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An Enigma of Lower Airway Mucormycosis Infection

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ABSTRACT

Saprophytic zygomycetes (e.g., Mucor, Rhizopus) are occasionally found in tissues of compromised hosts, in persons suffering from diabetes mellitus (particularly acidosis), extensive burns, leukemia, lymphoma or other chronic illness or immunosuppression. Rhizopus species, Mucor species and other zygomycetes invade the walls of blood vessels, producing thrombosis. This occurs commonly in paranasal sinus, the lungs and result in ischemic necrosis of surrounding tissue with an intense polymorphonuclear infiltrate. The organisms are rarely cultured during life but are seen in histologic preparations of tissues as broad nonseptate, irregular hyphae in thrombosed vessels or sinuses with surrounding leukocyte and giant cell response.

Keywords: Zygomycosis, *Rhizopus arrhizus*, posaconazole, coronary artery disease, hyperuricemia, dyselectrolytemia, bronchogram, hemodialysis

Cell wall of fungus contains chitin, a polymer of N-acetylglucosamine, rather than peptidoglycan. Mucormycosis refers to a fungal infection caused by fungi in the order Mucorales. Species in genera Mucor, Rhizopus, Absidia and Cunninghamella are often the cause of infection. Mucormycosis commonly infects the sinuses, brain or lungs. Uncontrolled diabetes is a focal point in accelerating mucormycosis. Zygomycosis and mucormycoses occur in soil and their airborne spores often contaminate food and laboratory specimens and produce infections. Common symptoms include thrombosis and tissue necrosis. The diagnosis can be confirmed by staining with toluidine blue, silver stain, periodic acid-Schiff stain or an immunofluorescence assay shows the characteristic cysts. Antifungal drug therapy and surgery help in removing the infected tissue. Mucormycosis occurs in patients with increased serum iron. Improvements in therapeutic and diagnostic options are helping clinicians prevent invasive fungal infection. The mold is unaffected by antibiotics. The degree of infection varies in different sites of the body, like lungs, skin, gastrointestinal tract and brain. The invasive mold causes serious mucormycosis disease in immunocompromised patients.

Posaconazole is the drug of choice in the management of pulmonary mucormycosis in diabetic patients. Fever, hemoptysis and tissue infarction is characteristic of pulmonary mucormycosis. Fungus enters into lung and produces mucormycosis. Fungi will enter into sinonasal cavities by spores inhalation. Neutropenia, glucocorticoid therapy and diabetes are the risk factors for invasive mucormycosis. In immunocompromised patients, mucormycosis is a life-threatening condition. The incidence of pulmonary mucormycosis is up to 24% among all cases of mucormycosis. Most fungi are harmless saprophytes, but some species may, in certain circumstances, infect human tissue or promote damaging allergic reactions. The term mycosis is applied to disease caused by fungal infection. Predisposing factors include metabolic disorders, such as diabetes mellitus, toxic states such as chronic alcoholism,

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diseases such as leukemia and myelomatosis in which immunological responses are disturbed. Treatment is done with corticosteroids and immunosuppressive drugs, and radiotherapy.

The damage or necrosis and the elimination of the competitive influence of a normal bacterial flora by antibiotic may also facilitate fungal infection. The pulmonary mycoses are difficult to treat. The administration of antibacterial drugs should be stopped, and antifungal agents substituted. Nystatin or natamycin by inhalation may control the more superficial respiratory mycoses involving the trachea and bronchi. For grave pulmonary infections, amphotericin, a potent but highly toxic antifungal agent may have to be given intravenously. Flucytosine and the antifungal imidazoles may also be useful. The effective dose of amphotericin, and thus its toxic effects on the kidney, can reduced by combining it with flucytosine. Surgical treatment may have to be considered if severe hemoptysis occurs.

Presented here is the case of a 65-year-old man with poorly controlled diabetes who was diagnosed with mucormycosis.

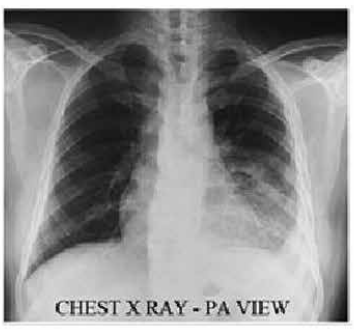
CASE REPORT

A 65-year-old male patient with complaints of fever and cough associated with hemoptysis since 1 week presented to the emergency. He was on medical management for diabetes mellitus, hypertension and coronary artery disease. He was evaluated with relevant investigations which showed – Hyperglycemia (614 mg%), poorly controlled diabetes (HbA1c - 12.8%), anemia (Hb - 9.1 gm%), elevated TLCs - 24,600/mm^3, azotemia (creatinine - 3.21 mg% and urea - 212 mg%), hyperkalemia (7. 6 mEq/L), hyponatremia (123 mEq/L), hyperuricemia (uric acid - 10.2 mg%), CUE-1 + Protein,1 + Glucose. Chest X-ray showed homogenous opacity in left lower zone and left CP angle with fluid tracking along left lateral chest wall – Pleural effusion with underlying lung collapse (Fig. 1).

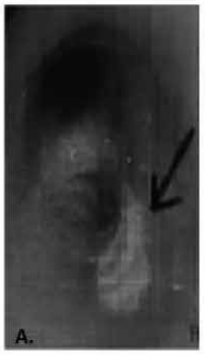
There were no significant changes in ECG. 2D Echo high-resolution CT chest (Fig. 1) showed - patchy parenchymal opacity with few areas of cystic changes and air bronchogram in the superior and inferior lingular segments; vague ground-glass opacities in lower lobe and medial basal segments of right lower lobe; atelectatic bands in the basal segments of left lower lobe; left pleural effusion. Features were suggestive of infective etiology. Sputum cultures grew multidrug-resistant Klebsiella. Bronchoscopy was done which revealed – whitish membranes present in the left lingular orifice; endobronchial biopsy suggestive of mucormycosis (Fig. 1); bronchoalveolar lavage (BAL) fungal stain showed fungal elements and galactomannan was not detected; BAL cultures grew Klebsiella. USG-guided pleural fluid tapping done for microbiology, reports were inconclusive. He was managed with glycemic control, hemodialysis, dyselectrolytemia, specified antibiotics, antifungals, stress ulcer prophylaxis, comorbidity management, oxygen and supportive care.

Patient's attendants were counseled about the infection – regarding management, and prognosis with (~70-90% mortality) and without surgery (~100% mortality) was explained. Patient developed arrhythmia (AF). Cardiologist's opinions were taken and posaconazole was switched to amphotericin B. Lobectomy/pneumonectomy was planned, explained to attendants in detail and consents were taken. Left upper lobe wedge resection was done, biopsy was sent for histopathological examination, implantable cardioverter-defibrillator (ICD) was placed and was uneventful. Post-op recovery was good and patient was extubated. On post-op Day 2, patient became drowsy and hypertensive. Inotrope supports were given, chest X-ray showed new opacities; antibiotics were escalated. He was intubated and bronchoscopy was done which revealed thick white color mucus plaques adherent to mucosa, present in the left upper lobe and BAL was collected from the left lower lobe and upper lobe. Surgical tissue biopsy revealed mucormycosis with angioinvasion. He developed empyema; ICD drained around 600 mL pus.

Patient gradually deteriorated, family was prognosticated. Patient vitals worsened further and he developed cardiac arrest. Cardiopulmonary resuscitation (CPR) was started immediately according to the advanced cardiac life support (ACLS) protocol and continued. In spite of all the efforts, return of spontaneous circulation (ROSC) was not achieved, pupils became dilated, BP was not recordable, ECG showed flat line. Patient was declared dead at 9:37 pm on 14/11/2019 due to cardiorespiratory arrest, secondary to pulmonary mucormycosis, uncontrolled diabetes mellitus, acute kidney injury and sepsis. Pathology slides showed broad, nonseptate, irregular hyphae in contrast to *Aspergillus fumigatus*, a group of mycoses, in tissues, exudates or sputum. Aspergillus species occur as filamentous, septate structures that usually branch dichotomously.



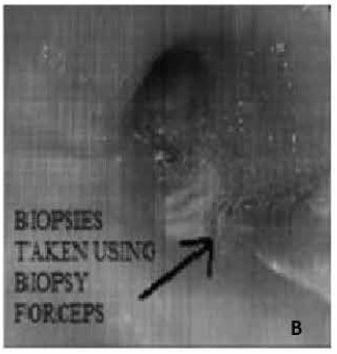
Left-sided effusion with collapse consolidation

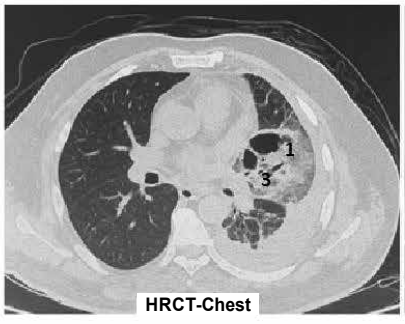


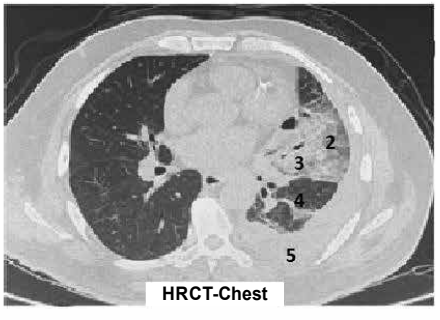
Bronchoscopy-

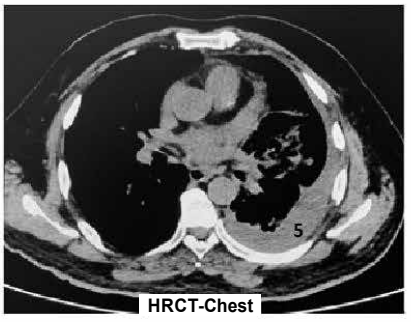
A. Whitish membranes in the left lingular orifice

B. Biopsies taken from the whitish membranes using biopsy forceps

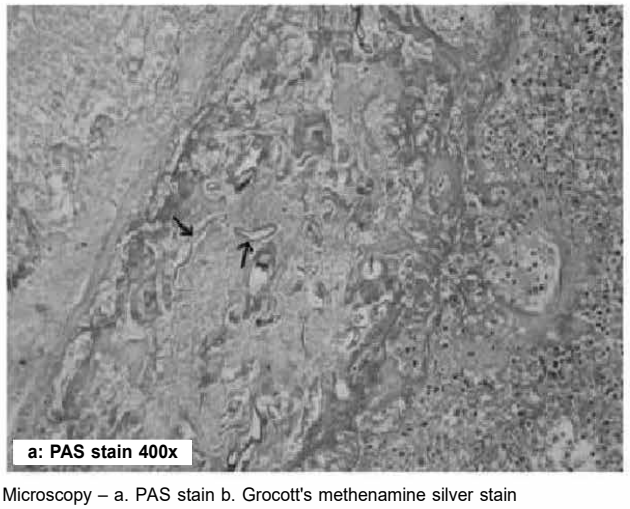


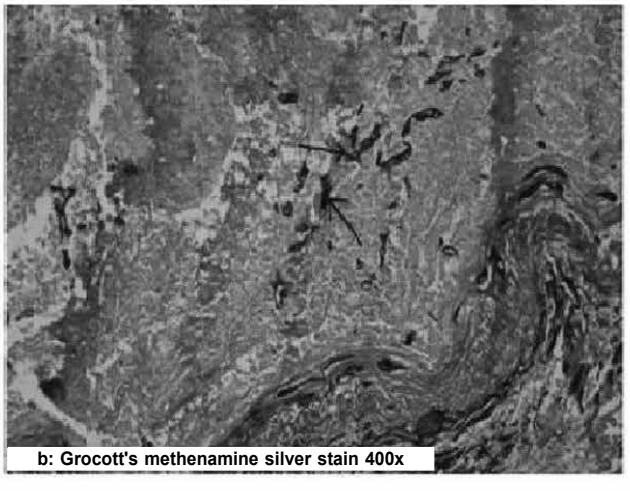






HRCT-Chest – Patchy parenchymal opacity with areas of necrosis with cavity changes (1), ground-glass opacities (2) consolidation (3) in the superior and inferior lingular segments, atelectatic band (4) in the basal segments of left lower lobe and left pleural effusion (5).





Microscopy – a. PAS stain b. Grocott's methenamine silver stain

Angioinvasive mucormycosis showing nonseptate broad fungal hyphae in the blood vessel.

Figure 1. Findings on various investigations.

DISCUSSION

Several factors contribute to the predisposition to Mucor infection in patients with diabetes mellitus. Impaired neutrophil function and high blood glucose concentration favor fungal growth. Adequate treatment of Mucor infection is dependent on early diagnosis. Mucor should be suspected when a patient with diabetes mellitus has orbital cellulitis or sudden visual changes. The underlying disease process must be aggressively controlled, correcting hyperglycemia and acidosis. Medical therapy also includes intravenous antifungal agents, usually amphotericin. Hyperbaric oxygen was shown in two small studies to be effective by decreasing tissue hypoxia and tissue acidosis. Early recognition increases the chance of successful medical and surgical treatment. Patients with high HbA1c levels, poor clinic attendance and risk-taking behaviors, are at greater risk for developing this devastating infection. A multimodality treatment approach with antifungal

agents and surgical debridement has been shown to improve outcomes. Other immunocompromised patients at risk include those using corticosteroids or deferoxamine, or long-term voriconazole prophylaxis, or with iron overload.

The organisms are normally saprophytic and phycomycetous, usually Absidia, Rhizopus or Mucor. The infection develops into cellulitis with the organism showing a predilection for blood vessels as Aspergillus does when invading the lungs. Sinus infections spread rapidly to the orbit and brain and most cases have been fatal. The phycomycetous are common free living fungi with nonseptate hyphae and reproduce asexually by the production of large number of spores within a sporangium, which develops at the end of an aerial hyphae. They grow and sporulate rapidly. Wounds very rarely become infected with filamentous fungi. Though mucormycosis exhibits several syndromes with isolated involvement of the gastrointestinal system, skin, kidney and central nervous system, the commonest and most devastating manifestations are rhino-orbital cerebral and pulmonary syndromes. These fungi have a ketone reductase enzyme that permits a high-glucose environment. Concomitant sinusitis and voriconazole prophylaxis are significantly associated with development of pulmonary mucormycosis. Cavitary lesions with the air crescent sign are rare. The high mortality observed in pulmonary mucormycosis may be related to delays in the diagnosis, poor host response (e.g., neutropenia) and limited available therapy.

CONCLUSION

Mucormycosis refers to a fungal infection caused by fungi in the order Mucorales. Uncontrolled diabetes is a focal point in accelerating mucormycosis. The diagnosis can be confirmed by staining with toluidine blue, silver stain, periodic acid-Schiff stain or an immunofluorescence assay shows the characteristic cysts. Antifungal drug therapy and surgery help in removing the infected tissue.

The present case represents the enigma associated with mucormycosis infection in a patient with underlying diabetes mellitus, hypertension and coronary artery disease. The case report emphasizes the significance of adequately controlling hyperglycemia in diabetes patients and the importance of early diagnosis in Mucor infection.

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Pregnant Women Show Fewer COVID-19-related Symptoms

DG Alerts: According to new findings published in the *British Medical Journal*, pregnant and recently pregnant women with COVID-19 have lesser odds of exhibiting COVID-19-related symptoms of fever and myalgia. However, they may have a higher risk for admission to intensive care units (ICUs) and invasive ventilation, in comparison with nonpregnant women of reproductive age.

The living systematic review and meta-analysis also suggested that mothers with pre-existing comorbidities appeared to have a greater risk for severe COVID-19, along with those who were obese and of older maternal age. Preterm birth rates seem to be higher in pregnant women with COVID-19, compared to those without it, and their neonates have a higher likelihood of being admitted to a neonatal unit.

Overall, 77 cohort studies, including 55 comparative and 22 noncomparative, were included in the systematic review. The studies included 13,118 pregnant and recently pregnant women with COVID-19, and 83,486 nonpregnant women of reproductive age with the disease. Forty cohort studies, including 13,018 pregnant and 85,084 nonpregnant women, reported on clinical manifestations; 45 studies, involving 14,094 pregnant and 85,169 nonpregnant women, reported on COVID-19-related maternal outcomes and 35 studies, with 6,279 women and 2,557 neonates, reported on pregnancy-related maternal and perinatal outcomes.

Reference: https://www.bmj.com/content/370/bmj.m3320

Every citizen of India should have the right to accessible, affordable, quality and safe heart care irrespective of his/her economical background

HEART CARE FOUNDATION OF INDIA
A Not-For-Profit Organisation

Sameer Malik Heart Care Foundation Fund

An Initiative of Heart Care Foundation of India

E-219, Greater Kailash, Part I, New Delhi - 110048 E-mail: heartcarefoundationfund@gmail.com Helpline Number: +91 - 9958771177

"No one should die of heart disease just because he/she cannot afford it"

About Sameer Malik Heart Care Foundation Fund

"Sameer Malik Heart Care Foundation Fund" it is an initiative of the Heart Care Foundation of India created with an objective to cater to the heart care needs of people.

Objectives

- Assist heart patients belonging to economically weaker sections of the society in getting affordable and quality treatment.
- Raise awareness about the fundamental right of individuals to medical treatment irrespective of their religion or economical background.
- Sensitize the central and state government about the need for a National Cardiovascular Disease Control Program.
- Encourage and involve key stakeholders such as other NGOs, private institutions and individual to help reduce the number of deaths due to heart disease in the country.
- To promote heart care research in India.
- To promote and train hands-only CPR.

Activities of the Fund

Financial Assistance

Financial assistance is given to eligible non emergent heart patients. Apart from its own resources, the fund raises money through donations, aid from individuals, organizations, professional bodies, associations and other philanthropic organizations, etc.

After the sanction of grant, the fund members facilitate the patient in getting his/her heart intervention done at state of art heart hospitals in Delhi NCR like Medanta – The Medicity, National Heart Institute, All India Institute of Medical Sciences (AIIMS), RML Hospital, GB Pant Hospital, Jaipur Golden Hospital, etc. The money is transferred directly to the concerned hospital where surgery is to be done.

Drug Subsidy

The HCFI Fund has tied up with Helpline Pharmacy in Delhi to facilitate patients with medicines at highly discounted rates (up to 50%) post surgery.

The HCFI Fund has also tied up for providing up to 50% discount on imaging (CT, MR, CT angiography, etc.)

Who is Eligible?

All heart patients who need pacemakers, valve replacement, bypass surgery, surgery for congenital heart diseases, etc. are eligible to apply for assistance from the Fund. The Application form can be downloaded from the website of the Fund. http://heartcarefoundationfund.heartcarefoundation.org and submitted in the HCFI Fund office.

Important Notes

- The patient must be a citizen of India with valid Voter ID Card/ Aadhaar Card/Driving License.
- The patient must be needy and underprivileged, to be assessed by Fund Committee.
- The HCFI Fund reserves the right to accept/reject any application for financial assistance without assigning any reasons thereof.
- The review of applications may take 4-6 weeks.
- All applications are judged on merit by a Medical Advisory Board who meet every Tuesday and decide on the acceptance/rejection of applications.
- The HCFI Fund is not responsible for failure of treatment/death of patient during or after the treatment has been rendered to the patient at designated hospitals.
- The HCFI Fund reserves the right to advise/direct the beneficiary to the designated hospital for the treatment.
- The financial assistance granted will be given directly to the treating hospital/medical center.
- The HCFI Fund has the right to print/publish/webcast/web post details of the patient including photos, and other details. (Under taking needs to be given to the HCFI Fund to publish the medical details so that more people can be benefitted).
- The HCFI Fund does not provide assistance for any emergent heart interventions.

Check List of Documents to be Submitted with Application Form

- Passport size photo of the patient and the family
- A copy of medical records
- Identity proof with proof of residence
- Income proof (preferably given by SDM)
- BPL Card (If Card holder)
- Details of financial assistance taken/applied from other sources (Prime Minister's Relief Fund, National Illness Assistance Fund Ministry of Health Govt of India, Rotary Relief Fund, Delhi Arogya Kosh, Delhi Arogya Nidhi), etc., if anyone.

Free Diagnostic Facility

The Fund has installed the latest State-of-the-Art 3 D Color Doppler EPIQ 7C Philips at E – 219, Greater Kailash, Part 1, New Delhi.
This machine is used to screen children and adult patients for any heart disease.

Free Education and Employment Facility

HCFI has tied up with a leading educational institution and an export house in Delhi NCR to adopt and to provide free education and employment opportunities to needy heart patients post surgery. Girls and women will be preferred.

Laboratory Subsidy

HCFI has also tied up with leading laboratories in Delhi to give up to 50% discounts on all pathological lab tests.

Help Us to Save Lives

The Foundation seeks support, donations and contributions from individuals, organizations and establishments both private and governmental in its endeavor to reduce the number of deaths due to heart disease in the country. All donations made towards the Heart Care Foundation Fund are exempted from tax under Section 80 G of the IT Act (1961) within India. The Fund is also eligible for overseas donations under FCRA Registration (Reg. No 231650979). The objectives and activities of the trust are charitable within the meaning of 2 (15) of the IT Act 1961.

Donate Now...

About Heart Care Foundation of India

Heart Care Foundation of India was founded in 1986 as a National Charitable Trust with the basic objective of creating awareness about all aspects of health for people from all walks of life incorporating all pathies using low-cost infotainment modules under one roof.

HCFI is the only NGO in the country on whose community-based health awareness events, the Government of India has released two commemorative national stamps (Rs 1 in 1991 on Run For The Heart and Rs 6.50 in 1993 on Heart Care Festival- First Perfect Health Mela). In February 2012, Government of Rajasthan also released one Cancellation stamp for organizing the first mega health camp at Ajmer.

Objectives

- Preventive Health Care Education
- Perfect Health Mela
- Providing Financial Support for Heart Care Interventions
- Reversal of Sudden Cardiac Death Through CPR-10 Training Workshops
- Research in Heart Care

Heart Care Foundation Blood Donation Camps

The Heart Care Foundation organizes regular blood donation camps. The blood collected is used for patients undergoing heart surgeries in various institutions across Delhi.

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This Fund is dedicated to the memory of **Sameer Malik** who was an unfortunate victim of sudden cardiac death at a young age.

- HCFI has associated with Shree Cement Ltd. for newspaper and outdoor publicity campaign
- HCFI also provides Free ambulance services for adopted heart patients
- HCFI has also tied up with Manav Ashray to provide free/highly subsidized accommodation to heart patients & their families visiting Delhi for treatment.