Clinical Spectrum of Pulmonary Mucormycosis*

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Pulmonary mucormycosis is an uncommon, but important, opportunistic fungal pneumonia which is often diagnosed post-mortem. This review emphasizes clinical and pathologic characteristics of pulmonary mucormycosis that differentiate this infection from other fungal pneumonias. The most common clinical presentation of pulmonary mucormycosis is a rapidly progressive pneumonia with diffuse infiltrates on chest radiographic examination of a patient with an underlying hematologic malignancy treated with immunosuppressive drugs. Other immunocompromised hosts at risk for pulmonary mucormycosis include patients with diabetes mellitus who may develop a distinctive endobronchial form of this disease. Early consideration of this diagnosis, along with aggressive diagnostic evaluation, are critical to effective therapy and patient survival. While treatment with amphotericin B is the mainstay of therapy for pulmonary mucormycosis, diabetes with endobronchial disease may benefit from early, aggressive surgical resection of the involved lung tissue.

Mucormycosis is a term applied to a distinct group of infections caused by fungi which belong to the order Mucorales in the class Zygomycetes. Although first described by Peltauf in 1885, these infections were virtually unrecognized in the lung until the advent of antimicrobial, immunosuppressive, and antineoplastic therapy. These infections are still uncommon, but their incidence in the immunocompromised host has increased significantly.1,2 The two most common clinical presentations of mucormycosis are the rhinocerebral and pulmonary forms.3,4 In this article, we will review the pulmonary form of this disease and discuss the microbiology, pathology, predisposing factors, clinical presentation, diagnosis and treatment.

Microbiology and Pathology

Mucorales are ubiquitous saprophytic fungi found in soil or decaying organic matter. Three genera are described as human pathogens: Rhizopus, Absidia and Mucor. Production of spores, which become airborne, leads to the primary route of inoculation in man, the respiratory tract. The term Phycomycoses has been used in the past to describe infections caused by these organisms, but this term is no longer favored.6 Although the members of the family Mucorales belong to the class Phycomycetes, there are other pathogens in this class which are not Mucorales. These other pathogens have different microbiology with distinct and different pathology in man that does not involve the lung.

Mucorales are capable of growth under aerobic, anaerobic, and microaerophilic conditions, but cultures from clinical specimens are most often negative.6 The presence of this organism in a culture from the respiratory tract of an immunocompromised patient, with clinical evidence of pulmonary infection, is highly suggestive of invasive mucormycosis, but is not diagnostic.7 Identification of fungi which belong to the order Mucorales in clinical biopsy material (stained with methenamine silver or periodic acid-Schiff stains) is based on visualization of the characteristic broad (5-50 micron), non-septate (coenocytic) hyphae with right-angle branching (Fig 1).8 Histopathologically, mucormycosis is characterized by invasion through blood vessel walls, thrombosis, and hemorrhagic infarction.5

Predisposing Factors

These saprophytic fungi have rarely been reported to be pathogenic in normal people.10-13 However, pulmonary mucormycosis is clearly an infection that has increased with the development of modern medicine.14 Numerous predisposing clinical factors have been described, including diabetes, diabetic ketoacidosis, corticosteroid therapy,4 leukemia, lymphoma,4 immunosuppressive therapy,5 neutropenia,3

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Support in part by the Institutional NRSA no. HL-07185 and Pulmonary Vascular SCOR no. 31555.
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antibiotic therapy,4 salicylate-induced acidosis,13 elastoplast bandages,14,15 renal failure,5,18 prolonged postoperative course,14,17 solid tumors,4 agammaglobulinemia,18 and burns.19 Although a consistent common element for these factors is not overtly obvious, host cell defense and white blood cell function appear to be very important.8

CLINICAL PRESENTATION

The most common presentation of invasive pulmonary mucormycosis occurs in patients with an underlying hematologic malignancy being treated with immunosuppressive or antimicrobial drugs.3,5,6,9 These patients often present with an acute illness at their neutropenic nadir, consisting of fever, cough, and variable sputum production. Pleuritic chest pain is common. Chest examination may demonstrate rales with evidence of pulmonary consolidation; pleural friction rubs are not uncommon. Sputum, when present, may be white, yellow, blood-tinged, or grossly bloody. Patients are often profoundly ill, with marked gas-exchange abnormalities and rapidly advancing respiratory failure despite therapy with conventional antibiotics. The following is an illustrative case:

CASE REPORT

A 44-year-old man with a nine-month history of hairy cell leukemia was admitted to the hospital with fever, right-sided chest pain, and hemoptysis. He had been treated with chlorambucil 4 mg per day, but was not responding to therapy. On examination, he appeared acutely and chronically ill with respiratory distress. His temperature was 39°C; chest examination revealed findings of consolidation and a friction rub in the right lateral chest. Total white blood cell count was 300 cells/cu mm with 55 percent neutrophils. He had marked hypoxemia and chest radiographic film revealed two nodular densities in the right lung (Fig 2A), but this rapidly progressed over five days to acinar infiltrates in the right upper, lower, middle, and left lower lobes (Fig 2B). Tobramycin, cefotaxime, vancomycin, and amphotericin B drug therapies were instituted. Results of routine cultures, acid fast smears, and KOH preparation were negative. Bronchoscopic examination with transbronchial biopsy revealed broad, non-septate hyphae with right-angle branching, diagnostic of mucormycosis. Sputum samples subsequently grew Mucorales. The patient failed to improve on therapy with amphotericin B and died on the eighth hospital day with widely disseminated mucormycosis.

DISCUSSION

Pulmonary mucormycosis may also develop in patients with poorly controlled diabetes mellitus and ketoacidosis with a clinical syndrome similar to patients with hematologic malignancies. Donohue30 has reported that there is an additional, distinct clinical syndrome of mucormycosis in diabetic patients. These
patients have evidence of an endobronchial lesion with confinement of the lung pathology to a discrete area. Serious complications develop because the organism invades the airways and hilar vessels which may result in atelectasis, abscess formation, or hemorrhage. The following patient illustrates this clinical syndrome.

Case Report

A 59-year-old diabetic woman with a long history of asthma was hospitalized with ketoacidosis and an upper gastrointestinal hemorrhage. She had been treated with corticosteroid drugs intermittently in the past for control of her asthma; at the time of admission, she was on therapy with a tapering dose of prednisone. Physical examination revealed a woman who was afebrile with postural hypotension and guaiac positive material in a gastric aspirate. White blood cell count was 28,800/cu mm; serum glucose level was 574 mg/dl with a mild metabolic acidosis. Chest film appeared normal except for a right paratracheal prominence (Fig 3A). She was treated with insulin, bronchodilator and intravenous methylprednisolone therapy and she rapidly improved. However, five days following admission, she complained of hoarseness and had difficulty expectorating her secretions. A temperature of 38°C was noted, and repeat chest radiographic examination revealed trilobar consolidation of the right lung (Fig 3B). She was treated with clindamycin for a presumptive bacterial aspiration pneumonia. The following morning, she expectorated three tablespoons of bright red blood. Five hours later, massive hemoptysis occurred and the patient died. Post-mortem examination revealed necrotizing tracheobronchitis with a chronic, right paratracheal abscess (Fig 4), extensive necrotizing pneumonia, and massive intrabronchial hemorrhage. Microscopic examination revealed mucormycosis with the characteristic broad non-septate hyphae with right angle branching in all areas of the lung, including the right paratracheal abscess.

Comment

There are 11 reported cases in the literature of primary major airway involvement with invasive mucormycosis.20-27 Nine of these patients were diagnosed antemortem, eight by bronchoscopic examination. Of the cases with specific pulmonary locations reported, seven of ten patients had lesions of the right lung and two had tracheal lesions. In nine patients diagnosed antemortem, five survived. Four of these five were managed by surgical resection. One case was treated successfully with amphotericin B alone. Of the seven patients who died, all expired secondary to massive hemoptysis. Hoarseness was a symptom in two cases. Of the 11 patients with endobronchial disease reported in the literature, nine were diabetic.

It is apparent that diabetics with pulmonary mucormycosis have a striking tendency to develop major airway lesions. This can lead to invasion of the airway wall and hilar vessels with infarction or massive hemoptysis. Diagnostic clues to major airway involvement include hoarseness, gross hemoptysis, or mediastinal widening evident on chest film. The available data

Figure 3. Anterior-posterior chest radiographic films of patient described in the second case report. A) (left) Note that the lung fields are clear but there is a right paratracheal prominence indicated by the arrow. B) (right) Diffuse infiltrates have developed five days later in most of the right lung field, with two cavities apparent in the mid-lung field (both confirmed at autopsy).

Figure 4. Post-mortem photograph of the trachea seen from posterior view. The cricoid cartilage is at the left and the incised portion of the trachea shows the gross appearance of the right paratracheal abscess seen on chest radiographic film (Fig 3A).
suggest there may be a predilection for involvement of the right lung in these patients. Bronchscopy appears to be a reliable tool in the diagnosis of major airway involvement. Sudden, massive hemoptysis is a common fatal complication, but with aggressive surgical management in patients with surgically approachable lesions, cure is possible.  

**Radiographic Features**

The radiographic presentation of pulmonary mucormycosis has been previously well reviewed. Reported chest radiographic abnormalities include nodular, lobar, or wedge-shaped infiltrates (Fig 2 and 3); mediastinal widening; bronchopneumonia; solitary nodule; miliary pattern; cavitation; fungus ball; and pleural effusions. The more typical findings on chest radiographic examination are those of vascular invasion by fungus. This may begin as a nodular or nonspecific acinar infiltrate which subsequently develops into a wedge-shaped density or, in some instances, lobar consolidation. Despite this, the radiographic variability is vast and pulmonary mucormycosis cannot be diagnosed or excluded on radiographic grounds alone.

**Diagnosis**

Antemortem diagnosis has been made infrequently in pulmonary mucormycosis because of the acute course of the illness, lack of consideration of the diagnosis, and the need for tissue to establish the diagnosis. Result of sputum culture is usually negative, but a positive culture for Mucorales from sputum is highly suggestive of invasive infection in the appropriate host. Definitive diagnosis, however, requires histologic demonstration of tissue invasion with characteristic broad, nonseptate hyphae with right-angle branching. Culture of histologic material gives variable results.

Often, there is reluctance on the part of the clinician to pursue an invasive procedure in a severely ill patient with acute respiratory failure. Successful diagnostic modalities have included percutaneous needle biopsy, open lung biopsy, and pleural fluid culture. As demonstrated by the first case, bronchoscopic examination is often chosen as a relatively safe and less invasive technique that often yields histologic material for diagnosis. However, bronchoscopic results may be negative in patients with large areas of lung infarction secondary to vascular invasion with mucormycosis.

**Differential Diagnosis**

There are many opportunistic pathogens capable of causing pulmonary disease in the immunocompromised host. This subject has been reviewed extensively in previous literature. Other fungi, especially Candida and Aspergillus, can cause invasive pneumonia and may mimic the presentation of pulmonary mucormycosis. No serologic test is available which adequately establishes the diagnosis of any fungal pneumonia. Candida is differentiated from Mucorales by a somewhat different clinical setting, usually suggesting widely disseminated disease, and blood cultures which often yield positive results. Sputum culture for Candida is not helpful because of frequent colonization of the upper respiratory tract in patients being treated with broad spectrum antibiotics. To establish definitively the diagnosis of an invasive Candida pneumonia, biopsy material must demonstrate narrow (5 micron), septate, club-shaped pseudohyphae with the presence of blastospores. Invasive aspergillosis causes a clinical syndrome indistinguishable from mucormycosis in the lung, often with hemoptysis and rapidly progressive infiltrates on chest radiographic examination. Biopsy material demonstrates smaller hyphae (up to 15 microns) which are septate and have acute angle branching. Culture for Aspergillus from biopsy material often yields positive results.

**Management**

Experience in the management of patients with pulmonary mucormycosis has been limited to date because most cases are diagnosed post-mortem. As a greater percentage of patients are diagnosed antemortem, the need for more effective therapy has become apparent. Control of the patient's underlying disease, although probably the most important factor, is often the most difficult objective. Withdrawal of immunosuppressive agents and corticosteroid drugs are advised when possible, as well as control of hyperglycemia and correction of acidosis. Amphotericin B remains the only antimicrobial agent with evidence of antifungal efficacy in mucormycosis. This is complicated by variability in sensitivity from isolate to isolate, as well as between spore and hyphal forms, unknown penetration into infarcted tissue, and poor host immunocompetence.

Aggressive, early surgery for localized disease appears to offer the best chance of recovery, especially in diabetics with hemoptysis. Of the 18 survivors with pulmonary mucormycosis reported in the literature, 11 were managed with surgery alone. Although six cases were reported as cured with amphotericin B therapy alone, two cases may have improved due to extensive surgical resection at the time of open lung biopsy. Review of the literature suggests that patients with endobronchial disease may have surgically remediable disease and may do well with an aggressive early surgical procedure. Patients with hematologic malignancy often progress despite early diagnosis and therapy with amphotericin B. This reflects the severity of the underlying illness and its failure to improve following the development of mucor-
mycosis.

In conclusion, it is important to recognize that the presentation of pulmonary mucormycosis depends on the associated clinical disorder. Patients with leukemia and lymphoma often have diffuse parenchymal disease refractory to medical and surgical therapy; it is also apparent that occasional patients with serious, but non-malignant, underlying medical illness may develop diffuse disease. Some diabetics, however, may have local disease amenable to therapy with surgery and amphotericin B.® There are specific diagnostic clues to the presence of large airway disease, and the diagnosis can be confirmed by bronchoscopic examination in a high percentage of cases.® Early identification of this group of patients with large airway involvement in mucormycosis should lead to earlier diagnosis, appropriate medical and surgical therapy, as well as an increased survival rate.

ACKNOWLEDGMENT: We appreciate the secretarial assistance of Sharon Udovich and Shirley Letten in the preparation of this manuscript.

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CHEST / 89 / 3 / MARCH, 1986 439