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Original Research Article

COVID Associated Mucormycosis –A Clinicoepidemiological Study in a Tertiary Care Centre

Dr. Megha Annigeri[1], Dr. Laxmi Purushothama[2], Dr. Lyra Joy[3], Dr. Annapurna S. Mushannavar[4]

[1]Assistant Professor, Department of Otorhinolaryngology, KMCRI, Hubballi, Karnataka, India.
[2]Senior Resident, Department of Otorhinolaryngology, KMCRI, Hubli, Karnataka, India.
[3]Assistant Professor, Sree Mookambika Institute of Medical Sciences, Kulashekaram, Kanyakumari, Tamil Nadu, India.
[4]Assistant Professor, Department of Otorhinolaryngology, Karnataka Medical College & Research Institute, Hubballi, Karnataka, India.

Corresponding Author
Dr. Annapurna S. Mushannavar, Assistant Professor, Department of Otorhinolaryngology, Karnataka Medical College & Research Institute, Hubballi, Karnataka, India.

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ABSTRACT

Background
Mucormycosis is a life-threatening opportunistic angioinvasive fungal infection seen in immunocompromised states. It's raise in covid -19 infected individuals was of concern & the entity was termed as covid associated mucormycosis (CAM). The disease that was previously present endemically was blown to an epidemic. The purpose of this study is to present the epidemiological & clinical profile of the cases of CAM that were treated at a tertiary care centre.

Methods
The present observational study was conducted at department of ENT of a tertiary care centre during the study period of April 2021-December 2021. Convenience sampling method was used & 305 patients with suspected mucormycosis were selected for the study. Complete history of patients was taken & laboratory along with histological & radiological tests were performed. Results were analyzed using SPSS version 25.0.

Results
The mean age of patients was 51.76±6.3 years. Number of female patients was 21.9% & number of male patients was 78.03%. Only 6.5% patients had taken first dose of vaccine & 0.98% had taken two doses of vaccine. All the patients (100%) had diabetes as a comorbidity. Average duration of disease was 6.8 years. Mean HbA1c was 9.23±1.7. Maximum (64.5%) patients were taking OHA drugs. 78.1% patients had taken steroids for the treatment of COVID. Mean duration of steroids taken was 10.2 days. 11.5% had taken antifungals & 80.6% had taken antibiotics to cure the infection. Significant association was found between severity of disease & RBS, HbA1C & total count ($P<0.05$). 20 (7.21%) had rhinocerebtal type of mucormycosis, 15 (4.92%) had

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rhinoorbital & 270 (88.52%) had sinonasal mucormycosis. 100% had DM of which 95 (31.1%) were recently diagnosed(<6 months)

Conclusion

The immunosuprressive nature of Covid along with DM has led to CAM ;factors like prolonged dry oxygenation may have added to the severity of the disease. Amultidisciplinary approach to early diagnosis & clearance were indispensable in the management of CAM.

Keywords- antibiotics, covid-19, diabetes, mortality, mucormycosis, steroid

INTRODUCTION

Due to the global COVID-19 pandemic, mucormycosis—a uncommon & potentially fatal fungal infection—saw an unusual rise in cases. India, which has a large population impacted by SARS-CoV-2, reported the most mucormycosis cases, particularly during the second wave of COVID-19.[1,2] As of 2021, India reported 40,845 instances of mucormycosis, according to records from the Union Health Ministry.[3] The disease's impact was so great that the government used the Epidemic Diseases Act of 1897 to declare "mucormycosis" a sickness that needed to be reported.[4]

Angioinvasive fungal infections like mucormycosis are brought on by fungi that are members of the Mucorales order. Rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, or other illnesses can be used to describe the presentation, including uncommon forms including endocarditis, osteomyelitis, peritonitis, & renal disorders. It usually targets immunocompromised people, such as diabetics, recipients of transplants, & those on steroid therapy.[5] Poorly managed diabetes is a greater cause in developing countries like India than post-transplant recipients, which is more common in the developed world.[6] Fungal infections, such as Aspergillus flavus, Candida glabrata, & Candida albicans, have been connected to COVID-19.[7] India had a sudden & unexpected rise in mucormycosis cases among COVID-19 patients during the second wave of the virus, accounting for 71% of all mucormycosis cases worldwide. Koehler et al. [8] found that five out of nineteen critically ill COVID-19 patients had invasive lung aspergillosis.[9] In the context of a COVID-19 infection, poorly controlled diabetes, corticosteroid & immunosuppressive medication administration, & other factors create an environment that is favorable to the development of mucormycosis.[10]

With this background, this study was specifically designed to present the clinic-epidemiological profile of the COVID Associated Mucormycosis cases admitted & managed in our tertiary care centre.

MATERIAL & METHODS

The current observational study was carried out from April 2021 to December 2021 at an ENT department of a tertiary care facility. Before the study started, institutional ethics committee approval was obtained. After being fully informed about the operation, patients were requested to sign an informed permission form.

305 patients with probable mucormycosis were chosen for the study using the convenience sample approach. The identification of broad aseptate hyphae by direct microscopic examination using potassium hydroxide (KOH) wet mount or histopathological analysis of nasal swabs (crusts & discharge) & excised sterile tissue (Eschar) in individuals displaying clinically compatible

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symptoms were characteristics of probable mucormycosis cases. Additionally, predisposing risk factors (such as diabetes mellitus, glucocorticoid therapy, transplantation, malignancy, & immunosuppression), baseline demographic information, COVID-19 status at admission, previous medical history, & clinical characteristics relevant to SARS-CoV-2 infection & mucormycosis, as well as COVID-19 vaccination status, were taken from hospital records. Other comorbid conditions, such as hypertension & ischemic heart disease, were also included..

Laboratory parameters assessed were hemogram, liver function tests, creatinine levels, serum potassium, blood glucose, HbA1c, Ferritin, D-Dimer, CRP, ESR, TC, Neutrophil, Lymphocyte, IL-6 & RBS. The site of infection by Mucorales was determined through clinical & radiographic evaluation, utilizing contrast-enhanced computed tomography (CECT) of the paranasal sinuses & orbit, as well as contrast-enhanced MRI of the brain & paranasal sinuses with orbit.

All patients were screened for SARS-CoV-2 by RT-PCR & HRCT chest at admission, with the exception of those who had previously had a positive SARS-CoV-2 RT-PCR result, as long as the patient had not shown any symptoms associated with COVID-19 & 15 days had elapsed since the positive result. We collected data on the therapy (antifungal medication, dosage, & duration) & investigated the relationship between CAM & risk factors.

Samples of excised tissue were analyzed histopathologically & microbiologically. Concurrently, fungal elements in tissue samples were identified by direct microscopy & KOH wet mount. Two sets of Sabouraud's Dextrose agar (SDA) were used to infect the tissue samples, which were then incubated in a Biological Oxygen Demand (BOD) incubator at 25 °C. The causal Mucorale was identified using standard mycological methods, including growth characteristics & lactophenol cotton blue (LPCB) wet mount examination, after the medium had grown. The tissue samples that were submitted for histological examination were evaluated using the Grocott methenamine silver staining, periodic acid-Schiff, or hematoxylin & eosin staining methods.

A multidisciplinary team called the COVID-19 associated fungal study group was formed by the institution to monitor all recruited patients.

The patients were treated in accordance with the institution's policy & the availability of posaconazole & amphotericin B. The damaged tissue was thoroughly surgically debrided in the patients. A nasal endoscopy was done at discharge & two to three weeks after surgery. Insulin was used to treat diabetes in the beginning, but oral hypoglycemic drugs eventually replaced it. Additionally, when necessary, a low dosage of atorvastatin (10 mg) was given.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), Version 25.0 (IBM Corp., NY), was used to do the statistical analysis. For quantitative data, descriptive statistics (mean ± standard deviation) were used, whilst frequency & percentage distribution were used for categorical variables. The chi-square test & Fisher's Exact Test were used in the statistical analysis for several categorical parameters. Additionally, the means or medians of two groups were compared using the Mann Whitney U test & the Student's t-test. Statistical significance was defined as a P-value of less than 0.05.

RESULTS

The mean age of patients was 51.76±6.3 years. Number of female patients was 21.9% & number of male patients was 78.03%. Out of all the patients 36.7% had been in home isolation. Mean

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duration at ward was 7.5 days & at ICU was 8.7 days. Only 6.5% patients had taken first dose of vaccine & 0.98% had taken two doses of vaccine shown in table 1.

Baseline data		**Values**
Age (years)	Range	58-80
	Mean	51.76±6.3
Gender	Male	238 (78.03)
	Female	67 (21.9)
Home isolation	No	193 (63.2)
	Yes	112 (36.7)
Mean duration at ward (days)		7.5±2.6
Mean ICU stay (days)		8.7±2.7
Vaccination status	No	282 (92.4)
	First dose	20 (6.5)
	Second dose	3 (0.98)
Mean SPO2		94.03±10.3
Mean duration on oxygen(days)		8.23±2.9
Use of humidifier		130 (42.6)

Table 1: Mean spo2 delivered, mean duration of oxygenation, & use of humidifier

All the patients (100%) had diabetes as a comorbidity of which –95 (31.1%) were newly detected.(<6 months. Average duration of disease was 6.8 years. Maximum (64.5%) patients were taking OHA drugs.

Variable		**N (%)**
Diabetes		305 (100)
Duration of diabetes (year)		6.8±2.4
Diabetes patients with duration `<6 months		95 (31.1)
Anti diabetic drug	No drug taken	13 (4.26)
	Insulin	67 (21.9)
	OHA	197 (64.5)
	Insulin+OHA	26 (8.5)

Table 2 Patient data on diabetes

Different laboratory parameters assessed with mean value were Ferritin (394.5±23.1), D-Dimer (741.9±45.2), CRP (72.8±3.67), ESR (33.0±1.1), TC (12376.7±215.8), Neutrophil (72.9±8.5), Lymphocyte (17.9±1.9) , IL-6 (21.0±2.9), RBS (265.11±24.5) & HbA1C (9.23±1.7). Patients having mucormycosis have a positive correlation with laboratory parameters showing increase in values with severity of disease.

Laboratory parameters	**Values**
Ferritin	394.5±23.1
D-Dimer	741.9±45.2

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CRP	72.8±3.67
ESR	33.0±1.1
TC	12376.7±215.8
Neutrophil	72.9±8.5
Lymphocyte	17.9±1.9
IL-6	21.0±2.9
RBS	265.11±24.5
HbA1C	9.23±1.7

Table 3: Assessment of laboratory parameters

On the basis of microscopic examination KOH was positive or 61.9% of patients & was negative for 38.1% of patients as shown in figure 1.

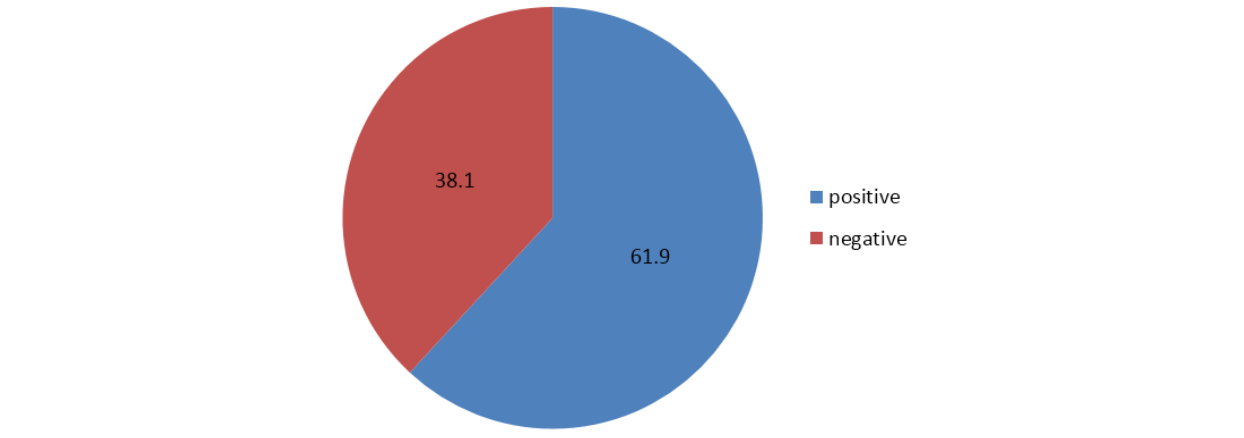

Figure 1: Distribution of patients on the basis of microscopic examination

78.1% patients had taken steroids for the treatment of COVID. Mean duration of steroids taken was 10.2 days. 11.5% had taken antifungals & 80.6% had taken antibiotics as a part of treatment for CAM. Surgery was done in 290 (95.08%) patients as shown in table 4.

Treatment given	**Values**
Steroids	78.1
Mean duration of steroids (days)	10.2±3.8
Antifungals	35 (11.5)
Antibiotics	246 (80.6)
Surgery	290 patients (95.08%)

Table 4 Treatment taken by patients

Significant association was found between severity of disease & RBS, HbA1C & total count ($P<0.05$) as shown in table 5.

Severity of disease	RBS	HbA1C	Total count
Mild (≤8)	219.10±24.2	7.13±1.0	12105.3±203.5
Moderate (9-15)	248.12±12.9	9.21±1.6	12352.7±211.8

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Severe (16-25)	289.18±21.6	10.26±1.8	12757.3±216.4
P value	0.016	0.019	0.034

Table 5 Association of severity of disease with risk factors

20 (7.21%) had rhinocerebtal type of mucormycosis, 15 (4.92%) had rhinoorbital & 270 (88.52%) had sinonasal mucormycosis. Sinus involved were maxillary 40(88.8%), ethmoid 33 (73.3%), 35 frontal (77.7%) & sphenoid 37 (82.2%) as shown in table 6.

Variable		N (%)
Type of mucormycosis	Rhinocerebral	20 (7.21)
	Rhinoorbital	15 (4.92)
	Sinonasal	270 (88.52)
Sinus involved	Maxillary	40 (88.8)
	Ethmoid	33 (73.3)
	Frontal	35 (77.7)
	Sphenoid	37 (82.2)

Table 6: Type of mucormycosis & sinus involved

DISCUSSION

The recent COVID-19 outbreak caused an unusual rise in mucormycosis patients. Steroid use & uncontrolled diabetes mellitus were common contributory factors seen in patients in several Indian states & institutions.

Mucormycosis in COVID-19 infections is caused by a number of reasons. One of the main causes of this problem is poorly managed diabetes. COVID-19 & diabetes mellitus interact in both directions, which has detrimental consequences. Serious COVID-19 infections are caused by diabetes, a pro-inflammatory disease.[11] Because SARS-CoV-2 directly affects pancreatic islet cells, it causes a reduction in insulin production. Additionally, it results in a transient hyper-inflammatory state that leads to insulin resistance.[12]

Male patients with poorly controlled diabetes made up the majority of our patients. 95 (31.1%) of our patients had recently received a diabetes diagnosis while they were ill with mucormycosis or COVID-19. The results are consistent with earlier studies carried out in India, which show that over 76% of patients have insufficient glycaemic control & that 42% of people with diabetes go untreated.[13, 14] Since India has the second-highest population of diabetics worldwide, raising public awareness of the importance of early diabetes diagnosis & strict diabetes control is crucial to preventing mucormycosis in the future.

According to the study, patients during the second wave of COVID-19 in India did not receive enough testing, & silent COVID-19 infections may also make them more susceptible to mucormycosis. On March 1, 2021, the Government of India launched the second phase of the COVID-19 immunization, making almost all of our patients eligible. This phase allows those over 60 & those over 45 with comorbidities to obtain the vaccine.However, 92.4% of our patients did not receive any doses of the vaccine, suggesting vaccine hesitancy in this group.

78.1% of participants in our study used steroids, suggesting widespread misuse of these drugs during the second COVID-19 wave. According to a comprehensive analysis of CAM cases,

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India has a far higher rate of steroid abuse than other countries worldwide.[16] Even in the absence of hypoxia, mild cases with a persistent fever or cough may be treated with low-dose steroids, according to the National guidelines published in May 2021.[17] It is known that corticosteroids increase the incidence of mucormycosis by aggravating hyperglycemia & impeding fungal phagocytosis.[18] For COVID-19 symptoms, 80.6% of patients were treated with antibiotics. The abuse of antibiotics was common during COVID-19.[19] During the first wave of the COVID-19 epidemic, the Indian National Guidelines also recommended antibiotics like azithromycin.[20] Because the nasal microbiome prevents Rhizopus from adhering & invading, drugs promote fungal growth & invasion via altering the microbiome.[21, 22].Most common type of mucormycosis was of sinonasal type (88.52%) Total cell count, RBS, & HbA1C were significantly correlated with illness severity. According to a study by Riad et al., only 44.5% of the patients exhibited clinical symptoms & severity, demonstrating the seriousness of COVID-19 as a predictor of mucormycosis.

CONCLUSION

The abuse of steroids & antibiotics during infections, in the context of uncontrolled hyperglycemia, may have exacerbated this epidemic amid the COVID-19 pandemic. Timely identification of diabetes with effective hyperglycemia management will significantly reduce the future occurrence of mucormycosis.

The immunosuprressive nature of Covid along with DM has led to CAM ;factors like prolonged dry oxygenation may have added to the severity of the disease.A multidisciplinary approach to early diagnosis & clearance were indispensable in the management.

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