

DISCRIPTIVE STUDY OF MUCORMYCOSIS AND COVID 19 IN DELTA REGION, THANJAVUR, TAMILNADU, INDIA.

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Abstract

Background: Second wave of COVID-19 was very severe because of increased incidence of Fungal infections especially Mucor mycosis. This is mainly related to increased usage of Steroids and Oxygen during this wave in the management. Early Endoscopic Debridement and Inj. Amphotericin plays major role in preventing the dreadful complications. Study about the Types of Mucormycosis, Involvement of various Para Nasal Sinuses, Orbital involvement and its association with Steroid Usage, Oxygen Therapy and Diabetes Mellitus and Effectiveness of Earlier Surgical Debridement. Descriptive Study, Analytical Study. **Materials and Methods:** Study was conducted in Government Thanjavur Medical College, Thanjavur, Tamil Nadu, India in Mucor Mycosis ward and ENT Department from May 2021 - July 2021. Total Number of patients are 295. All patients are Evaluated, Processed, and Classified into various types of Mucormycosis. Rhino-Orbital type of cases are taken for Endoscopic Sinus Surgery followed by Amphotericin injection and discharged and followed regularly. **Result:** Mucormycosis of Nose and Paranasal Sinus involvement are large in numbers, followed by Rhino –Orbital Mucormycosis, and Rhino-Cerebral types. Pulmonary, Cutaneous and Intestinal Mucor Mycosis are very few only. Males are more affected. Most of the cases associated with Diabetes. Excellent Recovery and Reduced Recurrence is witnessed in Earlier Surgical Debridement cases than later one. Sino Nasal type of Mucormycosis is large in number. Very early Diagnosis with Suspicious Clinical Symptoms and Signs and Supportive Evidence by Endoscopic and Radiological investigation especially by MRI is very effective in management part. Earlier removal of Dead tissue and Adequate Amphotericin coverage leads to excellent outcome. HPE and Fungal Culture is Essential. Glycaemic Control is essential for Good Results. Steroid use and Oxygen therapy are not having Significant impact in the development of Mucor in our study but commonly associated with western countries. Regular weekly Follow-up, Endo- Clearance, Nasal Douching with Hypertonic Saline and Salvage therapy with Tablet Posaconazole, and Diabetes Management Significantly reduces the Recurrence. **Conclusion:** Earlier Diagnosis and Effective Surgical Debridement and Adequate Antifungal treatment and Good Diabetic Control is the standard protocol of Mucormycosis treatment. Regular Follow-up is important by that Recurrence is minimized.

INTRODUCTION

Mucor mycosis belongs to Zygomycetes family. Common type in Covid-19 is Rhino-orbito-cerebral Mucor mycosis is usually rare incidence only. But when the patient is Immunologically weak the occurrence will be more common. Very commonly affects in Uncontrolled Diabetes especially with Ketoacidosis.^[1]

Route of entry for this fungus was Nose and Paranasal Sinus. It can extend to adjacent vital

regions like Cranial cavity and Orbit and resulting dangerous complications with Grave prognosis. Eschar is a characteristic feature of Mucor. It was due to Angioinvasion of arteries leading to thrombus formation resulting in Necrosis of the soft tissues and underlying bone called as Eschar.^[2] The other group of Zygomycetes was Entomothorales are common in Immunologically strong patients and leads to mild form of fungal infections like Superficial and Mucocutaneous types.

Most commonly the Rhizopus variety is responsible for majority type of infections in Mucoraceae group.

The strong Host defence is produced by Phagocytes against Mucormycosis.^[3] Corticosteroid treatment, patients with pronged period of Immunosuppressant treatment like Renal dialysis, on Chemotherapy treatment affects the ability of macrophages to prevent the germination of spores of Mucormycosis. COVID 19 is a Negative sense RNA virus without segmentation and causes reduction of Lymphocyte count. Extensive endothelial barrier disruption, Dysfunctional Alveolar-Capillary Oxygen transmission and Impaired Oxygen Diffusion Capacity are characteristic features of COVID 19 especially in Second wave.^[4]

Ocular Manifestations of Mucormycosis ranging from Simple Conjunctivitis to restricted eye ball movements, Optic Neuritis and Oculomotor Cranial (III) neuropathies.^[5] Steroids and High Flow Oxygen are very essential in treatment protocol. Steroids suppress the immune system and will lead to increased chances of secondary infections especially fungal infections, latent Diabetes Mellitus, and many adverse effects. Mucormycosis is potentially lethal infection mostly in patients suffering from immunodeficient conditions like Diabetes Mellitus, Leukaemia, and Lymphoma.^[6]

Incidence rate of Mucormycosis worldwide is around 0.005 to 1 per million.^[7] But in India it was about 0.14 per 1000 populations, which was 80 times higher than Developed Countries. Death rate of this condition was about 40% to 45%. But it was very high upto 60-75% when it was associated with high-risk groups like Immunocompromised and Intracranial involvement conditions.

High Clinical Suspect and awareness of Earlier Clinical symptoms like Numbness in infraorbital region, Ptosis and reduced eye ball movement and Diagnostic Nasal Endoscopic findings like Black coloured Eschar is confirmatory of this condition.^[8]

Radiological Investigations like CT and MRI is very important by that the extension of infection can be assessed and planned for Earlier and Forcible Debridement. Histopathological Confirmation and Fungal Culture of the Debrided tissue is always mandatory. Inj. Amphotericin and Salvage therapy with T. Posaconazole are important. Good control of Diabetes and other immunocompromised conditions also equal important in this management protocol.

Objectives:

To Know about

1. Types of Mucormycosis involved,
2. Para Nasal Sinuses involvement,
3. Orbital involvement and Cerebral Involvement.
4. Association with risk factors like Steroid Usage, Oxygen Therapy and Diabetes Mellitus
5. Earlier Endoscopic Surgical Debridement role,

Study Design: Descriptive study, analytical study.

MATERIALS AND METHODS

Study was conducted in Government Thanjavur Medical College, Tamil Nadu, India in

MucorMycosis ward and ENT Department from May 2021 - July 2021. Total Number of patients are 295. All cases are Evaluated by Clinical features, Endoscopic Examination, Radiological Investigation and Prepared for Earlier Surgical treatment after getting various Opinions from Diabetology, Dept of Eye, Neurosurgery, Neuromedicine, Dental Surgery, ThoracicMedicine and Anaesthesia Departments.

Mucormycosis was Classified into Rhino Mucor, Rhino Orbital, Rhino Orbito Cerebral types. Rhino-Orbital Mucormycosis cases alone taken for surgical debridement. Depending upon the extent of infection by Radiological investigation, Surgical procedures are varied from Endoscopic Sinus Surgery, Endoscopic assisted Debridement, ESS with Orbital Decompression, Endoscopic Medial Maxillectomy, and Total Maxillectomy.

Histopathological Confirmation and Fungal Culture are very important for the Initiation of Inj. Amphotericin Post operatively. For Orbital involved cases Amphotericin has to be extended for 2 weeks than the other types of Mucor cases, in the dosage of 5mg per Kg bodyweight per day. Retro Bulbar Amphotericin injection was given for all Orbital involved cases.

All post operative patients are subjected to Diagnostic Nasal Endoscopic Examination after 7 days and Depending upon the finding they are discharged with the Advice of T. Posaconazole 300mg BID for first day followed by 300mg OD daily for 4 to 6 weeks. Weekly Follow up for Regular Endocleaning upto 6 to 8 weeks is made compulsory for all patients.

Recurrence cases are Readmitted and evaluated and revision surgery was performed, some cases underwent Maxillectomy of various types depending upon of the involved walls of Maxillary Sinus.

RESULTS

In this study, [Table 1 and Figure 1] shows the distribution of various types of Mucormycosis. Among the 295 cases 58% of cases around 171 belongs to Rhino mucor followed by Rhino-Orbital 84 cases (28%), Rhino-Orbito-Cerebral Mucor 22 cases (7%), Pulmonary Mucor 15 cases (5%) and Intestinal Mucor 3 (2 %) cases.

[Table 2 and Figure 2] reveals that 78% of cases are Males (212) and the rest are Females 83 cases (28%). Age group of 41-60 years are affected around 197 which was 67 %. Next group was 21-40 years 72 cases (24%), above 60 years 21 cases (7%) and 0-20 years contribute 5 cases (2%), it was explained in [Table 3 and Figure 3].

[Table 4 and Figure 1] shows the Para Nasal Sinus involvement. Ethmoid and Maxillary Sinus are involved in high number of (173) cases. Maxillary Sinus alone involved in 53 cases. Maxillary, Ethmoid and Frontal Sinus are involved in 43 cases. Pan Sinusitis are seen in 26 cases. Bilateral Sinus involvement is more common (179 cases) which was

61% than Unilateral Sinus involvement 116 patients contributing 39%.

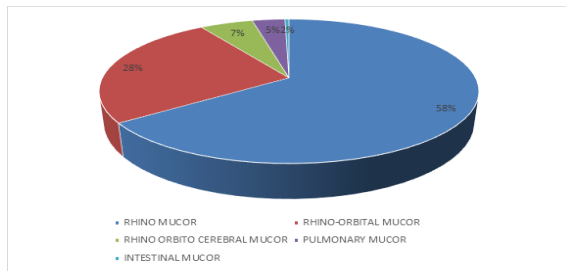


Figure 1: Types of Mucormycosis

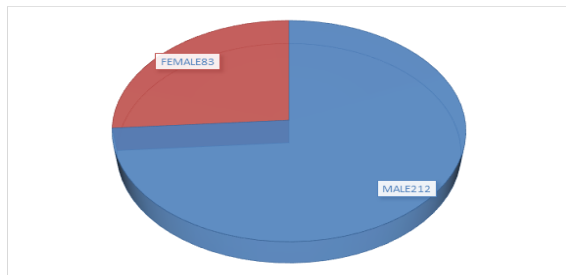


Figure 2: Sex Distribution

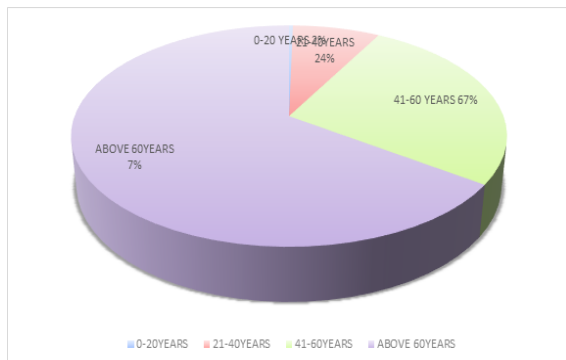


Figure 3: Age Wise Distribution

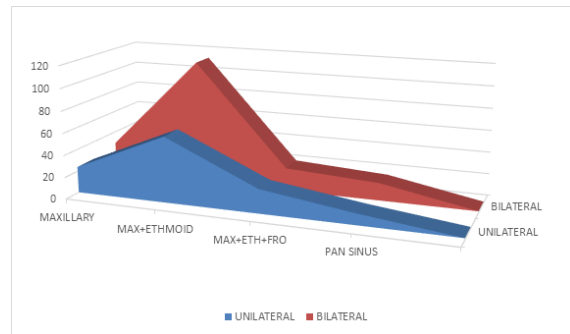


Figure 4: Paranasal Sinus Involvement

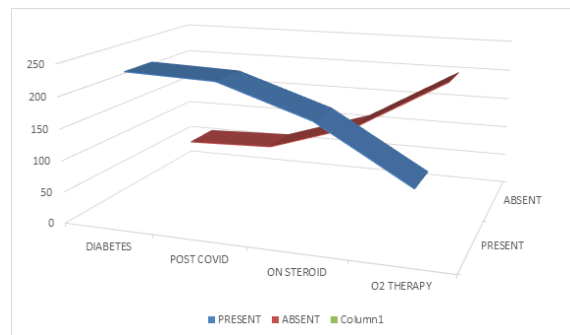


Figure 5: Risk Factors

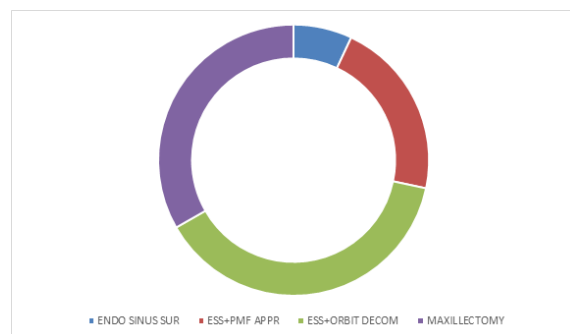


Figure 6: Types of Surgery

Table 1: Types of Mucormycosis

Types of mucormycosis	Number of cases
Rhino mucor	171
Rhino- orbital mucor	84
Rhino-orbito-cerebral mucor	22
Pulmonary mucor	15
Intestinal mucor	3

Table 2: Sex Distribution

Sex of the patient	Number of patients
Male	212
Female	83

Table 3: Age Wise Distribution

Age group	Number of patients
0-20 years	5
21-40years	72
41-60years	197
Above 60years	21

Table 4: PARA Nasal Sinus Involvement

Sinuses	Unilateral	Bilateral
Maxillary	24	29
Maxillary & ethmoid	60	113
Maxillary ðmoid&frontal	22	21
All sinuses	10	16

Table 5: Risk Factors Distribution

Risk factors	Yes	No
Steroid Usage	86	155
Oxygen Treatment	90	151
Diabetes Mellitus	211	30
Covid-19	169	72
Prolonged Immunosuppression	9	232
Covid Vaccination	8	233

Table 6: Types of Surgeries

Types of Surgeries	Number Of Cases
Endoscopic Sinus Surgery	186
Ess Plus Pterygomaxillary Fossa Exposure	25
Ess Plus Orbital Decompression	45
Various Types of Maxillectomy	39

Figure 7: Chances of Recurrence

Early debridement& inj. Amphotericin	Minimal chance
Early debridement & inj. Amphotericin & t. posaconazole	Very minimal chance
Early debridement & without inj. amphotericin	Medium chance
Late debridement & ampho	Medium chance
Regular post op endocleaning	Very minimal chance
Irregular follow up& endo cleaning	High chance
Good glycaemic control	Minimal chance
Poor glycaemic control	Medium chance

[Table 5 and Figure 2] explains about the relationship of risk factors. Strong Positive association with Diabetes Mellitus (231) was Obvious in our study. it was around 78%. 64 patients are having normal Blood Glucose level.

Mucor mycosis are seen in 226 patients with Post Covid infective status, which was 77% of total cases. Non Covid-19 related Mucormycosis (69 cases) contributes 23%. Patient on prolonged steroid usage related mucor cases are 178 (60%). In our study there was Negative Association with Oxygen therapy. Development of Mucormycosis without Oxygen therapy was seen in 203 cases, which was 69%.

Only 15 cases are received Covid-19 Vaccination, and only 7 received both doses. Prolonged Immunosuppressive Therapy related Mucormycosis are seen in 34 cases.

[Table 6 and Figure 6] explains the types of Surgeries performed. Majority of cases underwent Endoscopic guided Sinus surgery in the form of Aggressive Debridement. 186 cases done under this category and it was 63%. Endoscopic Sinus Surgery with Orbital Decompression done for (45 cases). Endoscopic Sinus Surgery with Pterygo Maxillary Fossae Exposure was done for 25 cases. Various Types of Maxillectomies are done for 39 cases.

[Table 7] reflects types various treatment option and expected chances of recurrences. the recurrence chances in various modalities of treatment options. Early Surgical Debridement and Inj. Amphotericin and Salvage Therapy with T. Posaconazole was very effective one by that it has very minimal Recurrence compared to other types of treatment options. Regular weekly Follow up and Endo cleaning has very high cure rate. Good Glycaemic Control is related to low Recurrence. In Contrast Irregular Follow up and without Endo Cleaning, Irregular

Antifungal Treatment and Poor Glycaemic Control Favours High chance of Recurrence.

DISCUSSION

Post Covid, Un controlled diabetes and on prolonged Steroid usage and its association with Mucor was well established in our study. Fungal hyphae were destroyed by the formation of some Oxydative metabolites and Defensins which was derived from Phagocytes. So conditions related with poor or Dysfunctional phagocytic activities such as immunodeficient states vulnerable for severe form fungal infections. Prolonged use of Steroids leads to Lymphopenia affecting more T cells than B cells.

Post COVID-19 infected patients are in a Pro Coagulable state with high risk of Thromboembolic episodes. Angioinvasion of Mucormycosis was hastened rapidly after this Covid. Arterial invasion was more common than venous invasion. Mucor grows along the Internal Elastic Lamina and causes Thrombosis and later on Infarction of the concerned region. Covid-19 leads to Severe Pulmonary disease and subsequent development of Alveolo-Interstitial pathology and increased the risk of Fulminant Fungal infections.^[9]

Orbital involvement can occur after a period of 7 to 10 days. Symptoms are Numbness over Infra Orbital Region, Ptosis, eye ball movement restriction. Because of the empirical use of Antibiotics and Steroids and Oxygen treatment for Covid-19. the possibility of Fungal infection is very high.

Nose is the portal of entry. Adjacent regions are involved by direct spread or by Vascular invasion. Intracranial involvement occurs through Superior Orbital Fissure, Ophthalmic Vessels, Cribriform plate, Carotid artery or through Perineural route.^[10]

The Symptoms of Mucormycosis are Facial pain, numbness, Headache, Periorbital swelling, Nasal Obstruction, Eyelid drooping followed by Ptosis, External and Internal Ophthalmoplegia, Visual Loss and Black Necrosis of Palate and Nasal Mucosa (Eschar). Lamina Papyracea is easily vulnerable for mucor invasion. Later on vision loss by Optic Nerve involvement or Invasion of Retinal Artery.

Intracranial Involvement may occur through the Erosion of Sinus walls, Cribriform plate, Superior and Inferior Orbital Fissures or through Blood stream. Cavernous Sinus Thrombosis also common in Mucormycosis and results in Palsies of Cranial Nerve III, IV, VI, V2, V1.

Computerised Tomography and Magnetic Resonance Imaging are very important to assess the extension and prognosis of the condition. Findings are varying from Opacities of involved Sinuses, Bony Destructions of sinus walls, Alterations of Intra Orbital tissue Signals with or without Focal Mass, Cavernous Sinus Filling defect, Alteration of Meningeal Signal.

It was confirmed by Blackish Necrotic Eschar in nasal cavity and Palatal region, which was confirmed by Histopathological Examination and Fungal Culture. Stains used for Confirmation of Mucor are Eosin and Haematoxylin, Periodic-Acid-Schiff (PAS), and Gomori Methenamine Silver (GMS) stain.^[11]

HPE reveals Broad Non Septate hyphae with right angle branches, Necrotizing granulomatous inflammation, and Vasculitis together with the presence of mucor hyphae within the Vessel wall or Lumen.

Posterior group of Ethmoidal Sinuses and Sphenoid sinus involvement are more prone for Orbital Apex related problems. Mortality was increased in intracranial involved cases. Early suspicious of symptoms, Diagnostic Nasal Endoscopy, Control of the risk factors, Aggressive Debridement of Necrotic Tissues, Appropriate Systemic and Oral Antifungal Therapy and Regular PostOperative Follow up and EndoCleaning. Systemic Amphotericin with its Liposomal Formulation is the drug of choice followed by Step-Down therapy with Oral Antifungal T. Posaconazol. This regime significantly improves the survival rate.^[12] Irrigation of Involved sinuses with Diluted Amphotericin solution and also with Hypertonic Saline wash also supportive one.

Orbital Exenteration is the treatment of choice for Intra orbital involved cases and with Extensive intra ocular necrotic tissues. Retro Orbital Amphotericin Injection also effective if it was started earlier.

Pterygo Maxillary Fossae exposure and removal of Necrotic tissues are very important when the disease spreads beyond the Posterior wall of Maxillary sinus and extends to Infra Temporal Fossae. Fat tissues in PMF are totally necrotic and the space filled with purulent discharge and most of the time the Internal Maxillary Artery found as Cord like Structure due to Thrombosis. Proper ligation of that

major vessel is Mandatory to avoid unnecessary Post Operative complications like massive Bleeding.

In our study, many cases presented with Isolated Necrosis of Anterior part of Middle Turbinate and Posterior part of Middle Turbinate due to involvement of Anterior and Posterior Ethmoidal Artery respectively. Some cases are presented with necrosis of Posterior end of Septum due to involvement of Posterior Septal branch of Sphenopalatine Artery.

Various types of Maxillectomies are carried out depending upon the wall of Maxillary sinus involved. Endoscopic Medial Maxillectomy (Denker's Procedure), Extended Medial Maxillectomy, Sub Total Partial Maxillectomy, and Total Maxillectomy.

CONCLUSION

Uncontrolled Diabetes Mellitus and Post COVID_19 status and Prolonged Steroid usage was having strong correlation with mucor was clearly confirmed in our study. Oxygen usage in treatment of Covid-19 and further development of Mucormycosis is not proved in our study.

Ethmo Maxillary component involvement are more common. Bilateral involvement is more common. Endoscopic Sinus Surgery with debridement is the most common procedure in our study than other types like Orbital Decompression or Maxillectomy.

Early Diagnosis with Clinical findings, Supportive Evidence by Radiological Imaging followed by Aggressive Endoscopic Sinus Surgery with Debridement and Histopathological Confirmation and Fungal Culture, followed by Injection Amphotericin and Salvage Therapy with T. Posaconazole results in Excellent outcome.

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