High Mortality Fungal Co-Infection of Covid 19-Mucormycosis: A Case Review

Short Title: Fungal co-infection-Mucormycosis

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Abstract:

The immunocompromised patients who have uncontrolled diabetes, transplants, or long-term corticosteroid therapy are the ones who contract mucormycosis the most frequently, but it can also affect those who have been injured, have pathology, or use injectable drugs. The study summarises the consequences, diagnosis, and prevention of mucormycosis in COVID-19-positive hospitalized diabetic patients, as well as the ramifications of the pandemic. Only occurrences or case series reports with appropriate information regarding risk factors, clinical presentation, course, diagnosis, therapy, and prognosis were included in this research because it was conducted using material found on PubMed. We identified eight patients with pulmonary Mucormycosis and six patients with rhino-orbital-cerebral disease. Despite the fact that 10 (71%) of the patients were males with a median age of 58.5 years (IQR 38-79) and 29% of them were females with a median age of 46.5 years, 8 (8/14, or 57% of the patients) had risk indicators for severe COVID-19 (IQR 32-61). Co-infection is prevented and controlled by using a sterile mask, avoiding touching of the nose, eye mouth, control over steroid medication, and controlling diabetes and other conditions in an exceedingly regulated manner.

Keywords: Mucorales, Rhinocerebral, Mucormycosis, Diabetes, Covid-19

Highlights:

- Mucormycosis is a potentially lethal fungal infection that is carried out by mucormycetes.
- Angioinvasion, mycotic thrombosis, and ischemia necrosis of tissues are all symptoms of mucormycosis of the orbit, which is a vision-threatening and potentially fatal illness.
- Uncontrolled diabetes mellitus, hematologic malignancies, transplants, and long-term corticosteroid therapy are major risk factors of mucormycosis.
- The most common clinical manifestation is Rhinocerebral mucormycosis.
- Early identification, elimination of risk factors and underlying conditions, surgical debridement, and prompt intravenous antifungal medication etc. are all advised for the control of the infection.

Introduction: Over 130 million people worldwide have been impacted by the COVID-19 epidemic, which is caused by the severe acute respiratory syndrome virus 2 (SARS-CoV-2). As of the publication date of this article, over 3.0 million people have died as a result of the epidemic. However, serious COVID-19 problems have been related with aspergillosis (the entity is coined COVID-19-associated aspergillosis or CAPA). The mechanism and precise scope of CAPA are still unknown because there aren't many cases of the same that have been biopsy-documented (1,2).

Furthermore, poorly managed Diabetes Mellitus (DM) and other co-morbidities are risk factors for both severe COVID-19 and Mucormycosis (MCR), and corticosteroids are frequently used to treat serious/critical COVID-19, therefore Mucorales infections seem to be a matter for concern. A risk factor for MCR has been discovered as COVID-19 (3,4). This deadly fungus is produced by moulds from the Mucoromycotina subphylum of the Mucorales order (5). However, it has also been seen in immunocompetent adults with diabetes, penetrating trauma, iron overload, and injectable medication use. Mucormycosis is most common in immunocompromised patients, such as those with hematologic malignancies, transplants, or long-term corticosteroid usage (6). In MCR, infections frequently occur in the skin, gastrointestinal tract, lungs, sinuses, and skin.

T lymphocytes are affected by SARS-CoV-2 infection, mainly CD4+ and CD8+ T cells, which are thought to be particularly significant in the pathological state of COVID-19 infection (7). According to the most severe COVID-19 cases, the stressful consequence is associated with a significant decline in the absolute number of lymphocytes, particularly T cells, and it may put patients at an elevated risk of contracting opportunistic infections (8). Mucormycosis can be perplexing for immunocompromised patients. Solid organ transplants and neutropenia, which are frequently documented in patients with haematological malignancies, were the only patients with pulmonary Mucormycosis risks, according to a recent systematic analysis by Jeong et al (9). Researchers studied a group of COVID-19 patients who had been hospitalised for moderate to severe acute respiratory distress syndrome (ARDS) and had developed invasive pulmonary aspergillosis as a result of immunological paralysis brought on by SARS-CoV-2 infection (10). As a result, it's possible that SARS-CoV-2 infection can cause an immunological condition, putting the patient at risk of getting opportunistic infections like moulds. Mucorales is a fungal problem with an extremely hostile

potential for contiguous spread and a bleak prognosis if it is not accurately and promptly identified and controlled (11). Angioinvasive hyphae arise as a result of spore inhalation and/or planting onto the airways or any other susceptible epithelium. Host variables such hyperglycemia, ketoacidosis, iron overload, and neutropenia that promote endothelial damage, resulting in local haemorrhage, thrombosis, and necrosis, as well as eventual dissemination to various organs, dictate the persistence and severity of the MCR infection (12,13). Even in healthy people, steroid medication (such as Dexamethasone) can cause hyperglycaemia, which can develop to corticosteroid-induced diabetes. Immunosuppression, cytokine storms, excessive spore load, and hyperglycaemia are the main problems for Mucormycosis patients in Covid-19 (14,15). Hyperglycemia, acidosis, and high dose corticosteroid therapy paralyse the capacity and phagocytic capacities of phagocytes, the principal host defence mechanism against Mucormycosis (16,17).

Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia are some of the fungi that can cause angioinvasive mucormycosis. With an estimated prevalence of 0.14 cases per 1000 persons, mucormycosis is approximately 80 times more prevalent in India than in wealthy nations. Fungal infection and COVID-19 infection have been associated (18,19). It's more common in immunocompromised people, and complications including orbital and cerebral involvement are more frequent in diabetic ketoacidosis and when steroids are taken at the same time. The most common complication of Mucormycosis in India is ocular problems (20). Only a few cases of Mucormycosis have been recorded in the context of the COVID-19 pandemic, however there are no known verified examples of abrupt start of vision loss associated with incidental COVID-19 infection in young non-ketonic diabetic patients (21).

Mucormycosis diagnosis requires a high conceptualization index, knowledge of host factors, and fast evaluation of clinical symptoms. On radiography, mucormycosis is associated with many (10) nodules and pleural effusion (22). Another X-ray (CT) scan finding that seems to point to the presence of Mucormycosis is the reverse halo sign (RHS) (23). In a recent study of sequential thoracic CT images in leukemic patients with neutropenia, the RHS was observed in 15 of 16 patients (94%) within the first week of the disease. Later, further radiologic abnormalities such as many nodules appeared (24). Another recent imaging technology that may eventually help in the diagnosis and treatment of Mucormycosis is Positron Emission Tomography-Computed Tomography (PET/CT) (16) with F-fluorodeoxyglucose (FDG) (25). When possible, endobronchial ultrasound-guided fine needle aspiration is another effective diagnostic method (26). Microscopy (direct and histopathological) and culture of diverse clinical specimens are used to identify

mucormycosis. Galactomannan, histoplasma antigen, and beta-d-glucan (BDG) are examples of fungal antigens that can be found in bodily fluids and are regarded to be clinically useful for a minimum of invasive fungal infection presumptive diagnosis. Numerous fungal organisms, such as the often-observed Candida species, Aspergillus species, and Pneumocystis jirovecii, have the antigen -d-Glucan (27). With repeated negative BDG and X-ray, CT scan & microbiology tests, infections of these fungal infections can be differentiated from other fungal infections.

As a result, the study's main goal was to look at the complications and diagnosis of mucormycosis in diabetic patients hospitalised with COVID-19, as well as the implications of results made throughout the pandemic. The secondary goal was to investigate the diabetic patients' overall observations and experiences throughout their stay, as well as to discover areas for improvement in diagnosis, prevention, control, and enlightenment towards future pandemics. Mucormycosis is a very dangerous complication that is also extremely difficult to diagnose and cure in a pandemic situation. The review summarises the diseases' pathophysiology, diagnosis, therapy, and complications, allowing health professionals to think critically and successfully manage the condition.

Materials and Methods

The present review has been carried out on the basis of information recorded on the PubMed (December 2020 - May 2021) by "COVID-19", "SARS CoV-2", "new coronavirus infection", "Mucormycosis", "Mucorales", "non-aspergillus mould", "Mucor", "Rhizopus", "Rhizomucor", "Cunninghamella", and "Lichtehimia" ("Absidia"). Original studies, case or case series reports, reviews with enough information about Mucormycosis and COVID-19, and targeted publications from India were included in this review.

Results

As a result, 14 patients were found, as shown in Tables 3 and 4. We discovered six patients with rhino-orbital-cerebral illness and eight patients with pulmonary Mucormycosis. 10 (71%) of the participants had a median age of 58.5 years (IQR 38-79) and 29% had a median age of 46.5 years (IQR 38–79). (IQR 32-61). There were eight patients who showed COVID-19 risk characteristics (8/14, or 57%).

Six patients (6/14, 43%) had diabetes, two (2/14, 14%) had uncontrolled diabetes prior to admission, three (3/14, 21%) had newly started diabetes, one (1/14, 7%) was in diabetic

ketoacidosis (DKA), and the others had diabetes with normal blood sugar levels at the time of presentation.

Six patients had "moderate" COVID-19, while thirteen (13/14, 93%) of the 14 patients with information on COVID-19 severity had "critical" COVID-19, requiring mechanical breathing or non-invasive ventilation. Despite the fact that only six patients had accessible neutrophil and lymphocyte counts, only one experienced neutropenia (neutrophil count 500/microliter) and three experienced lymphocytopenia (total lymphocyte count 1000/microliter). On genus-level identification of Mucorales (14 patients; 77%), Rhizopus species were isolated in 10 people. The patients had an average of 19 days before receiving the MCR diagnosis.

It was also discovered that cilizumab was given to two of the nine individuals who got systemic corticosteroids (64%). Six of the 14 patients (43%) had rhino-orbital-cerebral disease (1.7%), rhino-cerebral disease (5.36%), or rhino-orbital disease (7.41%), whereas eight (57%) had pulmonary MCR. Three out of every six DM patients had rhino-orbital or rhino-orbital-cerebral illness. Two patients had vancomycin-resistant *Enterococcus* sp. and *Bacteroides fragilis*; however, one patient had *Aspergillus* and Candida, and another had methicillin-resistant *Staphylococcus aureus* and *Klebsiella pneumoniae* in a ventilator-associated pneumonia.

MCR was diagnosed antemortem in 13 of 14 cases (93%) and by autopsy in one case. Antemortem MCR found that Amphotericin B-based treatment was given to 12 of the 14 patients; it was given with Posaconazole in two patients, voriconazole in two patients, and avuconazole in one patient. Seven of the 14 individuals who gave data on when antifungal therapy should be started in response to an MCR diagnosis received empiric treatment; seven (50%) of those patients underwent adjunct surgery (sinus and chest cavity debridement, orbital exenteration, decortication, and lung resection). In the hospital, there were 64% deaths (as on 09/14).

Discussion

Blood vessel invasion along with mucormycosis causes ischemic necrosis. It has the capacity to enter a variety of biological systems, causing a variety of clinical symptoms that swiftly get worse. Co-infections that are opportunistic, including invasive fungal infections, can be fatal in COVID-19 illness. Health care professionals, particularly doctors, must therefore be cautious, aware of the risk of infection, and take the required precautions (42).

There have been numerous further reports of rhino-orbital mucormycosis. According to Waizel-Haiat et al., a 24-year-old Mexican woman who tested positive for COVID-19 had a history of obesity (43). She was sent to the emergency room after displaying symptoms of left lid edoema and maxillary hypoesthesia within two days and complaining of left midface pain for at least six days. After oral amoxicillin-clavulanate failed to provide relief, a contrast-enhanced CT scan of the head and chest was performed, which revealed an invasive fungal infection. Acute renal injury brought out by disseminated intravascular coagulopathy and metabolic acidosis with pulmonary insult were further COVID-19 issues this patient had. These issues ultimately led to multi-organ failure and death from septic shock. According to the researchers, this patient was susceptible to COVID-19 and mucormycosis co-infections because of an immunological condition caused by diabetic ketoacidosis. Her inadequate care and delayed diagnosis contributed to her terrible outcome (44). Studies indicate that ICU patients with ARDS are not routinely screened for respiratory fungal infections, which may have contributed to the co-infection of mucormycosis. The study also examined the length of time (up to a month from diagnosis to focused therapy at ICU) and contributed to the development of preventative methods (45).

In Bangalore, India, a study was done on a multi-centric retrospective investigation in 18 diabetes patients with positive SARSCoV-2 infections. For COVID-19 therapy, 15 of the 18 patients had uncontrolled diabetes and were all given corticosteroids. Surprisingly, 12 of the 18 patients suffered from vision loss, with seven of them required orbital exenteration as a result. According to the findings of the study, there were 16 cases of mucormycosis, one case of aspergillosis, and one case of mixed fungal infection. Eleven patients made it through, one was unidentifiable, and six people passed away. Researchers believe that there is a clear relationship between immunosuppression and corticosteroid use since they found that diabetics had a much greater prevalence of fungal infections ($p = 0.03$) (43).

According to Karimi-Galougahi *et al*., a 61-year-old woman with no prior medical history was hospitalised for two weeks due to COVID-19 infection. Remdesivir, interferon-alpha, and a systemic corticosteroid were given to her during her hospitalisation. Neither mechanical ventilation nor intubation were necessary for this patient. One week after being discharged, the patient experienced right hemifacial discomfort without any other sinonasal symptoms, hemifacial numbness, decreased visual acuity, and chemosis, prompting her second hospital stay. The diagnostic sinonasal endoscopy, MRI, and noncontrast CT of the paranasal sinuses all showed evidence of an invasive mucormycosis fungus infection. Despite the fact that the patient was healthy, researchers discovered that corticosteroid treatment

resulted in hyperglycemia and immunosuppression, as well as immunological dysregulation induced by COVID-19, which led to invasive mucormycosis, advising doctors to diagnose the disease early (35, 44).

In this review, steroids-induced immunosuppression, which causes MCR, was an example of a premorbid situation where the clinical presentation of MCR was quite comparable to that of premorbid MCR. The well-known risk factor for MCR, DM, is connected to greater morbidity and mortality in COVID-19 (46). Patients with COVID-19 are more likely to develop DKA than those with other severe illnesses. Evidence suggests that SARS CoV-2 damages pancreatic islets, causing abrupt hyperglycemia and DKA (47). The "diabetogenic state" in SARS CoV-2 infection may be explained by the elevated expression of angiotensin-converting enzyme 2 receptors in pancreatic islets and increased insulin resistance brought on by cytokine storm (48). Compared to the national prevalence of type 2 DM and DKA in the general population, COVID-19 exhibited a higher prevalence of DM (31%) and DKA (2%). Patients' frequent use of corticosteroids, which worsen glucose homeostasis, may have made them more susceptible to MCR. The usage of corticosteroids is considered to be a significant risk factor for MCR and other opportunistic mycoses.

In addition to hyperglycemia, a shift in iron metabolism also occurs in severe COVID-19 (4, 48). In severe COVID-19, a high ferritin level may be a sign of a major systemic disease or a factor influencing pathophysiology, however it is not known whether this is the case.

Regardless of their function, high ferritin levels cause an excess of intracellular iron, which generates reactive oxygen species and damages tissue. IL-6 in particular increases ferritin production and decreases iron export as a result of the severe infection and DKA, which causes intracellular iron overload and worsens the sickness. Free iron is released into the bloodstream as a result of the tissue damage. Iron overload and excess free iron found in academic settings were two major and separate risk factors for MCR (49).

According to the findings of the studies, clinicians treating COVID-19 patients should exercise particular vigilance in numerous areas in order to reduce the occurrence of mucormycosis and enhance their survival rates. We highly suggest practising physicians to think about and include the following in their protocols: All COVID-19 patients, including non-diabetics, should have their blood glucose levels checked on a regular basis. Special attention should be paid to people who are taking steroids. Educating all COVID-19 patients, whether hospitalised or not, on how to spot mucormycosis signs and findings (50) and also

suggested to follow the proper guidelines of COVID-19 and also specific government rules and dos and don'ts (see Tab.1 and 2).

Conclusion

The researchers focused particularly on patients' survival due to the association between a high death rate and a high index of suspicion, early diagnosis, and efficient care. In order to deliver the most effective, individualised care, it is critical to analyse the risk factors and kinds of invasive mycosis. The use of corticosteroids to treat severe/critical COVID-19 is a well-established risk factor for MCR as poorly managed diabetes mellitus (DM) and other co-morbidities are risk factors for both severe COVID-19 and mucormycosis (MCR). T lymphocytes, especially CD4+ and CD8+ T cells, which are believed to be crucial to the biological process of COVID-19 infection, could be damaged by SARS-CoV-2 infection. The most severe COVID-19 instances have several reductions in lymphocyte numbers, especially T cells, which are associated with the worst prognosis and may increase the risk of opportunistic infections in patients.

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Conflicts of Interest:

The authors declare no conflict of interest.

Author Contribution:

AKS conceived and wrote the manuscript. AV, PI, RR, SN compiled relevant information on Mucormycosis, Covid-19 and diabetes and helped in editing the manuscript. DS, JJ and KA assisted in the literature survey. MM provided critical feedback, guided the manuscript preparation, and assisted in language improvement.

All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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There is no ethical issue.

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Table 1: Prevention of Mucormycosis	
1.	When inspecting dusty building sites, wear masks.
2.	When working with soil, moss, or manure, wear shoes, long trousers, long sleeve shirts, and gloves.
3.	Maintain personal hygiene and take a scrub bath.
4.	Under control of diabetic condition.
5.	Use of corticosteroid under medical supervision.
Source: Ministry of Health.	

Table 2: Dos & Don'ts of Mucormycosis		
Sn	Dos	Don'ts
1.	Control Hyperglycaemia	Warning signals and symptoms should not be overlooked.
2.	Monitor blood glucose level post COVID-19 discharge and in diabetics.	In the setting of immunosuppression and/or COVID-19 patients on immunomodulators, do not assume that all episodes of blocked nose are bacterial sinusitis.
3.	Use of steroid wisely-correct timing, correct dose and duration or follow the medical practitioner instructions.	Hesitate to seek pathology laboratory help for further diagnosis
4.	Utilize clean, sterile water for humidifiers during oxygen therapy.	Lose key time to start treatment for Mucormycosis.
5.	Proper use antibiotics/antifungal	

	judiciously	
6.	Use daily cleaned/sterile/ new mask.	Don't use used masks or old one.
7.	Regular hand washing practice.	Touch your eye, nose, mouth with your fingers.
8.	Updated with outmost health instruction given by WHO and Gov Health authority.	Fellow the quack instructions.
9.	Use clean clothes	Share the clothes to others
10.	Stay away infected individuals.	Gather in public places.
Source: Ministry of Health & Family.		

Table 3: Patients having covid-19 infection with Mucormycosis risk factors

Sn	Age/Gender	Premorbid conditions if any	Type of viral pneumonia	Severity of disease/o2 supplementation with mechanical ventilator	Systemic corticosteroid therapy	Mucormycosis associated Risk factor
1	66/Male	Hypertension	Covid-19	Severe/yes	No	Covid-19 induced immunosuppression
2	56/Male	End Stage Renal Disease (ESRD)	Covid-19	Severe/yes	Yes	Steroid
3	60/Male	IDDM, HTN, Hyperlipidaemia	Covid-19	Severe/yes	Yes	IDDM
4	53/Male	AML, Myelodysplastic syndrome, Obesity & Stress	Covid-19	Severe/yes	Yes	Neutropenia, Steroid, Tocilizumab.
5	49/Male	N/A	Covid-19	Severe/yes	Yes	Tocilizumab, Steroid,
6	42/Female	DM	Covid-19	Mild/no	No	DM
7	61/Female	N/A	Covid-19	Mild/no	Yes	Steroid
8	55 /Male	Follicular lymphoma	Covid-19	Severe/yes	Yes	Steroid
9	68/Male	Ischemic cardiomyopathy leading to stage D Chronic systolic heart failure (IABP) and the	Covid-19	Severe/yes	Yes	Post OHT, DMD, Immunosuppressive therapy, steroid.

		insertion of a left ventricular assist device, followed by a heart transplant: Type 2 diabetes, hypertension, chronic renal disease, and obstructive sleep apnea are all symptoms of type 2 diabetes.				
10	33/Female	HTN/Asthma	Covid-19	Mild/no	No	DKA.
11.	32/Female	DMD	Covid-19	Mild/no	No	DMD
12.	79/Male	DMD/HTN	Covid-19	Severe/yes	Yes	Leukopenia, Lymphopenia, and T-cell dysregulation, DMD, Steroid.
13.	43/Male	DMD	Covid-19	Mild/no	No	DMD
14	38/Male	N/A	Covid-19	Mild/no	Yes	Steroid

Table 4: Clinical manifestations of MCR infection

Mucormycosis clinical symptoms	Mucor mycosis in its clinical state and the etiologic agent	The time between a diagnosis of viral pneumonia and a diagnosis of Mucormycosis (days)	Surgical \sdebridement Done	Antifungal treatment	Outcome	Reference
Pulmonary infiltrates and a parenchymal thickening	BAL/*Rhizopus spp*.	14 Days	No	AMB, ISZ	Death	(28)
Pleural effusion, necrotic parietal tissue, empyema, dyspnoea, generalized fatigue, haemoptysis, cardiac arrest.	Sputum/ *Rhizopus spp*.	19 Days	Yes	AMB	Death	(29)
ARDS, right globe proptosis with asymmetric	SINUS/ *Rhizopus spp*.	2 Days	No	AMP, CSP, PSZ	Death	(30)

retrobulbar-bar fat stranding and extensive opacification of the right maxillary, ethmoid, and frontal sinuses; invasive fungal rhinosinusitis with orbital involvement; ARDS, right globe proptosis with asymmetric retrobulbar-bar fat stranding and extensive opacification of the right maxillary, ethmoid, and frontal sinuses						
Increase of bilateral infiltrates, ARDS.	Pulmonary / *Rhizopus spp*.	Autopsy after 24 Days	No	VCZ	Death	(31)
Tachycardic, hypoxic, dyspnoeic, pneumothorax, right bronchopleural Fistula, necrotic empyema	Pulmonary / *Rhizopus spp*.	14 Days	Yes	AMP	DEATH	(32)
Pansinusitis with acute infarction in the left parieto-occipital area, ophthalmoplegia.	Sinus (Fess)/ *Rhizopus spp*.	Day-2	No	AMP	ALIVE	(33)
Right-sided proptosis, frozen eye, and fixed mydriasis, necrosis of the mucosa of the right lateral nasal wall, inferior and intermediate turbinates, and septum	Sinus/*Mucor sp*.	14 Days	Yes	AMP	ALIVE	(34)
Worsened Respiratory Status	Tracheal aspirate and broncho-alveolar lavage fluid [BALF]/	13	No	AMP	Death	(35)

	Aspergillus fumigatus and *Rhizopus microspores*					
Septic shock was diagnosed by a fever, purplish skin discoloration, and fluctuant edoema in the right axilla, where the IABP catheter had been inserted previously.	Chest fluid/ *Rhizopus microspores*	3 Months	Yes	AMP, PCZ	Death	(36)
Mild tachycardia, hypertension, and tachypnoea, left eye ptosis with proptosis, ophthalmoplegia, lower lobe consolidation consistent with pneumonia, moderate bilateral maxillary sinus mucosal thickening as well as ethmoid sinus mucosal thickening, and mucosal opacification of the osteomata units	*SINUS*/ *Mucor sp.*	-	Yes	AMP	Death	(37)
Complete left eye Ptosis, hemifacial pain, subperiosteal abscess with optic neuritis secondary to sinusitis.	Sinus/*Mucor spp*.	-	Yes	AMP	Alive	(38)
Fevers, rigours, dry cough, and progressive shortness of breath, as well as bilateral lung ground-glass opacities and infiltrates, hypoxic respiratory failure, and encephalopathy.	BAL/*Aspergillus, Rhizopus arrhizus*	14 Days	No	VCZ, AMP	Alive	(49)
Fever, hoarseness, productive cough and	Pulmonary / *Rhizopus*	4 Days	No	AMP	Death	(40)

haemoptysis, left lung pneumonia.	*arrhizus*					
Malaise, proptosis, chemosis, periorbital cellulitis, and restricted medial vision, partial ophthalmoplegia, swelling and pain in the left eye, partial ophthalmoplegia	Sino-Orbital/*Rhizopus oryzae*	18	Yes	AMP	Alive	(41)