Cardiac Tamponade Due to Primary Pericardial Lymphoma in a Patient With AIDS*

David M. Aboulafia, M.D.; Roger Bush, M.D.; and Vincent J. Picozzi, M.D.

Cardiac tamponade due to lymphomatous involvement of the heart is a dramatic and unusual complication. Because of their nonspecific clinical presentation, these tumors are seldom diagnosed antemortem. We report the case of a patient with AIDS who presented with signs and symptoms of cardiac tamponade. Emergency pericardioceintesis followed by staging studies revealed large cell B-lymphocyte lymphoma confined to the pericardial space. With combination chemotherapy, a durable complete response was obtained. This case illustrates the potential benefit of aggressive treatment of extranodal non-Hodgkin’s lymphoma in a patient with AIDS. The case is of particular interest because of the unusual development of isolated pericardial involvement as the sentinel sign of lymphoma.

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HIV=human immunodeficiency virus; KS=Kaposi’s sarcoma; NHL=non-Hodgkin’s lymphoma

Key words: AIDS, cardiac tamponade, extranodal lymphoma

Human immunodeficiency virus (HIV)-infected individuals develop non-Hodgkin’s lymphoma (NHL) at a frequency 60 to 100 times greater than expected in the general population.1,2 In 1985, the Center for Disease Control recognized the linkage between intermediate and high-grade lymphomas and HIV seropositivity and included this in the diagnostic criteria for AIDS. Some estimates project that 10 to 20 percent of all new NHL cases in the United States eventually may be related to AIDS.3 Their incidence continues to increase due in part to improved treatment and longer survival of AIDS patients.4,5

Roughly 90 percent of AIDS-related NHLs are of intermediate or high-grade B lymphocytes of either the immunoblastic or small noncleaved type. In the latter, the classic Burkitt’s or non-Burkitt’s lymphoma may be seen. In contrast, these high-grade types are expected in approximately 10 percent of the usual patients with lymphoma.6,7 When compared with the histologically similar NHLs arising in immunocompetent patients, systemic AIDS-related NHLs display distinctive features, including poor prognosis and frequent involvement of extranodal sites, particularly the gastrointestinal tract, central nervous system, and bone marrow.8,9

Cardiac abnormalities in HIV-infected individuals are common, occurring in 17 to 64 percent of cases evaluated by noninvasive means and in 31 to 77 percent in postmortem studies.10 These abnormalities include myocarditis with and without cardiomyopathy, endocarditis, pulmonary hypertension, and arrhythmias. However, NHL involving the heart or pericardium due to lymph-hematogenous spread in HIV patients is a most unusual development.11,12 In a study of 90 patients with AIDS who developed lymphoma, only one case involved the pericardium.13 Details regarding whether NHL was limited to the heart or was widely disseminated at the time of diagnosis were not provided. Non-Hodgkin’s lymphoma occurring as a primary cardiac or pericardial tumor in AIDS-related lymphomas is even more rare; most patients with this finding possess diffuse large cell or small noncleaved cell histologic findings.14-16 Clinical presentations vary with

REFERENCES

FIGURE 1. Chest roentgenogram showing large cardiac silhouette and bilateral pleural effusions.

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several reports describing intractable congestive heart failure, pericardial effusions, or arrhythmias as sentinel signs of cardiac involvement. The NHL that predominantly involves the heart rarely is detected antemortem and in many cases constitutes the immediate cause of death. In this study, the clinical course of a patient with AIDS and isolated cardiac lymphoma is reported and compared with the clinical courses of patients previously reported in the literature.

CASE REPORT

A 42-year-old white homosexual male developed a purplish plaque on his left arm in March 1989. A punch biopsy of the lesion demonstrated Kaposi's sarcoma (KS) and serologic testing for HIV proved positive. He was treated initially with zidovudine, then switched to didanosine 6 months later when he developed moderate neutropenia. In February 1990, he received external beam radiotherapy for advancing lower extremity KS. He also received intralesionally administered vinblastine and topically applied liquid nitrogen for cosmetically bothersome trunk and arm lesions. At the time of widespread tumor progression 6 months later, he began a regimen consisting of intravenously administered vincristine and vinblastine chemotherapy. In 1991, therapy with subcutaneously administered α-interferon, given three times weekly, was initiated when growth of cutaneous lesions accelerated.

In April 1992, the patient presented with a symptom complex including low-grade fevers and progressive dyspnea of several days in duration. Physical examination disclosed decreased breath sounds at the lungs bases, elevated jugular venous distention to the angle of the jaw, decreased heart tones, and hepatomegaly but without peripheral edema or adenopathy. Pertinent laboratory data included the following: hematocrit value, 33 percent; WBC count, 1700 cells/mm³, with 63 percent polymorphonuclear leukocytes, 16 percent band cells, 21 percent lymphocytes; platelet count, 81,000 cells/mm³. The CD4 count from several months earlier was 160×10⁹/L. Blood chemistry studies included a creatinine value of 1.8 mg/dl (normal, ≤1.2 mg/dl); alkaline phosphatase value of 144 IU/L (normal, ≤140 IU/L); aspartate aminotransferase, 113 IU/L (normal, ≤40 IU/L); lactate dehydrogenase level, 692 IU/L (normal, ≤300 IU/L); total bilirubin level, 0.8 mg/dl; and amylase, 73 IU/L. The electrocardiogram revealed a sinus tachycardia, low voltage, and QRS complex morphologic characteristics suggestive of right ventricular hypertrophy. A chest roentgenogram confirmed the presence of a bilateral pleural effusions and an enlarged cardiac silhouette (Fig 1). A transthoracic two-dimensional echocardiogram displayed a large pericardial effusion with evidence of both right atrial and right ventricular collapse consistent with cardiac tamponade. Computed tomography (CT) scans of the chest (Fig 2), abdomen, and pelvis confirmed the presence of tamponade and effusion plus the presence of ascites and small retroperitoneal adenopathy (unchanged since 1989) but no splenomegaly. Pericardiocentesis yielded 800 ml of exudative fluid with a lactate dehydrogenase value of 14,000 IU/L and cytologically contained cells characteristic of large cell immunoblastic lymphoma (Fig 3). Subsequent bacterial, viral, fungal, and mycobacterial stains and cultures were negative. Additional staging studies including bilateral bone marrow aspirates and biopsies, CT scan of the head, and lumbar puncture were negative for systemic lymphoma.

The patient was treated with cyclophosphamide, 750 mg/m² intravenously on day 1; mitoxantrone (Novantrone) 8 mg/m² intravenously on day 1; etoposide 75 mg/m² intravenously on day 1; vincristine, 2 mg intravenously on day 1; and prednisone, 50 mg/m² orally on days 1 through 7. Neutrophil counts were augmented with granulocyte colony-stimulating factor, 5 μg/kg, subcutaneously on days 2 through 14. Within days after the first cycle of therapy, the patient's symptoms had resolved. A repeat chest roentgenogram and echocardiogram one week later showed complete resolution of pleural and pericardial effusion. A total of six cycles of chemotherapy were given over a 6-month period. Detailed restaging, including CT scans and repeat bone marrow assessment, clinically confirmed that the patient was in complete remission. The patient died 12 months after his initial diagnosis of immunoblastic lymphoma but without evidence of recurrent tumor. An autopsy was not performed.

DISCUSSION

This article considers the case of a homosexual man with KS who presented with signs and symptoms of congestive heart failure. During initial evaluation, a cardiac echocardiogram demonstrated a large pericardial effusion with tamponade. Pericardiocentesis yielded a diagnosis of immunoblastic lymphoma. The tumor was not found in re-
Table 1—Cardiac Lymphoma in Acquired Immunodeficiency Syndrome*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Author</th>
<th>Age, yr</th>
<th>Cardiac Manifestations</th>
<th>Pathologic Description</th>
<th>Extent of Myocardial Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Holladay et al\textsuperscript{11}</td>
<td>30</td>
<td>SOB, biventricular CHF</td>
<td>LC</td>
<td>Multiple epicardial and myocardial nodules</td>
</tr>
<tr>
<td>2</td>
<td>Gill et al\textsuperscript{12}</td>
<td>37</td>
<td>Chest pain</td>
<td>SNL</td>
<td>Multiple nodules in pericardium, LV, IVS</td>
</tr>
<tr>
<td>3</td>
<td>Gill et al\textsuperscript{12}</td>
<td>39</td>
<td>None</td>
<td>SNL</td>
<td>Epicardial nodules with extension into papillary muscles</td>
</tr>
<tr>
<td>4</td>
<td>Gill et al\textsuperscript{12}</td>
<td>27</td>
<td>Acute SOB, tamponade</td>
<td>SNL</td>
<td>Solitary 4-cm pericardial mass</td>
</tr>
<tr>
<td>5</td>
<td>Gill et al\textsuperscript{12}</td>
<td>47</td>
<td>Acute SOB, tamponade</td>
<td>SNL</td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>6</td>
<td>Guarner et al\textsuperscript{14}</td>
<td>41</td>
<td>None</td>
<td>IBL</td>
<td>Multiple epicardial nodules infiltrating myocardium</td>
</tr>
<tr>
<td>7</td>
<td>Guarner et al\textsuperscript{14}</td>
<td>38</td>
<td>SOB</td>
<td>IBL</td>
<td>Single epicardial plaque</td>
</tr>
<tr>
<td>8</td>
<td>Constantino et al\textsuperscript{15}</td>
<td>34</td>
<td>Biventricular CHF</td>
<td>IBL</td>
<td>Multiple myocardial infiltrates</td>
</tr>
<tr>
<td>9</td>
<td>Goldfarb et al\textsuperscript{16}</td>
<td>30</td>
<td>SOB, right-sided heart failure, intermittent chest pain</td>
<td>LC</td>
<td>Bilateral atrial mass</td>
</tr>
<tr>
<td>10</td>
<td>Balasubramanyam et al\textsuperscript{19}</td>
<td>48</td>
<td>Biventricular CHF</td>
<td>IBL</td>
<td>Mass (M, E)</td>
</tr>
<tr>
<td>11</td>
<td>Balasubramanyam et al\textsuperscript{19}</td>
<td>51</td>
<td>Cardiac arrhythmias, systolic murmur, hypotension</td>
<td>DL</td>
<td>Multiple RA wall tumor masses</td>
</tr>
<tr>
<td>12</td>
<td>Andrews et al\textsuperscript{23}</td>
<td>40</td>
<td>SOB, chest pain, tamponade</td>
<td>SNL</td>
<td>RA mass</td>
</tr>
<tr>
<td>13</td>
<td>Dalli et al\textsuperscript{24}</td>
<td>36</td>
<td>SOB, cyanosis</td>
<td>SNL</td>
<td>Nodules in IVS and pericardium</td>
</tr>
<tr>
<td>14</td>
<td>Helfand\textsuperscript{25}</td>
<td>35</td>
<td>SOB, hypotension</td>
<td>SNL</td>
<td>Lobulated mass in anterior wall of RV</td>
</tr>
<tr>
<td>15</td>
<td>Kelsey et al\textsuperscript{26}</td>
<td>44</td>
<td>SOB, pleuritic pain</td>
<td>LC</td>
<td>Mass in RA and atrial septum</td>
</tr>
</tbody>
</table>

* M, myocardium; E, endocardium; CHF, congestive heart failure; LV, left ventricle; RA, right atrium; SOB, shortness of breath; SNL, small noncleaved; LC, large cell; IBL, immunoblastic; IVS, interventricular septum; RV, right ventricle.

Regional lymph nodes, the bone marrow, or in other body sites. Thus, the tumor fulfills the criteria set forth by McAllister and Fenoglio\textsuperscript{17} of a primary malignant lymphoma: an extranodal lymphoma involving only the heart and pericardium.

Using similar strict pathologic criteria, in 1989 Curtisinger et al\textsuperscript{18} surveyed the medical literature and were able to confirm only 15 of 55 reported cases that represented primary lymphoma as an extranodal lymphoma involving only the heart and pericardium. Only two of the 15 cases were diagnosed antemortem.\textsuperscript{18} In the first instance, Chou et al\textsuperscript{19} established the diagnosis by myocardial biopsy. The patient died before therapy could be offered.\textsuperscript{19} In the second, Pozniak et al\textsuperscript{20} recovered malignant lymphoid cells from a pericardial aspirate. Although chemotherapy was used, the patient's condition rapidly deteriorated, and he died 2 weeks later. In contrast, cardiac involvement in advanced disseminated lymphoma is not nearly so uncommon in HIV-seronegative patients with autopsy findings suggesting as many as 28 percent of NHLs involve the heart.\textsuperscript{21}

Recently, Holladay et al\textsuperscript{11} presented the case of a 30-year-old AIDS patient who developed fever, shortness of breath, followed shortly thereafter by death. Autopsy disclosed a diffuse large cell NHL of B lymphocyte phenotype with massive involvement of the pericardium and extension into the myocardium. A literature search revealed an additional 22 patients with cardiac lymphoma associated with AIDS, the vast majority of whom showed evidence of disseminated disease at the time of presentation.\textsuperscript{12,14-16,22-26} In 15 of 23 patients, detailed information allowed for tabulation of clinical findings. Twenty-two of the 23 were men and in 1 patient gender was not specified.\textsuperscript{27} Of the 16 patients for whom age was listed, the range was 27 to 51 years, with a mean of 39.5 years. This contrasts with non-HIV-infected patients for whom there is a near-equal incidence among males and females and the patients range in age from 3 to 80 years.\textsuperscript{17,19}

Pathologic descriptions of these tumors were available in 15 cases (Table 1). In all instances, NHLs were of B lymphocyte origin and of intermediate to high grade quality as evidenced by histologic features. The dominant features in eight include a diffuse lymphoma composed of large cells with vesicular nuclei with prominent nucleoli and the frequent presence of mitoses.\textsuperscript{11,14-16,22,26} The remaining seven cases of lymphoma were composed of small, noncleaved cells.\textsuperscript{12,23,24} In reported patients, the most common gross appearance was that of nodular or polypoid masses, predominantly involving the pericardium with variable myocardial infiltration.

Malignant cardiac lymphoma in AIDS patients presents in a variety of ways. There are no pathognomonic signs or symptoms characteristic of a primary tumor of the heart. Reviewed published reports reveal that of the 15 patients of whom clinical presentation was discussed, 7 (49 percent) initially had no symptoms referable to the cardiovascular system.\textsuperscript{10} As was true in our patient, when symptoms did occur, pleural and pericardial effusions were common. Electrocardiographic changes also were nonspecific with low voltage reported in 6 patients and some degree of atrioventricular block in 3 of 14. In some instances, the only clinical indication of a cardiac tumor was intractable con-
gestive heart failure without obvious cause.14,15,23,25

A collection of imaging studies were performed on these patients, but the results rarely prompted a concern for cardiac lymphoma. Chest radiographs were nonspecific; an enlarged cardiac silhouette was noted in 7 patients and pleural effusion in 5.10,14,18,23,25,26 The delay in considering NHL in the differential diagnosis of an AIDS patient with shortness of breath and effusions is understandable when one considers the rare finding of cardiac lymphoma in patients with enlarged cardiac silhouettes. In a retrospective study by Reynolds et al.28 of 14 AIDS patients presenting with large pericardial effusions 8 had evidence of mycobacterial disease. Cardiac lymphoma was found in one patient, but four others had KS. This and other studies serve to emphasize the malignancy most associated with cardiac disease in HIV-infected patients is KS. Like NHL, KS is most likely to be widespread by the time it is found to involve the heart.29,30 Autopsy studies have shown that KS most commonly invades the epicardium and, more rarely, the myocardium or pericardium.20,31 In contrast to NHL, KS of the heart often is asymptomatic. Ironically, the presence of disseminated KS does not ensure that neoplastic cardiac complications are due to KS. Like the report of our patient, Guarner et al.14 described two homosexual patients with widely scattered KS who at autopsy were found to have cardiac NHL.

In non-AIDS-related cardiac NHL, Chow et al.19 found that gallium scanning was useful in suggesting the presence of cardiac tumors. Although we can make no inference regarding the sensitivity or specificity of this technique, the three patients with AIDS-related cardiac lymphoma who underwent this procedure had intense myocardial uptake.11,15,22 Echocardiograms and CT scans of the chest were abnormal in all patients in whom they were obtained, with some instances demonstrating large pericardial effusions and others showing frank mass lesions. In a single case report, magnetic resonance imaging of the chest proved useful in delineating the extrapericardial extent of tumor.16

Cardiac tamponade is a distinctly unusual feature of AIDS-related NHL.12,25,29 In each of three previous reports, patients presented with rapid development of shortness of breath as their chief complaint, and they were found to have pleuropericardial effusions, congestive heart failure, and abnormal echocardiograms. Similar to our case, emergency pericardiocentesis yielded immediate benefit in at least one instance.23 Although 500 ml of chylous material was drained from the pericardial space, in this report no malignant cells were recovered. A diagnosis of high-grade lymphoma was established by biopsy of a right atrial mass via a femoral vein approach.

In a handful of instances has the diagnosis of cardiac lymphoma been made antemortem.12,16,23,25,26,32 As was true in our patient's case, the reported diagnosis of the disease was made during life either by cytologic examination of pericardial or pleural fluid or by endomyocardial biopsy, allowing for initiation of chemotherapy (Table 2). After diagnosis, survival is generally less than 6 months. The good response to chemotherapy seen in our patient, however, is not unique. Kelsey et al.30 treated a patient with cyclophosphamide, doxorubicin, vincristine, and prednisone, and at the time of their report 12 months post-completion of chemotherapy, the patient was still in remission. In the three reported cases where cardiac tamponade developed, the use of chemotherapy resulted in normalization of symptoms and echocardiographic findings within a week of beginning therapy.12,23 Several factors have been shown to imply poor prognosis in AIDS-related NHL, including (1) history of AIDS prior to diagnosis of lymphoma; (2) CD4 cells less than 200×10⁶/L; (3) bone marrow involvement; and (4) declining performance status.9,33 As shown by Levine et al.34 the median survival of patients with none of these risk factors was 11.3 months compared with 4.0 months in those with poor prognostic indicators.

To summarize, the differential diagnosis of cardiac abnormalities in HIV-infected subjects is broad and includes opportunistic infections, toxic effects of medications, and KS. Congestive heart failure, arrhythmias, or cardiac tamponade may be sentinel signs suggesting yet another complication of AIDS, cardiac involvement by NHL.35 Only with a high clinical awareness of this entity and the judicious diagnostic investigation of patients with cardiac involvement can antemortem diagnosis of this potentially treatable manifestation of AIDS be made. Although non-specific, chest radiographs and electrocardiograms should be done as clinically indicated for evaluation of specific problems in patients with unexplained dyspnea, tachypnea, or other chest complaints. Echocardiography is the most useful noninvasive procedure and should be done if previous studies are inconclusive or indicative of a cardiac problem such as an enlarged heart that needs further clarification. The presence of luminal masses, thickened

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**Table 2—Treatment of Cardiac Lymphoma**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Author</th>
<th>Diagnostic Procedure</th>
<th>Therapy</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gill et al12</td>
<td>Pericardial biopsy</td>
<td>Surgery only</td>
<td>&lt;1 mo</td>
</tr>
<tr>
<td>2</td>
<td>Gill et al12</td>
<td>Gastric biopsy</td>
<td>M-BACOD, cranial radiation</td>
<td>1.5 mo</td>
</tr>
<tr>
<td>3</td>
<td>Gill et al12</td>
<td>Lymph node and bone marrow biopsy</td>
<td>HD ara-C, HD MTX, CTX</td>
<td>6 mo</td>
</tr>
<tr>
<td>4</td>
<td>Goldfarb et al16</td>
<td>Transvenous right atrial biopsy</td>
<td>PRD, MTX, Doxo, CTX, VP-16</td>
<td>&lt;1 wk</td>
</tr>
<tr>
<td>5</td>
<td>Andress et al23</td>
<td>Transvenous right atrial biopsy</td>
<td>CHOP</td>
<td>5 mo</td>
</tr>
<tr>
<td>6</td>
<td>Helfand25</td>
<td>Pericardial biopsy</td>
<td>Vincristine</td>
<td>&lt;1 wk</td>
</tr>
<tr>
<td>7</td>
<td>Kelsey et al26</td>
<td>Thoracentesis</td>
<td>CHOP</td>
<td>&gt;12 mo</td>
</tr>
</tbody>
</table>

*Abbreviations: M-BACOP, methotrexate, leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; ara-C, cytosine arabinoside; MTX, methotrexate; CTX, cyclophosphamide; PRD, prednisone; Doxo, doxorubicin; VP-16, etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; HD, high dose.
myocardium or pericardial effusions may suggest neoplastic complications. Gallium scintigraphy also may be a useful adjunctive radiographic tool. As suggested by others, when unexplained pericardial effusions are detected in the symptomatic patient, attempts should be made to obtain fluid or tissue for culture and histologic preparation. When cardiac tamponade is present, drainage procedures should be performed for diagnostic and therapeutic purposes. The importance of establishing a timely diagnosis is highlighted by occasional favorable responses to multiagent chemotherapy.

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Delayed Onset Adult Respiratory Distress Syndrome in Babesiosis*

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