such as patients with immunosuppressive therapy associated with transplantation, poorly controlled diabetes mellitus, prolonged neutropenia, and high-dose corticosteroid treatment, are at increased risk [1]. Fungi within the genus Rhizopus are reported as the most predominant cause of mucormycosis human infections [2]. Diagnosis and treatment are challenging due to rapid progression, suboptimal culture recovery, and diminished tissue perfusion thus decreased antifungal penetration. In addition, many antifungal agents have troublesome side effects and/or drug-drug interactions that can be an obstacle during treatment. It is due to these issues that aggressive surgical intervention in combination with targeted antifungals is imperative for treatment success.
Table 1: Immunosuppression induction and maintenance therapy.

| Immunosuppression regimen prior to mucormycosis treatment | Patient 1 | Patient 2 | Patient 3 |
|-----------------------------------------------------------|-----------|-----------|-----------|
| Induction | Maintenance | Induction | Maintenance | Induction | Maintenance |
| Steroids | (1) Tacrolimus | Steroids | (1) Tacrolimus | Steroids | (1) Tacrolimus |
| (2) Mycophenolate mofetil 1000 mg every 12 hours | (2) Mycophenolate mofetil 1000 mg every 12 hours | (2) Mycophenolate mofetil 500 mg every 12 hours |
| (3) Prednisone 10 mg daily | (3) Prednisone 15 mg daily | (3) Prednisone 20 mg daily |

| Targeted FK506 level before and during mucormycosis treatment | Before: 8–10 ng/mL | Before: 6–8 ng/mL | Before: 6–8 ng/mL |
|---------------------------------------------------------------|---------------------|---------------------|---------------------|
| Induction | Maintenance | Induction | Maintenance | Induction |
| Oral medication formulation unless otherwise noted. 1Simultaneous liver-kidney transplant 20 months prior to mucormycosis event. 2Steroid induction followed by taper per institutional protocol: IV methylprednisolone 500 mg POD0, 200 mg POD1, 160 mg POD2, 120 mg POD3, 80 mg POD4, 40 mg POD5, and then prednisone 20 mg PO daily.
2. Case Reports

2.1. Patient 1. The first patient is a 34-year-old Caucasian female with a past medical history consisting of autoimmune hepatitis, type 1 diabetes mellitus requiring insulin pump, end-stage renal disease, history of deep vein thrombosis, peripheral vascular disease with femoral popliteal bypass, and extensive history of solid organ transplantations (previously underwent 6 organ transplants consisting of 3 kidneys and 3 livers) with the most recent being a simultaneous liver-kidney transplant 20 months prior to presentation. The patient was being maintained on tacrolimus, mycophenolate mofetil, and prednisone for immunosuppression (Table 1). Due to loss of previous graft from rejection, she was maintained on a high-dose triple drug immunosuppressive regimen to prevent recurrence of rejection. One month prior to diagnosis, she presented with acute left leg pain and swelling felt to be secondary to chronic pain from hardware repair of extremity several years ago. She continued to experience extremity pain and was subsequently admitted. On this admission, the patient was taken to the operating room (OR) for fasciotomy (Figure 1). No necrotic tissue was found, and she was sent home with a wound vacuum. Upon follow-up with her outpatient wound clinic, fat necrosis was identified leg and a debridement was completed.

A rapid genetic sequencing swab (MicroGen Diagnostics®) was run at the clinic showing 94% Rhizopus oryzae, 5% Enterococcus faecalis, and 5% Aspergillus flavus. The patient presented to our hospital for further work up of polymicrobial infection and potential invasive fungal disease.

On hospital day 2, she was started on intravenous (IV) isavuconazole 372 mg daily and returned to the OR for debridement. Preliminary tissue, fungal, and anaerobic culture reports from the OR grew diphtheroids, Klebsiella oxytoca, Enterococcus faecalis, and an unidentified mould. On hospital day 5, the cultures identified the mould as Rhizopus spp. Intravenous liposomal amphotericin B 3 mg/kg daily was added. The same day she went back to the OR for debridement, and a biopsy sample was sent to pathology. The pathology report confirmed organisms consistent with mucormycosis. On hospital day 15, she went back to the OR for another serial debridement and biopsy. That same day, fungal susceptibilities returned, displaying isavuconazole resistance (Table 2). She was switched to oral posaconazole 300 mg daily and IV micasfugin 150 mg daily in addition to amphotericin B. Three days later, her wound vacuum was replaced, and the pathology report showed multifocal fungal elements seen on a Grocott-Gomori methenamine silver stain consistent with clinical history of ‘Mucor/Rhizopus.’ There was necrotic tissue with no debridement, and a debridement was completed. A rapid genetic sequencing swab (MicroGen Diagnostics®) was run at the clinic showing 94% Enterococcus faecalis, 93% Rhizopus oryzae, and 5% Aspergillus flavus. The patient presented to our hospital for further work up of polymicrobial infection and potential invasive fungal disease.

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ascorbic acid 1000 mg tablet daily to help with absorption and therapeutic drug monitoring (Table 3) with plans to follow-up for the skin graft of the area. The patient remained *Rhizopus* spp. free at 1-year postdiagnosis.

2.2. Patient 2. Patient 2 is a 58-year-old Caucasian female with past medical history significant for obesity and upper gastrointestinal bleed who underwent an OLT secondary to chronic hepatitis C virus (HCV) infection and alcoholic cirrhosis. MELD-Na at time of transplant was 42. There were no immediate complications that occurred throughout the procedure. Immunosuppression consisting of a corticosteroid taper, tacrolimus, and mycophenolate mofetil (Table 1) was started on day of transplant per institution protocol. Infection prophylaxis consisted of sulfamethoxazole/trimethoprim (POD3), valganciclovir (POD1), and voriconazole (started 5 days prior to transplantation per protocol for high MELD-Na pretransplant patients in intensive care units) [3].

On POD10, department of infectious diseases was consulted for persistent leukocytosis and abdominal cramping. Notable findings included an endoscopy exhibiting ulcerations and old blood on POD18 and an indium scan exhibiting increased uptake in the abdomen; however, leukocytosis resolved and the patient was discharged to inpatient rehabilitation. Patient was then readmitted on POD30 for increased abdominal pain, and a computed tomography (CT) scan exhibited free air in her abdomen suspicious for gastric perforation (Figure 2). The patient was emergently taken to the OR for exploratory laparotomy with findings of a large necrotic ulcer in the antrum causing spillage of gastric contents. An OR biopsy sample resulted in *Rhizopus* spp., and on POD33, the patient was initiation on IV liposomal amphotericin B 3 mg/kg daily, micafungin 150 mg daily, and isavuconazole 372 mg every 8 hours. After 48 hours of therapy, the patient was transitioned from isavuconazole 372 mg every 8 hours to daily. In conjunction with the antifungal regimen, weekly OR debridement and washouts were performed which resulted in persistently positive margins. After two weeks of treatment (POD46), fungal susceptibilities resulted exhibiting azole resistance with amphotericin B minimal inhibitory concentration (MIC) of 4 mcg/mL (Table 4). Due to these results, amphotericin B was increased to 5 mg/kg and oral terbinafine 500 mg every 12 hours was added. Additionally, liposomal amphotericin B 250 mg/500 mL OR irrigation dwells for 30 minutes were performed by a four-quadrant wash with abdomen oscillation with each dwell taking place 5 days a week. After a total of 8 OR amphotericin B irrigation dwell completions and continued

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**Figure 2:** Patient 2 CT abdomen exhibiting bowel perforation secondary to mucormycosis.

**Table 4: Patient 2 susceptibilities.**

| Susceptibility report     | Specimen site: stomach | Specimen source: tissue |
|---------------------------|------------------------|-------------------------|
| *Rhizopus* spp.           | Amphotericin B 4 μg/mL | Itraconazole ≥16 μg/mL  |
|                           |                        | Posaconazole ≥16 μg/mL  |
|                           |                        | Voriconazole ≥16 μg/mL  |
|                           |                        | Micafungin ≥8 μg/mL     |
|                           |                        | Isavuconazole ≥16 μg/mL |
systemic combination antifungal therapy, the patient’s abdominal wall was closed on POD49. On POD53, isavuconazole was switched to IV posaconazole 300 mg every 12 hours with dose adjustments per therapeutic drug monitoring (Table 3) and nystatin 100,000 unit/mL suspension to be swallowed was added. The closure of the abdomen was complicated by dehiscence and necrotic appearing tissue at the incision site. After debridement, advancement of fasciocutaneous flap, and incisional wound vacuum placement, the amphotericin dose was transitioned to 7.5 mg/kg three times a week in preparation for discharge. Amphotericin B was continued outpatient until POD213 and posaconazole for a year from discharge. The patient remained *Rhizopus* spp. free at 1-year postdiagnosis.

2.3. Patient 3. The last patient is a 62-year-old Caucasian female with a past medical history of hypertension and coronary artery disease who underwent an OLT secondary
it to chronic HCV infection and alcoholic cirrhosis. MELD-Na at time of transplant was 51. Overall, the patient tolerated the procedure well. Due to intra-abdominal hemorrhage from ongoing coagulopathy, the patient’s abdomen was packed with a planned second operation for completion of the biliary anastomosis on POD2. Immunosuppression with a corticosteroid taper, tacrolimus, and mycophenolate mofetil was started on the day of transplant per institution protocol (Table 1). Infection prophylaxis consisted of sulfamethoxazole/trimethoprim (POD3), valganciclovir (POD1), and voriconazole (started 24 days prior to transplant). Hepatitis B total core antibody resulted positive, and tenofovir and voriconazole (started 24 days prior to transplant). Hepatitis C treatment dosing, and inhaled amphotericin B was started. POD12 observation of a lesion on the patient’s abdomen was a major component of the therapy plan that led to successful treatment in these 3 patients.

3. Discussion

We present three cases of *Rhizopus* spp. invasive fungal infection in OLT recipients with high MELD-Na at time of transplant. In treatment of these infections, surgical intervention is imperative. Mortality has been shown to double in patients who received systemic antifungal therapy alone versus in addition to surgical intervention (55% vs. 27%) [2]. Aggressive surgical intervention to remove necrotic tissue is crucial to limit the spread of this rapidly evolving infection. Not only does this limit the spread but also helps to remove the necrotic tissue which is problematic for systemic antifungal success. The necrotic tissue exhibits decreased blood flow to the site of infection thus in turn results in a decrease in systemic antifungal concentrations. To further increase infection site antifungal concentration, unique strategies were employed in our three patients. All three patients received amphotericin B locally in the form of wound vacuum irrigation, abdominal irrigation dwells, or nasal packing, respectively (Table 6). Amphotericin B is nephrotoxic requiring pre- and posthydration. This strategy provides high concentrations at the target site as well as possibly limits nephrotoxicity. The localized therapy allowed the treatment team to achieve high concentrations of amphotericin B without an increase in the IV dosage. We believe this was a major component of the therapy plan that led to successful treatment in these 3 patients.

### Table 6: Summary of presented cases.

| Patient | Site of infection | Systemic therapy | Local therapy | Surgical therapy |
|---------|------------------|------------------|---------------|------------------|
| 1       | Left lower       | (1) Isavuconazole 372 mg daily then switched to posaconazole 300 mg daily | Amphotericin B deoxycholate 50 mg/1000 mL irrigation through wound vacuum | Fasciotomy and debridement |
|         | extremity        | (2) Liposomal amphotericin B 3 mg/kg daily | | |
|         |                  | (3) Micafungin 150 mg daily | | |
| 2       | Abdominal        | (1) Isavuconazole 372 mg every 8 hours for 2 days then 372 mg daily | Liposomal amphotericin B abdominal irrigation dwells | Serial OR debridement and washouts |
|         |                  | (2) Liposomal amphotericin B 3 mg/kg daily | | |
|         |                  | (3) Micafungin 150 mg daily | | |
| 3       | Sinuses          | (1) Posaconazole 300 mg every 12 hours | Amphotericin B deoxycholate 1 mg/mL nasal packing | Rhinectomy, resection of intranasal contents, and multiple debridement sessions |
|         |                  | (2) Liposomal amphotericin B 7.5 mg/kg daily | | |
|         |                  | (3) Micafungin 150 mg daily | | |

Initiation date of therapy included in case series body. OR: operational room.

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**Table**: Summary of presented cases. **Patient**: 1 Left lower extremity; 2 Abdominal; 3 Sinuses. **Systemic therapy**: (1) Isavuconazole 372 mg daily then switched to posaconazole 300 mg daily; (2) Liposomal amphotericin B 3 mg/kg daily; (3) Micafungin 150 mg daily. **Local therapy**: Amphotericin B deoxycholate 50 mg/1000 mL irrigation through wound vacuum; Liposomal amphotericin B abdominal irrigation dwells; Micafungin 150 mg daily. **Surgical therapy**: Fasciotomy and debridement; Serial OR debridement and washouts; Rhinectomy, resection of intranasal contents, and multiple debridement sessions.
Another strategy utilized was the combination of 3 systemic antifungal agents. All 3 patients were treated with amphotericin B, an azole, and an echinocandin. No prospective randomized studies for optimized treatment of mucormycosis have been performed due to the rarity and heterogenous nature of these infections [2]. Amphotericin B is the cornerstone of systemic antifungal treatment of mucormycosis as this agent has reliable activity. Posaconazole and isavuconazole are both active against *Rhizopus* spp.; however, interestingly all 3 of our patients had strains that were resistant to isavuconazole (MIC $\geq 16 \mu g/mL$). The addition of echinocandins is controversial in literature. A case-control study completed at MD Anderson Cancer Center investigated early liposomal amphotericin B monotherapy versus combination therapy. The most common combination therapy received was liposomal amphotericin B plus an echinocandin at 46%, with posaconazole or triple therapy following behind at 27% each. However, the authors did not find any survival benefit for combination therapy over early administration of amphotericin B [4]. Echinocandins have an overall benign side effect profile and *Rhizopus* spp. have been shown to express the site of action, $\beta$(1,3)-D-glucan, making triple therapy a reasonable possibility in treatment of these aggressive infections [5].

The last treatment strategy performed in our patients was reduction of immunosuppression (Table 1). Our patients were high MELD-Na recipients receiving immunosuppression at time of diagnosis of the mucormycosis. To aid the antifungal therapy plan, net state of immunosuppression was decreased to enable the host’s immune response to strengthen. This strategy must weigh the risk versus benefit with the possibility of transplant organ rejection. Of note, azole antifungals inhibit CYP3A4 in the liver which is a major component of drug metabolism in the human body. This can lead to the possible side effect of hepatotoxicity and drug-drug interactions. It is important to consider this when starting azole antifungals and adjusting immunosuppression as tacrolimus is metabolized by CYP3A4. These drug-drug interactions present an additional challenge in the treatment of mucormycosis, but with vigilant monitoring can be administered safely.

In conclusion, mucormycosis is an aggressive fungal infection with a high mortality rate without equally aggressive treatment. Although surgical intervention is a mainstay of therapy, other additional strategies such as localized antifungal concentrations, triple antifungal therapy, and a decrease in immunosuppression can be beneficial with successful outcomes in orthotopic liver transplant recipients with mucormycosis.

Data Availability

Data is not publicly available but was collected retrospectively under approval from the Institutional Review Board.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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