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Research Paper

Post-Covid Mucormycosis With Management: A Case based Review

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ABSTRACT: The rise in mucormycosis in India appears to be the result of an unholy trifecta of diabetes (high hereditary incidence), excessive corticosteroid use (increases blood glucose and opportunistic fungal infection), and COVID-19 (cytokine storm, lymphopenia, endothelial damage). To limit the incidence of deadly mucormycosis, all efforts should be taken to maintain optimum hyperglycemia, and only prudent evidence-based use of corticosteroids in patients with COVID-19 is advocated.As the coronavirus disease 2019 (COVID-19) pandemic is evolving, more complications associated with COVID-19 are emerging. In this case report, we present a case of rhinosinoorbital mucormycosis concurrent with COVID-19 pneumonia in a 45-year-old man with a history of type 2 diabetes mellitus (T2DM). COVID-19 pneumonia was diagnosed with reverse transcription-polymerase chain reaction (RT-PCR). He was promptly treated with steroids and antibiotics , as this was the recommended regional COVID-19 practice patterns at the time. After that, mucormucosis was developed as a secondary infection due to the immunosuppressed condition.This case was treated with prompt antifungal therapy and FESS(Functional Endoscopic Sinus Surgery).

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I. INTRODUCTION:

Mucormycosis is a rapidly progressive lethal form of fungal infection, formally known as Zygomycosis. This is an angioinvasive fungal infection caused by Mucorales fungus. This infection tends to occur most often who has weakened immunity from an illness or poor health condition. It is classified as rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, or other depending on the clinical presentation which includes unusual types such as endocarditis, osteomyelitis, peritonitis, renal, and so on. The condition was initially documented in 1876 by Fürbinger in Germany, who described a patient who died of cancer and had a hemorrhagic infarct in the right lung with fungal hyphae and a few sporangia. Arnold Paltauf described the first case of disseminated mucormycosis in 1885, calling it "Mycosis mucorina". The presence of sporangiophores and rhizoid-like structures in his illustrations of the etiologic agent led to the conclusion that the infection was most likely caused by Lichtheimia corymbifera. More instances have been diagnosed throughout time, and the disease's incidence has risen. After Aspergillus, Mucorales fungi are the next most frequent mould pathogens, causing invasive fungal illness in individuals with cancer or transplant recipients. Mucormycosis has also become more common in persons with diabetes, which is the most frequent underlying risk factor worldwide. However, doctors are now noticing a rise in mucormycosis amongst the people hospitalized for or recovering from COVID-19.(1) (8)

II. MUCORMYCOSIS AND COVID-19:

The correlation between COVID-19 and Mucormycosis can be due to diabetes mellitus which is also a high-risk factor for COVID-19. Secondly, steroids that suppress immunity are the only treatment that decreases COVID-19 mortality. So it is the combination of COVID-19, with decreased immunity and the steroids which probably predisposing factor to have the infection of Mucormycosis. A perfect environment of low oxygen (hypoxia), high glucose in the blood (steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins), and decreased phagocytic activity of white blood cells appears to be facilitating Mucorales spores to germinate in people with COVID-19 due to immunosuppressed condition (SARS-CoV-2 mediated, steroid-mediated or some comorbidities) coupled with

several other shared risk factors including prolonged hospitalization with or without mechanical ventilators. (3)(4)

III. PATHOGENESIS:

(i) Presence of DM with or without DKA increases the risk of contracting mucormycosis and DM is often associated with an increased severity of COVID-19,

(ii) Corticosteroid use is frequently associated with uncontrolled hyperglycemia and the onset of DKA. Acidosis causes a low pH, which is ideal for mucor spores to grow. Furthermore, steroid use decreases WBC phagocytic activity (both first and second line defensive mechanisms), impairs bronchoalveolar macrophage migration, ingestion, and phagolysosome fusion, and makes a diabetic patient particularly prone to mucormycosis.

(iii) COVID-19 often causes endothelialitis, endothelial damage, thrombosis, lymphopenia, and reduction in $CD4^+$ and $CD8^+$ T-cell level and thus predisposes to secondary or opportunistic fungal infection,

(iv) Free available iron is an ideal resource for mucormycosis. Hyperglycemia causes glycosylation of transferrin and ferritin, and reduces iron binding allowing increased free iron. Moreover, increase in cytokines in patients with COVID-19 especially interleukin-6, increases free iron by increasing ferritin levels due to increased synthesis and decreased iron transport. Furthermore, concomitant acidosis increases free iron by the same mechanism and additionally by reducing the ability of transferrin to chelate iron,

(v) Mucor growth is aided by high glucose, low pH, free iron, and ketones in the presence of reduced WBC phagocytic activity. It also increases the expression of the endothelium's glucose-regulator protein 78 (GRP-78) and the fungal ligand spore coating homolog (CotH) protein, allowing angio-invasion, hematogenous spread, and tissue necrosis.

IV. A CASE OF MUCORMYCOSIS: POST COVID COMPLICATION:

Case History: A 45 years male patient with moderate diabetes, had taken treatment for COVID 19 after his RT-PCR report was positive. He came to our hospital with a high fever, dyspnea, sore throat, headache, diarrhea. He had taken medicines from the physician of our hospital.
On admission (21 March 2021, around 8 pm), He was being prescribed the following medicines: (Treatment of Covid -19):
1. Azithromycin 500 mg 1-0-0
2. Cefixime 200 mg 1-0-1
3. T. Dexamethasone 6 mg 1-0-0
4. T. Acetaminophen 650 mg SO
5. T. Vitamin C 500 mg 1-0-1
6. T. Pantoprazole 40 mg 1-0-0
7. C. Becosule – Z (Vitamin B Complex+ zinc) 1-0-0
8. Syp. Grilinctus (Guaifenesin, Chlorpheniramine maleate, and Ammonium chloride) 2 tsp 1-1-1.

The above medications were continued for 14 days and fever and other symptoms were subsided then he was advised to do few diagnostic tests for routine monitoring to assess the complications.

	Results	Reference range	Units
1.Quantified D-Dimer test	less than 140	0-198	ng/ml
2. Interleukin -6	291.10	Upto 7	pg/ml
3. Serum Creatinine	1.24	0.72-1.25	mg/dl
4. Serum Potassium	3.80	3.5-5.1	mmol/l
5. CRP	41.9	less than 5	mg/l
6. Serum Ferritin	468.6	21.81-274.66	ng/ml

The patient was in ICU set up and as his fever and cough were subsided but Oxygen level has decreased some medicines were cut off from previous medication. Newly prescribed medicines were-

1.Metformin 400 mg BD for 10 days to control blood sugar level.
2.Tocilizumab (single IV intravenous dose of tocilizumab 8mg /kg actual body weight up to 800mg)
3.Dexamethasone 6 mg daily for up to 10 days

4.Moist O2 inhalation support
5. Vit C and Zn

After day 21, there was a development of Right-sided facial swelling, proptosis, decreasing of the vision, dilated pupil as shown in the following figure:

V. INVESTIGATIONS:

Nasal Endoscopy Findings:

Fig 2.Right nasal cavity infection

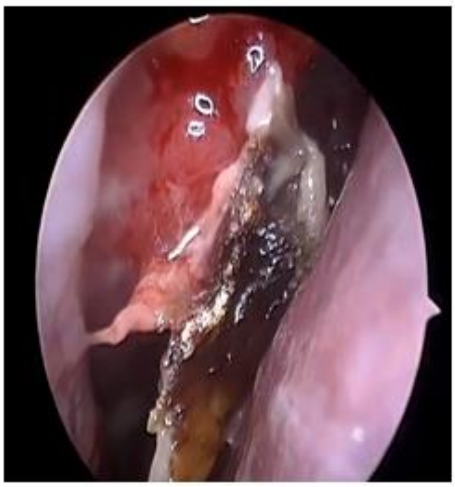
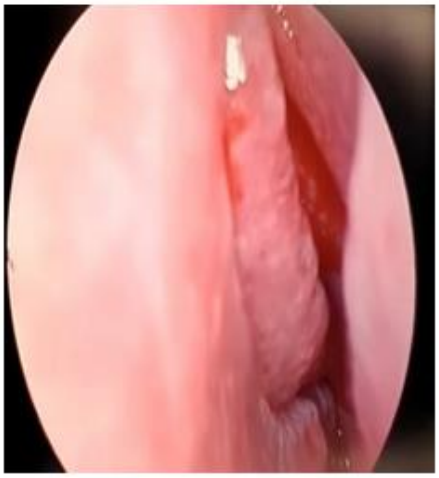


Fig 3: The left nasal cavity is normal



After examination of that patient, He was sent to the ENT and Surgery department of our hospital and it was diagnosed as a confirmed case of Mucormycosis after MRI. MRI impression suggested also here that there was inflammation in the maxillary sinus and ethmoidal sinus.

VI. MANAGEMENT:

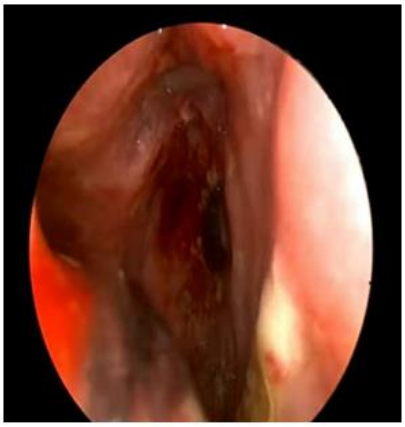
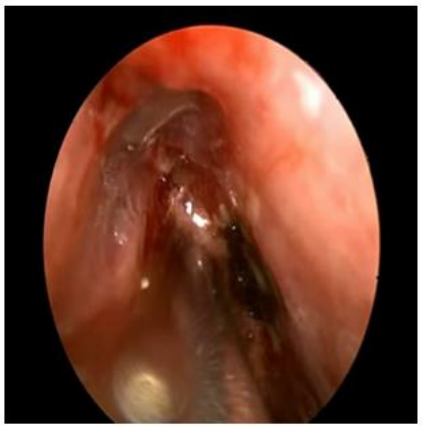
Immediately, the patient was given Injectable Amphotericin B 300 mg/day and finally the case was finally managed by surgical debridement (FESS) of the necrotic tissue and the necrotic tissue was sent for microbiological and histopathological investigation.

After Functional endoscopic sinus surgery (FESS), the nasal vestibule and nasal sinus are cleaning by irrigation of fluid and antifungal solution. Debridement and Amphotericin B lavage (1 mg/mL) was given. After cleaning the nasal crust and pus, Betadine and Amphotericin B-based nasal packing was given to the patient for 48 hours. Then Post operation check-up was done for sinonasal wash routinely and to check the nasal ventilation and nasal obstruction. Then repeatedly ESR (Erythrocyte sedimentation rate) and CRP (C-reactive protein) were done to check the presence of any active infection in the body.

After the course of completion of IV Liposomal Amphotericin -B, the patient was advised to take Isavuconazole orally 100 mg twice daily for 18 days. (Routine liver function test was done to check the increasement of SGOT and SGPT because sometimes isavuconazole orally can cause rising of the liver enzyme). Then after 20 days, the nasal septum changes were free from the fungal crust and necrotic debris.(7)(Fig 3 and Fig 4)

Others antifunal drugs are also used to control mucormycosis such as amphotericin B, posaconazole, or isavuconazole according to the case.(6)(7). Incase of high uncontrol glucose level,anyone can use insulin drip as emergency control of diabetes.

Post Operation picture of nasal septum of Right Nose:

VII. DECLARATION OF PATIENT CONSENT:

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her clinical information to be reported in the journal. The patient understood that his name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed

VIII. DISCUSSION:

Here Amphotericin B was used to control the fungal infection and prevent the fungal spread. Amphotericin B is a potent nephrotoxic drug so it was used in a controlled manner. Other treatments for covid 19 are also included here. Mucormycosis is an invasive fungal disorder. FESS is a minor procedure for taking out the necrotic fungal debris from the nasal septum. after IV amphotericin b course completion, the patient is shifted to isavuconazole orally.Careful use of amphotericin B is necessary because this drug has potent toxic effect on kidney. chronic monitoring is necessary for oral administration of isavuconazole because it causes increasement of liver enzymes as a side effect.(5)(6).

The rise in mucormycosis in India appears to be the result of an unholy trifecta of diabetes (high hereditary incidence), excessive corticosteroid use (increases blood glucose and opportunistic fungal infection), and COVID-19 (cytokine storm, lymphopenia, endothelial damage). To limit the incidence of deadly mucormycosis, all efforts should be taken to maintain optimum hyperglycemia, and only prudent evidence-based use of corticosteroids in patients with COVID-19 is advocated.

IX. CONCLUSION:

It is an overview study of Mucormycosis is the present situation demanding study which includes literary review as well as a case study with the management but needs further extensive study and research in this field. COVID-19 is linked to a high rate of secondary infections, both bacterial and fungal, most likely as a result of immunological dysregulation. Furthermore, frequent use of steroids, monoclonal antibodies, and broad-spectrum antibiotics in the fight against COVID-19 could lead to the development or worsening of pre-existing fungal illnesses. (12) Physicians should be aware of the possibility of invasive secondary fungal infections in patients with COVID-19 infection, especially in those with previous risk factors, and should consider early detection and treatment to reduce death and morbidity. The use of therapeutic drugs should be closely managed to achieve a therapeutic result at the lowest possible dose and for the shortest possible time. The use of broad-spectrum antibiotics, especially in the absence of infection, should be reconsidered. (1)(2)(8)

X. DECLARATION:

9.1 Financial support and sponsorship:
Nil.
9.2 Conflicts of interest:
There are no conflicts of interest.
9.3 Code availability

Not applicable
9.4 Authors' contributions
Conceptualization: [Debasish Ghosh], [Rajdeep Ghosh]; Methodology: [Debasish Ghosh], [Rajdeep Ghosh]; Formal analysis and investigation: [Debasish Ghosh], [Rajdeep Ghosh]; Writing–original draft preparation: [Rajdeep Ghosh], [Debasish Ghosh]; Writing–review and editing: [Debasish Ghosh]; Funding acquisition: [N/A]; Resources: [N/A] ; Supervision: [Debasish Ghosh]
9.5 Ethics approval
Not applicable
9.6 Consent to participate
All the authors mutually agree to participate in this work.

Consent for publication
All the authors mutually agree to submit the manuscript for publication.

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