

An Observation of Association Between Steroid Treated COVID-19 Patients and Mucormycosis

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Abstract

Background: Mucormycosis is a life-threatening angio-invasive fungal infection mostly observed in patients with uncontrolled Diabetes-mellitus and immune compromised patients. Mucormycosis progress rapidly and destructive in nature. The aim of our study is to analyse whether systemic steroid therapy is the contributing factor for COVID-19 associated Mucormycosis. **Methods :** We have 25 patients who were admitted to mucor-mycosis ward in Rajendra Institute of Medical Sciences, Ranchi. Data regarding age, sex of the patient, history of COVID-19 infection, history of diabetes mellitus, duration of diabetes mellitus and history pertaining to systemic steroid therapy during COVID-19 infection (type and dose of steroid given, duration of treatment), blood sugar level and HbA1C of the patients were also included in the study. **Result:** All our 25 patients were COVID-19 infected. 23(92%) were Male and 2(8%) were female patient. The most common affected age group was between 41-50 years (12,44%). 14(56%), 9(36%) and 2(8%) patients were known case of type 2 diabetes mellitus, newly diagnosed case of DM, and non-diabetic respectively. Among the 23 diabetic, 17(74%) had poor glycaemic control. 21(84%) patients out 25 received systemic corticosteroid therapy as a part of standard treatment of COVID-19 infection. The common steroid used in our study group was Dexamethasone administered via the intravenous route with an average dose of 12.3 per day in 18(86%) patients. Methylprednisolone was prescribed for 4(20%) patients with dose of 0.5-1mg/kg/day per orally. For 6(29%), 11(52%) and 4(19%) patients, steroid was administered for a duration of <10days, 10-19 days, >20 days respectively. **Conclusion:** The immune dysregulation and hyperglycaemic state due to the COVID-19 infection, diabetes mellitus and systemic steroid therapy caused the epidemic outbreak of mucor-mycosis cases. This dreadful situation can be overcome by administering glucocorticoid at possible lowest dose for shortest duration on alternate days and by maintaining proper glycaemic control of COVID-19 infected patient on systemic steroid therapy.

Keywords: COVID-19-associated mucormycosis, Rhino- orbital- cerebral mucor-mycosis, Invasive fungal infection, systemic corticosteroid therapy

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Introduction

COVID-19 is a viral disease caused by Novel SARS-COV2, is a SARS- related Coronavirus. On March 11, World Health Organization (WHO) declared the novel coronavirus as a Pandemic [1]. Various ENT manifestations such as sore throat, anosmia, tonsillar enlargement, pharyngeal edema, rhinosinusitis, recently mucormycosis are also being noted during infection and recovery among the patients as its site of entry via nose. This disease led to dramatic loss of human life globally and presented health system with an unprecedented challenge. Till to this date there is no specific treatment for this disease. Various clinical trials are being done to evaluate the potential treatment. One among them is the Randomized Evaluation of COVID-19 Therapy (RECOVERY) Trial, showed that mortality rate was lower for patients who received dexamethasone than the control group [2]. After this trial, corticosteroids are considered as one of the effective drugs against COVID-19 infection and they are readily available globally at low cost.

Widespread use of this drug unfortunately led to secondary bacterial and invasive fungal infection in high-risk individuals. One among them is dreadful infection with the fungi of order Mucorales which includes mucor, Rhizopus, rhizo-mucor etc. Now, Mucormycosis has become an emerging concern for the patient with uncontrolled diabetes mellitus [3] and severe/critical COVID-19 infection due to the corticosteroid therapy [4].

Aim of the study

To analyze the association between systemic steroid therapy and COVID-19 associated Mucormycosis.

Material & methodology

Study Area

Mucormycosis ward, Department of ENT & HNS, Rajendra Institute of Medical Sciences (RIMS), Ranchi.

Study Design

Observational study

Study period

May, 2021

This observational study is conducted in our institute with aim to analyze whether systemic steroid therapy is the contributing factor for COVID-19 associated Mucormycosis. This study was conducted on the patient fulfilling the mentioned inclusion and exclusion criteria. Detailing history was taken emphasizing on the age, sex, time of onset of symptoms, time of presentation to our institute, past history of

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Diabetes mellitus, history of COVID-19 infection, systemic steroid therapy for COVID-19 infection/ other causes and patient blood

sugar, HbA1C value at the time of presentation was also noted. And the following data was evaluated.

INCLUSION CRITERIA	EXCLUSION CRITERIA
<ul style="list-style-type: none"> • Age >18yr to <80yrs • Patient with past/ present history of COVID-19 infection • Rhino-orbital-cerebral type of mucor-mycosis (ROCM) • Patient willing to give informed written consent 	<ul style="list-style-type: none"> • Age <18yr >80yr • Mucor-mycosis not associated with COVID-19 infection • Mucor-mycosis of other form except ROCM • Patient refuses to participate in the study • On steroid therapy except for COVID-19

Results

In our study, out of 36 patients admitted in mucor-mycosis ward 25 patients fulfilling the above-mentioned inclusion and exclusion criteria were studied. Age distribution of study population is represented in the Fig 1, with mean age of 49.6 years and range of 26 – 75 year. Fig2, depicts the gender predilection with male predominance (23, 92%).

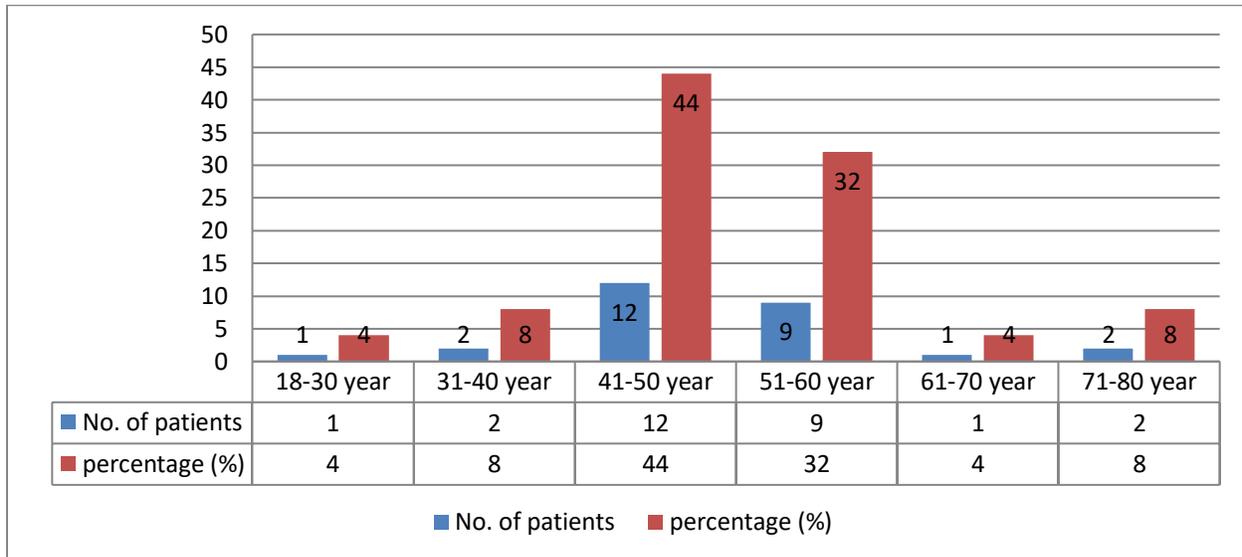


Fig 1:Age distribution

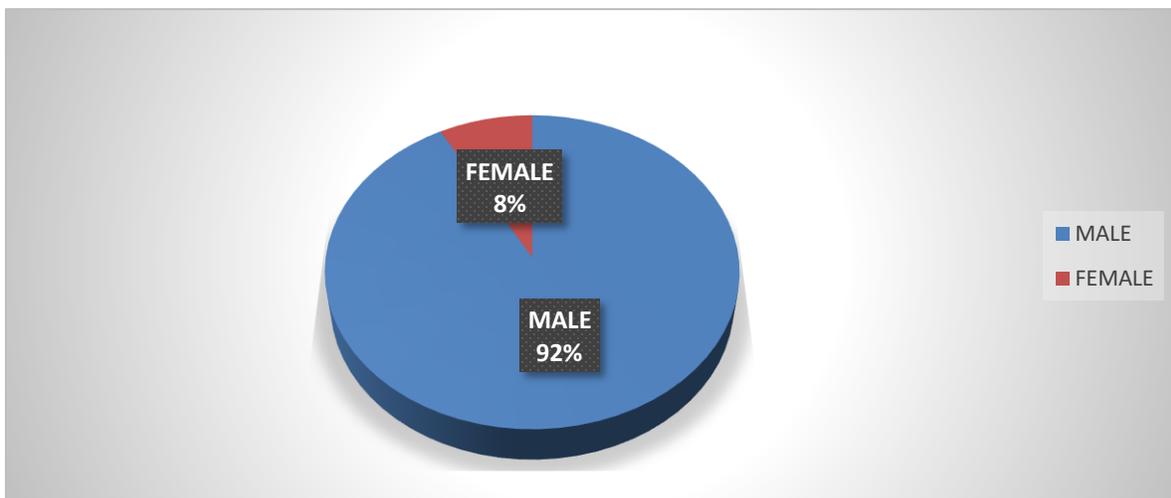


Fig 2:Gender prediction

In our study group, all the patient had COVID-19 infection either previously (22.88%) or at the time of admission (3,12%). 14 (56%) of our patients were known case of diabetes mellitus, 9 (36%) were newly diagnosed to have hyperglycemia and 2 (8%) were Non-Diabetic. The Blood sugar level of patients at the time of presentation is represented in the Fig 3 about 60% of patients are between the range of 301-500mg/dl.

The HbA1C value of the 23 diabetic patients are tabulated in the Table 1, shows about 74% of patients have poor glycemic control.

Table 1: Glycemic control of diabetic patients.

GLYCEMIC CONTROL (HbA1C)	NO. OF PATIENTS	PERCENTAGE (%)
GOOD (6.1-7.0%)	2	9
FAIR (7.1-8.0%)	4	17
POOR(>/=8.1%)	17	74

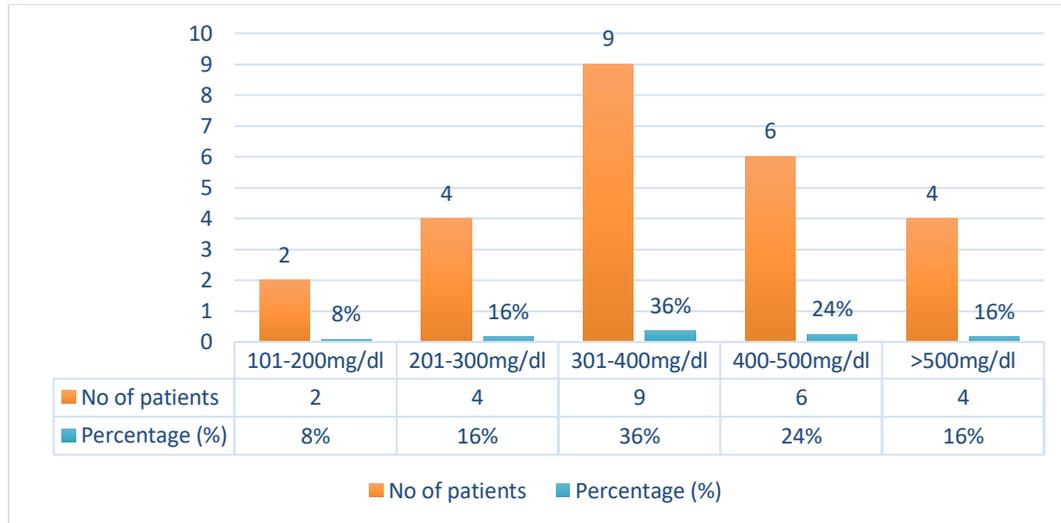


Fig 3:Blood glucose level

Systemic steroid therapy

Out of 25 patient, 21 (84%) patients received systemic corticosteroid therapy as treatment for COVID-19 infection.

Among these 21 patients, 17 (81%) patients had Dexamethasone, 3 (14%) had Methylprednisolone and 1 (5%) had both Dexamethasone and Methylprednisolone.

Route of administration: Intravenous (17, 81%), Oral (3,14%) and 1(5%) patient were initially on Intravenous steroid and then switched over to oral route.

Dose of steroid used: Patients (18,86%) those who were on only Dexamethasone got 8mg/day, 12mg/day and 16mg/day by 9(50%),8(44%) and 1(6%) patient respectively, with mean of dosage of 12.3 per day. Methylprednisolone was prescribed at the dose of 0.5 – 1mg/day for 4 (20%) patients.

Duration of therapy given is represented in Fig 4.

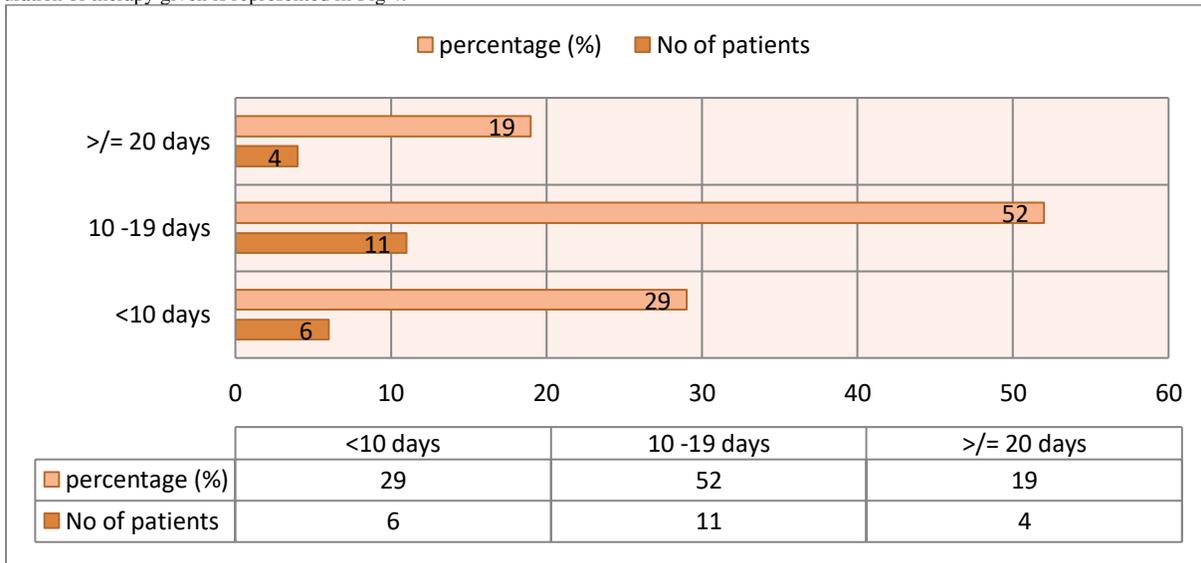


Fig 4:Duration of steroid therapy

Discussion

Mucor-mycosis is an acute and fatal fungal infection caused by the fungal species of order Mucorales belonging to the class Zygomycetes [5]. Their fungal spores are found everywhere in the environment such as soil, decomposing organic matter, animal manure etc. Human

transmission occurs via the inhalation of fungal spores. Once the condition is favorable such as uncontrolled diabetes mellitus, glucocorticoid therapy, underlying lung pathology the seeded spores in nasal mucosa germinate into an invasive fungal hyphae [6]. In normal immunocompetent host, the spores and hyphae will be

destroyed by macrophage phagocytosis and oxidative cytotoxic mechanism by polymorphonuclear leucocytes (PMNs) [7].

Recently there is an upsurge of Mucor-mycosis cases among the COVID-19 infected population globally. This phenomenon apparently because both the disease shares the same pathogenesis of causing angio-invasion, endothelial damage, thrombosis, necrosis [6,8] making the individuals more susceptible. Other possible causes are acute cortisol stress response in COVID-19 infection, making the glycemic control a difficult one in both diabetic and non-diabetic patients [9] and alteration of innate immunity by causing reduction of CD4+ and CD8+ T-Lymphocytes count [10]. Rhino-orbito-cerebral mucor-mycosis is the commonest form of presentation in COVID-19 patients, which is also the fatal one [11]. In our study, most common affected age group is of 5th decade (44%) with the mean age of 49.6 years with Male predominance (92%) which was similarly observed by Fatchi Elzein et al [12] and M.M.Roden [13] et al. Out of 25 patients, 14 (56%) and 9 (36%) were known case and newly diagnosed cases of Diabetes mellitus respectively. Around 60% of the patients presented with the blood glucose level between 301-500 mg/dl. Among the diabetics' patients (23), 74% have poor glycemic control (HbA1C \geq 8.1%) Making diabetes the most common predisposing factor in our study which was also observed by Prakash H et al [3]. The greater frequency of infection in diabetic patient is mainly because of the hyperglycemic environment favoring the immune dysregulation. 21 (84%) patients out of 25 underwent systemic glucocorticoid therapy as a standard treatment protocol for COVID-19 infection. The Glucocorticoids have become an inevitable drug in management of COVID-19 infection to reduce the mortality and hospital stay by their immunosuppressive and anti-inflammatory property. But these properties made the individuals susceptible for secondary bacterial/ fungal infections. Glucocorticoids on administration causes depletion of CD4+ and CD8+ lymphocytes [14], dysregulation of T-helper cells by suppressing the phagocyte effector cell function [15], inhibit PMN apoptosis [16] and prolong the survival of dysfunctional neutrophils [16] which makes individual at high-risk for Invasive fungal infections. Among 21 patients on steroid therapy, 17 (81%) were on Intravenous dexamethasone, 3 (14%) were on oral methylprednisolone and 1 (5%) was initially treated with intravenous dexamethasone then switched over to tablet methylprednisolone.

Out of 18 patients on intravenous dexamethasone received dose of 8mg/day, 12mg/day and 16mg/day by 9 (50%), 8 (44%) and 1 (6%) patient respectively.

Methylprednisolone oral preparations were administered at the dose of 0.5 to 1mg/kg/day. About 52% (11) are treated for a duration of 10-19 days followed by <10 days and \geq 20 days by 29% (6) and 19% (4) respectively. Invasive fungal infection associated with glucocorticoid therapy depends on route of administration, dose, potency and duration of treatment given. Dexamethasone is a long-acting high potent corticosteroid shown to cause marked functional defect in lymphocyte-mediated cytotoxicity [17] while methylprednisolone is an intermediate acting high potent steroid causes suppression of lymphocyte proliferation and cytotoxicity [18]. According to RECOVERY trial, recommended dose of dexamethasone for intubated/suspected/ confirmed cases of COVID-19 was 6mg/day intravenous or per oral [2]. For our patients, dose administered was higher than the recommended dose. Coming to methylprednisolone, high-dose regimen (0.5-1mg/kg/day) was given which is a known risk factor for invasive fungal infection [19]. Dale DC et al stated that restriction of steroid usage to less than 21 days at lowest possible dose and alternate day administration allowing intermittent normal leucocyte kinetics reduces the susceptibility to invasive fungal infection [20].

Conclusion

The immune dysregulation and hyperglycemic state due to the COVID-19 infection, diabetes mellitus and systemic steroid therapy caused the epidemic outbreak of mucor-mycosis cases. This dreadful

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situation can be overcome by the following measures. Primarily by administering glucocorticoid at possible lowest dose for shortest duration on alternate days to achieve desired therapeutic effect. Then by maintaining proper glycemic control of COVID-19 infected patient on systemic steroid therapy. As our study conclusion was drawn by observing only 25 patients, this subject need further detailed evaluation in larger study group to substantiate this.

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