

Effectiveness of COVID-19 Vaccination against COVID-associated Mucormycosis

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ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) infections may be associated with a wide range of opportunistic bacterial and fungal co-infections. Both *Aspergillus* and *Candida* have been reported as the main fungal pathogens for co-infection in people with COVID-19. During the COVID-19 pandemic, another threat has emerged as a challenge to India was in the form of COVID-associated mucormycosis.

Aim: To study the incidence of COVID-associated rhino-orbital mucormycosis in vaccinated and unvaccinated patients.

Materials and Methods: A prospective observational study was carried out at Gajra Raja Medical College and Jay Arogya Hospital, Gwalior, Madhya Pradesh, India, over a period of two months (May to June 2021). A total of 94 patients with post-COVID rhino-orbital mucormycosis were reported in the institute during the study period. Biopsy or postoperative surgical specimens were received for histopathological examination with a proper history of diabetes mellitus, steroid intake, and vaccination status. Histologically confirmed COVID-associated rhino-orbital

mucormycosis cases were included in the study and its incidence was compared in vaccinated and unvaccinated patients.

Results: Total 94 patients were confirmed histopathologically, with mucormycosis. It was noted that mucormycosis was more common in males as compared to females. Of the total number of cases, 71 (75.5%) cases had a history of diabetes mellitus and 73 (77.7%) had a history of steroid intake. Eighty-six (91.5%) cases were unvaccinated while only 8 (8.5%) were either completely or partially vaccinated. Incidence of mucormycosis was found to be more amongst unvaccinated patients as compared to vaccinated patients.

Conclusion: Mucormycosis is one of the major post-COVID threats. Diabetes mellitus and steroid intake were found to be the main risk factors for post-COVID mucormycosis. However, it has also been noted that mucormycosis can occur without a previous history of diabetes and steroid intake. Incidence of mucormycosis was found to be higher amongst unvaccinated patients as compared to vaccinated patients. Hence, vaccination against COVID-19 is likely to be effective in the prevention of COVID-associated mucormycosis.

Keywords: Corticosteroid, Coronavirus disease-2019, Diabetes mellitus, Fungal infection, Histopathological examination, Hyphae, Incidence, Steroid

INTRODUCTION

After the COVID-19 pandemic another threat has emerged as a challenge to India in the form of COVID-associated mucormycosis [1]. Mucormycosis is caused by a group of moulds called Mucormycetes, which are rare but potentially fatal if inadequately treated [2]. Mucormycosis is popularly known as “black fungus”. Cases were reported in almost every state of India following COVID-19. Most patients presented with complaints of headache and facial pain. Hard palate involvement was observed in patients and unilateral presentation was more common. Various research studies have been conducted to establish the risk factors and pattern of disease. The most common risk factors associated with post-COVID mucormycosis are diabetes and steroid intake [3,4]. However, a number of cases had no history of diabetes or steroid intake. Various states have quickly undertaken measures to control the situation by setting up special task forces, issuing guidelines, arranging separate wards in hospitals for the management of mucormycosis cases, and procuring the drugs required for treatment. Now the disease is under control with less number of cases are being reported.

Now COVID-19 vaccines are widely available, which have reduced the disease burden significantly [5]. Although various studies have reported that diabetes mellitus or immunocompromised state are the major risk factors of mucormycosis, there have been cases without such a history [3,4]. Researchers have hypothesised that immediate vaccination will help in generating herd immunity, thereby reducing the chances of black fungus infection and its associated severe health complications [6].

The aim of the study was to investigate the incidence of COVID-associated rhino-orbital mucormycosis in vaccinated and unvaccinated patients. This would help to establish the efficacy of vaccination in preventing COVID-associated rhino-orbital mucormycosis. Another objective was to find out the associated risk factors predisposing to post-COVID mucormycosis.

MATERIALS AND METHODS

A prospective observational study was conducted at Gajra Raja Medical College and Jay Arogya Hospital, Gwalior, India, over a period of two months (May to June 2021). The study was approved by the Institutional Ethics Committee (IEC) (Approval no. P/412/21). Informed consent was obtained from the participants.

Inclusion criteria

- Histopathologically confirmed mucormycosis cases.
- Either post-COVID or presently COVID-positive mucormycosis patients.

Exclusion criteria

- Incomplete medical history.
- Patient suspected to be a case of mucormycosis but not histopathologically confirmed.

Procedure

The samples from patients who were admitted in the mucormycosis ward between May-June 2021 were submitted for histopathological examination. Their medical history was taken for current COVID-19 status, history of diabetes mellitus, steroid intake, and vaccination

status and the data was recorded. Total 95 histopathological samples were submitted to the Histopathology Department. Proper history of one patient could not be obtained and hence excluded from the present study.

All histopathological specimens with suspected COVID-associated rhino-orbital mucormycosis received in the Department of Pathology, which were either COVID-positive or had recovered from COVID-19, were included in the study. A total of 94 patients with COVID-associated rhino-orbital mucormycosis were reported during the study.

All samples were fixed in 10% neutral buffered formalin, embedded in paraffin blocks, and stained with Haematoxylin and Eosin (H&E) stain. All histopathologically confirmed cases of mucormycosis were then compared with their COVID vaccination status, history of diabetes mellitus and steroid intake during management of COVID-19.

STATISTICAL ANALYSIS

Descriptive data were entered in Microsoft excel and were analysed using the Statistical Package for the Social Sciences (SPSS) version 20.0 and mean age, gender distribution and percentage were analysed.

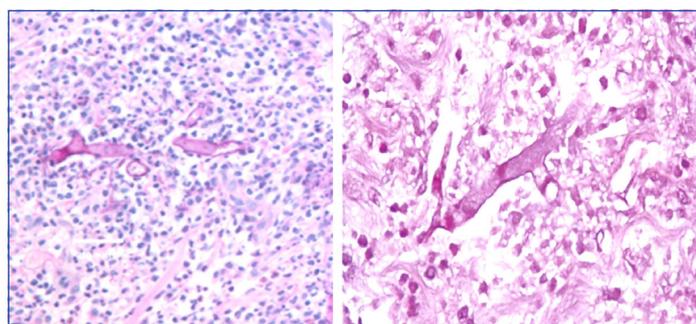
RESULTS

The mean age of the patients in the present study was 45.2 years, although there was a wide spectrum of age varying between 28-81 years. Out of 94 patients, 70 were males and 24 were females, indicating that there was a male predominance. Out of 94 mucormycosis patients, 23 (24.5%) had no history of diabetes mellitus, while 71 (75.5%) were diabetic. Twenty-one patients had not taken steroid in any form, while 73 had a history of steroid use. Total 86 (91.5%) patients were unvaccinated, while five had received their 1st dose of COVID-19 vaccine. The data showed that only three patients had received two doses of the COVID-19 vaccine. The frequency of COVID-associated mucormycosis was much higher in unvaccinated patients as compared to vaccinated patients [Table/Fig-1].

Variables	n	Percentage
Male patients	70	74.5
Female patients	24	25.5
History of diabetes mellitus	71	75.5
History of steroid intake	73	77.7
Unvaccinated against COVID-19	86	91.5
1 st dose of COVID-19 vaccine	05	5.3
Both doses of COVID-19	03	3.2

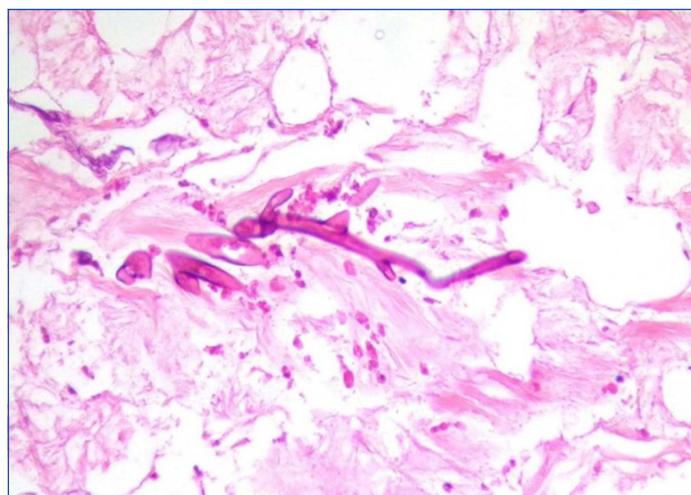
[Table/Fig-1]: Number of cases with various findings.

Histopathological examination: Broad aseptate fungal hyphae with large areas of necrosis, mycotic infiltration of blood vessels, tissue infarction, haemorrhage, giant cell reaction, and acute neutrophilic infiltrate. Periodic acid-Schiff (PAS) stain was used in a few cases to identify fungi [Table/Fig-2-4].



[Table/Fig-2]: Broad hyphae with inflammatory infiltrate (H&E stain 10X).

[Table/Fig-3]: Broad aseptate hyphae with necrotic background (H&E stain 40X). (Images from left to right).



[Table/Fig-4]: Thick hyphae with PAS stain (PAS stain 40X).

DISCUSSION

Although mucormycosis is an extremely rare condition in healthy people, immunocompromised individuals are at a higher risk of infection. These include co-morbid and other conditions, such as diabetes mellitus, haematological and other malignancies, organ transplantation, prolonged neutropenia, immunosuppressive drugs, such as corticosteroids, [7] as well as other drugs like deferoxamine and voriconazole, severe burns, Acquired Immune Deficiency Syndrome (AIDS), drug abuse, malnutrition, and open wounds following trauma [8]. The recent surge in mucormycosis cases have been observed in post-COVID patients, largely due to excessive use of immunosuppressive steroids to treat the condition.

Histologically, giant cell invasion, thrombosis, and eosinophilic necrosis of the underlying tissues are the pathological hallmarks of mucormycosis. Pathological examination of biopsy samples can identify the hyphae based on diameter, presence or absence of septa, branching angle (right or acute branching), and pigmentation, which differentiates it from other fungal infections [9]. Special stains like PAS or Grocott Methenamine Silver (GMS) can be used to highlight the microbe.

A systematic review by Singh AK et al., showed male predominance comprising of 78.9% male patients. There was a history of diabetes mellitus in 80% and steroid intake in 76.3% of patients [7]. This data was in concordance with the present study, which showed that 74.5% were male patients. Data on risk factors, such as history of steroid intake and diabetes in the present study have also been presented in [Table/Fig-1].

As of 28th May 2021, when India had 14,872 mucormycosis cases, most of them had diabetes mellitus and prolonged steroid intake. This Indian epidemiological study showed that 55-76% of mucormycosis patients had diabetes [10]. In comparison, the present study showed that 75.5% of patients had diabetes. The variation may be attributed to the difference in sample sizes.

In another study, Arakeri G et al., showed a male predominance. They also showed that 68.3% of patients had a history of uncontrolled diabetes and 46% for steroid intake. Moreover, only two cases were fully vaccinated [11]. Comparison of this study with the present study show that the results were similar with reference to vaccination status, as most of the cases were unvaccinated in both the studies, as well as the fact that diabetes and steroid intake were both contributing risk factors.

There are not many studies related to mucormycosis incidence in vaccinated and unvaccinated patients. However, one survey conducted in Hyderabad showed that 86% of mucormycosis patients were not vaccinated against COVID-19 [12]. In the present study, 91.5% of patients with mucormycosis were not vaccinated against COVID-19, while 5.3% had taken the 1st dose and only

3.2% were fully vaccinated [Table/Fig-1]. The results of these two studies are somewhat similar.

The most notable finding of the present study was that the majority of mucormycosis cases were unvaccinated, which is also true for a study conducted by Joshi PK and Jadhav KK [13]. In this study also, males were more prone to COVID-associated mucormycosis and the incidence was observed more in unvaccinated patients than vaccinated patients.

Limitation(s)

The sample size was quite small. Also, there was no data on actual incidence of mucormycosis as only histopathologically confirmed cases were included.

CONCLUSION(S)

Males are more prone to COVID-associated mucormycosis. Also, diabetes and steroid intake are the most common risk factors, although this isn't true for all cases. Most importantly, it is highly plausible that vaccination against COVID-19 is likely to reduce the incidence of COVID-associated mucormycosis.

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