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Original Article

Absence of Case of Mucormycosis (March 2020–May 2021) under strict protocol driven management care in a COVID-19 specific tertiary care intensive care unit

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ABSTRACT

Aims: With a sudden increase in cases of mucormycosis seen in Covid –19 patients, we conducted a retrospective analysis of all admitted patients in a tertiary care covid-19 hospital looking at incidence of mucormycosis.**Methods:** Intensive care unit daily rounds data stored in an electronic format was retrieved by one of the consultants, looking for incidence of mucormycosis, diabetes mellitus, adherence to protocol for steroid use, glycemic control and use of monoclonal antibodies. Also, patients follow up data base of post covid Outpatients Department was searched for cases of mucormycosis.**Results:** A total of 5248 patients were admitted between March 2020 to May 2021, of which 1027 were in ICU and 4221 in wards. Of the 1027 patients admitted in Intensive care unit, 915 received steroids and 417 had diabetes as existing co-morbidity. No case of mucormycosis was reported during the stay in the hospital and during immediate outpatient department follow up. The low dose steroids were administered as per state government protocol for treating COVID 19, a nurse driven strict glycemic control regime (blood glucose level was maintained between 140 and 180 mg/dl through the admission in ICU and was achieved consistently in 842 (82%) patients, followed along with minimal use of other immunomodulatory like monoclonal antibodies.**Conclusion:** A strict adherence to protocol of low dose steroids coupled with strict glycemic control helped in eliminating the risk and incidence of mucormycosis in a tertiary care dedicated covid-19 hospital.

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Introduction

Mucormycosis is a rare but serious infection caused by a group of moulds called as mucormycetes. These moulds live throughout the environment. It is an angio-invasive opportunistic infection, characterised by tissue infraction and necrosis which can be fatal if not detected early. Uncontrolled diabetes mellitus has been shown to be the most important risk factor [1]. The rhino-orbital-cerebral (ROCM) form of mucormycosis is commonly seen in diabetic population as opposed to pulmonary mucormycosis which is

commonly seen in patients with hematological malignancy and transplant recipients [1–3]. A computational modelling done by A Chakrabarti et al. [4] suggested an incidence of around 14 per 100,000 Indian populations which is almost 70–80 times higher than the rest of the world. In the last few months there has been a significant, exponential rise of the rhino-orbital-cerebral mucormycosis in the patients who have recovered from COVID-19 or still undergoing treatment for COVID-19. Though the exact incidence is still unknown, the Government of India has taken the cognizance of the issue and has made mucormycosis as a notifiable disease as per the Epidemic Diseases Act 1897 Govt. of India. In a recent review by A K Singh et al. [6] of mucormycosis cases reported worldwide and in India the main reasons for Mucorales growth in COVID-19 patients is reported as conducive environment in form of hypoxia

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Table 1
Steroid protocol.

Day	C-Reactive Protein (CRP)	Steroid	Dose	Duration
Day 1	Hypoxia Saturation < 93% or PaO ₂ /FiO ₂ Ratio < 300		Methyl Prednisolone 1 mg/kg not more than 40 mg twice daily	3 days
Day 4	If CRP > 50 mg/L	Continue	Continue	For 2 days more (total of 5 days)
Day 4	If CRP < 50 mg/L	Continue	40 mg Daily	For 2 days
Day 6		Prednisolone	30 mg/day	Wean over 5 days

(Low Oxygen), diabetes mellitus, poor glycemic control, high ferritin and decreased phagocytic activity of white blood cells (WBC).

Methods and materials

Fortis Hospital Mulund, Mumbai a tertiary care center, has been admitting COVID-19 patients since the start of pandemic. The covid ICU is 36 beds unit divided in 3 pods of 12 patients each, admitting around 800 patients every year, with an average LOS of 9 days. The daily ICU rounds data is stored in electronic data sheet and was retrieved by an ICU consultant looking specifically at incidence of mucormycosis, diabetes mellitus, adherence to protocol for steroid use, glycemic control and use of monoclonal antibodies. Similarly post covid outpatient's department follow up data base was searched for incidence of mucormycosis. In the current study since March 2020, every patient admitted with COVID-19 for treatment was evaluated retrospectively. The study looked at the incidence of mucormycosis in our admitted patients in wards and intensive care units. Every case had adherence to treatment protocol as per the local and Maharashtra state task force guidelines, especially in context of steroid use, blood glucose control, Oxygen Humidification methods and use of monoclonal antibodies in admitted patients. The hospital also has a strong award-winning antimicrobial stewardship program.

Our steroid protocol (Table 1) included use of Methyl Prednisolone in a dose of 1 mg/kg/day not exceeding 40 mg twice a day maximum for 3 days. The steroids were initiated only when patient was hypoxic as evident by saturation below 93% or PaO₂/FiO₂ ratio below 300 or exercise induced hypoxia. A C-Reactive Protein (CRP) level was done every day and dose was reduced to 40 mg once daily on day 4 if CRP was below 50 mg/L. If CRP persisted above 50 mg/L, then methylprednisolone was continued in twice daily dose for 2 more days and then reduced to daily dose. Regardless on day 6 the steroids were changed to 30 mg Prednisolone oral and this was weaned over the next 5 days. In patients with septic shock, sepsis replacement hydrocortisone 200 mg/day in 4 divided doses or by infusion was given. A nurse driven glycemic control regime targeting blood glucose level between 140 and 180 mg/dl was continued using Intravenous insulin infusion and once on oral steroids it was shifted to subcutaneous regime as per an insulin sliding scale regime. In the initial few months of pandemic Tocilizumab was used for cytokine storm in addition to steroids, in patient who remained hypoxic despite steroids for 24 h, with a high CRP (>50 mg/L) and IL6 level above 100 pg/ml.

Results

Between March 2020 to May 2021 a total of 1027 patients were admitted in the Intensive Care Unit (ICU) and a total of 4221 patients were admitted in the wards for treatment of COVID-19. There was no case of Mucormycosis seen in admitted patients or on their post discharge follow up. Of the 1027 patients admitted in the ICU, 915 received steroid therapy as follows, 827 patients received Methylprednisolone, 74 received Hydrocortisone and 5 received

Dexamethasone. There were 417 patients of Diabetes Mellitus out of 1027. Total of 67 patients received a single dose of Tocilizumab a monoclonal antibody in addition to steroids for cytokine storm. The blood glucose level was maintained between 140 and 180 mg/dl through the admission in ICU and was achieved consistently in 842 (82%) patients. A total of 536 patients were treated with High Flow Nasal Cannula (HFNC) using an inbuilt humidified circuit, 227 on invasive mechanical ventilator using Heat Exchange Moisturizing (HME) filters, 56 patients needed Noninvasive Ventilation using HME, the rest 147 received dry Oxygen 133 via nasal cannula and 14 using non rebreather mask. Our center conducts a regular post covid outpatient service, and each case was periodically assessed telephonically or on follow up visit to ascertain nonoccurrence of Mucormycosis.

Discussion

In this brief report of retrospective data, we show that under strict protocol driven use of steroids and nurse driven tight control of glycaemia, occurrence of mucormycosis can be totally avoided. These results are noteworthy, given major escalation of cases of mucormycosis seen in other ICUs and Covid-19 centers.

The possibly reasons and rationale has been discussed here. The zero incidence of mucormycosis was seen in our patients because we believe there was a strict adherence of protocol for steroid dosing and duration of steroids. Nityanandam S [5] et al. also have reported that 88% patients who had Rhino Orbital Cerebral Mucormycosis (ROCM) were having diabetes mellitus. This brings us to the importance of controlling blood glucose level better. This was achieved in 82% of our group of patients. The reason been it was nurse driven and had a strict level of vigilance at the bed side. The use of other immunomodulatory drugs in our patients was also very low, with only 67 patients receiving a single dose of Tocilizumab. It is also important to note the strict quality of oxygen humidification protocols and biosafety by nursing care. This may further hypothesize the point that less of immunomodulation may have helped in preventing mucormycosis. Current literature analysis of mucormycosis across the globe shows the diabetes and steroid use is responsible for mucormycosis and both were address as standard of care as a part of routine in patient and critical care [6].

Conclusion

A strict adherence to protocol of low dose steroids coupled with strict glycemic control helped in eliminating the risk and incidence of mucormycosis in a tertiary care dedicated covid-19 hospital.

Conflict of interest declaration

This is to state that we have NO conflict of interest of any form in the manuscript titled "Absence of Case of Mucormycosis (March 2020–May 2021) under strict protocol driven management care in a COVID-19 specific tertiary care intensive care unit".

References

- [1] Prakash H, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J, et al. A prospective multicenter study on mucormycosis in India: epidemiology, diagnosis, and treatment. *Med Mycol* 2019;June 1;57(4):395–402. <https://doi.org/10.1093/mmy/myy060>.
- [2] Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005;41:634–53.
- [3] Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, Chen SCA. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clin Microbiol Infect* 2019;25:26–34.
- [4] Chakrabarti A, Sood P, Denning D. Estimating fungal infection burden in India: mucormycosis burden as a case study. Available online, <https://www.gaffi.org/wp-content/uploads/P1044.pdf>.
- [5] Nithyanandam S, Jacob MS, Battu RR, Thomas RK, Correa MA, D'Souza O. Rhino-orbito-cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes. *Indian J Ophthalmol* 2003;51:231–6.
- [6] Singh Awadhesh Kumar, Singh Ritu, Joshi Shashank R, Misra Anoop. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. *Diabetes & Metabolic Syndrome: Clin Res Rev* 2021. <https://doi.org/10.1016/j.dsx.2021.05.019>.