Acute Community-Acquired Pneumonia due to Aspergillus in Presumably Immunocompetent Hosts*

Clues for Recognition of a Rare but Fatal Disease

Cornelius J. Clancy, MD; and M. Hong Nguyen, MD

This article reports a case of acute community-acquired pneumonia due to *Aspergillus fumigatus* in a healthy patient and reviews 11 previously reported cases occurring in presumably immunocompetent hosts. The diagnosis was delayed for all patients; mortality was 100%. Clues that might suggest *Aspergillus* as a pathogen in community-acquired pneumonia include a chest radiograph revealing diffuse infiltrates or new cavitation; lack of bacterial or viral cause; a preceding influenza A infection; and respiratory secretion cultures positive for *Aspergillus*. When these clues are present, the physician should consider an early biopsy of lung tissue. Increased recognition and more timely diagnosis in future cases will improve the outcome of this rare but fatal infection.

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Key words: Aspergillus pneumonia; fungal pneumonia; immunocompetent

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cute invasive pulmonary infection due to *Aspergillus* species, principally *A. fumigatus*, is well-recognized in the immunocompromised host. This illness pursues a rapidly progressive course, usually resulting in death. Aspergillus also can cause pneumonia in immunocompetent hosts. The classic presentation has been recognized for over 60 years: a chronic necrotizing pneumonia, which progresses insidiously over months to years.1-6 Underlying lung disease and systemic illness are factors predisposing to this entity. Acute community-acquired pneumonia in immunocompetent hosts is much less common. Recently, an otherwise healthy patient died from acute pulmonary aspergillosis; in this case, the diagnosis was delayed by a failure to recognize *A. fumigatus* as a potential pathogen. The case reported here and a review of the literature about this entity are presented in order to provide clues for the recognition of this rare but fatal disease.

METHODS

Study Data

Previous case reports were identified through a Medline search of the English-language literature from 1986 to the present. Terms searched were: Aspergillus or fungus, and fungal, pneumonia, and immunocompetent. Reports referenced in articles identified through the search also were reviewed.

Case Definition

All cases included in this review fulfilled the following criteria: (1) onset of respiratory symptoms within 14 days of presentation to a health care provider; (2) no underlying medical condition or medications associated with immunosuppression; (3) histopathologic study of tissue obtained by biopsy or postmortem examination revealing hyphal elements within the lung parenchyma; and (4) culture of tissue from a respiratory site positive for *Aspergillus*.

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CASE REPORT

A 58-year-old previously healthy woman presented to the hospital with a nonproductive cough, fever, and nonspecific flu-like symptoms, starting suddenly 5 days prior to admission. These symptoms did not respond to treatment with clarithromycin. She had no significant past medical history, although she did have a 50 pack-year history of cigarette smoking. She was not taking any medications prior to her illness; she did not smoke marijuana or take other illicit drugs.

Upon admission, laboratory evaluation revealed a WBC count of $41.1 \times 10^9/mm^3$. A Gram stain of a sputum sample revealed abundant polymorphonuclear leukocytes without a predominant organism. A chest radiograph revealed an interstitial infiltrate in the lower lobe of the right lung. Therapy was started with ceftriaxone disodium and clarithromycin; these were discontinued after the first hospital day due to worsening symptoms, and ceftazidime sodium therapy was begun. On the third hospital day, the chest x-ray film showed bilateral lower lobe infiltrates with evidence of a new cavitary lesion at the site of the initial infiltrate (Fig 1). On the fourth hospital day, the patient required mechanical ventilation. Sputum cultures obtained on the day of admission and on the subsequent days yielded *A. fumigatus*. This was believed to represent contamination, and erythromycin was added empirically to the antimicrobial regimen.

The patient did not improve, and a follow-up chest x-ray film revealed bilateral diffuse, nodular infiltrates. BAL was performed on the 8th hospital day, and cultures from three different sites involving both lungs yielded *A. fumigatus*. Due to uncertainty about the significance of these findings, a transbronchial biopsy was undertaken on the 11th hospital day. Histopathologic examination of tissue revealed necrotizing pneumonia with evidence of parenchymal invasion by hyphal elements (Fig 2); culture yielded *A. fumigatus*. Therapy was initiated with amphotericin B, 1 mg/kg/d, and itraconazole, 600 mg/d, on the 13th hospital day. The patient’s condition, however, progressively worsened, and she died on the 22nd hospital day. The family did not grant permission for an autopsy.

DISCUSSION

Including this report, only 12 cases of invasive pulmonary aspergillosis presenting as acute community-acquired pneumonia in apparently immunocompetent hosts have been reported in the English-language literature (Table 1).7-15 All patients were infected with *A. fumigatus*. Patients ranged in age from 14 months to 67 years old (median: 41 years); 6 patients were female. Nine patients were previously healthy, one had chronic obstructive pulmonary disease, one had cirrhosis, and one had hypertension. Three patients were noted to have antecedent farm-related exposures to a heavy inoculum of Aspergillus; one patient was exposed to hay and two sisters were exposed to artificial manure. *A. fumigatus* was recovered from the patients and the environmental sources.7,14 Among the 9 adult patients (more than 16 years old), 3 were heavy cigarette smokers and three had a history of heavy alcohol consumption. Alcohol has long been recognized as a predisposing factor for pneumonia;16 it impairs mobilization,17 adherence,18 phagocytosis,19 and superoxide production20 of alveolar macrophages as well as migration of polymorphonuclear cells.21

For three patients, antecedent or concurrent influenza A infection was diagnosed by serologic studies,10,12 suggesting that acute influenza illness might predispose otherwise healthy individuals to invasive aspergillosis. Influenza A causes necrosis of columnar ciliated epithelium to the level of the bronchioles and alveoli, rendering the airways susceptible to secondary opportunistic invaders;12 furthermore, influenza suppresses phagocytosis and killing of organisms by alveolar macrophages.22,23 With worsening pneumonia following influenza A infection, Aspergillus should be added to the list of potential secondary pathogens such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, particularly if bacterial or viral pathogens are not evident.

![Figure 1. Chest radiograph taken on the 3rd hospital day revealing bilateral lower lobe infiltrates with evidence of a new cavitary lesion in the lower lobe of the right lung.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21811/)

![Figure 2. Gomori's methenamine-silver stain of lung tissue removed at transbronchial biopsy revealing multiple acute-angled branching hyphal elements within the lung parenchyma. Fruiting bodies, diagnostic of *A. fumigatus*, are evident within the mass of hyphal elements in the right lower corner of the figure. The diagnosis was confirmed by growth on tissue culture.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21811/)
### Table 1—Clinical Data on 12 Presumably Immunocompetent Hosts With Acute Community-Acquired Pneumonia due to Aspergillus*

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (yr)/Sex</th>
<th>Presenting Symptoms</th>
<th>Chest x-ray Film</th>
<th>Respiratory Culture Results†</th>
<th>Further Workup</th>
<th>Antifungal Therapy</th>
<th>Outcome</th>
<th>Autopsy</th>
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</thead>
<tbody>
<tr>
<td>Strelling et al†</td>
<td>4/F</td>
<td>SOB, fever, cough×2 d</td>
<td>Patchy infiltrates, bilateral</td>
<td>Sputum, negative</td>
<td>Needle biopsy of lung negative</td>
<td>None</td>
<td>Died, HD 14 Disseminated: lungs, liver, spleen, nodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/F</td>
<td>SOB, fever</td>
<td>Fluffy infiltrates, bilateral</td>
<td>Sputum, negative</td>
<td>N/S</td>
<td>None</td>
<td>Died, HD 14 Disseminated: lungs, spleen, nodes</td>
<td></td>
</tr>
<tr>
<td>Zellner, et al°</td>
<td>35/M</td>
<td>Fever, chills×5 d; SOB, cough×1 d</td>
<td>Homogenous infiltrates, bilateral</td>
<td>Sputum, positive</td>
<td>None</td>
<td>None</td>
<td>Died, HD 4 Pulmonary necrosis; cultures positive for A fumigatus</td>
<td></td>
</tr>
<tr>
<td>Zimmerman &amp; Miller°</td>
<td>16/M</td>
<td>Fever, cough×2 wk</td>
<td>Diffuse infiltrates, bilateral</td>
<td>N/S</td>
<td>N/S</td>
<td>None</td>
<td>Died, HD 1 Disseminated: lungs, brain, kidney, GI tract, liver, spleen</td>
<td></td>
</tr>
<tr>
<td>Fischer &amp; Walker°</td>
<td>59/F</td>
<td>&quot;Influenza-like&quot;×10 d</td>
<td>Alveolar infiltrates, bilateral</td>
<td>Sputum, positive</td>
<td>TBBs: hyphal invasion of bronchial wall; positive culture</td>
<td>N/S</td>
<td>Died, HD 14 Pulmonary necrosis and infarcts, pulmonary vascular invasion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>47/F</td>
<td>&quot;Influenza-like&quot;×14 d</td>
<td>Interstitial infiltrates, bilateral</td>
<td>Sputum, positive</td>
<td>N/S</td>
<td>None</td>
<td>Died, HD 10 Disseminated: systemic infarcts; pulmonary vascular invasion</td>
<td></td>
</tr>
<tr>
<td>Brown et al†</td>
<td>61/M</td>
<td>Fever, chills, SOB, cough, wheezing</td>
<td>RLL infiltrate on HD 6</td>
<td>Sputum, positive</td>
<td>TBBs: invasive hyphae and necrosis</td>
<td>AmB on HD 8 (1 mg/kg/d)</td>
<td>Died, HD 15 Necrotizing bronchitis and pneumonitis with invasive hyphae; multiple abscesses</td>
<td></td>
</tr>
<tr>
<td>Lewis et al‡</td>
<td>28/F</td>
<td>Fever, chills, cough, sore throat×7 d</td>
<td>Patchy infiltrates, bilateral→upper lobe cavitation, HD 10</td>
<td>Sputum, positive</td>
<td>TBBs: necrotizing pneumonia, focal invasive hyphae</td>
<td>AmB on HD 10 (total: 170 mg)</td>
<td>Died, HD 16 Disseminated: organizing pneumonia and myocardial Aspergillus abscesses</td>
<td></td>
</tr>
<tr>
<td>Karam &amp; Griffin°</td>
<td>66/M</td>
<td>Fever, SOB, cough, wheezing×7 d</td>
<td>Focal infiltrate→cavitation, HD 3</td>
<td>Sputum, positive</td>
<td>None</td>
<td>AmB on HD 5</td>
<td>Died, HD 6 Pulmonary necrosis; hyphal invasion of blood vessels</td>
<td></td>
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<tr>
<td>Mecker et al‡</td>
<td>19/M</td>
<td>Fever, chills, cough</td>
<td>Diffuse nodular infiltrates, bilateral</td>
<td>Sputum, positive for bacteria only; BAL, positive for A fumigatus</td>
<td>TBBs: negative; open-lung biopsy; invasive hyphae</td>
<td>AmB on HD 5 (80 mg/d)</td>
<td>Died, HD 12 Not performed</td>
<td></td>
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<tr>
<td>Thommi, et al°</td>
<td>67/M</td>
<td>Fever, cough, pleuritic pain</td>
<td>R upper lobe cavitation→bilateral diffuse infiltrates</td>
<td>Sputum, positive; BAL, positive</td>
<td>TBBs: necrotizing pneumonia; invasive hyphae</td>
<td>AmB×3 d prior to death</td>
<td>Died Pulmonary abscesses and upper lobe cavity</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>58/F</td>
<td>Fever, cough, flu-like×5 d</td>
<td>R lobar infiltrate→diffuse nodular infiltrates→bilateral cavitation on HD 3</td>
<td>Sputum, positive; BAL, positive</td>
<td>TBBs: necrotizing pneumonia; invasive hyphae</td>
<td>AmB, itra on HD 13</td>
<td>Died, HD 22 Not performed</td>
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*Abbreviations used are as follows: SOB=short of breath; RLL=right lower lobe; HD=hospitalization day; R=right; L=left; N/S=not stated; TBBs=transbronchial biopsy; AmB=amphotericin B; itra=itraconazole.

†All positive cultures yielded A fumigatus.
The presenting symptoms and time course of acute Aspergillus-caused pneumonia were nonspecific and were indistinguishable from those of acute bacterial or viral pneumonia. Fever was noted in all patients. Nine patients presented with a cough; for seven patients, this was nonproductive. In addition, dyspnea was noted for five patients and nonspecific “flu” symptoms were documented for four. The median duration of symptoms prior to presentation was 7 days (range: 2 to 14 days).

Initial chest radiographs revealed bilateral diffuse infiltrates for eight patients and localized infiltrates for three patients (Table 1). Within 3 days of the initial chest x-ray film, all patients with localized infiltrates progressed to showing diffuse infiltrates. One patient had no infiltrate upon admission but developed a localized infiltrate over the ensuing 6 days; within a few days, this infiltrate became diffuse. Such diffuse patterns of infiltrate are nonspecific and could be caused by a variety of organisms including Legionella and Mycoplasma.

In addition to infiltrates, four patients had evidence of new cavitary lesions as noted by some studies as well as the present report. For one patient, the cavity was evident upon admission. The remaining patients had new cavitary lesions diagnosed on the 3rd hospital day (2 patients), and on the 10th hospital day (1 patient). Although cavitary lesions might be more suggestive of aspergillosis, they could also be encountered in cases of pneumonia due to other fungi or bacteria.

The diagnosis of invasive pulmonary aspergillosis requires the demonstration of hyphae within tissue and the growth of fungus from tissue. The presence of Aspergillus in a smear or culture of sputum or respiratory secretions is not necessarily indicative of invasive infection since these organisms are ubiquitous in the environment and can colonize the respiratory tree.

In this series, only five patients were definitively diagnosed antemortem, four following transbronchial biopsy and one following open-lung biopsy. Overall, the sensitivity of transbronchial or open-lung biopsy was 83% (5 of 6). The most common findings of histopathologic study were hyphal invasion of lung parenchyma (all patients) and necrotizing pneumonia (three patients). Two other patients were suspected of having pulmonary aspergillosis antemortem based on cultures of sputum or fluid removed by BAL, these suspected cases were confirmed by findings at postmortem examination.

The diagnosis was delayed in all patients. Among the patients in whom the diagnosis was made antemortem, the median time from onset of symptoms to definitive or presumptive diagnosis was 15 days (range: 10 to 17 days). In addition, four patients were not suspected of having aspergillosis antemortem and were only diagnosed at postmortem examination. In one of these cases, no abnormalities were found with a needle-guided lung biopsy.

A Gram stain of sputum revealed hyphal elements in only one patient. Sputum cultures, on the other hand, were positive for Aspergillus in seven of the ten patients for whom culture results were reported. For six of these patients, Aspergillus was identified as the sole pathogen. Furthermore, all three patients for whom cultures of BAL washings were reported demonstrated A. fumigatus. Despite the sensitivity of respiratory cultures, diagnosis based on these results alone is limited by low specificity. Nevertheless, in cases of acute diffuse or cavitary pneumonia of uncertain cause, repeated sputum cultures positive for Aspergillus are suggestive of pulmonary aspergillosis and cannot be routinely dismissed as contaminants. Such findings are a compelling argument for immediate lung biopsy. Conversely, a negative sputum culture does not exclude the possibility of pulmonary aspergillosis. The diagnosis must still be contemplated if alternative diagnoses cannot be established, and early lung biopsy to exclude the diagnosis is justified.

The overall mortality rate was 100% (12 of 12). Death occurred a median of 14 days after hospital admission (range: 1 to 22 days). Antifungal therapy was not effective; the six patients who received amphotericin B died a median of 7 days after starting therapy (range: 1 to 9 days). The lack of response to amphotericin B likely resulted from a combination of the ineffectiveness of the drug against Aspergillus and the delay in making a diagnosis until infection was far advanced.

At present, the options for antifungal therapy are limited. Liposomal preparations of amphotericin B have been effective in some neutropenic patients with pulmonary aspergillosis who failed to respond to conventional amphotericin B. Liposomal preparations might permit higher doses of amphotericin B to be administered with less systemic toxicity.

Due to the poor response to therapy with amphotericin B, combination regimens of antifungal agents might be considered. In vitro and animal model studies have demonstrated synergy or indifference between amphotericin B and fluconazole. Any clinical evidence of superiority of combination therapy over therapy with amphotericin B alone is anecdotal. Nevertheless, this combination might be considered given the limited therapeutic alternatives.

Itraconazole has been effective in the treatment of aspergillosis in selected populations of patients. Whether this agent is effective in cases of invasive pulmonary or disseminated infections is not known. One of the major limitations of itraconazole is its unreliable absorption. Although in vitro data about the efficacy of combination regimens of amphotericin B and itraconazole is conflicting and in vivo data are limited, such an approach might be considered given the shortcomings of single-drug therapy.

A new triazole, voriconazole, presently in phase II trials, appears to have heightened activity against Aspergillus and might offer an improvement over the current agents. Experience with this agent at present is too limited to draw conclusions.

All of the patients in our series suffered from advanced infection at the time of diagnosis, as demonstrated by the diffuse infiltrates noted on a chest x-ray film. This was confirmed by the findings at postmortem examination. All ten patients for whom autopsies were performed exhibited extensive, multifocal pulmonary infection, and five patients had disseminated infection. The best hope at
present for improving outcome might be increased recognition of this entity and earlier diagnosis and institution of therapy.

Due to the uniform mortality for patients with acute community-acquired pneumonia due to Aspergillus despite antifungal therapy, new approaches to therapy also need to be investigated. As an example, establishing a diagnosis while infection remains localized to one region of the lung might permit an aggressive combined approach of surgical resection and antifungal therapy to eradicate the infection. Such combined modality therapy has been demonstrated to be effective in neutropenic patients with localized pulmonary aspergillosis.37

Another approach might include immunomodulating therapy with agents such as colony-stimulating factors or interferon-gamma, which can improve the functional activity of macrophages and polymorphonuclear leukocytes.35,39 A phase I trial of macrophage colony-stimulating factor used in combination with antifungal agents documented resolution in 50% (6 of 12) of bone marrow transplant recipients with biopsy-proven fungal infection.40 Clinical experience with interferon-gamma is more limited. To our knowledge, only two reported cases of invasive aspergillosis refractory to conventional antifungal therapy were successfully treated with adjunctive interferon-gamma.41,42

In order to establish invasive pulmonary infection, inhaled Aspergillus conidia must bypass two primary lines of host defense. First-line host defense is provided by alveolar macrophages, which phagocytose conidia; if conidia evade macrophage ingestion, second-line host defense against hyphal elements in tissue is provided by polymorphonuclear leukocytes.43 Why the apparently immunocompetent hosts described in this report succumbed to fulminant Aspergillus infection is not known. It is possible that these patients had some unrecognized defect in macrophage or neutrophil function that permitted invasive infection to develop.44 Physicians might consider studies of macrophage and neutrophil function in patients diagnosed with invasive aspergillosis to clarify this issue, particularly since immunomodulating therapy might be a therapeutic alternative in the future.

CONCLUSION

Acute community-acquired pneumonia due to Aspergillus is a rare infection in immunocompetent hosts that carries a uniformly fatal prognosis. Aspergillus should be considered as a possible etiologic agent in patients with acute onset of diffuse bilateral pneumonia, cavitary pneumonia, or localized pneumonia rapidly progressing to diffuse pneumonia despite therapy with broad-spectrum antibiotics or with worsening pneumonia following influenza infection. Aspergillus recovered from cultures of sputum in such settings cannot be routinely dismissed as contaminants, particularly if no other pathogens can be identified. Lung biopsy should be performed immediately if pulmonary aspergillosis is considered in the differential diagnosis, and tissue should be submitted for histopathologic evaluation and culture. If the uniform mortality of this infection is to be reduced, improvements in antifungal therapy and more timely diagnosis prior to extensive progression of infection will be needed.

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**Enuresis and Obstructive Sleep Apnea in Adults***

Naomi R. Kramer, MD; Alice E. Bonitati, MD, FCCP; and Richard P. Millman, MD, FCCP

Adult enuresis is an unusual symptom of obstructive sleep apnea (OSA). Although it is described as a classic symptom of childhood OSA, enuresis is encountered infrequently in adult sleep medicine. Five adults with enuresis associated with sleep apnea presented to our Sleep Disorders Center. In all five cases, the onset of enuresis was associated with the progression of sleep apnea symptoms. In each case, the enuresis resolved with treatment with nasal continuous positive airway pressure. Current medical literature on the postulated mechanisms of nocturia and enuresis in sleep apnea is reviewed. Based on the experience of the authors and review of the medical literature, one may conclude that severe OSA may lead to new-onset enuresis in adults and that effective treatment of OSA is associated with resolution of enuresis.

*(CHEST 1998; 114:634–637)*

**Key words:** adults; enuresis; obstructive sleep apnea

**Abbreviations:** ANP=atrial natriuretic peptide; CPAP=continuous positive airway pressure; OSA=obstructive sleep apnea

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