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Case Study

Challenges in Perioperative Anaesthetic Management of Post COVID Mucormycosis

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Abstract

Following the second wave of Covid 19 pandemic, there has been a surge in cases of post-Covid Mucormycosis. The cause of this rise has been variously attributed to underlying (and uncontrolled) diabetes, with or without the use of steroids and industrial grade oxygen cylinders. It is a highly lethal, locally-invasive infection with severe tissue destruction involving multiple organs. Rhino-orbital-cerebral mucormycosis is the most common presentation with patients complaining of fever, nasal congestion, purulent nasal discharge. It is seen to rapidly spread to contiguous structures, such as the palate, orbit, and brain over the course of a few days.

Successful treatment of mucormycosis is dependent on four key principles: early diagnosis, treatment of underlying predisposing factors, administration of antifungal therapy and surgical debridement of necrotic tissue while keeping in mind the toxic effects of systemic amphotericin B and its interaction with anaesthetic agents.

Surgical debridement is specially challenging to anaesthesia providers who share the airway. Particular attention must be made for the maintenance of an adequate mean arterial pressure and cardiac output while concomitantly avoiding further renal insults. A heightened awareness for renal, electrolyte, coagulopathy, hemodynamic, and respiratory aberrancies is warranted for when treating patients receiving Amphotericin therapy.

Keywords: *Covid-19; Mucormycosis; Amphotericin B; Anaesthetic Management; Surgical debridement*

Introduction

Among the post- Covid complications in the second wave of Covid 19 pandemic, we had seen a surge of cases of Mucormycosis around this part of the world. The cause of this rise is being attributed to underlying (and uncontrolled) diabetes, use of steroids and industrial-grade oxygen cylinders being pulled into use in view of shortage of medical oxygen cylinders.

Pathogenesis

Mucormycosis (previously called zygomycosis) is a rare but serious fungal infection caused by a group of moulds called mucormycetes found in soil and decaying vegetation. The genera most commonly found in humans are *Cunninghamella*, *Rhizopus*, *Mucor*, *Rhizomucor*; *Absidia* (now reclassified as *Lichtheimia)*. These fungi release a large numbers of airborne spores, which are inhaled. In healthy individuals, cilia transport these spores to the pharynx and are cleared through the GI tract. In immuno-compromised individuals, it starts as a locally invasive infection with severe tissue destruction due to endothelial invasion and then, involves multiple organs through hematological spread. Difficult airway and hemodynamic instability is seen in almost all the cases, carrying a high percentage of mortality [1,2].

Among the recognized host conditions for mucormycosis colonization are persistently high blood glucose levels with or without acidosis, solid organ transplants, malignancies and use of immune-suppressants like glucocorticoids. Host defenses are compromised by

microvascular degeneration and impaired fungicidal activity of neutrophils. Uncontrolled blood sugar also suppresses a group of immune proteins called beta-defensins. Elevated serum free iron as well as raised glycogen and ketones produce an acidic milieu thereby supporting growth of fungal hyphae. The fungal hyphae produce an enzyme, *ketone reductase* which allows the fungi to thrive in acidic conditions [3,4].

The iron chelator deferoxamine deserves special mention. It chelates both iron and aluminum in-vitro and has immune-modulatory and anti-oxidant actions by directly inhibiting IL-6 synthesis through decreasing NF-kB. The deferoxamine-iron chelate, called feroxamine, increases iron uptake by the fungus since it is a siderophore for the species *Rhizopus.* This stimulates fungal growth leading to tissue invasion [3,56].

Clinical features

Thrombosis, ischemia and necrosis of the surrounding tissues are the classical features of mucormycosis [3,7]. Infection usually begins in the nasal turbinates' or the alveoli, then the fungal hyphae adheres to arterial walls and grows along the internal elastic lamina. Unless the patient has an underlying hematologic malignancy with neutropenia, there is no hematogenous spread to other organs including lungs and gastrointestinal tract.

Though Rhino-orbital-cerebral (ROC) and pulmonary infections are the most common syndromes reported, cases of facial numbness due to infarction of sensory branches of the fifth cranial nerve, altered sensorium due to spread to the cavernous sinus or frontal lobe, have also been reported [3,8].

Successful treatment of mucormycosis is dependent on four key principles [5,9]

- Early diagnosis
- Administration of antifungal therapy
- Treatment of underlying predisposing factors
- Surgical debridement of necrotic tissue.

Indications of surgical resection for mucormycosis includes overwhelming infection with tissue necrosis [9-11].

Antifungals such as voriconazole, fluconazole and echinocandins have nil or limited effect against mucormycosis. Injectable Liposomal amphotericin B (0.5 to 1 mg/kg/day), posaconazole, or isavuconazole are generally recommended. Side effects of Amphotericin B range from fever, shivering, hypotension, hypoxia, hypokalemia, hypomagnesaemia to arrhythmias and nephrotoxicity [5].

Other considerations also include management of diabetic ketoacidosis (DKA) with insulin and volume repletion. Use of colony-stimulating factors helps in reversing neutropenia associated with hematologic malignancy. With-holding cytotoxic chemotherapy, immunosuppressive drugs and replacing deferoxamine with Hydroxypyridine chelating agents also helps to improve neutrophil counts [5,12,13].

A review of 179 cases of ROC mucormycosis found that 70 percent of the patients had diabetes mellitus with ketoacidosis at the time of presentation [14]. The RetroZygo study in France found following predisposing factors of mucormycosis [15].

- Hematologic malignancy - 50%
- Diabetes mellitus - 23%

- Trauma - 18%.

Most of the patients managed in our Institution presented as acute pan-sinusitis with fever and purulent nasal discharge, which rapidly spread to contiguous structures, such as the palate, orbit, and brain within a few days. Only 15% cases had cerebral and 5% cases had GI Mucormycosis in addition to ROC involvement. All developed onset of symptoms within 01 month of initial treatment of covid, while almost 95% patients had received oxygen therapy and steroids.

60% of patients had moderate covid with unenhanced chest Computerized Tomography (CT) COVID-19 Reporting and Data System (CO-RADS) Score between 12-18. Majority had pre-existing diabetes mellitus and only 15% patients were fully vaccinated when they tested positive for covid.

All patients had received Amphotericin therapy and 60% of cases demonstrated increased creatinine levels, out of which, 35% required haemodialysis prior to surgery. Local examination showed tissue necrosis resulting in eschars visible in the palate or skin overlying the orbit (Figure 1-4).

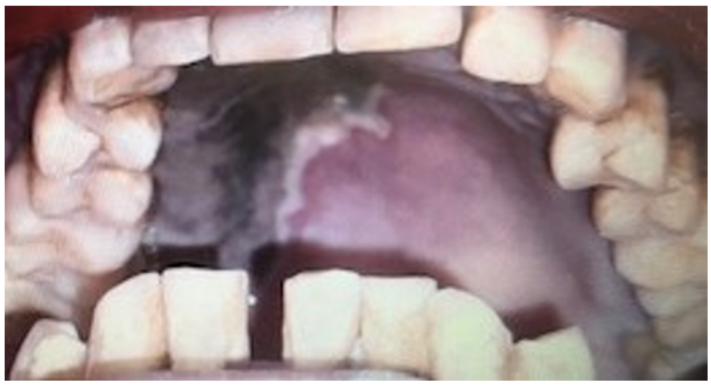

Figure 1: *Hard Palate Necrosis and Eschar.*

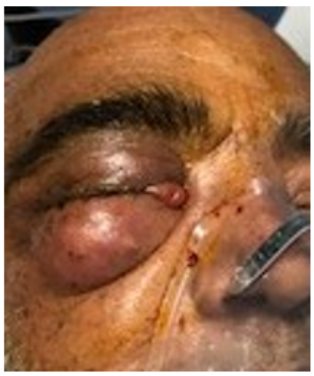

Figure 2: *Orbital involvement of Mucormycosis.*

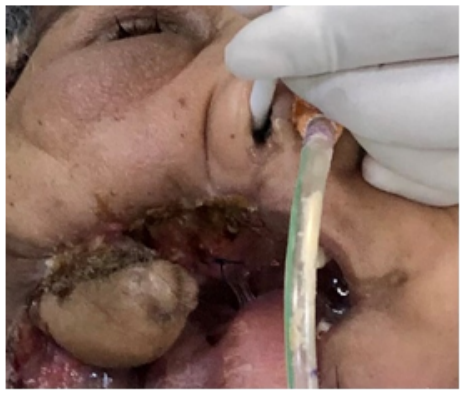

Figure 3: *Facial Deformity due to Tissue Necrosis and Surgical Excision.*

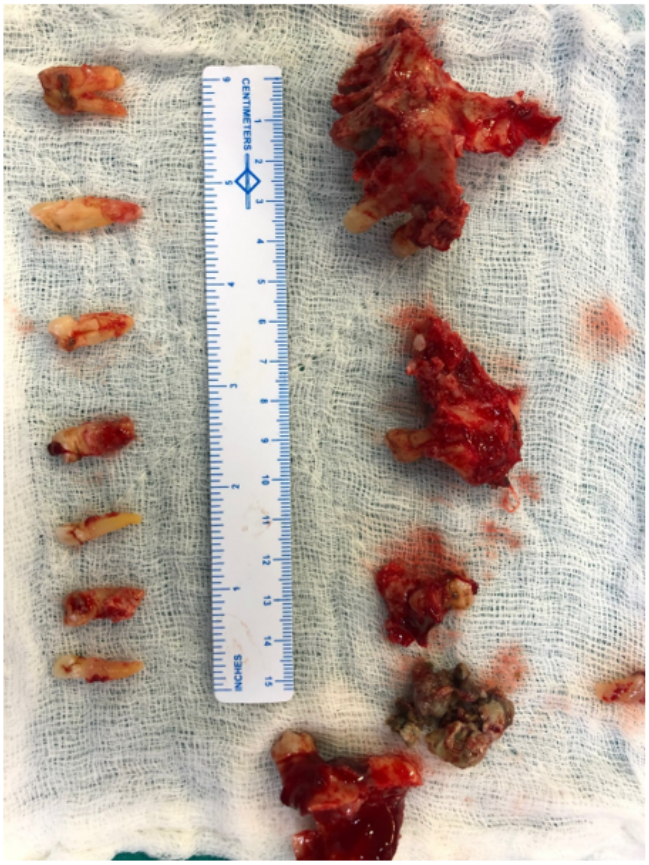

Figure 4: *Wide local Excision of affected tissue.*

Perioperative anaesthetic management

Preoperative evaluation [1,5.9,11]

- **Airway evaluation**: ROC mucormycosis may present with difficult mask ventilation and/or difficult intubation scenarios due to palatal perforation, supraglottic edema associated with fungal debris in the oropharyngeal region and co-existing oedema of periorbital and maxillary areas.
- **Pulmonary evaluation**: Pulmonary functions and residual lung damage should be evaluated in all post Covid cases by Pulmonary Function Tests and CT chest.
- **Cardiac evaluation:** Cardiac evaluation with preoperative 2D Echocardiography should be done as the use of corticosteroids, Amphotericin B and digitalis glycosides may potentiate cardiac dysfunction and arrhythmias.
- **Renal function evaluation**: Serum potassium, magnesium and creatinine levels are important confounders affecting mortality in mucormycosis. Care to be taken in patients on Amphotericin B therapy.
- **Haemodynamic monitoring**: To prevent the progression of renal damage, adequate renal perfusion in the perioperative period should be maintained by preventing hypotension and ascertaining hemodynamic stability.
- **Arterial cannulation:** Mucormycosis is a vaso-occlusive disease. Continuous measurement of arterial blood gas values and intermittent biochemical analyses are essential due to the metabolic condition, fluid-electrolyte imbalance, and coagulopathy.
- **Central venous cannulation (CVC)**: Patients with mucormycosis usually have coexisting diffuse sepsis, multiple organ failure and immunosuppression which increases morbidity and mortality.[1,16] In patients with ROC involvement, the internal jugular vein is not the primary choice for CVC due to its proximity to the infected site. Subclavian vein cannulation by infraclavicular approach or femoral access is preferred so as to minimize the risk of contamination by the patient's secretions during insertion.

Advantages of using peripherally inserted central catheters include

- No risk of pleuropulmonary complications even in severe respiratory distress
- No risk of bleeding in anticoagulated patients
- No interference with the respiratory management in patients on NIV
- No interference in management of the exit site in pronated patients.

To reduce the thrombotic risk in patients with central lines and in the absence of contraindications, low molecular weight heparin is given in prophylactic (100 units/kg/24 h) or therapeutic (100 units/kg/12 h or 150 units/kg/24 h) doses [16,17].

Patient counselling

Surgical resection of ROC mucormycosis is an aggressive procedure, resulting in cosmetic deformity, which in turn may lead to severe anxiety in patients. Emphasis should be given to preoperative counselling and administration of anxiolytics.

Anaesthetic management

Aggressive intraoral surgical debridement is performed under general anaesthesia with American Society of Anaesthesiology III risk stratification. In order to avoid need for mask ventilation and regurgitation, Rapid Sequence Induction (RSI) using disposable circuits and HEPA filter barrier is recommended.

Premedication

An antisialagogue (Inj Glycopyrrolate 0.2 mg over 1-2 minutes) is used to reducing secretions and preventing reflex bradycardia.

- Other premedications include anxiolytic-hypnotic-sedative agents like benzodiazepines. Midazolam is a benzodiazepine with anxiolytic, muscle relaxant, anticonvulsant, sedative, hypnotic, and amnesic properties. The initial *dose* in adults is 2-2.5 mg given 5-10 minutes before the start of the procedure.

- Opioid agonists like Fentanyl (2 mcg/kg), also provide analgesia and sedation, but should be used cautiously in post-CoVid respiratory situations due to its adverse effects on respiratory rate and alveolar ventilation.

Preoxygenation

Following recovery from moderate-severe CoVid, rapid desaturation is seen with RSI. In patients breathing room air and maintaining an arterial partial pressure of oxygen (PaO_2) of ≈90 to 100 mm Hg), rapid desaturation occurs (within 45-60 seconds) between sedative/paralytic administration and airway placement, despite 100% oxygen at high flow. Because of their exhausted compensatory mechanisms, patients with acute hypoxemic respiratory failure have minimal respiratory reserves, hence preoxygenation is must in order to bring the saturation as close to 100% as possible. Denitrogenation also increases the residual capacity and maximize the oxygen storage of the lungs. Three minutes' of tidal-volume breathing is the acceptable duration of preoxygenation for most patients.

Induction and intubation

Appropriate induction agent is administrated in the form of propofol (0.5-2 mg/kg) or thiopental (5 mg/kg) followed by a muscle relaxant. Palatal perforation or eschar, if any, are covered with gauze. Intubation is done with appropriate sized cuffed reinforced endotracheal tube by the most experienced anaesthesiologist in minimum possible time and confirmed using capnography.

Because of short and predictable time of onset and its rapid recovery time, succinylcholine, is preferred as depolarising neuromuscular blocking agent for RSI. However, the kyperkalemic effects of succinylcholine may be exaggerated by the use of exogenous catecholamines leading to fatal arrthymmias. Also, prolonged ICU stay may precipitate critical illness myopathy, which is a relative contraindication for the use of depolarising agents. In cases of severely decreased PO_2/FiO_2 ratio, a modified RSI can be done with low pressure ventilation before intubation.

Royal College of Anaesthetists, Difficult Airway Society, Faculty of Intensive Care Medicine, and Intensive Care Society have jointly recommended use of Rocuronium for emergent intubation of critically ill as well as CoVid patients' [18].

Serum potassium levels should be closely monitored while administering amphotericin. If the patient develops ventricular ectopics, suitable treatment should be instituted using FiO_2 of 1.0, withdrawal of amphotericin infusion, injection lidocaine (1.5 mg/kg bolus dose repeated by 0.5 mg/kg dose 5-10 minutes later) or Injection amidarone (in standard recommended dosage) [1,5,11].

Maintenance

Total intravenous anaesthesia with airway protection has been advocated in place of inhalational agents due to lack of disposable vaporizers in a Covid scenario and cost concern. In case volatile anaesthetic agents are used, Isoflurane is selected as in-vitro studies have demonstrated its antibacterial and antifungal activity [19]. Nitrous oxide is avoided in case of low pre-operative saturations. Lung Protective Ventilation as per ARDS protocol should be followed with optimal positive end expiratory pressure (PEEP) and a plateau pressure (Pplat) <35 mmHg to achieve a SpO_2 >90% and admissible hypercapnia [1,5]. Muscle relaxation is maintained with appropriate neuromuscular blocking agent (NMBA).

Extubation

The threshold to extubate should be low in patients with ROC mucormycosis Patients who achieve spontaneous respiration (respiratory rate > 12/min, tidal volume > 5 mL/kg), have a SpO_2 levels of > 95% and show good response to verbal commands can be considered for extubation.

Failure to extubate may be due to liberation failure (i.e., the inability to ventilate spontaneously without ventilator support) or extubation failure (i.e., the inability to tolerate removal of the endotracheal tube) or both. Post-Covid lung changes may cause the former and pre-operative supraglottic edema increases the incidence of reintubation. Additionally, RSI can lead to ulcerations and damage to the vocal cords.

Reintubation

Presence of postextubation stridor is a potentially fatal condition and reflects a narrowing of the airway lumen of more than 50 %. Hence airway assessment is mandatory before extubation in ROC mucormycosis. Cuff-Leak Test (CLT) which is the best indicator of glottis oedema, is an easy-to-perform, non-invasive test which should always be done prior to planned extubation [5,11,20].

Prevention

Deliberate efforts to eliminate possible risk factors helps to prevent post-operative stidor and reintubation. An adequate-size endotracheal tube should be used. Cuff pressures should be maintained at 22-25 cm H_2O to prevent formation of glottis edema and pressure ulcers. The duration of intubation should be kept minimum possible. The application of NIV might facilitate early extubation.

Intravenous or nebulized corticosteroids (methylprednisolone 20-40 mg or dexamethasone 5 mg) with at least 4-48 hours between administration of corticosteroids and extubation have shown to decrease the incidence of stidor by more than 50% [20]. Reintubation should be performed without delay in the presence of respiratory insufficiency.

Post-operative management

Multimodal analgesia is preferred for pain relief. Inhalation corticosteroids should be given to prevent lung fibrosis. Regular chest physiotherapy and incentive spirometry should be continued, if possible.

				Remarks
1	Pre op			
		Medical Management	Antifungal, Diabetic Control Stop Steroids, Correct Fluid loss	Amp B Insulin
		Airway Assesment	Difficult Airway	
		Renal Function Evaluation	S. Potassium and Creatinine	Since AmB is Nephrotoxic
		Cardiac Evaluation	Potassium toxicity	Due to AmB use
		Pulmonary Evaluation	PFT & HRCT Chest	Residual lung damage due to Covid
		Investigations	CBC, Blood Sugar, RFT, LFT CT Chest, ECG, 2 D ECHO	
2	Intra Op			

		Airway Management	Difficult Airway Cart	Rapid sequence Intubation
		Haemodynamic monitoring	Arterial line	Electrolyte and Blood gases monitoring
		CVC Cannulation	Prefer Sub clavian or Femoral access. Avoid JVC	Due to proximity of Jugular vein to the infected site and risk of pulmonary hematoma associated with thrombocytopenia
		Muscle Relaxant	Prefer Vecuronium	Cardiac stable
		Inhalational Anaesthetic	Prefer Isoflurane	Isoflurane has antifungal properties
		Ventilation	ARDS Protocol	Lung protective Ventilation
		Monitoring	Potassium levels	
		Extubation	After Cuff leak Test	
3	Post Op			
		Post op care	Elective Ventilation in ICU or NIV	Difficult airway post resection and AmB use.
			Inhalation Corticosteroids	Post Covid Fibrosis
			Lung Expansion Exercises	Incentive Spirometry

Table 1: *Considerations for Perioperative management of Mucormycosis.*

Conclusion

With the increase of mucormycosis as a result of post-covid complications, a large number of cases are coming up for surgical resection, this being the primary lifesaving treatment. Medical management is by Amphotericin B, which is a highly nephrotoxic drug.

The aim of this writeup is to highlight the need for early diagnosis and surgical debridement of necrotic tissues in Mucormycosis while keeping in mind the toxic effects of systemic amphotericin B and its interaction with anaesthetic agents.

Anaesthesia providers must pay particular attention for the maintenance of an adequate mean arterial pressure and cardiac output while concomitantly avoiding further renal insults. A heightened awareness for renal, electrolyte, coagulopathic, hemodynamic, and respiratory aberrancies is warranted while treating patients receiving Amphotericin B therapy.

Ethical Clearance

Institutional clearance was taken from the Ethical committee to use the patient Data. Patient's permission was taken to use the photographs.

Acknowledgement

The manuscript was compiled by corresponding author and edited by the first author. There is no conflict of interest.

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