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Original Research Paper

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COVID-19 WITH RHINO-ORBITO-CEREBRAL MUCORMYCOSIS : A SUDDEN SURGE

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ABSTRACT Recently an increase in the incidence of mucormycosis is noticed in COVID-19 cases. The main aim of this study is to present our experience of rhino-orbito-cerebral mucormycosis in COVID-19 patients and thereby aid its early diagnosis and treatment. This is a prospective study of 12 cases diagnosed as Rhino-orbito-cerebral mucormycosis . Presentation of mucormycosis in COVID-19, their temporal association and outcome of treatment was studied. Pre-existing comorbidities were seen in 91.67% patients, Diabetes Mellitus (83.33%). Previous history of COVID-19 infection and treatment for the same in 41.67% cases, concomitant infection in 16.67% and asymptomatic undiagnosed covid (antibodies positive) was detected in 41.67%. All patients showed improvement in general and nasal condition (100%). Early diagnosis is must.

KEYWORDS : Mucormycosis, COVID-19, Rhino-orbito-cerebral

INTRODUCTION

Mucormycosis (zygomycoses) is an opportunistic fungal infection caused by fungi belonging to *Mucor* species[1]. Mucormycosis affects many different systems in immunocompromised hosts. According to anatomical site, it is divided into rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated and miscelleneous[2]. Rhino-orbito-cerebral and pulmonary infections are commonly reported[3]. The annual incidence in India and Pakistan is about 140 cases in 1,000,000[4].

In the ongoing COVID-19 pandemic, few studies report the concurrent presence of mucormycosis in COVID-19 cases[5-8]. Individually Mucormycosis and COVID-19 are diseases with known morbidity and mortality. Thus, the rising incidence of this co-infection needs to be studied to provide early diagnosis and treatment.

The main aim of this study is to report our experience of the rising incidence of rhino-orbito-cerebral mucormycosis in COVID-19 cases and the positive outcome secondary to its early diagnosis and treatment.

METHOD

This prospective study of 12 cases diagnosed as Rhino-orbito-cerebral mucormycosis was carried out in department of ENT, GMCH Nagpur from November 2020 to February 2021. Patients with signs and symptoms of mucormycosis were registered. After taking consent, detailed history and examination findings were recorded. Oropharyngeal swabs were sent for COVID-19 RT-PCR testing. COVID-19 antibody tests were performed in negative cases. Nasal endoscopy, CT Scan and MRI was done. Nasal swab for KOH and tissue for fungal staining, culture and histopathology were collected to confirm mucormycosis. Treatment comprised of Inj. Amphotericin B 1mg/kg/day or Inj Liposomal Amphotericin 5mg/kg/day x 6 weeks, treatment for comorbidities, antibiotics and surgical endoscopic debridement.

RESULTS

There were 9(75%) male and 3(25%) females. Male: Female ratio 3:1. Age was between 32yrs to 82 yrs. Commonest presenting complaint was nasal obstruction in 8(66.67%) followed by loss of vision in 4(33.33%) and swelling around eye in 3(25%) cases. Other complaints were nasal discharge (16.67%), decreased vision (16.67%), facial pain (16.67%), pus discharge from gums and palate (8.33%), nasal bleed (8.33%), Fever (8.33%) and headache (8.33%). Most frequent associated comorbidity was DM in 10(83.33%) cases. DM alone was seen in 6(50%) patients, DM+HTN in 2(16.67%), DM+HTN+CKD in 1(8.33%), DM+liver cirrhosis in 1(8.33%). Pulmonary TB+CKD was seen in 1(8.33%) patient. Comorbid association was not found in 1 patient (8.33%) (table 1).

Table 1: Clinical Profile, Management And Outcome

CHARACTERISTICS	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6
AGE/GENDER	55/F	58/M	61/M	50/M	82/M	41/M
HISTORY						
SYMPTOMS	Lt nasal obst. , blurring of vision	Lt nasal obst,bleed	Lt nasal obst, loss of vision, , fever, headache	Lt nasal obst, disch	Lt eye loss of vision	Rt nasal obst, disch
CO-MORBIDITIES	DM	HTN, DM, CKD	DM	PTB treated, CKD	DM	DM
PAST HISTORY OF COVID POSITIVE STATUS AND TREATMENT	-	+	-	+	+	-
COVID RT-PCR POSITIVE ON ADMISSION	+	-	-	-	-	-

COVID ANTIBODIES POSITIVE	NOT NECESSARY	NOT NECESSARY	+	NOT NECESSARY	NOT NECESSARY	+
EXAMINATION						
NASAL CAVITY AND PALATE	Blackish crusting	Black crust in left nasal cavity with B/L necrosed turbinate	Purulent disch ,blackish crusting, ulcer over hard palate	Purulent disch, blackish crusting, palatal perf	Crusting	Crusting, necrosis of turbinate, palatal perf
V/A	FC 4M	Normal	NO PL/PR	Normal	No PL	Normal
EYEBALL	Proptosis	Normal	Proptosis	Proptosis	Proptosis	Proptosis
EYELID	Ptosis, oedema	Normal	Ptosis ,oedema	Normal	Normal	Oedema
CONJUCTIVA	Congested	Normal	congested, chemosis	Normal	Mild congestion	Chemosis, congestion
PUPILLARY LIGHT REFLEX	+	+	+	+	+	+
EYE MOVEMENTS	Restricted	Normal	Restricted	Normal	Restricted	Normal
FUNDUS	Papilledema	Normal	not possible (mature cataract)	Normal	Not possible (cataractous lens)	Normal
CRANIAL NERVES	WNL	WNL	5th (I) nerve palsy	WNL	WNL	WNL
MANAGEMENT						
RDAIOLOGICAL FINDINGS	Soft tissue density in left maxillary, ethmoid sinus ,nasal cavity with medial maxillary wall erosion, orbit-intraconal fat stranding	Complete opacification of all sinuses, and lt nasal cavity, widening of lt maxillary ostium, architectural distortion of turbinate	Mucosal thickening in all sinuses, retro-orbital fat stranding , preseptal oedema, Lt cavernous sinus thrombosis	Mucosal thickening in left maxillary ,ethmoid sinus, erosion of floor of maxillary sinus	Preseptal oedema , extraconal fat stranding in left orbit, mild mucosal thickening in ethmoid sinus	Soft tissue density in rt maxillary, ethmoid and sphenoid sinus, erosion of medial wall and floor of maxilla, preseptal oedema
NASAL SWABS FOR KOH	Pos	Pos	Neg	Neg	Pos	Neg
TISSUE FOR CULTURE AND HISTOPATHOLOGY	Mucor	Mucor	Mucor	Mucor	Mucor	Mucor
MEDICAL AND SURGICAL TREATMENT	Inj Amphotericin B, Inj Insulin, Inj Methyl prednisolone, Inj piperacillin+tazobactum, Inj metronidazole Endoscopic debridement	Inj Liposomal Amphotericin, Inj Insulin, Inj Meropenem, Inj metronidazole Endoscopic debridement	Inj Amphotericin B, Inj Insulin, Inj Mannitol, Inj piperacillin+tazobactum, Inj metronidazole Endoscopic debridement	Inj Liposomal Amphotericin, Inj Meropenem, Inj metronidazole Endoscopic debridement	Inj Amphotericin B, Inj Insulin, Inj piperacillin+tazobactum, Inj metronidazole Endoscopic debridement	Inj Amphotericin B, Inj Insulin, Inj piperacillin+tazobactum, Inj metronidazole Endoscopic debridement
OUTCOME	Cured	Cured	Cured	Cured	Cured	Cured

CHARACTERISTICS	**CASE 7**	**CASE 8**	**CASE 9**	**CASE 10**	**CASE 11**	**CASE 12**
AGE/GENDER	55/F	32/M	35/M	61/M	56/F	50/M
HISTORY						
SYMPTOMS	Lt nasal obst, eye swelling	Rt eye blurring of vision, nasal obst	Lt eye swelling and loss of vision	Rt facial pain	Rt eye loss of vision, swelling	Lt facial pain, pus discharge from gums palate, nasal obstruction
CO-MORBIDITIES	DM	Nil	Liver cirrhosis,DM	DM, HTN	DM, HTN	DM
PAST HISTORY OF COVID POSITIVE STATUS AND TREATMENT	-	-	-	+	-	+
COVID RT-PCR POSITIVE ON ADMISSION	+	-	-	-	-	-
COVID ANTIBODIES POSITIVE	NOT NECESSARY	+	+	NOT NECESSARY	+	NOT NECESSARY
EXAMINATION						
NASAL CAVITY AND PALATE	Mucosal oedema with minimal crusting in lt middle meatus	Rt middle meatus crusting with necrosis, palatal perf	Black crust in lt cavity with necrosed turbinate	Black crust in rt middle meatus	Mucopurulent Discharge and crusting in rt middle meatus	B/L nasal cavity crusting, lt maxillary tenderness, Multiple sinuses and slough over palate, upper alveolus, loose tooth

V/A	Normal	FC 2M	No PL/PR	Normal	No PL/PR	Normal
EYEBALL	Normal	Proptosis	Proptosis	Normal	Proptosis	Normal
EYELID	Oedema, erythema	Oedema	Oedema erythema	Normal	Oedema ptosis	Normal
CONJUCTIVA	Normal	Mild congestion	Congested, chemosis	Normal	Chemosis	Normal
PUPILLARY LIGHT REFLEX	+	+	-	+	+	+
EYE MOVEMENTS	Normal	Restricted	Restricted	Normal	Restricted	Normal
FUNDUS	Normal	papilledema	Papilledema	Normal	Normal	Normal
CRANIAL NERVES	WNL	WNL	5th (I) nerve palsy	WNL	WNL	WNL
MANAGEMENT						
RADIOLOGICAL FINDINGS	Mucosal thickening in lt maxillary sinus with OMC widening, subtle erosion of medial wall of maxilla, no extramaxillary extension	Soft tissue density in ethmoid, sphenoid sinus, soft tissue extension into rt extra and intraconal compartment of orbit, lamina papyracea , breech, soft tissue density in frontal lobe	Mucosal thickening in lt maxillary, ethmoid ,sphenoid sinus. Erosion of lamina papyracea, intra and extraconal fat stranding with bulky extraorbital muscles, preseptal oedema	Mucosal thickening in rt maxillary sinus, ethmoid sinus, frontal sinus	Mucosal thickening in rt maxillary and ethmoid sinus, lamina papyracea rarefaction, orbital intra and extraconal fat stranding, extraorbital muscle bulky	Soft tissue density in B/L maxillary, ethmoid sinus
NASAL SWABS FOR KOH	Neg	Pos	Neg	Neg	Pos	Neg
TISSUE FOR CULTURE AND HISTOPATHOLOGY	Mucor	Mucor	Mucor	Mucor	Mucor	Mucor
MEDICAL AND SURGICAL TREATMENT	Inj Amphotericin B, Inj Insulin, Inj piperacillin+tazobactum, Inj metronidazole Endoscopic debridement	Inj Amphotericin B, Inj Methyl Prednisolone, Inj Mannitol, Inj piperacillin+ tazobactam, Inj metronidazole Endoscopic debridement	Inj Amphotericin B, Inj Insulin, Inj piperacillin+tazobactum, Inj metronidazole Endoscopic debridement	Inj Amphotericin B, Inj Insulin, Inj piperacillin+tazobactum, Inj metronidazole Endoscopic debridement	Inj Amphotericin B, Inj Insulin, Inj piperacillin+tazobactum, Inj metronidazole Endoscopic debridement	Inj Amphotericin B,Inj Insulin, Inj piperacillin+ tazobactam, Inj metronidazole Endoscopic debridement
OUTCOME	Cured	Cured	Cured	Undergoing treatment	Undergoing treatment	Undergoing treatment

(Obst- obstruction, disch-discharge, Neg -negative, Pos-Positive, Pul- pulmonary, DM-diabetes mellitus, RPD- renal parenchymal disease, perf- perforation, WNL-Within normal limit)

Table 2: Association Of Covid-19 Infection With Mucormycosis (n=12)

Development of symptoms of mucor	Duration gap between diagnosis of covid and mucormycosis symptom onset (days)	No. of patients (Percentage)
Concomitant presentation	0	2 (16.67)
During treatment of covid	6-10	1 (8.33)
After recovery from covid	18-20	4 (33.33)
Asymptomatic undiagnosed covid (antibody test positive)	Cannot be assessed	5 (41.67)

On examination blackish nasal crusting and necrosis was seen in all patients (100%). Palatal involvement in the form of ulcer or swelling with single or multiple perforation seen in 5(41.67%) and purulent nasal discharge was seen in 3(25%) cases. Ophthalmic involvement was documented in 9(75%) cases (FIG 1). Eyeball proptosis being the most common seen in 8(66.67%) followed by eyelid oedema in 7(58.33%). Conjunctival congestion with or without chemosis was in 7(58.33%), restricted eye movements in 6(50%), abnormal fundus examination (papilledema) in 3(25%), ptosis in 3(25%), loss of vision in 4(33.33%) and decreased vision in 2(16.67%)(FIG 1). Loss of touch sensation over forehead was in 2(16.67%) cases. Cerebral involvement was seen in 2(16.67%) cases.

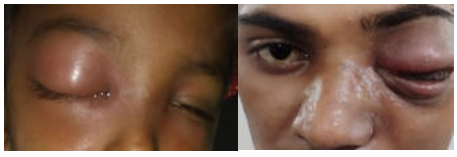

Fig 1: clinical presentation

Nasal swab for KOH was positive in 5(50%) cases. Tissue culture, special stains and histopathological examination revealed aseptate broad hyphae with aerial mycelium and sporangiophores consistent with mucor in all(100%) (FIG 2).

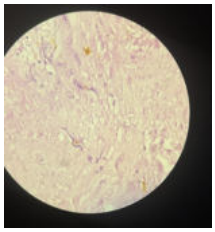

Fig 2: Fungal Hyphae On Pas Stain (10x)

When association with COVID-19 was studied, 4(33.33%) were already diagnosed and treated for COVID-19(18-20 days), 1(8.33%) had onset of mucormycosis symptoms during the hospital stay (within 6-10 days), 2(16.67%) presented simultaneously for COVID-19 and mucormycosis and their treatment was continued in dedicated COVID-19 setup in our hospital. COVID-19 antibody test was positive in remaining 5(41.67%) patients suggestive of past undiagnosed COVID-19 infection. The patients with diagnosed COVID-19 (7 cases) received Inj remidesivir, Inj methylprednisolone, Inj azithromycin and Inj LMWH for treatment of covid pneumonia.

For mucormycosis, Inj Amphotericin B , Inj Piperacillin+ Tazobactum, Inj Metronidazole and treatment of comorbidities (inj insulin, antihypertensive medication, diuretics) wherever needed were given . Amphotericin B was administered in Normal Saline slowly over a period of 4-6 hrs with adequate hydration. Regular monitoring of electrolytes and renal function was done. Patients with kidney disease were treated with Inj Liposomal Amphotericin, Inj Meropenem and Inj Metronidazole. In patients with cerebral involvement Inj Mannitol was given. Those with Papilledema were given Inj Methylprednisolone. All cases were subjected to endoscopic debridement.

Follow up of 1 month is completed in 9(75%) cases. At the end of 1 month, improvement in vision was seen in 2(16.67%) cases who had blurring of vision and 4(33.33%) cases with complete loss of vision did not show any improvement. Improvement in general condition with reduction in nasal necrotic tissue and inflammation is noted in all cases (100%).

DISCUSSION

Mucormycosis is an acute invasive opportunistic fungal disease seen in patients with impaired immunity. The host defence constitutes hyphal damage by phagocytosis, oxidative and non-oxidative mechanism by macrophages and neutrophils[9]. Steroid induced immunosuppression, hyperglycaemia induced defective neutrophilic phagocytosis and chemotaxis, acidosis increasing free iron levels etc all promote fungal opportunistic infection[10,11]. Their ability of angio-invasion leads to thrombosis, infarct and tissue necrosis making them fatal.

While the medical community is still at war with the COVID-19 virus, adding to its woes is the mucor. Of the limited literature available, few studies claim the increasing incidence of co-infection of mucor with COVID-19[5-8].

Mehta S et al reported a case of DM with Covid pneumonia[6] where patient developed rhino-orbital mucormycosis during the hospital stay. Hanley B et al in their post-mortem study documented the presence of disseminated mucormycosis[7]. In other study Werthman-Ehrenreich A documented a case of simultaneous presentation of covid and mucormycosis[8]. A study conducted by Sen M et al included 6 patients where 1 patient presented with concomitant infection while the remaining 5 patients were treated for COVID-19 infection[5]. The mean duration between diagnosis of COVID-19 and development of mucormycosis symptoms in this study was 15.6 days. In present study, this duration was 6-10 days in 8.33%, 18-20 days in 33.33%. Simultaneous infection was seen in 16.67%. Undiagnosed covid infection was seen in 41.67% where duration could not be assessed. These studies showed that mucormycosis can present at any stage of COVID-19 infection[5-8].

An interplay of various factors like immunosuppression caused by cytokine storm, use of steroids for the treatment, risk of hospital acquired infection, pre-existing diseases etc has been thought to have a role in development of secondary bacterial or fungal infection in the COVID-19 patients. In our study pre-existing co-morbidities were seen in 91.67%. In other studies, the patients had history of DM similar to our study where 10(83.33%) patients had pre-existing DM.

Antifungals with surgical debridement is the mainstay of treatment for mucormycosis. Inj Amphotericin B, Liposomal Amphotericin and Posaconazole are the first line drugs. Isavuconazole may be used when there is no response to other drugs[12]. In present study we have used Inj Amphotericin B (10 cases) and liposomal amphotericin (2 case with renal disease) along with adequate surgical debridement in all cases.

Identification of the risk factors, suspicion based on symptoms, early diagnosis and treatment of mucor infections in patients with COVID-19 is necessary to alleviate morbidity and mortality.

CONCLUSION

The knowledge about the COVID-19 pandemic is being updated every minute which is of paramount importance in dealing with the virus. Rhino-orbito-cerebral mucormycosis can present at any stage of COVID-19 infection which adds to its already existent lethality. A constant vigilance, early diagnosis and treatment can reduce this morbidity and mortality. Hence a fast and co-ordinated effort is needed.

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