To,
The Editor

**Sub:** Submission of Manuscript for publication

Dear Sir,

We intend to publish an article entitled "FIGHTING FIRE WITH FIRE: RARE PRESENTATION OF AN UNCOMMON DISEASE" in your journal as Letter to editor.

On behalf of all the contributors I will act and guarantor and will correspond with the journal from this point onward.

- Prior publication- Nil
- Support - Nil
- Conflicts of interest- Nil
- Permissions- Nil

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Thanking you,

Yours’ sincerely,

Signature

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FIGHTING FIRE WITH FIRE: RARE PRESENTATION OF AN UNCOMMON DISEASE

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**Introduction**
Sir,

Mucormycosis is caused due to infection with moulds of the order Mucorales. They are ubiquitous, found in soil and decaying plant matter. The most common genera associated with mucormycosis are Rhizopus and Mucor. The moulds gain access to body via inhalation, skin penetration and ingestion. They cause a spectrum of illness including skin and soft tissue infection, rhino-orbital-cerebral, lower respiratory tract, gastrointestinal and disseminated infections. The disease is extremely lethal with mortality rate as high as 96% in patients with disseminated disease. The disease which recently rose to public fame as the “black fungus” complicating the on-going Covid 19 pandemic affects immunocompromised host, especially diabetics, patients with haematological malignancies and those on long term immunosuppressive therapy. The presence of pulmonary mucormycosis in non-immunocompromised patients is extremely rare with only 15 case reports describing about 16 patients been reported till date to the best of our knowledge. Herein we report a case of pulmonary mucormycosis in a non-immunocompromised lady with no predisposing factors which was diagnosed and managed at our centre.

72-year-old female with no known comorbidities, presented to our OPD with complaints of intermittent fever and non-productive cough of one month duration, associated with pleuritic chest pain of one week duration. There was no history of fever, night sweats, weight loss, wheeze, hemoptysis or connective tissue disorders. Patient gave history of multiple outpatient visits at another hospital over the last one month wherein she was managed symptomatically with anti-pyretic and oral antibiotics. The patient’s history as well as examination of her medical records over the previous one year showed no use of corticosteroids, other immunomodulatory agents, surgical interventions or hospital admission. On examination her vitals were stable, with no evidence of respiratory distress, peripheral stigmata of tuberculosis or connective tissue disorders. Respiratory examination revealed decreased movement of left hemithorax with no signs of volume loss. There were bronchial breath sounds over left infraclavicular and mammary region.

On evaluation, patient was anaemic (Hb 9.7 gm/dl, microcytic hypochromic anaemia) with all other haematological and biochemical parameters within normal range. Serological work up for Human Immunodeficiency Virus, Hepatitis B Virus and Hepatitis C Virus were negative. Her Anti-nuclear antibodies (ANA), anti-cyclic citrullinated peptide (anti-CCP), C-reactive protein (CRP) and Rheumatoid factor workup were also negative. Chest radiography taken as a part of evaluation showed homogenous oval opacity with well-defined borders in left middle zone (Figure-1a). High resolution computed tomography (HRCT) of the chest showed air space opacities in the left upper lobe anterior and posterior segments with surrounding ground glass opacities (Figure-1b). There was no significant mediastinal lymphadenopathy. Sputum Gram stain, fungal stain and Ziehl- Neelsen stain did not show any micro-organisms. Sputum cartridge based nucleic acid amplification test for mycobacterium tuberculosis was negative. Ultrasonographic evaluation of kidney showed normal sized kidneys, normal echotexture and corticomedullary differentiation with a non-obstructive left renal calculus measuring 5mm. Video bronchoscopy done on the patient showed a normal tracheobronchial tree with bronchoalveolar lavage (BAL) negative for bacteria
and fungi. BAL fluid cytology showed predominantly alveolar macrophages (55%), neutrophils (30%) and lymphocytes (15%) with no evidence of any atypical cells. Due to her advanced age, non-resolving pneumonia status and radiological appearance of lesion, patient was suspected to have pulmonary malignancy and computed tomography guided biopsy of the lesion was performed which revealed broad aseptate hyphae with right angle branching (Figure-1c,d). Based on the histopathological report, patient was diagnosed to have pulmonary mucormycosis. Patient was reviewed by ENT specialist and presence of sino-nasal mucormycosis was ruled out. Nasal swab potassium hydroxide mount was negative for fungal hyphae. Patient was reviewed by ophthalmologist and orbital/ocular mucormycosis was also ruled out.

The patient was counselled regarding the disease and the therapeutic options. She was started on liposomal amphotericin B at a dose of 3 mg/kg which was infused over two hours at a concentration of 0.5 mg/ml. On the third day of liposomal amphotericin B therapy, patient had infusion related adverse effects in the form of fever and chills towards the end of infusion which was managed with iv corticosteroids and antihistamines. On day seven of liposomal amphotericin B therapy, patient developed acute kidney injury, raised transaminases, hyponatremia and hypokalaemia due to which the liposomal amphoteric B was with-held. Her condition deteriorated further with development of upper gastrointestinal bleed, hyperchloremic normal anion gap metabolic acidosis. Patient was diagnosed to have amphotericin B induced Type IV renal tubular acidosis. She was managed with IV fluids, bicarbonate therapy, proton pump inhibitors, packed red blood cells infusion and antibiotics but she did not respond to the therapy and succumbed to multi-organ dysfunction.

Pulmonary mucormycosis is a sinister infection caused by Mucorales and is characterised by angioinvasion leading to tissue necrosis and massive hemoptysis. This rapidly growing fungi is ubiquitous in nature and releases large number of airborne spores which are constantly inhaled by humans. Even with this constant exposure infection is rare due to the effectiveness with which intact immune system clears the spores. Almost all human infections occur in the presence of an underlying immunocompromising condition which makes the host ineffective in clearing the inhaled spores. A meta-analysis of 851 mucormycosis patients by Jeong et al described underlying conditions and predisposing factors for mucormycosis like diabetes mellitus, haematological malignancies, aplastic anemia, solid organ transplant, haematopoietic stem cell transplant, liver disease, corticosteroid use, neutropenia, major trauma, biological therapy, chemotherapy, calcineurin inhibitors and renal replacement therapy.\[^{2}\] The disease is extremely rare in patients without any underlying predisposing factors with systematic review of data between 01 Jan 2010 to 10 Oct 2020 revealing only 15 published articles describing 16 patients.\[^{3}\] This makes our case report an extremely rare description of a deadly disease wherein our patients was extensively evaluated but was found to have no comorbidities that predisposed her to pulmonary mucormycosis.

To the best of our knowledge, two such cases have been reported from India.\[^{6,7}\] Both these patients were suspected to have malignancy and the diagnosis of mucormycosis was made on tissue biopsy. Both these patients were successfully treated with liposomal Amphotericin B.
Epidemiological review of 929 cases of mucormycosis showed a mortality of 76% in patients with pulmonary mucormycosis. The mortality was around 43% in immunocompetent patients with mucormycosis. If left untreated the disease is universally fatal with the angio-invasive hyphae causing massive haemoptysis and tissue necrosis. Mucormycosis causing bilateral pulmonary artery aneurysm has also been reported. A combined surgical and medical therapy has mortality benefit over lone medical management but as the patient was unwilling for surgery and as immediate treatment initiation improves survival, patient was started on Inj liposomal Amphotericin B as per recommendation of European Society for Clinical Microbiological and Infectious Disease guidelines. The ECMM mucormycosis registry had reported liposomal amphotericin B at a median dose of 5mg/kg/day (range 3 – 10 mg/kg/day) showed good response rates. Even though the recommended dose was 5 mg/kg/day; patient was started at a lower dose of 3 mg/kg/day with a plan to escalate the dose as per drug tolerance of patients. The medication was constituted at company recommended concentration of 0.5mg/ml (0.2 – 2 mg/ml) and was given using a controlled infusion device over a period of 120 min. Despite the best of intentions and careful drug monitoring, patient didn’t tolerate the therapy with development of adverse effects like drug induced renal tubular acidosis, liver injury and upper gastrointestinal bleed which proved fatal.

Pulmonary mucormycosis is an opportunistic fungal infection of immunocompromised host. It can rarely affect immunocompetent host and therefore biopsy taken even from a patient with no predisposing factor should be subjected to fungal stains. The disease is extremely lethal and so is its therapy and when faced with a dilemma of whether to treat fire with fire, there is enough evidence to suggest that physician should go ahead with the therapy.

Statements:

Acknowledgement - Nil

Statement of Ethics

The written informed consent to publish the case was taken from the Next of Kin and the study protocol was approved by the departmental and institute’s committee of medical research
References


Figure Legends:

Figure-1a: Chest radiograph of the patients showing a homogenous oval opacity with well-defined borders in left middle zone.

Figure-1b: High resolution computed tomography of chest showing air space opacities in the left upper lobe anterior and posterior segments with surrounding ground glass opacities.

Figure 1c,d: Grocott-Gomori’s methenamine silver stain of lung biopsy showing broad, aseptate hyphae with irregular branching.