Review Article

SARS-CoV-2 Infection and Incidence of Mucormycosis

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Abstract

With COVID 19 becoming a most important worldwide cause of concern, it is significant to comprehend the various manifestations of the disease to fully accomplish it. No country is untouched by the plague of this new disease which was first reported from Wuhan, China in December 2019. It is an infectious disease caused by novel coronavirus i-e; SARS-CoV-2. The rapid spread of this disease as well as the illness and mortality associated with this disease has led to unprecedented research into the various aspects of this disease. While respiratory catalogs are the most predominant feature of this disease, with time it has been initiate that the virus can include almost any organ in the human body. Covid-19 has overcome human wellbeing worldwide while also vigorously affecting the worldwide economy. SARS-CoV-2 has influenced more than 220 nations and domains, with roughly 4176,185 deaths so far across the globe.

Recently, Mucormycosis made serious disarray in India during the second wave (among April and June 2021) of the tragical COVID-19 upsurge by its startling and severe overflow with up to half the death rate. Mucormycosis is a deadly parasitic infection brought about by a kind of uncommon yet deft contagious microorganism called mucormycetes. While the specific reason for its sharp ascent out of nowhere and explicitly during the second wave stays disputable, it has been noticed that individuals who are diabetic and have recuperated from COVID-19

disease are more inclined to Mucormycosis. In this review, we will briefly discuss the relation between COVID-19 and Mucormycosis.

Keywords: SARS-CoV-2, Mucormycosis, Fungal infection, Mucormycetes, Black fungus

1. Introductıon

Mucormycosis is uncommon parasitic contamination brought about by openness to mucor form regularly found in soil, fertilizer, plants, rotting foods grown from the ground, air, and surprisingly in the bodily fluid of solid individuals. It influences the sinus, mind, and lungs and can be dangerous in diabetic or seriously immune compromised people. The year 2020 was annihilating for worldwide wellbeing as an extraordinary infection ruined around the world, arising quickly as one of the top executioner's discovery the insufficiencies of the wellbeing frameworks. Today, wellbeing administrations in all districts are battling to handle COVID-19 and furnish individuals with crucial consideration. India kept on keeping a descending pattern in everyday COVID-19 cases until the number of cases drifted over 3,00,000 in the lethal second rush of the contamination. As of June 7, 2021, the nation has recorded 28,252 instances of mucormycosis from 28 states. There are 24,370 cases with a background marked by COVID-19 and 17,601 cases with a past filled with diabetes. India had recorded its most elevated number (6329) of mucormycosis cases [1]**.** Mucormycosis (likewise called zygomycosis) is a serious disease carried by a gathering of molds called mucormycetes. Mucormycosis, or the destructive black fungus, is a perilous parasitic infection taken about by organisms that has a place with the subphylum Mucoromycotina and mandate Mucorales [2]. Mucorales growths are the most widely recognized parasites found in hematological malignancies, hematopoietic immature microorganism transplantation, and strong organ transplantation after Aspergillus [3]. Eleven varieties and ~27 species under the demand Mucorales cause mucormycosis [4]. Among the prevalent genera that cause mucormycosis, Rhizopus is the most well-known followed by Mucor and Lichtheimia. Mucorales are by and large found in soil, rotting food, fertilizer, and residue [5].

The principal method of disease of mucormycosis is through the inward breath of spores, utilization of defiled food, and vaccination of the organisms into scraped areas or cuts on the skin [6]. This condition can be grouped into six structures remain specific rhino-orbital cerebral mucormycosis (ROCM), pneumonic, cutaneous, gastrointestinal, spread, and exceptional locales dependent on the area of their event. Among them, ROCM is the most generally happening one. Among the species that cause mucormycosis, the Rhizopus species was connected with ROCM. Simultaneously Cunningham Ella was found in the pneumonic or dispersed structure, while Apophysomyces and Saksenaea were found in the cutaneous sort [3]. The growths start by attacking the veins, which brings about apoplexy and localized necrosis of the tissue. At the point when the spores of the growth, interacts with the endothelial cells, angioinvasion happens. More connection with the receptors of these cells brings about cell harm and infectious spread [7].

2. Condition Accompanying Mucormycosis

Mucormycosis has been related to different basic conditions that incline a person to the disease. A portion of these components incorporates diabetes, neutropenia, organ or foundational microorganism transplantation, injury and consumption, hematological problems, steroidal use, metabolic acidosis, intravenous medication utilization, renal

deficiency, a wide range of anti-infection agents, expansion in iron in the framework, lack of healthy sustenance, use of voriconazole [8]. Among the various types of mucormycosis, ROCM has been accompanying by the presence of diabetes. The cutaneous structure was more conspicuous in people with injury, and organ relocation was identified with the aspiratory, gastrointestinal, and dispersed sort. Moreover, fundamental hematological malignancies were available in dispersed sort and neutropenia in the pneumonic structure [3].

Mucormycosis happens predominantly in people with uncontrolled diabetes, and this is because the inborn invulnerability in these people, impacts the polymorphonuclear phagocytes to annihilate the growths. In patients with diabetes, the sinus was the most influenced region followed by the aspiratory regions [9]. People with hematological malignancies were additionally inclined to mucormycosis during the neutropenia period of the disease. The presence of mucormycosis in hematological malignancies can be credited to chemotherapy and the use of voriconazole utilized in the treatment of aspergillosis [10]. Transplantation treatments have additionally been analyzed as hazard factors for mucormycosis. In any case, the rate of the condition changes depending on the sort of organs that are being relocated. Since beneficiaries of transplantation treatments are directed immunosuppressants and high portions of steroids, it makes them more defenseless against mucormycosis [11]. Steroid-managed people also fall under the high-hazard class. Undeveloped cell treatment patients are treated with voriconazole which impacts the event of mucormycosis when utilized prophylactically [12]. Another factor adding to mucormycosis is iron over-burden and deferoxamine treatment, which is being utilized to treat patients with diabetic ketoacidosis, hemodialysis, and renal disappointment. Despite that, this deferoxamine treatment makes the patients bound to create mucormycosis. The iron that is taken out by the medication is utilized by the organisms to develop making a good condition for its turn of events [13]. Curiously, mucormycosis isn't simply seen in patients with comorbid conditions, and it can also be found in people after a medical procedure, presumably after utilizing sullied items [3].

3. COVID-19 and Mucormycosis

COVID-19 has sprung up the world's horde of conditions and inconveniences [14]. Mucormycosis is another achievement included COVID-19, which has arisen as a lethal inconvenience related to COVID-19. In March 2021, 41 instances of COVID-19 related mucormycosis has been accounted for worldwide and 70% were from India. There is a flood in these cases during the second wave in India [15]. The mucormycosis coming from COVID-19 affected role more commonly saw in patients with a background marked by diabetes mellitus and 95% of people with serious or basic COVID-19 [16]. A patient with intense myeloid leukemia (AML) endured mucormycosis after the COVID-19 contamination [17]. Although these components like diabetes, organ transplantation, and hematological variables are generally related to mucormycosis. Furthermore, it has been seen that individuals with no set of experiences of any hidden condition can similarly be determined to have mucormycosis post-COVID-19 disease [18]. The immunosuppressants and corticosteroid drugs that are justified in COVID-19 can contribute altogether to the event of mucormycosis [19]. Further, anyhow hyperglycemia, COVID-19 also adds to changes in iron digestion. High ferritin levels have been seen in COVID-19; the high iron fixations discharge responsive oxygen species while harming the close-by tissue. The

cytokines delivered during COVID-19 further increment intracellular iron and spillage of iron into the course, acting as a danger factor for the improvement of mucormycosis [20]. In this condition, it is clear that the utilization of anti-infection agents and steroids might be perilous for certain patients as they might trigger the beginning of these hazardous parasitic contaminations. It is critical for the specialists' treating patients with COVID-19 to be aware of patients with fundamental sicknesses and endorsed steroids or immune suppressants [21]. There are many COVID- 19 patients that have Mucormycosis. Some of the cases are discussed below.

4. Gastrointestinal Mucormycosis in COVID-19 Patient

Assimilation of the microorganisms of fungus is caused by Mucormycosis of the gastrointestinal tract. The immune competent host has infrequently stated in Mucormycosis cases of GI and the mortality rate in these cases is 85% [22]. Fever, abdominal pain, nausea, GI bleeding, and perforation are the symptoms of Mucormycosis of GI. Gastric Mucormycosis is usually a large ulcer with necrosis difficult to diagnose correctly because of non-significant clinical symptoms [23].

A case is reported of an 86-year-old male that has a history of arterial hypertension with symptoms of acute diarrhea, cough, fever dyspnea started five days ago when they diagnosed COVID-19 and admitted to the emergency room. After 5 days of admission in the emergency room, the patient's hemoglobin level is dropped from 14.3 to 5.3mg/dL after this patient requires three units of red blood cells. Esophagogastroduodenoscopy EDG showed that he has two giant gastric ulcers with necrotic debris and a deep hemorrhagic base without active bleeding and the biopsy's confirmed Mucormycosis. Unfortunately, the patient died after 36 hours of EDG [23].

5. Pulmonary Mucormycosis due to Rhizopus microspores in COVID-19 Patient

A case of the 53-year-old male patient has been reported with a medical history of obesity and depression and diagnosed with secondary acute myeloid leukemia AML and admitted to the hospital for further treatment in January 2020. After five weeks of the hospital, the patient suffers from symptoms of fever, dyssomnia, sore throat, and paralgesia and the test of RT nasal PCR confirmed SARS-CoV-2 at day 54 after orientation of chemotherapy. The patient was admitted to the intensive care unit after five days of diagnosis of SARS-CoV-2 and for the development of severe acute respiratory distress syndrome. During this period the patient suffered from severe neutropenia, lymphocyte count, or platelet count, and the patient was released from extubating as he stabilizes on day 18. But after the rapid respiratory destruction on day 22 the patient was again admitted to the ICU due to a negative nasopharyngeal swab for SARS- CoV-2 and bronchoalveolar level. The patient died on day 24 due to bad hemodynamic conditions a full autopsy was done and showed invasive Rhizopus microspores on lung tissue and to know about the fungal tissue an internal transcribed spacer ITC sequencing was performed on lung tissue and the test confirmed 100% DNA homologous to Rhizopus microspores. The patient was diagnosed in postmortem with severe pulmonary Mucormycosis to Rhizopus microspores. This report in this case tells us about the fast detection and treatment of Mucormycosis [25].

6. Rhino orbital Mucormycosis against COVID- 19

A 28-year-old male patient gave a 5-day history of abrupt vision misfortune and expanding of the right eye alongside a past filled with hack and fever. He denied any past visual injury or nasal manifestations. His past clinical diagrams administered any reason for immune suppression aside from a background marked by intense viral hepatitis-A 5 years back. The general assessment was mediocre. The visual assessment uncovered proptosis of the right eye with a conjunctival clog, chemosis, erythematous, and enlarged upper and lower eyelids. He kept discernment from getting light on the right eye with a properly expanded understudy and complete ophthalmoplegia. Assessment of another eye and nose was unexceptional. An oropharyngeal swab for turnaround transcriptase PCR (RT-PCR) was positive for SARS-CoV-2 infection with a cycle limit worth 30. The standard blood examinations were mediocre. The fasting and 2-hour postprandial glucose esteem were inside typical cut-off points with a hemoglobin A1C worth of 5.5%. A difference improved CT sweep of the nose and Paranasal sinus with circle showed right intraoral and retrobulbar delicate tissue thickness alongside mucosal thickening in the right ethmoid sinus. His chest radiograph showed diffuse reciprocal ground-glass opacities predictable with Coronavirus pneumonia. An orbital biopsy uncovered expansive aseptate contagious hyphae reminiscent of mucormycosis. Safe inadequacy disorders including HIV (ELISA test) and hypocomplementemia were precluded attributable to the presence of a pioneering contagious disease in a solid grown-up. Intravenous expansive range anti-infection agents (meropenem 500 mg threefold every day and teicoplanin 200 mg two times per day) were regulated for likely bacterial superinfection of Coronavirus pneumonia alongside liposomal amphotericin-B for rhino-orbital mucormycosis.

The presence of dynamic fulminant mucormycosis blocked the utilization of corticosteroid treatment. The patient went through right-side orbital exenteration and ethmoid sinus debridement under broad sedation with widespread insurances utilizing the ideal individual defensive gear. He had finished the course of parenteral antifungal treatment and was clinically sickness-free at 2-month follow-up period post Coronavirus recuperation. Rhino-orbital mucormycosis is an intense and fulminant parasitic contamination brought about by the Angio invasive growths of the family Mucoralean and seen ordinarily among immune-compromised subjects and patients with decompensate diabetes [26]. However, the essential site of contagious immunization is the nose and Paranasal sinuses, these forceful organisms multiply and spread to the circle and mind by direct augmentation or through hematogenous course causing rhino-orbital or the dangerous rhino-cerebral mucormycosis. The SARS-CoV-2 disease itself initiates an immunosuppressive state by influencing the T-lymphocytes causing lymphopenia, especially CD4+ and CD8+ Lymphocytes which assume an essential part in cell-intervened invulnerable reactions and cause a change of neutrophil to lymphocyte ratio [27]. The more elevated levels of incendiary cytokines saw among instances of serious Coronavirus, presence of comorbid sicknesses like diabetes mellitus and the utilization of simultaneous glucocorticoid treatment and other immune modulatory drugs for the administration of moderate to extreme cases potentiates the net condition of immune suppression inclining the patient to pioneering contagious contamination throughout illness [28]. The distributed writing on the uncommon relationship of obtrusive rhino-orbital mucormycosis among Coronavirus patients is restricted to not many case reports referring to uncontrolled diabetes as the inclining hazard factor

dissimilar to this patient who comes up short on any prior immunosuppressive state [29]. A tissue biopsy from a circle or nose showing the presence of stretched aseptate hyphae with tissue attack affirms the determination of mucormycosis, while contrast-improved CT and X-ray of the nose and Paranasal sinuses with circle and mind can distinguish the degree of contamination and difficulties. Fundamental antifungal treatment, early complete careful debridement, and the board of hidden inclining conditions are the backbone of treatment [30]. A clinical and radiological observe-up is obligatory to preclude any repeat and regardless of ahead of schedule and forceful therapy, rhino-orbital mucormycosis conveys a helpless forecast.

7. Discussion

The SARS-CoV-2 disease may adjust the resistant background by influencing T lymphocytes, especially CD4+ and CD8+ T cells, which may be exceptionally engaged with the obsessive course of COVID-19 contamination [31]. The critical decrease of without a doubt the number of lymphocytes and explicitly of T cells depicted in the most extreme COVID-19 cases is related with the most exceedingly terrible result and may open patients to a higher danger of creating shrewd contaminations [32]. Mucormycosis which is a parasitic disease is brought about by an impedance of bronchial alveolar macrophages; however, a job of T-cells was portrayed as a feature of the versatile invulnerable outline, in a concise report on a gathering of hematological patients who experienced mucormycosis portrayed Mucorales-explicit T-cells (CD4+ and CD8+), that were dynamic against Mucorales by delivering cytokines, for example, IL-4, IL-10, IL-17 and IFN-γ, which could straightforwardly harm Mucorales hyphae [33].

Moreover, SARS-CoV-2 contamination itself may trigger a modification of the invulnerable framework and this is the main announced instance of astute co-disease brought about by Rhizopus spp including lungs with broad parenchymal harm [31]. In one study, the appearance of COVID 19 caused SARS CoV2 contamination in patients admitted to the intensive care unit. Moderate to severe respiratory distress (ARDS) induced closed pneumonia aspergillosis as a result of confirmed loss of resistance was observed [34]. Also, in the current case, neither corticosteroids nor immunosuppressant treatments were managed, however, the patient showed an extreme type of COVID-19 with numerous organ dysfunctions and a critical and supported lymphopenia with N/L proportion change; the last has been as of late depicted to be exceptionally connected with the most serious clinical show and the most noticeably awful result [31]. In actuality, the patient's oxygenation started to further develop when lymphocytes expanded and N/L proportion diminished, and the aspiratory cavitary injury opened into the pleural space. In spite of the fact that molds couldn't be secluded in the pleural radiation, careful investigation to eliminate necrotic sores ought to be considered to annihilate the form contamination and further develop the patient's result [35]. The European Confederation of Medical Mycology Mucormycosis Guidelines emphatically proposes an early careful therapy to eliminate the tainted tissue (either through nearby debridement or complete resection) anyhow fundamental antifungal therapy [30].

8. Conclusion

Coronavirus has placed the whole world in unrest circumstances, and an accurate solution for this dangerous disease has not been found at this point. The COVID-19 influenced patients who are more defenseless to these diseases are immune

compromised, have diabetes, and are recommended weighty steroids. As mucormycosis is Angio invasive when breathed in, its spores start to develop, and the contagious hyphae attack the veins, further adding to tissue localized necrosis, corruption, and apoplexy. This parasitic disease is perilous as it happens among the individuals who have immunosuppression went with diabetic ketoacidosis, neutropenia, expanded serum levels of iron, overabundance arrival of sugar due to overwhelm of steroids which at last outcomes in a diminishing in degrees of WBCs, T-cells and other immune modulatory cells and triggers the cytokine storm that harms the cell organs. Consequently, specialists and medical care experts ought to expeditiously control this mucormycosis disease by understanding its impact and scope of seriousness, particularly on COVID-19 patients. A multidisciplinary approach ought to incorporate brief findings, treatment with antifungals, any suitable careful counsel, and treatment, which might turn around the basic condition. Henceforth lively examinations to accentuate the underlying driver of mucormycosis, explicitly in COVID-19, ought to be under the extent of the exploration. An indicative report for this entrepreneurial microbe ought not to be overlooked in the event that the patient is COVID-19 positive and immunosuppressed.

Contribution

All authors contributed equally.

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