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Fatal Rhinocerebral Mucormycosis in a Non- Adherent Diabetic Patient

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ABSTRACT

A case was reported involving a 50-year-old woman with poorly controlled diabetes mellitus and a history of medication non-adherence. She initially presented to a peripheral hospital with metabolic acidosis and was treated for diabetic ketoacidosis. However, her condition deteriorated rapidly, necessitating transfer to a multidisciplinary care facility. Upon arrival at the emergency department, a bluish-black rash was observed on the right upper side of her face, which had developed over the preceding 48 hours. The appearance of this rash raised a strong suspicion of invasive fungal infection, specifically mucormycosis.An urgent ENT consultation was obtained, and a smear from the palate revealed the presence of septate hyphae. Intravenous amphotericin was initiated alongside continued management of diabetic ketoacidosis. Surgical intervention involving extensive debridement of the affected skin, with the possibility of enucleation, was advised but declined by the patient's family. Despite intensive medical management, the patient's condition progressively worsened, leading to brain death within three days, followed by terminal extubation. This case highlights the severe and often fatal complications of mucormycosis in individuals with uncontrolled diabetes mellitus.

Keywords: Sinusitis, Hyphae, Brain.
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INTRODUCTION

Mucormycosis, often referred to as black fungus, is an aseptate fungal infection that has a hundred percent mortality in immunocompromised patients[1]. Typical symptoms encompass nasal congestion, headaches, facial edema, mild fever, proptosis, tissue destruction in the periodontal area, and the formation of a necrotic black patch in regions like the hard palate, oral cavity, or maxillary regions. The mechanism by which it enters the bloodstream is through the inhalation of spores by the mouth, nostrils, or skin incisions [2]. Nonetheless, early diagnosis and effective patient management can mitigate the risk of mortality[3]. This case is of a diabetic patient who developed life-threatening

mucormycosis with diabetic ketoacidosis. Despite aggressive medical and surgical interventions, the patient was not able to survive.

CASE PRESENTATION

A 52-year-old woman known case of poorly controlled diabetes mellitus for ten years. She underwent a tooth extraction at a dental clinic a week ago. After the dental procedure, she started running a fever associated with myalgias, for which she received analgesics and empirical antibiotics. As her symptoms worsened, she was transferred to a specialized clinic, where it was determined that her blood sugar levels were aberrant, necessitating an adjustment in her insulin dosage. Due to her drowsiness, she was referred to a neurologist, who recommended neuroimaging, yielding normal results. Consequently, she was admitted for the management of her unstable blood sugar levels. During her stay at a periphery hospital, she developed severely deranged blood sugars and metabolic acidosis, which was managed on lines of diabetic ketoacidosis for two days before being transferred to our tertiary care facility. Upon her arrival at our facility, she presented with drowsiness, localized responses observed in her left upper extremity, marked tachypnea and tachycardia, accompanied by an oxygen saturation level of 88%. Most notably, within the past 48 hours, a distinctive bluish-blackish rash had manifested on her face. **Figure 1**.

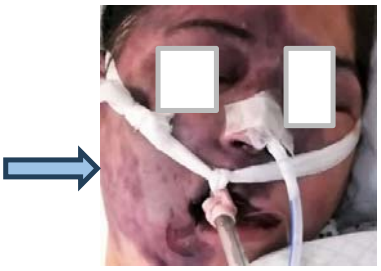

Figure 1: **The arrow shows Bluish-Blackish Mucor Rash Involving the Face of the Patient**

The patient was promptly mechanically ventilated in the emergency. There, she received a regimen of broad-spectrum antibiotics and an insulin infusion. The characteristic rash, strongly suggestive of Mucormycosis rhinosinusitis, prompted a referral to an ear, nose, and throat (ENT) specialist, who advocated for a CT scan of the paranasal sinuses (PNS). The CT scan revealed mucosal thickening in all the visualized sinuses, indicative of fungal sinusitis. Given the strong suspicion of mucor, the ENT team performed Functional Endoscopic Sinus Surgery (FESS) as a life-saving measure, involving debridement. A histopathological examination of a fungal smear taken during FESS from

her palate affirmed the presence of aseptate hyphae suggestive of mucor. Amphotericin B therapy at a dosage of 1.5 mg/kg/day was initiated without delay. Subsequent CT imaging of her head and neck displayed an escalation in diffuse sinusitis compared to the prior scan, along with evidence of erosion of the lamina papyracea; however, cerebral extension was not observed.

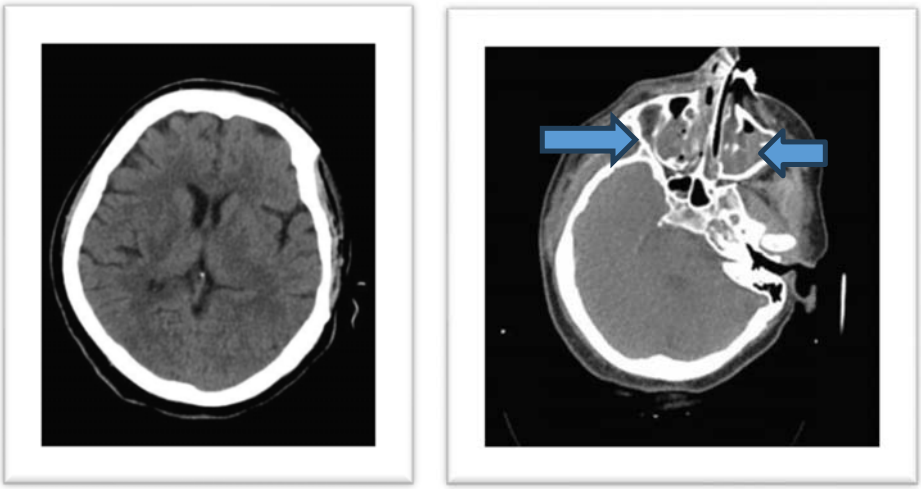

Figure 2a: CT Head (plain) Normal (2b) CT Paranasal sinuses. Bilateral maxillary sinusitis with the possibility of fungal infection. (marked by the arrows) Erosion of the Lamina papyracea(medial wall of the orbit) on the right side.

Table 1: Comprehensive Laboratory Workup

CSF Detailed Report		
Glucose	170 mg/dl	400 mg/dl in serum
Protein	134 mg/dl	45 mg/dl
White cell count	1325 /cumm	0-5/ cumm
Differentials	70 % lymphocytes	-
Complete Blood Count		

Hemoglobin	10 mg/dl	12-13 mg/dl
TLC	12.3 /cumm	4-11 /cumm
Platelets	299 /cumm	150-300 /cumm
Creatinine	1.7 mg/dl	0.7-1.4 mg/dl
Bicarbonate	17 mmol/L	22-28 mmol/l
Sodium	145 mmol/l	135-145 mmol/l
Potassium	2.3 mmol/l	3.5- 5 mmol/l
Urea	101 mg/dl	7-20 mg/dl
C-reactive protein	39.06 mg/dl	< 10 mg/dl
HbA1c	11.1 %	4-5.6%
Urine D/R		
Ketones	150 mg/dl	Trace
Glucose	1000 mg/dl	Trace

Detailed lab workup can be seen in **Table 1**. Her CSF studies showed significantly raised WBC count with low sugars and high proteins. She was simultaneously covered for bacterial and fungal meningitis.

Despite initial treatment, her symptoms rapidly deteriorated. Both ENT and ophthalmological specialists recommended a cautious approach due to the potential necessity for enucleation of both eyes and maxillary sinuses during surgery, rendering a skin flap unfeasible. Expert opinions from plastic surgeons concurred with this assessment. As her clinical condition continued to deteriorate, her family opted to proceed with terminal extubation, ultimately leading to cardiac arrest.

DISCUSSION

Mucormycosis encompasses various infections caused by fungi from the Zygomycetes class, characterized by their branching, ribbon-like hyphae, and sexual reproduction through zygospores. These pathogens are widely present in fruits, soil, and feces, and can also be isolated from the oral cavity, nasal passages, and throat of healthy individuals. A subtype of Zygomycetes, Mucorales, is responsible for specific clinical infections. These fungi are generally non-virulent and become pathogenic only when the host's immune resistance is significantly compromised. In the maxillofacial region, mucormycosis can enter through mucosal ulcerations or extraction wounds in the mouth, especially in immunocompromised individuals[4,5].

Patients with poorly controlled diabetes face an elevated susceptibility to infections, particularly from opportunistic fungal pathogens such as mucormycosis. Diabetes mellitus disrupts the body's natural immune response to infections through various mechanisms. Hyperglycemia, in addition to promoting fungal proliferation, inhibits chemotaxis and the effectiveness of phagocytosis, permitting typically benign species to flourish within an acidic environment. The pathophysiology of diabetes-induced susceptibility to infections is multifaceted. Chronic hyperglycemia impairs neutrophil function, reducing their ability to adhere, migrate, and perform phagocytosis and microbial killing. Furthermore, high glucose levels lead to non-enzymatic glycation of proteins, which in turn impairs the complement pathway and reduces the efficiency of the immune response. Diabetic patients also exhibit a state of chronic low-grade inflammation, characterized by elevated levels of pro-inflammatory cytokines such as TNF-alpha, IL-6, and CRP, which can paradoxically impair effective immune response[6].

In addition to these immune impairments, diabetic patients often suffer from vascular complications, including microangiopathy and macroangiopathy, which compromise tissue perfusion and oxygenation. This ischemic environment further predisposes tissues to infection and hinders the effective delivery of immune cells and antimicrobial agents to the site of infection. Poor wound healing, another hallmark of diabetes, exacerbates the risk of secondary infections. The presence of neuropathy in diabetic patients can lead to unrecognized injuries, providing entry points for pathogens[7].

Moreover, mucormycosis is particularly insidious in diabetic patients due to the ability of mucorales to thrive in hyperglycemic and acidic environments. The fungus produces an enzyme called ketoreductase, which enables it to utilize ketone bodies for growth. This is particularly problematic in patients with diabetic ketoacidosis (DKA), where elevated ketone levels provide an optimal growth

environment for the pathogen. DKA itself, a severe complication of diabetes, is associated with profound immune suppression, further facilitating the invasion and dissemination of mucorales.In our case, the patient's diabetes was poorly controlled, which was the primary reason for the development of this life-threatening mucor infection.

While these organisms are common commensals in the nasopharynx of healthy individuals, they become opportunistic pathogens in diabetics with severely compromised immune systems, invading adjacent structures before spreading to the paranasal sinuses and, if left untreated, potentially the central nervous system (CNS).

In our patient, the cerebrospinal fluid (CSF) picture was pyogenic with significantly high cell counts. This unusual presentation prompted us to continue bacterial coverage alongside antifungal therapy. The radiographic visualization of the disease's progression can be achieved through neuroimaging, encompassing CT scans of the head and paranasal sinuses with contrast enhancement, which effectively documents the extent of the spread and perineural invasion by the fungus. Definitive diagnosis in our patient was established by obtaining nasal scrapings via endoscopic sinus surgery, which revealed aseptate hyphae, consistent with mucormycosis as the causative agent[8].

While the most common route of CNS involvement is the direct spread through the orbital bones and sinuses, dissemination through vessels from distant sites of infection can also lead to CNS involvement. Fungi can infect periorbital tissues and the cavernous sinus via emissary veins, although mucormycosis originating from the ethmoid sinus is exceptionally rare[9,10]. The management of rhinocerebral mucormycosis is grounded in three fundamental principles: addressing underlying predisposing conditions, initiating antifungal therapy promptly, and resorting to surgical debridement when necessary. In our case, the prompt combination of antifungal and antibacterial therapy, alongside managing the patient's hyperglycemia, was crucial. Despite the necessity of surgical debridement for effective management, our patient's family did not permit surgical intervention. They later withdrew ventilatory support due to the grave nature of the disease, highlighting the importance of family counseling and discussions regarding prognosis in severe cases of mucormycosis. Deferasirox has also shown promise as salvage therapy in cases of rhinocerebral mucormycosis[11]. The recent approval of the triazole isavuconazole by the European Medicines Agency and the US FDA expands the available antifungal options. A poorer prognosis is associated with the progression of the disease, and central nervous system involvement is considered fatal[12]. Additionally, literature highlights the necessity of an interdisciplinary approach in managing such complex cases, involving endocrinologists, infectious disease specialists, neurologists, and ENT surgeons to optimize patient outcomes, as the clinical differential diagnosis of such lesions could be squamous cell carcinoma,

chronic granulomatous infections like tuberculosis, syphilis, or other deep fungal infections like candida[12].

The experience underscored the need for heightened awareness among clinicians regarding the potential severity of mucormycosis in diabetic patients, especially those with poorly controlled glucose levels. Early diagnosis and a comprehensive treatment strategy are paramount in improving survival rates in these patients.

CONCLUSION

Allgrove syndrome is an uncommon condition, so uncommon that numerous cases remain undetected or are incorrectly diagnosed. Therefore, when a child exhibit any of the three primary symptoms, Allgrove syndrome should be considered, and the child should be monitored closely.

In addition, the dental management is also very important for these patients along with reinforcement of oral hygiene instructions. Early diagnosis and dental management can improve the quality of oral health.

CONSENT

Informed consent was obtained from the patient for publication of the case report and accompanying images.

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None

CONFLICT OF INTEREST

None

AUTHORS' CONTRIBUTION

SAT was responsible for data collection, literature review, and initial draft preparation, and **SZ** did study conception, supervision, critical revision of the manuscript, and final approval.

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