Invasive Aspergillosis in Patients With Acquired Immunodeficiency Syndrome: Report of 33 Cases

OLIVIER LORTHOLARY, M.D., MARIE-CAROLINE MEYOHAS, M.D., BERTRAND DUPONT, M.D., JACQUES CAUHANEL, M.D., DOMINIQUE SALMON-CELON, M.D., Paris, France, DOMINIQUE PEYRAMOND, M.D., Lyon, France, DANIEL SIMONIN, M.D., Le Mans, France, and Centre d’Informations et de Soins de l’Immunodéficience Humaine de l’Est Parisien, for the French Cooperative Study Group on Aspergillosis in AIDS*

PURPOSE: Acquired immunodeficiency syndrome (AIDS)-associated invasive aspergillosis (IA) is a rare condition, which is mainly reported as isolated cases either antemortem or at autopsy. The role of AIDS itself is controversial, because many of the reported patients exhibited the classic risk factors such as neutropenia and steroid therapy. The aims of this study were to report 33 patients with IA during AIDS and their outcome, focusing on the risk factors and the value of diagnostic procedures.

PATIENTS AND METHODS: Thirty-three patients from 17 different medical centers in France were retrospectively included in the study. For pulmonary IA, we defined two types of patients: those with “confirmed IA,” describing all the patients with histologically proven disease, and those with “probable IA,” who had the development of a new pulmonary infiltrate on chest radiograph and a positive bronchoalveolar lavage (BAL) fluid culture for Aspergillus species without identification of other pathogens. For extra-pulmonary IA, the diagnostic criteria included both positive histology and culture.

RESULTS: Of the 33 cases included in this series, 91% were recorded during the last 3 years (1989 to 1991), suggesting that aspergillosis is an emerging complication in AIDS. Approximately 50% of the patients did not exhibit any classic risk factor, i.e., neutropenia and steroid treatment; almost all patients had a CD4 cell count less than 50/mm³. The mycologic culture from BAL was the method of choice for the diagnosis of invasive pulmonary disease because it was known to correlate well with histologic findings obtained either antemortem or postmortem. Of 28 patients with a positive BAL culture for Aspergillus, 15 underwent a biopsy or autopsy and 14 were positive at histology. Serum antigen detection was positive in only 4 of 16 tested patients. Clinical and radiologic signs did not differ from those observed in neutropenic patients without human immunodeficiency virus, except for the higher incidence of neurologic complications in AIDS. Interestingly, we observed three cases of invasive necrotizing tracheobronchial aspergillosis with acute dyspnea and wheezing. The use of amphotericin B (0.5 mg/kg/d) and/or itraconazole (200 to 600 mg/d) was most often unsuccessful. Only four patients experienced clinical and radiologic improvement. The mean interval between the diagnosis of IA and death was 8 weeks (range: 3 days to 13 months).

CONCLUSIONS: This study suggests that aspergillosis is an important life-threatening condition in the advanced stage of AIDS. It requires an early diagnosis with BAL fluid culture and careful therapeutic evaluation.

Invasive aspergillosis (IA) is a life-threatening complication in patients with prolonged neutropenia or neutrophil dysfunction, or in those receiving steroids [1]. Surprisingly, IA is generally not mentioned in reviews on mycoses in acquired immunodeficiency syndrome (AIDS) [2,3]. AIDS itself is not considered to be a full risk factor because the cellular defect mainly concerns T lymphocytes and less so neutrophils and macrophages, of which the latter two are involved in the defense against Aspergillus [3,4]. Five cases (0.16%) were included among 3,170 cases of AIDS in the United States reported to the Centers for Disease Control between May 1983 and June 1984 [5], just before the deletion of IA from the list of AIDS-associated infections [4]. Between 1984 and 1991, a few documented [6-21] and undocumented reports [22], in addition to postmortem data [23,24], were published. Three studies, involving 33 patients, were
recently published [25–27]. In the present report, we describe 33 AIDS patients with IA and their outcomes. As previously described, all patients were severely immunocompromised. IA is extremely difficult to diagnose before death, and sputum culture was of little value in human immunodeficiency virus (HIV)-infected patients [27]. We emphasize the value of the various diagnostic procedures in patients with new pulmonary lesions, such as the culture of bronchoalveolar lavage (BAL) fluid, and Aspergillus antigen in BAL fluid and serum. Patients with classic risk factors for aspergillosis are described in addition to those (48.5%) without either neutropenia or steroid therapy. In light of our results, we believe that Aspergillus is a serious and increasingly prevalent pathogen during the advanced stage of AIDS, as recently reported [26–28].

PATIENTS AND METHODS

All the French infectious diseases wards of university hospitals (37 centers) were contacted between July 1991 and December 1991 to find out whether or not they had observed cases of IA during AIDS since the beginning of the epidemic. All centers participated in this study; 8 centers included a total of 21 patients.

Nine other medical or intensive care units, working with us for complementary mycologic tests, were also contacted and included 12 patients. For pulmonary IA, we used the criteria defined by Denning et al [25]. “Confirmed IA” describes all the patients with histologically proven disease, either antemortem, by biopsies during endoscopy and surgery, or at autopsy. “Probable IA” describes all patients who had the development of a new cavity in previously normal lung, or localized or diffuse infiltrates or nodules, and a positive BAL culture for Aspergillus species without the identification of other pathogens. Mycologic cultures were positive for 28 of 28 BALs performed. For “extrapulmonary IA,” the diagnostic criteria were positivity of both histology and culture.

Neutropenia was defined as an absolute neutrophil count less than or equal to 500/mm³ within 3 months of isolation of Aspergillus species. Corticosteroids were considered as a risk factor when administered at a dosage greater than or equal to 0.5 mg/kg/d for 8 days or more within 3 months of the diagnosis of IA. Antibiotic treatment was considered as a risk factor when prescribed for 8 days or more within 3 months of the diagnosis of IA. Aspergillus antigen detection was determined by the latex method described by Dupont et al [29] on fresh samples. Antibody detection in serum was performed by counterimmunoelectrophoresis. Serum itraconazole concentrations were determined by a microbiologic method in a bioassay [30].

RESULTS

Patients

Ninety-one percent of cases (30 of 33) were recorded during the last 3 years. No case was recorded before 1986. One patient with IA was diagnosed each year in 1986, 1987, and 1988; 11 in 1989; 9 in 1990; and 10 in 1991. Among the 33 patients, 30 were men and 3 were women. The mean age was 35 years (range: 27 to 53 years). The mode of acquisition of HIV was homosexuality or bisexuality for 19, drug addiction for 8, and heterosexual for 6. All the patients had full-blown AIDS at the time of diagnosis. For five of them (15%), AIDS and IA were diagnosed during the same month. The mean interval between the diagnosis of AIDS and aspergillosis was 13 months (range: 0 to 48 months). The T4 cell count was usually low (median: 27/mm³; range: 1 to 152/mm³). Details are recorded in Table I.

Diagnostic Procedures

BAL culture was positive each time it was performed. Positivity was correlated with histology findings. No other pathogen grew in 27 patients. The species were Aspergillus fumigatus in 28 patients, Aspergillus flavus in 2, and both A. fumigatus and A. flavus in 1. The species could not be determined for the two diagnosed postmortem cases, but antemortem clinical, radiologic, and histologic features were highly suggestive of aspergillosis. Results of diagnostic procedures are given in Table II.

Among the 22 patients with positive BAL cultures and new pulmonary infiltrates without positive antemortem histology, 8 had a positive histology at autopsy, 4 experienced clinical and radiologic improvement with negative results of mycologic culture, and 2 had a positive antigen detection in serum. Eight patients died within the following months without definitive proof of IA or other pathogens.

Aspergillus antigen detection in the serum was performed in 16 cases, and was negative in 12 cases and positive in 4. The same method was used for three BAL fluid samples and was always positive. Serology by counterimmunoelectrophoresis was performed in six cases, but the result was always negative.

Predisposing Factors

Sixteen patients (48.5%) did not have either severe neutropenia or steroid treatment during the 3 months before diagnosis. Ten patients experienced at least 1 episode of severe neutropenia during the 3 months before diagnosis. Five patients received steroid therapy and had severe neutropenia. Neutropenia was related to specific therapy for toxoplasmosis in five, antineoplastic chemotherapy for...
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Months Since AIDS Diagnosis</th>
<th>Last CD4 Count/mL</th>
<th>Past Medical History</th>
<th>Extent of Aspergillosis</th>
<th>Symptoms</th>
<th>Radiographic Appearance</th>
<th>Source of Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1†</td>
<td>10</td>
<td>6</td>
<td>ATB, PCP</td>
<td>Trachea, bronchi, lungs</td>
<td>Fever, dyspnea, cough, wheezing, splenomegaly</td>
<td>Bilateral nodular in lower lobes, mediastinal and hilar adenopathies</td>
<td>Lavage, bronchial biopsy, serum Ag-</td>
<td>Amphotericin B, 6 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>39</td>
<td>ATB, nondocumented pneumonia, AP</td>
<td>Lungs</td>
<td>Fever, dyspnea, cough, myocardiitis, chest pain, pericarditis, CNS disorders, hepatosplenomegaly</td>
<td>Bilateral, diffuse infiltrates in both lobes, cardiomegaly</td>
<td>Lavage, tracheal biopsy</td>
<td>Amphotericin B, 4 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>6</td>
<td>ATB, neutropenia, AP, CMV retinitis</td>
<td>Lungs</td>
<td>Fever, dyspnea, cough, CNS disorders</td>
<td>Bilateral cavity in upper lobes</td>
<td>Lavage, autopsy</td>
<td>Amphotericin B, 2 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>5</td>
<td>PCP, bacterial pneumonitis, AP</td>
<td>Lungs</td>
<td>Fever, cough, chest pain, myocardiitis, pericarditis, CNS disorders</td>
<td>Unilateral cavity and nodular in upper lobe, bilateral pleural effusion, cardiomegaly</td>
<td>Lavage, autopsy, serum Ag-</td>
<td>Amphotericin B 4 weeks, then itraconazole 6 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>42</td>
<td>Steroids, ATB, neutropenia, CMV pneumonia</td>
<td>Lungs, heart, kidney, brain, lymph nodes</td>
<td>Fever, cough, dyspnea, chest pain</td>
<td>Bilateral, diffuse infiltrates, cavity in lower lobe</td>
<td>Lavage, autopsy</td>
<td>Amphotericin B, 1 week</td>
<td>Death</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>54</td>
<td>ATB, PCP</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea</td>
<td>Bilateral, diffuse infiltrates, cavity in upper lobe</td>
<td>Lavage, autopsy, serum Ag i</td>
<td>Itraconazole 2 weeks, then amphotericin B 6 days</td>
<td>Death</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>G</td>
<td>ATB, AP</td>
<td>Lungs</td>
<td>Fever, cough</td>
<td>Unilateral, cavity in upper lobe</td>
<td>Lavage, lung surgical biopsy</td>
<td>Amphotericin B, 1 week</td>
<td>Death</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>32</td>
<td>ATB, PCP, AP</td>
<td>Lungs, heart</td>
<td>Fever, cough, dyspnea, chest pain, hemoptysis</td>
<td>Bilateral, diffuse infiltrates and cavity in both lobes</td>
<td>Lavage, autopsy</td>
<td>Amphotericin B 4 weeks, and itraconazole 4 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>72</td>
<td>ATB, PCP, CMV retinitis</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea, CNS disorders, hepatosplenomegaly</td>
<td>Bilateral, diffuse infiltrates and nodular lesions, unilateral cavity in upper lobe</td>
<td>Lavage, autopsy, serum Ag-</td>
<td>Amphotericin B, 1 week</td>
<td>Death</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>6</td>
<td>ATB, neutropenia, PCP, AP</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea</td>
<td>Bilateral, diffuse infiltrates</td>
<td>Lavage, bronchial biopsy</td>
<td>No</td>
<td>Death</td>
</tr>
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</table>
### TABLE I (Cont'd)

Identification of Patients With Risk Factors for HIV, Past Medical History, Clinical Symptoms and Radiographic Appearance, Extent of Aspergillosis, Source of Diagnosis, Treatment, and Outcome, in 33 AIDS Patients With Invasive Aspergillosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Months Since AIDS Diagnosis</th>
<th>Last CD4 Count/mL</th>
<th>Past Medical History</th>
<th>Extent of Aspergillosis</th>
<th>Symptoms</th>
<th>Radiographic Appearance</th>
<th>Source of Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (M, 34, Homo)</td>
<td>0</td>
<td>25</td>
<td>ATB, PCP</td>
<td>Lungs</td>
<td>Fever, cough</td>
<td>Bilateral, diffuse, nodular infiltrates</td>
<td>Lavage, autopsy, serum Ag-</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>22 (M, 29, Homo)</td>
<td>2</td>
<td>10</td>
<td>CMV retinitis, AP</td>
<td>Lungs</td>
<td>Fever, cough</td>
<td>Unilateral cavitary in upper lobe</td>
<td>Lavage, autopsy, serum Ag-</td>
<td>Amphotericin B 2 months, then itraconazole 2 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>13 (M, 32, Homo)</td>
<td>13</td>
<td>2</td>
<td>Neutropenia, bacterial pneumonia, CMV retinitis</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea</td>
<td>Bilateral diffuse infiltrates</td>
<td>Autopsy</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>14* (M, 51, Homo)</td>
<td>10</td>
<td>10</td>
<td>Neutropenia, steroids, pulmonary Kaposi, PCP, AP</td>
<td>Bronchial, lungs</td>
<td>Fever, cough, dyspnea, wheezing</td>
<td>Unilateral infiltrates, bilateral pleural effusion</td>
<td>Autopsy</td>
<td>Nu</td>
<td>Death</td>
</tr>
<tr>
<td>15 (M, 34, Homo)</td>
<td>41</td>
<td>14</td>
<td>ATB</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea</td>
<td>Bilateral nodular in both lobes</td>
<td>Lavage, transbronchial and bronchial biopsies, autopsy, serum Ag-</td>
<td>Amphotericin B 2 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>16* (M, 29, Homo)</td>
<td>19</td>
<td>3</td>
<td>ATB, neutropenia, AP, Pulmonary Kaposi, bacterial pneumonia</td>
<td>Trachea, lungs</td>
<td>Fever, cough, dyspnea, chest pain, hemoptysis, wheezing</td>
<td>Bilateral nodular infiltrates, mediastinal adenopathies</td>
<td>Lavage, tracheal biopsy</td>
<td>Amphotericin B 1 week</td>
<td>Death</td>
</tr>
<tr>
<td>17† (F, 39, Hetero)</td>
<td>6</td>
<td>50</td>
<td>ATB, neutropenia, CMV retinitis, nondocumented pneumonia</td>
<td>Mastoidis</td>
<td>Fever, cough, hearing loss, ear pain</td>
<td>Destruction of middle ear and mastoidis</td>
<td>Ear liquid, histology of total mastoidectomy, serum Ag-</td>
<td>Amphotericin B 4 weeks, and itraconazole 13 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>18† (M, 36, Hetero)</td>
<td>0</td>
<td>152</td>
<td>None</td>
<td>Spleen</td>
<td>Fever, splenomegaly</td>
<td>None</td>
<td>Surgical biopsy of spleen</td>
<td>Amphotericin B 2 weeks, and itraconazole 2 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>19† (M, 30, Homo)</td>
<td>9</td>
<td>19</td>
<td>PCP</td>
<td>Kidney</td>
<td>Fever, cough, hematuria</td>
<td>Unilateral cavitary in the pelvis of the kidney, unilateral pleural effusion</td>
<td>Surgical biopsy of the kidney, serum Ag-</td>
<td>Itraconazole, 4 months</td>
<td>Alive after 4 months</td>
</tr>
<tr>
<td>Patient No. (Sex, Age, Risk Factors for HIV)</td>
<td>Months Since AIDS Diagnosis</td>
<td>Last CD4 Count/mL</td>
<td>Past Medical History</td>
<td>Extent of Aspergillosis</td>
<td>Symptoms</td>
<td>Radiographic Appearance</td>
<td>Source of Diagnosis</td>
<td>Treatment</td>
<td>Outcome</td>
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</tr>
<tr>
<td>20 (M, 34, Homo)</td>
<td>12</td>
<td>7</td>
<td>Bacterial pneumonia, AP</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea, axillae, hepatosplenomegaly, CNS disorders</td>
<td>Unilateral, cavitary in upper lobe, bilateral pleural effusions, mediastinal adenopathies</td>
<td>Lavage, serum Ag-</td>
<td>Itraconazole, 2 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>21 (M, 34, Homo)</td>
<td>34</td>
<td>19</td>
<td>Neutropenia, AP, CMV colitis</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea</td>
<td>Bilateral infiltrates in upper lobes</td>
<td>Lavage</td>
<td>Itraconazole, 12 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>22 (M, 37, Hetero)</td>
<td>48</td>
<td>10</td>
<td>Steroids, ATB</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea, hemoptysis, CNS disorders, myocarditis</td>
<td>Bilateral nodular lesions</td>
<td>Lavage</td>
<td>Amphotericin B, 5 days</td>
<td>Death</td>
</tr>
<tr>
<td>23 (M, 34, IVD)</td>
<td>10</td>
<td>3</td>
<td>Bacterial pneumonia, PCP, AP, CMV colitis and esophagitis</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea, hemoptysis, pancreatitis</td>
<td>Unilateral nodular lesions in upper lobe</td>
<td>Lavage</td>
<td>Amphotericin H, 5 days</td>
<td>Death</td>
</tr>
<tr>
<td>24 (M, 40, Homo)</td>
<td>10</td>
<td>2</td>
<td>Steroids, ATB, neutropenia, AP, CMV retinitis</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea</td>
<td>Bilateral, diffuse infiltrates and unilateral cavitary in lower lobe, unilateral pleural effusion</td>
<td>Lavage, serum Ag+</td>
<td>Itraconazole, 6 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>25 (F, 27, IVD)</td>
<td>16</td>
<td>1</td>
<td>Steroids, ATB, neutropenia, PCP, bacterial pneumonia</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea, CNS disorders</td>
<td>Bilateral nodular lesions</td>
<td>Lavage</td>
<td>Amphotericin B, 2 days</td>
<td>Death</td>
</tr>
<tr>
<td>26 (M, 59, Homo)</td>
<td>14</td>
<td>11</td>
<td>ATB, neutropenia, AP</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea, chest pain</td>
<td>Bilateral, diffuse infiltrates</td>
<td>Lavage</td>
<td>Amphotericin B, 2 days</td>
<td>Death</td>
</tr>
<tr>
<td>27 (M, 53, Homo)</td>
<td>20</td>
<td>70</td>
<td>Neutropenia, AP, PCP</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea</td>
<td>Bilateral diffuse nodular infiltrates, unilateral cavitary lesions in upper and lower lobes, bilateral pleural effusion</td>
<td>Lavage</td>
<td>Itraconazole, 6 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>Patient No.</td>
<td>Months Since AIDS Diagnosis</td>
<td>Last CD4 Count/mL</td>
<td>Past Medical History</td>
<td>Extent of Aspergillosis</td>
<td>Symptoms</td>
<td>Radiographic Appearance</td>
<td>Source of Diagnosis</td>
<td>Treatment</td>
<td>Outcome</td>
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</tr>
<tr>
<td>22 (M, 34, IVD)</td>
<td>22</td>
<td>32</td>
<td>Neutropenia, AP, PCP</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea</td>
<td>Unilateral infiltrates and cavitary lesions in upper lobe</td>
<td>Lavage, serum</td>
<td>Itraconazole, 4 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>29 (F, 32, Homo)</td>
<td>14</td>
<td>7</td>
<td>ATB, neutropenia, AP, PCP</td>
<td>Lungs</td>
<td>Fever, cough, hemoptysis</td>
<td>Bilateral diffuse infiltrates and unilateral nodular lesions, unilateral cavitary in upper lobe</td>
<td>Lavage, serum</td>
<td>Itraconazole, 11 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>30 (M, 46, Homo)</td>
<td>0</td>
<td>121</td>
<td>PCP</td>
<td>Lungs</td>
<td>Fever</td>
<td>Bilateral infiltrates in upper lobes</td>
<td>Lavage, serum</td>
<td>Itraconazole, 13 months</td>
<td>Death</td>
</tr>
<tr>
<td>31 (M, 32, Homo)</td>
<td>10</td>
<td>21</td>
<td>PCP, AP</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea</td>
<td>Bilateral diffuse infiltrates</td>
<td>Lavage</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>32 (M, 32, Homo)</td>
<td>17</td>
<td>8</td>
<td>Steroids, ATB, PCP, AP</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea, pericarditis</td>
<td>Bilateral, nodular diffuse infiltrates, unilateral cavitary in upper lobe, cardiomegaly</td>
<td>Lavage, serum</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>33 (M, 77, Hetero)</td>
<td>6</td>
<td>17</td>
<td>Steroids, ATB, neutropenia, bacterial pneumonia</td>
<td>Lungs</td>
<td>Fever, cough, dyspnea</td>
<td>Bilateral diffuse infiltrates</td>
<td>Lavage, negative bronchial and transbronchial biopsies, serum</td>
<td>Amphotericin B 4 weeks, then itraconazole 3 months</td>
<td>Alive after 4 months</td>
</tr>
</tbody>
</table>

PCP = Pneumocystis carinii pneumonia; ATB = antibiotic treatment; AP = aerosolized pentamidine; CMV = cytomegalovirus; IVD = intravenous drug abuser; Hetero = heterosexual; Homo = homosexual or bisexual; Ag = antigen; CNS = central nervous system.

*Tracheobronchial invasive aspergillosis.

†Isolated extrapulmonary disease.
TABLE II

Diagnostic Procedures (33 Patients)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pulmonary invasive aspergillosis (30/30)</th>
<th>Positive BAL fluid culture (28/28)*</th>
<th>Positive histology antemortem (6/7)</th>
<th>Bronchial biopsy</th>
<th>Tracheal biopsy</th>
<th>Bronchial and transbronchial biopsies</th>
<th>Open lung biopsy</th>
<th>Positive histology at autopsy (9/9)+</th>
<th>Positive histology at autopsy alone (2) (cultures not performed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized extrapulmonary aspergillosis (3/33) with positive histology and culture (3/3)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
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<td>Spine</td>
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BAL = bronchoalveolar lavage.
*For 27 patients, Aspergillus species was found as a single pathogen; and for 1 (Patient 11), Pneumocystis carinii was found in association, but autopsy revealed invasive aspergillosis.
+The patient with positive bronchial and transbronchial biopsies also had a positive histology at autopsy (Patient 15).

Kaposi's sarcoma in four, ganciclovir in four, zidovudine in three, and an unknown cause in two. Two patients received steroids for more than 8 days during the 3 months before diagnosis.

Possible Predisposing Factors, Underlying Diseases, and Associated Treatment

Medical history revealed at least 1 episode of infectious pneumonia for 24 patients (73%), 21 of whom were diagnosed during the last year before infection with Aspergillus. Causative organisms were Pneumocystis carinii (PCP) for 17 patients; mycobacteria for 3; Streptococcus pneumoniae for 2; and Legionella pneumophila, Haemophilus influenzae, Pseudomonas aeruginosa, and cytomegalovirus (CMV) for 1, respectively. The pathogen could not be identified in 2 cases. Two patients had pulmonary Kaposi's sarcoma. CMV infection was diagnosed in nine patients (retinitis for six, gastrointestinal tract for two, and histologically proven pneumonitis for one). Four other patients had CMV in the BAL fluid. One patient smoked marijuana. Monthly aerosolized pentamidine was administered as primary or secondary prophylaxis of PCP pneumonia in 20 patients (61%). Twenty patients (61%) received broad-spectrum antibiotics for more than 8 days during the 3 months before diagnosis of aspergillosis (Table I).

Pulmonary IA

Body temperature was always elevated, with a median of 39°C. Cough was found in 29 patients (97%), dyspnea in 24 (80%), chest pain in 6 (20%), and hemoptysis in 5 (17%).

Three cases of tracheobronchial IA were observed: two for which endoscopy revealed fungal necrotic pseudomembranes, and one for which diagnosis revealed at autopsy the same macroscopic features. Before they died, all three patients had acute dyspnea and wheezing that mimicked asthma, as well as associated pulmonary involvement (Figure 1).

Other associated signs and symptoms were central nervous system (CNS) abnormalities in seven, splenomegaly in four, liver enlargement in three, myocarditis in three, pericarditis in three, pancreatitis in one, and ascites in one. By definition, chest radiographs or thoracic computed tomographic scans were abnormal (Figure 1). Newly diagnosed cavitating pulmonary lesions were found in 14 cases, 12 of which were located in the upper lobes. In 12 patients, there were nodular lesions, which were disseminated in 9. Bilateral interstitial infiltration of the lungs was observed in 18 patients, and a localized infiltrate was found in 2 cases. Pleural effusion was found in five cases and was bilateral in four; mediastinal or hilar lymph node enlargement was observed in three cases. Extrapulmonary symptoms were also present at the time of diagnosis. They were probably underestimated, because an exhaustive examination was not performed for all the patients. The organs involved at autopsy were lungs in 11, myocardium in 2, bronchial tissue in 1, kidney in 1, brain in 1, and lymph nodes in 1, but a systematic search was not performed for specific fungal extrapulmonary lesions, which probably underestimates the potential involvement of organs other than the lungs.

Localized Extrapulmonary IA

There was one patient with specific otomastoiditis with related symptoms, one with pelvis of the...
kidney aspergillosis and macroscopic hematuria, and one with spleen involvement and splenomegaly. Two of the patients had a cough, one of whom had positive sputum. Chest radiographs were normal in two cases, whereas the patient with renal aspergillosis had a unilateral pleural effusion, which resolved after removal of the kidney (Table I).

Outcome
Among the 33 patients, 31 died during the follow-up period. The mean interval between diagnosis and death was 8 weeks (range: 3 days to 13 months). Death was directly related to aspergillosis in 13 patients, with a mean interval of 5.5 weeks between diagnosis and death. Eleven patients (37%) died with CNS abnormalities. Two patients were alive and still under observation 4 months after diagnosis (one with negative and one with positive cultures). Six patients became culture-negative, and four experienced clinical and radiologic improvement.

Treatment
Six patients did not receive any treatment. The other patients received specific treatment that was not administered as a function of the patient’s clinical status.

Twelve patients received amphotericin B alone, 8 of them for less than 15 days, and 4 for 15 days or more. Only four patients were evaluable because they received a mean total dose of 1,200 mg with a dose of 0.5 mg/kg to 1 mg/kg for each infusion. One patient had a negative culture and two did not; for the last patient, follow-up cultures were not performed.

Eight patients received itraconazole alone for 15 days or more (greater than or equal to 300 mg/d), and three had sterile cultures of BAL fluid (peak serum level determined for two = 1.25 mg/L). Four did not attain negative cultures (peak serum level in three patients = 2.5, 0.90, and 0.31 mg/L). Follow-up cultures were not performed for the last patient.

Three patients received amphotericin B and itraconazole in association for 15 days or more, without sterile cultures in two; the peak serum level of itraconazole was 2.5 mg/L in one patient, and no follow-up cultures were performed for the last case, because it was a localized splenic aspergillosis.

Three patients received amphotericin B alone for more than 15 days (two with negative culture results), then itraconazole (greater than or equal to 300 mg/d) alone for 15 days or more, with cultures remaining negative for the same two patients. For one patient, the culture remained positive and the itraconazole peak serum level was 0.05 mg/L.

One patient received itraconazole alone for 15 days, then amphotericin B alone for 6 days without becoming culture-negative.

COMMENTS
This report presents the largest study on AIDS-associated IA. In a shorter previously reported series, 89% of patients exhibited predisposing factors. In contrast, Minamoto et al [26] reported 6 of 18 patients without classic risk factors, and in our series, only 16 of 33 (48.5%) patients exhibited such risk factors (i.e., neutropenia and steroid therapy) [1,31].

Qualitative defects of neutrophils and/or alveolar macrophages, which are the major cells for host defense against Aspergillus [31-38], could be involved; impaired neutrophil function in patients with AIDS was previously reported [39,40].

In our study, 73% of patients had a past history of pulmonary infection, which could impair pulmonary macrophage function [36] and increase the frequency of colonization by Aspergillus [1]. It is possible that cystic pulmonary lesions during AIDS [41] represent a new risk factor for IA. Monocyte dysfunction has been noted in AIDS [36,37]; the fungicidal activity of monocytes but not alveolar macrophages against Aspergillus was normal in one study [38].

We cannot exclude the potential role of aerosolized pentamidine, which was given to 61% of our patients and to 90% of the IA patients in the literature. The use of broad-spectrum antibiotics and CMV infection as single factors is still discussed [42,43], but a direct role of marijuana seems unlikely [42].

All patients had a very low T4 cell count, usually below 50/mm^3, a finding in agreement with recent reports [26,27]. A direct effect of T4 cells on the function of neutrophils and macrophages was advocated by Denning et al [25]. The mean interval between the diagnosis of full-blown AIDS and IA was 10 months in a recent report [26] and 13 months in the current study.

Autopsy showed that the antemortem diagnosis of AIDS-associated IA is often underestimated [21,44]. Twenty-nine percent of the cases were diagnosed at autopsy in the literature [25].

In light of the poor prognosis of AIDS-associated IA, attempts to make an early diagnosis are interesting. Biopsy is the optimal means for diagnosis, but is often difficult to perform for seriously ill patients with AIDS and may be nondiagnostic [26].

The positivity of sputum cultures is not always correlated with IA [45], because colonization of the airways with Aspergillus species is not uncommon in patients with AIDS [27]. In contrast, results of BAL fluid culture were always positive (28 of 28) in
our study, with no other pathogen discovered in 27 of 28 patients. For six of seven patients, the BAL fluid culture correlated with the histologic findings obtained antemortem, and for nine of nine patients (including one with positive antemortem histology in whom autopsy was performed), the BAL fluid culture correlated with the histologic findings obtained at autopsy, which revealed characteristic features of invasion. For the other patients without histologic confirmation, either antemortem or at autopsy, four experienced clinical or radiologic improvement in association with negative results of mycologic cultures during antifungal treatment, six had new cavitary pulmonary lesions without any other documented pathogen, and two had positive detection of antigen in serum. Six deaths could be directly attributed to aspergillosis. At least, colonization could not be excluded for the other patients; however, it seems unlikely because Aspergillus was the only causative agent isolated in these patients with suggestive clinical and radiologic features. Interestingly, we observed no false-positive BAL results. This might explain why only 6% of our patients were diagnosed at autopsy. Because we have not taken into account patients who had BAL fluid specimens that did not grow Aspergillus, whose pulmonary disease was not clarified and who died without autopsy, the frequency of IA may be underestimated. Twenty-eight of 30 patients had a diagnosis by BAL. The value of BAL is similar to what has been reported in other immunocompromised patients [46,47]. Aspergillus antigen detection in BAL fluid can be helpful in AIDS: it was positive for three of three tested patients. This finding is also in agreement with the results obtained in patients without AIDS [48]. In our study, serum antigen detection was not helpful in contrast with data from non-AIDS patients with IA [49]. Antibody detection by counterimmunoelectrophoresis was negative in six of six cases. Clinical and radiologic signs are not different from that seen in patients without AIDS. A cavitary lung disease, especially in the upper lobe, should now alert physicians to IA in AIDS. Invasive necrotizing tracheobronchial aspergillosis should also be emphasized: in three of our cases this was observed in association with lung involvement. Two cases of invasive bronchial aspergillosis without lung involvement [9,24] and four cases of noninvasive obstructive bronchial aspergillosis have also been reported [25,48]. It does not seem useful to differentiate invasive from noninvasive tracheobronchial aspergillosis. One patient with the noninvasive form of aspergillosis did not receive any treatment initially and later presented with the invasive form, dying of cerebral aspergillosis [25].

In the literature, extrapulmonary involvement was often discovered during postmortem examinations. The most common sites involved are as follows: heart [7,10,13,18,20,26]; brain [7,8,13,20,21,26]; spleen [20]; kidney [8,13,20,21,26]; pancreas [19,20]; pleura [8]; medulla [8]; bronchi [9,26]; sinus [9,26], liver [11]; trachea [13]; lymph nodes [13]; and thyroid [13,21]. Isolated invasive external otitis [16] and otomastoiditis [17] have also been reported. CNS involvement appears to be more frequent in HIV-infected patients than in others, who have an incidence of 10% to 20% [6]. Thirty-seven percent of our patients died with CNS clinical abnormalities. We observed one case of pelvis of the kidney aspergillosis in a nondiabetic patient [50].

The overall outcome of AIDS-associated IA is poor. Indeed, in the study of Denning et al [25], the patients died a mean of 4 months after the diagnosis, and after 2 months in our study. The precise clinical activity of antifungal agents is difficult to assess [51]. Indeed, in the literature, only 10 patients received appropriate treatment (15 days or more) with amphotericin B, but 8 died with either clinical symptoms suggestive of IA or with a confirmed evolutive disease [7,8,18,25,26]. In our study, four evaluable patients received amphotericin B alone for 15 days or more, and we observed only one mycologic cure. In the literature, six patients received itraconazole for more than 15 days and treatment failed in four of them [15,25], whereas two were apparently cured [25]. In our series, eight patients received itraconazole alone for more than 15 days, and three became culture-negative. Itraconazole represents an attractive therapy in AIDS because it is orally active and is safe [52,53] for patients in whom amphotericin B-induced renal toxicity is a major concern. The poor results obtained in AIDS could be partially due to absorption defects, but we could not correlate the serum level with the outcome. Interaction of itraconazole and rifampin was documented in our study in two cases (peak serum level less than or equal to 0.05 mg/L), as previously reported [25]. Interestingly, one patient who received a combination of itraconazole and ansamycin also had a very low itraconazole serum concentration (0.03 mg/L), which increased after administration of the second drug was discontinued (1.25 mg/L). In light of these poor results, new therapeutic strategies must be emphasized, such as new galenic forms of amphotericin B or itraconazole. The use of immunomodulating agents, especially interferon-γ, could be promising [54,55].

CONCLUSION

Aspergillosis is a growing problem, which may reflect the retrospective and not the comprehensive
nature of the study. It particularly occurs in the advanced stage of AIDS, in patients with very low T4 cell counts, but not particularly in those with classic risk factors (i.e., neutropenia or steroid therapy). Mycologic culture after BAL is the method of choice for diagnosis in cases of suggestive chest radiographs. Clinical and radiologic signs are similar to what was reported in patients without AIDS, except for the higher frequency of CNS involvement in AIDS. Conventional treatment is most often unsuccessful; therefore, new therapeutic strategies should be defined, such as the use of immunomodulating agents in association with antifungal agents. AIDS patients with sputum samples positive for *Aspergillus* without evolutive IA should be carefully monitored.

**APPENDIX**

French Cooperative Study Group on Aspergillosis in AIDS


**REFERENCES**


