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Original Article

Pathology Section

Clinicopathological Study of Mucormycosis in COVID-19: A Cross-sectional Study from a Tertiary Care Centre in North Kerala, India

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ABSTRACT

Introduction: Mucormycosis is an angioinvasive disease associated with high morbidity and mortality caused by fungi of the order Mucorales. The rise in the incidence of mucormycosis, along with the surge of Coronavirus Disease-2019 (COVID-19), justifies reassessment of associated risk factors and the susceptible population. The present study aims to highlight the specific clinicopathological features and risk factors of mucormycosis in COVID-19 patients.

Aim: To investigate the histopathological features, key clinical findings in mucormycosis, and the predisposing factors associated with mucormycosis in post-COVID-19 patients.

Materials and Methods: This descriptive cross-sectional study was conducted at the Department of Pathology, Government Medical College, Manjeri, Malappuram, Kerala, India, in the Department of Pathology. It included all histopathologically proven Mucormycosis specimens from confirmed COVID-19 positive and post-COVID-19 cases in this Medical College from January 1, 2021, to December 31, 2021, amounting to a total of 30 cases. The type of tissue reaction, fungal hyphae, angioinvasion, necrosis, and fungal co-infections were assessed. Histopathologic analysis was performed using routine Haematoxylin and Eosin (H&E) slides, followed by special stains such as Periodic Acid Schiff (PAS) and Grocott Methenamine Silver (GMS). Data was collected using a proforma, and the clinical details were obtained from the request form received along with the biopsy specimen and case sheets. Age, gender, site of involvement, and risk factors were assessed and subjected to descriptive tabulation and analysis.

Results: The mean age was 49.5 years with a male-to-female ratio of 1.30:1. The major risk factors observed in the present study were Diabetes Mellitus (DM) and steroid therapy, 30 all cases (100%), along with others such as chronic kidney disease 2 cases (6.67%) immune disorders, and renal transplantation 1 case each (3.33%). The most commonly involved site was sinuses 27 cases (90.00%). Multiple sinuses were affected in 22 cases (73.33%), with the ethmoid sinus being the most common site 24 cases (80.00%), followed by the maxillary sinus 21 cases (70.00%). The most common reaction pattern observed was acute inflammation 15 cases (50.00%). Angioinvasion was noticed in 19 cases (63.33%) and necrosis was present in 28 cases (93.33%). Co-infection with fungal pathogens was observed in 8 cases (26.67%), with aspergillus being the most common co-infection in all except one of the eight cases. Fungal hyphae were visible on H&E slides in 28 cases (93.33%), while the remaining cases were identified only through special stains (PAS and GMS).

Conclusion: Mucormycosis infection is strongly associated with DM and steroid therapy. A more even distribution between males and females was noted, deviating from the male predominance described in most studies. The histopathological appearance of angioinvasion was less frequent compared to most studies, consistent with previous studies on the Indian population. Higher rates of co-infection and the presence of granulomatous inflammation were observed. Further studies are needed to explore the relationship between host immunity, morphological patterns, and their influence on prognosis.

Keywords: Angioinvasion, Coronavirus disease-2019, Diabetes mellitus, Histopathological features, Risk factors

INTRODUCTION

As COVID-19 cases have surged, there has been a dramatic rise in mucormycosis infections among patients infected with or recovered from COVID-19. Mucormycosis is an angioinvasive disease associated with high morbidity and mortality. It is caused by fungi of the order Mucorales, which includes Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia. Rhizopus oryzae is the most common type and responsible for nearly 60% of mucormycosis cases in humans, accounting for 90% of the Rhino-Orbital-Cerebral-Mucormycosis (ROCM) form. The mode of contamination occurs through the inhalation of fungal spores [1].

The prevalence of mucormycosis in India is approximately 0.14 cases per 1000 population, which is about 80 times higher than the prevalence in developed countries [1]. In a prospective multicentre study conducted by Patel A et al., from January 1, 2016, to September 30, 2017, at 12 tertiary care centres across India [2], Rhino-Orbital Mucormycosis (ROM) was reported as the most common presentation of mucormycosis. Diabetes mellitus was identified as the most common predisposing factor. The study also reported that disseminated mucormycosis and ROM with cerebral extension, shorter duration of symptoms, shorter duration of antifungal therapy, and treatment with amphotericin B deoxycholate (as opposed to liposomal) were independent risk factors for mortality. The changing epidemiology of mucormycosis due to the increased incidence during COVID-19 necessitates a reassessment of associated risk factors and susceptible populations. The principal risk factors for mucormycosis include diabetes mellitus with or without ketoacidosis, haematological malignancies, organ transplant, chronic kidney or liver disease, immunological disorders, prolonged corticosteroid therapy, deferoxamine therapy, and trauma [3,4]. Limited published studies from a pathologist's perspective in this part of South India are available [5,6]. Therefore, the present study aims to highlight the specific clinicopathological features and risk factors of mucormycosis in COVID-19 patients.

Mucormycosis has been classically described as an aggressive opportunistic infection occurring in immune-compromised patients. Fungal co-infections associated with the global COVID-19 pandemic, based on a retrospective analysis by Song G et al., [7],

have been reported. They presented the epidemiology of fungal co-infections in COVID-19 patients based on a Worldwide Web search and suggested the possibility of neglected fungal co-infections in COVID-19 patients, drawing ideas from Severe Acute Respiratory Syndrome (SARS) and influenza worldwide data. Sen M et al., reported six cases of ROM with a mean age of 60.5 years [8]. The major risk factors reported were uncontrolled type 2 diabetes with systemic corticosteroids for COVID-19 in all patients. Mehta S and Pandey A, Mekonnen ZK et al., and Werthman-Ehrenreich A each presented a case of concurrent COVID-19 infection with invasive ROM [9-11].

Different pathophysiological models have been proposed on the pathogenesis of mucormycosis in COVID-19. In a SARS-CoV-2 infected individual, numerous factors have been shown to be involved in the pathogenesis of COVID-19 Associated Mucormycosis (CAM). Mucorales invades vessels through its spore coat protein (CotH3) with Glucose-regulated 78 KDA Protein (GRP78) on the human endothelial cells acting as a receptor for vascular invasion. Hyperglycaemia, diabetic ketoacidosis, and the presence of iron are the key factors promoting this interaction. SARS-CoV-2 directly increases GRP78 expression, precipitating diabetic ketoacidosis, and might alter innate immune cell functions [12]. Glucocorticoids used in the treatment can worsen the scenario by causing hyperglycaemia and immunosuppression. An increase in mucormycosis in the Indian context has been linked to a triad of diabetes, widespread use of corticosteroids, and COVID-19, mainly through cytokine storm, lymphopaenia, and endothelial damage [13].

Sree Lakshmi I et al., reported that histopathological features of mucormycosis, such as angioinvasion, perineural invasion, severe fungal load, and large areas of necrosis, were directly proportional to the mortality rate [6]. Diabetes and a history of corticosteroid intake for the treatment of COVID-19 were identified as the two most common predisposing factors for the development of mucormycosis.

Hence, the present study aimed to study the histopathological features of mucormycosis and the associated risk factors of mucormycosis in patients with COVID-19.

MATERIALS AND METHODS

The present descriptive cross-sectional study was conducted in the Department of Pathology, Government Medical College, Manjeri, Malappuram, Kerala, India. All histopathology-proven Mucormycosis specimens in confirmed RT-PCR COVID-19 positive and post-COVID-19 cases at the study institution from January 1, 2021, to December 31, 2021, were included after obtaining approval from the Institutional Ethics Committee (IEC number-IEC/GMCM/93).

Inclusion criteria: All histopathology-proven Mucormycosis specimens in confirmed RT-PCR COVID-19 positive and post-COVID-19 cases were included.

Exclusion criteria: COVID-19 cases diagnosed with positivity in the rapid antigen test and autopsy cases of COVID-19 were excluded.

Study Procedure

Data were collected using a proforma. The clinical details were obtained from the request forms received along with the biopsy specimen, including age, gender, site of involvement, and risk factors such as diabetes mellitus, steroid therapy, immunological disorders, organ transplant, etc. Histopathologic analysis of routine H&E slides, PAS, and GMS stained slides of Mucormycosis specimens in COVID-19 and post-COVID-19 cases was performed. Assessment included the type of tissue reaction, presence of fungal hyphae, angioinvasion, necrosis, and fungal co-infections on H&E stained slides, followed by special stain studies including PAS and GMS.

STATISTICAL ANALYSIS

The data, which included age, sex, risk factors, site, interval between COVID-19 and mucor presentation, histopathological findings, and co-infections, was entered into an excel sheet and subjected to descriptive tabulation and analysis.

RESULTS

In the present study, a total of 30 cases were included. The subjects had an age range from 23 to 76 years. Most of the subjects (10 out of 30, 33.33%) belonged to the age group of 51 to 60 years. Of all the thirty study subjects, 17 (56.67%) were males and 13 (43.33%) were females. The mean age in the present study was 49.5 years with a male-to-female ratio of 1.30:1. The age and sex distribution of cases in the present study are given in [Table/Fig-1].

Age (in years)	Number of cases
21-30	1
31-40	2
41-50	3
51-60	10
61-70	9
71-80	5

[Table/Fig-1]: Age distribution of cases.

The major risk factors observed in the present study were diabetes mellitus and steroid therapy in all the cases (100%), followed by chronic kidney disease in 2 cases (6.67%), immune disorder, and renal transplantation in 1 case each (3.33%) [Table/Fig-2].

Risk factors involved	No. of cases (n)
Diabetes mellitus	30
Steroid therapy	30
Chronic kidney disorder	2
Immune disorder	1
Renal transplant	1

[Table/Fig-2]: Risk factors associated with COVID-19 Associated Mucormycosis (CAM) (N=30).

Most of the patients presented in the second week (7-13 days) after commencement of COVID-19 treatment 12 cases (40%), followed by the first week (0-6 days, 11 cases (36.67%) [Table/Fig-3].

Interval between COVID-19 treatment commencent and presentation of mucor symptoms	No. of cases (n)	Percentage (%)
0-6 days (First Week)	11	36.7
7-13 days (Second week)	12	40
14-20 days (Third week)	6	20
21-27 days (Fourth week)	1	3.33

[Table/Fig-3]: Interval between COVID-19 treatment commencent and presentation of mucor symptoms.

The sites involved were sinuses in 27 cases (90.00%), followed by the nasal cavity 17 cases (56.67%), orbit 5 cases (16.67%), pterygopalatine fossa 4 cases (13.33%), and brain in 1 case (3.33%) [Table/Fig-4]. Multiple sinuses were involved in 22 out of 30 cases in the present study (73.33%). The most common sinus involved was the ethmoid sinus 24 cases (80.00%), followed by the maxillary sinus 21 cases (70.00%), sphenoid sinus in 18 cases (60.00%), and frontal in 6 cases (20.00%). All the sinuses were involved in 6 cases (20.00%).

Microscopic examination showed various histopathological reactions [Table/Fig-5]. The most common reaction pattern observed was acute inflammation, which was seen in 15 cases (50.00%), followed by chronic inflammation in 8 cases (26.67%), granulomatous reaction in four cases (13.33%), foreign body reaction in 2 cases (6.67%), and eosinophilic reaction in 1 case (3.33%). Angioinvasion was noticed

in 19 cases (63.33%) and was absent in the remaining 11 cases (36.67%). Necrosis was present in 28 cases (93.33%) and absent in 2 cases (6.67%). The presence of co-infection was observed in 8 cases (26.67%), out of which seven were Aspergillus. Co-infection with the bacteria Actinomycosis was seen in one case [Table/Fig-6].

Sites	No. of cases (n)
Nasal cavity	17
Ethmoid sinus	24
Maxillary sinus	21
Sphenoid sinus	18
Frontal sinus	6
Orbit	5
Pterygopalatine fossa	4
Brain	1

[Table/Fig-4]: Sites involved and distribution among sinuses (N=30).

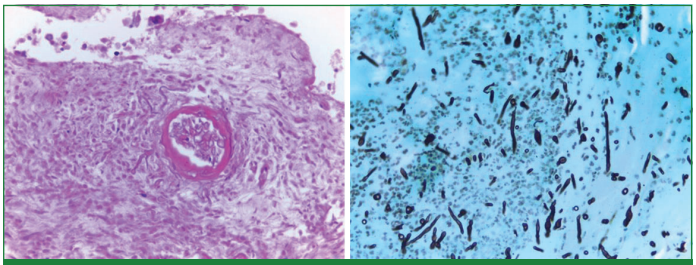
Histopathological features	No. of cases (n)
Acute inflammation	15
Chronic inflammation	8
Granulomatous reaction	4
Eosinophilic reaction	1
Foreign body reaction	2
Presence of angioinvasion	19
Presence of necrosis	28

[Table/Fig-5]: Histopathological Features noted in cases of COVID-19 Associated Mucormycosis (CAM) (N=30).

Co-infection	No. of cases
Aspergillus	7
Actinomycosis	1
Absent	22

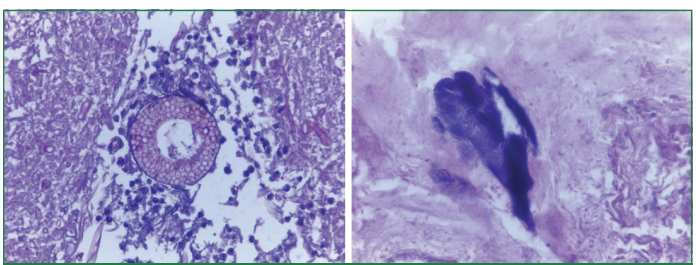
[Table/Fig-6]: Presence of co-infection and organisms involved (N=30).

The authors were able to identify the fungal hyphae on H&E slides in 28 cases (93.3%) [Table/Fig-7], and in the remaining 2 cases (6.67%), hyphae were identified only on special stains (PAS and GMS) [Table/Fig-8].



[Table/Fig-7]: Fungal hyphae with angioinvasion, 40x, H&E.
[Table/Fig-8]: GMS stain highlighting hyphae, 40x. (Images from left to right)

Nine out of the 30 patients (30%) died during the period of the present study. Co-infection with actinomycosis and aspergillosis was present [Table/Fig-9,10]. The clinical presentation of mucormycosis cases can be seen in [Table/Fig-11-13].



[Table/Fig-9]: Aspergillus fruiting body co-infection with mucor, 40x, H&E.
[Table/Fig-10]: Actinomycosis- co-infection with mucor, 40x, H&E. (Images from left to right)

[Table/Fig-11]: Case presented with supra-orbital and infra-orbital swelling.

[Table/Fig-12]: Case of Rhino-Orbital-Cerebral Mucormycosis (ROCM).
[Table/Fig-13]: Case presenting as orbital cellulitis diagnosed as mucormycosis on biopsy. (Images from left to right)

DISCUSSION

The study included a total of 30 cases during the study period. RT-PCR positivity was considered as the operational definition of a case. Most of the cases in the present study belonged to the age group of 51 to 60 years (33.33%). The youngest person was 23 years old, and the oldest was 76 years old. Out of the thirty study subjects, 17 (56.67%) were males, and 13 (43.33%) were females. In comparison to the present study, a much stronger male predominance has been noted in most studies. In a multicentre observational study of mucormycosis in India, conducted by Patel A et al., on a total of 287 individuals, 74.6% were men, and only 25.4% were women [14]. Mucormycosis was more common in males (73.60%) with a mean age of 46.8 years in a study by Jain K et al., among patients in a rural tertiary setting in central India [15]. The mean age of the entire study population was 53.4 years in the study by Patel A et al., [14]. In comparison, the mean age in the present study is 49.5 years. According to a systematic review of COVID-19 cases from 18 countries by Hoenigl M et al., 78% of CAM cases reported were males [16].

The rhino-orbital (ROM) area was the most common site involved in the present study. All the cases studied (100%) involved this area. The common sites involved were sinuses in 27 cases (90.00%), followed by the nasal cavity 17 cases (56.67%) and the orbit 5 cases (16.67%). Hoenigl M et al., reported that rhino-orbital cerebral infection was the most frequent presentation of the disease (74%) [16]. This study noted that ROCM infection was particularly common in patients from India, where 41 out of 42 patients (98%) had rhino-orbital cerebral infection, compared with 18 out of 38 patients (47.37%) from outside India. The results from our study are in line with this finding.

A systematic review on CAM by Muthu V et al., reported that ROM and ROCM accounted for 89% of cases in India, while globally, they accounted for only 64% [12]. Proof of cerebral involvement was found in 11 (27%) of these 41 patients in the study mentioned above by Hoenigl M et al., whereas authors only had one case involving the brain in the present study. Multiple sinuses were involved in 22 out of 30 cases in the present study (73.33%), with the most common sinus involved being the ethmoid sinus 24 cases (80.00%), followed by the maxillary sinus 21 cases (70.00%), the

sphenoid sinus in 18 cases (60%), and the frontal sinus in 6 cases (20.00%). A prospective observational study conducted by Lakshmi I et al., also showed the ethmoid sinus to be the most common site, followed by the maxillary sinus [6]. Authors did not have any cases involving the lung in the present study. The study by Muthu V et al., also pointed out that pulmonary, disseminated, and other sites were less frequently reported from India [12]. Several explanations for the observed preponderance of rhino-orbital cerebral infection in India have been put forward, the most important being the difference in the distribution of species, with Rhizopus arrhizus being the most common species in India, compared to Cunninghamella spp. being the most common species in countries like Spain [16]. Pulmonary disease almost exclusively occurred in the Intensive Care Unit (ICU) setting and was present in 50% of patients reported from outside India, with most of the cases being from Europe and the USA, as per the study by Hoenigl M et al., [16].

As observed in most studies, DM and corticosteroid therapy were the most common risk factors in the present study as well. All cases (100%) were diabetic and had received steroid therapy. A systematic review of 101 cases reported worldwide by Singh AK et al., found that pre-existing DM was present in 80% of cases [13]. Diabetes was the most prevalent condition overall in Hoenigl M et al., review of cases, reported in 66 (83%) of 80 cases overall [16]. However, the same study also noted the almost ubiquitous presence of Diabetes CAM in cases from India (present in 95%) and reported a higher prevalence of diabetes as a risk factor in Indian patients compared to patients from other countries (40 of 42 patients in India (95%) vs 26 of 38 (68%) from outside). The present study also reported that ROCM was mostly seen in patients with diabetes. According to this study, 93% of patients with rhino-orbital cerebral disease were diabetic, compared to pulmonary cases which showed a weaker association (55%). Authors did not have any pulmonary cases in the present study for a similar comparison.

The mainstay of treatment offered in the present hospital was steroids, liposomal amphotericin B, oxygen, and supportive therapy. Corticosteroid intake for the treatment of COVID-19 was reported in 76.3% of cases in India, as reported by Singh AK et al., in a systematic review of cases reported worldwide and in India. The review also reported an association with the intake of remdesivir (20.6%) and tocilizumab (4.1%) as therapy [13]. However, none of the patients received remdesivir or tocilizumab.

Among the patients, 2 had chronic kidney disease (6.67%). This is comparable to Hoenigl M et al., study, which reported chronic kidney disease in 6% of cases [16]. One case in the present study had a history of organ transplantation (3.33%). Muthu V et al., reported solid organ transplant in five out of the 233 Indian cases they studied (2.14%) [12]. Regarding other well-studied risk factors, the authors did not have any cases with haematologic malignancy developing CAM. Muthu V et al., reported 2 cases among 233 cases from India (0.9%), while the association was stronger in patients outside India (four out of 42 cases, 9.52%). Hoenigl M et al., study reported 5 cases out of 80 CAM cases (6.25%) having a haematological malignancy [16].

Most of the patients in the present study presented in the second week (7-13 days) after commencing COVID-19 treatment, accounting for 12 cases (40%) in our study. Mucormycosis was diagnosed at a median of 10 days (range: 0-90 days) after the diagnosis of COVID-19 in the study conducted by Hoenigl M et al., [16]. In another multicentre observational study conducted by Patel A et al., [14], the number of days between the diagnosis of COVID-19 and CAM was 18.

Out of the 30 patients in the present study, 9 (30%) died during the study period. In the study by Hoenigl M et al., [16], all-cause mortality occurred in 39 (49%) out of 80 patients. The mortality rate reported in the present study, however, was 37% in patients with Rhino-Orbital-Cerebral Mucormycosis (ROCM), which was comparable to the present study where all cases were Rhino-Orbital in nature. The fatality rate of cases reported from India (36.5%) was lower than the globally reported cases (61.9%), probably due to the predominance of Rhino-Orbital-Mucormycosis (ROM) as per a multivariate analysis of 275 cases of CAM, of which 233 were reported from India and 42 from the rest of the world by Muthu V et al., [12]. A lower value of 16% mortality was reported in the study by Sree Lakshmi I et al., [6].

Among the histopathological findings in the present study, an inflammatory background consisting of neutrophils, lymphocytes, and plasma cells was observed in 50% of the cases, whereas the presence of a granulomatous response (13%), eosinophilic response (3%), and foreign body reaction pattern (5%) was less frequent. In the present study, granulomas did not show necrosis in the centre in any of the cases. Frater JL et al., [17] have described inflammation in mucormycosis, where a neutrophilic response was seen in 50% of the cases, pyogranulomatous response in 25%, only granulomatous response in 5%, and no inflammation in 20% of the cases. The presence of granulomatous response is consistent with other studies in the Indian population, such as those by Ganesan N and Sivanandam S and Sree Lakshmi I et al., which reported granulomatous inflammation at 23% and 11%, respectively [5,6]. Angioinvasion was noted in 63% of the cases in the present study, which was lower than in many of the previous studies, and necrosis was observed in 95% of the cases. Frater JL et al., [17] identified angioinvasion in 100% of the cases, while studies in the Indian population by Ganesan N and Sivanandam S, found it in 71.67% of the samples, which is closer to the present findings [5]. Angioinvasion was present in only 24% of the patients in the study by Sree Lakshmi I et al., [6].

In the present study, authors found 8 cases (26.67%) of co-infection. Out of these cases, seven were Aspergillus and one was Actinomycosis. The study by Ganesan N and Sivanandam S, identified Aspergillus in 20% of the cases and Candida in 13.33% [5]. One of the cases in the present study had a fungal ball of Aspergillus. Co-infection with Actinomycosis was not described in the mucor-related articles that authors could find in the published literature. The histomorphology of these cases was confirmed by special stains and culture.

Limitation(s)

The limitations of the present study were that we could not obtain all the clinical information, such as the mode of presentation and follow-up after the study period. Additionally, the study sample size was small. Another limitation was the inability to include culture confirmation in all cases due to its unavailability.

CONCLUSION(S)

Mucormycosis infection was found to be overwhelmingly associated with DM and steroid therapy. The association was much stronger than what was identified in previous studies, especially in study populations outside India. Male preponderance was much lower in our study compared to most available studies. The histopathological appearance of angioinvasion was less frequent compared to most studies, although it is consistent with previous studies conducted on the Indian population. The unexpected findings were higher rates of co-infection and a higher incidence of the granulomatous type of inflammation. Further studies need to be conducted to investigate the relationship between host immunity and morphological patterns, and how it influences the prognosis.

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