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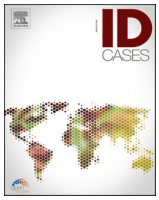

Case report

An unexpected case of disseminated mucormycosis following pacemaker placement and brief course of oral corticosteroids

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ABSTRACT

Mucormycosis is a rare opportunistic fungal infection with a high degree of morbidity and mortality. It classically presents with rapidly progressing, necrotic rhinocerebral mucocutaneous lesions in the setting of an immunocompromised host, especially with concomitant uncontrolled diabetes. We report the case of a 67-year-old man with well-controlled non-insulin dependent diabetes and brief steroid exposure who presented in sepsis with a tender posterior shoulder skin lesion. The initial lesion enlarged and progressed over several days, developing central areas of ecchymosis and bullae, with several other large lesions appearing at various distant sites. He also experienced an array of systemic symptoms, including fever, malaise, weakness, and acute encephalopathy. A diagnosis of mucor was made by histopathological examination of the initial skin lesion. Despite initiation of amphotericin B and aggressive surgical debridement including transfer to specialist tertiary burn center, the patient passed away less than a week after definitive diagnosis. This is a unique case of disseminated mucormycosis given his lack of chronic immunosuppression or uncontrolled diabetes, and with no risk factors for inoculation except for pacemaker placement 2 months prior to admission. The case highlights the importance of considering mucormycosis in the early differential diagnosis of rapidly progressing skin lesions, as rapid detection and treatment is critical to mitigate the deadly effects of this fast-moving fatal fungus. Moreover, the case serves as a testament to the unpredictable progression of disseminated disease, while also demonstrating an unusual potential mode of introduction and a rare but fatal consequence of prescribing corticosteroids in an infected host.

Introduction

Mucor, also known as 'black mold' or 'bread mold', is an opportunistic pathogenic fungus within the class of zygomycetes that is ubiquitously found in animal feces, decaying food, and most commonly soil [1]. Inhalation of airborne spores classically leads to rhinocerebral mucormycoses, which is the most common anatomic location for infection especially in diabetic patients [1,2]. Pulmonary infection is the second most common presentation of mucormycosis, whereas gastrointestinal, cutaneous, and disseminated mucor infections are rarely observed [2]. General risk factors include immunocompromising conditions such as uncontrolled diabetes, hematopoietic stem cell transplant, solid organ transplant, chronic steroid exposure, persistent neutropenia, iron chelation therapy, intravenous drug use, or malnourishment [3]. In fact, the combination of poorly controlled diabetes and prolonged steroid therapy during the COVID-19 pandemic has led to a recent surge of rhinocerebral mucormycosis cases in India, increasing the relevance of clinician awareness of this disease entity amidst a global pandemic [4]. Burns, surgical wounds, or skin trauma typically precede a cutaneous infection, while inhalation of environmental spores may lead to pulmonary disease [2]. Following inoculation and proliferation, angioinvasion rapidly leads to thrombosis and tissue necrosis, if not further dissemination via hematogenous spread [4,6].

The prognosis of mucormycosis infection is highly contingent upon prompt diagnosis, which is usually made by visualization of their distinct broad hyphae with irregular septate branching on histopathology [1–3]. They are easily differentiated from the more common Aspergillus mold, which has narrow hyphae, regular branching, and many septations. Culture is typically not clinically relevant given the speed of disease progression and tests such as beta-D-glucan or galactomannan have no role in detection of mucor. While DNA-based methods may offer some promise for future diagnostics, there are

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currently no widely available serologic standards for diagnosing mucormycosis [5,6]. Pharmacologic treatment options include liposomal amphotericin B, posaconazole, or isavuconazole, although some data suggests voriconazole may play a role in increasing the risk of disseminated mucormycosis [7]. However, most cases fail to respond to antimicrobial therapy alone, with emergent and aggressive surgical debridement of infectious foci serves as the mainstay of therapeutic intervention. Even in disseminated disease, localized mucocutaneous lesions require elaborate surgical debridement for source control, often resulting in significant deformity and disfigurement. Unsurprisingly, this imparts a relatively high mortality rate of 46–50 % for rhinocerebral disease, which approaches an alarming 96 % in disseminated disease [2].

In this report, we present a unique case of an ostensibly immunocompetent patient with a myriad of nonspecific symptoms including malaise, pain, diarrhea, and worsening encephalopathy, noted for multiple large, rapidly evolving skin lesions. The patient's overall condition declines as the lesions progress and spread to additional distant locations before a diagnosis of mucormycosis is made.

Case presentation

A 67-year-old man with a history of chronic obstructive pulmonary disease (COPD), type 2 non-insulin-dependent diabetes, and stage 3B chronic kidney disease (CKD3B) presents with sepsis following a three-week history of upper respiratory and sinus symptoms. His review of systems is positive for malaise, productive cough, abdominal pain, nasal congestion, headache, back pain, nausea, vomiting, diarrhea, fevers, and mild unintentional weight loss. A week prior, he presented with sinus symptoms that failed to improve despite a seven-day course of levofloxacin and prednisone for presumed acute bacterial sinusitis. He has no burns, trauma, recent travel, deferoxamine use, solid organ/stem cell transplant, prolonged steroid exposure, intravenous drug use, history of malignancy, unusual hobbies, and no environmental or occupational exposures. His labs on admission were noted for white blood cell (WBC) count of 19,500/mm3 (86.9% polymorphonuclear leukocytes), erythrocyte sedimentation rate (ESR) is 70 (ref range 0–15), lactate of 1.7, creatinine of 2.6, hemoglobin A1c of 7.3%, and glucose is 316. Physical examination is remarkable for tenderness and erythema related to large (16 cm × 13 cm), well demarcated lesion of the left posterior shoulder (Fig. 1). A CT scan of his chest reveals mild adenopathy with a lesion in the left suprahilar region (Fig. 4). Vancomycin and meropenem are started empirically with IV fluids, with a relatively broad differential diagnosis that includes *Clostridioides difficile*, acute COPD exacerbation, osteomyelitis, and various other bacterial skin or soft tissue infections. Infectious disease specialists are consulted at this time for recommendations for a suspected infectious process.

Over the next two days, the patient remains febrile with complaints of malaise and generalized weakness, and progressively worsening encephalopathy. Of note, his skin lesion enlarges centrifugally, developing an indurated and ecchymotic appearance. New skin lesions develop on the right flank, left flank (Fig. 2), right thigh (Fig. 3), and right lower abdomen, which are similarly tender to palpation, enlarging and noted for development of bullae in some lesions. Given the appearance of his skin lesions and new concern for possible vasculitis, he is given a one-time dose of IV methylprednisolone and a punch biopsy is performed for histopathological analysis. Pulmonology is also consulted and plans for tentative bronchoscopy to evaluate the hilar lesion seen on CT imaging. Meanwhile, blood cultures remain negative at 72 h and a transthoracic echocardiogram reveals mild reduction of left ventricular systolic function (EF 40–45 %), with no valvular abnormalities or vegetations. His acute kidney injury fails to improve despite aggressive intravenous fluid resuscitation throughout his admission.

By day four, the lack of response to aggressive broad-spectrum antibiotics narrows the differential diagnosis to include Sweet's syndrome, calciphylaxis, and disseminated fungal infection. He is started on IV voriconazole before preliminary hematoxylin and eosin stain from a shoulder punch biopsy shows broad, non-septate hyphae with right-angle branching, consistent with mucor (Fig. 5). This includes visualization of hyphae within lymphovascular structures, which supports the argument for disseminated disease (Fig. 6). Infectious disease immediately initiates amphotericin B and general surgery is consulted for emergent surgical debridement of multiple large lesions in various anatomic locations (right flank 16 × 13 × 5 cm, right thigh 15 × 20 × 3 cm, right abdomen 15 × 20 × 2 cm, left shoulder 16 × 13 × 2 cm, and left flank 18 × 13 × 3 cm), many of which penetrate deep into underlying fascia and skeletal muscle. Unfortunately, comprehensive CT imaging to evaluate for occult lesions was not able to be performed prior to surgical intervention. Immediately following surgery, he requires pressor support and mechanical ventilation in the ICU prior to transfer to the nearest burn center for further management. Over the next 6 days he undergoes two additional surgical debridements for attempted source control with continued administration of IV antifungal agents. He ultimately expires secondary to hemodynamic instability and general failure to improve despite all attempted resuscitative measures.

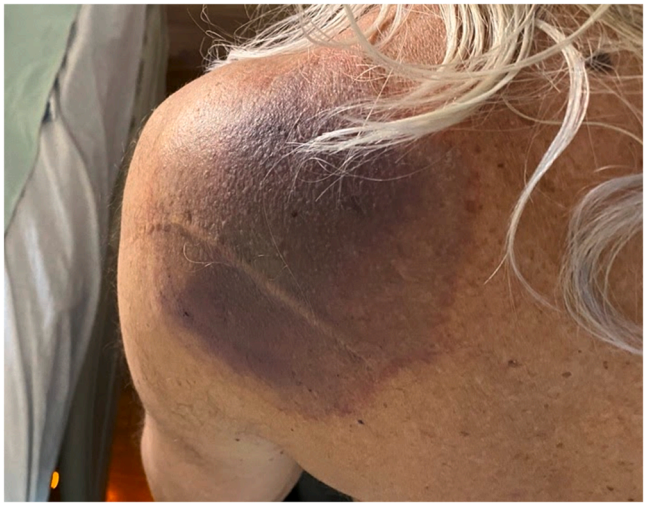

Fig. 1. Photo taken on Day 3 of hospitalization illustrating left shoulder lesion. The erythematous rim extended centrifugally with new development of internal ecchymosis.

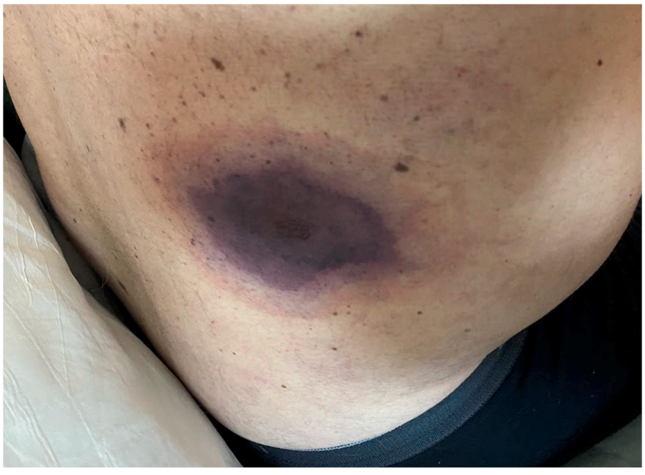

Fig. 2. Photo of right flank was also taken on Day 3. Note the outer erythematous rim with internal ecchymosis and a single bullae. Moreso than the shoulder lesion, this lesion highlights classic necrosis seen with cutaneous mucormycosis.

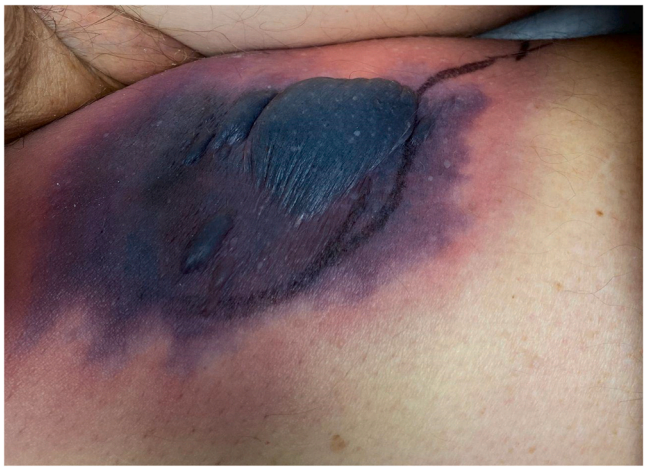

Fig. 3. : Photo of ecchymotic lesion located in right goin/thigh area on day 3 of admission. Note the development of bullae and the rapid spreading of lesion beyond the boundary of initial line of demarcation.

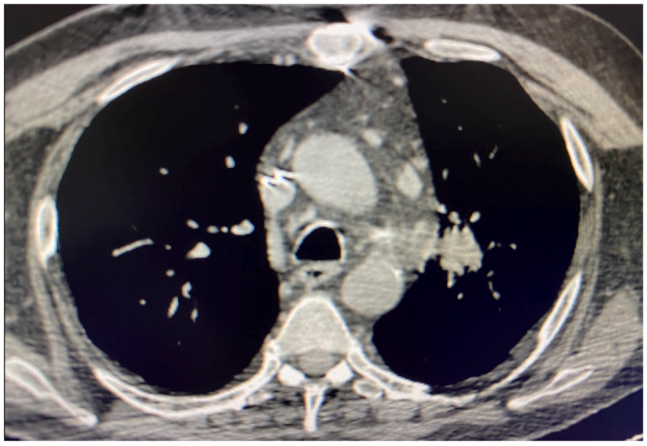

Fig. 4. : CT scan of the chest on admission, demonstrating an abnormal airspace density in the left suprahilar region, concerning for either inflammatory or neoplastic etiology. The lesion is occult on plain chest radiograph.

Discussion

The high mortality associated with disseminated mucormycosis necessitates a high clinical suspicion and rapid diagnosis. It is worth noting that while fungal skin infections are common, these are typically due to dermatophytes and candida, which have a low mortality and generally remain localized and slow progressing. This case reinforces the notion that mucor is not necessarily a disease of the overtly or chronically immunocompromised patient. One could perhaps make an argument that the patient experienced a relatively mild degree of immunosuppression following his course of corticosteroids. However, this was a relatively brief course of therapy including only five-days of oral prednisone in the outpatient setting, with a one-time dose of IV methylprednisolone on the third day of admission. Moreover, this is a patient with stable glycemic control, adequate nutritional status, and relatively limited risk for developing disseminated disease overall.

Ultimately, this raises the question of exactly what mode of inoculation may have occurred that could progress to disseminated disease? On further questioning to explore this following his death, his wife mentioned that he had underwent placement of implanted pacemaker device approximately 2 months prior to his original upper respiratory symptoms. In the absence of any other identifiable inoculation event, it is possible that mucor was introduced perioperatively at the time of his

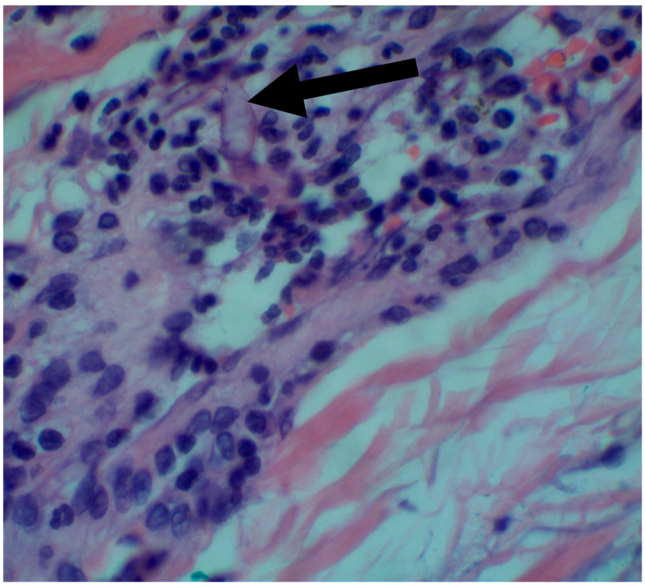

Fig. 5. : This H&E slide of a skin biopsy demonstrates the classic broad and non-septate hyphae of mucor (arrow). The approximately 90-degree angle of branching helps differentiate it from the acute branching of aspergillus.

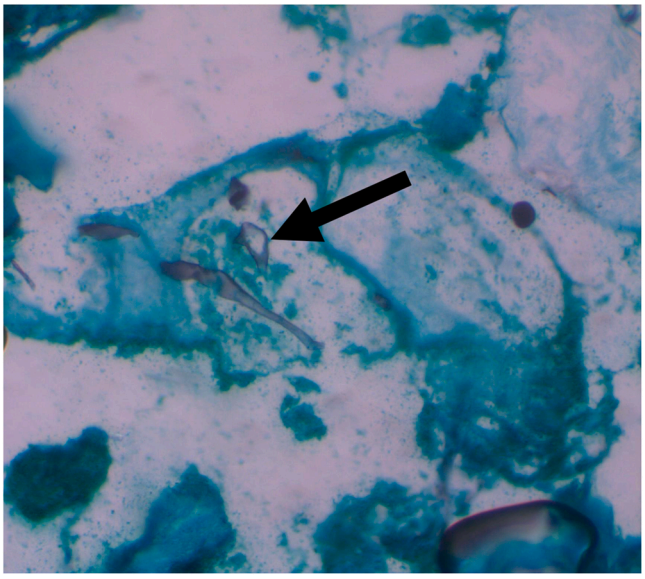

Fig. 6. : The Grocott Methenamine-Silver Nitrate Stain (GMS) is useful in staining carbohydrates and thus highlights the polysaccharide-rich cell walls of fungi. This image was also obtained by skin biopsy and shows a mucor hypha en face (arrow) within a lymphovascular vessel.

device placement, followed by gradual hematologic seeding and acute proliferation when he was treated with steroids for his sinus complaints. Alternatively, it was speculated that a lung nodule was the potential primary source of infection, although he was not able to undergo bronchoscopy and biopsy during his hospitalization to confirm this. In hindsight, the rapid progression of his skin lesions despite broad-spectrum antibiotics could have warranted earlier tissue biopsy. Instead, brief exposure to IV corticosteroids was recommended due to concern for an autoimmune process, which likely only led to mild immunosuppression and hyperglycemia, both of which would encourage fungal proliferation. In retrospect, the patient likely would have benefitted from tissue biopsy on admission, especially given the ease of the procedure and low likelihood of complications.

Unfortunately, the rare nature of disseminated disease combined with its atypical presentation led to a brief and potentially fatal delay in diagnosis and appropriate care. We hope to raise the index of suspicion for this disease entity, especially given the increased incidence of both localized and disseminated disease during the COVID19 pandemic [8].

Conclusions

Disseminated mucormycosis is a relatively uncommon clinical entity with an extremely rapid disease course and exquisitely high mortality. The success of clinical intervention is highly contingent upon prompt recognition and emergent surgical intervention, even when combined with the most aggressive antifungal therapies available. While classically associated with poorly controlled diabetics or immunocompromised individuals (i.e., transplant recipients, chronic steroid use, etc.) a high index of suspicion is required to facilitate prompt recognition and intervention. Moreover, it should be considered as an important part of the differential diagnosis for any patient presenting with sepsis in the setting of rapidly progressing mucocutaneous lesions that fail to improve despite initiation of aggressive broad-spectrum antibacterial coverage, even in the absence of identifiable risk factors or exposures. Early tissue biopsy and recognition of pathognomonic histopathology is the most direct path to diagnosis, especially given that until necrosis occurs lesions may resemble noninfectious causes such as vasculitis, which would be managed counterproductively with systemic corticosteroids. Although disseminated mucormycosis is exceedingly rare, giving passing thought to this fast-spreading and highly deadly fungal infection is imperative, even when investigating other more common etiologies. This case also exemplifies a rare but potentially fatal justification for judicious utilization of corticosteroids and immunosuppressant therapy, an argument that is increasingly pertinent given the increased utilization of these agents amidst the global COVID19 pandemic.

CRediT authorship contribution statement

Chadley Froes: Conceptualization, Writing - original draft, review & editing. Data curation. **Matthew Gellatly**: Data curation, Writing – original draft. **Brian Watson**: Data curation, Writing – review.

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Consent

Verbal and written informed consent were obtained from the patient 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.

Guarantor

Chadley Froes.

Conflicts of interest

None to disclose.

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