Annals of Clinical Case Reports

Research Article
Published: 02 Oct, 2023

Rhino-Orbito-Cerebral Mucormycosis - A Retrospective Review of 246 Cases for Clinicoradiological Sites of Predilection

*Neelima G**

Department of ENT, UCMS and GTB Hospital, Delhi, India

Abstract

Aim: To determine the sites of predilection of the rhino-orbito-cerebral mucormycosis, an otherwise rare and opportunistic infection.

Methods: The study was a retrospective review of 246 patients of microbiologically confirmed mucormycosis from April 2021 to October 2021 were included in the study.

Observations: Among the 234 patients who could undergo radiological assessment of extent of disease, 51 (21.79%) had sinonasal disease, 110 (47.01%) had rhino-orbital disease, 12 (5.13%) had rhino-cerebral disease and 61 (26.07%) had rhino-orbito-cerebral disease at presentation. At the time of presentation, 53 (21.54%) tested positive for COVID-19. Most common comorbidity found was diabetes mellitus (n=200, 81.3%) followed by anemia (n=171, 69.51%). Most common presenting complaint was eyelid swelling (n=153, 62.2%) followed by cheek swelling (n=124, 50.41%). Most common finding on diagnostic nasal endoscopy was black crusts (n=177, 71.95%) and mucopurulent secretions (n=133, 54.07%). Rhizopus was identified in culture in 113 (45.93%) as the most common causative agent. *Cunninghamella* (n=6, 2.44%), *Lichtheimia* (n=1, 0.41%) was also found. Median (IQR) of hospital stay was 37.5 (41.5) days during which 79 (32.11%) patients expired.

Conclusion: Maxillary sinus was the most common site involved followed by the ethmoid air cells. We observed that the key to a better prognosis was early identification and aggressive treatment involving surgical debridement and intravenous amphotericin B.

Keywords: Mucormycosis; COVID-19; Mucorales; Rhino-orbito-cerebral

OPEN ACCESS

Correspondence:
Neelima Gupta, Department of ENT, UCMS and GTB Hospital, Delhi, India, Tel: 011-8595288086

Received Date: *13 Sep 2023*
Accepted Date: *27 Sep 2023*
Published Date: *02 Oct 2023*

Citation:
Neelima G. Rhino-Orbito-Cerebral Mucormycosis - A Retrospective Review of 246 Cases for Clinicoradiological Sites of Predilection. Ann Clin Case Rep. 2023; 8: 2489.
ISSN: 2474-1655.

Introduction

Mucormycosis is a rare, opportunistic infection which surged in the Indian subcontinent during the pandemic of COVID-19 to the extent of being declared an epidemic. The reason for the surge in cases may be attributed to the cocktail of COVID-19, rampant and unregulated use of corticosteroids during the pandemic, and the high prevalence of diabetes mellitus in the Indian subcontinent. Hot and humid atmosphere of the region provided the necessary adjunct to the favorable host environment which led to the growth of ubiquitous fungi. Mucormycosis is caused by ubiquitous fungi of the order Mucorales which grow aggressively and invade the tissues and blood vessels. On the basis of anatomical site involved, Rhino-Orbito-Cerebral Mucormycosis (ROCM) is the commonest form of mucormycosis in India [1]. This is a retrospective study conducted in a tertiary care center in India which aimed at studying the sites of predilection of this potentially fatal disease.

Materials and Methods

Sample size

Taking the prevalence percentage of clinical and radiological signs from case series of Payne et al. [2] and the then reported cases in Delhi [3], the sample size was calculated for infinite population. A minimum sample of 88 was calculated when a finite population was considered. The article presents data for 246 cases from April 2021 to October 2021.

Data collection and statistical analysis

Anonymized data of patients was collected and entered in a google sheet. Patient demographics,

Table 1: Demographics, risk factors and comorbidities, details of hospital stay in patients of Mucormycosis.

		All patients	Sinonasal	RO	RC	ROC
		(n=246)	(n=51)	(n=110)	(n=12)	(n=61)
		n (%)	n (%)	n (%)	n (%)	n (%)
Age (years)	Median (IQR)	50 (16)	50 (7)	50 (15.5)	57.5 (24.25)	51 (20)
Sex	Male	149 (60.57%)	29 (56.86%)	67 (60.91%)	7 (58.33%)	37 (60.66%)
	Female	97 (39.43%)	22 (43.14%)	43 (39.09%)	5 (41.67%)	24 (39.34%)
Risk factors associated with COVID						
COVID positive when mucormycosis diagnosed		53 (21.54%)	16 (31.37%)	16 (14.55%)	2 (16.67%)	9 (14.75%)
Severity of COVID	Mild	17 (6.91%)	6 (11.76%)	6 (5.45%)	0 (0%)	2 (3.28%)
	Moderate	15 (6.1%)	2 (3.92%)	7 (6.36%)	1 (8.33%)	3 (4.92%)
	Severe	21 (8.54%)	8 (15.69%)	3 (2.73%)	1 (8.33%)	4 (6.56%)
Use of remdesivir		5 (2.03%)	2 (3.92%)	1 (0.91%)	0 (0%)	1 (1.64%)
Use of tocilizumab		1 (0.41%)	1 (1.96%)	0 (0%)	0 (0%)	0 (0%)
History of mechanical ventilation		5 (2.03%)	1 (1.96%)	2 (1.82%)	1 (8.33%)	1 (1.64%)
History of hospitalization in last 3 months		100 (40.65%)	26 (50.98%)	38 (34.55%)	4 (33.33%)	15 (24.59%)
History of oxygen use	During hospital stay	84 (34.15%)	25 (49.02%)	31 (28.18%)	4 (33.33%)	14 (22.95%)
	Home-based oxygen therapy	10 (4.07%)	3 (5.88%)	2 (1.82%)	0 (0%)	2 (3.28%)
Comorbidity						
Diabetes Mellitus		200 (81.3%)	29 (56.86%)	98 (89.09%)	9 (75%)	54 (88.52%)
Hypertension		81 (32.93%)	14 (27.45%)	44 (40%)	3 (25%)	17 (27.87%)
Tuberculosis		4 (1.63%)	1 (1.96%)	2 (1.82%)	1 (8.33%)	0 (0%)
Chronic Obstructive Pulmonary Disease		3 (1.22%)	0 (0%)	1 (0.91%)	1 (8.33%)	1 (1.64%)
Coronary Artery Disease		13 (5.28%)	4 (7.84%)	5 (4.55%)	3 (25%)	0 (0%)
Chronic Kidney Disease		8 (3.25%)	2 (3.92%)	2 (1.82%)	2 (16.67%)	0 (0%)
Chronic Lung Disease (other than COPD)		1 (0.41%)	0 (0%)	0 (0%)	0 (0%)	1 (1.64%)
Chronic Liver Disease		2 (0.81%)	1 (1.96%)	0 (0%)	0 (0%)	0 (0%)
Cerebrovascular Disease		9 (3.66%)	1 (1.96%)	4 (3.64%)	1 (8.33%)	3 (4.92%)
Malignancy		2 (0.81%)	0 (0%)	1 (0.91%)	0 (0%)	0 (0%)
Hypothyroidism		16 (6.5%)	6 (11.76%)	4 (3.64%)	1 (8.33%)	2 (3.28%)
Anemia		171 (69.51%)	29 (56.86%)	86 (78.18%)	7 (58.33%)	43 (70.49%)
Others		16 (6.5%)	4 (7.84%)	8 (7.27%)	0 (0%)	4 (6.56%)
Surgically managed		147 (59.76%)	22 (43.14%)	79 (71.82%)	6 (50%)	40 (65.57%)
Duration of hospital stay median (IQR)		37.5 (41.5) days	30 (33.5) days	44.5 (37.5) days	30.5 (54.25) days	37 (47) days
Expired during hospital stay		79 (32.11%)	10 (19.61%)	27 (24.55%)	5 (41.67%)	27 (44.26%)

comorbidities, clinical presentation, radiological and microbiological investigations at presentation were recorded along with the duration of hospital stay, treatment received and outcome at the time of discharge. All patients with complaints suggestive of invasive fungal rhinosinusitis underwent diagnostic nasal endoscopy at presentation. Nasal swab of secretions or crusts were sent for microbiological evaluation. The sample was examined for fungal elements on Potassium Hydroxide (KOH) mount and was cultured on Sabouraud dextrose agar with antibiotics. A negative KOH mount in a clinically suspicious patient was followed by a histopathological examination of the sample for fungal elements. Patients with clinical suspicion underwent a contrast enhanced computed tomography of nose, paranasal sinuses, head and orbits, for radiologic evidence and extent of disease. A patient was diagnosed with mucormycosis if the patient had disease clinically or radiologically with or without microbiological confirmation. Analysis was done using SPSS v20.0.

Observations and Results

Anonymized data of 274 patients was collected, of which, 11 were admitted for evaluation of mucormycosis on basis of clinical suspicion and positive fungal stain or culture but were eventually not found to have mucormycosis, and 17 were patients who were already operated for mucormycosis before admission at the study center. These patients were excluded from analysis and final data of 246 patients was analyzed. Of 246 patients, 12 patients could not undergo a radiological assessment for the disease due to the critical condition and expired before a full evaluation. Among the rest 234 patients, 51 (21.79%) had sinonasal disease, 110 (47.01%) had Rhino-Orbital disease (RO), 12 (5.13%) had Rhino-Cerebral disease (RC) and 61 (26.07%) had Rhino-Orbito-Cerebral disease (ROC). Among the 12

Table 2: Clinical presentation of mucormycosis.

		All patients	Sinonasal	RO	RC	ROC
		(n=246)	(n=51)	(n=110)	(n=12)	(n=61)
		n (%)	n (%)	n (%)	n (%)	n (%)
Laterality of Disease	Unilateral	122 (49.59%)	23 (45.1%)	56 (50.91%)	5 (41.67%)	34 (55.74%)
	Bilateral	124 (50.41%)	28 (54.9%)	54 (49.09%)	7 (58.33%)	27 (44.26%)
Presenting symptoms and signs						
Systemic	New onset fever	29 (11.79%)	7 (13.73%)	9 (8.18%)	4 (33.33%)	6 (9.84%)
Cerebral	Altered Sensorium	40 (16.26%)	3 (5.88%)	3 (2.73%)	4 (33.33%)	21 (34.43%)
	Focal Neurological Deficit	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Seizures	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nasal	Nasal blockage	54 (21.95%)	11 (21.57%)	24 (21.82%)	4 (33.33%)	10 (16.39%)
	Nasal discharge	40 (16.26%)	10 (19.61%)	17 (15.45%)	2 (16.67%)	8 (13.11%)
	Foul smell	16 (6.5%)	2 (3.92%)	11 (10%)	0 (0%)	2 (3.28%)
Orbital	Eyelid swelling	153 (62.2%)	17 (33.33%)	74 (67.27%)	6 (50%)	49 (80.33%)
	Eyelid echhymosis/blackening	25 (10.16%)	3 (5.88%)	10 (9.09%)	1 (8.33%)	10 (16.39%)
	Sudden loss of vision	97 (39.43%)	5 (9.8%)	46 (41.82%)	3 (25%)	39 (63.93%)
	Proptosis	83 (33.74%)	3 (5.88%)	42 (38.18%)	1 (8.33%)	32 (52.46%)
	Restriction of ocular movements	108 (43.9%)	4 (7.84%)	54 (49.09%)	2 (16.67%)	45 (73.77%)
	Conjunctival congestion	102 (41.46%)	4 (7.84%)	51 (46.36%)	5 (41.67%)	36 (59.02%)
	Chemosis	112 (45.53%)	10 (19.61%)	56 (50.91%)	3 (25%)	38 (62.3%)
	Ptosis	122 (49.59%)	8 (15.69%)	58 (52.73%)	5 (41.67%)	46 (75.41%)
	Diplopia	4 (1.63%)	0 (0%)	3 (2.73%)	0 (0%)	1 (1.64%)
Facial	Paresthesia over cheek	6 (2.44%)	2 (3.92%)	2 (1.82%)	0 (0%)	2 (3.28%)
	Anesthesia over cheek	72 (29.27%)	4 (7.84%)	37 (33.64%)	3 (25%)	26 (42.62%)
	Cheek swelling	124 (50.41%)	16 (31.37%)	68 (61.82%)	5 (41.67%)	35 (57.38%)
Regional Pain	Facial Pain	111 (45.12%)	24 (47.06%)	53 (48.18%)	6 (50%)	27 (44.26%)
	Retro-orbital pain	105 (42.68%)	5 (9.8%)	63 (57.27%)	6 (50%)	27 (44.26%)
	Worsening headache	122 (49.59%)	25 (49.02%)	59 (53.64%)	5 (41.67%)	31 (50.82%)
Oral	Loosening of teeth	12 (4.88%)	1 (1.96%)	10 (9.09%)	0 (0%)	1 (1.64%)
	Palatal erosion/ulceration	72 (29.27%)	9 (17.65%)	32 (29.09%)	4 (33.33%)	27 (44.26%)
Facial nerve palsy		20 (8.13%)	2 (3.92%)	8 (7.27%)	0 (0%)	8 (13.11%)
Diagnostic Nasal Endoscopy findings	Crusts	177 (71.95%)	34 (66.67%)	77 (70%)	8 (66.67%)	48 (78.69%)
	Mucopurulent Secretions	133 (54.07%)	20 (39.22%)	68 (61.82%)	6 (50%)	31 (50.82%)
	Fungal Debris	19 (7.72%)	6 (11.76%)	10 (9.09%)	0 (0%)	3 (4.92%)
	Pallor of Mucosa	4 (1.63%)	1 (1.96%)	1 (0.91%)	1 (8.33%)	1 (1.64%)

patients who could not undergo a radiological assessment, nine had intracranial extension of mucormycosis, one developed sepsis as a result of severe COVID-19 infection, one had hepatic encephalopathy and one had end stage renal disease.

The median (IQR) of age of the patients was 50 (16) years. Of them, 149 (60.57%) were male and 97 (39.43%) females. Table 1 summarizes the comorbidities and risk factors identified in patients, along with duration of hospital stay and outcome. Diabetes mellitus was the most common comorbidity identified followed by anemia. Surgical debridement was performed in 147 (59.76%). Overall mortality during the hospital stay was seen in 79 (32.11%) patients which was maximum in ROCM cases. Among the 'Other' comorbidities, 5 had HCV infection, 2 were on anti-retroviral therapy for HIV, 2 were morbidly obese, 1 had recovered from severe dengue in past one month, and 1 each had pancytopenia, leprosy, Hepatitis B, autoimmune hepatitis, and deep vein thrombosis.

Table 2 depicts the clinical presentation (Figure 1). Most common symptom was eyelid swelling followed by cheek swelling, worsening headache and ptosis. Palatal ulceration was seen in 72 (29.27%) patients. Table 3 describes radiological extent and site involvement of disease (Figure 2). Maxillary sinus was involved in most cases in all categories followed by ethmoidal sinus.

Among the 246 patients, 295 causative organisms were isolated. Table 4 describes the result of Potassium Hydroxide (KOH) mount and isolated organisms on culture both preoperatively and postoperatively. All patients were started on injection liposomal amphotericin-B on the basis of presence of aseptate hyphae on KOH mount and clinical and radiological findings. Those who developed an

Table 3: Radiological sites of involvement in mucormycosis.

		All patients	Sinonasal	RO	RC	ROC
		(n=234)	(n=51)	(n=110)	(n=12)	(n=61)
		n (%)	n (%)	n (%)	n (%)	n (%)
Radiological Investigation	NCCT	45 (19.23%)	11 (21.57%)	20 (18.18%)	5 (41.67%)	9 (14.75%)
	CECT	147 (62.82%)	32 (62.75%)	71 (64.55%)	5 (41.67%)	37 (60.66%)
	CE-MRI	78 (33.33%)	13 (25.49%)	37 (33.64%)	4 (33.33%)	24 (39.34%)
Sites involved (radiologically)	Ethmoidal Cells	210 (89.74%)	35 (68.63%)	105 (95.45%)	11 (91.67%)	59 (96.72%)
	Maxillary Sinus	221 (94.44%)	40 (78.43%)	108 (98.18%)	12 (100%)	61 (100%)
	Sphenoid Sinus	177 (75.64%)	27 (52.94%)	86 (78.18%)	10 (83.33%)	54 (88.52%)
	Frontal Sinus	155 (66.24%)	21 (41.18%)	75 (68.18%)	11 (91.67%)	48 (78.69%)
	Premaxillary Region	150 (64.10%)	17 (33.33%)	80 (72.73%)	6 (50%)	47 (77.05%)
	Retromaxillary Region	129 (55.13%)	8 (15.69%)	76 (69.09%)	3 (25%)	42 (68.85%)
	Pterygopalatine Fossa	129 (55.13%)	8 (15.69%)	76 (69.09%)	3 (25%)	42 (68.85%)
	Masticator Space	29 (12.39%)	1 (1.96%)	20 (18.18%)	0 (0%)	8 (13.11%)
	Infratemporal fossa	44 (18.80%)	0 (0%)	27 (24.55%)	0 (0%)	17 (27.87%)
	Orbit	171 (73.08%)	0 (0%)	110 (100%)	0 (0%)	61 (100%)
	Orbital floor	145 (61.97%)	0 (0%)	94 (85.45%)	0 (0%)	51 (83.61%)
	Extra-ocular muscles	75 (32.05%)	0 (0%)	47 (42.73%)	0 (0%)	28 (45.9%)
	Lamina papyracea	114 (61.54%)	0 (0%)	71 (64.55%)	0 (0%)	43 (70.49%)
	Intracranial Extension	73 (31.96%)	0 (0%)	0 (0%)	12 (100%)	61 (100%)
	Cribriform plate	29 (12.39%)	0 (0%)	0 (0%)	5 (41.67%)	24 (39.34%)
	Cavernous Sinus Thrombosis	44 (17.09%)	0 (0%)	0 (0%)	7 (58.33%)	37 (60.66%)
	Palate	72 (30.77%)	9 (17.65%)	32 (29.09%)	4 (33.33%)	27 (44.26%)
	Nasal dorsum	9 (3.85%)	2 (3.92%)	3 (2.73%)	1 (8.33%)	3 (4.92%)

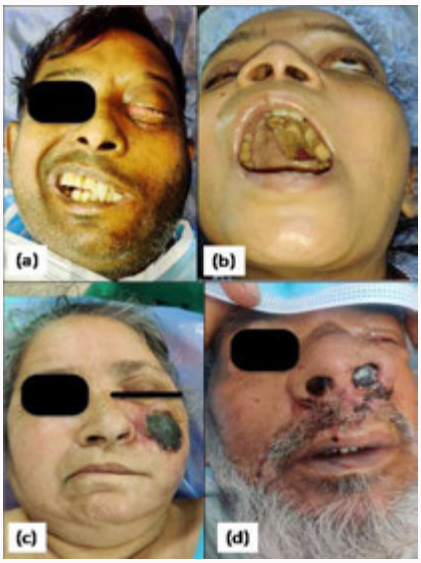

Figure 1: (a) Left Rhino-orbital mucormycosis with left facial nerve palsy. (b) Left rhino-orbital mucormycosis with left facial nerve palsy and palatal erosion. (c) Left rhino-orbito-cerebral mucormycosis with necrosis of skin over left maxillary region. (d) Bilateral rhino-orbito-mucormycosis with fungating mass seen in the left nasl vestibule.

allergic reaction to amphotericin-B or had deranged kidney function tests or serum electrolytes were given tablet Posaconazole. The patients were administered a daily dose 5 mg/kg of liposomal amphotericin-B intravenously with pre and post transfusion hydration during their stay at the hospital. Subsequently these patients were taken up for surgical debridement.

Thirty-three patients underwent endoscopic debridement and 114 patients were taken up for debridement by external approach. Orbital exenteration was done in 16 patients. Eleven patients with intracranial extension were operated in conjunction with neurosurgery department. The median (IQR) stay in hospital was 37.5 (41.5) days and patients were discharged on tablet Posaconazole for a period of 3 months. The patients were followed up regularly for 6 months.

Discussion

Mucormycosis is nearly 70 times more prevalent in India than the rest of the world, and Rhino-Orbito-Cerebral Mucormycosis (ROCM) is its most common form (45%-74%) in terms of the anatomical site involved [1]. The trend of mucormycosis was already reported to be on the rise before COVID-19 [4,5]. The rate increased during the first wave of COVID-19 in India but remained under-reported and did not gather much attention [6]. The alarming rate of 28,252 cases reported in second quarter of 2021 alone, brought the disease to limelight and created panic by the popular name of "black fungus" disease [7]. This sharp rise in number of cases can be attributed to the favorable agent and host environment created during the pandemic.

Host, agent and environment interplay

India being a damp tropical country also has a high prevalence of fungi in environment. Aero-mycological studies have shown that mucoromycetes have an outdoor mean (SD) spore count (cfu/

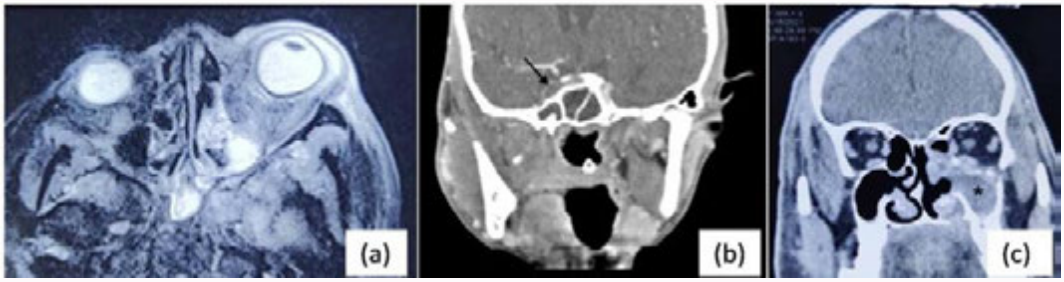

Figure 2: (a) T2 weighted magnetic resonance imaging of nose and orbit showing heterogenously hyperintense polypoidal mass lesion involving the posterior ethmoid air cells and extending anteriorly and laterally into both intraconal and extraconal compartment of left orbit with intracranial extension posteriorly. The lesion is causing proptosis on left side (b) Contrast enhanced computed tomography of nose, paranasal sinus and brain shows heterogeneously enhancing opacities in bilateral sphenoid sinuses and pterygopalatine fossa regions along with filling defect in right cavernous sinus (arrow) suggestive of right cavernous sinus thrombosis. (c) Contrast enhanced computed tomography of nose, paranasal sinuses, orbit and brain, showing heterogenous enhancing mass epicentered in left maxillary sinus (asterisk), medially extending to left nasal cavity and left posterior ethmoid sinuses, and superiorly causing erosion of floor of left orbit with loss of fat plane between left inferior and medial rectus.

Table 4: Microbiological evaluation of causative agents of mucormycosis.

		All patients	Sinonasal	RO	RC	ROC
		(n=246)	(n=51)	(n=110)	(n=12)	(n=61)
		n (%)	n (%)	n (%)	n (%)	n (%)
Result of KOH mount	Septate	4 (1.63%)	1 (1.96%)	2 (1.82%)	0 (0%)	1 (1.64%)
	Aseptate	195 (79.27%)	42 (82.35%)	84 (76.36%)	10 (83.33%)	51 (83.61%)
	Aseptate+septate	6 (2.44%)	0 (0%)	2 (1.82%)	0 (0%)	1 (1.64%)
	Negative	41 (16.67%)	8 (15.69%)	22 (20%)	2 (16.67%)	8 (13.11%)
Result of fungal culture	No growth	33 (13.41%)	2 (3.92%)	17 (15.45%)	0 (0%)	11 (18.03%)
	Rhizopus	113 (45.93%)	29 (56.86%)	47 (42.73%)	4 (33.33%)	30 (49.18%)
	Mucor	14 (5.69%)	2 (3.92%)	9 (8.18%)	1 (8.33%)	2 (3.28%)
	Aspergillus flavus	58 (23.58%)	15 (29.41%)	29 (26.36%)	2 (16.67%)	11 (18.03%)
	Aspergillus fumigatus	14 (5.69%)	3 (5.88%)	9 (8.18%)	0 (0%)	2 (3.28%)
	Aspergillus niger	19 (7.72%)	5 (9.8%)	6 (5.45%)	4 (33.33%)	4 (6.56%)
	Aspergillus terreus	2 (0.81%)	0 (0%)	1 (0.91%)	0 (0%)	1 (1.64%)
	Aspergillus	12 (4.88%)	2 (3.92%)	8 (7.27%)	0 (0%)	2 (3.28%)
	Alternaria	17 (6.91%)	2 (3.92%)	9 (8.18%)	3 (25%)	4 (6.56%)
	Bipolaris	4 (1.63%)	1 (1.96%)	2 (1.82%)	1 (8.33%)	0 (0%)
	Candida albicans	5 (2.03%)	1 (1.96%)	2 (1.82%)	0 (0%)	2 (3.28%)
	Candida krusei	1 (0.41%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Candida parapsilosi	1 (0.41%)	0 (0%)	0 (0%)	1 (8.33%)	0 (0%)
	Candida rugosa	1 (0.41%)	1 (1.96%)	0 (0%)	0 (0%)	0 (0%)
	Candida tropicalis	1 (0.41%)	0 (0%)	0 (0%)	0 (0%)	1 (1.64%)
	Candida	10 (4.07%)	2 (3.92%)	6 (5.45%)	0 (0%)	1 (1.64%)
	Cunninghamella	6 (2.44%)	2 (3.92%)	1 (0.91%)	0 (0%)	2 (3.28%)
	Fusarium	6 (2.44%)	3 (5.88%)	2 (1.82%)	0 (0%)	0 (0%)
	Lichtheimia	1 (0.41%)	1 (1.96%)	0 (0%)	0 (0%)	0 (0%)
	Synephalastrum	1 (0.41%)	1 (1.96%)	0 (0%)	0 (0%)	0 (0%)
	Trichosporon	6 (2.44%)	0 (0%)	5 (4.55%)	0 (0%)	1 (1.64%)
	Yeast	4 (1.63%)	1 (1.96%)	0 (0%)	0 (0%)	1 (1.64%)

m^3) of 0.73 (0.96) to 8.60 (5.70) across different seasons. In hospital, the mean spore count varied from 0.68 (1.07) to 1.12 (1.07) and 0.88 (1.01) to 1.72 (2.17) respectively for wards with and without air-conditioning [8]. Spore counts have also been reported to be increased significantly during outdoor construction which may also be a contributory factor for the outbreak as COVID-19 pandemic saw rapid constructions of new centers for patient care. Mucorales do no not infect individuals but higher fungal hyphal load may overwhelm the polymorphonuclear response, causing hyphal damage and thus the disease [9].

India is the diabetic capital of the world and COVID-19 led to an increase in prevalence of diabetes by causing new onset diabetes and uncontrolled hyperglycemia often leading to diabetic ketoacidosis. COVID-19 and diabetes also weaken the innate immunity. Diabetes mellitus was the most common comorbidity found in our study (n=200, 81.3%). Diabetes also leads to increased expression of Glucose Related Protein 78 (GRP78), a heat shock protein, expressed on the surface of endothelial cells. Mucorales bind to GRP78 using their coat protein CotH3 and invade blood vessels. Angioinvasion, a hallmark of mucormycosis, plays an important role in locoregional spread by causing ischemic necrosis, and hence the characteristic black crusts and eschar. Invading blood vessels also provides a highway for distant spread of the organism [10,11]. Although, mucormycosis is mainly a disease of immunocompromised, but 21 (8.54%) were immunocompetent. They had no history of any other condition affecting immunity other than history of hospitalization for COVID-19.

COVID-19 also causes hyperferritinemia due to increased inflammation. Iron has an important role to play in the survival and growth of Mucorales [11]. Patients with iron overload are particularly susceptible [12]. The triad of hyperglycemia, hyperferritinemia and lowered innate immune defense creates a favorable environment for the fungus to grow.

Symptoms and signs

When favorable conditions prevail, fungal spores germinate in the sinonasal lining and grow to invade the tissues and blood vessels causing ischemic necrosis of tissue, and forming a black eschar presenting as crusts. Black crusts and mucopurulent discharge are the most common findings on nasal endoscopy as confirmed in our study. The agent grows to involve the orbit laterally, pterygopalatine fossa posteriorly, palate inferiorly and cranium superiorly. Presentation at an advanced stage is common because the symptoms at an early stage can be non-specific and ubiquitous, like, nasal blockage, discharge or facial paresthesia or hypoesthesia.

Pathways for orbital involvement

The pathways of spread to the orbit is by direct erosion of medial and inferior walls of orbit (n=171, 73.08%). In cases with orbital involvement orbital floor was more commonly found eroded (n=145, 61.97%) than lamina papyracea (n=114, 61.54%), which can be correlated with the finding that maxillary sinus was more commonly involved (n=221,94.44%) than the ethmoid sinus (n=210, 89.74%). Nine (5.26%) patients had maxillary sinus involvement and orbital extension of disease but there was no erosion of floor or medial wall of orbit. Among them, 2 (1.17%) patients had cheek involvement and 1 (0.58%) had involvement of the pterygopalatine fossa and 2 (1.17%) had involvement of both, suggesting the possible path to be the infraorbital canal and fissure. Four (2.34%) patients who did not have premaxillary or retromaxillary extension but had orbital disease could be attributed to the extension along perivascular channels (anterior and posterior ethmoid arteries) as all had ipsilateral involvement of ethmoid sinuses. Another possible pathway that has been proposed is *via* the nasolacrimal duct [13]. Infratemporal fossa involvement is also seen exclusively in orbital involvement, the possible pathway for which is the inferior orbital fissure.

Pathways for intracranial involvement

Among patients with intracranial involvement (n=73), anterior cranial fossa was involved by erosion of posterior wall of frontal sinus (n=1, 1.36%), or cribriform plate (n=29, 39.72%) resulting in extension into frontal lobe (n=2, 2.74%) or extension into olfactory fossa respectively. Middle cranial fossa involvement was noted by cavernous sinus involvement (n=44, 60.27%) through orbit or lateral wall of sphenoid sinus, causing loss of vision with or without internal carotid artery thrombosis along the optic nerve (n=6, 8.22%), or superior extension from the infratemporal fossa *via* the foramina in the greater wing of sphenoid, causing temporal extension (n=2, 2.74%); into the posterior cranial fossa, by erosion of clivus (n=2, 2.74%) causing cerebellar abscess in 1 (1.37%) patient.

Causative agents, treatment and outcome

Extensive surgical debridement followed by intravenous amphotericin B is the recommended treatment in ROCM. The patients were started empirically with amphotericin B, on basis of suggestive symptoms, characteristic signs on nasal endoscopy and KOH mount results, with adjunctive roles of radiological findings and fungal culture results. *Rhizopus arrhizus* species were the most common organisms isolated. Complementing other studies, the most common organism isolated is *Rhizopus* in our study [5,14]. Fungal culture in our study also revealed the presence of yeast, *Candida*, *Trichosporon*, *Bipolaris* and *Fusarium* which can be saprophytic fungi present over the debris due to mucormycosis. The mortality at the study center was 79 (32.11%) which is lower than most reported mortality rates. Despite all efforts, the mortality rate remains significant and especially high in case of intracerebral involvement.

References

1. Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. Microorganisms. 2021;9:523.
2. Payne SJ, Mitzner R, Kunchala S, Roland L, McGinn JD. Acute invasive fungal rhinosinusitis: A15-year experience with 41 patients. Otolaryngol Head Neck Surg. 2016;154:759-64.
3. Jha DN. 1,044 black fungus cases in Delhi, 89 deaths so far. 2021. (Accessed January 11, 2023).
4. Chakrabarti A, Das A, Mandal J, Shivaprakash MR, George VK, Tarai B, et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. Med Mycol. 2006;44:335-42.
5. Prakash H, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J, et al. A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. Med Mycol. 2019;57:395-402.
6. Muthu V, Rudramurthy SM, Chakrabarti A, Agarwal R. Epidemiology and pathophysiology of COVID-19-associated mucormycosis: India versus the rest of the world. Mycopathologia. 2021;186:739-54.
7. Back Black Fungus: These 2 states account for nearly 42% of India's 28,252 mucormycosis cases. 2021. (Accessed January 11, 2023).
8. Prakash H, Singh S, Rudramurthy SM, Singh P, Mehta N, Shaw D, et al. An aero mycological analysis of Mucormycetes in indoor and outdoor environments of northern India. Med Mycol. 2020;58:118-23.
9. Antachopoulos C, Demchok JP, Roilides E, Walsh TJ. Fungal biomass is a key factor affecting polymorphonuclear leucocyte-induced hyphal damage of filamentous fungi. Mycoses. 2010;53:321-8.
10. Ibrahim AS. Host-iron assimilation: Pathogenesis and novel therapies of mucormycosis. Mycoses. 2014;57 Suppl 3:13-7.
11. Gumashta J, Gumashta R. COVID-19 associated mucormycosis: Is GRP78 a possible link? J Infect Public Health. 2021;14:1351-7.
12. Maertens J, Demuynck H, Verbeken EK, Zachée P, Verhoef GEG, Vandenberghe P, et al. Mucormycosis in allogeneic bone marrow transplant recipients: Report of five cases and review of the role of iron

overload in the pathogenesis. Bone Marrow Transplant. 1999;24:307-12.

13. Khullar T, Kumar J, Sindhu D, Garg A, Meher R, Goel R. Coronavirus disease 2019 associated mucormycosis meandering its way into the orbit: A pictorial review. J Laryngol Otol. 2021;135:942-6.

14. Hussain S, Baxi H, Riad A, Klugarová J, Pokorná A, Slezáková S, et al. COVID-19-Associated Mucormycosis (CAM): An updated evidence mapping. Int J Environ Res Public Health. 2021;18:10340.