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"Incidence, Clinical Profile, Treatment Protocol and Outcome of Rhino-Maxillary Orbital Mucormycosis in Government Medical College Hospital, Nizamabad, Telangana, India: A Prospective Study and Mini – Review of Literature"

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Abstract:

Introduction: mucormycosis (ROCM) is a aggressive infection and in patient with co-morbidities, the mortality rises upto 50%. Rhino-orbitocerebral mucormycosis (ROCM) is the more common in patients with poor diabetic control and usually manifests itself as nasal stuffiness, nasal discharge, facial pain. Eye signs involve opthalmoplagia, proptosis and in advanced stages loss of vision.

Material & Methods:

This is a prospective, cross-sectional study involving patients who reported to our centre and those patients who were referred from other hospital for treatment of mucormycosis during the second of COVID-19 during april – june 2021.

Results:Majority of the patients were above 50 years of age and the most common co-morbidity was diabetes. Maxilla was more commonly involved than mandible. Posaconazole along with surgical debridement effectively controlled the disease process. All the patients were disease free at 6 months follow up

Discussion: Combined team work, creating a task force team for mucormycosis, effective anti-fungal therapy along with surgical debridement played a key role in management of mucormycosis with no recurrence. Control of co-morbidities remained as part of the patient care and has helped in control of the disease process and prevention of secondary infections.

Introduction:

Mucormycosis is an aggressive, acutely infective opportunistic granulomatous fungal infection caused by fungi[1,2,3]. These fungi belong to class Zygomycetes, order Mucorales and family Mucoracae[3]. COVID -19 poses a big challenge to the health care workers and their infra-structure across the globe. The virus has taken the world by surprise causing wide spread loss in terms of health, infra-structure, economy and development. The development has slowed-down if not paused by this pandemic. COVID-19 patients afflicted with mucormycosis are specifically seen in patients with immunocompromised conditions. Diabetes mellitus, neutropenia, severe trauma, immunosuppression following transplantation are few of the predisposing factors for mucormycosis[4,5,6,7].

Rhinoorbitocerebral mucormycosis (ROCM) is a aggressive infection and in patient with co-morbidities, the mortality rises upto 50%. In COVID patients, the pathophysiology is mainly dictated by a) markedly raised proinflammatory CD4 T cells and CD8 toxic granules b) cytokine surge c) hemoglobinopathy and hypercoagulable state d) increase in iron overload due to disturbed iron metabolism[8,9,10,11]. Mucor is an angiotrophic fungus and invades to cause thrombosis and endothelial damage. Since thrombosis is the hallmark of mucormycosis, platelets play an important role in the innate immunity against the fungus. Fungus on the skin/mucosa present on the basement membrane with the aid of laminin interacts with the endothelial cells through GRP78 receptor which facilitates fungal endocytosis. The fungal ligand which helps in binding the GRP78 during early invasion of mucor is CotH3[12,13].

Rhino-orbitocerebral mucormycosis (ROCM) is the more common in patients with poor diabetic control and usually manifests itself as nasal stuffiness, nasal discharge, facial pain. Eye signs involve opthalmoplagia, proptosis and in advanced stages loss of vision. As the fungus involves dento-alveolar complex and the maxillary bone, multiple draining sinuses from the gums, loosening of the teeth, bad oral hygiene are evident. Infact, the entire segment or the dento-alveolar complex becomes mobile and patients complain of difficulty in chewing and swallowing.

Diagnosis is relatively simple and easy for mucor cases post covid-19. This is mainly because of the fact that almost all of the patients had history of COVID-19, poor diabetic status, 3-5th decades of life and history of oxygen support during COVID-19 treatment. Careful clinical examination and history will reveal blackish “eschars”, multiple draining sinuses, nasal congestion and headache along with mobility of teeth. Tissue Biopsy remains to be the “Gold Standard” for confirmation of diagnosis. 10-20% KOH staining gives relatively quick results. Though conventional radiographs help in detection of the disease, CT scan involving facial bones and sinuses aids in effective treatment planning, the progress of the disease and the structures involved precisely. Early diagnosis, combined medical and surgical intervention and correction of co-morbidities is the key for effective treatment and reducing the morbidity involved. Complications involve intra-cranial spread, need of orbital exenteration and dissemination to distant organs.

Material & Methods:

This is a prospective, cross-sectional study involving patients who reported to our centre and those patients who were referred from other hospital for treatment of mucormycosis during the second of COVID-19 during april – june 2021. Every patient was screened by the mucormycosis task force team

which involved specialists from General Medicine, ENT, Maxillofacial Surgery, Neurosurgery, Opthalmology. The cases were admitted in the mucor ward after initial examination and CT scan interpretation. All the patients were evaluated by the same team members and data recorded in the case sheets. Treatment planning was done and executed through an inter-disciplinary committee headed by the Superintendent of the hospital. Total number of patients admitted, screened were recorded in a data sheet. Patients receiving anti-fungals, patients undergoing FESS (functional endoscopic sinus surgery) and those undergoing maxillectomy as primary or secondary surgery were recorded. Intra-oribital injections given for patients with extra-ocular muscle involvement were recorded and progress monitored.

The total incidence, patients with co-mobidities, primary involvement of the jaw, type of surgery performed is analyzed and displayed and discussed in the present study.

Inclusion Criteria:

1. All patients who were presented with signs and symptoms of mucormycois during april to July 2021
2. All patients screened for covid-19 with oral, nasal and ophthalmic involvement of the disease process
3. Patients who were treated for mucormycosis at a different centre and referred to our centre for anti-fungal treatment and/or surgical intervention

Results:

As shown in figure 1, out of 257 patients screened, 129 patients were confirmed with manifestations of mucormycosis. Figure 2 shows that majority of patients (128 out of 129) had maxillary involvement and only 1 patient had mandible involved. Figure 3 shows distribution of diabetic status (Hb1Ac) values. 19 patients had Hb1Ac value between 6-9, 93 patients had in the range of 10-14 and 17 patients had values above 15.

Figure 4 shows patients distribution according to age group. Majority of the patients were in the age group of 51-65 (62 patients), followed by 47 patients in the age group of 36-50, 14 patients above the age of 65 years and only 6 patients were in the age group of 21-35 years.

Figure 5 shows the type of surgery perfomed primarily. 80 patients underwent FESS (functional endoscopic sinus surgery) alone, 41 patients underwent FESS followed by maxillectomy. For 8 patients, maxillectomy was the only mode of treatment and 12 patients underwent maxillectomy followed by FESS.

Figure 6 shows treatment done for orbital involvement patients. For 23 patients, retrobulbar amphotericin injection was given, 1 patient underwent orbital exenteration and 18 patients were treated by orbital floor exploration during FESS surgery or during maxillectomy procedure such that the globe was preserved.

Discussion:

Mucormycosis is an uncommon life-threatening fungal infection primarily involving immunocompromised or trauma patients. Due to its intrinsic ability to invade blood vessels, the fungus causes thrombosis and ischaemia to the region affected[14]. As stated by Jose A *et al.*, thrombosis is the hallmark of mucormycosis and platelets play an important role in the innate immunity against the fungus[8].

In patients with hyperglycemia (without ketoacidosis), due to defective innate Immunity defective, there is inhibition of neutrophil migration, chemotaxis and decreased phagocytosis.

Further, the inhibiting of the action of iron sequestering proteins and upregulation of GRP78 and CotH3 ligand which is present on the endothelial cells of blood vessels causing increased load of free iron. This free iron acts as a rich medium for the growth of fungus.

For patients with diabetes with ketoacisosis, there is 50% more probability of mucormycosis[15]. According to Sen M et al., in their expedited publication, corticosteroids also precipitate hyperglycemia and Diabetic ketoacidosis. Hyperglycemia causes glycosylation of transferring and ferritin and reduces iron binding. By reducing the ability of transferring to chelate iron, acidosis presents an additive effect causing an overall increase in free iron levels, thereby allowing the mucor to thrive[15]. According to AcCarthy M *et al.,* predisposing factors such as corticosteroid therapy should be discontinued, and blood sugar must be controlled restrictevely[16]. Garg D *et al.* ,in their systemic review stated that multiple risk factors along with the additional immunosupression caused by glucocorticoids predisposes to invasive mold infections[17]. Kumar M *et al.,* in their study mentioned that the indiscriminate use of steroids, antibiotics and zinc as a self-medication during COVID-19 pandemic have promoted the dysbiosis of gut thereby inducing immune-suppression and making the risk group highly susceptible to this mycotic disease[18]. Alom Shahnaz *et al.,* in their comprehensive review on mucormycosis and its association with COVID-19 stated that the most common risk factor for mucormycosis in Asia is diabetes mellitus while in North America and Europe, organ transplant and hematological malignancies are the common risk factors[19,20,21,22,23]. Few leading national newspapers reported that water used for oxygenation regularly in COVID-19 patients, use of sterile cannula and oxygen masks must be examined very carefully to prevent the entry of mucormycosis[24]. In the present study also, majority of the patients were diabetics with Hb1Ac values above 10. Most the studies have not reported the age group affected with mucormycosis. In our present study, we have distributed the patients affected with mucormycosis according to age group. Majority of the patients (more than 2/3rds of the patients) were above 50 years of age. This explains lowered immune response, diabetic status with increasing age as a causative factor for mucor post COVID-19.

Sen M *et al.,* in their expedited publication stated that there is no formal staging system for the disease and no evidence based protocol for the management of this condition, leaving medical teams grappling in an unchartered territory[15]. However, during the outburst of mucor during COVID pandemic, many institutions have devised their own staging and classifications according to their convenience and as a guide for diagnosis and treatment planning. Almost all of these staging and classification systems are based on the involvement of eye signs, superior extension into the cranium and the extent of surgical debridement and surgery dictated. This statement is based on the several webinars and clinical discussions attended by the team of authors involving different specialties in this manuscript.

Corzo-Leon *et al.,* proposed an algorithm for the diagnosis and treatment of rhino-orbito-cerebral mucormycosis in patients with diabetes mellitus[25]. The red flags/warning signs in this algorithm are cranial nerve palsy, diplopia,sinus pain, proptosis,periorbital swelling,orbital apex syndrome or a palatine ulcer.any of these signs must prompt the clinician for immediate further testing and initiation of anti-fungal therapy and to devise a surgical protocol. Definitive diagnosis is based on examination of histopathological specimens for fungal hyphae. It aids in differentiating mucor from Aspergillus species due to its wide and acute angle branching septae[26]. Moreover, histopathology gives a clear picture whether vessels are invaded – angioinvasion.KOH wet mounts is a rapid and inexpensive method to demonstrate fungus. Though it does not

differentiate the species of fungus, it is of high importance intra-operatively to demonstrate clear margins during surgical resection. Blood cultures are rarely positive[2]. Development of quantitative polymerase chain reaction (PCR) systems is still evolving and may enable more rapid diagnosis[27].

Treatment for mucormycosis is both medical – anti-fungal therapy combined with aggressive surgical debridement and in advanced cases resection. Amphotericin B 5mg/kg body weight in divided doses is the drug of choice[15,19,28,29]. Due to its nephrotoxic potential, liposomal form (LAMB) is preferred. FDA has approved posaconazole (POSA) for treatment of mucormycosis[30,31]. Due to acute shortage of LAMB during the pandemic, POSA was used as an alternate drug. Oral tablet form in the dosage of 800 mg daily in divided doses by oral route is more preferred than the suspension since it has better higher absorption potential. In our case series, all the patients were administered POSA in oral form. The dosage continued till the sequential CT scans were disease free post-surgery on a weekly review upto three months. Patient compliance was good and none of the patients had recurrence. Deferasirox, an iron chelating agent has also been widely mentioned in the literature with promising results. However, we have confined our protocol of treatment to POSA and surgical management. However, for patients with extra-ocular muscle swelling/involvement and patients with orbital floor involved, LAMB was instituted as a peri-orbital injection in the recommended dosage of 3.5 mg diluted in 10 ml saline.

Surgical management in our cases involved a functional endoscopic sinus surgery (FESS) followed by surgical resection in indicated cases. Majority of our patients had the indication of FESS alone as the patients were referred at an early stage of disease and treatment was instituted at the earliest. This along with aggressive control of co-morbidities have effectively controlled the disease and reduced the morbidity involved with salvage surgery. Those patients who had undergone partial to sub-total maxillectomy also had good response and remained disease free at six months follow up. Similar to cases reported in literature, mandible was remotely involved and the only patient who had presented with mandibular osteomyelitis has undergone sequestrectomy and primary closure with and uneventful recovery.

Combined team work, creating a task force team for mucormycosis, effective anti-fungal therapy along with surgical debridement played a key role in management of mucormycosis with no recurrence. Control of co-morbidities remained as part of the patient care and has helped in control of the disease process and prevention of secondary infections.

Conclusion:

1. Majority of the patients were above 50 years of age and the most common co-morbidity was diabetes
2. Maxilla was more commonly involved than mandible
3. Posaconazole along with surgical debridement effectively controlled the disease process
4. All the patients were disease free at 6 months follow up

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Figure 1: Incidence of Mucormycosis

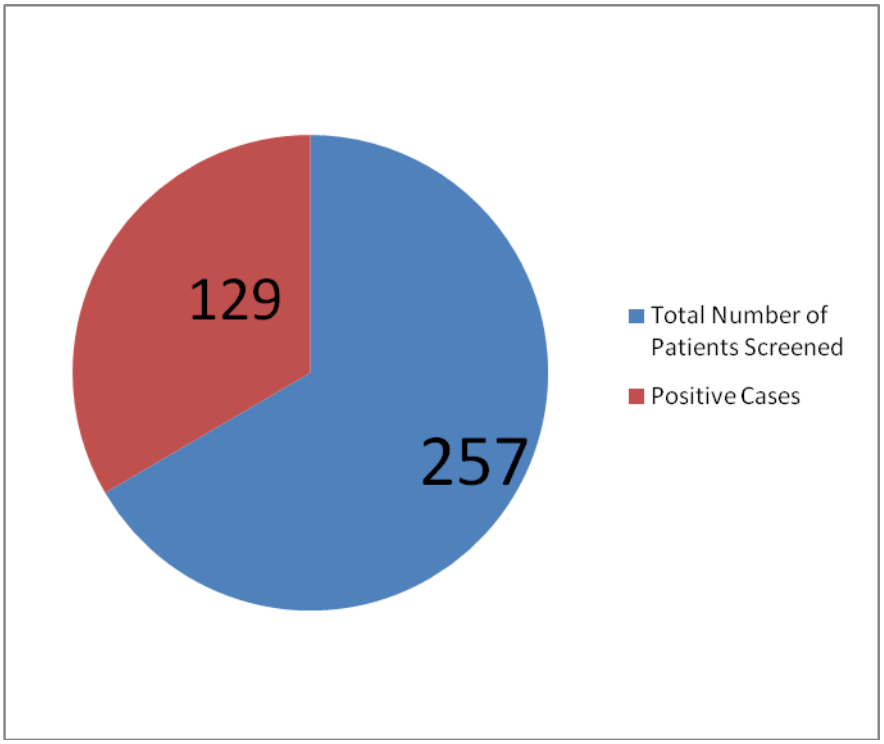

Figure 2: Distribution of patients according to the site involved

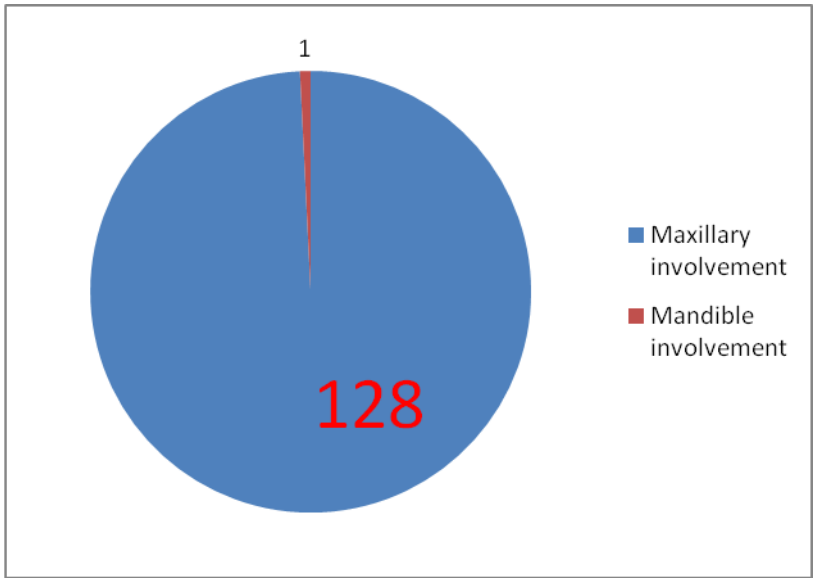

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Figure 3: Distribution of patients according to Diabetic status

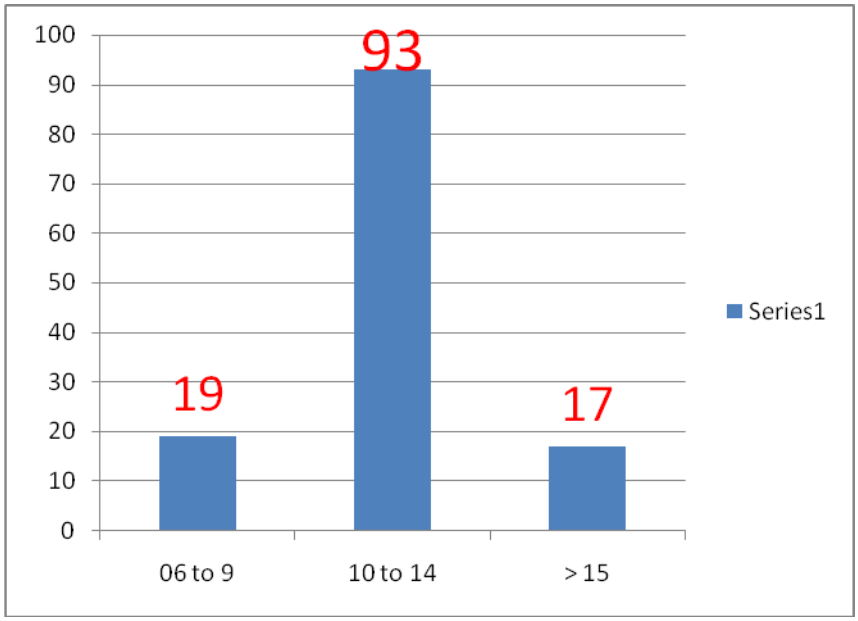

Figure 4: Distribution of Patients according to age group

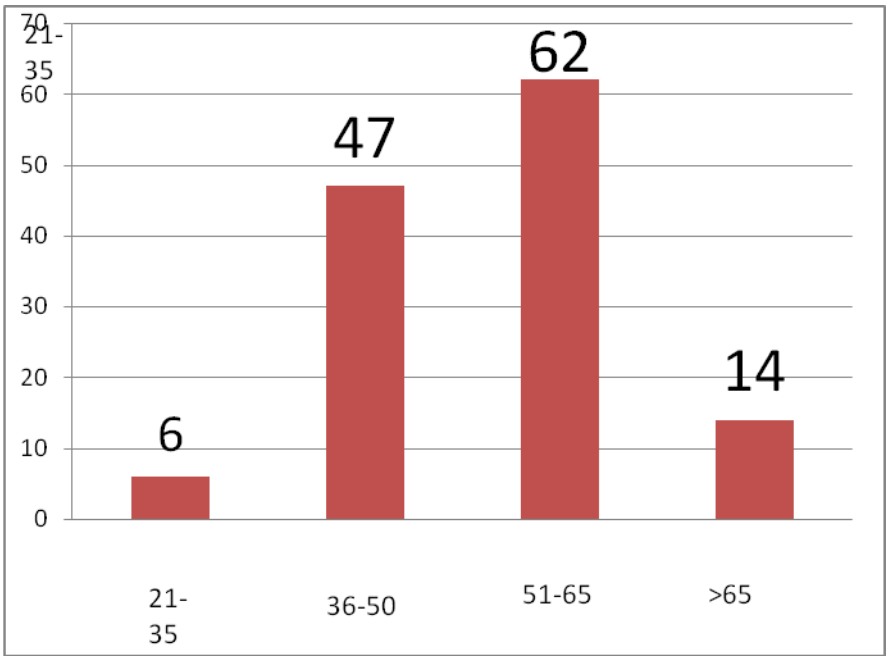

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Figure 5: Distribution of Patients according to type of surgical procedure

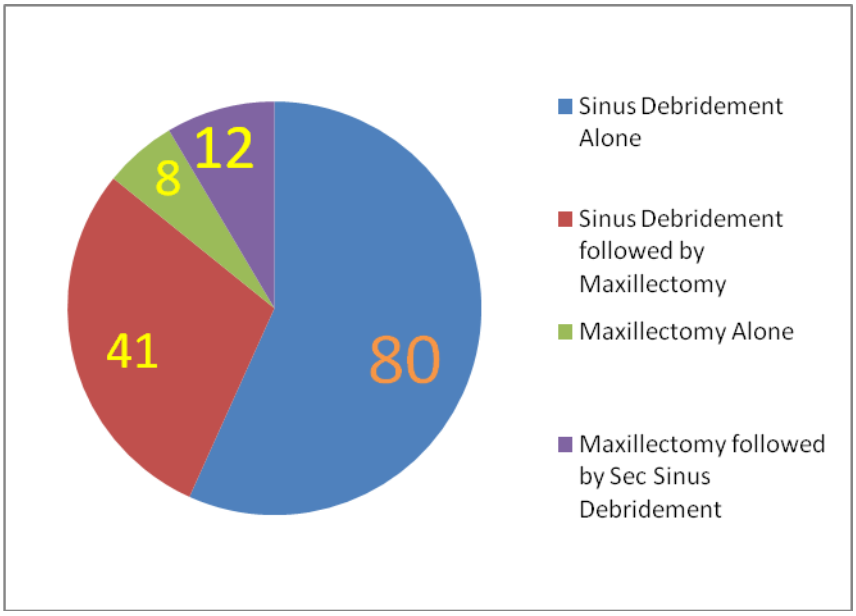

Figure 6: Distribution of Patients according to orbital involvement