

**Mucormycosis in Covid -19**

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**Abstract**

Mucormycosis remains a devastating invasive fungal infection, with high mortality rates even after active management. The disease is being reported at an alarming frequency over the past decades from India. Indian mucormycosis has certain unique features. Rhino-orbito-cerebral presentation associated with uncontrolled diabetes is the predominant characteristic. Isolated renal mucormycosis has emerged as a new clinical entity. *Apophysomyces elegans* and *Rhizopus homothallicus* are emerging species in this region and uncommon agents such as *Mucor irregularis* and *Thamnostylum lucknowense* are also being reported.

**Keywords:** Mucormycosis, Diabetes Mellitus, Rhinocerebral, Desforaxamine.

**Introduction**

Fungi belonging to the class Zygomycetes and order Mucorales often cause devastating angioinvasive fungal infections, primarily in patients with underlying risk factors.(1) These moulds gain entry into the human body via respiratory tract or skin, and less commonly through the gastrointestinal tract, eliciting an acute inflammatory response.(2) Under favourable conditions such as those in immunocompromised hosts, they invade the blood vessels, causing extensive vessel thrombosis and ischaemic tissue necrosis.(2-3) Most of these infections are rapidly progressive and exhibit high mortality (~50%) even after active management; the mortality rates approach nearly 100% among patients with disseminated disease.(3-6) The principal risk

factors implicated in mucormycosis include uncontrolled diabetes and diabetic ketoacidosis, prolonged steroid therapy, persistent neutropaenia, desferoxamine therapy, haematological malignancies, illicit use of intravenous drugs, autoimmune disorders, prophylaxis with voriconazole or echinocandins, and the breach of cutaneous or mucous membrane barrier due to trauma, burns and surgical wounds.(1,2) However, it has also been described in patients with no underlying disease.(1, 2)

The emergence of mucormycosis is being reported globally, with an alarming rise in the number of cases from developing countries including India. (7-9) The precise epidemiology of this disease in developing world is not well known due to limited data as a result of sub-optimal awareness, inadequate reporting and diagnostic facilities at many of the healthcare centers.1 However, the available literature suggests a considerable variation between the developing and developed nations, with differences in the prevalence, risk factors and causative agents involved. (4-7) Certain peculiarities have been observed in cases of mucormycosis in India compared with the western world, including a high incidence of this disease; uncontrolled diabetes and diabetic ketoacidosis as the principal risk factor; rhino-orbitocerebral (ROC) form as the most common clinical presentation; isolated renal mucormycosis as a new entity; and a wide and varied spectrum of pathogens involved in such infections. Seasonal variations in incidence of mucormycosis with respect to temperature, rainfall and humidity have also been noted.(10) In this review, we highlight these distinct features of mucormycosis with reference to India.

Mucormycosis is a rare opportunistic infection invariably affecting immunocompromised patients. The

organism implicated to cause mucormycosis is a saprophytic fungus, mainly rhizopus or mucor. It is the most deadly and rapidly progressive form of fungal infection affecting humans (1).Clinical presentation of mucormycosis depends upon the site of entry of micro-organism and the organ systems involved. The most common form includes rhinocerebral, which involve the nose, paranasal sinuses, orbits and central nervous system. Other forms of mucormycosis are cutaneous, gastrointestinal, pulmonary and disseminated (2). Oral mucormycosis is usually caused by inhalation of spores or direct contamination of open oral wound. Oral mucormycosis affecting immunocompromised patients, mainly diabetes mellitus has been reported in literature (3). However those occurring subsequent to tooth extraction are rare (4). In view of the serious and potentially fatal complication of tooth extraction, this paper reports two such cases of mucormycosis presenting as oroantral fistula and non-healing extraction socket respectively, in healthy adult patients.

### **High incidence**

An upsurge of mucormycosis is being reported throughout the world over the past two decades; however, the rise in developing countries including India has been phenomenal. Three consecutive case series on mucormycosis have been reported from a single tertiary-care centre in India: 129 cases over 10 years (1990–1999), 178 cases during the subsequent 5 years (2000–2004) and then 75 cases in an 18 month period during 2006–2007. Many other Indian centres have also subsequently published multiple series of this disease in different risk groups.(10-13) This increasingly high incidence of mucormycosis in India has been attributed primarily to a continued increase in the patient population with uncontrolled diabetes, which is a one of

the major risk factors for this disease in developing countries.<sup>1</sup> In fact, India has the second largest diabetic population globally (65.1 million) (14) with nearly 70% of these cases being those of uncontrolled diabetes.<sup>(15)</sup> Environmental factors, such as tropical and sub-tropical humid climate and high environmental temperature in most parts of India, further provide an optimum set-up for survival of these fungi, and perhaps contribute to the disease prevalence. Better awareness, expertise and diagnostic facilities in many of the healthcare centres have also significantly contributed to an increased recognition of this disease over the past years.<sup>(3)</sup>

Based on the clinical presentations, Rhino-orbitocerebral (ROC) is the most common form of mucormycosis in India, possibly due to its association with uncontrolled diabetes and diabetic ketoacidosis.<sup>(16-20)</sup> According to the multiple case series reported from our tertiary care centre in North India, the prevalence of different clinical types amongst mucormycosis cases is: ROC (48–55%), cutaneous (13–15%), pulmonary (7–17%), disseminated (5–12%), gastrointestinal (5–13%) and isolated renal (5–14%).<sup>(4-6)</sup> Likewise, in a meta-analysis of all the zygomycosis cases reported from India, Diwakar et al. describe an overall prevalence of ROC (58%), cutaneous (14%), pulmonary (6%), disseminated (7%), gastrointestinal (7%) and isolated renal (7%).<sup>(21)</sup> This is consistent with the global trend, wherein pulmonary and sinus infections (with/without central nervous system involvement), followed by cutaneous type have been found to be the most prevalent.<sup>(22-25)</sup> Cases of necrotising fasciitis due to zygomycetes, occurring via contaminated intramuscular injections, are also a common finding.<sup>(26)</sup> This happens due to compromise in healthcare practices and the use of

contaminated needles. In addition, majority of the patients (60%) with cutaneous infections due to *Apophysomyces elegans* are from India. <sup>(27)</sup> The patients are usually immunocompetent individuals, who acquire the infection following penetrating trauma or burns. However, no correlation between the environmental prevalence of this fungus and clinical cases has been described yet. Furthermore, nosocomial mucormycosis is also being reported from this country, though traditionally the disease was considered to be community acquired. In a study from our centre, 9% of all mucormycosis cases were found to be nosocomial in origin. These patients acquired infection either at the site of the ECG leads or the adhesive tapes, or from contaminated intramuscular injections, or from air in the hospital environment.<sup>(4)</sup>

In India, 3–26% of mucormycosis cases are recorded from the immunocompetent host compared to 18–19% globally. Cases in India often present with cutaneous or isolated renal mucormycosis. Trauma is a risk factor in 7.5–22% of mucormycosis cases in India. Majority of the patients present with cutaneous mucormycosis after trauma, burns, and nosocomial infections at the surgery or injection site. Chander et al. from North India reported cutaneous mucormycosis in patients with post-intramuscular injections in the gluteal region <sup>(28)</sup>. Another study from North India reported that 9% of the mucormycosis cases are nosocomial in origin <sup>(29-31)</sup> Contaminated intramuscular injections and surgery, adhesive tapes, and endobronchial tubes were sources of infection in nosocomial mucormycosis. In General Risk groups for mucormycosis include persons with compromised immunity, Like suffering from covid 19, HIV, AIDS, cancer, with Transplant of organ/stem cell, skin trauma, burns, or surgical wounds; iron overload;

excessive intravenous drug use; malnourishment; and premature infants, low number of white blood cells (Neutropenia). Steroids are given to COVID-19 patients who are at risk which increases the sugar level both in diabetic and non diabetic patients. It means it suppresses the immune system and should only be given if it is very necessary. The following table shows the percentage data in the tabular form.

Types of mucormycosis	% Of patients suffering in India	Deceased patients
Rhinoorbital cerebral mucormycosis <sup>17,18</sup>	72-78	Diabetic patients
	22	Unhygienic tooth extraction process
Pulmonary mucormycosis <sup>19</sup>	40-45	SOT patients
	15-20	Hematological malignancy
	11	Diabetes

**Diabetes as a risk factor**

The risk factors for mucormycosis differ significantly amongst the developed and developing world. (1, 7) While haematological malignancies and transplants are designated as the key risk factors for mucormycosis in developed nations, the disease is majorly associated with uncontrolled diabetes with or without ketoacidosis in developing countries including India. (1, 7) Nearly 24–64% of the mucormycosis cases reported from India are in patients with uncontrolled diabetes, with or without ketoacidosis. (4-6), (21) Although other risk factors have also been implicated, the overwhelming number of mucormycosis cases with uncontrolled diabetes overshadows their role. (1, 7) This is possibly linked to a large diabetic population in such countries, as discussed previously. Unless complication develops, these patients avoid seeking medical attention. (3) In India, a

considerable number (16–23%) of diabetics remain undiagnosed of their underlying disease before presentation of mucormycosis; mucormycosis, in fact, acted as diabetes-defining illness in those cases. (4, 5) The mean informed duration of diabetes was found to be 6.7 ± 4.6 years before acquiring mucormycosis. (16)

Amongst the diabetic patients, poorly controlled type II diabetes is the most common risk factor for mucormycosis, being involved in nearly 44–88% of the cases mainly from north to south India, with nearly half of them exhibiting ketoacidosis. Type I diabetes (10–15%) and secondary diabetes have also been detected in some patients. In contrast, diabetes was the risk factor in only 36% of the global series of 929 cases, 17% of the Trans-European series, 16% of France series, 30.6% of Belgium series <sup>31</sup> and 18% of Italy series. (23)

It has been observed that the testing should be done from lower respiratory track in the lungs to track the infection for Aspergillus galactomannan antigen and fungal culture. Health care associated infections such as blood streams infections by Candida <sup>27,30</sup> has been also reported for hospitalized patients. Limited resources of health care facilities like gloves, gowns are also a key factor of the fungal spread like C. Auris. Medical workers should consider Pneumonias causing respiratory illness due to fungal infections if a person particularly is negative for Covid 19.

**Conclusions**

The epidemiology of mucormycosis in India is intriguing, and varies significantly from the developed nations. The estimated number of cases in India seems to be alarmingly high, with uncontrolled diabetes being the most important risk factor. Certain confounding factors like renal failure and hepatic diseases have also been

detected along with diabetes in mucormycosis patients; a detailed multicentric study is therefore warranted to precisely determine the association of diabetes with this invasive mycosis in India. ROC form remains the most common clinical presentation, albeit due to its association with diabetes. Isolated renal mucormycosis amongst immunocompetent, young individuals is an emerging entity in India. Although isolated renal infections have been reported from China as well, but the majority of patients in China have pre-disposing risk factors for developing mucormycosis, except the paediatric population. The disease is highly aggressive but the mode of acquisition and spread of the fungus through the body are not yet known, and demand urgent investigation. Cutaneous infections in apparently healthy individuals due to traumatic implantation of *Apophysomyces elegans* are also a common finding in India, although uncommon in other countries. The precise ecology, epidemiology and taxonomy of this fungus are not well understood and further studies on these aspects would provide valuable insights into the presence of mucoralean agents in environment, the susceptible hosts and the mode of fungal acquisition and spread.

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