AN UPDATE ON PATHOPHYSIOLOGY, DIAGNOSIS AND MANAGEMENT OF COVID 19 ASSOCIATED MUCORMYCOSIS

Dr. Devendra Palve1, Dr. Shilpa Warhekar2, Dr. Deepali Mohite3, Dr. Vinanti Bodele4

1Professor and Head, Department of Oral and Maxillofacial Pathology, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Nagpur, (M.S). INDIA.
2Associate Professor, Department of Public Health Dentistry, Government Dental College and Hospital, Nagpur, (M.S). INDIA.
3Associate Professor, Department of Oral and Maxillofacial Pathology, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Nagpur. (M.S). INDIA.
4Post Graduate Student, Department of Oral and Maxillofacial Pathology, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Nagpur (M.S). INDIA.
1dhpdevendra@gmail.com

ABSTRACT

WHO declared COVID-19 as a pandemic on March 11, 2020, the. The pandemic had caused enough fatality, yet the misfortune did not stop there and got exaggerated with the occurrence of other complication and one of those is COVID-19 associated mucormycosis, a deep fungal infection. The association of the infection with the disease is a matter of certain predisposing factors like ill-advised use of steroids for the treatment of COVID-19 or systemic conditions like diabetes, immunocompromised states etc. Since, the COVID-19 pandemic is itself new and not much time has lapsed for sufficient literature to get cumulated, the reported cases of mucormycosis further seem to be lesser. An eagle’s eye toward the occurrence of mucormycosis in COVID-19 patients with the predisposing factors has been advised for an early diagnosis and initiation of treatment. Therefore, the clinicians are strongly encouraged to report the cases of COVID-19 associated mucormycosis for sufficient research to be conducted in the area to determine the burden of disease and to save the lives of patients.

Key Words : COVID-19, diagnosis, pathophysiology.

I. INTRODUCTION:

The zygomycoses are infections caused by fungi of the class zygomycetes, comprised of the orders mucorales and entomophthorales.[1] Mucormycosis, previously called zygomycosis, refers to various different diseases caused by infection with fungi in the order mucorales. The most common causative organism species is rhizomucor. The other genera along with mucormycosis include mucor, cunninghamella, apophysomyces, lichtheimia, saksenaea, rhizomucor and other species. Most of the mucormycosis infections are life-threatening and the risk factors such as diabetic ketoacidosis and neutropenia are present in most of the cases. Its involvement in the pulmonary, cutaneous, and gastrointestinal infections is wellrecognized.[2] The epidemiology of invasive fungal disease due to filamentous fungi in immunocompromised patients and host groups is shifting with changing clinical practice.

On December 31, 2019, the Chinese authorities reported an emerging novel coronavirus (CoV) in patients in Wuhan, Hubei province, to the World Health Organization (WHO).[5] This Virus has by now become one of the major pathogens, primarily targeting the human respiratory system and its associated organs. The outbreaks of coronavirus include the severe acute respiratory syndrome(SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV, already characterized as agents those are real threat to humans.[6] With the rapidly increasing number of cases and increased risk of global public health, the WHO declared it as a health emergency globally on January 30, 2020. For prevention of SARS-CoV-2 transmission, measures such as quarantining the infected patients and their family members, social distancing, closure of schools and colleges were implemented, yet the infection could not be controlled. Hence, on March 11, 2020 the WHO declared COVID-19 as a pandemic.[5] With lapse of time, we are now encountering newer complications associated with this pandemic,
along with the primary pathogenic manifestations. One such recent and most dreadful complications is Mucormycosis. This review focuses on this complication encountered vastly in the second wave of COVID-19 pandemic.

**Pathogenesis of Mucormycosis**

The pathogenesis of mucormycosis includes host defenses, both mononuclear and polymorphonuclear phagocytes of normal hosts, that kill *mucorales* by the generation of oxidative metabolites and cationic peptide defensins. The phagocytes being the major host defense mechanism against mucormycosis, patients with dysfunctional phagocytes are at higher risk of developing mucormycosis. Hyperglycemia and acidosis are known to impair the ability of phagocytes to move towards and kill the organism by both oxidative and non-oxidative mechanisms. The exact mechanism by which ketoacidosis, diabetes or steroids impair the function of these phagocytes remain unknown.

**Role of iron in pathogenesis**

An elevated serum iron level in patients with mucormycosis was recently thought to be another identified clinical feature. But, it is now clear that iron chelation is not the mechanism by which deferoxamine enables mucormycosis infection. Patients with diabetic ketoacidosis are at a higher risk of developing rhinocerebral mucormycosis. This was backed up with the finding that simulated acidotic conditions decreased the iron-binding capacity of sera collected from normal volunteers, suggesting that acidosis temporarily disrupts the iron-binding capacity of transferrin. Thus, an increased susceptibility to mucormycosis of patients with diabetic ketoacidosis is likely, at least in part, due to an elevation in available serum iron during diabetic ketoacidosis.

**Role of fungal-endothelial interactions**

Presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis is the hallmark of mucormycosis infections. The angioinvasion is associated with the ability of the organism to hematogenously disseminate from the original site of infection to other target organs. This is a critical step in the organism’s pathogenic strategy. The precise mechanisms by which the spores or the organism mediate the tissue injury remain unclear. The evidence of the presence of spore or the organism in the tissue, thereby simply advocating the killing of the spores or the organism may not prevent subsequent tissue injury, perhaps, in part, explaining the lack of efficacy of fungicidal agents during clinical disease. 

**Epidemiological data of COVID-19**

At the beginning of the outbreak, only elder persons were found to be affected. But as the outbreak continued, number of cases increased irrespective of elder or younger ages. The mean incubation period was of approximately 5.2 days. There were few parameters like higher sequential organ failure assessment (SOFA) score and d-dimer>1 µg/millilitre. The presence of coronary artery disease, diabetes and hypertension were considered to be risk factors. Majority of patients died from multi-organ failure, shock, acute respiratory distress syndrome. The reported number of COVID-19 patients was highest in U.S, followed by Spain, Italy, Germany, France and China. The number of children affected by this pandemic was less as compared to that of elderly. Only 73% developed fever, cough, or shortness of breath. There were equal number of cases among males and females.

**Morphology and pathophysiology of COVID-19**

Coronaviruses are non-segmented, enveloped viruses with single-stranded RNA (ssRNA) ranging between 26 to 32 kd in length. Their genomes are the largest among the RNA viruses. These viruses have spherical shape, with a diameter ranging from 60-140nm and an outer surface studded with distinctive 9-12nm long spikes that gave virions an appearance resembling a solar corona. The viral envelope is coated by spike(S) glycoprotein, envelope(E), and membrane(M) proteins. The pathogenesis includes viral entry and interaction with the target cells. SARS-CoV-2 binds to ACE2, the host target cell receptor, and then there occurs active replication and release of the virus into the cells of lungs leading to certain non-specific symptoms such as fever, myalgia, headache and respiratory symptoms causing transient damage to the cells in the olfactory epithelium leading to olfactory dysfunction exhibited as temporary loss of taste and smell. After the viral entry, the initial inflammatory cells attract the virus-specific T cells to the infected site, where the infected cells are eliminated before the spread of the infection.
Fig 1- (1) The virus binds to ACE 2 as the host target cell receptor in synergy with the host’s transmembrane serine protease 2 (cell surface protein), which is principally expressed in the airway epithelial cells and vascular endothelial cells. This leads to membrane fusion and releases the viral genome into the host cytoplasm. (2) Stages (3–7) show the remaining steps of viral replication, leading to viral assembly, maturation, and virus release.

There are some virulence factors of mucorales for mucormycosis-

1. Calcineurin- Involved in the transition of Mucor circinelloides from the yeast form to hyphae.

2. Rhizoferrin- It is secreted by R.oryzae in the presence of acidic pH via receptor mediated energy dependent process. It disrupts the capacity of transferrin to bind Fe by proton mediated displacement.

3. High affinity Iron permeases- Mononuclear and polymorphonuclear cells clear spores and germings. The fungal acquisition of free iron supports growth of hyphal forms.

4. Host defense-(Mononuclear and PMNL’s)- Due to decrease pH in hyperglycemia there is impaired chemotaxis and defective killing by oxidative and non-oxidative mechanisms.

5. Angioinvasion- Uniform presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis. This angioinvasion is associated with the ability of the ability of the fungi to hematogenously disseminate from the original site of infection to other target organs[8].

In young patients, presence of mucus plugs with fibrinous exudate is seen, which is due to the overproduction of pro-inflammatory cytokines accumulating in the lungs, eventually damaging them. Cytokines mediate and regulate immunity, inflammation, and haematopoiesis. However, an excess exacerbation of immune reaction and accumulation of cytokines in organs leads to extensive tissue damage or a cytokine release syndrome (cytokine storm), leading to capillary leak, thrombus formation, and organ dysfunction. Some patients had septic shock and multi-organ dysfunction.

Phases of COVID-19 infection

The first phase is incubation which starts from the entry of the virus and lasts up to the onset of symptoms, for around 2 and 11 days. The incubation time is almost 6 days, with patients likely to be infectious from 1-3 days before the development of symptoms. There is a significantly increased risk of viral transmission in the first phase.

The second phase involves characteristic onset of certain symptoms such as fever, dyspnea, and then eventually typical symptoms of upper respiratory infections such as sore throat, nasal congestion and rhinorrhea. Some
patients show progressive respiratory involvement seen on chest computed tomography.[9] There occurs silent or happy hypoxemia especially in the elderly patients along with respiratory failure without other signs of respiratory distress.[10]

The third phase includes focal and systemic inflammation depicting direct cytopathic lung injury caused by viral replication in pulmonary parenchyma, the pro-inflammatory phase is then characterized by an abnormal, exaggerated host response, either local or systemic. The SARS-CoV-2 infection of dendritic cells and macrophage triggers and gets activated leading to secretion of vast array of pro-inflammatory cytokines such as interleukins 6, 2, and 7, MCP-1, MIP1-α, GSF,C-X-C motif chemokine 10, and TNF-α. Evolving lymphopenia may be associated with antiviral defect and immune regulation. This highly abnormal immune-inflammatory response is universally defined as “cytokine storm.” This phase may show some signs of direct viral injury and inflammatory infiltrates in organs like heart, kidney, liver, and intestine.

The final stage shows progressive stage characterized by onset of microvascular and macrovascular thrombosis triggered by and exaggerated focal and or systemic inflammation. It depicts pro-thrombotic effects of hyperinflammation in veins and arteries, disturbing many pathogenetic mechanisms (endothelial dysfunction, etc.) resulting in the development of microvascular and macrovascular thrombosis. Even in younger patients, significant thrombotic events have been reported, including large vessel stroke that is thought to be direct cause of mortality.[8] Death is then attributable to ARDS, pulmonary thrombosis, acute renal failure, acute cardiac injury, superinfection and or multiple organ failure.[11] The virus mainly spreads from person to person through respiratory droplet transmission when in close contact with someone who is coughing or sneezing. Transmission may also be because of fomites used by the infected individuals. During the incubation period of 6 days or up to 14 days, the pre-symptomatic period, the individuals no longer can transmit the virus. Patients initially complain of fever, body ache, breathelessness, malaise, dry cough, and may be asymptomatic or present with mild, moderate, or severe disease. Few patients show gastrointestinal symptoms such as abdominal pain, vomiting, and loose stools.[12]

Ketoacidosis (diabetic or other), iatrogenic immunosuppression, especially when it is associated with neutropenia and also graft vs. host disease in certain haematological patients, ongoing therapy with corticosteroids or deferoxamine, disruption of mucocutaneous barriers by catheters and other devices and also even on exposure to bandages that are contaminated by fungi mucormycosis become the risk for the further complication of mucormycosis,[13-19]

COVID-19-associated Mucormycosis and Oral Health:

Chakraborty T et al have recently reviewed the scarce yet available literature on the prolonged post-COVID-19 symptoms and discussed their effect on oral health. After a thorough review of the literature, they enlisted the symptoms pertaining to oral health and in patients with diagnosed COVID-19, with the associated mucormycosis being one of the others like xerostomia, HSV-1 infections, ulcerations etc. Further, they opined that as a dentist, one must keep a keen eye and be very suspicious of finding COVID-19 associated mucormycosis in a severely ill patient with COVID-19 superadded with being a known case of diabetes mellitus, especially if rhino-orbital or rhino-cerebral symptoms are evident.[20] John T et al, further added that it is attributed to occur as a consequence of steroid therapy and in patients with uncontrolled diabetes.[21]

Supporting this suggestion is a recently report by Pauli MA et al who reported a case of a 50-year-old female patient, diagnosed of COVID-19 around 8 days prior to her consultation. Although she was not prescribed steroids and was only under non-opiod analgesics, she had a medical history of type 2 diabetes mellitus. The chronological presentation of the lesion was that it started as a small symptomless ulcer on hard palate, which increased in size over a period of 5 days along with mild pain, and the pain exaggerated severely by day 7, irradiating to middle third of face. Clinically, the lesion was surrounded by an erythematosus halo, lobulated borders, and exposed bone. On a biochemical examination, her fasting blood sugar level was found to be 28 mg/dl. A local debridement with intravenous amphotericin B helped the patient recover within 10 days after discharge from the hospital.[22]

Another supporting report to the discussed so far is the case of a 60-year-old male patient reported by Mehta S and Pandey A, who was diagnosed with COVID-19 with associated lung involvement on CT. His medical history revealed the patient being a longstanding diabetic (>10 years) and had been on oral antihypoglycemic tablets. Furthermore, his right foot revealed a non-healing ulcer, typical of a diabetic peripheral vascular disease. A
Turkish Journal of Physiotherapy and Rehabilitation; 32(3)  
ISSN 2651-4451 | e-ISSN 2651-446X

rigorous medical management of COVID-19 was initiated alongwith a steroid therapy. However, on day 10, the patient exhibited signs of rhino-orbital edema and a thorough investigation revealed it to be an infection with mucormycosis. The authors suggested the use of broad spectrum antibiotics and steroids judiciously to reduce the number of such COVID-19-associated mucormycosis.\[23\]

**Differential Diagnosis:**
A presentation of mucormycosis can be misdiagnosed as necrotizing sialometaplasia, a reactive and inflammatory condition. However, there are, at times, chances that the lesion could actually be a necrotizing sialometaplasia, which could progress rapidly or worsen because of the COVID-19, it being a systemic inflammatory condition. Because the common oral presentation of mucormycosis is ulcer, it may also be looked upon as a malignancy. Other infections of soft tissue like paracoccidioidomycosis, leishmaniasis and osteomyelitis. Furthermore, even the oral manifestation of COVID-19 as a primary cause must be considered in the differential diagnosis.\[24,25\]

**Diagnosis of COVID-19 associated Mucormycosis:**
The foremost step toward the diagnosis of COVID-19-associated mucormycosis is the establishment of the COVID-19 status of the patient with the help of RT-PCR. Simultaneously, the patient must be subjected to imaging investigations like computed tomography to assess the amount and extent of destruction caused by the lesion. The confirmatory diagnosis can be made on histologic examination of a biopsy of the ulcerated lesion. The histological picture may show areas of necrosis, especially the coagulative necrosis, intense inflammatory cell infiltrate, especially the cells of acute inflammation, and areas of hemorrhage. The blood vessels or the surrounding connective tissue may show nonseptate hyphae with branching at 90° even in hematoxylin and eosin staining. KOH mount & microbial culture, biopsy are other methods aids in diagnosis of fungal infections. The organisms can be better appreciated with Grocott’s methamine and special stains for fungi like the periodic-acid Schiff stain.\[23\] Furthermore, the systemic status of the patient with respect to diabetes or immunocompromised state must be assessed with thorough biochemical examinations and with an enquiry about the medical history.

**Management of COVID-19 associated Mucormycosis:**
In the report presented by Pauli M et al, the patient was immediately referred for hospitalization after the confirmation of the diagnosis of mucormycosis. An intensive treatment with intravenous amphotericin B and hydrocortisone was initiated. After 10 days of intravenous medication, the lesion was superficially debrided, and diabetes was brought under control. A period as long as 1½ months at hospital was needed to reach a recovery enough to be discharged. A complete recovery of the lesion seemed further 10 days after the discharge.\[22\]

According to the guidelines issued by the Directorate General of Health Services regarding the management of COVID-19 associated mucormycosis, it has been suggested that a high index of suspicion should always be there in cases of predisposing conditions associated with COVID-19. A multidisciplinary approach and a timely diagnosis with the initiation of treatment reduces mortality. The basic treatment modality is a surgical debridement of the lesion or involved area along with antifungal therapy. The therapy has been advised to be continued till the resolution of the signs and symptoms of the infection, along with resolution of radiological signs of active disease and elimination of any predisposing factors involved.

Furthermore, the Clinical Infectious Disease Society of India has advised to discontinue the steroids or any other immunosuppressive drugs. It also suggested that the use of steroids be reserved only for the patients of COVID-19 with hypoxemia and only in the recommended dose and duration. Also, it added that any immunosuppressive agents that are not clinically proven for treating COVID-19 must be avoided.

II. CONCLUSION:
COVID-19 itself has emerged as a life threatening condition throughout the world. There are several guidelines on the use of steroids in the treatment of the disease. However, unnecessary or prolonged administration of the steroids in such patients may predispose to the occurrence of another life threatening deep fungal infection, mucormycosis. Furthermore, extreme caution must be exercised in COVID-19 patients who report clinical risk factors like diabetes or immunocompromised states to aid in the prevention of the occurrence of mucormycosis and, if not, at least in the early diagnosis and initiation of treatment against the another deadly association of COVID-19. Since not much time has elapsed since the occurrence of the pandemic, there is scarcity of literature. Further, the scarcity is even more with respect to the associated complication like mucormycosis. Thus, more
reporting of such cases of COVID-19 associated mucormycosis is encouraged to aid in the research directed towards prevention, early diagnosis, and a successful treatment of mucormycosis.

REFERENCES


