Pulmonary invasive aspergillosis in patients infected with the human immunodeficiency virus: Report of two cases

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Patients infected with the human immunodeficiency virus (HIV) have an increased frequency of invasive aspergillosis. We report two cases of invasive pulmonary aspergillosis in patients infected with HIV. Patients had less than 10 CD4 (helper cell) cells/mm3 (2/2), presented with fever (2/2), dyspnea (1/2), and abnormal chest radiograph (2/2). Diagnosis was established by transbronchial biopsy (1/2) and autopsy (1/2). Patients died in spite of treatment with intravenous deoxycholate amphotericin B. Prognosis of invasive pulmonary aspergillosis among patients infected with HIV remains dismal, even with aggressive antifungal treatment. (Heart Lung®1998;27:63-6)

Invasive aspergillosis is a significant cause of morbidity and death in immunocompromised patients, especially those with hematologic malignancies and organ transplantation. Human immunodeficiency virus (HIV)-infected individuals are also at increased risk for invasive aspergillosis; the disease was initially included among the acquired immunodeficiency syndrome (AIDS)—defining infections by the Centers for Disease Control.1-3

We report two new cases of pulmonary invasive aspergillosis and discuss the clinical characteristics, treatment, and prognosis of the infection.

CASE REPORTS

Case No. 1. A 28-year-old woman who acquired HIV by heterosexual transmission first received a diagnosis of HIV-infection and Pneumocystis carinii pneumonia 3 years before admission. Her subsequent clinical course was notable for disseminated Mycobacterium avium-intracellulare, cytomegalovirus retinitis, oral thrush, adenovirus esophagitis, and wasting syndrome.

She was admitted to undergo placement of a Hickman catheter for parenteral nutrition because of viral esophagitis. Her last CD4 (helper cell) count was less than 10 cells/mm3. Medications on admission included morphine as needed for esophageal pain, ranitidine, dapsone, megesterol, fluconazole, clarithromycin, rifabutin, ganciclovir, and acyclovir. On admission, she was afebrile and physical examination was significant for cachexia. Her white blood count (WBC) was 8400/mm3, with 62% segmented neutrophils. Chest radiograph and urinalysis on admission were normal. The Hickman catheter placement was complicated by cardiac arrest, and she was admitted to the intensive care unit (ICU). Intermittent fevers up to 39.5° C and persistent bilateral pulmonary infiltrates (Fig. 1) developed in the patient on the second day in the ICU. WBC increased to 16,600/mm3, with 58% segmented neutrophils. Chest radiograph and urinalysis on admission were normal. The Hickman catheter placement was complicated by cardiac arrest, and she was admitted to the intensive care unit (ICU). Intermittent fevers up to 39.5° C and persistent bilateral pulmonary infiltrates (Fig. 1) developed in the patient on the second day in the ICU. WBC increased to 16,600/mm3, with 58% segmented neutrophils and 26% band forms. Multiple blood and urine cultures yielded no growth. Sputum Gram's stain and bronchoalveolar lavage (BAL) revealed septate branching hyphae, and cultures of those specimens grew Aspergillus fumigatus. The patient received broad-spectrum antibiotics
and amphotericin B (1 mg/kg/day), but continued to have severe fever up to 40°C. On the seventh day after admission in the ICU, the patient died. Autopsy, excluding the brain, was performed and revealed generalized aspergillosis involving the lungs, spleen, liver, and right kidney.

**Case No. 2.** A 39-year-old man was admitted to our institution as a result of fever and dyspnea. The patient had received a diagnosis of HIV 3 years before, and had met the clinical and laboratory (CD4 count) criteria for AIDS 2 years before this admission. His medical history was also significant for hepatitis B, *Mycobacterium avium-intracellulare*, cytomegalovirus retinitis, and *Pneumocystis carinii*. Medications on admission included clarithromycin, ciprofloxacin, ganciclovir, and dapsone.

Fever and dyspnea had started 10 days before admission. On admission, WBC was 5600/mm³, with 62% segmented neutrophils, 25% bands, and 4% lymphocytes. His CD4 count was less than 10 cells/mm³. Urine, blood, and cerebrospinal fluid cultures for bacteria, mycobacteria, and fungi were negative. Chest radiograph revealed a new infiltrate at the left upper lobe with probable cavitation (Fig. 2). Sputum and BAL on admission showed septate, branching hyphae on Gram stain. Cultures of those specimens grew *Aspergillus fumigatus*. Histologic examination of transbronchial biopsy showed chronic inflammation and septate, branching hyphae consistent with *Aspergillus*. The patient received amphotericin B (1 mg/kg/day) on the first hospital day. His general condition remained stable, with intermittent fever up to 39°C. Twelve days after his admission, and after receiving a total of 0.7 gm of amphotericin B, the patient experienced progressively increasing lethargy, and on the next day had a single episode of generalized tonic-clonic seizures. On clinical examination, the patient had a temperature of 39°C and was unresponsive and anisocoric. A computerized tomography of the head with normal results at the time of admission revealed a poorly defined area of low density deep in the right basal ganglia and a large gray–white matter of low density at the posterior left parietal lobe. The patient remained unresponsive through the next 24 hours and amphotericin B was continued, but on the fifteenth hospital day he died. In accordance with his wishes, no attempt for cardiac resuscitation and no autopsy were performed.

**DISCUSSION**

The prevalence of invasive aspergillosis among patients infected with HIV has been lower than in other immunocompromised patients, affecting almost exclusively patients with advanced immunosuppression and CD4 count less than 50 cells/mm³. A review of 12 major autopsy series among patients infected with HIV demonstrated a prevalence between 0% to 12%, whereas five cases (0.16%) were included among the 3170 cases of HIV-infection in the United States that were reported to the CDC in the early and mid-1980s. There was lung involvement in more than 70% of the cases. Brain, sinus, thyroid, liver, renal,
Invasive pulmonary aspergillosis in two patients infected with HIV

<table>
<thead>
<tr>
<th>Case No., sex, age</th>
<th>CD4 count (cells/mm³)</th>
<th>Medical history</th>
<th>Extent of Aspergillus infection</th>
<th>Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, F, 28 yr</td>
<td>&lt; 10</td>
<td>MAL, oral thrush, CMV retinitis</td>
<td>Lungs, spleen, liver, r. kidney</td>
<td>Fever</td>
<td>BAL, autopsy</td>
<td>Amphotericin B X 5 days</td>
<td>Death</td>
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<tr>
<td>2, M, 39 yr</td>
<td>&lt; 10</td>
<td>MAL, PCP, hepatitis B, CMV retinitis</td>
<td>Lungs ± CNS</td>
<td>Fever, dyspnea, seizures</td>
<td>Lavage, transbronchial biopsy</td>
<td>Amphotericin B X 14 days</td>
<td>Death</td>
</tr>
</tbody>
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F, Female; M, male; MAL, Mycobacterium avium-intracellulare infection; CMV, Cytomegalovirus; PCP, Pneumocystis carinii pneumonia; CNS, central nervous system.

Predisposing factors for invasive aspergillosis among patients infected with HIV include sustained neutropenia, treatment with steroids, malignancy, and cytotoxic chemotherapy. In addition, prior opportunistic infections, prolonged treatment with broad-spectrum antibiotics, marijuana use, and alcoholism may also contribute to the infection. In the cases we describe, both patients had a low CD4 count, previous opportunistic infections, and prolonged use of broad-spectrum antibiotics.

Fever, cough, dyspnea, pleuritic chest pain, and hemoptysis are the most common presenting symptoms. Chest radiograph almost always shows abnormalities, but appearances may vary. The radiologic findings include localized or diffuse infiltrates and nodules. Cavitary lesions, as in the second case, are relatively distinctive. Pleural effusions may occasionally be present.

The diagnosis of invasive pulmonary aspergillosis remains a challenge. The microorganism is infrequently isolated from blood cultures. The evaluation of the sputum was nondiagnostic in all 10 patients described by Klapholz et al., including nine patients with pulmonary involvement. Pursell et al. reported a series of 45 patients with respiratory cultures positive for Aspergillus. Invasive aspergillosis was documented in only four of these patients and strongly suspected in an additional patient.

Although histologic documentation is needed to definitively establish the diagnosis of invasive pulmonary aspergillosis, patients with the infection often have unstable conditions. A BAL specimen may provide helpful data for the early initiation of treatment, before a definitive diagnosis based on histology, is established.

Treatment of pulmonary and disseminated aspergillosis is usually based on intravenous administration of deoxycholate amphotericin B with or without flucytosine. The usual beginning dose is 0.8 to 1 mg/kg/day, and further dosage is adjusted based on the toxicity of deoxycholate amphotericin B. Newer forms of amphotericin B have comparable in vivo activity, but the clinical experience is limited. Hiemenz and Walsh suggest that their use could be considered in the management of invasive fungal infections in patients with dose-limiting renal insufficiency, in patients who are intolerant of amphotericin B, and in patients with severe fungal diseases that progress despite treatment with deoxycholate amphotericin B. Recently published data lend more support to
early use of liposomal amphotericin B as a component of therapy for invasive aspergillosis, although the data are not conclusive, and the relative efficacy in comparison with deoxycholate amphotericin B is still under investigation. 20-23 The experience with the use of itraconazole for the treatment of invasive aspergillosis is also limited. This azole is approved by the United States Food and Drug Administration as second-line treatment for invasive aspergillosis in patients who are unable to tolerate deoxycholate amphotericin B or for whom treatment fails. 24

The outcome of invasive pulmonary aspergillosis among patients with AIDS is poor, as seen in the patients we described and as noted in previous reports. 25,26 All 30 patients with invasive pulmonary aspergillosis presented by Lortholary et al. 5 died within 12 weeks of diagnosis. The poor outcome, however, may reflect in part the advanced stage of AIDS in patients with invasive pulmonary aspergillosis. 3

Invasive aspergillosis is a life-threatening complication in patients with advanced AIDS. The lungs are the most commonly involved organ. Diagnosis is difficult, and BAL, percutaneous needle aspiration, or biopsy is necessary. Intravenous deoxycholate amphotericin B is the mainstay of treatment. Physician-awareness is needed because early diagnosis and treatment remain the only available means by which the currently poor prognosis of pulmonary aspergillosis may improve.

REFERENCES