

Mucormycosis and Covid: Why in India?

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Abstract

Background: CAM (COVID-19 associated invasive Mucormycosis) has been increasingly documented in patients with coronavirus disease 2019 (COVID-19). Predisposing factors include diabetes, steroid use, neutropenia, malignancies, and immunocompromised individuals. The etiology and the exact route of entry for CAM in COVID patients are poorly understood. In India, the incidence of CAM in COVID patients is on the rise. Repeated use of steam inhalation with herbal medicines might cause nasal mucosal trauma which leads to CAM

Patients and Methods: Analytical cross-sectional study was conducted to determine the cause for CAM. COVID positive patients with and without Mucormycosis admitted to our hospital were included in the study. A detailed history about the practice of steam inhalation, comorbid illnesses like Diabetes Mellitus (DM), and the use of steroids were assessed and analyzed.

Results: 63 CAM patients and 154 Non-Mucormycosis COVID positive patients were taken for the study and analyzed. Injudicious use of steam inhalation (84.1% vs 40.9%) multiple times per day (> 3 times) are strongly associated with CAM among COVID-positive patients (P value 0.0001). Uncontrolled DM (P-value 0.011) and prolonged duration of steroids > 8 days (P-value <0.001) were significantly associated with CAM when compared to control groups. Early diagnosis and treatment improved the outcome of CAM patients.

Conclusion: Injudicious use of steam inhalation can cause nasal mucosal trauma which can result in Invasive Mucormycosis in already immune depleted COVID positive patients

Keywords: CAM COVID-19 associated invasivemucormycosis); Coronavirus disease 2019 (COVID-19); Steam inhalation.

Introduction:

CAM(COVID-19associatedinvasive mucormycosis) is a rare life threatening opportunistic infection with high morbidity and mortality.¹ It commonly affects immune depleted individuals like uncontrolled Diabetes Mellitus (DM), malignancy, patients on long term steroids, and immunosuppressive

medications.² The global pandemic of coronavirus disease 2019 (COVID 19) and its management leads to an immunocompromised state which invites opportunistic infections like CAM. Worldwide, the prevalence of Mucormycosis varied from 0.005 to 1.7 per million population.³ In India, its prevalence is nearly 80 times higher (0.14 per 1,000), as per recent

estimate from 2019-2020.^{4,5} CAM is characterized by devitalization of host tissues that results from thrombosis of vasculature by fungal hyphae.⁶ The exact etiology and route of entry of CAM are poorly understood.

The fungus causing mucormycosis is commonly present in the environment. We hypothesize that damage/breach in nasal mucosa facilitates entry of Mucormycosis in COVID 19 patients. We believe that the indiscriminate use of steam inhalation in the COVID 19 pandemic cause's mucosal trauma thereby increases the incidence of CAM infection especially among Covid positive patients in India.

This study aims to evaluate the possible causes and risk factors for the high incidence of CAM in India during this global COVID pandemic.

Patients and Methods: This study is an analytical cross-sectional study conducted in Government Stanley Medical College Hospital from April 2021 to June 2021 for 3 months. COVID positive patients with and without CAM admitted to our hospital were included in the study. A detailed history about the risk factors and practice of steam inhalation, comorbid illness like Diabetes Mellitus (DM), and duration and use of steroids were evaluated and analyzed. Data about demographics, clinical features, co-morbidities, laboratory investigations, histopathology, management, and outcomes were collected after obtaining informed consent from all patients. The study was approved by our institutional ethics committee.

The diagnosis of COVID 19 was based on a real-time polymerase chain reaction (RT-PCR) test from nasopharyngeal and/or oropharyngeal swabs. In clinically suspected patients, the presence of fungal hyphae was detected by direct examination in 10% Potassium Hydroxide (KOH) from scrapping and was subsequently proved based on microbiological culture. Apart from establishing COVID 19 status and ascertaining CAM, imaging like computed tomography (CT) and/or magnetic resonance imaging (MRI) of the orbit, brain, and/or paranasal sinuses were performed for all cases to assess the extent of involvement due to CAM.

Statistical analysis:

Data were entered in the excel spreadsheet and variables were coded accordingly. The statistical analyses were performed using SPSS version 20

software. All continuous variables were expressed as mean and Standard deviation and categorical variables were expressed as proportion and percentages. Chi-square test/Fisher's exact test and unpaired t test were used as tests of significance. p value <0.05 was considered statistically significant.

Sample size: n=63 (CAM group); n=154 (control groups)

Sample calculation: from study done by Moorthy *et al*, Bangalore

Formula

$$n = \frac{z^2 pq}{d^2}$$

Where n=sample size

z=1.96 (statistical significant constant for 95% CI)

p=83% (proportion of covid 19 mucormycosis patients who are having DM as a risk factors))

q= (100-p) 17%

d=13% relative precision (i.e., 13% of 83=10.79 approx)

Results:

Sixty-three CAM patients (case n=63) and 154 Non-Mucormycosis COVID positive patients (control n=154) were taken for the study and analyzed. The baseline characteristics like age and sex between the two groups were comparable.

Table 1: Comparison of baseline characteristics between the groups

Parameter	Case group (n=63)	Control group (n=154)	P value
Age in years (mean ±SD)	54.57±10.8	50.1±17.1	0.124
Sex distribution			
Male (n,%)	32 (50.8)	81 (52.6)	0.881
Female (n,%)	31 (49.2)	73 (47.4)	

The COVID 19 patients with Mucormycosis are case group and without Mucormycosis are control group. Unpaired 't' test was used to compare the mean age between the groups (t=1.55; df=215). Chi square test was used to compare the gender distribution between the groups (X²=0.451; df=2).

Table 2: Description of various parameters of COVID 19 patients with Mucormycosis observed in the study.

Parameter	n	%
Steam inhalation		
Present	53	84.1
Absent	10	15.9
Use of native medication while steam inhalation*		
Amur坦jan	5	9.4
Herbal products (without scientific evidences)	25	47.2
Plain water only	23	43.4
Use of corticosteroids		
Present	44	69.8
Absent	19	30.2
Presence of diabetes		
Present	38	60.3
Absent	25	39.7
ENT mucormycosis infection present	50	79.4
Eye mucormycosis infection present	40	63.5
Type of antifungal therapy given		
Amphotericin-B alone	49	77.8
Amphotericin-B + Posaconazole	2	3.2
Amphotericin-B + FESS	2	3.2
Amphotericin-B + Meropenem	3	4.8
Posaconazole alone	7	11.1
Positive fungal culture present	46	73
Outcome observed		
Recovered	55	87.3
Died	8	12.7

The total N = 63 except * where the = 53 (as only patients who took steam inhalation was included

Based on imaging, nose and paranasal involvement.

Were about 50 patients (79.4%), orbital involvement of about 40 patients (63.5%). Positive fungal cultures were in 46 patients (73%) among CAM.

The various sites of nasal and paranasal sinuses involved based on imaging were shown in Table-3.

Table 3: Description of types of sites of ENT Mucormycosis observed in the study (N=63).

Site of ENT Mucormycosis involvement	n	%
All sinuses	6	9.5
Bilateral ethmoid, sphenoid frontal sinusitis	3	4.8
Bilateral maxillary sinusitis	1	1.6
Bilateral maxillary sinusitis, ethmoid, sphenoid sinusitis	1	1.6
Black turbinate sign in inferior turbinate left side	1	1.6
Ear crust, hyperemia, nasal turbinate hypertrophy	1	1.6
Edematous and hyperemic laryngeal mucosa	1	1.6
Edematous turbinate	3	4.8
Epistaxis, black discoloration of nasal bridge	1	1.6
Epistaxis, nasal discharge, edematous mucosa	1	1.6
Erythema of nasal mucosa ,hypertrophied turbinates	1	1.6
Erythema of nasal skin, foul smelling discharge. Mucosal edema	1	1.6
Foul smelling nasal discharge, epistaxis, Bilateral facial edema, black discoloration of nasal bridge	1	1.6
Invasive Rhino cerebral and Ocular Mucormycosis	1	1.6
Mild fungal sinusitis in right maxillary and ethmoid sinus	1	1.6
Nasal crusting, turbinate hypertrophy	1	1.6
Nasal foul smelling discharge, nasal bridge black discoloration+	8	12.7
Nasal mucosal edema, turbinate hypertrophy	1	1.6
Normal	13	20.6
Oral mucosal hyperemia, turbinate hypertrophy	1	1.6
Palate black discoloration	1	1.6

Similarly, orbital involvement was described in Table 4 of CAM patients. The duration of COVID related symptoms between the groups (7.27 ± 2.8 days in case Vs 6.58 ± 1.98 in control) were significant (P-value 0.044)

Table 5: Comparison of parameters between the case and control groups.

Parameter	Case group (n=63)	Control group (n=154)	Test used	Statistic value	df	P value
Duration of Covid symptoms in days (mean \pm SD)	7.27 \pm 2.8	6.58 \pm 1.98	Unpaired t test	t=2.02	215	0.044*
Presence of steam inhalation, n(%)	53 (84.1)	62 (40.9)	Fisher's exact test	X ² =33.5	1	<0.0001*
Number of times steam inhalation done per day (median \pm IQR)	3 (2 - 4)	2 (1 - 2)	Mann Whitney U test	U=414.5	--	<0.0001*
Use of native medication during steam inhalation						
Amur坦jan, n(%)	5 (7.9)	4 (2.6)				
Herbal, n(%)	25 (39.7)	28 (18.2)	Fisher's exact test	X ² =0.504	2	0.7772 (NS)
Plain water only, n(%)	23 (52.4)	30 (19.5)				
Use of steroid, n(%)	44 (69.8)	110 (71.4)	Chi square test	X ² =0.055	1	0.871 (NS)
Duration of use of steroid in days (mean \pm SD)	8.43 \pm 2.67	7 \pm 0.1	Unpaired t test	t=5.65	152	<0.001
Presence of diabetes, n(%)	38 (60.3)	63 (40.9)	Fisher's exact test	X ² =6.79	1	0.011*

*Indicates p<0.05 and considered statistically significant. The 'n' for row 4 was 53 and 62 for case group and control group respectively. The 'n' for row 6 was 44 and 110 for case group and control group respectively.

Table 4: Description of types of sites of ophthalmomycosis observed in the study (N=63)

Site of ophthalmomycosis involvement	n	%
Bilateralsevere NPDR, CSME	1	1.6
Bony erosion medial wall of orbit/proptosis	1	1.6
Diplopia, restricted movements	3	4.8
Left orbit edema	1	1.6
Left eye peri orbital edema	1	1.6
Left ophthamoplegia	1	1.6
Left orbit exentration done	1	1.6
Left orbital cellulitis	4	6.3
Normal	23	36.5
Orbital cellulitis	2	3.2
Periorbital edema	3	4.8
Ptosis+proptosis	1	1.6
Right orbit exentration done	1	1.6
Right orbital cellulitis	2	3.2

The practice of steam inhalation includes the use of native medications (medications without scientific

evidences) like amur坦jan, other herbal products, or with plain water and the number of times per day used were compared between two groups (Table 5).

It was found that steam inhalation and its usage of more than 3 times/day was found to be significant 84.1% in the case group and 40.9% in the control group) between two groups (P-value 0.0001).

The impact of usage of steroids for moderate and severe COVID illness on CAM (Table 5) were analyzed and it was found that intravenous steroids use was not positively correlated with CAM, however, the prolonged duration of steroid use for more than one week (8.43 \pm 2.67 days in case Vs 7 \pm 0.1 days in control) was found to give a significant difference between the two groups (P-value 0.0001).

The presence of comorbid illness especially Diabetes Mellitus (DM) (Table 5) were compared between the two groups as a predisposing factor for opportunistic CAM. It showed that 38 patients (60.3%) in the CAM group had DM as compared to 63 patients (40.9%) in the control group and the results were statistically significant (P-value 0.011).

Table 6: Calculation of odd ratio for various risk factors identified in the study.

Risk factor for mucormycosis	Mucor developed group (n=63)	No mucor group (n=154)	Odd's ratio	95% confidence interval	P value
Presence of diabetes	38 (60.3)	63 (40.9)	1.74	1.14 to 2.68	0.011*
Use of steam inhalation	53 (84.1)	62 (40.3)	7.86	3.7 to 15.8	<0.001*
Presence of both diabetes and steam inhalation	33 (52.4)	28 (18.2)	4.95	2.6 to 9.1	<0.001*

Data are expressed as n (%). *indicates p<0.05 and considered statistically significant

The odds ratio for various risk factors like the presence of diabetes, use of steam inhalation, and both (DM and steam inhalation) identified in the study were calculated and found that presence of Diabetes Mellitus 38 (60.3%) among CAM versus 63 (40.9%) among non CAM, their odds ratio of 1.74 (CI 1.14 to 2.68), use of steam inhalation 53 (84.1%) among CAM versus 62 (40.3%) in control groups, their odds ratio was 7.86 (CI 3.7 to 15.8) produced significant association among CAM patients. The presence of both diabetes and steam inhalation was also produced significant results (odds ratio 4.95, CI between 2.6 to 9.1 with P-value <0.001).

Data about the outcome (table 2) were also analyzed and 55 patients (87.3%) were recovered

and about 8 patients (12.7%) succumbed to illness which showed that appropriate diagnosis and intervention improved the outcome of CAM.

Discussion:

CAM is a rare superinfection in immunocompromised individuals caused by invasion of fungal hyphae resulting in ischemic necrosis of host tissues.⁶ The most common clinical presentation of Invasive Mucormycosis (CAM) is a rhino orbital cerebral infection, due to invasion of spores into the paranasal sinuses of immune depleted individuals.⁷ Cytokine storm, uncontrolled DM and prolonged steroids amidst Covid 19 infection causes immunocompromised states which lead to CAM.⁸

Table 7: Criteria for Proven Invasive Fungal Disease (Donnelly *et al.* Clinical Infectious Diseases 2020)

Microscopic Analysis: Sterile Material	Culture: Sterile Material	Blood	Serology	Tissue Nucleic Acid Diagnosis
Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage	Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding BAL fluid, a paranasal or mastoid sinus cavity specimen, and urine	Blood culture that yields a mold (eg, <i>Fusarium</i> species) in the context of a compatible infectious disease process	Not applicable	Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue

Infection usually begins with flu-like symptoms, spreads to all the sinuses and then invade contiguous structures like the palate, orbit, and brain results in worsening of clinical symptoms.⁹ Early recognition of warning symptoms and timely interventions are vital to avoid morbidity and mortality in this lethal condition. The diagnosis of CAM (Table-7) was made as per Criteria for Proven Invasive Fungal Disease made in "Revision and Update of the Consensus Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium".¹⁰

In the multicentric study by Moorthy *et al.*, the incidence of mucormycosis is not age or gender-dependent, and the significantly higher number of males might be a reflection of the higher COVID 19 prevalence of males in India. In India till 25 May 2020, approximately 66.8% of COVID-19 cases were identified to be males.¹¹ In the present study mean age affected was 54.57±10.8 years, gender

distribution was 32 (50.8%) were males as against 31 (49.2%) were females in CAM group. The mean duration between the diagnosis of COVID 19 and the appearance of Mucormycosis in our study was 7.27 ± 2.8 days, which is consistent with a previous study.¹²

Our study included patients with Rhino-orbital Cerebral Mucormycosis as case group (n=63) compared to Non Mucormycosis covid positive patients as the control group (n=154).

Computed tomography (CT) is the first diagnostic imaging of choice used to assess the status of sinuses, although the extent of extra-sinus spread is best judged with magnetic resonance imaging (MRI).¹³ In our study, all suspected CAM patients had undergone CT paranasal sinuses and MRI (Fig. 1, 2, 3) which showed significant findings in 50 patients (79.4%), orbital involvement in 40 (63.5%) patients, both paranasal sinuses, and orbital involvement in 19 (30.1%) patients.



Fig. 1: Computed Tomography Para Nasal Sinuses (PNS) (reformatted coronal view) shows soft tissue opacification in right maxillary sinus with erosion of lateral wall of sinus and extension to right pterygopalatine fossa.

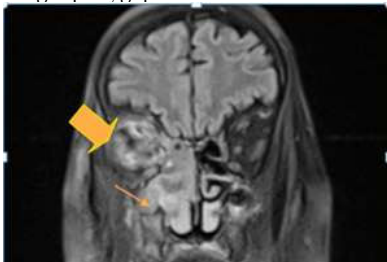


Fig. 2: MRI brain (FLAIR coronal section) shows soft tissue thickening in the right maxillary sinus with extension to the right nasal cavity (Arrow) and right orbit (Bold Arrow). Intraconal and extraconal fat stranding in the right orbit with premaxillary edema.

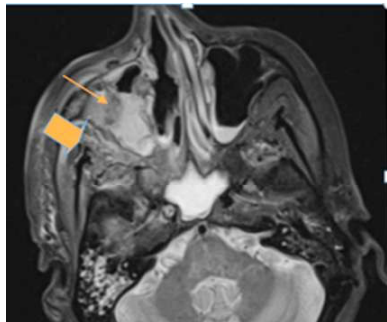


Fig. 3: Magnetic Resonance Imaging brain (axial section) shows mucosal thickening with air fluid levels noted in bilateral maxillary sinus (Arrow) (right more than left). Mucosal thickening in sphenoid sinus (Bold Arrow). Edema noted in right premaxillary and retro maxillary region

A definitive diagnosis of CAM as the causative fungal species is achieved by histologic examination of the biopsy specimen and culture as per criteria for Proven Invasive Fungal Disease.¹⁰ KOH examination may be used only as a screening tool to identify the presence of mucormycosis.¹⁴ All suspected CAM patients were subjected to biopsy as well as culture for fungal hyphae. It showed that 46 patients (73%) had a positive culture for fungal hyphae.

We have postulated this sudden increase in CAM infection with COVID 19 contributing in more than

one way. Firstly, this fungus usually resides as a commensal of the nasal mucosa, for the fungus to cause invasion into sinuses, there can be a breach in nasal mucosa like trivial trauma. Overenthusiastic use of steam inhalation to get rid of COVID 19 infections, multiple times per day might cause nasal mucosal trauma, which causes invasion of fungus into sinuses. Traditionally steam inhalation is used to practice once or twice a day at a temperature of 40-42°C. Injudicious use of steam inhalation with high temperature and multiple times per day will cause nasal trauma and conjunctival congestion which may lead to fungal invasion into sinuses.

Secondly, uncontrolled DM favors the spread of opportunistic fungal infection. People with type 2 diabetes are increasing in every country, but more than 80% live in developing countries such as India, Bangladesh, Bhutan, Pakistan, Sri Lanka, the Philippines, and Indonesia.¹⁵ In our study 38 patients (60.3%) in the CAM group had DM as compared to 63 patients (40.9%) in the control group, which favored the spread of opportunistic fungal infection.

Thirdly, intravenous steroids have been used considerably to reduce hospital stays and mortality related to COVID 19. Systemic steroids like dexamethasone and methylprednisolone are major part of COVID 19 management guidelines especially in moderate to severe cases. Owing to its immunosuppressive nature, COVID-19 patients are vulnerable to opportunistic infections like CAM.^{16,17} In our hospital we found the use of that intravenous steroid was not positively correlated with CAM, however, the prolonged duration of steroid use for more than one week (8.43 ± 2.67 days in case Vs 7 ± 0.1 days in control) was found to give significant results for CAM (P-value 0.0001).

The first line antifungal agents for CAM are Amphotericin B (liposomal) or posaconazole. Isavuconazole is regarded as salvage therapy for refractory cases.^{18,19} Combination therapy can also be given for recalcitrant cases. Surgical debridement of devitalized tissues and FESS (Functional Endoscopic Sinus Surgery) associated lavage helps to contain the spread and allows better pharmacokinetics of intravenous drugs.²⁰ In our study, we started Amphotericin B (liposomal) and posaconazole as a second-line drug for all suspected CAM and confirmed by following the Criteria for Proven Invasive Fungal Disease.

The prognosis of the infection is poor with the overall mortality ranging between 33.3 and 80%.^{21,22} In the present study total of 8 (12.7%) out of 63 patients died due to CAM.

The Strength of our Study:

Our study is one of the unique study about CAM in this part of our country. The fact that this study was done in comparison with the control group (1:3) added weightage to the results of the study.

Limitation:

Though the sample size was taken for the study was sufficient statistically, to establish a finer causal relationship between various risk factors, future study should be done with a higher sample size covering various strata's of the general population.

Conclusion

Injudicious use of steam inhalation amidst the COVID pandemic causes nasal mucosal trauma which resulted in CAM in already immune depleted covid positive patients. Early diagnosis and timely intervention improved the outcome of CAM.

Caution needs to be exercised in judicious use of steam inhalation. Stringent glycemic control, avoidance of inadvertent use of steroids can reduce the incidence of CAM.

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Availability of data and material (data transparency): The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval: The study was approved by the institutional ethical committee No: ECR/131/Inst/TN/2013/RR19, EC/NEW/INST/2020/461

Authors' contributions: "All authors have

contributed equally to the work".

Consent to participate: Informed consent was obtained from all individual participants included in the study. (consent form included)

Consent for publication: Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/ relative of the patient.

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