Clinical Characteristics And Outcomes of 16 Cases With COVID19 and Mucormycosis: Experience From A Tertiary Care Center In India and Review of Literature

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Abstract

Background-The sharp uptick in the cases of mucormycosis in the background of the COVID19 pandemic is a cause of concern and the reasons and it's impact remains to be seen. We studied the clinical characteristics in patients with mucormycosis and COVID19 co-infection and performed a literature review.

Methods-This retrospective study was conducted at tertiary centre in India. All patients admitted with COVID19 and mucormycosis were included, clinical details were obtained from hospital records. We did review of literatures using the terms "SARS-CoV2" OR "COVID19" AND "Mucormycosis" AND "co-infection" on Pubmed published before February 20, 2021.

Results-Sixteen cases (M:F–13:3), mean age 46·5 years (24-75years), were included. Fourteen had known risk factors for mucormycosis, the most common being diabetes mellitus. Most patients (n=14) were symptomatic with mucormycosis before diagnosis of COVID19. There was delay in surgery by 22.5 days (IQR–>17.75–29.5), pending SARS-CoV-2 RT-PCR negativity. There were six deaths in this cohort, unrelated to the COVID19 severity. The literature review revealed eleven case reports on co-infection. Patients who had developed mucormycosis were found to have history of mechanical ventilation.

Conclusion-The apparent increase in the incidence of mucormycosis may be due to decompensation of underlying comorbidities (decreased access to healthcare), and increased use of immunosuppressants in COVID19. Patients with co-infection were noted to have poorer outcomes.

Introduction

Even after more than one year following the origin of the pandemic the pathogenesis of COVID19 remains partially understood and understanding of the same continues to evolve with time. As the highly infectious virus continues to give rise to new cases globally, one of the biggest concerns is co-existing infections. Co-infections or superinfections are deemed to occur as the pandemic tends to overlap with geographical realm and seasonality for few infections or due to the encounter with other community or nosocomial pathogens (during hospitalisation for COVID-19). However, information on co-infections in COVID19, especially with relation to invasive fungal infections, is lacking.

Multiple cases of invasive pulmonary aspergillosis (CAPA - COVID19 associated pulmonary aspergillosis) and invasive candidiasis (CAC – COVID19 associated candidiasis) have been reported in patients with severe COVID19 (1). This has been linked to the use of steroids, long-term antimicrobials, prolonged mechanical ventilation, and the extended duration of hospital stay in these patients. There is growing concern over the increase in cases of mucormycosis in COVID19 as well. Mucormycosis is an angio-invasive disease caused by opportunistic fungi of the order Mucorales in immunocompromised patients.(2) Untreated mucormycosis is almost always fatal. It remains to be seen if this increasing incidence of mucormycosis in COVID19 is related to the illness itself, the steroids and immunomodulators administered for treatment, or the worsening of underlying predisposing factors in the socio-economic upheaval caused by the pandemic. Further, it is unknown how the co-existence of COVID19 would affect the natural history and treatment of patients with mucormycosis.

To answer some of these questions, we performed a retrospective clinico-epidemiological study on patients with COVID19 and mucormycosis co-infection.

Methods

This was a retrospective, observational study, conducted at All India Institute of Medical Sciences, New Delhi, India. Patients admitted between March 20, 2020 and January 31, 2021 with current, recent, or remote history of COVID19 AND diagnosed mucormycosis were included in the study. The diagnosis of mucormycosis was based on either the histopathological demonstration of hyphae consistent with mucormycetes, i.e., hyaline, broad, aseptate, or pauci-septate, ribbon-like hyphae with right/obtuse-angled branching in the hematoxylin and eosin (H & E)/ Periodic Acid Schiff's (PAS)/ Gomori's methenamine silver (GMS) staining or on culture isolation of the mucormycetes, in the tissue specimens obtained from suspected sites, as per the ECMM/MSG-ERC-2019 (European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium) diagnostic criteria.

Patients without microbiological or histopathological evidence of mucormycosis were excluded from the study. Written informed consent was obtained in all cases. Hospital records were scanned, and missing details were filled in through telephonic or direct interviews with patients. Information on demography, clinical features, investigations, treatment, and outcomes was collected. Mucormycosis was classified based on the site of involvement into sino-nasal disease, rhino-orbital, rhino-orbito-cerebral, or pulmonary disease. Sino-nasal disease was defined as infection limited to sinus and nasal cavities only without orbital or intracranial extension. Rhino-orbital or rhino-orbital-cerebral disease included fungal invasion into orbit or intracranial cavity to involve orbital contents or intracranial structures, respectively. Orbital involvement was defined as vision diminution or ophthalmoplegia and definitive radiological evidence of the same. Brain parenchymal involvement was defined as focal neurological deficits or altered mentation with radiological evidence of intracranial extension. Pulmonary disease was defined as radiological, histopathological, or microbiological evidence of fungal infection in the lung parenchyma. The protocol for the study was approved by the Institutional Ethics Committee.

Results

Between March 20, 2020 and January 31, 2020, 6250 cases of COVID19 were admitted at our centre. Of these, sixteen patients were (M: F 13:3) with a mean age of 46·5 years (SD, 14·5) were diagnosed with mucormycosis and were included in our study (Table 1). Fifteen patients had one or more comorbidities (Table 3), most commonly uncontrolled diabetes mellitus (n = 12), chronic kidney disease (n = 2), solid-organ transplantation (n = 1), hematological malignancy (n = 1), decompensated chronic liver disease (n = 1) and chronic granulomatous disease (n = 1). Three out of twelve diabetic patients had presented with diabetic ketoacidosis.

Table 1
– Demography, clinical features, management, and outcom

	Patient 1	Patient2	Patient 3	Patient 4	Patient 5	patient 6	patient 7	Patie
Age/Sex	62/M	70/M	53/M	47/M	38/M	37/M	32/M	48/M
Comorbidities	DM	DM	DM CKD-3	DM	Post renal transplant on immune-suppression, DM	Decompensated CLD (Child C), DM	CGD	DM
COVID-19 severity	Mild	asymptomatic	asymptomatic	Not known	severe	asymptomatic	Mild	Mild
RT-PCR positivity duration	30 days	10 days	10 days	NA	28 days	24 days	16 days	18 da
Duration of symptoms	10 days	12 days	10 days	15 days	15 days	6 days	20 days	40 da
Temporality of diagnosis of mucormycosis to COVID-19	Pre-COVID-19	Pre-COVID-19	Pre-COVID-19	Pre-COVID-19	**Post COVID-19**	Pre-COVID-19	Pre-COVID-19	Pre-C
Clinical features	Right periorbital swelling with oculopareis, diminution of vision, multiple C.N palsy, necrotic palatal ulcer, DKA	Left facial pain, mucopurulent nasal discharge	Left sided periorbital and malar swelling, proptosis and external ophthalmoplegia, diminution of vision, necrotic palatal ulcer, Right hemiparesis	Right periorbital and malar swelling, proptosis, ophthalmo-plegia, diminution of vision, left hemiplegia, altered sensorium; DKA	Left sided periorbital swelling, proptosis, diminution of vision	Altered sensorium, nasal discharge, epistaxis	Right eye proptosis, ophthalmo-plegia, diminution of vision, multiple C.N palsy	Right perio mala swell ophth plegi dimi visio multi palsy
Site involved	Rhino-orbital-cerebral	Sino-nasal	Rhino-orbito-cerebral	Rhino-orbito-cerebral	Rhino-sino-orbital	Sino-nasal	Rhino-orbito-cerebral	Rhino cereb
Mycological	KOH +	KOH +	KOH +	*Rhizopus arrhizus*	KOH +	KOH +	KOH +	KOH
Histopathology	Angio-invasion present	Angio-invasion with necrosis	Angio-invasion with perinural invasion, osteonecrosis	NA	angioinvasion with perineural invasion, chronic inflammation	NA	angioinvasion	chron infla
Radiology	Pan-sinusitis, Lateral rectus involvement, orbital, Palatal bony erosion	Pan-sinusitis with sinus bony erosion	Acute infarct of left parietal, centrum semiovale, optic nerve infiltration, left inferior, medial, lateral rectus involvement	Right fronto-parietal infarct, B/L pansinusitis with bony destruction	Pansinusitis with invasion of medial, lateral, inferior rectus and optic nerve	Pansinusitis with Dural enhancement of B/L frontal region	Pan ophthalmitis with pansinusitis, 2.3x2cm frontal lobe abscess	Pans with erosi pan ophth acute front parie occip
Lab abnormalities	Leucocytosis, lymphopenia, raised CRP, elevated D-Dimer	Lymphopenia Raised CRP, IL-6, elevated D-dimer	Lymphopenia, Raised CRP, IL-6, elevated D-dimer	Leucocytosis, Lymphopenia, Raised CRP, elevated D-dimer	Lymphopenia thrombo-cytopenia Raised CRP, IL-6, elevated D-dimer	Lymphopenia IL-6, elevated D-dimer	Leucocytosis,	Lymp thron cytop Raise
Antifungal	LAmB (5mg/kg) –> stepdown Tab Posaconazole 300 mg OD	LAmB (5mg/kg) –> stepdown Tab Posaconazole 300 mg OD	LAmB (3mg/kg) + intraorbital Ampho B (1.5mg x 10days)	LAmB (5mg/kg)	LAmB (3mg/kg) –> stepdown Tab Posaconazole 300 mg OD	LAmB (4mg/kg) –> stepdown Tab Posaconazole 300 mg OD	LAmB (5mg/kg) –> stepdown Tab Posaconazole 300 mg OD	LAm (5mg stepd Posa 300 m

DM – Diabetes mellitus, DKA – diabetic keto-acidosis, CAD – coronary artery disease, CKD – Chronic kidney disease, CLD – chronic liver disease, CGD – chro

	Patient 1	Patient2	Patient 3	Patient 4	Patient 5	patient 6	patient 7	Patie
Surgery	Infra-structural maxillectomy	Infra-structural subtotal maxillectomy	Total maxillectomy with coronoid-ectomy	-	Total maxillectomy with orbital exenteration	FESS with complete sinus debridement and posterior ethmoid-otomy + sphenoidotomy	Orbital exenteration with sinus debridement	Hem bulec with maxi etmo orbit exen
Time lag between diagnosis and surgery	Day 40	Day 16	Day 17	Not done	Day 25	Day 7	Day 19	Day
ICU admission	Yes	No	No	Yes	Yes	No	No	No
Outcome	Expired 2 weeks after discharge	Discharged and under follow up	Expired	Expired	Discharged and under follow up	Discharged and under follow up	Discharged and under follow up	Disch and u follo
Cause of death	Unknow cause (died at home)	-	Hospital acquired pneumonia	DKA with sepsis	-	-	-	-
Duration of stay	49 days	66 days	48 days	3 days	40 days	31 days	94 days	49 da
LAmB cumulative dose	7.8gm	5.3gm	6.5gm	0.6 gm	6.4gm	4.5 gm	13.7gm	7.8gr
Amphotericin-B toxicity	Hypokalemia, acute kidney injury	Hypo-kalemia, hypo-magnesemia, acute kidney injury, acute infusion reaction	Hypo-kalemia, Acute kidney injury, Pan-cytopenia	NA	Hypo-kalemia, hypomagnesemia	Pancytopenia	Acute kidney injury	Acut injur
DM – Diabetes mellitus, DKA – diabetic keto-acidosis, CAD – coronary artery disease, CKD – Chronic kidney disease, CLD – chronic liver disease, CGD – chro								

Table 3
Risk factor for pre-existing mucormycosis (n = 16)

Risk factors	Number of cases(percentage)
Uncontrolled Diabetes mellitus	10 (75%)
Chronic kidney disease	2 (12.5%)
Post renal transplant (immunosuppressive agents)	1 (6.25%)
Chronic liver disease	1 (6.25%)
Pulmonary Tuberculosis (MDR-TB)	1 (6.25%)

All patients had confirmed COVID19 illness using SARS CoV-2 RT-PCR on nasopharyngeal or oropharyngeal swabs. Two patients were diagnosed with mucormycosis during convalescence from COVID19, whereas the rest had features suggestive of mucormycosis even before the diagnosis of COVID19. The median duration of symptoms was 15 days (range, 6–60 days). Laboratory abnormalities have been summarised in Table 2. The severity of COVID19 ranged from asymptomatic infection (n = 5, 31·25%), mild (n = 7, patients, 43·75%), moderate (one patient, 6·25%), and severe COVID19 requiring steroids and anticoagulation (n = 2, 12·5%). Most of our patients had sino-nasal mucormycosis (n = 15) with or without orbital or intracranial involvement, with only one patient with pulmonary disease. Out of the fifteen patients with sino-nasal disease, five patients had localised disease, three had orbital involvement, and seven patients had evidence of intracranial spread. The diagnosis was established by demonstrating the fungal hyphae, in KOH mount and calcofluor fluorescent staining, with the characteristic feature of mucormycetes, while the fungus could be cultivated and identified as *Rhizopus arrhizius* in two cases and *Rhizopus* spp. in one case. While six cases had histopathological features of acute disease process i.e., coagulative necrosis or angioinvasion or perineural invasion, seven cases had granulomatous inflammation with giant cells, features suggestive of chronic mucormycosis. Radiological (CECT or CE-MRI) findings have been summarised in Table 1.

Table 2
Laboratory abnormalities of 16 patients with COVID-19 and mucormycosis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	patient 6	patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patie 13
Hemoglobin	11.8	13.5	12	11.8	13.3	12.8	12.3	12.2	8.5	9.9	10.7	8.7	16
TLC	14850	8900	6690	15340	7170	6330	13400	7200	7340	13080	14900	10200	1770
ALC	787	676	1210	782	638	1196	1742	936	653	1124	2682	1632	1416
Platelets	3.7Lac	2.47Lac	2.04Lac	3.13lac	0.91Lac	0.52Lac	3.21Lac	0.95Lac	1.83Lac	2.43Lac	2.93Lac	0. 61Lac	2.47L
Urea	36.4	27	71	34	64	23.5	10	51	34.2	74.9	25	36	86
Creatine	0.8	0.9	1.78	1.25	1.1	0.39	0.8	1.3	1.5	5.3	0.5	1	0.72
Potassium	3.6	4.3	4.04	6.3	4	4	4.7	5.1	4	4.6	3.9	2.3	6.6
SGOT	34	29	65	20	21	21	28	26	19	164	11	19	39
SGPT	35	30	62	15	51	21	24	39	8	9	10	29	82
Ferritin	1091	1954	838	1590	789	258	-	785	1175	-	370	508	-
CRP	10.9	12.59	6.3	21.1	1.22	0.3	-	6.7	12.75	11.87	16.82	15.74	-
IL6	-	14.1	27	-	621.9	1.6	-	-	25.6	-	59.9	12.85	-
LDH	-	309	234	451	560	241	-	232	143	282	175	-	-
D-dimer	557	3428	456	538	1238	2016	-	-	1308	682	-	300	-
Fibrinogen	523	624	-	702	193	255	-	-	417	289	-	-	-

All patients were managed with Liposomal Amphotericin B (Fungisome) with or without surgical debridement. It was started at a dose of 3 mg/kg and escalated to 5 mg/kg if tolerated well. Adverse events necessitating alteration or discontinuation of therapy were nephrotoxicity (n = 9, 56·25%), hypokalaemia (n = 8, 50%), hypomagnesemia (n = 2, 12·5%) and bone marrow suppression (n = 2, 12·5%). Surgical intervention was done following two consecutive negative SARS CoV-2 RT-PCR results (at least 24 hours apart). Twelve patients (75%) underwent surgery, two patients had fulminant disease and succumbed before medical stabilisation, and surgical intervention could be undertaken, one patient was planned for surgery, and one patient was lost to follow up. Surgical approaches included maxillectomy, orbital exenteration, and functional endoscopic sinus surgery, alone or in combination. The median duration of SARS CoV-2 RT-PCR positivity was 16 days (IQR 10–24 days). The median duration between diagnosis of mucormycosis and surgical debridement was 22·5 days (IQR 17.75–29.5 days).

Out of the sixteen patients, five patients required admission to the intensive care unit (ICU), two due to severe COVID19, two patients due to diabetic ketoacidosis with severe metabolic acidosis, and one due to sudden drop in sensorium (due to progressive mucormycosis) (Table 1). The median duration of hospitalization was 40·5 days (IQR 27–49 days). There were six (37·5%) mortalities in this cohort, all of them attributable to mucormycosis. Seven patients (43·75%) patients have been discharged with step-down long term maintenance therapy with oral Posaconazole tablets (at a dosage of 300 mg OD). Two patients (6·13%) were still admitted at the time of writing.

A literature search on pubmed for articles, published before February 20, 2021, using the terms “SARS CoV2” OR “COVID19” AND “Mucormycosis” AND “co-infection”, yielded 11 published cases of COVID19 and mucormycosis. We analysed these twenty-seven cases (eleven case reports, sixteen cases from our study and divided them into categories based on if they developed mucormycosis before or after the COVID19 infection (Table 5). In patients with pre-COVID mucormycosis, sino-nasal disease (with or without orbital or cerebral involvement) was the most involved site, whereas in patients with post-COVID mucormycosis, the most common site was the lungs. Moreover, the need for mechanical ventilation was more common in post-COVID patients ($p < 0.05$).

Table 5 Characteristics of cases with Pre COVID vs Post COVID mucormycosis (n = 27)

	Pre COVID mucormycosis	Post COVID mucormycosis	
Number of cases*	17 (14 + *3*)	10 (2 + *8*)	
Age (years)	45.3 (median 47, range - 24-75)	54 (median 54, range - 34-86)	
Sex	M : F - 14:3	M : F - 8:2	
Severity of COVID-19			
Asymptomatic	4	1	
Mild	7	1	
Moderate	3	0	
Severe	**2**	**8**	
Unknown	1	0	
Site of mucormycosis			
Sino-nasal (orbital or intracranial extension)	16	3	
Pulmonary	1	6	
Gastro-intestinal tract	0	1	
Others	0	0	
Risk factors			
Pre-existing			
Diabetes mellitus	11	4	
Chronic kidney disease	1	2	
Chronic liver disease	1	0	
Haematological malignancy	1	2	
Solid organ transplant	0	1	
MDR Pulm TB	1	0	
PID	1	0	
None	1	3	
COVID-19 hospitalisation related	**N=17**	**N=10**	
Lymphopenia (<1500/ul)	9 (56.3%)	8 (80%)	
Steroids	6 (35.3%)	7 (70%)	
Anti-IL-6 agents	0	3 (30%)	
Mechanical ventilation	1(5.9%)	7 (70%)	**p value - 0.000426**
H/O repeated nasopharyngeal or oropharyngeal swabs (>=2)	16 (94.1%)	4 (40%)	
Outcomes			
Expired	7	8	**p value – 0.0499**
Discharged	8	2	
Admitted	2	0	

* italicized number represent the number of cases published

Discussion

This study summarizes the experience of co-existing mucormycosis and COVID19 from our center and those reported in the literature so far. The incidence for the specific at-risk population for mucormycosis varies between 0·005 to 1·7 per million population (2). A recent multicentric study on the epidemiology of mucormycosis from India reported an increase in incidence rates from 24·7 to 89 cases per year (3); while another single-center based survey on people with diabetes reports an incidence of 0.15 % (4). Only a few cases of COVID19-mucormycosis co-infection have been reported in literature to date (5–16). In our centre, the occurrence rate of co-existing COVID19-mucormycosis was 2·56 per 1000 COVID19 patients; the incidence rate of mucormycosis following COVID19 was 3·2 per 10,000 COVID19 patients.

Comparing with the data prior to year 2020, current data is suggestive of increasing case of mucormycosis. There may be many causes for the increase in the incidence of COVID19. As part of the pandemic control strategy, active tracing of all contacts of COVID19 cases was being carried out along with screening of all cases, presenting to out-patient or emergency services, for SARS CoV-2 infection. As per national recommendations, all patients who tested positive were admitted regardless of symptomatology (17). This possibly explains the clustering of cases with mucormycosis in hospitals that were otherwise asymptomatic or previously undiagnosed. In our study, fourteen patients had symptoms suggestive of mucormycosis at admission, while the remaining two patients developed rhino-orbital mucormycosis nearly one month after the resolution of COVID19. The duration of diagnosis was variable, ranging from one week to three weeks.

Common mucormycosis (CM) occurs following inhalation of spores or inoculation of spores in wounds inflicted during trauma e.g., bomb blast injuries or road traffic accidents (18, 19). However, hospital acquired mucormycosis (HAM) secondary to surgical intervention, adhesive bandages, wooden tongue depressors, osteomy bags or contaminated linen etc. also has been reported (20, 21). Most common sites involved in HAM were skin followed by intrabdominal disease. The increased incidence of mucormycosis in the COVID19 may have many causes. The pandemic has caused widespread sociological and economic disturbances, severely restricting adequate access to healthcare. This has caused decompensation of previously well-controlled comorbidities in patients with chronic illnesses, like diabetes and chronic kidney disease. Furthermore, the incidence of hospital-acquired mucormycosis (HAM) has increased due to more exposure of at-risk individuals to Mucorales, in the setting of an altered host-immune response. Pre-existing conditions such as uncontrolled diabetes mellitus, solid organ transplants, haematological malignancy, neutropenia, or use of immunosuppressants predispose to the development of mucormycosis. It is noteworthy that exposure to molds is common in ICUs or wards close to construction sites, which was common in our case, where several newly built or previously unused buildings were repurposed as COVID19 facilities. Moreover, contaminated air, equipment, or linen may serve as sources of spores. Interventions such as swab tests (along with use of wooden tongue depressors), Ryle's tube insertion, insulin injections, etc. serve as a mode of inoculation into human tissues. The situation is further complicated using steroids or immunomodulators for severe COVID19, worsening glycaemic status, rampant use of antibiotics and voriconazole (empirically for CAPA), prolonged mechanical ventilation as well as prolonged hospitalisation.

In our cohort, sites of involvement were sino-nasal (with or without orbital or cerebral involvement) or lung parenchyma. Of the two patients (at our center) who developed mucormycosis following COVID19, one on immunosuppressants for renal transplant (and had received steroids for severe COVID19), and the other had end-stage renal disease. Both patients were diagnosed with rhino-orbital mucormycosis.

Amongst the cases reported in the literature, eight patients had risk factors for mucormycosis, i.e., diabetes mellitus (n = 6) and hematological malignancy (n = 2) (Table 4). Moreover, eight cases received steroids for moderate to severe COVID19. Six had pulmonary mucormycosis, four had rhino-orbital-cerebral disease, and one patient had gastro-intestinal mucormycosis. Ten patientswere on mechanical ventilation before the diagnosis, while no such intervention was noted in the one with gastro-intestinal mucormycosis. Noteworthy here is the case reported by Pasero et. al. who developed pulmonary mucormycosis without any known risk factors; severe COVID19 and mechanical ventilation are potential risk factors in this case. Mechanical ventilation was a significant risk factor for developing post-COVID mucormycosis (Table 5). We did not find any patient developing mucormycosis, following COVID19, in the absence of obvious risk factors or severe COVID19 (possible use of steroids, mechanical ventilation). Lymphopenia is a common finding in COVID19, than neutropenia, whether COVID19 illness itself predisposes to mucormycosis is unclear yet (22, 23). According to one study, a protective role of Mucorales specific CD4 and CD8 T cells have been hypothesized during active mucormycosis (24). However, it will be interesting to know, whether COVID-19 related lymphocytopenia, results in impaired T cell Mucorales specific response and predispose to mucormycosis (25). It is worth noting that thirteen patients (81·25%, n = 16) had an absolute lymphocyte count less than 1500 cells/cumm (Table 2), however, the difference was not significant between pre-COVID and post-COVID mucormycosis cases (Table 5).

Table 4
Summary of published case reports of co-infection COVID-19 and Mucormycosis (n = 11)

Author	Alekseyev et al	Bellanger et al	Garg et al	Khan et al	Mehta - Pandey	Monte Junior et al	Pasero et al	Placik et al
Country	USA	France	India	USA	India	Brazil	Italy	USA
Age/Sex	41/M	55/M	55/M	44/F	60/M	86/M	66/M	49/M
Comorbidities	Diabetes mellitus	Follicular lymphoma, Post HSCT	Diabetes mellitus, Hypertension, Ischemic heart disease, Chronic Kidney disease	Diabetes mellitus	Diabetes mellitus	Hypertension	Hypertension	None
Clinical presentation	Cough, dysgeusia, Nasal pain with palatal eschar	Fever Respiratory distress	Fever, cough, dyspnea New onset expectoration	Altered sensorium. Respiratory distress	Fever, dyspnea, malaise Altered mentation, Right eye proptosis, Left eye loss of vision	Malena, Abdominal tenderness	Dyspnea, respiratory distress	Fever, coug dyspnea Pneumotho with bronchople fistula
COVID-19 severity	Moderate (no hypoxemia)	Mild	Severe	Severe	Severe	Severe	Severe	Severe
Timing of Features s/o Mucormycosis	At admission	19 days after admission (13 days after COVID-19 diagnosis)	17 days after admission due to COVID-19	13 days after admission due to COVID-19	10 days after admission due to COVID-19	7 days after admission due to COVID-19	14 days after admission due to COVID-19	14 days aft admission to COVID-1
Site of mucormycosis	Rhino-cerebral	Pulmonary	Pulmonary	Pulmonary	Rhino-orbital mucormycosis	Gastrointestinal	Pulmonary	Pulmonary
Risk factors for mucormycosis	Uncontrolled diabetes mellitus Diabetic ketoacidosis	Hematological malignancy, Mechanical ventilation	Uncontrolled glycemic status, Steroids	Uncontrolled diabetes mellitus, Steroids	Steroids - Tocilizumab	Steroids	None No steroids	Steroids, Tocilizuma
Imaging	MRI: Sinusitis with B/L infratemporal abscess and cavernous sinus enhancement	non-specific bilateral ground glass opacities	Thick-walled cavity in right upper lobe with minimal pleural effusion	GGO with right multiple cavitation	Sinusitis with bulky extraocular muscle and proptosis	Esophagogastro-duodenoscopy: Two gastric ulcer with haemorrhagic base	Left lung cavitatory lesion with maxillary sinusitis	large bronchople fistula of th right upper lobe with associated necrotic empyema
Basis of diagnosis	KOH mount on debrided tissue	*Aspergillus fumigatus* and *Rhizopus microsporus*	Culture – *Rhizopus microsporus*	HPE of endobronchial biopsy specimen	Biopsy and culture from nasal mucosa	HPE of specimens from ulcers	Culture - *Rhizopus spp.*	Culture - *Rhizopus s*
Management	Amphotericin-B lipid complex + Sinus debridement	Liposomal Amphotericin-B (5mg/kg)	Liposomal Amphotericin-B (3mg/kg) Awaiting surgery	Liposomal amphotericin-B (5mg/kg)	Amphotericin-B (0.5mg/kg)	No antifungal or surgical therapy	Liposomal Amphotericin-B (5mg/kg) and Isavuconazole	Amphoteric B + Right middle thoracotom resection o diseased a + fistula rep and pleurodesis
Outcome	Discharged	Died	Discharged	Died	Died	Died	Died	Died

The starkest aspect of co-existing mucormycosis and COVID19 was the impact on the management of mucormycosis. Mucormycosis is a fulminant disease and a surgical emergency. Its management requires a combination of extensive surgical debridement to remove infected tissue as well as medical therapy (2, 18, 26). Despite both surgery and antifungal, it is associated with high mortality and morbidity. It has been observed that surgery performed during active COVID19 disease is associated with poor outcomes (27, 28). Furthermore, there is a risk to operating room personnel during surgery due to aerosol-generating

procedures like intubation and endotracheal tube suction. A general consensus during COVID-19 pandemic is to postpone all elective surgeries, while all emergency surgery requires utmost consideration to indication, urgency of surgery, surgical approach, risk of aerosol spread, and availability of staff and resources (29, 30). All our patients were started on medical management with antifungal agents at diagnosis. We found that in most cases, surgery was delayed till medical stabilisation and RT-PCR negativity. The median duration between diagnosis of mucormycosis and surgical debridement was 22·5 days (IQR 17.75–29.5 days). Surgery was performed in twelve cases. Two patients deteriorated rapidly and could not be taken up for surgery; one was lost to follow up, and one patient was awaiting surgery following medical stabilisation. Our cohort had six mortalities, including four patients who had undergone surgical debridement. Of these, five were of sino-nasal mucormycosis, while one patient had pulmonary involvement. In reported literature, two out of eleven cases, had rapidly worsening severe COVID19 and succumbed to severe illness before surgery or medical therapy. Other patients were managed medically with one or more antifungals, i.e., Liposomal Amphotericin B or isavuconazole. Surgery was undertaken in only three patients, while the rest were deemed medically unfit for surgical intervention. Ten out of eleven patients died despite medical therapy and surgery.

This study is the largest account of COVID19 and mucormycosis co-infection available in the literature. Having been done at a tertiary care centre equipped to diagnose and treat both COVID19 and mucormycosis with alacrity, our study is uniquely equipped to identify disease-related, patient-related, and treatment-related factors leading to poor outcomes. Limitations of our study include a descriptive design. The lack of a non-COVID19 infected control group limits our ability to distinguish COVID19 specific considerations in the broader background of the socio-economic upheaval caused by the pandemic. Further research is required to establish if COVID19 itself predisposes to mucormycosis.

Conclusion

There has been an apparent increase in the incidence of mucormycosis in patients of COVID19. The causes for this are multi-factorial, including decreased access to healthcare leading to decompensation of underlying comorbidities, increased exposure to healthcare facilities leading to more Hospital Acquired Mucormycosis (HAM), and increased use of immunosuppressants in the setting of COVID19. Patients with mucormycosis with COVID19 co-infection have poorer outcomes which may be related to immunosuppression administered for the COVID19 infection and delays in access to adequate surgical management.

Declarations

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