

Post-traumatic cutaneous mucormycosis in an immunocompetent patient

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Fungi of the class Zygomycetes, order Mucorales, cause deep-seated infections in immunosuppressed individuals, such as those with hematologic malignancies, renal failure, diabetes mellitus, and patients on immunosuppressive therapy.¹ Typically an airborne disease, primary infection is initiated in the upper or lower airways and is associated with the clinical development of sinusitis, rhinocerebral mucormycosis, or pulmonary infection.² Dissemination to other sites may occur if patients do not receive aggressive surgical and medical therapy. Primary cutaneous mucormycosis is uncommon and has been associated with the use of elasticized surgical bandages, burns, and trauma.^{1,3,4} We report a case of cutaneous mucormycosis due to *Rhizopus microsporus* in a young immunocompetent patient following a severe traumatic injury to his lower limb.

Case

A 20-year-old male was admitted to Hamad General Hospital in November 2002 after being involved in a rollover road traffic accident. On arrival to the emergency room he was in severe pain, with a blood pressure 117/70 mm Hg, pulse rate 70/minute, and temperature 37.1°C. His physical examination revealed a swollen, markedly tender right forearm, a deeply lacerated 10×12 centimeter cut wound on the lateral aspect of the right thigh with small pieces of metal inside the wound. Laboratory investigations revealed hemoglobin 14.1 gm/L, white blood cell count (WBC) 20 500 /mm³, platelets 331 000/mm³, a random blood sugar of 7.8 mmol/L, and serum creatinine 66 µmol/L. Plain x-ray films showed fractures of the right iliac crest, a displaced comminuted fracture of the right femur, and fractures of the right radius and ulna. Computed tomographic (CT) scans of the abdomen and pelvis were unremarkable. Debridement of the right thigh wound with removal of foreign bodies and dead tissues was done. A few days after operation he developed a fever. All cultures were negative except wound cultures, which grew *Enterobacter cloacae* and *Pseudomonas aeruginosa*. He was given intravenous imipenem/cilastatin 500 mg every 6 hours. Fever persisted, and a blackish discoloration of the wound was noticed. Wound debridement was done again. A direct smear of the debrided tissue using KOH revealed irregularly broad, non-septate hyphae with right-angle branching suggestive of Zygomycetes. Culture on Sabouraud dextrose agar (SDA) yielded fungal colonies within 48 hours. The cottony aerial mycelia were at first white and then acquired a gray, speckled appearance. Microscopically the colonies were composed of broad coenocytic hyphae with stolons, which bore rhizoids and brown sporangio-phores at the same intervals on the stolons but on opposite sides, in a manner consistent with members of the genus *Rhizopus*. Identification of the fungus isolated from the patient as *Rhizopus microsporus* was conducted by Centraalbureau voor Schimmelcultures, Utrecht, The

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Netherlands. Specimens of similar unused adhesive tape cultured on SDA medium failed to yield any fungi. Amphotericin B (1 mg/kg/day) was given, and repeated surgical debridement of the wound was done. The patient's condition improved gradually and repeated tissue cultures became negative for the fungus. A total of 2.5 gm of amphotericin B was given. Skin grafting was done before discharge.

Discussion

Human infection with members of the family Mucoraceae, known as mucormycosis, is most commonly caused by species of *Rhizopus*, *Absidia*, and *Rhizomucor*. Patients who develop mucormycosis generally have predisposing factors that reduce their immunity and make them more susceptible to the infection, although cases developing in immunocompetent individuals have been reported.⁵ Factors that have been most commonly associated with mucormycosis include diabetes mellitus, neutropenia, malignancy, corticosteroid therapy, desferoxamine therapy, metabolic acidosis, and thermal burns.^{6,7} The clinical manifestations of mucormycosis are categorized as rhinocerebral, pulmonary, disseminated, gastrointestinal, cutaneous, and miscellaneous.⁸ Cutaneous mucormycosis is rare. It is less likely to be associated with severe systemic illness compared to other forms, and usually local predisposing factors like burn, trauma, surgery, needlesticks, and others play a major role.⁹ A large outbreak of cutaneous mucormycosis in the 1970s associated with the use of contaminated Elastoplast bandages focused attention on this mode of transmission. Following that outbreak Elastoplast bandages have been irradiated with cobalt to ensure their sterility.^{4,10} Patients with pulmonary or other forms of mucormycosis can develop skin lesions distant from the site of primary pathology.¹¹ Cutaneous mucormycosis has been described rarely in trauma patients.¹² Members of the genus *Rhizopus* have been the most common causative agents of wound mucormycosis.³

Our patient is the first case of post-traumatic cutaneous mucormycosis seen in our hospital over the last 15 years despite the large number of trauma patients admitted each year. This conforms to reports in the international literature which indicate that post-traumatic mucormycosis is very rare.¹² Cocanour et al,¹² in 1992, reported eleven patients over a ten-year period, and found another nine patients in a review of the international literature since 1962.

In trauma patients, initial cutaneous soil contamination of traumatized tissue leads to fungal

proliferation and invasion of subcutaneous tissues, muscles, and fascias. The mucorellae have a peculiar affinity for blood vessels and cause tissue necrosis.¹³ Besides local invasion, systemic factors such as hyperglycemia, acidosis, acute renal failure, or antibiotic use have been proposed as contributors to the spread of such infections following trauma.¹³

The portal of entry of *Rhizopus* in our patient was most probably wound contamination at the time of accident. The possibility of a contaminated adhesive pad, although not completely excluded, is unlikely in view of the negative culture from a similar unused adhesive pad. Initial wound cultures in our patient were negative for *Rhizopus*, but the presence soft tissue damage and the use of broad-spectrum antibiotics contributed to later multiplication of the fungus.

The clinical manifestations of cutaneous mucormycosis are variable, ranging from mild chronic infection to severe acute fatal infection. It may resemble that of ecthyma gangrenosum. In patients with open wounds, mucormycosis has a cottony, "bread mold" appearance.^{8,12} The most lethal form of cutaneous mucormycosis is a phycomycotic gangrenous cellulites, which closely resembles necrotizing fasciitis.¹⁴ Characteristically there is a central blackened necrotic eschar surrounded by reddish-purple soft tissue induration.

Cutaneous mucormycosis is diagnosed by culture or biopsy. A potassium hydroxide preparation of the biopsy may allow direct microscopic identification of the characteristic nonseptate, thick-walled hyphae with right-angle branching. Hyphae are also seen in tissue sections with standard staining methods such as hematoxylin-eosin and Gomori's methenamine silver.¹² A fluorescent microscopy stain using calcofluor white has been developed for the fast identification of fungi in frozen sections.¹⁵ Vascular invasion is the hallmark of mucormycosis and commonly is associated with thrombosis of vessels and necrosis of surrounding tissue.^{1,2,16}

Treatment of cutaneous mucormycosis requires aggressive debridement and intravenous amphotericin B.^{3,12,13} Debridement is the cornerstone of cure. In immunocompetent patients debridement alone or the use of the topical antifungal agent amphotericin B has occasionally been successful.¹⁷ Limb amputation is often required to control infection.³ Adjunctive use of hyperbaric oxygen in the treatment of mucormycosis remains unproven, but reports suggest that it may be beneficial.¹⁸ Correction of metabolic acidosis and control of underlying disease is essential in successfully treating cutaneous mucormycosis. Amphotericin

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B is the most effective parenteral antifungal agent. It is given in a dose of 1 to 1.5 mg/kg/d. Lipid formulations of amphotericin B are an appropriate alternative to conventional amphotericin B in patients who are intolerant or develop nephrotoxicity related to its use.¹⁹ Mucorellae are usually resistant to ketoconazole, itraconazole, and fluconazole.¹³ The newer azole antifungal drug posaconazole has demonstrated good in vitro sensitivity against *Rhizopus* species, *Mucor* species, and other *Zygomycetes*. Tobon et al²⁰ recently reported the successful treatment of invasive zygomycosis with posaconazole in a heart-kidney transplant recipient who failed to respond to amphotericin B (deoxycholate).

The prognosis of post-traumatic mucormycosis is dismal. Of the 20 patients reviewed by Cocanour et al,¹² 6 patients died (30%), and 7 required limb amputation (35%). Most fatalities were among patients with head and or trunk involvement. The outcome

in our patient was favorable, and limb amputation was avoided. Factors that contributed to this favorable outcome were limb involvement, the fact that the patient was young and immunocompetent, and there was early diagnosis and institution of antifungal therapy and wound debridement.

In conclusion, post-traumatic mucormycosis remains a rare condition. However, with the increasing number of immunosuppressed patients, more cases may be seen in the future. Because the presentation may be mild and atypical, especially in the less severely immunosuppressed, the diagnosis may be missed or delayed. The key to successful treatment is early diagnosis and correction of the underlying predisposing condition. Aggressive debridement and amphotericin B are the cornerstones of treatment. The availability of the new broad-spectrum azoles with activity against *Zygomycetes* may offer a safer alternative to amphotericin B in the future.

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