Primary cutaneous mucormycosis (zygomycosis) caused by *Apophysomyces elegans*

I. S. Reddy, N. Raghupathi Rao[1], V. M. Shankar Reddy[1], Ratna Rao[2]
Departments of Dermatology, [1]General Surgery and [2]Microbiology, Apollo Hospital, Hyderabad, India

Address for correspondence: Dr. I.S. Reddy, B- 13, Madhura Nagar, S.R. Nagar Post, Hyderabad - 500 038, India. E-mail: drreddyis@gmail.com

ABSTRACT

A 53 year-old male diabetic presented with a month-old, painful ulcer with necrotic margins over the right thigh. Wound debridement was done twice and the ulcer showed recurrent growth of a white, cottony filamentous structure. Cutaneous mucormycosis was suspected and confirmed by histopathology and a culture isolate of *Apophysomyces elegans*. The patient was treated with liposomal amphotericin-B and itraconazole followed by partial thickness skin grafting, and then discharged after being prescribed posaconazole syrup for three weeks. Regular follow-up was done and during the last visit after six months following discharge, the ulcer was found to have healed well with no recurrence of the fungus.

Key Words: Amphotericin-B, *Apophysomyces elegans*, Posaconazole, Mucormycosis, Wound debridement

INTRODUCTION

Primary cutaneous mucormycosis is an uncommon infection caused by saprophytic fungi of the order Mucorales (class Zygomycetes), which occurs most often in diabetics, in patients with thermal burns, and in immunocompromised patients.[1] The primary cutaneous form has a better prognosis than the more deeply invasive form, but is still associated with fatality and long-term morbidity if not diagnosed early and treated adequately. We report here a case of primary cutaneous mucormycosis in a diabetic caused by *Apophysomyces elegans* after a road traffic accident.

CASE REPORT

A 53 year-old male diabetic was admitted for the evaluation of a month-old, painful ulcer over the right thigh. He had been the victim of a road traffic accident, denied any penetrating injury, and had subsequently developed an indurated swelling, the center of which formed a blister and a thick, hemorrhagic crust. The crust and surrounding necrotic tissue were excised by a local doctor. On removal of the dressing, the entire desloughed area showed white, cottony and filamentous growth, and the patient was subsequently referred to this hospital.

Clinical examination showed a well-defined, oval ulcer 15 cm x 10 cm in size over the anterior aspect of the lower 1/3rd of the right thigh. The skin around the ulcer was erythematous, edematous, and indurated. Inguinal lymph nodes on the right side were enlarged, tender, and firm.

Exploration of the ulcer and debridement of necrotic tissue were done under spinal anesthesia. Histopathological examination of the debrided tissue showed a few elongated, broad, nonseptate hyphae in the necrotic adipose tissue. In view of the morphology of the hyphae, underlying diabetes mellitus, and preceding traumatic injury, cutaneous mucormycosis was suspected and the patient was started on intravenous liposomal amphotericin-B 250 mg daily and itraconazole 200 mg twice daily. One week after the initiation of amphotercin-B and itraconazole, the floor of the ulcer continued to show growth of the fungus and extension of necrosis around the wound [Figure 1]. Radical debridement

How to cite this article: Reddy IS, Rao NR, Reddy VMS, Rao R. Primary cutaneous mucormycosis (zygomycosis) caused by *Apophysomyces elegans*. Indian J Dermatol Venereol Leprol 2008;74:367-70.
Received: August, 2007. **Accepted:** December, 2007. **Source of Support:** Nil. **Conflict of Interest:** None Declared.

was planned and the entire ulcer, the surrounding necrotic area, a narrow zone of normal skin, subcutaneous fat, deep fascia and a part of the quadriceps muscle were excised under spinal anesthesia.

Histopathological examination showed necrosis with dense neutrophilic collection that formed abscesses. Inflammation was seen extending into the underlying subcutis and muscle. Numerous, broad, nonseptate hyphae were seen in the periphery of the necrotic areas [Figure 2]. Vascular invasion was not seen and the deep and lateral margins of the excised specimen were free of inflammation and hyphae.

Sabouraud's dextrose agar with chloramphenicol, plain Sabouraud's dextrose agar and Sabouraud's dextrose agar with cycloheximide were used at 26º and 37ºC to cultivate the organism from the excised tissue. All inoculated plates showed profuse growth of woolly mycelium in 2-3 days. The surface of the colony was white initially and turned brownish gray or yellowish [Figure 3]. Microscopy showed nonseptate, broad hyphae with rhizoids and sporangiophores. The apices of the sporangiophores widened to form funnel-shaped apophyses. Typical pyriform (pear-shaped) sporangia with the characteristic, half-circled columella of *Apophysomyces elegans* were observed [Figure 4]. As sporulation of *A. elegans* was poor on routine culture media, the water culture technique was used. Sporangia were scanty and were observed two weeks after incubation.

Amphotericin-B and itraconazole were continued for two weeks after radical debridement. Regular dressing of the wound was done taking strict aseptic precautions and there was no recurrence of any growth of the fungus, which was confirmed by potassium hydroxide wet mount preparation and culture of the wound. Split-thickness skin grafting was done ten days after radical debridement; the graft was

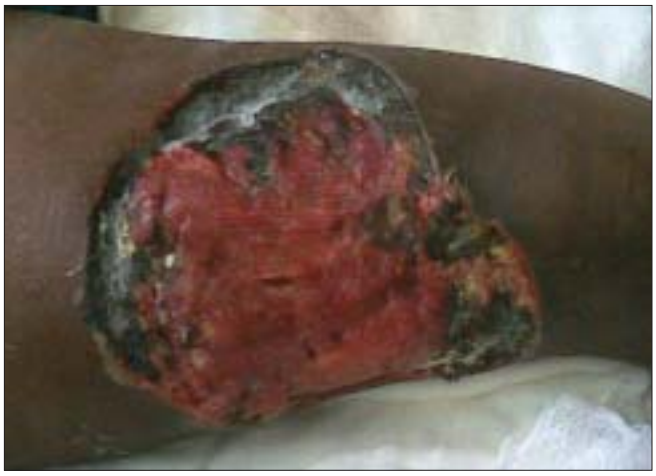

Figure 1: The ulcer with necrotic margins and the floor showing white, cottony, filamentous growth

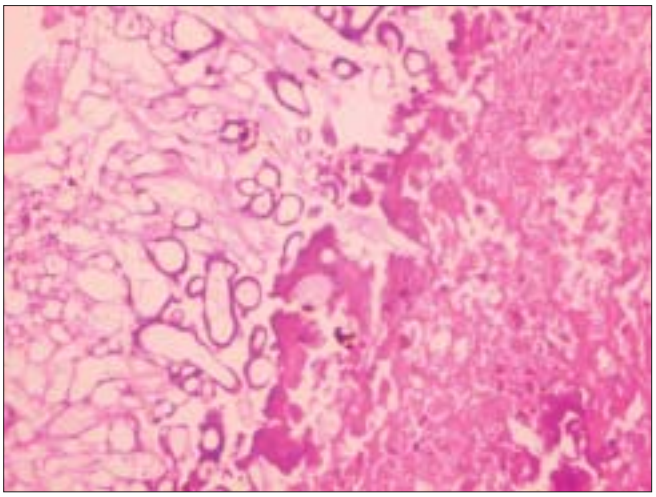

Figure 2: Numerous, broad, a septate hyphae in longitudinal and in cross sections in close proximity to necrotic tissue (H&E, x400)

Figure 3: Sabouraud's dextrose agar showing white, cottony colonies

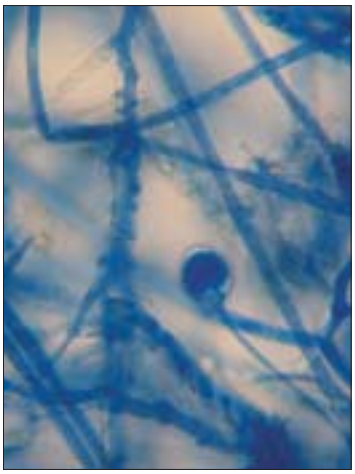

Figure 4: Microscopic appearance showing sporangiophores, rhizoids and characteristic pyriform (pear-shaped) sporangia of *Apophysomyces elegans* (Lactophenol cotton blue, x 400)"

accepted well. The patient was discharged and prescribed posaconazole syrup 400 mg twice daily for three weeks. The patient was followed up regularly and during his last visit (six months after discharge), the grafted site was found to have healed well and there was no evidence of any recurrence.

During the hospital stay, the patient's diabetes was managed with insulin. Renal and hepatic parameters as well as electrolytes were monitored regularly. The patient tested negative for HIV infection; his urine did not show any ketone bodies and a general evaluation showed no systemic involvement.

DISCUSSION

Zygomycosis is a broad term used for diseases caused by the fungi classified under the orders, Mucorales and Entomophthorales of class Zygomycetes under the phylum Zygomycota. Mycoses caused by members belonging to the order Mucorales are called mucormycoses while mycoses caused by fungi belonging to the order Entomophthorales are known as entomophthoromycoses or subcutaneous phycomycoses.[2] Mucorales are saprophytic fungi characterized by broad, aseptate, thick-walled hyphae found ubiquitously in the environment, particularly in the soil and decaying vegetable matter.[3,4]

The genus *Apophysomyces elegans* of the family Mucoraceae was first isolated in 1979 by Mishra and colleagues from soil samples from mango orchards in India and this has now emerged as a significant cause of mucormycosis.[2]

Several clinical types of mucormycosis have been described-rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated forms. The cutaneous form is further divided into primary and secondary types. The rhinocerebral form is the most common and fulminant form seen commonly in diabetics with ketoacidosis. *Rhizopus arrhizus* is the most common species isolated from patients in a ten-year study of mucormycosis in India.[5] The primary cutaneous form is the least common and the primary cutaneous mucormycosis caused by *A. elegans* and *Saksenaea vasiformis* manifests as bullous and necrotic lesions within a few days of traumatic injury due to potential contamination of wound with dust or soil. Mucormycosis can also manifest as Zosteriform lesions[6] with the lesions resembling superficial granulomatous pyoderma[7] and bull's-eye cutaneous infarcts.[8]

Risk factors for the development of mucormycosis include diabetic ketoacidosis,[9] corticosteriod use, organ transplantation, HIV infection,[10] neutropenia[11] and chronic renal failure. Local risk factors include burn wounds, surgical wounds, IV drug abuse, adhesive elastoplast dressings,[12] motor vehicle trauma[13] and insect bite.[14]

Touch preparation with PAS stain may help in rapid diagnosis.[8] Skin biopsy and routine hematoxylin and eosin (H and E) staining show characteristic fungal morphology and culture is required to identify the species.

Successful treatment of cutaneous mucormycosis requires a combination of surgical debridement, antifungal therapy and medical management of the underlying predisposing condition.[15] Amphotericin-B in both the conventional and liposomal forms, has been used successfully to treat zygomycosis. The liposomal form can achieve higher concentrations of the drug without causing nephrotoxicity. One *in vitro* study comparing the activity of posaconazole, itraconazole, voriconazole, fluconazole and amphotercin-B on 31 isolates of zygomycosis showed that the mean inhibitory concentration (MIC) was lowest for Amphotericin-B and second lowest for posaconazole.[16]

For many decades, amphotericin B used to be the drug of choice in the treatment of zygomycosis. The recent past has seen the introduction of newer antifungals and other modalities of treatment for invasive and systemic forms of mucormycosis.

Among triazoles, posaconazole has emerged as an important antifungal agent since 2005.[17] Combinations of antifungal agents such as amphotericin B, liposomal nystatin with granulocyte macrophage-colony stimulating factor and hyperbaric oxygen have been used in the management of rhinocerebral and disseminated mucormycosis.[18]

It is now established that iron metabolism plays a central role and iron chelation using deferiprone is a promising novel therapeutic strategy for refractory mucormycosis.[19]

This case is being presented because of its rarity and to emphasize the role of early diagnosis and appropriate treatment, which saved the limb and life of the patient.

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