

COVID-19 associated mucormycosis and its effect on oro facial region- A review and future perspectives

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Abstract:

Corona virus is caused due to severe acute respiratory syndrome corona virus-2. In symptomatic patients, 81% have mild to moderate symptoms, while 14% develop severe symptoms and 5% suffer critical symptoms. Mucormycosis is a significant, but rare opportunistic and life-threatening fungal infections mainly caused by *Rhizopusarrhizus* with higher case fatality rates, mucormycosis belongs to a group of saprophytic fungi growing on decaying vegetation and food containing high sugar content, it is observed in the many post COVID cases. Recent increase in the number of COVID-19 patients with mucormycosis infection are mostly due to uncontrolled diabetes and excessive use of steroids for the treatment of Coronavirus infection. The triad of coronavirus, corticosteroid use and uncontrolled diabetes mellitus have been evident for significant increase in the incidence of maxillofacial mucormycosis

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I. Introduction

Corona virus is caused due to severe acute respiratory syndrome corona virus-2. It is an, enveloped RNA beta coronavirus that emerged in wuhan, china in December 2019. It is a global public health crisis associated with substantial mortality and morbidity worldwide.⁽¹⁾ World health organisation (WHO) on march 11, 2020 has declared the novel corona virus (COVID-19) outbreak a global pandemic.⁽²⁾ It is noted that, about 1/3 of infected people are asymptomatic. In symptomatic patients, 81% have mild to moderate symptoms, while 14% develop severe symptoms and 5% suffer critical symptoms.⁽³⁾

Mucormycosis belongs to a group of saprophytic fungi growing on decaying vegetation and food containing high sugar content.⁽⁴⁾ Recently, Mucormycosis is observed in the many cases post COVID. The primary reason appears to be facilitating Mucorales spores to germinate in people with COVID- 19 is an ideal environment of low oxygen, high glucose, hyperglycaemia, steroid induced hyperglycaemia, high iron levels, decreased phagocytic activity of white blood cells due to immunosuppression coupled with several other share risk factors including prolonged hospitalisation with or without mechanical ventilators.⁽⁵⁾ The occurrence of Mucormycosis may vary depending on the nature of population, co-morbidities such as blood pressure and diabetes, and also medical facilities used to treat the patients with presence of these infections. The direct form of transmission of this disease is through cough or sneeze or droplet transmission.⁽⁴⁾

Mucormycosis is a significant, but rare opportunistic and life-threatening fungal infections mainly caused by *Rhizopusarrhizus* with higher case fatality rates. Mucormycosis has been recognized as complication of the SARS- CoV-2 infection that has wide spread in COVID era, although not infectious but prompt early diagnosis and treatment are necessary to avoid high rates of mortality and morbidity particularly in patients during or post COVID recovery phase. Mucormycosis caused by the inhalation of filamentous fungi especially in the patients who are with less immunity.

COVID - 19 patients are prescribed with heavy doses of steroids resulting in weakened immune system and are susceptible to mucormycosis.⁽⁶⁾ Following a sharp rise in the number of COVID-19 patients infected with mucormycosis, the Indian health ministry has advised all the states to declare mucormycosis itself as epidemic.⁽⁷⁾ The most observed type of Mucormycosis is rhino-maxillary disease in which patients might report firstly to a dental practitioner for oral related problems. As the dentists treat the oral diseases, there is a high risk of exposure to COVID-19. Maintenance of oral health should be given extreme importance for the prevention of these kind of diseases.⁽⁸⁾

Recent increase in the number of COVID-19 patients with mucormycosis infection are mostly due to uncontrolled diabetes and excessive use of steroids for the treatment of Coronavirus infection.⁽⁹⁾ The triad of coronavirus, corticosteroid use and uncontrolled diabetes mellitus have been evident for significant increase in the incidence of maxillofacial mucormycosis.⁽¹⁰⁾

Epidemiology

Invasive “black fungus” (Mucormycosis) is creating an epidemic within a global pandemic.⁽¹¹⁾ Globally, the reported burden of mucormycotic cases (71% of the global cases) is highest in India. It has been estimated that more number of cases of Mucormycosis in India is nearly 70 times that of the global incidence. The prevalence of mucormycosis in India is about 80 times the prevalence in developed countries, being approximately 0.14 cases per 1000 population.⁽¹²⁾ Currently, in India diabetes mellitus is the most prevalent underlying comorbidity associated with Mucormycosis followed by haematological neoplasms or malignancy, and solid organ transplantation. It has been found that patients suffering from renal diseases (namely chronic kidney diseases in the form of renal failure) as well as pulmonary tuberculosis are at a higher risk for contracting mucormycosis infections.⁽¹¹⁾

Common Affected Sites

The most commonly effected sites are rhinoorbital/ rhino-cerebral mucormycosis.⁽¹⁰⁾ Mucormycosis involving nose and sinuses (88.9%) is most common followed by rhino-orbital (56.7%). Pulmonary mucormycosis is observed in about 10% of patients.⁽¹³⁾

Mortality

Infection with mucormycosis is associated with high mortality primarily due to complications such as cavernous sinus thrombosis, disseminated infection, osteomyelitis, and death. The overall mortality is reported upto 50% to 66.7% in the recent studies among affected patients.^(14,15)

Indian Scenario

Till 15th July 2021, 432 cases of Mucormycosis have been reported and uploaded on COVID 19 portal of India. Most common types reported in India are Rhinocerebral(77.6%), cutaneous (4.3%), and pulmonary (3%). Among these 84.4% patients had the positive test for COVID 19 infection. States highest affected in the decreasing order are Maharashtra, Gujarat, Madhya Pradesh, Haryana, Delhi, Utter Pradesh, Bihar, Chhattisgarh, Karnataka and Telangana. **Pathogenesis**

Fungal inoculation into the host tissues leads to the activation of both innate and adaptive immune responses. However, in the presence of hyperglycemia the innate immune system is defective resulting in the inhibition of neutrophil migration, chemotaxis and decreased phagocytosis. Diabetes with ketoacidosis [DKA] is 50 percent more likely to develop mucormycosis than without DKA. Ketone bodies by virtue of its high pH increase the availability of free iron by inhibiting the sequestration of iron by transferrin and ferritin. This high pH and increased availability of free iron promote fungal growth in a susceptible host.

Hyperglycaemia also increases the risk of mucormycosis by the following mechanisms: (i) inhibiting the action of iron sequestering proteins, (ii) impaired phagocytosis and chemotaxis by neutrophils, and (iii) by weakening the oxidative and non-oxidative pathways. Rhino-cerebral mucormycosis is almost always associated with diabetic ketoacidosis. While hematological malignancies and neutropenia cause pulmonary disease, trauma usually leads to cutaneous mucormycosis.⁽¹⁶⁾

It is confirmed that the patients with ketoacidosis are at a higher risk of developing rhino-cerebral mucormycosis. The mechanisms which predispose the diabetic ketoacidosis to rhino-cerebral disease are unknown. Other observations in DKA like impaired neutrophil chemotaxis and phagocytosis cannot be consistently applied to the increased rhino-cerebral cases due to the fact that neutropenic patients frequently develop pulmonary and disseminated disease rather than rhino-cerebral disease.⁽¹⁶⁾

In COVID-19 patient's studies have shown that the glycemic control is not only poor but also necessitates insulin to be utilized in exceedingly high doses for their management. This transient elevation of glucose during the course of disease can be possibly linked to insulin resistance caused by increased levels of inflammatory cytokines in the body.⁽¹⁷⁾

Hyperglycemia, ketoacidosis, increased availability of free iron and impaired phagocytic action mainly leads to an environment conducive for the growth of fungi. Similarly, increased serum iron cause the endothelial damage predisposing the host to fungal invasion.⁽¹⁶⁾

Apart from the viral-induced hyperglycemia, systemic steroids and antiviral agents used in the treatment of COVID-19 can also be considered as a factor responsible in the worsening of hyperglycemia. There is an increased incidence of mucormycosis infections in diabetic patients treated for COVID-19, who used corticosteroids during the course of treatment. Corticosteroids and immunosuppressive agents are risk factors

and prolonged high dose (>3 weeks) of corticosteroids predisposes an individual to mucormycosis infection.⁽¹⁸⁾ The propensity of corticosteroids to impair migration, ingestion and phagolysosome fusion in macrophages may explain suppressed immunity in such patients. There is a positive correlation between coronavirus and mucormycosis of the paranasal sinuses which must be taken into consideration.

Clinical Presentation

The patients complaints of pain and redness around eyes and/or nose, fever, headache, coughing, shortness of breath, bloody vomitus, altered mental status, facial pain, pain over sinuses, pain in teeth and gums, altered sensation over half of face, blackish pigmentation of skin over nasolabial groove, nasal crusting and nasal discharge which could be blackish or blood tinged, c periorbital swelling, blurring of vision/ diplopia, loosening of teeth/ discoloration of palate/ gangrenous inferior turbinates, worsening of respiratory symptoms, hemoptysis, chest pain, alteration of consciousness, headache.⁽¹⁹⁾ The median time interval between COVID-19 diagnosis and the first evidence of mucormycosis infection is 15 days.⁽¹²⁾

Clinical suspicion should be kept high if COVID patient present with sinusitis - nasal blockade or congestion, nasal discharge (blackish/bloody), local pain on the cheek bone, one sided facial pain, numbness or swelling, blackish discoloration over bridge of nose/palate, toothache, loosening of teeth, jaw involvement, blurred or double vision with pain, fever, skin lesion, thrombosis and necrosis, chest pain, pleural effusion, haemoptysis, worsening of respiratory symptoms.⁽¹³⁾

Risk Factors

Uncontrolled diabetics mellitus in ketoacidosis, other forms of metabolic acidosis, corticosteroid treatment (high-dose glucocorticoids), organ or bone marrow transplantation, neutropenia, trauma and burns , malignant hematologic disorders and defoxamine therapy in heamodialysis patients, use of occlusive dressings/ boards, tounge blades, blast injury, malt/ lumbar industrial workers, construction workers, malnutrition and poor wound care are all major risk factors for Mucormycosis.^(20,21) The probable percentage of patients to get affected with Mucormycosis of following risk factors are, diabetics mellitus(96.7%), COVID - 19 (61.2%), intravenous methylprednisolone (61.2%), hypertension (54.8%), ischemic heart disease (3.22%) and kidney disease(6.45 %).⁽²²⁾

A systematic review of the studies and cases reported worldwide suggested that Mucormycosis was predominantly seen in males (78.9%), both in people who were active (59.4%) or recovered (40.6%) from COVID-19. Pre-existing diabetes mellitus (DM) was present in 80% of cases, while concomitant diabetic ketoacidosis (DKA) was present in 14.9%. Corticosteroid intake for the treatment of COVID-19 was recorded in 76.3% of cases.⁽⁵⁾ Further, prolonged hospitalisation, patient on ventilator, patient on high flow mask or Bipap machines for prolonged period are also high-risk patients, presence of an open wound, HIV/AIDS, cancer, and organ transplant, mucormycosis can result in a severe invasive fungal infection. It is speculated that the promiscuously use of steroids, antibiotics and zinc as a self-medication practice that increased during the COVID-19 epidemic may have promoted the imbalance of gut microbiota thereby inducing immune-suppression and making the risk group highly susceptible to this mycotic disease.⁽¹⁹⁾

Types of Mucormycosis:

Rhino orbital cerebral Mucormycosis [ROCM]

Maxillary Mucormycosis

Pulmonary Mucormycosis

Gastro intestinal Mucormycosis

Cutaneous Mucormycosis

ROCM is again divided into ⁽²³⁾

- possible ROCM
- Probable ROCM
- Proven ROCM

Diagnosis

COVID-19 infection may induce significant and persistent lymphopenia, which in turn increases the risk of opportunistic infections. It is also noted that 85% of the COVID- 19 patients' laboratory findings showed lymphopenia. This means that patients with severe COVID-19 have markedly lower absolute number of T lymphocytes, CD4+T and CD8+ T cells and, since the lymphocytes play a major role in maintaining the immune-homeostasis, the patients with COVID-19 are highly susceptible to fungal co-infections.⁽¹⁵⁾

Prevention

Control diabetes and diabetic ketoacidosis.
Reduce steroids (if patient is still on) with aim to discontinue rapidly.
Discontinue immunomodulation drugs.
No anti-fungal prophylaxis needed.
Extensive surgical debridement - to remove all necrotic materials.
Rational use of antibiotics.
Timely start of medical treatment.
Install peripherally inserted central catheter.
Maintain adequate systemic hydration.
Monitor patients clinically and with radio-imaging

Management

The most commonly used drug for the management of mucormycosis infection is Liposomal Amphotericin B. It is the first line chemotherapy, also involves Amphotericin B lipid complex. Second line treatment includes Posaconazole, isavuconazole and combination therapy of Liposomal Amphotericin B or Amphotericin B with caspofungin.. In addition to traditional anti fungal and surgical therapies hyperbaric oxygen therapy is also used. This therapy provides reduction in tissue hypoxia and acidosis and also provides high oxygen concentration that are considered fungistatic, resulting in wound healing while enhancing neutrophilic action. The treatment for patients with respiratory problems like breathlessness and cough are periodic recording of oxygen saturation for a week by the patient prior to treatment, continuous monitoring of oxygen saturation by pulse oximeter during the treatment, practice of breathing techniques [inspiration to expiration ratio of 1:2], bilateral mandibular blocks should not be administered, antitussives or lozenges for immediate cough suppression.

The suggested dental recommendations and management for symptoms like inflammatory reactions [salivary glands and tongue], pain, periodontal disease are dental follow ups of recovered patients, acetaminophen [not exceeding 60mg/ day or 3 mg/ day], oral health hygiene respectively. The most common treatment for maxillary mucormycosis and rhinocerebral mucormycosis is right total maxillectomy, bilateral subtotal maxillectomy, partial maxillectomy, left subtotal maxillectomy.

Liposomal amphotericin B in initial dose of 5mg/kg body weight is the treatment of choice. Each vial contains 50 mg. It should be diluted in 5% or 10% dextrose; it is incompatible with normal saline/ ringer lactate. It has to be continued till a favourable response is achieved and disease is stabilized which may take several weeks following which step down to oral posaconazole or isavuconazole can be done. Early surgical debridement or excision plays an important adjunctive role.⁽²⁴⁾

Conclusion

Rhino-orbital-cerebral mucormycosis is a rapidly progressive and lethal infection, with increasing incidence COVID-19 pandemic. Thus, it is very important that early warning signs and symptoms of mucormycosis are recognized so that appropriate treatment can be started at the earliest and patient survival can be enhanced.

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