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Mucormycosis: A Short Dental Review

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Review Article

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ABSTRACT

Mucormycosis is a severe and often fatal fungal infection that primarily affects immunocompromised patients. This serious infection is caused by a group of molds found in our environment called mucormycetes. Those with reduced ability to fight infections are most at risk including those with uncontrolled diabetes and malignancies. Historically, this fungal infection was rare, however, in recent years the prevalence has increased and the need for further discussion is warranted. The prevalence of Mucormycosis is significantly higher in India compared to other countries. In the wake of COVID-19, an increased number of cases have been reported in India, bringing additional attention to this deadly disease. Mucormycosis is categorized by the area of infection and includes five major clinical forms; pulmonary, disseminated, rhinocerebral, cutaneous, and gastrointestinal. Due to a high mortality rate, aggressive treatment is recommended to improve patient outcomes. Early diagnosis along with combination treatment is vital for patient survival. This paper intends to provide a brief overview and discussion of recent advances. The main aim and purpose of this review is to increase awareness and understanding of this disease to improve early diagnosis and outcomes.

Keywords: COVID-19, Diabetes Mellitus (DM), Fungal Infection, Immunocompromised, Rhinocerebral Mucormycosis.

Introduction

The term Mucormycosis was introduced by American pathologist R.D. Baker. Originally referred to as Zygomycosis, it has also been called Black Fungus by popular media due to the presence of black necrotic tissue. It is defined as a severe but rare fungal infection caused by a group of molds known as mucormycetes. These fungi live throughout the environment and can commonly be found in soil and decaying organic matter such as leaves, compost piles, or rotten wood.[1] Infections may develop when fungal spores enter the human body by inhalation, ingestion, or direct inoculation.[1] Although these fungi are common within the environment, they are non-pathological in immunocompetent individuals. At risk population includes those with weakened immune systems at any age, including individuals with diabetes, malignancies, transplant recipients, or premature infants.[2] The infection is not contagious and cannot be spread from one person to another. Incidence rates for Mucormycosis globally range from 0.005 to 1.7 per million population.[3] In India, the prevalence is estimated to be 80 times higher

with rates projected to be 140 per million population.[4] The incident rate has also been affected by the recent COVID-19 pandemic resulting in more cases throughout the country. The following paper will provide a brief review of this rare disease in order to spread awareness and increase the recognition and early diagnosis among affected individuals.

Classification

The presentation of an infection will be dependent upon the classification. Generally, mucormycosis is classified into five main types according to the body parts affected. This includes rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated. Of these classifications, rhinocerebral and pulmonary infections are the most common.[5-7]

Rhinocerebral Mucormycosis affects the sinuses and the brain. The mechanism of infection includes inhalation of the fungus. Symptoms include necrotic tissue in the sinuses or inside of the mouth, facial swelling, headache, and nasal or sinus congestion. The beginning phases may appear similar to sinusitis. More severe cases include symptoms such as cranial nerve palsies, fever, lethargy, seizures, slurred speech, and partial paralysis.

Pulmonary Mucormycosis affects the lungs and is caused by inhalation of fungal spores into the lower airway tract. Symptoms include cough, chest pain, shortness of breath, fever, and hemoptysis.

Gastrointestinal Mucormycosis is less common and is known to affect the gastrointestinal tract including the stomach and intestine. This may be caused by ingestion of spores. The stomach was the most common site followed by the colon. It is rare to find infections in the esophagus and ileum.[8] Symptoms include abdominal pain, nausea, vomiting, and gastrointestinal bleeding.

Cutaneous Mucormycosis is known to affect the skin this primarily occurs at a site of injury including burns or open wounds. The mechanism of infection is typically direct inoculation at the site of a weakened skin barrier. Individuals at risk include those with recent trauma, burn victims, and post-surgical patients. Also at risk are individuals with poorly controlled DM due to diabetic foot ulcers. Symptoms include skin lesions that resemble blisters or ulcers that may progress to necrotic tissue. Other symptoms include pain, warmth, excessive redness, or swelling around a wound.

Disseminated Mucormycosis is a widespread infection that spreads to other areas of the body via the blood. This is a very progressive presentation of the disease and is difficult to treat. The presentation of symptoms will be unique to the areas affected.

Ecology

The group of fungi that cause Mucormycosis is called mucormycetes and belongs to the scientific order Mucorales. While there are several different types of fungi in this classification, the most common types that cause mucormycosis are Rhizopus species and Mucor species.[9] Other less common examples of Mucorales include Rhizomucor species, Syncephalastrum species, Cunninghamella bertholletiae, Apophysomyces, Lichtheimia, Saksenaea, and Rhizomucor.

Mucorales fungi are thermotolerant and can be found in a variety of environments. They are more common in soil than in air and are widely found in organic materials such as compost piles, crop debris, agricultural soils, and animal excreta.[1] Growth patterns also indicate they may favor the summer and fall seasons.(10) The optimal environment for the growth and sporulation of this fungus is 27°C and high humidity.[1-2] Some speculate an increased incidence in Southeast Asian countries may be linked to the tropical climates where fungal spores are more likely to cultivate as well as increased agricultural land.[11]

Mucorales release sporangiospores and are easily aerosolized. Sporangiospores may enter the body through the airway and be deposited in the nasal turbinates or inhaled into the pulmonary alveoli. The respiratory tract is the most common route of entry to the body. In the case of cutaneous mucormycosis, sporangiospores may come into contact with open wounds leading to infection.

Epidemiology

The first case of mucormycosis was described by Friedrich Küchenmeister in 1876 in a German cancer patient who presented with a hemorrhagic infarct with fungal hyphae.[12] Over time, increased awareness of the disease led to more cases being identified and diagnosed. It primarily affects immunocompromised individuals and has been most strongly associated with diabetes, especially those with a history of diabetic ketoacidosis. Other risk factors include cancer, organ or stem cell transplant, and long-term corticosteroid use.[9,5,13]

Although still considered a rare disease, there is no doubt that the incidence of mucormycosis is increasing. While population studies are difficult to execute, multiple case series aim to review the prevalence. The first large literature review was published in 2005 by Roden et al. reviewing 929 cases from 1940-2003.[9]

In the past several years publications reviewing this topic have increased with the aim to spread awareness and improve diagnosis and treatment. As this disease is still somewhat rare, many cases may go undiagnosed and for this reason, case studies are often retrospective and the vast majority of studies rely on postmortem diagnosis. Despite the challenges in this area of research many strive to improve understanding of this rising disease.

Current research has focused on the rising number of cases being reported in India.[14,15] Chakrabarti et al. published three consecutive studies that illustrate the rising prevalence. In a retrospective analysis of cases from a single center in Chandigarh India, the incidence of mucormycosis increased from 12.9 cases/year in the 1990s to 50 cases/year in 2007.[16,17,18] Furthermore, a more recent country-wide spike in cases includes a 2.1-fold increase in mucormycosis from 2019 to 2021 due to the recent Covid-19 pandemic.[19]

The rise of cases is multifactorial. Firstly, improving diagnostic testing and awareness can lead to more accurate diagnoses. Secondly, due to the nature of this opportunistic infection, it is reasonable to relate incidence rates with that of an underlying disease such as diabetes, cancer, and other immunocompromising comorbidities. It is theorized that if immunocompromising diseases become more widespread, mucormycosis would subsequently increase as well. This is evident in the association between DM as well as Covid-19.

Association with Diabetes

Currently, Diabetes Mellitus (DM) is the most common underlying comorbidity globally.[2,9,14] Studies show that DM is a predisposing factor for mucormycosis in 36%-88% of cases.[9,15,16] Patients with uncontrolled DM, particularly those with ketoacidosis are most at risk. Rhinocerebral mucormycosis has a strong association with DM and is the most common presentation.[9] Studies show that out of patients with rhinocerebral mucormycosis, 81% had uncontrolled DM and of these patients, 41% were diagnosed with DM for the first time.[16] The International Diabetes Foundation estimates that 1 in 2 adults in Southeast Asia living with diabetes are undiagnosed.[20] This is suspected to be exacerbated by the recent pandemic due to individuals not seeking care. This illustrates the importance of multidisciplinary care and consideration of comorbidities when screening for mucormycosis.

It is evident that DM is closely linked to mucormycosis in India and other Southeast Asian countries, however, risk factors vary when comparing data from other regions of the world. Western countries do not see as much of an association with DM and report hematologic

malignancy emerging as a leading risk factor.[22,23] Researchers speculate that the use of statin to treat DM in the West may contribute to a decreased incidence due to some statins being active against some Zygomycetes.[21]

Association with Covid-19

During the pandemic, a remarkable increase in mucormycosis has been observed. A 2021 study discussing Coronavirus-Associated Mucor-mycosis (CAM) found a 2.1-fold increase in mucormycosis in 2021 when compared to 2019 which is attributed to the increase in COVID cases.[19] According to the national registry, Gujarat and Maharashtra are the most affected accounting for 22% and 21% of all reported cases of CAM respectively.[24]

Speculations suggest that this rise is due to multiple factors including an increase in uncontrolled DM, the overuse of corticosteroids, as well as an increase in immunocompromised individuals suffering from Covid-19. During the pandemic, otherwise healthy individuals became more susceptible to fungal infections due to weakened immune systems while fighting Covid-19.

The use of Corticosteroids is being considered for its role during this time. Corticosteroids are known to suppress the immune system making patients more susceptible to infections. A 2021 retrospective observational study by Sen et al. included patients from across India and found that corticosteroids were used to treat 87% of COVID-19 patients, with 21% treated for longer than 10 days.

This study also highlighted the prevalence of DM in these cases with 78% of patients being diabetic.[24] These cases require extra care and consideration. These emerging reports highlight the benefit of a multidisciplinary approach and the importance of healthcare providers considering fungal infections in these patients.

Natural Disasters

Mucormycosis has been known to be linked to natural disasters. This is evident in the rise of cases following the 2004 Indian Ocean tsunami.[25] Victims of natural disasters that sustain trauma are often exposed to contaminated environments. This results in an increased risk of cutaneous mucormycosis due to direct inoculation of contaminated materials with fungal elements. Contaminated water sources have been known to spread infection as they may mix with contaminated soil and spread fungal spores.[26] Moreover, Mucoraceouse molds are known to produce aerial growth when the surrounding air is extremely damp and is found to be more prevalent in water-damaged buildings.[1]

Diagnosis

Identifying mucormycosis in the early stages is pivotal for patient survival rates. Early diagnosis and treatment resulted in a 2-fold increase in survival rate compared to a 12-week delay in therapy (82.9% vs 48.9%).[13] Familiarity with predisposing factors assists in identification and it is vital to have a high index of suspicion when multiple risk factors are present. Among the most significant risk factors are diabetic ketoacidosis, COVID-19, prolonged glucocorticosteroid therapy, and persistent immunocompromising conditions.[26]

Dentists are perfectly poised to be the first line of defense against rhinocerebral mucormycosis. A physical examination and review of symptoms is the first step in identification. Tissue necrosis is a classic sign of mucormycosis which can be represented as tissue discoloration around the maxillofacial region.

During an oral examination, dentists may also notice palatal ulcers. These patients may complain of periorbital swelling and pain. If the infection is spread to the pulmonary system patients may present with dark-colored nasal discharge or sputum along with chest pain and difficulty in breathing.[27]

Pathological diagnosis is very important for confirmation of the disease. This can be done by collecting nasal discharge or biopsy specimens from the affected site and sending it to the pathology lab. This procedure should be done with extra consideration. It is recommended to collect specimens in sterile containers and avoid using swabs as the cotton fibers may interfere with identification.[27] Samples should be kept at room temperature as fungi may not survive at colder temperatures.[27]

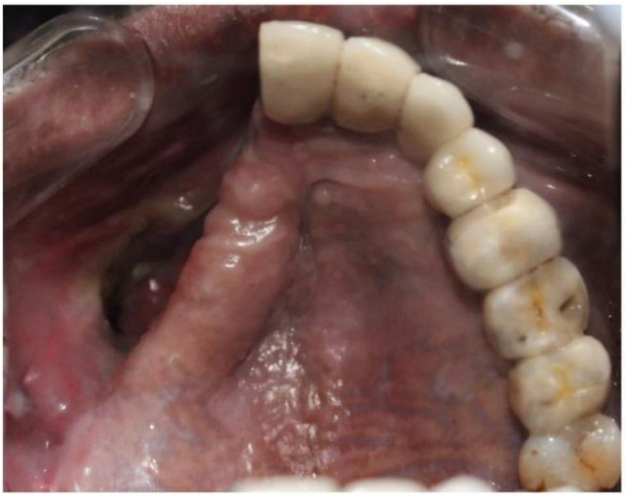

Figure 1: lesion caused by necrosis of buccal mucosa and hard palate.

Treatment

Effective treatment of this disease relies on a multidisciplinary approach and may benefit from dentists, clinicians, histopathologists, microbiologists, and oral surgeons. Currently, the recommendations for treatment heavily rely on case studies and retrospective reviews. Due to the low frequency and high mortality rate, studies are limited. It has been shown that monotherapy has been largely ineffective compared to combination therapy thus making it unethical to perform prospective randomized control trials to compare single treatments. Evidence shows that a combination of treatment approaches is the most effective to enhance survival rates.[7] Standard treatment regimens include antifungal therapies, surgical debridement, and management of the underlying disease.

Antifungal Therapy

Established antifungal therapies include Amphotericin B deoxycholate (AmB) as the most commonly used, followed by Liposomal amphotericin B (LAmb), and Amphotericin B liquid complex (ABLC). AmB is widely used due to its affordability and availability. The recommended dose of Amphotericin B deoxycholate is suggested to be 1 to 1.5 mg/kg/day.[7] Unfortunately, this dosage has a very high toxicity rate. A 2022 study looking at the side effects of this medication in India revealed that out of 57 patients, 68.4% developed hypokalemia, and 59.6% developed AKI while being treated with Amphotericin B deoxycholate.[29] While these side effects are typically reversible they should be considered when managing these cases.

Liposomal amphotericin B is significantly less nephrotoxic than amphotericin B deoxycholate, however, it can be much more expensive and not readily available in developing areas. Ostrosky-Zeichner proposed Liposomal amphotericin B be adopted as the gold standard however some argue that the increased cost is not justified.[30-31]

Surgery

Due to the numerous agents leading to mucormycosis, antifungal therapy alone may not be sufficient as different strains may have a higher drug resistance. Necrosis of the tissue may also result in poor perfusion rates at the site of infection. For these reasons, surgical debridement should be considered when appropriate.

In regards to rhinocerebral mucormycosis, early surgical debridement can impact survival rates significantly, and prevent the infection from spreading.[32] A case study from Khor et al. compared treatments for rhinocerebral mucormycosis showing that antifungal medication alone had a survival rate of 20% compared to a survival rate of 94% in cases receiving both antifungal medication and surgical debridement.[33] In the presence of necrotic tissue surgical debridement is necessary and should be performed with urgency. Following surgical intervention, continuous exploration of the sinuses may be warranted to ensure the infection has not progressed.

Adjunct Therapies

Clinicians must consider the treatment of the underlying risk factors associated with mucormycosis. This includes glycaemic control for patients with diabetes as well as medications to increase WBC in patients with neutropenia. Another consideration should be the overall management of prescription medications. If a patient is on corticosteroids, a diligent review of the duration of use may be warranted.

Another recent area of research includes Iron levels and the efficacy of Iron chelators as an adjunct therapy.[34] Iron is known as a key element in the growth of fungal infections. This is currently being studied in various populations including those with diabetic ketoacidosis. It is theorized that medications affecting iron levels may be beneficial, however, more research is needed in this area.

Hyperbaric oxygen may be considered an adjunct treatment for patients with rhinocerebral mucormycosis.[10,35] While there is not substantial evidence to support the effectiveness, early case reports suggest that it may be beneficial. It is theorized that higher oxygen improves the function of neutrophils and decreases the ability of fungal spores to germinate.[10,35,36]

Conclusion

Mucormycosis has undoubtedly become more prevalent in recent years. With such a high mortality rate it is imperative that dentists and health care workers be vigilant and familiarize themselves with this disease. Understanding how to recognize symptoms and identify at-risk patients is the first step to early diagnosis. If mucormycosis is suspected, a multidisciplinary team may be beneficial to consult on the plan of care. When considering treatment options it is important to use a combination of treatments for the best patient outcomes. A general dentist may be the first line of defense when screening and diagnosing individuals. While additional research is warranted, an increased awareness has the potential to significantly impact a patient's prognosis and potentially save lives.

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