



Mucormycosis in Post COVID-19 Patients: A Case Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Introduction: Acute respiratory distress syndrome (ARDS) is a common complication of severe pneumonia virus, such as the flu and COVID-19, which requires critical treatment, including asthma support, corticosteroids, and other treatments to prevent acute respiratory tract inflammation. Although steroid treatment is limited to the treatment of viral pneumonia, it is usually a double-edged sword, leading to increased morbidity and mortality. Mucormycosis is a fungal emergency with a high tendency for contagious spread and a poor prognosis if not detected and treated promptly. Mucormycosis is believed to be caused by uncontrolled diabetes mellitus (DM) and other immunosuppressive disorders, such as corticosteroid therapy.

Aim: To discuss causality factor of mucormycosis in COVID-19 infection.

Conclusion: COVID-19 is correlated with a high rate of secondary infections, both bacterial and fungal, most likely as a result of immune dysregulation. Furthermore, the widespread use of steroids and broad-spectrum antibiotics as part of the COVID-19 remedy can result in the production or exacerbation of pre-existing fungal diseases. Physicians should be mindful of the likelihood of invasive secondary fungal infections in patients with COVID-19 infection, especially in those that have pre-existing risk factors, and should be able to detect and treat these infections early in order to reducing mortality and morbidity.

Keywords: *Mucormycosis; Apophysomyces elegans; immunosuppression; dm; second-line fungal therapy and corticosteroid therapy.*

1. INTRODUCTION

As our country fights COVID-19 the issue of post COVID-19 sepsis has become such a significantly huge problem that India bears the dubious distinction of being both the mucormycosis as well as the world's capital of diabetes [1]. Considering the severity of mucormycosis, it is not wise to put it among other general fungal infections as the disease is spreading at an alarming rate in post COVID patients in India. Indian mucormycosis has a few distinguishing characteristics. The most common signs is rhino-orbito-cerebral presentation, which is linked to uncontrolled diabetes. Mucormycosis sometimes is known as the diabetes-defining illness, and remains one of the most devastating complications in uncontrolled diabetics. As a rare but severe fungal infection, it usually affects those with weakened immune systems, such as cancer patients, those with severe diabetes, or those who have undergone multiple organ surgeries. Chronic diabetics with severe foot ulcers should exercise extreme caution, as harmful external particles laden with dirt can easily enter the body through the injured skin tissues [2]. As it is now showing in several COVID post-recovery cases, it reflects how COVID infection affects our immune system deeply.

Mucormycosis, previously termed as zygomycosis, is a rare fungal ailment, born out of mucormycete mould, that occurs extensively in soil, leaves, decayed wood and putrefied manure, *Apophysomyces elegans* and *Rhizopus homothallicus* are emerging species and uncommon agents such as *Mucor irregularis* and *Thamnostylum lucknowense* are also being discovered [3].

Its infection starts in the nasal area, throat, and then soon spreads to the eyes, brain, and finally, the entire body. It also spread through cut wounds and skin. Once the COVID patients inhale these fungal spores and ingest it into their systems, they can have a very lethal and life-threatening infection as this fungus is quite angioinvasive, meaning that it is a predilection or preference for the blood vessels. As it enters the blood vessels, it induces necrosis of the tissue and vessels, resulting in a lack of blood flow to the tissues. As a result, the patient can develop an aggressive infection, necessitating treatment

with an antifungal and/or surgical debridement, which may result in tissue or organ death, potentially leading to higher mortality rates [4].

It becomes life-threatening until it infects a patient's brain. Its high rate of dissemination aggravates the patient's condition, and if left unchecked or untreated at the appropriate time, it can lead to multiple organ failure. In the meantime, the patient's immunity is eroded, other infections are aggravated, and the patient becomes infection-prone, lowering the patient's survival rate dramatically. The connection between COVID-19 and mucormycosis is not unexpected to us since the most common cause of mucormycosis is uncontrolled diabetes, which is also a high-risk factor for COVID-19. Furthermore, steroids, which inhibit immunity, are the only drug that has been shown to reduce COVID-19 mortality. Therefore it is the combination of COVID-19, usage of steroids leading to suppressed immunity which probably predispose a patient to mucormycosis [5].

One major and observed cause of mucormycosis in post COVID patients is due to the fulfillment of the adequate amount of O₂ requirements which is met by high FiO₂ and along with a high pressure. If sustained conditions given above persist, it causes destruction and degradation of the mucosal membrane or MALT (mucosal associated lymphoid tissue). This exposes the epithelium below which results in fine injuries which are not visible to naked eye. The fungal spores entering the respiratory track directly take entry into blood stream and rapidly multiply. Thus, post COVID patients are more prone towards Mucormycosis.

Due to immunosuppression the host becomes susceptible to a large variety of bacterial, fungal or viral infections. In the beginning, characteristic symptoms of mucormycosis affect only the part of the body through which the fungus invades the system and the tissues that it eventually occupies. But, as the infection spreads to various tissues and organs, multiple types of indications are shown by the affected person such as [6]:

- 1) The patient will have Fever followed by persistent cough.
- 2) The patient will have nasal discharge of blood and mucous.

- 3) The patient may suffer from Stuffy nose[7].
- 4) The patient may suffer from Proptosis (abnormal protrusion of the eyeball).
- 5) The patient may experience Ptosis (weakness of eyelid muscle).
- 6) The patient may suffer from Periorbital swelling.
- 7) The patient may have impaired vision.
- 8) The patient may develop complete blindness.
- 9) The patient may suffer through hemicranial pain [8].
- 10) The patient may go through complete headache.
- 11) The patient may develop swelling of gums.
- 12) The patient may have loosening of teeth.
- 13) The patient may suffer from toothache.
- 14) Altered mentation.
- 15) The patient may experience Drowsiness.
- 16) Intracranial parenchymal involvement [9].

2. CASE STUDY

A-60-year old male patient who is diabetic, hypertensive since last 10 years was diagnosed and treated for COVID-19 and SARS COV2 and left the hospital. After that, the patient noted left eye redness with irritation with left nostril congestion. Symptoms were progressive and noted periorbital edema, blurred vision in left eye, left sided headache with bloody mucous discharge from left nostril. Patient consulted to ENT (Ear, Nose and Throat) specialty in seven star hospital where he was advised Computerized Tomography (CT) scan of the Paranasal Sinuses (PNS) and ophthalmologist opinion. Ophthalmologist seen the patient and noted his findings. It suggested of left eye lid edema, proptosis of left eye, restriction of eye ball movement with impaired vision. Left eye fixed and non-reactive pupil.

CT PNS suggested of moderate mucosal thickening with abnormal soft tissue involving left maxillary sinus, left ethmoid sinus suggested of Sinusitis. This patient was referred to tertiary care center where Nasal Endoscopic diagnosis and treatment was possible. ENT surgeon did Nasal Endoscopy suggested of Extensive Invasive fungal Sinusitis. Patient was advised to go under Endoscopic Radical Debridement with left orbital decompression. Prior surgery opinion of Retina specialist was taken, there was drastically decrement of vision with involvement of Lateral, Medial Rectus muscle with almost completely fixed eye. Neuro physician's opinion

was taken and Magnetic resonance imaging (MRI)of brain was performed to check involvement of brain/ Infra Cranial Extension. MRI brain suggestive of no evidence of intracranial involvement/ extension. As patient is 60 year old and known case of Diabetes Mellitus and Hypertension. Cardiologist's opinion and bed side 2D ECHO done. ECHO suggested LVEF 60percent, no RCOMA, and Grade-1 Diastolic Dysfunction. Nephrologist's opinion was taken, advised adequate hydration and daily KFT. Mild to moderate risk to undergo surgery.

CBC – HB 11.2gm%, TLC 16400, Platelets 2.63Lac
 KFT- Sr Creat 1.4mg/Dl, Urea 51mg/Dl, Sr Na 136mEq/L , Sr K 3.9mEq/L
 Urine R& M- Albumin 1+, Pus cells absent
 PCT- 1.23
 CRP- 58
 D dimer- 1202
 X-ray Chest- PA Bilateral lower zone consolidation
 Coagulation profile- Within normal range
 HIV- Negative
 HCV- Negative
 HBSAg- Negative

IV antibiotic Piperacillin tazobactam 4.5mg IV TDS, IV Liposomal amphotericin started from 250mg OD (ACCORDING TO NEW GUIDELINES FOR MUCORMYCOSIS THE DOSE IS 250mg/DAY FOR 50KG PERSPON, 5mg/Kg/day). IV Pantosid 40, capsule Posaconazole 300mg OD, IV Tramadol for pain management, IV Paracetamol for additional pain management and other supportive medications that consists of vitamins and trace elements. The patient was supported with IV fluid at the rate of 80ml/hour. Patient was diabetic so his sugar was controlled according to his random blood sugar level. Fractional doses of HAI (human actrapid insulin) given. Patient posted for surgery next day. Patient kept NBM for 12 hours prior surgery. IV fluid was given on next morning with all due high risk consent under general anesthesia Endoscopic radical debridement with Left orbital decompression done with ethmoidectomy.

Nasal cavity packed with antiseptic and haemostatic solution. During surgery, biopsy and pus was collected and sent for histopathology and microscopy examination suggestive of filamentous fungal hyphae suggestive of mucormycosis. This patient improved symptomatically after surgery. From post of day to edema, swelling, redness of eye decreased



Fig. 1. Left orbital decompression



Fig. 2.



Fig. 3.

Fig. 2, 3. Nasal cavity during surgery

but vision was not improves. It was as previous as before the surgery. Again nasal endoscopy done and surgical syringing and flushing done known as nasal clearance. Endoscopy suggestive of no active fungal invasion, granulation of tissue seen. This patient was admitted for 14 days in seven stars hospital for IV antibiotic, antifungal doses under Physician's and Nephrologists' guidance. There was slight increase in his serum creatinine from 1.4mg/Dl to 1.8mg/Dl hence IV antifungal and antibiotic doses were titrated according to creatinine clearance. Adequate hydration maintained, RBS was tightly controlled with fractional doses of HAI (HUMAN ATRAPID INSULIN).

On 15th day of hospitalization, patient discharged in haemodynamically stable condition. Patient was advised follow-up every week for nasal clearance

3. DISCUSSION

The novel Coronavirus has already swallowed up more a million lives worldwide. Absence of an effective vaccine or antiviral therapy in such tremendous situations, supportive care plays a vital role in the management of this disease. Glucocorticoids and remdesivir are the only drugs proven to be beneficial in this disease [10].

However, glucocorticoids may increase the risk of secondary infections. Moreover, the immune dysregulation caused by the virus and the use of concurrent immunomodulatory drugs such as tocilizumab could further increase the risk of infections in Corona in patients. The corona virus infection might affect and alter the immune system by affecting T lymphocytes, particularly CD4+ and CD8+ T cells, which usually are highly involved in the pathological process of COVID infection [11]. This drastic decrease of lymphocytes, especially T-cells, as seen in the most serious COVIDcases, is linked to the worst outcomes and puts patients at a higher risk of contracting opportunistic infections like mucormycosis. Mucormycosis is a fungal infection caused by the *Mucormycetes*, a group of fungal molds [12]. While bronchial alveolar macrophage dysfunction is the most common cause of fungal infection, T-cells have been identified as a component of the adaptive immune system. Mucorales-specific T-cells (CD4+ and CD8+) were shown to be active against Mucorales by developing cytokines such as IL-4, IL-10, IL-17, and IFN-, which were able to specifically destroy Mucorales hyphae in a study on a group of mucormycosis patients. It's possible that lymphopenia increases the chance of invasive mucormycosis, while increasing lymphocyte numbers improves the adaptive

immune system and induces the development of Mucorales-specific T-cells, which could help regulate the invasive infection [13].

Mucormycosis is more prevalent in immunocompromised patients. In particular, a new systematic study by Jeong et al. found that solid organ transplantation and neutropenia, which is generally seen in patients with haematological malignancies, were the only independent risk factors for pulmonary mucormycosis [14]. Furthermore, SARS-CoV-2 infection can alter the immune system, and this is the first case of opportunistic *Rhizopus* spp co-infection involving lungs with severe parenchymal injury. In a retrospective report, Koehler et al. looked at a population of COVID-19 patients who had mild to extreme acute respiratory distress syndrome (ARDS) and experienced intrusive pulmonary aspergillosis as a result of the immune-paralysis caused by SARS-CoV-2 infection. Similarly, no corticosteroids or immunosuppressive drugs were used in this situation, but the patient had an extreme type of COVID-19 with multiple organ dysfunctions and a major and long-term lymphopenia with a change in the N/L ratio [15]. Following that, it's possible that SARS-CoV-2 infection could cause an immunosuppressive condition, putting the patient at risk of infections like mold. These infections are often linked to the worst outcomes, especially when the immune system response does not improve [16]. However, once the immune system has recovered, opportunistic infections can be managed, as shown by the present case, which showed an increase in clinical symptoms, especially respiratory dysfunction [17]. As lymphocytes increased and the N/L ratio reduced, and the pulmonary cavitary lesion opened into the pleural room, the patient's oxygenation improved dramatically. Surgical exploration to extract necrotic lesions should be considered to cure the mould infection and increase the patient's result, even if the molds could not be separated in the pleural effusion [18].

In addition to systemic antifungal therapy, the European Confederation of Medical Mycology Mucormycosis Guidelines highly recommends early surgical treatment to remove infectious tissue (either by local debridement or full resection) [10].

Infections, such as the mold infection seen in this instance, should be examined as possible

causative agent when clinical effects do not change after wide-spectrum observational therapy or when a compromised immune response caused by SARS-COV-2 is detected [19]. As a result, antifungal agents should be used in antimicrobial therapy, and pharmacological medication should be combined with surgical action to eliminate mold-associated necrotic lesions wherever possible where results indicate a mucormycosis [17,20-23].

4. CONCLUSION

COVID-19 is linked to a high rate of secondary infections, both bacterial and fungal, most likely as a result of immune dysregulation. Furthermore, the widespread use of steroids, monoclonal antibodies, and broad-spectrum antibiotics as part of the COVID-19 armamentarium can result in the production or exacerbation of pre-existing fungal diseases. Physicians should be mindful of the likelihood of invasive secondary fungal infections in patients with COVID-19 infection, especially in those that have preexisting risk factors, and should be able to detect and treat these infections early, reducing mortality and morbidity. The use of therapeutic agents should be closely supervised in order to produce the best possible therapeutic outcome at the lowest possible dosage and for the shortest possible time. The use of broad-spectrum antibiotics should be reconsidered, particularly in the absence of infection.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline Patient's consent and ethical approval has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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