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Mucormycosis: A Life Threatening Public Health Disease

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Abstract

The alarming Coronavirus which affected the whole world has resulted in various complication affecting majority of population throughout the world. The pandemic COVID 19 has led to surge of potentially life threatening invasive fungal disease (IFD) called Mucormycosis. It is one of the aggressive devasting disease and is considered as oppurtunistic fungal infection affecting immunocompromised individuals. Mucormycosis, so called Black Fungus is caused by mucormycetes group of molds. India has declared mucormycosis as notifiable disease in May 2021 as rate of COVID 19 associated mucormycosis cases has increased tremendously. This review article presents the causes of this infection,the mode of spread ,sign and symptoms in the human body, and its diagnosis with available recent therapies. The diagnosis and identification of the infection were made possible through various latest medical techniques.

Keywords: Fungal; Mucormycosis; Transmission; Variant; Isolation

1. Introduction

American pathologist R. D. Bakeer coined the term Mucormycosis. It is also known as Zygomycosis[1,2] . The class Zygomycetes is divided into two orders, Mucorales and Entomophthrales. These two orders produce dramatically different infections. Genera from the other mucorales (rhizopus, mucor, rhizomucor, absidia, apophysomyces, cunninghamella and saksenaea) cause an angio invasive infection called Mucormycosis.It is a rare disease but increasingly recognized in immune-compromised patients. It can be categorized into rhino-orbito-cerebral, cutaneous, disseminated, gastrointestinal and pulmonary types. Immuno-compromising states includes haematological malignancy, bone marrow or peripheral blood stem cell transplantation, neutropenia, Solid organ transplantation, diabetes mellitus with or without ketoacidosis, Corticosteroids and deferoxamine therapy. Mucorales can gain entry to a susceptible host through inhalation, ingestion of contaminated food, or abraded skin. One of the characteristic features of mucormycosis is its angio-invasive property, resulting in vascular thrombosis and ultimately tissue necrosis [3].

2. Discussion

Corona virus (Cov) belongs to the Corona viridae family, Nidovirales order. The subfamily *Corona* viridae has four genera, Alpha-corona virus *(*229E, NL63), Beta-corona virus *(OC43,* HKU1), Gamma-corona virus and Delta-coronavirus [4]. The name of the genus "corona" means crown, as the virus appears with crown-like projections on its surface. Cov can lead to a range of conditions as mild as the common cold, fever and cough and as severe as pneumonia, respiratory distress kidney failure or even death. These viruses are zoonotic, ie.they are transmitted between animals and humans [5]. A couple of corona viruses were previously identified as MERS- COV (Middle East Respiratory Syndrome –corona virus) and it was transmitted form dromedary camels to humans.

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SARS-Cov (Severe Acute Respiratory Syndrome – corona virus) was transmitted from civet cats to humans.[6,7] In the late 1960s, it was first isolated from patients suffering from common cold, named as B814 and visualized under an electron microscope. The key reservoirs of the virus are bats, palm civets, livestock and animals.According to the Canadian study I 2001[5] approximately 500 patients were identified as Flu-like symptom. 17-18 cases of them were confirmed as infected with corona virus strain by polymerase chain reaction. Corona was treated as simple non fatal virus till 2002. In 2003, various reports published with the proofs of spreading the corona to many countries such as United States of America, Hongkong, Singapore, Thailand, Vietnam and in Taiwan. Several case of severe acute respiratory syndrome caused by corona and their mortality rate is more than 1000 patient was reported in 2003. In 2012, Saudi Arabian reports were presented several infected patient and deaths. COVID-19 was first identified and isolated from pneumonia patient belongs to Wuhan, China [6,7].

Viruses and other pathogens are known to mutate and differentiate by nature. According to WHO, a virus replicated or makes copies of itself. These changes, by definition are called "mutations". A virus with one or more new mutations is referred to as a "variant" of the original virus [8,9]. Corona viruses have all their genetic material in something called RNA (ribonucleic acid). RNA has some similarities to DNA, but they aren't the same. When the viruses infect you, they attach to your cells, get inside them and make copies of their RNA, which helps them spread. If there's a copying mistake, the RNA gets changed. Scientists call those changes mutations[9].

The three infamous COVID variants which are said to carry the most risks-ones which have emerged from Kent, UK (B.1.1.7 variant), South Africa (B.1.351 variant) and Brazil (B.1.1.28.1 or P.1 variant) are all variations of the original virus strain. The double mutant variant first identified in the state of Maharashtra is considered to be a cross between E484Q and L452R mutations. While the E484Q mutation is domestic, the L452R mutation was traced back to the US [8,9]

The clinical features of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress syndrome and multi-organ dysfunction which may appear 2-14 days after exposure. The period after exposure and before having symptoms is called incubation period[10,2,13].Common symptoms can include as fever, cough .Early symptoms of COVID-19 may include as loss of taste or smell, pain and tightening in the chest[10,11].Other symptoms can include as shortness of breath or difficulty in breathing, muscle aches, chills, sore throat, runny nose, headache, chest pain, pink eye (Conjuctivitis), nausea, diarrhoea and rash. COVID-19 can also cause blood clots, brain fog, mood changes, visual disturbance, kidney damage, heat palpitations. Severe impact on lungs may include as difficulty in breathing, low levels of oxygen in the blood, lung injuries, pneumonia, and pulmonary edema. In addition, having COVID-19 can increase the risk of damage to blood, kidneys, nervous system and brain, cardiovascular system, gastrointestinal system.

Diagnostic test for evaluation of COVID 19 includes the following [14,15]

2.1. Nucleic Acid test

RT-PCR (reverse transcription-polymerase chain reaction) used to detect the viral RNA from samples obtained through specimen sites.

2.2. Antigen test

To detect the presence of SARS-CoV-2 nucleocapsid protein antigen on the viral surface form nasopharyngeal and oropharyngeal swabs.

2.3. Antibody test

It detects specific antibodies (IgG and IgM) produced against SARS-CoV-2 in the serum, plasma or whole blood of the host in response to the viral infection.

2.4. Image-based test

HRCT (High Resolution Computed Tomography) -Scan has played a pivotal role in the diagnosis and treatment of the disease. (Ground glass opacities are the predominant pattern of abnormalities seen after the onset of symptoms).The reversed halo sign located in the peripheral portion of lungs suggest the diagnosis of pulmonary mucormycosis and indicates the initial phase to start the antifungal therapy.

Investigations suggested are Chest X-Ray, Lung Ultrasound were also recommended.Other Laboratory Assessment includes Complete blood count , Comprehensive Metabolic Panel (CMP), Erythrocyte Sedimentation Rate, C-Reactive Protein (CRP), Ferritin, Lactate dehydrogenise, D-Dimer and Pro-calcitonin.

Symptomatic cases should be admitted to hospitals and treated effectively.They should follow strict isolation and prevention protocol measures. General supportive therapy including oxygenation and fluid management should be followed. Drugs like Corticosteriods (e.g.:dexamethasone 6mg/day) and Chloroquine /Hydroxychloroquine , an anti-malarial drug is used in the treatment of MERS-Cov and SARS-Cov which also provides post- transcriptional inhibition in HIV patients.

Lopinavir/ Ritonavir are protease inhibitors used as anti-HIV drugs. In Cov patients, responsible for viral replication . Ivermectin has multifaceted property with its anti-microbial and anti-cancer actions. In Cov patients, it is responsible for viral protein transmission into the host cell nucleus within 48hrs of initiating ivermectin treatment. Due to limited clinical trial it is still pending for approval[16]. Favipiravir is a purine nucleoside analogue used against influenza A and B (used as a trial in Cov). Oseltamivir (Tamiflu) neuraminidase inhibitor approved for treating influenza A and B (still under clinical trial used with the combination of chloroquine and Favipiravir). Antibiotics should be used only in patients presenting with severe clinical respiratory insufficiency for a maximum of 5days. Adjunctive therapy: Anticoagulants such as low molecular weight heparin (LMWH) to treat DIC or thromboembolism in critically ill COVID-19 patients .VitaminC is an essential co-factor, antioxidant and immunomodulator.

Treatment for COVID leads to various post COVID complications[17] .Post-COVID conditions are a wide range of new, returning, or ongoing health problems people can experience more than four weeks after first being infected with the virus that causes COVID-19.Some of the complications being witnessed in patients recovered from Covid-19 include impact on lungs, kidneys, heart, and cases of a black fungal infection, called Mucormycosis.Long COVID is now a widely recognised and reported phenomenon wherein symptoms include fatigue, tiredness and breathlessness for prolonged periods of time.One instance of this is Mucormycosis or black fungus, which is affecting people recovering from Covid-19. The state of Rajasthan has declared it an epidemic, and Maharashtra has reportedly said it will seek doses of the antifungal drug amphotericin B from the Centre[17,18]

The common signs and symptoms of mucormycosis depend on the part of the body where the fungus is growing. The symptoms of mucormycosis that affect the sinus and the brain are swelling on one side of the face, headache, nasal and sinus congestion, blackish discolouration on the nose bridge and palate , scabbing on the nose may also be seen, fever, toothache, swelling in the eyes and nose , blurry or double vision.The symptoms of mucormycosis that affect the lungs are fever, cough, shortness of breath, worsening of respiratory symptoms, also common in COVID-19, chest pain. Other symptoms of mucormycosis that affect the skin and the patient's gastrointestinal system are nausea, vomiting, pain in the abdominal region, blisters or ulcers on the skin, followed by the infected area turning black. Redness or swelling around the wound, sputum in the blood.

The 1950 Smith and Krichner criteria for the clinical diagnosis of mucormycosis are still considered to be gold standard [19,20] and include black, necrotic turbinate's easily mistaken for dried, crusted blood, blood-tinged nasal discharge and facial pain, both on the same side, Soft peri-orbital or peri-nasal swelling with discoloration and induration, ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia and multiple cranial nerve palsies unrelated to documented lesions. Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported world-wide, in particular from India.

The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment for low oxygen (hypoxi*a*), high glucose (diabetes, new-onset hyperglycaemia),steroid-induced hyperglycaemia ,acidic medium (metabolic acidosi*s*, diabetic ketoacidosis (DKA) , high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immune suppression (SARS-Cov-2 mediated, steroid-mediated or background comorbidities coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators [21,22]

Treatment for Mucormycosis includes rapid accurate diagnosis, surgical debridement, and administration of drugs, adjunctive application of hyperbaric oxygen, recombinant cytokines or transfusion of granulocyte and prosthetic obturator. According to Spell berg et al [23,24] currently available monotherapy shows high mortality rate especially with haematology patients and hence proposed the choice of "Combination therapy" for Mucormycosis.Antifungal therapies include (Amphotericin) AmB Deoxycholate, Liposomal AmB (5-10mg/kg), AmB lipid complex, AmB colloidal dispersion, Posaconazole (400mg bid) and manage of core conditions. Second-line treatment includes combination of caspofungin and lipid AmB, mixture of lipid AmB and Posaconazole, not grouping with Deferasirox is suggested.In case of soft tissues, cerebral disseminated, localized pulmonary lesion and rhino-orbito- types surgical treatment should be considered.

3. Conclusion

Mucormycosis is an oppurtunistic disease caused due to fungal spores which is prone to attack immunocompromised individual.Hence it is necessary to strengthen the immunity of each and every individual to fight against such infection.Mortality rate related to this disease is increased due to delay in seeking medical assistance and diagnosis of the condition.Hence it is necessary to follow the recommended treatment protocols to overcome this disease.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

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