Original Article

Post COVID-19 Rhino-Orbito-Cerebral Mucormycosis : Retrospective Clinical Observational Study & Analysis of the Patients Presenting in Kheda District, Gujarat, India

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Background : Mucormycosis is a rare, life threatening fungal infection having an increased incidence during this COVID-19 pandemic, especially in the second wave in India. The state of Gujarat leads in the number of rhino-orbito-cerebral mucormycosis cases Post COVID-19 infection.

Aims and Objectives : Rhino-orbito-cerebral fungal infections are being reported as a post COVID-19 sequelae. This observational study explores correlation between mucormycosis, diabetes-mellitus and corticosteroid therapy, with the aim to understand disease pattern, predisposing factors, presenting features and outcomes with surgical and anti-fungal therapy.

Materials and Methods : This retrospective clinical analysis includes data collection of 50 patients from an Otorhinolaryngology hospital located in Kheda district of Gujarat, India from 1st April, 2021 to 31st May, 2021. All these were post COVID-19 patients presented after varying number of days postinfection and had undergone indoor treatment at various hospitals.

Results : Of the 51 patients, 14 were from Nadiad itself, rest were from peripheral areas and aged between 20 and 75 years. All the patients had diabetes mellitus Pre-COVID except one and majority underwent corticosteroid medications and supplemental oxygen therapy during COVID treatment. Mucormycosis infection was observed with palatal involvement in 26 patients (50.98%) and 10 patients (19.60%) with eye involvement.

Conclusion : Close correlation was observed between invasive rhino-orbito-cerebral mucormycosis, diabetes mellitus and corticosteroids administration in COVID-19 positive patients. Possible follow up and larger sample size will be needed to justify this results more.

[*J Indian Med Assoc* 2024; **122(5):** 14-8]

Key words **: COVID-19 Sequelae, Mucormycosis, Diabetes Mellitus, Corticosteroids, Black Fungus.**

Assessment of placement of human pathogen named 2019-nCoV was done by Coronaviridae Study Group (CSG) which then classified viruses and taxons of the Coronaviridae family. CSG recognizes that this virus forms a clade to human prototype and bat causing Severe Acute Respiratory Syndrome-Related Coronavirus (SARS-CoV-2) on the basis of phylogeny and taxonomy.

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Received on : 24/06/2022
Accepted on : 28/03/2024

Editor's Comment :

- Viral infections like COVID-19 are akin to immunosuppressive states making the patient more prone for superadded infections like Mucormycosis.
- Strict Control of Diabetes & early surgical intervention in the patient of Mucormycosis resulted in better patient outcomes.
- Besides Lyophilized Amphoterin the newer Anti Fungals like Posaconazole & Isavuconazole exhibited equally good efficacy in treating patients of Mucormycosis with lesser side effects & cost.

Dominant pandemic SARS-CoV-2 associated pneumonia, stroke, kidney dysfunctions and vascular thrombosis had afflicted and succumbed more than millions of people worldwide in few years. Recent viral storm in India noticed severe devastating co-infection named *Mucormycosis*, a "Black fungus" caused by *Mucorales* species in patients who are recovering from COVID-19[2]. Duration of time in which this infection occurred was couple of days to weeks from COVID recovery. Involvement of maxillofacial area has led to worse outcome during a deep COVID crisis in immuno-compromised patients with uncontrolled diabetes and subsequent corticosteroid therapy[2-4]. Tissue necrosis is the sign of mucormycosis[5] along with severe pain,

necrotic ulcer at palate, ocular swelling, visual problems as blurring and/or loss of vision, cough and shortness of breath are all associated clinical signs and symptoms[2,6]. Lethality was increased with rhino-cerebral (brain and sinus) involvement[7].

Alarming rise in mucormycosis cases in post-COVID-19 phase has stressed to think some triggering causative factors beyond the steroid use and immuno-compromised status by diabetes mellitus or other diseases[8]. Diagnosis by MRI, superintendence of contributory factors, Functional Endoscopic Sinus Surgery (FESS)[5], conservative management by anti-fungal drugs and surgical debridement are the best treatment protocol[2]. The aim is to analyse 51 cases of mucormycosis for correlating between causative factors to help clinicians workout through the evolving disease pattern, considering the poor prognosis of the disease and its short time spread.

Materials and Methods

This is a retrospective, uni-centric study of 51 cases of rhino-cerebro-orbital mucormycosis treated between April till June and were followed up till the end of July, 2022. The study followed compliance with Helsinki statement and exemption was made due to its retrospective nature. Standard informed consent to participate and publish were obtained for every patient.

All these patients were treated at ENT hospital in Nadiad, Gujarat, India. Maxillary sinusitis, headache, necrosis of palatal bone/mucosa or acute loss of vision are some of the common complaints patients get presented with. All but five of the total patients were known cases of previous COVID-19 infection. Every patient was treated with corticosteroids as a part of a standard COVID-19 drug regime. Exclusion criteria had patients with history of chemotherapy, granulocytopenic patients, radiotherapy, history of medication-related osteo-necrosis of jaw, osteo-radionecrosis or those on other immuno-modulator drugs.

Routine blood investigations, ECG, chest X-ray, CT scan and MRI of the face (including orbits) and brain were done (Fig 1).

Sinusitis with mucosal thickening of ethmoidal and maxillary sinuses, facial swelling, sudden dental pain and teeth mobility, headache, ophthalmoplegia, epiphora, edema of extraocular muscles, orbital cellulitis, etc were few clinical features that the patients presented with. Ophthalmology reference was taken for those patients having orbital extension.

Punch biopsy from the oral cavity especially the necrotic palatal part and/or collection of infected tissue/ nasal discharge is/are sent for (KOH test) to screen for any fungal hyphae. KOH test is a rapid method of identifying the presence of fungal hyphae or yeast compared to the fungal culture which takes weeks for reporting and thus was done for all our patients. Histopathologic examination as well as fungal and bacterial culture were also done from the tissue samples. From surgical debridement to maxillectomy (partial, subtotal, total) till orbital exenteration, the surgical intervention varies depending on the orbital involvement.

Once Mucormycosis was confirmed, within 72 hours, surgery was performed as well (Fig 2). Post surgery, either Amphotericin B therapy was instituted if it was available and if it was not available then either orally Posaconazole (200 mg q8h) was administered or Isavuconazole at a loading dose of 372 mg orally every 8 hours and maintenance dose of 372mg orally once a day. Inj Amphotericin B was administered at 3-5 mg/kg. Daily renal function tests had to be performed due to possible nephrotoxicity of Amphoterecin B. Those who could afford, liposomal Amphotericin B injections were given which had lesser renal complications. Alteration in dosage was adjusted according to renal tolerance. Amphotericin B was not available in private clinic/hospitals but only available in government hospitals. Those who were ready to get

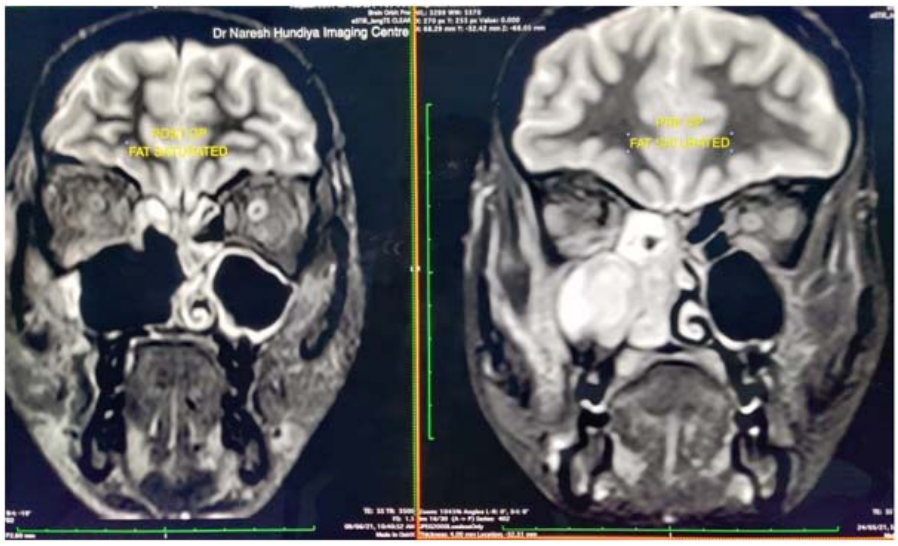

Fig 1 — Pre-operative and Postoperative coronal MRI slice

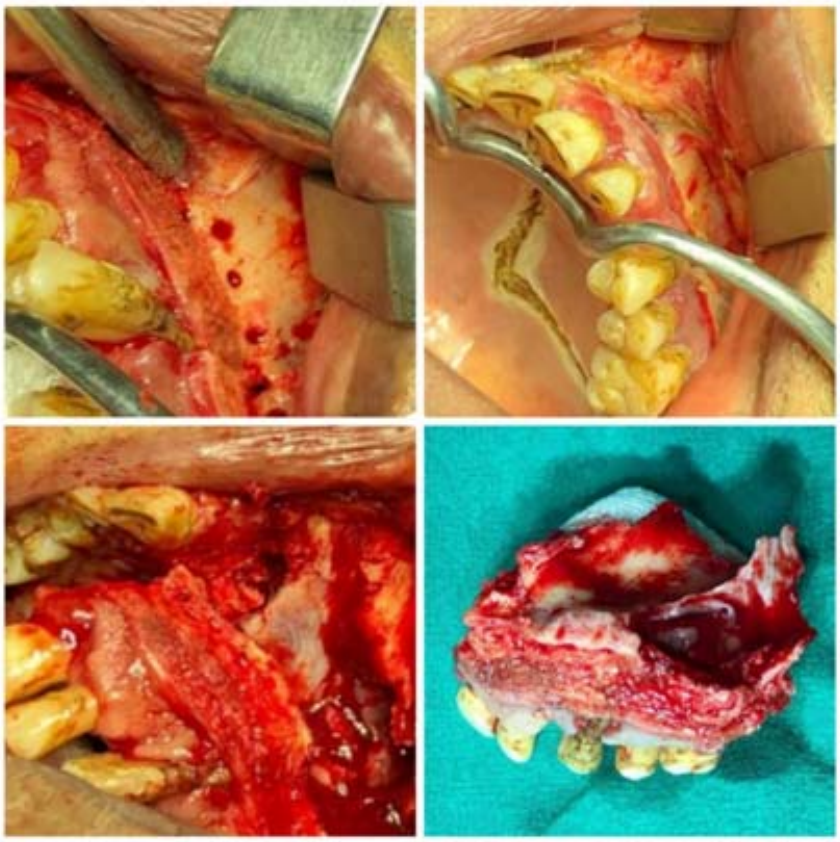

Fig 2 — Collage representing resection with debridement of the maxillary lesion and lastly providing an obturator

admitted in Government hospital for further treatment were sent to Government hospitals for Amphotericin B while rest others were subject to oral medicaments.

Results

Data was collected from ENT Hospital indoor and outdoor case records. Of the 51 patients, 14 were from Nadiad itself, rest were from peripheral areas and aged between 20 and 75 years with a mean age of 49.74 years. This study was performed from the start of April 2021, with most of the patients seen and operated in May and few in June and they all were followed up till July end. In the study, there were 43 male patients while eight were female patients. Out of the 51 patients in the study, 40 (78.43%) patients had diabetes mellitus pre-covid and all the diabetic patients underwent steroid therapy. Supplemental oxygen was provided to 24 (47.05%) patients. For those having involved maxillary sinus, FESS was performed; those having palatal or alveolar bone involved, thorough debridement / maxillectomy was performed while those having eye involvement, orbital exenteration was performed.

Fortynine patients (96.01%) presented with involvement of maxillary sinus. Mucormycosis infection was observed with palatal involvement in 26 patients (50.98%) and 10 patients (19.60%) with eye involvement. Of the 26 patients having palatal bone involvement, 23 patients have undergone maxillectomy. Three patients developed intracranial extensions. All but two patients having mucormycosis, received steroid therapy during the COVID treatment. By the end of July till the last follow up, it was observed that 12 patients were deceased out mainly due to other causes like six patients refused treatment, two patients died due to brain haemorrhage, one patient died due to abdominal distension, 2 patients had sudden cardiac arrest, one had hemoptesis due to hypovolemia. Of the 39 surviving, 32 are disease free while seven patients had been showing some osteomyelitic changes and are currently undergoing the therapy but are medically doing fine.

Discussion

Mucormycosis is a aggressive and lethal infection caused by Mucoraceae belonging to class of Zygomycetes[9,10]. The fungus has a likeliness to affect the nasal mucosa and mostly seen in immuno-suppressive conditions like diabetes, ketoacidosis, solid organ transplant, severe burns, etc. Germination is seen in the nasal and paranasal sinuses ultimately involving the palate, orbit and brain causing death[11]. Mucormycosis in patients can be also contributed to excessive and long term use of steroids[12].

Decrease of phagocytic function, diabetic ketoacidosis and fungal heme-oxygenase elevating iron uptake for metabolism are some pathogenic mechanisms responsible for aggression of the fungal disease[13].

There have been few case reports published presenting co-relation between COVID-19, diabetes and steroids[14-17]. Moorthy published a case study having 18 patients which is by far, the largest case series on role of COVID-19, steroid and uncontrolled diabetes causing mucormycosis in 2021.[4] Of the 18 patients, 16 patients received steroids. Out of these 16 patients, 15 were diabetic as well. Blindnesss truck

12 of the 18 patients and orbital exenteration was carried out in seven patients. The fungi in 16 patients was noted as mucormycosis, one patient had as per gillosis while one patient had a mixed fungal infection. Eleven of the patients survived, six died and one got lost to follow-up.

Basically, in susceptible hosts, standard defense mechanisms slows down. Suppose, in diabetic ketoacidosis, the serum pH is acidic causing dissociation of free iron from the sequestering proteins. The liberation of free iron leads tofaster fungal growth. Further invasion of the fungus is caused by mechanisms like neutropenia or functional defects because of corticosteroids or hyperglycemia or acidosis due to diabetic ketoacidosis. Sequentially, adherence and damage to the endothelial cells because of fungus allows fungal angioinvasion and thrombosis of vessels causing necrosis of tissue by fungal infection[18].

In India till May 2020, 66.8% of the COVID-19 cases were males[19]. Rhino-cerebro-orbital (44-49%) was the type most commonly found, followed by cutaneous (10-19%), pulmonary (10-11%), disseminated (6-11%) and gastrointestinal (2-11%)[20]. But in our case study, all the cases occurring with COVID-19, diabetes and steroids led to rhino-cerebro-orbital mucormycosis. Patients usually presented with headache, fever, unilateral facial swelling, orbital cellulitis with the presence of palpebral oedema, chemosis, ptosis and ophthalmoplegia[21]. The prognosis is poor with about 33.3%-80% being the overall mortality rate[21,22]. CT scan is usually the first diagnostic tool to check the status of sinuses, although best way to detect extra-sinus spread is using Magnetic Resonance Imaging (MRI)[9]. A definitive diagnosis of mucormycosis as the causative species is achieved only by histological examination of the biopsy specimen. Culture and KOH examination may be used only as a suggestive tool for noting the presence of mucormycosis.

We feel the acute increase to be due to infection with COVID-19 contributing in more than one way. Firstly, the reduced numbers of T lymphocytes, CD4 + T and CD8 + T cells suggestive of immune dysregulation may alter innate immunity leading to secondary fungal infections[23]. Secondly, the pathogenesis of COVID-19 kind of mimics the spectrum of Thrombotic Microangiopathies (TMA) leading to angioinvasion and endothelial damage much like that of mucormycosis, aggravating the disease[24]. Thirdly, glucocorticoids have been used extensively to reduce hospital stay and mortality related to COVID-19. In most of the protocols fortreating moderate to severe cases of COVID-19 infection, Dexamethasone and methylprednisolone have both been used[25, 26]. Due to the immuno-suppressive nature of gluco-corticoids, patients become more susceptible to secondary infections.

Due to the high mortality rate, need of early intervention by aggressive surgical debridement, systemic antifungal medications and management of underlying illness are much essential for a better rate of survival. A standard blanket protocol of steroid administration for COVID-19 infection may need to be evaluated again and an emphasis on strict blood sugar control during and after COVID-19 infection should be put.

Both central ciliary and retinal artery occlusion can be caused by mucormycosis[27]. Orbital exenteration can be done to reduce the disease burden and prevent the intracranial spread in cases where blindness is delayed even if having a clear radiological picture of involvement of the orbital cavity. Some cases even mandate partial or total maxillectomy. Repeated surgical debridement may be needed for local control of the disease and an aggressive surgical approach seems to improve patient survival. It is important to note that once the diagnosis is suspected, all immuno-suppressive therapy should be reduced or discontinued if it is possible and Amphotericin B should be therapeutically started[28].

Conclusion

This clinical observational survey includes few points to be considered in priority are possible avoidance of glucocorticoids in mild COVID-19 cases (without hypoxemia) or maintained doses of glucocorticoids in critical cases of COVID. Antifungal medications, surveillance of immuno-compromised status of diabetes mellitus in all patients, screening of COVID-19, early diagnosis of fungal co-infection, focus on triggering contributor factors and timely required treatment are a valuable means to control disease and its severe outcome.

Funding :

The authors did not receive support from any organization for the submitted work.

Compliance with Ethical Standards :

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Informed consent had been signed by all the patients but this being a retrospective study, it doesn't require ethical approval.

No new research has been done on any human beings or animals.

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