

# Mysterious alarming mucormycosis: Anesthetic challenges in a series of four cases

## ABSTRACT

The sudden epidemic of mucormycosis amid COVID-19 pandemic has significantly challenged our understanding of the disease while affecting the whole medical and surgical management. Overzealous use of steroids in the management of covid-19 and uncontrolled diabetes mellitus has resulted in a tremendous rise in mucormycosis cases further burdening the already strained health care infrastructure and health care workers, especially the anesthesiologists. While working in a tertiary care institute of the country, we have been facing multiple challenges in its anesthetic management on a daily basis. This article is a case series involving four different patients who were operated for rhino-orbito-cerebral mucormycosis with a brief discussion on various aspects of this multisystem epidemic.

**Keywords:** Amphotericin B, COVID-19, diabetes mellitus, mucormycosis, rhino-orbital-cerebral mucormycosis, steroids

## INTRODUCTION

India has witnessed a high incidence of the disease in the The occurrence of mucormycosis in the setting of Covid 19 is relatively new pandemic. We are standing at a crossroads where the tussle between our burden of huge population and the developing nation has made it an area of concern. Adding to it is the struggle with a fungal infection called mucormycosis. It is a rare fungal infection known to occur in diabetics and immunocompromised patients. Our huge population and lack of public health awareness where diabetes is underreported have become the perfect culture media for the ubiquitous fungus to grow. India has a high prevalence rate of type 2 diabetes mellitus (8.9% of adults, 77 million patients), which is a well-known risk factor.<sup>[1]</sup>

The acidotic medium secondary to raised lactate of COVID, impaired immune system postinfection, high sugar level, and irrational use of steroids helps the Mucorales to grow in closed sinus, orbits, and cerebrum. A prolonged high dose of steroids was accounted for another fungal infection called invasive aspergillosis.<sup>[2]</sup> The exact cause of the mucormycosis is yet to be ascertained of.

The treatment recommendations can be supported by the global guideline for the diagnosis and management of mucormycosis in 2019 by the European Confederation of Medical Mycology which supports an early debridement in addition to systemic antifungal treatment.<sup>[3]</sup> Hence, we face a string of problems and constellation of challenges which can happen while providing general anesthesia to the patients.

## CASE REPORTS

### Case report 1

A 62-year-old male patient reported to the ENT outpatient department (OPD) with chief complaints of drooping

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of eyelids, restricted eye movements for 2 weeks, and swelling and pain in the left jaw for 1 week. The patient was infected with COVID-19 infection 7 days post-COVID vaccination and had positive reverse transcription–polymerase chain reaction (RT-PCR). Then, he had received antibiotics (beta-lactams), injection hydrocortisone 200 mg IV stat f/b 100 mg IV OD, and injection enoxaparin 0.6 ml sc BD during his course of illness. High-resolution computed tomography (HRCT) thorax was done on the 10<sup>th</sup> day of symptom onset; the CTSS was 10/25. The patient maintained a saturation of above 93% and above on room air without respiratory distress. He was a known case of diabetes and hypertension for the last 2 years and was on oral medications but had discontinued drugs during infection. His HbA1c was 9.4% and red blood cell (RBS) of 514 mg/dl. Features of left axis deviation were present on electrocardiography (ECG). Chest X-ray (CXR) revealed peripheral opacities and bilateral basal lung zone involvement. Magnetic resonance imaging (MRI) brain was suggestive of left sinonasal orbital cerebral mucormycosis involving the hard palate. Cerebral vein thrombosis and intracerebral abscess in the left temporal area were involved. The patient was on amphotericin B for the last 3 days. He underwent surgical debridement of palate and sinuses and evisceration of eyes.

#### Case report 2

A 43-year-old female presented to ENT OPD with restricted eye movement and blurring of vision for 1 week, toothache and facial swelling for 1.5 months, and loss of hearing for 1 month. The patient had fever and myalgia 50 days back which subsided with antipyretics, and she did not undergo any hematological testing then. On evaluation, she was found to be diabetic with HbA1C of 9%. Her hemoglobin was 9 mg/dl, and peripheral blood smear showed macrocytosis suggestive of pernicious anemia. Her COVID biomarkers were marginally raised. ECG and CXR were normal. She was a diagnosed case of hypothyroidism secondary to Hashimoto's thyroiditis for 5 years with elevated anti-TPO antibodies levels, and was on tablet levothyroxine 50 mcg daily. The current laboratory report showed a TSH of 26. MRI brain showed invasive fungal sinusitis with infraorbital premaxillary, palatal, and infratemporal fossa extrusion. The patient was on oral posaconazole 300 mg for the last 4 days. Surgical debridement of palate and sinuses was done under general anesthesia.

#### Case report 3

A 48-year-old female presented to ophthalmology OPD with chief complaints of blurring of vision/double vision on the left side for the last 20 days and mild-to-moderate headache for the last 25 days. She had mouth ulcer 40 days back and was prescribed oral prednisolone 60 mg for 1 day followed

by 30 mg for 6 days. There was no history of fever, myalgia, malignancy, or any other immunosuppressive therapy. There was no contact history with the COVID-positive case as well. The patient had type 2 DM and hypertension for the last 13 years on regular medications but irregular follow-up. Her current HbA1C was 13.4%, RBS = 330 mg/dl, Hb 8.9 gm/dl, platelet count 1, 2 lakhs, total count was 7100, but neutrophil-to-lymphocyte ratio (NLR) was more than 9. RT-PCR came negative, but her COVID biomarkers were raised with D-dimer (933 ng/ml), IL-6 of 111 pg/ml, and C-reactive protein of 39 mg/l. MRI showed bilateral maxillary, sphenoid, ethmoid, and left frontal sinusitis with orbital and intracranial extensions. The patient was immediately started with liposomal amphotericin B 275 mg. The patient was posted for emergency surgical debridement of sinuses and evisceration of the left eye.

#### Case report 4

A 61-year-old female presented to ENT OPD with chief complaints of cough for 4 days and swelling of the left eye with blurred vision for 5 days. She had a high-grade fever and shortness of breath for 15 days with positive RT-PCR for COVID. She was hospitalized and was on oxygen support through face mask of 7 L/min maintaining a saturation of above 95%. Her COVID biomarkers were significantly raised. HRCT on the 9<sup>th</sup> day showed features of ground-glass opacities with CTSS of 12/25. The patient had received injection ceftriaxone (1 g) and injection Doxycycline 100 mg for 7 days. Inhalational steroid fludrocortisone 400 mcg was given four puffs twice daily. Her current white blood cell count was 1030/ $\mu$ l with NLR of 3, Hb of 9.3 mg/dl, and platelets within normal limits (WNL). CXR showed bilateral opacification with right > left, and Arterial blood gas (ABG) showed a PaO<sub>2</sub> of 68 mmHg with lactate of 3 mmol/dl. The patient was a known case of diabetes for the last 3 years with on-off medications. Currently, HbA1C was 11% with RBS of 299 mg/ml. MRI revealed left maxillary sinusitis with palatal invasion. Liposomal amphotericin B 150 mg was started, and surgical debridement was planned under general anesthesia.

#### Anesthetic management

The high-risk consents were obtained from all patients after giving proper explanations. A large working cannula was instituted and crystalloid infusion started at the rate of 20 ml/kg. If found necessary, triple lumen central venous catheters were used too. In the operation theater, ASA recommended monitoring such as SPO<sub>2</sub>, ECG, Non invasive blood pressure (NIBP), Heart rate (HR), and ETCO<sub>2</sub> were applied. IBP and NMT monitoring were also done in these patients to account for multiple comorbidities and associated hemodynamic derangements under general anesthesia. Besides, temperature and urine output monitoring were

also done. Preoxygenation of 5 min was done in all patients. All patients received injection midazolam 1 mg, fentanyl 2 mcg/kg, and propofol 1–2 mg/kg, followed by succinylcholine 2 mg/kg or rocuronium 1.2 mg/kg, and rapid sequence induction and intubation was done. The appropriate size-cuffed endotracheal tube was placed and tube position confirmed ETCO<sub>2</sub> monitoring and bilateral chest auscultation. Lung-protective ventilation strategy was used in these patients. They received injection paracetamol 15 mg/kg and injection ondansetron 4 mg IV 15 min before completion. Neuromuscular blockade reversal was done with injection neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg, and the patients were extubated after demonstrating adequate neuromuscular recovery. All patients were sent to intensive care for observation and further optimization.

## DISCUSSION

India is said to be the diabetic capital of the world.<sup>[1]</sup> With the rising number of rhino-orbito-cerebral mucormycosis, India has become the capital of this disease too. In our institute too, a large number of such patients are getting operated every day and anesthesiologists are facing a number of unique challenges in their management.

Airway management is difficult both due to the disease itself and due to diabetes-associated glycosylation of tissues leading to limited mouth opening and neck movements. Some of these patients are presenting with palatal perforation which has the same anesthetic implication as of cleft palate patients undergoing surgery.

Diabetic patients are at increased risk of developing nephropathy. Amphotericin B is the recommended treatment of mucormycosis, which is nephrotoxic. Daily assessment of renal function test and electrolyte balance has been recommended in these patients.<sup>[4]</sup> Hypokalemia can occur due to amphotericin B use which can exaggerate neuromuscular blockade. It is better to avoid longer acting muscle relaxants, and the use of NMT would be helpful. Drugs with exclusive renal clearance should be avoided, or dose modifications are necessary. Adequate hydration should be maintained to avoid prerenal failure.

Our first case was a known diabetic and hypertensive. Preoperative assessment for cardiac risk stratification is mandatory. The highly raised sugar in the perioperative period poses various challenges to both anesthesia and surgical outcomes. To add to the problem, the risk of general anesthesia in the post-COVID patient causing lung damage results in prolonged hospital stay. Uncontrolled diabetes

increases the risk of aspiration secondary to gastroparesis due to diabetic autonomic neuropathy necessitating rapid sequence intubation. Furthermore, in lieu of anticipated difficult airway, limited functional reserve post cover sequelae, the presence of senior anesthetist, preoxygenation, and the use of video laryngoscope come in our first line of airway management. Because of labile blood pressure secondary to autonomic involvement, preoperative preparedness of both vasopressors, inotropes, and anti-hypertensive medications is a must. As this patient was an uncontrolled hypertensive and was found to have left axis deviation in the electrocardiogram, a preoperative screening two dimensional echocardiogram may be necessary. Due to emergency nature of the surgery, adequate preoperative optimization is not possible. Judicious fluid management and advanced haemodynamic monitoring can provide better perioperative outcomes. Episodes of hypotension have to be avoided to prevent renal injury. Furthermore, hypotension may further worsen the already existing ventilation-perfusion (V/Q) mismatch of the post-COVID compromised lung. Lung-protective ventilatory strategy was used to prevent further barotrauma and volutrauma in an already insulted lung.

Increased blood pressure intraoperatively can cause increased bleeding, especially in Indian population where a frequently nutritional-deficiency anemia leaves very less scope of maximal allowable blood loss. Subsequently, one has to decide between the risks of transfusion-associated lung injury in a compromised lung and the lower down oxygen-carrying capacity due to anemia.

Intraoperative, temperature monitoring and prevention of hypothermia is a must to avoid lactic acidosis. Careful positioning of the patient is needed to prevent nerve compression and pressure sores.

Intraoperatively, glucose monitoring has to be done hourly to prevent both hypoglycemia and hyperglycemia. A high vigilance was kept to avoid precipitation of diabetic ketoacidosis as well as hyperosmolar coma as the stressors were present. Since the patient was on amphotericin B, electrolyte and fluid therapy were taken care of.

The second case was a known case of uncontrolled diabetes with Hashimoto's thyroiditis with pernicious anemia. As we know COVID-19 is associated with immune dysfunction, there was flaring up of the autoimmune disease postinfection. During preoperative evaluation, Thyroid stimulating hormone(TSH) was 26 signifying underoptimized hypothyroidism. Furthermore, autoimmune condition as pernicious anemia coexisted. We tried to evaluate other

autoimmune disorders like rheumatic arthritis which poses a threat to airway. A complete treatment history and detailed systemic examination along with laboratory parameters were done. It was challenging to give general anesthesia to a patient with a combination of the four well-defined ill-controlled comorbidities. We had to be careful on drug dosing as clearance is delayed in hypothyroidism. The bleeding tendency is higher in hypothyroidism. Meticulous surgical technique and the use of hemostatic agent should be instituted. It will be challenging to diagnose coma whether secondary to diabetic ketoacidosis or myxedema coma or prolonged effect of the anesthesia drugs. Since the patient had pernicious anemia, we avoided the use of nitrous oxide.<sup>[5]</sup> Hypothyroidism is associated with lymphocyte dysfunction, so strict aseptic precautions need to be taken.<sup>[6]</sup>

The third case is an interesting case who was asymptomatic COVID patient just presenting with mouth ulcer and was prescribed steroids. On further evaluation, we found his anti-SARS-CoV-2 immunoglobulin M antibody was high, suggesting infection in the absence of history of vaccination. So, it was a miss and overzealous use of steroids would have caused the opportunistic infection. This patient was a long ill-controlled diabetic and hypertensive whose implications have been discussed. NLR >9 in this patient indicates increased severity of the COVID as per the literature.<sup>[7]</sup> The inflammatory biomarkers were significantly raised, which signified the patient was in active cytokine storm. In cytokine storm, oxygen requirements increase manifold and at the same time the inflammatory injury to the lung decreases lung compliance. These factors contribute to increased risk while administering general anaesthesia. D-dimer was significantly raised, and the patient was not on any anticoagulation. Hence, intraoperative mechanical and pneumatic thromboprophylaxis was used. Furthermore, thromboprophylaxis was immediately started in the postoperative period with consultation with a surgeon on risk of bleeding. Intraoperatively, airway pressures were raised, so lung-protective ventilation was used. The patient was on active storm where steroids are the only proven treatment which is to be weighed against the further aggravation of fungal infection.

The fourth case needed oxygen therapy, and inhaled steroids were used. There is possibility of the deposition of the inhalational steroids in the nasal and oral cavity resulting in the formation of ideal cultivation field for the seeded

Mucorales to grow. We posted this as our first case of Operation theatre (OT) list due to her low Total leucocyte count (TLC) to minimize cross-infection.

## CONCLUSION

Rhino-orbital-cerebral mucormycosis has emerged as a leading cause of morbidity in COVID-19 patients requiring urgent surgeries. The emergency nature of these surgeries in association with various exaggerated or uncontrolled systemic diseases makes the anesthetic management challenging. A thorough knowledge about the problems is a foremost requirement for a successful outcome.

## Declaration of patient consent

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

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## Conflicts of interest

There are no conflicts of interest.

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