16 Medical Management of Patients with Rhino-Orbito-Cerebral Mucormycosis

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In the year 2019 world encountered COVID-19 pandemic. The first wave hit the world in 2019, the second one being more lethal hit India in 2021. In the second wave, a large number of individuals were affected and required critical care too. Soon we were facing an unprecedented tsunami of mucormycosis. We were familiar with a deadly fungal disease in the past, but this time's magnitude and extent threw new challenges in patient care. There are a variety of factors that make COVID-19 patients more susceptible to mucormycosis. Management of mucormycosis involves a multidisciplinary team approach. This chapter describes the role of a physician in the evaluation and management of this devastating disease.

16.1 Evaluation of the Patient

16.1.1 Initial Workup

All the patients admitted to the hospital are thoroughly investigated in the first 24 h to know the extent of the disease. KOH staining, fungal and bacterial cultures from the areas affected, and rapid molecular tests should be sent. Computed tomography and magnetic resonance imaging are ordered to ascertain the stage of the disease. Patients with extensive involvement of sinuses, orbit and brain need to be managed more aggressively as mucor gives very little time to save the life.

16.1.2 Treatment of COVID

16.1.2.1 The Exact Date of Onset of Infection

It is necessary to know the exact date of onset of illness as the likelihood of developing cytokine storms decreases as time elapses.

16.1.2.2 Hospital-Based Treatment (ICU/HDU/Ward) or Home Isolation

The previous history of hospitalization for COVID helps us know the nature and extent of COVID pneumonia, oxygen requirement and other organ involvement. Previously hospitalized patients are more prone to have hospital-acquired bacterial infections. So it helps us in deciding the empirical selection of antibiotics till we have the culture reports.

16.1.2.3 Use of Steroids

The history of steroid usage has an important implication. We should make a note of the dose and duration of the steroid. The indications of

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steroid usage during COVID treatment should also be documented.

16.1.2.4 Use of Immunosuppressants

Severe COVID pneumonia has put us in place to use immunosuppressants to manage the dysregulated host immune response. Many patients with severe COVID-19 do not respond to steroids and other adjuvant therapies. The magnitude of cytokine storm compels the healthcare provider to use immunosuppressants to save human life in limited cases. There are a plethora of immunosuppressants used in this pandemic like tocilizumab, bevacizumab, tofacitinib and baricitinib. These drugs helped us save a few patients but put the patients at risk of opportunistic infections by lowering the host immunity. So knowledge of their usage helps us to tailor the treatment.

16.1.2.5 Respiratory Evaluation

A careful evaluation of the respiratory system should be done as the patient's oxygen requirement seriously affects the treatment protocols. Those patients still suffering from severe COVID pneumonia requiring high-flow oxygen or ventilator support will be the most difficult to manage. Many of these patients will not be medically fit for any surgery or debridement for mucormycosis. High-resolution computed tomographic scan of the chest should be done in all such patients to know the CT severity index of COVID pneumonia. The severity of previously underlying chronic lung diseases like asthma, chronic obstructive pulmonary airway disease and interstitial lung disease should be accommodated in the treatment protocols.

16.2 Pulmonary Mucormycosis

Pulmonary mucormycosis is a rare opportunistic infection caused by this fungus and generally affects the hosts with poor immunity. This infection has a high mortality (40–76%) [1–3] and is a source of serious morbidity as the fungus causes extensive tissue destruction rapidly. It presents with fever, cough, haemoptysis and rapidly deteriorating lung functions causing life-threatening hypoxia. Radiologically it presents with multiple cavitary lesions in lungs especially in those individuals who have poorly controlled diabetes and are immunocompromised due to associated comorbidities. Fibreoptic bronchoscopy in expert hands can be used to obtain biopsy from the suspected lung lesions. A combined approach of surgical resection and amphotericin B therapy is the best possible treatment option in such scenario right now. Future studies are needed to evaluate treatment protocol and outcomes in patients suffering from this disease.

With the involvement of lungs, although rare, we have seen cases of fungal pneumonia in this pandemic. A few patients, on rare occasions, can have disseminated mucor infection in the lungs too. The presence of fungal pneumonia will pose a further challenge in the treatment of these patients. Serial chest X-ray and arterial blood gas analysis should be carried out. Patients with mucormycosis who are stable and not on oxygen support should be subjected to pulmonary function testing and 6-min walk test for the evaluation and fitness of surgery if required.

16.3 Blood Tests

All patients suffering from mucormycosis should undergo routine blood investigations like complete blood count, kidney function tests, liver function tests, thyroid function tests, glycosylated haemoglobin, C-reactive protein quantitative and D-Dimer. Procalcitonin, blood culture, urine culture and galactomannan assay should also be done in seriously ill patients.

16.3.1 Evaluation of Diabetes

Extensive diabetic and stress hyperglycaemia evaluation should be carried out in all the patients. Hyperglycaemia in mucormycosis patients further propagates the disease and hampers recovery. Random blood sugar levels more than 200, fasting blood sugar levels more than 124 and HbA1c levels more than 6.4 are diagnostic of diabetes mellitus [4, 5]. Some of the patients do not

fit into these criteria on admission but develop random blood sugar levels more than 200 later in the course of disease due to stress hormones or the use of steroids. So it is necessary to check the blood sugar levels regularly, even in non-diabetic patients. Such patients should also be managed like a diabetic patient till their blood sugar levels are normal.

16.3.2 Evaluation of Comorbidities

Extensive evaluation of all the patients of COVID-19 and mucormycosis should be done for the underlying comorbidities like coronary artery disease, chronic liver disease (CLD), chronic obstructive airway disease (COAD), chronic kidney disease (CKD), hypertension, stroke, post organ transplant, post chemotherapy. Patients already on antiplatelets should be offered anticoagulants in lower doses than necessary. Patients with CLD and CKD have alrered baseline coagulation profile, so PT and aPTT should be tested before beginning anticoagulants and should be monitored later on. The advice of concerned subspeciality should be sought as all these are immunocompromised states, and any new organ failure will further jeopardize patients' complete care and prognosis.

16.4 Management

16.4.1 Management of Mucor

Mucormycosis is a devastating disease and spreads very rapidly. This fungus is angio-invasive and leads to infarction of tissue. If not treated appropriately, it can prove fatal. Patients should be first categorized based on the severity. Those aged 60 years and above, with ocular and neural involvement, immunosuppressed, uncontrolled diabetes, and severe COVID pneumonia requiring high flow oxygen or ventilator support should be treated more aggressively. Antifungal therapy and surgery remain the mainstay of treatment. For those patients who are unfit for surgery, medical management continues until they become fit for surgery. Surgery should be planned as early as the conditions permit.

16.4.2 Treatment of COVID Pneumonia

Treatment of COVID pneumonia includes anticoagulation, oxygen, and ventilator support to all patients suffering from active COVID pneumonia.

Steroids should be avoided as far as possible if the patient is not on supplemental oxygen or ventilator therapy. Patients requiring supplemental oxygen and ventilator therapy, steroids can be considered in minimal possible doses, i.e. 0.5 mg/kg of methylprednisolone. The dose and duration should be tailored according to the clinical scenario and tapered off quickly.

Immunosuppressants like tocilizumab and baricitinib should be avoided in the management of such patients as it will risk the flare-up of mucormycosis.

Antibiotics: Routine and prolonged use of broad-spectrum antibiotics should be discouraged. Broad-spectrum antibiotics can be considered empirically in seriously ill patients till the report of bacterial culture is awaited. Afterwards, the de-escalation of the antibiotic regime according to the culture report should be instituted.

16.4.3 Management of Diabetes

The prevalence of diabetes in India is 11.8% [6]. The high prevalence and absence of routine health checkups have put a large number of asymptomatic, previously undiagnosed, uncontrolled diabetic patients at risk of severe COVID infection and, later on, mucormycosis. Steroid usage is recommended and life-saving for severe COVID-19 pneumonia, but their indiscriminate overuse also poses a challenge for the control of diabetes. High blood sugar levels, steroids, malnutrition, immunosuppression and COVID-19 infection per se set the stage for mucormycosis. So it is imperative to control blood sugar levels tightly to prevent the onset of mucormycosis and

prevent its complications. Basic principles for the control of diabetes in such patients are as follows.

1. Insulin infusion is the mainstay of therapy for seriously ill patients requiring vasopressors and ventilator support and a very high blood sugar more than 400 [7, 8].
2. The basal bolus regimen is ideal for all stable patients taking regular meals or on RT feeding.
3. Oral hypoglycaemic agents can be adjuvants in stable patients with previously controlled diabetes or requiring large doses of insulin therapy. Long-acting insulin secretagogues and SGLT2 inhibitors should be avoided [9]. DPP4 inhibitors and metformin can help manage diabetes in such patients [9].

The target glucose levels are 140–180 irrespective of the meal [9]. Insulin infusion should be considered in seriously ill patients admitted to intensive care units with very high blood sugar levels.

16.4.3.1 . Insulin Infusion

Insulin infusion can be prepared by mixing 50 units insulin regular in 49 CC of normal saline and should be administered with the help of an infusion pump [10, 11]. The initial rate of infusion should be blood glucose divided by 100. The rate of infusion should be titrated every hour to maintain blood glucose between 140 and 180. Once the patient gets stabilized, transition to subcutaneous insulin should be planned. The basal insulin (degludec, glargine and detemir) should be added first. The starting dose of basal insulin can be 20–30% of the total daily requirements [10, 11]. The basal insulin dose should be less in patients with underlying comorbidities like chronic liver disease, chronic kidney disease and heart failure.

16.4.3.2 Sliding-Scale Insulin Regimen

Sliding-scale insulin regimen is not a good regimen for inpatient diabetes management. It does not provide a stable control of blood glucose levels but can be used in limited settings where oral intake is deficient and blood sugar levels are not so high. It can be used in patients whose blood sugar levels are <250, but it provides a roller-coaster kind of control with excursions sometimes and low sugar levels at other times so it should be better avoided.

16.4.3.3 Oral Hypoglycaemic Agents

Oral hypoglycaemic agents can be used in the limited settings of hospitalized patients like stable patients taking regular meals, those who have high insulin requirements, high insulin resistance, and patients with no underlying chronic kidney disease or chronic liver disease. Currently, metformin can be used in non-critically ill patients with preserved renal and hepatic functions. It primarily acts on the liver and prevents gluconeogenesis, and it increases insulin sensitivity, so it helps in the control of fasting blood glucose. The initial dose of metformin should be 500 mg per day, and it can be titrated up to 2000 mg per day depending on the tolerability of the patient. DPP4 inhibitors like sitagliptin, vildagliptin, alogliptin, saxagliptin and linagliptin can be used in stable patients [9–12]. They should be avoided in patients with past history of pancreatitis. Dose modification will be required in hepatic and renal impairment. They mainly affect postprandial blood glucose levels.

Patients with uncontrolled blood glucose levels at the time of admission should be discharged on insulin and oral hypoglycaemic agents. As insulin is an anabolic hormone, it helps in the recovery of the patients and it should be continued at least 4–6 weeks after the patient's discharge from the hospital.

16.4.4 Anticoagulation in COVID

COVID-19 leads to thrombosis in microvasulature of lungs and other internal organs leading to ischaemic changes. These ischaemic changes can manifest as pulmonary thromboembolism, deep-vein thrombosis, myocardial infarction, ischaemic stroke and renal artery thrombosis in rare cases. The incidence of thrombotic disease in

individuals affected by COVID-19 is reported as high as 31% [13, 14]. So it is imperative to use anticoagulants to prevent these complications in high-risk individuals as well as to treat these complications.

Those patients who are taking anticoagulant or antiplatelet therapies for their medical disorders should continue these drugs if they get COVID-19 infection.

Hospitalized adults with COVID-19 should receive prophylactic dose anticoagulation.

There is currently insufficient evidence to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients [14, 15].

Patients with COVID-19 who experience thromboembolic event (deep-vein thrombosis or pulmonary embolism, cavernous sinus thrombosis, renal or splenic artery thrombosis, ischaemic stroke) or who are highly suspected of having thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy.

Low-molecular-weight heparin is the preferred agent for anticoagulation. The therapeutic dose is 1 mg/kg/dose twice daily. Unfractionated heparin can be used in patients with altered kidney functions with serial monitoring of aPTT. aPTT should be kept around twice the normal upper limit.

16.4.5 Amphotericin B-induced Nephrotoxicity

Amphotericin B can cause nephrotoxicity in the form of acute renal failure and hypokalaemia. So it is necessary to measure kidney functions and electrolytes on a daily basis to evaluate for such damage. Patient's hydration should be well maintained, and any other nephrotoxic drug should be avoided. On discontinuation of antifungal therapy the renal functions are gradually regained. New preparations of the drug, such as liposomal amphotericin B, are very less nephrotoxic.

In a nutshell, mucor and COVID are a deadly combination. The addition of other comorbidities further complicates the clinical scenario and hampers the adequate management of patients. So it is of utmost importance to evaluate and treat the patient in toto to achieve the desired outcome. Further prospective randomized controlled studies are needed for a better understanding of treatment options and their adequate duration.

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