Symptomatic Metastatic Right Atrial Lymphoma in a Patient With AIDS Presenting With Pulmonary Embolization

Navneet Lather, MD, MPH,* Mohamed Islam, MBBS,† Icilma V. Fergus, MD, FACC†

*Department of Medicine and †Division of Cardiology, Columbia University, Harlem Hospital Center, New York, NY

Tumors involving the heart are rare, and the majority of them are benign. Secondary lymphoma with localization to the heart is the third most common malignant heart tumor and is more common, by far, than primary cardiac lymphomas. In patients with human immunodeficiency virus, the risk of development of systemic lymphoma is 60 to 200 times higher than in the general population. Symptoms usually consist of chest pain and dyspnea. Patients can also present with obstructive symptoms, based on the location and size of the tumor, and signs such as elevated jugular venous pressure, peripheral edema, ascites, and hepatomegaly. Transthoracic echocardiography is the initial modality of choice for diagnosis of cardiac lymphomas because it is readily available and helps localize the tumor, but transesophageal echocardiography and magnetic resonance imaging remain the best tests for evaluation. Treatment consists primarily of chemotherapy, and anticoagulation can be used in certain cases where embolization of the tumor is likely. This case review describes a 37-year-old man with past medical history significant for herpes zoster and stage 1 syphilis who presented with complaints of weight loss, intermittent fevers, and vague chest pains of 1-month duration.
[Rev Cardiovasc Med. *2008;9(4):275-279*]

Key words: Right atrial mass • B-cell lymphoma • AIDS • Pulmonary embolism

A 37-year-old man with distant medical history of herpes zoster and stage 1 syphilis, active polysubstance abuse, and irregular follow-up presented to the emergency department with complaints of intermittent fevers, weight loss, and vague chest pains of 1-month duration. He had a temperature of 101°F, heart rate of 128 beats/min, blood pressure of 100/66 mm Hg, and respiratory rate of 16 breaths per minute. His oxygen saturation was 98% on room air. Examination was significant for generalized lymphadenopathy and oral thrush.

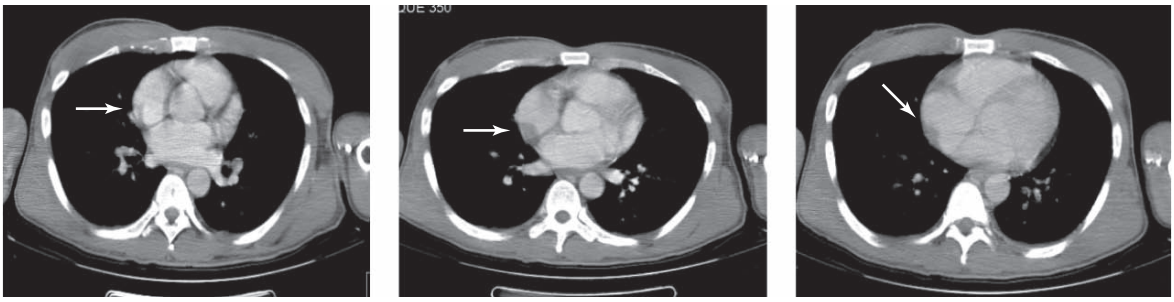

Figure 1. *A contrast-enhanced computed tomography scan of the chest shows a filling defect in the right atrium measuring 2.2 × 2.1 cm in the transverse section invading the atrial wall.* www.medreviews.com

Oral swab testing was positive for human immunodeficiency virus (HIV) infection. His CD4 count was 166, and his viral load was more than 500,000 copies. The evaluation for the chest pains suggested a nonischemic etiology. A diagnosis of acquired immunodeficiency syndrome (AIDS) was made, and the patient was discharged home to follow up as an outpatient in the infectious disease clinic with initiation of highly active antiretroviral therapy (HAART).

Outpatient follow-up 1 week later in the infectious disease clinic revealed persistent fevers, new onset pain in the right calf, and intermittent headaches. His vital signs were blood pressure of 90/65 mm Hg, heart rate of 125, respiratory rate of 22 breaths per minute, and temperature of 104°F. The patient continued to have generalized lymphadenopathy with new findings of visible inflammation of the right leg and negative signs of meningitis. He was readmitted to the hospital to rule out underlying lymphoma. Heparin was started prior to obtaining ultrasound of the legs for presumed deep vein thrombosis. Doppler ultrasound of the right leg was negative for deep vein thrombosis. Lumbar puncture was negative for meningitis. Laboratory data were consistent with normocytic anemia and lymphopenia. The lactate dehydrogenase (LDH) levels were elevated, at 550 U/L.

The hematology and oncology service recommended that clinicians obtain a bone marrow and lymph node biopsy. The patient subsequently underwent a computed tomography scan (CT) of the chest and abdomen, which showed a small filling defect in the right atrium measuring 2.2 × 2.1 cm, along with diffuse lymphadenopathy in the mediastinum and abdomen and trivial pericardial effusion. It also showed the presence of multiple pleural and subpleural nodular opacities of variable sizes suggestive of the embolic process (Figure 1). Anticoagulation was started again after initial discontinuation.

A transthoracic echocardiogram (TTE) performed on the same day did not show any mass in the right atrial cavity. The patient continued to be hypotensive on the subsequent days and kept receiving intravenous fluids to maintain blood pressure. On the seventh hospital day, he was found to be in acute respiratory distress and had developed a harsh systolic murmur at the left lower sternal border. He was also noted to have a right basal infiltrate and increasing cardiac silhouette on the chest x-ray. Intravenous antibiotics for hospital-acquired pneumonia were started. The patient underwent a repeat chest CT scan to rule out worsening pulmonary embolization. Again, the scan showed the right atrial mass, which had increased in size—despite anticoagulation in the past—to 5.0 × 3.0 cm, and there was interval appearance of moderate pericardial effusion. The CT scan again showed the presence of multiple pleural and subpleural opacities of variable sizes, which had increased in size from the previous study (Figure 2).

A TTE performed at that time, again to rule out infective endocarditis, showed a right atrial mass measuring 5.0 × 3.1 cm. The mass was attached to the superior aspect of the right atrium and appeared to infiltrate the wall. TTE also showed right ventricular dilatation, tricuspid regurgitation, and moderate pericardial effusion without any evidence of a tamponade. The estimated pulmonary artery pressure was 46 mm Hg, and there was no evidence of vegetations (Figure 3).

The swelling of the right calf and the high-grade fevers persisted. The platelet count had significantly decreased since admission; therefore anticoagulation had to be discontinued. The LDH levels increased to 1540 U/L. The histopathology on biopsy of the bone marrow, enlarged left axillary lymph node, and right gastrocnemius muscle showed infiltration of the malignant cells in the bone marrow, lymph node, and gastrocnemius muscle, which stained positive for CD20 and

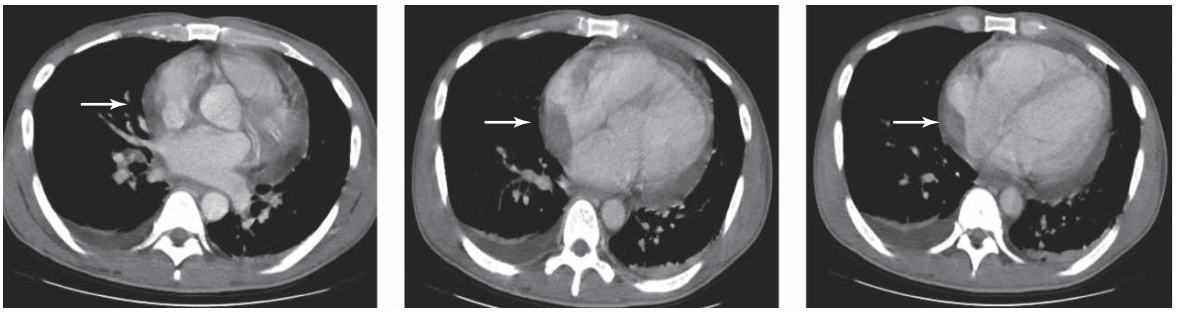

Figure 2. *Contrast-enhanced computed tomography scan of the chest shows the presence of a filling defect in the right atrium measuring 5.0 × 3.0 cm.* www.medreviews.com

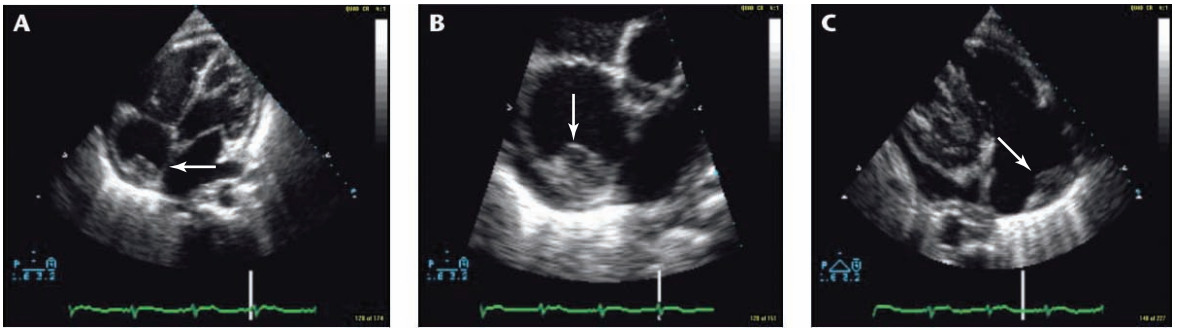

Figure 3. *Apical view of the heart* **(A)** *showing the tumor attached to the right atrial wall measuring 5.0 × 3.1 cm. The magnified view shows invasion into the wall* **(B)**. *The right ventricular inflow view shows the presence of the mass* **(C)**. www.medreviews.com

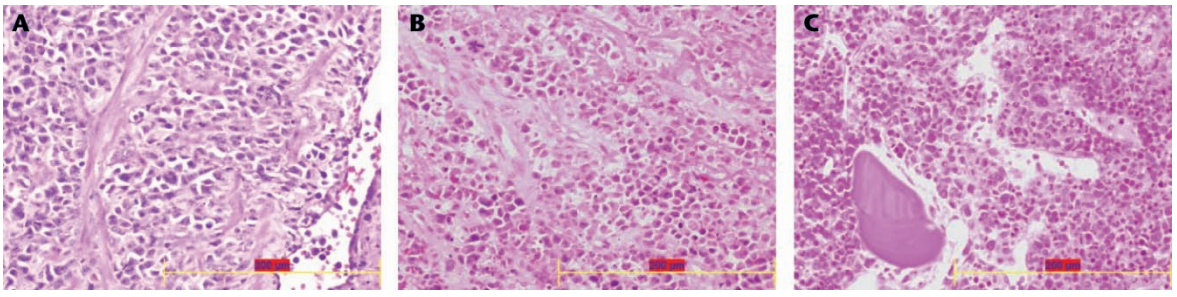

Figure 4. *This histopathology shows magnified views of the lymph node* **(A)**, *muscle* **(B)**, *and bone marrow* **(C)**, *showing the infiltration by the malignant cells with an increased nuclear-to-cytoplasmic ratio that is positive for CD20 and negative for CD3, which is consistent with B-cell lymphoma* **(B)**. *These images also demonstrate the predilection for tumor cells to invade blood vessels.* www.medreviews.com

Ki-67, and it provided confirmation of aggressive B-cell lymphoma (Figure 4).

The patient was started on chemotherapy with intravenous steroids and cyclophosphamide, along with allopurinol to prevent tumor lysis syndrome. His condition, however, continued to deteriorate, and he developed increasing dyspnea related to pericardial effusion and resistant hypotension, which was not responding to intravenous fluids. The patient was transferred to the intensive care unit and began vasopressor support. He was intubated for airway protection. However, he was noted to have severe lactic acidosis and became unresponsive on the 15th hospital day. All resuscitation measures failed to revive him.

Discussion

Tumors involving the heart, benign or malignant, are rare, and the majority of them are benign. The most common primary benign cardiac tumor is myxoma, and the most common primary malignant cardiac tumors are usually sarcomas followed by lymphomas.[1] Only about 2% of cardiac tumors are primary cardiac lymphomas. Secondary lymphoma

with localization to the heart is the third most common malignant heart tumor, seen in 8% to 26% of autopsy cases, and is more common by far than primary cardiac lymphomas.[2] Both primary and secondary cardiac lymphomas occur more commonly in immunocompromised individuals.[3] In HIV-infected patients, the risk of development of systemic lymphoma is 60 to 200 times higher than in the general population.[4] AIDS-related diffuse large B-cell lymphoma is the most common histology type and usually affects patients with advanced immunodeficiency. Kaposi sarcoma is another common malignancy associated with AIDS and other immunocompromised conditions, and it usually presents with associated mucocutaneous involvement.[5] Lymphoma very often presents with widespread tumors, with an approximately 80% predominance of extranodal localizations. The central nervous system, bone marrow, and gastrointestinal tract are the most frequently involved sites, but other sites can also be involved.[6]

The spread to the heart is usually hematogenous, although direct spread from the mediastinum can also occur.[7] Metastatic cardiac lymphomas are rarely diagnosed based on symptoms but usually discovered on autopsy. Symptoms usually consist of chest pain and dyspnea, as in the patient described here.[7,8] They can also present with obstructive symptoms, based on the location and size of the tumor, and signs such as elevated jugular venous pressure, peripheral edema, ascites, and hepatomegaly. Other associated signs are pericardial effusion with or without tamponade, arrhythmias, hypotension, and pulmonary embolization.[9-11] Acute myocardial infarction may be simulated by diffuse myocardial infiltration. Because the incidence of non-Hodgkin's lymphoma is more common in people with HIV infection, a large solitary right atrial mass in conjunction with pericardial effusion in a patient with HIV should be considered lymphoma until proven otherwise.[12] Cardiac tumor in the right atrium and pericardial effusion with pulmonary tumor embolism and obstructive symptoms, as in our patient, is a very unique presentation, making it more difficult to treat and to prevent embolization from the cardiac tumor.[13]

Diagnosis is based on clinical suspicion. Laboratory data show elevated LDH and decreasing cholesterol levels as the tumor progresses. Other laboratory findings can be related to involvement of bone marrow in metastatic lymphoma. Chest x-ray can show cardiomegaly suggestive of pericardial effusion or the right atrial enlargement.[2,14] The electrocardiogram may show tachycardia, arrhythmias, ST-T wave changes, conduction delay, and low-voltage QRS.[14] TTE is the initial modality of choice for diagnosis of cardiac lymphomas because it is readily available and helps localize the tumor.[7] It also provides information on the possibility of embolization and any obstructive mass effects due to the tumor. Transesophageal echocardiography (TEE) is considered superior to TTE and can help visualize masses missed on TTE.[15] However, in our patient, TTE clearly showed the mass in the atrial cavity attached to the superior wall and was diagnostic. Cardiac magnetic resonance imaging (MRI) has been described as the best diagnostic procedure, offering precise data on localization and size of the tumor, and it has been regarded as better than a CT scan with contrast.[15,16] T1- and T2-weighted images can identify the chemical

Main Points

- Diffuse large B-cell lymphoma related to acquired immunodeficiency syndrome is the most common histology type and usually affects patients with advanced immunodeficiency.
- Symptoms usually consist of chest pain and dyspnea. Patients can also present with obstructive symptoms, based on the location and size of the tumor, and signs such as elevated jugular venous pressure, peripheral edema, ascites, and hepatomegaly.
- Because the incidence of non-Hodgkin's lymphoma is more common in people with human immunodeficiency virus (HIV) infection, a large solitary right atrial mass in conjunction with pericardial effusion in a patient with HIV should be considered lymphoma until proven otherwise.
- The information provided by echocardiography and cardiac magnetic resonance imaging or a computed tomography scan is generally sufficient to enable physicians to make a decision regarding the need for biopsy or surgery, which can establish a definitive histological diagnosis.
- B-cell lymphomas are very sensitive to chemotherapy, and the addition of highly active antiretroviral therapy in the HIV population has improved survival.

microenvironment within the tumor and help identify the type of tumor.[16] The information provided by echocardiography and a cardiac MRI or CT scan is generally sufficient to enable physicians to make a decision regarding the need for biopsy or surgery, which can establish a definitive histological diagnosis.

Transvenous endomyocardial biopsy can provide specimens for definitive histopathological diagnosis. Infiltration into the myocardium by malignant cells that are CD20–positive and CD3–negative are characteristic of B cell lymphoma. A positive Ki-67 stain indicates an aggressive nature of the lymphoma.[12] When cardiac lymphomas are not diagnosed antemortem, the diagnosis is often made on autopsy.

Before the widespread availability of HAART, treatment outcomes for patients with HIV-associated lymphomas were very discouraging.[17] But studies have found that the tolerance for HAART is much better than for chemotherapy, and HAART is now the standard of care.[18] Treatment with the conventional CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin [vincristine], prednisone) regimen with rituximab, an anti-CD20 monoclonal antibody, has shown much promise.[12] Autologous hematopoietic stem cell transplantation with high-dose chemotherapy has become possible recently due to the availability of HAART.[19] In a phase II National Cancer Institute trial, chemotherapy with EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) showed a survival rate of 73% at 33 months.[20] B-cell lymphomas, as mentioned, are very sensitive to chemotherapy, but chemotherapy itself can make a tumor fragile via tissue necrosis and raise the risk of embolism. Sudden death has occurred early after chemotherapy due to massive pulmonary embolism.[21] Anticoagulation has been recommended along with chemotherapy to prevent embolization for certain cases.

Conclusion

Secondary heart involvement should be suspected in non-Hodgkin's lymphoma patients who present with even mild nonspecific heart symptoms. Because the incidence of non-Hodgkin's is more common in people with HIV infection, a large solitary right atrial mass in conjunction with pericardial effusion in a patient with HIV should be considered lymphoma until proven otherwise. The hematogenous route is the most common pattern of involvement, so even extrathoracic lymphomas can present with heart dissemination. Appropriate imaging procedures to evaluate the mass include echocardiography, preferably TEE. TTE, however, was conclusive and diagnostic in this patient. Treatment primarily consists of chemotherapy, and the addition of HAART helps build up hematological reserve, especially for patients with advanced immune dysfunction. ■

References

1. McAllister HA Jr, Hall RJ, Cooley DA. Tumors of the heart and pericardium. *Cur Prob Cardiol*. 1999;24:57-116.
2. Delmas-Marsalet B, Molinie V, Jary L, et al. Cardiac localization of non-Hodgkin's lymphoma: two case reports and review of the literature. *Nouv Rev Fr Hematol*. 1995;37:223-230.
3. Sanna P, Bertoni F, Zucca E, et al. Cardiac involvement in HIV-related non-Hodgkin's lymphoma: a case report and short review of literature. *Ann Hematol*. 1998;77:75-78.
4. International Collaboration on HIV and Cancer. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst*. 2000; 92:1823-1830.
5. Levison DA, Semple P. Primary cardiac Kaposi's sarcoma. *Thorax*. 1976;31:595-600.
6. Levine AM. Clinical aspects of HIV-associated lymphomas. In: Magrath IT, ed. *The Non-Hodgkin's Lymphomas*. 2nd ed. London, England: Arnold; 1997:975-988.
7. Meng Q, Lai H, Lima J, et al. Echocardiographic and pathological characteristics of cardiac metastasis in patients with lymphoma. *Oncol Rep*. 2002;9:85-88.
8. Duong M, Dubois C, Buisson M, et al. Non-Hodgkin's lymphoma of the heart in patients infected with human immunodeficiency virus. *Clin Cardiol*. 1997;20:497-502.
9. Van Vooren JP, Renard M, Dargent JL, et al. Cardiac tamponade: the first manifestation of a generalized lymphoma in a patient with HIV infection. *Eur J Haematol*. 1995;55:274.
10. Araoz PA, Eklund HE, Welch TJ, Breen JF. CT and MR imaging of primary cardiac malignancies. *Radiographics*. 1999;19:1421-1434.
11. Rolla G, Bertero MT, Pastena G, et al. Primary lymphoma of the heart: a case report and review of the literature. *Leukemia Reserve*. 2002; 26:117-120.
12. Kaplan LD, Afridi NA, Holmvang G, Zukerberg LR. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 31-2003. A 44-year-old man with HIV infection and a right atrial mass. *N Engl J Med*. 2003;349:1369-1377.
13. Kosugi M, Ono T, Yamaguchi H, et al. Successful treatment of primary cardiac lymphoma and pulmonary tumor embolism with chemotherapy. *Int J Cardiol*. 2006;111:172-173.
14. Balasubramanyam A, Waxman M, Kazal HL, Lee MH. Malignant lymphoma of the heart in acquired immune deficiency syndrome. *Chest*. 1986;90:243-246.
15. Moore AJ, De Ran PB, Minor R, et al. Transesophageal echocardiographic evaluation of intracardiac lymphoma. *Am Heart J*. 1992;124: 514-516.
16. Galli R, Fiorani V, Ferlito M, et al. Tumori secondari del cuore e dei grossi vasi. *Cardiol Pratica*. 1992;Clin 2:83-92.
17. Thorley-Lawson DA. Epstein-Barr virus: exploiting the immune system. *Nat Rev Immunol*. 2002;1:75-82.
18. Ratner L, Lee J, Tang S, et al. Chemotherapy for human immunodeficiency virus–associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. *J Clin Oncol*. 2001;19:2171-2178.
19. Krishnan A, Molina A, Zaia J, et al. Autologous stem cell transplantation for HIV-associated lymphoma. *Blood*. 2001;98:3857-3859.
20. Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood*. 2003;101:4653-4659.
21. Rolla G, Bertero MT, Pastena G, et al. Primary lymphoma of the heart. A case report and review of the literature. *Leukemia Res*. 2002;20: 117-120.