

Clinicoepidemiological Study of Intracranial Extension of Rhino-Orbito-Cerebral Mucormycosis in a Tertiary Care Hospital

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1. Introduction

Coronavirus disease 2019 (COVID-19) a deadly pandemic which first originated in Wuhan (SARS-CoV-2) spread across the entire globe. It was observed that there was a notable surge in fungal rhinosinusitis post second wave of covid. Injudicious use of steroids led to an extended immunocompromised state, thereby increasing susceptibility to fungal rhinosinusitis. The disease originates in the nasal/sinus mucosae after inhalation of fungal spores and takes a rapidly progressive course extending to neighboring tissues, including the orbit, and sometimes to the CNS. Rhino-orbital-cerebral mycosis (ROCM) is a life-threatening fungal disease associated mostly with Mucoralean fungi. The infection presents as headache, vision loss, proptosis, ptosis, painful ophthalmoplegia, and peripheral face palsy, with a high morbidity (>80% for infections that spread to the CNS) and severe mortality, such as eyeball exenteration and vision loss. Early suspicion, rapid diagnosis, and initiation of treatment are the most important factors that determine prognosis in the management of mucormycosis. Imaging forms the cornerstone of management in patients with rhino-orbital-cerebral mucormycosis (ROCM). Impaired delivery of the antifungal drugs to the site of infection because of vascular thrombosis and limited aggressive surgery because of the complex anatomy of the rhino-orbital region cautions for early diagnosis and aggressive management in these patients. The main objective of this study is to evaluate patients with intracranial extension of ROCM and find a possible correlation of early intervention with outcome at our tertiary care center, Government medical college, Akola from February 2021 to August 2021.

2. Methods

It is retrospective study, from February 2021 to April 2022 done in tertiary care center, Government medical college Akola. Detailed history and thorough clinical examination (including dental and ophthalmologic evaluation) was done for all patients clinically suspicious of AIFRS. All patients underwent diagnostic nasal endoscopic examination at time of presentation, and nasal biopsy or swab for KOH and fungal culture was taken. Necessary radiological investigation (CT contrast PNS with orbit and/or MRI PNS with orbit and Brain) was done. All patients underwent surgical debridement and tissue sample send for histopathological examination.

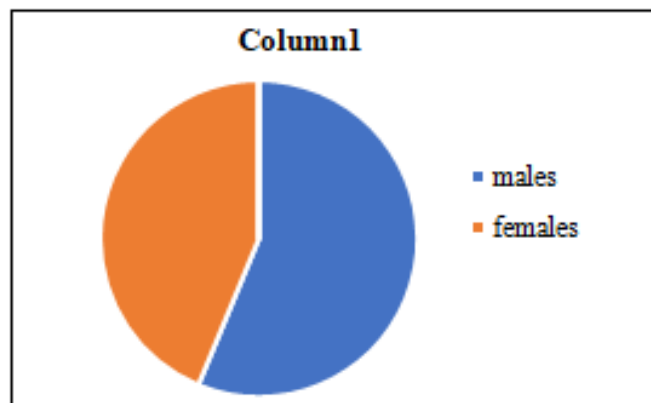
Inclusion criteria: Case records of all patients with a clinical acute invasive fungal rhinosinusitis were evaluated. Only those patients that showed intracranial involvement on CT / MRI were selected for study.

Review endoscopy was carried out in all patients at regular interval. Those suspicious of recurrence were advised repeat scan. Patients showing intracranial involvement in subsequent scans were also selected for the study

Exclusion criteria: Patients not having intracranial extension on CT /MRI i.e. patients with isolated Nasal, palatal and / or orbital involvements were excluded from the study.

Methods

136 patients of AIFRS were admitted in our hospital., Out of which 16 patients who showed intracranial involvement were selected for the study. 10 patients were males and 6 were females. Majority of the patients belonged to age group of 50- 70, youngest patient being 27 and oldest 75.



Maximum number of patients were already diabetic or were newly diagnosed diabetic

Comorbidities	Number of patients
Known diabetic	8
New diabetic	6
Hypertensive	3
CKD	2
Cardiovascular disorder	2
Depressive disorder	1

It was noted that 14 patients had a recent history of COVID 19. 12 patients were given steroids during COVID admission (8 patients were given MPS / 4 were given dexa). Further evaluation revealed that Only 2 patients were fully

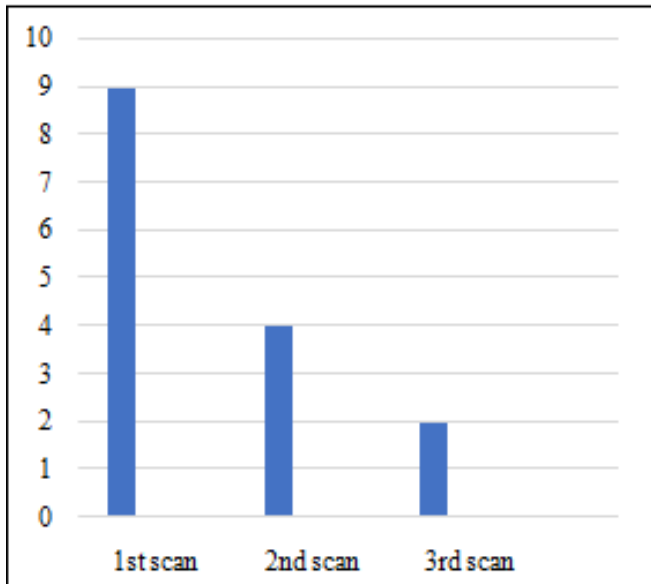
vaccinated. The gap between COVID discharge and onset of symptoms/ clinical suspicion of mucormycosis ranged between 5 days to 1 month. 4 patients however showed symptoms while they were admitted for COVID 19

Most patients had a history of facial pain and nasal blockage. These symptoms were often associated with dental pain and loose teeth. Some patients also gave complaints of diminution of vision and periorbital swelling.

General Symptoms	
Nasal blockage	16
Nasal discharge	5
Facial pain	7
Dental pain	8
Headache	15
Facial swelling	2

CNS Related Symptoms	
Blurring of vision	10
Periorbital swelling	3
Altered sensorium	3
Facial palsy	2
meningism	1

A diagnostic nasal endoscopy was performed in patients presenting with such complaints and a CT / MRI was advised. CBCT was advised in those showing extensive palatal involvement. 9 patients showed intra cranial involvement on the 1st scan. Whereas 5 and 2 patients showed intracranial involvement on 2nd and third scans respectively.



The involved areas were studied and all patients showed sinusitis, predominantly maxillary sinus involvement.

Area involved	Number of patients
Maxillary sinus	16
Ethmoid sinus	13
Sphenoid sinus	7
Frontal sinus	4
palate	14
orbit	13

CNS involvement on CT Scan

Cavernous sinus	13
Cribriform plate	3
Pterygopalatine fossa	4
Temporal lobe	5
Cortical	4
Sub cortical	3
Basal ganglia	2
Cerebral crus	1
Meckels cave	2
Infratemporal fossa	2
Basifrontal	4
ICA	1

8 patients were graded 4d, whereas 4 patients were of grade 4b and 4c on the basis of intracranial involvement

4b	8
4c	4
4d	4

Palatal involvement was present in 14 patients and orbit was involved in 13.

Cavernous sinus was the predominant intracranial site of involvement present in 81% of the cases 4 patients showed infratemporal involvement. Meckels cave was involved in 2 patients. All these patients were immediately started on 5 - 10 mg per kg body weight liposomal amphoterecin B, and simultaneously posted for surgery as per AIIMS Hrishikesh protocol.

Many patients showed reaction on administration of deoxycholate/lipophilic amphoterecin b ranging from a mild gastric discomfort to severe chills and rigors. This led to withholding of amphoterecin B. Patient serum creatinine and serum potassium was monitored. Derangement of these parameters also led to delay in medical management.

An 8 hourly monitoring of Blood sugar levels of these patients was done, and patients were administered injectable insulin as per sliding scale. Physician opinion was taken when required, and patients with severely deranged blood sugars were started on fixed doses of long-acting insulin.

Extensive debridement of involved areas was carried out. Endoscopic sinus surgery was done and diseased mucosa was exenterated.

Maxillectomy partial or complete was carried out depending upon palatal involvement. Orbital decompression was carried out in those who needed it. Removed tissue was sent for both histopathological and microbiological examination A 3 dose Retroorbital injection of amphoterecin b was given in patients that had Orbital involvement

Endoscopic sinus surgery	16
Maxillectomy	14
Orbital decompression	13
Skull base drilling	1
Clivus drilling	2

Post surgery liposomal Amphoterecin b was continued. Amphotercin soaked Nasal packs were placed post op and removed on pod 2, alkaline nasal douching was immediately

started. Close monitoring of kidney function and electrolyte of these patients was done and doses were adjusted accordingly.

On histopathological examination mucorales were isolated in 13 patients. 1 patient showed aspergillus and 2 patients showed mixed infection.

Mucorales	13
Aspergillus	1
Mixed	2

Check Nasal endoscopies were done in all patients after 7 days interval and patients were advised repeat scans if any residual pathology was suspected 4 patients showed intracranial involvement on 2nd scan. 3 patients out of these 4 had AKI due to amphoterecin b and their doses had to be tapered due to same.

2 patients showed intracranial involvement on 3rd scan. One of who was known case of CKD and his surgical fitness was delayed due deranged renal parameters. Other patient was a 75 year old male with multiple comorbidities.

Amphoterecin was continued till a total dose of 3.5 to 5 g based on the extent of disease and patient response.

On discharge patients were given tablet posaconazole on discharge for 21 days (300 mg BD on day 1 / 300 mg OD day 2-21) Mortality rate in our patients was 18 %. Cause of death in one cardiorespiratory arrest as a result of post COVID pneumonia, while 2 suffered cardio- respiratory arrest with ARDS while still COVID.

3. Discussion

Mucormycosis is an invasive, potentially fatal, opportunistic fungal infection, caused by saprophytic fungi of the order Mucorales. A rapid surge in its incidence has been witnessed in the second wave of the COVID-19 pandemic in India. The proposed predisposing factors include hypoxia, uncontrolled blood sugars either steroid induced or due to diabetes mellitus, and prolonged multipronged immunosuppression³.

The rhinocerebral form of the disease is most often found in uncontrolled diabetics or profoundly dehydrated children. Infection usually begins in the nose and progresses through the paranasal sinuses, invading the orbit and CNS secondarily

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The earliest symptoms in this series were lethargy, fever, and headache, which were universal. Facial swelling developed soon after the initial headache, with subsequent proptosis. External ophthalmoplegia was present in 11 of our

patients and developed as a later manifestation in all but two patients. Dehydration and acidosis were predominant findings indicative of the poor control of diabetes in this group. Both nondiabetic patients were profoundly dehydrated and acidotic.

In a comparative study by Harold Et al it was found that the presenting complains was headache, present in 100 % of the patients. Present study showed 93.5 % patients with headache

Patients who are immunocompromised or who have metabolic anomalies are prone to mucormycosis. P Chetchotisakd et al in their study of 11 patients found that 8 patients had Diabetes mellitus and 5 patients had renal failure¹

Recent onset diabetes was seen in 37.5 % patients as opposes 20.6 % as found by sen et al

In our study 87.7 % had palatal involvement, while 81 % had orbital involvement In a study by ketenki et al On initial examination, nine (64 per cent) patients had cutaneous and/or palatal necrosis (three had both palatal and skin necrosis); of these, five (35 per cent) also had ophthalmoplegia and blindness. Four (29 per cent) patients also had facial palsy⁸

Contrast-enhanced MRI is the imaging modality of choice. It allows delineation of soft tissue involvement earlier and is better than a CT scan, especially in the setting of orbital and cerebral involvement. Contrast-enhanced CT scan is relatively faster and can be used for patients where MRI is not feasible. Mucormycosis leads to tissue necrosis, and bone erosion is not a common finding, so a CT scan may not support an early diagnosis.⁴

75 % of our patients showed positive MRI finding, and the remaining 25 % showed finding on CECT.

Diagnostic nasal endoscopy allows a quick inspection and sampling from the nasal cavity. It is a simple, bedside yet powerful tool to diagnose suspected cases in stage 1 and early stage 2 before the clinical and radiological signs are evident.

A study by Kaushik et al found cavernous sinus to be the predominant site. Present study shows that 81 % patients had cavernous sinus involvement.

The possible routes of intracranial involvement are

- Direct erosion of pterygopalatine fossa and sphenoid sinus wall
- Through nasal vein and basi-cranial vein
- Entering orbital vessels or optic canal through maxillary or ethmoidal sinus.
- Disseminated infection

The widely accepted treatment of choice for mucormycosis is amphotericin B. When administering amphotericin B, it is essential to monitor kidney function due to its high nephrotoxicity incidence. When extensive disease occurs, second-line therapies may be contemplated. A combination

therapy with echinocandins and amphotericin B is a second-line therapy that is recommended. When echinocandins are combined with amphotericin B, they add a polyene backbone, which increases the success of therapy. Some of the other second-line accepted antifungals include the triazoles, posaconazole and isavuconazole⁵

Spellberg et al mention in their studies of covid 19 associated ROCM that liposomal amphotericin B formed the mainstay of their treatment whereas adjuvant treatment was given with Posaconazole⁶ similar medical management lines were followed in present study.

Surgical debridement mainly endoscopic sinus surgery formed the core of the management strategies. In a study carried out by jyoti et al on a group of 20 patients. Approaches used for debridement of paranasal sinuses were endoscopy (75 %), lateral rhinotomy (10 %), Caldwell Luc (20 %) and combined approach (20 %). Diagnostic nasal endoscopy were done twice weekly to diagnose recurrence of disease, if recurrence was found debridement of necrotic tissue was carried out⁶

Amphotericin B was continued till a total dose of 3.5 – 4 g. In a study by Sandeep et al of 23 patients were administered amphotericin B, in a dose of 1 mg/kg body weight to the total dose of 2.5–4.0 g. The onset of nephrotoxicity, and electrolyte imbalance was the usual cause for limiting the dose of amphotericin B.⁷

Mortality rate in present study was 18.75 %. In a study by palejwala et al the survivability was as low as 3 %. The key to management of this rapidly progressive fulminant disease is swift commencement of multidisciplinary treatments. These patients should be treated in tertiary care centers with the availability of otolaryngology, ophthalmology, neurosurgery, and infectious disease specialists so as to execute efficient and expeditious treatment. We feel that the rapid initiation of an aggressive multifaceted surgical and medical treatment regiment can confer an improved overall prognosis, and propose treating rhinocerebralmucormycosis as any other neurosurgical emergency¹⁰

4. Conclusion

Diabetes super imposed with COVID-19 is a harbinger for severe immunosuppression which may increase the danger to develop opportunistic infections. Early detection of symptoms for mucor should be reported immediately. Furthermore, if a scan or DNE is suspicious for mucormycosis fungus, then there's a gold standard treatment through surgical debridement. Clinical suspicion and prompt treatment are fundamental to realize the cure of the disease. These aided with appropriate medical management ensure better patient outcomes

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