An unusual ulcer: A case of cutaneous mucormycosis caused by *Rhizopus oryzae*

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A R T I C L E I N F O

A B S T R A C T

Mucormycoses are high-mortality infections feared by clinicians worldwide. They predominantly affect immunocompromised hosts and are associated with a spectrum of disease. We describe a case of cutaneous mucormycosis caused by *Rhizopus oryzae* in a patient with multiple risk factors cured with complete surgical excision and a short course of antifungal therapy.

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1. Introduction

The diverse agents of mucormycosis (members of the subphylum Mucormycotina) are ubiquitous fungi found in environmental reservoirs associated with decaying matter worldwide. They have a broader, more heterogenous population of human hosts than other opportunistic molds but tend to affect the immunocompromised. Risk factors have been well described and include diabetes mellitus, malignancy, solid organ transplantation, iron overload, neutropenia and prednisolone use [1,2]. Classification of these fungi has changed over the years, leading to some confusion with nomenclature – the term zygomycosis, which was previously applied to these fungi, is now obsolete. *Rhizopus oryzae* is the most common agent, found in approximately half of reported culture positive cases. Mucormycosis is associated with a spectrum of disease of which the rhinocerebral form is the best characterized – however pulmonary, gastrointestinal, central nervous system, cutaneous and disseminated forms are also recognized [3].

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) have recently released comprehensive guidelines for the diagnosis and management of mucormycosis [4]. However even with optimal diagnostic and therapeutic strategies, mortality remains as high as 40% [1].

We describe a case of cutaneous mucormycosis secondary to *R. oryzae* in a patient with irreversible risk factors cured by surgery and a short course of antifungal therapy that illustrates the difficulties in managing this complex condition.

2. Case

A 69-year-old man presented (day 0) with a 4-day history of a skin lesion on his right lower leg which was initially erythematous, became black and necrotic, then broke down into an ulcer. He had no systemic symptoms, and could not recall any trauma or injury to the leg. His past history included poorly controlled type 2 diabetes mellitus, metastatic non-small cell lung cancer for which he had received chemotherapy and radiotherapy, chronic obstructive pulmonary disease, recurrent pulmonary emboli, peripheral vascular disease, and chronic renal impairment. He had received large doses of prednisolone for radiation pneumonitis and exacerbations of his airways disease, and had previously been a heavy smoker.

Physical examination revealed reduced pulses on his right lower leg but was otherwise unremarkable. The ulcer is shown in Fig. 1. When there was no improvement with empiric broad-spectrum antibiotics, biopsy of the ulcer was performed (day 4) and H&E stains (Fig. 2) revealed extensive dermal necrosis with a

heavy neutrophilic infiltrate, with narrow-angled branching fungal hyphae with occasional septae seen under high-power magnification. Cultures were positive within 24 h for a cotton-like, white–gray fungus without reverse pigment growing at 28°, 37° and 40° but not 42 °C. Microscopically (Fig. 3) the isolate had broad aseptate hyphae, a white to gray–brown thallus formed from stolons with long unbranched sporangiophores which were sub-globose to ellipsoidal with longitudinal striations, up to 1500 μm. Simple rhizoids were positioned opposite the sporangiophores. It was later confirmed to be *R. oryzae* with DNA sequencing of the ITS1-5.8S-ITS2 region (100% sequence identity in both Genbank and CBS databases).

Fig. 1. Appearance of the ulcer on hospital admission (day 1).

Subsequent broth microdilution antifungal susceptibility testing revealed minimum inhibitory concentrations (MICs) of amphotericin 0.25 mg/L, 5-flucystosine > 64 mg/L, fluconazole > 256 mg/L, itraconazole 1.0 mg/L, voriconazole > 8.0 mg/L, posaconazole 1.0 mg/L, caspofungin > 8 mg/L, anidulafungin > 8 mg/L, micafungin > 8 mg/L [5].

Because of concern about pre-existing renal impairment, empiric therapy with posaconazole was commenced on day 15 and excision of the ulcer was performed on day 21. Liposomal amphotericin B (5 mg/kg) was added on day 20 due to concerns about posaconazole absorption but ceased when renal function deteriorated on day 24. As fungal hyphae were seen histologically out to the margins of the initial specimen, a second wide local excision was performed on day 24 with subsequent skin grafting (Fig. 4). Therapy also consisted of a right femoro-popliteal bypass to restore vascular supply to the limb, temporary cessation of prednisolone, and optimization of blood glucose control with insulin. There was no evidence of disseminated disease elsewhere on clinical assessment or on positron emission tomography (PET) imaging.

Despite 200 mg qid dosing with meals, cessation of pantoprazole and high fat intake, posaconazole levels > 0.5 mg/mL could not be achieved. Antifungal therapy was ceased two weeks following the second excision given histologic margins were clear of fungal hyphae, and the wound progressively healed over several months (Fig. 5). The patient's malignancy however continued to progress despite treatment that included prednisolone and he died as a consequence of metastatic disease 9-months later, at which time there was no evidence of mucormycosis at the excision site or elsewhere. No post-mortem examination was performed.
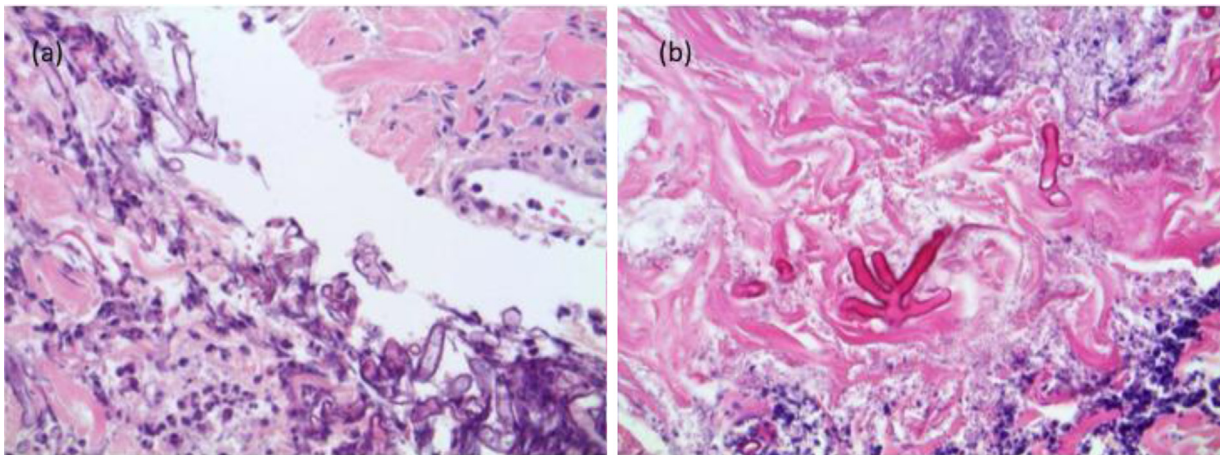

Fig. 2. Biopsy of ulcer performed on day 4: H&E stain, 400 × (a) and PAS stain, 400 × (b) showing narrow-angled branching fungal hyphae invading into necrotic dermis.
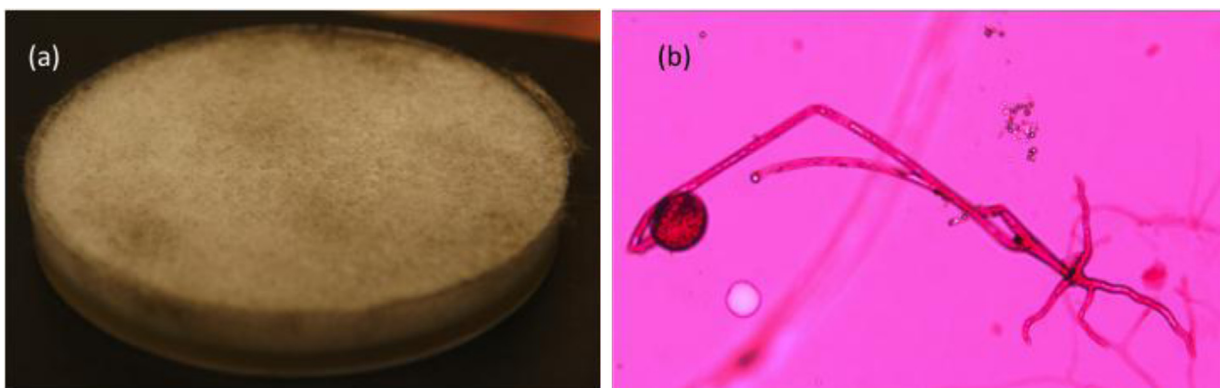

Fig. 3. Sabouraud agar plate following 24 h incubation (a) and view from slide culture (40 ×) showing the presence and orientation of rhizoids (b).
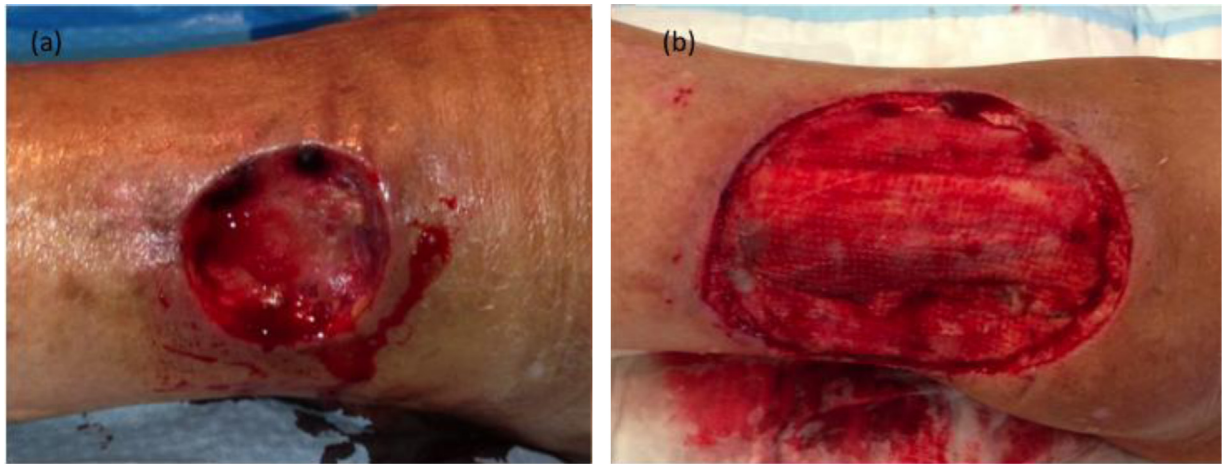
Fig. 4. Post-operative appearance (a) following initial surgery on day 21 and (b) following second wide local excision on day 24.

Fig. 5. One month following grafting showing wound healing, complete graft take and no evidence of residual infection.

3. Discussion

Cutaneous mucormycosis typically results from direct spore inoculation or exposure of compromised skin (e.g. burns or trauma) and starts as erythema and induration, progressing to necrosis with a black eschar. It can extend into deep fascia and muscle layers, and necrotizing fasciitis has been reported [6]. A notable outbreak in mostly normal hosts injured during a tornado occurred in 2011 with a 14-day mortality rate of 38% [7]. Although our patient could not recall a history of trauma, cases have been reported from an injury as minor as an insect bite [8].

Diagnosis is challenging given the non-specific signs and symptoms, and a high index of suspicion is required in susceptible populations. Fungal growth alone is insufficient as it may represent colonization or contamination; histopathological evidence of invasive disease is required. Although our patient did have a typical presentation the non-specific nature of this and broad differential diagnosis of infectious and non-infectious etiologies demonstrates the importance of early biopsy with adequate amounts of specimen sent for both histology and microbiology.

Treatment principles revolve around (1) timely diagnosis, (2) reversal of underlying predisposing factors, (3) early surgical debridement of infected tissue and (4) rapid initiation of effective, high-dose systemic antifungal therapy (2). Amphotericin B remains the most active agent as *Rhizopus* spp. have intrinsic resistance to fluconazole, voriconazole, 5-flucytosine and the echinocandins. MICs to itraconazole, terbinafine and posaconazole are variable [9], and given the lack of interpretive breakpoints the value of routine susceptibility testing

has been questioned (4). Amphotericin has been shown to be clinically effective, with response rates of 39–71% [10–12].

Although there is less experience with posaconazole, it has lower toxicity, supportive animal data [13], and demonstrated efficacy in salvage therapy [14,15]. Oral bioavailability is low often resulting in low plasma levels, however skin concentrations have been shown to be equivalent to plasma concentrations [16]. Newly available high-bioavailability oral and intravenous formulations hold promise. The only randomized trial for any treatment strategy in mucormycosis examined the role of deferasirox iron chelation therapy, which showed increased mortality in the treatment group (82% vs 22% at 90 days) and also demonstrated the challenges of conducting RCTs in rare infectious diseases in complex, unwell patients [17].

Early, aggressive surgery is considered vital to prevent dissemination and achieve cure, and has been associated with increased survival [1,4,12]. There is limited evidence to guide the specifics of excision in cutaneous mucormycosis. Excision margins should be clear and wide yet judicious, preserving form and function wherever possible. Multiple procedures may be necessary, and skin grafting or other wound closure techniques should be individualized [18–20].

In summary, we have described a patient with a typical presentation of cutaneous mucormycosis caused by *R. oryzae* successfully cured with rapid wide local excision and a short course of antifungal therapy. Our case illustrates the importance of prompt, adequate surgery to achieve rapid cure in patients with irreversible risk factors who cannot tolerate medical therapy.

Conflict of interest statement

There are no conflicts of interest to declare.

Acknowledgments

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