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Cutaneous mucormycosis in the immunocompromised host: An important cause of persistent post traumatic skin lesions

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ABSTRACT

We describe a case of a 31-year-old man with a history of ocular non-Hodgkin's lymphoma who presented with a large 12-cm non-resolving traumatic skin lesion on his back. Biopsy showed fungal elements, and on fungal culture, *Rhizopus arrhizus* (formerly *R. oryzae*) was isolated. Cutaneous mucormycosis is an important diagnostic consideration for a non-resolving skin lesion in an immunocompromised host. Early tissue sampling is key, and diagnostic certainty is particularly important because first line therapy, liposomal amphotericin B, has significant systemic toxicities, notable renal toxicity, and is therefore challenging to continue empirically. Surgical debridement is an integral part of therapy, highlighting the need for early multidisciplinary care in patients with cutaneous mucormycosis.

1. Introduction

Mucormycosis is an uncommon fungal infection caused by fungi belonging to the order Mucorales (phylum Mucoromycota). *Rhizopus arrhizus (previously known as R. oryzae)* is the most common organism isolated from patients with mucormycosis – found in about 70% of cases [1]. Intact mucosal and endothelial barriers are key in protecting against invasion; therefore, the disruption of these barriers is important in fungal pathogenesis. In particular, trauma to the skin leading to local breakdown is a risk factor for cutaneous mucormycosis, usually but not always in the immunocompromised individual. Cutaneous mucormycosis is the third most common type after pulmonary and rhinocerebral [2] and is responsible for 10-19% of all mucormycosis [3].

Immunocompromising conditions such as malignancy, organ transplantation, chemotherapy, hematologic disorders, neutropenia and treatment with corticosteroids increase the risk of developing mucormycosis [4]. Patients experiencing iron overload states or taking deferoxamine are particularly susceptible to mucoralean fungi, which possess virulence factors that help them obtain iron from their hosts. Iron is essential to cellular growth and development. In situations such as the ketoacidosis associated with decompensated diabetes, acidic environments increase iron availability and thus increase patient susceptibility. Deferoxamine, used in patients with iron overload, seems to be assimilated as a xenosiderophore by mucoralean opportunists, a unique compatibility not seen in other fungal opportunists such as members of the genera *Candida* and *Aspergillus* [5].

2. Case

A 31-year-old man with history of ocular non-Hodgkin's lymphoma presented with a non-resolving traumatic skin lesion on his back, about a week after a traumatic incident. He had previously received radiotherapy for his malignancy as well as chemotherapy (CHOP regimen: cyclophosphamide, doxorubicin, vincristine, prednisone) but was off all therapy at the time of presentation. However, he was not yet considered in remission from his malignancy and was neutropenic on admission to hospital (absolute neutrophil count of 0.16 x 10^9 per litre).The patient had sustained trauma to his back, he had been kicked and the shoe had gone through his clothing, creating a laceration and broken skin. He had then fallen to the sidewalk in a way that caused the laceration to contact

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the ground. He presented (on day 0) with a non-resolving skin lesion on his back that had grown from 10 to 12 cm in diameter, despite topical care and antibiotherapy targeting skin flora. He did not have any other skin lesions on presentation. Biopsy showed fungal elements, and on fungal culture, *Rhizopus arrhizus* was isolated. Fungal identification was confirmed with DNA analysis of the ribosomal internal transcribed spacer region. The patient was diagnosed with cutaneous mucormycosis. He was initiated on liposomal amphotericin B but within 5 days had developed *Pseudomonas aeruginosa* bacteremia that was ultimately fatal. He died within 2 days of rapid decompensation, which is likely the time at which he became bacteremic. An autopsy did not reveal involvement of any other organ system but the skin at the site of inoculation. (seeFigs. 1–3).

3. Discussion

Our patient presented with primary cutaneous mucormycosis. Cutaneous mucormycosis can occur in both immunocompetent and immunocompromised patients. It can be primary, often due to trauma leading to skin breakdown and inoculation of the fungal spores into the dermis, or secondary, acquired through dissemination from another primary site [5]. With respect to etiology, primary cutaneous mucormycosis has been associated with traumatic injuries (70%), surgery (15%), burns (3%), and hospital materials such as intravenous lines, adhesive tapes, wooden tongue depressors and linens [3].

Cutaneous mucormycosis usually appears as a single, painful, erythematous area. In patients with open wounds, tissue necrosis may occur. Dissemination and deep tissue involvement are unusual complications [6]. Primary cutaneous mucormycosis is reported to have a dissemination rate of approximately 20%, while the incidence of secondary cutaneous involvement from another source is only 3%. Mortality rates are circa 10% with cutaneous mucormycosis when dissemination is not present as opposed to 94% when it is present [7].

In patients with immune compromise, such as our patient, there is often an absence or dysfunction of neutrophils, or there is some other type of immunoregulatory dysfunction conducive to cutaneous mucormycosis. Our patient was neutropenic on presentation and was also not considered in remission from his malignancy. In patients with diabetes mellitus, locally invasive infection is likely associated with incidental inoculation into skin and deep soft tissue, coupled with poor wound healing [8].

In the immunocompetent patient, inoculation is usually due to trauma, and, in addition, local and systemic immune impairment are likely at play. Local neutrophil dysfunction is key through mechanisms such as impaired host neutrophil chemotaxis and dysfunctional pH control of phagolysosomes [8].

In both immunocompromised and immunocompetent hosts who have experienced trauma, there is often a direct injury leading to necrosis and impaired blood flow, along with inoculation of foreign material such as soil. The introduced Mucoralean fungus found in soil then causes cutaneous mucormycosis and establish a biofilm that can attract bacteria and increase the likelihood of local inflammation and infection [8]. The fungus invades the walls of blood vessels and proliferates, leading to thrombosis and then to infarction of the vessel involved, reducing blood supply into an already inflamed and infected lesion, reducing the likelihood of healing [9] and leading to tissue necrosis [4].

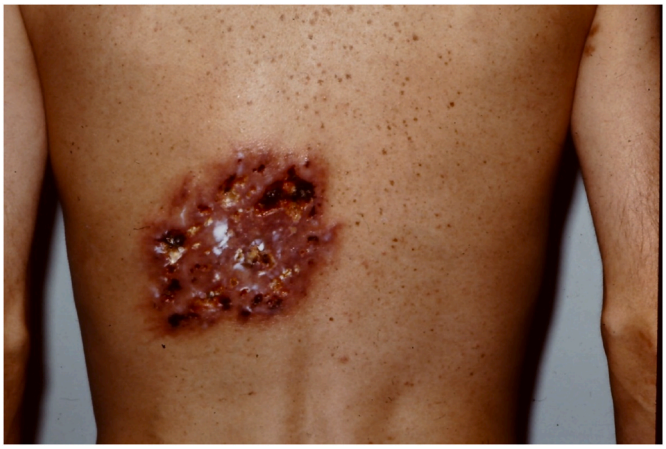

Fig. 1. A 12cm skin lesions secondary to *Rhizopus arrhizus*.

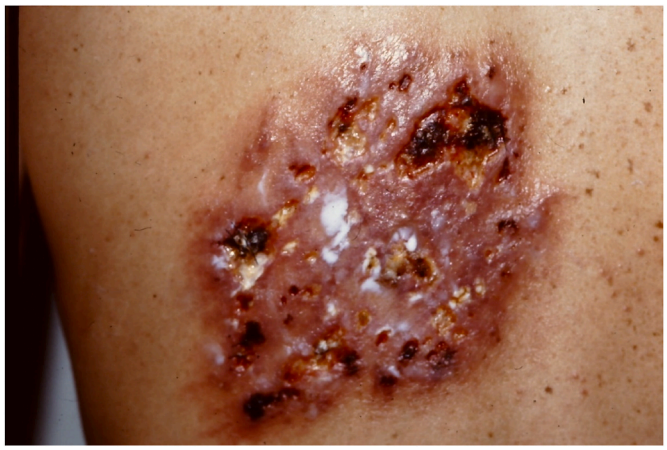

Fig. 2. A 12cm skin lesions secondary to *Rhizopus arrhizus* – A close-up photograph.

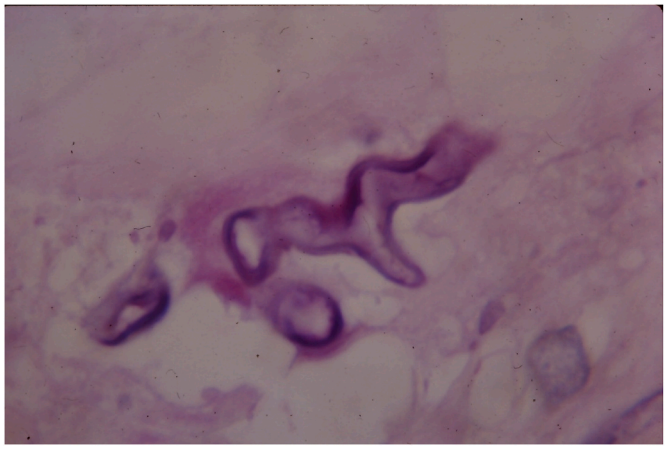

Fig. 3. Microscopy of skin tissue biopsy: broad irregular hyphal fragments, no septae visible. Hematoxylin and eosin stain.

Surgical debridement and antifungal drugs are the cornerstones of therapy for cutaneous mucormycosis. Liposomal amphotericin B is strongly recommended as first line therapy, with renal toxicity an important possible side effect. Use of amphotericin B deoxycholate is discouraged due to increased risk of side effects. Isavuconazole is an alternative first line therapy for which there is a moderate recommendation, and posaconazole may also be used with a weaker recommendation, although both drugs are recommended for first line salvage therapy. No definitive data are available for combination antifungal therapy. Duration of therapy is unclear but is weeks to months [9,10].

This case highlights an important diagnostic consideration in all cases where there is a non-resolving skin lesion in an immunocompromised patient. Key learning points include broadening the differential diagnosis early on in such patients, recognizing the importance of getting a tissue sample to guide diagnosis and treatment, and rapid surgical debridement as the cornerstone of therapy.

Diagnostic certainty is particularly important in mucormycosis where the first line therapy is the relatively uncommonly used liposomal amphotericin B, which is known to have significant systemic toxicities and is therefore challenging to continue empirically for more than a few days.

Unfortunately, our patient died 5 days after presentation to hospital, before significant effect was seen from his antifungal therapy and before a discussion regarding debridement could be had with the appropriate surgical service. His significant immune compromise from his underlying malignancy and subsequent neutrophil dysfunction likely contributed to his unfavourable outcome.

Funding source

Nothing to declare.

Consent

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Note: the patient passed away over 20 years ago and unfortunately there was no available contact info for his family; For this reason we were unable to obtain written consent for this case but felt that it was significant enough that it was worth writing up despite of the fact that no formal consent could be obtained.

Declaration of competing interest

None to declare.

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