Bangladesh Journal of Medicine (BJM)
ISSN : 1023 - 1986
eISSN : 2408 - 8366

CASE REPORT

POST-COVID PULMONARY MUCORMYCOSIS: FIRST CASE REPORT FROM BANGLADESH

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Abstract:

Mucormycosis is an invasive fungal infection caused by different saprophytic environmental fungus occurring predominantly among immunosuppressed patients. Pulmonary mucormycosis is the second most common form after rhino-cerebral mucormycosis and may accompany with other infections. Coronavirus disease 2019 (COVID-19) itself and its treatment with immunosuppressive drugs and oxygen delivery systems etc. are setting the scenes for opportunistic and co-infections with fungus and other pathogens. A middle aged Bangladeshi man, with background diabetes mellitus, hypertension, bronchial asthma and COVID-19, presented with fever, respiratory symptoms and cavitary lung lesion. Diagnostic work-up confirmed pulmonary mucormycosis and he responded with liposomal amphotericin B. To the best of our knowledge, this is the first case of post-COVID mucormycosis reported from Bangladesh.

Key words: *COVID-19, diabetes mellitus, mucormycosis, pulmonary mucormycosis.*

Received: 3.6.2021 *Accepted: 5.6.2021*
DOI: https://doi.org/10.3329/bjm.v32i2.53802

Citation: *Afroz F, Barai L, Rahim MA, Kanta SS, Hossain MD. Post-Covid Pulmonary Mucormycosis: first case report from Bangladesh. Bangladesh J Medicine 2021; 32: 156-160.*

Introduction:

Mucormycosis is an invasive fungal infection, caused by different environmental saprophytic fungus, occurring predominantly among immunosuppressed patients like patients with haematological malignancy, transplant recipients, diabetes mellitus and patients receiving steroids and other immunosuppressive drugs for some other indications. Pulmonary mucormycosis is the second most common form after rhino-cerebral mucormycosis and may accompany with other infections.[1] Coronavirus disease 2019 (COVID-19) itself, its treatment with corticosteroids and other immunomodulators, invasive and non-invasive ventilatory supports and other oxygen delivery systems, prolonged hospital stay and comorbidities, all are setting the scenarios for opportunistic infections and co-infections with fungus and other pathogens. In recent weeks, increasing numbers of identified and reported mucormycosis cases among patients with history of recent infection by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), has created panic among patients with COVID-19 and also among general people. Here, we report a case of post-COVID mucormycosis from Bangladesh.

Case Report:

A 53-year-old businessman from Satkhira, a south-western coastal district of Bangladesh with adjacent Indian border, was referred to our center because of 16-days history of fever and cavitary lung lesion. He is a known case of type 2 diabetes mellitus with poor glycaemic control (glycated haemoglobin, HbA1c 11.4%), systemic hypertension and bronchial asthma and denied any recent history of overseas travel.

Two months ago (April 3, 2021), he was detected as having COVID-19 [8-days history of fever, cough and shortness of breath and positive reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2], 39 days after receiving the first dose of COVID vaccine. He was hospitalized in Khulna and required intensive care unit (ICU) transfer because of hypoxia (required up to 70 liters of oxygen/min through high flow nasal cannula) and around 60% lung involvement on computed tomography (CT) scan of chest (Fig.-1).

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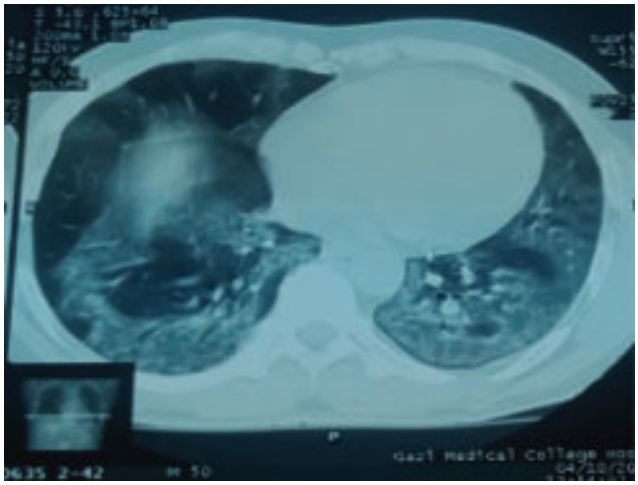

Fig.-1. *HRCT scan of chest showing ground glass opacity*

That time, his medications included remdesivir (5 days), dexamethasone (20 mg/day for 10 days), tocilizumab (one dose), enoxaparin (60 mg/day) along with antibiotics (ceftazidime and moxifloxacin). After 8-days stay in ICU, he was shifted to cabin and 3 days later he was discharged without any supplemental oxygen requirement and his discharge medication included dexamethasone 6 mg/day for another 10 days.

His present illness started 10 days after discharge and he was evaluated by a pulmonologist at Khulna. He had neutrophilic leukocytosis (total white cells 13000/cmm with 79% neutrophils), raised C-reactive protein (CRP) (92 mg/L, ref. <6 mg/L), sputum Gram stain and culture, acid fast bacilli (AFB) stain and GeneXpert were negative but CT chest revealed a caviatry lesion in right upper lobe (Fig.-2) which was not present during his hospital stay with COVID-19 (Fig.-1).

Depending on clinical and radiological features, he was started with category-1 anti-tubercular chemotherapy along with broad spectrum antibiotics without any benefit. Subsequently, he was prescribed voriconazole empirically.

Admission evaluation at our facility revealed that, he was toxic with a temperature of 105°F and had intractable cough with mucoid sputum production. He was tachycardic (pulse110 beat/min), tachypnoeic (respiratory rate 22 breaths/min) and chest auscultation revealed bilateral scattered course crepitation. There was neutrophilic leucocytosis and lymphopenia (total white cells 18,000/cmm, neutrophils 85%, lymphocytes 7.5%) with raised CRP (92 mg/L) and erythrocyte sedimentation rate (ESR) (70 mm in 1st hour). Piperacillin-tazobactum combination was started after sending blood culture and oral voriconazole was continued at a dose of 200 mg 12 hourly with other symptomatic management. Liver and renal biochemistry were unremarkable. A repeat CT chest at our center revealed increase in size and wall thickness of the cavitary lesion (Fig.-3).

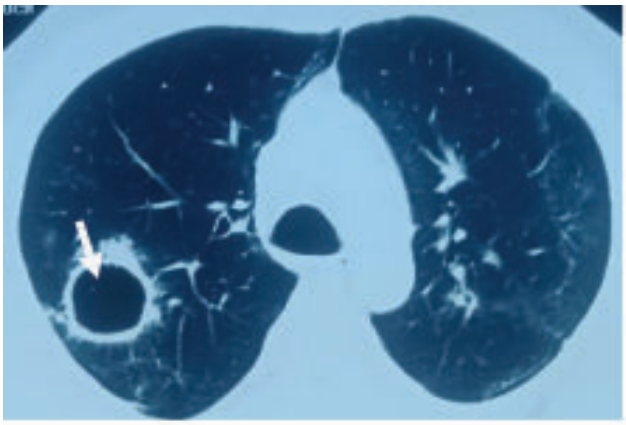

Fig.-2. *Cavitary lung lesion in right upper lobe on CT scan of chest (arrow)*

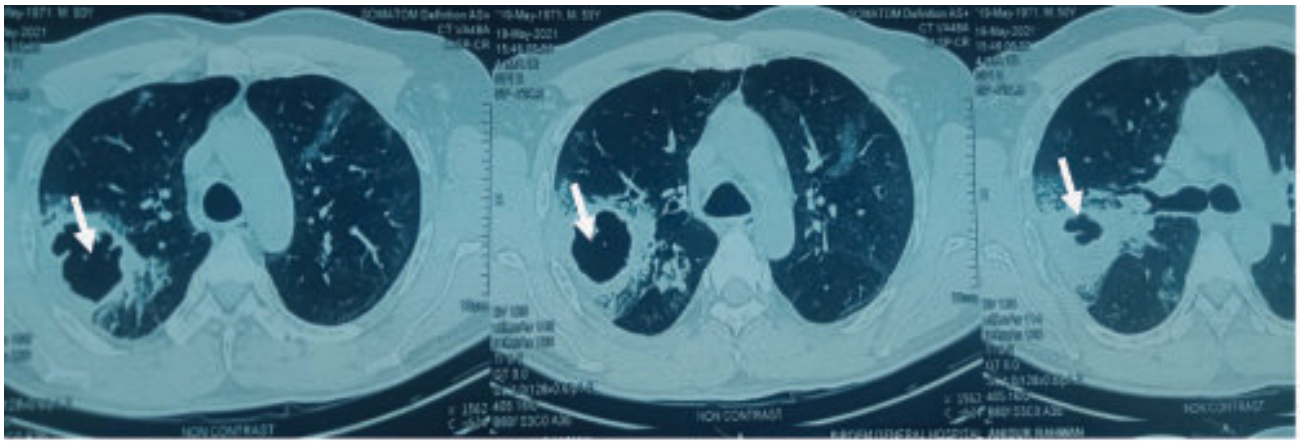

Fig.-3: *Cavitary lung lesion in right upper lobe on CT scan of chest (arrow)*

As we were dealing a poorly controlled diabetic man having non-resolving cavitary lung lesion with recent history of critical COVID-19, invasive fungal infection appeared as an important differential. The 1st sputum sample showed budding yeast, which could be normal flora. Blood and urine cultures did not reveal any growth, he had normal procalcitonin level, he tested negative for antibody against human immuno-deficiency virus (HIV) and repeat sputum for AFB and GeneX-pert appeared negative.At this stage, we pursued microbiologists for a second sputum sample and that showed typical hyphae of mucormycosis on 22nd April, 2021 (Fig.-4).

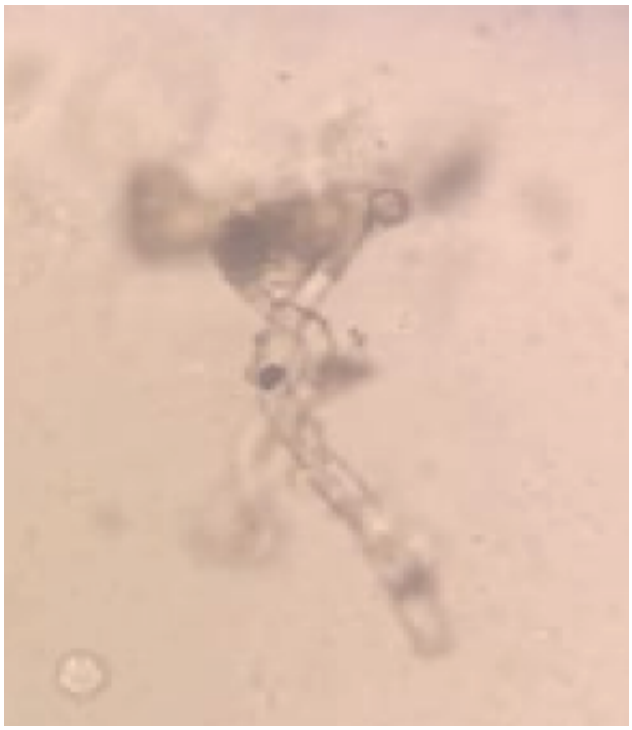

Fig.-4: *Broad, irregular, aseptate and twisted hyphae characteristics of mucormycosis on direct microscopy*

Injectable liposomal amphoterecin B (5 mg/kg/day) was started. On 24th April, 2021, sputum culture grew *Pseudomonas* and *Klebsiella* and both were sensitive to colistin only, which was started. Bronchoscopy did not show any definite endobronchial lesion, no contact bleeding but there were multiple whitish plaques, scattered over vocal cord and trachea (Fig.-5). Bronchoalveolar lavage (BAL) also revealed mucormycosis (Fig.- 6 & 7) without any AFB or malignant cells. So, treatment was continued.

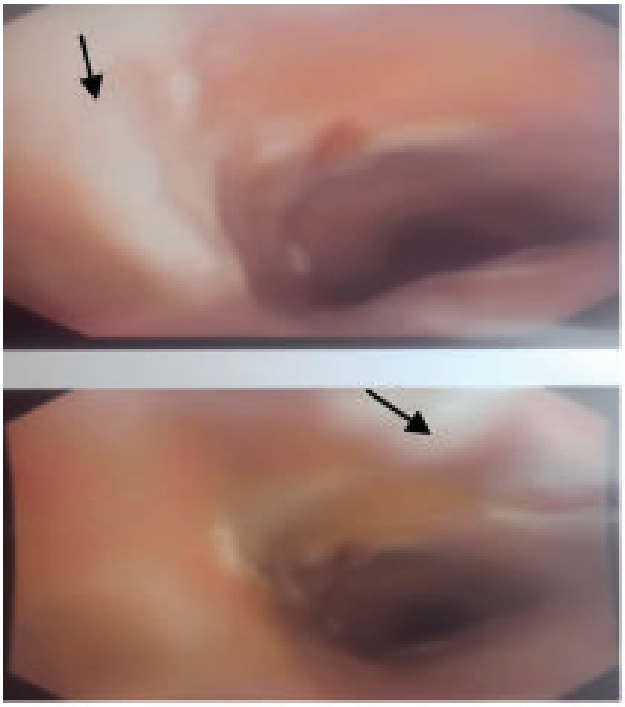

Fig.-5: *Bronchoscopic view of the whitish plaque of the fungus (arrow)*

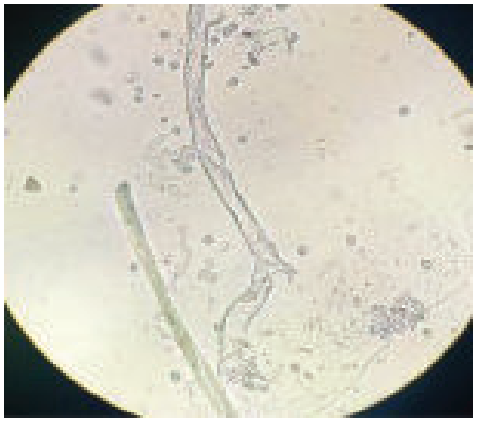

Fig.-6: *Direct microscopy of BAL*

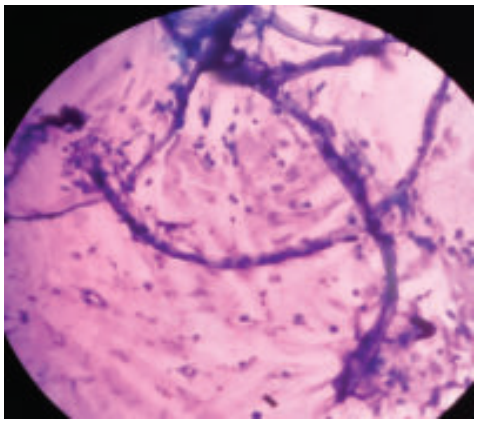

Fig.-7: *Giemsa stain of BAL*

Patient became afebrile and his cough improved after 6 days of amphoterecin B treatment along with radiological (Fig. 8 & 9), respectively showing improvements on chest X-rays) and hematological parameters (total white cells 11350/cmm, neutrophils 72.4%) and inflammatory markers (ESR 22 mm in 1st hour, CRP 14 mg/L).

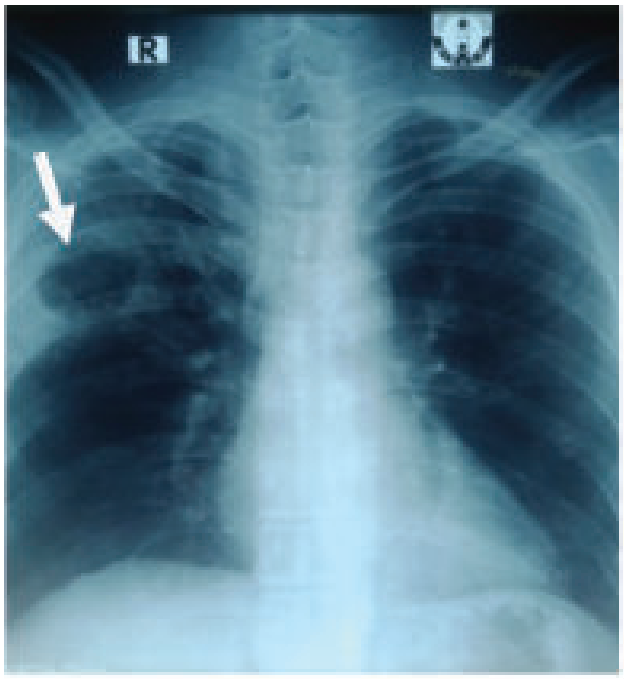

Fig.-8. *Chest X-ray postero-anterior view showing cavitary right lung lesion (first X-ray)*

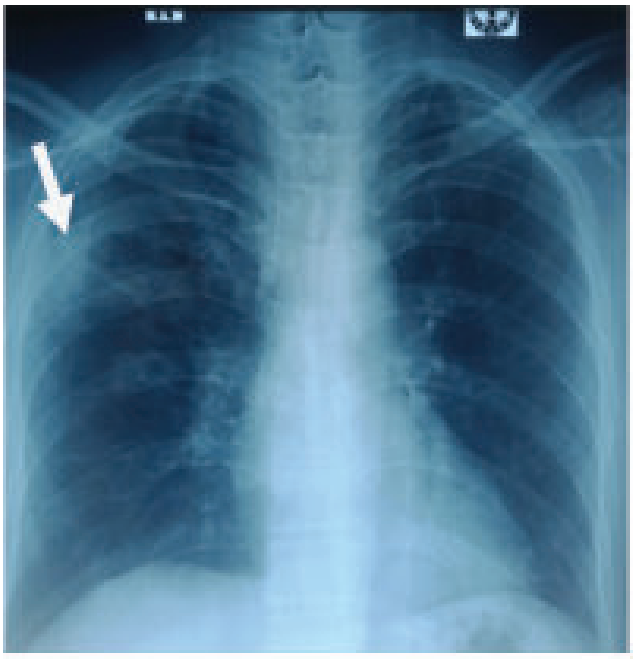

Fig.-9: *Chest X-ray showing improvement of right lung lesion (follow-up X-ray)*

No drug reaction from amphoterecin B was observed. Finally, on 1st June, 2021, sputum and BAL culture reports were available but did not show growth of any fungus. Till the time of writing this report, injectable liposomal amphoterecin B is being continued, his blood glucose is well controlled with premixed insulin and there is no feature suggesting any other organ involvement or dissemination or deterioration of any clinical or laboratory parameters.

Discussion:

Though mucormycos is is an uncommon disease, its prevalence in India is 70 times the world wide estimated rate.[1] No clear racial or age factors that predispose people to mucormycosis exist. However, a review of all published cases of pulmonary mucormycosis performed by Lee et al showed a male-to-female ratio of 3:1.[2]

Mucormycosisis an opportunistic infection, caused by the order Mucorales. Rhizopus species are the most common causative organisms. In descending order, the other genera with mucormycosis-causing species include Mucor, Cunninghamella, Apophysomyces, Lichtheimia (formerly Absidia), Saksenaea, Rhizomucor and others.[3] Mucorales species are ubiquitous saprophytes and soil is believed to be the main habitat of most of these fungi. The sporangiospores released by Mucorales range from 3 to 11 ìm in diameter and can be aerosolized to disperse in the environment, leading to an airborne infection in the upper or lower airways.[4] These fungi can invade the nose, sinuses, brain, gastrointestinal tract, skin and lung or even disseminate throughout the body.

Risk groups include patients with diabetes mellitus, specially uncontrolled one with or without diabetic ketoacidosis, haematological and other malignancy and treatment with chemotherapeutic agents, organ transplant recipients, patients with HIV infection/ acquired immunodeficient syndrome (AIDS) and patients receiving immunosuppressive medications. However, immune-competent patients are not immune against mecormycosis, though the reported cases of pulmonary mucormycosis in immunocompetent patients are very low.

COVID-associated invasive fungal infections are being identified and reported in literature. Emerging associations are proposed like COVID-associated pulmonary aspergillosis (CAPA) and COVID-associated pulmonary mucormycosis (CAPM). Several factors are proposed to be responsible for increased incidence of post-COVID invasive fungal infections including severe pulmonary alveolar damages in COVID-19 may facilitate fungal invasion, immune dis-regulations may facilitate infections, invasive mechanical ventilations may facilitate opportunistic infections and immunosuppressive drugs used in COVID-19 further helps in invasive fungal infections.[5]

COVID-associated mucormycosiscases are mostly involving the rhino-orbital-cerebral area. The largest

case series (pre-print), so far,which is awaiting to be published in Lancet, revealed 80 cases of COVID-associated mucormycosis (CAM), with 42 of them from India and almost all are of rhinocerebral variety.[6] Pulmonary cases are uncommon and may be missed because of lack of awareness to the condition in post-COVID patients, because of symptom sharing; fever, cough, haemoptysis, all can occur in COVID-19 and in pulmonary mucormycosis and also in other differentials, including bacterial infections. Unlike our patient, He J et al reported isolated pulmonary mucormycosis in a patient who did not have any of the afore-mentioned risk factors and similar to other reported cases, it was assumed that he may have pneumonia or tuberculosis, until BAL fluid culture confirmed the growth of Absidia. A high index of suspicion, including the fact, that, non-response or poor-response to broad spectrum antibiotics should raise the suspicion. Fungal staining of true representative respiratory samples may indicate the disease, tissue diagnosis may be possible and cultures may fail to identify cases, though being gold standard and are time consuming.[7]

Management includes a prompt diagnosis, removing or reversing predisposing factors, surgery or debridement, if indicated and antifungal drugs. Liposomal amphotericn B is the drug of choice and oral posaconazoles are also effective. Antifungal drugs are not widely available and high cost of liposomal amphotericin B appears as a barrier to effective therapeutic outcomes.

Though uncommon, mucormycosis poses significant challenge because of high mortality reaching up to 50% or even more in this COVID era. The mortality rate associated with rhinocerebral disease is 50-70%. Pulmonary and gastrointestinal (GI) diseases carry an even higher mortality rate, because these forms are typically diagnosed late in the disease course. Disseminated disease carries a mortality rate that approaches 100%. Animal excreta may be responsible for cutaneous cases and carries the lowest mortality rate (15%). Also, mucormycosis leaves significant morbidity including organ damage among the survivors. A retrospective report from Bangladesh revealed histopathologically diagnosed 13 patients with invasive fungal rhinosinusitis between 2007 and 2011, with 37.5% (3 out of 8 patients with Mucoraceae and died) mortality.[8] Rapid diagnosis, early and aggressive management including combined antifungal and surgical interventions and reversal of underlying risk factors along with a high index of suspicion can save lives.[9]

Preventive strategies should be stressed including strict glycaemic control, judicious use of corticosteroids and safe use of ventilator and oxygen delivery system are important. Patients recovering from COVID-19 should be educated regarding symptoms suggestive of mucormycosis like nasal blockage, blackish nasal discharge, haemoptysis etc. and report immediately for evaluation. Physicians should be aware that in the COVID era, increasing mucormycosis cases is a reality, but it should not cause panic and an early diagnosis and appropriate management strategy can result to a good outcome as in the present case.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study

Funding:

No specific funding was received for this study.

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