



Mucormycosis: An Epidemic Associated with Pandemic- A Systematic Review

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Different infections have been presenting danger to mankind every once in a while and in 2019 a serious respiratory illness (COVID-19) reported in Wuhan, Hubei province of China, became a threat to general wellbeing not only in China but all the nations throughout the world. COVID-19 disease which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is found to be associated with a wide range of opportunistic fungal and bacterial infections. Candidial and aspergillus infections leading to mucormycosis and orbital compartment syndrome have been reported to be the main co-infections in COVID-19 patients, which must be recognized and treated promptly to avoid any morbidity and mortality. Low oxygen environment, acidic medium, high glucose, decreased phagocytic activity and increased ferritin levels in addition to prolonged hospitalization with or without mechanical ventilators are considered as the main risk factors. Thus, the main aim of the article is to briefly survey and discuss about the types, causes, methods to prevent and treatment modalities of main co-morbidity of COVID 19 i.e. mucormycosis.

KEYWORDS: COVID-19, Fungal Infection, Mucormycosis, Steriods

INTRODUCTION

Coronavirus, an outsized family of viruses, noted to cause diseases which range from simple cold to more severe diseases like severe SARS (2002 – 2004) and MERS (2012) (WHO, 2020). A much recent, Novel coronavirus (COVID-19) caused by similar family of viruses is an infectious disease primarily associated with symptoms ranging from mild to severe life-threatening conditions particularly pneumonia.¹ First ever case was recorded in Wuhan city of China during the ending month of 2019 and has been associated with myriad of fungal, bacterial and viral co-infections. While the pathophysiology is still under investigation, new indicative manifestations and complications of the same continue to be identified and described in medical literature.²

Since the beginning of this pandemic, a large number of studies have centered on quick diagnosis, advancement, and redirection of new treatment plans. In many cases, it was found that SARS-CoV-2 is something much more than a respiratory disorder. Significant degrees of endogenous substances delivered by this infection are capable of producing changes and disturbances influencing the target tissues. They even go past the hindrances of protection of the innate tissue immunity, reaching the systemic level through hematogenous transmission.³ This signalling animates immunity cells associated with

constant chronic inflammatory process that can promptly lead to fibrosis of lungs, loss of function, pulmonary degeneration, oxygenation impairment, culminating the delayed hypoxic state, anoxemia and hypoxemia and ultimately leading to death. Patients having metabolic diseases such as diabetes mellitus, autoimmune diseases, cardiopulmonary diseases, or patients undergoing chemotherapy, corticotherapy or radiotherapy have a higher danger of death.⁴

Apart from arrhythmias, thrombo-embolic complications, cardiac injury (acute), and strokes, secondary opportunistic infections including white fungus (candidiasis) and black fungus (mucormycosis) are much prevalent.

MUCORMYCOSIS

Zycomycosis or Phycomycosis was first described by Paltauf in 1885 and later changed to Mucormycosis by Baker (American pathologist) in 1957 due to severe form of infection caused by Rhizopus. Fungi which belong to the order Mucorales are distributed into six families and all are responsible for cutaneous and deep infections.⁵ Head of the fungal pathogenesis group at the institute for medical research, Julie Djordjevic described it as a "NATURE'S DECAYER".⁶

The Rhizopus Oryzae type is responsible for nearly



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60% of mucormycosis cases in humans and 90% of the Rhino-orbital-cerebral form. It is usually uncommon but can occur as an opportunistic severe fungal infection in people who have altered immune system and affects the sinuses, lungs and brain leading to life threatening conditions in cancer patients, diabetic patients, or people suffering from HIV or AIDS. These pathogens are commonly present in soil along with association with decaying organic matter, such as rotten wood, compost piles, or leaves. It is commonly transmitted through inhalation of these fungal spores.⁷

PATHOGENESIS

Both mononuclear and polymorphonuclear phagocytes of ordinary hosts kill Mucorales by the creation of metabolites and the cationic peptides defensins. Clinical proof exhibits that these phagocytes are the significant host defense system against mucormycosis. For instance, neutropenic and phagocytic dysfunctional patients are at expanded danger of creating mucormycosis. The capacity of phagocytes to engulf these fungi by their oxidative and nonoxidative components is disabled by hyperglycemia (diabetes mellitus) and acidosis. Furthermore, corticosteroid treatment influences the capacity of broncho alveolar phagocytes to prevent germination of the spores in vitro or after in vivo contamination initiated by intranasal inoculation. The specific components by which ketoacidosis, diabetes, or steroids impede the capacity of these phagocytes stay obscure.⁵

CLINICAL PRESENTATION

The clinical sign of this disease (mucormycosis) is vascular invasion leading to tissue necrosis and thrombosis. Mucormycosis practically consistently happens in people with defects in host defense mechanism and/or potentially with increased available serum iron, albeit uncommon cases have been accounted for in evidently normal hosts. This disease is determinedly progressive and results in death except if treatment with a careful surgical debridement and antifungal drugs is started instantly.⁸

According to the clinical presentation and the involvement of a specific anatomic site, mucormycosis has been divided into at least six clinical classifications: (1)pulmonary, (2)disseminated, (3)cutaneous, (4)gastrointestinal, (5)rhinocerebral, and (6)miscellaneous (table 1).

PREDISPOSING CONDITION	PREDOMINANT SITE
Neutropenia	Pulmonary And Disseminated
Diabetic Ketoacidosis	Rhinocerebral
Deferoxamine	Disseminated
Corticosteroids	Pulmonary, Disseminated, Or Rhinocerebral
Malnutrition	Gastrointestinal
Trauma, Catheter/Injection Site, Skin Maceration	Cutaneous/Subcutaneous

Table 1. Relationship between predisposing conditions and site of infection⁵

SYMPTOMS

Sinusitis along with clogging of the nasal tract with blackish or bloody mucus emission from the nose is the main indication of mucormycosis. Blackish discoloration on the bridge of the nose, along with pain on one side of the face, cheekbone and lack of sensation and bulging of the involved area are observed. Abnormal clotting of blood tissue thrombosis, damage or injury to the skin and/or necrosis of the dermal cells are also seen. Impairment of respiratory functions, pain in chest, excessive build-up of fluid in lungs and haemoptysis are also observed.⁹

Blood clots with blocked vessels, blindness and nerve damage prove mucormycosis is deadly if not treated. Due to its rare nature, the exact mortality is unknown but an overall estimate is roughly around 45%. The likelihood of patient's death depends on the body part affected.¹⁰

DIAGNOSIS

The exact time for the presentation of this disease in covid patient is usually around third week of onset of its symptoms. Physical examination, swab test, followed by tissue biopsy and radiographic imaging (CT or MRI) are used to detect the extent of it.

Specific investigations include 1. Non-contrast

computed tomography scan of the sinuses particularly paranasal sinuses (NCCT PNS) to detect the bony erosion; 2. High resolution computed tomography chest (HRCT chest) and CT Angiography and 3. MRI of the brain for better delineation of CNS involvement.

Diagnosis includes 1. KOH staining and microscopy, followed by histopathology of the debrided tissues and culture; 2. Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry if available and 3. Presence of ribbon like aseptate hyphae (5-15 μ), branching at right angles.¹¹

PREVENTION AND TREATMENT

Ensuring proper oral hygiene, wearing face shields and masks, maintaining hand hygiene, regular changing of masks and avoiding unnecessary visits to crowded and dirty or polluted environments are main prevention goals in preventing any co-morbidity related to covid.

For prevention of mucormycosis, it is important to control hyperglycemia, discontinue any immunomodulating drug and reduce the use of steroids. Maintaining the adequate systemic hydration, normal saline (IV) infusion followed by amphotericin B and anti-fungal therapy for at least 4-6 weeks is required. In case of diabetic and covid patients, it is very much important to control hyperglycemia and regularly monitor blood glucose levels during and after Covid treatment. Steroid use must be judicious with correct dosage, timing and duration.⁶

The major treatment part includes antifungals but depending upon the severity, surgery is the end treatment. Mucormycosis can cause damage to upper jaw and even eye. Loss of functions including facial aesthetics, chewing, swallowing and loss of self-esteem can lead to the detrimental effect on the patients mental health. Hence management of covid patients with mucormycosis approach involving team of professionals such as microbiologist, internal medicine specialist, ENT specialist, ophthalmologist, dental surgeon (oral and maxillofacial surgeon for reconstruction) and others.²

METHOD

A systematic search of literature was done in the electronic database of SCOPUS, PUBMED, COCHRANE and EMBASE, using keywords SARS CoV-2, COVID 19 and MUCORMYCOSIS. Details of articles that reported confirmed and suspected patients with

mucormycosis, so far till June 2021 were retrieved. Characteristic of the subjects were analysed on various endpoints and outcomes (table 2).

DISCUSSION

Though been an extremely rare case (mucormycosis) in healthy individual, severe immunocompromised patients predispose it. Uncontrolled diabetes mellitus with or without diabetic ketoacidosis, organ transplantation, hematological and various other malignancies, corticosteroid therapy, prolonged neutropenia, iron overload, voriconazole prophylaxis for transplantation patients, AIDS, and malnutrition are main predisposing factors. Nose, sinuses, CNS, orbit, lungs, GIT, skin, joints, jaw bone are the areas involved, though rhino-orbital-cerebral (ROC) form is more common among all. ROC form is frequently observed in association with uncontrolled diabetes and diabetic ketoacidosis, whereas pulmonary involvement is often seen in patients suffering from neutropenia, and hematological malignancies while GIT involvement is seen in malnourished individuals.²⁶

Eosinophilic necrosis, thrombosis, and giant cell invasion of the underlying area is the main pathological symptom of mucormycosis. Its gold standard criteria for clinical diagnosis was given by Smith and Krichner in 1950 which included: black and necrotic turbinate, easily misdiagnosed for crusted, dried blood. Blood tinged nasal discharge with facial pain, soft peri-orbital swelling, ptosis and proptosis of the eye with a multiple number of cranial nerve palsies.²⁷

Prakash et al.²⁸ (2019) and Patel et al.²⁹ (2020) have found that rhino-orbital-cerebral was the utmost presentation which was followed by pulmonary and cutaneous type in patients with uncontrolled hyperglycaemia. Systematic review by John et al reported 41 cases in people with COVID-19 and diabetes was found in 93% of the cases and 88% were on steroid therapy. These findings were consistent with that of Awadesh et al, where they found that 80% of the mucormycosis cases were hyperglycemic and 76.3% received corticosteroids.³⁰ No studies are available that compared patients of mucormycosis with/without confounding factors.

LIMITATION

Various limitations were seemed to be found while conducting this systematic review, using case reports

AUTHOR	YEAR	PLACE OF REPORT	N	CO-MORBIDITIES	CONFIRMED/SUSPECTED CASES	LOCATION	OUTCOME
Mehta et al ¹²	Sep,2020	Mumbai	1	Diabetes	Confirmed	Nasal, Orbit	Death
Hanley et al ¹³	Oct,2020	UK	1	Nil	Confirm, Autopsy	Lung	Death
Placik et al ¹⁴	Nov,2020	USA	1	Nil	Confirmed	Lung	Death
Monte Junior et al ¹⁵	Nov,2020	Brazil	1	Nil	Confirmed	GIT	Death
Zurl et al ¹⁶	Jan,2021	Austria	2	Leukemia	Confirmed	Bone	Death
Sarkar et al ¹⁷	Apr,2021	Puducherry	10	Diabetes	Confirmed:6 Suspected:4	Nasal, Orbit, CNS	Death:4 Improved:2 Unchanged:4
Sharma et al ¹⁸	Apr 2021	Jaipur	23	Diabetes	Confirmed	Nasal, Orbit, CNS	Death: 0 Lost To Follow Up:2 Alive:21
Veisi et al ¹⁹	Apr, 2021	Iran	2	Diabetes	Confirmed	Nasal, Orbit, CNS	Death:1 Recovered:1
Garg et al ²⁰	May,2021	Chandigarh	1	Diabetes	Confirmed	Lung	Improved
Mishra et al ²¹	May,2021	Bangalore	10	Diabetes	Confirmed	Nasal, Orbit, Bone	Death:4 Improved:2 Unchanged:4
Satish et al ²²	May,2021	Bangalore	11	Diabete:10 Leukemia:1	Confirmed	Nasal, Orbit	Death:2 No Medical Advice:5 Improved:4
Johnson et al ²³	Jun,2021	USA	1	Diabetes	Confirmed	Lung	Improved
Sen et al ²⁴	2021	Mumbai	6	Diabetes	Confirmed:5 Suspected:1	Nasal, Orbit, CNS	Improved
Wetherman et al ²	2021	USA	1	Nil	Confirmed	Nasal, Orbit	Improved
Sargin et al ²⁵	2021	Turkey	1	Diabetes	Confirmed	Nasal, Orbit, CNS	Death

Table 2. Characteristic of the subjects reported by various authors analysed on the basis of various endpoints and outcomes

and series which are subjected to publication biases with considerable diversity of the reported cases. The active and recovered SARS CoV-2 cases and its correlation to the onset of mucormycosis is difficult due to the less sensitivity of confirmatory reverse transcriptase polymerase chain reaction. Lack of denominator value, does not allow the real estimation of the incidence of mucormycosis.

CONCLUSION

COVID-19 is found to be associated with significant incidence of opportunistic bacterial and fungal infections due to immune dysfunction. Additional due to steroid therapy, broad spectrum antibiotics, monoclonal antibodies lead to exaggeration of pre-existing fungal diseases. While still, there is no major outbreak, physicians should be aware of the possibility

of invasive opportunistic infections in patients with SARS CoV-2 and pre-existing risk factors. Use of therapeutic agents should be monitored to achieve the effect at the minimal dose and for the momentary duration for maximum efficacy. Thus, it becomes very much essential to make the judicious use of drugs and reducing major outbreak with decreased mortality.

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