

A study of mucormycosis in second wave of COVID-19

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Abstract: *Background:* During the second wave of Covid 19 infection in India, we witnessed a pandemic within an epidemic – that of mucormycosis in Covid-19. Hence, we performed a study on the patients admitted under our care. *Objectives:* To study the risk factors and clinical presentations of Covid 19 associated mucormycosis; and to know the treatment outcome. *Methods:* 112 patients with clinical diagnosis of mucormycosis were subjected to diagnostic nasal endoscopy (DNE) and KOH mount. This was followed by contrast MRI and estimation of HbA1c, and levels of various inflammatory markers – D-dimer, LDH, serum ferritin, IL-6 and CRP. All underwent endoscopic/ external clearance of disease with anti-fungal therapy. Patients were followed up for 3 months. *Results:* The common presenting complaints were headache and facial pain. DNE showed unhealthy mucosa with blackish discoloration of septum or turbinate, mucopurulent discharge, and crusting. 23 patients had palatal involvement; 24 patients had orbital involvement of whom 13 had complete loss of vision during the course of the disease. 63 of the patients had poor glycemic control, with HbA1c >10. Levels of inflammatory markers were all elevated. Maxillary and ethmoid sinuses were most commonly affected sinuses, with intracranial involvement in 18 patients as per MRI. Revision surgery was required in 12 patients. The mortality rate in our study was 8%. *Conclusion:* Covid associated mucormycosis is a fulminating disease which requires immediate diagnosis and emergent management with both medical and surgical modalities without which patient has high morbidity and mortality.

Keywords: Amphotericin B, Covid 19, Mucormycosis, ROCM (Rhino-Orbital-Cerebral Mucormycosis), CAM (Covid Associated Mucormycosis), Posaconazole.

Introduction

Rhino-orbital-cerebral mucormycosis (ROCM) is a rapidly progressive opportunistic fungal infection occurring in patients with co-morbid conditions like uncontrolled diabetes, ketoacidosis, malignancy, blood dyscrasias, trauma and burns [1]. As the occurrence of disease itself is rare, the understanding of etiopathogenesis, risk factors and course of the disease and effectiveness of existing therapeutic options are limited.

During first wave of Covid-19 (March 2020 to July 2020 in India), there was a mild spike in the cases of mucormycosis globally [2]. However, not many alarming cases were reported by any tertiary centres during that time [3]. During the second wave of Covid-19 (March 2021 to July

2021 in India), there was a huge surge of ROCM which took a serious toll parallel to Covid-19 incidence in Indian population. The reported number of cases were very high as compared to elsewhere in the world. The rising cases of Covid-19 along with mucor cases has necessitated us to find out the associated risk factors, and to learn the course of the disease for early diagnosis and effective management with the least possible morbidity and mortality.

ROCM was always considered to be a rare infection commonly affecting immunosuppressed individuals of uncontrolled Diabetes. The other etiological factors were immunocompromised patients either secondary to chronic steroid usage or post

chemo-radiation therapy for malignancies [5]. Artis in 1982 suggested that patients with diabetic ketoacidosis were more susceptible to mucormycosis secondary to free iron in the serum due to reduced binding capacity of transferrin [6]. The most common etiologic agent of mucormycosis is *Rhizopus Oryzae* in more than 60% of all cases of Mucormycosis, and the causative agent in 90% of rhinocerebral mucormycosis [7]. Several studies have documented the presenting features of ROCM - Nasal discharge, headache, black necrotic turbinates, palatal ulceration, periorbital swelling, edema of eyelids, decreased vision secondary to ophthalmoplegia, multiple cranial nerve palsies, altered sensorium, sometimes even acute unilateral or bilateral vision loss [8-9].

Biopsy of specimens from clinically affected sites is necessary for diagnosis. Demonstration of hyphae by direct microscopy in clinical samples is essential because it is rapid and highly suggestive of the disease. Specimens can be observed after treating with Potassium hydroxide, staining with an optical brightener Calcofluor white or with Gomori methenamine silver [10]. Contrast-enhanced MRI is the preferred imaging modality. The classic "black turbinate" on contrast-enhanced imaging represents mucormycosis. A common radiological feature of advanced disease is non-enhancing, necrotic soft tissue at the sinonasal, orbital and skull base areas [11].

The treatment is to be immediate as impending visual loss or extension into cranial area is common. Management is both medical and surgical for all clinico-radiologically or histopathologically probable, possible or proven cases according to guidelines of code Mucor [12]. Amphotericin B is the antifungal drug of choice for mucormycosis. Intravenous doses of Amphotericin B deoxycholate in the range of 0.25 to 1.0 mg/ kg once daily (most commonly 0.4 to 0.7 mg/kg/day) in 5% dextrose solutions usually are recommended. Maximum daily doses of 1.2 mg/kg/day. Liposomal Amphotericin B is relatively well tolerated and 3 to 5 mg/kg/day is recommended [13]. Posaconazole and Isavuconazole are other drugs which are used [14]. However, mucormycosis has been known to cause acute fulminant disease. Naureen M et al reported a high mortality rate of 54.5% [4].

Aims and Objectives:

1. To study the risk factors associated with mucormycosis infection in second wave of Covid-19
2. To study different presentations and clinical features of mucormycosis of second wave of Covid-19.
3. Treatment outcome

Material and Methods

A cross sectional study was conducted by Department of Otolaryngology and Head and Neck Surgery at BLDE deemed to be University, Shri B M Patil Medical College Hospital & Research Centre, Vijayapura, from March to July 2021.

Inclusion criteria:

1. Patients diagnosed with mucormycosis secondary to Covid 19 infection
2. Willing to give consent for study and to come for follow up for at least 3 months

Those patients who did not give consent for either surgery or medical treatment and had inadequate follow up were excluded from the study.

Methodology: A Semi structured proforma was prepared and recorded to assess risk factors, different presentations and course with following parameters.

1. Socio-demographic data like age and sex distribution
2. Co morbid conditions like diabetes mellitus, details of Covid infection in 2nd wave
3. Possible etiological factors like steroid treatment, oxygen supplementation
4. Presenting complaints
5. Signs and symptoms
6. Findings on nasal diagnostic endoscopy and oral and ophthalmic examination
7. KOH mount reports
8. MRI Scan
9. Investigations like serum ferritin, CRP, D-dimer, HbA1C, urine ketone bodies
10. Surgical interventions, postoperative complications
11. Postoperative histopathology report
12. Outcome of treatment with follow up for 3 months

Statistical analysis: The data was recorded in a Microsoft Excel worksheet and analysed using SPSS software (Version 21).

Results

At our centre, patients with mucormycosis were aged from 18 years to 80 years (mean 49.5). Our results showed that the most common age range of presentation was between 40 to 49 years (27.7%), followed by 50 to 59 years (26.8%). Majority of our patients were males (74.1%) (Table 1).

Table-1: Demographic data		
Distribution of Cases according to Age		
Age(yrs)	N	Percent
< 20	1	.9
20 – 29	3	2.7
30 – 39	17	15.2
40 – 49	31	27.7
50 – 59	30	26.8
60 – 69	25	22.3
70+	5	4.5
Total	112	100.0
Distribution of Cases according to Sex		
Sex	N	Percent
Males	83	74.1
Females	29	25.9
Total	112	100.0
History of Covid 19 infection, steroid usage and oxygen supplplantation**		
Second wave Covid 19 infection	112	100
Steroid administered during Covid infection	69	61.6
Oxygen support during Covid infection	48	49.2
Diabetes		
Newly diagnosed	46	41.1
Known diabetic	53	47.3

The mean time interval of presentation of mucormycosis after initial diagnosis of Covid infection was 3.2 weeks, wherein 4 patients had active Covid infection at time of admission. 69 (61.6%) patients had been administered steroids during the course of Covid infection, and 48 (42.9%) patients had required oxygen support. 53 patients (47.3%) were known to be diabetic prior to Covid infection, whereas 46 (41.1%) were newly diagnosed with diabetes during Covid-19

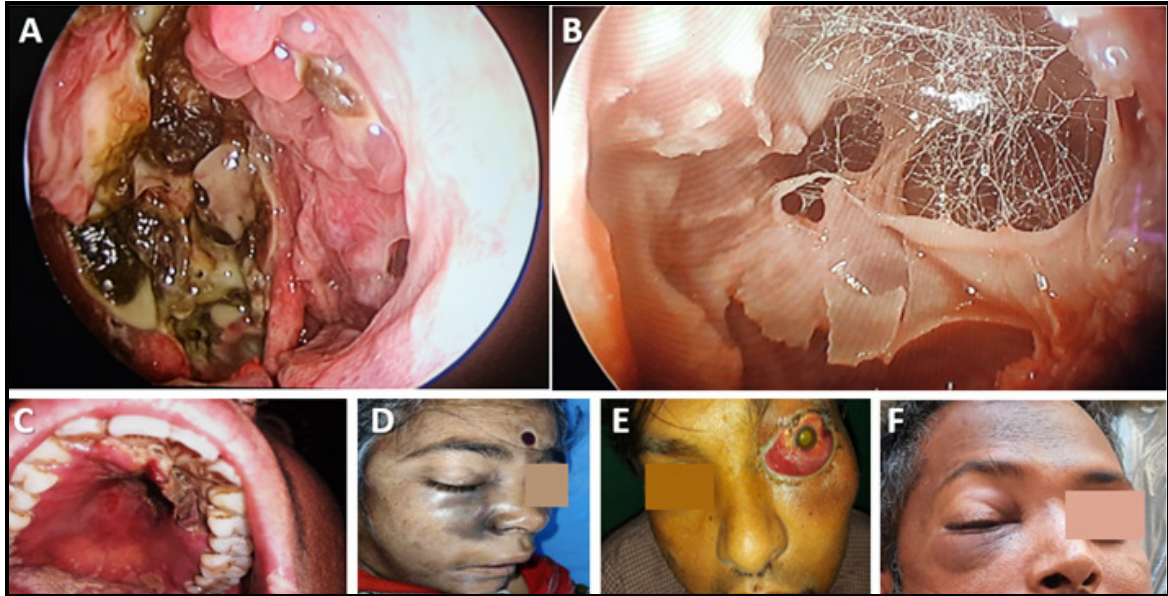
infection. Also, 7 patients (6.3%) had diabetic ketoacidosis at the time of admission.

Table-2: Clinical features		
Presenting Complaints**	N	Percent
Headache	39	34.8
Facial Pain	29	25.9
Tooth Ache/loosening of teeth	15	13.4
Facial Swelling	14	12.5
Eye Lid Swelling	13	11.6
Eye pain/ retro-orbital pain	10	8.9
Blurring Vision	8	7.1
Nasal Obstruction	5	4.5
Vision Loss	4	3.6
Nasal Bleeding	2	1.8
Fever	2	1.8
Facial Palsy	1	0.9
Skin change	1	0.9
On DNE		
Nasal cavity findings**	N	Percent
Unhealthy mucosa	60	53.6
Mucopurulent discharge	30	26.8
Crusting	16	14.3
Blackish turbinate	11	9.8
Septum blackish changes	2	1.8
Palatal involvement		
On one side	14	12.5
Crossing midline	9	8.0
Not involved	89	79.5
Skin affected		
Nasal skin discoloration	4	3.6
Malar skin discoloration	3	2.7
Not involved	105	93.7
Orbital involvement** (N = 24)		
Lid oedema	8	7.1
Chemosis	7	6.3
Proptosis	6	5.3
Complete loss of vision, unilateral	13	11.6
** percentage may add up more than 100 in view of patients having multiple findings		
Vision impairment		
Blurring	4	3.6
CF – 4 metres	1	0.9
CF – 3 metres	2	1.8
PL +	2	1.8
PL -	13	11.6

The most common presenting complaints were headache and facial pain (Table 2). Other complaints were loose tooth, facial swelling, eye

pain and/ or swelling, and blurred vision. Facial palsy and skin changes were uncommon (Figure 1).

Fig-1: A) Unhealthy nasal mucosa seen in DNE. B) Fungal growth on DNE. C) Palatal necrosis. D) Skin discoloration. E) Left eye chemosis. F) Right eye swelling



On diagnostic nasal endoscopy (DNE), nasal cavity had unhealthy mucosa in 60 patients (53.6%), mucopurulent discharge in 30 (26.8%), crusting 16 (14.3%), blackish turbinate 11 (9.8%), septum blackish changes 2 (1.8%). One case showed fungal growth like cotton woolly appearance (Figure 1). Involvement of the palate on one side was seen in 14 patients (12.5%), 9 patients (8%) had extensive palatal involvement (Figure 1). Involvement of nasal skin was seen in 4 patients (3.6%), malar skin was discoloured in 3 (2.7%) patients. In our case series, orbital involvement was seen in 24 patients; vision was unaffected in 88 patients, 13 had complete loss of vision during the course of the disease.

63 of the patients had poor glycemic control, with HbA1c >10. Also, 7 patients (6.3%) had diabetic ketoacidosis at the time of admission. Levels of inflammatory markers were all elevated. D- dimer was >500 in 84 patients (81.5%), lactate dehydrogenase (LDH) was >246 in 34 (65.3%), interleukin-6 (IL-6) was elevated in 57 patients (90.5%) and C reactive protein (CRP) on admission were elevated and more than 10 in 94 patients (89.5%). Serum ferritin was elevated in males 49 patients (62%), but the same in females was within normal limits (Table 3).

Table-3: Investigations		
HbA1c		
Value	N	Percent
5.70 – 6.49 Prediabetes	5	4.7
6.50+ Diabetes	101	95.3
>10 Poor glycemic control	63	59.4
Total	106	100.0
Data unavailable	6	
D Dimer		
< 500.00 Normal	19	18.4
> 500.00 Elevated	84	81.5
Total	103	100.0
Data unavailable	9	
Serum ferritin – Males		
< 434.00 Normal	30	38.0
> 434.00 Elevated	49	62.0
Total	79	100.0
Serum ferritin – Females		
< 278.00	17	63.0
278.00+	10	37.0
Total	27	100.0
Data unavailable	6	

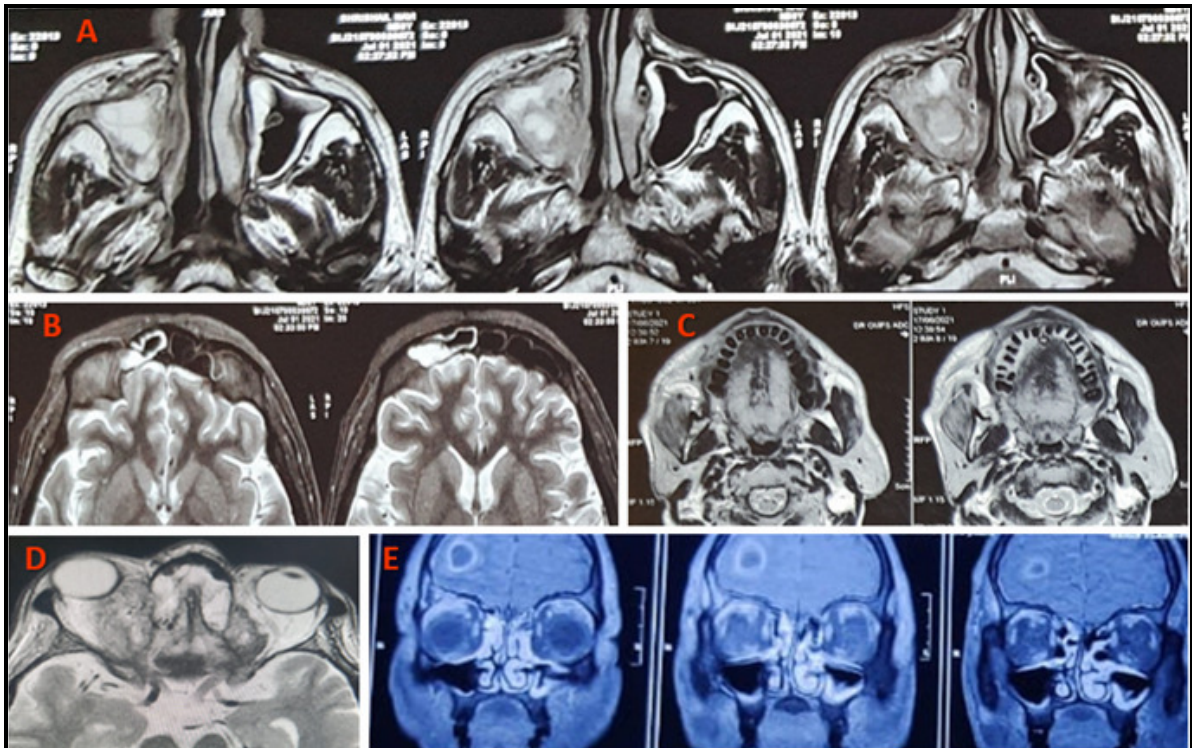
CRP		
Value	N	Percent
< 10.00 Normal	11	10.5
10.00+	94	89.5
Total	105	100
Data unavailable	7	
LDH		
< 120.00	3	5.8
Normal 120-246	25	48.1
> 246.00+	34	65.3
Total	52	100.0
Data unavailable	50	
IL 6		
<= 6.39 Normal	6	9.5
> 6.40 Elevated	57	90.5
Total	63	100
Data unavailable	49	

involved; frontal in 27(unilateral) and 31 (bilateral), sphenoid in 29 patients. Premaxillary tissues were involved in 11 patients. Likewise, pterygopalatine fossa was involved in 7 patients, Infratemporal fossa in 8 patients, parapharyngeal space in 4 patients. (Figure 2, Table 4).

Part involved		Unilaterally involved Cases	Bilaterally involved cases
Paranasal sinuses	Maxillary	33	78
	Ethmoid	34	67
	Frontal	27	31
	Sphenoid	29	
Orbit		21	1
Pterygopalatine fossa		7	
Infratemporal fossa		8	
Premaxillary tissues		11	
Parapharyngeal space involved		4	

MRI was done for all patients. The maxillary 33(unilateral), 78 (bilateral) and ethmoid sinuses 34 (unilateral), 67(bilateral)were most commonly

Fig-2: MRI showing A) Right maxillary sinus involvement, B) Right frontal sinus involvement, C) Palatal necrosis, D) Right intraconal involvement, E) Frontal lobe abscess.



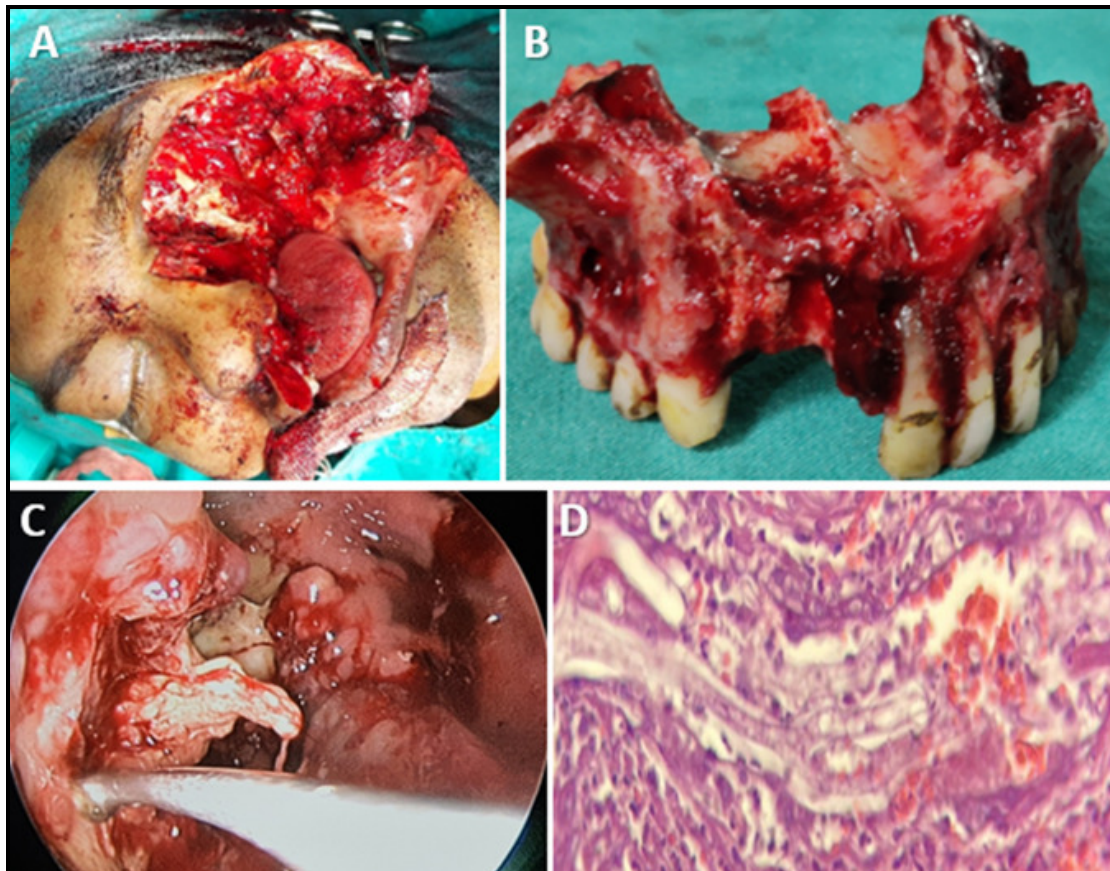
Intracranial involvement was present in 18 cases as per MRI/ One patient having an incidental finding of pituitary macroadenoma.

Injection Amphotericin B was started empirically upon clinical and radiological correlation in symptomatic patients in a COVID-19 setting while awaiting culture and histopathology confirmation. Antifungal therapy was continued for a period of 4 to 6 weeks. Liposomal Amphotericin B was the drug of choice and all efforts were for giving the same, but most of the patients received deoxycholate Amphotericin B injections in our study. Topical application of Amphotericin B was also encouraged, as was described by Ferguson BJ [7]. Patients also received supportive therapy for correction of electrolyte imbalance, and anti-coagulants in view of elevated D- Dimer levels along with control of glycemic status. Regular monitoring of serum creatinine levels was done, and Amphotericin B therapy was temporarily withheld if creatinine levels were >2. Intra-orbital injections of Amphotericin B were also

administered to patients having orbital extension of disease.

Some patients had poor tolerance to Amphotericin B (4 patients-3.6%), which did not reduce on pre-medication with paracetamol and diphenhydramine prior to infusion. They were administered tablets of Posaconazole as per recommended guidelines [14]. Extensive and expedite surgical debridement was done for all patients. All but one patient underwent Endoscopic sinus surgery with debridement (51.8%) or with modified Denkers (45.5%), palatal resection in 14 (12.5%) with maxillectomy in 2 (1.8%), alveolectomy in 1 (0.9%) and orbital decompression in 17 (15.1%). Orbital exenteration was done in 4 cases (3.6%), orbital enucleation in 1 case (0.9%). Disease clearance from pterygopalatine fossa was done in 2 patients. One patient also underwent craniotomy. External approach via lateral rhinotomy was done in one patient (Figure 3).

Fig-3: A) External approach via Weber Ferguson incision. B) Partial Maxillectomy and palate excision. C) Endoscopic debridement. D) Post Op HPR suggestive of Mucormycosis.



All patients were subjected to postoperative day 3 and 7 endoscopic suction clearance to look signs of persistence of disease. After the first surgery, revision surgery was required in 12 patients for progression of disease in palate, requiring palatal resection in 9 patients, 3 patients underwent disease clearance from pterygopalatine fossa. Major postoperative complications after surgery were pulmonary thromboembolism in 1 patient, delayed extubation or prolonged ventilator support in 3 patients, 4 patients had epistaxis post-surgery. Even though preoperative KOH was positive in only 17 patients, postoperatively tissues sent for HPR showed fungal elements. (Figure 3) HPR for mucor was positive in 72 (64.3%), Only *Asperigillus* was found in 7 (6.3%) Mixed with *Asperigillus* in 4 (3.57%), Mixed with candida in 2 (1.8%) patients, data was unavailable for 27 patients.

We also observed varied presentations of the disease in our patients post admission, when they were undergoing treatment. They were quadriplegia in 2 cases, hemiparesis in 2 cases, 7th nerve palsy in 4 cases, 9th and 10th nerve palsy in 3 cases, myocardial infarction in 2 cases, suspected pulmonary embolism in 1 case, bronchopneumonia and respiratory failure in 4 cases each. The mortality rate in our study was 9 out of 112 (8%). The causes of death were- Respiratory failure in 3 cases (2.7%), 4 patients (3.6%) expired due to sepsis, Myocardial Infarction in 1 (0.9%) case, suspected pulmonary embolism in 1 case (0.9%).

Discussion

Spores of the Mucorales are ubiquitous in nature, and everyone is exposed to them. When inhaled, the nasal ciliary clearance system, transports these spores into the nasal cavity, down the pharynx, to be cleared out by the gastrointestinal tract. Spores inhaled into the lungs are cleared by phagocytes. In the susceptible individuals, the infection usually begins along the middle or inferior turbinate [7]. The fungus shows marked predilection for vascular invasion. It directly invades the walls of large and small arteries and sometimes veins, causing thrombosis. This contributes to the necrotic ischemic and escharotic appearance so characteristic of advanced disease. It is important to note that systemic Amphotericin B does not achieve

fungistatic levels at the eschar, and hyphae continue to grow and to recolonize [7]. Hence, surgical debridement along with supportive Amphotericin B remains the mainstay of treatment.

The age and sex distribution of our patients were similar to demographics of other studies of Covid 19 associated ROCM like Moorthy A et al [15], Sen M et al [16]. All but one patient were diabetics, with HbA1c ranging from 5.9 to 16.1, mean HbA1c being 10.5. Sen M et al reported a similar range of HbA1c from 4.8 to 17.1, with a mean of 9.8. [16] We had 7 patients in ketoacidosis at admission. Selarka et al, however, reported no patients with diabetic ketoacidosis in their study of 47 patients, where 36 (76.6%) were diabetics [17]. All our patients had a history of Covid infection during the second wave, presenting with mucormycosis after a time interval ranging from 1 week to 8 weeks. Moorthy A et al [15] reported a time interval ranging from 1 to 12 weeks, similar to Sen M et al [16].

Our patients most commonly presented with frontal headache, followed by facial pain. Joshi S et al reported facial pain to be the most common presenting symptom, followed by headache [18]. Bhanuprasad K et al studied the risk factors predisposing to mucormycosis in Covid 19, and concluded that steroid use in Covid 19 was significantly associated with mucormycosis [19]. They also noted that serum ferritin levels were markedly elevated among patients with mucormycosis secondary to Covid 19. COVID-19 infection with possible alteration in iron metabolism may have predisposed to mucormycosis [20-21]. Moorthy et al stated that 14.28% had no abnormalities on DNE, while a majority of patients had purulent discharge, the others had crusting in the nasal cavity. Also 34.65% had palatal involvement clinically and radiologically [15].

On MRI, most common sinus involved was maxillary (70% patients), followed by ethmoid (60%) in our study. Intracranial extension of mucormycosis was seen in 14.28% of our patients. Sen M et al reported cavernous sinus thrombosis to be the most

common intracranial finding 285 patients out of 2826(53%), followed by internal carotid occlusion/ stenosis in 95 patients (18%), brain abscesses: temporal (66 patients-12%) frontal lobe (15 patients-2.8%) and skull base osteomyelitis in 38 patients (7.1%) [16]. Moorthy et al [15] stated intracranial extension in 13.8 % patients, of whom 8 patients had intracranial abscesses. They also reported 21.22% patients having disease extending to the retromaxilla, or pterygopalatine or infratemporal fossa. Skin involvement was noted in 4 patients, similar to our study.

In the study by Sen M et al [16], 67% (1585 of 2358) of patients underwent ESS/PNS debridement, of whom 27% (346 of 1286) underwent multiple sessions to clear the residual/recurrent disease, orbital exenteration was performed in 15% and simultaneous PNS debridement and orbital exenteration was performed in 17%. They concluded that Corticosteroids and DM are the most important predisposing factors in the development of COVID-19-associated ROCM. The follow up of Covid -19 patients should be robust even after recovery [16].

In our study, the patients were assessed for predisposing factors, presenting signs and symptoms, sites of extension, the extent of surgical debridement, as well as the outcome. Ocular, sinonasal and facial soft tissue involvement was common. Orbital extension of disease was noted in 17.46% of our patients. Selarka et al reported a much higher involvement of 40.4 [17]. Aditya Moorthy et al also showed positive prediction of poor outcome in Orbital extension [15]. Extension into the orbit and facial soft tissues usually follows the route either by maxillary or ethmoids. According to Hosseini et al, Pterygopalatine fossa seems to be the route from which orbit gets involved [22]. But our MRI

denote lesser involvement of this fossa (7 patients only).

In the series by Honavar and Sen et al, 67% (1585 of 2358) of patients underwent FESS/PNS debridement, of whom 27% (346 of 1286) underwent multiple sessions to clear the residual/ recurrent disease, orbital exenteration was performed in 15% [16]. In our cases 12 patients (10.7%) required revision surgeries. Kumari A et al reported 1 patient having facial palsy in a study of 20 patients with mucormycosis in Covid 19 patients [23]. Reddy YM et al concluded that facial palsy is also a common finding in ROCM OF 2 ND wave of covid-19 pandemic wherein they reported a very high percentage of 53 patients out of 300 patients [24]. Keeping an eye out for the red flag symptoms and signs, high index of clinical suspicion, prompt diagnosis, and early initiation of treatment with Amphotericin B, aggressive surgery including orbital exenteration, are essential for a good outcome. This study had a mortality rate of 8%. Different studies have mentioned a mortality rate ranging from 18 to 41%. [15, 25-26].

Conclusion

Covid-19 associated mucormycosis is a fulminating disease which requires immediate diagnosis and emergent management with both medical and surgical modalities without which patient has high morbidity and mortality.

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