

Rising concerns of Mucormycosis (Zygomycosis) among COVID-19 patients; an analysis and review based on case reports in literature

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Abstract. As the world continues to struggle with the pandemic of COVID-19 (coronavirus disease 2019), several cases of mucormycosis have been reported in these patients with a high mortality rate. We conducted a review of literature and found 19 articles with 20 patients who developed mucormycosis during their COVID-19 infection. 14 (70%) were males, and 6(30%) were females. While their mean age was 52.2 ± 17.3 years, affected men were older than females. Ten (50%) patients also had diabetes. Common clinical findings included ophthalmologic complaints, fever, shortness of breath, and facial pain. Amphotericin B was the most common antifungal used and around 40% of cases needed surgical management of the infection. Steroid use was reported in around 12 cases (60%). Unfortunately, the mortality rate was 65% in this group of patients. Several changes in care should be brought for a consistent prevention, early diagnosis, and strong management of mucormycosis in COVID-19 patients.

Key words: Mucormycosis, COVID-19, Fungal infection, Amphotericin B.

In late 2019, a new virus was identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) after several patients in Wuhan, China were hospitalized with atypical symptoms resembling pneumonia. The disease was eventually called COVID-19 (coronavirus disease 2019) (1, 2). The virus became a pandemic as more than 206 million people have been tested positive, and 4.3 million lost their lives globally (3). COVID-19 can present with a range of symptoms and has multiple risk factors influencing the outcome (4-7).

Fungal infections are typically considered as opportunistic infections, meaning they thrive when

the host immune system is compromised. Initially, at the start of the pandemic, many patients started showing signs and findings of pulmonary aspergillosis while admitted suffering from severe COVID-19 (8). However, in recent months, reports of mucormycosis infections involving COVID-19 patients have expanded fast across multiple countries (9). The management and treatment of mucormycosis can be expensive and challenging for several developing countries that are already struggling to control the spread of COVID-19. Mucormycosis was designated as an epidemic by the Rajasthan government in India on May 19, 2021, and numerous states are also seeing

an increase in new cases and deaths connected to the fungus. (10, 11). Therefore, we conducted a review to, first, know the disease in general, and then further used published case reports from the literature to better understand the symptoms, prognosis, management, and possible risk factors of this condition in patients with COVID-19.

What is Mucormycosis?

Mucormycosis, previously known as Zygomycosis, is a life-threatening infection caused by the filamentous fungi of the order of “Mucorales” (12). Multiple species that have been identified in humans, such as “*Apophysomyces* (*A. variabilis*), *Cunninghamella* (*C. bertholletiae*), *Lichtheimia* (*Absidia*) (*L. corymbifera* *L. raosa*), *Mucor* (*M. circinelloides*), *Rhizopus* (*R. arrhizus* (*oryzae*) *R. microsporus*), *Rhizomucor* (*R. pusillus*), and *Saksenaia* (*S. vasiformis*)” (13). Mucorales can be present in rotting materials such as fruits and vegetables, and in the soil. It is very resistant to high temperatures too. The *Rhizopus* species tend to be the most common one involving up to 70% of cases of mucormycosis in immunocompromised patients (13–15). The *Apophysomyces* species was first identified in India in 1979 and is believed to prefer tropical and subtropical climates. Several developing countries in those climatic areas are, thus, potentially at risk of this infection (16).

There are several routes of infection. The spores can enter the nose and lungs when inhaled, can be present in the gastrointestinal tract if present in contaminated food, or can be present in wounds or skin breaks (17). Once the spores have made their entry into immunocompetent patients, they are eaten up by neutrophils that eventually break them down. Therefore, patients with low levels of neutrophils or with impaired function of neutrophils are at very high risk (13, 16). Some studies further pointed out that patients with AIDS did not have a higher risk of developing the infection, and this confirmed that neutrophils were the primary mechanism of host defense instead of T cells (15).

Mucormycosis has also been observed in several immunocompetent hosts such as trauma patients. Diabetics who have uncontrolled management of

their blood sugar levels and previous history of diabetic ketoacidosis (DKA) are also at a higher risk (14). *Rhizopus arrhizus* species contain ketone reductase, which enables the fungi to overcome the acidic environment in DKA patients. The ability for the fungi to take up unbound iron from the host has also been linked with the pathogenesis (15, 18).

The presentation of the infection usually relies on the route of entry of the spores. Patients can have rhinocerebral mucormycosis with symptoms of “facial numbness, ocular pain, and dysfunction, fever, as well as intranasal painless ulcerations with necrotic tissues”. Pulmonary mucormycosis may lead to pneumonia and include “fever, shortness of breath, and even hemoptysis”. The cutaneous form of this infection, which can occur from sites of injury, can start as cellulitis that eventually becomes necrotic. Ingestion of spores can lead to gastrointestinal symptoms, including nausea, vomiting, diarrhea. Severe cases can even include hematemesis and melena (13, 15).

Since routine blood work is not very helpful in diagnosing the infection, biopsy samples are usually taken. On histopathology, the fungi is identified as a “non-septated or minimally septated broad-based hyphae” (13). Management includes anti-fungal therapy via Amphotericin B, surgical debridement if needed, and symptomatic care and therapy. The primary cause of infection should also be addressed. Several other anti-fungal therapies, such as Posaconazole or isavuconazole have also been considered in the past. However, mucormycosis can be very deadly and have a mortality rate that varies between 25–87% (13, 15, 17).

Method

We used the keywords “COVID-19”, “SARS-CoV-2”, “Coronavirus”, “Mucor”, and “zygomycosis” to identify cases of mucormycosis in COVID-19 patients published in English, French, Chinese, and Spanish between 2019 and 10th May 2021 on PubMed. The age, gender, presence of risk factors such as hypertension, diabetes, obesity, immunosuppression, and the treatment used for the fungal infection were all recorded. Manuscripts that were not accessible or that did not provide enough information for our review

were rejected. The authors performed their search as two teams, and each team eventually presented their findings and discussed the results to set up a final choice of cases.

Results

The initial search provided 34 results, and both teams read 33 of them. One of the manuscripts was inaccessible at that time. After filtering cases for individual patient level-data, we found 19 articles (table 1) that involved 20 patients (19-37). Among the 20 patients, 14 (70%) were males, and 6 (30%) were females. The mean age of the patients was 52.2 ± 17.3 , with ages ranging from 22-86 years. However, the mean age of the female patients was 38.0 ± 14.1 years, while the mean age for male patients was 57.3 ± 15.8 years. Geographically, six cases (30%) were from the USA, five (25%) from India, three (15%) from Iran, and one from Austria, Brazil, Franca, Italy, Mexico, and UK each. 10 (50%) patients had a history of diabetes and 7 (35%) had hypertension. Other comorbidities that were present included end-stage renal disease/chronic kidney disease (3 patients, 15%), obesity (3 patients, 15%), asthma (2 patients, 10%), and immunosuppressed states/ malignancy (three patients; one for Acute myelogenous leukemia, follicular lymphoma and heart transplant each).

The time of diagnosis of mucormycosis varied drastically for the patients between on admission to even three months after hospitalization for COVID-19, while one patient was even diagnosed during his post-mortem analysis (35). The common findings involved ophthalmologic complaints, fever, shortness of breath, and facial pain. One patient with Gastrointestinal mucormycosis also had abdominal pain, anemia and melena (22). 16 (80%) patients used non-invasive Oxygen supply, and eventually, a total of 11 (55%) patients were intubated for mechanical ventilation. The fungi affected multiple systems. Ten patients (50%) had rhino/sino/paranasal/orbital mucormycosis, while mycotic mycosis and gastrointestinal mucormycosis were reported in one patient each. Six patients (30%) had pulmonary mucormycosis, amongst which one also had aspergillosis. Mixed

infection due to both aspergillus and Rhizopus was found in one patient (5%) (26). Hanley et al. even reported a case of disseminated mucormycosis that reached the patient's lungs, hilar lymph nodes, kidneys, and brain (summarized in table 1) (36).

Several different approaches were used for the management of the fungal infection. Amphotericin B was the most common drug used, while other drugs such as Voriconazole, Posaconazole, Isavuconazole, Caspofungin, itraconazole were also being considered. Around 40% of cases also needed surgical debridement of the infection. Steroid use was reported in about 60% of cases, and may have been higher if unrecorded in the case reports but given during their hospitalization or during early management of COVID-19. Unfortunately, 13 patients (65%) died, while 7 patients (35%) survived. The mean ages of the deceased and survival cases were 51.8 ± 18.2 years and 53.2 ± 16.8 years each.

Discussion

Several developing countries are struggling to contain the spread of COVID-19 (11), and the high mortality rates and rising numbers of mucormycosis infections are crippling their health care system (38, 39), as well as their economic balance. Our analysis provides several vital points that should raise further questions on the screening, planning, and management of such patients.

While mucormycosis is typically known to infect diabetic patients (15), 50% of cases reported in literature for COVID-19 patients were non-diabetics. Therefore, further research should be undertaken to determine whether hyperglycemia occurred during the hospitalization of non-diabetic patients as a result of their steroid use for the management of COVID-19 symptoms or as a result of the stress of their severe disease. (40). Physicians should also be encouraged to have regular random blood glucose checks for these non-diabetic patients along their diabetic cases of COVID-19. More males were affected than females in our study. Previously, while some studies have reported a balanced distribution of cases between the two sexes in non-COVID-19 patients (41), Mignogna et al. found a higher male to female ratio (42). A larger

Table 1. Cases of mucormycosis among COVID-19 patients in literature

Author	Age (years)	Sex	Diabetes	Died	Treatment used for mucormycosis	Non-invasive O2	Intubated or on ventilator	Other major co morbidities	Symptoms	System/organ affected by mucor
Mehta S et al.(19)	61	M	Yes	Yes	N/A	Yes	Yes	Diabetes and Non-Healing Ulcer	"Fever before admission, afebrile on the day of admission, Shortness of breath, Orbital Cellulitis, Conjunctivitis, Keratitis Periorbital Edema"	Rhino Orbital Mucormycosis
Werthman-Ehrenreich A. et al.(20)	33	F	Yes	Yes	Amphotericin B, Surgical debridement	Yes	No	Asthma, hypertension	"Shortness of Breath, Altered mental status, Fixed Dilated Pupil with Complete Ophthalmoplegia"	Rhino Orbital Mucormycosis
Pasero D et al.(21)	66	M	No	Yes	Liposomal Amphotericin B, Isavuconazole, Surgery	Yes	Yes	Hypertension	"Shortness of Breath, COVID symptoms"	Pulmonary Mucormycosis
Monte Junior ESD et al.(22)	86	M	No	Yes	N/A	Yes	Yes	Hypertension	"COVID symptoms, fever, shortness of breath, Acute Diarrhea, Melena, Profound Anemia, Abdominal Pain"	Gastrointestinal Mucormycosis
Mekonnen ZK et al.(23)	60	M	Yes	Yes	Liposomal Amphotericin B, Caspofungin, Surgery, Posaconazole	Yes	Yes	Asthma, Hyperlipidemia, Hypertension	"Shortness of breath, Fixed Pupil, Conjunctival Chemosis, Edema of Eyelids, Proptosis"	Rhino Orbital Mucormycosis
Garg D et al.(24)	55	M	Yes	No	Liposomal Amphotericin B, Itraconazole, Posaconazole	Yes	No	Ischemic Cardiomyopathy, End-Stage Renal Disease on Dialysis, Hypertension	"Fever, Shortness of breath, Cough with Expectoration"	Pulmonary Mucormycosis
Placik DA et al.(25)	49	M	No	Yes	Amphotericin B	Yes	Yes	Bronchopulmonary Fistula, pneumothorax developed During Hospitalization	"Fever, Cough, Dyspnea"	Pulmonary Mucormycosis
Bellanger AP et al.(26)	55	M	N/A	Yes	Liposomal Amphotericin B	Yes	Yes	Follicular Lymphoma	"Fever, Dyspnea"	Mixed Mold Infection due to Aspergillus and Rhizopus
Maini A et al.(27)	38	M	No	No	Amphotericin B, Surgery, Tobramycin, Nepalact	Yes	No	N/A	"Fever, Shortness of breath, Body ache, u Swelling and Pain in Left Eye"	Sino Orbital Mucormycosis

(Continued)

Author	Age (years)	Sex	Diabetes	Died	Treatment used for mucormycosis	Non-invasive O2	Intubated or on ventilator	Other major co morbidities	Symptoms	System/organ affected by mucor
Khatri A et al.(28)	68	M	Yes	Yes	Liposomal Amphotericin B, Posaconazole, debridement	Yes	Yes	Heart Transplant, Chronic Kidney Disease, Obstructive Sleep Apnea, Hypertension	"Nonproductive Cough, Fever, Non-Bloody Diarrhea, Sternal Wound Discharge"	Mycotic Aneurysm
Saldanha M et al.(29)	32	F	Yes	No	Amphotericin B, Surgery	No	No	N/A	"Left Eye Prosis and Facial Pain"	Paranasal Mucormycosis
Veisi A et al.(30)	40	F	No	Yes	Surgery, Amphotericin B	Yes	No	N/A	"Bilateral Visual Loss and Periorbital Pain"	Rhino Orbital Mucormycosis
Veisi A et al.(30)	54	M	Yes	No	Amphotericin B, Surgery	Yes	No	N/A	"Left Orbital Pain, Periorbital Swelling and Vision Loss"	Rhino Orbital Mucormycosis
Johnson AK et al. (31)	79	M	Yes	No	Voriconazole	Yes	No	Hypertension	"Fever, Dyspnea, COVID-symptoms"	Pulmonary Mucormycosis And Aspergillosis
Karimi-galogahi M et al.(32)	61	F	No	No	Anti-Fungal and Surgery	No	No	N/A	"Right Hemifacial Numbness, Decreased Visual Acuity, Chemosis"	Rhino Orbital Mucormycosis
Waizel Haiat S et al.(33)	24	F	Yes	Yes	Impipenem, Linezolid, Amphotericin B	Yes	Yes	Obesity	"Pain in Left Mid Face, Left Lid Swelling, And Maxillary Hypoesthesia"	Rhino Orbital Mucormycosis
Kanwar A et al.(34)	56	M	No	Yes	Isavuconazole, Posaconazole	Yes	Yes	End Stage Renal Disease	"Fatigue, Dyspnea, Hemoptysis"	Pulmonary Mucormycosis
Zurl C et al.(35)	53	M	No	Yes	Voriconazole	Yes	Yes	Acute Myelogenous Leukemia, Obesity, Depression	"Fever, Sore Throat, Parageusia, Dysosmia, Dyspnea"	Pulmonary Mucormycosis
Hanley B et al.(36)	22	M	N/A	Yes	Caspofungin, Linezolid, Meropenem And Tigecycline		Yes	Obesity and Hypothyroidism	"Multisystemic, COVID-related, difficulty breathing"	Disseminated
Revannavar SM et al.(37)	N/A Middle age	F	Yes	No	Amphotericin B	No	No	N/A	"Fever, Left Eye Ptosis and Facial Pain and Fever"	Rhino Orbital Mucormycosis

N/A= not available, M= male, F= female

sample size may help clarify this finding. A gap in age difference between males and females was also observed in our study, and since the male group had one outlier at 22 years of age, the gap may be more significant than reported. Older men and younger women were the prominent cases recorded.

Patients with immunosuppression, malignancy, chronic inflammatory states, on dialysis, chronic kidney disease/ renal insufficiency, and obesity have all been linked with a more severe outcome for COVID-19, and they are also at a higher risk of developing fungal infections (43-46). Therefore, these groups should be appropriately sequestered during their hospitalizations to reduce the risk of nosocomial infections and fungal infections from other patients. Since half of the cases had ophthalmologic complaints and involved the rhino/sino/paranasal/orbital area, several changes can be brought in the protocols of management of COVID-19 patients. A thorough examination on admission, as well as daily examinations should be performed. However, given the rising cases of COVID-19 and the decreasing physician-to-patient ratio in developing countries, the physicians should also educate the patients to report symptoms that could hint towards the infection and be shown how to check for any such infections.

Mucormycosis has a high mortality rate (47), and in our study only 35% of the patients survived. Since Amphotericin B was used in most patients, protocols should also include a close eye on the possible side effects and a regular check on the patient's electrolytes. The causes of death of these patients were not properly described in the case reports, and it is, therefore, difficult to hypothesize if the drugs used for their management could have been a precipitating factor for their deaths. Amphotericin B can cause several electrolyte imbalances such as hypokalemia, which can eventually lead to Torsades de Pointes and other cardiac arrhythmias. Close cardiac monitoring for patients and reporting their results may help understand the impact in such cases (48).

Conclusion

In summary, our analysis shows that several areas may need extra caution by physicians treating

COVID-19 patients that can help lower the incidence of mucormycosis and improve their survival rates. We strongly advise the following to be considered by the treating physicians and to be included in the protocols:

- Regular blood glucose monitoring in all COVID-19 patients, including non-diabetics. Special attention to those receiving steroids.
- Educating all COVID-19 patients, hospitalized or non-hospitalized, on simple ways to locate symptoms and findings of mucormycosis.
- Encouraging physicians to anticipate side effects of antifungal therapies and correct them in a timely manner, before the onset of additional symptoms.

With proper preventive measures, early diagnosis, and appropriate care, the world will eventually be able to handle the new complication of this pandemic.

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