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Original Research Article

Epidemiology, clinical profile, management and outcome in patients of post covid mucormycosis at a tertiary care center in eastern UP

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ABSTRACT

Background: The second wave of covid 19 in our country has seen rhino orbital cerebral mucormycosis reach an epidemic level. It is an opportunistic fungal infection with high morbidity and mortality.

Objective: This study aimed to determine the patient's demographics, risk factors, symptoms and signs, treatment and the outcome at our tertiary care centre.

Materials and Methods: In this retrospective observational study the case records of 43 patients with biopsy/culture proven invasive rhino-orbital mucormycosis who were admitted in the post covid phase between May 2021 and July 2021 were reviewed.

Observation/Result: Mean age was 52.4 years with 65.11% of patients being male. 83.7% belonged to the rural background. 37 (86.05%) had history of diabetes while 25 (58.15%) used steroids and only 13 (30.23%) patients needed oxygen. Only 3 (6.97%) had RBS below 200mg/dl with 2 patient showing HbA1C level below 6.4. All patients had proptosis and ptosis while only 28 had chemosis and 26 had loss of vision. Chemosis showed significant association in our study with HbA1c with significant p value of 0.000126. and loss of vision showed a significant association with steroid use (p value 0.03) and oxygen requirement (p value 0.008). All the patients had involvement of orbit. Treatment included IV liposomal amphotericin B in all patients, Retrobulbar amphotericin B and endoscopic orbital debulking in. Significant improvement was seen in patients with stage >3b with Retrobulbar amphotericin B and orbital debulking.

Conclusion: Patients with rhino orbital mucormycosis can be managed with orbital debulking with perilesional, intralesional and Retrobulbar amphotericin B with IV amphotericin B and functional endoscopic sinus surgery to avoid distressing surgery like exenteration.

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1. Introduction

COVID – 19 which is caused by coronavirus is a highly transmissible and pathogenic disease. It was first reported in Wuhan, China in 2019 and is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ It spreads faster than its related viral strains SARS-CoV and MERS-CoV and this rapid human to human transfer resulted in a worldwide pandemic.² Covid-19 leads to decrease in the total number of lymphocytes

which in turn inhibits body's cellular immune function,^{3,4} which along with the complex interaction of different factors like preexisting comorbidities (diabetes mellitus, kidney disease), use of immunosuppressive drugs leads to secondary infection in patients.⁵

India has seen a sudden rise in cases of a rare but notoriously fatal disease, rhino-orbital-cerebral mucormycosis during the second wave of covid-19 with contributing as high as 82% of the total global burden.⁶ First described by Paltauf, ROCM is caused by zygomycosis of order Mucorales⁷ which is an angioinvasive nonseptate filamentous fungus generally found in soil,

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decaying organic matter.⁸ It commonly affects orbit via invasion of paranasal sinuses or via direct inoculation and hematogenous spread.⁸ Immunocompromised state, diabetes, solid organ transplantation, neutropenia, long-term systemic corticosteroid use, and iron overload are the associated risk factors.^{9,10}

Early diagnosis of mucormycosis which is based on clinical history and examination, imaging, microbiology and histopathology is important as medical and surgical treatment can reduce morbidity and mortality.¹¹ MRI/CT findings are often nonspecific but are used to delineate the extent of disease.¹² Confirmation of diagnosis is done by KOH (fungal hyphae), culture and histopathology shows pathognomonic broad, irregular, non-septate, and right-angle branching hyphae along with evidence of angioinvasion and tissue infarction.¹²

In this study we aim to determine the patient demographics and population at risk, symptoms and signs, role of comorbidities and medication, treatment and outcome.

2. Materials and Methods

We performed a prospective study on patients admitted in post covid fungal ward as clinically and microbiologically proven case of mucormycosis with past history of COVID-19 infection. The demographic and clinical data were collected with the consent of the patients. The diagnosis of COVID-19 was based on RT-PCR test on nasopharyngeal/oropharyngeal swabs. Proven mucormycosis was defined as histopathologic, cytopathologic or direct microscopic examination showing fungal hyphae in biopsy specimen with associated tissue damage, or a positive culture result.⁶

Patients were admitted on the basis of clinical suspicion and a deep nasal swab and tissue from diagnostic nasal endoscopy was sent for KOH mount and fungal culture. Systemic antifungals were started on the basis of initial reports after consultation with ENT specialists. Magnetic resonance imaging (MRI) orbit, brain, and paranasal sinuses was performed for assessing the extent of disease. After getting the confirm culture report as mucormycosis all the patients underwent Retrobulbar injection Amphotericin B on 3 alternate days in dose 3.5 mg/ml. MRI was repeated after 1 week and based on clinical and radiological finding patients were divided into two groups, first group which showed regression of disease and second group where stable or progressive disease was seen. Second group then underwent endoscopic orbital debulking. All the patient also underwent endoscopic sinus debridement with biopsy and specimen was sent for histopathology, microbiology for culture and sensitivity test. Patients were then followed up for a period of 3 months to determine the outcome. Demographic and clinical characteristics were represented by frequencies and percentage. Fischer test was used to

calculate P-value and significant p value was taken as <0.05.

3. Observation

The study group consisted of 43 patients with a mean age of 52.4 years. Maximum patients belonged to age group of 41-50 years (30.2%) with a gender ratio of 1.8:1. 28 (65.11%) patients were male while 15 (34.88%) were female. 36 (83.7%) patients belonged to rural background while 37 (86.05%) patients presented with concurrent history of diabetes out of which 5 had more than 1 risk factor.

27 (62.79%) patients had history of Covid-19 which was RTPCR confirmed whereas 16 (37.2%) had Covid defining symptoms like fever, malaise, breathlessness and sore throat with chest X-ray suggestive of covid-19 but never got tested. While 20 (66.67%) patients suffered for a duration less than 8 days, 25 (58.15%) and 13 (30%) needed steroids and oxygen respectively. Out of 25 patients, 11 used oral steroids, 6 used IV steroid and 8 used both oral and injectable steroids with mean duration of steroid use for 9.1 days. None of the patients in our study used any immunomodulatory drugs during illness.

All the patients presented to us with nasal stuffiness, swelling and pain on one side of face and periorbital area, headache, proptosis and ptosis. 28 (65.11%) patient had chemosis and 26 (60.46%) had loss of vision at the time of presentation. MRI of all the patients was done which showed sinus disease with orbit involvement.

Routine blood investigation was done and 18 (41.86%) patients had RBS in range of 200-300mg/dl, 11 (25.58%) patients had RBS in the range of 300-400mg/dl, 11 (25.58%) patients had RBS >400mg/dl while only 3 (6.97%) patients had RBS below 200mg/dl. Similar trend was seen with HbA1c with only 2 (4.65%) patient showing HbA1c in pre-diabetic range of 5.7-6.4. Rest of the patients had HbA1c level above 6.4 where a staggering 20 patients showed HbA1c above 10.

Out of 28 patients where chemosis was present, 19 patients had HbA1c level more than 10 and 18 had history of use of steroids. Chemosis showed significant association in our study with HbA1c with significant p value of 0.000126. No significant association was found between chemosis and steroid use with p value of 0.26 and between chemosis and oxygen use with p value of 0.307.

Out of 26 patients where loss of vision was present, 19 patients had history of use of steroids and 12 had history of oxygen requirement. Loss of vision showed significant association in our study with steroid use and oxygen requirement with significant p value of 0.03 and 0.008 respectively. No significant association was found between loss of vision and HbA1c with p value of 0.66.

On MRI, maximum 29 patient showed unilateral diffuse Para nasal sinus involvement whereas only 6 showed unilateral maxillary and ethmoid involvement and 8 showed bilateral involvement. Similarly, 2 patient showed

involvement of medial orbit i.e. stage 3a whereas, only 1 patient had stage 3d i.e. bilateral orbit involvement. Out of 39 patients who had diffuse unilateral orbit involvement 13 were in stage 3b and 26 in stage 3c.

All the patients underwent Retrobulbar amphotericin B injection and MRI was done after 1 week, all the 3 patients in stage 3a showed regression. Out of 9 patients in stage 3b, 7 showed regression whereas 6 patients who showed stable/progressive disease then underwent orbital debulking and showed regression. Similarly, all the patient in stage 3c underwent orbital debulking where 12 showed regression of disease, 11 showed stable and 3 showed progressive course. 1 patient in stage 3d showed regression to stage 3c with retrobulbar and intralesional amphotericin B injection and a further stable course after orbital debulking.

4. Discussion

The COVID-19 pandemic started in wuhan, China back in December 2019.¹³ A novel coronavirus was identified by the Chinese Center for Disease Control and Prevention (CDC) on 7 January 2020. Coronavirus consumes immune cells (CD4+, CD8+ and Lymphocytes) leading to decrease in the total number of lymphocytes which in turn inhibits body's cellular immune function,¹³ which along with the complex interaction of different factors like preexisting comorbidities (diabetes mellitus, kidney disease), use of immunosuppressive drugs, hospital acquired infection leads to secondary infection in patients.¹⁴

The mucorals are angioinvasive, they have affinity for arteries and grow along the internal elastic lamina, causing thrombosis and necrosis of host tissue.¹⁵ Progression of the disease is either direct through the thin lamina papyracea of the ethmoid bone, infratemporal fossa, inferior orbital fissure, or orbital apex or leads to the vascular occlusion of the orbital contents.¹⁵ Intracranial involvement occurs also from the invasion by the way of the superior orbital fissure, ophthalmic vessels and cribriform plate, through the carotid artery, or possibly via a perineural route.¹⁶

The use of immunosuppressant drugs and immunomodulators in COVID also increases the risk of secondary infection. Currently the use of intravenous methylprednisolone 0.5-1 mg/kg/day for three days in moderate cases and 1-2 mg/kg/day in severe cases is recommended by Government of India (GOI)¹⁷ and use of dexamethasone (6 mg per day for a maximum of 10 days) in patients on supplemental oxygen is recommended by The National Institute of Health.¹⁸

Mucormycosis is likely to develop during the middle and later stages of COVID-19.¹⁹ Most common association was found between diabetes mellitus and mucormycosis in India. In a large meta-analysis on 851 cases presence of DM was found to be an independent risk factor (Odds ratio [OR] 2.69; 95% Confidence Interval 1.77–3.54; $P < 0.001$) and the most common species isolated was *Rhizopus* (48%).²⁰

Voriconazole use was also found to be a predisposing factor in mucormycosis in the same study. While long term use of corticosteroids has often been associated with several opportunistic fungal infection, even a short course of corticosteroids has been reported to link with mucormycosis especially in people with DM.²¹ In a retrospective observational study on 2826 patients from all over India by Sen, Mrityika et al⁶ in July 2021, they found that maximum cases were reported from Gujarat (22%) and Maharashtra (21%) with a male predilection and a mean age of 51.9 years. Majority of patients were diagnosed when presented in stage 3 (involvement of orbit). They concluded that DM and use of corticosteroids are important and independent risk factor for mucormycosis along with covid which in itself is an immunocompromised state. In a systemic review of cases of mucormycosis from all over world and india, Singh AK et al²² concluded that increase in cases in india during covid second wave is due to the trinity of diabetes who have high prevalence genetically, rampant use of corticosteroid which increases blood glucose and opportunistic fungal infection and COVID-19 the disease itself which leads to cytokine storm, lymphopenia, endothelial damage. In a similar study done by Gupta SK²³ in 2017, mean age was found to be 50 years with male preponderance. He concluded that uncontrolled diabetes is the biggest risk factor for rhino orbital mucormycosis.

The mean age of our study is 52.4 years with male predominance similar to the study done by Sen, Mrityika et al. Most of the patient in our study were rural area where the lack of proper care and rampant use of steroids is prevalent. 5 patients had more than 1 risk factor, out of which 1 patient had history of long term steroid use which in itself is a risk factor for mucormycosis. All the patient presented in stage 3 after the involvement of orbit. Diabetes mellitus was the most common underlying predisposing factor in our study and steroid use the second most common with as many as 25 patients who needed steroids during their covid illness similar findings were also observed by Sen, Mrityika et al¹⁵ and Singh AK et al.²² The mean duration of steroid use was 9.1 days (short duration). Use of oxygen was found only in 13 patients.

All the patients presented to us in stage 3 disease with nasal stuffiness, swelling and pain on one side of face and periorbital area, headache, proptosis and ptosis. MRI of all the patients showed sinus disease with orbit involvement. Most patients in our study had uncontrolled diabetes with only 3 patients having RBS below 200mg/dl at the time of presentation and only 2 patient having HbA1c below 6.4 whereas a staggering 20 patients had HbA1c above 10.

Use of steroid and oxygen increases with the increase in severity of covid-19 illness along with the use of broad spectrum antibiotics and antifungal in hospital setup. With increasing severity of covid-19 and use of steroid long with uncontrolled diabetes, severity of symptoms

Table 1: Clinical-demographic profile

S.No.	H/O DM	HbA1C	Covid +Ve	Steroid	O2	Age	Sex	RBS	R/U	Proptosis	Ptosis	Chemosis	Loss of vision
1	No	13.2	Yes	Yes	No	74	M	214.5	R	Yes	Yes	Yes	No
2	Yes	13.7	Yes	Yes	No	45	F	354.7	R	Yes	Yes	Yes	Yes
3	Yes	8.7	Yes	No	Yes	80	M	362.6	R	Yes	Yes	No	Yes
4	Yes	8.6	Yes	No	Yes	50	F	277	R	Yes	Yes	No	Yes
5	Yes	10.2	No	Yes	No	56	M	302.2	R	Yes	Yes	Yes	No
6	Yes	11.6	No	Yes	No	60	F	555	R	Yes	Yes	Yes	No
7	Yes	10.2	Yes	Yes	No	62	M	213	R	Yes	Yes	Yes	Yes
8	No	7	Yes	Yes	YES	45	M	436	R	Yes	Yes	No	Yes
9	Yes	13.2	No	No	No	40	M	190.7	R	Yes	Yes	Yes	No
10	Yes	11.8	Yes	No	No	34	F	223	R	Yes	Yes	Yes	Yes
11	Yes	8.8	Yes	Yes	Yes	56	F	304.2	R	Yes	Yes	No	Yes
12	Yes	12.6	Yes	Yes	No	60	M	242.9	R	Yes	Yes	Yes	Yes
13	Yes	12.2	Yes	No	No	55	M	444	R	Yes	Yes	Yes	Yes
14	Yes	8.8	No	No	No	51	M	254.4	R	Yes	Yes	No	No
15	NO	10.2	Yes	No	No	45	M	338.4	R	Yes	Yes	Yes	Yes
16	Yes	11.1	Yes	Yes	No	36	F	238.5	R	Yes	Yes	Yes	Yes
17	Yes	10.2	No	No	No	48	M	275	R	Yes	Yes	Yes	No
18	Yes	10.8	Yes	Yes	No	48	M	333.3	U	Yes	Yes	Yes	Yes
19	Yes	8.1	Yes	Yes	Yes	45	M	198.9	R	Yes	Yes	Yes	Yes
20	Yes	8.6	No	No	No	40	F	224.4	R	Yes	Yes	No	No
21	No	6.1	No	No	No	60	F	336.7	R	Yes	Yes	No	No
22	Yes	7.8	Yes	Yes	Yes	72	M	221.1	U	Yes	Yes	No	Yes
23	Yes	7.1	No	No	No	43	M	456	R	Yes	Yes	No	No
24	Yes	8.9	Yes	Yes	No	66	M	246	U	Yes	Yes	Yes	Yes
25	Yes	13	No	No	No	74	M	450	R	Yes	Yes	Yes	No
26	Yes	14.6	Yes	Yes	YES	69	M	380.9	R	Yes	Yes	Yes	Yes
27	Yes	8.2	Yes	Yes	No	35	F	224	R	Yes	Yes	No	Yes
28	Yes	12.4	Yes	Yes	Yes	40	M	178.7	R	Yes	Yes	Yes	Yes
29	Yes	8.8	Yes	Yes	Yes	40	M	461.8	R	Yes	Yes	Yes	Yes
30	Yes	12.8	Yes	Yes	No	55	F	224	R	Yes	Yes	Yes	Yes
31	Yes	7.9	Yes	Yes	No	42	M	314	U	Yes	Yes	No	No
32	Yes	8.9	No	Yes	No	50	M	444	R	Yes	Yes	No	Yes
33	Yes	12.6	No	No	No	39	f	254.9	U	Yes	Yes	Yes	No
34	No	5.8	No	No	No	40	F	202	R	Yes	Yes	Yes	No
35	Yes	14.4	Yes	Yes	Yes	45	M	502.7	R	Yes	Yes	Yes	No
36	Yes	6.4	No	No	No	50	M	371	R	Yes	Yes	No	Yes
37	Yes	8.9	Yes	Yes	No	66	M	222	U	Yes	Yes	Yes	No
38	Yes	6.7	No	No	No	70	M	524	R	Yes	Yes	No	Yes
39	Yes	7.7	Yes	Yes	Yes	50	M	377	R	Yes	Yes	Yes	Yes
40	Yes	9.8	Yes	Yes	Yes	55	F	226	R	Yes	Yes	Yes	Yes
41	Yes	11.3	Yes	Yes	Yes	36	F	666	R	Yes	Yes	No	Yes
42	No	6.6	No	No	No	62	M	276	R	Yes	Yes	Yes	No
43	Yes	8.9	No	No	No	65	F	495	R	Yes	Yes	Yes	Yes

for mucormycosis also increases and hence the grave consequences. All the 43 patients were alive at 3 month follow –up.

5. Conclusion

Patients with rhino orbital mucormycosis can be managed with orbital debulking with perilesional, intralesional and Retrobulbar amphotericin B with IV amphotericin B and functional endoscopic sinus surgery to avoid distressing

surgery like exenteration.

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None.

8. Conflict of Interest

None.

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