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Rhino orbital cerebral mucormycosis: A life-threatening complication of coronavirus diseases 2019 in an uncontrolled diabetic patient

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Abstract:

Mucormycosis is a progressive and life-threatening disease that has been increasingly reported in patients infected by coronavirus diseases 2019 (COVID-19). We describe a case of rhino-orbital mucormycosis with central nervous system involvement resulting in bilateral blindness and intracranial extension in a patient with uncontrolled diabetes mellitus (DM) and mild COVID-19 infection. A 35-year-old obese male, recently diagnosed with DM, presented to the emergency department suffering from dizziness, headache, speech difficulty, and facial weakness. His glycosylated hemoglobin was 10.4% and his reverse transcriptase–polymerase chain reaction (PCR) test came positive for COVID-19. Ocular examination revealed left eye proptosis, ophthalmoplegia, and lid edema with no ocular movement. Imaging studies showed pansinusitis and periorbital and orbital cellulitis with intracranial involvement. Histopathology and biopsy examination confirmed mucormycosis. Medical management included glucose control and liposomal amphotericin B therapy. Septoplasty and functional endoscopic sinus surgery was performed as emergency procedures. The patient survived with bilateral blindness. In this case, we described the importance of considering mucormycosis in COVID-19 patients with uncontrolled diabetes, particularly those presenting with sinusitis, headache, and orbital edema symptoms. Despite intensive antifungal therapy and surgical intervention, it is a serious opportunistic fungal infection associated with long-term complications.

Keywords:

Coronavirus diseases 2019, case report, diabetes, fungal infection, mucorales, rhino-orbital-cerebral mucormycosis

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) is the strain of coronavirus that causes coronavirus diseases 2019 (COVID-19) and it is highly associated with severe fungal infection.[1] Mucormycosis, known as the black fungus, is a rare, life-threatening angioinvasive fungal infection caused by groups of molds called mucoromycetes. Since early 2021, COVID-19-associated mucormycosis (CAM) has been rising worldwide mainly in immune-impaired patients, particularly those with uncontrolled diabetes mellitus (DM) or treated with corticosteroids.[2] Rhino-orbital-cerebral mucormycosis (ROCM) is the most common clinical presentation of mucormycosis.[3] Symptoms of ROCM include headache, facial

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pain, facial/orbital swelling, and/or nasal eschar. Progressive ROCM infection results in necrosis of the head and neck, paranasal sinuses, proptosis of the eyeball, and/or ptosis of the eyelid with possible central nervous system (CNS) involvement.[4,5] ROCM is a rapidly progressive disease that even with aggressive antifungal therapy and surgical intervention, mortality risk is very high which ranges from 50% to 100%.[6] A recent review of several case reports, identified 80 cases of CAM from 18 countries.[2] In our report, we describe a case of ROCM with CNS involvement in a patient with uncontrolled DM and mild COVID-19 infection which was not treated with corticosteroid.

Case Report

A 35-year-old obese male with a body mass index of 37.35 kg/m², known history of hepatitis C infection, and recently diagnosed with DM had presented to the emergency department with dizziness, headache, speech difficulty, and left-sided facial weakness and was admitted as a case of suspected stroke. The patient's medical record showed no history of COVID-19 vaccination.

A nasopharynx reverse transcriptase–polymerase chain reaction test for COVID-19 was performed on admission and the result came positive with variant (BA.4/BA.5). Other significant laboratory results include refractory hypokalemia (potassium level were 2.0, 1.9, and 1.8 mmol/L), normal magnesium (2.94 mg/dL), hyperglycemia (point of care test was 421mg/dL and glycosylated hemoglobin (HbA1c) was 10.4%) and interleukin-6 was (175.00 pg/mL). Human immunodeficiency virus was ruled out by the enzyme-linked immunosorbent assay test. Chest X-ray showed clear costophrenic angles [Figure 1], but brain computerized tomography scan with contrast

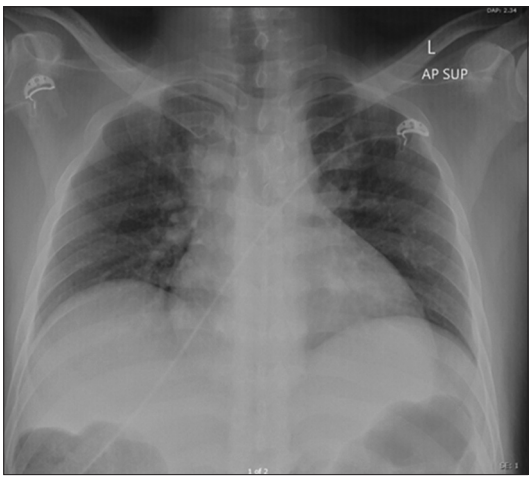

Figure 1: X-ray image on admission. Diagnosis: Normal cardiac configuration, both lung felids show increased bronchovascular markings; however, no detected pulmonary opacities and clear costophrenic angles

concluded features of pansinusitis with left side facial and periorbital inflammatory process (cellulitis) with left proptosis but no evidence of cavernous sinus thrombosis. No bacterial growth was detected from blood culture test, where candida albicans was detected in urine culture.

Given the suspicion of CNS infection, the patient was prescribed broad-spectrum antibiotic regimen (piperacillin–tazobactam, vancomycin, and metronidazole). Insulin therapy was started immediately for hyperglycemia management and supportive therapy (dexamethasone was started then ceased due to mucormycosis suspicion) for COVID-19 complications management.

On the next day of admission, the patient developed a sore throat and increased left eye swelling. Otherwise, he was stable with no fever and maintained oxygen saturation in room air. Ocular examination showed left eye proptosis, ophthalmoplegia, and lid edema with no ocular movement. The pupil was dilated and fixed/relative afferent pupillary defect. Nasal examination indicated septal deviation and black discoloration.

Nasal/sinus endoscopy revealed a black right middle turbinate with no pus or polyps. Various nasal biopsies for the fungal study were collected and sent to laboratory for microscopic culture growth and examination, and liposomal amphotericin 5 – 10 mg/kg/day was started as mucormycosis was suspected.

Later during admission, brain magnetic resonance imaging (MRI) scan with contrast revealed invasive sinonasal mucormycosis with orbital and cerebral extension and intracranial involvement [Figure 2]. The patient underwent emergency septoplasty and functional endoscopic sinus surgery. During the surgery, sinuses were opened, pus was drained, necrotic tissues were removed, and biopsies were collected for further histopathological tests. Histopathological examination confirmed mucormycosis, as culture reports indicated Rhizopus arrhizus and methicillin-resistant *Staphylococcus aureus* (MRSA) growth. Nasal MRSA PCR was not detected.

During the hospital stay, voriconazole was given in combination with liposomal amphotericin which was stopped because of not being effective against the Mucorales. The patient developed bilateral ophthalmoplegia, proptosis, and blindness, and necrotic eschar of the left ear [Figure 3]. Oral cavity examination revealed an extensive spread of Mucor.

On day 17, the patient had a drop in the Glasgow coma scale and developed a labored breathing pattern, thus he was transferred to the intensive care unit (ICU) for intubation. Repeated MRI scan for the brain revealed a complicated abscess formation. After being discharged

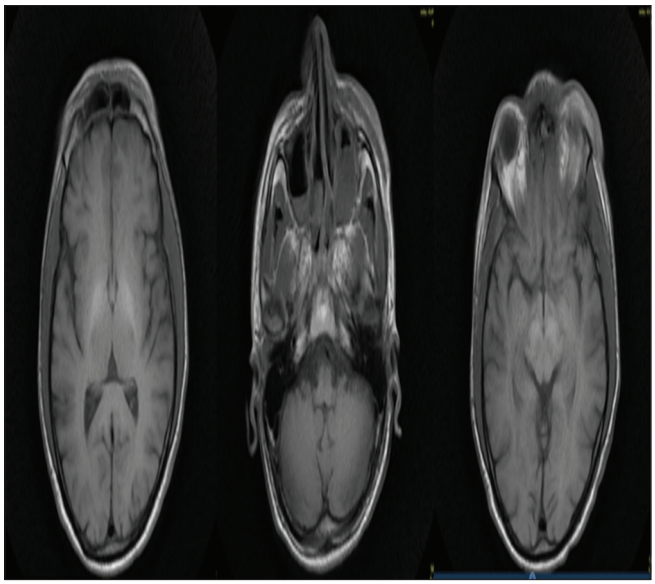

Figure 2: MRI brain scan with contrast. Conclusion: A case of invasive sinonasal mucormycosis showing orbital and cerebral extension. Orbital involvement: Periorbital and orbital cellulitis as described. No intraorbital abscess formation. Intracranial involvement: Regional focal bilateral frontal lobe early cerebritis as described likely due to perineural spread along olfactory nerve root. No current evidence of intracerebral abscess formation. MRI: Magnetic resonance imaging

from the ICU, the patient is in a stable condition with bilateral blindness. We obtained written informed consent from the patient's family.

Discussion

ROCM is a rare but fatal fungal infection involving the cerebellar and orbital sinuses as proposed by Champion early in 1969.[3] A sudden and rapid rise in mucormycosis incidence was observed during the second wave of the COVID-19 pandemic. The global prevalence of mucormycosis before the COVID-19 pandemic ranges from 0.005 to 1.7 per million population and it is almost 80 times higher in India (0.14/1000) compared to other world regions.[7] Before the era of COVID-19, there were a total of 310 cases of mucormycosis reported within the Middle East and North Africa region, whereas less than ten cases were reported from the United Arab of Emirates (UAE).[8] However, there were no cases reported related to CAM within the UAE regions.[9]

DM was often detected as an underlying disease; poor glycemic control might be a definite predictor of COVID-19 associated ROCM complication. A recent review reported that up to 87% of patients who developed ROCM were presented with uncontrolled DM.[2] As our patient presented to ER with an uncontrolled DM (HbA1c of 10.4%). One explanation for this association could be hyperglycemia stimulated inflammatory state which could be potentiated by concurrent COVID-19 infection.[10] In COVID-19 patients, several divergent

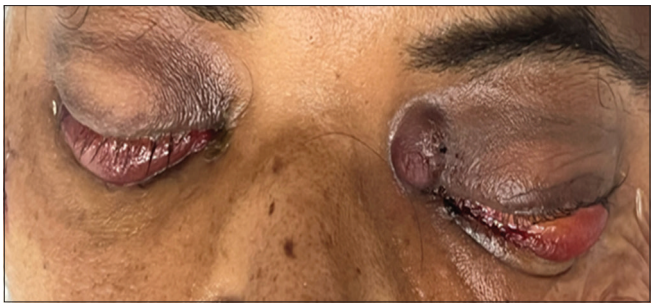

Figure 3: Ophthalmoplegia of both eyes, bilateral proptosis, and bilateral blindness

inflammatory pathways could act together to create an inflammatory environment that is greatly permissive to the development of CAM, potentiating the expression of specific virulence factors and related host damages. COVID-19 causes markedly raised proinflammatory CD4 T cells and CD8 toxic granules and cytokine. With the presence of hyperglycemia, the risk of mucormycosis increases due to several mechanisms such as upregulation of glucose-regulated protein 78 and fungal protein, impaired phagocytosis and chemotaxis by neutrophils and weakening the oxidative and nonoxidative pathways. Hyperglycemia, ketoacidosis, increased availability of free iron and impaired phagocytic action invariably result in an environment favorable for the growth of fungi. SARS-CoV-2 could possibly trigger diabetes, which could clarify COVID-diabetes as a causative factor in the pathogenesis of mucormycosis.[10]

Corticosteroid use is one of the risk factors for CAM. These agents are often given indiscriminately to COVID-19 patients, whereas most cases of CAM were detected after recovery of COVID-19.[2] Corticosteroids are known to lower patients immunity and put them at high risk of opportunistic infections, but their use was proposed to reduce risk of COVID-19 complications.[11,12] The current case was admitted with clinical signs of ROCM, where COVID-19 was detected positive at the time of admission, and he received dexamethasone before it was stopped for mucormycosis suspicion.

Mucormycosis management is based on three critical steps; controlling risk factor, extensive surgical debridement of necrotic infected tissue and proper antifungal therapy.[13] For those with uncontrolled DM, glycemic control is essential in limiting risk of CAM with better prognosis.[2] Lipid formulation of amphotericin B therapy, with a dose of 5–10 mg/kg/day, is recommended as initial therapy because it has better CNS penetration and lower nephrotoxicity compared to other formulations.[13] Isavuconazole and posaconazole, azole antifungals, can be an alternative regimen in two situations: as oral step-down therapy or as salvage therapy.[4,11] These agents are better choice for an individual with renal impairment and who cannot

tolerate amphotericin. Other azole antifungal agents like fluconazole, voriconazole, and flucytosine are not effective against Mucorales.[4]

The mucormycosis mortality rate ranges between 50% and 80% depending on the site of involvement.[14] Intracranial involvement, disseminated disease, and the presence of underlying comorbidities are associated with higher mortality. A recent review reported that 62% of patients with ROCM and CNS involvement had a median survival time of 26 days.[2]

This report raises some clinical questions regarding CAM such as whether there is any relationship between obesity and the risk of CAM, or whether the COVID-19 vaccine lowed the risk of CAM. These questions require further studies to be answered. In recent research, 58% of 73 patients with CAM were not vaccinated against COVID-19, whereas five patients received only one dose of the vaccine.[15] The current report, with the findings of the reported research, highlighted the importance of COVID-19 vaccine in reducing risk of morbidity and mortality associated with CAM.

One limitation of this case is that it was hard to determine the exact time of being infected with COVID-19, as the infection was confirmed once the patient was presented to the hospital, even thought he was not presenting with COVID-19 symptoms. However, COVID-19 infection was expected to be recent, especially because most of these complications were developed after admission.

Conclusion

In this complicated case of ROCM with intracranial involvement, uncontrolled diabetes with concurrent COVID-19 infection contributed to this opportunistic fungal infection which requires quick diagnosis and immediate intervention for a better prognosis. Despite the early diagnosis and aggressive antifungal treatment, mucormycosis is associated with long-term morbidity. Future research is necessary to develop immunotherapy to target this life-threatening pathogen.

Author contributions statement

HAHA (Lead): Conceptualization (lead), writing original draft (lead), reviewing, and editing the final draft (equal). AAAQ: reviewing and editing the final draft (equal). ZFA: supervised the case management (lead), reviewing and editing the final draft (equal).

Conflicts of interest

None Declared.

Consent to Participate

Patient consent for publication was obtained

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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