International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at http://www.ijmscrr.in Volume 7|Issue 03 (May-June) |2024 Page: 404-415

Review Paper

Prevalence and Management of Mucormycosis in India- A Post Pandemic Analysis

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Article Received: 08-March-2024, Revised: 28-March-2024, Accepted: 18-April-2024

ABSTRACT:

Background: The emergence of SARS-CoV-2 has increased Mucormycosis cases, which was perceived to be a rare infection caused by belligerent fungi belonging to order Mucorales. It is also called the black fungus and is exhibited as one of the seven variants such as rhino-cerebral, cutaneous, pulmonary, renal, gastrointestinal, disseminated or miscellaneous, leading to the debilitation of systemic wellness often associated with a reduction in functional efficiency and characterized by organ failure due to necrosis necessitating early diagnosis and timely treatment. **Aim**: Hence, to sustain the quality of life during the pandemic, this review was aimed for a better understanding of Mucormycosis which is the need of the hour for efficient management to overcome global crises. **Materials and Methodology**: A theoretical review was carried out on existing literature over three decades involving data in India as well as its global comparison, especially in terms of incidence and prevalence for enabling a scientifically evidence-based comprehensive analysis. **Results**: Indians have higher risk to Mucormycosis due to its large diabetic population when compared globally. It is evident that the rhino cerebral variant is the most commonly prevalent with a recent surge due to the pandemic. **Conclusion**: Both the incidence and prevalence of mucormycosis cases in India have always been very higher and has escalated even further due to the outbreak of SARS-CoV-2. It is recommended that appropriate modalities have to be adopted in individuals with immunocompromised conditions to safeguard them from contracting any reinfection as they are more susceptible to high-risk exposure.

Keywords: Mucormycosis, Review, Covid, Fungal Infection, Variants, Management

INTRODUCTION:

Mucormycosis is a rare and aggressive fungal infection that is angioinvasive in nature. It is caused by the fungi belonging to the order Mucorales and group Mucormycotina. The earlier scientific term for these fungi was Zygomycota which has changed recently [1-2]. Mucormycosis is also known as zygomycosis. It is the third leading cause of invasive fungal infection after Candidiasis and Aspergillosis [3]. Among all the present species under the Mucorales order, Rhizopus and Apophysomyces are the leading causes of Mucormycosis. It is claimed that 60percent of the world's cases of Apophysomyces infections are reported from India [4]. The name "black fungus" was given to it in recent times as it refers to the dark and necrotic tissues seen in patients affected by this disease [5]. Humans are infected by it either from inhaling the spores or consuming food or liquids contaminated by the fungus. Thus, it is referred to as a "fungal emergency" and is a devastating disease with a high mortality rate beyond 40percent even after its active management is carried out. It is mostly seen in patients with immune-compromised status due to conditions like uncontrolled diabetes, haematological diseases,

malignancies, and transplant recipients. A phenomenal increase in the case rate has been observed in India due to high numbers of reported uncontrolled diabetics [6].
It has been observed that COVID-19 patients are more susceptible to secondary infections, especially during the intermediate and later stages of the disease. In addition, critically ill patients, especially those admitted to the intensive care unit (ICU) and needing mechanical ventilation or who had a history of hospitalization up to 50 days, were more likely to develop fungal co-infections [7].
In terms of its spread on the oral cavity mainly involves the maxillary region, and it spreads rapidly, leading to necrosis followed by perforation of the palatal bone [7]. However, other parts of the mouth may also be affected based on the source of infection.

THE DESCRIPTION OF MUCORMYCOSIS VARIANTS:

Mucormycosis may affect several organ systems. It commonly affects the paranasal sinuses and brain, which is referred to as Rhino-cerebral Mucormycosis. Rhino cerebral Mucormycosis involves the nasal, paranasal sinuses and the brain. In addition, pulmonary, primary cutaneous, renal, gastrointestinal, miscellaneous, and disseminated forms have also been identified [8].

Rhino cerebral Mucormycosis:

This is the most common variant and constitutes about a 39percent of all variants. Based on the tissues affected, it may be of subtypes such as rhino-orbital or rhino-orbito-cerebral Mucormycosis. The former usually presents with periorbital or retro-orbital oedema, pain, proptosis, ophthalmoplegia and decreased vision. At the same time, the latter may be characterized with symptoms such as unilateral facial pain, cognitive disturbances and chemosis associated with periorbital oedema, fever, diplopia, cranial nerve palsies, necrotic tissue formation palatal perforation [9,10]. The novel COVID associated Mucormycosis (CAM) is linked with the highest case fatality rate of approximately 50percent due to cerebral involvement.

Pulmonary Mucormycosis:

This is the second most common variant with a high mortality rate of up to 80percent. The secondary infection among post covid individuals is associated with initial symptoms such as nasal obstruction and black crust like formation on the nose. It is characterized by clinical features such as neutropenic fever, dyspnoea, cough, haemoptysis, chest pain and, in certain cases, maybe in co-presentation of other diseases like concurrent bacteraemia. Radiological findings may be seen like nodules, mass, consolidation, cavitation, and ground-glass infiltrate or as that of pleural effusion. Other rarer findings may be air-crescent or reverse halo sign or presentations similar to pneumothorax [11, 12].

Cutaneous Mucormycosis:

The variant commonly affects the limbs and sometimes the scalp, face, thorax, back, abdomen, breast, neck and gluteal area. It is transmitted either by direct inoculation or through the usage of contaminated dressings, adhesive tapes, wooden tongue depressors, ostomy bags, vascular devices, nitro-glycerine patches, insulin syringes etc. It may be acquired during surgery, burn injury, road traffic accident or at an injection site. It usually presents itself in primary or secondary forms. The former localized occurs due to an infection spread by direct inoculation. At the same time, the latter is characterized by dissemination of the primary infection to a distant site that is mostly the rhino cerebral region [11]. The primary variant is gradual in onset and has varying clinical presentations. Some appear as indurated reddish to purple plaques that may become necrotic with an erythematous halo. This might further change to eschar in certain cases or appear ulcerated with tender nodules, swollen scaly plaques, cellulitis, necrosis, purpuric or target lesions. Another pattern regarded is the infection at deep sites [13, 14].

Renal Mucormycosis:

This has been reported to have two clinical presentations, of which the first is the dissemination from a primary source observed in up to a 22percent of cases and is the most common. The other may be an isolated renal infection among healthy individuals in India with acute symptoms like fever, haematuria or anuria and flank pain, about which the existing reported literature available are meagre [15,16].

Gastrointestinal Mucormycosis:

This is the rarest variant of all. The most commonly affected portions of the tract are the stomach, followed by the colon, small intestine and oesophagus, characterized by bleeding from the gut, abdominal pain, fever and alterations in bowel habits. This uncommon variant is often missed or delayed in its diagnosis and is identified at the autopsy stage in most cases [17, 18].

Miscellaneous variants of Mucormycosis:

These involve infection of the bone, breasts or mediastinum. Inadequate literature exists about its features as very few cases have been documented.

Disseminated variants of Mucormycosis:

This indicates the involvement of two or more non-contiguous organ systems through a haematogenous spread. It is commonly seen in neutropenic patients with haematological malignancies. Sites of dissemination are primarily to the brain following the heart, skin and spleen. The detection is usually done at the advanced stage or sometimes even during autopsy as this variant is rare but with the highest case fatality

rate. Survival of the individual is often challenging due to the aggressive potential of the fungus [15, 19].

INCIDENCE:

There has been an unprecedented increase in the incidence of Mucormycosis in the past two decades. The incidence levels depend on the risk factor and the variant involved. Uncontrolled diabetes and haematological disorders are the major predisposing factors for Mucormycosis [4]. An additional contributing factor can be the exposure to co-infections during the course of treatment with mechanical ventilation, antibiotic therapy, monoclonal antibodies and the use of corticosteroids [20].

The highest number of cases are documented in developing countries, especially India and China, as they comprise large populations having uncontrolled diabetes with immune-suppressed conditions [21]. However, in a review conducted by Roden *et al*. between 2000 to 2017, it has been observed that 34percent of the cases were observed in the European population, followed by Asia with 31percent, North America and South America with 28percent while Africa, Australia, New Zealand reported 3percent cases individually [22].

Since 2019, a new cause of the disease has also come into being as comorbidity following COVID -19. This has increased the global incidence of Mucormycosis greatly [4, 23]. This can be due to the individual's reduced immunity following SARS CoV-2 infection. Hence there is an increase in opportunistic infections such as oropharyngeal candidiasis, pneumocystis jiroveci pneumonia (PCP), pulmonary aspergillosis, bloodstream candida and infections caused by gram-negative bacteria, Staphylococcus aureus etc.

Over the 31 years, several pieces of research have been conducted in India to understand the cause and spread of mucormycosis in the native population. In three epidemiological studies carried out by Chakrabarti at PGIMR in Chandigarh *et al*. between 1990-2004 and 2006-2007, a total of 382 cases were observed in a span of 15years and 6months with a mean annual incidence of 24.5percent. This survey also revealed that 129 cases were diagnosed with an annual incidence of 12.9 cases between1990-1999 [24]. In the study conducted from 2000 to 2004, an annual incidence of 35.6 cases was found with the detection of 178 cases [25]. A total of 75 cases of zygomycosis were reported from 2006 to2007 [16].

At CMC in Vellore, Tamil Nadu, a total of 184 cases were detected with a mean annual incidence of 18.4percent in a ten-year study done by Manesh *et al*. from 2005 [26].

A four-year prospective observational study carried out at the government medical college and hospital in Chandigarh by Chander *et al*. from 2010 revealed that a total of 82 patients presenting with symptoms of mucormycosis with a mean annual incidence of 16.4percent [27].

In a two-year retrospective study at Ahmedabad, Gujrat by Patel *et al*. from 2013, which was conducted according to the European Organization for Research and Treatment of Cancer Mycoses study group criteria (EORTC/MSG), a total of 27 cases were detected [28,29].

In a prospective observational study by Patel A *et al*. in 2016, till 2017 held across 12 tertiary care centres across India, it was found that mucormycosis was diagnosed in 465 individuals [30].

An epidemiological prospective and multicentric research by Prakash *et al*. took place for two years from 2013 across four major tertiary care centres across India, of which two were located at Chandigarh, and New Delhi in the North and two at Bengaluru and Hyderabad in the Southern regions were included. The results led to the finding of 388 mucormycosis cases. The area-wise distribution observed was 321 and 67 cases in the northern and southern centres, respectively [4].

A total of 38 cases were found with an annual mean incidence of 9.5percent in a four-year retrospective observational study conducted by Priya *et al*. from 2015 in Tamil Nadu [31].

Sharma *et al*. studied the relationship between COVID-19 and mucormycosis in 2019 at a tertiary care centre in Jaipur, which led to the finding of 23 cases among individuals who were tested positive [23].

After the first SARS-CoV-2 wave, a review by John *et al*. to evaluate the total number of mucormycosis cases between the last month of 2019 to April 2021 reported 43 cases [32].

A sudden rise in mucormycosis cases between March and May 2021 was reported by Raut *et al*. This time period coincides with the second wave of SARS-CoV-2, during which approximately 14872 cases were detected [33]. Following this, a total of 45374 cases were declared positive in India as of 21 st of July, based on a BBC report.

PREVALENCE:

The result after a thorough search of past and existing literature was the observation of a higher prevalence of Mucormycosis in the Indian population when global comparisons were made. These numbers have only exaggerated with the recent SARS-CoV-2 pandemic [34].

The findings of the LIFE (Leading International Fungal Education) on the global estimation of the annual prevalence of mucormycosis excluding India were found to be approximately 10000 cases which drastically increased to 910000 cases after its inclusion [35].

The rate of cases for every 100,000 population was 14 within India while it was 0.2 in other countries, as reported by Prakash *et al*. in 2019[1, 36].

As the immune status and comorbidities influence prevalence, diabetes especially with diabetic ketoacidosis, haematological diseases, malignancies,

long term steroid or immunosuppressive agents use, kidney transplant, premature birth, alcoholic chronic liver disease, breach of skin, HIV infection, graft versus host disease, renal failure, metabolic acidosis, intensive care unit stay, neutropenia and ageing are some of the predisposing factors [37].

Out of all the factors, diabetic patients make up the largest population to develop mucormycosis. However, this does not reflect the actual tendency of acquiring the disease. A systematic review conducted by Chegini *et al*. in 2020 indicated a positive relationship between cerebral mucormycosis and diabetic patients [38]. A ten-year study conducted by Barati *et al*. in 2010 in Tehran, Iran, revealed that patients with non-insulin-dependent diabetes mellitus were more susceptible to mucormycosis [39]. A retrospective case-control study by Sarvestani *et al*. in Iran showed that patients with good glycaemic control had a better prognosis and lower predisposition compared to uncontrolled diabetic cases [40].

A study by Saeedi P. *et al*. in 2019 estimated that by 2030, the Indian diabetic population may rise to approximately 454 million, which is expected to cause a simultaneous rise in mucormycosis cases [41].

Uncontrolled diabetes was found to be a risk factor in 56.8percent of individuals, with a majority (65.7percent) having ROC variant while 18percent of them had diabetic ketoacidosis as a comorbidity in the study by H.Prakash *et al*. in 2019[5]. This result was also confirmed by Ramazan *et al*. in 2013 and S. Gupta *et al*. in 2020, showing a high correlation between rhino-orbito-cerebral mucormycosis and diabetic ketoacidosis [42, 43].

According to Chakrabarti *et al*. in their 15-year study in North India, the prevalence of different clinical variants of mucormycosis is 48–55percent for ROC (rhino-orbito-cerebral), 13–15percent for cutaneous, 7–17percent for pulmonary, 5–12percent for disseminated, 5–13percent for gastrointestinal and 5–14percent isolated renal variants [15].

Rhino-orbito-cerebral (ROC) variant exhibited the highest prevalence in India owing to its large diabetic population [43]. The cutaneous variant is the most common in immunocompetent children [44]. In a review by Skiada *et al*. in 2009, among children with this variant, 40percent of were immunocompetent while 23percent suffered from haematological malignancies [45]. In a 25-year study by Pamidimukkala *et al*. in 2020, immunocompetent individuals who had trauma due to road traffic accidents were found to be the most susceptible [46]. Pulmonary mucormycosis is a rare fungal disease that is difficult to diagnose during its early stages and lacks effective, timely treatment[47].In contrast to the cutaneous variant, it usually affects severely immunocompromised individuals, including patients with high-risk hematologic malignancies, recipients of hematopoietic stem cells and organ transplants[48].In the epidemiological study by Prakash *et al*., this variant was usually observed in 37–44percent solid organ transplantation recipients, 10–26percent patients with haematological malignancies and 10–14percent individuals with diabetes mellitus in the Indian population, which also is in agreement with data analyzed globally[21,22,49].

Renal involvement is usually described as the disseminated form of zygomycosis, while isolated renal disease has been infrequently documented [50, 51]. It is seen usually in immunocompromised patients [52]. However, some case series from India have reported 33–100percent of renal mucormycosis cases in immunocompetent individuals as well [53]. Chakrabarti *et al*. found renal involvement in 14percent of patients, out of which 23percent were apparently healthy and 35percent were diagnosed during autopsy [27].In the epidemiological study by Prakash *et al*., renal involvement was seen in 0.5–9percent of individuals [1].

The gastrointestinal variant involves complexity in its diagnosis due to its non-specific clinical signs and symptom. Nevertheless, its incidence has been reported as 5-13percent of all mucormycosis cases. Reliable incidence rate cannot be estimated as the majority of the cases are diagnosed accidentally during surgery or post –mortem [4].

In a study by Kaur *et al*., variation in the prevalence rate was based on the organs involved. Intestinal involvement was the most common (64.2percent), of which the large and small intestines were affected in 43.2percent and 28.4percent of the cases, respectively, followed by the stomach in 33percent. Colon (84.0percent), cecum/rectum (22.4percent) and appendix (7.8percent) were the regions of the large intestine in the order of infectious occurrence, whereas it was the Ileum (68.4percent), jejunum (10.5percent), duodenum (7.9percent) and combination of Ileum and jejunum (10.5percent) of the small intestine. The organ to be often involved was stomach in adults and intestine in children. About 50.6percent of cases were reported from Asia when global GI mucormycosis data was collected. It accounts for 2–8percent of all mucormycosis cases in India. This variant was present in 60percent of the paediatric group, of which 83percent were premature neonates [54]. The significant risk factors determined were diabetes mellitus (24percent), peritoneal dialysis (16percent), broad-spectrum antibiotic usage among adults and malnourishment (26percent) in children [55].

In recent times, COVID-19 associated mucormycosis (CAM), which is mostly exhibited in the rhinoorbitocerebral regions, is increasing globally due to the emergence of the new SARS-CoV-2 variants (B.1.617.2 and B.1.617.2.1 or AY.1) in the terminally ill ICU hospitalized patients with 35percent having contracted invasive pulmonary aspergillosis that is linked to prior uncontrolled corticosteroid therapy [56-58]. A systematic review by Pal *et al*. reported that 72percent in a total of 99 CAM cases was of Indian origin with diabetes mellitus as a comorbid condition

in 85percent of the cases. A median interval of 15 days existed between the initial diagnosis of COVID-19 and the appearance of initial signs of infection in 37percent of the patients [59]. The nasal cavity and facial sinuses were the common sites of infection in 88.9percent of the cases as per the study reported by Sigh *et al*. in 2021[60]. The rate of prevalence observed was 0.27percent among hospitalized COVID-19 patients in a multicentric retrospective study conducted by Patel *et al*. in 2020, which also noted a 2.1-fold rise during 2019 and a strong association of COVID19 in 32.6percent of mucormycosis cases [61].

DIAGNOSIS:

It is delayed since the clinic features are similar to that of aspergillosis and non-specific clinical presentations, lack of distinctive imaging, difficulty in collecting samples from deep tissues in neutropenic and hemodynamically unstable patients with a coagulopathic state, absence of biomarkers, inadequacy in standardized molecular techniques is detected to be the various factors hindering the establishment of specific mucormycosis diagnosis [62,63]. Excessive radiation exposure in children, cranial and chest CT is the regular investigation required to identify infiltrates suggestive of mucormycosis [64-66].

Recognition of specific clinical manifestations along with risk factors and carrying out a timely histopathological microscopic investigation of the specimen using 10percent potassium hydroxide wet mounts is vital due to its reliability in its culture positivity detections enables early diagnosis [67]. However, thorough knowledge among clinicians is the need of the hour for its final diagnosis.

A range of molecular tools such as polymerase chain reaction, (PCR) based platforms, PCR coupled with electrospray ionization mass spectrometry (PCR/ESI-MS), high-resolution melt analysis (HRMA), matrix-assisted laser desorption ionization-time of flight analyzer-mediated mass spectrometry (MALDI-TOF/MS), breath-based metabolomic diagnostic test and metagenomic shotgun approaches have been recently adopted for accuracy in diagnosis[68-74].

MANAGEMENT:

Medical management with conventional or non-conventional therapeutic agents of anti-Mucorales among the high-risk population and surgical approaches are the available treatment modalities, and the choice for the best prognosis depends upon the accessibility to drugs and appropriateness in the surgical techniques involved. Acquired facial defects secondary to mucormycosis is resolved through maxillofacial prosthetic rehabilitation [75, 76].

Prophylaxis:

Primary prophylaxis is recommended in neutropenic patients (lesser than 500 cells/µl for greater than seven days) and individuals with graft versus host diseases. An oral suspension of 200 mg of Posaconazole four times a day or 300 mg delayed-release tablet or via intravenous route at a dosage frequency of twice a day initially followed by once thereafter is prescribed. Monitoring of its serum level is imperative to check for adequate antifungal drug absorption, and response to therapy as inadequate serum level increases the chance of breakthrough infections. Isuvaconazole via an oral suspension or intravenously at a dosage of 200 mg thrice each day for the first two days followed by a single dosage per day or 200 mg once daily throughout the course is the drug of choice in cases of prolonged neutropenia, lung and heart solid organ transplant (SOT) in adults. However, the dosage differed based on the response from infected individuals. Despite its cost-effectiveness, the increase in the total number of invasive fungal infections following its use was of great concern [77-79].

Secondary prophylaxis is recommended for immunocompromised individuals who have been exposed to mucormycosis previously. In those cases, continuation or recommencement of the last effective drug, mostly either Isuvaconazole or amphotericin B or a preventive surgical resection or a combination of both medical and surgical modalities, are often advocated in most of the patients. It was found that the transition from amphotericin B to Posaconazole after 3-6 weeks was suggested [65, 77].

Treatment:

Both the suspected and confirmed cases of mucormycosis are treated as emergencies. Systemic antifungal treatment, resection or debridement's are usually repeated as and when indicated. The first-line therapy involves a recommendation of lipid formulations of amphotericin B (LAMB) and Isuvaconazole. Salvage therapy is suggested if the standard first-line treatment with LAMB/AMB fails. The general principle adopted is either one of the two courses of action, such as increasing the dosage of LAMB or switch over to Posaconazole or Isuvaconazole [80-82].

The exact duration of treatment delivery is uncertain as immunosuppressive drugs are tapered and then stopped with control of the immune-compromised condition. However, it is carried out until the resolution of signs and symptoms with radiographic improvement. The average treatment duration with Isuvaconazole or salvage therapy is approximately three months (IV/oral/both). Several studies reported that the duration of treatment with Posaconazole via oral suspension form varied from a week to 3 years as its range was based on the organs involved and risks from underlying conditions [81-84].

CONCLUSION:

Indians have higher risk to mucormycosis due to its large diabetic population when compared globally. It is evident that the rhino cerebral variant is the most

commonly prevalent with a recent surge due to the pandemic. Both the incidence and prevalence of mucormycosis cases in India have always been very higher and has escalated even further due to the outbreak of SARS-CoV-2. It is recommended that appropriate modalities have to be adopted in individuals with immunocompromised conditions to safeguard them from contracting any reinfection as they are more susceptible to high-risk exposure. This review thus helps us to understand the pattern of widespread distribution of mucormycosis in India thus enabling gain of knowledge on epidemiological background to prioratize delivery of health care service.

DATA AVAILABILITY STATEMENT:

Total numbers of references are submitted with DOI below (The entire data is extracted from articles available online to public access)

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