A 29-year-old man with hospital-acquired cavitary pneumonia

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Learning objectives
• To underscore health care-associated pulmonary mucormycosis.
• To review pulmonary mucormycosis management.

CanMEDs Competency: Medical Expert

Pretest
• What are the risk factors for pulmonary mucormycosis?
• How would you treat a patient with pulmonary mucormycosis?

CASE PRESENTATION

A 29-year-old East Asian immigrant male was admitted with acute hypoxic respiratory failure that required intubation and mechanical ventilation. Admission chest x-ray and computed tomography (CT) scans are shown in Figures 1 and 2. He also had new-onset acute renal failure that required hemodialysis. The work-up for this pulmonary-renal syndrome included microbiological testing, which was negative, serological testing for connective tissue diseases and bronchoscopy. The bronchoscopy cytology was nonspecific and cultures were negative for bacterial, mycobacterial, viral and fungal agents. A thoracoscopic left lower lobe open lung biopsy was performed. Findings were consistent with nonspecific, organizing pneumonia without evidence of active infection (Figure 3). Serological testing was consistent with systemic lupus erythematosus (SLE). He was started on high-dose methylprednisolone and cyclophosphamide. His condition showed slow improvement and he was liberated from mechanical ventilation. Six days after the biopsy, he started complaining of worsening cough, shortness of breath, fevers and pleuritic left-sided chest pain.

His medical history was otherwise negative. He was single, recently released from prison and he had no history of smoking.

On examination, the patient was a thin male in mild respiratory distress. Vital signs were as follows: temperature 38.7°C; heart rate 115 beats/min (regular); blood pressure 99/56 mmHg; respiratory rate 28 breaths/min; and oxygen saturation 91% on 4 L/min of oxygen via nasal cannula. Significant physical examination findings included left lung base rales; regular heart sounds without murmurs or gallop; and clean left-sided lung biopsy incision.

Pertinent laboratory findings included white blood cell count 4.2×10^9/L (83% neutrophils and 15% lymphocytes); hemoglobin level 89 g/L; platelet count 86×10^9/L; creatinine 34 mg/L; repeated airway cultures and blood cultures were negative; and HIV test was negative. Liver enzyme levels and coagulation studies were within normal limits.

The patient’s fever continued despite multiple days of broad-spectrum antibiotics. Chest imaging showed cavitary pneumonia in the left lower lobe (Figures 4 and 5). He underwent computed tomography-guided lung biopsy, which showed granulomatous inflammation with broad pauci septate fungal hypae consistent with mucormycosis (Figure 6). In light of the location of the fungal infection in relation to the lung biopsy and the initial extensive work-up that was negative for...
infectious agents, he was diagnosed with health care-associated pulmonary mucormycosis that complicated the open lung biopsy. His immunosuppression regimen was reduced and he was started on liposomal amphotericin B and posaconazole. His condition continued to deteriorate and he ultimately died from the infection.

**Figure 2** Admission computed tomography scan cross-section showing alveolar opacities without evidence of cavitation

**Figure 3** Hematoxylin and eosin-stained open lung biopsy showing alveolated lung parenchyma with intra-alveolar fibrinous exudate consistent with nonspecific organizing pneumonia. No granulomas or fungal microorganisms are apparent (original magnification ×200)

**Figure 4** Follow-up chest x-ray showing improving right-sided pulmonary opacities but a new cavitary lung mass in the middle zone of the left hemithorax. Surgical staples on the left side, a left internal jugular hemodialysis catheter and a right-sided peripherally inserted central catheter are visualized

**Figure 5** A and B Follow-up computed tomography cross-sections showing improving right-sided pulmonary opacities but a new cavitary left lower lobe lung mass abutting the chest wall

**Figure 6** Hematoxylin and eosin-stained computed tomography-guided lung biopsy showing broad pauciseptate fungal hyphae within multinucleated giant cells surrounded by granulomatous inflammation (original magnification ×400)
Mucorales are ubiquitous filamentous fungi that can cause a life-threatening infection characterized by angioinvasion with subsequent thrombosis and tissue necrosis (1). They are found in soil and rotten food, and spores enter the host through the aerodigestive tract or, less commonly, direct inoculation. Predisposing conditions include diabetes mellitus, malignant hematological diseases, stem cell and organ transplant, neutropenia, iron overload, major trauma, immunosuppressive medications, HIV infection and chronic liver disease (1).

‘Zygomycosis’ was classically used to describe infections caused by species in the orders Mucorales and Entomophthorales (2). Evolving changes in nomenclature and molecular taxonomy favour the use of ‘mucormycosis’ over the inclusive name ‘zygomycosis’ to describe these two clinicopathologically different infections (2).

Mucormycosis is rarely reported in SLE (1). Based on anatomical location, the infection can cause one of six forms of infection: rhino-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated and uncommon presentations. In SLE patients, disseminated mucormycosis has often been reported and the mortality rate is very high.

Mucormycosis complicating health care procedures is an emerging entity (3). Skin and the gastrointestinal tract are the most common sites of infection. Portal of entry has been attributed to surgical procedures and medical devices including chest tubes. Health care-associated mucormycosis outbreaks have been tracked back to adhesive bandages, wooden tongue depressors and ostomy bags.

Few cases of hospital-acquired pulmonary mucormycosis have been reported but none after a lung biopsy. Nosocomial pulmonary mucormycosis claimed the lives of two premature infants in a neonatal care unit due to an adjacent area of hospital renovation (4). Disseminated mucormycosis killed a 19-year-old woman shortly after a liver transplant for her fulminant Wilson disease (5). A 46-year-old woman survived a right main-stem anastomosis site mucormycosis infection following a double lung transplant for idiopathic pulmonary fibrosis (6). A 59-year-old woman developed and, ultimately, succumbed to a right-sided pleural mucormycosis caused by a biliary drain that traversed the right hemidiaphragm following cholecystectomy (7). Pulmonary mucormycosis complicated chemotherapy-induced neutropenia in a 60-year-old woman and a 51-year-old man with acute lymphoblastic leukemia, and a 55-year-old man with T cell lymphoma (8). Of those three patients, all but the latter died from their fungal infections. A 61-year-old woman died as a result of pulmonary mucormycosis during treatment of an acute rejection of a renal transplant (8).

Clinical features of pulmonary mucormycosis are nonspecific and include fever that does not respond to broad-spectrum antibiotics, dyspnea, dry cough, pleuritic chest pain and hemoptysis (1,9). Pulmonary mucormycosis has the propensity to invade adjacent organs such as the pericardium, chest wall and mediastinum. Early recognition of this lethal condition relies on a high index of suspicion that is based on the patient’s risk stratification and presentation, followed by appropriate imaging. Radiological studies may show consolidation, nodules, caviation, air crescent sign, halo sign and reversed halo sign. Definite diagnosis, however, hinges on obtaining appropriate bronchoscopic or percutaneous tissue samples for culture and histopathological identification. Molecular diagnostic modalities for mucormycosis are under development.

Successful treatment of this infection requires a multidisciplinary approach: reversing underlying immunosuppression (if feasible), instituting systemic antifungal therapy and surgical debridement. The successful treatment of this infection requires a multidisciplinary approach: reversing underlying immunosuppression (if feasible), instituting systemic antifungal therapy and surgical debridement. Liposomal formulations of amphotericin B are favoured owing to lower toxicity and better efficacy. Recent studies show higher mortality with antifungal monotherapy, especially in patients with hematological malignancies (10). Given the above, there has been a growing trend toward combination therapy. The combination of amphotericin B and an echinocandin, such as caspofungin, has been most promising (11). It has shown synergy and improved survival in animal studies, as well as a small, retrospective clinical study (11). In contrast, posaconazole-containing regimens are plagued by significant variability in serum levels and poor activity against some of the most common fungal species that cause mucormycosis (12). However, in many instances, posaconazole, which is an oral agent, is used to continue therapy in the outpatient setting. Of note, a double-blinded, randomized placebo-controlled trial failed to demonstrate a benefit of combining deferasirox to liposomal amphotericin B against mucormycosis in a heterogeneous group of patients (13).

Patients are treated for several months; however, the exact duration of therapy needs to be individualized based on patient’s response.

Post-test
• What are the risk factors for pulmonary mucormycosis?
Multiple risk factors have been associated with the development of pulmonary mucormycosis including: diabetes mellitus, malignant hematological diseases, stem cell and organ transplant, neutropenia, iron overload, major trauma, immunosuppressive medications, HIV infection and chronic liver disease.
• How would you treat a patient with pulmonary mucormycosis?
The successful treatment of this infection requires a multidisciplinary approach: reversing underlying immunosuppression (if feasible), instituting systemic antifungal therapy and surgical debridement. Liposomal formulations of amphotericin B are the drugs of choice. Alone or in combination with an echinocandin or posaconazole, they are given for several months to ensure the complete eradication of this potentially fatal infection.

DISCLOSURES: The authors have no financial disclosures or conflicts of interest to declare.

REFERENCES
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