



VARIATIONS IN INVOLVEMENT OF STRUCTURES IN PATIENTS WITH COVID-19 ASSOCIATED RHINO-ORBITO-CEREBRAL MUCOR MYCOSIS

Dr. Jitendra Singh Yadav

Professor & Head, Department of Otorhinolaryngology, M.L.B. Medical College, Jhansi U.P., India.

Dr. Shankar Lal

Assistant Professor, Department of Otorhinolaryngology, Rani Durgawati Medical College Banda, U.P., India.

Dr. Haraprathap Yelishetty

Junior Resident, Department of Otorhinolaryngology, M.L.B. Medical College, Jhansi U.P., India.

Dr. Shraddha Gupta*

Junior Resident, Department of Otorhinolaryngology, M.L.B. Medical College, Jhansi U.P., India. *Corresponding Author

ABSTRACT

Mucormycosis or black fungus previously called as zygomycosis is not a common fungal disease. It occurs in the patients with low neutrophil counts, severe malnutrition and hematological malignancies. Mucor mycosis also common in patients with tuberculosis, diabetes mellitus, COVID-19 and steroid therapy since all these conditions lead to low immunity. Mucormycosis involves different body organs like nose, orbit, brain, skin, gastrointestinal tract, lung, blood and is classified accordingly. Infection mainly enters in the body through nose and mouth or through cuts present over the skin. In case of rhino-orbito-cerebral type of mucormycosis the clinical feature might be from nasal blockage and crusting to life threatening complication like brain abscess and meningitis. The treatment for mucor mycosis might be antifungal drugs alone or combined with surgical debridement depending upon involvement of vital structure and complications. After covid-19 infection, incidence of rhino-orbito-cerebral mucor mycosis increased. The rare disease is to be common due to multiple factors in covid-19 infected patients. Diabetes was a major etiological factor because high blood glucose level and acidosis is responsible for virulence and survival of the fungi. Most common clinical feature was nasal blockage and crusting of nasal cavity mucosa and most common involved sinus was maxillary sinus while involvement of maxillary sinus with ethmoid sinus was highest.

KEYWORDS : COVID-19, mucormycosis, Biopsy

INTRODUCTION

Mucormycosis is a fungal infection of the sinuses, brain, or lungs occurs in people with a low immunity. It is caused by different kinds of fungi which are found in decaying organic matter such as spoiled bread, fruit, and vegetables, as well as soil and compost piles. Most of the people come in contact with the fungus in the environment. It is an angio-invasive fungal infection and is caused by fungi of the order Mucorales. Among all genera in this order, genera *Rhizopus oryza* solely responsible for approximately 70% of all cases of mucormycosis followed by genera *Lichtheimia* (~20%) and rarely (3%) by *Apophysomyces*^[1]. Out of all genera causing mucormycosis, the most fatal infection is also caused by *Rhizopus oryza*^[2,3,4]. The spores of the mucor found mainly in dump and moist environment e.g. rotten breads, cow dung and soil. . Diagnosis of mucor mycosis made by identifying mold in the affected tissue by mounting with KOH and confirmed by biopsy taken for histo-pathological examination^[5]

The prevalence of mucor mycosis in developing country like India is more than in developed countries. Globally, Diabetes mellitus is the main underlying cause especially in low and middle-income countries^[6]. Rhino-orbito- - cerebral mucormycosis almost always occurs in immunocompromised persons including uncontrolled diabetes mellitus with its complications (acidosis or ketoacidosis), steroid therapy, solid organ or hematopoietic stem cell transplant recipients, chemotherapy, hematologic dyscrasias , retroviral disease, and malnourishment^[6,7]. In addition to this new risk factors like post covid-19 infection, post-pulmonary tuberculosis and chronic kidney disease also play a pivotal role in occurrence of mucormycosis. The preponderance also noted in the patients on deferoxamine therapy, iron overload state, and intravenous drug abuse. Cases of rhino-orbital cerebral mucormycosis have been reported following facial burns or scleral buckling procedures^[8].

TYPES - According to the involvement of tissue , it may be categorizes as follows^[9].

1. Rhino-orbito-cerebral[4%]
2. Cutaneous[57%]
3. Gastro-intestinal[15%]
4. Pulmonary[8%]
5. Disseminated[16%]

Since the rhino-orbito-cerebral types is least common but is the most fatal with mortality of approximately 54-60 % [9,10] .

PATHOGENESIS -

Individuals who lack phagocytes or have impaired phagocytic functions are at higher risk of mucor mycosis e.g. severely neutropenic patients. In the presence of hyperglycemia and low pH i.e. diabetic ketoacidosis (DKA), phagocytes are dysfunctional that leads to impaired chemotaxis and defective intracellular killing by both oxidative and non-oxidative mechanisms^[10]. *Rhizopus* grows rapidly in the hyperglycemic environment because phagocytosis is significantly impaired in a high blood sugar state. The ketone reductase system in the fungus helps successfully for survival in the acidotic environment in diabetic ketoacidosis. Moreover acidosis causes dissociation of iron from sequestering proteins in the serum which promotes virulence and survival. Phagocytosis also get impaired notoriously in the patients with neutropenia and steroid therapy. The iron-rich state caused by deferoxamine (iron-chelating agent) also favors the fungal growth by acting as a siderophores to the fungus. Many of the patients suffering from diabetes with minimal or no acidosis also encounter with mucormycosis because hyperglycemia itself favors fungal growth by at least three mechanisms first one is hyper-glycation of iron sequestering proteins with impaired iron sequestration second enhanced expression of GRP 78 (a mammalian protein receptor) which increases binding to Mucorales and finally the decreased phagocytosis associated with high blood sugar state^[11].

CLINICAL FEATURE-

Clinical features of mucormycosis depend on the location of the infection in the body. Infection usually begins from the nose or mouth and enters the central nervous system via the cribriform plate and foramina present in skull base and eyes^[12]. If the fungal infection begins from nose or sinus and extends to brain then clinical features may include one-sided orbital pain or headache that may be accompanied by pain and numbness over the face, fever, loss of smell, blocked nose or bloody nasal discharge. Sometimes patients may also appear to have sinusitis^[13]. The face may look swollen with rapidly progressing "black lesions" across the nasal cavity, turbinates, floor of nose and hard palate (Fig-1). Ipsilateral eye may look swollen, bulging and vision may be blurred. In case of pulmonary type of mucor mycosis prominent clinical feature are fever, dry cough, chest pain, difficulty in breathing and coughing out of blood while in gastrointestinal type stomach ache, nausea, vomiting and bleeding might occur. If skin get involved then a dusky reddish tender patch with a darkening centre (due to tissue death) and painful ulcer may present. Invasion into the blood vessels can result in thrombosis that leads to loss of blood supply of subsequent tissue and ultimately necrosis of tissue. Widespread (disseminated) mucormycosis typically occurs in people who are already suffering from other medical conditions so it can be difficult to know which symptoms are related to mucormycosis. People with disseminated infection in the brain can develop changed mental status or coma^[13].



Fig 1- Black Lesion On Hard Palate

The basic principle of the management is debridement of necrotic tissue with post operative antifungal drugs like Amphoterecin B and azoles like Posaconazole. In spite of all these aggressive efforts it's not necessary that the patient's health get improved as expected because diabetic status parse is a great barrier for the healing and responsible for poor immunity that might lead to the nosocomial infection.

METHODOLOGY –

All 40 patients with post covid mucor mycosis came to ENT Department, M.L.B.M.C. Jhansi underwent for proper history taking for whether he was pre covid-19 diabetic or post covid-19 newly diagnosed diabetic, whether he was treated in ICU or general ward, whether patient underwent for oxygen therapy or not. After history taking patients went for proper local and systemic examination followed by radiological investigation like CECT and gadolinium MRI of paranasal sinuses with orbit and brain.

Since clinical feature are little bit obvious so Inspection become very important part of examination of the patients. After inspection, next important clinical examination is diagnostic nasal endoscopy which reveals the necrotic changes in the turbinates, floor of nasal cavity and septum. After that patient underwent for KOH mount for confirmation of fungal etiology and types of genera of fungus. Radiological investigations(CT PARANASAL SINUSES AND Gd contrast MRI) become necessary for assessment of structure got

involved and to differentiate between rhino sinusitis and invasive fungal rhino sinusitis so that a surgeon can proceed accordingly.

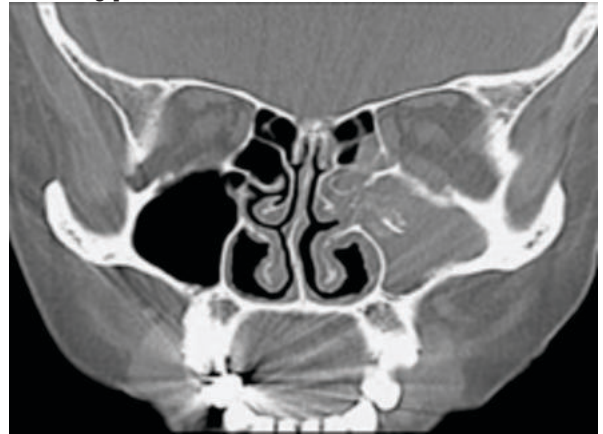


Fig 2- Rhinosinusitis

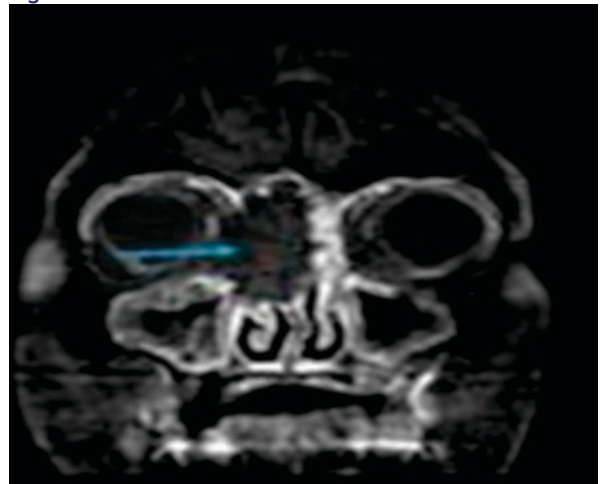


Fig 3- Rhino-orbital mucormycosis

Fig - 2 and 3 shows no bony erosion in case of sinusitis but bony erosion is obvious in rhino mucormycosis (blue arrow).

OBSERVATION –

In our study all 40 patients presented with the variation in etiology, clinical features, radiological imaging and intra-op findings.

Table 1- Etiology Causing Rhino-orbital Mucormycosis

. Etiology	No.	Percentage
1. Diabetic	18	45
	Newly diagnosed	19
	Pre covid diabetes	47.5
2. Non diabetic	3	7.5
3. Hospitalized	27	67.5
4. Steroid therapy	22	55
5. O ₂ therapy	15	37.5
6. ICU patient	10	25

Table 2- Clinical Features

S.No.	Sign and symptoms	No.	Percentage
1.	Nasal blockage/crusting	35	87.5
2.	Facial numbness and pain	26	65
3.	Fever	25	62.5
4.	Anosmia	22	55
4.	Headache	15	37.5
5.	Cranial nerve palsy	13	32.5
6.	Blood stained nasal discharge	12	30
7.	Periorbital edema	12	30
8.	Exophthalmia	6	15
9.	Diplopia	8	20

10.	Decreased vision	4	10
11.	Blepharoptosis	4	10

Table 3- Cranial Nerve Involvement

S. No.	Cranial nerve	N	Percentage
1.	Trigeminal nerve	29	72.5
2.	Olfactory nerve	22	55
3.	Oculomotor nerve	14	35
4.	Facial nerve	12	30
5.	Abducent	8	20
6.	Optic nerve	4	10

Table 4- Structure Involved In Mucor Patients

S.No.	Structure involved	No.	Percentage
1.	Maxillary sinus with ethmoid sinus	30	75
2.	Maxillary sinus	25	62.5
3.	Maxillary with ethmoid and frontal sinus	26	65
4.	Ethmoid sinus	18	45
5.	Orbit (40%)	Right	4
		Left	2
		Both	10
6.	Pansinus	15	37.5
7.	Hard Palate	13	32.5
8.	Frontal sinus	10	25
9.	Pterygoid process	6	15
10.	Pterygopalatine fossa	5	12.5
11.	Infratemporal fossa	4	10

DISCUSSION

The incidence of rhino-orbito-cerebral mucor mycosis increased in the patients after covid-19 infection. In patients with covid-19 infection multiple factors simultaneously played a significant role that made this rare disease to common. Those factors are shown by table no.1 and its obvious that diabetes(82.5%) was a major etiological factor because high blood glucose level and acidosis is responsible for virulence and survival of the fungi. Hospitalization of the patients was another major etiology because who were hospitalized, they necessarily underwent for steroid therapy which itself causes low immunity and high blood glucose. All hospitalized patient didn't underwent for oxygen therapy because their oxygen saturation were maintained at room air but who were on oxygen therapy whether admitted in general ward or in ICU, encountered with mucor mycosis because humidified oxygen leads to moistening of tubes that become favorable habitat for fungus.

Nasal blockage and crusting (87.5%) in nasal cavity occurred due to necrosis of the tissue that leads to impaired mucociliary action in nasal cavity mucosa. Patients presented with facial pain and numbness (65%) due to involvement of infra-orbital division of maxillary nerve (V2) which is 2nd branch of 5th cranial nerve i.e. trigeminal nerve. Since the bone barrier is major factor that prevent extension of disease so when this barrier got destroyed by disease leads to cranial nerve palsy (32.5%). Patients with covid -19 developed anosmia(55%) because supporting cells (microvillar cells, sustentacular cells, globular basal cells, olfactory sensory neurons) in the olfactory apparatus having ACE 2 and TMPRSS-2 receptors and covid -19 virus binds to these receptors and hamper the metabolism of these cells. Oculomotor nerve (III CN) is the motor type of cranial nerve and it has motor fiber(supplies levator palpebrae superioris) in its center and parasympathetic fiber in periphery . Since Covid -19 infection causes angiopathy to the blood vessel of motor component that supplies the central part of oculomotor nerve and leads to blepharoptosis(10%). Maxillary nerve gives posterior-superior alveolar nerve and infraorbital nerve(continuation of maxillary nerve) which gives middle and anterior superior alveolar nerve ,all these three nerves supplies upper alveolus and hard palate that's why involvement of maxillary nerve

causes pain and necrosis over upper gingivum and hard palate.

In case of isolated sinus involvement ,Maxillary sinus was the most commonly (62.5%)involved sinus because this is the sinus which encountered first while isolated frontal sinus involved only in 25 % of patients. Less commonly sphenoid sinus involvement was found because it situated most posteriorly. In case of combined sinus involvement maxillary and ethmoid sinus involvement found in 75% of cases which was the highest.

Since the disease progression depends on the low immunity and delaying of treatment so in patients with very low immunity and delay in treatment, Orbital involvement was high (40%) because lamina papyracea is very thin bony plate between nasal cavity and orbit which get engulfed as the disease progresses. Pterygoid process (15%) involvement was found due to passage of maxillary nerve through foramen rotundum. Infratemporal fossa(10%) were also got involved. In 32.5% cases hard palate involvement was found due to branches of maxillary nerve which supplies hard palate and upper gingivum. Involvement of orbit and palate are point to get worried because debridement of hard palate and exenteration of orbit both need a very skilled surgical hand. All patients with hard palate and orbital involvement underwent for surgical debridement and exenteration of eye respectively followed by intravenous antifungal liposomal amphoterecin B which gave very impressive results.

CONCLUSION-

It is quite obvious that all the patients got rhino-orbito-cerebral mucor mycosis but there were great variation in etiology, clinical feature and structure got involved. Although diabetes was played a great role in occurrence of mucor mycosis but other factor enhances the chance to get infected. The major things in case of covid -19 associated mucor mycosis is that covid-19 infection itself causes high serum ferritin level and the thrombosis in blood vessel that leads to necrosis of the tissue, both these factors provide favorite place for rhizopus to grow. Because of involvement of maxillary nerve commonly, majority of the patients presented with facial numbness and pain. The most common clinical feature was nasal blockage and crusting of nasal cavity mucosa and most common involved sinus was maxillary sinus while involvement of maxillary sinus with ethmoid sinus was highest. If the surgical debridement and antifungal drugs given timely then the life of the patient can be escaped from this life threatening disease.

Declaration-

I don't have any financially or personal relationship with third party by which my submission would be influenced. On behalf of all authors, the corresponding author states that there is no conflict of interest.

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