Study of Correlation between Covid-19 and Mucormycosis during current pandemic situation

Shivangi Srivastava[1], Anupama Ojha[2], Sarad Kumar Mishra[3]

[1]*Postgraduate, Department of Biotechnology, Deen Dayal Upadhyaya Gorakhpur University, Gorakhpur, Uttar Pradesh, India.*

[2]*Post Doctoral Fellow, Department of Biotechnology, Deen Dayal Upadhyaya Gorakhpur University, Gorakhpur, Uttar Pradesh, India.*

[3]*Head, Department of Biotechnology, Deen Dayal Upadhyaya Gorakhpur University, Gorakhpur, Uttar Pradesh, India.*

Corresponding Author: saradmishra5@gmail.com

Abstract: - Mucormycosis is an opportunist and invasive fungal disease. It is also known as "black fungus" caused by spores of Mucorales order, mainly *Rhizopus oryzae.* It damages lungs, brain, skin and other organs of the body. In this pandemic situation of Covid-19, most of the patients developed mucormycosis during or after the complete treatment of infection. It was observed that the infection of SARS CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) in the individuals leads to increases the risk of fungal diseases mainly mucormycosis due to increase in risk factors like GRP 78 over expression, increased iron levels, weakened immune system, etc. It was observed that the cases of mucormycosis increases rapidly in the 2nd wave of Covid-19 in India as well as in other countries of whole world also. Antifungal drugs or surgeries or other therapies are adopted to save the lives of patients of mucormycosis or Covid-19 associated mucormycosis. But the fatality rate is still higher due to rapidly spreading of fungal infection in the body and brain of the patients. This article review that the possible mechanism of mucormycosis in covid as well as normal individuals, possible links between mucormycosis and Covid-19 & the factors responsible for the development of mucormycosis in Covid-19 affected individuals and the biotechnological approaches to reduce the infection rate of mucormycosis in Covid-19 infected individuals. This article also reviews currently used treatment methods for mucormycosis.

Key Words: —*Mucormycosis, Covid-19 associated mucormycosis (CAM), Amphotericin B, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2), Posaconazole, isavuconazole.*

I. INTRODUCTION

In the present situation, whole world is dealing with the global pandemic of coronavirus disease-19 (Covid-19) (World Health Organization, 2020). Covid-19 is very contiguous and highly spreading disease. It can spread very easily from one to another person by making any contact to the infected person. It belongs to the family of Coronaviridae and order Nidovirales. It is a small virus in size and it contains RNA as its genetic material. Special type of spike protein is present at the surface of the virus. These spike proteins are responsible for the attachment to the surface of the human cells and infect them.

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It is also called as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses., 2020). Symptoms of the infection include fever, dry cough, tiredness, etc. These are the most common symptoms but the patient with severe infection of the Covid-19 dealing with heavy breathing problems. The diagnoses of the coronavirus disease are done by collecting swab from the nose and mouth of the infected person and send it for RT PCR test. Some rapid antigen test kits are also available for the rapid testing of the virus (Li C et al., 2020).

Currently in this pandemic situation, Mucormycosis is seen as an emerging disease. It is also known as black fungus due to its symptoms (Dyer, 2021). Mucormycosis is a disease caused by filamentous fungi (commonly forms hyphae) belonging to the order Mucorales (Hibbett et al., 2007). Fungi in this order are omnipresent (means that present everywhere) and eleven genera, six families and ~ 27 species of this order are responsible of causing human infection. Rhizophus spp. is

mainly responsible of causing mucormycosis (Ribes et al., 2000). This disease is associated with angio-invasive, life-threatening and highly mortality rate. The spores are producing from these molds are dispersed in air and it is inhaled by the humans. Cases of mucormycosis increased in India in the second wave of Covid-19 and in May 2021, India had recorded at least 14,872 cases of mucormycosis (Kumar S et al., 2021). The increasing number of cases of mucormycosis in Covid-19 patients was reported from worldwide (USA, Austria, Brazil, Mexico, Italy, France, Iran and India). Other clinical forms of mucormycosis are rhinocerebral (sinus and brain), pulmonary, cutaneous, disseminated and, gastrointestinal mucormycosis.

The diagnosis of the disease is very difficult and that's why its confirmation is made at the very late stage of the illness. The treatment of the disease requires use of antifungal therapy or medications and in some severe cases surgery is required.

The present study is to reveal the correlation between Covid-19 and Mucormycosis during this pandemic situation through online survey.

II. PATHOGENESIS OF MUCORMYCOSIS

Pathogenesis of mucormycosis is the mechanism of action of mucormycosis in the individual's body. Spores of Mucorales entered in the body of humans via inhalation of spores, percutaneous inoculation or ingestion. If the spores are able to penetrate the lungs or subcutaneous tissues, the first line of defense i.e., mononuclear and polynuclear phagocytes start killing spores of Mucorales by oxidative and non-oxidative mechanism in the body of healthy individual but if the individual is not healthy, spores are able to cross the first line of defense very easily. In the immunocompromised individuals, these phagocytes are dysfunction and they losses the capacity of lysis which results the invasion of spores in the vessels (E. Bouza et al., 2006).

2.1Pathogenesis of Mucormycosis in the normal/immuno compromised individuals

Free iron is abundantly released which makes perfect environment for the growth of mucormycosis. They consume iron (high affinity iron permease) and transport free iron to the development sites of the fungi. They damage epithelial cells and increased platelet derived growth factor receptor B (PDGFRB) which helps in the development of fungi. After the entering of spores of Mucorales in the body, they start producing Mucorales specific T-cells which generates interleukins (IL-4, IL-10 and IL-17) and IFN-γ and damages the host cell. The fungal hyphae also decrease the release of various immunomodulatory molecules such as RANTES [regulated upon activation, normal T-cell expressed and secreted] (Mahalaxmi et al., 2021). This pathogenesis mechanism in normal/immunocompromised individuals shown below in the fig.1.

2.2 Pathogenesis of Mucormycosis in Covid-19 infected patients

It can be due several reasons. The infection of corona virus makes individual's body to provide a favorable environment for the growth of mucormycosis. Reasons for the development of mucormycosis in the Covid-19 infected patients are patient with diabetes or uses of immunosuppressant or uses of steroids or neutropenia patients. Most of the studies of Covid-19 associated mucormycosis suggested that the patients with diabetes are on the high risk of development of mucormycosis and use of steroids to reduce the infection of Corona virus makes the patient's body immunocompromised which gives good chances to develop mucormycosis and other factors are also responsible of this infection. These factors or reasons act as an opportunity for the mucormycosis (Mahalaxmi et al., 2021).

This pathogenesis mechanism in the Covid-19 infected patients shown below in the fig. 2. Few case studies on Covid-19 associated mucormycosis have been presented in Table-1.

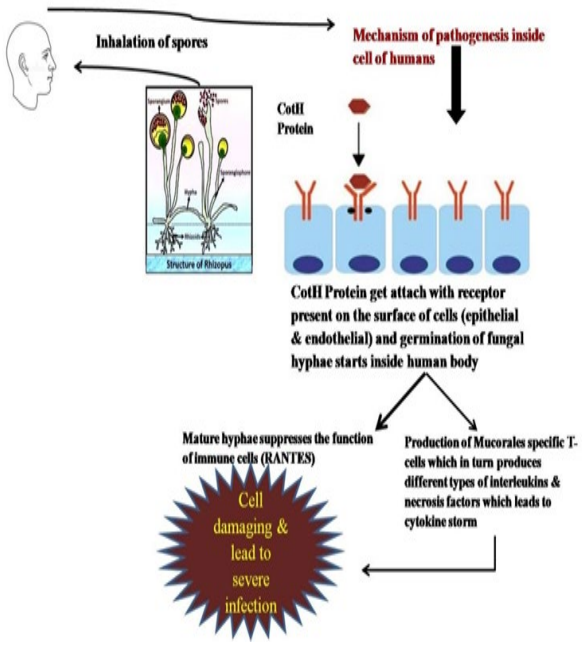

Fig.1. pathogenesis mechanism in normal/immunocompromised individuals

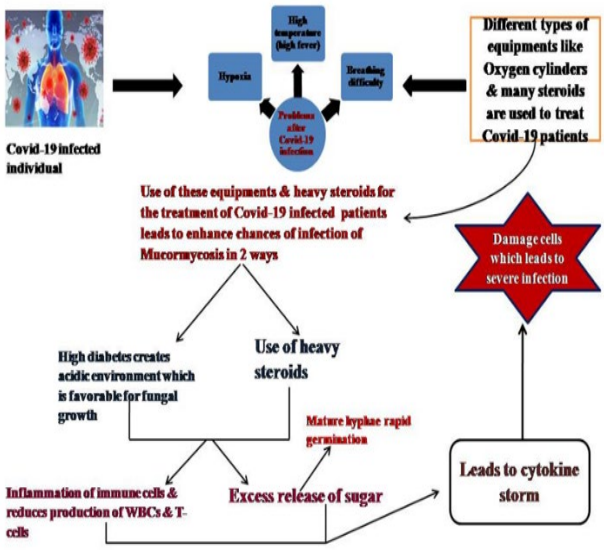

Fig.2. pathogenesis mechanism in the Covid-19 infected patients

Table.1. Case studies of Covid-19 associated Mucormycosis (CAM)

S.No.	Age/Sex	Multiple illness	Diagnosis of mucormycosis (when patient is live)	Organs affected	Author/country
1.	-	Heart disease	Yes	-	Khatri et al., 2021
2.	Middle age/female	Non-ketotic diabetes	Yes	-	Mallikarjun et al., 2021
3.	55/male	Diabetes, blood deficiency & end stage renal disorder	Yes (after 14 days of covid-19 infection)	Lungs	D. Garg et al., 2021/India
4.	60/male	Diabetes, vascular diseases	Yes (after 10 days of covid-19 infection	Rhino-orbital	Mehta et al., 2020/India
5. (i). (ii). (iii).	33/female, 49/male, 60/male	Hypertension, asthma - Diabetes, hypertension & asthma	Yes Yes (after 14 days of covid-19 infection) Yes (after 10 days of hospitalization)	Rhino-cerebral Pulmonary (lungs) Rhino-orbital	Werthman-Ehrenreich 2020/USA Placik et al., 2020/USA Mekkonen et al., 2020/USA
6.	86/male	Hypertension	No (postmortem diagnosis)	Gastro-intestinal	Monte junior ESD et al., 2020/ Brazil
7.	22/male	Obesity & hyperthyroidism	No (postmortem confirmation)	Multiple organs affected	Hanley et al., 2020/UK
8.	66/male	Hypertension	Yes (after 14 days of ICU admission)	Lungs & maxillary sinus	Pasero et al., 2020/Italy

III. Possible Link Between Covid-19 and Mucormycosis

Corona virus induces or increases some risk factors for mucormycosis infection in the patients. These factors create the linkage between Covid-19 and mucormycosis. Factors for mucormycosis infection in the patients which makes possible linkage between Covid-19 and mucormycosis includes surface receptors of epithelial & endothelial cells, increased iron levels, immune dysfunction due to use of several steroid therapy. These factors are explained in detail below:

3.1 Surface receptors of epithelial & endothelial cells

SARS-CoV-2 get entry in the host through ACE-2 (Angiotensin-Converting Enzyme-2) receptor and GRP78 (Glucose Regulated Protein) co-receptor is also responsible for the entry of the Corona virus in the host body. These receptors mediated the binding of spike protein of Corona virus on the host cell and allow entry of the virus which results in the endothelial damage. Like corona virus, mucormycosis causing fungal spores also takes entry via GRP78 in the host cell and start invasion. It is shown that the Covid-19 infected patients have increased level of GRP78 in comparison to normal individuals. This increased levels of GRP78 mark as a high-risk factor for mucormycosis in the Covid-19 infected patients. GRP78 is also responsible in stabilizing the binding of ACE-2 receptor and spike protein of Corona virus. The endothelial lining damaging in the Covid-19 infected patients is due to activation of inflammatory factors and increased in the levels of pro-inflammatory factors like interleukins (IL-1β, IL-6, and IL-8) and tumor necrosis factor (TNF) which leads to endothelial cell apoptosis, alternation in blood coagulation factors and inflammation in various organs leads to multi organ failure. This endothelial damaging and increased level of GRP78 receptor acts as a high risk of mucormycosis infection in the Covid-19 infected patients. Both increases the chances of entry of fungal spores in the host cell which causes mucormycosis. Fungus which cause mucormycosis have a coat protein CotH on their surface which acts as a fungal ligand for the receptor present on the endothelial cells of host, this CotH coat protein is a conserved part in all Mucorales order fungi. Increased level of GRP78 and CotH coat protein May increases the chances of binding of Mucorales fungal spores so, inhibition of GRP78 or using antibody against GRP78 and CotH results in reduction in corona virus as well as mucormycosis (Prakash et al., 2021) This surface receptor mechanism is shown in fig.3 below.

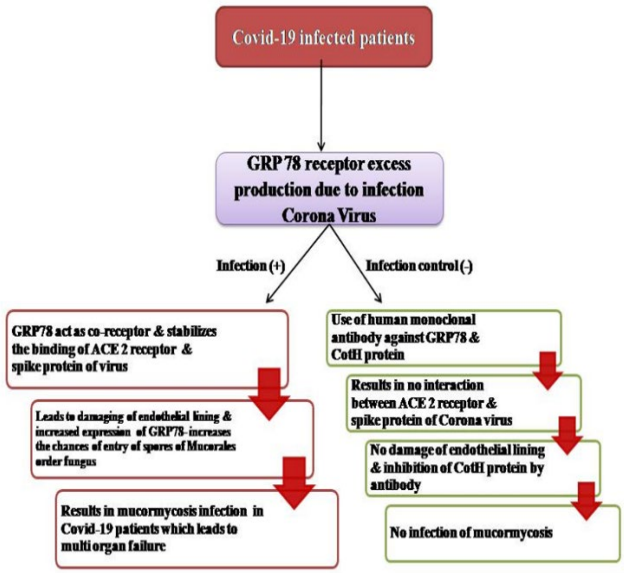

Fig.3. Flow chart shows the role of GRP78 in the pathogenesis of Covid-19 and mucormycosis

3.2 Increased Iron levels

Increase level of free iron plays an important role in the survival and development of mucormycosis in the patients. Patients with high glucose level or uncontrolled diabetes may act as a risk factor for mucormycosis. DKA (Diabetic ketoacidosis) patients have more chances to get infected to mucormycosis. Normally iron binds with some binding molecules like ferritin, transferrin, etc. During Covid-19 infection, iron gets dissociated from heme molecule which results in hyperferritinaemia which causes overload of iron in the body. Due Covid-19 infection and hyperglycemia in the patients leads to this hyperferritinaemia (high ferritin inside cells) results in release of oxygen radicals in high concentration which leads to tissue damage and release of free iron in the blood. This free iron favors the growth of the fungus causing mucormycosis in the blood of host.

Mucorales have some genes for gaining iron from the host for their survival is high affinity iron permease (FTR1), multi-copper oxidase and ferric reductase or some genes are also present to gain iron from heme molecules. This FTR1 plays an important role in the survival of Mucorales in low iron concentration and pathogenesis of mucormycosis. Some reports suggested that the use of RNA interference or antibody against this FTR1 gene helps to reduce the mucormycosis infection in DKA patients as well as in Covid- 19 infected patients. During Covid-19 infection, iron chelation therapy can also be used to treat hyperferritinaemia which results in reduction of mucormycosis in the Covid-19 infected patients. Some iron chelators such as deferoxamine, deferasirox and deferiprone. But use of these iron cheletors in covid 19 infected patients to treat hyperferritinaemia is still in clinical trials (Prakash H. et al., 2021).

3.3 Several Steroid therapy

Different types of steroids are used to treat Covid-19 infection in the patients. World Health Organization (WHO) recommended the manageable use of corticosteroid only in the critical Covid-19 infected patients (6 mg of dexamethasone orally/intravenously daily or 50 mg of hydrocortisone intravenously every 8 h) for 7 to 10 days. Glucocorticoids are the most commonly used as anti-inflammatory and immunosuppressive drugs but the use of steroids for long time results in severe side effects like suppression or inactivation of immune cells such as macrophages, T-cell, neutrophils or platelets. The suppression of these cells results in the development of infection very rapidly in the host body. Steroids treated Covid-19 infected patients have higher risk of development of mucormycosis. Some experimental evidences are reported that the use of steroids in the treatment of patients leads to increase the expression of GRP78 in the patients which results in the development of mucormycosis (Prakash H. et al., 2021).

IV. TREATMENT METHODS USED IN COVID-19 ASSOCIATED MUCORMYCOSIS

Different treatments strategies are used to reduced or treat the mucormycosis. It includes antifungal therapy treatment and surgery of the affected part or organ of the patient.

4.1 Antifungal Agents or drugs

Antifungal drugs are used to treat mucormycosis in the infected patients. Antifungal drugs mainly include polyenes and triazoles for the mucormycosis treatment e.g., amphotericin B and its lipid formulations, posaconazole and isavuconazole. Amphotericin B and its lipid derivatives and isavuconazole are used as first line therapy but posaconazole is used as salvage therapy for the treatment of mucormycosis. In some cases these antifungal drugs are used as monotherapy or as combination therapy (Sipsas, N.V et al., 2018). 2D and 3D structures of several antifungal drugs are generated using online chrome software which is shown in fig. 4 & 5 below and several antifungal drugs are listed below in table 2.

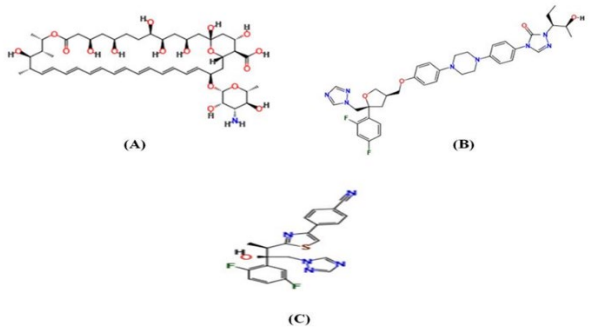

Fig.4. 2D Structures {(A) Amphotericin B; (B) Posaconazole; (C) Isavuconazole} are generated by using online chrome software
Source- (online chrome software) https://molview.org/?cid=5280965

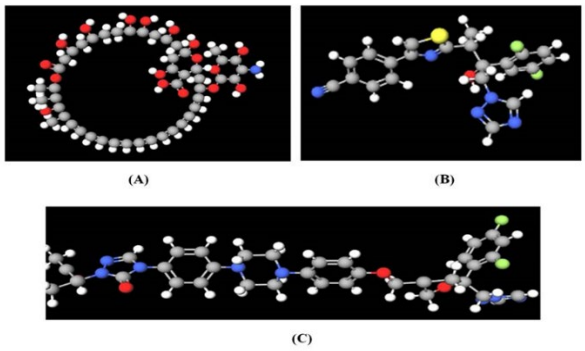

Fig.5. 3D Structures {(A) Amphotericin B; (B) Isavuconazole; (C) Posaconazole} are generated by using online chrome software
Source- (online chrome software) https://molview.org/?cid=5280965

Table.2. Various antifungal drugs and their mechanism of action

S.No.	Antifungal drugs	Drugs name	Chemical formula	Molar mass (g/mol)	Mode of action	References
1.	Polyenes	Amphotericin B, liposomal amphotericin B, amphotericin B lipid complex	$C_{47}H_{73}NO_{17}$	924.091 g/mol	It binds to the ergosterol (main component of the cell membrane of fungal cells) leads to formation of pores, the membrane permeability & produce free radicals which results in fungal cell death. This mechanism shown in fig. 6	Nett & Andes (2015); Noor A, Preuss CV (2021)
2.	Triazoles	Posaconazole	$C_{37}H_{42}F_2N_8O_4$	700.8 g/mol	Triazoles mainly inhibit the synthesis of ergosterol. It blocks the cytochrome P450 dependent enzyme C-14 alpha-demethylase which is responsible for converting lanosterol to ergosterol. This mechanism shown in fig. 7	Nett & Andes (2015); Sipsas, N.V et al., (2018); Edward C Oldfield III (2013)
3.	Triazoles	Isavuconazole	$C_{35}H_{35}F_2N_8O_5S$	717.77 g/mol		
4.	Echinocandins	Echinocandins B	$C_{52}H_{81}N_7O_{16}$	1060.24 g/mol	It disrupts the fungal cell wall by inhibiting the synthesis of β-1, 3 glucan (essential polysaccharide component of fungal cell wall)	Nett & Andes (2015)

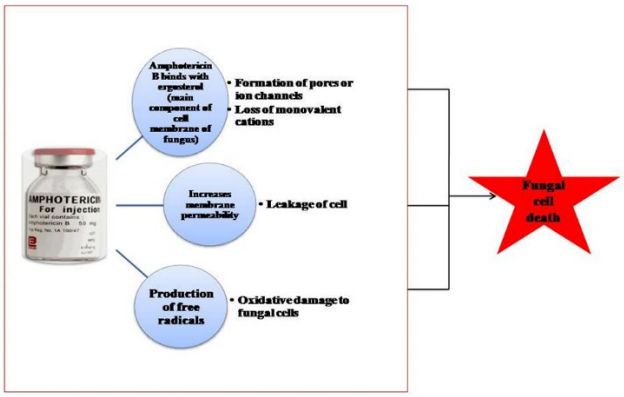

Fig.6. Mechanism of action Amphotericin B to kill fungal cell

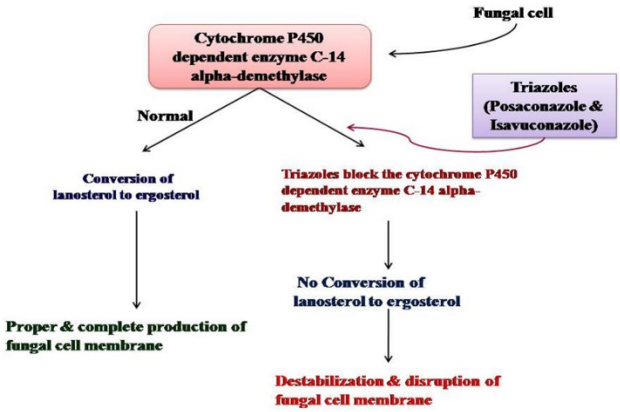

Fig.7. Mechanism of action of triazoles (posaconazole & isavuconazole) to kill fungal pathogens

4.2 Combination Therapy

Some case series reveals that the monotherapy of several antifungal drugs does not show higher activity against mucormycosis causing fungus. So, in this type of cases a combination therapy of antifungal drugs is used to treat patients. This therapeutic approach includes combination of polyenes and triazoles mainly amphotericin B and posaconazole or isavuconazole and also includes combination of polyenes and echinocandins. This therapeutic approach has both advantages as well as disadvantages like benefits of this approach is cooperative effect and wide coverage and disadvantages are cost, toxicity and drugs interaction. But due to lack of clinical data and proper evidences this combination therapy approach is not being used on humans for the treatment of mucormycosis (Sipsas, N.V et al., 2018).

4.3 Surgery

Surgery is done to remove the infected or necrotic tissues from the patient's body. It is the main treatment

approach for the treatment of mucormycosis infected patients. Surgery along with the systemic use of antifungal drugs enhances the chances of survival of the patients compared to the alone use of antifungal drugs for the treatment (Sipsas, N.V et al., 2018).

V. Discussion

The article discusses about various case studies or case reports, links between Covid-19 and mucormycosis, types of mucormycosis, fatality rates, and treatments. India had approx. 24,370 cases of mucormycosis with Covid-19 history in 2021 (Adil 2021; Mahalaxmi et al., 2021). Different states of India reported high number of mucormycosis cases till June 2021 (Barnagarwala 2021; Mukherjee 2021; Ali 2021; Josephine 2021; Mahalaxmi et al., 2021. All case studies from different countries of whole world reveals that several risk factors are arises which are responsible for the development of mucormycosis in Covid-19 infected patients. First & main causes are uncontrolled diabetes in the patients and use of several steroids or immunosuppressant drugs which highly responsible for mucormycosis. Rhinocerebral & Pulmonary mucormycosis are common in Covid-19 patients & cutaneous mucormycosis is also very common during this Covid-19 pandemic era. Pathogenesis of mucormycosis starts by inhalation or inoculation or ingestion of Mucorales spores. If the individual is immune competent then he/she is easily able to kill the spores of Mucorales through his/her defense mechanism of the body but if the individual is immunocompromised, spores start developing in the body due to the presence of favorable environment for the growth & development of mucormycosis in the host body (Mahalaxmi et al., 2021). Pathogenesis of mucormycosis in Covid-19 infected patients is due to several factors which are responsible for the development & surviving of Mucorales spores in the host body. SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) provides favorable environment for the growth & development of Mucorales spores (Mahalaxmi et al., 2021). Some of the factors are responsible for creating the possible linkage between Covi-19 & mucormycosis like endothelial cells receptors (ACE-2 & GRP 78 receptors). In the Covid-19 infected patients GRP78 receptor expression is increased due to several factors which increase the risk of entry of the fungal pathogens. Risk of mucormycosis is reduced by inhibiting GRP 78 or using antibody against CotH (Prakash H. et al., 2021). An increased level of serum iron in the body of Covid-19 infected patients is also a major risk factor for the growth & development of mucormycosis. Over load of iron in the tissues of host releases free iron is due to hyperferritanemia and provides favorable environment for the development of Mucorales spores in the host body (mainly in the uncontrolled keto-diabetic patients). Using iron chelation therapy to reduce risk factor or infection rate of mucormycosis in the host body & different types iron chelators are used for this therapy such as deferoxamine, deferasirox and deferiprone. Using antibody against the genes (which are responsible of gaining free iron from the host body) is also helps in reducing or preventing from mucormycosis infection (Prakash H. et al., 2021). Use of steroids for the treatment of Covid-19 infected patients is also increases the risk for the development mucormycosis in the patient's body. Steroids suppressed or inactivate or dysfunction the immune cells like T-cells, neutrophils, platelets, macrophages. These cells help in killing the spores of Mucorales but in Covid-19 infected patients, these cells are not able to kill spores of fungus that results in growth & development of mucormycosis. Some reports are revealed that the use of steroids increases the expression of GRP 78 which leads to mucormycosis infection (Prakash et al., 2021).

Antifungal drugs are used to treat mucormycosis infected patients mainly includes amphotericin B & its lipid formulations and triazoles (posaconazole & isavuconazole). They attack on fungal cell membrane and stop the synthesis of ergosterol (essential component of cell membrane of fungus). These drugs are also caused oxidative damages and leakage of cells of fungus which ultimately kill the fungus. These drugs are used as monotherapy or combination therapy to enhance the efficacy of the drugs. Surgery of necrotic or damages tissues are also done with use of systemic antifungal drugs to enhances the chances of survival.

VI. Conclusion

The article concluded that the cases and risk of mucormycosis increases during this pandemic situation of Covid-19 due to several risk factors are increased in the Covid-19 infected patients. Factors like surface receptors (ACE-2 & GRP 78); steroid used for the treatment of Covid-19 patients, immune compromised individuals during and after infection of SARS CoV-2 viruses, increased serum iron levels in the body. Post Covid-19 effects are also responsible for the development of mucormycosis. Most susceptible individuals to mucormycosis are keto-diabetic or uncontrolled diabetic patients, weak immune system individuals, Covid-19 infected

individuals, etc. After the treatment mucormycosis is not fully cured or less chances of survival of the patients.

Future Prospects:

More research is required to find out the cause of Mucormycosis in Covid-19 patients. Study is needed to find out the entry of this fungus into the body through possible receptors/ways. Study of steroid treatment in stimulation of mucormycosis is needed to find the role of steroids in generation of mucormycosis. More research is needed to study the efficiency of Mucorales to cause infection in immune compromised individuals. Role of metabolic deficiency in generation of mucormycosis is also a thirst area. The use of biotechnological approaches to treat mucormycosis includes antisense technology to suppress the expression of genes which is responsible for gaining free serum iron from the host body. A use of antibody against GRP 78 receptor or CotH protein is also a required area for treatment of mucormycosis or reducing the infection rate. More iron chelating approaches are required to reduce the gaining of available iron by spores of Mucorales for their growth and development in host body.

REFERENCES

[1]. Adil, A., 2021. Over 28,200 'black Fungus' Cases Recorded in India. Anadolu Agency, 2021.

[2]. Akshay Khatri, Kai-Ming Chang, Ilan Berlinrut and Frances Wallach, 2021. Mucormycosis after Coronavirus disease 2019 infection in a heart transplant recipient–case report and review of literature. J. Med. Mycol. 101125.

[3]. Ali, M., 2021. Telangana: Black Fungus Patients Losing Sight. The Hans India.

[4]. Amanda Werthman-Ehrenreich. 2020. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med.

[5]. Barnagarwala, T., 2021. Mucormycosis: 2,245 Cases So Far in Maharashtra, 30 Dead in Last Six Days. Indian Express.

[6]. Bouza E, Munoz P, Guinea J., 2006. Mucormycosis: an emerging disease? Clinical Microbiology and Infection. 12 (suppl 7).

[7]. Brian Hanley, Kikkeri N Naresh, Candice Roufosse, Andrew G Nicholson, Justin Weir, Graham S Cooke, Mark Thursz, Pinelopi Manousou, Richard Corbett, Robert Goldin, et al., 2020. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. Lancet Microbe 1, e245–e253.

[8]. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 5, 536–544 (2020).

[9]. Daniel A. Placik, Wesley L. Taylor and Nathan M. Wnuk., 2020. Bronchopleural fistula development in the setting of novel therapies for acute respiratory distress syndrome in SARS-CoV-2 pneumonia. Radiol. Case Rep. 15, 2378–2381.

[10]. Daniela Pasero, Silvana Sanna, Corrado Liperi, Davide Piredda, Gian Pietro Branca, Lorenzo Casadio, Raffaella Simeo, Alice Buselli, Davide Rizzo Francesco Bussu, Salvatore Rubino and Pierpaolo Terragni, 2020. A challenging complication following SARS-CoV-2 infection: a case of pulmonary mucormycosis. Infection 1–6.

[11]. Deepak Garg, Valliappan Muthu, Inderpaul Singh Sehgal, Raja Ramachandran, Harsimran Kaur, Ashish Bhalla, Goverdhan D. Puri, Arunaloke Chakrabarti and Ritesh Agarwal., 2021. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. Mycopathologia. 186:289–298.

[12]. Dyer O (May 2021). "Covid-19: India sees record deaths as "black fungus" spreads fear". BMJ. 373: n1238.

[13]. Edward C Oldfield III., 2013.Treatment of Systemic Mycoses. Hunter's Tropical Medicine and Emerging Infectious Disease (Ninth Edition).

[14]. Epifanio Silvino do Monte Junior, Marcos Eduardo Lera dos Santos, Igor Braga Ribeiro, Gustavo de Oliveira Luz, Elisa Ryoka Baba, Bruno Salomão Hirsch, Mateus Pereira Funari and Eduardo Guimarães Hourneaux de Moura, 2020. Rare and fatal gastrointestinal mucormycosis (Zygomycosis) in a COVID-19 patient: a case report. Clin Endosc; 53: 746–749.

[15]. Hariprasath Prakash, Anna Skiada, Raees Ahmad Paul, Arunaloke Chakrabarti and Shivaprakash Mandya Rudramurthy., 2021. Connecting the Dots: Interplay of Pathogenic Mechanisms between COVID-19 Disease and Mucormycosis. Journal of Fungi, 7, 616.

[16]. Hibbett, D. S., Binder, M., Bischoff, J. F., Blackwell, M., Cannon, P. F., Eriksson, O. E. ...& Zhang, N. (2007). A higher-level phylogenetic classification of the Fungi. Mycological research, 111(5), 509-547.

[17]. Iyer Mahalaxmi, Kaavya Jayaramayya, Dhivya Venkatesan, Mohana Devi Subramaniam, Kaviyarasi Renu, Padmavathi Vijayakumar, Arul Narayanasamy, Abilash Valsala Gopalakrishnan, Nachimuthu Senthil Kumar, Palanisamy Sivaprakash, Krothapalli R.S. Sambasiva Rao and Balachandar

Vellingiri., 2021. Mucormycosis: An opportunistic pathogen during COVID-19. Environmental research; DOI: 111643.

[18]. Jeniel E. Nett and David R. Andes., 2015. Antifungal Agents Spectrum of Activity, Pharmacology, and Clinical Indications. Infect Dis Clin N Am;

[19]. Josephine, S.M., 2021. 1,196 Cases of Mucormycosis in T.N., More Drugs Required. The Hindu.

[20]. Julie A. Ribes, Carolyn L. Vanover-Sams and Doris J. Baker. 2000. Zygomycetes in human disease. Clinical microbiology reviews, 13(2), 236-301.

[21]. Kumar S, Ache ST, Syed M, Dutta J, Khan FA, Mali AP., 2021. Mucormycosis: A New Threat in Pandemic. Journal of Advanced Medical and Dental Sciences Research; Vol. 9(6):131-135.

[22]. Li C, Zhao C, Bao J, Tang B, Wang Y, GU B. 2020. "Laboratory diagnosis of coronavirus disease-2019 (COVID-19)". Clinica Chimica Acta; International Journal of Clinical Chemistry. 510: 35–46.

[23]. Muhammad Adnan Shereen, Suliman Khan, Abeer Kazmi, Nadia Bashir and Rabeea Siddique., 2020. COVID-19 infection: Emergence, transmission, and characteristics of human corona viruses. Journal of Advanced Research 24.

[24]. Mukherjee, M., 2021. Inside Black Fungus Wards in Rajasthan: amid Injection Shortage, Increasing Patients, Many End up Losing Vision. Indian Express.

[25]. Nikolaos V. Sipsas, Maria N. Gamaletsou, Amalia Anastasopoulou, and Dimitrios P. Kontoyiannis. 2018. Therapy of Mucormycosis. Journal of Fungi; 4(3):90.

[26]. Salil Mehta and Abha Pandey, 2020. Rhino-orbital mucormycosis associated with COVID-19. Cureus 12.

[27]. Shweta Mallikarjun Revannavar, Supriya P S, Laxminarayana Samaga, Vineeth V K., 2021. COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world? BMJ Case Rep; 14: e241663.

[28]. World Health Organization (WHO) 2020. "Naming the coronavirus disease (COVID-19) and the virus that causes it". Archived from the original on 28 February 2020. Retrieved 13 March 2020.

[29]. Zesemayat K. Mekonnen, Davin C. Ashraf, Tyler Jankowski, Seanna R. Grob, M. Reza Vagefi, Robert C. Kersten, Jeffry P. Simko and Bryan J. Winn, 2020. Acute invasive rhino-orbital mucormycosis in a patient with COVID-19-associated acute respiratory distress syndrome. Ophthalmic Plast. Reconstr. Surg. 37, e40–e80.