

Original Research Article

A prospective study on emergence of mucormycosis in recently recovered COVID-19 patients

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ABSTRACT

Background: Mucormycosis is an angio-invasive fungal infection with high morbidity and mortality. This infection seems to be increasing during the second wave of COVID-19. Objectives of this study were to identify and characterise the fungal species causing post-covid-mycosis, to analyze the cases for underlying co-morbidities if any and to correlate the associated risk factors with the progression of disease.

Methods: Prospective observational study which constituted conventional fungal culture of 188 tissue specimens collected from clinically suspected mucormycosis patients who had history of COVID.

Results: This study noted the occurrence of disease with predominance of males (72.03%). Most common symptoms were facial/periorbital swelling, followed by facial pain and headache. Among co-morbid conditions, diabetes mellitus was the most common (71.17%). Use of steroids (65.25%), antivirals therapy (22.86%), oxygen support (11.86%) used in management of COVID patients were found to be risk factors in post-covid-mucormycosis. radiological diagnosis showed involvement of paranasal sinuses (77.11%), followed by orbit (16.94%) and brain (5.90%). *Mucor* spp. was isolated in 21 cases. Although commonest fungus isolated was *Aspergillus*, analysis of the data for last 5 years showed a significant rise of Mucormycosis cases. Mortality was seen in 17.79% cases.

Conclusions: Fungal aetiology should be kept in mind in patients with above clinical presentations with history of recent COVID-19 infection especially who received steroids.

Keywords: Aspergillosis, COVID-19, Diabetes mellitus, Post-covid-mucormycosis, Steroid

INTRODUCTION

Though the spread of COVID-19's infection is not yet stopped, the number of new cases is not significant. Despite this, COVID-19-related problems are beginning to surface, with the fungus mucormycosis becoming a significant problem in India due to its uncharacteristic rise and high morbidity.¹ Based on the literature from December 2019 to the beginning of April 2021, approximately 71 percent of all cases of mucormycosis in

patients with COVID-19 were from India.² The mucoromycetes family of moulds, which are common decomposers of organic materials found in soil and dust, produce the fungal infection known as mucormycosis.³ Patients who have specific predisposing medical factors, such as immunosuppression and diabetes mellitus, are more likely to develop mucormycosis.⁴ The most common site of rhinocerebral mucormycosis is the paranasal sinuses, orbit, facial bones, and cranial cavity.⁵ The initial signs that are frequently presented to facial

and periorbital swellings, facial pain and headache. By harming the endothelial lining of blood vessels, mucormycosis in the bone marrow may stimulate fungal growth, resulting in vascular insufficiency, bony necrosis, and fungal osteomyelitis. Platelet-derived growth factor signalling has been linked to greater expression of mucormycosis' angioinvasive nature.⁶ Even with active therapy, fatality rates for serious infections are more. It is strongly advised to conduct appropriate imaging to determine the severity of the disease when mucormycosis is suspected, followed by surgical debridement. High-dose liposomal amphotericin B is recommended as the first line of treatment.⁷ The Indian Health Ministry has encouraged all States to designate mucormycosis itself an epidemic in response to a dramatic increase in the number of COVID-19 patients infected with the disease.⁸ We evaluated the information on patients with post-COVID-mucormycosis from the tertiary care hospital in Mumbai in order to further investigate the risk variables.

METHODS

This was the prospective observational study conducted at Mycology section of department of Microbiology, Grant Government Medical College, Mumbai from March 2021-June 2021 for four months.

Necessary ethical approvals, permissions were obtained from Institutional Ethical Committee of our Tertiary care hospital in Mumbai. A total of 188 specimens (tissue, crust, swabs) were collected from clinically suspected post-Covid-Mucormycosis patients. All the patients were COVID 19 positive confirmed by RTPCR test. These patients were further analyzed with respect to their clinical presentation; associated co-morbidities, radiological aspects, fungi isolated and outcome. Patients of this study mainly belonged 14 years and above age group and both genders were found to be affected. The major and minor criteria of Lanza and Kennedy were also applied to study these patients.⁹

Inclusion criteria

The major criteria included patients with facial pain/fullness, nasal obstruction, postnasal discharge, hyposmia/anosmia and fever; minor criteria included ear pain/fullness, headache, halitosis, fatigue, dental pain, and cough.

Exclusion criteria

Exclusion criteria were age group below 14 years, patients who were unwilling to comply with this study, patients with underlying paranasal sinus malignancy, congenital mucocilliary disorders, atrophic rhinitis. Statistical analysis was done from Open Epi, version 3, open-source calculator-SS proportion.

Conventional identification of fungi

Routine microscopic identification was carried out via direct microscopic identification using KOH mount. All the clinical specimens were directly inoculated on Sabouraud's dextrose agar and Sabouraud's dextrose agar with chloramphenicol and cycloheximide in duplicate. All the culture media were incubated at two different temperatures (37°C and 30°C). Culture readings for Yeasts were taken at 24, 48, 72 hours, 5th day and 7th day. The growth was observed for rate of growth, colour, texture, diffusible pigment, aerial and submerged hyphae, and colony topography. The growth on colonies were confirmed with lactophenol cotton blue (LPCB) mounting or by slide culture for speciation. Genus and species level of identification of the yeast colonies obtained was done by germ tube test, testing for growth at higher temperature and by dalmau colony morphology/assimilation and fermentation wherever required.¹⁰⁻¹³

RESULTS

This study noted the occurrence of disease with predominance of males (72.03%) and in females (27.09%). We observed existence of more than one symptom in the patients. Most common symptoms were facial/periorbital swelling in 60 cases, followed by facial pain in 54 cases and headache in 30 cases. In patients with involvement of orbit, other symptoms were drooping of the eyelids, proptosis and or diminution of vision. Among the associated co-morbid conditions, diabetes mellitus (71.17%) was the most common. Even in some cases new onset of diabetes (27.11%) was seen. Use of steroids (65.25%), antivirals therapy (22.8%), oxygen support (11.86%) used in management of COVID patients were found to be risk factors in post-Covid-mucormycosis. Radiological diagnosis showed involvement paranasal sinuses (77.11%), followed by orbit (16.94%) and brain (5.90%) (Table 1).

Out of 188 specimens processed for fungal culture, 62 (33%) specimens showed growth of fungi. Remaining 125 showed no growth while one specimen grew contamination.

Table 1 shows the fungi isolated in this study. *Aspergillus spp.* (16%) predominated followed by *Mucor spp.* (11%) and *Candida spp.* (4%). A single isolate of *Fusarium spp.*, *Scedosporium apiospermum* and *Syncephalastrum racemosum* was also grown. Repeated isolation and multiple slant growth of same fungus helped to rule out contamination.

Table 2 shows different fungi isolated in rhinosinusitis cases in last 5 years in our hospital. This five years analysis clearly shows the sudden increase in *Mucor* isolation in 2021. Even with prompt surgical and or medical treatment, mortality was seen in 17.7% mucormycosis cases. Out of 21 mortalities, in 16 cases

Mucor was isolated and in 5 cases *Aspergillus spp.* were isolated. The study also shows commonest predisposing factor associated with these cases was diabetes mellitus

(71%) irrespective of the isolate. Maximum death cases were due to complications leading to orbital involvement (61.9%) followed by intracranial involvement.

Table 1: Various parameters of the patients.

Parameter	Value (%)
Age (years)	19 to 64 years
Male: Female	7:2
Clinical Presentation	Cases
Facial/ Periorbital swelling	60
Facial pain	54
Headache	30
Diminution of vision	21
Dental pain	20
Fever	12
Drooping of eyelid	11
Nasal discharge	02
Associated co-morbid conditions	
Diabetes mellitus	52 (44.06)
New onset DM	32 (27.11)
Hypertension	25 (21.18)
Renal failure	4 (3.38)
Haematological malignancy	2 (1.69)
Pulmonary TB	2 (1.69)
Asthma	1 (0.08)
Risk factors due to use of	
Steroids	77 (65.25)
Antivirals	27 (22.86)
Oxygen support	14 (11.86)
Radiological findings	
Pansinusitis	91 (77.11)
Orbit involvement	20 (16.94)
Intracranial involvement	7 (5.90)
Fungus isolated	
<i>Aspergillus spp.</i>	31(16)
<i>Mucor spp.</i>	21 (11)
<i>Candida spp.</i>	7 (4)
<i>Fusarium spp.</i>	1 (0.5)
<i>Scedosporium apiospermum</i>	1 (0.5)
<i>Syncephalastrum racemosum</i>	1 (0.5)

Table 2: Isolation of different fungi in rhinosinusitis cases in last 5 years in a tertiary care hospital.

YEAR	<i>Mucor spp.</i>	<i>Aspergillus spp.</i>	<i>Candida spp.</i>	<i>Rhizopus spp.</i>	<i>Absidia spp.</i>	<i>Fusarium spp.</i>
2018	3	6	4	1	0	0
2019	1	12	1	1	1	1
2020	1	11	3	1	1	0
2021	21+6*	58	10	1	1	5
2022	1	5	2	3	0	0

DISCUSSION

As shown in Table 1, COVID-19 patients with diabetes mellitus who were using glucocorticoids were susceptible to mucormycosis. Similar findings were noted by

a comprehensive study of 101 Covid-19 patients in north India in June 2021 found findings that were similar.¹⁴ It revealed that the two main risk factors for developing mucormycosis were male preponderance (78.9%) and diabetes mellitus (83.3%). Additionally revealed a history

of taking corticosteroids in 76.3% of cases, followed by the use of antivirals such remdesivir (20.6%). The paranasal sinuses were involved in 88.9% of cases, followed by the orbit in 56.7% and rhino-orbito-cerebral mucormycosis in 22.2%, according to radiological results. Overall mortality was noted in 30.7% of the cases. A second study conducted in South India in June 2021 on 28 patients revealed that the majority (78.57%) of the patients were male and that the mean age of the participants was 49 years. Diabetes mellitus was the most common comorbidity (96%) and was followed by hypertension in 8 cases. In 17 patients (61%), oxygen was administered, and 46% received steroid medication. Pansinusitis and maxillary osteomyelitis were detected on radiology.¹⁵ The COVID-19 epidemic emphasises the significance of understanding the challenging biology of conditions like diabetes. The fact that COVID-19 patients had pathological pancreatic alterations shows that SARS-CoV-2 might cause pancreatic injury, which may help to explain why COVID-19 patients with no history of diabetes have high blood sugar levels. When the SARS-CoV-2 virus, diabetes mellitus, and steroid medication are combined, it appears to start a vicious cycle of immunosuppression and hyperglycaemia that can lead to risky fungus colonisation such mucormycosis.

Aspergillus species were the most frequently isolated fungi in this investigation among the 62 cultures (Table 1), followed by *Mucor species* in 21 specimens and *Candida species* in 7 specimens. While reviewing our institute's most recent five years of data, we noticed a considerable increase in opportunistic infections such mucormycosis brought on by the COVID 19 pandemic (Table 2). However, *Aspergillus spp* more specifically *Aspergillus flavus*, is already the most frequent etiological factor causing rhinosinusitis.¹⁶

All 21 of the cases where the outcome was death are listed in Table 3 in detail. The most frequent predisposing factor in these patients appears to be diabetes mellitus. Most cases were brought on by *Mucor*. Stress factors favour the spread of a mucormycotic infection, according to McNulty and Blitzer.¹⁷ The fungus gets a large portion of its metabolic needs from a ketone-reductase enzyme system in a person with ketoacidosis, which explains our findings.

Limitation of this study was shorter duration of the study.

CONCLUSION

A high suspicion of fungal aetiology should be kept in mind in patients with recent COVID-19 infection who receive steroids. Prompt diagnosis and early management are vital for a favourable outcome. It is crucial to identify this infection at an early stage in order to notify treating physicians of this debilitating and lethal infection and possibly reduce soft and hard tissue necrosis and severe complications.

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