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Original Research Article

Mucormycosis coinfection associated with global COVID-19: a case series from India

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ABSTRACT

Background: Mucormycosis is a life-threatening fungal infection that occurs in immunocompromised patients. There has been increasing number of mucormycosis cases during COVID pandemic and also as post COVID sequelae. Our study aimed at scrutinizing a possible coinfection of invasive mycoses and COVID -19 and also its management
Methods: We did a retrospective case study of 25 patients presenting as invasive fungal infection from March - December 2020. Majority of patients were immunocompromised, since they presented during the pandemic, all patients were subjected to rapid antigen and RT -PCR testing for COVID.
Results: 11 patients tested COVID positive out of 25. Diagnosis of mucormycosis was based on clinical features, culture, and histopathology from sinus biopsy. COVID positive patients were managed in the high dependency units and COVID wards. Severe COVID -19 positive patients were empirically started on IV Amphotericin based on clinical suspicion of mucormycosis and were taken up for debridement once stable. Negative patients underwent surgical debridement and were started on IV Amphotericin postoperatively.
Conclusions: There have been lot of case reports from India showing COVID recovered patients presenting with invasive fungal infections, this could be because of their immunocompromised status and long-term corticosteroid use. In our case series we had three patients with post COVID mucormycosis. There was a surge in COVID positive mucor cases during August and September which also coincided with the maximum peak of cases in India, thereafter, there has been a declining trend. There have been significant challenges in treatment modality and outcome due to the pandemic.

Keywords: Mucormycosis, COVID 19, Supplied air respirator, Fungal infections, Post COVID sequelae

INTRODUCTION

SARS COV-19 has affected millions worldwide. It is predominantly a respiratory illness and ranges from a common cold to more severe disease including pneumonia. The mode of human to human transmission is via droplet infections which are either inhaled or enter the body by touching infected surfaces. It has presented to us with a global health crisis.[1]

The lack of evidence in literature has put clinicians into a dilemma as patients come with varied presentations. COVID-19 patients especially the severely ill and immunocompromised have a higher probability of suffering from invasive mycoses. Mucormycosis is a life-threatening fungal infection that occurs in immunocompromised patients. Neutropenic and immunocompromised patients like COVID positive are at increased risk of developing mucormycosis. Due to the COVID positive status patients were on corticosteroids

which worsened the hyperglycemia and hence were more prone to invasive fungal infections.

Objectives

Our study aimed at scrutinizing a possible coinfection of invasive mycoses and COVID-19 and also its management. We assessed the impact of COVID on invasive mycoses management including surveillance and monitoring and current strategies adopted to mitigate them.

METHODS

Study design

This is a retrospective chart review.

Patient selection

Patient included in this study presented to department of ENT and Emergency medicine in a tertiary hospital (St Johns medical College Hospital, Bangalore) over a period of 10 months (March 2020 to December 2020). 25 patients, most of whom presented with unilateral facial swelling, retro-orbital pain, ptosis and headache. A diagnosis of acute invasive fungal sinusitis was made clinically.

All patients were immunocompromised, 2 were immunocompetent.

Since they presented during the pandemic, all patients were subjected to rapid antigen and RT -PCR testing for COVID, however none of our patients presented with symptoms of COVID, some of these patients eventually developed complications and were categorised as severe and moderate COVID.

Crusts taken from nasal cavity was sent for Calcoflour KOH stain to rule out invasive fungal sinusitis (mucormycosis), A contrast enhanced CT scan of nose and Paranasal sinuses including orbital cuts was done to look for rhino-orbital involvement, in patients with suspected cerebral involvement a CT scan of brain was also included.

Statistical analysis

The data collected was entered in to Microsoft excel and analysed. Descriptive Data was presented in the form of frequency and percentage using pie chart and bar diagrams.

Ethical approval

Ethical approval was obtained from the Institutional Ethics Committee.

RESULTS

Out of 25 patients, 3 were female and 22 were male, age group varying from 30 -74 years. Majority of the patients were diabetic and hypertensive, with underlying IHD and CKD. One patient was a known case of leukemia undergoing chemotherapy.

Figure 1: Surgeon with PPE and SAR.

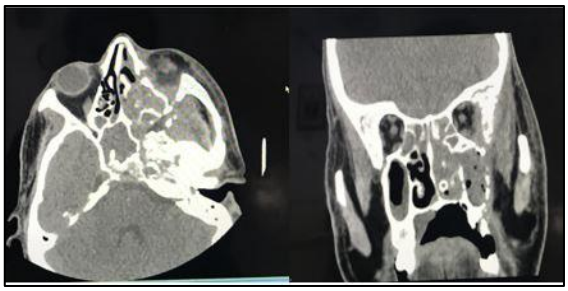

Figure 2: Contrast enhanced CT Scan of a patient showing features of osteomyelitis of left maxilla with air foci with bilateral ethmoid and sphenoid sinus involvement.

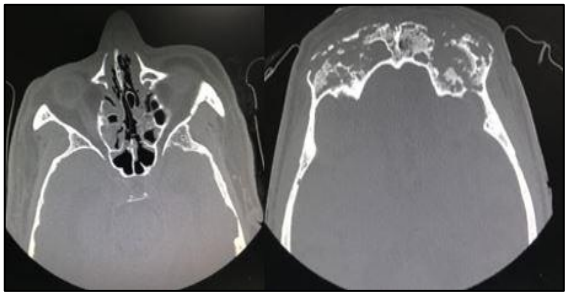

Figure 3: Contrast enhanced CT Scan of a patient showing features of soft tissue opacification of bilateral frontal and ethmoid sinuses with associated fragmented bony destruction and remodelling/sclerosis of frontal bone with multiple intraosseous air foci.

11 out of 25 patients tested positive for COVID -19 (Table 1).

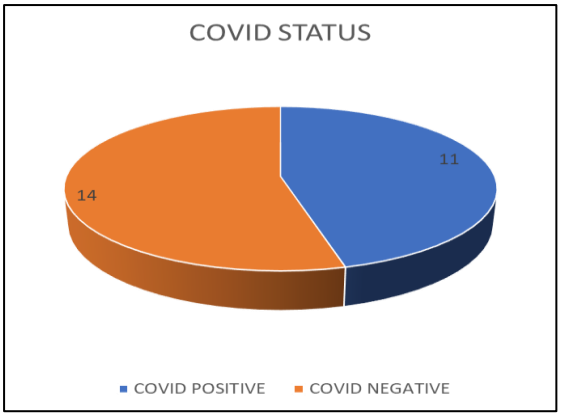

Figure 4: Number of COVID positive and negative mucor patients.

On KOH mount 12 patients grew broad aseptate fungus, 7 patients had a negative KOH report who later tested positive for zygomycetes on histopathological examination. Of the total 20 patients who underwent debridement 7 patients were found to have angioinvasion in the tissue sample and 4 out of them were COVID positive

Most of the COVID positive mucormycosis patients had a glycated haemoglobin (HbA1c) ranging from 7-15 with majority having HbA1c of above 10, COVID negative mucor patients had HbA1c ranging from 6-13, with majority values below 10.

Out of our 25 patients, majority presented with rhino-orbital mucormycosis, remaining 6 patients presented with rhino-orbito-cerebral and 7 with nasal mucormycosis.

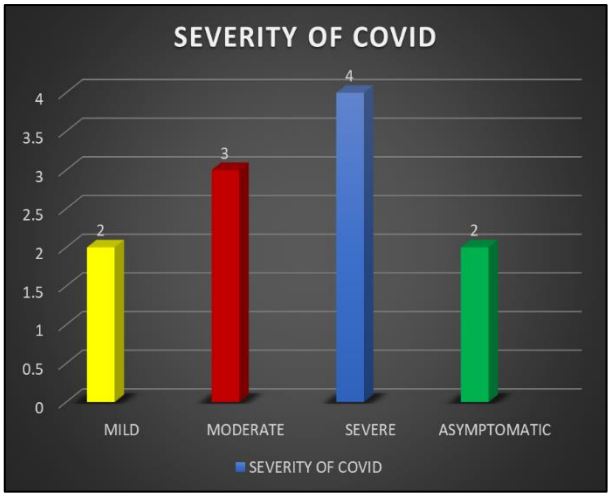

Figure 5: Severity of COVID in mucor patients.

Majority of positive patients were managed in the high dependency units and COVID wards. All patients were started on IV Amphotericin (50 mg/day) with cumulative dose of 1.5-2 gms. Post operatively all patients were advised local diluted Amphotericin douching.

Severe COVID -19 positive patients were empirically started on IV Amphotericin based on clinical suspicion of mucormycosis and were taken up for debridement once stable.

On follow up we had 2 mortalities, one patient with leukemia and the other who presented as severe COVID. 20 Patients underwent surgical debridement, 5 patients went against medical advice. One patient presented one month later with vision loss and underwent redebridement. Some patients were lost to follow up.

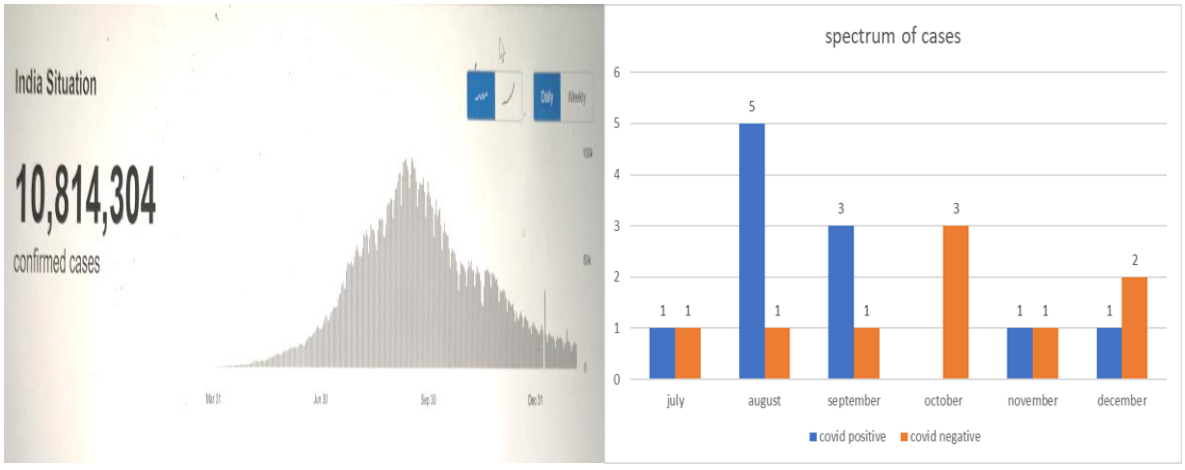

Figure 6: Peak in COVID positive mucor cases during august September in our hospital in comparison to WHO database of COVID in India.

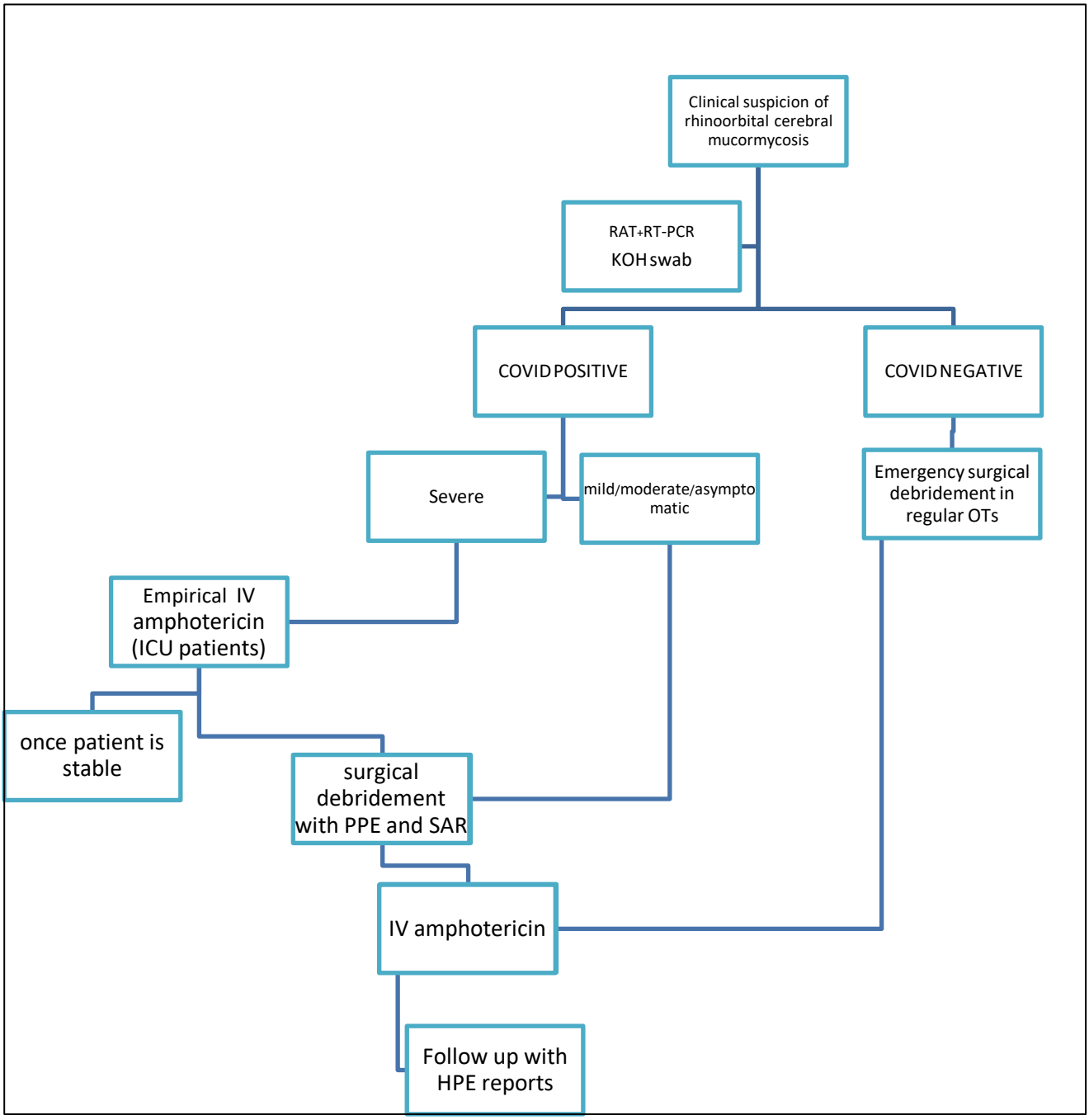

Figure 7: Our management protocol mucormycosis during Covid-19.

DISCUSSION

Severe acute respiratory syndrome coronavirus (SARS-CoV) was first reported in China's Hubei province in December 2019.

The COVID-19 pandemic due to novel coronavirus SARS-CoV-2 is predominantly a respiratory illness and ranges from a common cold to more severe disease including pneumonia. The mode of human to human transmission is via droplet infections which are either inhaled or enter the body by touching infected surfaces.

Emerging data suggests that COVID-19 is common in patients with Diabetes, Hypertension, and Cardiovascular disease (CVD). Patients with diabetes are predisposed to infections in general, there are several specific factors responsible for increased risk and severity of infection with SARS CoV2 in diabetes.

a) Increased ACE-2 Expression
b) Increased Furin
c) Impaired T-Cell function
d) Increased Interleukin-6 (IL-6).[2]

Diabetes and associated complications can increase the risk of morbidity and mortality during acute infections due to suppressed innate and humoral immune functions. The levels of glycated hemoglobin (HbA1c) >9% have been linked to a 60% increased risk of hospitalization and pneumonia-related severity during bacterial infection.[2] Past viral pandemics have witnessed the association of diabetes to increased morbidity and mortality. In our case series we have observed patients with extensive mucormycosis had elevated levels of glycated haemoglobin (>10%), and these were the patients who were also COVID positive.

Treatment of diabetes poses challenges in the current times when the world is going through an unprecedented pandemic with 'lockdowns" in most places, people were confined at home with no opportunities for exercise and regular walks and there is also considerable mental stress with alterations in the daily routine which could affect the dietary intake as well. All these factors could have led to glucose dysregulation and could predispose the patients to complications like in our study invasive fungal infections.[2]

The zygomycoses are infections caused by fungi of the class Zygomycetes, comprised of the orders Mucorales and Entomophthorales. Mucormycosis is a life-threatening fungal infection that occurs in immunocompromised patients.

Phagocytes are the major host defense mechanism against mucormycosis. Hyperglycemia and acidosis are known to impair the ability of phagocytes to move toward and kill the organisms by both oxidative and nonoxidative mechanisms, hence predisposing such patients to mucormycosis. Neutropenic patients like COVID positive are at increased risk of developing mucormycosis, furthermore these covid positive patients were on corticosteroids which worsened the hyperglycemia.

A hallmark of mucormycosis infections is the presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis, hence damage of and penetration through endothelial cells lining blood vessels is likely a critical step in the organism's pathogenetic strategy which also causes hematogenous dissemination from the original site of infection to other target organs.[3]

Rapid diagnostic methods include biopsy, KOH mount and Calcofluor stain. Mucor is difficult to routinely culture. Biopsy remains the mainstay of diagnosis.

Treatment principles include surgical debridement and antifungal agents. Amphotericin B has been the standard of treatment for invasive mucormycosis

The treatment recommendations can be supported by the global guideline for the diagnosis and management of mucormycosis in 2019 by European Confederation of Medical Mycology (ECMM) and Mycoses Study Group Education and Research Consortium which generally supports an early complete surgical treatment for mucormycosis whenever possible, in addition to systemic antifungal treatment. Amphotericin B, lipid complex, liposomal Amphotericin B and posaconazole oral suspension are treated as the first-line antifungal monotherapy, while isavuconazole is strongly supported as salvage treatment.[4]

The optimal time of surgery to reduce the operative risk to the patient with COVID-19 and the risk of transmission to the operating team is a challenging issue.

Patients with mild to moderate COVID illness had reduced infectivity after ten days, patients with severe illness after fifteen days and critically ill patient after twenty days.[5]

Timely surgical debridement is required in rhino-orbito-cerebral infection mainly for biopsy of tissue as well as to clear the disease to prevent further spread and complications. During COVID pandemic we faced a lot of challenges in the treatment of mucormycosis due to coinfection with COVID 19. In our case series there was a significant delay in the surgical management of moderate to severe COVID patients due to their lack of fitness for general anaesthesia hence they were started on empirical IV Amphotericin and once stable were taken up for surgical debridement. Patients with mild to moderate COVID disease were taken up for emergency biopsy and debridement in designated covid OTs.We had a dedicated floor for COVID OTs which had negative pressure (Figure 7).

All aseptic precautions were taking during preparation for the procedure the surgical team wore an adequate complete PPE along with sterile surgical gown, cap and mask over the complete PPE with double surgical gloves were used to ensure asepsis during the procedure. We additionally used a supplied air respirator (SAR) to prevent aerosol generation in positive cases. The SAR is a well fitted air Visor which has a connection port to medical air supply at a pressure of 4 bar and 7 bar, which provides excellent protection, comfort and ease while operating. After each use the connector was disinfected in hypochlorite solution and visor was cleaned with mild disinfectant and allowed to dry in a well ventilated area. Due to the use of SAR none of the surgeons who operated on the covid positive mucor cases were infected. COVID negative patients were debrided in regular OTs (Figure 1).

Some patients left the hospital against medical advice due to the anticipated cost, morbidity of surgery and prognosis majority of whom were COVID positive.[5]

India closed its international borders and enforced an immediate lockdown on March 24, 2020, for 21 days and it further extended till May 31, 2020. Due to this timely intervention, there was no rapid increase in cases during that time. Once Lockdown was lifted, there was a rapid increase in cases which peaked during August and September in accordance with WHO statistics.[6] In our case

series also majority of the COVID positive patients were seen during August and September (Figure 6). We saw a declining trend of positive cases from October onwards, the reason for which could be the population being more aware of COVID and its complications, non-pharmaceutical interventions such as social distancing, patient isolation, face masks and hand hygiene, have proven effective in controlling the circulation of the virus. The use of antiviral drugs also helped in reducing the viral load, this could become significant for epidemic control in the coming months. This is until vaccines become available, which will allow us to reach herd immunity in the safest possible way.[7] There have been lot of case reports from India showing COVID recovered patients presenting with invasive fungal infections, this could be because of their immunocompromised status and long-term corticosteroid use. In our case series we had three patients with post COVID mucormycosis.

The pathophysiology of COVID-19 may also account for unprecedented co-morbidity with Invasive Fungal Infection. First, the high aggressive feature of the SARS-CoV-2 virus to the lung tissue and the large bilateral alveolo-interstitial lesions make the occurrence of Invasive Fungal Infection very likely, specifically those with a primary pulmonary entry and an airborne route of infection such as Invasive Pulmonary Aspergillosis, pneumocystosis (PjP) and mucormycosis, also the absolute number of T lymphocytes, CD4+T and CD8+T cells are markedly lower in severe COVID-19 cases than moderate cases, associated with markedly higher levels of IL-2R, IL-6, IL-10, TNF-alpha and some other inflammatory markers .In many post covid patients mucormycosis can be underdiagnosed.[8]

There is a need to sensitize specialist teams dealing with COVID-19 patients to look for early signs in cases so that there is no delay in diagnosis. A nasal swab for KOH mount and culture can be done as a bedside procedure along with simple tests like vision, pupil, ocular motility, sinus tenderness and palatal examination for eschar can be part of routine physical evaluation of a COVID-19 patient hospitalized with moderate to severe infection or diabetics with COVID-19 or those receiving systemic corticosteroids. Development of unilateral facial or orbital pain, headache, periocular swelling, double vision or diminution of vision should prompt even the COVID-19 recovered patients to seek immediate medical attention. Follow-up of high-risk patients with COVID-19 for sequelae is imperative.9

Limitation of the study

5 COVID positive patients most of whom were severe COVID went against medical advice and among the patients who underwent surgery some of them were lost to follow up after discharge, as a result of which their outcome could not be monitored.

CONCLUSION

Already immunocompromised patients with superadded COVID-19, have shown increased surge of mucormycosis. There was a surge in COVID positive mucor cases during August and September which also coincided with the maximum peak of cases in India, thereafter there has been a declining trend. There have been significant challenges in treatment modality and outcome due to the pandemic. Treatment outcome was variable due to concomitant COVID management. Clinicians were in a dilemma in completing all modalities of treatment. Due to increasing case reports of post COVID fungal infections, follow up of high risk patients with COVID-19 for sequelae is imperative.

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