Aspergillosis in the Acquired Immunodeficiency Syndrome

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The role of Aspergillus species as a pathogen in acquired immunodeficiency syndrome (AIDS) has not been clearly defined. From 1984 to 1989, more than 2,000 AIDS patients were seen at Beth Israel Medical Center, New York. Aspergillus was isolated in ten patients; seven had invasive disease and three had noninvasive disease. Invasive pulmonary aspergillosis (IPA) was diagnosed in six patients and invasive renal aspergillosis was found in one patient. Five were homosexual men and two were intravenous drug users. At presentation, all ten had fever, seven had cough, eight had dyspnea, and five had pleuritic chest pain. Chest roentgenograms revealed focal infiltrates in six patients, bilateral interstitial infiltrates in two patients, and bilateral pneumothoraces in one patient. Predisposing conditions included corticosteroid therapy in four, granulocytopenia (<1,000/cu m) in two, and broad-spectrum antibiotic therapy in five. Three of the four patients receiving corticosteroids received them as adjuvant therapy for Pneumocystis carinii pneumonia (PCP). Aspergillus was identified ante-mortem in eight patients, in bronchoalveolar lavage (BAL) fluid in six, in transbronchial biopsy specimen in three, in open lung biopsy specimen in one, and postmortem in one patient. Six of seven patients had at least one concomitant pulmonary process. Six underwent necropsy and findings showed IPA in three, disseminated aspergillosis in two, and PCP in one. Invasive aspergillosis, although significant, is uncommon in AIDS. When Aspergillus is isolated in the setting of corticosteroid therapy, antibiotics, or granulocytopenia, one must suspect invasive disease.

(Chest 1991; 100:1614-18)

ELISA = enzyme-linked immunosorbent assay; HIV-1 = human immunodeficiency virus 1; IA = invasive aspergillosis; IPA = invasive pulmonary aspergillosis; IVDU = intravenous drug user; KS = Kaposi's sarcoma; PCP = Pneumocystis carinii pneumonia; TBBx = transbronchial biopsy

Invasive aspergillosis (IA) is a significant cause of morbidity and mortality in severely immunocompromised hosts. Patients with hematologic malignant neoplasms and prolonged neutropenia, organ transplant recipients receiving cytototoxic therapies and high-dose corticosteroids, and patients with chronic granulomatous disease are at particularly high risk. Isolated case reports of invasive pulmonary aspergillosis (IPA) have been reported in patients with the acquired immunodeficiency syndrome (AIDS). The relationship between invasive aspergillosis and human immunodeficiency virus 1 (HIV-1) infection has not been fully elucidated. Invasive aspergillosis was previously included in the Centers for Disease Control case definition for AIDS but was later removed because it was believed not to be an infection predictive of the cellular immune deficiency of AIDS. We retrospectively reviewed our experience with the isolation of Aspergillus from patients infected with HIV-1. An attempt was made to characterize the clinical settings in which Aspergillus was considered a significant pathogen.

MATERIALS AND METHODS

The study site was the Beth Israel Medical Center, a 900-bed teaching hospital in New York City, an area of high prevalence of HIV infection. The study period was January 1984 through June 1989. Cases were identified through (1) records of infectious diseases and pulmonary consultation services, (2) computer search of patients with primary and secondary hospital discharge diagnosis of aspergillosis, and (3) microbiologic reports. Identified charts were reviewed using a standard data collection instrument. Cases were included in the study if they had both (1) evidence of Aspergillus infection by either culture, cytology, or histology, and (2) CDC-defined AIDS or serologic evidence of HIV infection by enzyme-linked immunosorbent assay (ELISA) and Western blot assays. Invasive aspergillosis was defined as the presence of characteristic closely septate hyphae with repeated acute angle branching in either biopsy materials or percutaneous tissue aspirates other than lung. Hyphae were identified using hematoxylin-eosin and methanamine silver stains. Invasive aspergillosis was further divided into pulmonary and extrapulmonary disease. Noninvasive aspergillosis was defined as the presence of hyphae in bronchoalveolar lavage (BAL) fluid with no evidence of tissue invasion. Aspergillus infection refers to the identification of characteristic hyphae without regard to the presence or absence of invasion.

RESULTS

Background Data

During the study period, more than 2,000 patients with symptomatic HIV-1 infection were seen at our institution. Aspergillus infection was identified in ten patients. Seven patients (70 percent) had IA and three
Table 1—Clinical, Diagnostic, and Necropsy Findings of Ten Patients with HIV and Aspergillosis*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Risk Factor</th>
<th>HIV Stage</th>
<th>PMNs/10^9L</th>
<th>Symptoms</th>
<th>Steroids</th>
<th>Chest Roentgenogram</th>
<th>Diagnosis</th>
<th>Necropsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Homosexual</td>
<td>IV C</td>
<td>4.6</td>
<td>Fever, dyspnea, pleuritic chest pain</td>
<td>+ Bilateral reticular infiltrate LUL consolidation†</td>
<td>BAL: + asper hyphae</td>
<td>IA: lungs, mediastinal nodes</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Homosexual</td>
<td>IV C</td>
<td>1.3</td>
<td>Fever, dyspnea, cough, pleuritic chest pain</td>
<td>+ Bilateral pneumothorax</td>
<td>BAL: + PC</td>
<td>TBBx: + IPA</td>
<td>IA: lungs, pleura</td>
</tr>
<tr>
<td>3</td>
<td>Homosexual</td>
<td>IV C</td>
<td>0.7</td>
<td>Fever, dyspnea, cough</td>
<td>+ Bilateral reticular infiltrate bilateral patch consolidation†</td>
<td>BAL: + asper hyphae</td>
<td>TBBx: ND</td>
<td>CMV: lungs</td>
</tr>
<tr>
<td>4</td>
<td>Homosexual</td>
<td>IV C</td>
<td>2.0</td>
<td>Fever, dyspnea, cough, pleuritic chest pain</td>
<td>+ Consolidation of posterior segment of RUL and cavity</td>
<td>BAL: + asper hyphae</td>
<td>TBBx: + IPA</td>
<td>CMV and KS: lungs</td>
</tr>
<tr>
<td>5</td>
<td>Homosexual</td>
<td>IV C</td>
<td>0.8</td>
<td>Fever, dyspnea, cough</td>
<td>- Bilateral patchy consolidation</td>
<td>BAL: asper hyphae</td>
<td>TBBx: + IPA</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>Homosexual</td>
<td>IV C</td>
<td>4.0</td>
<td>Fever, dyspnea</td>
<td>- Bilateral reticulonodular infiltrates</td>
<td>BAL: ND</td>
<td>TBBx: ND</td>
<td>IA: lungs</td>
</tr>
<tr>
<td>7</td>
<td>IVDU</td>
<td>IV C</td>
<td>9.5</td>
<td>Fever, flank pain</td>
<td>- Normal CT: heterogeneous left kidney mass</td>
<td>PCRs: + invasive renal asper</td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>Homosexual</td>
<td>IV C</td>
<td>5.2</td>
<td>Fever, cough</td>
<td>- Patchy consolidation of RML</td>
<td>BAL: + asper and H influenzae</td>
<td>TBBs: nonspecific inflammation</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>Homosexual</td>
<td>IV C</td>
<td>3.4</td>
<td>Fever, dyspnea, cough</td>
<td>- Bilateral reticular infiltrates</td>
<td>BAL: + asper hyphae and PC</td>
<td>TBBs: PCP</td>
<td>PCP</td>
</tr>
<tr>
<td>10</td>
<td>Homosexual</td>
<td>IV C</td>
<td>1.8</td>
<td>Fever, dyspnea, cough, pleuritic chest pain</td>
<td>- Patchy consolidation and cavity in RUL</td>
<td>BAL: + asper hyphae</td>
<td>TBBs: QNS</td>
<td>ND</td>
</tr>
</tbody>
</table>

*BAL = bronchoalveolar lavage; TBBx = transbronchial biopsy; OLBx = open lung biopsy; PCRx = percutaneous renal biopsy; PMNs = polymorphonuclear leukocytes; IVDU = intravenous drug user; IA = invasive aspergillosis; IPA = invasive pulmonary aspergillosis; PC = Pneumocystis; PCP = Pneumocystis pneumonia; KS = Kaposi's sarcoma; CMV = cytomegalovirus; ND = not done; QNS = quantity not sufficient; HIV = human immunodeficiency virus; LUL = left upper lobe; RUL = right upper lobe; CT = computed tomography; RML = right middle lobe,asper = Aspergillus.

(30 percent) had noninvasive disease. Pertinent clinical data are summarized in Table 1. All patients were male, eight were homosexuals, and two were intravenous drug users (IVDU). Of the seven patients with IA, all had prior CDC stage IV HIV-1 infection for more than a year (mean, 15 months; range, 12 to 48 months).

**Predisposing Factors**

Significant risk factors included neutropenia, prior antibiotic therapy, and/or corticosteroid therapy. In three patients (patients 1, 2, and 3) IA occurred during high-dose adjunctive corticosteroid therapy for *Pneumocystis carinii* pneumonia (PCP) (mean daily methyprednisolone dose of 400 mg for a mean duration of two weeks). New pulmonary infiltrates evolved in two of the three patients. All three patients were also receiving broad-spectrum antibiotics (mean duration, 19 days) and one had a granulocyte count of 700/µm while receiving zidovudine and ganciclovir. Patient 4 presented with fever, cough, and pleuritic chest pain and consolidation of the posterior segment of the right upper lobe two weeks after a 14-day course of dexamethasone (mean daily dose of 16 mg). Corticosteroids were employed for the treatment of cerebral edema for cerebral toxoplasmosis. Patient 5 presented with a recurrence of respiratory symptoms and new bilateral patchy consolidation three weeks after a 14-day course of broad-spectrum antibiotics for a Pseudomonas pneumonia; his granulocyte count was 800/µm while receiving zidovudine and ganciclovir. Patients 6 and 7 were both IVDUs. Neither had granulocytopenia or had received corticosteroids.

Patients 8 and 9 had noninvasive infection. Both presented with respiratory symptoms and pulmonary infiltrates (bilateral reticulonodular infiltrates in one
and patchy right middle lobe consolidation in the other). Neither was granulocytopenic or had previously received antibiotics or corticosteroids. In patient 10, IA was strongly suspected but not proven. Fever, cough, and pleuritic chest pain and a cavitary right upper lobe infiltrate were noted. Bronchoalveolar lavage fluid revealed Aspergillus hyphae, but the transbronchial biopsy (TBBx) yielded insufficient specimens for detailed analysis. Despite a strong suspicion for IA, this patient was included in the analysis as having noninvasive disease. No obvious predisposing factor was evident in this patient.

Four (66.6 percent) of the six patients with IPA received high-dose corticosteroids (mean daily methylprednisolone dose of 376 mg for a mean duration of 17 days) within two weeks of the diagnosis. Five (83.3 percent) of the six patients had received broad-spectrum antibiotics (mean duration, 19 days) within four weeks of the diagnosis. Granulocytopenia (<1,000/cu mm) was present in two patients who had been receiving zidovudine and ganciclovir. Five (83.3 percent) of the six patients had recent antecedent pulmonary processes and included the following: PCP (four patients), Pseudomonas pneumonia (one patient), and pulmonary Kaposi’s sarcoma (KS) and radiation therapy to the lung (one patient). The one patient with renal aspergillosis was neither granulocytopenic nor receiving corticosteroids.

Of the three patients with non-IPA, two had concomitant lung processes at the time of the diagnosis of Aspergillus infection: PCP (one patient) and bronchiectasis (one patient). No patient received corticosteroids or broad-spectrum antibiotics within four weeks of the diagnosis. None was a granulocytopenic or had a history of intravenous drug use.

In those patients with IA, five of seven (71.4 percent) had predisposing risk factors as outlined above. These risk factors were absent in those with noninvasive disease.

Clinical Presentation

The clinical features at the time of presentation were primarily pulmonary in nine (90 percent) patients. All nine (100 percent) patients had fever, eight (88.9 percent) had dyspnea, seven (77.7 percent) had cough, and five (55.5 percent) had pleuritic chest pain. Hemoptysis was absent in these patients. One patient presented with fever and flank pain and was found to have invasive extrapulmonary (renal) aspergillosis. There were no differences in symptoms between the invasive and the noninvasive group.

Roentgenographic Findings

Chest roentgenographic presentations were variable. Six (85.7 percent) of seven patients with IPA had focal infiltrates; two of these were cavitary. In two patients, chest roentgenograms revealed only bilateral interstitial infiltrates. One patient presented with bilateral pneumothoraces. The patient with renal aspergillosis had a heterogeneous left renal mass on computed tomographic (CT) scan and a normal chest roentgenogram. There were no differences in chest roentgenographic findings between the invasive and noninvasive groups.

Initial Diagnosis

Routine sputa were nondiagnostic in all ten patients. Eight (80 percent) patients underwent fiberoptic bronchoscopy. Bronchoalveolar lavage revealed only Aspergillus in six of eight (75 percent) patients and both Pneumocystis and Aspergillus in one of eight (12.5 percent). TBBx was performed in seven of eight (87.5 percent) patients undergoing fiberoptic bronchoscopy and confirmed IA in three of seven (42.8 percent), did not demonstrate IA in three of seven (42.8 percent), and yielded insufficient material in one of seven (14.3 percent). The overall yield for Aspergillus in BAL and TBBx was 87.5 percent (seven of eight) and 42.8 percent (three of seven), respectively. The diagnosis of invasive renal aspergillosis was made by percutaneous renal biopsy specimen. In two patients, the diagnosis of IPA was made only at open lung biopsy or autopsy.

Treatment/Survival

A premortem diagnosis of IA was made in five (50 percent) of the ten patients. Four of these five and one patient with Aspergillus infection, in whom invasive disease was suspected but not proven, received a total of at least 1 g of amphotericin B. Among the five treated patients, three (60 percent) died of their illness. Two (40 percent) of the five treated patients, one with IPA and one with invasive renal disease, improved satisfactorily and were discharged from the hospital. Postdischarge survival was three weeks and six months, respectively; autopsies were not performed.

Five of the ten patients did not receive amphotericin B. Three were treated for PCP and died; autopsy revealed PCP alone in one (case 9) and IPA in one (case 6) and IPA, PCP, and KS in one (case 3). One patient was treated for Hemophilus influenzae pneumonia, improved, and was discharged from the hospital. One patient died within 48 hours of the diagnosis of IPA; autopsy confirmed the premortem diagnosis.

Seven (70 percent) of the ten patients with aspergillosis died during the initial hospitalization and six of ten (60 percent) had autopsies. Autopsy confirmed the premortem diagnoses of IPA in three patients. In two the diagnosis of IPA was only made at autopsy. In addition, the autopsy showed dissemination beyond the lungs and mediastinal lymph nodes in two and concomitant lung processes in all (cytomegalovirus [CMV] in three; KS in two; and aspiration pneumonitis...
DISCUSSION

Invasive aspergillosis occurs primarily in individuals with severe granulocytopenia or defects of cell-mediated immunity usually resulting from cytotoxic chemotherapy or high-dose corticosteroids.\(^1\)\(^-\)\(^4\) IPA has also been reported in patients with chronic granulomatous disease and other qualitative neutrophil defects.\(^5\)\(^-\)\(^6\) and in some instances in apparently normal hosts.\(^17\)\(^-\)\(^19\) IPA has also been reported to occur in association with chronic alcoholism and cirrhosis, hepatic failure, diabetes mellitus,\(^30\)\(^21\) and more recently with AIDS.\(^6\)\(^-\)\(^10\) The nature of the relationship between IA and HIV-1 infection has not been fully defined.

In this series, the lung was the predominant site of involvement in both the invasive and noninvasive aspergillosis groups. The clinical features at the time of presentation were persistent fever (100 percent), dyspnea (88.8 percent), cough (77.7 percent), and pleuritic chest pain (55.5 percent). Interestingly, hemoptysis was absent in our series. Although the roentgenographic abnormalities were variable, focal pulmonary infiltrates with or without cavitation were most common. Diffuse interstitial infiltrates and bilateral pneumothoraces were also noted, but could have been attributed to concomitant PCP. The clinical symptomatology and the pulmonary infiltrates described were temporally related to either a course of corticosteroids or an episode of granulocytopenia in five of seven patients. It should be noted that three of four (75 percent) patients receiving corticosteroids were receiving them as adjunctive therapy for PCP.

Fiberoptic bronchoscopy has been shown to be a useful tool in the diagnosis of IPA in patients with other immunocompromised states.\(^22\) Bronchoalveolar lavage is an effective way of detecting Aspergillus in IPA. Kahn et al\(^23\) reported a yield of 53 percent in the lavage fluid of immunocompromised patients with IPA. Transbronchial biopsy produced a yield of 18 percent in the same study. Eight of ten patients in our study underwent fiberoptic bronchoscopy. The overall yield for Aspergillus hyphae in BAL and TBBx was 87.5 percent and 42.8 percent, respectively. The yield in those with IPA undergoing bronchoscopy was four of five (80 percent) for BAL and three of three (100 percent) for TBBx. In four (patients 1, 3, 4, and 5) with granulocytopenia or adjuvant high-dose corticosteroid therapy, BAL accurately predicted invasive disease in all. The three remaining patients with positive BAL were neither granulocytopenic nor receiving corticosteroids. Two of these three (patients 8 and 9) did not have IPA. In the third (patient 10), the TBBx yielded insufficient specimens, the patient died, and there was no autopsy. Therefore, the precise diagnosis remains uncertain. While the specificity and predictive value of BAL for IPA cannot be determined from these limited data, the presence of Aspergillus hyphae, especially in the setting of granulocytopenia or corticosteroids, should alert the clinician to the possibility of invasive disease.

Rubin\(^24\) has emphasized the importance of both barrier and cellular host defenses against Aspergillus. A breach in the integrity of the skin, mucous membranes, or respiratory epithelia may render these tissues susceptible to Aspergillus infection. Granulocytes and cells of the monocyte-macrophage line are also important in the defense against Aspergillus.\(^25\) Following the delivery of spores to susceptible tissues, infection may progress to invasive disease in the setting of concomitant defects in cellular host defenses. A recent report of invasive cutaneous aspergillosis in a group of leukemic and bone marrow transplant patients with Hickman catheters supports this notion.\(^26\)

Among ten cases of IA in AIDS in the published literature,\(^6\)\(^-\)\(^10\) four were granulocytopenic and three were receiving high-dose corticosteroids. In two cases, severe emphysema was believed to be a predisposing risk factor for the development of IPA. The remaining patient was an IVDU who developed Aspergillus mitral valve endocarditis. It is noteworthy that the granulocytopenia in two of the published cases and in two in this study occurred in patients receiving both ganciclovir and zidovudine.

Five of the seven patients with IA whose cases are reported herein did not use intravenous drugs. All had defects in both mucosal defenses (ie, recent antecedent lung processes) and cellular defenses (either granulocytopenia, high-dose corticosteroids, or both), which predisposed to IA. Two patients were IVDUs; one developed IPA and one developed invasive renal aspergillosis. Neither was granulocytopenic or had received high-dose corticosteroids. Direct bloodstream inoculation may have led to IA in these two patients. The three patients with BAL positive for Aspergillus but with no proof of invasive disease had no history of IVDU, granulocytopenia, or high-dose corticosteroid therapy. It is noteworthy that the mean daily dose of corticosteroids used, as adjuvant therapy for PCP, was high and the duration of therapy was prolonged. At the time the study was undertaken, there was no unanimity concerning the dose or duration of corticosteroid therapy.

In summary, IA was uncommon in AIDS patients in our institution, occurring in approximately 0.3 percent (7/2,000) patients over a 4½-year period. Invasive aspergillosis in AIDS usually presents with symptoms and roentgenograms consistent with a focal pulmonary process or at times, PCP. Two of the seven patients with IA had disseminated disease, a rate comparable to that in the series of Meyer et al.\(^3\) Fiberoptic bronchoscopy with TBBx and BAL is an
effective method of detection in those with invasive disease. In our series, IA was a late complication of HIV-1 disease, occurring after a diagnosis of AIDS in all patients. Invasive disease in AIDS occurred only in the presence of risk factors previously known to be associated with IA, ie, granulocytopenia, corticosteroids, or intravenous drug use. This suggests that immunosuppressive factors in addition to HIV-1 infection are required for the development of IA. Patients suspected of having PCP and receiving adjunctive corticosteroid therapy are especially at risk for this complication. IA should be considered in the differential diagnosis of pulmonary infiltrates in HIV-1-infected individuals, particularly in the presence of Aspergillus hyphae in BAL fluid in the presence of granulocytopenia or corticosteroid use.

References