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RESEARCH

Successful treatment of cutaneous mucormycosis in a young diabetic with end-stage renal disease using combination systemic antifungal agents

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This article reports successful eradication of isolated cutaneous mucormycosis in a young poorly controlled type 1 diabetic patient with end-stage renal disease using a combination of systemic antifungal agents and aggressive surgical debridement.

Keywords: cutaneous mucormycosis, diabetic, echinocandin, fungal, liposomal amphotericin-B, Mucorales, polyene-caspofungin combination, posaconazole

Introduction

Mucormycosis is a rare life-threatening opportunistic infection caused by environmentally acquired fungi found in soil and decaying vegetation.[1] Diseases caused by fungi of the order Mucorales are mainly encountered in immunocompromised patients.[2] Among poorly controlled diabetic patients, specifically those who are in a persistent ketoacidotic state, rhinocerebral mucormycosis is the most common and devastating form of disease and often presents a rapidly progressive aggressive course. Ketone reductase, the enzyme present in Rhizopus organisms, allows for rapid growth in a high-glucose, acidotic environment.[3] Other manifestations of disease include pulmonary, gastrointestinal, cutaneous and disseminated mucormycosis.[4] Cutaneous mucormycosis is almost always associated with disruption of the dermis by trauma or wounds and direct inoculation of spores resulting in rapidly progressive locally invasive disease into the subcutaneous tissue, fascia, muscle and bone.[1] The angio-invasive nature of mucormycosis may also result in disseminated disease due to haematogenous spread. Of the different forms of mucormycosis, cutaneous mucormycosis has the lowest mortality rate (15%) and most favourable outcome.[1] Early recognition, expeditious surgical debridement, antifungal treatment and management of predisposing conditions is imperative to prevent disseminated disease and improve survival.[1] Most of the available literature supports the use of high-dose intravenous liposomal amphotericin-B (LAmB) as monotherapy and to date there have been no definitive guidelines regarding the use of systemic antifungal agents in cutaneous mucormycosis.[5] However, a few case studies have reported promising outcomes with combination antifungal therapy.[6] We report successful eradication of isolated cutaneous mucormycosis using a combination of systemic antifungal agents and aggressive surgical debridement.

Case report

A 21-year-old Caucasian female known to have poorly controlled type 1 diabetes mellitus diagnosed at age 2 and complicated by proliferative diabetic retinopathy, peripheral neuropathy, autonomic dysfunction and diabetic nephropathy presented with a history of allegedly sustaining a spider bite on her back one week prior to presentation. At presentation she also complained of headaches, backache, fever, dysuria and nausea. In the months leading to her presentation her physician had regularly attended her with regard to her poor glycaemic control and progressively worsening renal function. She had also been started on antihypertensive agents in January 2014.

At presentation her fasting blood sugar was 21 mmol/l. She had a wide anion gap metabolic acidosis due to renal impairment and sepsis, but no ketones were present on urine examination. She was haemodynamically stable. An area of well-demarcated necrotic tissue was present on her right flank at the site of the spider bite. A large erythematous area surrounded this (Figure 1). The patient and her family stated that the lesion progressed rapidly over a period of five days. On clinical suspicion of a necrotising process, surgical debridement was done immediately. Histopathological examination revealed broad aseptate hyphae, which branched at 90 degrees with Periodic Acid-Schiff (PAS) stain and fungal spores as well as foci of angioinvasion involving the deep dermis and subcutaneous tissue. These features were indicative of the presence of *Mucor* Spp (Figure 2). Tissue was also sent for fungal culture, but yielded no growth. The patient had, however, been on a broad-spectrum antibiotic for several days at the time of biopsy, which could have affected the culture yield.

In conjunction with the histopathologist and microbiologist a diagnosis of mucormycosis was made based on the typical histopathological features and appropriate clinical scenario. She was treated with an initial course of intravenous LAmB (5 mg/kg daily) in combination with intravenous caspofungin (70 mg on day one, followed by 50 mg daily) and aggressive repeated surgical debridement at days 23, 35 and 51 of intravenous LAmB therapy. A nephrologist was consulted prior to initiation of intravenous LAmB and caspofungin and the decision was made to start haemodialysis immediately in view of the presence of intractable metabolic acidosis, hyperkalaemia and oliguria. A number of tunnelled dialysis catheters were placed during her stay. Placement of a long-term dialysis catheter was delayed until confirmation of eradication of the cutaneous mucormycosis. The caspofungin was limited to a fourteen-day course. Daily Actisorb® silver 220 dressings were applied.

A decision was made to continue intravenous LAmB until the culture at the time of debridement showed no fungal growth. This resulted in a total of 56 days of intravenous LAmB (a cumulative dose of 16.8 g). A long-term dialysis catheter was inserted in

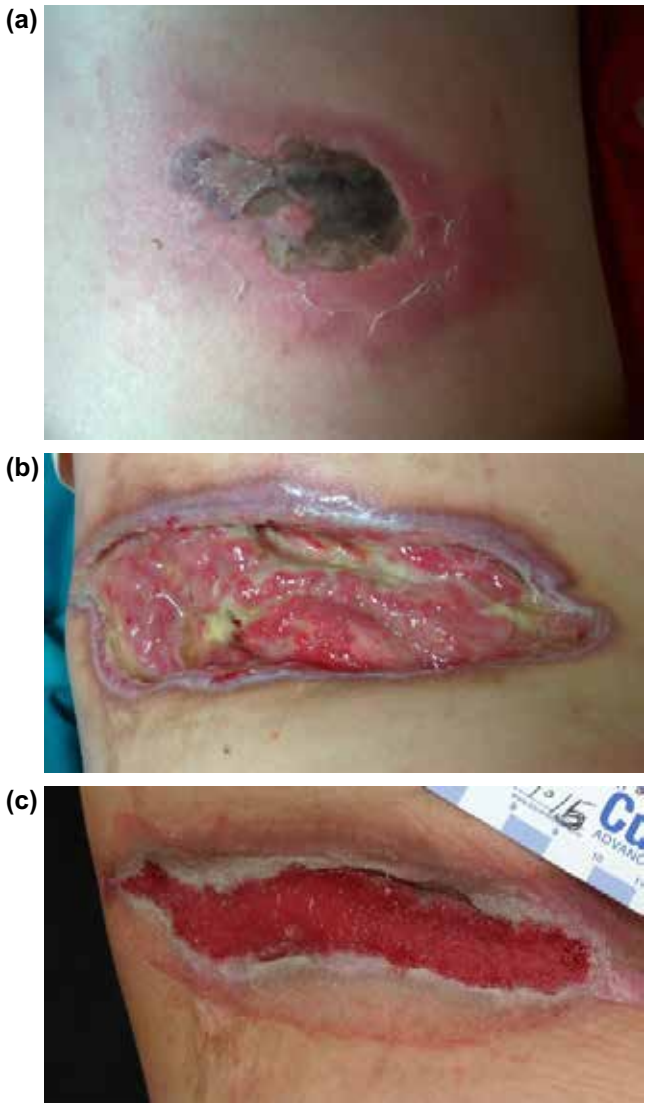

Figure 1: (a) A well-demarcated necrotic lesion on the right flank surrounded by an area of induration and erythema as captured 72 h after initial insult. (b) Lesion after second debridement showing signs of wound healing. However, hyphae still present on histopathological evaluation. (c) Wound demonstrating adequate granulation at eight weeks post-debridement.

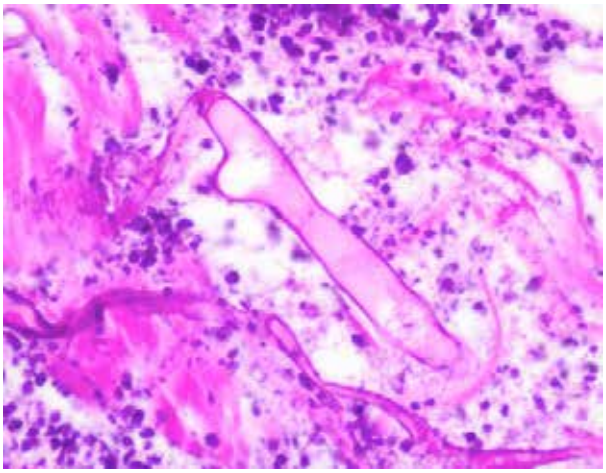

Figure 2: (a) Histological section stained with PAS highlights cell wall of mucormycosis within the tissue biopsy with necrosis of the tissue and degenerate inflammatory cells surrounding the hyphae (400x magnification).

the right subclavian vein after eradication of the mucormycosis. She was discharged at day 56. She is currently receiving haemodialysis as an out-patient. Wound care was also done on an out-patient basis. There was excellent clinical resolution and regular cultures obtained from the wound site at follow-up visits showed no fungal growth. Secondary wound closure was done after two months of oral posaconazole therapy.

Discussion

Mucormycosis is a relatively uncommon yet aggressive saprophytic opportunistic infection.[2] Clinical data are indicative that patients with phagocytic dysfunction are mostly at risk.[1] Phagocytes eliminate the hyphae and spores via oxygen-dependent and oxygen-independent mechanisms. Patient populations mostly affected are immunocompromised individuals such as diabetics, particularly those with ketoacidosis, patients with haematological malignancies, and those undergoing haemopoietic and solid organ transplantation.[1] Other risk factors include iron overload, treatment with iron chelators, trauma, burns, malnutrition and intravenous drug abuse.[3] The prevalence of mucormycosis is low in patients with AIDS, suggesting that neutrophils, but not necessarily T lymphocytes, play a role in the defence against fungal spores.[7] It has, however, infrequently been reported in immune-competent patients.[3]

The incidence of mucormycosis has increased over the past 20 years. This is most likely due to the fact that the population at risk for the development of mucormycosis is growing steadily.[1] Cutaneous mucormycosis occurs through direct inoculation of spores into damaged dermal barriers. It has been reported after surgical procedures, placement of intravenous catheters, tattoos, traumatic injuries, insect bites and burns. In our patient the site of entry was believed to be a spider bite.[1] It usually presents as an indurated area of cellulitis and rapidly progresses to an area of necrotic tissue due to ischaemia and tissue infarction as a result of the angioinvasive nature of the fungal hyphae. Although rarely encountered, cutaneous mucormycosis may lead to disseminated disease if not treated promptly.[8] The rapidly progressive course, poor glycaemic control and persistent acidotic state placed mucormycosis very high on our list of differential diagnoses. The diagnosis of mucormycosis is based on the histopathological demonstration of broad, aseptate hyphae that branch at right angles and the presence of angiolymphatic invasion resulting in tissue necrosis and infarction. Fungal cultures of specimens confirm the diagnosis. Some 70–80% of cases of mucormycosis are caused by *Mucor*, *Rhizopus* and *Lichtheimia* species of the order Mucorales.[2]

After correct identification of mucormycosis at histological examination, a thorough review of the available literature was undertaken to determine the best combination of systemic antifungal agents to use in conjunction with extensive surgical debridement and correction of underlying metabolic abnormalities in view of a possible favourable outcome with early aggressive management strategies in isolated cutaneous mucormycosis.[9] In the absence of clear guidelines regarding antifungal pharmacotherapy intravenous LAmB was chosen with caspofungin as adjunctive therapy. This decision was based on the following deciding factors: high-dose amphotericin B remains the drug of choice for mucormycosis.[6,10] The lipid formulation was chosen in view of the patient's poor renal function. Ibrahim et al. demonstrated a potential benefit of echinocandins in the treatment of Rhizopus oryzae, the most common cause of zygomycosis.[11] A standard 14-day course of caspofungin was given. The duration of LAmB administration was based on the

persistent presence of typical hyphae on histopathological examination. After no fungal elements were demonstrated at the time of final debridement on day 51 and fungal cultures were negative, the azole posaconazole was commenced and intravenous therapy discontinued on day 56. Oral posaconazole (400 mg daily) was given for 12 weeks. Although no clear guidelines exist regarding the use of posaconazole as step-down therapy in cutaneous mucormycosis, we based the duration of therapy on a retrospective study by Van Burik et al. reporting a 60% success rate when using posaconazole for 12 weeks in a patient with zygomycosis refractory to or intolerant of other antifungal agents.[1]

We conclude that the chosen combination of intravenous polyene-caspofungin therapy and aggressive surgical debridement followed by a further 12 weeks of oral posaconazole as step-down therapy successfully eradicated the cutaneous mucormycosis in our patient. Despite successful eradication we acknowledge the cost implications of this regimen. This is of particular concern in a resource-limited setting.

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