Cutaneous mucormycosis infection owing to *Rhizomucor variabilis* presenting as recurrent lower limb ulceration and cellulitis in a diabetic patient

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Abstract

Primary cutaneous mucormycosis is caused by environmental fungi and may complicate leg ulcers or traumatic wounds even in immunocompetent individuals. This case report highlights recurrent lower limb ulcers and cellulitis in a patient with type two diabetes mellitus, which was unresponsive to conventional antibiotic treatment. Histopathology revealed the diagnosis of cutaneous mucormycosis, and fungal cultures identified *Rhizopus variabilis* as the causative organism. Initial courses of oral azole antifungals yielded only partial response and he eventually required more aggressive treatment with i.v. amphotericin B and oral posaconazole. Good treatment outcomes for this condition require a high index of clinical suspicion, early histopathological and microbiological diagnosis, targeted systemic antifungal therapy, and surgical debridement if necessary.

Keywords: cutaneous, diabetes, immunocompetent, mucormycosis, Rhizopus variabilis

Introduction

Cutaneous mucormycosis is a rare but serious fungal infection. While fungal infections are usually opportunistic in nature and affects largely the immunocompromised population, mucormycosis may still cause lethal infection in people with greater immunocompetency such as those with diabetes mellitus [1]. In this article, we present an interesting case of cutaneous mucormycosis presenting as recurrent lower limb ulcers and cellulitis in an elderly patient with poorly controlled Type 2 diabetes mellitus.

Case Synopsis

We report a 73-year-old man with cutaneous mucormycosis. He presented with painful, enlarging bilateral lower limb ulcers, with surrounding cellulitis of a few months' duration (**Figure 1**). He had no constitutional symptoms of fever, chills, or rigors. His background medical history was significant for poorly controlled type 2 diabetes mellitus [glycated hemoglobin A1C (HbA1C) 8.6%, normal target in diabetics is <7.0%] complicated by peripheral neuropathy which resulted in repeated minor trauma to the limbs at the same areas where these ulcers formed. He also had chronic bilateral lower limb lymphoedema (arising from sonographically-confirmed superficial venous incompetencies). In the preceding two years, he had multiple hospital admissions for lower limb cellulitis, including a

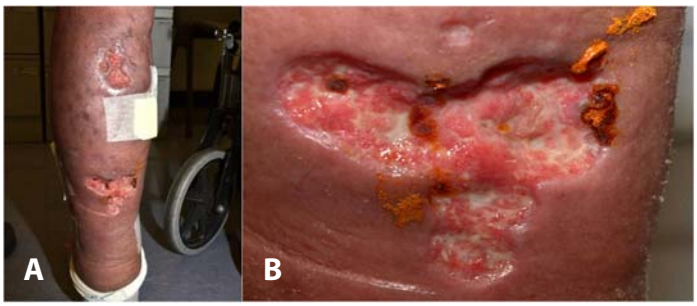

Figure 1. ***A)*** *Multiple irregularly shaped, deep, coalescing ulcers are seen on the calf, with surrounding cellulitis and induration.* ***B)*** *A close-up photo of an ulcer with cadexomer iodine applied.*

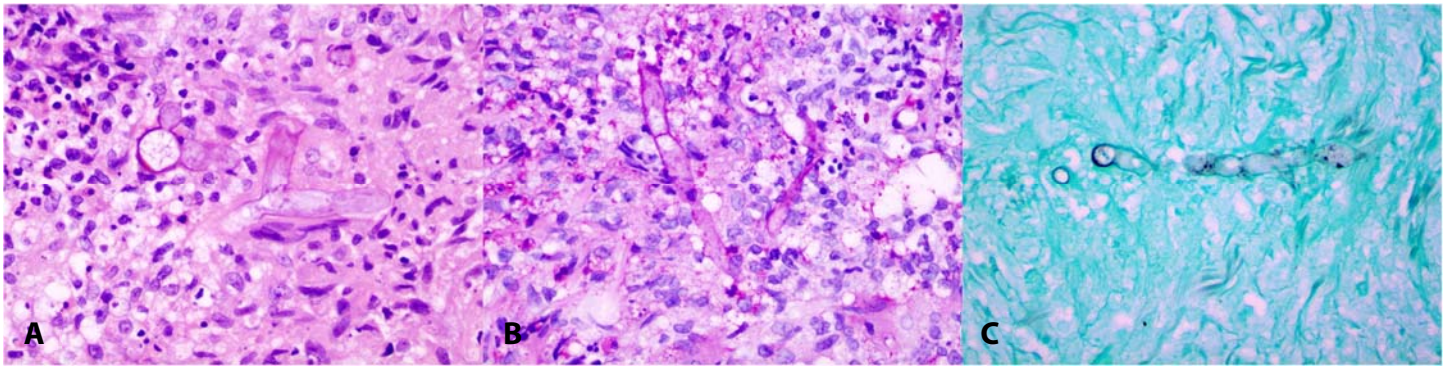

Figure 2. ***A)*** *Broad (15cm diameter), non-septated fungal hyphae branching irregularly at 90º are seen clearly on the hematoxylin and eosin stain. There is an accompanying infiltrate of lymphocytes, histiocytes and neutrophils, 400×.* ***B)*** *Broad fungal hyphae stain positively on* ***B)*** *periodic acid–Schiff stain, and* ***C)*** *Grocott methenamine silver stain stains, 400×.*

severe episode where a fasciotomy was done for suspected right lower limb necrotizing fasciitis.

Blood investigations excluded systemic sepsis and magnetic resonance imaging excluded any underlying abscess or necrotizing fasciitis. A skin biopsy was done and demonstrated epidermal hyperplasia with a dense superficial and deep perivascular and periadnexal infiltrate of lymphocytes, histiocytes, plasma cells, and neutrophils. Multinucleated giant cells were admixed within the infiltrate. There were broad, non-septate fungal hyphae 10-15 micrometers in diameter which branched at 90° (**Figure 2A**). These were readily seen on routine hematoxylin and eosin stain and stained positively for periodic acid–Schiff stain and Grocott methenamine silver (**Figure 2B**, **C**). Angioinvasion was not observed in the 4mm punch biopsy specimen. Bacterial cultures from the wound yielded methicillin-resistant *Staphylococcus aureus*, whereas the fungal culture showed *Rhizomucor variabilis*. Mycobacterial and nocardia cultures were negative.

He was treated intravenous vancomycin for his methicillin-resistant *Staphylococcus aureus* wound infection with clinical improvement. After the skin biopsy results were known, he was started on empiric oral itraconazole 200mg twice daily for two weeks, then oral fluconazole 150mg once daily, with partial improvement. He was subsequently lost to follow up and was admitted a month later for worsening of lower limb ulceration and cellulitis. The repeat skin biopsy yielded similar findings and the tissue culture was consistent again with *Rhizomucor variabilis*. He was thus started on i.v. amphotericin B and oral posaconazole. Intravenous amphotericin B treatment was discontinued 5 days later as he developed acute renal failure (creatinine159μmol/l, normal 54-101μmol/l) and hypokalemia. He completed 36 days of posaconazole as an inpatient with clinical improvement and was discharged to complete a full three months of oral antifungal treatment.

Case Discussion

Mucormycosis is caused by infection with fungi in the order of Mucorales. *Rhizopus* species are the most common causative organisms, accounting for 47% of all infections [1]. Other genera with mucormycosis causing species include *Rhizomucor*, *Absidia*, *Mucor*, and *Saksenaea*. These fungi are frequently found in natural environments and in decaying organic matter. Host characteristics determine the primary site of infection and clinical course.

The major clinical forms of mucormycosis are namely: rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated. Uncommon presentations include endocarditis, osteomyelitis, peritonitis, and renal infection.

In a large retrospective review by Roden et al. [1], primary cutaneous mucormycosis accounted for 19% of all infections. The majority of patients with cutaneous infection were either non-neutropenic or had no underlying conditions. Independent risk factors for localized cutaneous infection were female

sex, no underlying medical condition, prior surgery, and HIV infection. Direct inoculation from penetrating trauma, burns, falls, or motor vehicle accidents accounted for 46% of cases, whereas nosocomial causes (dressings, surgery) accounted for 30%. This explains why cutaneous mucormycosis is an important cause of morbidity and mortality following a natural disaster [2]. However, even innocuous procedures like intravenous cannulation [3], and insulin injections [4] have been implicated.

Primary cutaneous mucormycosis can be classified as: localized or disseminated. Localized cases can be superficial and only involve skin and subcutaneous tissue or deep and show involvement of muscle, tendon, or bone. Disseminated disease occurs with involvement of another non-contiguous organ, owing to the vasotropic properties of these fungi, which allow them to cause tissue infarction and invasive/disseminated disease, especially in immunocompromised hosts. The reverse (disseminated disease localizing to the skin) is rare. In immunocompetent hosts, dissemination can also occur, but the prognosis is better [5]. The disease course can be gradual, slow, or fulminant leading to gangrene and hematogenous dissemination. The typical presentation would be initial erythema and induration of the skin that typically progresses to necrosis with a black eschar [6]. Primary cutaneous mucormycosis can present as enlarging lower limb ulcers in the setting of immunocompromise or in healthy individuals. They may also complicate diabetic ulcers [7], or traumatic wounds. Conditions in the differential diagnoses which need to be considered and include pyoderma gangrenosum, bacterial synergistic gangrene, and other infections by bacteria/fungi.

Histologically, the hyphae are broad with diameters ranging from 10 to 20 micrometers, non-septate, and branch at right angles [8]. They are often clearly seen on routine hematoxylin and eosin stains, and highlighted on periodic acid–Schiff and Grocott methenamine silver stains. Angioinvasion is a feature often seen associated with mucormycosis.

A multidisciplinary approach should be taken for optimal treatment of cutaneous mucormycosis. Successful treatment entails prompt correction of underlying metabolic abnormalities, judicious surgical debridement of devitalized tissue, early microbiological/ histopathological diagnosis, and targeted systemic antifungal therapy [9]. This patient initially was resistant to oral itraconazole and then fluconazole were chosen based on a previous report of treatment success with such a regime [10]. However, clinical improvement was limited and short-lived and he was re-admitted and eventually required intravenous amphotericin B and posaconazole therapy.

Conclusion

Mucormycosis can manifest as a variety of different symptoms in humans, particularly in immunocompromised patients and those with diabetes mellitus. Diabetes is a common predisposing condition for mucormycosis. Herein, we present an interesting case of cutaneous mucormycosis presenting as recurrent lower limb ulcers and cellulitis in an elderly patient with poorly controlled type 2 diabetes mellitus. He was initially treated with empiric oral itraconazole 200mg and then oral fluconazole 150mg but this only yielded partial improvement and patient was lost to follow up. He later presented again with worsening of lower limb ulceration and cellulitis and was thus started on i.v. amphotericin B and oral posaconazole. Mucormycosis requires aggressive treatment and a multidisciplinary approach should be taken for optimal treatment of cutaneous mucormycosis. Successful treatment entails prompt correction of underlying metabolic abnormalities, judicious surgical debridement of devitalised tissue, early microbiological/histopathological diagnosis, and targeted systemic antifungal therapy.

Potential conflicts of interest

The authors declare no conflicts of interest.

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