Research Article

Superinfection of Mucormycosis in Post-COVID-19 Patients with Diabetes at Tertiary Care Hospital in Eastern Uttar Pradesh

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Abstract

Introduction and Objectives: To determine the prevalence of mucormycosis in post COVID-19 patients. To understand the risk factor mainly diabetes and its association with post COVID-19 mucormycosis.

Method and Material: This a retrospective observational study of post-COVID-19 patients associated with mucormycosis which were managed in a tertiary care centre of Eastern UP from March 2021 to February 2022. The tissue sample for study was taken from surgical and medicine wards of the centre and the study was conducted in Microbiology Department. The procedures followed to process the sample were: 10% KOH mount after teasing the tissue. Culture on Sabouraud dextrose agar (SDA) with chloremphenicol and the fungal growth was stained with lactose phenol cotton blue (LPCB) for microscopy

Conclusion: There has been a surge in cases of mucormycosis in COVID-19 era. Uncontrolled diabetes and other immunocompromised states predispose to its development mainly in adult patients where diabetes is the most important predisposing factor. Although, early presentation and intervention play a very important part. Tight glycemic control, Amphotericin B and surgical debridement can lead to favourable outcomes.

Keywords: Amphotericin B, COVID-19, Diabetes, Immunocompromised, Mucormycosis.

Introduction

Coronavirus disease 2019 (COVID-19) was caused by severe acute respiratory syndrome coronavirus2 (SARS-CoV-2). It has been associated with wide range of bacterial and fungal superinfections.[1] Mucormycosis, *Aspergillus* and *Candida* have been reported as the main fungal pathogens causing co-infection in people with COVID-19 were found to be mucormycosis, *Aspergillus* and *Candida*.[2] Several cases of mucormycosis in people with COVID-19 were reported worldwide, particularly in India. The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium metabolic acidosis, diabetic ketoacidosis (DKA), overuse of zinc, high iron levels (increased ferritin) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators. Studies have implicated poorly controlled type-2 diabetes as the main risk factor for mucormycosis in COVID-19 patients (Table 1). These types of co-infections were common in patients with comorbidities like diabetes mellitus, COPD, prolonged corticosteroid therapy, etc. The second wave of COVID-19 along with its variants, affected the global population at its worst, causing undue complications. COVID-19 and mucormycosis, also known as black fungus, cause a lot of

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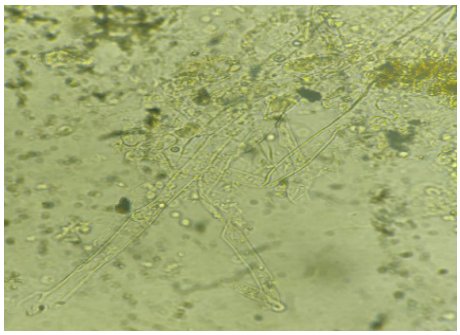

Figure 1: KOH mount of mucor (40X)

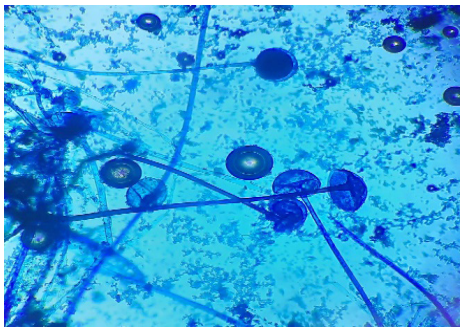

Figure 2: Lactose phenol cotton blue mount of mucor (40X)

morbidity and mortality and affect all sorts of populations. Paltauf in 1885, first described mucormycosis microbiologically and previously called it as *Phycomycosis or Zygomycosis*.[3] Later in 1957, Baker renamed it as mucormycosis.[4] It is a fungal infection caused by a mould of family mucormycetes which is widely distributed in the environment. These fungi are ubiquitous in soil and their spores are distributed in air and dust. The principal species associated with human infections include *Rhizopus, Mucor and Absidia*. These are most commonly associated with opportunistic infections in immunocompromised people. They develop a systemic infection following dissemination from the upper respiratory tract or nasal cavity. Angio-invasiveness is a characteristic of zygomycosis which makes it a cause of fatal disease, particularly affecting orbit, sinuses or the brain. Surveys and metanalysis suggested that mucormycosis is prevalent in a population of 0.005 to 1.7 per million globally.[5] India had the highest global burden of mucormycosis, accounting for 14 cases per one lakh of the population. Along with the increase in COVID-19 cases in India, there has been an alarming increase in COVID-19-associated mucormycosis in India. The prevalence of COVID-19-associated mucormycosis has increased 80% in India. In this state, the government of India reported COVID-19-associated mucormycosis as an epidemic in several states, including Uttar Pradesh. One of the causes of increased mucormycosis in India may be as India has the second largest cases of diabetes and diabetes (uncontrolled) is the most important factor associated with mucormycosis worldwide with a high mortality rate of 46%.[6,7] Also long-term use of steroids predisposes to opportunistic fungal infections, including mucormycosis.

All these findings need to be seen in relation to the COVID-19 pandemic and the enormous increase of mucormycosis cases mainly in India. These can lead to an impact on public health as the morbidity and mortality of COVID-19-associated mucormycosis is very high. Early diagnosis and immediate treatment is the only modality that can decrease the percentage of mortality in these cases. Even diagnosis is possible with minimal setting and an expert microbiologist. All this can lead to a better approach to a patient with suspected mucormycosis.

To address these issues of COVID-19-associated mucormycosis, we planned this study in our setting. The main concern was to find out the risk factors and to diagnose and treat mucormycosis in COVID-19 patients as soon as possible. Hereby we present our overall experience with mucormycosis in COVID-19 patients.

Materials and Methods

Study Setting

A prospective observational study was planned in the department of Microbiology and Level-3 ward of a tertiary care hospital in North India, enchanting various COVID-19 cases. Study was done between March 2021 to February 2022 (1-year). Case positivity month wise is shown in Table 2. The study population included all COVID/Post COVID patients with suspected mucormycosis with diabetes**.** Clinical data and consent were taken from all the patients or attendants on a performed proforma.

Table 1: Distribution of mucormycosis cases

Attributes no. of patients (n = 62)	*Number (%)*
Age (in years)	
<18	02 (03.2%)
18–45	11 (18%)
45–60	10 (16.1%)
>60	39 (63%)
Sex	
Male	41 (66.1%)
Female	21 (34%)
Comorbidity	
Diabetes	54 (87%)
Prolonged antibiotics	48 (77.4%)
Hospital stay of>14 days	58 (94%)
Anti-viral drug given	12 (19.3)
Oxygen support	48 (77.4)
Steroid usage	49 (79%)
Zinc 53	52 (84%)
Extent of involvement	
Sinus	33 (53.2%)
Orbital	26 (42%)
CNS involvement	03 (5%)

Table 2: Case positivity month-wise

Month	*Total samples received*	*mucormycosis detected*
March 21	37	05
April 21	38	13
May 21	23	18
June 21	18	11
July 21	15	06
August 21	5	02
September 21	4	01
October 21	2	00
November 21	1	00
December 22	8	02
January 22	5	02
February 22	00	00

Table 3: Species-wise distribution of mucormycosis in COVID-19

Species	*No of patients*
Mucor	35
Rhizopus	18
Absidia	9
Rhizomucor	0

Sample Collection

Samples (biopsy or scraping) of COVID-19 patients suspected of mucormycosis were obtained in normal saline from the affected area. The Institutional Ethical Committee approved the study, which follows the Indian Council of Medical Research (ICMR) ethical guidelines for biomedical research on human subjects.

Microbiological Methods

All samples received in the laboratory were seen for sample size and were divided into two parts. One part was put in 10 to 20% KOH for 2 to 4 hours and the other was cultured on SDA with an antibacterial agent without cycloheximide at 37°C for 7 to 14 days (Figure 1). KOH samples were subjected to microscopy and all broad aseptate hyphae samples were reported as suspected mucormycosis immediately. Samples cultured on SDA were looked into daily for growth. Colonies with thick, fluffy, cottony surfaces were followed by lactose phenol cotton blue staining and microscopy (Figure 2). Broad aseptate fungal hyphae with fruiting bodies containing sporangiophores and sporangiospores were seen. Further speciation was done according to the presence of spores/ rhizoids. Species wise distribution of mucormycosis in COVID-19 is shown in Table 3.

Exclusion Criteria

All patients with following conditions were excluded:

- Prolonged steroid therapy
- Chemotherapy

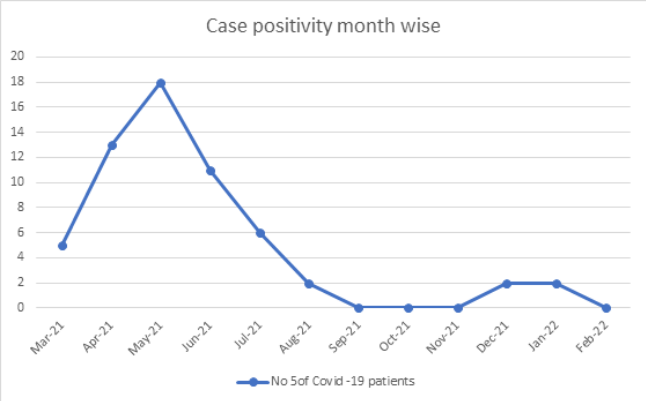

Figure 3: Case positivity month-wise

- Metabolic disorders other than diabetes nellitus.

Results

Of the total 156 samples of COVID-19 patients with suspected mucormycosis received. Case positivity month wise is shown in Table 2 and Figure 3.

In our laboratory, 62 patients with mcormycosis were diagnosed.

Discussion

Mucormycosis is an invasive fungal infection. It is rare in humans. Uncontrolled diabetes mellitus with or without DKA, hematological and other malignancies, organ transplantation, prolonged neutropenia, immunosuppressive and corticosteroid therapy, iron overload or hemochromatosis, deferoxamine or desferrioxamine therapy, voriconazole prophylaxis for transplant recipients, severe burns, acquired immunodeficiency syndrome (AIDS), intravenous drug abusers, malnutrition and open wound following trauma and other immunocompromised states predispose patients to develop mucormycosis.[8]

Mucormycosis can involve nose, sinuses, orbit, central nervous system (CNS), lung (pulmonary), gastrointestinal tract (GIT), skin, jaw bones, joint, heart, kidney and mediastinum, but rhino-orbital-cerebral is the most common type seen in the cases of mucormycosis.[8] Microbiological identification of the hyphae based on diameter, presence or absence of septa, branching angle (right or acute branching), and pigmentation differentiates it from other fungal infections. The 1950 Smith and Krichner[9] criteria for the clinical diagnosis of mucormycosis are still considered to be gold standard and include:

- Black, nectrotic turbinates easily mistaken for dried, crusted blood.
- Blood-tinged nasal discharge and facial pain, both on the side.
- Soft peri-orbital or peri-nasal swelling with discoloration and induration,
- Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia,

- Multiple cranial nerve palsies unrelated to documented lesions.

In 2019, a multi-centeric study of 388 confirmed or suspected cases of mucormycosis in India prior to COVID-19, by Prakash *et al*. was done nationwide. It was found that 18% cases has DKA and 57% of patients had uncontrolled DM.[10] Another study Tawfiq et al. concluded that the triad of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), corticosteroid use and uncontrolled diabetes mellitus have been evident for significant increase in the incidence of angioinvasive maxillofacial mucormycosis.[11]

Mucormycosis infection can be attributed to supplemental oxygen therapy, indiscriminate use of steroids or prolonged admission in hospital wards. Although the exact etiology remains unclear, a state of prevailing hyperglycemia seems to serve as an important association.

Out of 58 patients diagnosed with mucormycosis, 52 had diabetes. Diabetes is the most important predisposing factor. And most of the patients were of >60 years of age.

Although early presentation and intervention play a important part, strict glycemic control, Amphotericin B and surgical debridement can lead to favorable outcomes.

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Conflict of Interest

There are no conflicts of interest.

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