Cardiac Aspergillosis in Patients With Acquired Immunodeficiency Syndrome

A Case Report and Review of the Literature

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Cardiac aspergillosis is uncommon in patients with acquired immunodeficiency syndrome (AIDS) in the absence of open heart surgery. We report a unique case of a 62-year-old man with AIDS who developed Aspergillus pancarditis with Aspergillus vegetations on mitral valve without evidence of pulmonary aspergillosis. There was extensive embolization to the brain and multiple foci of Aspergillus infection in kidneys and adrenal glands. There are only 10 documented cases of cardiac aspergillosis in the literature (1966–2003) in severely immunocompromised AIDS patients with CD4 T lymphocyte counts ranging from 10 to 121 cells/µL. The cardiac aspergillosis could result from invasive pulmonary aspergillosis, either by hematogenous dissemination or by direct invasion, and skin Aspergillus infection can be carried through the bloodstream to the right heart in intravenous drug abusers. Most of the reported cases of cardiac aspergillosis were diagnosed at autopsy. Mortality among AIDS patients with cardiac aspergillosis is 100%, despite appropriate therapy. (Arch Pathol Lab Med. 2005;129:511–515)

Aspergillosis was initially included in acquired immunodeficiency syndrome (AIDS)–defining opportunistic infections by the Centers for Disease Control in 1982. However, it was subsequently excluded from the revised case definition of AIDS, because patients with CD4 lymphopenia showed no predisposition for or increase in the incidence of developing invasive aspergillosis. However, the world literature that we reviewed, including our case, shows that AIDS patients with cardiac aspergillosis without exception had marked CD4 T lymphopenia (Table). There is close association between marked CD4 T lymphopenia and increased incidence of developing cardiac aspergillosis in patients with AIDS. These findings support the view that cardiac aspergillosis should be reconsidered as an AIDS-defining condition.

Although cardiac aspergillosis is very rare in patients with AIDS who have not undergone open heart surgery, it carries a very high mortality rate. The first case of cardiac aspergillosis as an AIDS-related opportunistic infection was reported in 1985. Ever since, there have been a few reports, mostly from North America and Europe. Patients with cardiac involvement have frequently previously experienced pulmonary aspergillosis with Aspergillus endocarditis and myocarditis (Table). Our patient with AIDS had Aspergillus pancarditis (endocarditis, myocarditis, pericarditis with pericardial effusion) embolizing and infecting multiple organs in the absence of pulmonary aspergillosis. The unique case is presented in this report. We also reviewed the literature from 1966 to 2003 and did a thorough analysis of the 10 cases previously reported of AIDS patients with Aspergillus infection in the heart.

REPORT OF A CASE

A 62-year-old male AIDS patient with recent Pneumocystis carinii pneumonia was admitted to our hospital for fever, shortness of breath, and productive cough. The tests showed CD4 lymphocyte count of 79 cells/µL and human immunodeficiency virus (HIV) viral load of <400 copies/mL. He was on highly active antiretroviral therapy and Pneumocystis carinii pneumonia prophylaxis. He was a smoker and alcohol abuser. His past medical history included diabetes mellitus (type I) and hypertension, for which he was on insulin and antihypertensive medications. At the time of admission his temperature was 38.0°C. Lungs had decreased breath sounds at bases bilaterally. Cardiovascular examination revealed a 3/6 holosystolic murmur audible at the mitral area. Laboratory tests revealed white blood cell count, 23.2 × 10^3 cells/µL (23.2 × 10^3 cells/L), with 89% neutrophils; hemoglobin, 13.7 g/dL (137 g/L); platelet count, 286 × 10^9 cells/µL (286 × 10^9 cells/L); glucose, 174 mg/dL (9.7 mmol/L). Chest radiography indicated bilateral pneumonia. The patient was treated empirically with broad-spectrum antibiotics and continued anti-HIV therapy. He experienced ventricular tachycardia with cardiogenic arrest and was successfully resuscitated. Subsequent echocardiogram showed large vegetation on the atrial surface of the posterior mitral valve leaflet with severe mitral regurgitation. Blood cultures were negative for bacteria or fungi. Vancomycin and gentamicin were added for presumed bacterial endocarditis. On the 7th day, his pupils were not reactive to light with Doll eye sign; there was bilateral facial asymmetry and right-extremities paralysis with positive Babinski sign. Head computed tomography revealed an extensive low density, compatible with infarctions, in the left temporal, parieto-occipital lobe, with evidence of mass effect and midline shift. There was also extensive right basal ganglia infarct. Toxoplasmosis was suspected at this stage and appropriate treatment started. His condition progressively deteriorated. He expired on the 15th hospital day.
Pathologic and Clinical Features of Documented Cardiac Aspergillosis in Patients With Acquired Immune Deficiency Syndrome (AIDS)*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Source, y</th>
<th>Age, y/Sex</th>
<th>HIV RF/Interval Between AIDS and Asp, mo</th>
<th>Last CD4 count, cells/μL</th>
<th>ANC or WBC, cells/μL</th>
<th>Echocardiogram Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Henochowicz et al, 1985</td>
<td>32/M</td>
<td>IVDU/12</td>
<td>NA</td>
<td>NA</td>
<td>A 1 × 1-cm vegetation on MV/NA</td>
</tr>
<tr>
<td>2</td>
<td>Asnis et al, 1988</td>
<td>44/M</td>
<td>IVDU/1</td>
<td>NA</td>
<td>ANC 60</td>
<td>Small PE/NA</td>
</tr>
<tr>
<td>3</td>
<td>Minamoto et al, 1992</td>
<td>43/M</td>
<td>Homosexuality/3</td>
<td>NA</td>
<td>ANC 1800</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>Cox et al, 1990</td>
<td>31/M</td>
<td>Homosexuality/1</td>
<td>12</td>
<td>WBC 7200</td>
<td>Globular mass in LV cavity/NA</td>
</tr>
<tr>
<td>5</td>
<td>Schonheyder et al, 1992</td>
<td>50/M</td>
<td>Homosexuality/13</td>
<td>272 (7 mo previous)</td>
<td>WBC 1200</td>
<td>NA/trial flutter, ICRBBB</td>
</tr>
<tr>
<td>6</td>
<td>Lortholary et al, 1993</td>
<td>29/M</td>
<td>NA (neutropenia, steroid)/0</td>
<td>42</td>
<td>NA/neutropenia</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>Lortholary et al, 1993</td>
<td>41/M</td>
<td>NA/1</td>
<td>32</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>Staples et al, 1995</td>
<td>47/NA</td>
<td>NA/NA</td>
<td>10</td>
<td>Normal</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>Petrosillo et al, 2001</td>
<td>35/M</td>
<td>IVDU/1</td>
<td>121</td>
<td>ANC 3100, WBC 4700</td>
<td>Vegetation on TV/CRBBB</td>
</tr>
<tr>
<td>10</td>
<td>Petrosillo et al, 2001</td>
<td>39/M</td>
<td>IVDU/1</td>
<td>72</td>
<td>ANC 1617, WBC 2100</td>
<td>A mass on AV with regurgitation/NA</td>
</tr>
<tr>
<td>11</td>
<td>Present report</td>
<td>62/M</td>
<td>NK/1</td>
<td>79</td>
<td>ANC 20 648, WBC 23 000</td>
<td>A large vegetation on MV with MR/VT</td>
</tr>
</tbody>
</table>

* HIV indicates human immunodeficiency virus; RF, risk factor; Asp, aspergillosis; ANC, absolute neutrophil count per mm²; WBC, white blood cell; IVDU, intravenous drug abuse; NA, data not available; MV, mitral valve; ASP, Aspergillus; A F, Aspergillus fumigatus; AmB, amphotericin B; PE, pericardial effusion; LV, left ventricle; PCP, Pneumocystis carinii pneumonia; ICRBBB, incomplete right bundle branch block; NHL, non-Hodgkin lymphoma; LN, lymph node; CMV, cytomegalovirus; TV, tricuspid valve; CRBBB, complete right bundle branch block; CS, cardiogenic shock; AV, aortic valve; NK, not known; MR, mitral regurgitation; VT, ventricular tachycardia; and MI, myocardial infarct.

**MATERIALS AND METHODS**

A complete autopsy was performed. The gross and histologic findings of all organs were available for studies. Hematoxylin-eosin-stained sections and Gomori methenamine silver-stained sections were evaluated. Aspergillus was microscopically confirmed based on the characteristic features of small and regular fungal hyphae with dichotomous branching at acute angles and distinct cross-septa.

We did a MEDLINE search for reports of cardiac aspergillosis. All reported cases in the literature, including the present case, are summarized in the Table. Ten of the total 11 patients are male. In one case, the patient's gender was not mentioned. Patient ages ranged from 29 to 62 years, with mean of 41 years. All cases were confirmed as cardiac aspergillosis at autopsy. Aspergillus fumigatus was recovered from 6 patients, either from preremoent blood culture and biopsy tissues or at postmortem tissue culture. The mean interval between the diagnosis of AIDS and aspergillosis was 3.5 months (range, 0 to 13 months). Details of cardiovascular features of documented AIDS patients with cardiac aspergillosis are recorded in the Table.

**PATHOLOGIC FINDINGS**

At autopsy, there was 100 mL of serosanguineous pericardial effusion. The heart weighed 660 g and showed biventricular hypertrophy and right ventricular dilatation. The mitral valve showed a large, polylobular, fungating, reddish vegetation (3.0 × 2.0 × 1.5 cm) on the atrial surface of the posterior leaflet, extending to the left atrial endocardium just above the annulus of the posterior leaflet (Figures 1 and 2). Multiple small vegetations (0.5 cm in greatest dimension each) were attached along the line of closure of the posterior leaflet (Figure 2). The vegetations did not extend onto the chordae. The mitral valve itself, except for the vegetations, and the rest of the cardiac valves were unremarkable. The myocardium revealed a pale-gray ovoid infarcted area (0.7 × 0.6 × 0.4 cm) in the ventricular septum. All coronary arteries were unremarkable. Microscopic findings of the heart include endocarditis with characteristic Aspergillus fungal elements in necrotic debris on both the anterior and posterior leaflets, Aspergillus myocarditis with micro-abscess formations in the left ventricle and left atrium (Figure 3), and foci of Aspergillus aggregates in necrotic debris present in the thickened pericardium in the left ventricle and atrium (Figure 4), as well as microscopic old myocardial fibrous foci in the ventricular septum and left ventricle. The specificity of the morphologic identification of Aspergillus in tissue was based on the regular hyphae with dichotomous
inflammation with micro-abscesses containing sampling. Kidneys showed extensive chronic interstitial halation. Physical barriers and entrapment by bronchial solized, are responsible for pulmonary infection after in-

have been described to date. Conidia, which are readily aero-
pulmonary fibrosis, pulmonary edema, hemorrhage, and

branching at 45° angles and distinct cross-septa (Figure 3,
invasion or by direct invasion, and skin

Aspergillus species were recovered by culture were infect-

but less effective against A. fumigatus, which has small (2-
to 3-μm) conidia and is therefore the most common cause

most common site of invasive aspergillosis is the lung (91%),

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Comment

More than 180 species within the genus Aspergillus have

been described to date. Conidia, which are readily aero-
solized, are responsible for pulmonary infection after in-
halation. Physical barriers and entrapment by bronchial

mucus are efficacious against species with larger conidia

Aspergillus species were recovered by culture were infect-

of invasive aspergillosis through a respiratory route. No other

Aspergillus species were recovered by culture were infect-

invasion or by direct invasion, and skin

Aspergillus hyphae; thromboemboli of intramural arteries

invasive aspergillosis from 17 different medical centers in

Aspergillus hyphae; thromboemboli of intramural arteries

Extensive cerebral infarction in the left temporal parieto-occipital lobes (Figure 5) and focal infarct in the right basal ganglia were found grossly. There was subfalcine herniation (inset in Figure 5). Microscopically, infarcted areas demonstrated coagulative necrosis, containing sporadic Aspergillus fungal clusters with scattered areas of micro-abscesses. The left middle cerebral artery was almost completely occluded by fungal emboli. There was diffuse mycotic arteritis in the left middle and posterior cerebral arteries (Figure 6). The posterior cerebral arteries also showed severe atherosclerosis, with approximately 85% luminal narrowing. There was approximately 1000 mL of serosanguineous pleural effusion bilaterally. The lung revealed bilateral diffuse interstitial pulmonary fibrosis, pulmonary edema, hemorrhage, and congestion. No fungal elements were identified by histopathology or tissue cultures of both lungs after extensive sampling. Kidneys showed extensive chronic interstitial inflammation with micro-abscesses containing Aspergillus. The right adrenal gland showed focal aspergillosis.

COMMENT

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solized, are responsible for pulmonary infection after in-
halation. Physical barriers and entrapment by bronchial
Although the infective form of *Aspergillus* is conidia, usually acquired through a respiratory route, hyphal growth results in disease in tissue and extrapulmonary dissemination. Patient 9, an intravenous drug abuser, had large *Aspergillus* vegetation on the tricuspid valve, which caused pulmonary embolism and infarction. The *Aspergillus* infective route was most likely directly from skin through blood to heart. His pulmonary aspergillosis was likely secondary to *Aspergillus* endocarditis of right heart. Once the left endocarditis with *Aspergillus* vegetation was present, it could cause infarction of the myocardium and other organs, particularly the brain, as seen in our case.

The first line of cellular defense against *Aspergillus* conidia are macrophages, which ingest conidia, kill germminating cells, and secrete cytokines and chemokines to coordinate secondary cellular defenses. Germinating conidia and hyphae that escape macrophage surveillance are destroyed primarily by neutrophils and monocytes. Patients in the early stage of HIV infection usually reserve the macrophage functions and maintain normal counts of neutrophils and monocytes, which will enable them to protect against *Aspergillus* infection. However, T lymphocytes mediate the effector function of macrophages. During the late stage of disease, AIDS patients with severe T lymphocytopenia eventually will have defense systems ineffective against *Aspergillus*. In this review, 8 of 11 patients with documented CD4 T-lymphocyte counts had CD4 lymphopenia. Markedly decreased CD4 counts were present in 7 of 11 patients whose last T4 cell counts were recorded, ranging from 10 to 121 cells/μL. Patient 5 had a CD4 count of 272 cells/μL measured 7 months before his death. This count does not represent the relation between onset of cardiac aspergillosis and level of last CD4 number. Only 3 of 8 patients with CD4 lymphopenia had documented leukopenia. The data suggest that severe CD4 lymphopenia in patients with AIDS should be considered a risk factor for cardiac aspergillosis.

The clinical presentation may include fever, features of cardiac dysfunction, or embolic phenomena. Most of the reported cases of cardiac aspergillosis were diagnosed at autopsy. *Aspergillus* species are not commonly isolated from premortem blood cultures. Six of 11 patients were given amphotericin, itraconazole, or fluconazole therapy, most likely with the purpose of complete coverage, not specifically for cardiac aspergillosis. Patients with cardiac involvement frequently have widespread, disseminated aspergillosis. Because of the difficulty reaching a diagnosis, specific immunologic tests and molecular techniques have been developed for early detection of *Aspergillus*. However, these tests are not readily available in every medical facility. Mortality among AIDS patients with cardiac aspergillosis is 100%, despite antifungal therapy. This is partly because the diagnosis is often made late or because there is no really effective treatment.
References