Original Article

Mucormycosis and Its Correlation with Raised Ferritin Levels

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Abstract:

Background: Mucormycosis has emerged as an epidemic within the COVID-19 pandemic due to widespread use of corticosteroids and immune-modulators like Tocilizumab, in the management of COVID-19 pneumonia. It is an invasive fungal disease which spreads by angioinvasion and rapidly spreads to adjacent tissues. If untreated its outcomes are dangerous and often fatal. Uncontrolled diabetes, malignancies and dialysis are predisposing factors. Raised blood iron is an important factor in pathogenesis and rapid progression of fungal invasion that needs to be investigated. **Aim**: To establish a correlation between raised serum ferritin level and aggressiveness of Mucormycosis. **Methodology**: A retrospective study was done from February 2021 to February 2022 of patients diagnosed with mucormycosis by middle meatal biopsy and microscopy along with CT & MRI scan of PNS with brain. They were treated either surgically or conservatively. All the blood parameters including serum ferritin level, were carried out. A comparison was done on extent of disease in patients in-relation to their serum ferritin level. **Results**: Our study suggested that higher levels of ferritin are often associated with aggressive form the disease. Zygomycetes are dependent on environmental iron for their growth. Higher the serum ferritin level, more aggressive & widespread is mucormycosis. **Conclusion**: Serum free iron aggravates mucormycosis. Measures should take to control the serum ferritin in patients under risk for mucormycosis. Iron chelating agents or novel methods like anti-ftr1 immune serum should be developed for controlling the disease at its earlier stages.

Keywords: Mucormycosis, Ferritin level, Raised Serum ferritin level, Mucormycosis & Iron overload

Introduction:

Mucormycosis has been known as an opportunistic, but dangerous and often fatal fungal infection. It is caused by a fungus of Class- Zygomycetes, Order- Mucorales and Genus- *Mucor, Rhizopus, Rhizomucor, Cunninghamella and Absidia.* Most common infections are caused by *Rhizopus arrhizus* (previously known as *Rhizopus oryzae*). In India, second most common infection is caused by *Apophysomyces sp*.[1]

Mucormycosis is mostly seen in immune-compromised patients and raised blood sugar level has been often linked with contracting this invasive fungal disease. Immuno-suppression was observed in many patients undergoing treatment for COVID-19, along with change in many serum parameters like C-Reactive protein, erythrocyte sedimentation rate, D-Dimer and ferritin. With the emergence of epidemic of Mucormycosis during COVID-19 pandemic, other factors need to be studied to understand the spectrum of presentation of this fungal infection. Many factors like use of steroids and raised blood sugar level, are explored for rise of Mucormycosis epidemic but iron overload and raised ferritin levels in COVID-19 patients' needs further analysis.

Epidemiology: In 1885, Arnold Paltauf published the first case of disseminated mucormycosis which he named "Mycosis mucorina".[2] However the first recorded human infection was a case of pulmonary mucormycosis reported by Sluyter in 1847. Furbinger in 1876 described a case of a patient who died of cancer and showed hyphae and sporangia in his right lung.[3] Since then with the global pandemic of Diabetes and use of immune-modulating drugs for cancer and organ transplants, the numbers of cases of mucormycosis are ever being rising.

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ISSN No. *: (p) 2348-523X, (o) 2454-1982*

DOI: 10.46858/vimshsj.9202

Date of Published : *30th June 2022*

Before the emergence of COVID-19 caused by SARS –CoV-2, mucormycosis was usually seen in patients with immune deficiency, patients on immunosuppressant or in patients having uncontrolled diabetes. COVID-19 itself is known for causing immune dysregulation, but when a large number of patients with complications of COVID-19, required oxygen supplementation and were managed with high doses of steroids, the number of cases of mucormycosis increased considerably in many countries particularly India, Brazil, Chile, USA and United Kingdom.

The prevalence of Mucormycosis in India before Covid-19 era was 0.14 cases per 1000 population, which was 80 times the prevalence of mucormycosis in developed countries.[4] During September to December 2020, in a multicentre study in India, among 287 patients of Mucormycosis, 187 patients had Covid Associated Mucormycosis. It shows a 2.1-fold increase in incidence of mucormycosis as compared to same period in 2019.[5] In our institute at Ahmadnagar, a 300 fold times increase in the incidence of Mucormycosis has been observed in 2021 as compared to previous records.

Pathophysiology & Iron Dependency of Mucormycosis: Mucorales are opportunistic infections in humans. In Immuno-competent individuals, mucorales spores are killed by phagocytes. Thus, patients with neutropenia and impaired phogocytic functions are at higher risk of mucormycosis. In contrast, patients with AIDS are comparatively less susceptible for mucormycosis.[6] Both mononuclear and polymorphonuclear phagocytes of normal hosts are capable of killing mucorales spores by oxidative metabolites and cationic peptides.[7-9] However in Diabetic ketoacidosis (DKA), due to low pH and high glucose levels, chemotaxis and oxidative mechanism of intracelluclar killing by phagocytes gets impaired and mucorales spores germinate into hyphae.[10] But only impaired phagocytic function cannot be attributed to increased incidence of mucorales in patients with DKA, as incidence of mucormycosis is increased more than the incidence of infections caused by other pathogens in these patients. This indicates towards other specific characteristics of mucorales which help them to exploit the host's suppressed immune response. One such characteristic is to acquire iron from the host tissues.[11]

Aims & Objectives:

The aim of our retrospective study is to find out the correlation between raised ferritin levels and aggressiveness and extent of spread of mucormycosis in patients who were diagnosed with mucormycosis and were managed either conservatively with anti-fungal therapy or with surgical debridement.

Methodology:

- This retrospective study was conducted at Gajanan Hospital, Advanced Endoscopic ENT Surgery & Snoring Treatment Centre, Ahmadnagar, from February 2021 to February 2022.
- The study includes 182 patients whose Nasal swabs and Middle meatal biopsies were tested positive for zygomycetes. Microbiological identification of the hyphae was based on diameter, presence or absence of septa, branching angle (right or acute) and pigmentation, which differentiates it from other fungal infections.
- All these patients, diagnosed with mucormycosis underwent CT & MRI scans (with and without Contrast) of Para-nasal sinuses & brain to find out the extent of disease.
- All the blood parameters including complete blood count, ESR, Sr. Creatinine, CRP, Sr. Billirubin, Sr. Electrolytes (Na+, K+, Cl), Sr. Ferritin, blood sugar (R), ABG, HbA1c, HIV & HBsAg were done.
- Informed consent was taken and surgery was planned depending upon the extent of the disease under aggressive control of blood sugar and D-Dimer (if raised).

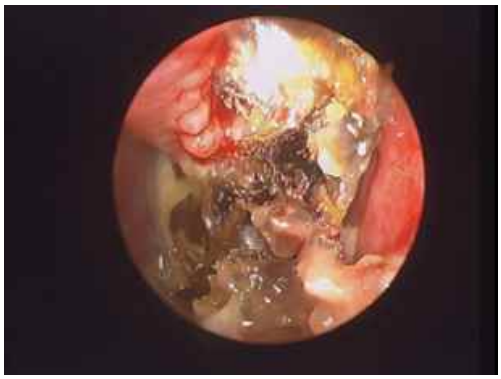

Fig.1: Endoscopic Image nasal mucormycosis with crusts & pus and inflamed inferior turbinate

- Radical FESS was carried out depending upon disease extension. Orbital exenteration was done, if orbit was involved and hemi or complete palatal bone resection was done if palate was involved. DRAF III and skull base dissection were other radical procedures that were carried out to remove the disease completely.
- Post operatively nasal douching was done with Conventional Amphotericin –B solution. Intravenous liposomal Amphotericin B was continued and suctioning was done every 5th day. The current guideline for the management of mucormycosis recommends liposomal Amphotericin B at a dose of 5-10 mg/kg per day. In the absence of central nervous system involvement, a dose of 5mg/kg is suggested.[12] In case of Intra-cranial extension of Mucormycosis, 7 mg/kg body weight of liposomal Amphotericin B is indicated.
- MRI was repeated on 7th day and biopsy was repeated, if required. If biopsy was positive for zygomycetes hyphae then Liposomal Amphotericin B was continued and if it were negative in two successive biopsies then Posaconazole 300 mg was given for 3 months. Triazoles like Posaconazole and isavuconazole, are available in both oral and parentral forms and are used in step down or salvage therapy in patients who can't tolerate Amphotericin B.

Due to aggressive nature of the mucor, it has a tendency to spread rapidly to adjacent tissues or structures. Thus, proper management of cases of Mucormycosis requires a team effort from medical experts of various specialities like Medicine, ENT surgeons, ophthalmologists, dental surgeons, Neurologists & neuro-surgeons. Even the role of Radiologists, Pathologists & Microbiologists is undeniable.

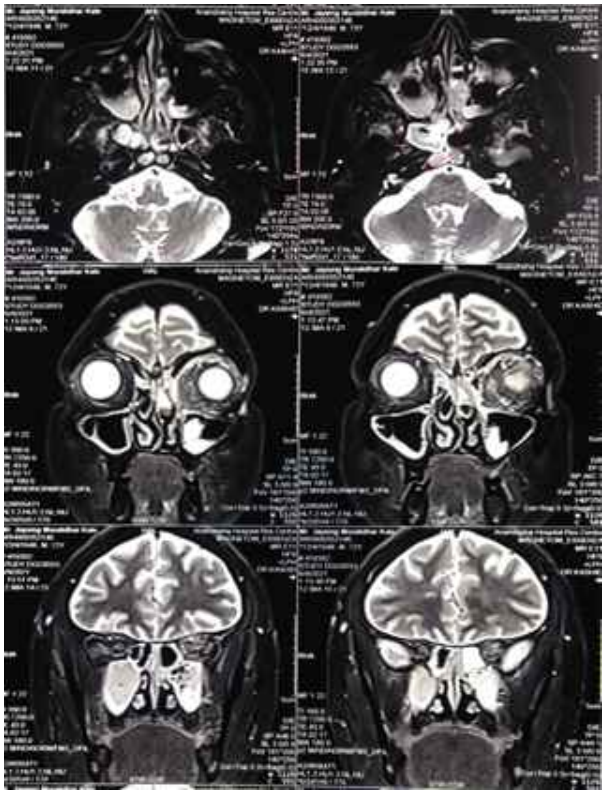

Fig. 2: Pre-operative MRI Scan showing involvement of Paranasal sinuses & Left Orbit

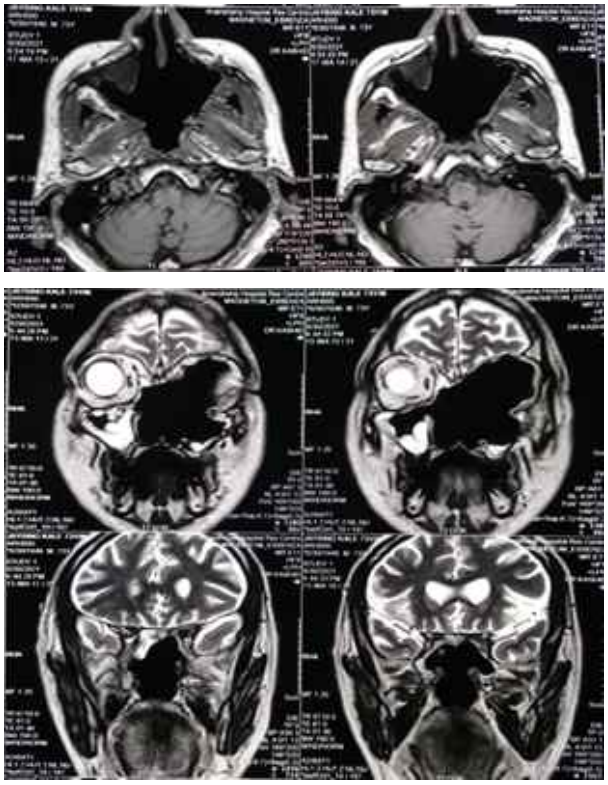

Fig. 3: Post operative MRI scan of the same patient with radical FESS & orbital exenteration

The statistical analysis to find out the significant co-relation between various blood parameters and severity and extension of mucormycosis was done using Mann –Whitney U Test. U-values, Z- Scores and pValues for various parameters under study is given in Table 1.

Table no. 1: Statistical Analysis

Parameter	U value	Z score	p value
Serum ferritin	2036.5	5.85185	<.00001
BSL	3849	-0.38905	0.69654
HbA1c	3476.5	1.78395	0.07508
D-Dimer	3656.5	-1.38194	0.16758

Results:

In our study of 182 patients who were diagnostically confirmed with mucormycosis, 83 patients were treated conservatively on antifungal Inj. Amphoteicin –B (Control group) and 99 patients underwent surgery (Study group) depending upon the severity & extension of the disease. Criteria for deciding the treatment protocol, whether patient needs to be treated conservatively or needs surgical intervention was dependent upon the symptoms, clinical and radiological extension of disease and blood profile of the patient.

- **Disease extension-** patients with limited nasal mucormycosis (limited to nasal mucosa of nostrils) were treated on liposomal Amphotericin-B and Posaconazole. Whereas patients with extensive nasal and paranasal extension or with involvement of adjacent structures were candidates for surgical debridement.
- As all the patients during this period had developed mucormycosis after COVID-19. Thus, D-Dimer levels were also considered before taking the patients for surgery. Post COVID mucormycosis patients with high D-Dimer values were managed with Enoxaparin (Clexane) while taking for surgical procedures.
- Patients with recurrence of mucormycosis and raised ferritin levels were preferentially treated with aggressive surgical debridement.

Table 2. Gender Distribution

	MALES	FEMALES
STUDY GRP	77	22
CONTROL GRP	60	23
TOTAL	137	45

We divided the patients into two groups. The first group included patients who underwent surgical intervention (Study group) and the second group (Control group) included those patients who were managed conservatively.

In our retrospective study, 137 patients were male & 45 patients were female with a gender ratio of 3:1 (Table.2). 157 patients were above 40 years of age group.(Fig.4)

The oldest patient diagnosed with mucormycosis and successfully treated was 80 years old. Youngest patient was 19 years old female who had poor prognosis at the time of diagnosis of Mucormycosis.

This patient had developed severe pneumonia during COVID-19 acute phase, had received high doses of steroids and had cerebral extension of mucormycosis. In spite of successful debridement, this patient couldn't survive due to severe pneumonia, haemodynamic unstability and intra-cranial complications.

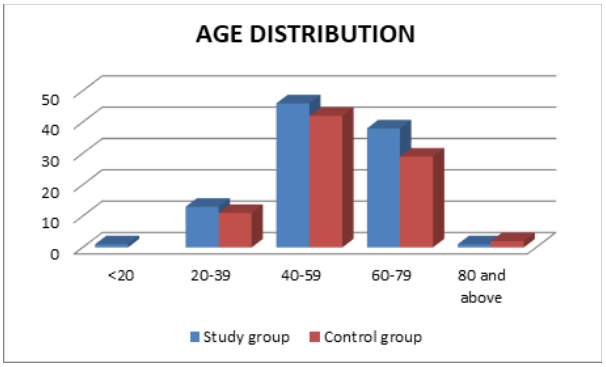

Fig 4: Diagram showing number of patients in different age groups

All the patients had history of COVID-19. Most common presenting complaint was headache (84%) followed by facial swelling (79%). Nasal blockage (65%) was most common associated feature with these two symptoms.

Table 3: Chief Complaints

Complaints	Percentage
Headache	84
Facial swelling	79
Dental pain	22
Eye swelling	19
Nasal blockage	18

Few patients also presented with tooth ache and numbness (22%), which on examination was often associated with palatal oedema. Other important symptom was pain in eyes (19%) which often rapidly progressed to blurring of vision.(Table.3)

Table 4: MRI Findings

Site of involvement	Percentage of patients
Nasal cavity and PNS	95
Floor of maxilla	25
Orbit	23
Pterygomaxillary area	42
Petrous apex	8
Infra-temporal fossa	6
Intra-cranial extension	2

On radiological studies about 57% patients had only nasal mucormycosis. 29% patients had either orbital or palatal invasion along with sino-nasal involvement. 14% patients presented with extensive form of mucormycosis with involvement of more than two entities i.e Rhino-orbito-palatal/cerebral (Fig.5). Among these 14% (26 patients), 5 patients had cerebral extension of disease. They were operated and made disease free successfully.

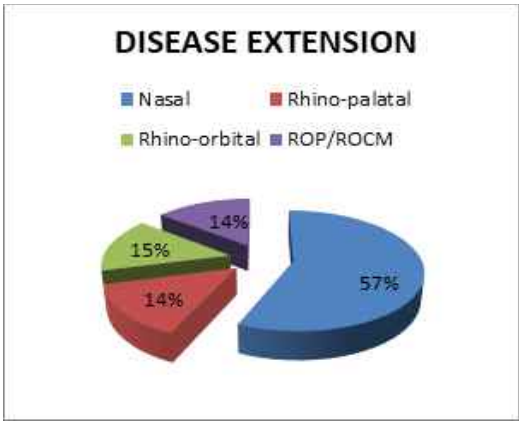

Fig 5: Diagram showing percentage of patients with extension of disease in facial structures. ROP-Rhino-orbital, ROCM- Rhino-orbito-cerebral Mucormycosis

Non-specific inflammatory markers like ESR and CRP were found to be elevated in all patients. Though non-specific but both ESR and CRP have good predictive values in the severity of the disease.

Serum ferritin, the important parameter of our study, was raised in majority of the patients. Normal range of serum ferritin is 20-250ng/ml in females and 30-350 ng/ml in males. About 66 patients had serum ferritin level more than 350ng/ml in study group, whereas only 16 people in the control group had raised ferritin levels.(Fig.6)

29 and 67 patients in study and control groups respectively, had serum ferritin levels between 50-350 ng/ml. Out of these, 10 female patients in study group and 3 female patients in control group had serum ferritin levels more than 250 ng/ml. (normal serum ferritin level in females- 20-250 ng/ml). Thus 76 patients in study group and 19 patients in control group had raised ferritin levels.

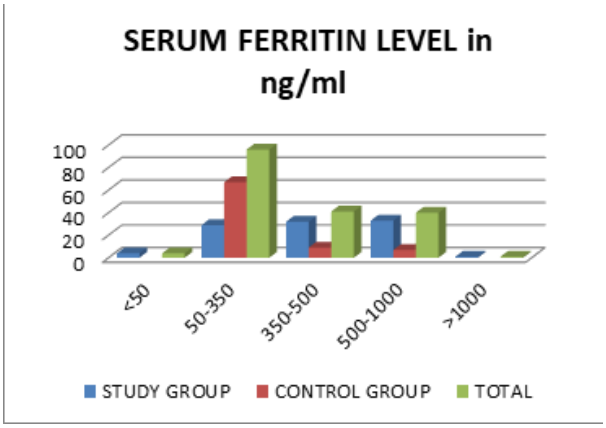

Fig 6: Diagram showing number of patients in each ferritin- level group

All patients were either previously diabetic or developed diabetes during the treatment of COVID-19 phase. Thus, they were either on oral hypoglycemic drugs or on insulin.

Table 5: HbA1c Levels

Groups	Upto6.4	More than 6.4
STD Group	27	72
CTR Group	23	60

Raised blood sugar levels have been proven etiologic factors for contracting mucormycosis, but no significant difference noted in blood sugar levels of control and study group to correlate raised blood sugar level with the aggressiveness of the disease as we strictly controlled blood sugar levels in all our patients. In our study, about 132 patients were having raised HbA1c level (Table.5) at the time of diagnosis of mucormycosis and 127 patients (65 in study group and 62 in control group) had raised blood sugar levels.(Fig. 7)

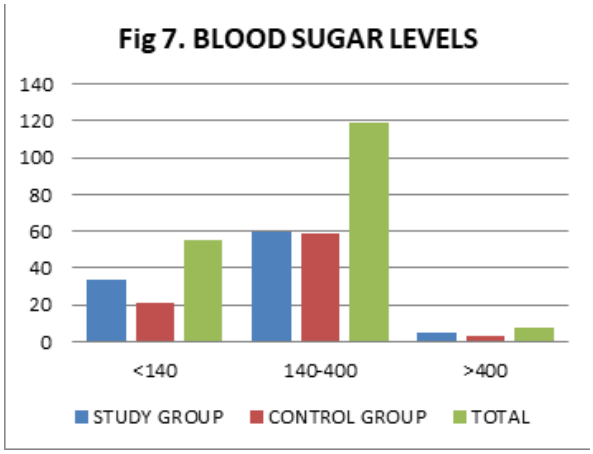

Fig 7: Diagram showing number of patients in each blood sugar level group

D-Dimer was raised (>500ng/ml) in 43 patients in the study group and in 47 patients in the control group. Again no significant association was found between the raised D-Dimer levels and aggresiveness of the mucormycosis.(Fig. 8)

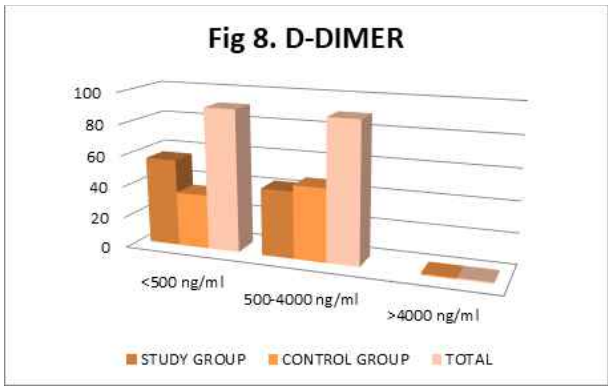

Fig 8: Diagram showing number of patients with varying D-Dimer levels

With 6 months regular follow-up, all patients in the control group are doing good, but 11 patients in study group, who were having extensive mucormycosis expired during 0-3 months follow up period.

Discussion:

Mucormycosis is an opportunistic infection and it has been usually observed in patients with immune-compromised state, malignancies, organ transplantation or patients on dialysis. Certain viral infections including SARS-CoV2, decrease the immunity during acute stage of the disease. Besides this, administration of high doses of steroids and other immune-modulator drugs like Tocilizumab in COVID-19 patients lead to hyperglycemic stage and diabetic-ketoacidosis. All these factors contributed to immune-compromised status in Post covid convalescence period. But out of many opportunistic infections why mucormycosis was most prevalent in these patients, has been a subject of curiosity among the health care professionals. Mostly it has been linked with raised blood sugar levels. Though raised blood sugar is important parameter in pathogenesis of mucormycosis, but not all patients with raised blood sugar levels have rapid progression and severe extension of the disease. In our study we tried to find out other important factor that is, raised serum ferritin levels associated with the extent of mucormycosis

Free iron can exist in Ferric (Fe3+) or ferrous (Fe2+) forms. These free iron forms can damage the tissue, so in Human hosts, the iron is bound to carrier proteins like Ferritin, Transferrin etc. In DKA, acidic pH of blood decreases the binding of iron to transferrin probably by proton mediated displacement of ferric iron.[13]

Recent studies have shown that free iron in serum promotes the virulence of mucormycosis in patients with DKA.[14,15] In experimental studies, when mice with DKA was administered with iron chelators like deferiprone and deferasirox (which are not used by mucorales as xenosiderophores), R. arrhizus failed to cause mucormycosis.[16,17] However patients on dialysis who are treated with iron chelator-Deferoxamine, are uniquely susceptible to mucormycosis.[18,19] Deferoxamine is a bacterial siderophore which is used by R. Arrhizus (xenosiderophore) for acquiring host iron. Another example of iron dependency of zygomycetes is Myelodysplastic syndromes where excessive iron in blood predisposes patients to deadly mucormycosis.[20]

Zygomycetes have developed many mechanisms for acquiring iron. One such mechanism includes high affinity permeases. These permeases convert less soluble ferric ions into more soluble ferrous ions, which is then stored in protein complexs.[21,22] Ibrahim *et al* have shown in their studies that gene encoding these high permeases is *FTR1*gene and inhibition of this gene by RNA-I reduces the virulence of fungus.[23]

Rhizopus also secretes a siderophore Rhizoferrin, but the contribution of this siderophore in acquiring iron from host is minimal. Third mechanism of acquiring iron from host is through use of heme. Studies have shown that *R. arrhizus* has 2 homologues of heme oxygenase[23]. These help the *R. arrhizus* to obtain iron from host haemoglobin and explain it's the angio-invasive nature. The FTR1 may act as cytoplasmic memberane permeases that helps heme uptake which is then followed by release of ferric ions through degradation with heme oxygenases.[24]

Mucormycosis spreads by angioinvasion. Subsequently there is thrombosis and tissue necrosis. COVID-19 induced Cytokine-storm leads to high levels of IL-6 that causes hyperferritenemia and macrophage activation. This immune response results in increased free iron within cells resulting into endothelial cell destruction. Endothelitis promotes angioinvasion by the fungus and its rapid spread. *Ibrahim et al* found that *R. arrhizus* adhere to human umbilical vein endothelial cells in vitro and invade these cells by induced endocytosis.[25] A Glucose related protein GRP78 mediates penetration of fungus by endocytosis and damage of endotheilial cells.[26] GRP78 expression increases in glucose starvation. Thus, elevated levels of glucose and iron, and increased expression of GRP78 in DKA are consistent with increased infectivity of mucorales in patients with DKA.

Associated uncontrolled diabetes, causes glycosylation of iron carrier proteins like ferritin and transferrin and decreases their iron-binding capacity, resulting in increased serum free iron levels. Higher serum ferritin level is suggestive of iron overload in blood which in turn is favorable for the growth of fungus of Order mucorales. In patients with raised blood sugar or Diabetic keto-acidosis, mucormycosis is specifically due to raised blood iron levels which promote the growth of this fungus. Though primary site of inoculation and growth of mucormycosis is nasal cavity, but due to its angioinvasive nature, it rapidly progresses to adjacent structures like sinuses, orbit, palate or brain.

In our retrospective study of 182 patients', we divided the patients into two groups. First group included those patients which on clinical and radiological examination urgently required surgical intervention. The other group included those patients in which extension of disease was not severe, disease was limited to nasal cavity & nasal mucosa, and were managed conservatively on antifungals. First group comprised 99 patients which had extensive invasion of mucormycosis in nasal cavities, paranasal sinuses or in adjacent vital structures where surgical debridement was necessary to avoid impending complications. In the second group those patients were included whose mucormycosis invasion was localized within nasal cavity, and it was feasible to treat them with antifungal therapy which included Liposoamal Amphotericin-B and Posaconazole. Among 182 patients, 95 patients (76 in study group and 19 in control group) had serum ferritin level above normal physiological range at the time of their presentation.

In the second group of patients, irrespective of their day of presentation after the onset of presenting complaint, serum ferritin levels were found to be below 350ng/ml in 67 patients. On the other hand, patients with extensive spread of mucormycosis in paranasal cavities, pterygopalatine fossa, orbit, palatal bones or dural extension showed higher levels of serum ferritin levels (above 350 ng/ml). About 76 patients in this group had serum ferritin levels higher than the physiological range. 8 out of 9 patients who underwent revision surgeries for debridement after recurrence of

mucormycosis had serum ferritin level higher than 350 ng/ml.

Higher serum ferritin level is associated with more invasive form of mucormycosis. This is because mucorales growth is promoted in a media where iron concentration is more. Boelart et al.[18] had found in their study that the incidence of mucormycosis was higher in patients on dialysis, due to use of iron chelator deferoxamine. Mucorales can use this iron chelator as xenosiderophore for acquiring iron for their growth. Ibrahim et al.[16,17] showed that use of iron chelators like deferiprone and deferasirox (that cannot be used as xenosiderophores by mucorales) can inhibit the progression of mucormycosis.

D-dimer, which is an important marker for the severity of COVID-19, doesn't show statistically significant difference in our two groups under study.

Early diagnosed patients in our study had disease limited to nasal cavity and sinuses, while other cases had involvement of other structures like orbit, skull base, palate or brain due to invasive nature of the fungus and raised ferritin levels. The India-centric guideline by ECCM (European Confederation of Medical Mycology) and the International Society for Human and Animal Mycology has suggested for extensive debridement of infected tissues and bones infected with mucormycosis.[27] It also suggests repeated procedures in case of recurrence.

In our institute, depending upon the extent of disease suggested in radiological studies (CT & MRI scan, with & without contrast), necessary and extensive debridement of sinuses, skull base, palatal bone or orbit was carried out to make the patient disease free. In a multivariate study of 929 reported instances of mucormycosis, Roden et al. found that antifungal medication with surgery results in better survival rates (69%) while death was practically certain (97%) for patients who got no treatment at all.[28]

Conclusion:

Mucormycosis has been a deadly disease because of its invasive nature and rapid progression. Though effective antifungals like Liposomal amphotericin-B and triazole (like Posaconazole) and surgical debridement have helped in reducing mortality, still management with anti-fungal drugs has its own systemic side effects and surgical debridement leads to disfigurement in many cases. Association of iron overload and progression of mucormycosis is an important aspect of research for controlling the disease at earlier stages. FTR1 gene encodes iron permeases of R. arrhizus that help in obtaining iron from environment. Passive immunization with anti-Ftr1p immune serum has shown efficacy in protecting mice with DKA from infection with R. arrhizus. Such passive immunotherapy is a promising strategy to improve outcomes of mucormycosis11. Iron chelators like deferiprone and deferasirox which cannot be used by mucorales as xenosiderophores can be protective in patients on dialysis or patients with DKA. Proper financial support and research work is required for developing such interventions to minimize disability and morbidity caused due to present medical and surgical methods.

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