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A 70 YEAR OLD DIABETIC MALE WITH POST COVID-19 MUCORMYCOSIS- A CASE REPORT

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ABSTRACT

The most common causes attributed to the rise of mucormycosis in COVID-19 patients are uncontrolled diabetes, the excessive use of corticosteroids for immunosuppression, and long term stays in the intensive care unit. Even though no official figures about mucormycosis in COVID-19 cases were released by the Union Health Ministry during the first wave of COVID-19, India contributed to approximately 71% of the global cases of mucormycosis in patients with COVID-19 based on published literature from December, 2019, to the start of April, 2021. Bangladesh has reported two cases of mucormycosis at BIRDEM Hospital in patients who have recovered from Covid-19, a worrying sign as neighboring India reports widespread infections. One of the patients, aged 45 was detected on May 8 and the other, aged 60, was detected on May 23. Here we present a 70 year old diabetic male, who has recovered from Covid-19 and presented with severe respiratory distress, fever and cough. He received steroid, Tocillizumab and Ramdisivir as treatment of Covid in another hospital. He had neutrophilic leukocytosis, thrombocytopenia, acute kidney injury, very high inflammatory markers, CXR(Chest X-Ray) demonstrated bilateral peripheral patchy opacities, RT-PCR(Real Time Polymerase Chain Reaction) for COVID-19 was negative, Bronchoscopy revealed black and white fungus and histopathology confirmed Mucormycosis. He was treated accordingly and subsequently improved. He was discharged with treatment and advice. Since the world has a greater population of diabetic patients in most regions and steroid therapy being used as a potential drug for COVID-19 infection, the warmer and humid regions where COVID-19 and diabetes are prevailing can be an immediate health hazard, especially in low-income and middle-income countries.

KEYWORDS: Mucormycosis, Covid-19, Post Covid-19, Diabetes mellitus.

INTRODUCTION

Covid-19 cases in Bangladesh are approaching 1,576,001 while death has surpassed 27980 on Nov 29, 2021. Total patient recovered during this period is 1,540,597 and second dose of vaccination completed in 33,792,415 no of people.[1] Bangladesh has reported two cases of mucormycosis at BIRDEM Hospital in patients who have recovered from Covid-19, a worrying sign as neighboring India reports widespread infections. One of the patients, aged 45 was detected on May 8 and the

other, aged 60, was detected on May 23[2]. Covid-19 patients, those who are diabetic, take steroids, have cancer or transplanted organs, and other comorbidities are susceptible to an infection, they added.[2]

CASE REPORT

Mr. X, 70 year of age, male patient hailing from Nikunjo, Khilkhet, Dhaka, Bangladesh got admitted to Anwer Khan Modern Medical College Hospital(AKMMCH) Non Covid Intensive Care Unit (ICU) on 8.10.21 at 12.40 AM with the complaints of severe respiratory distress, fever and cough. On query patient's attendance state that, he has been suffering from fever and cough from 19.8.21. He was Covid-19 positive 21.8.21 and negative on 7.9.21. He was admitted to ICU of another hospital from 20.8.21 to 7.10.21, During his stay in that hospital he developed acute kidney injury (AKI) and started hemodialysis on 25.8.21. After receiving several sessions of (8-9 sessions) hemodialysis (Sustained low efficacy dialysis), his renal function improved. He was intubated on 3.9.21 due to Type 2 Respiratory Failure and tracheostomy done on 22.9.21. Patient received Methyle-prednisolone, Ramdisivir, Tocillizumab on 21.8.21 for Covid-19 in that hospital.

As patient's condition gradually deteriorated patient's relative shifted the patient to non Covid ICU (Intensive Care Unit) of AKMMCH on 8.10.21 after getting DORB (Dis-charged on risk bond) from that hospital. Patient was discharged on tracheostomy tube, MV(Minute ventilation) Day 16, Mode- PCMV(Pressure controlled mandatory ventilation), FiO_2(Percentage of oxygen in the air mixture) 40-60%, RR(Respiratory rate) 20 breaths/min, PEEP(Positive end expiratory pressure) 5, PIP(Peak inspiratory pressure) 40, Blood Pressure(BP)-110/70, HR(Heart rate)- 75 beats/min, RR(Respiratory rate) 24 breaths/min, SPO2(Oxygen saturation) 95%, Temperature(Temp) 98^0F.

On admission to AKMMCH, his pulse was 112/min, BP 140/80 mm of Hg, Temp 98^0 F, Respiratory rate 20 breaths/min, SPO2 96%, Random Blood Sugar(RBS) 7.2 mmol/L, P^H 7.3, Partial pressure of Carbon di oxide(PCO_2) 57.3 mm of Hg, Partial pressure of Oxygen(PO_2) 76 mm of Hg, Hematocrit (Hct) 29.6, Bi-carbonate($HC0_3$) 28.7mmol/L. Patient could not tolerate SIMV (Synchronized intermittent mandatory ventilation) trial on MV, due to repetitive Carbon di oxide(CO_2) retention, he was well maintained in controlled mode without sedative and paralytic agents.

On 8.10.21 patient's investigations revealed, Complete blood count (CBC) Hemoglobin (Hb%)- 10.10gm%, Erythrocyte Sedimentation Rate(ESR) 19mm in 1st Hour, Total count of White Blood Cell(WBC)- $10x10^9$ U/L(Neutrophil- 78%, Lymphocyte- 16%), Total count of Red Blood Cell(RBC)- $4.07x10^{12}$ U/L, Total Platelet count $215x10^9$ U/L, Mean corpuscular hemoglobin (MCH)-25pg/U, S. Creatinine 1.8mg/dl, B. Urea 78mg/dl, S. Uric Acid 4.3mg/dl, S. Calcium 9.6mg/dl, S. Phosphate 1.0mg/dl, Serum glutamic pyruvic transaminase(SGPT) 21U/L, S. Electrolytes- Sodium-143mmol/L, Pottasium-4.1mmol/L, Chloride-101mmol/L, Bicarbonate-26mmol/L, S. Albumin-36g/L, D Dimmer 0.17mcg/mL, S. Lactate 1.68mmol/L, C-reactive protein (CRP) 25.8mg/L, Procalcitonin(PCT) 0.6ng/ml, Interleukin-6 (IL-6)- 31.7pg/ml, S. Ferritin 906.4ng/ml, Pro- B type Natriuretic Peptide(Pro-BNP) 6043pg/ml, Albumin creatinine ratio(ACR) 2700mg/g, HbA1c 7%, Troponin-I 33.45pg/ml, Routine Examination of Urine(Urine R/E) Albumin++, Pus cell 6-8mm^3, Red Blood Cell(RBC)-Plenty, Activated partial thromboplastin time(APTT) 49 sec(Control 28 sec), Prothrombin time(PT) 15.8 sec(Control 12 sec), International normalized ratio(INR) 1.29, High-resolution computed tomography(HRCT) Chest-Bilateral Pneumonia.

During ICU stay patient received stem cell therapy on 12.10.21 and 17.10.21. On 15.10.21, he developed fever, reduced urine output, bleeding from suction of tracheal tube and patient was deteroriated. His Platelet count reduced to $115x10^9$ U/L and S. Creatinine increased to 4.2mg/dl and B. Urea 91mg/dl. IT Tube C/S (Culture and sensitivity) – Growth of Klebsiella pneumonea, Tracheal aspirate C/S- Growth of Pseudomonous aeroginosa, Nasal swab C/S- Escherichia Coli(E. Coli). Blood C/S and Urine C/S reveals no growth. All his drugs were adjusted according to estimated Glomerular filtration rate (GFR). Broncho-alveolar lavage (BAL)- Ziehl Neelsen(ZN) stain-Acid-Fast Bacilli(AFB) not found. On 17.10.21 Bronchoscopy done and revealed black and white fungus and biopsy taken, Histopathology-Mucormycosis confirmed and Amphotericin B and Anidulafungin (with renal dose adjustment) added and continue for 14 days. After 14 days Bronchoscopy done again and only white fungus found.

We adjusted different antibiotics according to C/S reports. 3 units of Packed cell transfusion given. He developed yellowish dis-coloration of skin, sclera and mucous membrane on 18.10.21. He was Anti HBc (Hepatitis B core antigen) Total positive and S. bilirubin was 1.8mg/dl, 24 hours Halter monitoring revealed Atrial fibrillation, Vitamin D level was 14ng/ml. And he was treated accordingly. He was then shifted to cabin and was discharged on 18.11.21 with supportive treatment, tracheostomy tube, oxygen saturation was maintained in room air and was advised to take support from portable ventilator in PCV and SIMV mode alternatively, whenever needed.

Operational Definition

SIMV: Synchronized intermittent mandatory ventilation is a type of volume control mode of ventilation. With this mode, the ventilator will deliver a mandatory (Set) number of breaths with set volume while at the same time allowing spontaneous breaths.[3]

MV: Minute ventilation (or respiratory minute volume or minute volume) is the volume of gas inhaled (inhaled

minute volume) or exhaled (exhaled minute volume) from a person's lungs per minute. It is an important parameter in respiratory medicine due to its relationship with blood carbon dioxide levels.[4]

PCMV: Pressure control mandatory ventilation (CMV) is a mode of mechanical ventilation in which breaths are delivered based on set variables. Still used in the operating room, in previous nomenclature CMV referred to controlled mechanical ventilation.[5]

PCV: Pressure control ventilation, the ventilator generates the present pressure during present inspiratory time at the present respiratory rate. The pressure is constant during the inspiratory time and the flow is decelerating.[6]

PEEP: Positive end expiratory pressure is a pressure applied by the ventilator at the end of each breath to ensure that the alveoli are not so prone to collapse. This 'recruits' the closed alveoli in the sick lung and improves oxygenation. So PEEP reduces trauma to the alveoli.[7]

PIP: Peak inspiratory pressure is the highest level of pressure applied to the lungs during inhalation. In mechanical ventilation the number reflects a positive pressure in centimeters of water pressure (cm H_2O).[8]

FiO_2: Percentage of oxygen in the air mixture that is delivered to the patient.

Flow: Speed in liters per minute at which the ventilator delivers breaths.

Compliance: Change in volume divided by change in posture.[9]

DISCUSSION

The incidence of mucormycosis has risen more rapidly during the second wave compared with the first wave of COVID-19 in India, with at least 14872 cases as of May 28, 2021. The state of Gujarat alone contributed to the highest number of cases, with at least 3726 cases of mucormycosis in patients with active and recovered COVID-19, followed by the state of Maharashtra. Since the communication from the Health Minister of Maharashtra on May 19, 2021, there have been 90 deaths attributable to mucormycosis. Other states such as Rajasthan, Andhra Pradesh, Karnataka, Haryana, Madhya Pradesh, Uttarakhand, and Delhi have also shown a steady rise in the number of mucormycosis cases and deaths related to it; with multiple states already having declared it as an epidemic and a notifiable disease to the national health authorities.[10]

The Indian Council of Medical Research released guidelines for the screening, diagnosis, and management of mucormycosis in patients with COVID-19.[11] The most common causes attributed to the rise of mucormycosis in COVID-19 patients are uncontrolled diabetes, the excessive use of corticosteroids for immunosuppression, and long term stays in the intensive care unit. Even though no official figures about mucormycosis in COVID-19 cases were released by the Union Health Ministry during the first wave of COVID-19, India contributed to approximately 71% of the global cases of mucormycosis in patients with COVID-19 based on published literature from December, 2019, to the start of April, 2021.[12]

Bangladesh has reported two cases of mucormycosis at BIRDEM Hospital in patients who have recovered from Covid-19, a worrying sign as neighboring India reports widespread infections. One of the patients, aged 45 was detected on May 8 and the other, aged 60, was detected on May 23[2]. Covid-19 patients, those who are diabetic, take steroids, have cancer or transplanted organs, and other comorbidities are susceptible to an infection, they added.[2]

Here we present a 70 year old diabetic male, who has recovered from Covid-19 and presented with severe respiratory distress, fever and cough. He received steroid, Tocillizumab and Ramdisivir as treatment of Covid in another hospital. He had neutrophilic leukocytosis, thrombocytopenia, acute kidney injury, very high inflammatory markers, CXR(Chest X-Ray) demonstrated bilateral peripheral patchy opacities, RT-PCR(Real Time Polymerase Chain Reaction) for COVID-19 was negative, Bronchoscopy revealed black and white fungus and histopathology confirmed Mucormycosis. He was treated accordingly and subsequently improved.

What is Mucormycosis and how does it transmit?

Clinical Forms of mucormycosis

Mucorales fungi are seen as aseptate hyphae, with some 11 genera and 27 species are known to cause human infection. Mucormycosis belongs to class Phycomycetes which is subdivided into genera Absidia, Rhizopus, and Mucor.[13,14]

Transmission of the Disease

Mucormycosis is caused by the fungus mucor that requires a wet surface to adhere, therefore, a humid environment is an ideal condition for it to prevail.[15] It could transmit through the hospital bed linen, unsterilized oxygen pipes, and hospital ventilators.[15] Mucormycosis infection targets immune-compromised patients, low levels of neutrophils, cancer patients, organ transplants, and patients who underwent stem cell transplants.[16] Steroids are used for the treatment of COVID-19 infections while heavy steroid use induces immunosuppression can potentially increase chances of opportunistic infection of which is mucormycosis.[16] The spores are commonly found in organic matter particularly food, soil, and plants which require humidity to grow.[16] The inhaled spore forms hyphae that invade the para-nasal sinuses, extending further through anatomical sites within the skull causing rhino-orbital or rhino-cerebral infection. COVID-19 patients are highly susceptible to develop opportunistic mucormycosis, due to weakened immune systems by decreased levels of CD4+T and CD8+T cells.[16,17] Other factors that increase the vulnerability of COVID-19 patients include prolonging hospital stay, iatrogenic corticosteroid therapy with uncontrollable diabetes mellites, and diabetic ketoacidosis.13 and pulmonary infections.[18] In

India, the usual time to fumigate ICU is around 14 days, however, due to COVID-19, complete fumigation remains a challenge at large.[19]

Symptoms of Mucormycosis

Indian Council of Medical Research (ICMR) has released signs and symptoms of mucormycosis that may include pain and redness around the eyes and nose, cough, fever, headache, disorientation, dyspnea, hematemesis, sinusitis, toothache, facial pain and numbness, hemoptysis, blackish discharge from nose and visual disturbances including unspecified vision loss.[20] ICMR has given strict instructions that any patient experiencing the mentioned symptoms must immediately seek the medical attention.

Prakash and Chakrabarti (2021) discussed the anatomical localization of mucormycosis with rhino-orbital-cerebral (ROCM) commonest area, followed by cutaneous, pulmonary, renal, gastrointestinal, disseminated, breast, ear, spine, heart, and bone.[21] In a study conducted by Pagano et al. (1997) through eighteen hematology departments, fever, thoracic pain, cough, and shortness of breath were the main symptoms presented in the patient, while 89% of the patients were neutropenic at the time of onset.[14] Talmi et al. (2002) found bloody nasal discharge and black nasal eschar as a sign of the infection, meanwhile, malaise was seen as the most common symptom in 89% of the cases.[22]

Mucormycosis in Pre-Covid-19 and During Covid-19

In the Pre-COVID-19 era, Prakash et al. (2019) discussed hematological malignancies to be the foremost global indicator for mucormycosis infection, while, diabetes mellitus was the forerunner reason the cases in India.[23] Other comorbid conditions involve skin trauma, human immunodeficiency virus, peritoneal dialysis, iron overload, deferoxamine therapy, illicit drug infusion, and voriconazole therapy.[21] Pagano et al. (1997) found the lungs to be the most affected site for the infection, followed by chronic nerve compression, sinus, liver, kidney, heart, orbital space, and large intestine.[14] However, currently in the mucormycosis epidemic in India, orbital space is the common site of infection followed by other organs.

Prognosis and Outcomes

Outcome of Infection

In the study conducted by Pagano et al. (1997), the outcome of the infection resulted in thirty patients dying within 3 months of the treatment, out of which, 28 died due to mucormycosis.[14] Talmi et al. (2002) discussed the orbital compromise exhibits the advancement of the fungal infection into cranial fossa leading to the option of orbital exenteration, however, this may lead to mutilation and irreversible loss of vision.[22]

Prognostic Factors

Pagano et al. (1997) found Phycomycetes to be resistant to triazoles and nystatin.[14] Pagano et al. (1997) found the increase in neutrophils after post-chemotherapy aplasia and amphotericin B treatment was closely associated with the prognosis from the infection.[9] However, oral antimycotic prophylaxis failed to prevent mucormycosis.[14] Controlling the environmental exposure to neutropenic patients showed positive outcomes in restricting the development of filamentous fungal infection. Isavuconazole is a new antifungal remedy for the treatment of mucormycosis, which was unavailable in India in 2018, but recently introduced in India, therefore, it lacks research on the efficacy in long-term, however, during the limited timeframe, it has shown efficacy as compared to amphotericin B.[23] Talmi et al. (2002) noted palatal involvement in the patients with poor prognosis. Talmi et al. (2002) discussed the use of granulocyte colony-stimulating factor (G-CSF) in neutropenic patients to hold value.[22]

Mortality Rate

Before COVID-19 the mortality rate from mucormycosis in India was 46.7%, where, the mortality rate in North India was higher compared to South India.[23] Prakash and Chakrabarti (2021) discussed that the mortality rate in the clinical presentation of mucormycosis is 64-97% in patients with gastrointestinal comorbidity, 61-77% in pulmonary, 62-79% in disseminated, 31-49% in ROCM, 23-57% in cutaneous cases.[21]

Incidence and Prevalence of Mucormycosis

There is a rise in mucormycosis cases globally, the rate of infection is further higher in developing countries including India.[24] Prakash and Chakrabarti (2021) debated on the exact incidence of mucormycosis in India due to a deficit in a population-based study, however, with the aid of the computational-model-based method, the prevalence is 14 cases per 100,000 in India.[10] Prakash and Chakrabarti (2021) in their research discussed that prevalence of mucormycosis is 70 times higher in India as compared to global.10 It was 13 cases per year from 1990 to 1999, 36 annual cases from 2000 to 2004, 50 annual cases from 2006 to 2007, and 89 annual cases from 2013 to 2015.[10] One reason Prakash and Chakrabarti (2021) discussed is improvement in the diagnosis of the disease.10 In other studies, discussed by Prakash and Chakrabarti (2021) the yearly incidence is 18 cases in Southern India (Tamilnadu) from 2005 to 2015, while, 9.5 cases from 2015 to 2019.[10] Talmi et al. (2002) mention that seasonal presence may contribute towards the incidence with the peak in fall and early winter.[23]

Was it the case of an emerging pathogen, rise during the covid-19?

Mucormycosis is not a new infection, neither it has been reported recently. It had its presence but the condition remained as rare.[14,21,22] However, the steroid treatment in COVID-19 patients is causing an immunosuppressed condition, together with the conditions in which mucormycosis infects humans.

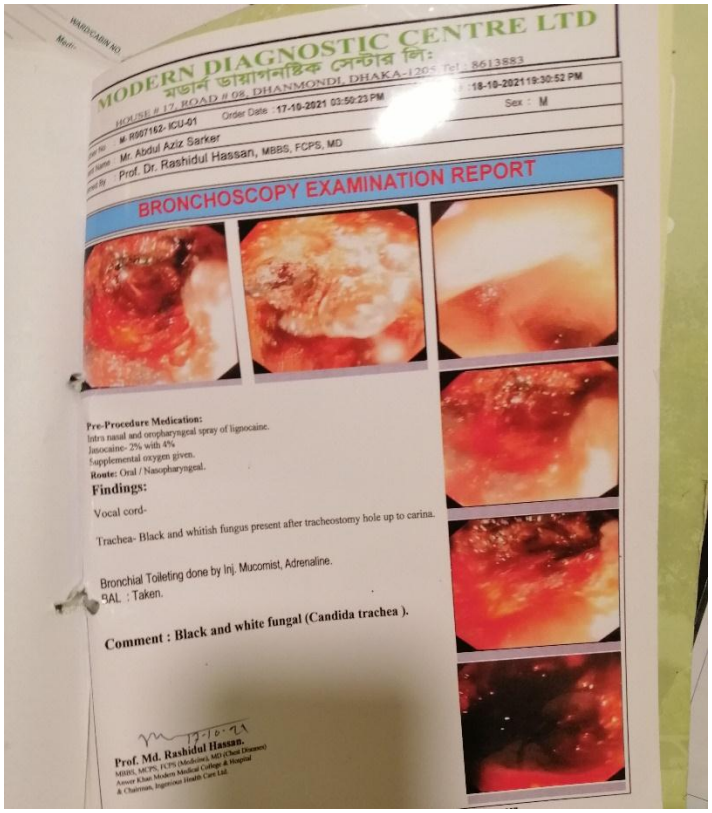

Fig. Bronchoscopy of the Patient.

CONCLUSION

The burden of COVID-19 in Bangladesh has affected millions, which has been an emergency throughout the country during the second wave. The mucormycosis infection has been increased vulnerability of COVID-19 recovered patients with corticosteroid therapy and diabetes mellitus. Since the treatment is expensive, the burden of infection is increased on the health care system. The mortality rate of mucormycosis is much higher than of COVID-19 infection alone. Since the world has a greater population of diabetic patients in most regions and steroid therapy being used as a potential drug for COVID-19 infection, the warmer and humid regions where COVID-19 and diabetes are prevailing can be an immediate health hazard, especially in low-income and middle-income countries.

Conflict of interest: None.

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