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Case report

Successful treatment of rhino-cerebral mucormycosis with dual antifungal therapy and minimal surgical debridement

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ABSTRACT

The authors report the case of a 42-year-old female with history of type I diabetes mellitus and recent episode of diabetic ketoacidosis who presented with symptoms of epistaxis, gastrointestinal upset, hyperglycemia, confusion, and a cough. She was found to have rhino-cerebral mucormycosis with associated multi-focal strokes and a left internal carotid artery pseudoaneurysm. Her infection was successfully treated with dual-antifungal therapy consisting of liposomal amphotericin B and isavuconazole, and required only minimal surgical debridement.

Introduction

Mucormycosis is an invasive fungal infection most often caused by the pathogens of the *Rhizopus* genus which thrive in decaying compost and soil [1–5]. Rhino-orbito-cerebral is the most common form of infection, occurring in almost 50% of cases [5–7]. Diagnosis is established using histological biopsy, often in conjunction with nasal endoscopy and surgical debridement, showing fungal hyphae at right angles [8,9]. Early diagnosis is essential as invasive mucormycosis entails mortality rates around 50%, which can rise to 90% when the infection is intracranial or disseminated [10–13]. Herein, we present the case of a 42-year-old female found to have rhino-cerebral mucormycosis who was treated with primarily medical therapy, including dual-antifungal treatment with liposomal amphotericin B and isavuconazole, with only minimal surgical debridement, as well as improved diabetes mellitus control.

Case presentation

A 42-year-old female with type I diabetes mellitus (most recent hemoglobin A1c of 14.3%, three-months prior to sentinel admission) presented to our emergency department with symptoms of epistaxis, diarrhea, nausea, vomiting, hyperglycemia (blood glucose 256 mg/dL), and a one-month long cough.

She initially presented three-months prior for management of diabetic ketoacidosis accompanied by several weeks of sinus pressure. At that time, computed tomography (CT) scan of the head and neck with contrast showed edema within the superficial facial soft tissues and fluid within the left lateral nasopharynx recess, with no clear evidence of invasive fungal disease. She was seen in otolaryngology clinic one-month prior to presentation due to development of left facial paresthesia and muffled hearing. Laryngoscopy revealed a friable left nasopharyngeal mass with a small amount of mucous and clot, partially obscuring the left eustachian tube, which was thought to be most likely malignant. She was scheduled to undergo a surgical biopsy of the mass in the operating room under general anesthesia later that month; however, she re-presented to the emergency department (ED) for the sentinel admission prior to this procedure.

On presentation, temperature was 36.6 °C, blood pressure was 134/89 mmHg, heart rate was 82 beats-per-minute, and respiratory rate was 18 breaths-per-minute. Exam was notable for mild confusion, recurrent vomiting of dark brown emesis, and diffuse abdominal tenderness. Laboratory testing revealed a white blood cell count of 20.96 cells/uL, absolute neutrophils 17.51 cells/uL, hemoglobin 14.1 g/dL, and glucose of 193 mg/dL. Her electrolytes, anion gap, ferritin, and beta-hydroxybutyrate were all within normal limits. Hemoglobin A1c had

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decreased to 6.8%. COVID-19 polymerase chain reaction (PCR) was negative. Electrocardiogram demonstrated normal sinus rhythm at 84 beats-per-minute. A chest x-ray was unremarkable.

While in the ED, the left nasopharyngeal mass started bleeding and she hyperventilated and syncopized. A few hours later she was found to have a left-sided Horner's syndrome, left facial droop, right arm weakness, dysarthria, and expressive aphasia. Computed tomography angiography (CTA) of the head and neck demonstrated invasive disease in the left nasopharynx, which was considered nasopharyngeal carcinoma or less-likely invasive fungal disease. Magnetic resonance imaging (MRI) of the head and magnetic resonance venography (MV) were obtained which demonstrated acute infarction of the left frontal, parietal, and occipital lobes; occlusion of the left sphenoid sinus and left jugular vein consistent with thrombosis; and edema and enhancement in the soft tissues around the left nasopharynx including anterior to the base of the skull. She was neither a candidate for tissue plasminogen activator nor thrombectomy, and was started on a heparin drip.

On hospital day 1, otolaryngology performed a surgical debridement and exploration via rhinoscopy and found a rubbery, pale mass with surrounding necrosis concerning for invasive fungal infection. Debridement of the involved deeper skull base sites of infection was not performed during this procedure. Intraoperative histopathology was consistent with mucormycosis, though fungal culture of the mass resulted in no growth. Fungal and routine bacterial blood cultures were negative. She was started on liposomal amphotericin B 7.5 mg/kg IV daily as well as intravenous isavuconazole 372 mg IV q8 hours x 6 doses (loading dose), then 372 mg IV daily. After discussion with multiple surgeons locally and at quaternary care centers, the extent of disease into the skull base was deemed prohibitory to further debridement due to overwhelming risk of morbidity from surgery, so no further debridement procedures were performed. This meant that deep-seated mucor infection remained un-debrided through much of the left skull base and surrounding structures. MRI of the head and endoscopy with otolaryngology were performed weekly.

On hospital day 7, MRI head demonstrated a new outpouching measuring approximately 9 mm within the left internal carotid artery concerning for a pseudoaneurysm. On hospital day 8, CTA confirmed the pseudoaneurysm arising from the distal petrous segment of the left internal carotid artery (ICA). On hospital day 10, neurointerventional radiology performed a bilateral diagnostic cerebral angiogram with balloon occlusion of the left ICA, which demonstrated preserved left cerebral circulation through the circle of Willis. On hospital day 11, she underwent successful selective cerebral and cervical angiograms and stent assisted coiling of the left ICA mycotic pseudoaneurysm. She was started on aspirin 325 mg PO daily and clopidogrel 75 mg PO daily thereafter. On hospital day 12, she developed right groin pain. A right groin pseudoaneurysm, likely a complication of endovascular intervention for the left distal ICA pseudoaneurysm, and right femoral deep vein thrombosis (DVT) were found on ultrasound. On hospital day 15, ultrasound showed recurrence of the right common femoral artery pseudoaneurysm, and vascular surgery subsequently performed an ultrasound-guided thrombin injection on hospital day 16.

On hospital day 18, MRI head showed evidence of new acute and subacute infarcts throughout, thought to potentially be secondary to previous interventional radiology procedures. Acute kidney injury (AKI) developed on hospital day 24 with a creatinine of 1.08 (baseline 0.7), thought to be secondary to antifungal toxicity. Lisinopril was held and her renal function improved. Her right femoral pseudoaneurysm recurred and was treated with an additional thrombin injection on hospital day 26, which subsequently resolved. Also, on hospital day 26, MRI head showed interval development of a parenchymal hematoma centered in the left posterior external capsule, thought to be due to anticoagulation. The hematoma was associated with vasogenic edema, narrowing of the right lateral ventricle, and mild leftward midline shift. A new subarachnoid hemorrhage in the right superior frontal sulcus and central sulcus and a possible mycotic aneurysm were also evident. All anticoagulation medications were held with discovery of the hematoma. Repeat CT on hospital day 32 showed no changes in hematoma size. Aspirin 81 mg PO daily was restarted and additional anticoagulation was held. Ondansetron, marinol, decadron, compazine and low-dose dexamethasone were used for severe nausea and vomiting treatment throughout hospitalization, thought to be secondary to infection, medications, long-standing diabetes mellitus, constipation, and acute illness. Ultrasound showed resolution of the left internal jugular vein thrombus and an interval decrease in right lower extremity DVT. On hospital day 33, total parenteral nutrition (TPN) was started due to persistent low PO intake. On hospital day 34, heparin was restarted. Enoxaparin 25 mg BID was started on hospital day 36. CT and MRI head on hospital day 37 and 38, respectively, were performed for lower extremity weakness and were found to be stable. On hospital day 42, visible coils from the left ICA aneurysm were seen on surveillance rhinoscopy, which appeared more visible on hospital day 53, though no intervention was made. TPN was discontinued on hospital day 51. The final dose of amphotericin was given on day 54, and intravenous isavuconazole was transitioned to 372 mg PO daily on day 55. She was discharged on hospital day 56 on an indefinite course of oral isavuconazole and plans for monthly LFTs, monthly brain MRIs, follow-up with otolaryngology, endocrinology, neurology, hematology, infectious diseases, and excellent blood sugar control. Additionally, before discharge, the patient and her family were counseled that blood glucose control was critical to her ongoing recovery.

Three months after discharge, she continues to take isavuconazole daily, serial MRIs show continued improvement, and she is making an excellent clinical recovery with full resolution of the initial presenting symptoms of epistaxis, sinus pressure, and paresthesia.

Discussion

Mucormycosis is a rare opportunistic infection caused by several species of fungi belonging to the order Mucorales, which thrive in decaying vegetation, animal excreta, and unprocessed foods [1–4]. Mucormycosis is the third most common invasive fungal infection after aspergillosis and candidiasis [4,14]. The estimated prevalence of mucormycosis hovers around 0.01–0.2 cases per 100,000 individuals in the United States and Europe, while that of India is about 80 times higher [9,15,16]. However, the true incidence is unknown, due to its non-specific clinical picture, low sensitivity in diagnostic testing, and difficulty collecting samples [5,17,18]. The type of infection is characterized by its location: 1) rhino-orbito-cerebral (33–49%), 2) cutaneous (10–16%), 3) pulmonary (10–11%), 4) disseminated (6–12%), and 5) gastrointestinal (2–11%) [12,19,20]. Rhino-orbito-cerebral is the most common site of infection, potentially because the heme present in red blood cells is an important substrate and the head and neck regions have a rich blood supply [21]. Overall, it has a global mortality rate of about 50% [19,22]. Infections associated with the best prognosis include cutaneous, pulmonary, and sinus infections, while intracranial, disseminated, and gastrointestinal infections are often fatal with morality rates as high as 90–100% [1,13,15,23,24].

Important aspects of mucormycosis pathophysiology involve elevated levels of serum iron and impaired host immunity [25]. Globally, the most common risk factor for mucormycosis infection is diabetes mellitus, especially states of uncontrolled diabetes and diabetic ketoacidosis, which is present in about 75% of cases [9,11–15,17,19,26–34]. Acidotic states promote the unbinding of iron from proteins leading to increased levels of serum iron which promotes fungal growth [25]. In addition to impaired iron sequestration, hyperglycemic states favor fungal growth through decreased phagocytosis associated with hyperglycemia [1,10,15,35,36]. Of those with diabetes, about 80% have type II, while about 20% have type I [7,9,14,18,24,26,33,36–39]. Uncontrolled diabetes was the main risk factor for the patient presented here, due to lack of access to insulin. As the global prevalence of diabetes continues to rise, from 366 million in 2011 to 522 million predicted in

2030, mucormycosis is likely to follow a similar trend [17]. Although diabetes is the most common risk factor, hematological malignancy (i.e., acute myeloid leukemia) and immunosuppression have replaced diabetes as the predominant risk factor in developed countries, and, unfortunately, are associated with high mortality because the immune defect which predisposes individuals to mucormycosis usually cannot be quickly reversed in these conditions [4,9,15,17,22,26,27,37]. In these disease states, mucormycosis thrives due to impaired function of phagocytes and neutrophils which normally would inhibit fungal growth[40].

Other medical risk factors that promote infection include states of iron overload (ie, dialysis, multiple transfusions, cirrhosis, hemochromatosis) [3,6,9,15,19,37,41], chronic kidney disease [9,26], severe neutropenia [9,11,12,15,21,22,26,37,41], transplantation [9,22,26,41], COVID-19 [4,22,42], trauma [9,15,37], intravenous drug use [9,17,37], neonatal prematurity [6,9,17,26,37], malnourishment [9,17,37], and human immunodeficiency virus [17,26]. Additionally, mucormycosis has been reported to have a male predominance with a ratio as high as 5:1 [3,4,7,10,11,23,28,36,38,41,43].

Initially patients with mucormycosis may present with non-specific symptoms, which can delay diagnosis [20,44]. Often the first signs of rhino-orbito-cerebral infection include ophthalmic signs, such as blindness, decreased visual acuity, diplopia, proptosis, and retroorbital pain [2,5–7,9,16,19–21,28,30,33,37–39,43,45,46], or sinusitis commonly of the ethmoid and maxillary sinuses, including nasal congestion, epistaxis, and sinus tenderness [1,3,4,7,11,12,14,16,24,35,37,38,43]. Facial weakness, facial swelling, cranial nerve palsy, and facial pain are also typically present [2,4–6,9,11,16,19–21,28,30,32,35,37,39,41, 43]. Other symptoms may include shortness of breath [37], fever and chills[16,19,33,37], headache [2,4,5,16,19,35,45], and progression of symptoms despite treatment with antimicrobials [26]. Confusion and altered mental status are often associated with cerebral involvement and indicate a later stage of disease, often indicating intracranial spread [3,6,19,28,31]. Necrotic tissue is also present in more advanced disease [2,3,16,19,30,33–35,37]. Additionally, aneurysms, hemorrhage, dissection, and strokes can occur, as the fungus damages blood vessels and invades the arterial lamina [6,19,22,30,34,35,37].

Early diagnosis, as well as medical and surgical management, are essential [1,2,20,22,24,26,37,47]. Diagnosis requires histology obtained from a direct tissue biopsy. On histopathology of clinical specimens, mucormycosis show fungal hyphae at right angles with necrotic debris from angioinvasion [8,18]. However, cultures have a low sensitivity and can be falsely negative in 50% of cases, as the long filamentous structures can be destroyed by tissue homogenization, part of standard procedure for tissue culture preparation, if the laboratory is not aware of a possible mucormycosis diagnosis [4,5,20,44]. Blood cultures often remain negative, although fungal DNA circulates in the blood [9]. Currently, research is being conducted on non-invasive methods, such as qPCR for detection of fungal DNA in blood and other bodily fluids [9]. Laboratory findings are often non-specific: leukocytosis is often present if the bone marrow is functional as well as high blood glucose with or without acidosis [1,6]. In regards to imaging, CT scans are useful for showing extent of disease, abscess, bony destruction, pulmonary disease, and mucosal thickening [1,6,12,17,20,22,24,26,37]; while MRI is used for evaluation of intracranial, intradural, and soft tissue inflammation [1,6,16,20,23,24,28]. Radiographic findings typically occur after clinical progression, so imaging may be nondiagnostic as seen in our case; thus, histology is the gold standard for diagnosis [6,8,18,34].

If mucormycosis is suspected, high dose liposomal amphotericin B (doses as high as 10 mg/kg daily) should be initiated promptly even without a confirmed diagnosis [1,6,19,22,26,30,36,37]. Medical management is often coupled with surgical debridement as vascular thrombosis can result in poor drug delivery to the site of infection and debridement can also prevent fungal extension [6,12,38,39,42,48]. The combination of medical management and surgical debridement versus only medical management often yields far better survival outcomes [6, 20, 22, 26, 35]. For example in one study, rhino-orbito-cerebral mucormycosis had a 58% mortality rate with solely medical management; however, when combined with surgical intervention, mortality improved to 17% [33]. The optimal amphotericin treatment duration is not currently known, but is suggested to be a minimum of six to eight weeks [1,20,43]. However, central nervous system involvement and dissemianted infections often require higher doses as well as a longer durations [4,8]. With high-dose liposomal amphotericin B, blood urea nitrogen, creatinine, electrolytes, and platelets should be checked regularly during treatment to monitor for amphotericin-related nephrotoxicity, hypokalemia, and thrombocytopenia [19,21,45]. Posaconazole and isavuconazole can be used as alternatives, salvage therapy, or in combination with amphotericin [1,5,6,18,20,26,31,41]. Of note, isavuconazole has good central nervous system penetration [31]. A study by Gebremariam et al., 2021 found combination therapy of liposomal amphotericin B and isavuconazole, the dual antifungal treatment used in this report, had greater reduction in fungal burden of mucormycosis compared to monotherapy [49]. The patient presented here was able to tolerate dual-antifungal treatment and could not undergo surgical debridement. A multidisciplinary team including otolaryngology, neurology, neurosurgery, infectious diseases, vascular surgery, as well as others, is essential for successful treatment [1,14,36]. Additionally, predisposing factors like neutropenia, acidosis, and hyperglycemia should be reversed [30,37,50].

One of the key aspects of treatment for our patient was improved diabetes mellitus control (A1c improved from 14.3% to 6.8%) with access to insulin. However, it is important to note that even with greatly improved glycemic control, the patient likely continued to have progression of disease, assuming her symptoms three months prior were due to early mucormycosis. Together, glycemic control with dual-antifungal therapy consisting of liposomal amphotericin B and isavuconazole offered an alternative to extensive surgical debridement which would have added significant risk for morbidity.

In conclusion, we present the case of a 42-year-old female with history of type I diabetes mellitus and recent diabetic ketoacidosis who was found to have rhino-cerebral mucormycosis with multi-focal strokes and left ICA pseudoaneurysm. We document the use of isavuconazole as an adjuvant used in conjunction with amphotericin B in the treatment of intracerebral mucormycosis infection. She was primarily treated with medical management as the site of her disease did not allow for full debridement. A diagnosis of mucormycosis should be high on the differential in a diabetic or immunocompromised patient presenting with ophthalmological or facial dysfunction. Antifungal therapy should be started with any clinical suspicion of infection and a biopsy should be obtained promptly to look for mucormycosis histology. In addition, we recommend considering the use of dual-antifungal therapy and tight glycemic control, in addition to debridement, for treatment of rhino-cerebral mucormycosis, as the patient presented here had good tolerability to medical therapy and could not undergo extensive surgical debridement due to the location of the infection.

Ethical approval statement

UVM institutional review board oversight was not required in this case report. Written informed consent for this manuscript was obtained from the patient.

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CRediT authorship contribution statement

Lauren Bougioukas: Conceptualization, Writing – original draft, Writing – review & editing. **Cindy D. Noyes:** Writing – patient care,

Writing – review & editing. **Katherine Peterson:** Writing – patient care, Writing – review & editing. **Lindsay M. Smith:** Writing – patient care, Writing – review & editing. **Andrew J. Hale:** Conceptualization, Patient care, Writing – original draft, Writing – review & editing.

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Consent

Written informed consent for this manuscript was obtained from the patient.

Authorship verification

All co-authors have seen and agree with the contents of the manuscript and have contributed significantly to the work.

Conflict of interest statement

None of the authors report any conflicts of interest.

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