Successful Surgical and Medical Treatment of *Rhizopus* Osteomyelitis Following Hematopoietic Cell Transplantation

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**abstract**

Mucormycosis has been reported in otherwise healthy individuals; however, it is primarily seen in immunocompromised patients, such as those with diabetes mellitus, malignancy, or chronic graft-versus-host disease, and has a high mortality rate. Because most cases of mucormycosis are associated with contiguous rhinocerebral infection, only 5 cases of isolated musculoskeletal *Rhizopus* infection have been reported in the literature. One patient underwent hematopoietic cell transplant, which resulted in a fatal outcome.

This article describes the successful treatment of isolated *Rhizopus* osteomyelitis in a patient who underwent hematopoietic cell transplant using a combined surgical and medical approach. A 33-year-old woman with pre-B cell acute lymphoblastic leukemia underwent hematopoietic cell transplant with few complications but developed chronic graft-versus-host disease 8 months posttransplant. She was treated with high-dose steroids for 6 weeks before she was admitted for severe right tibial pain in the absence of trauma. Early detection, aggressive therapies, and a multidisciplinary surgical and medical team allowed for the microbiologically confirmed resolution of the infection. Treatment included multiagent antimicrobial therapy with amphotericin B, daptomycin, and ertapenem. Several surgical irrigation and debridement procedures were also performed, with the eventual placement of amphotericin-impregnated polymethylmethacrylate cement beads and small fragment titanium screws. The patient continued taking postoperative antifungal treatment for 7 months after discharge. Six months following the discontinuation of antifungal therapy, the team's multidisciplinary approach achieved a continued resolution of the patient's infection and a return to a fully ambulatory and radiographically proven recovery without limb loss.

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nfections due to *Mucor, Rhizopus, Absidia,* and *Cunninghamella* species are collectively referred to as mucormycosis and are commonly defined based on the involvement sites: rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated.\(^1\) Mucormycosis has been reported in otherwise healthy individuals; however, it is primarily seen in immunocompromised patients, including those with diabetes mellitus, malignancy, or chronic graft-versus-host disease, and has a high mortality rate.\(^3\)

Although cases of mucormycosis osteomyelitis have been reported in patients with corticosteroid-dependent neutropenia/anemia and postrenal transplant, the majority of such infections are associated with contiguous rhinocerebral mucormycosis.\(^3,4\) A review of the PubMed database yielded 5 cases of musculoskeletal *Rhizopus* infection not associated with contiguous rhinocerebral mucormycosis.\(^2,6\) One case involved a patient who underwent hematopoietic cell transplant and had a fatal outcome.\(^5\) This current article describes the case of successful treatment of isolated *Rhizopus* osteomyelitis in a patient who underwent hematopoietic cell transplant using a combined surgical and medical approach.

**Case Report**

A 33-year-old woman with pre-B cell acute lymphoblastic leukemia underwent hematopoietic cell transplant from a matched related donor following a myeloablative conditioning regimen of fractionated total body irradiation and VP-16 (Etopophos; Bristol-Myers Squibb Co, Lisle, Illinois) in 2009, after which she received tacrolimus and methotrexate for 6 months for graft-versus-host disease prophylaxis. The early posthematopoietic cell transplant course was notable for low-grade fevers and transient partial small bowel obstruction that resolved at engraftment.

The patient had innumerable bilateral pulmonary nodules with associated ground-glass opacity suggestive of an infectious process during the acute lymphoblastic leukemia treatment. The nodules were nearly resolved by the time she underwent hematopoietic cell transplant, but she started taking voriconazole for anti-fungal coverage until 7 days preoperatively, when she was switched to 5 mg/kg of liposomal amphotericin B 4 times daily due to hepatic transaminitis. She continued taking amphotericin B until postoperative day 28, when oral voriconazole was restarted at 200 mg twice daily.

At 8 months posttransplant, while not taking immunosuppression drugs, she presented with a pruritic erythematous rash and moderately elevated hepatic transaminases consistent with a new onset of chronic graft-versus-host disease, which responded after the readministration of tacrolimus (1.5 mg daily) and prednisone (2 mg/kg daily). Prophylactic antimicrobials included voriconazole, trimethoprim-sulfamethoxazole, and acyclovir. Her course was also notable for H1N1 influenza infection, which responded after 15 days of oseltamivir for protracted symptoms. She achieved complete symptoms resolution, and immunosuppression was steadily tapered.

Six weeks after the original diagnosis of chronic graft-versus-host disease, she was admitted with a 1-week history of rapidly progressing severe pain, tenderness, warmth, and erythema over her right pretilial region. She reported no fever, chills, nausea, vomiting, or diarrhea. No superficial trauma to her leg was reported, but she had a chronically ingrown nail on her right great toe that was not inflamed or tender. She was unable to bear weight normally, and her pain was exacerbated by flexion and extension. Immunosuppression included prednisone (alternating 70 mg and 30 mg every other day) and tacrolimus (0.5 mg daily). Although plain bone radiographs demonstrated soft tissue changes without associated bony changes, magnetic resonance imaging (MRI) with contrast revealed narrow edema, periostitis, and inflammatory changes surrounding the proximal tibial metadiaphysis without evidence of an abscess (Figure 1). In collaboration with the orthopedic surgery team (R.A.), close observation without empiric therapy was planned.

Over the next 4 days, she had progressively worsening pain, erythema, and edema of the right lower leg. Repeat MRI...
revealed an interval increase in bone marrow edema and a complex fluid collection about the anterior lower leg (Figure 2). An aspiration of the fluid was collected, and repeat blood cultures were negative. She was empirically started on piperacillin-tazobactam, which was later replaced with ertapenem (1 g intravenously 4 times daily), daptomycin (295 mg intravenously 4 times daily), and caspofungin (50 mg intravenously 4 times daily) while her prophylactic antimicrobials were continued. Because she exhibited modest improvement and due to the suspicion of extensive disease, she underwent a planned 2-stage irrigation and debridement. During the first surgery, a medial and a lateral incision were created over the proximal lower leg. A large abscess containing chalk-like gray material was tracked along the anterior surface of the tibia, with destruction of the underlying periosteum but no obvious bone involvement. The anterior muscle compartment appeared to be healthy. The abscess and all devitalized tissues were debrided and, along with a core sample of bone, were sent to the microbiology lab for bacterial and fungal culture. A negative pressure dressing (Wound VAC; K.C.I., San Antonio, Texas) was applied over both incisions in anticipation of the second irrigation and debridement.

Postoperatively, her cellulitis and pain were significantly improved and cultures of bone were positive only for *Rhizopus* species. Voriconazole and caspofungin were replaced by amphotericin B (5 mg/kg daily, for a total of 363 mg given intravenously daily).

Three days postoperatively, the patient underwent a second irrigation and debridement. A cortical window was created along the proximal tibia using a Midas Rex high-speed burr (Medtronic, Minneapolis, Minnesota). The inside of the tibia was filled with gray-colored clay-like devitalized bone (Figure 3). This was debrided, and the tibia was irrigated with a combination of sterile saline and a saline mixed with amphotericin B. The ingrown great right toenail was also removed.

After 7 weeks of therapy with amphotericin B, daptomycin, and ertapenem, the patient presented with increased swelling around the tibial tuberosity. Repeat MRI revealed a rim-enhancing fluid collection in the intramedullary space extending into the soft tissues, which was concerning for abscess (Figure 4). Her prednisone had been tapered to alternating 50 mg and 20 mg every other day, with no change in her tacrolimus dosage. She underwent a repeat surgery with a more extensive debridement than was previously performed by enlarging the cortical window (Figure 5A) using a Midas Rex 9-mm high speed burr (Medtronic) to remove all traces of devitalized bone (Figure 5B), applying thermal ablation
with an argon beam coagulator (Covidien, Boulder, Colorado) (Figure 5C), and irrigating with half strength Dakin’s solution (bleach) (Century Pharmaceuticals, Inc, Indianapolis, Indiana). At the end of the procedure, a string of polymethylmethacrylate cement (Simplex P with 1 g of tobramycin beads; Stryker Orthopaedics, Kalamazoo, Michigan) impregnated with amphotericin (500 mg of amphotericin in one 40-g bag of cement) were inserted into the defect created in the proximal tibia (Figure 5D). However, bacterial and fungal cultures of the fluid obtained from this surgical procedure were negative.

Postoperatively, she was continued on amphotericin B and posaconazole (400 mg 4 times daily) for 6 weeks prior to the elective removal of the amphotericin beads, and tibial reconstruction with polymethylmethacrylate bone cement (Simplex P with 1 g of tobramycin; Stryker Orthopaedics) impregnated with additional vancomycin and amphotericin (2 g of vancomycin and 500 mg of amphotericin mixed in two 40-g bags of cement with manufacturer impregnated 1 g of tobramycin per bag). Two titanium screws (Synthes North America West Chester, Pennsylvania) were impacted into the cortical window to act as support struts for the medial tibial cortex (Figure 6A).

At the last surgery, immunosuppression was prednisone (50 mg alternating with 10 mg every other day) and tacrolimus (0.5 mg 4 times daily). No postoperative complications occurred, and the patient was discharged on continued amphotericin B alone. Approximately 7 months later, the patient had been tapered off of all immunosuppression and, after a repeat MRI that demonstrated no evidence of recurrent or progressive osteomyelitis, stopped taking amphotericin B.

Six months following the discontinuation of antifungal therapy, she was fully ambulatory without signs or symptoms of osteomyelitis, and radiographs demonstrated a well-aligned tibia without complication (Figures 6B, C).

**Discussion**

Although the mortality associated with mucormycosis worldwide has declined over the past half-century, outcomes remain poor for patients after hematopoietic cell transplant; mortality remains 91%. Early detection, aggressive therapies, and a multidisciplinary medical and surgical team help reduce potential morbidity and mortality caused by this rare infection.

Detection and diagnosis present a problem for cases such as this, where the infectious agent and the site of involvement are rare. The majority of *Rhizopus* disease starts as rhinocerebral or cutaneous infections but can disseminate to affect other vital organs due to their angiinvasive nature if they are not aggressively treated. Although the source of infection in the current case was unclear, no signs existed of rhinocerebral or cutaneous involvement.

Direct inoculation or local trauma have been implicated in the few cases of isolated osteomyelitis; however, no prior trauma to the right tibia was noted in the current case. The possibility exists of minor tibial trauma of which the patient was unaware because previous reports have noted the tibia to be particularly prone to osteomyelitis due to its large anterior subcutaneous surface and scant muscle coverage providing minimal protection and blood supply. It is also possible that the ipsilateral ingrown toenail was the portal of entry. Although the vast majority of mucormycoses result from the inhalation or ingestion of organisms, the pulmonary nodules in this patient remained stable in the absence of antifungal therapy effective against *Rhizopus* species, suggesting that the pulmonary nodules were not related to her fungal osteomyelitis.

Reported risk factors for the development of mucormycosis following hematopoietic cell transplant include high-dose steroid therapy for chronic graft-versus-host disease and infectious prophylaxis with voriconazole, which were likely contributors to the risk in the current case. The patient was taking therapeutic doses of tacrolimus, which has had protective effects against mucormycosis infections by inhibiting fungal homologues of calcineurin that play important roles in fungal growth and pathogenesis.

However, the classical rhinocerebral type of mucormycosis infection is not common in the posthematopoietic cell transplant population; therefore, providers must be aware of several possible infectious manifestations and must also be prepared to undergo early surgical identification and debridement because treatment delay is associated with worsened outcomes. One study showed that delayed initiation of an amphotericin B–based regimen (more than 6 days after diagnosis) was associated with a doubled mortality rate at 12 weeks.
Aggressive surgical debridement of infected and devitalized bone is widely accepted as critical for the successful management of many orthopedic problems, including open fractures, osteomyelitis, arthroplasty, and tumor surgery. The current case highlights the need to adhere to this basic concept even in the setting of high-dose steroids for graft-versus-host disease treatment; multiple debridements were performed, with the most successful outcome accomplished by opening a wide cortical window in the tibia to allow proper visualization of the full extent of infected and devitalized bone. The necrotic bone was thoroughly removed with curettes (Codman, Raynham, Massachusetts) and high-speed burring until healthy, bleeding, cancellous bone was encountered. Although adjuvants such as argon beam thermal ablation and Dakin’s solution were used, the adjuvants alone would not have been sufficient to eradicate the disease without an aggressive debridement. These surgical procedures occurred in the setting of ongoing steroid dosing for chronic graft-versus-host disease treatment without clinical consequences to recovery.

One key challenge in treating osteomyelitis is that antimicrobial penetration into bone tissue is significantly less than serum concentrations when necrosis is present. Because the cardinal feature of fungal osteomyelitis is angioinvasion, this challenge is potentially greater. A potential solution to this problem is the use of biodegradable or nonbioactive cement as a vehicle for tissue delivery. Several variables contribute to the elution of antibiotics from bone cement, including the dose of the antibiotic, the molecular structure of the drug, the mixing technique (eg, not using a vacuum and adding the antibiotic at the end of the mixing cycle), the surface-area-to-volume ratio of antibiotic cement beads (higher ratio favors improved elution), and multiple drug combinations. Fungal elution is considered similarly affected by these factors, but controversy exists regarding the effectiveness of antifungals, such as amphotericin B, used in these cements. Cui et al reported that amphotericin B remains active when used, whereas other reports indicate that the length of antifungal activity varies but is significantly diminished after 1 week. Several materials have been used to deliver antibiotic therapies in such situations, including polymethylmethacrylate, hydroxyapatite, and β-tricalcium phosphate, but data on the efficacy of antifungal delivery through these agents are limited. One study reported that the in vitro elution characteristics of most antifungals from bone cement spheres made from the aforementioned materials may not be optimal for the treatment of deep-seated fungal infections if the in vivo drug release was comparable. Although the biodegradable options (hydroxyapatite or β-tricalcium phosphate) reduce surgical risk and cost by eliminating the requisite cement removal surgery needed for nonbioactive materials, such as polymethylmethacrylate, no controlled trials have demonstrated improved therapeutic outcomes with local antifungal therapy. More research is needed to determine the effect of dosage, mixing technique, and multidrug cement combinations on the elution characteristics and ultimate role of amphotericin impregnated cement in the management of fungal osteomyelitis. The aggressive surgical debridement and use of amphotericin-infused cement beads and multiagent cement reconstruction appeared to contribute significantly to the successful treatment and functional recovery of the current patient.

CONCLUSION
Early recognition and treatment with aggressive systemic antifungal therapy and invasive cement delivery of local antifungals is important. A greater provider awareness of rare infections in hematopoietic cell transplant patients may be necessary and aggressive invasive therapy is possible during moderate- to high-dose immunosuppression. Future controlled clinical trials studying the efficacy of antifungal-embedded cement as therapy for osteomyelitis may bring greater therapeutic clarity to cases such as this.

REFERENCES


