Non-Hodgkin's Lymphoma of the Heart in Patients Infected with Human Immunodeficiency Virus

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Summary: A case of HIV-associated cardiac non-Hodgkin's lymphoma (NHL) is described, and the epidemiologic and clinicopathologic features of 21 cases previously reported in the literature are analyzed. All patients were homosexual males, and the cardiac NHL was the first acquired immune deficiency syndrome-defining condition in the majority. Patients were referred with nonspecific clinical findings including dyspnea and tachycardia, but rapid progression of cardiac dysfunction was frequent after symptoms appeared. Echocardiography constitutes the most useful noninvasive procedure in the diagnosis of cardiac NHL. Most of the patients had disseminated disease at initial presentation; pathologically, the lymphomas were of B lymphocyte origin and of high-grade subtypes. Prognosis of HIV-associated cardiac NHL is generally poor, although clinical remission has been observed with combination chemotherapy. Cardiac lymphomas in HIV-associated patients are typically high-grade and often disseminate early. Although the prognosis is poor, patients in whom dissemination has not occurred could have longer survival under systemic chemotherapy.

Key words: human immunodeficiency virus, non-Hodgkin's lymphoma of the heart, cardiac manifestations

Introduction

The frequency of non-Hodgkin's lymphomas (NHL) in patients with acquired immune deficiency syndrome (AIDS) is

increasing and is estimated to be 25 to 60 times greater than expected in the general population.¹ NHLs are observed in 5 to 10% of patients infected with human immunodeficiency virus (HIV) and constitute the first manifestation of AIDS in 3 to 4% of new cases.² The proportion of patients with extranodal involvement at presentation ranged between 70 and 85%; however, AIDS-associated NHLs have been reported to occur at virtually every anatomical site.³ Malignant lymphoma of the heart has rarely been observed in HIV-infected individuals and may occur as a primary cardiac tumor or as a secondary localization in disseminated disease.⁴⁻¹⁹ Because clinical presentation is nonspecific, the possibility of misdiagnosis exists if NHL is not considered in the differential diagnosis of heart disease in an HIV-infected patient. We report the clinical course of a patient with HIV infection and cardiac lymphoma and review the cases previously reported in the literature.

Case Report

A 31-year-old homosexual man was found to be HIV-positive in 1989. His medical history included chronic persistent hepatitis B. Until 1995, the patient was asymptomatic and his CD4 count was 540/mm³. In March 1995 he complained of shortness of breath and palpitations. Blood pressure was 130/70 mmHg, and pulse rate was 100/min. No cardiac abnormalities were seen on examination. The electrocardiogram (ECG) showed supraventricular tachycardia; chest roentgenogram and echocardiogram were normal. Oral digoxin was started, then replaced by disopyramide because of atrial flutter. One month later, the patient was admitted to our facility because of severe dyspnea, low-grade fever, and weight loss of 4 kg. He had persistent tachypnea with a respiratory rate of 25 to 30/min. Physical examination disclosed typical superior vena cava syndrome with jugular venous distension, edema of the face, neck, and arms, and collateral circulation of the chest; hepatomegaly and axillary lymphadenopathy were found. Hemoglobin was 11.1 g/dl, leukocyte count 4,100/mm³ with 62% of polynuclear neutrophils, platelet count 220,000/mm³, and CD4 count 258/mm³. Electrocardiography revealed atrial flutter. The echocardiogram displayed a bulky lobulated mass in the right atrium, which was dilated, with extension into the

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superior vena cava (Fig. 1). Right heart catheterization showed elevated right atrial and superior vena cava pressures. Transvenous biopsy of the mass yielded whitish, soft tissue fragments. On light microscopic examination, the tumor was highly cellular, composed of large, irregular, round to ovoid cells which possessed abundant, deeply basophilic cytoplasm. The lymphoid nature and B-cell phenotype were confirmed immunohistochemically by LN-2 and L26 positivity; in addition, few neoplastic cells expressed bcl-2. The tumor was classified as a large-cell immunoblastic lymphoma (working formulation). Using in situ hybridization for EBER RNA transcripts, EBV DNA had been detected in nearly all the neoplastic cells. Magnetic resonance imaging (MRI) of the heart demonstrated a tumor mass, 5 cm in size, infiltrating the external wall of the right atrium and extending into the superior and inferior vena cava (Fig. 2). Additional staging studies including computed tomography (CT) scan of the head, chest, and abdomen, and lumbar puncture were negative for systemic lymphoma, but tumor cells were found in the bone marrow. Thus, the lymphoma was staged IVB according to the Ann Arbor system. The patient was treated with two cycles of CHOP (vincristine, 2 mg intravenously on Day 1; cyclophosphamide, 750 mg/m² intravenously on Day 2; doxorubicin, 50 mg/m² intravenously on Day 3; and methyl-prednisolone, 60 mg/m² intravenously on Days 1 through 7). As there was no change in the tumor's size, combination chemotherapy was switched to ACVB (doxorubicin, cyclophosphamide, bleomycin, eldisine). After four cycles of ACVB, restaging studies showed absence of bone marrow involvement but only a tiny decrease of the mass. The patient progressed into severe biventricular cardiac failure and his general status rapidly deteriorated. He died after a course of high-dose methotrexate. At autopsy, the left and right lungs were markedly edematous, weighing 900 and 980 g, respectively. There were multiple firm, fleshy, pericardial

nodules measuring 0.5 to 1.5 cm in diameter. The right atrium and ventricle were dilated whereas the left cavities appeared normal. The valves and the coronary and pulmonary arteries were normal. A large tumor mass, 6 × 5 cm in size, was found within the posterolateral wall of the right atrium, completely infiltrating the endocardium, myocardium, and epicardium, with involvement of the ostium of the superior vena cava; in addition, partially necrotic tumor nodules were seen within the wall of the superior vena cava (Fig. 3). The lungs were devoid of nodules or tumor. Other organ systems were not studied.

Review of the Literature

Our review of the literature identified 21 cases of cardiac NHL associated with HIV infection.⁴⁻¹⁹ Relevant clinical information on these cases and from our case report are summarized in Table I. All patients were men; the average age was 39 years. Risk factors for HIV infection included homosexuality (14 cases), bisexuality (4 cases), heterosexuality (2 cases), and intravenous drug use (2 cases). HIV infection was diagnosed in 14 patients at the time of presentation with lymphoma. Of the other patients, half had history of a previous AIDS-defining condition (three patients had concomitant Kaposi's sarcoma and one had lymphoid interstitial pneumonitis).

Cardiac manifestations included dyspnea (14 cases), right-sided heart failure (4 cases), total heart failure (3 cases), chest pain (4 cases), tamponade (4 cases), and arrhythmias (3 cases). Dissemination was present at the time of diagnosis of NHL in most (15) patients. Only six patients had primary lymphoma involving only the heart and the pericardium.

Findings of chest radiographs were nonspecific, showing enlarged cardiac silhouette (9 cases) and pleural effusion (8 cases). The ECG revealed low voltage (9 cases), sinus tachy-

FIG. 1 Transoesophageal echographic image of the intra-atrial mass. LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle.

FIG. 2 Coronal magnetic resonance image after intravenous gadolinium injection. The lymphoma is seen as a voluminous lobulated mass arising from the external wall of the right atrium with extension into the superior vena cava.

FIG. 3 Coronal section of heart showing a voluminous tumor surrounded by multiple nodular masses with necrotic tumoral lesions in the superior vena cava (indicated by arrows). RA = right atrium, SVC = superior vena cava.

cardia (7 cases), arrhythmias or atrioventricular block (4 cases). The echocardiograms were more informative, demonstrating lesions suggestive of cardiac lymphomas. In 10 cases, they revealed a frank multilobulated mass and the tumor was mostly located in the right atrium, occasionally in the right ventricle, and rarely in the left cavities. Unique and multiple nodules were also detected within the cardiac wall (4 cases). Other aspects were reported, especially infiltrative forms of cardiac lymphoma: pericardial effusion (9 cases), limited thickening of the pericardium or the cardiac wall (9 cases), and decrease of the cardiac kinetic. The CT scans and MRI were performed in a limited number of patients and were useful in evaluating tumor extent.

According to the working formulation classification scheme, a high percentage of cardiac lymphomas were of B lymphocyte origin and of intermediate- to high-grade quality. Nine were small noncleaved cell lesions, six were immunoblastic, and three were large cell lesions. Only one patient had cardiac lymphoma of T lymphocyte origin. Eight patients were not treated because of severe degradation of their clinical status. Eleven patients were treated with systemic chemotherapy alone, one with surgery alone, one with both chemotherapy and surgery; one patient refused treatment. Systemic chemotherapy consisted of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for 4 of the 12 patients who received chemotherapy. Information regarding survival

time after diagnosis of NHL was available in 13 cases and ranged from 1 week to 12 months.

Discussion

We describe a case of a homosexual man infected with HIV who developed a cardiac lymphoma as the first manifestation of AIDS, and hypothesize that the neoplastic involvement of the heart occurred in two different patterns that followed one another. Initially, the lesion developed by infiltration within the wall of the right atrium and produced supraventricular paroxysmal tachycardia that progressed to atrial flutter. Second, it grew dramatically into a voluminous tumor that almost completely obstructed the right atrium, leading to a superior vena cava syndrome. The patient had disseminated lymphoma since bone marrow involvement was found at initial presentation. Cases of cardiac lymphoma are very uncommon but are encountered with increasing frequency; this is certainly due to more judicious diagnostic investigations of HIV-associated patients with cardiac symptoms and to a better awareness of this entity. Epidemiologic features noted in the 22 patients with cardiac NHL correlate with those described in large-scale studies of HIV-associated NHL with regard to the average age and the predominance of homosexual men.^{1, 20} In HIV patients, the occurrence of NHL does not correlate closely with an advanced stage of immunosuppression; this finding is particularly true for HIV-infected patients with cardiac lymphomas.

Clinical manifestations of cardiac NHL are nonspecific and include shortness of breath, cardiac heart failure, and tamponade. In fact, cardiac lymphoma as well as other cardiac complications of AIDS (opportunistic infections, congestive myocardiopathy, Kaposi's sarcoma) may present in a similar manner.^{21, 22} In addition, symptoms may not be due to the cardiovascular system and may be misinterpreted to be the result of noncardiac causes; this is especially true of the respiratory system because of the high incidence of multiple opportunistic infections in this organ. Finally, because of the severity of illness and the difficulty of diagnosis, many of the cases reported were discovered only at autopsy. Chest radiographs and ECG changes are nonspecific. Echocardiography is the corner-stone of the diagnosis, revealing intracardiac mass or nodular lesions within the three cardiac tunics. However, in infiltrative forms of cardiac NHL, it may underestimate the extent of myocardial involvement. Magnetic resonance imaging proves useful in delineating the extrapericardial tumor extension. In addition, CT scans and MRI of the chest provided a complete examination of the heart and the thorax. Prognosis of HIV-associated cardiac NHL is generally poor with very limited survival in most cases. Our data indicate that cardiac lymphomas in patients infected with HIV are most commonly high-grade disseminated lymphomas, almost always of B cell origin. In addition, prognostic factors must be taken into account in evaluating survival in the care of patients with HIV-associated NHL. A CD4 count of <100 cells/mm³, the pres-

TABLE 1 Clinicopathologic features of HIV-associated cardiac non-Hodgkins lymphoma (NHL)

Case no. (Ref.)	Age (years) /sex	HIV risk factor	Clinical stage of HIV disease	Cardiac manifestations
1 (4)	42/M	Homosexuality	AIDS(KS)	Dyspnea, tamponade
2 (5)	40/M	Homosexuality	AIDS (LIP)	Dyspnea, chest pain, tamponade
3 (6)	48/M	Homosexuality	NK	Congestive heart failure
4 (6)	51/M	Homosexuality	NK	Arrhythmia, systolic murmur, hypertension
5 (7)	33/M	IV drug use	Symptomatic	Dyspnea, superior vena cava syndrome
6 (8)	34/M	IV drug use	NK	Congestive heart failure
7 (9)	36/M	Bisexuality	NK	Dyspnea, cyanosis
8 (10)	71/M	Heterosexuality	Asymptomatic	Right-sided heart failure
9 (11)	37/M	Bisexuality	NK	Chest pain
10 (11)	39/M	Homosexuality	NK	None
11 (11)	27/M	Homosexuality	NK	Acute dyspnea, tamponade
12 (11)	47/M	Bisexuality	NK	Acute dyspnea, tamponade
13 (12)	30/M	Homosexuality	NK	Dyspnea, right-side heart failure, chest pain
14 (13)	41/M	Homosexuality	AIDS (KS)	None
15 (13)	38/M	Homosexuality	AIDS(KS)	Dyspnea
16 (14)	35/M	Homosexuality	NK	Dyspnea, hypotension
17 (15)	37/M	Homosexuality	NK	Arrhythmia
18 (16)	30/M	Homosexuality	NK	Dyspnea, congestive heart failure
19 (17)	48/M	Heterosexuality	NK	Dyspnea, tachycardia
20 (18)	44/M	Homosexuality	NK	Dyspnea, pleuretic pain
21 (19)	56/M	Bisexuality	Asymptomatic	Dyspnea, tachycardia, chest pain, jugular venous distension
22 (PR)	31/M	Homosexuality	Asymptomatic	Arrhythmia, dyspnea, superior vena cava syndrome

Abbreviations : HIV = human immunodeficiency virus; M = male; AIDS = acquired immune deficiency syndrome; IV = intravenous; PR = present report; um, LA = left atrium; RV = right ventricle; LV = left ventricle; MOI = multiple organ involvement; SNC = small noncleaved; MTX = methotrexate; Doxo = cyclophosphamide, vincristine, bleomycin.

ence of any previous AIDS-defining condition, the presence of bone marrow involvement, and a Karnofsky scale score of <70% constitute the major factors of poor prognosis.^{23, 24} Systemic chemotherapy is the therapeutic mainstay in cases of NHL in HIV-infected patients. However, at present, optimal combination chemotherapy for cardiac lymphomas in HIV-infected patients remains unknown. Intensive combination chemotherapy may prolong survival among patients with limited NHL and without poor prognostic factors, while low-dose chemotherapeutic regimens may be more efficient for others.

Conclusions

Although NHL is a frequent complication of HIV-infection, cardiac NHL has rarely been reported in HIV-associated patients. Signs and symptoms of cardiac NHL are nonspecific and can lead to initial misdiagnosis. Echocardiography is the diagnostic mainstay in cases of cardiac NHL; presence of an intracardiac mass or nodular lesions within the cardiac wall should raise the suspicion of malignancy and is a clear indication for prompt cardiac biopsy. Cardiac lymphomas in HIV-

Extent of cardiac involvement	Site of dissemination	Histologic classification	Treatment	Outcome
Pericardium	None	Immunoblastic	Novantrone, CTX, VP-16, vincristine, prednisone	Died 12 months after dg
RA	None	SNC	CTX, Doxo, vincristine, prednisone	Died 3 months after dg
Massive endocardial and myocardial involvement	MOI	Immunoblastic	CHOP	Alive at time of this report
RA	MOI	Large-cell	None	NA
RV, superior vena cava	Liver, pleura	NA	Refused	Died at dg
Myocardial involvement	None	Immunoblastic	None	Died at dg
Pericardium, RA	MOI	SNC	None	NA
RA, RV, pericardium	NA	Centroblastic	None	Died at dg
LV, interventricular septum, pericardium	MOI	SNC	BACOP	Died 1 month after dg
Pericardium, myocardium	MOI	SNC	M-BACOD	Died 1 month after dg
Pericardium	MOI	SNC	Surgery	Died after surgery
Pericardium	Liver, skin	SNC	Ara-C, MTX, cytoxan	Died 6 months after dg
RA, LA, RV, LV, pericardium	Pleura	SNC	Prednisone, MTX, Doxo, VP-16, CTX	Died after one cure
Massive epicardial and myocardial involvement	None	Immunoblastic	None	NA
Pericardium	None	SNC	None	NA
RV	None	SNC	Vincristine	Died at dg
Interatrial, AV septum	Lymph nodes, bone marrow	Lymphoblastic	None	Died at dg
Epicardial, myocardial involvement	Lung, skin	Large cell	None	Died 6 weeks after dg
RA, RV, pericardium	Lymph nodes, thymus	Immunoblastic	Surgery and chemotherapy	Died 8 months after dg
RA, interatrial septum	Lymph nodes, pleura	Large cell	CHOP	Died 12 months after dg
RA, LA, RV, interatrial septum	Lymph nodes, pleura	T-cell NHL	CHOP	Alive at time of this report
RA, superior and inferior vena cava	Bone marrow	Immunoblastic	CHOP ACVB, MTX	Died 5 months after dg

NK = not known at onset of NHL; KS = Kaposi's sarcoma; LIP = lymphoid interstitial pneumonitis; NA = not available; dg = diagnosis; RA = right atrium; Doxo = doxorubicine; CTX = cyclophosphamide; VP 16 = etoposide; CHOP = cyclophosphamide, doxorubicine, vincristine, prednisone; ACVB = adriamycin.

associated patients are typically high-grade and often disseminate early. Although the prognosis is poor, patients could have longer survival with systemic chemotherapy.

References

- Beral V, Peterman T, Berkelman R, Jaffe H: AIDS-associated non-Hodgkin lymphoma. *Lancet* 1991;337:805–809
- Gail MH, Pluda JM, Rabkin CS, Biggar RJ, Goedert JJ, Horm JW, Sondik EJ, Yarchoan R, Broder S: Projections of the incidence of non-Hodgkin's lymphomas related to acquired immunodeficiency syndrome. *J Natl Cancer Inst* 1991;83:695–701
- Raphael M, Gentilhomme O, Tulliez M, Byron P-A, Diebold J: Histopathologic features of high-grade non-Hodgkin's lymphomas in acquired immunodeficiency syndrome. *Arch Pathol Lab Med* 1991;115:15–20
- Aboulafia DM, Bush R, Picozzi VJ: Cardiac tamponade due to primary pericardial lymphoma in a patient with AIDS. *Chest* 1994; 106:1295–1299
- Andress JD, Polish LB, Clark DM, Hossack KF: Transvenous biopsy of a cardiac lymphoma in an AIDS patient. *Am Heart J* 1989;118:421–423

6. Balasubramanyam A, Waxman M, Kazal HL, Lee MH: Malignant lymphoma of the heart in acquired immune deficiency syndrome. *Chest* 1986;90:243–246
7. Beltinger J, Schonenberger R: Upper influx distension in a patient with HIV: Unusual localization of an HIV-associated lymphoma. *Schwz Rundsch Med Prax* 1995;84:76–81
8. Constantino A, West TE, Gupta M, Loghmanee F: Primary cardiac lymphoma in a patient with acquired immune deficiency syndrome. *Cancer* 1987;60:2801–2805
9. Dalli E, Quesada A, Paya R: Cardiac involvement by non-Hodgkin's lymphoma in acquired immune deficiency syndrome. *Int J Cardiol* 1990;26:223–225
10. Denis J, Hery B, Crépin V, Guillemot L, Guerzider P: Lymphome malin tumoral de localisation cardiaque dans l'infection à virus de l'immunodéficience humaine; diagnostic par échocardiographie. *Arch Mal Coeur* 1995;88:507–510
11. Gill PS, Chandraratna AN, Meyer PR: Malignant lymphoma: Cardiac involvement at initial presentation. *J Clin Oncol* 1987;5: 21–24
12. Goldfarb A, King CL, Rosenzweig BP, Feit F, Kamat BR, Rumancik WM, Kronzon I: Cardiac lymphoma in the acquired immunodeficiency syndrome. *Am Heart J* 1989;118:1340–1344
13. Guarner J, Brynes RK, Chan WC, Birdsong G, Herzler G: Primary non-Hodgkin's lymphoma of the heart in two patients with the acquired immunodeficiency syndrome. *Arch Pathol Lab Med* 1987; 111:254–256
14. Helfand J: Cardiac tamponade as a result of American Burkitt's lymphomas of the heart and pericardium. *Conn Med* 1990;54: 186–189
15. Herrero J, Artero A, Reedondo A, Vicente R, Guix J, Alcacer F: Linfoma cardiaco como presentacion inicial de un SIDA. *Ann Med Interna* 1991;8:52
16. Holladay AO, Siegal RJ, Schwartz D: Cardiac malignant lymphoma in acquired immunodeficiency syndrome. *Cancer* 1992;70: 2203–2207
17. Horowitz MD, Cox MM, Neibart RM, Blaker AM, Interian A Jr: Resection of right atrial lymphoma in a patient with AIDS. *Int J Cardiol* 1992;34:139–142
18. Kelsey RC, Saker A, Morgan M: Cardiac lymphoma in a patient with AIDS. *Ann Intern Med* 1991;115:370–371
19. Pousset F, Le Heuzey J-Y, Pialoux G, Rinaldi J-P, Hernigou A, Mousseaux E, Toty L, Dupont B, Guize L: Cardiac lymphoma presenting as atrial flutter in an AIDS patient. *Eur Heart J* 1994;15: 862–864
20. Orams GI, Grufferman S: Epidemiology of HIV-associated non-Hodgkin's lymphoma. *Cancer Surv* 1991;10:916–922
21. Acierno LJ: Cardiac complications in acquired immunodeficiency syndrome (AIDS): A review. *J Am Coll Cardiol* 1989;13: 1144–1154
22. Kaul S, Fishbein MC, Siegel RJ: Cardiac manifestations of acquired immune deficiency syndrome: A 1991 update. *Am Heart J* 1991;122:535–545
23. Ziegler JL, Beckstead JA, Volberding PA, Abrams DI, Levine AM, Lukes RJ, Gill PS, Burkes RL, Meyer PR, Metroka CE, Mouradian J, Moore A, Riggs SA, Butler JJ, Cabanillas FC, Hersh E, Newell GR, Laubenstein LJ, Knowles D, Odajnyk C, Raphael B, Koziner B, Urmacher C, Clarkson BD: Non-Hodgkin's lymphoma in 90 homosexual men: Relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome. *N Engl J Med* 1984;311: 565–570
24. Levine AM, Sullivan-Halley J, Pike MC, Rarick MU, Loureiro C, Bernstein-Singer M, Willson E, Brynes R, Parker J, Rasheed S, Gill PS: HIV-related lymphoma: Prognostic factors predictive of survival. *Cancer* 1991;68:2466–2472