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(REVIEW ARTICLE)

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Review on Mucormycosis the uprising infection and post COVID effect

Suvarna Patil [1], Pallavi Vijay Gupta [2, *], Saurabh Rajkumar Pandey [2], Komal Manoj Gupta [2], Harshit Pawankumar Shukla [2] and Amitkumar Ramprakash Jaiswar [2]

[1] *Department of Pharmaceutical Chemistry, Ideal College of Pharmacy and Research, Kalyan, India 421306.*
[2] *Ideal College of Pharmacy and Research, Kalyan, India 421306.*

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Abstract

Mucormycosis commonly called as Black Fungus is a fulminant angio-invasive infection that is caused by a distinctive group of fungi belonging to the genera of Class Zygomycetes and Taxonomic Order Mucorales, and is principally seen in immunosuppressed patients. It is an air-borne infection and primarily associated with upper and lower airways. It is a rare, infrequently and critically life-threatening fungal infection characterized by vascular invasion by hyphae and caused by the inhalation of its filamentous fungi, resulting in thrombosis, necrosis and infarction of tissue. The major risk factors that develop the infection include diabetic ketoacidosis, neutropenia, and protein-calorie malnutrition iron overload. Patients suffering from COVID-19 are more prone to have an infection due to low immunity power. Coronavirus disease causes an immunological disorder state and increases the risk of secondary infections like Mucormycosis. The mortality and morbidity rate caused by Mucormycosis has rapidly increased within the last decades, majorly in developing countries. Patients with Mucormycosis that endure surgical operation and who receive medical aid with IV Amphotericin B might have higher rates of survival. The work of the latest derivatives of azole within the treatment of Mucormycosis is unknown.

Keywords: Mucormycosis; COVID-19; Fungal infection; Diabetic Ketoacidosis; Amphotericin

1. Introduction

The term Mucormycosis was coined by R.D. Baker, An American Pathologist Mucormycosis is defined as an insidious fungal infection caused by members of Mucorales and zygomycotic species [1]. It is also called as Zygomycosis and commonly called as Black Fungus. This is an uncommon disease but serious fungal infection and is seen in people who have less resistance to fight infections or may be suffering through auto-immune diseases. It is caused by a group of molds called mucormycetes, order Mucorales. This fungus lives in the environment and is present in soils, decomposing organic matter, manure. There are mainly five kinds of Mucormycosis: Rhinocerebral (sinus and brain) Mucormycosis, Pulmonary (lung) Mucormycosis, Gastrointestinal Mucormycosis, Cutaneous (skin) Mucormycosis and Disseminated Mucormycosis. The fungi that mainly cause Mucormycosis are: Rhizopus species, Mucor species, Rhizomucor species, Syncephalastrum species, Cunninghamella. bertholletiae, Apophysomyces species, and Lichtheimia (formerly Absidia) species. In some cases the eye sockets may swell up and cause severe pain and also cause blurred vision which may lead to complete loss of vision. As the fungus grows it begins to discharge a black liquid through the nose. It is most likely to happen to people suffering from diabetes, as the fungus gets a suitable environment to produce itself. It may also happen due to unmonitored use of steroids, as it inhibits the immune system. To prevent it from happening or from spreading, a hygienic environment is a must. It can't spread from human to human, but can be transferred by the equipment used such as masks, nasal devices, etc. They can block the blood vessels leading to ischemic conditions in a tissue leading to its death. The brain surely can be infected through the nasal nerves that run along the nasal cavity. The death rate of the

* Corresponding author: Pallavi Vijay Gupta
Department of Pharmaceutical Chemistry, Ideal College of Pharmacy and Research, Kalyan, India 421306.

disease is 50% and may incline it proper medical conditions aren't provided which is quite expensive. In India, under the India epidemic acts the doctors have to report the cases and since the cases in India are soaring, hence it is declared as an epidemic in many states.

2. Epidemiology

Mucormycosis is an arising healthcare issue in the Indian population. A sudden alteration in the epidemiology of Mucormycosis has been noticed in the last few years with the increase in incidence, new causative agents and prone population [2]. The rise has been observed globally, but it is extreme in the Asian continent. Although diabetes overshadows all other risk factors in Asia, post-tuberculosis and chronic kidney failure have appeared as new risk groups [3]. Nevertheless, mucormycosis remains an uncommon disease, even in high-risk patients, and represents 8.3%–13% of all fungal infections encountered at autopsy in such patients [4]. The rhino-cerebral form of Mucormycosis is most noticeable in patients with diabetes mellitus, whereas, pulmonary Mucormycosis in patients with hematological malignancy and transplant recipients [3]. A new clinical organization, indolent Mucormycosis in nasal fossa, is recently perceived. The causes of Mucormycosis vary across different geographic places. New ((Prakash and Chakrabarti) causative factors such as *Rhizopus homothallicus*, *Mucor irregularis*, and *Thamnostylum lucknowense* are reported from Asia. In addition, this disease is increasingly recognized in recently developed countries, such as India, mainly in patients with uncontrolled diabetes or trauma. Epidemiological details on this type of mycosis are limited. Therefore, our ability to determine the burden of diseases is bounded [3]. Based on anatomic localization, Mucormycosis can be classified as one of 6 forms and they are as follows: [4].

- Rhinocerebral Mucormycosis
- Pulmonary Mucormycosis
- Cutaneous Mucormycosis
- Gastrointestinal Mucormycosis
- Disseminated Mucormycosis
- Uncommon Presentation

2.1. Rhinocerebral Mucormycosis

It can infect the sinuses and the brain lead to fever, inflammation of one side of the facial organ, black abrasion inside the mouth/outside the face, headache, and sinus congestion [5].

2.2. Pulmonary Mucormycosis

It mainly infects the lung leading to chest pain, difficulty in breathing, fever, and cough [5].

2.3. Cutaneous Mucormycosis

It causes Celleslitis (local skin infections) which cause ulcers or blisters, erythema and inflammation at the infected skin region [5].

2.4. Gastrointestinal Mucormycosis

It is unusual in adults, but more likely in premature infants leading to nausea, vomiting, gastrointestinal bleeding, and abdominal pain [5].

2.5. Disseminated Mucormycosis

It occurs in patients who are suffering from numerous medical complications impeding the symptomatic discrimination of Mucormycosis from other infectious diseases [5].

2.6. Uncommon Presentation

The rate of mortality and morbidity of Mucormycosis varies depending on the organ affected by the infection, the causative fungal species and the condition of the patient; Viz. 46% mortality was noticed in patients affected by sinus infections, and a death rate of 76% and 96% was reported for pulmonary and disseminated Mucormycosis infections, respectively [5].

A majority human infection arises from inhalation of fungal sporangiospores that have been liberated in the air or direct inoculation of organisms into disrupted skin or mucosa. Cases with Mucormycosis are reported from everywhere on

the planet. Seasonal fluctuations in Mucorales infection are possible. In a study from Israel, 16/19 reported cases of rhino-orbitocerebral Mucormycosis (ROCM) appeared in autumn. In further study from Japan, an indistinguishable seasonal variation among hematology patients was noted, with six of seven cases of pulmonary Mucormycosis having grown from August to September. Nevertheless, Mucormycosis remains an uncommon disease, even in high-risk patients, and represents 8.3%–13% of all fungal infections encountered at autopsy in such patients [4]. Postmortem prevalence assessment suggests that Mucormycosis is 10–50 times less common than candidiasis or aspergillosis, with a frequency of 1–5 cases per 10,000 autopsies [4].

Table 1 Incidence of mucormycosis in several countries all over the world [5].

Continent	Country	No. Of Mucormycosis cases per 1,00,000*	Reference	Years
Africa	Cameroon	0.2	23	2014–2017
	Senegal	0.2	24	2012–2014
Asia	China	0.1	25	2011–2012
	Jordan	0.2	25	2011–2013
	Nepal	0.2	26	2012–2013
	Qatar	1.23	27	2011
	Saudi Arabia	0.034	25	2011–2012
	Vietnam	1.2	28	2009–2012
Australia	Australia	0.1	25	2013–2017
Europe	France	0.1	29	2005–2007
	Norway	0.1	30	2015–2016
	Romania	0.04	31	2017
Latin America	Argentina	0.17	32	2014–2017
	Colombia	0.2	33	2005–2017
North America	Canada	0.1	25	1997–2006
	Mexico	0.1	25	2010–2013

*Refers to the total number of patients

3. Diagnosis

The diagnosis of Mucormycosis is very much challenging [6]. Early diagnosis of Mucormycosis may be possible if we can recognize the host we are dealing with and assess the signs and symptoms. Mucormycosis can be fatal if not detected at its earliest. Its fatality rate may be as high as 80%. It is rarely suspected among patients suffering from blood-related disorders. The mortality rate of this disease also depends upon underlying conditions such as diabetes with a mortality rate of 44%, patients with no conditions have a 35% mortality rate and the mortality rate is even higher in patients with malignancies by 66%.For testing the presence of fungus the enzyme 1, 3 β-D glucan is used Since it only detects Aspergillus sp. this test is not used. At present, there is no Polymerase Chain Reaction (PCR Test) for Mucormycosis. The other option is the biopsy, but it may not be possible for the patients suffering from cancer. A sample of sputum may also be taken [6]. This way of diagnosis doesn't work all the time but it helps in identifying the genus and the species that has been countered. Computed tomography of the region may be helpful compared to an X-ray [7]. If a patient suffers from diabetes and is Hyperopic or ophthalmodynia (pain in the eyes) and chest area may also be a sign, so without any further delay test samples should be sent for further testing methods. According to the most common clinical studies of Mucorales, the area which is most likely to be affected is Rhinocerebral, lungs, and connective tissues. The traditional hallmark of Mucormycosis is tissue necrosis but diagnosis lacks specificity and sensitivity as Aspergillus and Fusarium also produce the same signs the infection may spread rapidly and may be deadly in most cases [8]. In such cases, treatment is an obvious statement without wasting any time with proper care and antifungal agents to avoid any infections. The most common sites of invasive Mucormycosis are the sinus (39%), lungs (24%) and skin (19%).

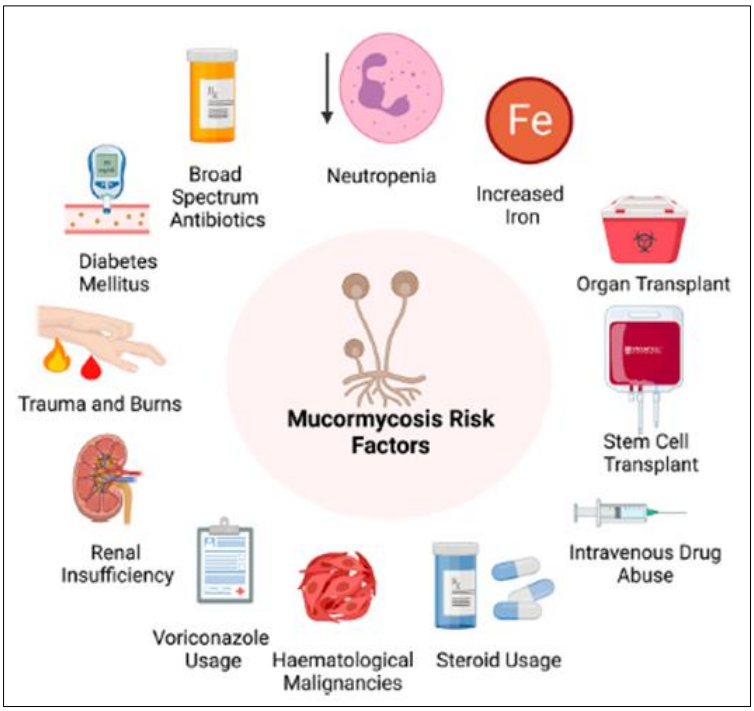

Figure 1 The risk factors associated with Mucormycosis [9]

4. Treatment

Mucormycosis can be managed successfully based on certain standards that can be followed to reduce the cause i.e. approaching various media to gain information, pre-understanding the symptoms, early treatment through antifungal agents, or in serious cases amputation of infected tissue be done [8]. Control of underlying condition includes control of diabetes, discontinuation of steroids. It is even more serious in the case of uncontrolled diabetes and immediate action is required to control the spread and severity. In such cases, Sodium bicarbonate is used to reverse ketoacidosis [10]. Corticosteroids and other immunosuppressive drugs are used in doses as low as possible. It is necessary to pre-prompt the diagnosis to initiate therapeutic action that reduces the cause of infection to the tissues [8].

5. Mode of entry

There are many common characteristics of Mucorales with other molds such as mode of entry i.e. via airways, mucosal area, and skin), host defense and histological and clinical features. Other forms of Mucorales that include Lichtheimia, rhizome, or and Mortierella spp. have distinct features that infect the patients with diabetic ketoacidosis and another acidosis, which enables a rare form of host-pathogens interactions compared to other Infections/fungi. Extensive angioinvasion characterizes Mucormycosis which leads to thrombosis and tissue necrosis. There are certain Mucorales like R.oryzae that have reduced the susceptibility that compromises the host defense compared to other fungi like Aspergillus or Candida, due to which these are more difficult to treat and hence increases fatality rates.

6. Drugs

Most antifungal in vitro are successful in resistance to Mucoraceous fungi that also includes Voriconazole. Amphoterin B is the most active drug along with Posaconazole and Isavuconazole [11] [12]. For patients who are intolerant to Amphotericin B in such cases, alternative agents like Posaconazole or Isavuconazole were administered. Itraconazole and Terbinafine are useful against certain strains of the fungi[13]. Due to a lack of information on drugs for Mucorales, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has recommended guidelines in the testing and treatment of Mucormycosis [14]. In the year 2016, The European Conference on Infections in Leukaemia (ECIL-6) has recommended the use of lipid formulations of Amphotericin B as the first line of therapy for Mucormycosis [14] [15]. The dose of liposomal amphotericin B is suggested as 5mg/kg/day and in extreme cases as high as 10mg/kg/day for Infections in the Central nervous system. The optimal dose of antifungal agents is still a case of issue. The European Conference on Infections in leukaemia (ECIL-6) recommended Posaconazole as maintenance therapy while according to European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines Posaconazole

can be used as the first line of treatment and the suggested dose is about 200 mg in the form of oral suspension. The most recent developed triangle is Isavuconazole that have high antifungal action [8].

7. Surgery

Surgery can be done if the spread of infection cannot be treated with medication but it can be aggressive. In this procedure, not only the necrotic tissues but also the surrounding healthy tissues are also removed to prevent the further spread of infection as the rate of extension of infections by Mucorales is immense [16]. Triggering Mucormycosis in patient's post-COVID-19 is the indiscriminate use of a high dose of steroids in COVID-19 patients, leading to spikes in the sugar level among diabetic patients which in turn renders them vulnerable that is why rational use of steroids is important. Steroids weaken the body of the patient and upon later being affected by Mucormycosis there is an increase in fatality rate.

8. In relation to COVID-19

Mucormycosis in itself is a deadly fungal infection and it is seen to be found in Covid-19 patients. The infection may develop within 10-14 days post-hospitalization and it spreads through blood and reaches other parts of the body. This may affect the brain or lungs of the patient along with Covid-19 infection. According to the Centre of Disease Control and Prevention (CDC), Mucormycosis has been divided as per their targeted area within the patient i.e. lungs, sinus, gastrointestinal, etc. The patients that recover from Covid-19 infection that have issues such as diabetes, more in ICU or medical oxygen use, Kidney disease, hematological malignancies, etc. are more at risk of getting infected with Mucormycosis [17]. These infections mainly spread due to unrestrained overuse of steroids and antibiotics in the treatment of Covid-19[18]. The combination of both the infections increased the mortality rate which is approximately 87% as compared to the previous Covid-19 mortality rate which was approximately 50% [19] [20]. All these infections were observed in immunocompromised Covid-19 patients which affects the immune system and causes unregulated and decreases the number of T lymphocytes [21].

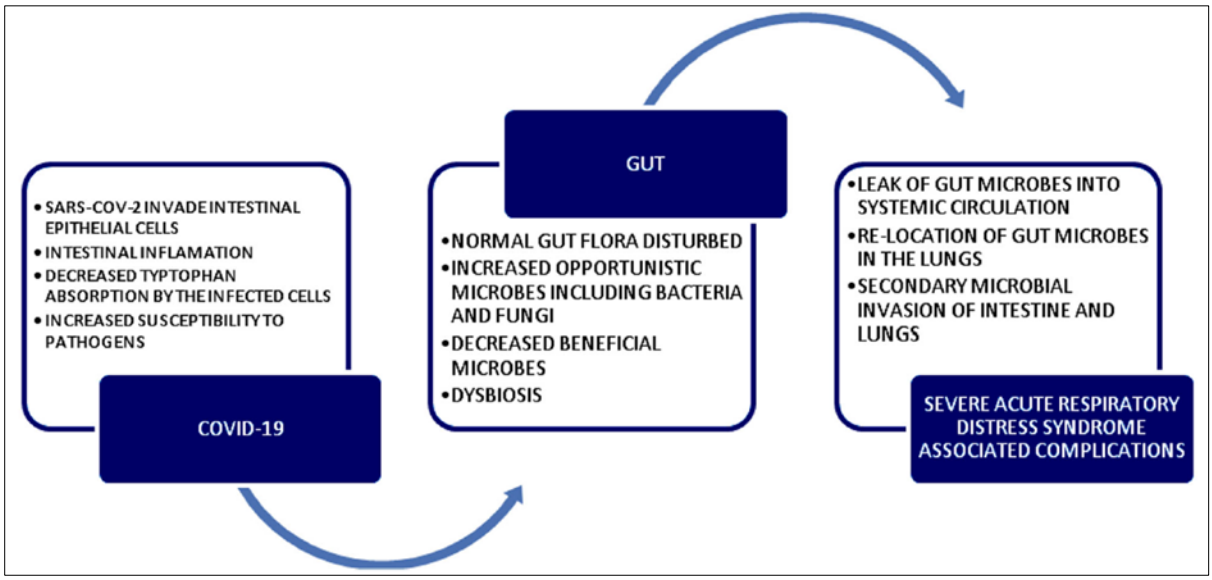

Figure 2 Gut microbiota and COVID-19 [22]

9. Conclusion

The COVID-19 Pandemic has put the entire world in turmoil and the proper cure for this is not yet discovered. The COVID-19 patients are more affected to this infection due to immunocompromised, diabetes, and heavy steroids. As Mucormycosis is angio-invasive if once inhaled the spores begin to grow, and the fungal hyphae conquer the blood vessels and this further contributes to tissue infarction, necrosis and thrombosis. This fungal infection is life-threatening because it occurs among people who have immunosuppression accompanied with diabetic ketoacidosis, neutropenia, increased serum levels of iron, excess release of sugar due to overtake of steroids that finally results in a decrease in levels of WBCs, T-cells and other immunomodulatory cells and triggers the cytokine storm that damages the cellular organs.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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