Pulmonary Mucormycosis: A Case Report and Systematic Review of the Literature

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The pulmonary mucormycosis (PMM) caused by Mucorales is a highly lethal invasive fungal infection in which early diagnosis and management is imperative. Otherwise, the mortality may exceed 80%. PMM does not have specific symptoms; hence, awareness of the disease and the treating physician’s suspicion can detect or diagnose it earlier. The fungal infection also needs to be differentiated from aspergillosis and other common fungal infections so an appropriate treatment is instituted.

Case Report: A 62-year-old male was admitted with a six-month cough with scanty expectoration and a short history of progressive breathlessness for the last five days. He had a known case of diabetes and also an old-treated case of tuberculosis. He had a history of COVID-19 pneumonia (without a positive report). No history of fever, chest pain and hemoptysis. However, chest X-ray and HRCT thorax revealed a fibro-cavitary lesion in the right upper lobe with sputum and CBNAAT negative for AFB. The FOB examination detected complete occlusion with protruded soft yellowish and black material in the right main upper lobe bronchus, which was reported as mucormycosis. The patient was treated with amphotericin and then with oral antifungal.

Discussion: An upsurge of mucormycosis was reported in our country during the COVID-19 era, leaving behind aspergillosis and another fungus. The rhino-orbit-cerebral is the most common site for this fungal infection and is essentially reported in an immune-compromised host as happened in our diabetic patient but as PMM. The Post TB sequelae with residual fibro-cavitary lesions, COPD and solid organ transplantation cases are the other risk factors and our country has enough of a vulnerable population. Our case was detected in the post-Covid period and required attention to epidemiological change or something else?

Conclusion: An early rapid diagnosis and management of mucormycosis is crucial to minimizing mortality. The treatment by amphotericin is the best choice followed by Posaconazole or Isavuconazole as step-down oral medication. The increasing incidence of this infection in our country is challenging.

Introduction

Humans are less prone to fungal infections than bacterial and viral infections. All fungal infections are usually opportunistic and relates to the decrease in or disruption in the immune system. The incidence of fungal infection globally has increased in the recent past. Among them, the four most common pulmonary invasive fungal infections in frequency are aspergillosis, candidiasis, coccidioidomycosis and mucormycosis.1 Pulmonary mucormycosis caused by mucorales is a highly lethal invasive fungal infection for the vulnerable group who has some underlying immune compromising condition, i.e., uncontrolled diabetes, HIV, organ transplant and, steroid therapy etc.2 The mucormycosis fungus grows rapidly, releases many spores in the environment, and is responsible for airborne infection. The Mucorales are thermotolerant saprophytic fungi and are also found in decaying organic matter and soil samples.3 The Mucormycosis hyphae are broad (5–15 micron diameter), irregularly branched, rarely have septations that can easily be distinguished on examination from the Aspergillus, by narrower hyphae (2–5-micron diameter), regular branching with many septations.

The rhino-orbito-cerebral mucormycosis is the most common (44–75%) site of involvement, followed by skin (10–31%) infection during trauma, lower respiratory tract (3–22%), renal (0.5–9%), gastrointestinal (2–8%), and

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disseminated infections 0.5 to 9%. However, the exact incidence of mucormycosis in India is not known however, Hariprasath Prakash et al. mentioned that it is estimated to be 70 times more prevalent in India than in global data. He further mentioned that the most common agent in our country is Rhizopus arrhizus. However, occasionally, other isolates are also detected. Tedder analyzed 255 cases of pulmonary mucormycosis (PMM), which revealed predisposing factors for the fungal infection in order of frequency were hematological malignancies, diabetes, chronic renal failure and organ transplantation as the underlying causes. Kumar et al. mentioned hyperglycemia, lymphopenia, hyper-ferritinemic and ketoacidosis, even in the absence of diabetes mellitus as common factors for PMM. The first phase of the Covid-19 pandemic recorded an association of pulmonary mucormycosis. Later, a massive upsurge in the second phase was characterized by CAM's angio-invasive and thrombotic nature. Pulmonary mucormycosis is a rapidly progressive infection that occurs after inhaling spores into the bronchioles and/or alveoli. This fungus leads to tissue necrosis, which is mainly responsible for the spread of infection to nearby structures, i.e., hilar lymph nodes, heart, mediastinum and even hematogenous dissemination. Pulmonary mucormycosis with Covid-19 remained the second common site after rhino-orbito and the risk factors for it could be the higher doses of steroids or use of other immunomodulator therapy like tocilizumab and or COVID-19 infection itself. However, the exact association with covid-19 is obscure. Somehow, the patients who develop unexplained worsening of clinical status or complications during the COVID-19 pandemic a strong suspicion lead to the cases being easily diagnosed as pulmonary mucormycosis. There is no specific symptom of pulmonary mucormycosis and most of the patients presented to have the usual symptoms i.e. cough, breathlessness, fever and hemoptysis (due to angio-invasive and necrosis of lung parenchyma) hence, awareness with an index of suspiciousness among treating physician can detect or diagnose it early.

India is a high burden country for TB with millions of patients are declared cured, and many of them are still suffering from symptoms pertaining to post-TB sequelae. These are in the form of residual bronchiectasis, persisting fibro-calcific and cavitary lesions leading to recurrent cough, expectoration and fever. These patients are the most vulnerable group for acquiring colonization and becoming a nidus for bacteria and fungus. The most common fungal infection is pulmonary aspergillosis however in the recent years, pulmonary mucormycosis have superseded it. An accidental detection of fungal growth during fiberoptic bronchoscopy (FOB) is not uncommon. It also happened in our case and instead of aspergillosis, a black necrotic material obstructing the right upper lobe bronchus was detected, even after the Covid-19 pandemic (in June 2023). The question comes to mind: Is the mucormycosis still prevailing or it become more common opportunistic infection than aspergillosis. Therefore the present case becomes an interesting and worthy to report.

Case Report
A 62-year-old male farmer was admitted to our hospital with the symptoms of cough with scanty expectoration since last 6 month, breathlessness since 5 days, no history of fever, chest pain or haemoptysis etc. He was a known case of type 2 diabetes mellitus since last 10 year and on regular oral hypoglycemic drugs. He was treated for pulmonary tuberculosis in the year 2020 for 6 month. A history of treatment for suspected Covid pneumonia was present, though the RTPCR test was negative. No history of HTN/Surgery/Thyroid/Asthma/Blood transfusion. The investigation revealed Hb-11.7 g/dl, WBC- 7300 and Platelets were adequate.

The serum examination for Urea, Creatinine, Liver profile, and electrolytes were within normal limits. Patient was negative for HIV and HBsAg. The sputum examination for AFB was negative on microscopy and CBNAAT examinations. Blood sugar was 102 mg/dl with HbA1C 6.7% and he was regular on anti-diabetics drugs. On examination bilateral air entry was present but diminished on right side with bronchial breath sound in the infra clavicular area and bilateral rhonchi were present. Chest X-ray & Computed tomography of thorax (Figure 1A & B) depicted fibro-cavitary lesion in right upper zone with volume loss and circumferential pleural thickening. The FOB examination revealed completely impacted fungal growth in the right upper lobe bronchus. The histopathological examination reported mucormycosis. The patient was started on Intravenous Liposomal Amphotericin. After 4 weeks of Liposomal Amphotericin therapy, patient improved and a repeat FOB (Figure 1C & D) showed patent upper lobe bronchus with inflammatory cytology negative for fungus. The patient was discharged on Posaconazole on step-down oral antifungal.

Discussion
The pulmonary mucormycosis is a rare disease with high morbidity and mortality if early diagnosis and
intensive treatment is not instituted. The mucormycosis is essentially associated with disruption of humeral or cell mediated immunity. The Covid Associated Mucormycosis (CAM) upsurge was observed during the Covid-19 era, and the incidence of mucormycosis increased many folds compared to aspergillosis in our country (India) compared to Europe. It became mandatory to differentiate both the fungus to ensure early appropriate treatment. The pathological samples stained with haematoxylin and eosin or periodic acid schiff stain and methenamine silver enable us to delineate characteristic broad pauciseptate hyphae with right angle branching which is the characteristic of mucormycosis (Figure 2). The Galactomannan assay a component of cell wall of Aspergillus help in diagnosis of invasive pathology.

Somehow till date no reliable biomarkers and molecular test etc is available for mucormycosis. Mucormycosis can easily be diagnosed clinically if the most common rhino-orbito-cerebral site is involved. The Time interval of diagnosis from Covid to mucormycosis was near 15 days; among them, only 10% were observed to have PMM. It remained difficult to diagnose isolated PMM cases during active Covid pneumonia but somehow it was reported with high mortality of >80% in the absence of early clinical suspicion and treatment. Most of these cases belonged to mechanical ventilator group, in association with diabetes, systemic high dose steroid, and other immunomodulator therapy like Tocilizumab, or with leucopenia and or lymphopenia.

In our case a history of covid treatment was present without the documentation of covid positivity. The fibrocavitary residual lesion in the upper lobe was a sequelae of pulmonary TB. This is a common site and nidus for bacterial and fungus, usually the Aspergillus. There are no specific symptoms of fungal infection except that at some occasion's haemoptysis due to fungal invasion and tissue necrosis, which were not present in our case. Our patient was diabetic and having long standing persisting cough so FOB was performed which detected completely occluded right upper lobe bronchus with a bulged out soft yellowish black material. The material was evacuated and sample was send to the laboratory and turned out to be Mucormycosis. The PMM was accidentally detected (June 2023) without involving it's other common site i.e. Rhino- orbito-cerebral even without the covid-19 pendemic for which an MRI head & neck was also performed. So is it a coincidence or still an epidemiologic change which was evident with many fold increase of mucormycosis observed during Covid era is still continued?. However the Hariprasath Prakash et al. mentioned that other predisposing factors associated with mucormycosis are chronic kidney disease (CKD), steroid therapy, pulmonary tuberculosis, solid organ transplant and COPD should also be considered for our country as new emerging risk factor apart from the most common uncontrolled diabetes. However none of above was present in the current case except a well-controlled diabetes and post TB sequelae. The Liposomal Amphotericin is the treatment of best choice followed

Figure 1: (A & B) CXR and HRCT shows fibrocavitatory lesion in Right upper lobe; (C) FOB examination revealed fungal plug in Right upper lobe bronchus; (D) After Amphotericin therapy, Right upper lobe bronchus was patent without any fungus.

Figure 2: Photomicrograph showing right angle branching broad pauciseptate hyphae of mucormycosis (H&E, x400)
by Posaconazole or Isavuconazole on step-down oral medication. At occasion, urgent surgical debridement may be beneficial in managing angio-invasive infection of Mucormycosis.

**Conclusion**

Pulmonary mucormycosis (PMM) in our country used to be uncommon and rare however, an increasing trend was observed even before an upsurge during Covid-19 period. An early rapid diagnosis and management is crucial to minimized mortality. An increasing incidence of PMM in developing countries like India is a matter of challenge and insisting we report all the sporadic cases.

**References**