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Post Covid 19 Symptom - A Deadly Combination of Mucormycosis and Diabetes Mellitus in Pandemic Spectrum.

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ABSTRACT

Fungal infections, including mucormycosis, aspergillosis and invasive candidiasis, have been reported in patients with severe COVID-19 or those recovering from the disease and have been associated with severe illness and death. India has reported a recent surge in mucormycosis cases. Prevention of COVID-19 associated mucormycosis needs to focus on aiming for better glycaemic control in COVID-19 patients and monitoring the use of systemic corticosteroids in treating severe cases. The survival rate for rhino-cerebral disease in patients without a systemic disease is about 75%; with other diseases is about 20%.; and in pulmonary disease is considered to be fatal. The incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million populations. Successful management of mucormycosis is based on a multimodal approach, including reversal or discontinuation of underlying predisposing factors (if possible), early administration of active antifungal agents at the optimal dose, complete removal of all infected tissues and the use of various adjunctive therapies. Uncontrolled, type II, diabetes is the most common type in diabetic patients with mucormycosis.

Keywords: Mucormycosis, Covid 19, Rhino cerebral mucormycosis

Introduction

American pathologist R.D. Baker coined the term 'Mucormycosis'. Another name for Mucormycosis is 'Zygomycosis'. It is an infection caused by fungi which belongs to the order Mucorales and zygomycotic species[1]. *Rhizopus oryzae* is the most common fungi isolated from patients with mucormycosis and is responsible for ~70% of all cases of mucormycosis. Mucormycotina are the common saprobes originating from the rotten matter or soils. Infections with Mucorales are categorized by rapid progression [1].

History

The German pathologist Paltauf, noted the first case of Mucormycosis in 1885 and named it as Mycosis Mucorina[2]. During 1980s and 1990s it is observed that, Mucormycosis was increasingly occurs in a patients who are immunocompromised[3]. Based on the prevalence rate, a study carried out in France reported amplification by 7.4% per year [4]. Worldwide occurrence along with the possibility of seasonal variation of zygomycotic infection has been reported [5].

Epidemiology

The most common agents of mucormycosis are *Rhizopus* spp., *Mucor* spp., and *Lichtheimia* (formerly *Absidia* and *Mycocladus*) spp. Genera of other Mucorales, such as *Rhizomucor*, *Saksenaea*, *Cunninghamella*, and *Apophysomyces*, are less common.[5] Etiology of mucormycosis varies considerably in different

countries. For example, *Rhizopus* spp. (34%), *Mucor* spp. (19%), and *Lichtheimia* spp. (19%) were most commonly identified in patients with mucormycosis in Europe.[6] In India, although *Rhizopus* species are the most common cause of the disease, *Apophysomyces elegans, A.variabilis* and *Rhizopus homothallicus* are emerging species and uncommon agents such as *Mucor irregularis* and *Thamnostylum lucknowense* are also being reported.[7,8] Another new species of *Apophysomyces*, namely, *A. mexicanus*, has been reported from Mexico.[9]

Most cases of mucormycosis result from inhalation of fungal sporangiospores that have been released in the air or from direct inoculation of organisms into disrupted skin or gastrointestinal tract mucosa. Seasonal variations affect the incidence of mucormycosis, with most infections occurring from August to November.[10] In a recent study, presenting the epidemiology of mucormycosis in Australia, trauma patients were more often infected with uncommon, non-*Rhizopus* spp.; the patients infected with *Apophysomyces* spp. or *Saksenaea* spp. were all immunocompetent, had predominantly acquired infection through trauma, and had infection frequently localized to the skin, soft tissues, and bones.[11] Necrotizing fasciitis due to *Apophysomyces variabilis or A.elegans*8 and *Saksenaea erythrospora,*[12] after intramuscular injections, have also been reported from India. *Cunninghamella* infection has been associated with poorer outcome. [13,14] The incidence of mucormycosis has been increasing in recent decades, mainly due to the growth of the number of severely immunocompromised patients.[2,3] Now mucormycosis cases are being reported from all over the world, but differences in the epidemiology seem to exist between developed and developing countries. In developed countries, the disease remains uncommon and is mostly seen in patients with hematological malignancies (HM). In contrast, in developing countries, especially in India, mucormycosis is more common and cases occur mainly in patients with uncontrolled diabetes mellitus (DM) or trauma.[7] Accordingly, the prevalence of mucormycosis varies from 0,01 to 0,2 per 100 000 population in Europe and the United States of America, and is much higher in India (14 per 100 000 population).[7]

Etiopathogenesis

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 [6]. Risk factors include uncontrolled diabetes mellitus, steroid use , especially ketoacidosis, AIDS , extremes of age, neutropenia; especially with haematological malignancy, , renal insufficiency, organ or stem cell transplantation, iron overload, skin trauma, broad-spectrum antibiotics, intravenous drug abuse, prophylactic voriconazole for aspergillosis and malnutrition [7].

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 [7]. 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 [8,9,10]. Ketone reductase in Rhizopus allows the organism to increase the glucose and acidic environment. In DM particularly with ketoacidosis all types of mucormycosis will occur[11,12,13,14].

Neutrophils play a major role in host defence against mucorales. Its function is impaired at different level in DM [10,11,15]. Ketoacidosis in diabetes accelerate the fungal invasion [16]. The acidic milie produces more free iron by reducing its binding to transferrin and low level of dialyzable inhibitory factor in diabetics present suitable conditions for fungal duplication[17]. Mortality rate was reported 90% or even more with Mucormycosis, before the administration of amphotericin B and radical surgery[18]. Severely neutropenic patients and those who lack phagocytic function are more prone for mucormycosis. But it's not same in the case of AIDS patients19. It implies that the

T lymphocytes are not significant for inhibiting fungal proliferation but only the neutrophils. Prolonged administration of voriconazole, principally among the patients with haematological malignancies and hematopoietic stem cell transplants are more prone for mucormycosis [20,21,22,23,24]. Moreover mucormycosis is also seen in patients without any obvious immune-deficiency [25]. In such conditions, it may be related with burns, trauma and or allied with iatrogenic factors [26,27].

Clinical Presentations and Manifestations Infection of Mucormycosis in human beings occurs in two types. 1 Superficial and Visceral and 2. Localized and Disseminated. Superficial form occurs in external ear, fingernails, skin. Visceral forms are manifested as pulmonary, gastrointestinal and rhino cerebral types. Entry of these spores may takes place either through cutaneous or respiratory route. (E.g. spread of spores during intake of soiled food or by tainted needles) [28].

Diagnostic Method

Diagnostic methods related to mucormycosis includes evaluation of clinical manifestations, utilization of computed tomography (CT) in the early stages, magnetic resonance imaging modalities, finest application of clinical microbiological technique and execution of molecular detection, specialist assessment of cytological and histological provision [29]. Detection of host factors contributes extensively to the estimation of a patient's possibility for invasive mucormycosis.

PAS stains, direct examination, calcofluor, histopathological examination, Gomori methenamine silver stain, culture, molecular methods and fluorescent in situ hybridization are the various laboratory techniques for detecting mucor[29]. According to Kontoyiannis et al., a major problem in the identification of mucormycosis includes its indefinable clinical appearance and recurrent occult distribution, and hence a need for a sensitive nonculture-based investigative method is required. Gold standard analytic technique for confirmation is the tissue-based analysis [20].

Differential Diagnosis

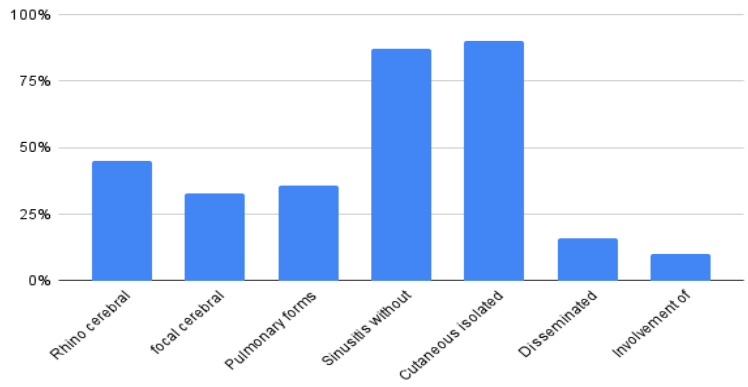
Differential finding of mucormycosis include maxillary sinus aspergillosis, maxillary sinus neoplasia, soft tissue radio necrosis, soft tissue infarction, other deep fungal infections [30].

Prognosis and Morbidity Rate

The prognosis generally depends on the extent of manifestation of the disease and effective treatment initiated in response to the diseases. The survival rate for rhino-cerebral disease in patients without systemic diseases is about 75%; with other diseases is about 20%.; and in pulmonary disease is considered to be fatal.

Survival rate varies with foci of the infection: rhino cerebral mucormycosis – 45%, focal cerebral mucormycosis – 33%, pulmonary forms –36%, sinusitis without cerebral involvement – 87%, cutaneous isolated – 90%, disseminated disease– 16%, and involvement of gastro intestinal form–10% [33, 34].

Better survival rate can be achieved in patients with low baseline serum concentration of iron / ferritin, neutropenia and malignant cases which is not associated with infection [30].



Treatment

Successful treatment for mucormycosis includes

1. Rapid accurate diagnosis
2. Surgical debridement
3. Administration of drugs
4. Adjunctive application of hyperbaric oxygen, recombinant cytokines or transfusion of granulocyte and prosthetic obturator
5. Antifungal therapies[31].

Successful management of mucormycosis is based on a multimodal approach, including reversal or discontinuation of underlying predisposing factors (if possible), early administration of active antifungal agents at the optimal dose, complete removal of all infected tissues and the use of various adjunctive therapies.[35–37] Rapid correction of metabolic abnormalities is mandatory in patients with uncontrolled diabetes and suspected of mucormycosis. In this respect, experimental evidence suggests that the use of sodium bicarbonate (with insulin) to reverse ketoacidosis, regardless of whether acidosis is mild or severe might be associated with better outcome with the disease due to reversal of the ability of Mucorales to invade host tissues.[38] Corticosteroids and other immunosuppressive drugs should be tapered quickly and to the lowest possible dose. Early diagnosis is crucial in order to promptly initiate therapeutic interventions necessary for preventing progressive tissue invasion and its devastating sequelae, minimizing the effect of disfiguring corrective surgery, and improving outcome and survival.[38,39] In this regard, Chamilos et al. showed that delaying effective amphotericin B-based therapy in patients with hematological malignancies for >5 days resulted in an approximately two fold increase in 12-week mortality (82.9% compared to 48.6% for those who started treatment immediately).[39]

Mucoraceous fungi are resistant to most antifungals in vitro, including voriconazole. Amphotericin B is the most active drug, except for some Cunninghamella and Apophysomyces isolates.[40–43] Posaconazole and isavuconazole are also active,[44] while itraconazole and terbinafine show some activity against certain strains. There seems to be some correlation between the degree of susceptibility of Mucorales isolates to amphotericin B and outcomes.

In a small study by Lamoth et al. MIC ≤0.5 μg/ml was significantly associated with better 6-week outcome.45 A similar correlation was reported in mice, where the efficacy of posaconazole was higher in animals infected with strains of Rhizopus oryzae that had lower MICs.[46] There are still not enough data to make a strong recommendation, but the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) / European Confederation of Medical Mycology (ECMM) guidelines recommend susceptibility testing to guide treatment of mucormycosis and to establish epidemiological knowledge.[36] Mucorales have many common characteristics with other moulds, including portals of entry (airways as well as disrupted mucosal and skin barriers), innate host defenses (polymorphonuclear neutrophil and mononuclear phagocytes, specific ligands in fungal spores such as pathogen-associated molecular patterns, and immune cells such as Toll-like receptors) as well as histopathological and clinical features.[47,48] However, R. oryzae and certain other Mucorales, including Lichtheimia, Rhizomucor, and Mortierella spp, are characterized by distinctive virulence factors that enable them to infect patients with diabetic ketoacidosis or other forms of acidosis, and exert unique host-pathogen interactions compared to other fungi, thus facilitating host evasion and disease progression despite treatment.[49]

In addition, mucormycosis is characterized by extensive angioinvasion that leads to vessel thrombosis and tissue necrosis.[50,51] Angioinvasion results in hematogenous dissemination of the organism, whereas necrosis of the affected tissues prevents penetration of immune cells and antifungal agents to the infection focus.[52] Certain Mucorales, such as R. oryzae, have reduced susceptibility to innate host defense as compared to other fungi, such as Aspergillus or Candida, making them more difficult to treat [53,54] and, therefore associated with increased mortality. The 2016

recommendations from the European Conference on Infections in Leukemia (ECIL-6), as well as the ESCMID/ECMM guidelines, advocate the use of a lipid formulation of amphotericin B as first-line therapy for mucormycosis. [35,36] The suggested dose for liposomal amphotericin B is 5 mg/kg/day and as high as 10 mg/kg/day for infection of the central nervous system. In the AmbiZygo study, performed by the French Mycosis Study Group, patients received 10 mg/kg/day of liposomal amphotericin B for the first month of treatment, in combination with surgery, where appropriate. The overall response rate was 36% at week 4 and 45% at week [12]. Renal function impairment as shown by doubling of serum creatinine level was noted in 40% of patients (transiently increased in 63%).[49]

The study was prospective, but uncontrolled, so its results should serve as a basis for further trials.The optimal doses for antifungal agents are still an issue of controversy. This is true for triazoles, such as posaconazole and isavuconazole. ECIL-6 recommends the use of posaconazole as salvage or maintenance therapy, while the ESCMID/ECMM guidelines propose its use as first line treatment (moderate recommendation) at a dose of 200 mg q6h of the oral suspension. The advent of the intravenous and tablet forms of posaconazole has led to enhanced bioavailability and increased drug exposure.[50] This may strengthen the position of this triazole in the antifungal armamentarium especially against difficult-to-treat mucormycosis. Isavuconazole is a recently developed triazole, with a wide spectrum of antifungal activity including Mucorales.[51] In a multicenter, open-label trial (VITAL trial) 21 patients with mucormycosis received isavuconazole 200 mg once a day (quaque die [qd]) (after six doses of 200 mg q8h) as primary treatment and were matched with contemporaneous controls from a registry of rare fungal diseases, who had received conventional or lipid amphotericin B at a median dose 70 or 325 − 250 mg qd, respectively as primary treatment.[52] Outcomes in the two groups were similar, and isavuconazole was thus deemed to be an alternative to amphotericin B, as first-line treatment of mucormycosis. Although the results are encouraging, the study has some limitations, that is, small size and external control matching, which should be taken into account.[53]

DIABETES AS RISK FACTOR-

Diabetes mellitus is the leading underlying disease in patients with mucormycosis globally [8,9]. According to the World Health Organization (WHO) "the global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980" [35]. Diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries.

The number of people aged 20–79 years with diabetes in 2011 was 61.3 million in India, and it is estimated to rise to 101.2 million in 2030 [36]. A great rise in the diabetic population is also predicted for China, Brazil, Japan, Mexico, Egypt and Indonesia [37]. Accordingly, the cases of mucormycosis are expected to increase. In the latest review by Jeong et al. diabetes mellitus was the most common underlying condition in 40% of cases and 20% had documented ketoacidosis [9]. Uncontrolled, type II, diabetes is the most common type in diabetic patients with mucormycosis. In a recent study comparing.

North and South India, diabetic ketoacidosis was found in 90% of cases from North India and 10% of cases from South India [29]. Diabetes has been reported as a risk factor for mucormycosis in 73.5% of cases in India [11], 75% [30] in Iran and 72% [12] in Mexico. In contrast, the percentages from the European ECMM study were 17% [14], from Italy 18% [27], from France 23% [10] and from Lebanon 35% [31]. In the Indian publications, mucormycosis was the unmasking disease for diabetes mellitus in 12–31% of patients [5,11,22,38.]

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