

Double trouble: A review on the ongoing mucormycosis crisis and the dental outlook

¹Dr. Aiman Haider, Department of Pediatric & Preventive dentistry, Rishiraj college of Dental sciences and Research center, Bhopal, Madhya Pradesh, India

²Dr. Priyanka Khadatkhar, Department of Pediatric & Preventive Dentistry, Rishiraj college of Dental sciences & Research center, Bhopal, Madhya Pradesh, India

³Dr. Pragya Kumari, Department of Pediatric & Preventive Dentistry, Rishiraj college of Dental sciences & Research center, Bhopal, Madhya Pradesh, India

⁴S. Suresh, Department of Chemical Engineering Maulana Azad National Institute of Technology, Bhopal- 462 003, Madhya Pradesh, India

⁵S. Arisutha, Energy Centre, Maulana Azad National Institute of Technology & Eco Science & Technology, Bhopal-462 003, India

Corresponding Author: Dr. Aiman Haider, Post graduate, Department of Pediatric & Preventive dentistry, Rishiraj college of Dental sciences and Research center, Bhopal, Madhya Pradesh, India

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Abstract

Mucormycosis is a rare fungal infection. It is present in the natural atmosphere and is found mainly in manure, soil, decaying fruits, and vegetables. Mucormycosis primarily affects the people on medication for uncontrolled diabetes and people on certain medications like cancer treatment, AIDS, which reduces their ability to fight environmental pathogens. Black fungus is now called COVID-associated mucormycosis. Its effects is severe on COVID-19 patients or post COVID-19 patients, with compromised immunity, resulting in disfiguration, and in some cases, life threatening. This

short communication covers root source of fungal diseases, characteristic features, causes and prevention of mucormycosis through dental perspective.

Keywords: Mucormycosis, black fungus, causes, dentist, preventive, clinical findings.

Introduction

With the outbreak of COVID-19 for more than one and half years globally, double trouble like a mutation of virus and risks associated with it, emerging infections, and other health issues. The recent pandemic coronavirus disease 2019 (COVID-19) results from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

This disease is mainly a severe respiratory tract infection in the patient. Due to this pandemic situation, globally, efforts are being made to know more about the virus, the targets of the virus, its mechanism, its cause, and transmission from one person to another, and many more things. The virus spread in many forms; as the infection enters a patient's body, it provokes a response in the immunity of affected organisms, resulting in the elimination of the virus[1].

As the virus is continuously changing, the risk of infection becomes severe. One of the recent and severe threats is Mucormycosis, the black fungus, in the COVID patients or post COVID patients. 'Black Fungus' is caused by a fungus named mucor, which is found on wet surfaces. Fungus is any member of eukaryotic organisms that obtains their food from dead and decaying material or other living things. The fungi that cause disease in humans or other organisms are pathogenic. Approximately 300 fungi are known to be pathogenic to humans.

Mucormycosis is also known as the black fungal infection, is a fungal infection caused by a special fungus, abundant in the environment, called micromycetes/mucor. The spores of a fungus (seeds of fungus) are ubiquitous in the air and get an entry into the body through inhaled air. Usually, the infection starts from sinuses (air pockets around nose beneath cheekbone and forehead). This also fungus is found in soil, plants, decayed fruits, and vegetables. The symptoms during this stage may be fever, facial pain, headache, stuffy nose, dental pain, bloody nasal discharge, facial swelling, or discolouration. If untreated and sometimes despite treatment, the infection spreads into surrounding areas such as orbit (around the eye) and brain[2]. During this stage, the symptoms may include eye swelling, pain, drooping of eyelids, and restriction of eye movements, decrease in vision, blackish

discolouration on the palate (roof of the mouth) and decrease in the level of consciousness[3][4].

The organism responsible for around 70% of all the cases of black fungus is rhizopus oryzae. This particular infection majorly affects the people on medication or those having health issues such as diabetes, heart problems, etc, which lowers the immunity, ability to fight germs, and sickness. It is believed that Mucormycosis has an overall mortality rate of 50%, which can be triggered by the use of steroids, a life-saving treatment for severe and critically ill Covid-19 patients. One reason is that with the increase in COVID-19 cases in general, moderate and severe COVID-19 patients are often treated with steroids, due to which Immunosuppression or loss in immunity is observed, by steroids, due to which more cases of black fungus are being reported.

Steroids reduce inflammation in the lungs for COVID-19 patients and appear to help or stop some of the damage that can happen when the body's immune system goes into overdrive to fight off coronavirus. But they also reduce immunity and push up blood sugar levels in both people with diabetes and non-diabetic COVID-19 patients. And also, person already having health issues, such as, if a diabetic patient with uncontrolled diabetes mellitus is given steroids as part of COVID-19 treatment; it increases the blood sugar level, resulting in complications. Hence, it is essential to manage the use of steroids and control sugar. Thus, resulting in immunosuppression.

A eye surgeon from Mumbai, Dr. Akshay Nair, says "fuel to the fire". It means steroids required to fight COVID-19 and Diabetes lowers the body's immunity system "the birth of Black fungus (Mucormycosis)". As medical experts say, this Mucormycosis occur mainly in patients who have suffered from diabetes diseases. The blaming factor comes through an overdose of steroids

while treating COVID-19 or SARS-CoV virus itself, helping the fungus spread due to immunosuppression.

Environmental fungi, especially Mucormycosis, causes of infections in human and increase nowadays globally, including US, Australia, India, and other countries. Effective treatment for COVID-19 is complicated in India due to a patient falling series of secondary infections like a fungal and bacterial disease[5] reported a new problem through black fungus during this pandemic situation. In Gujarat, 40 cases are recorded, and also 8 persons lost their eyes[6]. On 15th May 2021, 300 cases were recorded in the Gujarat state. Maharashtra state health minister said Mucormycosis patients rose around 2000 in the state on 11th May 2021[7]. In India, as experts say intense pressure in healthcare systems due to environment crowded which make chances more to spread.

Treatment of mucormycosis may require a team of doctors from multiple specialties including an ENT surgeon, Ophthalmologist, Neurologist, Intensivist, Endocrinologist, Microbiologist, Dental surgeon, and Maxillofacial surgeon. Since poor blood sugar control is the most important risk factor, treatment for control of blood sugars is a must. The treatment of infection itself requires a combination of medicines and surgery. Some antifungal drugs are effective in killing the virus and have to be started as soon as possible. Unfortunately, the medicines themselves are unable to fully control the infection and have to be combined with surgical removal of infected tissue.

This short communication covers root sources of fungus diseases, clinical features and characteristics of black fungus, causes and prevention through dentist's methods. Finally, the dentists have potential to control gems caused by black fungus. The information presented in this paper was searched from available literature in PubMed and Google Scholar database.

3. CLINICAL FEATURES OF BLACK FUNGUS

Mucormycosis' clinical presentation is linked to underlying conditions. Fungus can gain entry in the body through inhalation, ingestion of contaminated food, and contaminated wound on skin. Mucormycosis is ubiquitous and grows rapidly; it seldom causes infection in healthy individual. Other oral mycoses species are shown in illustration below [8].



Figure 1: Illustration of forms of oral mycoses apart from mucormycosis [8]

Clinical features [9]

1. Facial deformity is one of the most alarming features of fungal infection.
2. Excruciating headache- after entering in the body via inhalation, fungus molds and attacks the sinus cavities and nerves cause a person to experience persistent pain and headache.
3. Vision impairment- as the black fungus grows and spreads, vision can be distorted. Hazy or poor vision or blood shoot eyes can be seen in individual due to the involvement of cranial nerves III, IV, VI
4. Facial puffiness- swelling of the cheeks, eyes or parts of the face can be observed.
5. Multiple lesions- black fungal infection affects the skin and gives rise to multiple lesions.
6. Altered mental state- fungal infection makes its way to brain after inhalation and causes critical symptoms like – delirium, memory loss, altered mental state, neurological impairment.
7. Blackish discoloration around the bridge of the nose & palate- in the severe case of infection can result in the pain and growth of black patches around the eyes, nose& palate.

8. Fever
9. Shortness of breath
10. Bloody vomits.
11. Coughing
12. Chest pain
13. Pleural effusion

Dental examinations

Multiple carious teeth, severe toothache, black necrotic soft tissue such as- gingiva-mucosa and tongue, paresthesia of lip, horizontal bone loss or periodontitis, non-healing socket after extraction, halitosis, loss of teeth, jaw involvement, discoloration or ulceration of palate with medical condition such as- diabetes, leukemia, lymphoma, renal failure, immunosuppressive therapy, malnutrition, severe burns[10]

Classification of Mucormycoses according to anatomic location [11]



Figure 2

Characteristics of black fungus

One of the characteristic features of mucormycosis is its Angioinvasive property resulting in vascular thromboses and ultimately tissue necrosis. Angioinvasion was reported to be related to the interaction between a spore-coating protein family (cotH) on Rhizopus spp. Surface and endothelium glucose regulator protein 78 (GRP78) expressed at the surface of endothelial cells. The

interaction triggers host cell injuries and subsequent fungus hematogenous dissemination. Elevated level of serum glucose, iron and ketone bodies increases fungal growth, resulting in increased ability of Rhizopus to invade host tissues and explaining the susceptibility of diabetic and deferoxamine treated patient of mucormycosis[12]

Black fungus has some distinctive characteristics of Melanisation of their cell wall, morphological plasticity, incrustation of the cell wall with melanin and presence of other protective substance like carotenoids and mycosporines represent passive physiological adaptation which enable black fungus to be highly resistant against environmental stresses[12]

Causes

Mucormycosis is a fungal infection which is caused by Mucorales genera (Rhizopus, Mucor, Rhizomucor, Absidia, Apophysomyces, Cunninghamella, and Saksenaee)[13]. It is an angioinvasive infection (Saboo et al., 2021). Mucormycosis is also known as Zygomycosis. Mucor is saprophytic fungus and is widely found in nature such as soil, seeds, air, food and decaying organic material, as mucor has low virulence it is present in nasal mucosa of a healthy person as a commensal. In case if the healthy person becomes immunocompromised then the fungus will grow within the paranasal sinuses and spread intracranially or to other surrounded structures such as orbit. Intra-orbital involvement is more but intracranial involvement is seen rarely [14]. Mucormycosis affects people with lowered immune response [15]. It generally affects brain, sinuses or lungs [16]. Immunocompromised patients having uncontrolled diabetes mellitus, haematological malignancy, organ transplant, chemotherapy, chronic renal insufficiency, malnutrition, deferoxamine therapy, severe burns, HIV/AIDS, patients who have recovered from COVID-19 at least 6 weeks

back [15]. Patients who are recovering or have recovered from COVID-19 and were undergoing oxygen therapy, in which humidifiers were used, and there is exposure to moisture which put the patients at higher risk. So, it is better to use sterile water for oxygen therapy [17]. Other than host related risk factors, nosocomial mucormycosis has been connected with heavy fungal air load, contaminated air filters, healthcare related devices or procedures, for example contaminated wound dressing, intravenous catheter, tongue depressor, etc. Poor hygiene, unsanitary conditions, contaminated resources which includes food, access dose of steroids antibacterial drugs leads to these kind of fungal infection[18].

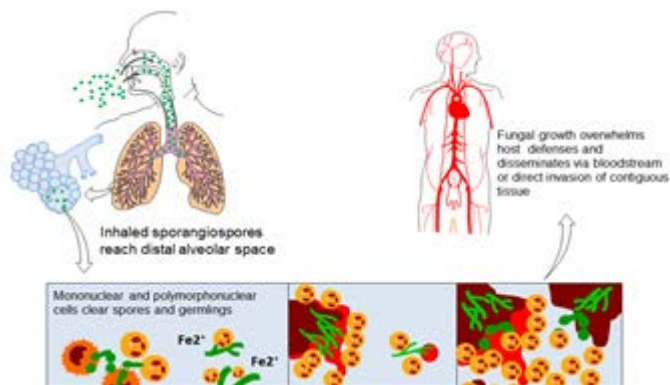


Figure 3
Predisposing Factors In Patients Of Mucormycosis

✚ Haematological malignancies or stem cell transplant (Dimitrios P. Kontoyiannis, Russell E Lewis, 2011)

- Prolonged (> 3 wk.) and severe (ANC < 200) neutropenia
- Monocytopenia (< 100 mm³)
- Prolonged (>3 wk.) high-dose systemic corticosteroids (e.g., prednisone or equivalent of >1 mg/kg/d)
- Iron overload (assessed by high iron indices, high iron storage by MRI, or high iron Staining in bone marrow biopsy)
- High-risk SCT (e.g., matched-unrelated donor SCT, haploidentical donor SCT, cord

Blood SCT, T cell-depleted SCT)

- Severe GVHD and its treatment (especially corticosteroids)
- Prolonged hyperglycaemia (fasting serum glucose > 200 mg/dL), corticosteroid-associated hyperglycaemia, diabetes mellitus
- Colonization by mucormycetes or heavy environmental exposure?
- Previous exposure to Aspergillus-active antifungal agents, especially voriconazole?
- Relapsed leukaemia

Among this condition acute myelogenous leukaemia (AML) are at higher risk, and the incidence range from 1%-8% and is less common in acute and chronic haematological malignancies[18].

✚ Diabetes mellitus and ketoacidosis

In this case the incidence ranges from 36%- 88%. Patients having uncontrolled hyperglycaemia with ketoacidosis have higher vulnerability to this infection. Patients having Type I, Type II and secondary diabetes are having high risk of getting infected by mucormycosis [18]. Mucormycosis in such patient is related to paranasal sinuses [14].

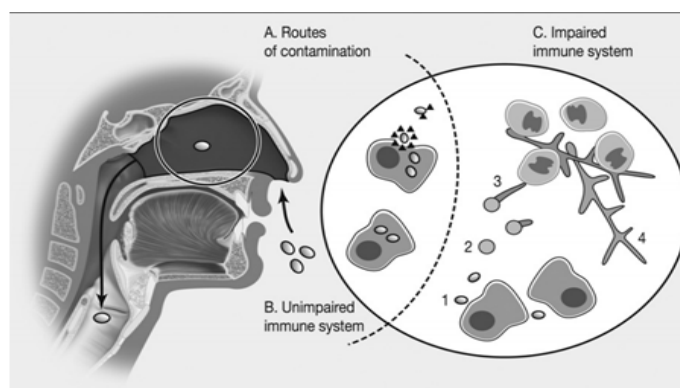


Figure 4
This picture shows impaired pathway responsible for Mucorales invasion in diabetic patient[19].

✚ Iron Load And Chelation Therapy With DFO

This therapy is one of the risk factors for angioinvasive mucormycosis. Iron chelator which are older like deferoxamine has contradictory higher vulnerability to have mucormycosis as the fungus has the potential to make use of chelator as a xenosiderophore to obtain free iron in vivo[20]. Opportunely use of DFO has been stopped as there are new iron chelator such as deferasirox (Exjade) and deferiprone, which do not influence patient to mucormycosis[18].

✚ HIV/AIDS

Patients with human immunodeficiency virus (HIV) or AIDS has lesser chances of getting infected by mucormycosis. There are less incidences of mucormycosis in patients with HIV compared to other immunocompromised population. Intravenous drug usage can be the cause of mucormycosis in patient of HIV[18].

✚ Use of Corticosteroids And Rheumatic Disease

Chronic use of corticosteroids causes defects in macrophages and neutrophils or steroids induced diabetes. Few patients of mucormycosis with systemic lupus erythematosus (SLE) which was informed in English-language literature, the infection can be exist in any clinical form, and disseminated mucormycosis was mutual and the mortality percentage was also high. Opportunistic mucormycosis is sometimes seen in patients with other autoimmune disorders, especially in patients with Wegener granulomatosis, there is reversion, as mucormycosis imitate the underlying disease and patients may go undiagnosed [18]

Prolonged Use of Voriconazole

Use of Aspergillus-active agents specially voriconazole which is administered in patient of HM's and recipient of hemopoietic stem cell transplant are related to higher risk of mucormycosis. A recent prospective randomized study which compares voriconazole with those using fluconazole or itraconazole in allogeneic transplant

recipient did not confirm finding for prophylaxis purpose. The controversy for use of voriconazole remains as, in both the studies patient enrolled were at low risk for invasive mold infection, including mucormycosis. Despite this risk clinicians should be aware of mucormycosis which can develop in high-risk patient who are receiving voriconazole, as double fungal infections are not uncommon[18].

✚ No Underlying Disease

Patients with no immunocompromised condition, these patients usually have initial cutaneous mucormycosis which may be related with burns or trauma. Authors have also stated iatrogenic factors as cause of mucormycosis which includes surgical trauma, using contaminated bandages, wooden tongue depressor, central venous catheter, adhesive dressings[18].

Mucormycosis in Children

It is rarely seen in children, Zaoutis et al has reviewed all available English language reports of mucormycosis in children before the year 2004. The total number of cases were 157 in which 64% were male with median range of 5 years. 28 (18%) had HM's (Haemoglobin malignancies) and remaining 9 (6%) has gone through HSCT (Hematopoietic stem cell transplantation). There were 30 more paediatric patients from 2004 to 2008.

Prevention

Practicing infection control habits at home and at hospital is highly recommended. Attention should be given during construction or renovation of the hospital facilities [20]. Use of mask is mandatory while visiting construction sites. Wear shoes, long sleeve shirt, long trouser and gloves while working in soil and doing other household work. Body should be scrubbed thoroughly while taking bath [21]. In recovered post-covid-19 patients it's necessary to change toothbrush once they test negative and mouth rinse should be used daily to avoid after

effects of the disease. Moreover, the same toothbrush holder should not be used for the entire family post-covid. [17].



Figure 5

Other than this blood sugar level should be monitored on regular basis. Use of clean and sterilised humidifier should be done at home for oxygen therapy. Use antibiotics, antifungal and steroids cautiously and as per doctors prescribed dose [21].

The Dentist: Gem of Control Black Fungus

The emergence of this COVID-19 pandemic has given rise to several other health conditions and mucormycosis or Black Fungus is one of them. Being a disease of fungal origin observed in COVID-19 patients who were on steroids or patients who have been taking medications of other illness such as- Diabetes. The intake of COVID-19 medications leaves the body stripped off with immunity and pushes up blood sugar levels in both diabetics and non-diabetics covid-19 patients which is said to be the main cause of this fungal disease[22].

As the infection spreads rapidly, early diagnosis is much needed for a better prognosis. A more precise dental examination & accurate history of present illness is the tool for diagnosis and therapeutic action [23].

Since all the virus and fungus enters the body through mouth, it is important take good care of oral hygiene and detect initial signs of black fungus before it turn fatal. Oral symptoms include discoloration of oral tissues-

tongue and gums, stuffy nose, severe pain, carious teeth, swelling on the face and heaviness in the region below eyes, headache and fever. Key points to keep in mind while dealing with covid-19 or post covid care-

Maintaining Oral Hygiene And Enhanced Use Of Tongue Cleaner And Toothbrush Everyday [22]

because of the fact that intake of steroids or medications enables the bacteria or fungus in the mouth to grow and leads to sinus. Taking care of oral hygiene is a necessity which can be ensured by regular brushing and even mouth rinsing can help exceedingly.

Conclusion

Early diagnosis is crucial for limiting the spread of infection. Dental surgeons and medical health care professionals must be fully aware with the ever changing signs and symptoms, diagnosis and treatment of this deadly disease. Hence, a multidisciplinary approach is required for treating the patients suffering from Mucormycosis.

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