International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
DOI: 10.22192/ijarbs Coden: IJARQG (USA) Volume 8, Issue 11 -2021

Review Article

DOI: http://dx.doi.org/10.22192/ijarbs.2021.08.11.003

Black fungus in India during COVID - 19: A systemic review

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Abstract

Mucormycosis which is commonly known as 'Black Fungus" is a very rare emerging infection with high mortality rate and has provoked great public concern in the context of Covid-19 pandemic. Generally caused by saprophytic mould (fungi). These fungi are commonly found in soil, plants, decaying fruits and vegetables due to its ubiquitous nature and found everywhere life is possible. The estimated prevalence of Mucormycosis in India brings endemic into this pandemic situation though Mucormycosis in India is not well known due to lack of frequent population-based studies. But it is around 70 times higher in India as comparable to global data. The main cause of this emerging endemic is rapid and uncontrolled use of steroids which is the only life-saving treatment for acute and critically ill covid-19 patients. The anti-inflammatory effect of corticosteroids might prevent lung injury and multisystem organ disfunction but it also leads to flare-up some secondary bacterial and fungal infections, Mucormycosis being an important one of them. It mainly effects sinuses lungs, brain and may become life threatening in diabetic or severely immunocompromised individual. Study highlights that the high occurrence of this infection in India is due to uncontrolled diabetes mellitus in contrast to hematological malignancy and solid organ transplant. Though awareness of the disease has gradually increased among public but mortality rate is still high. In conclusion the high rate of increased cases evoked a new risk factor as well as challenges in managing the disease in India. This time we need to follow the guidelines and maintain proper hygiene to protect us and our family members from mucormycosis and other fungal disease and also from COVID – 19.

Keywords: Anti-inflammatory, immunocompromised, hematological, corticosteroids.

Introduction

Angio invasive disease generally termed to fungal disease. *Mucormycosis* is no exception of that. This disease also characterized by tissue death or necrosis. This disease enormously increased in worldwide specially in India during this Covid period. ***Mucormycosis***is an uncommon but very deadly fungal infection that generally affects patients with altered immunity. These are mainly occurring in immune suppressed hosts, including those with hematological malignancies and those people who has uncontrolled diabetes mellitus. ***Rhizopus, Mucor, Cunninghamella, Absidia***, these are the main genus of the Mucormycosis which are cause infection in humans. These fungi are placed under Order of Mucovales and Zygomycetes class. Among them *Rhizopus oryzae* is most common fungi which is indebted for 60% mucormycosis cases in human body. Mucormycosis has an astonishment character that even a delay of 12 hours in the diagnosis could cause fatal for human life.

The second wave of COVID 19 is come like tsunami in India. 0.4 million positive cases have been recorded in a single day with 4 to 5 k daily death. Along with them Black Fungus or Mucormycosis is become new headache for health workers and for the public. It helps to increase the mortality rate of Covid 19. This is cause co infection in human body. Over 48000 cases of black fungus have been reported till the end of august 2021.With mucormycosis or black fungus, White and yellow fungus also occurred in India. Central Government of India has asked all the states to declare black fungus as an epidemic. Indian states like Rajasthan, Telangana and Tamil Nadu have been declared it as a notifiable disease under the Epidemic Disease Act 1897. Out of total cases of mucormycosis, 86% cases have a history of Covid 19 infection, and 62.3% cases have diabetes. Highest number of cases comes from Maharashtra. In this case report we also make focus on how these fungal disease increases in India and how this can be controlled or eliminated.

Etiology: -

The most threatened serious fungal infection in post covid scenario is Mucormycosis, previously known as Zygomycosis, caused by group of molds called Mucormycetes, mostly found in the soil and decaying organic matters such as leaves, compost piles, animal dung etc. belonging to the order Mucorales. The most common etiological agent of Mucormycosis is *Rhizopus oryzae*, isolated from the patient suffering from Mucormycosis and it is responsible for ~ 70% of the total cases of Mucormycosis (Ribes. JA, et al 2000),(Spellberg B, et al 2005; and Roden MM, et al 2005).

The other genera of this order causing this most frightening infection are ***Mucor, Cunninghamella, Apophysomyces, Lichtheimia, Saksenaea, Rhizomucor***etc. and the most frequently isolated species of these above genera are ***(M.circinelloides), (C.bertholletiae), (A. variabilis), (L.corymbifera), (S.vasiformis), (R. pusillus)*** subsequently. These are common environmental species, present everywhere and can infect only when fungal spores are inhaled by people or when these spores are entered through any exposing open wound.

In the background of CAM (Covid-19 associated Mucormycosis), it is reported that the main cause of this serious infection is the intake of steroid drug frequently during Covid treatment.

Person with weak immune system has affected frequently by black fungus, specially who takes medicines regularly for the treatment of any other disease.

As the body's immunity becomes low by taking frequent medicines to fight against any foreign particles it makes that person more susceptible to black fungus infection. Diabetic patients as well as covid patients are at great risk to develop this infection in the background of CAM.

Mode of Transmission: -

The spore can be transmitted into our body through: -

a. Inhalation
b. a cut or an open wound.
c. Recently transplanted organ.
d. Intake of contaminated food.

Clinical Presentation: -

Histopathological investigation reveals that mucormycosis is characterized by host tissue necrosis, angioinvasion and vessel thrombosis. Experimental data clearly indicate that people having low level of neutrophils (neutropenia), and people who are taking immunosuppressive drugs (suppress the body immune system) Specially for hematological cancer are at greater risk to develop Mucormycosis. On the basis of clinical manifestation and review analysis Mucormycosis can be classified as one of the major clinical forms, such as: -

1. Rhino-orbital-cerebral,
2. Cutaneous,
3. Pulmonary,
4. Renal,
5. Gastrointestinal and
6. Disseminated (Goodman NL,et al 1991) and (Alves SH , et al 1995).

People who have recently undergone through stem cell transplantation are also at high risk for developing this serious and rare infection. Case study reported that the most common invasive sites of Mucormycosis are sinuses, lungs and skin (average 27%) (J, et al 2007). Mortality rate of Mucormycosis varies in between 40-80%. In diabetic condition it is approx. 40%, 35% patients are with no underlying condition, 96% with disseminated, 85% with GI, and 76% with pulmonary infection died.

People with poorly controlled diabetes by producing diabetic ketoacids in their body and people who are overloaded with iron are also at higher risk of developing this infection.

Use of contaminated medical equipment and exposure of wound after organ transplantation and the inhalation of fungal spore through par nasal sinus of susceptible host are also the main cause of developing Mucormycosis.

Diagnosis: -

Diagnosis is the most important therapeutic tool to get particular and accurate information about the disease, to identify the history and nature of the causative agent for which the symptoms are expressed. Necessary information is typically collected from the concerned person seeking medical attention through details physical examination and previous history of disease.
The most indispensable clinical approach for the diagnosis of mucormycosis depends upon the high index of suspicion, prompt appraisal of developing signs and symptoms, culture, imaging studies, direct microscopic examination, molecular methods, histo pathological examination etc.

Early and prompt diagnosis is required to avoid the late treatment for this disease. But sometimes there is delay in treatment if Mucormycosis is misdiagnosed due to its non-specific signs and symptoms which are closely related with another disease like aspergillosis caused by other fungal genus like ***Aspergillus***, another common mold.

After successful identification of the causal agent and confirmation of the diagnosis, rapid initiation of treatment is necessary which can improve the consequences of invasive mycoses. But the first and foremost is the diagnosis process among these entire disease management act, on which early treatment is totally dependent, because only early diagnosis of Mucormycosis will be able to prevent the progressive tissue extension, proliferation as well as tissue necrosis which is the hallmark of Mucormycosis.

Though necrosis and vessel thrombosis may appear in immunocompromised people due to Mucormycosis, but differential diagnosis also include some other pathogenic agent such as ***Fusarim, Pseudallescheria***, etc.

So Mucormycosis must be distinguished from other invasive fungal disease with similar representation. Ecthyma gangrenosum caused by *Pseudomonas aeruginosa* also produce similar kind of symptoms as because all have the common nature of growing non-specific symptoms.

Host vulnerable to Mucormycosis, especially who are transplant recipients and receive antifungal therapy for prophylaxis with voriconazole shows result of receiving active agent against ***Aspergillus***but not Mucorales. Corzo- Leon et al. proposed an algorithm for the diagnosis of Rhinocerebral Mucormycosis in diabetic patients. Sinus pain, facial swelling, cranial neuropathy, T-cell lymphoma, proptosis, ulceration, cutaneous anthrax ect, are considered as ‘red-flag’ of Mucormycosis.

There are some potential markers favoring a diagnosis of Mucormycosis over a diagnosis of aspergillosis, such as multiple (> 10) nodules, pleural effusion are more common proposed by Chamilos et al.

Another finding reported that in pulmonary Mucormycosis, especially the neutropenic leukemic patient’s show the presence of RHS (reverse halo sign) on CT scan which is strong indicator of Zygomycosis.
Some another technique such as PCR,(PET/CT) [positron emission tomography with flurodeoxyglucose (FDG) and ITS sequencing for identification of Zygomycosis genus/ species from laboratory culture, infected tissue, frozen species are promising, challenging and under trial and also required well equipped laboratory.

However, the overall conclusion reviewed that delayed diagnosis resulted in a 2- fold increase in mortality rate within 12 weeks compared with early treatment.

Symptoms: -

Symptoms of Black Fungus diseases: -

The symptoms of mucormycosis depend on where in the body the fungus is growing. The most common presentation is a sinus infection (sinusitis) that is accompanied by nasal congestion, nasal discharge, and sinus pain. A fever and headache may also occur.

Type of Mucormycosis	Some common symptoms
Rhinocerebral (sinus and brain) mucormycosis	⁾ One-sided facial swelling. ⁾ Headache. ⁾ Nasal or sinus congestion. ⁾ Black lesions on nasal bridge or upper inside of mouth that quickly become more severe. ⁾ Fever. ⁾ Lethargy, seizures, slurred speech, partial paralysis.
Pulmonary (lung) mucormycosis	⁾ Fever. ⁾ Cough. ⁾ Chest pain. ⁾ Shortness of breath. ⁾ Hemoptysis.
Cutaneous (skin) mucormycosis	Skin lesion that resembles blisters or ulcers. The infected area may turn black. Other symptoms include pain, warmth, excessive redness, or swelling around a wound.
Gastrointestinal mucormycosis	⁾ Abdominal pain. ⁾ Nausea and vomiting. ⁾ Gastrointestinal bleeding.
Disseminated mucormycosis	Tends to occur in people who are already sick from other medical conditions, which makes it difficult to identify which symptoms are related to mucormycosis. Patients with disseminated infection in the brain may develop mental status changes or coma.

Table: - Types of Mucormycosis and their common symptoms

Symptoms of Yellow Fungus Disease: -

Symptoms of yellow fungus include weight loss, lethargy, and loss of appetite or no appetite. Other symptoms could be the formation and leakage of pus and sunken eyes. Due to the yellow fungus, the healing of wounds gets hindered and prolonged. It can also result in malnutrition, organ failure and necrosis in extreme cases.

Symptoms of White Fungus Disease: -

White fungus symptoms are said to be somewhat like COVID-19 symptoms. An HRCT (High-resolution computed tomography) test can be used to diagnose the infection. People with pre-existing medical conditions, such as diabetes, or those that have been on steroids for a long time are said to be at high risk of contracting white fungus.

- White patches on the inner cheeks, tongue, roof of the mouth and throat.
- Redness and Soreness.
- Cotton-like feeling in the mouth.
- Loss of taste.
- Pain while eating or swallowing.
- Cracking and redness at the corners of the mouth.

Treatment: -

Treatment for Black Fungus: -

Mucormycosis is a serious infection and needs to be treated with prescription antifungal medicine, usually amphotericin B, posaconazole, or isavuconazole. These medicines are given through a vein (amphotericin B, posaconazole, isavuconazole) or by mouth (posaconazole, isavuconazole). Other medicines, including fluconazole, voriconazole, and echinocandins, do not work against fungi that cause mucormycosis. Often, mucormycosis requires surgery to cut away the infected tissue.

Treatment for Yellow Fungus: -

More information about Yellow Fungus Infection Treatment could not be found right now as this infection is new in India. Presently, patients have been advised to use some common medicines. These drugs should be used only under the supervision of doctors. Amphotericin B injection, a broad-spectrum antifungal drug, is being used in current treatments by philanthropic doctors.

Treatment for White Fungus: -

Anti-fungal drugs can be used to treat patients infected with White Fungus. Candidiasis can be treated with fluconazole or itraconazole orally. Topical applications will be required for infections in the oral cavity or genitourinary regions. Serious infections in critically ill patients are treated with caspofungin or micafungin.

Occurrence in India: -

Mucormycosis occurrence rate starts in India from near about 8th May 2021. COVID – 19 second wave just peck in that time. A Mumbai based eye surgeon, Dr. Akshay Nair found something different while treating a 25-year-old women patient. He had inserted a tube in her nose and was removing tissues infected with *Mucormycosis*, a rare but dangerous fungal infection. After that the number of cases was increased. Dr. Nair who works in three hospitals in Mumbai one of the worst hit sites in COVID second wave says 40 patients suffering from that same infection from April 2021. Many of them are diabetes and who had recovered from COVID – 19.

Kunwar Singh a man in Uttar Pradesh's Ghaziabad, who diagnosed with black, white and yellow fungal infection along with Coronavirus disease, has died on 24th May 2021. This is the first and such a case where a person infected with all 3 funguses and with covid-19.

Till 26th May Black fungus cases rise up to 12000 in India. Maharashtra reported 2770 cases while Gujarat, Andhra Pradesh, Madhya Pradesh, Telangana logged 2859, 768, 752, 744 case respectively.

In the middle of June cases rise up to 28252. 86% of them has a history of COVID – 19 and 62.33% of them has diabetes. Maharashtra reported 6329 cases and Gujarat reported 5486 cases.

In the beginning of July most cases of Black fungus and most deaths are reported from Maharashtra. Total of 8367 cases in Maharashtra, Pune reported 1234 case and 93 deaths, Nagpur reported 1339 case and 104 deaths, Aurangabad has 945 cases and 79 casualties, Solanpur has 505 cases and 56 deaths, Nasik reports 557 cases of Black fungus and 60 deaths, Sangli has 269 case and 16 deaths, Thane reported 235 cases and 38 deaths.

Report coming from Uttar Pradesh in 1st July, 22 new black fungus cases recorded as a result state has total of 221 cases and among them 62 died.

In West Bengal situation is little bit stable but not easier. Till 8th July 2021, state has recorded a total of 77 black fungus cases and 18 casualties.

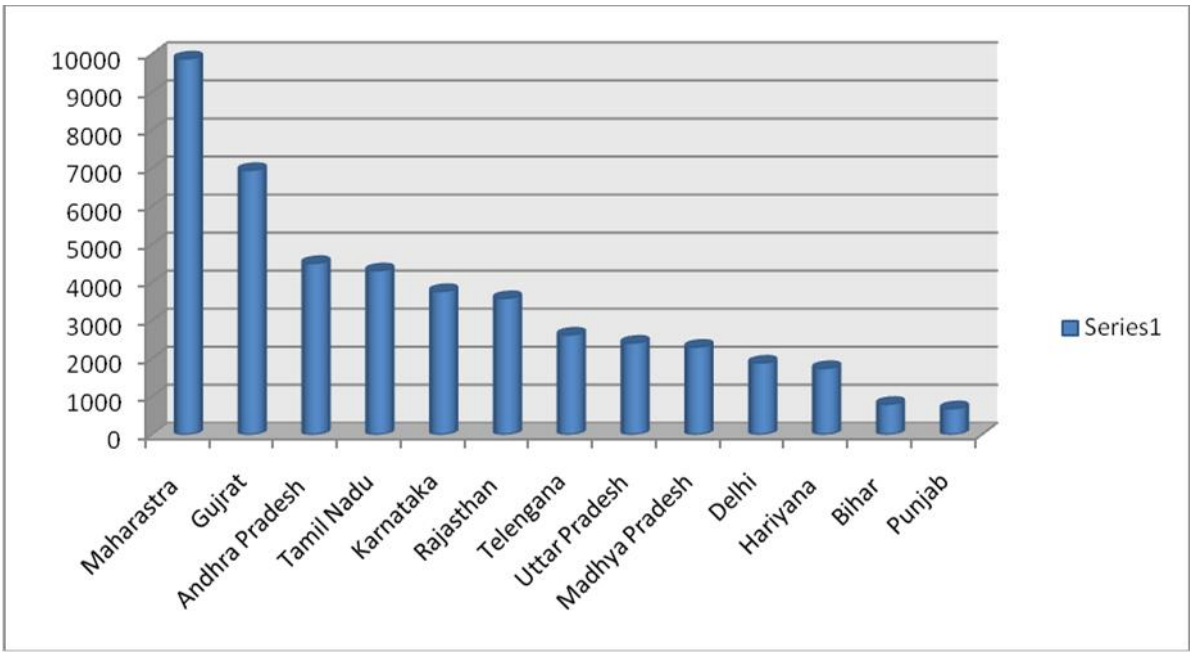
As of 12th July, a total of 303 lives have been lost due to Black fungus disease infection in Karnataka. 104 are from Bangalore. Facility rate is near about 8.6% in Karnataka. District wise Bengaluru urban reported 1109 cases, Dharwad has reported 279 cases, Vijaypura has 208 cases. Bangalore has reported highest mortality of 196 people. Kalaburgi district reported 23 deaths and Dakshini Kannada reported 20 deaths.

477 new cases of mucormycosis came from Rajasthan which has no COVID – 19 histories on 28th July. There is a total of 3471 black fungus cases came from Rajasthan and among them 14% came in last 2 month.

As of 21st July 2021, India has recorded 45374 total black fungus cases and more than 4300 people died because of it. Most of the death reports from Maharashtra and Gujarat where almost 2000 people have died.

As of 23rd August 2021, India has recorded more than 48000 total black fungus cases. Maharashtra topped the country with the highest of 9,878 cases of black fungus, of which 1,907 are under treatment, 6,501 cured and 1,286 deaths at 13 %Case Fertility Rate (CFR), followed by Gujarat 6,947 total cases, 415 under treatment, 5,128 cured, and 689 deaths at 10 % CFR, Andhra Pradesh 4,502 cases, 1,058 under treatment, 3,006 cured, 358 deaths at 8 % CFR, Tamil Nadu 4,308 cases, 2,047 under treatment, 1,788 cured, 370 deaths at 9 % CFR, Karnataka 3,765 cases, 1,209 under treatment, 1,729 cured, 411 deaths at 11 % CFR, Rajasthan 3,579 cases, 2,509 under treatment, 715 cured, 191 deaths at 5 % CFR, Telangana 2,619 cases,

2,593 under treatment, 13 cured, 4 deaths at zero CFR, Uttar Pradesh 2,407 cases, 1,162 under treatment, 957 cured, 249 deaths at 10 % CFR, Madhya Pradesh 2,301 cases, 707 under treatment, 1,448 cured, 142 deaths at 6 % CFR, Delhi 1,883 cases, 633 under treatment, 865 cured, 332 deaths at 18 % CFR, Haryana 1,741 cases, 591 under treatment, 809 cured, 264 deaths at 15 % CFR, and Bihar 800 cases, 36 under treatment, 577 cured, and 147 deaths at 18 % CFR. Punjab recorded 684 total cases so far, of which 236 are under treatment, 327 cured and 52 have since died at 8% CFR.



State wise *Mucormycosis* cases in India

Prognosis and Pathogenesis: -

Mucormycosis is an increasingly common infection in immunosuppressive patients. Major risk factors for Mucormycosis include uncontrolled diabetes in ketoacidosis, other types of metabolic acidosis, treatment with corticosteroids, transplantation or bone marrow transplantation, neutropenia, trauma and burns, severe hematologic diseases and treatment with deferoxamine receiving hemodialysis.

Pathogenesis of Mucormycosis: –

Patients with high serum iron levels, including those with diabetic ketoacidosis (DKA), are affected differently mucormycosis. High concentrations of glucose and iron, respectively detected during DKA, enhanced GRP78 expression GRP78 is a receptor that mediates penetration through and damage of endothelial cells by Mucorales. Patients who have dysfunctional phagocytes are at elevated risk for developing mucormycosis.

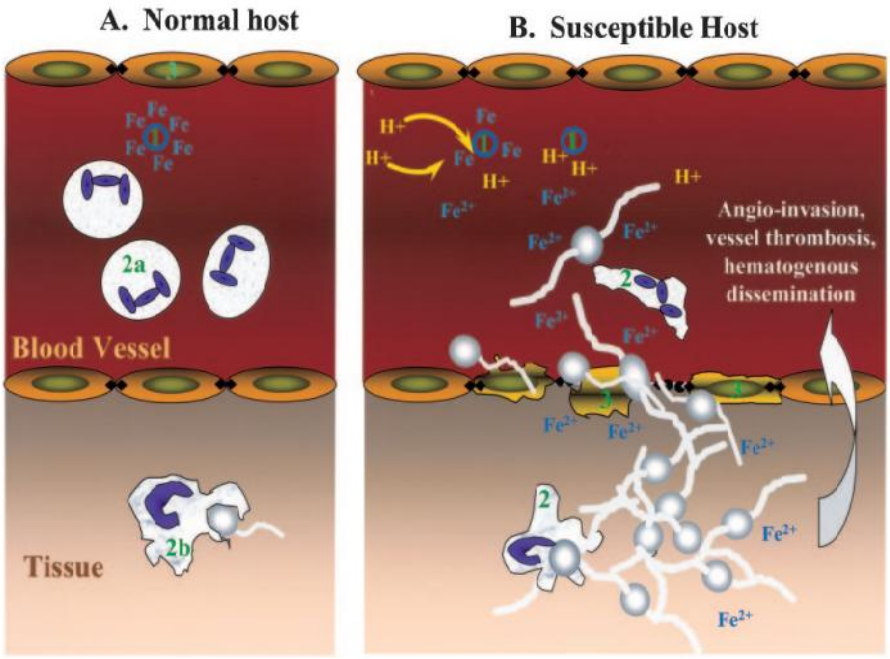


FIG: Proposed mechanism of pathogenesis and host defense mechanism of mucormycosis. In order to cause infections, agents of mucormycosis must take up sufficient iron for growth from the host body, must avoid phagocytic management methods, and must reach vasculature circulation A) In general administration, the main protective mechanisms against mucormycosis include the separation of iron from serum by special iron-binding proteins(1), phagocytes that regulate the circulation of neutrophils (2a) and macrophages (2b), as well as endothelial cells (3), regulate vascular tone to enter. Working in concert, these processes prevent the formation of tissue infections and subsequent endovascular attacks. B) In the normal hosts, the general defense mechanisms are deteriorating. For example, in diabetic ketoacidosis (DKA), serum acidic pH causes separation of free iron from trace proteins (1). This release of free iron allows for rapid fungal growth. Errors in phagocytic protection methods (2), for example, neutropenia or functional impairment caused by corticosteroids or hyperglycaemia and acidosis of diabetic ketoacidosis, allow for fungal proliferation. Finally, adhesion and damage to endothelial cells by the fungus (3) allows fungus angioinvasion and vessel thrombosis and tissue necrosis followed by the spread of fungal infections.
According to a clinical study report, in diabetic rats, bronchoalveolar macrophages can damage the hyphae of *R. oryzae* but serum factors elevate the spore germination and decrease the ability of macrophages attached to it.

Role of Iron (Fe) in pathogenesis-

Ina clinical study, it has been seen that the increased incidence of mucormycosis in patients with high serum iron levels**,** serumiron deferoxamine (Fe.DFO) allows for large iron intake by Rhizopus as well promotesit's in vitro growth. In conclusion, their study underscores the siderophore activity of Fe.DFO in the pathogenesis of DFO-induced mucormycosis, as it grows in humans, and in acute DFO mucormycosis, as seen in animals.Extraction of iron from the host by microorganisms is essential for the formation and continuation of infection because this substance is necessary for the survival of living cells. The patients having hyperglycaemia, Diabetic ketoacidosis (DKA) another forms of acidosis suffer from elevated level of serum iron.Excessive glycosylation of proteins such as trans-ferrin and ferritin, due to chronic hyperglycaemia found in reduced iron content of these sequesters leading to the release of free ions in the blood and tissues.

Prognosis: -

In a clinical studyRoden et al reported in a comprehensive literature review of 929 cases fulfilling prespecified criteria that the overall mortality of invasive mucormycosis in patients with diabetes mellitus was 44%; in those with no underlying condition, 35%; and in those with neoplastic disease, 66%.Mortality varies by location of infection:

Mortality occurs in 96% of contagious diseases, 85% of intestinal infections, and 76% of lung infections. Cerebral mucormycosis in immunocompetent adults showed that more than 85% had infection in basal ganglia. On May 9, 2021 India, The Council for Medical Research (ICMR) provided a warning of testing, determination and management of Black Fungus. It affects the sinuses, cerebrum and lungs and can be dangerous for people with diabetes or severe disabilities, such as malignant growth patients or people with HIV / AIDS. Majority of cases of mucormycosis have been reported from the state of Maharashtra followed by Rajasthan, Gujarat, Madhya Pradesh, Haryana, Delhi and Punjab of India.

Prevention: -

'Black fungus' has now become epidemic in pandemic due to sudden exponential surge in the number of coronavirus infection. Though it was very common in India, compared to the other country even before pandemic. As India represent the largest number of diabetes affected people about 66.8% than all other country. Recent report says that about 94% people who developed Mucormycosis after covid.

Though it is non- contagious, and due to ubiquitous in nature we cannot avoid inhalation of spores during breathing but can manage the disease by following few steps: -

1. Immunocompromised patient who are diabetic should control blood glucose level and diabetic ketoacids.
2. Reduction of steroids is another most important step to prevent this disease and continuous monitoring abd reduced of dosage is also required.
3. Avoid damp and dusty area.
4. Maintanance of hygiene properly such as surgical debridment is the process of removing and cleaning the wound as well as hyperkeratotic (thickened skin) infected, foreign debris tissue to help wounds.
5. Wearing of long-sleeve shirts, rubber gloves, full trousers, and full covering shoes during working in garden.
6. Avoid of eating contaminated food.
7. Recent research and experience by doctors include a point that sudden surge of black fungus is due to high demand and use of industrial oxygen (oxygen concentrators) and humidifiers as medical oxygen is far beyond the supply.

Current research says that few drop of methylene blue in the humidifier, moisturizing jar or concentrators through which oxygen usually passes can control all types of contamination even Mucormycosis also which is present in oxygen. One can be safe partially by following the above-mentioned steps by taking precautions accordingly.

Conclusion

It has been observed that diabetes mellitus was the dominant predisposition factor in all forms of mucormycosis. Mucormycosis cases were high and also the mortality during the initial stage of infection just because of delays in seeking medical attention and diagnosing the disease. Although India were stands strong through this epidemic lately. Frequent start of medical care and active research helps us to fight against these kinds of epidemics. The Drug Control General of India gave the nod to five pharmaceutical companies to manufacture Amphotericin B. which was widely used for treatment for mucormycosis. They also plan to study the role of antifungal agents like isavuconazole in the treatment of mucormycosis in Indian population.

ICMR released evidence based advisory in the time of COVID-19 to prevent mucormycosis and its management.

A group of scientists in West Bengal's South 24 Parganas district has developed the first indigenous testing kit to detect mucormycosis. The DiAGSure Mucormycosis Detection Kit has been prepared by the scientists at a laboratory. Diagnosis of black fungus with the available kit's costs around Rs 7,000-8000 because they are imported and the new technology will bring down this cost to Rs 1,000, claimed Raja Majumdar, the managing director of GCC Biotech Pvt Ltd, the company that developed the kit. As per the company, DiAGSure Mucormycosis Detection Kit was approved by the Central Drugs Standard Control Organisation (CDSCO) under the Directorate General of Health Services (DGHS), Union Ministry of Health and Family Welfare in August 2021.

Now this time we need to follow the guidelines and maintain proper hygiene to protect us and our family members from mucormycosis and other fungal disease and also from COVID – 19.

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How to cite this article:
Dipayan Dey, Sagarika Mukhopadhyay, Sudeshna Mukherjee. (2021). Black fungus in India during COVID - 19: A systemic review. Int. J. Adv. Res. Biol. Sci. 8(11): 19-28.
DOI: http://dx.doi.org/10.22192/ijarbs.2021.08.11.003