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Mucormycosis - A Review

[1]Dr. Aparna Paliwal, Professor and Head, Department of Oral Pathology and Microbiology, RKDF Dental College and Research Centre, Bhopal.

[2]Dr. Nidhi Chouda, Professor, Department of Oral Pathology and Microbiology, RKDF Dental College and Research Centre, Bhopal.

[3]Dr. Preeti Rajput, Reader, Department of Oral Pathology and Microbiology, RKDF Dental College and Research Centre, Bhopal.

[4]Dr. Shrenik Nahata, Postgraduate Student, Department of Oral Pathology and Microbiology, RKDF Dental College and Research Centre, Bhopal.

Corresponding Author: Dr. Shrenik Nahata, Postgraduate Student, Department of Oral Pathology and Microbiology, RKDF Dental College and Research Centre, Bhopal.

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Abstract

The second wave of COVID-19 pandemic in India has seen a sudden increase in cases of mucormycosis and associated complications of vision loss, brain abscess and stroke. Both morbidity and mortality are on a rise post this fungal infection. Mucor mycosis is one of the rare fungal infections, which has a high rate of morbidity and mortality. Its disease-causing fungi is Mucoromycetes and it belongs to the order Mucorales, subphylum Mucoromycotina. The aim of present review of literature is to discuss this newer threat in detail.

Keywords: Covid-19, Mucor mycosis, Zygomycosis

Introduction

American pathologist R.D. Baker coined the term Mucormycosis. It is also known as Zygomycosis. It can be defined as an insidious fungal infection caused by members of Mucorales and zygomycotic species. Mucoromycotina are the common saprobes originating from the rotten matter or soils. Infections with Mucorales are categorized by rapid progression.[1]

Recently, several cases of mucormycosis in people with COVID- 19 have been increasingly reported world-wide, in particular from India. Mucormycosis is one of the rare fungal infections, which has a high rate of morbidity and mortality. Its disease-causing fungi is Mucoromycetes and it belongs to the order Mucorales, subphylum Mucoromycotina.[2] Main challenge with mucormycosis is with the diagnosis and treatment of the disease, and with time there is a gradual increase in the incidence of the disease. The most common predisposing factor

discovered in developed countries is Haematological malignancies, while uncontrolled diabetes seems to be the most common condition in developing countries.[3]

The most common oral sign of mucormycosis is ulceration of the palate, which ends up from necrosis thanks to invasion of a palatal vessel. Extension from the sinuses into the mouth causes painful, black necrotic ulcerations within the surface. The lesion is characteristically large and deep, causing denudation of the underlying bone. Ulcers from mucormycosis have also been reported on the gingiva, lip and gum ridge. Oral manifestations of mucormycosis are frequently the primary clinical signs to arise, probably due to the highly vascularized structure of oral soft tissues. Furthermore, it's been suggested that vascular ruptures and bleeding thanks to dental extractions may create a portal of entry for fungi into the maxillofacial regions. Intraorally, the surface is typically affected due to its proximity to the infection of the nasal fossa and paranasal sinuses. Additionally, isolated intraoral involvement is extremely rare. The maxilla rarely undergoes necrosis thanks to its rich vascularity. Maxillary necrosis can occur thanks to bacterial infections like osteomyelitis, viral infections like herpes zoster or fungal infections like mucormycosis, aspergillosis etc. Location of mucormycosis on the palate may be a rare and late occurance.[4,5] The aim of present review of literature is to discuss this newer threat in detail.

Etiopathogenesis

Some of the common predisposing risk factors associated with Mucormycosis are haematological malignancy, AIDS, uncontrolled diabetes mellitus, especially ketoacidosis, steroid use, neutropenia; especially with renal insufficiency, organ or stem cell transplantation, extremes of age, broad-spectrum antibiotics, iron overload, skin trauma, intravenous drug abuse, prophylactic voriconazole for aspergillosis and malnutrition.[4] Mucorales attack deep tissues by means of ingestion or inhalation of spores, and percutaneous injection of spores. As soon as the spores penetrate into lung or cutaneous tissues, the first line of defence in the healthy host is capable of destroying the spores via oxidative metabolites and cationic peptides.[5] Risk factors include uncontrolled diabetes mellitus, especially ketoacidosis, steroid use, extremes of age, neutropenia; especially with haematological malignancy, AIDS, renal insufficiency, organ or stem cell transplantation, iron overload, skin trauma, broad-spectrum antibiotics, intravenous drug abuse, prophylactic voriconazole for aspergillosis and malnutrition.[5] In diabetic patients, mucormycosis occurs as a destructive and potentially critical condition due to augmented availability of micronutrients and diminished defence mechanism of the body. Various hypotheses include (i) Low serum inhibitory activity against Rhizopus species, (ii) Improved availability of iron for the pathogen at decreased PH level and (iii) Pulmonary macrophages of persons with diabetes mellitus show diminished facility to inhibit germination of Rhizopus species. Ketone reductase in Rhizopus allows the organism to increase the glucose and acidic environment.[7,8,9]

Clinical findings of mucormycosis[10, 11]

- One-sided facial pain, swelling, numbness
- Headache
- Nasal or sinus congestion
- Black lesions on nasal bridge or upper inside of mouth that quickly become more severe.
- Fever
- A bloody or blackish mucus discharge from the nose.
- Prominent aching in teeth, jawbone, degrading of tooth structures

- Sudden mobility of teeth especially in Maxillary arches.
- Hazy vision, with objects appearing blurred or in double, with eye pain
- Abnormal blood clotting or thrombosis of tissues, along with skin injury and damage or necrosis of dermal cells
- Further deterioration of respiratory functions, with chest pain, Excess fluid build-up in lungs i.e., pleural effusion and coughing up blood or haemoptysis

Diagnosis

Mucormycosis infections in human beings occurs in two types.

1. Superficial and Visceral and
2. Localized and Disseminated.

Superficial form is seen involving skin, fingernails and external ear whereas visceral forms are manifest as pulmonary, gastrointestinal and rhino cerebral types.17 Diplopia is considered to be a characteristic symptom seen in a patients with diabetes, whereas pleuritic pain is most commonly seen in a neutropenic host.[12] Corzo-Leon et al. proposed a list of signs and symptoms that must be considered as “red flags” that includes diplopia, sinus pain, proptosis, periorbital swelling, cranial nerve palsy, orbital apex syndrome, tissue necrosis and ulcers of the palate as an means to diagnose rhino cerebral mucormycosis in diabetic patients.[13] The infection begins from paranasal sinuses by inhalation of spores, extending to the brain and involving successively the sinuses, nose and eyes. Palatal and sinuses necrosis are the first clinical manifestation which further enters into the orbit before involving the intra-cranial structures. Fever, nose-bleed, exophthalmos, blindness, facial paralysis are the signs of invasion of the trigeminal nerve which are the most commonly seen symptoms. Unsettled rhino-sinus mucormycosis will be the reason for cavernous sinus thrombosis. Reddish - black nasal turbinate and septum along with nasal discharge is also seen. As the disease progresses into cranial vault it leads to blindness, lethargy and seizures followed by death.[14]

Radiographic investigation

Posteroanterior view of chest shows multiple (≥10) nodules, and pleural effusion in mucor mycosis. Computerized tomography (CT) scans, show a characteristic reverse halo sign (RHS) which is considered as gold standard and a strong indicator of pulmonary mucor mycosis. Positron emission tomography-computed tomography (PET/CT) with [18F] – fluoro deoxy glucose (FDG) imaging technique, aids in the diagnosis and management of mucormycosis. Endo bronchial ultra sound-guided fine needle aspiration is also a useful diagnostic tool when feasible. “Black turbinate sign” which refers to an area of non-enhancing mucosa on MRI is a characteristic image feature in cavernous sinus thrombophlebitis mucor infection.[15,16]

Histopathology

Histological evaluation of mucormycosis is the mainstay of diagnosis. Diagnosis occurs through observing non-septate or minimally septated broad, ribbon-like hyphae (10 to 20 micro meters) invading blood vessels. The microscopic examination should evaluate morphology, width, branching angle, and septation.[15]

Mucormycosis can be cultured on Sabouraud's dextrose agar medium but is confirmed by histo pathological examination using hematoxylin and eosin (H and E), PAS, and later by Grocott's Methenamine Silver (GSM) stains. Typical histo pathological picture of mucor mycosis shows the characteristic ribbon-like branching, smaller width non-septate (aseptate) fungal hyphae which are prominent and have long, acute-angled, or right-angled branching varying from 45° to 90°. As the fungus is angio-invasive, it is commonly found in close

proximity with the necrotic vessel walls. Usually, tissue shows nonspecific inflammatory cell infiltrate, with necrosis and granulation tissue along with the hyphae.[15]

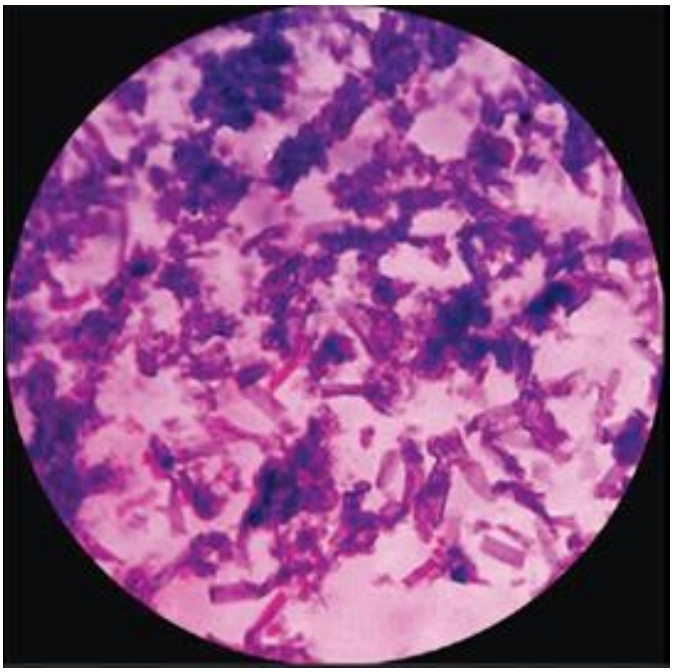

Fig. 1: Histological appearance of Mucormycosis

Management

The management of mucormycosis is based on multiple interventions occurring simultaneously, or with different timing and intensity. The basic principles of mucormycosis treatment include risk stratification for severity of the diseases, and intense attempts for early, clinical and laboratory diagnosis; timely initiation of an effective antifungal therapy (monotherapy or combination therapy) along with aggressive surgical debridement of necrotic lesions; reverse of immunosuppression (discontinuation of chemotherapy and increase of neutrophils), and control of the underlying medical condition. Early diagnosis and prompt therapeutic intervention may prevent progressive tissue invasion and its sequelae, may also reduce the need for extensive surgery and subsequent deformity, and may improve survival.[17]

In patients with uncontrolled diabetes rapid correction of metabolic abnormalities is mandatory also use of sodium bicarbonate (with insulin) so as to reverse ketoacidosis, even if acidosis is mild or severe it will help with a better outcome because it reduces the ability of Mucorales to invade the host tissues.[18]

European Society of Clinical Micro biology and Infectious Diseases (ESCMID) / Euro pean Confederation of Medical Mycology (ECMM) has given guide lines recommending use of susceptibility testing in order to guide the line of treatment in mucormycosis and to put together epidemiological knowledge.[19] European Conference on Infections in Leukemia (ECIL-6), and the ESCMID/ECMM guidelines, promote the use of a lipid formulation of amphotericin B as first-line therapy for treatment of mucormycosis.[19,20,21] The recommended dose for liposomal amphotericin B (AmB) is 5 mg/kg/day and as high as 10 mg/kg/day for infection involving the central nervous system.[19]

Use of hyperbaric oxygen is another adjunctive therapy in order to make a more-oxygen enriched cell environment in combination with administration of cytokines at the same time with the antifungal therapy. in vitro and some preclinical data on granulocyte-macrophage colony stimulating factor and/or interferon-γ has shown to enhance the immune response against certain Mucorales and thus can potentially help in treating the infection, as no clinical data is present to prove their efficacy, these therapies should be used with caution.[20]

Surgery management involves resection of necrotic tissues is the core of mucormycosis therapy. In pulmonary mucormycosis, surgical treatment along with appropriate systemic antifungal therapy has been shown to significantly improve survival compared to antifungal therapy alone.[22]

The prognosis is dependent on the extent of involvement of the disease and the time in which the treatment gets initiated in response to the disease.[5]

Conclusion

Mucormycosis, caused by a group of moulds called mucoromycetes, is a rare but potentially fatal infection if inadequately treated. Often referred to as the so-called black fungus, the incidence of mucormycosis has risen more rapidly during the second wave compared with the first wave of COVID-19 in India, with at least 14 872 cases as of May 28, 2021. The most common causes attributed to the rise of mucormycosis in COVID-19 patients are uncontrolled diabetes, the excessive use of corticosteroids for immunosuppression, and long-term stays in the intensive care unit. Rapid accurate diagnosis, administration of drugs, adjunctive application of hyperbaric oxygen, recombinant cytokines or transfusion of granulocyte, surgical debridement, and prosthetic obturator are the methods involved in successful management for mucormycosis.

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