

A Clinical Study on Mucormycosis Done During the Covid Pandemic in the Year 2021A. Geetha¹, K. Anjaneyulu², Y.M.S. Prasad³, K.V. Manasa⁴¹Associate Professor, Department of Ophthalmology, Government Medical College, Anantapur, Andhra Pradesh, India²Associate Professor, Department of Ophthalmology, Guntur Medical College, Guntur, Andhra Pradesh, India.^{3,4}Assistant Professor, Department of Ophthalmology, Government Medical College, Anantapur, Andhra Pradesh, India

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Conflict of interest: Nil

Abstract:**Background:** Mucormycosis is a angioinvasive fungal infection, mainly affecting patients with uncontrolled diabetes mellitus, those on chemotherapy and those who are suffering from a chronic illness. There has been a remarked increase in the incidence of Rhino-orbito-cerebral mucormycosis (ROCM) in association with the 2nd wave of COVID.**Methods:** The study was conducted in a tertiary care hospital. Data was collected from 200 cases of Rhino-orbito-cerebral mucormycosis which were admitted and treated in the period from June 1st to august 31st of 2021. Diagnosis was based on clinical features and histopathology of the biopsy specimen and staging was based on contrast enhanced MRI. Treatment included intravenous liposomal amphotericin B and surgical debridement of the necrotic tissue, retrobulbar amphotericin B injections as required.**Results:** Among the 200 patients under study 128 were male, 72 were female with the mean age being 50 yrs. All patients had history of covid with 159 of them having received oxygen inhalation and 167 of them had received systemic steroids. 174 patients were diabetic. Most of the patients belonged to stage 2 and stage 3.**Conclusion:** The usage of systemic steroids and uncontrolled diabetes mellitus are well known risk factors of mucormycosis, but the dramatic rise in the incidence in association with COVID probably suggests the immune compromised state caused by COVID. Early diagnosis and appropriate management are essential to control the spread of infection and decrease the morbidity and mortality associated with the disease.**Keywords:** mucormycosis, COVID-19, orbital infections, ROCM, amphotericin-B.

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Introduction

Mucormycosis is a fungal infection caused by fungus of the class Zygomycetes and of the order Mucorales. [1] It is a potentially fatal infection with rapid progression. The fungal hyphae invade the blood vessels of the host causing infection and necrosis of the tissues. It has been known to affect immunocompromised patients particularly those with uncontrolled diabetes. It can infect any site in the body based on which it can be classified as rhino-cerebral/ sino-orbital, pulmonary, cutaneous, gastrointestinal and disseminated. There has been an increased incidence of mucormycosis of the rhino-orbito-cerebral type in the people of India, in association with the second wave of COVID-19. [2] Early diagnosis and aggressive management by a multidisciplinary team is essential in improving the survival of the patient. [3] Naso-sinusoidal involvement results in nasal stuffiness, nasal discharge, foul smell, facial edema and pain.

Orbital involvement results in proptosis, ocular movement restriction and vision loss depending on the structures involved and staging. Cerebral involvement results in altered sensorium, paralysis and focal seizures. [4]

Materials & Methods

Data was collected from 200 cases of Rhino-orbito-cerebral mucormycosis which were admitted and treated in the period from June 1st to august 31st of 2021. The patients presenting with warning signs and symptoms like facial and orbital pain, edema, headache, proptosis, ptosis, ocular movement restriction were carefully evaluated. Detailed history was taken along with systemic, ENT, ophthalmic and neurological examination. The diagnosis of mucormycosis was confirmed by the presence of fungal hyphae on KOH mount of the specimen collected from deep nasal swab. Routine

blood tests were done to know the general condition of the patient including complete blood picture, LFT, RFT, fasting and post-prandial blood sugars, serum electrolytes. Contrast enhanced MRI was done in all patients to determine the extent of involvement and stage the disease. Intravenous liposomal amphotericin B was administered to all patients with monitoring of renal function. Daily monitoring of blood sugar levels with titration of the dose of insulin and oral hypoglycaemic agents was done. The surgical approach for patients in stage 2 included aggressive debridement of the paranasal sinuses along with turbinectomy and palatal resection in necessary cases. For patients with orbital involvement, retrobulbar amphotericin

B injections were given. For those with extensive orbital involvement with no useful vision i.e, with no perception of light, orbital exenteration was done along with debridement of paranasal sinuses. Prolonged step down antifungal therapy was given with oral posaconazole.

Endoscopy and suction clearance was advised weekly for 4 weeks and then monthly for a year. CT scan was advised after 1 month or with recurrence of symptoms.

Results

The age of the patients was ranging from 25-75 years, with the mean age being 50 years.

Table 1: Age distribution of mucormycosis

Age group	No. of patients
25-35	27
36-45	37
46-55	66
56-65	42
66-75	23
76-85	5

Of the 200 patients, 128 were male and 72 were female. The male: female ratio was 1.8:1.

Table 2: Gender distribution of mucormycosis

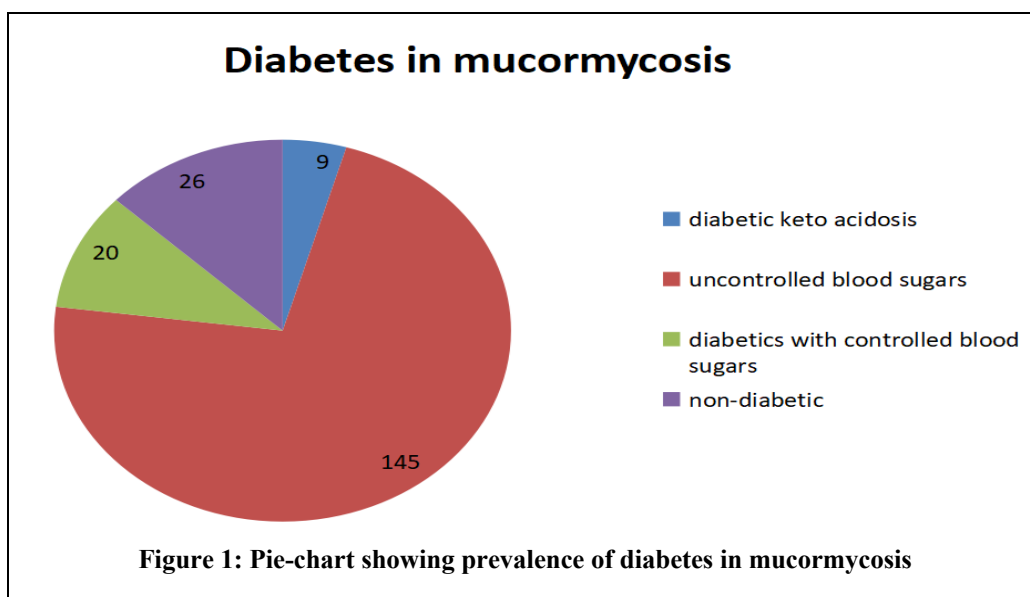
Gender	No. of patients
male	128
female	72

All of them had history of contracting covid, with hospital admission. Among them, 147 patients had oxygen inhalation either through nasal prongs or mask and 12 had continuous positive airway pressure ventilation for few days.

7 patients were unaware of the treatment they have taken, 26 patients have no history of steroid intake, and remaining 167 patients have taken systemic

steroids. Most of the patients had systemic steroids for a period of 6-10 days, with only 14 patients having taken steroids for more than 10 days. Of the 200 patients, 174 were diabetic.

Among them 9 had diabetic ketoacidosis and 145 patients had uncontrolled blood sugars and 20 had controlled blood sugars.



The stage of ROCM depends on the severity of spread of infection which can be best observed with contrast enhanced MRI.

Table 3: Stage distribution of ROCM based on contrast enhanced MRI

Stage of ROCM based on contrast enhanced MRI	No. of patients
2A	8
2B	23
2C	37
2D	12
3A	21
3B	26
3C	40
3D	9
4A	14
4B	6
4C	3
4D	1

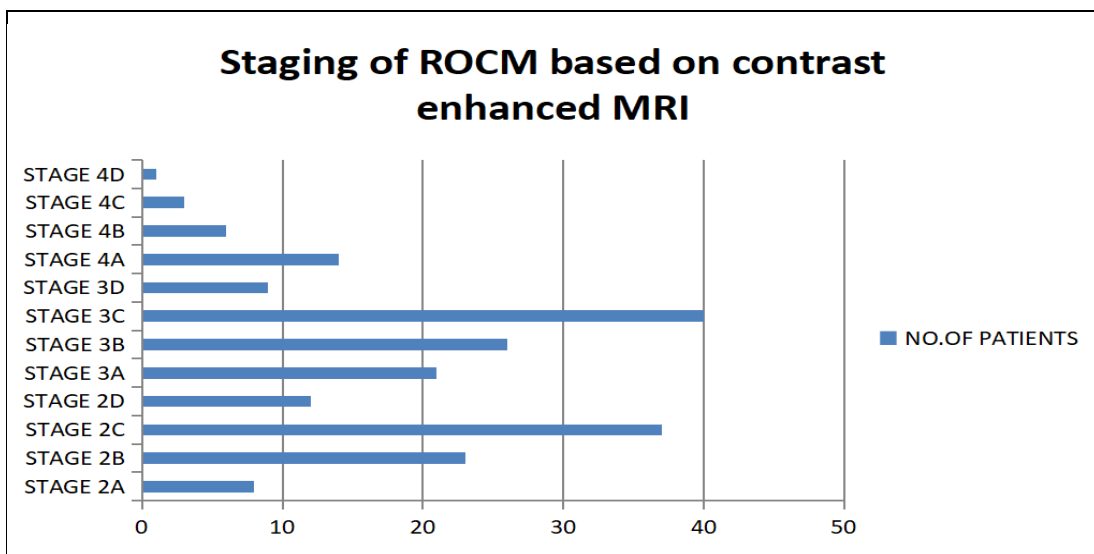


Figure 2: Bar diagram showing stage distribution of ROCM based on contrast enhanced MRI

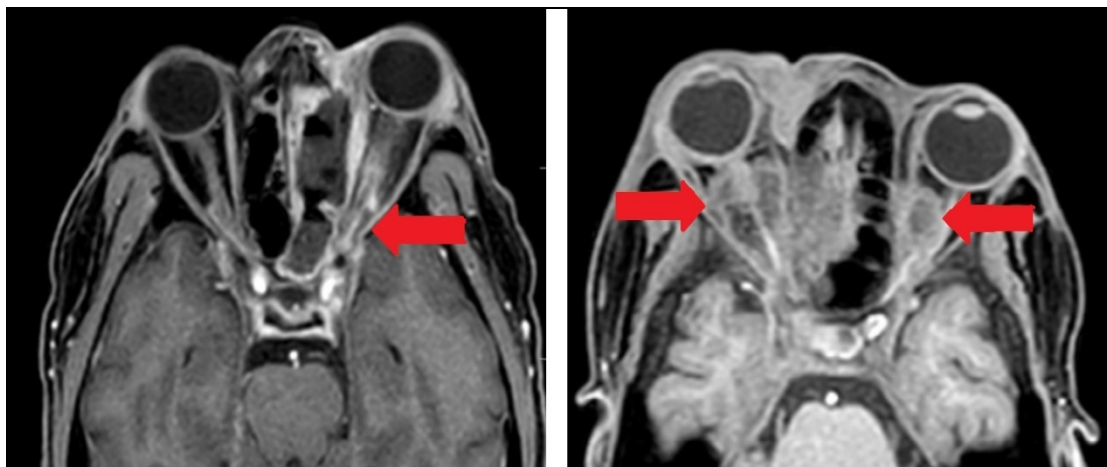


Figure 3: Image 1 (left side): contrast enhanced MRI image showing non-enhancing soft tissue in left orbital apex with thickened and enhancing optic nerve and proptosis. Image 2 (right side): contrast enhanced MRI image showing soft tissue enhancement in the intraconal compartment of bilateral orbits and proptosis on right side

Discussion

Mucormycosis is caused by filamentous fungi belonging to the family of mucoraceae of the order mucorales. The most common risk factors include uncontrolled diabetes mellitus, diabetic ketoacidosis and immunosuppressive states including usage of steroids and immunosuppressive drugs and haematological malignancies. There has been a surge in the mucormycosis in India during the 2nd wave of COVID-19 who were treated and recovered. The triad of covid, steroid usage and presence of uncontrolled diabetes mellitus was associated with increase in the incidence of mucormycosis. [5]

The initiating event is inhalation of sporangiospores. These spores invade the nasal mucosa and form coenocytic hyphae that spread rapidly in predisposed individuals. In healthy individuals, the macrophages phagocytose the fungal spores and prevent fungal infection. In immunocompromised individuals, the fungal spores evade the oxidative metabolites and defensins secreted by the macrophages and invade the endothelial cells of the blood vessels. The glucose regulated protein receptor GRP-78 are upregulated in the nasal endothelium in patients with diabetes mellitus. [6] Angioinvasion is the key mechanism in the spread of fungal hyphae and for tissue necrosis. [7] The hyphae grow in the paranasal sinuses first and then spread to the surrounding tissues by direct tissue invasion. From the sinuses the infection spreads to the orbital tissues through the lamina papyracea, naso-lacrimal duct, ethmoidal foramina or through the vascular channels. Rarely the infection spreads by destroying the bony orbital wall from the maxillary sinus. [2] Due to fungal invasion there is damage to the intima of the blood vessel causing thrombosis. This thrombosis can cause emboli and vascular occlusion leading to tissue necrosis. Lymphatics and veins are also involved. [6] Soft tissue involvement including retro orbital fat and extra ocular muscles are the signs of early orbital involvement. This causes proptosis. Further spread of infection causes superior orbital fissure syndrome which causes ophthalmoplegia and ptosis due to involvement of 3rd, 4th, and 6th cranial nerves. Orbital apex syndrome occurs due to involvement of optic nerve along with the superior orbital fissure. This leads to impairment of vision. Invasion of the central nervous system occurs due to spread from superior orbital fissure, optic canal, cribriform plate or blood vessels involving spread to cavernous sinus. [7]

Early diagnosis and early initiation of treatment are essential for improving the prognosis in a patient with rhino-orbito-cerebral mucormycosis. The awareness of red flag signs of ROCM (epistaxis, nasal stuffiness, headache, facial and

periorbital pain, loosening of teeth, diplopia, proptosis) is essential for high clinical suspicion of mucormycosis. Diagnosis is by direct microscopic examination using KOH mount. Culture can be done in brain heart infusion agar or sabouraud dextrose agar. Contrast enhanced MRI is preferred over CT scan to know the extent of involvement and staging. [4]

Initiation of antifungal therapy along with strict glycemic control is essential to halt the spread of fungal growth. Monitoring of renal function is essential while administering amphotericin-B. The surgical removal of necrosed tissues is essential as the antifungals can't reach the necrosed tissues which act as a nidus for fungal elements. Aggressive debridement of the paranasal sinuses is done. Turbectomy and palatal resection is advised in necessary cases. Retrobulbar amphotericin B injections are useful in cases with orbital involvement. In patients with no perception of light, orbital exenteration can be done along with debridement of paranasal sinuses. [8]

Although all the complications and sequelae of COVID-19 are not completely clear, there has been a rise in the incidence of secondary infections worldwide. This can be attributed to the decrease in CD4 count and immune compromised state seen in post-COVID patients. Hence they are more prone to fungal infections resulting in the increased incidence of rhino-orbito-cerebral mucormycosis. This explains the incidence of mucormycosis in patients who did not take systemic steroids and those who had judicious use of systemic steroids. However, use of systemic steroids in the treatment of severe COVID disease and association with diabetes mellitus further potentiates this risk of acquiring ROCM and the severity of spread of infection. [9]

Independent of the covid status, the usage of systemic corticosteroids and the presence of uncontrolled diabetes are considerably major risk factors for rhino-orbito-cerebral mucormycosis, it is important to have a judicious use of corticosteroids and perform aggressive monitoring and control of diabetes mellitus for the prevention and management of mucormycosis. [8]

Conclusion

Mucormycosis is an angioinvasive fungal infection which is rapidly progressive in nature. The incidence of ROCM has markedly increased in conjunction with the 2nd wave of COVID. Though the usage of systemic steroids and uncontrolled diabetes mellitus are well known risk factors, the dramatic rise in the incidence of ROCM in association with COVID probably suggests the immune compromised state caused by COVID. Early diagnosis and appropriate management are essential to control the spread of infection and

decrease the morbidity and mortality associated with the disease.

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