

Original Research Article

Rhino-orbital mucormycosis during COVID-19 pandemic: our clinical experience

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ABSTRACT

Background: The ongoing COVID-19 pandemic declared by the WHO was compounded by the sudden and unexpected increase of Rhino-orbital mucormycosis infections during the year 2021. Mucormycosis a life-threatening infection, with added COVID-19 infection further increases the morbidity and mortality of the disease. Our aim is to shed some light on possible risk factors, treatment options and outcomes when these diseases occur together.

Methods: 22 cases diagnosed with rhino-orbital mucormycosis with history of COVID-19 infection were selected. Cases underwent surgical and medical management. Patients were followed up for 3 months and were continued on medical treatment and regular post-operative DNE, CECT PNS and brain and relapses were treated accordingly.

Results: Of these 22 patients, 15 were males and 7 were females ranging between 31-60 years. 15 (68.18%) had history of DM, 16 (72.72%) gave history of oxygen therapy and 18 (81.82%) had history of high dose steroid therapy. 15 (68.18%), 4 (18.18%) and 3 (13.64%) respectively underwent Endoscopic debridement, Total maxillectomy and Medial maxillectomy. There were 3 cases of relapse which were managed with additional full course treatment with Intravenous Liposomal Amphotericin B.

Conclusion: COVID-19 and uncontrolled DM to both be probable pre-disposing factors for developing Mucormycosis. Oxygen therapy & high dose of steroids used in the treatment of COVID-19 may increase incidences of mucormycosis. Early treatment with surgery is necessary to reduce the need for more radical procedures and improving the recovery.

Keywords: COVID-19, Mucormycosis, Rhino-orbital-cerebral mucormycosis, COVID-19-associated ROCM

INTRODUCTION

COVID-19 is caused by SARS-COV-2 virus. It presents with varying severity ranging from asymptomatic cases to those requiring ICU admission.¹ It has been associated with opportunistic fungal infections like aspergillus, candida and mucormycosis. COVID-19 results in immunosuppression, which when combined with treatment with steroids, diabetic status of the patient and hypoxia, leads in increased risk of infection with mucorales.²

Based on tissue invasion, fungal sinusitis has been classified as follows: Tissue invasion: Invasive; Acute fulminant, Chronic invasive and Chronic granulomatous. Non invasive; Saprophytic fungal infestation, Fungal ball and Fungal related eosinophilic. Invasive fungal sinusitis is defined as the presence of fungal hyphae within the mucosa, submucosa, bone, or blood vessels on histopathology. Misdiagnosis or delayed diagnosis of this condition results in higher morbidity and mortality. Mucormycosis is an angioinvasive disease caused by

mold fungi of the genus *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella* and *Absidia* of Order- Mucorales, Class- Zygomycetes.³ The *Rhizopus Oryzae* is most common type and responsible for nearly 60% of mucormycosis cases in humans and also accounts for 90% of the Rhino-orbital-cerebral (ROCM) form.⁴ Mode of contamination occurs through the inhalation of fungal spores.

Mucormycosis is caused by mucorales. It can present as rhinocerebral, pulmonary, cutaneous, orbital and other manifestations. It was first described in 1876. 38 species have been associated with human infections out of which most common causative species is *Rhizopus arrhizus*. Some other fungi responsible for human infections are *Lichtheimia*, *Mucor*, *Rhizomucor*, *actinomucor* etc.⁵ Although incidence of mucormycosis is rare, COVID-19 infection predisposed individuals to fungal infection, hence, drastically increasing the incidence. Rhino-orbital-cerebral mucormycosis was the most common presentation of post covid mucormycosis.⁶ Mucormycosis being a life threatening infection on its own; the added burden of COVID-19 infection further increases the morbidity and mortality of the disease. Differentiating between the various types of fungal sinusitis, along with early identification of the aggressive fulminant type, are crucial to the management of patients with invasive fungal sinusitis. To improve the outcomes of invasive fungal sinusitis, several factors require to be addressed. Medical personnel education and training to achieve early diagnosis of disease and multi-disciplinary management, forms the crux of successful resolution of disease. Meticulous infection control practices, policies to control infection during construction and renovation of hospitals and early recognition of nosocomial outbreaks might be beneficial as well. Current study explains our clinical experience with COVID-19 and rhino-orbital mucormycosis and aims on determining the possible risk factors, treatment options and outcomes of the disease during the current global pandemic scenario.

METHODS

It was a prospective study conducted from March 2021 to October 2021. Cases diagnosed with rhino-orbital mucormycosis and having a previous history of COVID-19 infection confirmed by RTPCR testing and who underwent treatment in a rural hospital in Davangere, Karnataka were included in the study. A total of 22 patients were included in the study. Patients underwent thorough history taking and examination. Details regarding previous COVID-19 infection were noted. All patients were diagnosed as rhino-orbital mucormycosis through KOH mount taken from nasal cavity and Contrast Enhanced Computed Tomography of Paranasal sinuses (CECT PNS) and Brain. Once the patients were suspected of the disease they were started on intravenous Liposomal Amphotericin B at a dose of 5 mg/kg/day.⁷ All patients underwent surgical management depending on the extent of the disease spread. Surgery was performed endoscopically for unilateral involvement and open

approach was taken for bilateral involvement of the sinuses/bones/orbit. Post surgery confirmation of the diagnosis was done by histopathology and fungal culture from the intraoperative samples. Post operatively the patients were continued on intravenous Liposomal Amphotericin B, for 2 weeks, to achieve a cumulative dose of 4000 mg, blood samples were drawn regularly to check on serum sugar and serum potassium levels. Any Adverse Drug Reactions (ADRs) during the duration of treatment during the recovery/follow-up phase were documented and corrected accordingly. Patients were followed up for a period of 3 months during which they were continued on Tab Posaconazole 200mg for 2 months, along with regular post-operative DNE (Diagnostic nasal endoscopy), CECT PNS and Brain. Relapses were treated accordingly.⁷ Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

RESULTS

During this study, a total of 22 patients were diagnosed to have ROMC (Rhino orbital mucormycosis) post COVID-19, and underwent treatment for the same. Of which 15 (68.18%) were males and 7 (31.82%) were females. The minimum age was 37 years and maximum age was 60 years. The average duration of hospital stay was 25 days. Of these patients, 15 (68.18%) were found to have been known cases of Diabetes Mellitus (DM) and 2 of these patients were also known cases of Hypertension (HTN) on treatment. The diabetic patients were all found to have high sugar levels upon admission. There were 7 patients who didn't have any co-morbidity. Total 16 (72.72%) of the cases gave a history of receiving oxygen therapy and 18(81.82%) gave history of receiving high dose steroid therapy as a part of their COVID-19 treatment regimen in various hospitals. Among the 4 patients that didn't receive any steroid therapy only 1 didn't have any co-morbidity and the other 3 were known cases of DM. And among the patients that didn't receive oxygen therapy only 1 patient didn't have any co-morbidity, with the rest 5 patients having history of DM. Among the various symptoms the patients had presented with the most common symptoms were facial pain and facial swelling followed by eye pain and eye swelling, 16 (72.72%) and 12 (54.54%) respectively. The other presenting symptoms were headache, dental pain and vision disturbances. All the patients had paranasal sinus involvement with 13(59.1%) having unilateral and 9(40.9%) having bilateral involvement. 19 (86.36%) of these 22 patients also had unilateral orbital involvement and 7 (31.82%) had involvement of the hard palate. The patients had undergone various methods of surgical management, with 15(68.18%) undergoing Endoscopic debridement, 4

(18.18%) undergoing Total Maxillectomy and 3 (13.64%) undergoing medial maxillectomy.



Figure 1: A) Preoperative picture of patient A with right RCOM with palatal involvement; B) Preoperative image of patient A showing the palatal involvement; C) Immediate post operative picture of the patient A after open procedure; D) Patient A, after 2 months on follow-up, came for fitting for prosthesis.



Figure 2: A) Pre operative picture of patient B with left RCOM; B) Post operative followup picture of patient B at 2 months after undergoing endoscopic surgery.

Among 19 patients that had orbital involvement, 4 (18.18%) had to undergo orbital decompression along with the above-mentioned procedures. Also 4 patients required further debridement intraoperatively, with, 2 (9.09%) requiring Infratemporal endoscopic exploration and another 2 (9.09%) requiring pterygoid fossa exploration. During the hospital stay in the post op period only 1 patient had developed desaturation during the

immediate post operative period. This patient required ICU care for 3 days following which the patients' condition improved and was continued with the treatment in wards. All patients were continued on intravenous Liposomal amphotericin B post operatively as the main stay of treatment. Following Injection amphotericin B, 10 patients (45.45%) developed itching, erythema of skin, 11 patients (50%) developed hypokalemia for which correction was necessary. On discharge patients were put on Oral Posaconazole tablets 200 mg.

DISCUSSION

During the second wave of the COVID-19 pandemic in the year of 2020, there was an unexpected increase in the number of associated Mucormycosis. This had put an immense pressure on the health system of the country. Hardeep Singh Malhotra et al had proposed a guideline for diagnosis and classification of mucormycosis, as follows; Possible ROCM, Typical symptoms and signs in appropriate clinical setting, but No supportive evidence on diagnostic nasal endoscopy and/or GAD-MRI/CT scan.¹² Probable ROCM; Clinical supportive evidence, plus; Supportive diagnostic nasal endoscopy and/or GAD-MRI/CT scan and But no evidence on direct microscopy or culture or histopathology. Definite ROCM; Clinical supportive evidence, plus; Supportive diagnostic nasal endoscopy and/or GAD-MRI/CT scan; Plus and Confirmation on direct microscopy or culture or histopathology. In our study, the cases were among the Definitive ROCM category, these patients once clinically suspected of mucormycosis, underwent a CECT PNS and Brain, DNE and swab was taken for KOH mount. The patients suspected of RCOM were immediately started on intravenous Liposomal Amphotericin B, at a dose of 5 mg/kg/day. The patients underwent surgery and the intra operative specimens were sent again for a confirmatory culture. They were continued on intravenous liposomal amphotericin B for 2 weeks to achieve a cumulative dose of 4000 mg, and continued with Tab Posaconazole 200 mg upon discharge for 2 months.

In this study, a total of 22 cases were diagnosed and underwent treatment for mucormycosis. Amongst these, most of the cases were within the age group of 41-51 (15 cases), with the extremes of age being 37 years and 60 years. Along with this, it was also observed that most of these cases had other preexisting co-morbidities such as DM (15 cases) and HTN (2 cases) along with all of them being diagnosed as COVID-19 positive via RTPCR tests. This does show a probable risk factor of cases with co-morbidities. Especially uncontrolled DM to be was found to predispose to development of Mucormycosis. This is in line with most other studies done during this study as mentioned by Sen M et al.⁸ Mucor being able to produce Keto-reductase, helps it to grow in an acidic and glucose rich environment. This supports the claim that, DM could be a probable risk factor in these cases.⁹ The most common presenting symptoms in these cases was facial pain and facial swelling in 16 (72.72%) cases, followed

by eye pain and eye swelling in 12 (54.54%) cases and headache in 11 (50%) cases. The other presenting complaints were dental pain and vision disturbances. This vagueness of presenting symptoms shows that there is a high grade of suspicion needed for identifying and diagnosing of these cases. In the patients that we had operated, it was also noted that a majority of these patients had received high dose steroid therapy (18 cases, 81.82%) as a part of COVID-19 treatment protocol. This might have resulted in immunosuppression. Also, several patients had history of receiving oxygen therapy (16 cases, 72.72%). This could also be a probable risk factor. This was also supported by the study done by Ge Song et al.¹⁰

Out of these 22 patients, all 22 of them had PNS involvement, with 13 patients having unilateral and 3 patients having bilateral involvement. Several patients had other involvements or manifestations; 19 patients had unilateral orbital involvement, 7 patients had involvement of the hard palate and 2 patients had intracranial involvement. These patients had undergone surgical management depending on the manifestations. 15 (68.18%) patients underwent Endoscopic debridement, 3 (13.64%) patients underwent Medial Maxillectomy. Among the 19 cases with orbital involvement, 4 (18.18%) cases required Orbital Decompression. In cases which had extensive disease, Total Maxillectomy; 4 (18.18%) cases, Infratemporal endoscopic exploration; 2 (9.09%) cases) and Pterygoid fossa exploration; 2 (9.09%) cases were performed as deemed necessary. Thus, an early diagnosis and management would be advantageous in reducing the need for radical procedures. During the hospital stay in the post op period only 1 patient had developed desaturation during the immediate post operative period. This patient required ICU care for 3 days following which the patients' condition improved and was continued with the treatment in wards. The average duration of the hospital stay among these patients was found to be 25 days, showing a need for long term hospital stay needing a multi-specialty support team.

Post operatively the patients were continued on intravenous Liposomal Amphotericin B, for 2 weeks, to achieve a cumulative dose of 4000mg. Step down to Tab Posaconazole 200mg was done after this as part of Early Step-down therapy.⁷ During this duration of treatment some of the patients had developed ADR to the drug. As hypokalemia is one of the most common side effects of Amphotericin B, daily serum potassium was done during the therapy. 11 patients (50%) developed hypokalemia for which correction was necessary. 10 patients (45.45%) developed itching and erythema of skin which was managed with antihistamines. All the cases were kept on close follow up for duration of 3 months during which the patients were continued on Tab Posaconazole 200mg and repeat CECT PNS and Brain were done. There were 3 cases of relapse among these cases during the 3 month follow up period, which were managed with additional

full course treatment with Intravenous Liposomal Amphotericin B.

According to our experience during this pandemic, especially during the 2nd wave, we have found that, COVID-19 and uncontrolled DM are both probable pre-disposing factors for developing Mucormycosis. The high dose of steroids used in the treatment protocol of COVID-19 also seems to cause immunosuppression leading to increase incidence of mucormycosis among these patients. Oxygen therapy received during the COVID-19 treatment may also be a probable exposing factor when the humidifier is filled with portable water instead of sterile water. Due to the vague nature of the symptoms that the patient presents with, there should be a high degree of suspicion for the diagnosis of mucormycosis. Getting investigations like KOH mount of nasal swab and CECT PNS can help in early diagnosis of the same. Due to the rapid development of the disease which increases the morbidity and mortality, early treatment in the form of surgery is necessary to reduce the need for more radical procedures and improving the recovery. Post operative treatment with Inj Amphotericin B and early step down to oral medications also help in reducing the duration of hospital stay. During the treatment there should be a vigilant look out for any ADRs with intravenous Amphotericin B, especially Hypokalemia, which should be treated as soon as possible. The patients should also be kept on long term follow up to check for relapse cases using follow-up CECT scans.

Limitations

The main limitation that we found in this study was the low number of cases that took part, but considering the rare combination of both COVID-19 and ROCM occurring together in such a large number in a rural area, this limitation is quite expected. One of the other limitations would be the lack of long term follow up after 3 months' time, to assess the long-term effects of the disease and the probable psychological effects of the deformities to the patient caused by the disease.

CONCLUSION

COVID-19 and uncontrolled DM to both are probable pre-disposing factors for developing Mucormycosis. Oxygen therapy & high dose of steroids used in the treatment of COVID-19 may increase incidences of mucormycosis. Early treatment with surgery is necessary to reduce the need for more radical procedures and improving the recovery.

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