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Original Research Article

COVID associated mucormycosis: various trends, effects of treatment and sequelae

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ABSTRACT

Background: With second wave of covid-19 pandemic rapid rise in cases of covid associated mucormycosis (CAM) was detected. The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen, high blood glucose, acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA], high serum iron levels. Aim of this study is to evaluate the extent of disease, its causative factors, various associations and effect of treatment**.**
Methods: This is a prospective study done on 180 patients. Detailed history and diagnostic nasal endoscopic guided biopsies were taken and sent for histopathological and microbial examination. Computed tomography (CT) and MRI of paranasal sinus, orbit, skull base and brain were done. The data collected was entered in Microsoft excel and analyzed data was presented in form of frequency and percentage shown by bar chart and pie charts.
Results: The average age of the patients was 50.53 ± 11.280 years. Majority of patients were male (73.3%). Mean duration of onset was 19.28±11.482 days. The most common presenting symptom was headache(90%). 98.9% (N=178) patients were diabetics, 52.2% patients were known diabetics, newly diagnosed diabetics were 41.7%. 73.90% patients had history of steroid intake. 39 patients were certified dead with overall 21.7% mortality rate.
Conclusions: Increase in mucormycosis in Indian context appears to be an unholy intersection of trinity of COVID-19, Diabetes mellitus and corticosteroid. High suspicion, early diagnosis and rigorous management is the key to favourable prognosis.

Keywords: COVID associated mucormycosis, Surgical debridement, CAM, Fungal sinusitis

INTRODUCTION

COVID-19 was declared as a pandemic on March 11, 2020 by WHO and with its second wave cases of covid associated mucormycosis started being reported. The incidence of cases reported worldwide were high, with high morbidity and mortality that COVID associated mucormycosis (CAM) was itself declared as a pandemic and was kept under the category of notifiable diseases as per the epidemic diseases act 1897.

Mucormycosis is an angioinvasive disease caused by mould fungi of the genus rhizopus, mucor, rhizomucor, cunninghamella and absidia of order- mucorales, class-zygomycetes.[1] The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high blood glucose (diabetes, new onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis (DKA), high iron levels (increased S. Ferritin due acute inflammatory state) and decreased phagocytic activity of

white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.

Incidence and prevalence statistics

Mucormycosis per se, had a variable global incidence rate of 0.005 to 1.7 per million people in pre COVID era.[2] In India, the prevalence was 140 per million people, which is 80 times greater than in developed countries, with global mortality rate of 46%.[3] In comparision to above stated mucormycosis statistics, CAM had pooled global prevalence of 7 cases per 1000 population in European countries and 15 cases per 1000 population in Asian countries, which is 50 times higher than the prevalence of pre covid mucor in India (0.14 cases per million population). The all-cause mortality rate among CAM patients was 29.6%, which is lower than the reported mortality rate of pre covid mucormycosis in the U.S. (50%), India (45%), Iran (40.8%), and South Korea (33%).[4-7] The large discrepancy of prevalence of mucormycosis globally and in India is attributable to the fact that India is the country with second largest population with Diabetes Mellitus along with low socioeconomic status, late presentation and late diagnosis in Indian setup as compared to other developed countries. However, other factors such as immuno-compromised state, hematological malignancies and post transplant patients on immuno-suppresants were also found to contribute in causality of mucormycosis, which were more common in western world population with mucormycosis.

Estimated global incidence of pre COVID mucormycosis

The Leading International Fungal Education (LIFE) portal has estimated the burden of serious fungal infections globally. The estimated incidences per million populations in different continents were: Europe (from 0.2 cases in Denmark to 95 cases in Portugal), USA (3.0 cases), Canada (1.2 cases) and Australia (0.6 cases).

Aim and objectives

Current study is a prospective study of COVID associated mucormycosis patients: Various trends, associations, prognosis, effect of treatment and its sequalae

METHODS

Study design, location, duration and sample size

Prospective study conducted at Department of ENT and Head and Neck Surgery, NSCB Medical College Hospital, Jabalpur from 01 March 2021 till 31 August 2022. Sample size was calculated using Right size (China-Uganda-Zimbabwe version 2.0.0.0.2) statistical software with a final sample size of 180 was calculated.

Inclusion and exclusion criteria

All patients with previous history of COVID-19 infection presenting in ENT department with complaint complaints suggestive of fungal sinusitis were included. Patients with no history of COVID-19 infection were excluded.

Data collection

Patients with prior history of COVID-19 infection with symptoms and clinical findings suspicious of CAM were hospitalized and included in the study. Detailed history of COVID-19 infection, symptoms, medication, hospitalization and predisposing risk factors was taken. Diagnostic nasal endoscopy was performed in all cases with complete examination of nasal cavities and nasopharynx was done and endoscopic biopsies from most representative sites were obtained in all patients and sent for histopathological examination, KOH mount, fungal culture+sensitivity and pus culture+sensitivity. Ophthalmological consultations were done to assess vision status and fundus examination. Neurological /neurosurgical consultations were taken as per case requirement. Computed tomography (CT) paranasal sinus, orbit and skull base and T2 weighted gadolinium contrast inhanced MRI PNS, orbit and brain were done for assessing bony, soft tissue and intracranial extent of involvement and Cone Beam CT to assess involvement of maxilla and mandible. All the records were recorded by using structured schedule (Case Report form) and entered in Microsoft Excel Sheet.

Statistical analysis

The data collected was entered in Microsoft excel and analyzed. Analyzed data was presented in form of frequency and percentage shown by bar chart and pie charts.

Procedure

This is a prospective study done on 180 patients with prior history of COVID-19 infection with symptoms and clinical findings suspicious of CAM. Detailed history of symptoms, medication, hospitalization and predisposing risk factors was taken. Diagnostic nasal endoscopic guided biopsies were taken and sent for histopathological examination, KOH mount, fungal culture+sensitivity and pus culture+sensitivity. Computed tomography (CT) paranasal sinus, orbit and skull base and T2 weighted gadolinium contrast inhanced MRI PNS, orbit and brain were done. The data collected was entered in Microsoft excel and analyzed. Analyzed data was presented in form of frequency and percentage shown by bar chart and pie charts.

RESULTS

The average age of the patients was 50.53±11.280 years. Most of the patients were under 50-60 yrs age group (32.8%).

Table 1: Comparative analysis of present study with other studies.

First author	Place (of report)	N	Duration of study	Age, range, M/F (in years)	Gender	Comorbidities				C/S COVID-19	Treatment received for COVID-19			Onset duration	C/S Mucor	Location of mucormycosis			Outcome
						DM	HTN	CVA	Cancer		Steroid	Tocilizumab	Remdesivir			Nasal/ Sinus	Orbit	CNS	
Case study/report/series from India																			
Mehta et al	Mumbai	1	N/A	60	M	Y	N/A	N/A	N	C	Y	Y	N	N/A	C	Y	Y	N	Death
Garg et al	Chandigarh	1	N/A	55	M	Y	N/A	N/A	N	C	Y	N	Y	N/A	C	N	N	N	Improving
Maini et al	Mumbai	1	N/A	38	M	N	N/A	N/A	N	C	Y	N	Y	N/A	C	Y	Y	N	Improved
Saldanha et al	Mangalore	1	N/A	32	F	Y	N/A	N/A	N	C	NR	NR	NR	N/A	C	Y	Y	N	Improved
Revannavar et al	Mangalore	1	N/A	Middle age	F	Y, NDD	N/A	N/A	N	C	N	N	N	N/A	C	Y	Y	Y	Improving
Sen et al	Mumbai	6	N/A	46.2–73.9	M=6, F=0	Y: All	N/A	N/A	N	C	Y: 5 N: 1	N	N	N/A	C: 5, S: 1	Y: All	Y: All	Y: 5 N: 1	Improving
Sarkar et al	Puducherry	10	N/A	27-67	M=8, F=2	Y: All, DKA: 9 (90%)	N/A	N/A	N	C	Y: 10	N	Y: 5 N: 5	N/A	C: 6, S: 4	Y: All	Y: All	Y: 1	Death: 4, Improved: 2, Unchanged: 4
Mishra et al	Bangalore	10	N/A	37-78	M=9, F=1	Y: 8 N: 2	N/A	N/A	N	C	Y: 6 N: 4	Y: 1 N: 9	Y: 6 N: 4	N/A	C: All	Y: All	Y: 2	N	Death: 4 Improved: 5 LFU: 1
Satish et al	Bangalore	11	N/A	30-74	N/A	Y: Majority	N/A	N/A	Y#	C	N	N	N	N/A	C: All	Y: Majority	Y: Majority	Y: NR	Death: 2 LAMA: 5 Improving: 4
Moorthy et al	Bangalore	17	N/A	39-73	M=15, F=2	Y: 15 N: 2	N/A	N/A	N	C	Y: 15 N: 2	N	N	N/A	C: All	Y: All	Y: 11 N: 6	Y: 8 N: 9	Death: 7 Alive: 9 LFU: 1
Sharma et al	Jaipur	23	N/A	NR	M=15, F=8	Y: 21 N: 2	N/A	N/A	N	C	Y: All	N	N	N/A	C: All	Y: All	Y: 10	Y: 2	Death: 0 LFU: 2 Alive: 21
Ramaswami et al	India	70	6/5/2021 to 1/06/2021	38-55.5 (Mean 44.5)	M=42, F=28	DM=70%	HTN= 24.3%	N/A	N	C	N/A	N/A	N/A	13.5-25 days, mean= 20 days	C	Y: 36.65%	Y:81.4%	N/A	Death=23%
Mishra et al	India	32	12/4/2021 to 31/05/2021	58.28±8.57	f=46.90%, m=53.10%	DM=87.5%	N/A	N/A	N	C	N/A	N/A	N/A	17.28± 11.76 days	C	Y= 62.5%	Y=56.2%	N/A	Death=12.5%
Patel et al	India	53	1/9/2020 to 31/12/2021	N/A	N/A	DM+	N/A	N/A	N	C	N/A	N/A	N/A	N/A	C	N/A	N/A	N/A	N/A
Selarka et al	India	47	3/1/2021 to 27/3/21	55±12.8	M=24.50%, F=25.50%	DM:76.6%	HTN: 57.4%	N/A	N	C	N/A	N/A	N/A	12.1± 4.6 days	C	N/A	Y:25.5%	N/A	Death=23.40%
Present Study 2022	Jabalpur	180	1/3/2021 to 31/08/2022	20-90 (50.53±11.28)	M=132, F=48	Y=178 (98.9%), N=2, K/C=103 (57.2%), NDD= 75 (41.7%), DKA=55(30.6%	Y=39, N=141	Y=10, N= 170	N	C	Y=133 (73.9%)	N/A	N/A	Mean 19.28± 11.482 days	C=132 (MF =95, AF= 37, Infl Ts=33, N/A=15)	Y=72	Y=73	Y=34	Death=39 (21.70%), Alive=126, LFU/LAMA=15

C: Confirm; S: Suspect; Y: Yes; N: No; #:1 (leukaemia)

Majority of the patients were male (73.3%) with male to female ratio of 2.75: Most of the patients (36.7%) presented in 10-20 days of getting covid positive with mean duration of onset 19.28±11.482 days.

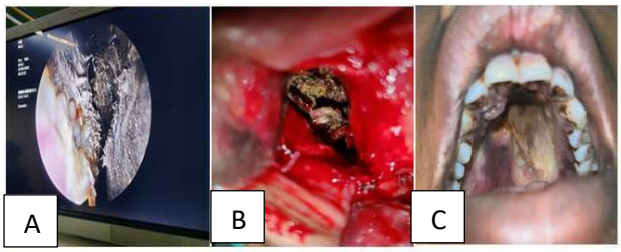

Figure 1: Various subsites with black crusts; A) Black nasal cavity crusting with underlying pus discharge on nasal endoscopy, B) Intra-op black necrotic tissue in maxillary sinus via Caldwell Luc approach, C) Palatal necrotic patch in a patient with covid associated mucormycosis.

Figure 2: Aggressive spread of COVID associated mucormycosis within hours. Within 36 hours of presentation the erythematous skin patch developed vescicular lesions and turned into necrotic skin patch.

Almost 98.9% (N=178) patients were, about 52.2% patients were known diabetics, newly diagnosed diabetics were 41.7%. 30.6% patients presented with diabetic ketoacidosis. A total of 73.90% patients had history of steroid intake in the past. The most common presenting symptom in our study was headache, found in about 90% of the study population followed by nasal obstruction (82.8%), nasal discharge (80.6%), hyposmia and anosmia (80%) and facial swelling and numbness (78.9%). In our study we found that majority of the patients were in Sino-nasal (stage 1) (40.6%) and Rhino-orbital stage (stage 2) (40.6%) with equal distribution and 18.9% patients were in rhino-orbito-cerebral stage graded as stage 3. Highest mortality was observed among stage 3 pts (64.7%), followed by stage 2 patients (19.2%) and stage-1 patients with mortality of 4.2% only. Various sinus involvement were Maxillary sinus (95%) >Ethmoid sinus (87.8%) >Sphenoid sinus (47.2%) >Frontal sinus (37.8%). Regarding subsite involvement orbit was most common. Orbit (58.3%) >Palate (21.70%) >Intracranial (18.90%) >Dental (11.70%) >Cutaneous (7.8%).

Most of the study population underwent combined surgical and medical management (91.70 Most common causative organism was found to be mucor species of fungus (52.8%) with high morbidity and mortality rate of 20.6%, whereas Aspergillus was isolated only in 20.6% with mortality rate of 8.1% with p value of 0.01. The overall mortality rate in our study population, was found to be 21.7%. Highest mortality was observed among stage 3 pts (64.7%) >stage 2 patients (19.2%) >stage-1 patients with mortality of 4.2% only.

Figure 3: Intra-op. findings with extensive soft tissue destruction and necrotic bone caused by fungus. Patient was in rhino-orbital mucormycosis stage with blind eye.Patient underwent Right total maxillectomy with right alveolectomy and right orbital exenteration.

Figure 4: Post operative completely healed wound with residual facial defect after liposomal Amphoterecin-B therapy.

Figure 5: Reconstructive surgery for the same facial defect with anterolateral thigh flap.

Figure 6: Intra operative pictures of osteoplastic flap surgery for frontal sinus in a patient with isolated frontal sinus.

DISCUSSION

Mucormycosis is an oppurtunistic invasive fungal infection and is caused by Mucorales of zygomycete species of fungus. Infection by these fungi occurs pertaining to the immunocompromised, hyperglycaemic and hypoxic state of the patient. The fungi tend to proliferate along the elastic lamina of vascular channels dissecting the lamina away from media and causing direct invasion leading to endothelitis and endothelial thrombus formation with surround tissue infarcts and necrosis. The necrotic tissue further promotes fungal colonization and lower drug penetration. Few possible etiopathogenesis explations for Covid associated mucormycosis are- Evidence suggests SARSCoV-19 induces damage of pancreatic islets resulting in acute diabetes and DKA.[8] This is a possible explanation for the "diabetogenic state" in SARSCoV-2 infection, as there is a high expression of angiotensin-converting enzyme 2 receptors in pancreatic islets, along with increased insulin resistance due to cytokine storm.[9] Also, severe COVID-19 is a hyper-ferritinemic state. High ferritin levels lead to excess intracellular iron that generates reactive oxygen species resulting in tissue damage. Cytokines, especially IL-6, due to severe infection and DKA, stimulate ferritin synthesis and downregulate iron export resulting in intracellular iron overload, further exacerbating the process.[10] The resultant tissue damage leads to the release of free iron into the circulation.[11] Iron overload and excess free iron seen in acidemic states are one of the key and unique risk factors for CAM.[12] Another possible explanation for the association between COVID-19 and Mucormycosis is the "endothelialitis" observed in severe COVID-19. Endothelial adhesion and penetration are critical early steps in mucormycosis.[12] Interestingly, acidemic states and hyperglycemia induce the enthodelial receptor glucose-regulated protein (GRP 78) and the Mucorales adhesin spore coat protein homologs (CotH), creating a "perfect storm" for increased adhesion and penetration of Mucorales to the endothelium. Of interest, GRP 78 has been postulated as one of the receptors responsible for SARS-CoV-2 entry.[13] Although there is no predetermined age and sex preponderance of mucormycosis but in our study we found M:F ratio of 2.75:1 with mean age of 50±11 yrs, which can be explained with poor immunity and high DM-2 incidence with increasing age. Almost 98.9% (N=178) patients were diabetics among which known case of DM2-57.2%, Newly diagnosed diabetics-47.1%, DKA-30.6% (N=55). We also found a significant correlation between DKA and mortality and stage of patients with p value <0.01 for both. A total of 56.4% patients with DKA were certified dead. We also observed very rapid progression of disease in pts with DKA as compared to other patients. Diabetic ketoacidosis creates a very favourable environment of hyperglycemia and acidotic state for the rapid growth and faster invasion of the fungi, thereby leading to high mortality. Among the study population, a total of 133 patients (73.9%) had a history of steroid intake. However steroid intake did not show significant correlation with outcome (p value=0.08) and stage (p value=0.1). Other co-morbidities like Hypertension (N=39, 21.7%) and CVA (N=10, 5.6%) also showed significant correlation with stage as well as outcome of the disease. Mortality among hypertensives was found to be 33.3% and among CVA patients, mortality was 60%. Also CVA shows significant correlation with outcome (p value=0.01) as 60% of patients with CVA were in stage 3, 30% were in stage 2 and 10% were in stage 1. This can be attributed to the fact that poorer vascularity and infart zones in pts with CVA contributes to rapid invasion of disease. Few patients had history of hypothyroidism, some presented with dengue and typhoid but these were not as fatal as other co-morbidities such as patients with AKI, sepsis, CKD, and necrotizing fungal pneumonia and 100% of these patients were certified dead, showing detrimental effect of these comorbidities along with mucormycosis (p value=0.04). Most common symptoms found in Sino-nasal stage (stage 1) patients were nasal discharge (37.9%) and nasal obstruction (37.6%). In Rhino-orbital stage (stage 2) patients, facial swelling and numbness (45.1%) and anosmia /hyposmia (43.8%) were found to be the most common presenting symptom. In Rhino-orbito-cerebral stage (stage 3) patients, facial numbness and swelling (23.2%) and headache (21%) were the most common symptom. Upon correlation with outcome, facial swelling and numbness (26.1%) was found to be the most common presenting symptom among the patients who were certified dead, explaining the extensive angio-invasion and spread along the V2 division of trigeminal nerve and cutaneous vasculature involvement. Pansinusitis was found to be the most common overall sinus involvement, however talking about frequency distribution of individual PNS involvement showed the following trend, Maxillary sinus (95%) >Ethmoid sinus (87.8%) >Sphenoid sinus (47.2%) >Frontal sinus (37.8%). However, patients with Frontal sinus involvement showed maximum mortality followed by sphenoid sinus involvement. The infection typically starts in the nasal cavity or maxillary sinus and spreads to ethmoid or sphenoid sinus and less frequently to frontal sinus. An ulceration or extraction socket in alveolus commonly acts as the entry portal into maxillofacial region especially when the patient is immuno-compromised and diabetic, following which the fungus starts colonising in the potential spaces of sinus and spreads multifactorially via blood vessels (via branches of sphenopalatine artery),

foramens with nerve roots (foramen rotundum with V2 nerve intracranially, inferior orbital nerve) and direct local invasion through tissue and bone involvement. Orbital involvrment was the most common subsite involvement followed by palatal involvement reason being adjacent anatomical location of orbit and palate to the primary site of infection i.e nose and PNS and paper thin lamina papyracea which separates orbit from noasal cavity as compared to palatine bone which is much thicker comparably. Orbit (58.3%) >Palate (21.70%) >Intracranial (18.90%) >Dental (11.70%) >Cutaneous (7.8%)]. Palatal and dental involvement was mostly seen in patients with floor of nose and maxillary sinus involvement. Isolated palatal and dental involvement were very rare.

Regarding Vision status in the study population (N=180), 61.10% patients had intact vision, 27.20% had decreased vision, 11.70% patients were blind. However, among the patients with orbital involvement (N=105), 33.3% patients had intact vision, 46.6% patients had decreased vision, 20% patients were blind. Orbital spread can occur via dehiscence of lamina papyracea, ethmoid foramina or via nasolacrimal duct. Upon spread the disease showed extraoccular as well as intraocular spread with few cases of orbital apex involvement. These patients presented with conjunctival chemosis, retroorbital pain, ophthalmoplegia, diplopia, proptosis and even blindness. Direct invasion of central retinal artery and optic nerve attributes to blindness and even pathway for intracranial spread via the superior orbital fissure or optic canal. About 11% (N=21) patients in our study presented with multiple cranial nerve palsies of CN II , CN III, CN IV, CN V, CN VI and CN VII. These patients presented with, blindness or decreased vision, Periorbital swelling and discoloration, Proptosis, Ptosis, Conjunctival congestion, Facial anaesthesia, varying grades of Facial palsy and Absent corneal reflex. Out of which 10 patients had DKA and the rest had uncontrolled raised blood sugar levels. Aggressive surgical debridement with orbital exenteration (N=4), Orbital decompression (N=17). We were able to acheive cranial nerve function reversal in 10 patients with improvement of decreased vision status and return of perception of light in 3 patients. For patients with Sino-nasal stage of disease (stage 1), Endoscopic sinus surgery (ESS) along with sinus debridement with or without orbital clearance as per intra operative assessment was done. In stage 1 cases with palatal and dental involvement inferior maxillectomy with alveolectomy was done. For Rhino-orbital stage of disease (stage 2) with extensive sinus involvement (pterygopalatine fossa and infratemporal involvement) also involving the orbit, ESS with partial/total maxillectomy with orbital tissue decompression/debridement was done. In cases of intracranial disease extension with dead eye, a multispeciality surgical approach was opted with neurosurgeons and ophthalmologists and an open surgical sinus debridement with orbital exenteration with neurosurgical drainage of abcess/debridement was done. Intravenous Liposomal Amphoterecin-B therapy was given to all the patients, minimum for 6 weeks (a total of 5g dose over approximately 6 weeks. In certain patients there were unbearable adverse drug reactions and impaired renal function with AMP-B drug, such patients were managed with intravenous posaconazole via central line.

Limitations

Limitation of current study was patients with severe co-morbidities were transferred out for medical ICU management and therefore caused loss to follow up.

CONCLUSION

Increase in mucormycosis in Indian context appears to be an unholy intersection of trinity of COVID-19 (cytokine storm, lymphopenia, endothelial damage), Diabetes mellitus (high prevalence genetically), Rampant use of corticosteroid leading to newly diagnosed diabetes mellitus (all causing opportunistic fungal infection).Based on our study that the major prognostic factors for CAM in view that prescribed anti-fungal drugs are being given are severity of disease (U/L or B/L or orbital/ intracranial extension), glycaemic control, causative organism (mucor species being more aggressive and destructive),immunity status, early diagnosis and surgical debridement and other co-morbid conditions. Steroids only showed a role in causation of CAM, but not any significant role in outcome and stage of the disease. High suspicion for early disease diagnosis, aggressive surgical debridement and intravenous systemic antifungal therapy proves to give favourable outcome. Pre and post operative glycaemic control serve as the saviour and has significant effect on patient prognosis.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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