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CASE REPORT

Post-traumatic and post-surgical *Absidia corymbifera* infection in a young, healthy man

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KEYWORDS
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Mucormycosis;
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Summary *Absidia corymbifera* infection in a healthy individual is rare. Most of the infection occurs in immunocompromised patients or diabetic patients. Cutaneous and subcutaneous mucormycosis have been increasingly reported in the literature as a result of massive trauma with contaminated wounds. We present a case of cutaneous mucormycosis in a healthy, young patient after surgical amputation for a crush injury of the leg. We also highlight the importance of the high index of clinical suspicion in the diagnosis and treatment of this fungal infection in the hype of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in hospital setting these days. Despite an initial life-saving amputation, it was inadequate to ensure the eradication of *A. corymbifera* infection. A second amputation was required with parenteral liposomal amphotericin B to achieve a satisfactory cure.

Case report

A 19-year-old healthy young man was involved in a road traffic accident in a motor rally. He was a spectator hit by a rally car and sustained a Gustilo type IIIC (Fig. 1) compound fracture of his left tibia and fibula with gross contamination to the entire left lower limb. The distal segment of the leg was cold and pulseless with no Doppler signal beyond popliteal fossa. There was also a significant loss of soft tissue and bone with only an intact posterior myocutaneous flap.

On arrival to the hospital, his GCS was 15/15 and he was haemodynamically stable. A start dose of intravenous metronidazole 500 mg and cefuroxime 1.5 g was given in Accident and Emergency Department in view of the grossly contaminated wound. His X-ray revealed subluxation to the knee joint with dislocation of the superior tibiofibular joint, and comminuted fractures of both tibia and fibula.

He was brought to theatre immediately and the wound was washed with copious amount of normal saline on a pulsed-jet lavage. He had six units of red blood cells during the surgery. A through-knee amputation was performed with the stump end

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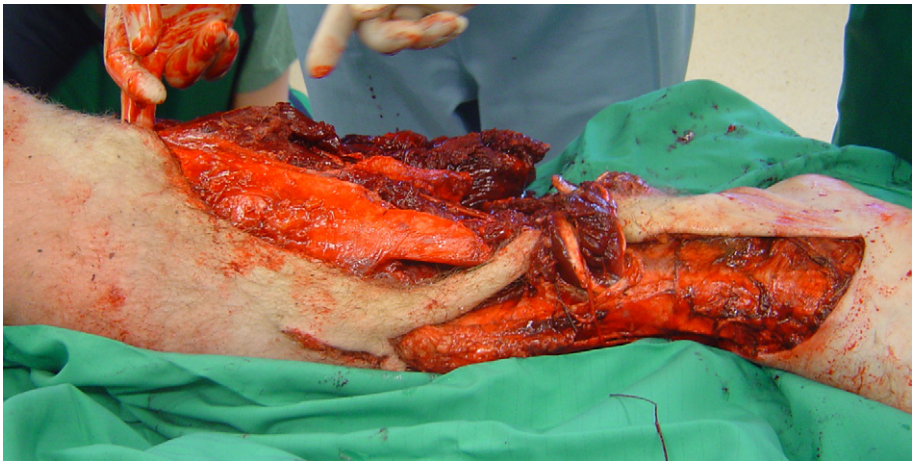

Figure 1 Gustilo type IIIC injury on the left lower limb after the accident.

covered by healthy posterior myocutaneous flap. Post-operatively, the patient was brought to ICU for 48 h for close monitoring and continued intravenous antibiotics.

Day 3 post-surgery, the patient developed a pyrexia at 38.6 °C. Cellulitis started to develop along the medial aspect of the wound with induration and erythema extending up to the thigh. There was also serous blistering along the wound edges. Wound culture swab was taken and empirical treatment with IV flucloxacillin 2 g qds, benzyl penicillin 2.4 g qds, clindamycin 600 mg qds, and ciprofloxacin 400 mg bd were commenced to provide a wide spectrum of antimicrobial cover.

CT scan of the stump showed the presence of gas within the subcutaneous tissue in the region of the stump. There were further collections of gas within the soft tissues overlying the anterior aspect of the distal half of the femur (Fig. 2).

Wound culture result (on day 4) showed coagulase negative *Staphyloccus* as well as a mucor species of uncertain significance. The microbiologist was consulted and IV vancomycin 1 g bd was added to cover the possibility of an MRSA infection. Intravenous liposomal amphotericin B 3 mg/kg/day was also instituted immediately.

On day 6, the pain got worse. Despite the improvement of cellulitis, the edges of the wound became necrotic. The patient was brought back to the theatre for immediate further debridement of the wound.

In the theatre, the wound was re-opened and explored. The pus collection on the medial aspect of the stump was evacuated. The necrotic wound edges were debrided down to healthy bleeding tissue and washed with hydrogen peroxide solution. The healthy subcutaneous tissue, fascia and muscles were closed in layers, and the wound was closed uneventfully.

Day 3 after the second surgery, the wound edges started to become necrotic and erythematous (Fig. 3). Gangrenous cellulitis later developed.

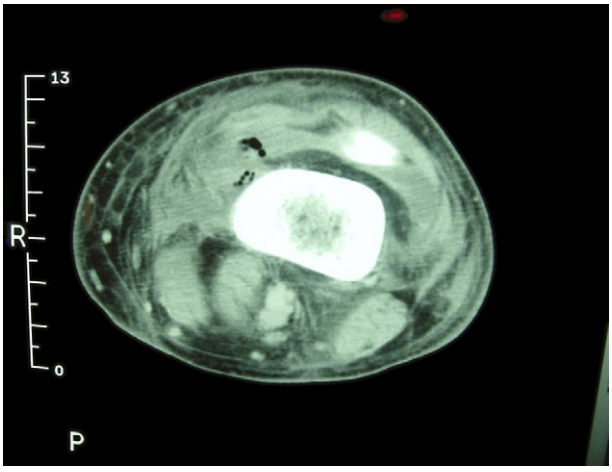

Figure 2 Gas was seen on both the subcutaneous tissue as well as within the soft tissues anterior to the femoral shaft.

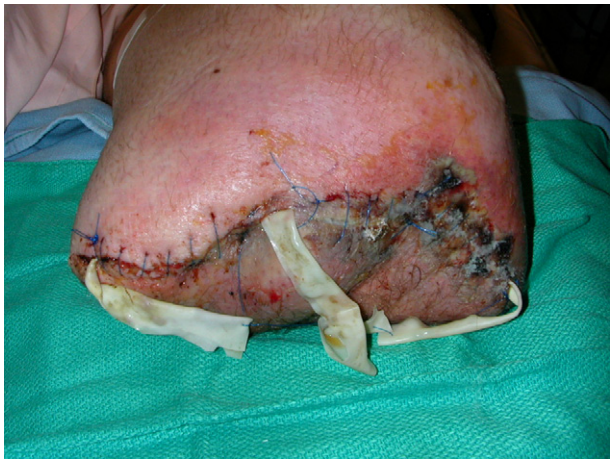

Figure 3 Necrotic wound edges with surrounding cellulitis and induration of soft tissue at the stump.

Infection by *A. corymbifera* was later confirmed by wound specimen of the second surgery. The patient was immediately brought back to theatre for a more aggressive debridement in the form of above-knee amputation (AKA). The necrotic subcutaneous tissues, fascias, and muscles were excised with an abundance of healthy tissue margin.

The patient made an unremarkable recovery and was discharged two weeks after AKA (Fig. 4). Liposomal amphotericin B (AmBisome) was continued parenterally for a full course of two weeks. His renal functions were normal throughout AmBisome treatment.

Discussion

Mucormycosis is the most aggressive and rapidly fatal fungal infection in humans.[1] Sometimes referred to as Zygomycosis, mucormycosis is an infection caused by ubiquitous fungi in the class Zygomycetes (formerly Phycomycetes) and of the order Mucorales.[1,2] The fungal agents within Mucorales responsible for infection in the humans include *Rhizopus* (about 90% of all cases), *Absidia*, and *Mucor*.[3,4]

Absidia spp. are filamentous fungi, ubiquitous in nature. They are found worldwide in soil and decaying vegetation, and can be isolated from food and indoor air environment. Of the genus *Absidia*, *A. corymbifera* (synonym: *Absidia ramosa*) is the only species pathogenic for humans.[3,5,6]

Worldwide, about 30 cases of various clinical forms of mucormycosis caused by *A. corymbifera* have been reported, following the first report by Hiller in 1874.[7] Of these, more than half represent the cutaneous form of zygomycosis.[7] Although uncommon, it deserves attention for its acute, necrotic, opportunistic infection, characterised by angioinvasion, vascular thrombosis and tissue necrosis.

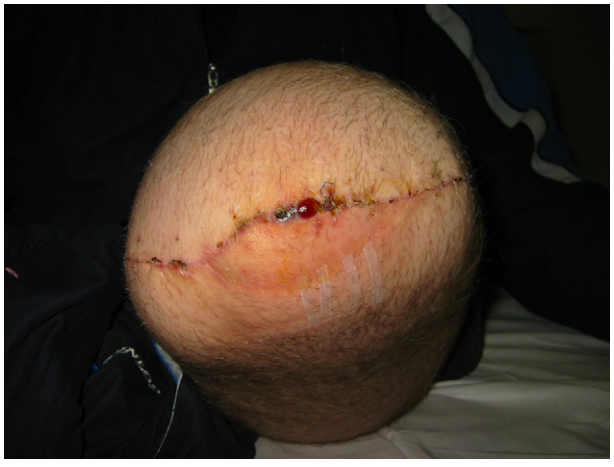

Figure 4 Two weeks after above-knee amputation, the wound healed satisfactorily.

Cutaneous mucormycosis comprises about 10—16% of all cases of mucormycosis.[1,7] It can be a primary infection or a manifestation of disseminated mucormycosis.[2,8] Disseminated mucormycosis can involve almost any organ, most frequently the lungs, CNS, spleen, kidneys, heart, and GIT.[2,3] Predisposing systemic and local risk factors are present in 50% and 86% of cases, respectively.[7]

Cutaneous mucormycosis has been largely described in the immunocompromised or the poorly controlled diabetic host, but is increasingly identified in patients without predisposing factors.[3,8,9] Most of these were cases of mucormycosis in traumatic wounds secondary to injuries following initial soil contamination.[3,8,9] They have also been reported in patients with massive trauma such as compound fractures, crush injuries, and severe burns.[10] Bony fractures, massive soft tissue disruption and haemorrhagic shock can induce immunosuppression and this explains the development of such an infection.

In trauma patients, initial cutaneous soil of traumatised tissue leads to fungal proliferation and invasion of subcutaneous tissues, muscles, and fascias. Then because of their peculiar affinity for blood vessels, mucorellae hyphae invade vascular structures and cause tissue necrosis and, in the nongranulocytopenic host, an acute suppurative inflammation. Microscopically, the lesions are characterised by coagulative necrosis, neutrophilic infiltration and blood vessel thrombosis. This is one reason of disease progression during treatment with systemic amphotericin B as in our case as this limits local tissue penetration of the chemotherapeutic agent. Angioinvasion can also lead to haematogeneous dissemination of disease.

Cutaneous mucormycosis has a better prognosis than pulmonary, disseminated or rhinocerebral mucormycosis.[7] Cocanour et al. reviewed the cases of nine patients hospitalised for blunt trauma injuries over a 9-year period who developed cutaneous mucormycosis.[9,11] In all cases infection was due to wounds contaminated with soil. Mortality was 30% (3/9), and it is noteworthy that mucormycosis involving the head and/or trunk was always fatal, while patients in whom the infection was limited to extremities have survived.[9,11]

The mortality due to these infections is high owing to frequent delayed diagnosis, and hence an inadequate management. Reported mortality rates range from 38% to 80%, the higher rates being associated mainly with delay in recognising the

nature of the infection.[12] Because of the mortality associated with mucormycosis, a high index of clinical suspicion and a low threshold for aggressive surgical and chemotherapeutic management should be instituted once the infection is suspected.

Other features such as continued expansion of the wound despite broad-spectrum antibiotic therapy, failure to isolate bacterial organisms and observation of a mould on the wound edges may also be of help in raising suspicion of this rare infection. Some have advocated wound biopsy as a more reliable method of detection than wound cultures, but our experience shows the history of the nature of injury, the clinical signs of wound infection and the progress of wound should be enough to raise caution for empirical treatment with antifungal agent.

Cutaneous mucormycosis diagnosis is usually confirmed by the finding of fungal hyphae in the histologic specimens and by fungal cultures. Despite being recognised as common laboratory contaminants,[1,6] these organisms are infrequently isolated in the clinical laboratory. *A. corymbifera* accounts for only about 2—3% of culture-confirmed cases of zygomycete infection.[3] Therefore, in patients with predisposing factors and/or clinical symptoms, the isolation of any mucorellae should be regarded as potentially significant. Hyphal invasion of the tissue specimen is the hallmark of the infection. As a rule, positive direct microscopy showing typical hyphae of a zygomycete should be considered significant, even if the laboratory is unable to culture the fungus, and empirical treatment should be instituted.[6]

The clinical presentation of cutaneous mucormycosis is extremely variable, ranging from indolent non-healing ulcers to rapidly progressing necrotising infections of the subcutis.[7] It has also been described to resemble that of ecthyma gangrenosum.[8,11] Others have reported cotton-like bread mould growing on wound edges as another form of presentation.[7,8,13] Our case presents as an increasingly painful, erythematous, necrotic wound with serous blisters within three days after surgery. Later, it developed into gangrenous cellulitis with characteristic morphology of central blackened necrotic wound surrounded by reddish-purple soft tissue induration.

Attempts have been made by some to separate cutaneous mucormycosis manifestation as two forms: a subacute 'superficial' form and a 'gangrenous' form.[1] The superficial form being the less aggressive, and the gangrenous form being the more severe and only reported in immunocompromised patients. These distinctions are unnecessary since both have the potential to disseminate and be fatal if inadequately treated. Both forms should represent a spectrum of disease rather than separate entity.

Although the optimal management is controversial, surgical debridement is essential. There is no existence of clinical guidelines on surgical margins of debridement even though many have used terms such as 'conservative debridement' and 'radical debridement'. More extensive studies are required to determine the 'safe' margin of debridement for cases of mucormycosis. In our case, a second more proximal level of amputation was necessary to control the infection.

The combination of surgical and antifungal chemotherapy remains the standard of care for cutaneous mucormycosis. Mucorales has a high incidence of antifungal resistance. They are susceptible to amphotericin B but resistant to ketoconazole, itraconazole, and fluconazole.[9,14] Therefore, the successful treatment of mucormycosis depends on the early recognition of the infection and control of the underlying disease coupled with aggressive early surgical debridement with complete resection of infected and devitalised tissues, and intravenous administration of amphotericin B especially in immunosuppressed or disseminated disease setting or multiorgan involvement.[7—9] Renal toxicity can be avoided by administering amphotericin in its liposomal form (AmBisome).[8,15] In our case, two weeks of parenteral administration of AmBisome was adequate although some recommend a duration of eight to 10 weeks.[6]

Treatments with the newer azole preparations, such as posaconazole or voriconazole, do not appear to be effective on their own, although experience has been limited.[12] Potassium iodide, granulocyte-colony stimulating factor, white cell transfusion, and clotrimoxazole have also been used successfully.[7] Anecdotal treatment with hyperbaric oxygen has been proposed, but its efficacy has yet to be proved.[1,9,12]

In the hype of MRSA in the hospital, it is important to have an open mind that other rare infections can occur in the hospital setting and high index of clinical suspicion is important. Due to the propensity of *A. corymbifera* to cause angioinvasion, wounds that are dirty and necrotic should be monitored closely and the possibility of mucormycosis should be borne in ones mind. It has been well documented that mucormycosis can cause disseminated disease and multiorgan system failure if not treated with great respect.

This case highlights the importance of a high index of clinical suspicion in the setting of a delayed healing of traumatic wound even after the initial

debridement and adequate antibiotic treatment in a healthy, non-suspecting immunocompetent host. It emphasises the importance of prompt action and aggressive wound debridement, and systemic liposomal amphotericin B in the management of cutaneous mucormycosis by *A. corymbifera*.

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