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Cutaneous mucormycosis with suspected dissemination in a patient with metastatic adrenocortical carcinoma

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ABSTRACT

Mucormycosis is a frequently lethal fungal infection that most commonly affects patients with poorly controlled diabetes or other immunosuppressed states. We report the case of a suspected disseminated *Rhizopus* infection in a patient who was pursuing naturopathic treatment including mud baths for metastatic adrenocortical carcinoma. He was empirically treated with liposomal amphotericin B but opted to stop treatment following multi-organ failure. The patient passed away on the tenth day of his hospital admission.

1. Introduction

Mucormycosis is a rare infection caused by fungi of the order Mucorales and class Zygomycetes that most commonly occurs in immunocompromised patients [1]. Most human infections are due to *Rhizopus*, *Mucor*, or *Lichtheimia* [2]. Infection can involve the skin, brain, lungs, and vascular system, often proving rapidly fatal [3]. The most common disease presentation is rhino-orbital-cerebral infection, which occurs after inhalation of fungal spores [4]. Cutaneous disease is often caused by trauma and is less frequently associated with disseminated infection. Lesions generally present as indurated plaques that may transform into tender nodules, ulcers, or necrotic eschars [5]. Mucormycosis is treated with surgical debridement and amphotericin B, although survival rates are low for disseminated infection [6]. In immunocompromised patients, lethal outcomes can occur over the course of days despite adequate treatment [7]. Little is known regarding the presentation and clinical course of mucormycosis in immunocompetent patients. This case emphasizes the importance of maintaining a high index of suspicion for mucormycosis early in the disease course, even despite the absence of classic signs of infection such as fever.

2. Case presentation

An afebrile 48-year-old man with adrenocortical carcinoma complicated by hepatic and peritoneal metastases was admitted to the hospital (day 0) for acute kidney injury following high dose vitamin C supplementation at a naturopathic treatment facility. The patient had previously undergone chemotherapy, partial adrenalectomy, and radiation therapy with continued disease progression and was not on active therapy at the time of presentation. His last chemotherapy session took place over one year ago. The patient was receiving valacyclovir for a dermatomal rash on his right flank that had been diagnosed at an outside hospital as a herpes zoster infection, although no vesicular lesions were reported and there had been no improvement in the rash after initiation of antiviral therapy. On admission, the patient was found to have two 3 cm ulcers with central eschars and peripheral retiform purpura on the right flank (Fig. 1). He also presented with multiple annular red to slightly golden-brown patches without overlying scale on bilateral thighs and nonpalpable petechiae on bilateral lower legs.

Initial differential diagnosis included calciphylaxis, cryoglobulinemia, ecthyma, and vasculitis. The following laboratory studies were normal or not clinically significant: rheumatoid factor, ANCA, antiphospholipid antibodies, cryoglobulins, protein C and S, C3/C4, CH50, ANA, ENA panel, and SSA. Results from a punch biopsy of the

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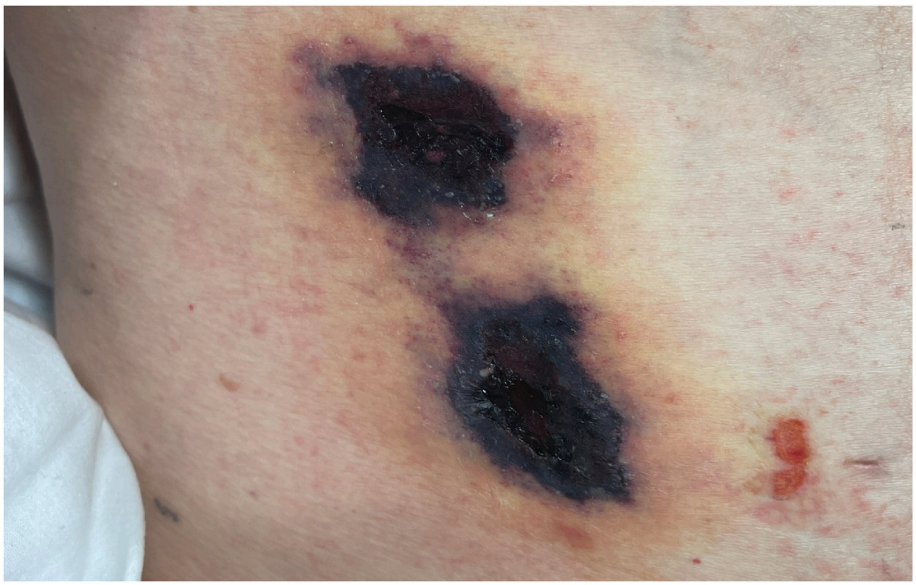

Fig. 1. Two 3 cm ulcers with central eschars and peripheral retiform purpura on the right flank of the patient on his first day of hospital admission.

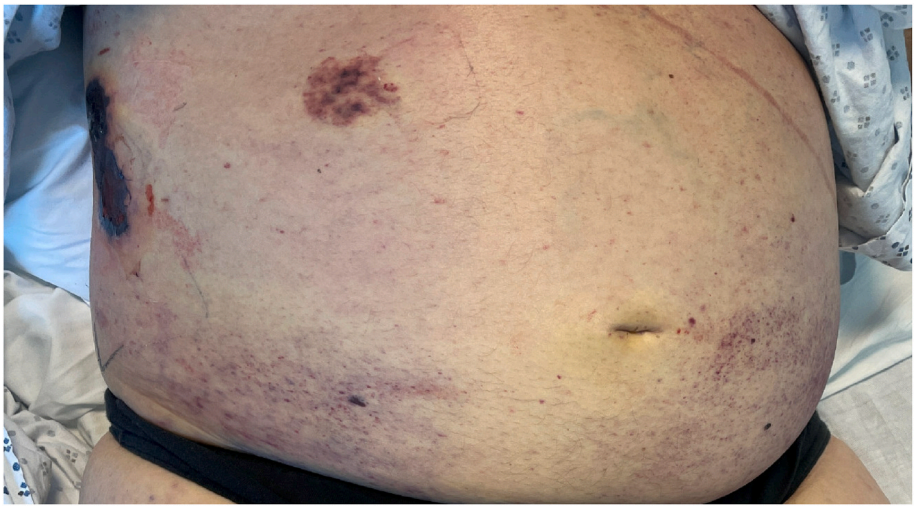

Fig. 2. Abdomen of the patient on his second day of hospital admission, with new 3 × 3 cm purpuric lesion on his right upper abdomen and magenta to purple macules and patches across his lower abdomen, raising suspicion for disseminated mucormycosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

right flank revealed deep tissue-invasive fungal forms with positive periodic acid-Schiff (PAS) staining, suspicious for angioinvasive disease (Figs. 3 and 4). The next day (day +1), the patient was found to have a new 3 × 3 cm purpuric lesion on his right upper abdomen (Fig. 2), raising concern for disseminated fungal infection. Repeat punch biopsies of the existing right flank and left leg lesions were obtained for fungal culture. The patient was empirically treated with intravenous liposomal amphotericin B 5 mg/kg daily for presumed disseminated fungal infection. Over the next three days (day +2, day +3, day +4), there was rapid progression of his cutaneous disease with new diffuse, and in some areas confluent, magenta to purple macules and patches across his lower abdomen. Although a serum (1->3)-β-D-glucan assay was positive at greater than 500 pg/mL (normal: <60 pg/mL), percutaneous blood cultures and *Aspergillus* antigen testing were negative. This was likely a false positive serum (1->3)-β-D-glucan assay, possibly due to albumin infusions that the patient had been receiving for his acute kidney injury. The tissue culture from the right flank lesion identified *Rhizopus* species. Additional biopsies and surgical debridement were deferred as these were felt to be futile interventions in the setting of suspected disseminated infection. The patient also had pulmonary infiltrates on chest CT and a worsening acute kidney injury, possibly related to mucormycosis or metastatic disease.

Due to multiorgan failure in the setting of suspected disseminated *Rhizopus* infection and metastatic adrenocortical carcinoma, further diagnostics to explore the extent of mucormycosis were declined. The patient opted to pursue no additional treatment and died on the tenth hospital day (day +10). Mud baths that the patient received as part of naturopathic treatment were the suspected source of *Rhizopus*.

3. Discussion

Fungi of the order Mucorales are identified histologically by their broad and irregularly branching hyphae with few septations, as well as PAS positive staining [8]. Zygomycetes characteristically produce very low levels of β-D glucan and galactomannan, unlike *Aspergillus*. The fungi causing mucormycosis are ubiquitous in soil and decaying

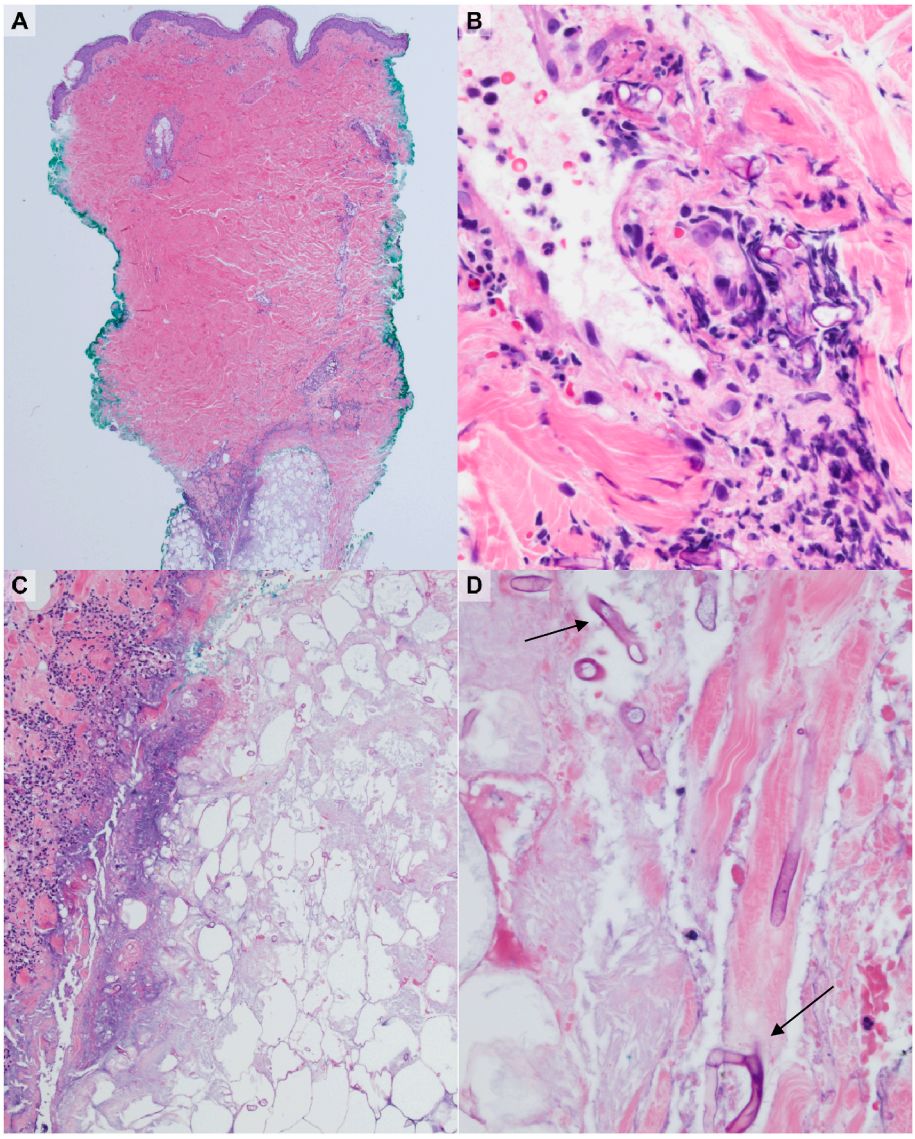

Fig. 3. Punch biopsy of the flank showing minimal superficial inflammation but prominent inflammation and necrosis of the subcutis (A, H&E, 20×). High-power image of a mid-dermal vessel with associated mixed inflammation and fungal forms in the surrounding tissue and abutting the endothelium (B, H&E, 400×). Necrotic subcutaneous tissue with associated acute inflammation and numerous broad, pauciseptate fungal forms (H&E; C, 100×; D, 400×).

vegetation [9].

Rhizopus is the most common cause of mucormycosis, which frequently affects patients with burn wounds, COVID-19 or HIV infection, hematologic malignancies, iron overload, organ transplantation, poorly controlled diabetes mellitus, and other immunosuppressed states [10]. Disseminated infection rarely occurs in immunocompetent patients, who are more likely to have cutaneous, pulmonary, or rhino-orbital-cerebral disease [11]. Cutaneous mucormycosis is often caused by direct trauma and uptake of spores, with subsequent dissemination occurring due to angioinvasive disease. Manifestations of mucormycosis vary depending on the organ systems involved, but generally include nonspecific symptoms such as abdominal pain, cough, or headache. Tissue biopsy is required for diagnosis, although treatment is often started empirically [12].

Classic signs of infection such as fever may be absent in mucormycosis [13]. Our patient remained afebrile throughout his admission, emphasizing the importance of high clinical suspicion for fungal infection in patients with rapidly progressing cutaneous lesions. Early biopsy of the lesion allowed for prompt diagnosis and empiric therapy, although not all biopsies were positive for *Rhizopus*, further highlighting the clinical complexity of the case. Amphotericin B and surgical debridement for non-disseminated disease are currently considered the gold standard of treatment. Incidence and mortality rates for mucormycosis, especially disseminated infection, remain elevated despite the development of novel antifungal therapies [14].

Rhizopus species grow rapidly and release large numbers of airborne spores. The most likely source of infection in our patient were the mud baths that he had taken as part of his naturopathic treatments. The patient had been receiving serial paracentesis for ascites, and it is plausible that these small injuries to the skin may have served as a portal of entry for the organism.

Ethical form

Please note that this journal requires full disclosure of all sources of funding and potential conflicts of interest. The journal also requires a declaration that the author(s) have obtained written and signed consent to publish the case report/case series from the patient(s) or legal guardian(s).

The statements on funding, conflict of interest and consent need to be

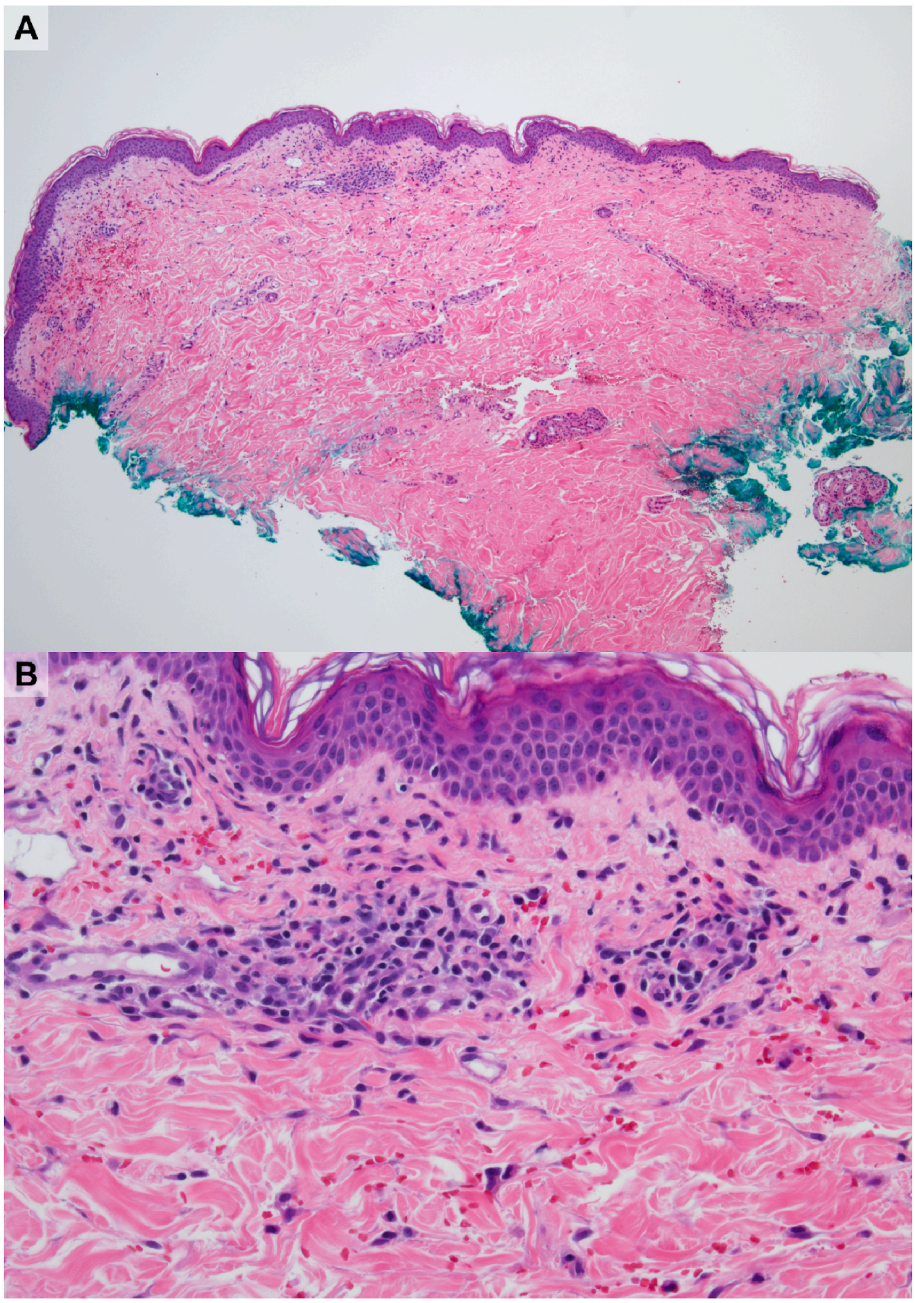

Fig. 4. Punch biopsy of the left leg showing superficial perivascular lymphohistiocytic inflammation and associated extravasated erythrocytes, consistent with a pigmented purpuric dermatosis, possibly related to the patient's thrombocytopenia. No fungal forms were identified (H&E, A, 40×; B, 200×).

submitted via our Ethical Form that can be downloaded from the submission site www.ees.elsevier.com/mmcr. **Please note that your manuscript will not be considered for publication until the signed Ethical Form has been received.**

CRediT authorship contribution statement

Nakul Dar: Conceptualization, Writing – original draft. **Abigail Wills:** Writing – review & editing. **Scott Berg:** Writing – review & editing. **Sarah E. Gradecki:** Data curation, Visualization. **Thomas G. Cropley:** Supervision, Writing – review & editing. **Darren Guffey:** Conceptualization, Writing – review & editing.

Declaration of competing interest

There are none.

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Nil.

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