International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 04-05-2023, Accepted: 18-05-2023, Published: 03-06-2023
Volume 8, Issue 2, 2023, Page No. 150-154

A comprehensive review on mucormycosis

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Abstract
Even after active treatment, mucormycosis remains a deadly invasive fungal illness with significant fatality rates. In India, the illness has been recorded at an alarming rate in recent decades. Indian mucormycosis has a few distinguishing characteristics. The most common symptom is rhino-orbito-cerebral presentation, which is linked to uncontrolled diabetes. Isolated renal mucormycosis is a novel clinical entity that has evolved. In this region, Apophysomyces elegans and Rhizopus homothallicus are developing species, as are unusual agents like Mucor irregularis and Thamnostylum lucknowense. This study focuses on the unique characteristics of mucormycosis that have been reported in India.

Keywords: mucormycosis, epidemiology, diabetes, rhizopus oryzae, apophysomyces elegans, renal infection

Introduction

Angioinvasive fungal infections are frequently caused by fungi belonging to the class Zygomycetes and the order Mucorales, especially in individuals with underlying risk factors.[1] These moulds enter the human body through the respiratory system or skin, and less usually, the gastrointestinal system, causing an immediate inflammatory reaction. [2] They infiltrate blood arteries under favourable conditions, such as those seen in immunocompromised hosts, producing widespread vascular thrombosis and ischemic tissue necrosis. [2, 3]

The majorities of these infections advances quickly and have a high death rate (50 percent) even after active treatment; fatality rates in individuals with disseminated illness approach over 100 percent. [3-6] Uncontrolled diabetes and diabetic ketoacidosis, prolonged steroid therapy, persistent neutropaenia, desferoxamine therapy, hematological malignancies, illicit intravenous drug use, autoimmune disorders, prophylaxis with voriconazole or echinocandins, and a breach of the cutaneous or mucous membrane barrier due to trauma, burns, or scalds are the main risk factors for mucormycosis. [1, 2] It has, however, been reported in people who have no underlying illness. [1, 2]

Mucormycosis is becoming more common throughout the world, with an alarming increase in the number of cases reported from developing nations like India. [1, 2, 4, 7, 9] The specific epidemiology of this disease in the developing world is unknown due to a lack of data as a result of poor awareness, reporting, and diagnostic facilities in many healthcare facilities.[1] However, the existing evidence reveals that there is a significant disparity in prevalence, risk factors, and causal agents between developing and industrialized countries. In comparison to the western world, India has a high incidence of mucormycosis, uncontrolled diabetes and diabetic ketoacidosis as the primary risk factor, rhino-orbito-cerebral (ROC) form as the most common clinical presentation, isolated renal mucormycosis as a new entity, and a wide and varied spectrum of pathogens in mucormycosis.[10] Seasonal fluctuations in mucormycosis incidence have been seen in relation to temperature, rainfall, and humidity.[10] With relation to India, we emphasise these specific aspects of mucormycosis in this review.

High incidents

Throughout the last two decades, mucormycosis has been on the increase all over the world, but the growth in emerging nations, such as India, has been remarkable. [1, 2, 4, 7, 9] A single tertiary-care centre in India has documented three consecutive case series on mucormycosis: 129 cases over ten years (1990–1999), 178 instances over the next five years (2000–2004), and 75 cases during an 18-month period in 2006–2007. [4, 6] Several additional Indian centres have since published many series of this illness in various risk categories. [10, 13] This rising mucormycosis incidence in India has been linked mostly to a rise in the patient population with uncontrolled diabetes, which is one of the key risk factors for this illness in developing countries. 1 In reality, India has the world's second-largest diabetic population (65.1 million). [14] The uncontrolled diabetes accounting for over 70% of all cases. [15] Tropical and sub-tropical humid climates, as well as high ambient temperatures in most regions of India, create an ideal setting for the survival of this fungus, and may contribute to disease prevalence. Improved knowledge, experience, and diagnostic facilities in many healthcare centers have also contributed to an increase in detection of this condition in recent years.

The vast majority of cases reported from India were those with confirmed mucormycosis, as determined by culture and histology. Only a few authors have included the possibility of mucormycosis in their work. However, because to the often non-specific clinical signs and symptoms associated with this illness and the limited sensitivity of the currently available diagnostic modalities, the number of confirmed cases would be fewer than the real magnitude of mucormycosis. The exact prevalence of mucormycosis in India is difficult to determine in the absence of a population-based investigation. The illness prevalence appears to be around 0.16 percent among diabetics and 1.2 percent among renal transplant recipients, based on data accessible from select categories of patients, with the majority of these instances appearing as the ROC form. [15, 16, 17] In one

facility, gastrointestinal mucormycosis is said to be found in approximately 20% of all operated cases of newborn enterocolitis. [18] At fact, gastrointestinal mucormycosis was found to be so common in that facility that doctors suspect the illness in any baby with intestinal perforation. We recently conducted a study of Indian literature from the 1960s to the 2012s and created a computer model to estimate the prevalence of mucormycosis. The findings show that India has a mucormycosis prevalence of 0.14 instances per 1000 people, with a prevalence range of 208 177 to 137 807 cases (Mean: 171 504; SD: 12 365.6; 95 percent CI: 195 777-147 688) and a mean of 65 500 (38.2 percent) related fatalities per year. [19] ROC is the most frequent type of mucormycosis in India, based on clinical manifestations, possibly because to its link to uncontrolled diabetes and diabetic ketoacidosis. [20] According to a multi-case dataset from our tertiary care centre in North India, the following clinical categories are prevalent among mucormycosis cases: ROC (48-55%), cutaneous (13-15%), pulmonary (7-17%), disseminated (5–12%), gastrointestinal (5-13%), and iso- lated renal (5-14%). (4)-(6). In a meta-analysis of all zygomycosis cases reported from India, Di-wakar *et al*. show an overall prevalence of ROC (58 percent), cutaneous (14 percent), pulmonary (6%), disseminated (7%), gastrointestinal (7%), and isolated renal (7%). (7 percent). [21] This is in line with a global trend, with lung and sinus infections (with/without central nervous system involvement) being the most common, followed by skin infections. [22–25] Necrotizing fasciitis caused by zygomycetes, which occurs as a result of contaminated intramuscular injections, is also a regular occurrence. [26] This occurs as a result of a breakdown in healthcare procedures and the use of infected needles. Furthermore, the majority of individuals with Apophysomyces elegans cutaneous infections (60%) are from India. [27] The patients are mainly immunocompromised people who get the illness as a result of penetrating wounds or burns. However, no link has been found yet between the fungus's presence in the environment and clinical cases. In addition, nosocomial mucormycosis has been documented in this nation, despite the fact that the disease was previously thought to be acquired in the community. According to a research conducted at our centre, nosocomial mucormycosis accounts for 9% of all mucormycosis cases. Infection was contracted at the location of the ECG leads or adhesive tapes, or through contaminated intramuscular injections, or from the air in the hospital setting.

Diabetes as a risk factor

Mucormycosis risk factors vary greatly across the industrialized and developing worlds. While in industrialised countries, haematological malignancies and transplants are identified as important risk factors for mucormycosis, in underdeveloped countries such as India, the condition is mostly linked to uncontrolled diabetes with or without ketoacidosis. Patients with uncontrolled hyperglycemia, with or without ketoacidosis, account for almost 24–64 percent of mucormycosis cases reported from India. 4, 6, and 21 Although additional risk factors have been highlighted, their importance is overshadowed by the large number of mucormycosis cases associated with uncontrolled diabetes. As previously discussed, this might be connected to a significant diabetes population in such nations. Unless a complication arises, these patients do not seek medical help. In India, a significant percentage of diabetics (16-23%) go undetected for their underlying condition before developing mucormycosis; in those situations, mucormycosis served as a diabetes-defining sickness. Before developing mucormycosis, the average informed length of diabetes was determined to be 6.7 T 4.6 years. Poorly managed type II diabetes is the most prevalent risk factor for mucormycosis among diabetic patients, accounting for about 44–88 percent of cases mostly from north to south India, with over half of them demonstrating ketoacidosis. Some individuals have been found to have Type I diabetes (10-15%) and secondary diabetes. [29,30] Diabetes, on the other hand, was a risk factor in only 36 percent of the 929 cases in the worldwide series, 24 % of the Trans-European series, 25 % of the France series, 30 % of the Belgium series 31, and 18 % of the Italy series. It should be mentioned, however, that renal failure and alcoholism-related chronic liver disease have been discovered in individuals with diabetes in India as confounding variables. The specific vulnerability of diabetic individuals to mucormycosis is due to a number of variables. For starters, diabetes and ketoacidosis cause phagocytic cells to malfunction. Under such conditions, both neutrophils and macrophages demonstrate reduced chemotaxis and faulty killing by both oxidative and non-oxidative routes, while the particular mechanisms driving this remain unknown. [31–32] Second, individuals with diabetic ketoacidosis have an acidic serum pH and high amounts of free iron, which is a key nutritional factor in mucosal sensitivity. [33- 36] Finally, increased glucose and iron levels, comparable to those seen in diabetic ketoacidosis, boost GRP-78 expression. GRP-78 is a glucose-regulated protein belonging to the HSP-70 family that is mostly found in the endoplasmic reticulum, where it functions as a chaperon mediating many cellular activities such as protein folding, misfolded protein degradation, calcium homeostatis control, and endoplasmic reticulum stress sensing. [37] According to recent investigations, a proportion of GRP-78 is translocated to the cell surface in numerous cell types where it works as a receptor facilitating Mucorales' penetration and destruction of endothelial cells, resulting in angioinvasion. Mice with diabetic ketoacidosis had higher levels of GRP-78 in their sinuses, lungs, and brains, and anti-GRP-78 serum can protect them from mucormycosis, suggesting that GRP-78 overexpression may play a role in diabetics' vulnerability to this condition. [38] Different clinical manifestations of mucormycosis are thought to be linked to different underlying risk factors, with ROC, pulmonary, gastro-intestinal, and cutaneous variants occurring in individuals with diabetes, haematological malignancies or neutropaenia, severe malnutrition, trauma, or burns, respectively. Uncontrolled diabetes, on the other hand, has been proven to be a prominent factor in all varieties of mucormycosis in India, save the isolated renal form, despite the fact that ROC manifestation is still the most prevalent clinical type and is strongly linked to uncontrolled diabetes. Because diabetes and metabolic acidosis are the most common risk factors in Indian patients, the primary care methods in such situations are hyperglycemia control and rapid reversal of ketoacidosis, as well as surgical debridement and amphotericin B treatment. It is thought that an increase in the use of statins in diabetic patients, as well as statins' inhibitory effect on mucoralean agents, has resulted in a decline in diabetes-associated mucormycosis in the United

States in recent years. [39] Despite the fact that insulin is routinely provided to diabetic patients in India, no decrease in the incidence of diabetes-related mucormycosis cases has been recorded. As a result, a comprehensive investigation is needed to determine the function of statins in the treatment of mucormycosis. Because of the potential of an early diagnosis, cutaneous and rhino-cerebral mucormycosis have a higher survival rate than other clinical kinds of mucormycosis. Despite the fact that the majority of Indian patients have rhino-cerebral manifestations, the mortality rate of mucormycosis in India is still significant (almost 50%). This is mostly due to a failure to seek medical help, diagnosis, and treatment in a timely manner.

Isolated renal mucormycosis

Isolated renal mucormycosis in seemingly healthy hosts has been described as a novel clinical entity in India, in addition to the typical clinical forms. [40] Despite the fact that the kidney is implicated in about 22% of cases with disseminated mucormycosis, isolated renal mucormycosis is seldom mentioned in the literature [41]. Aside from India, China has also recorded case series of isolated renal mucormycosis. [42] However, in India, the majority of patients with isolated renal mucormycosis (75%) seemed to be healthy individuals; in China, the majority of documented cases, with the exception of the paediatric population, had risk factors for developing mucormycosis. [43] These patients with isolated renal mucormycosis had acute presentations. Although renal tuberculosis, quickly advancing glomerulonephritis, and acute pyelo-nephritis can all show similarly, enlarged unilateral or bilateral infarcted non-functioning kidneys (no contrast excretion) with low attenuation regions on imaging clearly imply renal mucormycosis.[44] The bulk of these instances were detected antemortem at our tertiary-care centre in North India, thanks to greater awareness and a combination of clinical and radiologic signs, as seen in (76.2 %) of 42 patients in a meta-analysis. Despite the antemortem diagnosis, death was still significant (50%) due to the complexity of caring such individuals. It is still unknown how the fungus penetrates the kidney without causing damage to other organs in the vast majority of individuals. An extra focus in the lungs has been detected on autopsy in a few individuals, suggesting that the lungs are the portal of entrance. [45] An second lesion in the urinary bladder was found in a recent study, suggesting that the ascending pathway might possibly represent the portal of entrance. [46] Fungi can induce cortical and medullary infarction, which leads to renal failure, if they get into the major veins of the kidney. [47] To understand the mysterious pathogenesis of this mucormycosis, a thorough examination of such individuals is necessary.

Spectrum of mucorales fungi

Human infections are caused by a diverse range of mucoralean fungus. Rhizopus, Mucor, and Lichtheimia (previously Absidia or Myocladus) spp. are the most common causes of this illness worldwide, accounting for 70-80% of all cases [48] Rarely, Apophysomyces, Saksenaea, Rhizomucor, Cunninghamella, Cokeromyces, Actinomucor, and Syncephalastrum spp. have been found. After Rhizopus oryzae, Apophysomyces elegans is the second most prevalent causative agent in India. Although Mucorales are opportunistic infections, Apophysomyces elegans and Saksenaea vasifor- mis can cause illness in otherwise healthy hosts, often as a result of penetrating trauma in tropical and sub-tropical catastrophes. [49] The majority of these individuals have merely cutaneous mucormycosis and no underlying illness; only a few individuals had rhino-cerebral and pulmonary infections, as well as risk factors for mucormycosis. [50]

Surprisingly, Apophysomyces elegans does not readily develop spores in the environment; sporulation must be carefully generated in the laboratory. As a result, how individuals with pulmonary, renal, or disseminated mucormycosis get this toxin from the environment is unknown. In immunocompetent people, Cunninghamella bertholletiae, Rhizomucor pusillus, and Rhizopus microsporus can cause infections.

Infections in India have also been linked to a variety of unusual species. For the first time, Rhizopus homothallicus has been found in patients with cavitary pulmonary mucormycosis. Mucor irregularis has been found in a case of rhino-facial mucormycosis in India, which was previously thought to be associated with a new endemic cutaneous mucormycosis isolated to China. Thamnostylum lucknowense, a novel mucoralean fungus, was recently identified from a patient with rhino-orbital mucormycosis.

Conclusion

The epidemiology of mucormycosis in India is fascinating, as it differs greatly from that of affluent countries. The anticipated number of cases in India appears to be disturbingly high, with uncontrolled diabetes the leading cause. Certain confounding variables, such as renal failure and hepatic disorders, have been observed in mucosal mycosis patients, necessitating a comprehensive multicentric investigation to properly evaluate the association of diabetes with this invasive mycosis in India. The ROC form is still the most prevalent clinical presentation, despite its link to diabetes. In India, immunocompetent young people with iso-lated renal mucormycosis are becoming more common. Although isolated kidney infections have been documented from China, the majority of patients in China, with the exception of children, had pre-disposing risk factors for mucormycosis. The illness is extremely contagious, but the method of infection and propagation of the fungus throughout the body remain unknown, necessitating immediate research. Cutaneous infections in otherwise healthy people caused by traumatic Apophysomyces elegans implantation are also widespread in India, albeit less so in other nations. Further research into the presence of mucoralean agents in the environment, vulnerable hosts, and the mechanism of fungal acquisition and spread would give significant insights into the presence of mucoralean agents in the environment, vulnerable hosts, and the mechanism of fungal acquisition and spread.

Acknowledgments

The authors gratefully acknowledge the support provided by Principal and Teaching Staff of Nagpur college of Pharmacy, Nagpur

Disclosure of conflict of interest

The authors declare that there are no conflicts of interest.

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