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Mucormycosis and Role of COVID-19 in its Pathogenicity in India: A Review

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Abstract

Mucormycosis is a rising cause of invasive fungal infection but difficulty in diagnosis is the biggest detriment to early diagnosis. Rhinocerebral zygomycosis is most prevalent leading to vascular invasion, tissue necrosis, or even death. *Rhizopus arrhizus* is the most common causative agent of the disease, found on decaying organic matter but disease from *Cunninghamella* and *Rhizomucor* species should not be overlooked. The recent outbreak of COVID-19 pandemic has given rise to increasing patients of diabetes mellitus whose post-COVID immunocompromised state coupled with steroid use has led to rising numbers of mucormycosis patients in India. The establishment of a standard for permissible levels of microbial load in indoor environments has been suggested.

Keywords: Clinical microbiology, Environmental microbiology, Immunology, Infectious disease, Mucormycosis

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Introduction

Fungi from the order Mucorales are known to cause a rare infection called Mucormycosis which affects immunocompromised hosts primarily. Mucormycosis, also known as Zygomycosis, is still the third leading cause of invasive fungal infection, after Candidiasis and Aspergillosis.[1] The spread of this infection occurs mainly during the summer and autumn, and studies done between 1980 and 2000 have shown there to be a statistical significance in seasonal pattern, which are the earliest medical records of the occurrence of this infection. Atmospheric concentrations of Aspergillosis-causing *Aspergillus* have been documented to peak in autumn in several areas of the Western Mediterranean basin, Wales, Missouri USA and other Northern parts of Europe.[2] The study in Beirut had revealed that the onset of invasive mucormycosis is favored by a dry and warm weather which in India begins in April and lasts till June. Vasculotropism, which is the invasion of the blood vessels, is its key histopathological action leading to tissue infraction, or the formation of a thrombus due to obstruction of blood supply to the target organ.[3] The family Mucoraceae of the order Mucorales, class Zygomycetes have genera like *Absidia*, *Rhizopus*, *Mucor*, *Rhizomucor* and *Apophysomyce* which are responsible for causing this infection (Figure 1).[4]

The earliest medical records of 16 patients, eight male and eight female with a mean age of 50.7 years, show that 12 of them had rhinocerebral mucormycosis, the mortality of which was around 42% at that time, lower than the previously reported 50%.[5] Nine of these 16 patients were diabetic of whom two showed diabetic ketoacidosis. The rest were susceptible to chronic leukemia, hyperglycemia, and immunosuppression for renal transplant. The diagnosis of rhinocerebral mucormycosis was done by histopathological identification of large non-septate hyphae inside their blood vessels and tissues in biopsy of affected sites. It was seen that *Rhizopus* was growing in three of these patients. Both *Rhizopus* and *Aspergillus* were growing inside one patient with pulmonary mucormycosis, confirmed from biopsy of bronchoalveolar lavage showing growth of hyphae. The onset of symptoms for each of these patients was seen between August and December.[2]

In immunocompromised patients, mucormycosis is the second most susceptible and frequent mold infection but if infected, can spread rapidly in both immunocompromised and healthy individuals. However, the diagnosis of this infection in the laboratory and clinic remains problematic which leads to incorrect diagnosis and ultimately high mortality rates. To ensure a proper treatment and high survivability, early diagnosis, surgical debridement, antifungal therapy, and controlling the spread of infection are the most important factors.[4] Infections due to zygomycetes are divided into six clinical syndromes – rhinocerebral, pulmonary, disseminated, gastrointestinal, cutaneous, and miscellaneous.[6] Rhinocerebral zygomycosis is the most common,[7] described as an acute, rapidly progressive infection which is characterized by vascular invasion and large-scale tissue necrosis or death. When first reported, rhinocerebral zygomycosis was almost exclusively found in patients with diabetes mellitus, complicated by ketoacidosis.[8]

Of the various species in the *Absidia*, *Rhizopus*, *Mucor*, *Rhizomucor,* and *Apophysomyce* genera, *Rhizopus arrhizus* has been reported to be the most common pathogen responsible for infections and is found in 65% of all mucormycosis cases. They lead to hematological malignancies such as acute leukemia, lymphoma or chronic leukemia.[9] Among the less frequent causative agents of mucormycosis are *Cunninghamella*, *Apophysomyces*, *Saksenaea*, *Rhizomucor*, *Cokeromyces*, *Actinomucor,* and *Syncephalastrum*, these are responsible for fewer than 1–5% of reported cases.

This paper aims to study in minor details the pathogenesis, diagnosis, distribution, prevention, and management of the

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leading cause of mucormycosis and 2 lesser known causative organisms, and the sudden rise in patients of mucormycosis in India due to rising number of clinical diabetes brought about by the steroid treatment of COVID-19.

R. Arrhizus

It has already been established that hematological malignancies, neutropenia, intense steroid treatment, hyperglycemia, and forms of acidosis, deferoxamine therapy and trauma are risk factors for the onset of mucormycosis.[7] Differences in epidemiology of black fungus disease exist between developing countries and developed countries. In developed countries, the disease is uncommon and is mostly found in patients afflicted by diabetes mellitus and hematological malignancies undergoing chemotherapy[10] whereas in developing countries like India, the disease although sporadic is more common with patients of uncontrolled diabetes or trauma[11] and *R. arrhizus* has been claimed to be the most prevalent causative agent in these countries.[4]

Pathogenesis

A research finding had showed the increased susceptibility of patients with elevated available serum levels due to treatment by deferoxamine which is an iron-chelator to the onset of invasive mucormycosis.[12] It was further elucidated in another study that iron chelation is not the mechanism by which deferoxamine increases susceptibility of infections. While it is an iron chelator for a human host, *Rhizopus* can utilize deferoxamine as a siderophore to gain access to supply of iron for the growth of the organism itself. The fungus can accumulate 8–40-fold-greater amounts of iron in this manner than other fungi known to behave in the same way as *Aspergillus fumigatus* and *Candida albicans*. This utilization of iron leads to the proliferation of the organism in the serum of the host.[13] Moreover, animal model data show the exceptional requirement of iron for the growth of *R. arrhizus* since administration of deferoxamine worsens the survival of hosts infected with the fungi.[14]

Distribution

The majority of *Rhizopus* species are decomposers and are found on dead organic matter, although some are parasitic or pathogenic like *R. arrhizus*. The organism is characterized by branching mycelia composed of three types of hyphae – stolons, rhizoids, and sporangiophores. The black sporangia at the endings of sporangiophores produce numerous non-motile multinucleate spores for asexual reproduction. In warm countries, these fungi are found affecting plants and fruits causing a watery leakage rendering the inedible.[15] The organism can be found in the soil, near organic matter decomposition, and even indoor conditions when transported by individuals and can remain there for long hours if proper ventilation is not present. This condition worsens if an air conditioner is ran for long hours at a stretch which leads to formation of water droplets on surfaces when the AC is not in operation, lending areas for the growth of the organism unchecked.[16]

Management

Mononuclear and polymorphonuclear phagocytes or normal hosts are said to kill Mucorales by generating oxidative metabolites and

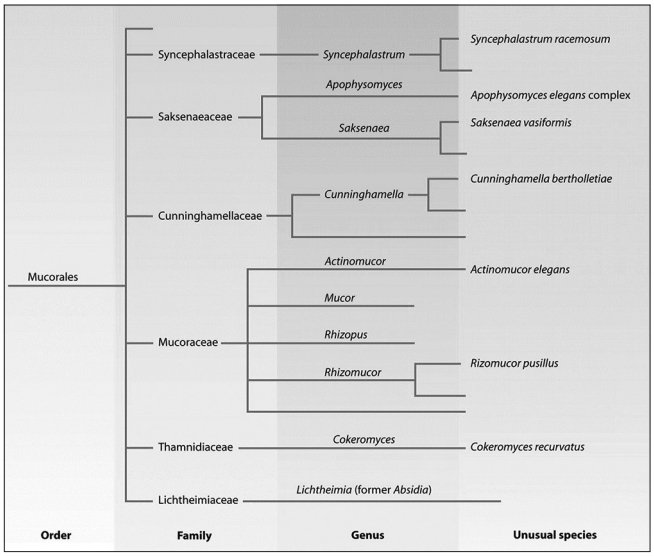

Figure 1: Classification of Mucormycosis-causing species[4]

cationic peptide defensins. Clinical evidence has demonstrated these phagocytes to be the major defense mechanism for the host against mucormycosis.[17] Oxidative and non-oxidative mechanisms brought about by persistent hyperglycemia and acidosis impair the functionality of the phagocytes.[18] Thus, corticosteroid treatment enhances the power of bronchoalveolar macrophages to prevent germination of spores *in vitro* or after *in vivo* onset of infection when the host has been inoculated by the virus.[17]

Prevention

VT1161 is a novel fungal-specific 14α-lanosterol demethylase fungal CYP51 inhibitor which was designed with a high potency for fungal identification and CYP51 inhibition of the fungal enzyme but not human CYP enzymes.[19] Thus, far after carrying out trials on a guinea pig model, it has been shown to have high effectiveness against yeasts and dermatophytes.[20] To present greater selectivity for fungal CYP51 against human cytochrome P450, VT1161 uses 1-tetrazole to bind the heme-iron within CYP51.[19] MIC of VIT1161 was determined against seven clinical isolates of *R. arrhizus* (lactic acid producer variety) and five clinical isolates of *R. arrhizus*, fumaric acid producer variety, and came out to be 0.5 μg/ml and >32 μg/ml, respectively.[21] The inhibitor increased the survival rate of neutropenic mice infected with *R. arrhizus,* treated until 3 days after onset of infection. They were sacrificed 24 h after the last dose and qPCR done on lung and brain tissue (primary and secondary target organs) showed 1 log decrease in fungal burdens as compared to placebo-treated controls.[22]

Cunninghamella bertholletiae and *Rhizomucor pusillus*

Pathogenesis

C. bertholletiae and *R. pusillus* like other agents of mucormycosis affect immunocompromised patients, as they enter the body through inhalation of spores causing pulmonary and disseminated infections with high rates of mortality. Immunocompromised hosts can be suffering from leukemia (which accounts for 51%

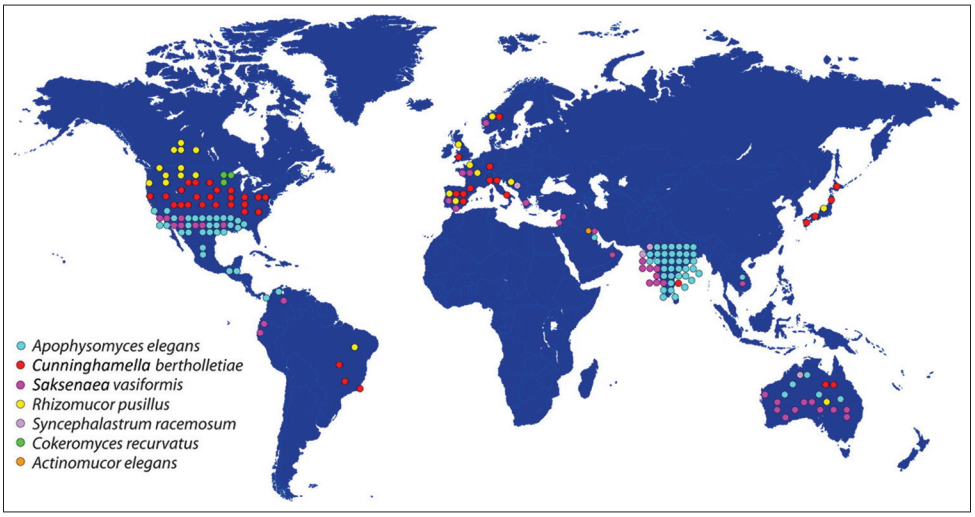

Figure 2: Geographic distribution of reported cases of mucormycosis by less abundant agents[4]

Undiagnosed diabetes globally

Region	% undiagnosed
Africa	59.7
South-East Asia (includes India)	56.7
Western Pacific	55.8
Middle East and North Africa	44.7
South and Central America	41.9
Europe	40.7
North America and Caribbean	37.8

*Data from 2019

Source: International Diabetes Federation BBC

Figure 3: Diagnosis of diabetes[55]

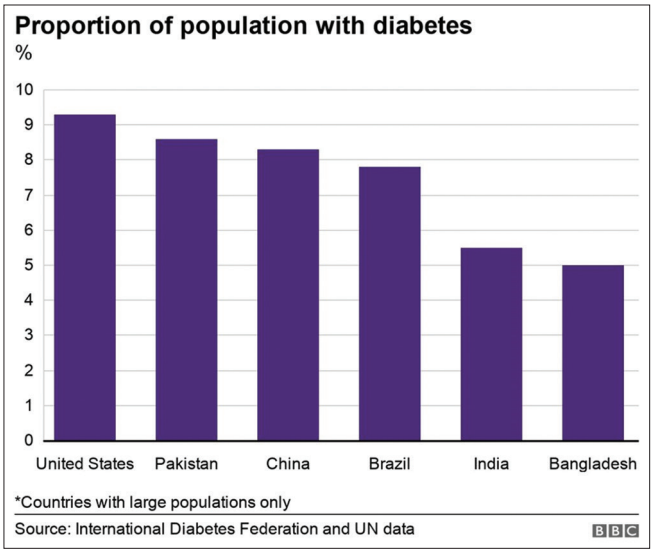

Figure 4: Population with diabetes in densely populated countries[55]

of the cases of *C. bertholletiae*), diabetes mellitus (19%), non-malignant hematological diseases (16%), organ transplantation (9%), or asplenia, hepatic cirrhosis, AIDS and IV drug abuse, and other chronic pharmacological immunosuppression from the action of drugs for the treatment of autoimmune diseases (5%).[23] This specie of *Cunninghamella* is found in many indoor environments including laboratories and hospitals and they grow very promptly at temperatures ranging from 30°C to 45°C within 48 h. Because it can grow at temperatures above 40°C, it can thrive in environments where *Caenorhabditis elegans* cannot. The longer the availability of immunocompromised patient in favorable environment of *C. bertholletiae*, the higher the chances of opportunistic mycosis.[6] Pulmonary cavity is the main localized site for *C. bertholletiae* infection in many reported cases.[24] With the exception of two reported cases of patients with infection, most other reported cases had an underlying hematological malignancy.[25] with the other two patients suffering from cardiopulmonary or rhinoorbitocerebral and pulmonary infections.[4] As reported, only six patients with pulmonary infections survived, giving it a mortality rate of 81% for lung-involved infections (Cohen-Abbo *et al*., 1993; Koyama *et al*., 2008; Mazade *et al*., 1998; Paul *et al*., 2006).

Diseases caused by *R. pusillus* are rare but dangerous. Because of its ubiquitous nature and capability to cause disease in many animals, its detection in the preliminary stages is difficult leading to further delay in administering medication or treatment. Despite being found much less frequently in the environment as compared to other species capable of causing mucormycetes in humans, *R. pusillus* is angioinvasive leading to thrombosis, hemorrhage, and tissue infarction.[26] Infections due to this agent are nosocomial or heath care related in a number of cases. While other less abundant agents such as *Apophysomyces elegans* and *Saksenaea vasiformis* cause disease in immunocompromised individuals too, *R. pusillus* cases are encountered when the patient is not only immunocompromised but has experienced tissue damage due to trauma leading to infections in the affected soft tissues.

Spores of *R. pusillus* are ubiquitous and are attached to various surfaces, getting transported onto the bodies of patients due to contact with air especially on the upper and lower airway mucosa.[26] As is the case with many mucormycetes infections, implantation of spores in the oral and nasal mucosa and the progressive extension to the rhinocerebral region is commonly seen in the case of infection due to this *Rhizomucor* specie. Dental

extraction sites are thus cited as a portal for the entry of the organism.[27] *R. pusillus* grows well between 20°C and 60°C, thereby making it well capable of inhabiting various climatic conditions and a wide variety of environments, indoor, and outdoor. Out of the 22 reported cases, the nosocomial route was responsible for 36% or eight of the patients' infections (Garner and Machin 2008; Kimura *et al*., 2009). Six patients showed symptoms of infection 1 week after admission into the hospital[28] or 3–7 days after discharge from hospital. This implicates hospital environments as potential sources of mold infections.[29] Entry of the organism is possible only when there is a lesion and thus availability of susceptible hosts are high in hospitals. An overall of 68% (15 out of the 22) cases were nasocomial or health-care-related routes of exposure of the fungi. Because of their ubiquitous nature, they are easily inhaled in and thus community-acquired cases are undiagnosed in most cases.[26] For their detection and identification, the patient has to be able to tolerate a biopsy which further increases the difficulty in histopathological identification of the agent.[30]

C. bertholletiae exhibited highest degree of pathogenicity in comparison to *R. pusillus*, and even *Mucor* species in a fly model of infection and can thus be claimed to be more virulent of the three.[31]

Diagnosis and Distribution

C. bertholletiae is found growing in a wide variety of nuts, seeds, and plants so direct ingestion of sporangioles is highly likely. It appears as branched sporangiophores ending at a swollen vesicle with spherical, ovoidal, or ellipsoidal sporangioes.[30] The infection has been found to spread from the gastrointestinal tract also in certain cases of disseminated infections. Accounting for 21 cases studied of *C. bertholletiae* infection, including autopsy results, almost all patients had their lungs compromised (81%), with heart (62%), spleen (57%), brain (48%), kidneys (38%), and liver,[29] gastrointestinal tract and skin (24%) being affected thereafter.[30] One of these patients showed early signs of pneumonia, further confirming that lungs are the most affected and vulnerable organ in case of *C. bertholletieae* infections.[32] It has been found that qPCR assay is more sensitive than culture analysis for the detection of infection in bronchoalveolar fluid. Whereas successful detection with culture analysis was around 67%, qPCR was successful at every attempt and could detect the organisms' DNA in 18 of 31 serial plasma specimens in as early as the 1st day after inoculation of the agent.[33]

Environmental isolates of *R. pusillus* can be found throughout the world in various places such as British Isles, Eastern Europe, North America, India, Japan, Indonesia, and even Africa (Figure 2). They can be found commonly in soil and garden composting, organic matter such as composted wheat and straw, dust from poultry, animal hairs, municipal waste dumps, manure beds, and also in air and water. Similar to *C. bertholletiae,* they are also found in grains, seeds, nuts, and beans,[30] and have not been confirmed using DNA-based techniques to be around areas of municipal compost.[34] They can very easily become airborne and reach the alveoli as they are around 3–5 μm in size. Because of their wide distribution and favorable size, they have been found in air conditioner air filters in Saudi Arabia[35] and in the indoor air of hospitals in United Kingdom,[36] Spain,[37] Canada,[38] and Italy.[39] Molecular techniques were used to diagnose *R. pusillus* in two outbreaks which showed their genetic relatedness to other more common agents of mucormycetes.[40] While *R. pusillus* affects the lungs and brain the most like *C. bertholletiae*, *R. pusillus* has caused several health-care associated infections too, like areas of needle insertion, catheter insertion, and areas on the skin in contact with adhesive paper tapes used to secure channels, IV and catheters.[41] Infections restricted to these soft tissues both with and without contagious osteomyelitis have 100% survival rates provided the infection is controlled, cleaned, and treated and the tissue is surgically debrided after a strict antifungal therapy.[42] However, in case of disseminated infections, especially in patients with leukemia, the case has been reported to be fatal.[43] Thus, like other mucormycetes, *R. pusillus* should be considered in the differential diagnosis of infections in patients if their infections are not responsive to antibacterial therapy, they are immunocompromised and are availing catheters and injections on a consistent basis.

Factors such has light make a difference in the distribution of all fungi in the soil or suspended spores in the air.[44] and hence there is a latitudinal relationship with their availability in the environment. Other meteorological parameters such as temperature and humidity have been found to be statistically significant in their correlation with bioaerosols[45] and this geographical pattern also plays a role in the composition of indoor fungal population which has been found to be more diverse in the temperate zones than in the expected tropics.[46]

Management

From the cases and reports reviewed, 33 or 77% of all patients with *C. bertholletiae* infection received antifungal therapy. AmB deoxycholate or lipid-based formulations of it were used on all patients solely (in 19), sequentially (in 8) or in combination with other antifungal drugs (in four patients). Only 11 or 33% of the patients who received these drugs survived. In addition, 14 patients were surgically treated in various ways of whom 8 recovered (57%) and only 2 of 18 patients (11%) recovered after antifungal therapy.[4] Studies have been done which show that *C. bertholletiae* is refractory to systemic antifungals and these results are in agreement with that finding. Survival rates are high only in the population who undergo surgical resection of the infected lesions after systemic antifungal therapy.[47]

From the studied cases, the overall mortality rate for *Rhizomucor* infections is significantly lower than that of *C. bertholletiae* infections (46% as compared to 77%).[28] Three patients did not receive antifungal treatment because the infections were diagnosed postmortem only. Otherwise, the infection has been found to be responsive to antifungal therapy.[43]

Prevention

The best way to prevent mucormycetes infections is still the reduction of environmental exposure, which due to their small size and large adaptability is a difficult task.[48] However, elimination of sources of infection and other interventional measures including use of antifungal prophylaxis have been shown to be effective control methods.[36] Outbreak of clusters of infections is more frequent with *R. pusillus* and *C. bertholletiae* if immunocompromised patients are inhabiting areas near construction sites associated with dust generation,[49] water-damaged environments, or have decaying organic matter near them.[50] Information obtained from these outbreak investigations has been the basis of formulation of control measures to prevent aspergillosis or mucormycetes from health-care-related causes.[49]

Fifteen outbreaks of mucormycetes, or clusters of it, have been reported in hospitals affecting immunocompromised patients affected by hematological malignancies, other forms of cancer,[38] transplants, or surgeries[36] in the United States, Europe, Canada, and China[51] between 1977 and 2010.[49] These cases could have been prevented by administering the quality of indoor air and ventilation systems (eight outbreaks), surfaces damaged by water and moisture (two outbreaks), and some of the materials used for dressing wounds and securing tubes (four outbreaks).[52] It can be suggested that whenever there is an outbreak of mucormycetes in areas around immunocompromised patients, the best way to combat the spread is to begin administering antifungal drugs and relocation of patients to a hygienic area away from the site of suspected outbreak.[52]

Black Fungus in India

After the outbreak of COVID-19 in India, around 12,000 cases of black fungus have been reported. These cases are mostly detected in patients recovering or suffering from the effects of COVID. Although previously reported to be very rare, currently new cases are on the rise. The prime reason hypothesized for the rising number of patients include hypoxia, a common symptom of COVID-19, and uncontrolled diabetes mellitus or the new onset of hyperglycemia due to rampant use of steroids for curing COVID-19. This leads to a condition of acidic medium and high levels of iron in serum and immunosuppressed state from the poor activity of phagocytic white blood cells.[53] About 94% of all who are suffering from black fungus in India are also suffering from diabetes[54] and as per the International Diabetes Federation, 57% of diabetic patients are undiagnosed in India, Nepal, Bangladesh, and Sri Lanka (Figure 3). It is this unreported occurrence of diabetes that is preventing early diagnosis of probable cases of black fungus in India.[55] It has been reported that microbiologists and doctors have claimed the indiscriminate use of steroids for the treatment of COVID to have a positive effect on contacting mucormycosis in India. Two widely prescribed drugs – dexamethasone and methylprednisolone – are being used on COVID patients to reduce inflammation due to immune response against the virus, but they are also responsible for reducing immunity of the patient and rising blood sugar levels of both diabetic and non-diabetic COVID-19 patients. (Figure 4)[56] Between December 2020 and February 2021, 58 new cases of the infection came up in five cities – Mumbai, Bangalore, Hyderabad, Delhi, and Pune. About 75% patients contacted the fungal infection within 12–15 days after recovery from COVID-19 and weakened nature of the immune system can be responsible for allowing entry of the pathogens.[57] Before the outbreak of COVID-19, Mumbai's Sion hospital experienced six cases of mucormycosis in a year which went up to 24 cases in 2 months. Eleven out of 40 diabetics suffering from mucormycosis have had an eye removed surgically, and six died. An unreported number have had their jawbones removed to prevent the spread of infection.[58]

A UK-based trail conducted on 2000 COVID-19 patients in controlled hospital setting showed administration of dexamethasone in treatment of the viral disease reduced mortality in those with moderate or severe infection but was harmful in those with mild onset of the disease. However, the drug has been included in many home-isolation kits and its use has been unchecked for a large portion of the population.[59]

Discussion

A work published in 2019 showed the diversity and abundance of fungal population in indoor environments of Kolkata, India. The study was done using an Andersen sampler to sample out air from various air conditioned public places and was successful in establishing the need to prepare a standard for permissible microbial load in workplaces of India. Two out of the five sites studied had microbial load higher than WHOs recommendation and all five were higher than the limit set by American Conference of Governmental Industrial Hygienists, with the values being in CFU/m^3. This showed us that rooms running any form of air conditioning for prolong periods of time on a daily basis suffer from lack of natural ventilation and serves as breeding grounds for fungal populations. This can be because of stale air in the room getting increased moisture once the air conditioning is switched off during non-working hours which supply the required water for growth of microorganisms. The study was aimed to prepare a risk-rating scale for fungal load by taking into account various growth-promoting factors present in the selected environment like moisture and temperature, and the variety of fungi present calculated by sampling and using Andersen formula. The risk rating of the five spots selected for the study was all between 50 and 70%. The sites being a computer laboratory, a library, a salon, a crèche, and a cafeteria, it increases the urgency to device a standard of allowable microbial load in public places, because hospitals too are air conditioned and suffer from lack of natural ventilation.[60] Buildings which do not run any form of air conditioning are also susceptible to fungal invasion as building materials and construction items can favor the growth of microorganisms by holding moisture in them and creating a condition of dampness,[61] and can even lead to asthmatic conditions in children[62] which during a COVID-19 pandemic can lead to further susceptibility.[63] Species of *Rhizopus* have been found in a non-air-conditioned cathedral[64] and an air-conditioned museum[65] of Kolkata, India growing on building materials and drapery which shows the ease at which these harmful species can enter places frequented by a crowd on a daily basis. Compounding this situation is the rising incidence of diabetes mellitus in India which has increased from 26 million in 1990 to 65 million in 2016[66] and has been estimated to rise to 100 million by 2030.[67] This can further complicate matters and give rise to an increasing population of susceptible people to mucormycetes.

Conclusion

Due to their adaptability and rising incidences in recent past, the black fungus disease or mucormycetes has become a global threat to all population but studies have shown that diabetes mellitus greatly improves the chances of onset as well as increase rates of fatality, or at least the need for surgical removal of affected organ. As our lifestyles have changed over the years so has the demand for air conditioning equipment in our homes and workplaces and the operation of such improves the chances of harboring pathogenic microorganisms in indoor environments which proliferate due to this lack of natural ventilation. These two conditions have led to a sudden rise in cases of black fungus in India during the COVID-19 pandemic where rampant use of drugs has caused sudden emergence of diabetes in people affected by the coronavirus and crowded hospitals have helped the pathogen grow on potential patients of the black fungus disease.

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