

A Study of Causation and Extent of Rhino-Orbito-Cerebral Spread of Mucormycosis in COVID-19 Treated Patients at a Tertiary Care Hospital in North India

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Abstract:

Background: The COVID-19 pandemic has resulted in immense devastation, with a staggering death toll of over three million worldwide. As a consequence, there has been a notable rise in opportunistic infections, with one of the most alarming being COVID-19 associated Mucormycosis (CAM). The lack of comprehensive guidelines for screening and managing this condition, coupled with delayed diagnoses and poor prognoses, have heightened concerns among healthcare professionals that an epidemic of CAM may occur alongside the existing pandemic.

Method: Twenty-one cases of invasive fungal infection from March to November 2021 were retrospectively examined. Demographic, clinical, laboratory, radiological, microbiological, pathological, and outcome data were then collected and analyzed.

Result: Twenty-one consecutive inpatients with COVID-19 associated Mucormycosis (CAM) had a 57% pre-existing diabetes mellitus rate. The most prevalent symptoms at the beginning of the disease included facial swelling (81%), periorbital edema (52%), fever (81%), and headache (57%). According to radiographic studies, the majority of patients showed thickening of the sinus mucosa, which was followed by inflammation of the periorbital muscles and cavernous sinus infiltration.

Conclusion: Steroid use, diabetes mellitus, and superadded COVID-19 infection induced immunodeficiency caused a higher incidence of Mucormycosis. The study highlighted the importance of early detection and proactive treatment, including surgical debridement and antifungal therapy, which significantly improved the long-term outcome and reduced the rates of mortality and morbidity.

Keywords: Mucormycosis, ROCM, COVID-19.

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Introduction

Mucormycosis is an uncommon and serious fungal infection caused by a fungus known as Mucorales. Currently, the rate of fungal infections is on the rise. Mucormycosis is the second most common fungal infection after *Aspergillus*. [1-3] This infection can rapidly worsen in people who have weakened immune systems or metabolic issues, leading to blood vessel blockage or involvement of the central nervous system. [4]

Neutropenic and immune-compromised patients, such as those who are Covid-positive, have an elevated risk of developing mucormycosis. The extensive use of corticosteroids in Covid-19-

positive patients can worsen hyperglycemia, making them more susceptible to invasive fungal infections. [5]

The most frequent underlying conditions that contribute to increased incidence include diabetes mellitus, the use of systemic steroids lymphoid malignancies, burns, long hospital stays, and kidney failure. [6,7]

Methods

Objective: The objective of our study was to examine the potential occurrence of simultaneous invasive fungal infections and Covid-19, and to

analyze the prevalence of ocular symptoms as well as other clinical characteristics and treatment outcomes.

Study Design: This is a retrospective observational study.

Sample Size: The study included 21 patients who were diagnosed with mucormycosis between March and November 2021.

Selection Criteria:

The patients underwent clinical and histological diagnosis. The clinical diagnosis of acute invasive fungal sinusitis was made based on symptoms and medical examination. To rule out invasive fungal sinusitis (mucormycosis), crusts from the nasal cavity were sent for Calcofluor KOH stain.

In order to assess the possible involvement of the nose, paranasal sinuses, and orbits, a contrast-enhanced CT scan was performed. Patients with suspected cerebral involvement also underwent a CT scan of the brain. For analysis purposes, data on the patient's baseline demographics, clinical signs, ophthalmic and other examinations to assess the extent of disease, nasal endoscopy with biopsy, and results of laboratory and radiological examinations were collected.

Statistical Analysis: The collected data was entered into Microsoft Excel for analysis. Descriptive data was then presented using pie charts and bar diagrams to show frequencies and percentages.

Ethical consideration: Ethical approval was obtained from the Institutional Ethics Committee.

Observation and Results

Presenting Characteristics: In our hospital, we had twenty-one cases of Mucormycosis. Among them, seven were female and fourteen were male. The average age of the patients was 55 ± 16 years, with an age range of 23 to 81 years.

It was surprising to note that all of these cases had recently experienced a COVID-19 infection. The severity of the COVID-19 symptoms ranged from moderate to severe, as per the WHO clinical classification. Additionally, 17 patients had previously undergone oxygen therapy, all of them had a history of steroid medication, and approximately half of the patients were administered Remdesivir during the management of their COVID-19 illness.

Diabetes Mellitus (DM) was the most prevalent comorbidity, and twelve patients had been undergoing treatment for approximately 2 to 26 years. The majority of the patients had inadequate glycaemic control, as evidenced by their high glycated hemoglobin (HbA1c) levels, ranging from 6-18 with a majority having HbA1c of above 9. One patient presented with a recent 1-month history of tooth extraction, and one has a history of chronic renal disease and underwent dialysis 2 months ago. Figure 1 shows the percentage of patients with various co-morbidities.

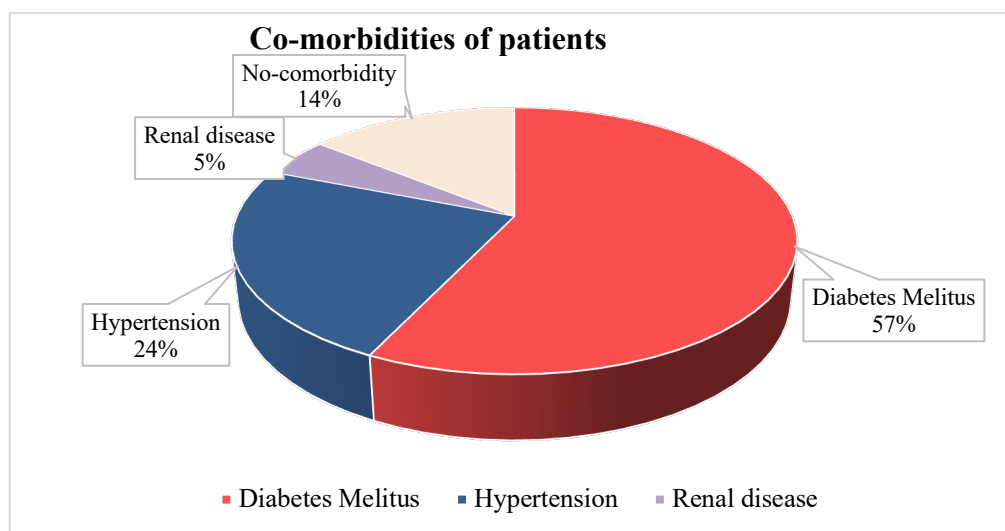


Figure 1: Co-morbidities of patients

The duration between the onset of COVID-19 and mucormycosis symptoms obtained from the patient's data ranged from 3 to 45 days with a mean of 17.3 days. Table 1 shows the site/extent of involvement of fungus revealed on clinical examination, laboratory findings, and imaging.

Table 1: Site/Extent of Involvement

Site of involvement	No. of cases	Percentage
Nasal	4	19.05%
Sino-nasal	6	28.57%
Sino-naso-orbital	5	23.81%
Rhino-orbital-cerebral	6	28.57%
Clinical involvement		
Orbital apex syndrome	6	28.57%

The graphical pie-chart representation of the site of fungal involvement is shown in Figure 2.

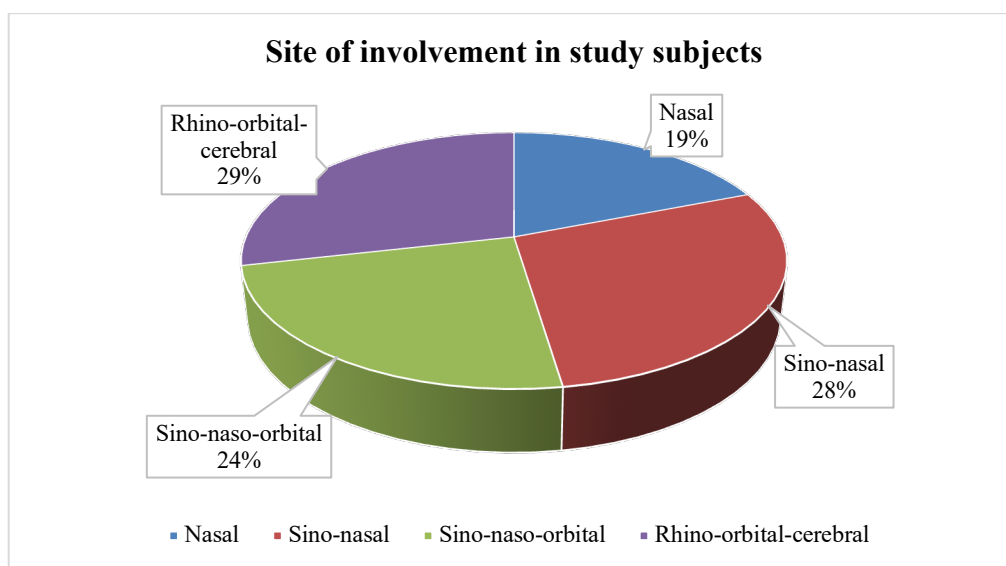


Figure 2: Site of involvement in study subjects

The radiological findings of the patients are shown in Table 2.

Table 2: Radiological imaging manifestation (CT/MRI)

Radiological Findings	No. of cases	Percentage
Thickening of sinus Mucosa	21	100.00%
Inflammation of the peri-orbital muscles	11	52.38%
Cavernous sinus infiltration	4	19.05%
Occlusion of the internal carotid artery	2	9.52%

The graphical representation of radiological findings is shown in Figure 3.

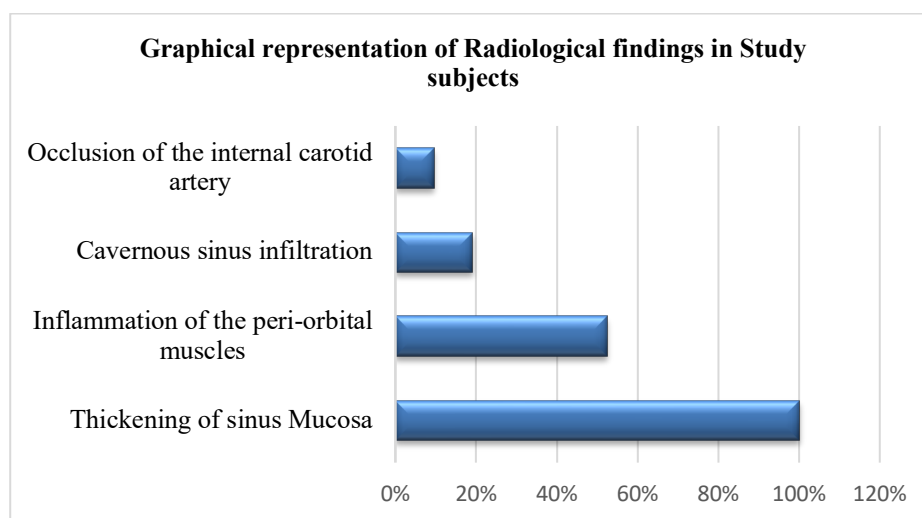


Figure 3: Graphical representation of Radiological findings in Study subjects

The most frequent sites affected were reported to be the nose, palate, and paranasal sinuses. This is followed by the orbit and can infiltrate the cavernous sinus, meninges and brain.

Upon the onset of sickness, the primary and frequent symptoms noted were fever, headache, swelling in the facial and peri-orbital areas, as well as

general constitutional discomfort. Tooth pain and nosebleeds were infrequently detected.

Of 21 cases of mucormycosis, the vision was altered in 9 patients including no perception of light in one case and only perception of light/hand moving in three cases. The clinical features of the study subjects are shown in Table 3.

Table 3: Clinical Features Observed in the Study subjects

Clinical features	No. of Cases	Percentage
Fever	17	80.95%
Headache	12	57.14%
Periorbital edema	11	52.38%
Facial swelling and pain	17	80.95%
Nasal obstruction	16	76.19%
Lacrimation	11	52.38%
Cranial nerve palsy	9	42.86%
Decreased vision	9	42.86%
No perception of light (PL-ve)	1	4.76%
Exophthalmia	6	28.57%
Diplopia	6	28.57%
Blepharoptosis	7	33.33%

The graphical representation of the clinical features of study subjects is shown in Figure 4.

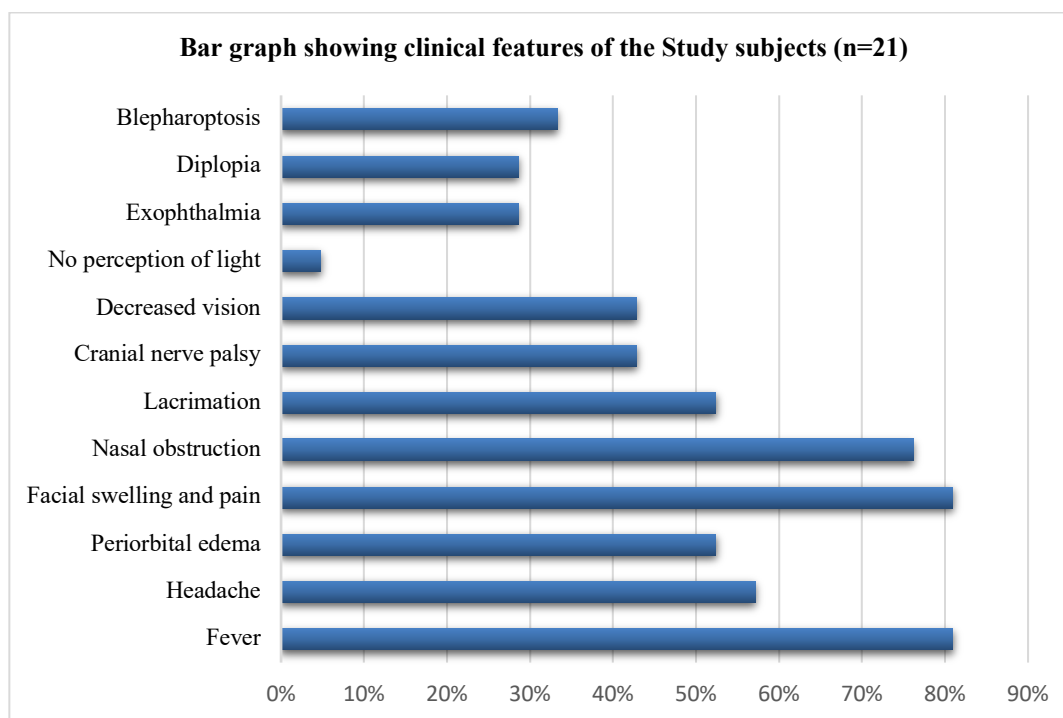


Figure 3: Bar graph showing clinical features of the Study subjects (n=21)

Intervention

Medical management with antifungals was the mainstay of treatment. Approximately all of the patients received different formulations of amphotericin B; followed by Posaconazole based on the availability and affordability of the patients.

Surgical intervention was the solution to hasten recovery from the disease. Most of the patients

underwent endoscopic debridement and maxillectomy. In one patient, orbital exenteration was performed to prevent the cerebral involvement of fungus.

Outcome

Out of 21 patients, fifteen patients were discharged asymptotically with follow-up advice and six succumbed to death. No recurrence has been

reported in 9 patients in six-month duration follow-up, while 6 patients lost follow-up.

Discussion

The second wave of COVID-19 in India resulted in a significant number of illnesses and deaths, with the emergence of a new condition called COVID-19 associated Mucormycosis (CAM). In our study, we found that the main demographic risk factors for CAM were being male, being older, and having poor hygiene. The most common and important risk factor for CAM was having diabetes with poorly controlled blood sugar levels, particularly when associated with diabetic ketoacidosis. We also discovered that the severity of COVID-19 infection and the extensive use of steroids and oxygen therapy were significant risk factors for CAM in the study subjects.

Rhino-orbito-cerebral mucormycosis (ROCM) occurs when sporangiospores from the paranasal sinuses enter the orbits, cavernous sinuses, and brain after germination. COVID-19 associated Mucormycosis is a life-threatening illness that requires extended treatment, especially when fungus reaches the cranial cavity. Our research revealed that 6 patients succumbed to cerebral fungus complications, while the remaining 15 received long-term therapy while being hospitalized. Mucormycosis, also known as Zygomycosis, is an uncommon yet severe fungal infection caused by Mucormycetes molds.[8] Our findings correlate with a comprehensive analysis of CAM, which showed that males faced a greater risk than females.

Additional risk factors for mucormycosis include diabetes mellitus (especially with diabetic ketoacidosis), chronic kidney disease, cancer, organ transplant, stem cell transplant, neutropenia, long-term corticosteroid use, injection drug use, iron overload or hemochromatosis, surgery-induced skin injury, burns, and other immune-compromised conditions.[9,10] In our study, we found that diabetes mellitus and poor glycemic control were significant risk factors for the development of mucormycosis. Additionally, one of our study subjects who recently underwent renal dialysis also acquired the infection, which aligns with previous studies.[10,11]

Corticosteroids were administered to treat moderate-severe COVID-19 patients, which also lower white blood cells and T cells, thereby reducing immunity. These steroids also contribute to hyperglycemia, which increases the risk of mucor growth. COVID-19 affects iron metabolism, causing elevated ferritin and reactive oxygen species. The cytokine storm also raises the levels of free iron in the circulatory system, encouraging mucor growth.[12] The most frequent symptoms reported in this study were swelling around the face and eyes, fever, headache, pain in the eye sockets, and a general feeling of illness. These findings align with

a previous study conducted by Kursun et al.[13] Another study also identified fever, swelling in the face, swollen eye sockets, facial pain, and difficulty breathing through the nose as the main complaints reported by study subjects.[14] Additionally, imaging revealed the presence of para-nasal sinus, orbital, cranial nerve, palate, and cavernous sinus involvement, similar to El-Khily et al.'s study.[15] CT scans can detect organ involvement, typically displaying mucosal thickening, edema, blood clots, and hemorrhages. Our study utilized surgical debridement as the primary treatment method for invasive fungal infection. Procedures such as functional endoscopic sinus surgery, maxillectomy, and orbital exenteration were performed on the patients, correlating to the previous study.[15]

Despite the intensive surgical and medical treatment approach, the mortality and morbidity rates associated with invasive fungal infections remain significantly high, spanning from 18% to 80%.[16] These rates are especially elevated in patients with cranial involvement of fungus. In our case, despite the implementation of aggressive management, six patients unfortunately succumbed to the infection, while the remaining individuals responded to the treatment.

Conclusion

Diabetes mellitus (along with diabetic ketoacidosis) and extensive steroid use were identified as the primary risk factors for COVID-19 associated mucormycosis (CAM) in this research. The study highlighted the importance of early detection and proactive treatment, including surgical debridement and antifungal therapy, which significantly improved the long-term outcome and reduced the rates of mortality and morbidity.

Limitations of the Study

The study's research limitations include being conducted in a single center, specifically a tertiary care hospital in North India. Additionally, the study had a relatively small number of cases and short-term follow-ups.

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