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A RETROSPECTIVE ANALYSIS OF INCIDENCE AND SEVERITY OF INVASIVE RHINO-ORBITAL MUCORMYCOSIS IN POST COVID PATIENTS, IN A TERTIARY CARE HOSPITAL.

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ABSTRACT:

Background
Recent COVID-19 infection is associated with increase in incidence of invasive fungal infection (Mucormycosis) among patients with uncontrolled T2DM, patients on steroids as part of treatment for COVID-19 infection. This is a report of incidence and severity of COVID-19 associated with mucormycosis in tertiary care hospital.

Method
We retrospectively investigated 19 cases of post COVID-19 rhino-orbital mucormycosis admitted in saveetha medical hospital between April 2021 to September 2021 during second wave of COVID-19 pandemic. The medical records of COVID-19 patients with rhino-orbital mucormycosis diagnosed in saveetha medical college included in the study.

Result
19 patients with post COVID-19 rhino-orbital mucormycosis, identified from April 2021 to September 2021. Comorbidities-T2DM(54.3 %), 63% of patients received corticosteroids for COVID. The sites of involvement were rhino-sino-orbital (83%) and rhino-sino (17%). Liposomal amphotericin B and retrobulbar amphotericin -B injection with surgical debridement of sinuses alone or with orbital decompression/orbital exenteration was first-line therapy. Overall mortality rate was found to be 2/19.

Conclusions
We found high incidence of mucormycosis among post COVID-19 patients. Diabetes mellitus and use of corticosteroid were predominant predisposing factors for mucormycosis. Mucormycosis is a life-threatening opportunistic infection; hence knowing signs and symptoms of disease and developing a planned approach for patients who are at risk is important for diagnosis and starting therapy on time. It is important to screen patients with comorbidities like uncontrolled diabetes mellitus and patients on immunosuppressive therapy who were affected by COVID-19 disease for mucormycosis.

Keywords: mucormycosis, COVID-19, rhino-orbital mucormycosis.

1. INTRODUCTION

Rhino-orbital mucormycosis is an invasive fungal disease associated with high morbidity and mortality rates which have life threatening complications[1] caused by the fungi family Mucoraceae, they have angioinvasive ability and causes thrombosis of blood vessel leading to tissue necrosis, and it is common in uncontrolled diabetic patients and immunocompromized

patients.[2,6] Other predisposing factors are malignant hematological disorders, long term deferoxamine and glucocorticoid therapy, metabolic acidosis, transplant patients , chronic renal failure, immunosuppressive therapies. Disease starts off in nose and PNS after inhalation of the fungal spores. Mucormycosis is highly capable of spreading to pharynx, orbital and intracranial cavity via the spores.[4] They proliferates and spread to PNS (sino-nasal mucormycosis) and orbits by direct extension or by hematogenous route (rhino-orbital mucormycosis) and brain (rhino-orbital-cerebral mucormycosis).

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated in Wuhan, China, in December 2019. The main reason for the invasive fungal infections in the post COVID-19 infected patients is due to impairment of innate defense mechanisms, like reduced ciliary clearance, lack of lymphatic immune response.[3] Use of corticosteroids against COVID-19 to reduce risk of mortality, most likely causes patients to be more prone to many opportunistic infections especially mucormycosis. Most people infected with the virus had mild to moderate respiratory illness and recover without any special treatment. However, some will became seriously ill and need medical attention. Older people and patients with underlying medical conditions like cardiovascular disease, diabetes, chronic respiratory disease, or cancer are the patients who were most likely to develop serious illness like mucormycosis.

The invasion is dangerous and usually it is rapidly progressive which needs a multidisciplinary approach and fast action on treatment. Mucor-derived angioinvasion especially in Post COVID-19 patients with rhino orbital mucormycosis presented with signs and symptoms of nasal stuffiness; mucoid, purulent, bloody or black nasal discharge; epistaxis; facial pain,facial edema or periocular edema and discoloration, nasal discolouration, vision impairment;blurring of vision,loss of vision and excruciating headache, nasal regurgitation of food,loosening of tooth, toothache.[5]

Diagnosis of disease was made based on the detailed clinical history, clinical manifestations, radiological findings, histopathological examination and culture.Systemic administration of antifungal Amphotericin B with surgical debridement of sinuses, retrobulbar amphotericin B and orbital exenteration and improvement of systemic condition of the patient is mainstay of treatment for mucormicosis.

2. METHODS

A retrospective observational study was conducted on all the rhino-orbital mucormycosis patients with a previous history of COVID-19 infection at saveetha medical hospital during the period from april 2021 to September 2021.Our study included patients diagnosed with COVID-19 who received treatment for COVID-19 infection and developed signs and symptoms of mucormycosis and was diagnosed with rhino-orbital mucormycosis .

Diagnosis of mucormycosis made on complete detailed history including severity and duration of COVID-19 infection,treatment undergone by patient-steroid administration, oxygenation,duration of stay in hospital,time of development of mucormycosis related symptoms from time of COVID-19 infection, clinical assessment by DNE,KOH mount and fungal culture and imaging CT and MRI to look for extent and bony erosion , breach of lamina papyracea and orbital extension, orbital cellulitis, orbital apex syndrome and histopathological examination. All data were collected and entered in a spreadsheet and analysed accordingly.

Teatment regimen included systemic liposomal amphotericin B injection, three doses of retrobulbar liposomal amphotericin B injection along with surgical debridement of the sinuses with or without orbital decompression and with or without exenteration.

Inclusion criteria:

1. Patients with a past history of COVID infection.

2. Age 20 to 70 years, either sexes.
3. With or without co-morbids.
4. Presenting with symptoms of headache,facial pain,loosening of tooth,blurring of vision ,loss of vision,Diplopia,nasal discharge,nasal bleed.

Exclusion criteria:

1. Patients who have symptoms, but diagnosed as chronic inflammatory conditions or chronic sinusitis by histopathological examination.
2. Acute sinusitis,chronic sinusitis,allergic fungal sinusitis, nasal polyps
3. Non COVID patients.
4. Patients not willing for the study.

3. RESULT

Out of 32 post COVID-19 patients who came to saveetha medical college with the signs and symptoms of mucormycosis and was evaluated and found positive for mucormycosis, 19(59.4%) patients had rhino orbital mucormycosis that is the involvement of the nasal cavity, paranasal sinuses and orbit. Of which were 12 male (63.2%) and 7 (36.8%) female. All cases that were reported as confirmed cases of mucormycosis by histopathological examination had a history of hospitalisation due to COVID-19. 15 (78.9%) out of 19 patients received corticosteroids as a part of treatment for COVID-19 infection and 4 (21.1%) out of 19 received oxygen therapy. All patients had T2DM (54.3%) as comorbidity. 10(28.6%) patients had SHTN as comorbidity, 4 (11.4%) patients had CAD, and 2 (5.7%) patients had CKD.

For diagnosis KOH mount demonstrated broad aseptate fungal hyphae with right angled branching and fungal culture and sensitivity on sabouraud's dextrose agar was positive for rhizopus in all cases.

Management of patients were done with antifungal therapy with oral T.Posaconazole 300 mg/day for 60 days and Inj.Amphotericin-B 1gm to 2.5 gms, surgical debridement of paranasal sinuses with orbital decompression or orbital exenteration. Renal parameters were daily monitored and diabetics were managed with insulin and oral hypoglycemic agents.

Hospital stay of these patients ranged from 15 to 50 days with an average of 32.5 days. 8 patients were admitted in ICU and 11 patients in ward. 3 patients were admitted in ICU for 5 to 6 weeks approximately .5 patients were admitted in ICU for 3 to 4 weeks. Of the 11 patients 4 patients recovered in 5 to 6 weeks 3 patients recovered in 6 to 7 weeks and 4 patients took 7 to8 weeks to recover. All patients were under regular follow up. The overall mortality in patients with only rhino-orbital mucormycosis was 2/19 patients.

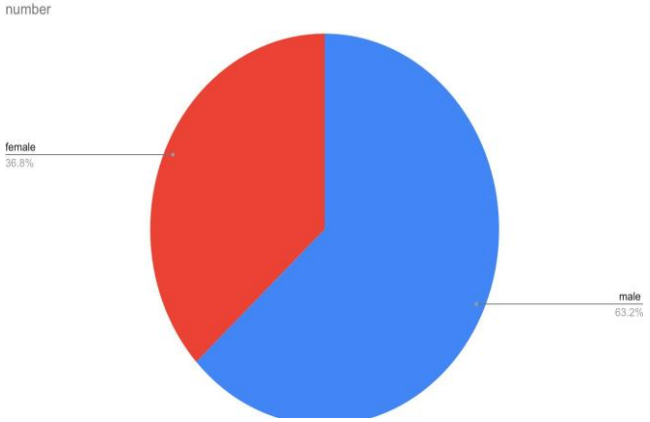

Fig1: Gender distribution of rhino orbital mucormycosis

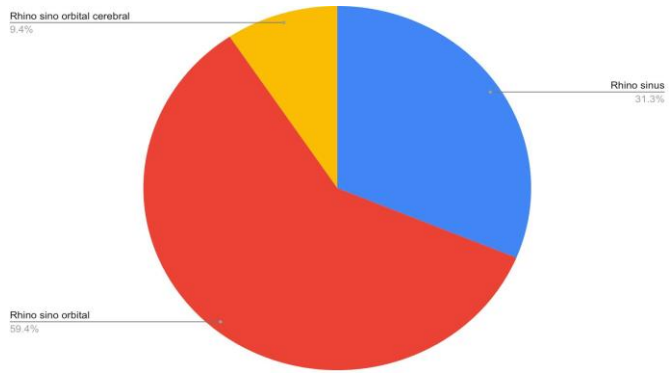

Fig 2: incidence of rhino-sino,rhino orbital and rhino-orbital-cerebral mucormycosis

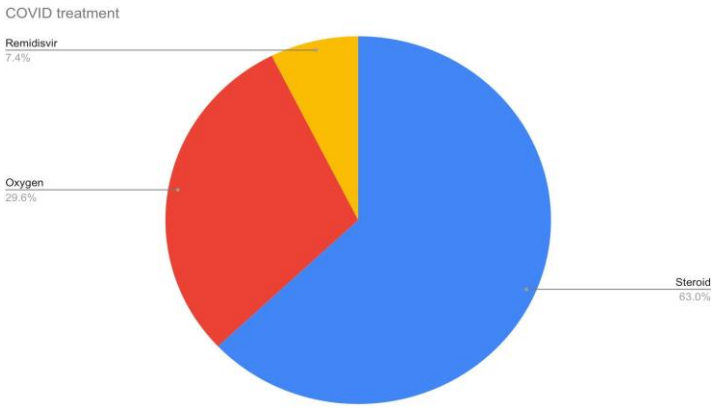

Fig 3: common treatment modalities during covid 19

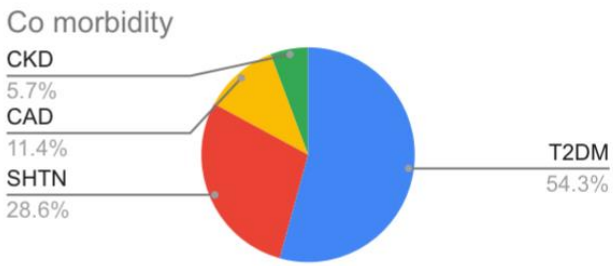

Fig4: Various Co-morbids in rhino orbital mucormycosis patients

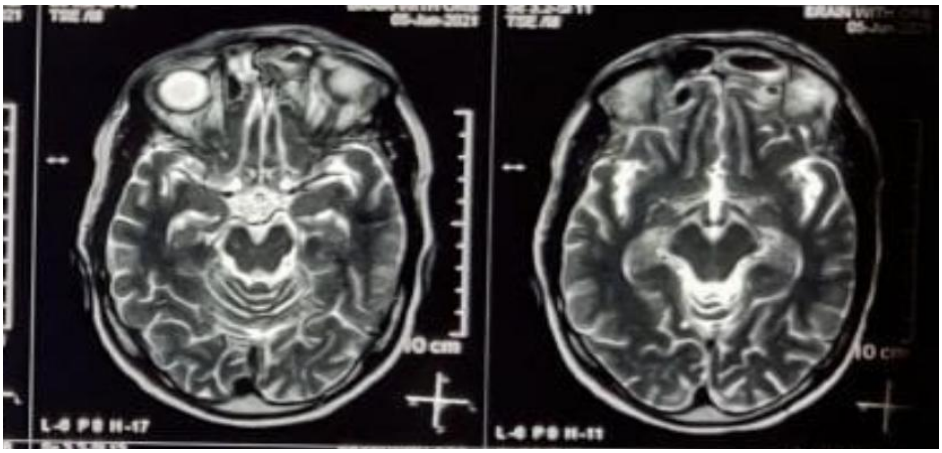

Fig5: CE-MRI showing Left periorbital involvement

Fig6: Bilateral periorbital swelling

Fig7: Right periorbital edema with alar necrosis

Table 1 Clinical presentation and treatment outcome of patients with rhino-orbital-cerebral mucormycosis

S.no	age/sex	covid RT-PCR	steroid use during covid treatment	oxygen use during COVID treatment	co-morbids	clinical features	KOH Mount	Fungal c/s	HPE	radiological findings	treatment	outcome
1	51/F	+	yes	yes	T2DM	Right sided facial pain,right eyepain	positive	rhizopus	positive	heterogenous soft tissue density in	A1, A4-2times A3	cured

										paranasal sinuses		
2	72/M	+	yes	yes	T2DM,CKD,CAD,HTN	left sided facial pain,left eye fixity	positive	rhizopus and candida yeast	positive	heterogenous soft tissue density involving the PNS and left orbit	A1 A2 A5 A3	cured
3	47/M	+	yes	no	T2DM	rhinorrhoea,right periorbital edema	positive	rhizopus	positive	soft tissue thickening in PNS	A1 A2 A4 A3	cured
4	26/M	+	yes	no	T2DM(newly diagnosed)	headache,Right eye swelling and edema	positive	rhizopus	positive	soft tissue thickening in PNS	A1 A2 A3 A4	cured
5	59/F	+	yes	no	T2DM(newly diagnosed)	left sided facial pain and swelling	positive	rhizopus	positive	soft tissue thickish in the PNS	A1 A2 A3 A4	cured
6	58/M	+	yes	no	T2DM	nasal discharge with progressive loss of vision in left eye	positive	rhizopus	positive	heterogenous soft tissue density in the PNS and left	A1 A2 A3 A6	cured

										orbit		
7	64/M	+	yes	no	T2DM	right sided facial pain,blood stained nasal discharge and right periorbital edema	postive	rhizopus	positive	soft tissue density in the PNS	A1 A2 A3 A4	cured
8	63/M	+	yes	yes	T2DM, SHTN, CAD	headache,nasal discharge and right peri orbital edema	positive	rhizopus	positive	soft tissue density in the PNS	A1 A2 A3 A4	cured
9	44/M	+	yes	no	T2DM	right retro orbital pain with right facial pain	positive	rhizopus	positive	soft tissue density in the PNS	A1 A2 A3 A4	cured
10	62/M	+	yes	no	T2DM,CKD,HTN	left sided facial pain with blurring of vision	positive	rhizopus	positive	soft tissue density in the PNS	A1 A2 A3 A5	cured
11	51/M	+	yes	yes	T2DM,SHTN	right eye swelling ,loss of	positive	rhizopus	positive	soft tissue density in	A1 A2 A3 A5	cured

						vision in right eye				the PNS		
12	54/F	+	no	no	T2DM,SHTN	headache with facial pain	positive	rhizopus	positive	soft tissue density in the PNS	A1 A2 A3 A4	cured
13	43/F	+	yes	no	T2DM	headache with nasal discharge, right eye pain and edema	positive	rhizopus	positive	soft tissue density in the PNS	A1 A2 A3 A4	cured
14	59/F	+	no	no	T2DM,HTN, CAD	right sided facial pain with periorbital edema	positive	rhizopus	positive	soft tissue density in the PNS	A1 A2 A3 A4	cured
15	60/F	+	yes	no	T2DM,SHTN	Right sided facial pain,blurring of vision in right eye	positive	rhizopus and candida	positive	soft tissue thicking in PNS with right orbital involvement	A1 A2 A3 A5	cured
16	64/M	+	no	no	T2DM	headache with retrorbital pain	positive	rhizopus	positive	soft tissue thicking in the PNS	A1 A2 A3 A4	expired

17	52/M	+	yes	no	T2DM, multiple sclerosis ,SHTN	left sided facial pain and left eye edema	positive	rhizopus	positive	soft tissue thicking in the PNS	A1 A2 A3 A4	cured
18	67/M	+	no	no	T2DM,SHTN, CAD	headache with left eye blurring of vision	positive	rhizopus	positive	soft tissue thicking in the PNS	A1 A2 A3 A5	expired
19	61/F	+	yes	no	T2DM,SHTN	headache with right facial pain	positive	rhizopus	positive	soft tissue thicking in the PNS	A1 A2 A3 A4	cured

A1- Systemic amphotericin-B 1.5G, A2-retrobulbar amphotericin- 3 days, A3- T.Posaconazole 300mg- 60 days, A4- Surgical debridement of Paranasal sinuses, A5-Surgical debridement of paranasal sinuses with orbital decompression,

4. DISCUSSION

The etiologic agents for mucormycosis are abundant in nature and thus it can be easily acquired especially in an immunocompromised patients, and its global epidemiological features has been studied by several researchers in India.[7,8] In India, the prevalence of mucormycosis is approximately 0.14 cases/1000 population[9] .It can present in various forms depending on immunological status of the patients. Due to the increasing cases of mucormycosis in the second wave of COVID-19 pandemic and due to severe complications and higher mortality rate in post COVID-19 patients, this rare disease is now a notifiable disease in India.[9]

Mucormycosis is rare in usually healthy individuals, but it is seen in patients with predisposing conditions like uncontrolled diabetes, hematological and other cancers, organ transplantation, immunosuppressive therapy and corticosteroid use, iron overload, deferoxamine therapy, severe burns, acquired immunodeficiency syndrome (AIDS) and similar immunosuppressive conditions. Diabetes mellitus is said to be a major predisposing factor for mucormycosis as described in a meta-analysis, in which 600 (70%) of 851 patients mucormycosis[10] .India harbours second largest diabetic population in world, and nearly 70% of these diabetics are uncontrolled[15].

Recent accumulating reports suggested an increasing prevalence of mucormycosis in COVID-19 patients[11] .Increasing mucormycosis cases may be due to increasing steroid use in COVID-19 patients. In the RECOVERY trial, dexamethasone at dose of 6 mg intravenous or oral once a day for treatment of COVID-19 was implemented. Systemic steroids further exaggerate the underlying glycemic control as well as decreasing the body's immune response system. The use of high dose corticosteroid has been found to be a cause of increase in the mucormycosis in post COVID-19 patients[12].

The infection begins by inhalation of spores into oral and nasal cavities. In people with good immune system infection very rarely develops because fungal spores are usually phagocytized by macrophages. However, in individuals with uncontrolled diabetes mellitus and in other immunocompromised status, infection develops as immune response is weak. From here infection would spread to paranasal sinuses and orbit through ethmoid air cells and maxillary sinuses causing orbital cellulitis. Fungus may also go to cavernous sinus and brain via cribriform plate, orbital apex and orbital vessel[13,14].

It is important to note that climate conditions can affect spread of mucormycosis[16]. Environmental factors of certain regions and humid climate and higher environmental temperature in India appears to be a reason for the disease prevalence and promotes growth of the Mucorales. COVID-19 infection adds a new risk to increasing mucormycosis cases[17,18].

Diagnosis of mucormycosis is made by clinical signs and symptoms and by broad aseptate hyphae with right-angled branching seen on KOH mount which is diagnostic. In this study, all patients on KOH smear, culture and Histopathology showed positive for mucormycosis. CT scan and MRI shows heterogeneous mucosal thickening, opacification of sinuses, orbit and intracranial involvement[19,20].In a study by Abdollahi et al. maxillary sinuses were most commonly involved sinuses (66.7%) followed by ethmoid[21].

5. CONCLUSION

High incidence of mucormycosis was found among COVID-19 infected patients during second wave. Early diagnosis of cases by proper history taking and examination, timely treatment with systemic antifungals, sinus debridement surgery, checking glycemic levels and proper use of corticosteroids are extremely important in successful eradication of mucormycosis and patient survival. Invasive rhino-orbital mucormycosis is a severe, fatal infection which requires a multidisciplinary approach.

It is also important for patients to be educated to identify early signs and symptoms of invasive mucormycosis.

Compliance with Ethical Standards

Conflicts of interest

All authors have declared that they have no conflict of interest.

Ethical Approval

The manuscript has been read and approved by all authors, the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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