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Case Report

A Case of Recovered Severe Rhino-Orbito-Cerebral Mucormycosis

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Running Title Challenging Case of Severe Mucormycosis

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ABSTRACT

Background: Mucormycosis is a rare disease with high morbidity and mortality, and its diagnosis is difficult and often delayed. Also, the disease tends to progress rapidly. Therefore, urgent surgical and medical intervention is lifesaving.

Case Presentation: A 24-year-old woman with diabetes since 3 months ago presented with excessive tearing in her left eye, unilateral headache with epistaxis, and loss of consciousness at Razi Hospital, Rasht City, Iran, in June 2021. A clinical and pathologic diagnosis of mucormycosis was established. Imaging the head and paranasal sinuses revealed extensive involvement of the brain, paranasal sinuses, and left orbit. Treatment with liposomal amphotericin B (5 mg/kg) was administered for about 50 days until discharge. During the treatment period, the patient underwent several surgical procedures, such as enucleation of the left eye, surgery on soft and hard palates, sinuses, and neurosurgery for debridement of necrotizing tissues. After 50 days of intensive medical and surgical treatments, the patient was recovered and discharged.

Conclusion: In the era of the COVID-19 pandemic, many diabetic patients acquire that infection. Physicians caring for these patients should be alert to mucormycosis as a complication of severe or mild COVID-19 infection. Early diagnostic and therapeutic interventions could be lifesaving for these patients.

Keywords: Mucormycosis, Diabetes mellitus, COVID-19

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Highlights

• We report the case of rhino-orbito-cerebral mucormycosis after the outbreak of the COVID-19 pandemic in a diabetic ketoacidosis patient who recovered.

Introduction

Mucormycosis is difficult to diagnose and is a rare disease with high morbidity and mortality. Depending on the site of infection and underlying predisposing factors, mortality rates may vary from 10% to 100% [1]. The diagnosis is often delayed, and the disease tends to progress rapidly. Urgent surgical and medical intervention is lifesaving. Suspected mucormycosis requires urgent intervention owing to the rapidly progressive and destructive nature of the infection. Delayed initiation of therapy is associated with increased mortality. Maximizing survival rates requires rapid diagnostic and therapeutic intervention, including immediate involvement of a multidisciplinary medical, surgical, radiological, and laboratory team [1]. This infection occurs mainly in immunocompromised patients, particularly with hematological malignancy, transplantation, or diabetes mellitus [2]. The most common form, rhino-orbito-cerebral mucormycosis (ROCM), is an abbreviated yet collective term used to denote the mucormycosis infections in sinus, sino-orbital, rhino-cerebral, and optical regions of the body [3]. The basic principles of mucormycosis treatment include risk stratification for the severity of the disease, intense attempts for early, clinical and laboratory diagnosis, and timely initiation of effective antifungal therapy (monotherapy or combination therapy), along with aggressive surgical debridement of necrotic lesions [4]. With the new pandemic of COVID-19, new challenges of previous severe infections like mucormycosis have been developed [5]. A strong association between COVID-19 and increased fungal infections can be observed. There are various possible reasons for this association, including the immunosuppression caused by COVID-19 infection and disease process or the extensive use of steroids and broad-spectrum antibiotics in managing COVID-19, leading to the development or exacerbation of a preexisting fungal disease [6]. Several case reports of newly diagnosed diabetes or diabetic ketoacidosis in previously diagnosed diabetes due to severe acute respiratory infection of COVID-19 triggered rhino-cerebral or pulmonary mucormycosis have been published to warn the possibility of COVID-19 as a trigger of severe fungal infections [7-12]. In this case report, we present a severe rhino-orbito-cerebral mucormycosis in a newly diagnosed diabetic patient with ketoacidosis.

Case Presentation

In June 2021, a 24-year-old female patient with a history of diabetes mellitus of pregnancy presented with 5 days duration of unilateral headache, excessive tearing of the left eye, and epistaxis to a local hospital. She has been on oral glucose-lowering agents (metformin 500 mg twice daily) since 3 months ago. At presentation, her blood glucose level was 400 mg/dL. She was referred to another hospital. During her transfer, she developed decreased consciousness. She was admitted to ICU, and treatment for diabetic ketoacidosis was administered. A COVID-19 PCR test on the nasopharynx was reported to be positive. In the subsequent few days, she developed lacrimation with purulent discharge, erythema and edema of the left eyelid, proptosis, and chemosis, and the patient was referred to our hospital, Razi, an academic hospital affiliated with Guilan University of Medical Sciences, Guilan Province, Iran, for better management of a presumed diagnosis of mucormycosis. On admission, she was lethargic with left orbit chemosis with purulent discharge. Treatment with amphotericin B liposomal (5 mg/kg), vancomycin (1 g BID), and cefepime (2g TID) was started. An ophthalmologic, otolarynffiggology, and endocrinologic consultation was requested. Thorax, brain, and sinus computerized tomographic scans were performed. Another COVID-19 PCR test was reported to be negative. Thorax CT scan did not show any signs of lungs COVID-19 involvement. Brain and sinus CT scans exhibited extensive opacities of the sphenoid, frontal, and left maxillary sinuses and hypodense opacities in the anterior cranial fossa. In subsequent days, infection progressed rapidly, and erythema and necrosis of hard and soft palates developed. She had pain, redness, lacrimation, purulent discharge, and blurred left-eye vision. Purulent and bloody discharge from nasal sinuses continued. Earache, vertigo, and signs of the left side facial nerve palsy developed. During the first week of admission, surgical debridement of the left maxillary sinus, a part of the nasal septum and anterior septum of sphenoid sinus, left nasal conchae, and a part of the left ethmoid sinus was done because of extensive necrosis of these tissues. Also, enucleation of the left globe was performed at an ear-nose-throat (ENT) and ophthalmology specialty center. Several tissue specimens sent for pathology diagnosis were reported to be mucormycosis (Figure 1). The

patient was transferred to another university hospital for surgical debridement of hard and soft palates destroyed by progressive mucormycosis. A brain magnetic resonance imaging (MRI) performed on the second week of admission revealed hypodense areas in the frontal lobe of the brain (Figure 2). The patient underwent neurosurgical debridement of necrotized brain tissues of frontal lobes. After 10 days, she was transferred to our hospital again, and medical therapy with amphotericin B liposomal was continued. She had lost more than 10 kg during her stay in the hospital. She could not eat solid food due to the destruction of her palate. After 50 days of intense medical, surgical, and rehabilitation treatments and numerous transfers between hospitals, she recovered and got alert in good mental condition. She was discharged and referred for reconstructive surgery of the hard palate. Six months after her discharge, she was in good physical and mental condition.

Discussion

Mucormycosis or zygomycosis, also called phycomycosis, is an uncommon, aggressive, invasive, rapidly progressive, and life-threatening fungal infection [5].

Rhino-orbito-cerebral (ROCM) and pulmonary mucormycosis are the predominant forms [2]. Among the various types of sinuses, the ethmoid and maxillary sinuses are the worst affected ones. Once the ethmoid sinus is affected, the infection progresses into the orbital region of the skull, where it affects the extraocular muscles and optic nerve, thereby causing the seeding of the brain, as was the case in our patient. In the mucormycosis of the maxillary sinus, the infection, apart from progressing into the orbital region, also progresses into the oral cavity. The hard palate becomes a hotspot, where painful black ulceration develops. In the orbital compartment, the optic nerve, ophthalmic artery, and ophthalmic nerve are invaded, leading to their inflammation followed by necrosis [3]. Cerebral mucormycosis is a rapidly progressive infection in diabetic patients and carries immense morbidity despite early diagnosis and treatment. The overall mortality in individual cases was 46.3%, and 64.2% of deaths were reported in patients with ketoacidosis diabetes [13]. Our case was a severe and rapidly progressive form of mucormycosis beginning in orbit that rapidly progressed to adjacent tissues of paranasal sinuses and soft and hard palates and then to cerebral tissue, producing severe tissue necrosis requiring aggressive surgical debridement.

COVID-19 is associated with a significant incidence of secondary infections, both bacterial and fungal, probably owing to the deterioration of immunity. The extensive use of steroids/monoclonal antibodies/broad-spectrum antibiotics as part of the COVID-19 treatment may lead to fungal diseases [5, 14]. Perhaps in the context where there is a widespread outbreak of mucormycosis, systemic corticosteroids should be more judicious in patients at high risk, such as those with diabetes, considering that systemic corticosteroids could aggravate hyperglycemia [15].

COVID-19 disease, followed by mucormycosis, carries a very high mortality rate, and timely detection, antifungal therapy, and aggressive surgical debridement remain key factors in the management [16].

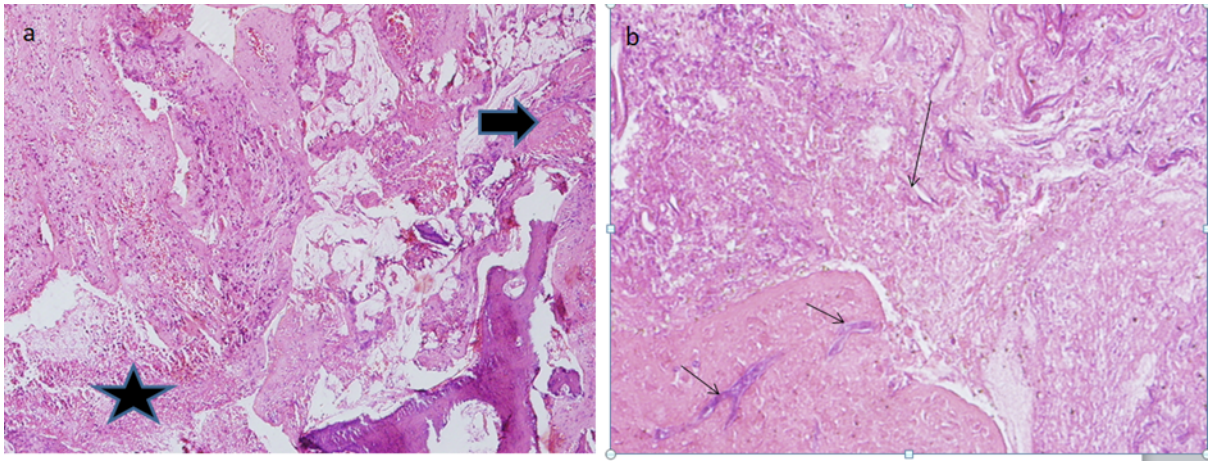

Figure 1. Bone trabecula and respiratory mucinous glands

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Intravascular thrombosis with massive hemorrhage and necrosis consistent with angioinvasion (Figure a). The fungal hyphae with broad, non-septate, and irregularly branching consistent with mucormycosis (Figure b, arrows).

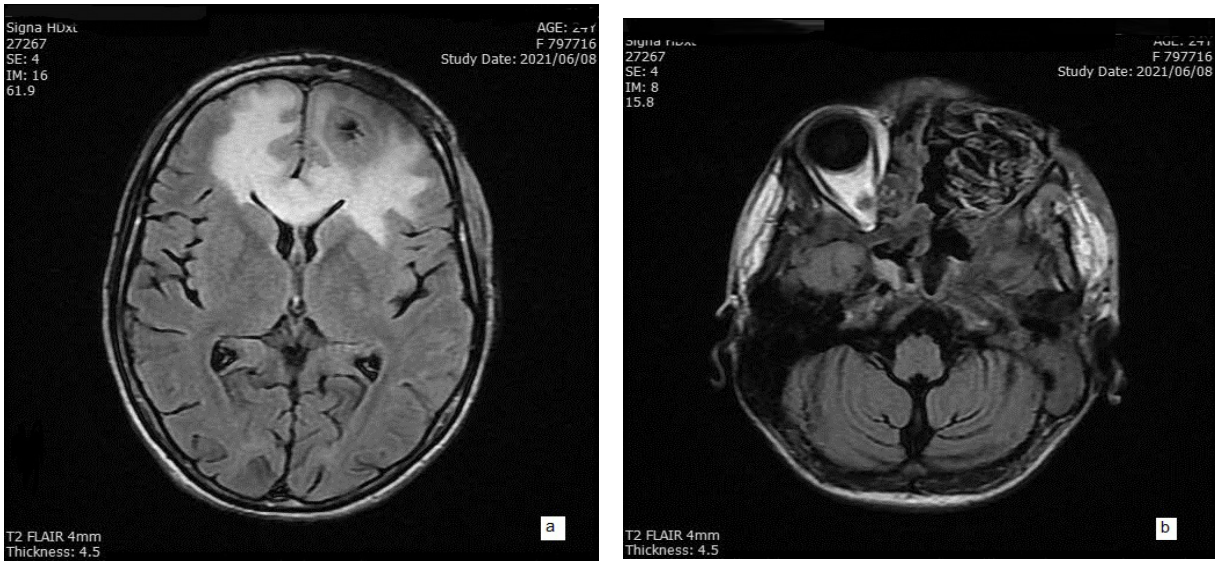

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Figure 2. Brain magnetic resonance imaging with and without contrast

T2 FLAIR (T2-weighted-fluid-attenuated inversion recovery) shows tissue involvement (mucormycosis) within the anterior cranial fossa on both sides with extension to superior temporal gyri.

a. tissue involvment, b. left globe.

Our case had a history of mild upper respiratory tract symptoms suspected of COVID-19 with a preliminary positive PCR test. Although she was not hospitalized and did not receive corticosteroids, she developed diabetic ketoacidosis as a predisposing factor for mucormycosis.

Intravenous amphotericin B is the drug of choice for the initial therapy of mucormycosis; a lipid formulation of amphotericin B (liposomal amphotericin B or amphotericin B lipid) is preferred to reduce the risk of nephrotoxicity. Posaconazole or Isavuconazole is used as the step-down therapy for patients who have responded to amphotericin B. Antifungal therapy should be continued until clinical resolution of the signs and symptoms, as well as resolution of radiographic signs of mucormycosis, is observed.

Our case was the first case of mucormycosis in the pandemic era of COVID-19, while we encountered the challenge of a shortage of amphotericin B, particularly lipid formulation of the drug, so providing continuous drug therapy to the patient was extremely difficult.

Our case was a severe acute rhino-orbito-cerebral mucormycosis with a fulminant and progressive course. In such severe and complicated cases, a multidisciplinary approach with infectious disease specialists working as a team with other specialists, such as endocrinologists for treating ketoacidosis, ENTs, ophthalmologists, neurosurgeons, reconstructive surgeons, pathologists, radiologists, and neurologists to deliver the best treatment modalities to save the patient's life, is indispensable. Another challenge we encountered was the lack of a multidisciplinary medical center in our province, and numerous transfer episodes between different hospitals complicated patient care management.

Conclusion

ROCM is a severe and poor prognosis form of mucormycosis with a high mortality rate. Physicians caring for COVID or post-COVID patients should be alert if symptoms, such as facial pain or swelling, decreased visual acuity, chemosis, proptosis, loss of consciousness, ophthalmoplegia, and numbness of skin over paranasal sinuses develop. Rapid diagnosis and appropriate treatment will be lifesaving.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki (2013).

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Authors' contributions

Investigation and original draft: Lida Mahfoozi; Conceptualization, resources, supervision, review, and editing: all authors.

Conflict of interest

The authors declared no conflict of interest.

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