Successful management of mucormycosis infection secondary to motor vehicle accident in a healthy adolescent: A case report

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ABSTRACT

Mucormycosis in healthy adolescents is a rare etiology of infection that does not have a commonly known protocol for management. This report describes an adolescent male who developed soft tissue mucormycosis secondary to a motor vehicle accident with severe lower extremity injuries. Treatment involved topical amphotericin B washouts and beads, serial aggressive debridement, and isavuconazole. To our knowledge, this is one of few documented cases of successful lower extremity salvage in an immunocompetent adolescent infected with mucormycosis and treated with isavuconazole.

1. Introduction

Mucormycosis is a rare fungal infection that typically does not arise in immunocompetent hosts. Infections may result from inhalation of spores into the nares or lungs, inoculation into disrupted skin or wounds, or ingestion of contaminated food. There are multiple subtypes of disease presentation, including rhinocerebral, pulmonary, gastrointestinal, oesotraarticular, cutaneous, and disseminated. Further, the mortality rate of this infection ranges from 32 to 70% [1]. In developed countries, mucor infection is uncommon unless the patient is severely immunocompromised (hematologic malignancies, organ transplant, autoimmune conditions). In developing countries, mucor is primarily prevalent in patients with poorly controlled diabetes and immunocompetent trauma [2]. Such cases typically involve extensive wound contamination for infection to occur [3]. An Australian case series discovered that motor vehicle accidents (MVAs) accounted for 78% of all trauma-related cutaneous mucormycosis cases studied, suggesting that MVAs may be a notable precipitant of the infection [4]. Because of the rarity of the infection in immunocompetent individuals and the aggressive nature of the fungus, little is known about treatment of cutaneous mucor, soft tissue, and bone infections in these populations. The aforementioned study, as well as few others, recommend aggressive debridement and decontamination as methods of prevention. We hope to add to the literature, particularly in North America, with our case [4,5]. Further, we show the utility of isavuconazole in a pediatric patient, which has limited reports in the literature.

This case report describes an adolescent male who developed cutaneous mucormycosis infection that progressed to the soft tissue and bone after an MVA with severe lower extremity injuries who presented to our academic institution in November of 2020. This progressed to osteomyelitis of the right tibia and left calcaneus. Treatment involved amphotericin B washouts, serial aggressive debridements, antibiotic impregnated cement and beads, intravenous isavuconazole, and a cross-leg flap. To our knowledge, while cases have been managed in adults, this is one of the only documented cases of successful lower extremity salvage in an immunocompetent adolescent infected with mucormycosis and treated with isavuconazole [6,7]. The work has been reported in line with the SCARE criteria [8].

2. Case

A restrained 17-year-old male with no previous medical history presented as a level 1 trauma after his vehicle collided with a tree. Extrication from the vehicle required 35 minutes. He sustained multiple severe injuries including bilateral Gustilo-Anderson Type 3A femur fractures, bilateral Type 3B tibia-fibula shaft fractures, left Type 3A open calcaneus and cuboid fractures, left medial soft tissue degloving injury of the plantar foot, left comminuted displaced radius and ulnar fractures,
left sacral ala fracture, and a left superior pubic ramus fracture. In addition, he sustained a large degloving injury involving most of the anteromedial aspect of his right leg with exposed fracture at the wound base. The left foot and posterior leg also had significant degloving injuries (see Fig. 1).

The left anterior tibial artery was occluded, and the right posterior tibial and peroneal arteries were discontinuous at the location of the comminuted and open tibia and fibula fractures. The right anterior tibial artery showed evidence of a dissection. Despite this, his foot remained well perfused and did not require vascular intervention. He was taken emergently for exploration of a hemoperitoneum due to superior mesenteric vein avulsion and a liver laceration on hospital day 1. His long bone fractures were initially treated with irrigation debridement and external fixation. He subsequently underwent intramedullary nailing of his femurs and tibias on hospital days 6 and 7. Following this, he required full pressor support and developed abdominal compartment syndrome from hemoperitoneum. The abdomen was left open and then closed 5 days later after serial abdominal explorations.

After intramedullary nailing and application of a cement spacer impregnated with gentamicin and vancomycin for the first stage of the masquelet technique, soft tissue coverage was required to cover the exposed hardware in the right leg. He was not stable enough to tolerate a prolonged surgery per the trauma service, nor did we feel he had adequate vessels for microsurgery given the zone of injury, one vessel leg on the right side, and radiographic findings. The soft tissue injury to the left posterior leg was in the proximal posterior calf with no exposed critical structures and provided enough remaining posterior skin for a flap. As a result, after significant irrigation and debridement of necrotic-appearing tissue, a cross leg flap was completed on hospital day 16 to allow for continued debridements and topical amphotericin due to continued clinical signs of soft tissue and bone infection. With the cross leg flap, shown in Fig. 2, only the medial edge of the flap was sutured down to the lateral right leg. This left a space underneath the flap and over the hardware which provided access to irrigate, debride, and pack the space with gauze. Once the infection cleared, the flap began to adhere to the underlying tissue from lateral to medial as we stopped packing it with gauze.

His lower extremity wounds were complicated by a polymicrobial infection, including Mucor and Pseudomonas osteomyelitis of his right tibia and left calcaneus isolated during this most recent debridement that was treated with a prolonged course of antibiotics, including piperacillin/tazobactam, linezolid, meropenem, and daptomycin, and antifungals, including topical amphotericin B washouts and beads and intravenous isavuconazole. Full thickness cortical debridement was completed to eradicate the fungal infection from the left calcaneus that did not compromise stability and from the right tibia fracture fragments and limited to the area of injury.

His mucormycosis diagnosis was made clinically based on the history and gross appearance of the infection, with Mucor growth confirmed on serial cultures. Amputation of the right leg was recommended given the severity of the infection and injury. Given his age, however, the patient and his mother wanted to continue with limb salvage procedures.

The left foot degloving was eventually closed primarily after clearing the osteomyelitis as above. He was separated at 4 weeks following negative bone and soft tissue cultures and definitive bone grafting was completed five months later.

To treat the underlying infection, antibiotic beads mixed with amphotericin B and gentamicin were placed under the cross-leg flap and in the left heel wounds. Tobramycin and vancomycin powders were placed within the wounds as well. The right leg was irrigated with an amphotericin B solution to further address his Mucor infection. He was started on intravenous isavuconazonium sulfate on day 19 of hospitalization, with a loading dose of 372 mg intravenous (IV) every 8 hours (x6 doses), followed by maintenance dosing of 372 mg IV every 24 hours based on his weight. The infection was successfully treated with resolution on subsequent cultures about 3.5 weeks after initiation of treatment, and his leg was salvaged despite initial recommendations to amputate. He continued his antimicrobial regimen even after closure of his lower extremity wounds for 3 months. A timeline of his surgeries and antifungal therapy is presented in Fig. 3.

Following discharge, the patient was prescribed a continued schedule of isavuconazonium sulfate to continue as an outpatient infusion via his peripherally inserted central catheter (PICC) at a rehabilitation facility and eventually was transitioned to oral therapy, and he has recovered extremely well since, regaining the ability to walk with his walker within 6 months after discharge despite suffering from anterior cord syndrome secondary to hypotension and abdominal compartment syndrome. The patient underwent his second stage of the masquelet technique with iliac crest bone graft placement within the pseudomembrane augmentative plating, shown in Fig. 4.

He was last seen 12 months after this graft placement, with his healed wound shown in Fig. 5.

3. Discussion

Mucormycosis is an opportunistic invasive fungal infection most commonly of Mucor or Rhizopus etiology, though because of the rarity of infection, these are not often specifically tested for. It is a fungus characterized by non-septate hyphae with 90-degree angle branching often

Fig. 1. Extent of degloving injury of the right lower leg (A, C, D) and left foot (B).

Fig. 2. Patient’s lower extremities post-cross-leg flap to the right leg and further separation.

Mucor and Pseudomonas osteomyelitis of his right tibia and left calcaneus isolated during this most recent debridement that was treated with a prolonged course of antibiotics, including
found in soil, plants, and decaying fruits and vegetables. Mucormycosis most commonly affects patients in the setting of immunocompromise, diabetic ketoacidosis, or iron overload, particularly those being treated for hematologic malignancies or organ transplant [9]. In immunocompetent hosts, mucormycosis infection has been associated with trauma and MVAs, specifically, though there are limited data on such infections, particularly in adolescents. "Mucor" infection secondary to trauma has been described briefly in the literature, and our findings are summarized in Table 1 [4,10,11]. In particular, motor vehicle accidents have been found to precipitate cutaneous "Mucor" infection in a number of cases. Of 16 documented cases in Australia across 15 years, 12 (75%) were immunocompetent, 9 (56%) were associated with trauma in general, and 7 (44%) were associated with MVAs. These cases, however, were mostly in adult patients with only one case in a patient under 18 years of age [4]. While "Mucor" infections secondary to trauma in adolescents is not unheard of, it is still fairly uncommon, and documented cases of successful treatment are even more rare.

In the literature, there are few documented cases of limb salvage following cutaneous, soft tissue, and bone "Mucor" infections, particularly in cases such as this with progression to osteomyelitis. Of the cases available for review, at least four described serial radical debridement as the single most important factor for successful salvage [1,4,12,13]. This was typically accompanied by intravenous or liposomal amphotericin B [1,3,12,13]. A study by Moran et al. described seven cases of cutaneous mucormycosis infection where four required eventual amputation due to severity of the degloving and infection, and other studies have reported similar injuries with the need for amputation, as well [13,14]. The patients with limb salvage had an average of ten debridements along with amphotericin [14].

Newer studies are investigating the utility of newer -azoles such as posaconazole and isavuconazole, though these are typically not considered to be first-line therapy [1,15]. One study, however, found that isavuconazole had treatment rates comparable to those of amphotericin, which makes it a promising drug to utilize in the future [9]. Data comparing the efficacy and side effect profiles of the two drugs are limited, however, and warrant future study with larger populations and in pediatric patients [9].

We chose to pursue newer therapy, including isavuconazole administered intravenously. This was because of isavuconazole's high

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**Fig. 3.** Timeline of hospital course.

**Fig. 4.** Flap elevation prior to bone grafting after completion of 3 months of isavuconazole.

**Fig. 5.** Healed right leg 12-months post-graft.
oral bioavailability when thinking forward to oral step-down therapy, as well as its linear pharmacokinetics, good tolerability, and broad fungal coverage. Although we ultimately proceeded with continued intravenous treatment via peripherally inserted central catheter, at the time of making this decision, this trajectory was not known to us. Thus, we chose this drug in order to give us the option to continue oral therapy outside of the hospital. Unfortunately, our transition to oral was delayed by rehabilitation center insurance requirements, so he had to remain on outside of the hospital. Unfortunately, our transition to oral was delayed by rehabilitation center insurance requirements, so he had to remain on outside of the hospital.

The mechanism of action for isavuconazole is inhibition of ergosterol biosynthesis, leading to accumulation of toxic sterols and cell death [9]. Conversely, amphotericin B acts by binding ergosterol to form pores in the membrane, causing leakage of ions and cell death. A major drawback of amphotericin B is that it is associated with nephrotoxicity. Conversely, the major advantages of isavuconazole are the good tolerability and limited drug-to-drug interactions, the possibility for the oral step down without dose adjustment, and the once-daily frequency of administration without the need for premedication and extensive monitoring during infusions [9]. In addition, when comparing isavuconazole to other newer therapies such as posaconazole, we elected for isavuconazole due to the potential for exacerbation of acute or chronic renal failure associated with the intravenous formulation. Considerations for isavuconazole therapy are monitoring for hypokalemia and elevated aspartate and alanine aminotransferases, which are rare but noted adverse effects [9]. When compared to the side effect profile of amphotericin, however, this was preferred by our team, particularly for a pediatric patient.

There is also debate in the literature about the utilization of early vs. delayed debridements and each one’s success in resolving mucor infections. Specifically, Saraiya et al. reported three fatalities with early debridement, defined as surgical intervention within the first ten days after injury, while they had five successful treatments with delayed debridement after ten days initiation of intravenous amphotericin first [16]. This is an interesting consideration to make when determining treatment plan for such patients, particularly because a majority of the literature promoting early radical debridement adjacent to amphotericin treatment was published before 1990. However, the controversy arises in patients like ours, whose initial cultures did not reveal any fungal growth. Thus, the question of whether to wait for culture prior to starting debridement or to start immediately to try and salvage as much tissue, and we found this to be an effective method of limb salvage. It is possible that our patient’s age and prior health contributed to the success, but it still suggests that this is a feasible method for patients in similar situations.

The use of the cross-leg flap allowed us to perform soft tissue coverage of the exposed hardware and bone while still giving us access to complete daily dressing changes with amphotericin-soaked gauze and no worry about a fresh anastomosis in the vicinity of the infection. This allowed us to topically address the infection to augment the intravenous coverage. While microvascular reconstruction tends to be the preferred reconstruction in these cases, the recipient leg was effectively a one.

### Table 1

| Study               | N | Location of Infection | Immune Status | Cause of Infection | Patient Age | Treatment | Outcome |
|---------------------|---|-----------------------|---------------|-------------------|-------------|-----------|---------|
| Kumbal et al., 2016 | 1 | Forehead and sinuses  | Competent     | MVA               | 30          | Systemic amphotericin B | Deceased |
| Ingram et al., 2014 | 16| Locations unspecified - 8 cutaneous wounds, 7 deep wounds, 1 sinus ulcer | 4 compromised, 12 competent | 8 MVA, 8 other traumas | 17, 22-74 | Systemic amphotericin B (11 liposomal), 3 combined amphotericin B with posaconazole, 3 untreated | 4 deceased, 12 locally improved |
| Jones et al., 2008  | 1 | Cutaneous forearm and ulna | Compromised   | Post-liver transplantation | 6 mos | Debridement, systemic amphotericin B, bone curettage, modification of immunosuppressants to cyclosporine, pig allograft coverage, STSG | Limb salvage |
| Kumar et al., 2003  | 1 | Right upper anterior abdominal wall | Competent     | Unknown, works in veterinary medicine | 50          | Debridement, systemic amphotericin B, STSG | Local improvement |
| Luo et al., 2013    | 1 | Right pretilbial       | Competent     | Injury by brick    | 58          | Debridement, systemic fluconazole e amphotericin B (renal toxicity) e iraconazole, STSG | Limb salvage |
| Moran et al., 2006  | 9 | Upper extremity        | 7 competent, 2 compromised | 3 MVA, 3 conveyor belts, 1 corn auger, 2 other traumas | 12, 28-70 | Debridement, systemic amphotericin B, STSG or amputation | 3 limb salvage, 4 amputation, 2 unknown |
| Paduraru et al., 2016 | 1 | Left anterior thigh   | Competent     | Unknown, works in veterinary medicine | 25          | Debridement, systemic liposomal amphotericin B e posaconazole | Limb salvage |
| Saraiya 2012       | 8 | 3 lower extremity, 1 buccal mucosa, 1 gluteal region, 1 upper extremity, 2 trunk wounds, 1 gluteal region | Unspecified   | 2 crush injury, 1 malignancy, 1 diabetic, 4 unknown | 25–71 | 3 immediate debridement, 5 delayed debridement, systemic amphotericin B, 1 amputation, 1 no surgery | 3 deceased, 5 improved |
| Singla et al., 2018 | 1 | Left flank            | Competent     | Railway accident   | 22          | Debridement and systemic liposomal amphotericin B | Deceased |
| Tehmeena et al., 2007 | 1 | Left gluteal region   | Competent     | Local injection trauma | 26          | Debridement and systemic amphotericin B, STSG | Local improvement |
| Tyl et al., 2015    | 1 | Left lower limb stump s/p amputation | Competent | MVA         | 38          | Local wound care, systemic liposomal amphotericin B | Re-amputation |
| Vitrat-Hincky et al., 2009 | 6 | Unspecified       | Unspecified   | 2 MVA, 4 farm accidents | 5–44 | Systemic amphotericin, debridement, 5 amputations | 5 amputations, 1 salvage |
| Wang et al., 2018   | 1 | Left chest wall      | Competent     | Unknown, but had skin lesion for 17 years | 37          | Systemic posaconazole | Local improvement |
| Kumar et al., 2012  | 1 | Right lower extremity | Competent     | Military combat   | 21          | Debridement, silver sponges, amphotericin-impregnated bone cement, systemic caspofungin e voriconazole e amphotericin B, STSG | Limb salvage |
| El Deeb et al., 2004 | 1 | Right thigh          | Competent     | MVA               | 20          | Debridement, systemic amphotericin B, STSG | Limb salvage |

Abbreviations: MVA = motor vehicle accident, STSG = split thickness skin graft.
vessel leg and the zone of injury extended effectively to the entire body limiting recipient vessels. The patient’s instability and pressor support also directed us to a procedure with a shorter operative duration. Although the cross-leg flap is a rather old technique, it is still a reliable option in certain reconstructive cases [17,18]. Despite anterior cord syndrome, the patient was able to walk with a walker at 6 months post-op and continues to build his strength.

4. Conclusions

Mucormycosis in previously healthy adolescents is a rare etiology of wound infection that consequently does not have a commonly known standardized protocol for treatment known to many clinicians. This brief demonstrates a case of mucormycosis of the lower limb secondary to MVA managed with continuous debridement, amphotericin B irrigation, antibiotic bead placement, intravenous isavuconazole, and cross-flap closure for the eventual outcome of a successful limb salvage. This case provides an example of effective management of a pediatric patient with a rare infection in order to increase awareness of this as a possible cause of wound infection not responsive to antimicrobials alone, as well as to delineate surgical planning for limb salvage as opposed to amputation utilizing a multidisciplinary team of infectious disease, orthopedics and plastic and reconstructive surgery. We understand that we will not know the full extent of his limb salvage for some time, but he is showing promise despite the long road ahead of him.

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Consent

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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