



AN OBSERVATIONAL STUDY OF MANAGEMENT OF INVASIVE FUNGAL SINUSITIS AS EXPERIENCED IN A TERTIARY CARE INSTITUTE

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ABSTRACT

1. To study the various clinical presentations, microbiological and radiological profiles in patients of invasive fungal sinusitis, to know about the underlying comorbidities or immunocompromised status and its relation to the disease. 2. To study the effect of timely surgery and long term antifungal therapy on prognosis of the patient. This is an observational prospective and retrospective study. Thirty adult patients diagnosed with invasive fungal sinusitis were studied. Our study also included patients who had past history of COVID 19 infection due to the ongoing pandemic. Diabetes mellitus was the most common underlying disease. Majority patients had a history of COVID 19 infection and had received intravenous steroids, as a part of the treatment for COVID-19 which led to deranged glucose levels, due to which these patients had increased risk of developing Invasive Fungal Sinusitis. Radiological imaging was done, that included CT and MRI. Patients were posted for debridement and the samples were sent for microbiological and histopathological examination. On KOH mount, aseptate hyphae were seen and on fungal culture most commonly isolated species was mucor and histopathological examination was suggestive of Acute invasive fungal sinusitis. Treatment protocol was administration of Injection Amphotericin B with endoscopic sinus surgery with debridement along with maxillectomy, orbital exenteration (depending on the extension) along with or without concurrent oral posaconazole. Majority of the patients improved clinically. Acute Invasive Fungal Sinusitis is a condition seen in patients with Diabetes mellitus and or other immunocompromised condition. COVID 19 infection is probably a predisposing factor due to covid induced hyperglycemia and use of steroids. Imaging plays a key role in early diagnosis and mapping of the disease extent. Timely initiation of antifungal therapy and aggressive surgical management and reversal of the immunocompromised status can significantly improve the clinical outcome.

KEYWORDS : invasive fungal sinusitis. immunocompromised patients. mucormycosis. COVID-19

INTRODUCTION

Fungal infections are one of the four major microbiological sub-groups. The most commonly encountered fungal species in medical practice are *Candida* species and *Aspergillus* species^[1]. The less commonly encountered, but known for their invasive potential, are fungi of the Zygomycota order (*Mucor*, *Rhizopus* et al.). These fungi are often implicated in immunocompromised individuals, as in the case of Mucormycosis^[2].

Acute invasive fungal rhinosinusitis (AIFR), although rare, is important because of its aggressive course and high mortality rates (around 50% but with some reports of up to 80%)^[3,4]. As the name suggests, AIFR (Acute Invasive Fungal Rhinosinusitis) differs from non-invasive forms of fungal rhinosinusitis in that there is invasion of primarily neural and vascular structures. A definition of AIFR has been proposed as 'the presence of fungal hyphae within the sinonasal mucosa, submucosa, vasculature or bone, in the setting of one month or less of sinusitis symptoms'^[4,5]. There are two common causative organisms of AIFR; these are typically from the *Aspergillus* species and *Zygomycetes*. AIFR is most commonly encountered in immunocompromised patients. Early diagnosis and initiation of treatment is paramount to improving survival in AIFR^[5]. Presentation may be with rhinorrhea (often clear), nasal congestion and facial pain or pressure and fever^[4]. Imaging-CT scan of the sinus and orbits is the imaging modality of choice, but in the early stages due to the fulminant nature of disease process changes may be very subtle or may not be evident. As the disease progresses, erosion of bone may be seen. While CT is ideal to assess bony changes, MRI is superior in evaluating retro-antral, intra-orbital or intracranial extension^[6]. To confirm the diagnosis a tissue biopsy is required. The most sensitive for biopsy, are the middle turbinate (75–86% sensitivity and 100% specificity)^[4,7]. The sample should be processed for histopathology and culture (although the sensitivity of culture is again very low)^[1]. KOH mount can be done for early diagnosis and initiation of treatment. The management of AIFR (Acute invasive fungal rhinosinusitis) has three arms: 1.Reversal of pre-disposing state (i.e., diabetes etc.). 2.Surgical management-Surgical

intervention is well recognised as a crucial element of management^[7,8,10]. 3.Antifungal therapy-Early instigation of systemic antifungal therapy has been shown to improve survival^[4].

MATERIALS AND METHODS

Inclusion Criteria

- 1.All patients above 18 yrs of age.
- 2.Diagnosed cases of invasive fungal sinusitis with histopathological features consistent with invasive fungal sinusitis.

Exclusion Criteria

- 1.Patients who are not consenting for the study.
- 2.Patients who are lost to follow up.

Study Design: A single site, prospective and retrospective observational study at Tertiary Health care

Duration of Study: 5 yrs -4 yrs retrospective study and 1 yr prospective study.

Sample Size: No formal sample size calculation has been done due to the ongoing COVID-19 pandemic

Methods of Sample Collection

The case will be collected by consecutive sampling method. The study will be carried out in 2 parts –

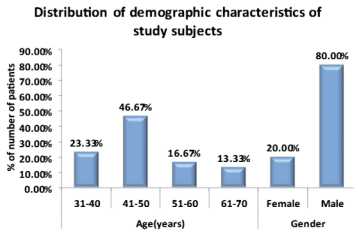
- A) In the Retrospective arm, records of all the patients treated for invasive fungal sinusitis at tertiary care hospital will be traced from the medical records section and from the department records in which the details of these patients are entered, the observations will be used for obtaining the data. As it will be difficult to contact these patients, we request for waiver of informed consent. Patients personal information will be confidential and his/her identity will not be revealed in any way.
- B) In the Prospective arm, all patients who satisfy the inclusion criteria will be enrolled in the study after obtaining a valid informed written consent. Detailed history and clinical examination and / or radiological investigation of all these patients will be done as per department protocols and relevant information regarding their presenting complaints and past illness will be

recorded in the case record form. These records and images will be documented and analysed as a part of the study. Patients will have to pay the routine hospital charges for the investigations as per the standard protocol. The patient will not be liable to pay any additional expenses. No incentive will be provided to the patients.

Assessment Parameters

1. Clinical improvement in symptoms and signs
2. Radiological imaging features

RESULTS



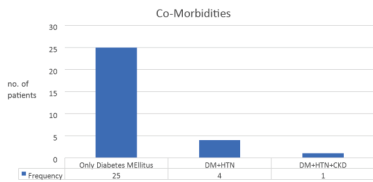
Distribution Of Unilateral/Bilateral Nasal Discharge And Nasal Obstruction Of Study Subjects

Unilateral nasal discharge was seen in 8 patients, Unilateral nasal obstruction was seen in 15 patients and bilateral nasal obstruction was seen in 6 patients out of 30 patients.

Distribution Of Headache/Facial Pain Of Study Subjects

Headache/facial pain	Frequency	Percentage
No pain	1	3.33%
Unilateral facial pain	13	43.33%
Unilateral headache	14	46.67%
Unilateral facial pain and headache	2	6.67%
Total	30	100.00%

Distribution Of Co-morbidities Of Study Subjects



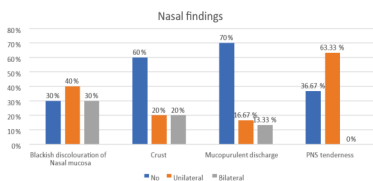
Distribution Of Past History And Use Of iv Steroids In Study Subjects

Out of 30 patients 19 patients had a history of COVID 19 infection and out of 19 patients who had a past history of COVID 19 infection, 14 patients had received intravenous steroids.

Distribution Of HbA1c Levels In Study Subjects

In all the patients HbA1c levels were raised with median of 11.3 and ranged between 8-15.8 %

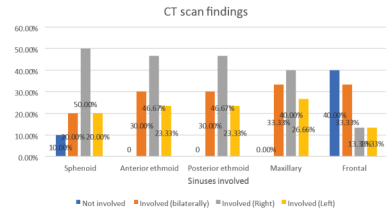
Distribution Of Nasal Findings On Anterior Rhinoscopy In Study Subjects



Distribution Of Ocular Findings In Study Subjects

ocular findings	Frequency	Percentage
Ptosis		
Normal	24	80.00%
Yes{Left}	3	10.00%
Yes{Right}	3	10.00%

Pupil		
Reactive to light	26	86.67%
Not reactive to light	4	13.33%
Vision		
Normal	22	73.33%
Diminision of vision/ No vision	8	26.67%
Extra ocular movements		
Normal	24	80.00%
Restricted	6	20.00%
Proptosis		
No	29	96.67%
Yes	1	3.33%



Distribution Of CT Scan Findings Of Study Subjects

Distribution Of Microbiology And HPR Of Study Subjects

Microbiology and HPR	Frequency	Percentage
KOH		
No fungal elements seen	18	60.00%
Broad aseptate hyphae	11	36.67%
Septate hyphae	1	3.33%
Fungal culture		
No growth	15	50.00%
Mucor species	9	30.00%
Rhizopus species	6	20.00%
HPR		
Acute invasive fungal rhinosinusitis	30	100.00%

Distribution Of Medical Management And Surgical Intervention Of Study Subjects

In present study (90%) of patients were discharged on T.Posaconazole 300 mg once a day and (10%) were discharged on syrup posaconazole 5ml three times a day.

Mean value of injection Liposomal Amphotericin B(mg) and injection Conventional Amphotericin B(mg) of study subjects was 10927.5 ± 3149.61 and 2746.92 ± 314.04 with median(25th-75th percentile) of 10,000(8090-13525.5) and 2,600(2500-3000) respectively.

In all the patients functional endoscopic sinus surgery with debridement was done. Exenteration of left eye and exenteration of right eye was done in 3 patients each. Left maxillectomy and right maxillectomy was done in 1 patient each. 2 patients received retro orbital amphotericin B. Diagnostic nasal endoscopy under local anaesthesia was done once weekly in all patients.

Distribution Of Side Effects Of Amphotericin B

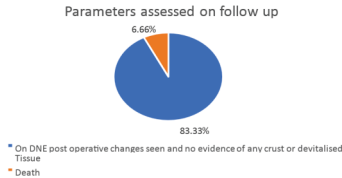
Serum creatinine(mg/dL)		
Normal{0.8-1.5mg%}	0	0
Deranged	30	100%
Mean ± SD		2.22 ± 0.54
Median(25th-75th percentile)		2(1.8-2.5)
Range		1.5-3.5
Serum potassium(mEq/L)		
Deranged	30	100.00%
Mean ± SD		2.24 ± 0.48
Median(25th-75th percentile)		2.45(1.85-2.675)
Range		1.5-2.8
Serum magnesium(mEq/L)		
Deranged	8	26.66%
Mean ± SD		1.16 ± 0.11

Median(25th-75th percentile)	1.2(1.1-1.2)
Range	1-1.3

Distribution Of Parameters Assessed After Treatment Of Study Subjects.

Parameters assessed after treatment	Frequency	Percentage
Patient improved symptomatically and on DNE post operative changes seen and no evidence of any crust or devitalised tissue	27	90.00%
Death	3	10.00%
Total	30	100.00%

Distribution Of Follow Up After 1 Months Of Study Subjects.



DISCUSSION

In present study, 14 patients (46.67%) belonged to age group 41-50 years followed by 7 patients (23.33%) belonging to age group 31-40 years, 5 patients (16.67%) belonging to age group 51-60 years, 4 patients (13.33%) belonging to age group 61-70 years. Mean value of age(years) of study subjects was 49.03 ± 9.5 with median (25th-75th percentile) of 49.5(42.5-54.25).

24 patients (80.00%) were males and 6 patients (20.00%) were females with a male:female ratio of 4:1

Study done by Liu YC et al.^[11] shows that the patient's ages ranged from 15 to 70 yrs with mean age of 50.9 yrs and male to female ratio of 3:1

Study done by Kaneria M V et al.^[12] shows that the patient's age ranged from 33 to 75 yrs with mean age of 55.4 yrs. A majority i.e (77.27%) of the patients in their study were expectedly males, as males have been preferentially targeted by SARS-CoV-2.

This male predominance in our study can be due to the fact that majority of patients i.e 19 patients (83.34%) had a history of COVID 19 infection and there by developing COVID-19 Associated Mucormycosis (CAM) which is consistent with the above study.

Presenting Symptoms

In present study the most common presentation was Headache/facial pain in 90% (27/30) followed by nasal obstruction in 70% (21/30)

As per study done by Dokania V et al.^[13] the most common presenting signs and symptoms were headache/facial pain in 18 patients (85.71%) and facial/periorbital swelling in 13 patients (61.90%)

As per study done by Sohail M A et al.^[14] the most common clinical symptoms were facial swelling, nasal obstruction, fever, headache and proptosis.

The most common presenting symptoms in our study were consistent with the above studies.

Co-morbidities

In present study all had Diabetes mellitus, 4 had Hypertension and 1 had chronic kidney disease in addition to diabetes mellitus and hypertension.

As per study done by Huang YF et al.^[15] Diabetes mellitus, hypertension and renal insufficiency were risk factors.

As per study by Bakhshae M et al.^[16] the most common underlying diseases were diabetes mellitus (50 %) and leukemia (44.44 %)

As per present study the most common underlying disease is Diabetes mellitus in 30 patients (100%) which is consistent with the above studies.

Past History

In present study 63.34% (19/30) had a past history of COVID-19 infection. Among that 46.67% (14/30) had a past history of COVID 19 infection + Use of IV steroids both followed by only COVID 19 infection in 16.67% (5/30).

As per M V Kaneria et al.[12] Diabetes mellitus (DM) was the commonest comorbidity observed in their study. A bidirectional relationship exists between COVID-19 and diabetes, which is fuelled by the exuberant use of steroids, the only treatment known to confer mortality benefits.

As per A Moorthy et al.[17] there is a significant increase in the incidence of angioinvasive maxillofacial fungal infections in diabetic patients treated for SARS-CoV-2 with a strong association with corticosteroid administration.

In our study the patients with a recent history of COVID-19 infection had increased risk of developing invasive fungal sinusitis which is consistent with the above studies.

HbA1C Levels

In all the patients, HbA1C levels(%) was deranged. Mean value of HbA1C levels(%) of study subjects was 11.53 ± 2.2 with median(25th-75th percentile) of 11.3(9.38-13.3).

According to study by Sekaran A et al.^[18] HbA1c levels in patients ranged from 6.8 % to 15%.

Our is consistent with the above studies.

Anterior Rhinoscopy Findings

In present study blackish discolouration of nasal mucosa (70%) was seen in majority of the patients followed by blackish crusts (40%), followed by mucopurulent nasal discharge (30%).

As per study by Piromchai P et al.^[19] the rhinoscopy findings were mucosal necrosis, black crust/debris, pus in middle meatus and septum involvement .

The findings in present study were consistent with the above study.

Ocular Findings

In present study most common sign was loss of vision/diminution of vision in 26.67% (8/30), followed by restriction of extraocular movements in 20.00% (6/30).

As per study by EL - kholy et al.^[20] ophthalmoplegia, and visual loss (63.9%) were the most common signs which is consistent with our study.

Diagnostic Nasal Endoscopy

In present study 63.34% (19/30) had necrosed middle or inferior turbinate and black crust in 40% (12/30) which was predominantly unilateral.

As per study by Valera FCP et al.^[21] The most common endoscopic findings were pale or necrotic mucosa. The middle meatus and middle turbinates were the sites most frequently involved.

The above findings in present study was consistent with above study.

Radiological Findings (CT Scan and MRI)

In our study bony erosion was present in all. Maxillary sinus was most commonly involved. Intraorbital involvement was seen in 13.33% (4/30), intracranial involvement seen in 10% (3/30).

In our study maxillary sinus (100%) was most commonly involved along with ethmoid sinus (100%) followed by sphenoid sinus (90%).

As per Study by Kaneria M V et al.^[12] the commonest sinus involved was the maxillary sinus, 54.54% had orbital involvement and 18.18% had intracranial involvement.

As per Valera FCP et al.^[21] Bony erosion is a clear sign that the disease is established but in generally this manifestation is seen only in later stages. They observed a predominance of unilateral disease with bone erosion, but orbital involvement was unusual.

In present study predominance of unilateral disease and bony erosion was seen, which is consistent with all the above studies.

Fungal Culture

In our study most common species isolated from culture was mucor in 30% (9/30). Rhizopus was seen in 20% (6/30).

As per study by Dokania V et al.^[13] Mucor species was the most common isolated fungus and was reported from 95.24% of patients.

As most of the patients in our study had a history of COVID19 infection, mucor species was more commonly isolated, which is consistent with above study.

Treatment

In present study 56.66% (17/30) received liposomal amphotericin B and 43.33% (13/30) received amphotericin B deoxycholate. In addition, out of 30 patients 13 patients received concurrent T.Posaconazole. On certain occasions there was a switchover between liposomal and deoxycholate amphotericin B, depending on the availability of antifungals after the adjustment of dose. The daily doses of amphotericin B deoxycholate ranged from 0.5-1.0mg/kg body weight and the cumulative dose ranged between 2.5 grams-3.5 grams in our study. The daily doses of liposomal amphotericin B ranged from 1-5 mg/kg body weight and the cumulative dose ranged between 8.05 grams-17.1 grams.

In all the patients functional endoscopic sinus surgery with debridement was performed. Orbital exenteration was required 20% (6/30). Maxillectomy was performed in 6.66% (2/30). 6.67% (2/30) were treated with Retroorbital amphotericin B. Diagnostic nasal endoscopy under local anaesthesia was performed once weekly in all patients. Patient were discharged on Tablet Posaconazole or syrup posaconazole depending on its availability, after the maximum recommended cumulative dose of amphotericin B had been reached. Out of 30, 90% (27/30) patients survived and improved symptomatically i.e on check diagnostic nasal endoscopy there was no evidence of any crust or devitalised tissue. 10% (3/30) expired during the treatment. Out of those that expired, 1 patient (3.33%) had intracranial extension of the disease and 2 patients (6.66%) had intraorbital extension who had undergone orbital exenteration.

According to Nagatepputaram P et al.^[22] treatment modalities included surgery, systemic antifungal drug Administration, and reversal of the pre-existing immunocompromised status. Amphotericin B is still the first line drug in the treatment of fungal infection. Early treatment of IFRS (Invasive Fungal Rhinosinusitis) significantly decreased

the mortality rate.

As per Raizada N et al.^[23] The daily doses of liposomal amphotericin B ranged from 2-5 mg/kg body weight while that of conventional amphotericin B was 0.5 to 1.0mg/kg bodyweight. Cumulative doses of liposomal amphotericin B ranged from 0.1 gm-16.6 gm while cumulative doses of conventional amphotericin B ranged from 0.1-3.0 gm. Posaconazole was used as a stepdown therapy in a daily dose of 800 mg in 3 cases for duration of 8-12 weeks. The cumulative dose of amphotericin B is variable and depends upon the time taken to achieve radiological and clinical response.

Adverse Effects of Amphoterecin B

In present study 60% (18/30) had infusion reaction like fever, chills, nausea, vomiting. In all patients, serum creatinine(mg/dL) and serum potassium(mEq/L) was deranged and 26.66%, serum magnesium(mEq/L) was deranged.

As per the study by Thiagarajan B et al.^[24], infusion reaction was seen in patients who received amphotericin b like fever with or without chills, headache, nausea, vomiting and anaphylaxis.

According to Haja Sherief S et al.^[25] hypokalemia, hyperkalemia, hypoglycemia, hyperphosphatemia, hypomagnesemia are electrolyte imbalances induced by amphotericin B. Hypokalemia was managed by oral or parenteral potassium chloride.

Follow Up After One Month

All these patients were further followed up after a month in terms of clinical improvement in signs and symptoms. Out of 27 patients, 2 expired whereas others showed clinical improvement in symptoms. On Diagnostic nasal endoscopy there was no evidence of any crusts. MRI was done after a month and on MRI there was resolution of disease and no further progression of the disease.

CONCLUSION

Acute Invasive Fungal Sinusitis is a condition seen in patients with Diabetes mellitus and or other immunocompromised condition. COVID 19 infection is probably a predisposing factor for AIFR (Acute invasive fungal rhinosinusitis) due to covid induced hyperglycemia and use of steroids. Imaging plays a key role in early diagnosis and mapping of the disease extent which is essential for appropriate management. Timely initiation of antifungal therapy and aggressive surgical management and reversal of the immunocompromised status can significantly improve the clinical outcome.

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