

Mucormycosis Review in Post Covid Patients

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Abstract

Mucormycosis (recently called zygomycosis) is a genuine however uncommon contagious disease brought about by a gathering of molds called mucormycetes. These molds live all through the climate. Mucormycosis essentially influences individuals who have medical issues or take drugs that bring down the body's capacity to battle microorganisms and disorder. A forceful fulminant intrusive contagious disease can happen in patients with different hastening variables like uncontrolled diabetes, renal disappointment, organ relocate, long haul corticosteroid and immunosuppressive treatment, cirrhosis, consumes, acquired immunodeficiency syndrome and malignancies like lymphomas and leukemia's. Deliberate audit of different examinations detailing presence of mucormycosis in post coronavirus patients was finished. The review was led to survey the effect of mucormycosis on patients experiencing an infection.

Mucormycosis can be isolated into somewhere around six clinical conditions: rhino-orbital-cerebral, aspiratory, cutaneous, gastrointestinal, spread, and various. Investigation of post Coronavirus patients showed four clinical indications rhino-orbital-cerebral disease (3 exploration papers revealing one case each and 1 examination paper with 4 patients); pulmonary disease (3 exploration papers with 4 cases); gastrointestinal disease (1 examination paper with 1 case) and disseminated (1 exploration paper with 1 case). Out of these complete thirteen patients, seven were accounted for dead. According to Worldometer, roughly 88 million instances of COVID19 have been accounted for so far of which almost 1.9 million surrendered to death. Albeit the announced information identifying with presence of mucormycosis in Covid patients is exceptionally small, yet the casualty rate is in excess of 50%. The circumstance is disturbing. Comprehensive investigations should be attempted as postponed determination and insufficient treatment might prompt higher danger of adverse results.

Keywords: COVID-19; COVID-19-Associated Mucormycosis (CAM); Mucormycosis

Introduction

Mucormycosis, the third intrusive mycosis arranged by significance after candidiasis and aspergillosis. The term '*Mucormycosis*' is utilized all through this survey of contaminations brought about by *Mucorales*. The class *Zygomycetes* is isolated into two orders, *Mucorales* and *Entomophthorales*. Individuals from the request *Mucorales* are the aetiological specialists of the sickness customarily known as '*Mucormycosis*', a fulminant illness with high paces of dismalness and mortality that chiefly influences immunocompromised patients. Nonetheless, types of the request *Entomophthorales* are liable for the persistent subcutaneous illness saw in immunocompetent patients in tropical and sub-tropical regions. The fundamental danger factors for the improvement of *Mucormycosis* are ketoacidosis (diabetic or other), iatrogenic immunosuppression, particularly when related with neutropenia and unite versus have illness in hematological patients, utilization of corticosteroids or deferoxamine, disturbance of mucocutaneous hindrances by catheters and different gadgets, and even openness to swathes debased by these fungi [1]. The aetiological specialists associated with the infection have been reclassified because of changes in scientific categorization and terminology, which likewise prompted fittingly naming the sickness '*Mucormycosis*' [2]. Patients getting this contamination consistently experience the ill effects of inclining conditions: acidosis, uncontrolled diabetes mellitus, leukemia, lymphoma, AIDS, extreme malnourishment, serious consumes, cytotoxic treatment, and resistant concealment from corticosteroid use. It has additionally been seen in patients with constant renal disappointment, liver issues, and dialysis patients on deferoxamine therapy. There are no realized inclinations dependent on age, race or sex. Most cases are intense careful crises, however a couple of persistent, inactive structures have been accounted for with signs and indications creating more than a 4-week time frame. The essential locales of attack are the paranasal sinuses, lungs, skin, and the GI tract. Clinical manifestations, signs, and neurotic discoveries are comparative in *Mucormycosis*, paying little heed to etiology.

These parasites show a preference for blood vessel attack, causing broad emboli and corruption of encompassing tissues.

Vein and lymphatic attack can happen later over the span of the infection. The acidotic, hyperglycemic climate existing in patients with ketoacidotic diabetes mellitus especially inclines toward the development of Rhizopus. It is believed that diabetic and immune compromised patients need ordinary phagocytic movement on their nasal and oral mucosal surfaces. This permits expansion of parasite, which doesn't happen in individuals with unblemished phagocytic movement, and the growth spreads through the veins. Rhino cerebral contamination is the most well-known structure, as a rule found in patients with ketoacidotic diabetes mellitus. This structure gives sinusitis, facial and eye torment, proptosis, advancing to indications of orbital construction inclusion. Necrotic tissue can be seen on the nasal turbinates, septum, and sense of taste. This might resemble a dark eschar. Intracranial inclusion creates as the parasite advances through either the ophthalmic vein, the predominant crevice, or the cribiform plate [3].

Epidemiology

The most widely recognized specialists of Mucormycosis are *Rhizopus spp.*, *Mucor spp.*, and *Lichtheimia* (previously *Absidia* and *Mycocladius*) spp. Genera of other *Mucorales*, like *Rhizomucor*, *Saksenaea*, *Cunninghamella*, and *Apophysomyces*, are more uncommon. Etiology of mucormycosis fluctuates extensively in various nations. For instance, *Rhizopus spp.* (34%), *Mucor spp.* (19%), and *Lichtheimia spp.* (19%) were most regularly distinguished in patients with Mucormycosis in Europe. In India, in spite of the fact that *Rhizopus* species are the most widely recognized reason for the illness, *Apophysomyces elegans*, *A. variabilis* and *Rhizopus homothallicus* are arising species and exceptional specialists, for example, *Mucor irregularis* and *Thamnostylum lucknowense* are additionally being reported. The rate of Mucormycosis has been expanding in late many years, predominantly because of the development of the quantity of seriously immunocompromised patients. Presently Mucormycosis cases are being accounted for from everywhere the world, however contrasts in the study of disease transmission appear to exist among created and agricultural nations. In created nations, the sickness stays remarkable and is for the most part found in patients with Hematological Malignancies (HM). Interestingly, in non-industrial nations, particularly in India, Mucormycosis is more normal and cases happen principally in patients with uncontrolled Diabetes Mellitus (DM) or trauma. Accordingly, the pervasiveness of Mucormycosis differs from 0,01 to 0,2 for each 100 000 populace in Europe and the United States of America and is a lot higher in India (14 for every 100 000 populace). The most widely recognized clinical introductions of mucormycosis are rhino-orbito-cerebral, pneumonic, cutaneous, and dispersed. In India rhino-orbito-cerebral show related with uncontrolled DM was the transcendent trademark, and separated renal mucormycosis has arisen as another clinical element. In a huge report from Mexico, looking into 418 cases, diabetes was the hidden illness in 72% of patients, and it was related with sinusitis. In the gathering of patients with basic malignancies, aspiratory and sinus introductions were similar [4].

Disease manifestation

Mucormycosis is more uncommon than other deft parasitic contaminations, for example, those brought about by *Candida* and *Aspergillus spp.* One populace based review assessed the frequency of mucormycosis to be 1.7 cases per million individuals per year, which means around 500 cases each year in the United States (126). In examination series, the pervasiveness of mucormycosis has gone from 1 to 5 cases for every 10,000 dissections, making the contamination 10- crease to 50- crease more uncommon than obtrusive *Candida* or *Aspergillus* diseases (56,154,178). At last, in patients at higher danger, for example, those going through allogeneic bone marrow transplantation, the predominance of mucormycosis has been depicted to be pretty much as high as 2% to 3% (90,96). In light of clinical show and the contribution of a specific anatomic site, mucormycosis can be isolated into no less than six clinical classes: (I) Rhinocerebral, (ii) aspiratory, (iii) cutaneous, (iv) gastrointestinal, (v) scattered, and (iv) random. Of note, these classes of obtrusive mucormycosis will quite often happen in patients with explicit imperfections in have protection. For instance, diabetics in ketoacidosis commonly create the rhinocerebral type of the illness, and considerably more once in a while foster pneumonic or scattered sickness. The system for ketoacidosis specially making powerlessness the rhinocerebral type of the illness stays hazy. As referenced before, patients in ketoacidosis, or without a doubt any foundational acidosis, have expanded accessible iron in serum because of separation of iron from sequestering proteins in acidic conditions. Notwithstanding, the dominating show of mucormycosis in the setting of deferoxamine treatment is dispersed sickness, demonstrating that expanded accessible iron can't, without help from anyone else, clarify the particular event of rhinocerebral illness in ketoacidosis. Besides, while it is realized that hyperglycemia and acidosis adversely sway neutrophil chemotaxis and phagocytic action, these perceptions can't clarify the particular event of rhinocerebral illness in diabetic ketoacidosis on the grounds that neutropenic patients more usually create aspiratory mucormycosis than rhinocerebral disease. Major hazard factors for mucormycosis in the transfer setting incorporate basic myelodysplastic disorder (potentially because of iron over-burden from rehashed blood bondings) and graft-versus-host sickness treated with steroids. Organization of antithymocyte globulin may likewise represent a danger for mucormycosis. Albeit not exactly 50% of these patients are neutropenic at the hour of illness beginning, drawn out neutropenia is a danger factor for mucormycosis in this setting, as are diabetes mellitus and steroid use. The job of antifungal prophylaxis in inclining patients to creating mucormycosis is progressively being depicted, as talked about further beneath. Prophylaxis with one or the other itraconazole or voriconazole has been embroiled in inclining to mucormycosis.

Rhinocerebral mucormycosis-Rhinocerebral mucormycosis keeps on being the most widely recognized type of the sickness, representing between 33% and one-half of all instances of mucormycosis. Around 70% of rhinocerebral cases (once in a while alluded to as craniofacial) are found in diabetic patients in ketoacidosis. All the more infrequently, rhinocerebral mucormycosis has likewise happened in patients who got a strong organ relocate or those with delayed neutropenia. As of

late, rhinocerebral infection has been an expanding issue in patients going through hematopoietic immature microorganism transplantation. These cases have to a great extent been related with steroid use for unite versus-have illness. The underlying indications of rhinocerebral mucormycosis are reliable with one or the other sinusitis or periorbital cellulitis and incorporate eye or facial torment and facial deadness, trailed by the beginning of conjunctival suffusion, hazy vision, and delicate tissue expanding. Fever is variable and might be missing in up to half of cases. White platelet counts are ordinarily raised, as long as the patient has working bone marrow. If untreated, disease as a rule spreads from the ethmoid sinus to the circle, bringing about loss of extraocular muscle work and proptosis. Checked chemosis may likewise be seen. The disease may quickly stretch out into the adjoining tissues [5].

Pathogenesis

Mucorales assault profound tissues through ingestion or inward breath of spores, and percutaneous infusion of spores. When the spores enter into lung or cutaneous tissues, the principal line of guard in the sound host is equipped for annihilating the spores through oxidative metabolites and cationic peptides. Hazard factors incorporate uncontrolled diabetes mellitus, particularly ketoacidosis, steroid use, limits old enough, neutropenia; particularly with hematological harm, AIDS, renal deficiency, organ or foundational microorganism transplantation, iron over-burden, skin injury, wide range anti-infection agents, intravenous illicit drug use, prophylactic voriconazole for aspergillosis and hunger. In diabetic patients, mucormycosis happens as a ruinous and conceivably basic condition because of expanded accessibility of micronutrients and decreased protection instrument of the body. Different speculations incorporate (i) Low serum inhibitory action against *Rhizopus* species, (ii) improved accessibility of iron for the microorganism at diminished PH level and (iii) pulmonary macrophages of people with diabetes mellitus show decreased office to repress germination of *Rhizopus* species. Ketone reductase in *Rhizopus* permits the life form to expand the glucose and acidic climate. In DM especially with ketoacidosis all sorts of mucormycosis will happen. Neutrophils assume a significant part in have protection against mucorales. Its capacity is debilitated at various level in DM. Ketoacidosis in diabetes speed up the parasitic invasion 16. The acidic milieu creates all the more free iron by lessening its limiting to transferrin and low degree of dialyzable inhibitory element in diabetics present reasonable conditions for parasitic duplication. Death rate was accounted for 90% or significantly more with Mucormycosis, before the organization of amphotericin B and revolutionary medical procedure. Seriously neutropenic patients and the individuals who need phagocytic capacity are more inclined for mucormycosis. However, it's not same on account of AIDS patients. It infers that the T lymphocytes are not critical for restraining contagious multiplication however just the neutrophils. Drawn out organization of voriconazole, mainly among the patients with hematological malignancies and hematopoietic undifferentiated cell transfers are more inclined for mucormycosis. Additionally mucormycosis is likewise found in patients with next to no conspicuous safe deficiency. In such

conditions, it could be connected with consumes, injury as well as aligned with iatrogenic factors [6].

Laboratory diagnosis

In a wide range of mucormycosis Neutrophils assume a significant part in have guard against mucorales. Its capacity is hindered at various level in DM 10,11,15. Ketoacidosis in diabetes speed up the contagious attack. The acidic delivers all the more free iron by decreasing its limiting to transferrin and low degree of dialyzable inhibitory variable in diabetics present reasonable conditions for parasitic duplication. Death rate was accounted for 90% or considerably more with mucormycosis, before the organization of amphotericin B and extremist medical procedure. Seriously neutropenic patients and the people who need phagocytic capacity are more inclined for mucormycosis. In any case, it's not same on account of AIDS patients 19. It suggests that the T lymphocytes are not huge for hindering contagious expansion however just the neutrophils. Drawn out organization of voriconazole, primarily among the patients with hematological malignancies and hematopoietic foundational microorganism transfers are more inclined for mucormycosis. Additionally mucormycosis is likewise found in patients with no conspicuous resistant lack. In such conditions, it very well might be connected with consumes, trauma [7].

The analysis of COVID-19 depended on RT-PCR test on nasopharyngeal/oropharyngeal swabs. Proven mucormycosis was characterized as histopathologic, cytopathologic or direct tiny assessment showing contagious hyphae in biopsy example with related tissue harm, or a positive culture result. Probable mucormycosis was closed as the presence of consolidated host factors and clinical measure with mycological proof and if by some stroke of good luck the models for a host factor and a clinical rule were met however mycological rules were missing, possible mucormycosis was diagnosed. a profound nasal swab was sent for KOH mount and parasitic culture dependent on the clinical doubt. Attractive reverberation imaging (MRI) circle, cerebrum, and paranasal sinuses with or without processed tomography (CT) was performed for surveying degree of the sickness. In view of the underlying report of nasal swab and radiographic elements, fundamental antifungals were started related to otorhinolaryngology and irresistible sickness subject matter experts. Liposomal amphotericin B (5 mg/kg/day, up to 10 mg/kg/day for CNS diseases; staying away from slow heightening) was given intravenously (IV) with checking of renal parameters [5]. Endoscopic sinus debridement with biopsy was performed and example was sent for histopathology, microbial science for culture, and affectability test. Oral antifungal, posaconazole (stacking portion 300 mg two times every day right off the bat, upkeep portion 300 mg orally one time per day, beginning the subsequent day) was started dependent on culture and histopathology report. Orbital exenteration was performed by the eyelid saving method with cross over blepharorrhaphy in patients with imperfect reaction to fundamental antifungals in 72 hours. Postoperatively, long haul oral antifungal treatment was continued [8].

Laboratory findings

The bacterial and contagious co-diseases have been reported in patients experiencing serious intense respiratory condition (SARS), Middle East respiratory disorder and flu, yet the information on co-contaminations especially parasitic diseases among basically sick COVID-19 patients is limited. Accordingly, focusing on deft contagious diseases in COVID-19 patients, with a rundown of inclining factors, is significant for medical care suppliers who are going up against the COVID-19 pandemic. COVID-19 patients experiencing ARDS, the individuals who require an extended stay in an emergency unit and mechanical ventilation, taking high dosages of corticosteroids, immunomodulators, interleukin adversaries and expansive range anti-toxins, are at complex danger to foster parasitic diseases like mucosal candidiasis, aspergillosis, mucormycosis, pneumocystis jiroveci pneumonia and candidemia. There is a scarcity of information in regards to the pace of COVID-19-Related Mucormycosis (CAM). In view of imaging, intra-usable endoscopic perception and histopathology assessment, Rhino-Orbital Mucormycosis (ROM) was the most incessant type of mucormycosis as proven in seven (47%) of COVID-19 patients, Sino-Orbital Mucormycosis (SOM) involved 33% of the patients, 13% had disconnected orbital association, and one patient (7%) was impacted by Sinonasal Mucormycosis (SM). No quiet had aspiratory mucormycosis. The most well-known type of paranasal sinus contribution was pansinusitis. In ten (67%) cases, mucormycosis was reached out to skull base spaces. Among patients, 53.3% had pterygopalatine fossa association. Huge sinus association created in seven cases (46%) [9].

Clinical records showed white platelets count was not exactly ordinary, C-Responsive Protein (CRP) raised (35 mg/dl; furthest cutoff standard 5 mg/dl), D-dimer at typical reach. Chest x-beam uncovered respective basal coarse reticular opacities. RT-PCR (Real-Time Polymerase Chain Reaction) from oropharyngeal swab was positive for crown. The patient conceded to ICU, showed further decay and hypoxemia (pO₂ 46 mmHg). There was an undeniable degree of Creatinine, raised neutrophils, CRP levels showed 140 mg/dl, white platelets actually raised (12.75*10⁹ per L) interleukins-6 was at 365 ng/ml and ferritin 450 ng/ml, just lymphocytes were ordinary [6]. Upon second day affirmation in ICU, the patient was additionally intubated and precisely ventilated. Chest x-beam uncovered movement in respective invades with aspiratory crumbling. Further, remain in ICU, endotracheal yearning was acquired from the patient and culture test was finished. Culture developed *Aspergillus* disinfects voriconazole with contagious like development. Horizontal stream gadget responded to *Aspergillus* explicit antigen however non colonized. Serum contagious markers gave positive indications of dark parasitic development. Galactomannan and 1,3-beta-D-glucan marker was utilized to distinguish the parasitic development. This parasitic development was exposed to treatment, in spite of endeavors the patient perished on the fifth day in ICU. Mucormycosis is dangerous causing loss of visual perception, hearing hindrance and extreme coronary failure and synapse misfortune. Each of the seven patients in various age gatherings, gentle or unforgiving parasitic disease have kicked the bucket. After broad hunt and concentrate on mucormycosis and with practically no aftereffect of diaries on this lethal

growth, one query item lead to another specialist, Yang et al. observed a little higher level of individuals impacted by this infection. Numerous patients were treated with hostile to parasitic medication however were to no end. One more German review related with COVID-19 tracked down 6 out of 19 patients contaminated with dark parasitic. In the Netherlands, there were new instances of dark organism, tainting with *A. fumigatus*. In France, there were 5 patients contaminated with *A. flavus* by tracheal suction culture.

Numerous occurrences in that period have found coronavirus with contagious disease increment from 16%-27%, with seriously sick patients passing on. Most level of them with mucormycosis has kicked the bucket since the start of this parasitic rate started. The beneath figure shows penicillin in mucormycosis. Some finding like anti-toxins has postponed this parasite. It is basic to focus on this mucormycosis in current COVID-19 patients [10].

Discussion

In enormous number of clinical cases, it has been accounted for that aspiratory mucormycosis as a perilous parasitic disease. It likewise bring about decimating and ongoing sickness result if neglect to analyze early and definitively. The whole drug; utilization of antifungal therapeutics depends on exact and early analysis of parasitic contamination. Here, during ongoing condition of aspiratory mucormycosis nasal cannula is fundamental for seven days. For this situation study, we report a steady state of patient yet need to intubate. Thinking about COVID 19 and relationship with lung 125 mg methylprednisolone was managed with lessening three portions of 40 mg for three every week. The case was overseen effectively with utilization of methylprednisolone. Further, a patient was gradually weaned off from O₂ backings. PICC line was held under clean aseptic precautionary measure. Irregular fever spikes were noted, blood culture sent from PICC line uncovered development of pain sensitive *Klebsiella*, proceeded with a similar anti-toxin imipenem. During the course, patient had hypokalaemia and hypomagnesemia, and the adjustment was given. Likewise, creatinine levels began rising, and the most extreme was up to 1.52. Hyponatremia was likewise there. Hidden diabetes has been overseen successfully. Rehash PET CT showed incomplete metabolic reaction when contrasted with the past examine. Following a month and a half, Liposomal Amphotericin B halted and changed to oral Posaconazole at release. The patient came for follow-up following one month of verbal Posaconazole course [11]. The greater part of the patients in our series were male, a pattern that has been reliably revealed in the event that series from various nations. The most widely recognized basic illness in our series was DM. DM is related with disabled neutrophil work, microvascular deficiency, and on account of ketoacidosis, other metabolic irregularities that advance parasitic development. *Rhizopus* species have an dynamic ketone reductase framework and flourish in high glucose and acidotic conditions. These patients likewise have diminished phagocytic movement as a result of debilitated glutathione pathway. Ordinary serum restrains *Rhizopus* while serum of the diabetic ketoacidosis patients invigorates its

development. Outstandingly, in our series, 4 patients gave diabetic ketoacidosis. In a progression of 28 MCM cases, 64% cases had DM and 55.6% of those cases had diabetic ketoacidosis, an extent like our discoveries. Nonetheless, in other series, difficulties related with DM represented just 17% of instances of MCM. Persistent renal inadequacy is another condition that inclines to MCM infection. In the biggest case series, patients with hematological malignancies (predominantly intense leukemia) address the gathering with the most noteworthy pervasiveness and with quickly expanding paces of MCM. In our series 6 of our patients had hematological malignancies, and in all cases these were intense leukemia (ALL and AML). In spite of the fact that neutropenia has additionally been hailed as a significant element in the advancement of MCM, just 2 of our patients with ALL gave neutropenia. The most normal signs and manifestations were fever, rhinorrhea, and migraine, while the most inauspicious indication was vision loss [12].

Microbiological and radiological determination alongside treatment got and Potassium Hydroxide (KOH) wet mount and contagious culture/affectability were finished from biopsy got during debridement or from nasal swab got during analytic nasal endoscopy. Microbiological finding of mucormycosis was demonstrated in six patients. Invert Transcriptase Polymerase Chain Response (RT PCR) tests for COVID 19 were positive in all the patients. All patients in our series were known diabetics. Diabetic Ketoacidosis (DKA) was evident in four patients during affirmation while five additional patients created DKA after the inception of corticosteroid treatment for COVID 19 sickness. All patients in our series had gotten intravenous dexamethasone for COVID 19 infection according to the national institute of health suggestion and Liposomal Amphotericin B for mucormycosis. Additionally, four patients got an infusion of Remdesivir, and nine patients needed ventilatory help during their medical clinic stay. The utilization of steroids, monoclonal antibodies, and broad spectrum anti-infection agents for the administration of COVID 19 disease can expand the odds of new onset of parasitic contamination or compound a prior one. All patients in our series had gotten intravenous dexamethasone. COVID 19 illness and Liposomal Amphotericin B for mucormycosis. Four patients in our series lapsed inside one month of the finding, five patients had agreeable foundational results, however with irreversible vision misfortune, while just a single patient had both visual and fundamental positive results. COVID 19 illness has an inclination to cause broad pneumonic infection and resulting alveolo interstitial pathology. This without anyone else may incline to intrusive parasitic contaminations of the aviation routes including the sinuses and the lungs. Furthermore, there is an adjustment of the inborn in susceptibility because of COVID 19 associated safe dysregulation described by diminished T cells, including CD4 and CD8 cells. All doctors including ophthalmologists ought to, hence, be aware of the likelihood of improvement of fungal infections such as mucormycosis in patients with COVID 19 illness, especially in those with comorbidities and on immunosuppressive agents in the coming future [13].

Conclusion

The development of mucormycosis can probably be attributed to the use of glucocorticoids and suggests a need for their judicious use. Thus, the use of glucocorticoids in mild COVID-19 cases (without hypoxemia) or the utilization of higher doses of glucocorticoids should be avoided. Further, in the absence of a clear benefit, drugs targeting immune pathways such as tocilizumab should be discouraged. Early diagnosis and timely management are necessary to improve outcomes in pulmonary mucormycosis [14].

In this context, new tools of molecular biology have been developed to obtain earlier diagnosis and start optimal medico-surgical treatment. Comparative studies are needed to better optimize induction and consolidation treatment [15].

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