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IP International Journal of Medical Microbiology and Tropical Diseases

Journal homepage: https://www.ijmmtd.org/

Original Research Article

A study unraveling the links between diabetes mellitus, COVID -19 and mucormycosis

Trupti Jansari[1]*, Jay Jansari[2], Vishwa Gevariya[2], Rachna Patel[3], Simran Jain[1]

[1]Dept. of Pathology, Sumandeep Vidyapeeth Deemed to Be University, Vadodara, Gujarat, India
[2]Dept. of General Medicine, Sumandeep Vidyapeeth Deemed to Be University, Vadodara, Gujarat, India
[3]Dept. of Microbiology, Sumandeep Vidyapeeth Deemed To Be University, Vadodara, Gujarat, India

Abstract

Background: Mucormycosis is a potentially fatal, angio-invasive infection by a fungus, mainly seen in persons with compromised immune system. After the COVID-19 pandemic, an increase in mucormycosis cases has been observed. We aimed to study the prevalence and distribution of mucormycosis cases among the post - COVID - 19 patients and to identify their link with patients with diabetes mellitus.
Materials and Methods: This study was retrospectiveand observational in type, which included 35 patients presenting with warning symptoms and signs at a tertiary care centre in Gujarat. All age – groups and both gender cases with a history of COVID - 19 were included. All the data regarding demography, co – morbid condition like diabetes mellitus, clinical examination, routine blood investigations, KOH and lactophenol cotton blue (LPCB) preparations, computed tomography (CT) scan- paranasal sinuses (PNS) and histopathological examinations (HPE) were collected and analyzed.
Results: Out of total of 35 patients highest number (16) of the patients was from age group 51-60 years (45.7%), males were 21 (60%) and females were 14 (40%). 31(88.6%) patients had diabetes mellitus and 04(11.4%) were non – diabetic. KOH and LPCB preparations from 29(82.9%) cases showed presence of fungal hyphae and 6(16.7%) cases were negative. On CT Scan – PNS, 30(85.7%) cases presented with rhino – orbital, 03(8.5%) cases with rhino – orbito – cerebral and 02(5.8%) cases with nasal type mucormycosis. Histopathological examination confirmed the diagnosis of mucormycosis.
Conclusion: Mucormycosis is associated with increased mortality rate. Once the diagnosis is confirmed, surgical debridement should be performed as soon as possible along with medical management.

Keywords: Diabetes mellitus, Mucormycosis, Post COVID - 19, Fungal infection.

Received: 22-05-2025; **Accepted:** 04-07-2025; **Available Online**: 04-09-2025

1. Introduction

Throughout the world, millions of people have been affected by SARS COV-19 virus. It is mainly a disease of respiratory system and clinical presentation may vary from as trivial as common cold to pneumonia and death. The transmission is via inhaled droplet infections or by entering the body through infected surfaces. SARS-CoV-19 was initially detected in December 2019 in Wuhan, China.[1] It has created the global health crisis claiming many lives.[2]

Mucormycosis is a rare angio - invasive, potentially fatal infection by fungus that occurs in patients with impaired immunity. e.g. in patients with human immunodeficiency virus infection, diabetes mellitus, haematological malignancies, iatrogenic immunosuppression as well as in patients with history of organ transplantation.[3]

Increased surge of mucormycosis cases during COVID – 19 pandemic and also as post COVID - 19 sequelae has been observed.[2] It can be classified into rhino-orbito-cerebral, renal, pulmonary, disseminated, cutaneous and gastrointestinal subtypes.[2-4]

Gujarat state has observed the highest number of mucormycosis cases in India. With more than 2000 cases and

*Corresponding author: Trupti Jansari
Email: dr.truptijansari@gmail.com

https://doi.org/10.18231/j.ijmmtd.v.11.i.3.13

more than 250 deaths due to mucormycosis. The Gujarat government declared the Mucormycosis an epidemic under the Epidemic disease Act 1857.[5]

There are some alarming features of mucormycosis (**Table 1**), of which the treating clinician should be aware of. Mucormycosis should be the suspicion if a patient exhibits any of the symptoms and signs listed in **Table 1**.[6]

Our aim was to study the prevalence and distribution of mucormycosis cases amongst the post COVID - 19 patients visiting a tertiary care center in Gujarat and to link its association with the presence of diabetes mellitus.

2. Materials and Methods

This retrospective observational study included 35 patients presenting with warning symptoms and signs of fungal infection at a tertiary care centre in Gujarat. Majority of patients were immunocompromised. The cases from all age – groups and both gender were included. All patients had a history of COVID - 19 positive test. The real time - polymerase chain reaction (RT – PCR) test was used to label patient as a COVID – 19 positive using the TRUPCR® SARS – CoV – 2 RT – qPCR Kit. All the demographic and co – morbid condition data were obtained and recorded. The data regarding diagnostic details e.g. clinical examination, routine blood investigations, blood sugar and HbA1c levels, KOH and lactophenol cotton blue (LPCB) preparations, computed tomography (CT) scan- paranasal sinuses (PNS) and histopathological examinations (HPE) were collected and analyzed. These data were entered into Microsoft excel and presented in the form of percentage, frequency, bar charts and pie charts.

3. Results

This study was retrospective and observational study that was carried out at a tertiary care centre in Gujarat. We included total of 35 patients with all age groups and both gender.

Highest number (16) of the patients was from age group 51-60 years (45.7%). Out of total 35 patients, males were 21 (60%) and females were 14 (40%). The male to female ratio was 1.5:1. (**Table 2**)

Out of 35 patients, 31(88.6%) patients had history of diabetes mellitus and 04(11.4%) were non – diabetic. (**Figure 1**). The mean random blood sugar and mean HbA1c of these diabetic patients were 268.5 mg/dl and 8.2% respectively. KOH and LPCB preparations from 29(82.9%) cases showed presence of mucorales species of organism characterized by broad, non – septate, ribbon – like and wide fungal hyphae with irregular branching and 6 (17.1%) cases were negative which later on turned positive for mucormycosis on biopsy examination. Among total 35 patients, 29 cases were positive by microbiology and all 35 cases were positive by histopathological examination of biopsy specimen for the hyphae of mucormycosis. On CT Scan – PNS, 30(85.7%) cases presented with rhino – orbital, 03(8.5%) cases with rhino – orbito – cerebral and 02(5.8%) cases with nasal type of mucormycosis.(**Figure 2**)

Table 1: Warning symptoms and signs of rhino-orbito-cerebral mucormycosis[6]

Nasal stuffiness	**Regional pain – orbit, paranasal sinus or dental pain**
Foul smell	Proptosis
Epistaxis	Sudden loss of vision
Nasal discharge - mucoid, purulent, blood-tinged or black	Facial paresthesia, anesthesia
Nasal mucosal erythema, inflammation, purple or blue discoloration, white ulcer, ischemia, or eschar	Sudden ptosis
Eyelid, periocular or facial edema, facial discoloration	Ocular motility restriction, diplopia
Facial pain	Facial palsy
Worsening headache	Fever, altered sensorium, paralysis, focal seizures

Table 2: Age and Gender distribution

Age group (years)	**Male**	**Female**	**Total**
Less than 20	0	0	0
20-30	0	0	0
31-40	0	0	0
41-50	3	1	4
51-60	10	6	16
61-70	4	5	9
71-80	4	2	6
Greater than 80	0	0	0
Total	21	14	35

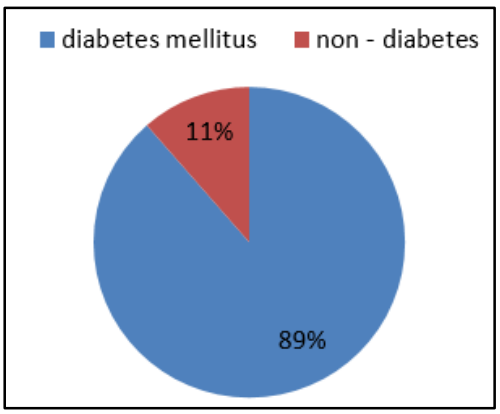

Figure 1: Cases with diabetes and non–diabetics

Histopathological examination from the biopsies of all cases revealed presence of mucosal lining epithelium, underlying stromal mixed inflammatory infiltrate, oedema and necrosis. There was presence of large, broad non - septate branching fungal hyphae at 45 – 90 degree angles with thin

wall infiltrating surrounding tissue.(**Figure 3**a,b) Diagnosis of mucormycosis was confirmed.

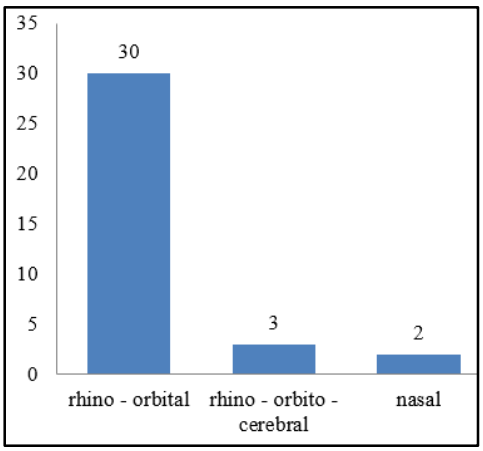

Figure 2: Type of mucormycosis

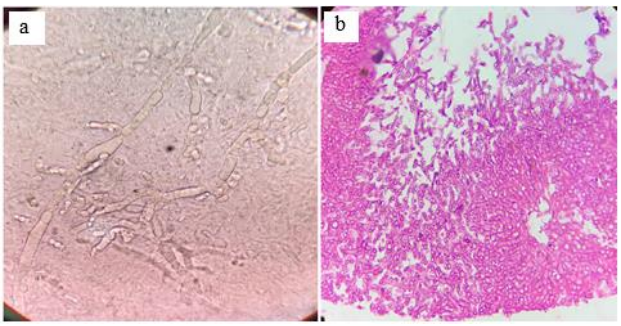

Figure 3: a: KOH Mount preparation; **b:** Broad, non-septate fungal hyphae (H & E stain, High power (40x).

4. Discussion

Paltauf in 1885, first described the mucormycosis. It is an aggressive fungal infection that generally affects patients with impaired immune system. It is a potential fatal fungal disease, with grave prognosis. The most common subtype is rhino - orbito – cerebral type.[7]

Despite of its low incidence, ranging from 0.005 to 1.7 per million populations, corona virus pandemic attributed to significant ride in its incident in recent times.[8] In India, the prevalence of mucormycosis is almost 80 times more than developed countries e.g. 0.14 per 1000.[1]

COVID - 19 patients has higher risk for invasive fungal infections specially in individuals with diabetes, malignancies, steroid therapy, respiratory diseases, intubation/mechanical ventilation, cytokine storm, HIV, transplants patients etc.[1]

Mucormycosis is one of the most rapidly growing and fatal forms of fungal infection, usually beginning in the nose and paranasal sinuses, followed by spore inhalation and possible extension to the brain, and then the sinuses, nose, and eyes. Its clinical presentation begins with palate and sinus necrosis, and then progresses to the orbit before affecting intracranial structures. Reddish-black nasal turbinate and septum, as well as nasal discharge, can be visible. The progression of the disease into the cerebral vault leads to loss of vision, lethargy, and seizures, followed by death.[1,4]

According to the emerging research, COVID-19 is prevalent in patients with diabetes, hypertension, and cardiovascular disease (CVD). Diabetes patients are prone to infections in general; however, there are numerous particular characteristics that contribute to the increased incidence and severity of SARS CoV2 infection in diabetes. For example, increased Furin, increased ACE-2 expression, increased Interleukin-6 (IL-6) and impaired T-cell activity.[9] Diabetes patients have high blood sugar levels and relatively acidic tissues, which creates an ideal habitat for mucorales fungi to flourish.[1]

The findings of the study done by Sharma M et al were similar to our study which showed that mucormycosis was more prevalent in diabetics as compared to non – diabetics.[3]

Phagocytes are the primary host defense mechanism against Mucormycosis. Hyperglycemia and acidosis are known to limit ability of phagocytes to move toward and kill organisms by both oxidative and nonoxidative pathways, predisposing these patients to mucormycosis. Neutropenic patients, such as COVID – 19 positive, are at a higher risk of developing mucormycosis; also, these COVID - 19 positive patients were on corticosteroids, which intensified the hyperglycemia.[2]Furthermore, COVID-19 patients have increased inflammatory cytokine levels and reduced cell-mediated immunity, with lower cluster of differentiation 4 and 8 positive T-helper (CD4+ T and CD8+ T) cell counts, indicating vulnerability to fungal co-infections.[10] Critically sick patients, particularly those referred to critical care units, those requiring mechanical ventilation, or those with extended hospital stays, were more likely to have fungal co-infections.[11] Excessive use of steroids in COVID-19 treatment can also reduce immunity that allows opportunistic fungal infections to thrive.[3]

Sharma M et al and Satish et al in their studies found high preponderance of mucormycosis in males which was comparable to our study that had male to female ratio of 1.5:1.[2-3]

Y.P. Talmi et al. described rhinocerebral mucormycosis as an infection of the sinuses that can migrate to the brain. This type of mucormycosis is more common in persons with uncontrolled diabetes and those who have undergone a renal transplant.[12] A study done by Satish D et al. showed most common type of mucormycosis was rhino – orbital type(48%) followed by rhino – orbito – cerebral (24%) and nasal (28%).[2] Our study also showed similar findings.

In April 2020, Song et al. investigated the link between COVID-19 and invasive fungal sinusitis and determined that a high number of individuals who were exposed to or recovered from COVID-19 are at an elevated risk of getting

invasive fungal infections.[10] According to a recent assessment, 8% of coronavirus-positive or recovered patients developed secondary bacterial or fungal infections during hospitalization, despite frequent administration of broad-spectrum antibiotics and steroids.[13]

Diagnosis was made by clinical examination, CT scan, KOH Mount, LPCB preparations, fungal cultures and HPE. Biopsy is the gold standard method to confirm the diagnosis.[4]

CT scan from majority of cases revealed non –enhancing hypodense mucosal thickening with multiple air foci without air-fluid levels in sinuses. In some cases bony destruction and erosion of the walls of sinuses were present with loss of right periantral fat planes. Intra – orbital spread and bilateral proptosis was noted in few cases which suggested possibility of invasive fungal sinusitis. KOH and LPCB preparation showed presence of non – septate, broad fungal hyphae. Hematoxylin and Eosin stained sections from biopsy showed the presence of large, non – septate, broad, branching hyphae at 45 – 90 degree angles with thin wall infiltrating surrounding tissue which confirmed the diagnosis of mucormycosis.[14]

Antifungal medications and debridement surgeries are among the available treatment strategies. The standard treatment for invasive mucormycosis has been Amphotericin B. These treatment recommendations are supported by the global guideline for the diagnosis and management of mucormycosis in 2019 by the European Confederation of Medical Mycology (ECMM) and Mycoses Study Group Education and Research Consortium, that supports an early complete surgical treatment whenever possible, along with systemic antifungal therapy. Antifungal therapy consists of IV Amphotericin B (50 mg/day) with a total dose of 1.5-2 gms, liposomal Amphotericin B (5-10mg/kg), lipid complex, and posaconazole (400mg bid).[2] The prognosis is largely determined by the extent to which the disease manifests itself and the effectiveness with which the therapy is initiated.[4]

Limitations of the study: Our study was a single center study that included the patients from limited geographic area. To make the findings more generalized to the population, multicentre study is required.[15]

5. Conclusion

Mucormycosis is a disease with high mortality rate. Increased surge of mucormycosis have been observed in patients having diabetes mellitus already having impared immunity with superadded COVID-19 infection. Explanation of warning indicators to patients and their families upon discharge following COVID-19 treatment may encourage them to seek immediate medical help. Awareness of and attention to warning indicators, a high index of clinical suspicion, and early diagnosis are critical to disease alleviation. Once the diagnosis is established, surgical debridement of the infected area should be undertaken as soon as possible, followed by medical management.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Jansari T, Jansari J, Gevariya V, Patel R, Jain S. A study unraveling the links between diabetes mellitus, COVID - 19 and mucormycosis. *IP Int J Med Microbiol Trop Dis*. 2025;11(3):312-315.