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Original Research Article

To Study the Occurrence of Mucormycosis in the Post Covid-19 Patients and its Association with Uncontrolled Diabetes Mellitus at a Tertiary Care Centre.

Jyoti Kasture[1], Rajendra Chaudhari[2], Devangana Rajyaguru[3], Preeti Bajaj[4], Apurva Ramteke[5]

[1]Associate Professor, Department of Pathology, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik.

[2]Associate Professor, Department of Pathology, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik.

[3]Associate Professor, Department of Pathology, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik

[4]Professor & Head, Department of Pathology, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik.

[5]JR-3, Department of Pathology, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik.

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Corresponding author: Dr. Preeti Bajaj
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Abstract

Introduction: Mucormycosis is becoming more prevalent among post COVID-19 patients. Diabetes mellitus (DM) is a risk factor for severe COVID-19 and mucormycosis on its own. Without prompt identification and treatment, the condition may advance quickly, with death rates from intra-orbital and cerebral complications recorded. AIMS AND Objectives: To study the spectrums of fungal infections in post Covid-19 patients on histopathology.

Materials and Methods: A total of 104 random subjects who were admitted for signs and symptoms of mucormycosis and had a history of COVID- 19 infection were included.

Results: The study revealed nasal and paranasal sinus involvement in a large number of patients. 73.08% patients had high BSL. DISCUSSION: In critically unwell patients with COVID-19 and DM, a high index of suspicion for Covid associated mucormycosis, especially if rhino-orbital or rhino-cerebral symptoms are present, is needed. Conclusion: We are learning more about the Covid-19 infection's novel and long-term manifestations.

Keywords: Mucormycosis, COVID-19, Diabetes, histopathology.

Introduction

A mystery pneumonia-like condition was discovered in Wuhan city of China, in December of 2019. The virus that caused the disease was designated coronavirus disease (COVID-19) by The International Committee on Taxonomy of Viruses, and the virus that caused it was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

COVID-19 is largely a respiratory disease, but it can also induce symptoms in the

gastrointestinal, neurological, renal, and cardiovascular systems. The SARS CoV-2 infection spread swiftly, posing a serious health risk to individuals all across the world, causing the World Health Organization to proclaim the disease a pandemic on March 11, 2020. [1]

For clinicians and researchers alike, this outbreak has been a challenge. The clinical features of COVID-19 infection range from asymptomatic to mild symptoms like fever, dry cough, dyspnea, myalgia, sore throat, and headache to more severe and emergent symptoms like confusion, chest pain, hypoxemia, pneumonia, and other complications that necessitate ICU admission and mechanical ventilation. In a few studies, diarrhoea, anosmia, and ageusia, as well as neurologic signs, have been recorded. [2] The reverse-transcriptase polymerase-chain reaction can be used to diagnose the 2019-novel coronavirus (RT-PCR).

In influenza, SARS, MERS, and other respiratory viral diseases, secondary infections are a well-documented phenomenon.

On the other hand, super-infections and co-infections in COVID-19 pneumonia are now being researched. [3] In hospitalised, critically ill Covid-19 patients, secondary infections are common, accounting for 10 to 30% of cases, with fungal infections being 10 times as likely. [3] It's impossible to say whether it is a complication of the condition or its treatment because the course of the illness is unknown.

Mucorales infections are also becoming a concern in COVID-19, as poorly controlled diabetes and other co-morbidities are risk factors for both mucormycosis [4] and severe COVID-19, and the use of corticosteroids in the treatment of severe/critical illnesses COVID-19.COVID-19 has been identified as a risk factor for MCR.

Mucormycosis (phycomycosis, zygomycosis) is an uncommon opportunistic fungus infection caused by mucorales order and mucoraceae family fungi. In 1885, Paultauf was the first to describe it. [5] It is the third most prevalent angioinvasive fungal infection, behind candidiasis and aspergillosis. [6] It usually affects immunocompromised persons, and it's only seen in healthy people on rare occasions. [7] Mucormycosis infection develops when the immune system of the compromised host is damaged, leading in rapid proliferation and invasion of fungal organisms in deeper tissues. [8]

Mucormycosis is caused by uncontrolled diabetes (especially in patients with ketoacidosis), cancers such as lymphomas and leukemias, organ transplant, renal failure, cirrhosis, burns, protein–energy malnutrition, long-term corticosteroid and immunosuppressive therapy, and acquired immune deficiency syndrome (AIDS). [9]

Source of infection is the inhalation of spores by the nose or mouth, or even a skin wound.

Individuals with weaker cellular and humoral defense mechanisms may not be able to respond properly.

The fungus can move to the orbit, meninges, and brain via direct extension from the paranasal sinuses. Some people with mucormycosis, on the contrary, have no known risk factors. [10] Early identification of the disease, as well as robust and rapid medical and surgical therapies, are required to avoid the high morbidity and death associated with this disease process. [11]

Mucormycosis sinus infection is a life-threatening invasive fungal sinusitis that primarily affects individuals who are immunocompromised, with a reduced neutrophilic response. Patients with uncontrolled diabetes, AIDS, iatrogenic immunosuppression, haematological malignancies, and organ transplant patients are all eligible. [12]

Mucormycosis is characterized by the appearance of hyphal infiltration of sinus tissue and a temporal course of less than four weeks. [13,14] If intracranial extension is present, rhinocerebral mucormycosis might present with unusual signs and symptoms similar to severe sinusitis, such as nasal blockage, crusting, proptosis, facial discomfort and oedema, ptosis, chemosis, and even ophthalmoplegia, as well as headache and fever. [15,16] A black eschar may be seen in the nasal cavity or on the hard palate, though is not typical. [17,18] Mycotic infiltration of blood vessels, vasculitis with thrombosis, tissue infarction, haemorrhage, and acute neutrophilic infiltrate are all histological characteristics. [19]

Mucormycosis is a deadly angioinvasive opportunistic infection in an immunocompromised host. Mucormycosis can come in a multitude of manifestations, including pulmonary, gastrointestinal, rhino-orbital-cerebral, cutaneous, and disseminated forms.

Diabetes is the most common metabolic disorder, and it is a risk factor for severe COVID-19 and mucormycosis on its own. Superinfection with mucormycosis in individuals with diabetes who have COVID-19 can result in a worse clinical outcome and a longer hospital stay. [20]

Even with quick diagnosis, treatment of underlying conditions, and vigorous medical and surgical intervention, care is frequently ineffective, resulting in infection spread and mortality.

The number of COVID-19 patients is continuing to rise over the world. Treatment in intensive care units (ICU) has become a major problem; as a result, early detection of severe forms is critical for patient triage. In addition, the number of cases of rhino-orbital Mucormycosis in persons with coronavirus disease 2019 (COVID-19) has increased, particularly in India. COVID-19 patients should be studied for better prevention and therapy of these opportunistic infections in order to reduce their prevalence and morbidity. Prophylactic treatment regimens, as well as the rational use of corticosteroids, must be devised.

This study aims to study occurrence of mucormycosis in the post covid-19 patients and its association with uncontrolled diabetes mellitus.

Aims and Objectives

1. To study the association of occurrence of mucormycosis with Diabetes Mellitus in post Covid-19 patients.
2. To study the spectrums of fungal infections in post Covid-19 patients on histopathology.
3. To study the distribution of Mucormycosis infection in post-COVID patients based on the age, sex, treatment given for COVID-19 infection and organs involved by Mucormycosis.

Material and Methods

The study was undertaken in the department of Pathology at Dr Vasantrao Pawar Medical College, Hospital and Research Centre, Nashik. All the patients suspected of mucormycosis infection, post COVID -19 were included in the study after they fulfilled the eligibility criteria.

Eligibility Criteria:

Inclusion Criteria for Patients:

- All suspected cases of mucormycosis of the rhino – orbital tract in post Covid-19 patients irrespective of age and gender.

Exclusion Criteria for Patients:

- All non Covid-19 patients irrespective of age and gender with suspected fungal infections of the rhino-orbital tract.
- All non Covid-19, known cases of Diabetes Mellitus, with signs and symptoms of mucormycosis, irrespective of age and gender.

All the patients satisfying eligibility criteria were included after taking well informed consent.

All the patients underwent operative procedures such as endoscopic biopsies, FESS operations, maxillectomies or exenteration as was decided by the ENT and Ophthalmology surgeons. The specimens received were subjected to routine histopathological examination.

Histopathological Examination:

The surgical specimens were evaluated grossly. The sections were taken from representative areas (in cases of maxillectomies, where the surrounding soft tissues were taken for examination and in cases of orbital exenterations where sections were taken from the grossly abnormal looking areas) or were submitted as whole for processing (in cases of soft tissues obtained from the nasal cavities, sinuses or nasal crusts). The tissue was fixed in 10% buffered formalin and then processed by the routine paraffin embedding techniques. Sections were cut at 4-5 microns thickness and stained with hematoxylin and eosin.

Results

A total of 104 patients were included in the study after they fulfilled the inclusion criteria.

Out of these, 77 patients were male (74.04%) whereas 27 patients were females (25.96%).

Table 1: Sex Wise Distribution

SEX	NO. OF PATIENTS	PERCENTAGE
MALE	77	74.04
FEMALE	27	25.96
TOTAL	104	100

The age groups of the patients ranged from 26 years to 84 years. The average age ranged from 50.33 years.

Table 2: Age Wise Distribution:

AGE GROUP	NO. OF PATIENTS
21-30	05
31-40	22
41-50	31
51-60	21
61-70	18
71-80	06
>80	01
Total	104

32 cases were known diabetics (30.77%), whereas 72 cases (69.23%) had no history of being diagnosed as diabetics.

The random blood glucose levels (BSL) of the patients on admission ranged from 80 to 509 mg/dL. The average BSL was 193.27 mg/dL. [Normal range of random BSL being 80 to 120 mg/dL]

76 patients (73.08%) had BSL levels above 120 mg/dL; out of which; 23 patients (30.26%) had BSL levels above 240 mg/dL.

46 patients (44.23%) patients had received oxygen therapy for the treatment of COVID-19, whereas 58 cases (55.77%) had not.

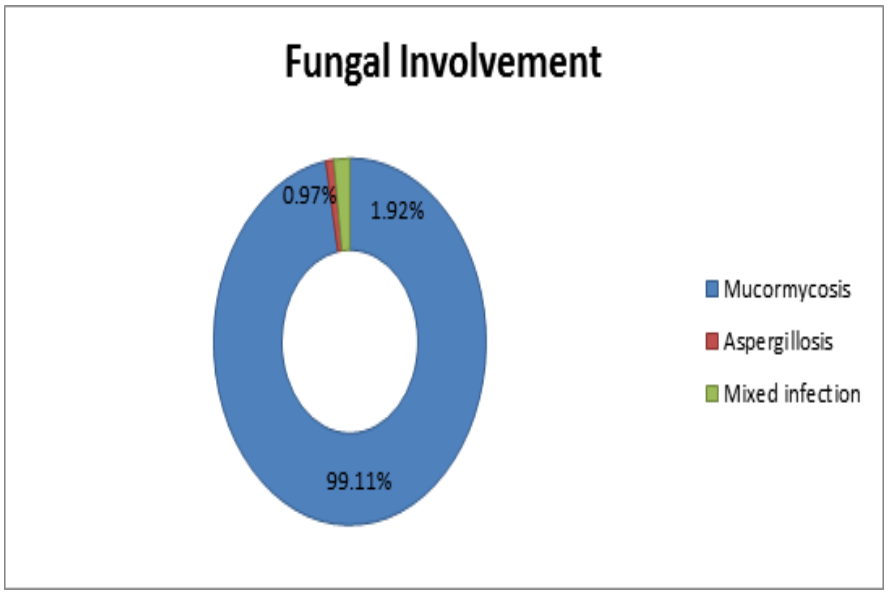
92 patients (88.46%) patients needed ventilators during the duration of the

treatment of COVID-19, whereas only 12 cases (11.54%) did not.

Parenteral steroids were used in the COVID-19 treatment for 47 patients (45.19%).

26 patients (25%) succumbed due to either the complications of uncontrolled diabetes or the invasive nature of the fungal infection.

Histopathological study revealed broad, aseptate hyphae [mucormycosis] in 101 patients (99.11%), acute angled, septate hyphae [Aspergillosis] in 01 case (0.97%) and mixed infection [aspergillosis and mucormycosis] in 02 cases (1.92%).



The fungal infestation showed involvement of paranasal sinuses, nasal cavities, palate, orbits (either bilateral or unilateral), and maxillas. Intracranial extension was also seen in very serious cases.
Foreign body type of reaction was also seen in 25 cases (24.03%).

Table 3: Distribution of lesions

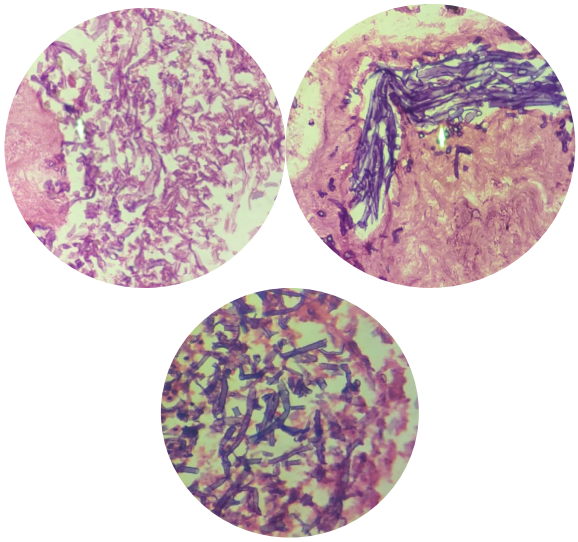
Site	NO. OF PATIENTS	PERCENTAGE
Nasal cavity	104	100
Paranasal sinuses	100	96.15
Maxilla	04	3.85
Orbits (Left/ Right)	25	24.04
Palate	03	2.89
Intracranial extension	06	5.78

These sites showed overlapping in majority of the cases.

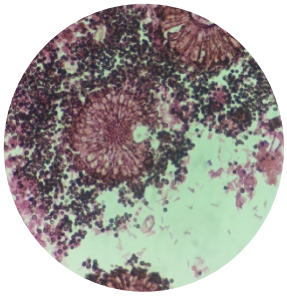
Images

Gross specimens of orbital exenterations in patients of mucormycosis. The cut open section of eyeball, shows necrotic, black soft tissue.

Histopathological microphotographs, stained with Hematolxylin & eosin staining showing broad, aseptate fungal hyphae suggestive of mucormycosis



Histopathological microphotographs, stained with Hematolxylin & eosin staining showing conidia, suggestive of aspergillosis



Discussion

Although mucormycosis is exceedingly rare in healthy people, it can be caused by numerous immunocompromised diseases. Uncontrolled diabetes mellitus with or without DKA, haematological and other malignancies, severe burns, deferoxamine or desferrioxamine therapy, prolonged neutropenia, iron overload or hemochromatosis, intravenous drug abusers, malnutrition, organ transplantation, immunosuppressive and corticosteroid therapy, voriconazole prohylaxis for transplant recipients, acquired immunodeficiency syndrome (AIDS), and open wounds. Mucormycosis

can affect the nose, sinuses, orbit, CNS, lungs (pulmonary), gastrointestinal tract (GIT), skin, jaw bones, joints, heart, kidney, and mediastinum (invasive kind), although Rhino-orbital-cerebral ***mucormycosis*** is the most prevalent variant observed in clinical practice around the world. [21] It's worth noting that the term "rhino-orbital-cerebral illness" encompasses the complete spectrum of diseases ranging from restricted sino-nasal disease (tissue invasion), limited rhino-orbital disease (progression to orbits), and rhino-orbital-cerebral disease (CNS involvement). [22] Due to the underlying illness, the extent of involvement may vary. For example, Rhino-orbital-cerebral ***mucormycosis*** is frequently associated with uncontrolled diabetes and DKA, lung involvement is frequently seen in patients with neutropenia, haematological malignancies, bone marrow and organ transplantation, and GIT involvement is more frequent in malnourished people. Mucormycosis is characterized by giant cell invasion, thrombosis, and eosinophilic necrosis of the underlying tissue. It is distinguished from other fungal diseases by microbiological identification of the hyphae based on width, branching angle (right or acute branching), presence or absence of septa and coloration. The Smith and Krichner [23] criteria for the clinical diagnosis of mucormycosis, published in 1950, are still deemed the gold standard, and include the following:

- Black, necrotic turbinate's easily mistaken for dried, crusted blood,
- Blood-tinged nasal discharge and facial pain, both on the same side,
- Soft peri-orbital or peri-nasal swelling with discoloration and induration,
- Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia and,
- Multiple cranial nerve palsies unrelated to documented lesions.

Prakash et al. observed 18 % had DKA and 57 % had uncontrolled DM in a countrywide multi-center survey of 388 confirmed or suspected cases of mucormycosis in India prior to COVID-19. [24] Similarly, Patel et al. [25] found that rhino-orbital presentation was the most common (67.7%), followed by pulmonary (13.3%) and cutaneous types in a study of 465 patients of mucormycosis without COVID-19 in India (10.5 %). In Indians, predisposing factors for mucormycosis include diabetes mellitus (73.5%), cancer (9.0%), and organ donation (7.7%) [25]. According to a prospective Indian study conducted prior to the COVID-19 pandemic, the presence of DM increases the risk of developing Rhino-orbital-cerebral ***mucormycosis*** by 7.5-fold (Odds ratio 7.55, P = 0.001). [26] In a recent systematic study conducted by John et al. [27] from April 9, 2021 to April 9, 2021, DM was recorded in 93 percent of verified mucormycosis cases in patients with COVID-19, while 88 percent were getting corticosteroids. These findings are congruent with those of a larger case series of 101 mucormycosis cases (95 confirmed and 6 suspected) in Covid-19, in which 80 percent of subjects had DM and more than two-thirds (76.3 percent) took corticosteroids. In persons with COVID-19, these findings reveal a common link between mucormycosis, diabetes, and steroid use.

It's difficult to demonstrate a causal effect association between COVID-19 and mucormycosis in relation to corticosteroids since no research have compared non-diabetic COVID-19 patients who did not receive steroids to COVID-19 patients who did receive steroids and developed mucormycosis. Still, there appear to be a number of factors that may cause mucormycosis in patients with COVID-19 when corticosteroids are used:

- The presence of DM, whether with or without DKA, increases the chance of acquiring mucormycosis, and DM is

frequently linked to increased COVID-19 severity.

- The use of corticosteroids is frequently linked to uncontrolled hyperglycemia and the development of DKA. Acidosis results in a low pH, which is optimal for the growth of mucor spores. Furthermore, steroid use reduces WBC phagocytic function (both first and second line defense mechanisms), affects broncho-alveolar macrophage recruitment, ingestion, and phagolysosome fusion, and increases the risk of mucormycosis in diabetic patients.
- COVID-19 frequently causes endothelialitis, endothelial damage, thrombosis, lymphopenia, and a decrease in CD4+ and CD8+ T-cell levels, predisposing to secondary or opportunistic fungal infection.
- For mucormycosis, free iron is an ideal environment. Hyperglycemia causes transferrin and ferritin to be glycosylated, which lowers iron binding and allows for more free iron. Furthermore, a rise in cytokines, particularly interleukin-6, increases free iron via increasing ferritin levels due to increased synthesis and decreased iron transport in COVID-19 patients. Concomitant acidosis also increases free iron through the same method, as well as by lowering transferrin's ability to chelate iron.
- The presence of diminished WBC phagocytic activity, high glucose, low pH, free iron, and ketones promote mucor growth. It also causes angio-invasion, hematogenous dissemination, and tissue necrosis by increasing the expression of the endothelium's glucose-regulator protein 78 (GRP-78) and the fungal ligand spore coating homolog (Cot H) protein. [28]

In their study, Awadhesh Kumar Singh et colleagues discovered that the rise in mucormycosis in the Indian setting appears to be the result of an unholy trinity of COVID-19 (cytokine storm, lymphopenia, endothelial damage), widespread corticosteroid use (increases blood glucose and opportunistic fungal infection) and diabetes (high genetic incidence), , and. To reduce the risk of fatal Mucormycosis, all efforts should be made to maintain optimal hyperglycemia, and in patients with COVID-19, only reasonable evidence-based corticosteroids should be used. [29]

Mucormycosis appears to be the junction of two crises: one of COVID-19 and the other of poorly controlled DM in the context of the pandemic, according to Teny M.John et al in their study. [30] Unlike COVID-19-associated pulmonary aspergillosis. (*CAPA*), the majority of Covid associated Mucormycosis instances are well recorded. In a critically unwell patient with COVID-19 and DM, clinicians should have a high index of suspicion and consider Covid associated Mucormycosis, especially if rhino-orbital or rhino-cerebral manifestations are present. In DM patients with COVID-19, cranial discomfort without swelling can be a neuropathic pain, and without facial asymmetry or necrosis, it should not be considered a sign of mucormycosis. [31] Although the effectiveness of preemptive antifungal therapy is yet to be proven, hyperglycemia control appears to be vital for mucormycosis prevention and management. [32]

In their study, S.Sharmaet al, stated that more is being learnt about the Covid-19 infection's novel and long-term manifestations. Its link to invasive mucormycosis sinusitis is worrisome, and it should be taken seriously. Uncontrolled diabetes and overuse of steroids are two of the most common causes of illness aggravation, and both must be addressed. In situations of post-coronavirus mucormycosis, early surgical intervention and intravenous anti-fungal treatment should be considered, as a favourable

prognosis and less fulminant disease course can be attained. [33]

Mucormycosis is usually seen because of immunosuppression or disabling conditions, according to Aastha Maini et al. Mold commonly enters the respiratory tract through the nose and sinuses in Head and Neck cases, with probable development into the orbital and cerebral structures. As a result, for a good prognosis and reduced morbidity, early diagnosis and intervention are necessary. On the basis of the clinical picture and direct smears, this can be accomplished. COVID-19 patients should be studied for better prevention and management of opportunistic infections in order to reduce their occurrence and morbidity. Prophylactic treatment regimens, as well as the reasonable use of corticosteroids, must be devised. [34]

Coronavirus disease 2019 (COVID-19) infections may be associated with a wide spectrum of bacterial and fungal co-infections, according to Salil Mehta et al's case report. The author presents the case of a patient with COVID-19 infection who developed rhino-orbital mucormycosis after treatment. After testing positive by RT-PCR for COVID-19, a 60-year-old diabetic man was admitted to the hospital for treatment during which he was given parenteral meropenem, oral oseltamivir, and parenteral methylprednisolone. During his hospital stay, he exhibited symptoms of orbital cellulitis.

On magnetic resonance imaging (MRI) of the brain, orbits, and paranasal sinuses, soft tissue swelling was detected in the right preseptal, malar, premaxillary, and retrobulbar regions with paranasal sinusitis. When a nasal biopsy revealed broad aseptate filamentous fungal hyphae, which were confirmed by culture, mucormycosis was suggested. Excessive use of steroids, monoclonal antibodies, and broad-spectrum antibiotics can lead to the development or exacerbation of a fungal infection. Physicians should be cautious of subsequent invasive fungal infections in patients with COVID-19 infection. [35]

In their investigation, Felin Ann Francis et colleagues discovered that mucormycosis is an uncommon fungal illness that affects immunocompromised persons, particularly those with untreated diabetes mellitus, producing orbital cellulitis. After a clinical examination, discussion with an ENT expert and an ophthalmologist regarding the appropriate diagnostic procedure, and an endoscopic nasal sample - which revealed fungal hyphae - the patient was diagnosed with diabetic ketoacidosis. [36]

In their study, RavindraV.Shinde et al, [37] and colleagues found that mucormycosis is still a serious infectious condition in diabetes people, with a significant fatality rate. Clinical diagnosis is frequently complicated and time-consuming.

Physicians should always pay special attention to infections inside the facial skeleton in diabetics, particularly those that do not respond to antibiotic therapy. To improve the prognosis, an early diagnosis along with medicinal and surgical intervention is required.

Rhino-orbital mucormycosis is a rare but life-threatening infection that most commonly affects people with diabetes and other immune system disorders. The disease is divided into two types: rhino-orbital and rhino-cerebral. Early detection and treatment are critical otherwise it can result in mortality in a matter of days. Although fungus infection of the nasal cavity is uncommon, it is becoming more common in patients with immune deficiencies.

Mucormycosis has become more common as a result of the prolonged survival of debilitated patients, as well as greater therapeutic use of antibiotics and immunosuppressive drugs.

Our heightened awareness of this devastating condition is the first step towards a more

favourable outcome in this disease.

Our study had various limitations. Due to the difficulty in making a microbiological or histological diagnosis, especially in a raging pandemic setting, reported cases of mucormycosis are likely to be an underrepresentation of the true burden. While some case reports included every last detail, others omitted critical information, such as the duration of diabetes and the unavailability of baseline HbA1c data in the vast majority of cases, limits the study. Second, the lack of a denominator value, compounded by the lack of control, may make it difficult to accurately estimate mucormycosis incidence in persons with COVID-19.

Thirdly, because to the decreased sensitivity of confirmatory RT-PCR, distinguishing active and recovered COVID-19 and its relationship to the beginning of mucormycosis may be tricky.

Furthermore, the study was retrospective, and the data came from a single clinical research site rather than many clinical research centres. Finally, analysing the results in people with mucormycosis and COVID-19 may be challenging at this time because many of these patients are still receiving treatment.

Multicentred and higher sample size clinical trials are needed to validate our findings for more accurate and precise results, as well as wider generalisability of the findings.

Conclusion

We're learning more about the Covid-19 infection's novel and long-term manifestations. Its link to invasive mucormycosis sinusitis is worrisome, and it should be taken seriously. Uncontrolled diabetes and overuse of steroids are two of the most common causes of illness aggravation, and both must be addressed. In situations of post-coronavirus mucormycosis, early surgical intervention and intravenous anti-fungal treatment should be considered, as a favourable prognosis and less fulminant disease course can be achieved.

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