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Mucormycosis in RT-PCR negative Covid 19 patient with newly diagnosed Diabetes Mellitus: A Case Report

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ABSTRACT

Corona Virus Disease 2019 (COVID 19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in Wuhan city of China in December 2019. Since then, the disease has spread very rapidly which has led to the current pandemic. Secondary infections are reported now a days during the illness in Covid-19 patients of any age and patients recovered from COVID 19. The high-risk conditions prone for opportunistic infections are uncontrolled blood sugar levels, prolonged steroid usage and oxygen therapy. Mucormycosis is highly invasive secondary infection. Early diagnosis along with surgical and medical intervention and control of all risk factors plays a crucial role. Delay in presentation of patient to medical care is really challenging to the physicians and ENT surgeons.

Key words: Mucormycosis; COVID 19; Diabetes Mellitus; Steroids

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INTRODUCTION

Mucormycosis is a mortiferous fungal infection caused by Mucoraceae family in the order Mucorales having seven families such as Mucoraceae, Lictheimaceae, Cunninghamellaceae, Thamnidiaceae, Mortierellaceae, Saksenaceae, Syncephalastraceae all of which can cause Mucormycosis. Risk factors for Mucormycosis are patients with diabetes mellitus, steroid induced hyperglycaemic states, solid organ or hematopoietic stem cell transplant, malignancy and other immunosuppressive conditions. A high index of suspicion to Mucormycosis is needed in patients with history of recent glucocorticoid usage or in hyperglycaemic states. Currently a triad of COVID 19 pneumonia, diabetes, corticosteroid usage is the leading cause of widespread fungal infection.[1] Mucormycosis can be divided into at least 6 clinical syndromes: rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated and miscellaneous. Patients with diabetes mellitus or steroid induced hyperglycaemic conditions usually develop rhino-orbital-cerebral form of disease. The initial symptoms are non-specific and include pain in the eye or face, facial paraesthesia, conjunctival chemosis, redness on eyes, stuffy nose, tooth ache, facial swelling, headache, nasal discharge, periorbital swelling, eyelid drooping, nasal swelling and proptosis, fever, vision loss, external and internal ophthalmoplegia. On Inspection, infected tissue

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appears normal in early stages later erythema develops and leads to black necrotic debris. Spread of infection from sinuses into mouth and entails necrotic ulcerations over hard palate.[2]

CASE REPORT

A 59-year-old male presented in AVBRH casualty with complaints of breathlessness at rest (NYHA Grade IV), dry cough, fever which is of low grade intermittent not associated with chills of multiple episodes, generalised weakness in the past 4 days. Patient has no other symptoms such as cold, loss of smell and taste, loose stools, body pains, chest pain, palpitations. Patient was newly diagnosed as diabetes mellitus type II. Patient has no other comorbidities such as hypertension, tuberculosis, bronchial asthma. On examination patient condition was moderate, afebrile with pulse rate of 80/minute and blood pressure of 120/80mmHg with saturation of 97% on 10litre oxygen. On systemic examination heart sounds S1, S2 heard, bilateral crepitations present over bilateral scapular, infra-scapular, axillary, infra-axillary areas, per abdomen was soft, non-tender, no organomegaly, conscious, oriented to time, place, person.

Chest X ray s/o bilateral heterogenous opacities (shown in Image 1). HRCT thorax was done suggestive of multiple ill-defined patchy areas of consolidation with surrounding ground glass opacities and septal thickening in bilateral lung fields' s/o infective aetiology possibility of atypical viral pneumonia. Imaging grading is CORAD-5 with CT Severity score-18/25(Severe) (shown in Image 2).

Ultrasonography Abdomen was done on first day of admission reveals raised cortical echotexture of bilateral kidneys with poor cortico-medullary differentiation suggestive of Grade III renal parenchymal disease, grade II fatty liver.

Blood parameters done on first day of admission s/o raised inflammatory markers such as Erythrocyte sedimentation rate- 105mm/hour, C-Reactive Protein- 27mg/dl, ferritin 1000 ng/ml, HbA1C 8.07%, azotaemia with blood urea 200 mg/dl, creatinine 8.0 mg/dl, sodium 144 mmol/litre, potassium 6.2 mmol/litre, ABG s/o metabolic acidosis and blood sugar levels were persistently elevated in the range of 400-450 with urine ketones mildly positive started treating as diabetes ketoacidosis with aggressive fluid management and insulin with regular monitoring of blood sugar, urine ketones and arterial blood gases.

Patient was started from first day on high flow oxygen, antivirals such as Remdesvir for 5 days, antibiotics such as

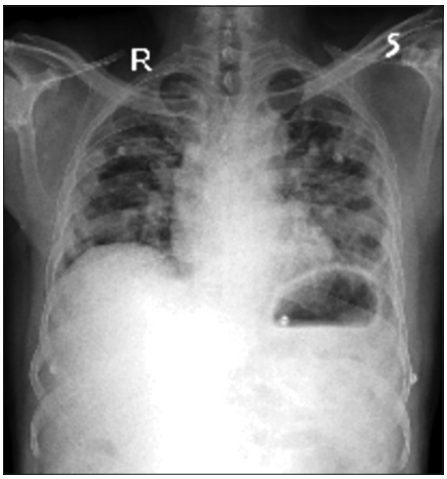

Image 1: Showing chest X ray suggestive of bilateral heterogenous opacities

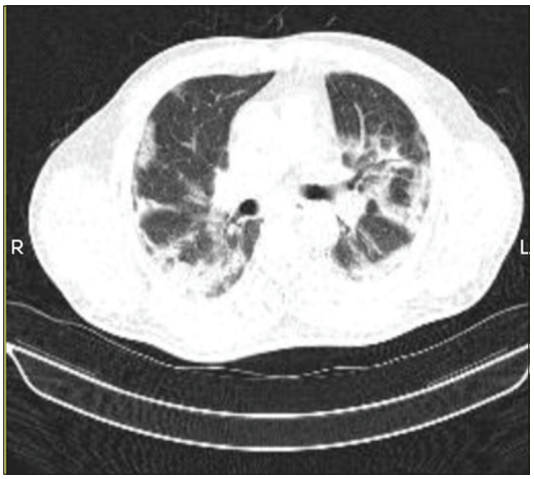

Image 2: Showing HRCT thorax with multiple ill-defined patchy areas of consolidation with surrounding ground glass opacities and septal thickening in bilateral lung fields

Piperacillin Tazobactam 4.5gm IV stat followed by 2.25gm TDS, Levofloxacin 750mg alternate day, doxycycline 100 mg BD for 7 days, steroids such as Dexamethasone for 7 days, anticoagulants such as low molecular weight Heparin for 14 days in view of COVID 19 and DVT prophylaxis as patient was bedridden, insulin, intravenous fluids and other supportive medication according to protocols and renal dosages. Later patient's creatinine and urea got normalised with intravenous fluids and ketones were negative and metabolic acidosis got improved and blood sugar levels got controlled.

After 1 week of treatment patient had sudden onset right upper eye lid swelling with conjunctival chemosis, inability to open the eye, eye pain, nasal stuffiness (shown in Image 3) so mucormycosis was suspected. Steroids were immediately stopped. To rule out it, CECT Paranasal sinuses was done on day 8 which revealed mucosal thickening in bilateral

maxillary sinus and ethmoid air cells with hyperdensities within it suggestive of sinusitis-probably fungal in nature.

Diagnostic nasal endoscopy was done on day 9 (shown in Image 4). Fungal tissue biopsy was taken and was sent for culture, KOH mount and Histopathological examination which was also s/o mucormycosis (shown in Image 5).

On day 9, patient has been started with antifungal injectable liposomal amphotericin B with dose of 3mg/kg/day in 500ml 5% dextrose over 6 hours after testing dose; given for 2 weeks Patient was then taken up for functional endoscopic sinus surgery on day 10 under general anaesthesia, debridement and curettage was done for sinuses and blackish necrotic tissue was scraped and debrided, sinuses were irrigated and cleaned. Procedure was uneventful. Patient was extubated on same day. Post operatively, patient was also started on antibiotics Clindamycin 600 mg BD, Linezolid 600 mg BD for 7 days.

Image 3: Showing right upper eye lid swelling, drooping of right eye lid, right sided facial swelling

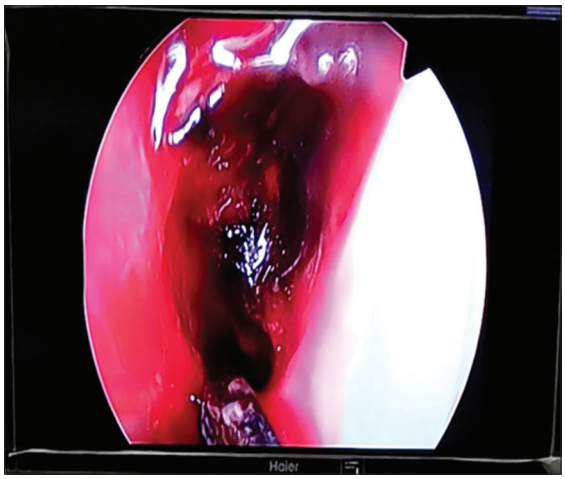

Image 4: Showing blackish necrotic debris in middle meatus with right sided deviated nasal septum in diagnostic nasal endoscopy

Patient has been taken for check endoscopy on day 14. Remained bits of mucormycosis was irrigated and cleaned. Patient improved, symptoms such as headache, nasal stuffiness relieved and swelling of right eye, right sided face, drooping of eyelid were reduced on 14th day (shown in Image 6). Patient has given amphotericin for 2 weeks and later patient got discharged with the advice to follow up for endoscopy and CECT paranasal sinuses after 7 days.

DISCUSSION

Mucormycosis is a life-threatening fungal infection infects oral and nasal cavities in immune dys-regulation conditions and also occurs as cutaneous or subcutaneous infection in immunologically normal conditions after traumatic implantation of soil or vegetation's or in nosocomial settings via IV catheters, SC injections or by moist dressing.[3]

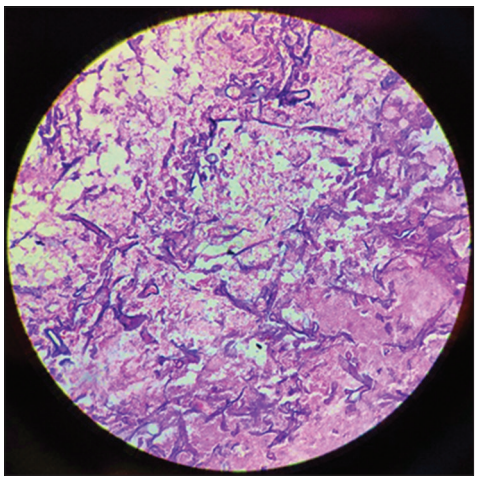

Image 5: Showing 40x histopathology shows broad aseptate hyphae budding at places and chronic inflammation at the background suggestive of mucormycosis

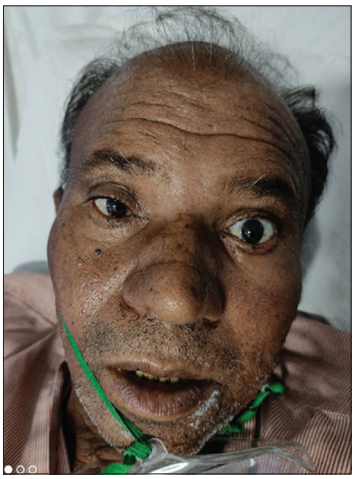

Image 6: Showing improvement of right sided facial swelling, eyelid swelling and patient able to open his eyes after FESS and medical treatment after 14th day

The phagocytic leukocytes help in the removal of these fungal spores in a person with healthy immune system. Conditions susceptible to Mucormycosis are uncontrolled diabetes mellitus or diabetic ketoacidosis, haematological malignancies, haematopoietic stem cell transplantation, autoimmune disorders, immunodeficient states.[4] In this presence of stimulus pathogen transforms into hyphae on which the phagocytic leukocytes have lesser effect, hence allowing rapid proliferation of these pathogens and angioinvasion resulting in thrombosis leads to ischemia and necrosis sets in. Hyperglycaemia becomes a culprit for development of mucormycosis by mechanisms such as hyper glycation of iron-sequestering proteins, disrupting normal iron sequestration, upregulation of mammalian receptor (GRP78) that binds to Mucorales, enabling tissue penetration, diminished phagocytic function, heightened action of CotH, a Mucorales-specific protein that brings into host cell invasion.[5] Dissemination of infection is directly into the paired sinuses of bone adjacent to nasal cavity and then it extends into orbital and intracranial spaces by direct invasion or via the bloodstream leading to rhinoorbito-cerebral mucormycosis which is common in diabetes mellitus or glucocorticoid induced hyperglycemic states and patients suffering from COVID 19 illness and in post recovery. Mucormycosis can also infects skin, lungs, gut and it can presents as disseminated form. In our study, COVID-19 infection, diabetes mellitus, corticosteroid therapy, oxygen support were the causative factors leading the patient to rhino-orbitocerebral mucormycosis. Vision loss and cavernous sinus thrombosis are the fatal complications.[6] Imaging techniques such as Contrast enhanced CT paranasal sinuses along with orbit and MRI Brain along with orbit helps in establishing diagnosis. Most common finding is sinusitis. MRI is more sensitive than CT for detecting orbital and CNS involvement.[7] Based on the infected region, the imaging findings may include paranasal sinuses inflammation itself in early stages later patient may develop bony destruction and invasion to orbital tissues causing intraorbital tissue signal alteration with or without focal mass finally it invades cavernous sinus via blood stream reveals cavernous sinus filling defect suggestive of thrombus, intracranial focal mass. Patients suspecting mucormycosis should always go through diagnostic nasal endoscopy and/or surgical exploration functional endoscopic sinus surgery, with biopsy and KOH mount of the areas of suspected infection. Mucormycosis can be confirmed by blackish necrotic tissue on diagnostic endoscopy.[8] Biopsy with histopathologic examination remains the most sensitive and specific modality for definitive diagnosis.

A histopathological examination reveals characteristic wide, thick walled aseptate hyphae that branch at right angles with inflammation in the background, and vessel inflammation together with the presence of mucor hyphae within the vascular wall and lumen.

Rhino-orbito-cerebral mucormycosis is a catastrophic infection in which mortality rises to 50%–85% in brain invasion. Prognosis in mucormycosis depends on early detection and diagnosis, recognition and removal of risk factors, curettage and scraping of necrotic tissues, irrigation of sinuses and systemic antifungals.[9] Most alarming thing is usage of corticosteroids and crucial step in management is discontinuation of corticosteroids and control of blood sugar levels and monitoring cautiously.

Amphotericin B is the first line drug in management of mucormycosis and significantly improves the survival rate. Liposomal formulation is less nephrotoxic and better CNS penetration but highly expensive. Posaconazole is a second line antifungal available as a salvage option. Surgical management includes detection of blackish necrotic tissue in endoscopy and debridement of paranasal sinuses and irrigation of sinuses and scraping the infected tissue which helps in preventing the propagation.[10] Orbital exenteration is preferred in late stages having mass or extensive necrotic tissues.

In our case, risk factors such as steroids were avoided, predisposing factors including diabetes mellitus was controlled, systemic amphotericin B was given, paranasal sinus necrotic tissue debridement was done. Debridement and scraping of necrotic tissues were continued intermittently. No gross detection of blackish necrotic tissue and tissue remains were also cleared and antifungal medical therapy was given later patients symptoms got improved as eye pain and facial pain subsided and facial swelling reduced, nasal stuffiness relieved, drooping of eyelid got improved, conjunctival chemosis got subsided. Early diagnosis and management help in preventing propagation and invasion of fungus to brain.

CONCLUSION

Incidence of secondary fungal infections has been increasing in COVID 19 illness as well as patients who had recovered from this illness probably due to immune dysregulation, diabetes mellitus or diabetic ketoacidosis, prolonged usage of corticosteroids. Hence, invasive secondary fungal infections in patients with COVID-19 infection or who recovered from COVID 19 should be diagnosed early and timely medical or surgical intervention should be done to reduce the morbidity and mortality associated with the disease.

TAKE HOME MESSAGE

Both Medical and Surgical Intervention plays a crucial role and good prognosis.

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