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Review Article

Epidemiology of Mucormycosis in India: A Notifiable Disease

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Abstract

Mucormycosis or the grimmer popular name, Black Fungus has evoked public concern in the context of the COVID-19 pandemic but the disease is not that uncommon, medical literature from India shows. Mucormycosis is an angioinvasive disease caused by saprophytic fungi of the order Mucorales. Rare, life threatening COVID-19 complications appear to be escalating in India, creating a fresh wave of critical medical challenges in a country that has already seen short supplies of oxygen and other basic needs. Hospital across India have been reporting several cases of Mucormycosis, a rare fungal infection, affecting patients who have recently recovered from COVID-19. Once considered a rare "opportunistic" fungal infection in Covid-19 patients, mucormycosis has emerged as a dramatic bellwether for a raft of secondary ailments symptomatic of India's inability to contain the world's fastest growing coronavirus outbreak. The exact incidence of mucormycosis in India is unknown due to the lack of population based studies. The estimated prevalence of mucormycosis is around 70 times higher in India than that in global data. Diabetes mellitus is the most common risk factor, followed by haematological malignancy and solid-organ transplant. The government has now declared it a 'Notifiable Disease'.

Key Words: Mucormycosis, Mucorales, Saprophytic Fungi, COVID-19, Coronavirus, Disease.

INTRODUCTION

Mucormycosis is an angioinvasive disease that is characterised by tissue infarction and necrosis (Frater et al., 2001; Prakash and Chakrabati, 2021). Mucormycosis, a rare but serious fungal infection, is being detected relatively frequently in Covid-19 patients across India. The disease, also known colloquially as "black fungus", was made notifiable by the government in the 3rd week of May 2021, making it mandatory for states to report both suspected and confirmed cases to the Integrated Disease Surveillance Programme (IDSP).

Mucormycosis (previously zygomycosis), a rare but serious fungal infection, is affecting some COVID-19 patients. The disease manifests in the skin, affects lungs and brain, and can lead to loss of the upper jaw or eye. It has been declared a notified disease in Haryana, Telangana, Maharashtra, Rajasthan and other states of India, the national COVID-19 task force has issued an advisory and the Union health ministry has asked states/UTs to declare Black fungus as an epidemic. A study from 2013-2015 at four major tertiary care hospital in India reported 388 mucormycosis cases, nearly 56% of whom were reported as having 'uncontrolled diabetes'. The next biggest risk factor was 'trauma' and reported in only 10% of the cases, which underlines the critical link of the disease to diabetes (Prakash et al., 2019; Patel et al., 2020; Skiada et al., 2011). India has among the highest global prevalence of diabetes with about 9% of India's adult population estimated to be diabetic according to Prakash and Chakrabati, 2021.

The pathogens associated with mucormycosis varies considerably between India and developed countries (Prakash and Chakrabati, 2019). Globally, Rhizopus arrhizus is the commonest cause of mucormycosis ((Prakash and Chakrabati, 2019; Jeong et al., 2019). The Apophysomyces species ranks second in India compared to the Lichtheimia species in developed countries (Jeong et al., 2019). Infections due to Rhizopus microsporus and Rhizopus homothallicus are rising in India (Jeong et al., 2019; Prakash et al., 2019; Patel et al., 2019). In the present review, we discuss the epidemiology, risk factors and underlying

diseases, causative agents, and clinical outcomes associated with mucormycosis in the Indian population.

Causative agent

Mucormycetes, the group of fungi that cause mucormycosis, are present throughout the environment, particularly in soil and in association with decaying organic matter, such as leaves, compost piles, and animal dung. They are more common in soil than in air and in summer and fall than in winter or spring. Most people come in contact with microscopic fungal spores every day, so it's probably impossible to completely avoid coming in contact with mucormycetes. These fungi aren't harmful to most people. However, for people who have weakened immune systems, breathing in mucormycete spores can cause an infection in the lungs or sinuses which can spread to other parts of the body. Several different types of fungi can cause mucormycosis. These fungi are called mucormycetes and belong to the scientific order Mucorales. The most common types that cause mucormycosis are Rhizopus species and Mucor species. Other examples include Rhizomucor species, Syncephalastrum species, Cunninghamella bertholletiae, Apophysomyces, Lichtheimia (formerly Absidia), Saksenaea and Rhizomucor (James and Berger, 2006; Jeong et al., 2019; Prakash and Chakrabarti, 2001). Lichtheimia species contribute 0.5% to 13% of cases from India. Chander et al. reported that most of the cases in India are due to L. ramosa (Chander et al., 2018). Other Mucorales associated with mucormycosis in India are Rhizomucor pusillus, Cunninghamella species, Mucor species, Syncephalastrum species, and Saksenaea species (Table 2). Mucormycosis due to rare pathogens such as Saksenaea erythrospora, Mucor irregularis and Thamnostylum lucknowense are also reported (Chander et al., 2018).

Prevalence and incidence

Covid triggered black fungus infection is raising in India. Reports showed an increasing trend of mucormycosis from a single centre at successive periods, with an annual incidence of 12.9 cases per year during 1990–1999 (Chakrabarti et al., 2001), 35.6 cases per year during 2000–2004(Chakrabarti et al., 2006), and 50 cases per year during 2006– 2007 (Chakrabarti et al., 2009). The overall numbers increased from 25 cases per year (1990–2007) to 89 cases per year (2013–2015) (Prakash et al., 2019). The rise in incidence over the years at that centre may be due to improved awareness and expertise in diagnosing the disease, though the possibility of a real rise in incidence cannot be ruled out. A 10-year study from Southern India (Tamilnadu) showed an annual incidence of 18.4 cases per year during 2005–2015 (Manesh et al., 2009). Another study from Tamilnadu reported 9.5 cases per year during 2015–2019 (Priya et al., 2020). A multicentre study across India reported 465 cases from 12 centres over 21 months; the study reported an annual incidence of 22 cases per year, and an average of 38.8 cases for each participating centre (Patel et al., 2020). Though invasive aspergillosis is given importance among invasive mould infections in intensive-care units (ICUs), a multicentre study in Indian ICUs reported mucormycosis in a considerable (14%) number of patients (Chakrabarti et al., 2019). Sindhu et al. reported mucormycosis at 12% in ICU patients at a single centre from North India (Sindhu et al., 2019). Without population-based estimates, it is difficult to determine the exact incidence and prevalence of mucormycosis in the Indian population. The computational-model-based method estimated a prevalence of 14 cases per 100,000 individuals in India (Chakrabarti et al., 2020). The cumulative burden ranged between 137,807 and 208,177 cases, with a mean of 171,504 (SD: 12,365.6; 95% CI: 195,777–147,688) and mean attributable mortality at 65,500 (38.2%) deaths per year (Prakash and Chakrabarti, 2019; Chakrabarti et al., 2020). The data indicates that the estimated prevalence of mucormycosis in India is nearly 70 times higher than the global data, which were estimated to be at 0.02 to 9.5 cases (with a median of 0.2 cases) per 100,000 persons (Prakash and Chakrabarti, 2019).

RISK FACTORS

Diabetes mellitus is the most common underlying disease, followed by haematological malignancies and solid-organ transplants (Prakash and Chakrabarti, 2021). However, mucormycosis in the immunocompetent host is an alarming threat in the Indian population. Infection is caused by Mucormycetes, a group of molds/fungus abundant in environment. It mainly affects sinuses/lungs of people with health problems or on medicines which lower body's ability to fight germs/sickness, including those with diabetes, cancer, organ transplant, hospitalised or recovering COVID-19 patients (treated with cheap steroid and other anti-inflammatory drugs). Steroid depresses the body's immune system, making patients more susceptible to secondary infections such as mucormycosis which may be triggered by mould tainted oxygen pipes and humidifiers. The prevalence of mucormycosis was reported at 0.16–1.72% in patients with diabetes mellitus from North India (Bhansali, 2004; Dayal et al., 2015). Prakash et al. reported a higher prevalence of diabetes mellitus as a risk factor in North India (67%) compared to South India (22%) (Prakash et al., 2019). However, no such regional variation was noted in recent case series with regard to South India (65.2–76.3%) (Manesh et al., 2019; Priya et al., 2020), North India (54–62.2%) (Manesh et al., 2019; Patel et al., 2020, Chander et al., 2018), and Western India (55.6%) (Patel et al., 2020). Similar to India, diabetes mellitus is a major risk factor in mucormycosis in Mexico (72%), Iran (75%), and the USA (52%) (Prakash and Chakrabarti, 2019). In comparison, the prevalence of diabetes in

mucormycosis is lower (17–23%) in European countries (Prakash and Chakrabarti, 2019).

Due to the lack of regular health check-ups in the Indian population, the diagnosis of mucormycosis unmasked diabetes in 43% of patients from North India, 40% in Western India (Patel et al., 2020), and 24% in South India (Manesh et al., 2019). These data signify the need for regular health check-ups in the Indian population. A recent estimate showed that 463 million adults (20–79 years), and 1 million children and adolescents under the age of 20 globally live with diabetes, which may rise to 578 million in 2030 (Williams et al., 2020; Prakash and Chakrabarti, 2021). China (116.4 million) and India (77 million) are at the top of the diabetes chart globally, followed by the USA (31 million). The situation is alarming in India, as the estimated diabetic population may rise to 101 million in 2030 (Williams et al., 2020; Prakash and Chakrabarti, 2021). A study from South India on acute myeloid leukaemia patients reported the prevalence of proven mucormycosis cases at 0.9%. Haematological malignancy (HM) is a risk factor in 1–9% of mucormycosis patients in India, compared to 38–62% in Europe and the United States (Prakash and Chakrabarti, 2019). Simultaneously, the expected rise of mucormycosis cases may worsen the condition.

CLINICAL SYMPTOMS

ROCM (Rhino-Orbital-Cerebral) mucormycosis is the commonest form (45–74%), followed by cutaneous (10–31%), pulmonary (3–22%), renal (0.5–9%), gastrointestinal (2–8%), and disseminated infections (0.5–9%). Other unusual sites of infection reported in the literature from India are breast (Kataria et al., 2016), ear (Prakash et al., 2019), spine (Hadgainkar et al., 2015; Shah and Nene, 2017), heart (Bharadwaj, 2017; Krishnappa et al., 2019), and bone infections (Bhatt et al., 2018; Urs et al., 2016). Diabetes mellitus is a common predisposing factor for the ROCM type of disease. A recent multicentre study from India reported that 77% of ROCM cases were in the diabetic population (Patel et al., 2020). Different case series focussed on ROCM cases from India reported diabetes as a risk factor in 80–100% of cases (Nithyanandam et al., 2003; Kolekar, 2015; Bakshi et al., 2020). Trauma is a risk factor for the ROCM type (15–52%), mainly after unhygienic dental procedures during tooth extraction (Prakash et al., 2019; Patel et al., 2020). Some other symptoms include Pain, redness around eyes and / or nose, fever, headache, coughing, shortness of breath, bloody vomits and altered mental status. The warning signs include toothache, loosening of teeth, blurred or double vision with pain, sinusitis (nasal blockade or blackish/bloody discharge), cheekbone or one sided facial pain or swelling, blackish discoloration of nose bridge/palate, thrombosis, skin lesion, chest pain Prakash and Chakrabarti, 2021).

Prevention

Use masks if you are visiting dusty construction sites. Wear shoes, long trousers, long sleeved shirts and gloves while gardening. Maintain personal hygiene (scrub bath). Control diabetes, monitor blood glucose level after COVID-19 treatment discharge, reduce steroid use, discontinue immunomodulating drugs and hydrate adequately.

Treatment and outcome

The treatment of mucormycosis involves the early initiation of therapy, the surgical debridement of infected tissue, antifungal therapy, and managing the underlying disease. Amphotericin B (AmB) is the first-line drug of choice; subsequently, posaconazole and isavuconazole are prescribed (Prakash and Chakrabarti, 2021). The major drawbacks in managing mucormycosis in India are a gap in treatment protocol and the financial constraints of patients that they cannot afford liposomal AmB (Patel et al., 2017; Patel et al., 2020). Existing data showed that the mortality rate was low in patients treated with a combination of AmB and surgical debridement of the infected tissue (19%–44%) compared with AmB monotherapy (50%–61%), these findings are in concordance with global data [76]. Posaconazole and isavuconazole were used as salvage therapy in the treatment of mucormycosis (Prakash and Chakrabarti, 2021). A study from South India assessed the safety and efficacy of posaconazole in ROCM patients. The study reported no mortality; 66.6% of patients had complete resolution of the disease, and the rest a significant reduction of the disease. The new anti-Mucorales drug isavuconazole showed comparable efficacy to AmB, however, it is recently introduced in Indian market and its efficacy is still to be assessed in this country. The mortality rate of mucormycosis in India is in the range of 28%–52% (Prakash et al., 2019; Prakash and Chakrabarti, 2021; Patel et al., 2020). The mortality rate in different clinical forms of mucormycosis reported from India are ROCM (31%–49%), pulmonary (61%–77%), cutaneous (23%–57%), gastrointestinal (67%–94%), and disseminated (62%–79%) ; these findings are similar to those in global data (Jeong et al., 2019; Prakash and Chakrabarti, 2021).

CONCLUSION

The fatality rate in mucormycosis cases is very high. As per data available thus far, mortality is as high as 80% if a patient goes untreated, or remains untreated long. If treated, it is still 40-50%. In cases where the infection is caught at the sinus stage itself, patients mostly completely recover. The exact prevalence of mucormycosis in India is unknown, though the estimated prevalence is much higher than that in developed countries. The possible reason for the high prevalence is the abundant presence of Mucorales in the community and hospital environment, large number of susceptible hosts especially diabetics, and the neglect for regular health check-ups of Indian population. A

considerable number of patients are ignorant of diabetes status till they acquire mucormycosis. Though uncontrolled diabetes is a common risk factor in all types of mucormycosis, it is significantly associated with ROCM type. Other emerging risk factors of mucormycosis are pulmonary tuberculosis, chronic kidney disease, and critically ill patients. Isolated renal mucormycosis in an immunocompetent host is a unique clinical entity and requires more studies on pathogenesis. Like in the global data, Rhizopus arrhizus is the most common causative agent isolated in all clinical forms of mucormycosis. However, the spectrum of agents causing the disease is considerably large in India. Apophysomyces and Saksenaea species are common agents causing cutaneous mucormycosis. Newer species like Rhizopus homothallicus, Rhizopus microsporus, Mucor irregularis, Thamnostylum lucknowense and Saksenaea erythrospora are emerging in India and require expertise in laboratory identification. The broad spectrum of agents emphasises the need to improve routine clinical laboratory facilities to identify rare Mucorales associated with mucormycosis. Mortality associated with mucormycosis in India is considerably high due to delays in seeking medical attention and diagnosing the disease, and challenges in managing the advanced stage of infection. It is necessary to conduct population-based studies in India to determine the exact prevalence of mucormycosis in diverse at-risk populations, which would help draw stakeholder attention to the early diagnosis and managing the disease. Though Amphotericin B is routinely used in the treatment of mucormycosis, in its absence second-line drugs like Posaconazole is also used. It is important to study the role of newer antifungal agents such as Isavuconazole in the treatment of mucormycosis in the Indian population.

Conflict of interest

Authors have no conflict of interest

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