

# Diabetic ketoacidosis and acute myeloid leukemia predisposing mucormycosis in a middle aged lady

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## Abstract

Mucormycosis is a rare but rapidly progressive opportunistic fungal infection. It is most often reported in patients with diabetes mellitus especially in the setting of ketoacidosis, but growing number of cases of mucormycosis are reported in patients with hematological malignancies such as leukemia and lymphoma. We report a case of a 43 year old diabetic lady who presented with Diabetic ketoacidosis and was found to have sino-orbital mucormycosis and acute myeloid leukemia. In spite of the unusual combination of two confounding risk factors, we managed to successfully treat both mucormycosis and acute myeloid leukemia in this patient.

**Keywords:** mucormycosis; acute myeloid leukemia; diabetes mellitus.

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## INTRODUCTION

Mucorales species are opportunistic fungi with a rapidly invasive nature. A rare disease, mucormycosis is most commonly reported in patients with diabetes mellitus, because of the favorable carbohydrate-rich environment allows the Mucorales fungi to flourish, especially in the setting of ketoacidosis. However, case reports over the past 20 years show that a growing number of cases of mucormycosis are occurring in patients with hematological malignancies and during treatment following bone marrow transplants (BMT). This is due to immuno suppression and prolonged treatment of these patients with steroids and chemotherapy. We are reporting a case of mucormycosis in a patient with diabetes and Acute myeloid leukemia. Both the conditions predisposes to increased incidences of

opportunistic fungi – mucormucosis. Liposomal amphotericin B treatment and posaconazole are two pharmacologic agents that seem to be effective against mucormycosis, but the inherently rapid onset and course of the disease, in conjunction with the difficulty in correctly identifying it, hinder prompt institution of appropriate antifungal therapy.

## CASE HISTORY

A 43 year old woman presented to us with history of fever, swelling of the right side of face including eye, and bleeding from the nose of 7 days duration. Her past history was significant for the history of diabetes mellitus diagnosed 6 months back for which she was on oral hypoglycemic drugs. On examination she had swelling and ecchymosis over her right maxillary region and proptosis and mechanical ptosis of right eye (Figure 1). She was febrile, pale and had a pulse rate of 120 beats/min. Fundus examination of the left eye showed nonproliferative diabetic retinopathy with Roth spots suggestive of leukemic fundus. ENT examination showed normal nasal mucosa with blood clots over palate and tongue. Examination of systems was within normal limits. Investigation revealed a 7.7 gm% hemoglobin, 122,460/mm<sup>3</sup> leucocyte count and 35,000/mm<sup>3</sup> platelet count. Her serum blood glucose was 349 mg/dL. Urine examination showed 2 plus sugar and 3 plus ketones.

Patients serum bicarbonate was 8mmol/dl Computed Tomography of paranasal sinus showed sinusoidal polyposis involving the paranasal sinuses on the right side with cellulitis of cheek, proptosis of right globe, with gross thickening of inferior rectus muscle (Figure 2). CT brain did not show any cerebral extension of the infection. A peripheral blood smear showed marked leukocytosis with predominantly blasts with increased nucleo-cytoplasmic ratio, 2-4 nucleoli and Auer rods, suggestive of acute myeloid leukemia. Bone marrow aspiration showed increased leucopoiesis showing 90% myeloblasts with scanty to moderate cytoplasm, along with nuclear clefting and myeloid: erythroid ratio of 22.5:1 suggestive of acute myeloid leukemia M2 (FAB) (Figure 3). A right maxillary sinus biopsy was also done which showed necrotic material consisting of non septate hyphae with neighbouring granulomatous inflammation suggestive of fungal granuloma (mucormycosis) and an adjacent proliferating population of cells probably of myeloid origin with scattered mitotic activity, suspicious of a leukemic involvement (Figure 4). However further

CKIT/CD117 (tyrosine kinase) studies showed no leukemic involvement. Patient was initially started on empirical broad spectrum antibiotics (piperacillin-tazobactam and linezolid) and antifungal (amphotericin B 1mg/kg/d) for suspected bacterial and fungal infections. Patient was also on insulin infusion with 2nd hrly CBG monitoring. She was also given packed cell and platelet transfusions and her diabetes was controlled with insulin. Once the diagnosis of AML was confirmed, she was given induction chemotherapy with cytarabine 160mg i.v. OD for 6 days and daunorubicin 80mg i.v. OD for 3 days. Patient was given 4 weeks of amphotericin B (cumulative dose of 1400mg) along with other supportive measures, including granulocyte colony stimulating factor. Surgical debridement was however not possible due to the poor general condition of the patient. Patient was discharged after 4 weeks of hospital treatment having shown good response in the form of reduction in the fungal infection and also good cytologic response for AML and was advised regular follow up.



Figure 1



Figure 2

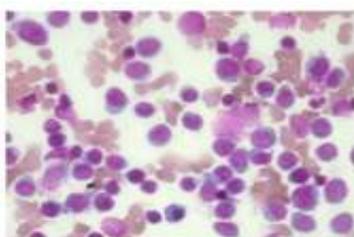


Figure 3

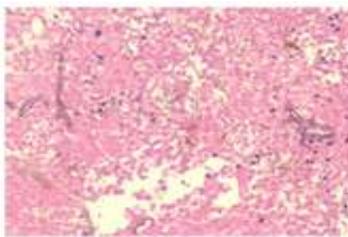


Figure 4

## DISCUSSION

Mucormycosis can be caused by any fungal species within the Mucorales order. This mold infection is also referred to as zygomycosis or phycomyosis in the literature. The most commonly seen genera in mucormycosis cases are *Rhizopus*, *Rhizomucor*, *Mucor*, and *Absidia*.<sup>1</sup> Although most cases of mucormycosis are seen in patients with uncontrolled diabetes mellitus, the numbers have been decreasing over the past 20 years and, instead, an increasing numbers of individuals with hematological malignancies are presenting with the infection. Recent studies indicate that 1–3% of bone

marrow transplantation patients present with mucormycosis.<sup>1,2,3</sup> The incidence of mucormycosis in adult leukemia patients is reported at around 2%.<sup>4</sup> Those leukemia patients who have developed neutropenia due to chemotherapy or the malignancy are most susceptible to the fungus. Mortality rates in patients with hematological malignancies who have mucormycosis is greater than 50%.<sup>5,6</sup> Mucormycosis commonly presents in six forms: pulmonary, sinus, cerebral, gastrointestinal, cutaneous, or disseminated. The majority of patients with malignancy present with pulmonary disease, whereas the majority of patients with diabetes have sinus disease.<sup>5</sup> Cases of

rhinocerebral mucormycosis present with facial pain, periorbital cellulitis, proptosis, visual deficiencies, black necrotic lesions and discharge from the nasal and palatal mucosa, and fever.<sup>1</sup> Mucormycosis can be a fatal infection and early diagnosis and treatment are of extreme importance for successful eradication of the infection and for patient survival. Diagnosis is most often done by identifying the fungus in histopathological specimens using Grocott-Gomori methenamine silver (GMS), hematoxylin and eosin or periodic acid-Schiff (PAS) stain. Invasion of the tissue by fungal hyphae and right-angle branching will be present in mucormycosis specimens.<sup>7</sup> Other diagnostic techniques include culture, PCR, serological testing, etc. Mortality rates among patients who have mucormycosis remain high despite antifungal therapy. Surgical intervention and debridement is the gold standard of treatment for eradicating the infection. However many of the clinical presentations do not allow for such methods of treatment and hence surgical debridement is most often used only as needed. The mainstay of treatment is systemic antifungals which include various amphotericin B formulations and posaconazole. Amphotericin B has been the drug of choice against mucormycosis for over 50 years due to its superior effectiveness compared to other therapies. The total dose that needs to be administered ranges from 2.0–4.0 g, depending on the specific case. Most cases that have been successfully treated have required approximately 5 weeks of therapy.<sup>8,9,10</sup> Treatment of our patient was a challenge because of the presence of three coexisting diseases, namely uncontrolled diabetes, acute myeloid leukemia and mucormycosis. Aggressive treatment of diabetes was possible with insulin and strict blood glucose monitoring. A high index of suspicion helped to make an early diagnosis of mucormycosis and thereby early initiation of appropriate antifungal therapy. Surgical debridement was not done in our patient mainly due to limitations imposed by the general condition of the patient and also due to the fortunate absence of cerebral or bone involvement. Treatment of AML had to be initiated with chemotherapeutic agents even though this had a risk of flaring up of the underlying fungal infection.

Fortunately for our patient, both mucormycosis and AML responded to the treatment initiated.

## CONCLUSION

A high index of suspicion, early initiation and appropriate dosing of antifungal therapy, surgical debridement whenever necessary, along with reversal of underlying predispositions are key to the successful outcome of therapy for this deadly opportunistic fungal infection, especially in the setting of more than one risk factors like diabetic ketoacidosis and acute myeloid leukemia.

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