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Original Research Article

A Study of Mucormycosis as an Extended Clinicopathological Spectrum of COVID-19 at a Tertiary Care Centre

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ABSTRACT

Background
Mucor mycosis is an emerging dreadful opportunistic angio-invasive fungal infection occurring predominantly in immunocompromised individuals. Popularly known as "Black fungus", it gained popularity due to its association with SARS-COVID-19. The aim of this study was to analyse various predisposing factors and histopathological features of COVID associated Mucor mycosis.

Methodology
This was a cross sectional retrospective study conducted at Department of Pathology, Government Kilpauk Medical College and Hospital, Chennai, over a period of six months, from April 2021 to September 2021. Maxillectomy and functional endoscopic sinus surgery (FESS) samples from 123 post COVID-19 patients were included in the study. Clinical details of systemic hypertension, diabetes, steroid and oxygen therapy were retrieved from case records.

Results
Our study comprised of 82 males and 41 females with male to female ratio of 2:1. Maximum number of cases were observed in the age group of 40 to 50 years (39%). Youngest patient was of 27 years and oldest age was 80 years. Facial pain was the most common symptom noted. In our study, 112 cases (91%) were diabetic, 71 cases (57.7%) were hypertensive and 116 cases (94.3%) had received systemic steroid therapy. Histopathological examination revealed increased fungal load with neutrophilic inflammation in 105 cases (85.36%), granulomatous inflammation in 18 cases (14.63%), mucosal invasion in 90 cases (73.17%), angioinvasion in 71 cases (57.7%), necrosis in 73 cases (59.3%) and infarct in 19 cases (15.6%).

Conclusions
Histopathological features such as high fungal load, angioinvasion and extensive areas of necrosis plays an important role in accurate diagnosis, assessing the prognosis and thereby reducing mortality and morbidity. We also conclude that high clinical suspicion in individuals with diabetes and steroid use is essential to facilitate early diagnosis and optimizing prompt treatment.

Keywords
Mucor mycosis, COVID-19, Fungal hyphae, Diabetes, systemic steroid therapy, hypertension

INTRODUCTION

The global pandemic of COVID-19 caused by severe acute respiratory syndrome corona virus 2 showed a sudden escalation of cases with Mucor mycosis particularly during the second wave.[1] Its incidence rate, globally, varies from 0.005 to 1.7 per million population. In India, its estimated prevalence is 140 per million population.[2,3] The fungus gains its entry through inhalation, ingestion, direct contact or traumatic inoculation of spores. Thus, individuals with uncontrolled diabetes, immuno-suppression, such as systemic corticosteroid therapy, chemotherapy, organ transplantation, malignancies, neutropenia, trauma and burns, were at high risk in acquiring post COVID-19 Mucor mycosis.[4] Mucor mycosis invades the tissues directly, causes necrosis and spreads from nasal and sinus mucosa

rapidly into orbit followed by cavernous sinus and cranium.[5] If left undiagnosed, Mucor mycosis can be fatal.[6] Most commonly patients present with nasal blockage, facial pain, proptosis, oedema, headache, fever, ophthalmoplegia and neurological symptoms, in case of intracranial extension.[7] Histopathological examination of affected tissues shows extensive necrosis with large, non-septate fungal hyphae branching at obtuse angles. The fungus is seen infiltrating the mucosa, submucosa into blood vessels causing infarction of tissues and hemorrhage.[8] Angioinvasion is the most common and important histological feature of invasive Mucor mycosis.[9] The aim of this study was to analyze various predisposing factors and histopathological features of COVID associated Mucor mycosis.

MATERIAL AND METHODS

This was a cross sectional retrospective study conducted at Department of Pathology, Government Kilpauk Medical College and Hospital, Chennai, over a period of six months, from April 2021 to September 2021. IEC approval was obtained before starting the study. Out of 154 maxillectomy and functional endoscopic sinus surgery (FESS) samples received during this period, samples from 123 post COVID-19 patients were included in the study. These samples were preserved in 10% neutral buffered formalin. Paraffin embedded 3-to-5-micron tissue sections stained with hematoxylin and eosin (H & E) were assessed. Special staining, such as Periodic Acid Schiff (PAS), Gomori Methenamine Silver (GMS) stain, was performed when required and the histopathological findings were recorded. Clinical details of systemic hypertension, diabetes, systemic steroid therapy was retrieved from case records.

RESULTS

The demographic data of 123 post COVID-19 Mucor mycosis comprised of 82 males and 41 females with male to female ratio of 2:1. Maximum number of cases were observed in the age group of 40 to 50 years (39%) (Table-1). Facial pain was the most common symptom noted, followed by facial swelling and headache (Table-2). In the current study, 112 cases (91%) were diabetic, 71 cases (57.7%) were hypertensive and 116 cases (94.3%) had received systemic steroid therapy. Figure-1 illustrates the overlapping risk factors of post COVID-19 Mucor mycosis in the present study. Histopathological examination revealed extensive necrosis along with numerous pale staining, flat, non-septate, large fungal hyphae frequently branching at right angles (Figure-2A). Staining with PAS and GMS (Figure-2C) was performed to highlight the fungal hyphae. Histopathological examination revealed increased fungal load with neutrophilic inflammation in 105 cases (85.36%) (Figure-2B), granulomatous inflammation in 18 cases (14.63%), mucosal invasion in 90 cases (73.17%), angioinvasion in 71 cases (57.7%) (Figure-2D), necrosis in 73 cases (59.3%) and infarct in 19 cases (15.6%) (Table-3).

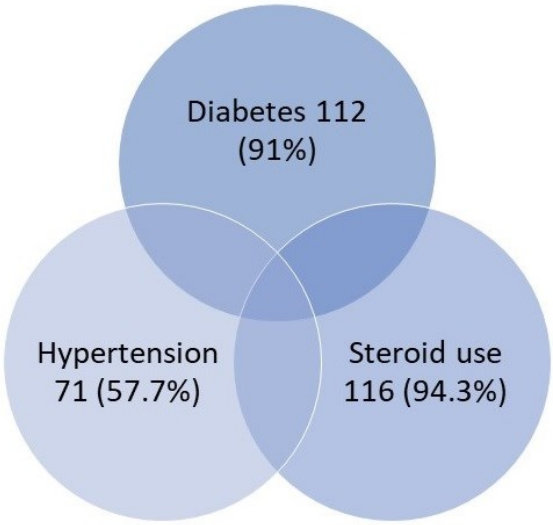

Figure-1: Overlapping predisposing factors in post-COVID-19 Mucormycosis patients

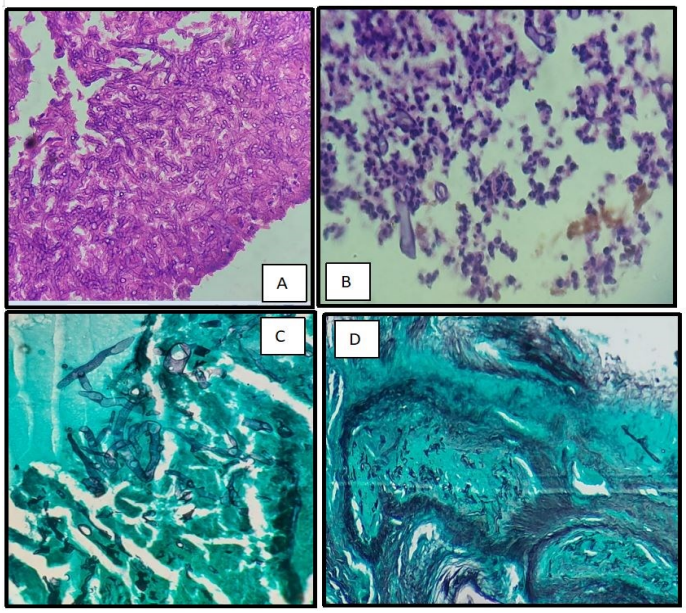

Figure-2:
A) Showing aseptate, broad, large fungal hyphae branching at right angles (H&E, X100)
B) Showing fungal hyphae admixed with neutrophilic inflammation (H&E X400)
C) Showing mucor fungal hyphae (GMS, X100)
D) Showing angio-invasion by the mucor fungal hyphae

Table-1: shows demographic data (N=123)

Age group in years	Number of cases (%)
21-30	2 (1.63%)
31-40	20 (16.26%)
41-50	48 (39.02%)
51-60	39 (31.71%)
61-70	11 (8.94%)
> 70	3 (2.44%)

Table-2: Clinical presentations in Rhino-orbital mucormycosis patients (N=123)

Clinical symptoms	Number of cases (%)
Facial pain	70 (56.91%)
Facial swelling	24 (19.51%)
Headache	14 (11.38%)
Black or blood-stained nasal discharge	4 (3.25%)
Decreased vision	4 (3.25%)
Facial numbness	3 (2.43%)
Nasal blockage	3 (2.43%)
Ptosis	1 (0.08%)

Table-3: Spectrum of micromorphological features in post-COVID-19 Mucor mycosis patients (N=123)

Histopathological features	Number of cases (%)
Acute inflammation	105 (85.36%)
Mucosal inflammation	90 (73.17%)
Necrosis	73 (59.3%)
Angioinvasion	71 (57.7%)
Infarct	19 (15.6%)
Granulomatous inflammation	18 (14.63%)

DISCUSSION

Globally, throughout the course of wide spread COVID-19 infection, the epidemiology of Mucormycosis has gradually evolved to limelight with mortality rate of 31-50%.[6] Mucormycosis, formerly known as zygomycosis, is ubiquitous fungal organisms infecting immunocompromised individuals.[10] Hypoxia, hyperglycemia, acidic conditions (metabolic and diabetic ketoacidosis), increased iron levels, and decreased phagocytic activity of white blood cells owing to immunosuppression are the primary causes for Mucormycosis to affect covid infected patients.[1] In our study, out of 123 post COVID Mucormycosis, we noted male predominance with male to female ratio of 2:1. Sreelakshmi et al[11] and Arora et al[12] also found similar male predominance in their studies. The possible contributing factor was increased outdoor exposure to fungal spores in males and estrogenic protective role in females.[13]

In the present study we noted predisposing factors such as diabetes (91%), including diabetic ketoacidosis (4%), systemic steroid therapy (94%) and hypertension (57.7%) which is similar to S Patil et al[14] who observed diabetes (76.6%), corticosteroid therapy (72.34 %) and hypertension (22.34%) in their study. Pakdel et al[15] from Iran, Fouad et al[16] from Egypt and Ponce-Rosas et al[17] from Peru also made similar observations of diabetes and corticosteroid therapy as predisposing factors. Thus, the basis of high Mucormycosis prevalence in India may be due to latent, poorly monitored and uncontrolled diabetes, new onset diabetes due to covid 19 affecting pancreatic cells and rampant usage of steroids in the treatment of COVID infection.[18] Diabetic ketoacidosis aids in the fungal multiplication by increasing the free iron concentration and reducing antifungal elements in the blood.[19]

The mainstay of diagnosis is the histopathological examination of the tissues as it differentiates from other fungal infections. Mucormycosis appears as large non septate pale staining fungal hyphae branching at wide angles. This is important for early initiation of therapy and favorable prognostic outcomes as studies have shown that delay in initiating treatment by only 6 days had increased twofold mortality rate.[20] In our study we noted extensive areas of necrosis, hemorrhage, infarction neutrophilic inflammation in 85% and granulomatous inflammation in 15%. Mucosal invasion was noted in 90% and angio-invasion was observed in 71% of the study population. Kavita et al[18] and Sree Lakshmi et al[11] found similar findings in their study. Shree Lakshmi et al[11] and Ashina Goel et al[21] found that angioinvasion had direct impact on the prognosis of the patient. Hemorrhage and infarction noted may be due to the angio-invasive nature of the fungal hyphae causing destruction of vessel wall and luminal invasion.[22] Thus, the present study emphasizes that histopathological examination can aid in the proper diagnosis, early treatment of Mucormycosis and thereby predicting the prognosis of the patient.

CONCLUSIONS

Histopathological findings, such as high fungal load, extensive necrosis and dense inflammation, along with mucosal and angioinvasion, can aid in predicting the prognosis at the time of diagnosis. Accurate diagnosis and early treatment can decrease disease progression and reduce mortality rate. High clinical suspicion about the association of diabetes and corticosteroid use is necessary to clinch the diagnosis and decrease the burden of Mucormycosis in post COVID-19 patients at an early stage.

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