Intracardiac Non-Hodgkin’s Lymphoma in an HIV-infected Patient

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ABSTRACT

We report a case of a 47-year-old HIV infected man that presented with progressive dyspnea for a month followed by left oculomotor nerve palsy and cauda equina syndrome after hospitalization. Transthoracic echocardiogram revealed moderate pericardial effusion, multiple pericardial and intracardiac masses at both right and left atria. CSF cytology reported numerous large atypical lymphoid cells which flow cytometry showed B-cell lymphoma. AIDS with non-Hodgkin’s lymphoma stage IV was diagnosed. He was treated with CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone) plus intrathecal methotrexate. Though there was complete recovery of left oculomotor nerve palsy with marked improvement of all intracardiac and pericardial masses and disappearance of pericardial effusion from transthoracic echocardiogram after chemotherapy, still he had paraplegia grade 2 until discharged from the hospital. Intracardiac lymphomas in HIV-infected patients are rare, but fatal if left untreated. Clinical awareness is important for a better outcome of the patient. (J Infect Dis Antimicrob Agents 2013;30:157-65.)

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INTRODUCTION

Cardiac tumors are rare; incidence at autopsy ranges from 0.0017 to 0.03%. In the past, such tumors are often left untreated and frequently diagnosed postmortem. Approximately 75% of primary cardiac tumors are benign and the remaining 25% are malignant. Among them, primary cardiac lymphoma is extremely rare. Only 35 cases have been documented since 1960. This accounts for only 5.6% of primary malignant cardiac tumors.¹ Although the incidence of cardiac lymphoma has increased in recent years, mainly because of HIV infection², intracardiac involvement is still less frequent than pericardial involvement.³ We present a rare case of primary intracardiac lymphoma in an HIV-infected patient.

CASE REPORT

A 47-year-old homosexual Thai man, from Rayong province, presented with progressive dyspnea for a month. He was first diagnosed with HIV infection with CD4 cell count of 471 cells/mm³.
one year ago due to disseminated herpes zoster infection. After that, the patient had been well and was lost to follow up from the hospital. One month prior to admission, he developed progressive dyspnea. No chest pain, paroxysmal nocturnal dyspnea or edema was detected. He noticed low grade fever every evening accompanied by non-productive cough, anorexia and weight loss of 4 kg within 1 month. He was admitted to the private hospital in Rayong province for 2 days. Chest radiograph at the private hospital showed cardiomegaly with bilateral reticulonodular infiltration. The patient was treated as *Pneumocystis jirovecii* pneumonia by co-trimoxazole single strength 3 tabs three times a day. Transthoracic echocardiogram at the private hospital reported moderate pericardial effusion with impending cardiac tamponade, mild tricuspid regurgitation and mixed 2 echogenic masses with stalk adhered to both atrial walls size 2.7 and 1 cm at right and left atrium respectively. The doctor planned to do the operation of intracardiac masses, but due to financial problem he decided to come to our hospital.

On examination, the patient was afebrile with temperature of 37°C, regular heart rate of 114/min, blood pressure of 110/80 mmHg, respiratory rate of 24 breaths/min and room air oxygen saturation of 99%. He had oral candidiasis and only 5 mm lymph node was palpable at right supraclavicular region. No pruritic papular eruption (PPE) or other skin lesion was seen. Cardiac examination revealed jugular venous pressure at 4 cm above sternal angle and PMI at sixth intercostals space; 1 cm lateral to midclavicular line without significant cardiac murmur. Abdomen revealed hepatosplenomegaly with liver span 13 cm. Respiratory and neurological systems were unremarkable.

At first presentation, an electrocardiogram showed sinus tachycardia rate 110/min and low voltage. We repeated transthoracic echocardiogram and it revealed moderate pericardial effusion at anterior apex 1.2 to 1.5 cm and posterior 1.5 to 2.3 cm without physiology of cardiac tamponade. There were thickened visceral pericardium with multiple hypechoic masses on pericardium, sized 2 cm at right ventricular apex and atrioventricular (AV) groove and sized 0.8 cm at left atrial side. Heterogenous echogenicity of multiple intracardiac masses at both right and left atria which 2 masses on tricuspid valve (TV) with turbulent flow during diastole, sized 1.5 cm at septum and sized 3 cm at posterior leaflet. A single mass in left atrium sized 1 cm adhered to anterior mitral leaflet and was also presented without mitral valve inflow obstruction. Left ventricular ejection fraction was 60% with eccentric left ventricular hypertrophy. No regional wall motion abnormality or significant valvular heart disease, except mild tricuspid regurgitation was demonstrated. (Figure 1, 2 and 3) The diagnosis of *Pneumocystis jirovecii* pneumonia was less likely, so then we reduced co-trimoxazole SS to 2 tabs once a day as a prophylactic dose while we tried to inspect the specific cause of the disease.

Three days after hospitalization, he developed complete ptosis of the left eye followed by progressive paraplegia. Neurological examination was significant for mydriasis, complete ptosis and limitation of medial, upward and downward gaze of left eye compatible with left oculomotor nerve palsy. Motor system examination showed flaccid tone at lower extremities without fasciculation, atrophy and motor weakness only at lower extremities, especially at distal more than proximal part. Deep tendon reflexes showed lower extremities grade 0. Per rectal examination showed loose sphincter tone.

A computed tomography (CT) scan and magnetic
Figure 1. Parasternal long axis view showed P: pericardial effusion, white arrow: single mass size 1 cm adhered to anterior mitral valve leaflet, RV: right ventricle, LV: left ventricle, RA: right atrium, LA: left atrium.

Figure 2. Parasternal short axis view at aortic valve level showed white thin arrow: 1.5 cm mass at septal side of tricuspid valve, white thick arrow: 3 cm mass at posterior leaflet of tricuspid valve, AV: aortic valve, RVOT: right ventricular outflow tract.
resonance imaging (MRI) of the brain were done with unremarkable results, while MRI spine showed diffuse mild enlargement and clumping of cauda equina root with prominent enhancement suggestive of radiculitis of cauda equina roots. Lumbar puncture then revealed clear cerebrospinal fluid (CSF) with opened and closed pressure of 30 and 23 cmH₂O respectively. White cell count 126 cells/μL with mononuclear cell count predominant of 99% and red cell count 100 cells/μL. CSF sugar was extremely low at 2 mg/dL with capillary blood glucose of 222 mg/dL. All CSF cultures were negative for aerobe, anaerobe, mycobacterium and fungus. CSF cytology revealed numerous large atypical lymphoid cells showing frequent mitoses which flow cytometry suggestive of B-cell lymphoma. (Figure 4) While transvenous endocardial biopsy was unsuccessful, CD4 cell count was 158 cells/mm³ (4%). No hepatitis B and C virus coinfection. Other
investigation was remarkable for a creatinine of 1.15 mg/dL, hemoglobin of 10.4 g/dL, hematocrit 32.4%, white blood cells of 8,060 cells/mm³ (neutrophil 46%, lymphocyte 49% and monocyte 5%) and platelets of 226,000 cells/mm³. Liver function test was total bilirubin 0.6 mg/dL, direct bilirubin 0.3 mg/dL, aspartate aminotransferase (AST) 69 μ/L, alanine aminotransferase (ALT) 65 μ/L, alkaline phosphatase (ALP) 342 μ/L, gamma-glutamyl transferase (GGT) 221 μ/L, serum albumin 2.3 g/dL and globulin 6 g/dL. Serum lactate dehydrogenase (LDH) level 637 μ/L. Hemocultures grew no growth for aerobe, mycobacterium and fungus. Sputum collection could not be inducible anyway.

Non-Hodgkin’s lymphoma was staging by bone marrow study and CT scan of chest and whole abdomen. The results revealed no bone marrow, but pulmonary and hepatic involvement besides the cardiac involvement as mentioned before. CT scan of chest showed focal consolidation at lateral segment of right lower lung, multiple small well-defined air space nodules in both lungs and lymphadenopathies at right supraclavicular, anterior mediastinum, both paratracheal, prevascular, subcarina, right hilar and left axilla regions. CT scan of whole abdomen also showed hepatomegaly without focal mass, diffuse enlargement of left adrenal gland, diffuse small bowel wall thickening, minimal ascites and multiple intraabdominal lymphadenopathies along paraaortic, mesenteric and hepatoduodenal ligament.

Diagnosis of AIDS with non-Hodgkin’s lymphoma (NHL) stage IV according to Ann Arbor staging was made and CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone) plus intrathecal methotrexate were started subsequently to antituberculous agents in case of the possibly concurrent pulmonary tuberculosis infection. Anti-retroviral treatment was deferred due to the increased liver enzyme more than 7 folds of upper normal limit, ALP and GGT more than 3 folds of upper normal limit during his admission. Three and six days after treatment, the physical examination showed neither ptosis nor ophthalmoplegia respectively, except for paraparesis motor power grade 1. The followed up transthoracic echocardiogram at 1 week after chemotherapy treatment showed markedly decreased heart size, decreased amount of pericardial effusion from 1.5 to 0.8 cm at apex, 2.3 to 0.8 cm at posterior and 1.2 to 0.5 cm at anterior aspect, decreased size of pericardial and all intracardiac masses at TV posterior leaflet from 3 to 2.1 cm, at septal leaflet from 1.5 to 0.6 cm and from 1 to 0.7 cm at anterior mitral leaflet. At 3 weeks after chemotherapy treatment, there were no pericardial effusion, no mass at mitral valve leaflet and markedly reduced size of intracardiac mass at TV anterior leaflet from 2.1 to 1.2 cm. Similarly, CT scan of chest and whole abdomen showed decreased focal consolidation at right lower lung and markedly decreased size of generalized lymphadenopathies in previous regions. So we decided to discontinue anti-tuberculous drug before discharging the patient from the hospital. And antiretroviral drugs; tenofovir (TDF), lamivudine (3TC) and efavirenz (EFV), were started 2 weeks afterward at out-patient clinic when the liver enzyme was decreased nearly 2 folds of upper normal limit. (Figure 5 and 6)

**DISCUSSION**

The differential diagnosis of intracardiac masses includes infection, tumor and thrombi. Cardiac thrombi and nonbacterial thrombotic endocarditis (NTBE), characterized by the deposition of thrombi on normal or superficially degenerated cardiac
valves in the absence of a bloodstream bacterial infection, are easily ruled out by echocardiography. The most common infectious causes are bacterial endocarditis and bacterial myocardial abscess. In a case of HIV infection, fungal endocarditis could also be considered, especially if CD4 cell count is very low. The fungi that most commonly infect the heart are *Candida albicans*, *Aspergillus fumigatus* and *cryptococcus*, but intracardiac fungal have been described mainly in association with aspergillus. In this patient, we could not find the evidence of such infection, so the diagnosis was less likely.
Intracardiac malignancies in an HIV-infected patient are different from the general population; Kaposi’s sarcoma and lymphoma are most commonly found respectively among this group of patients. Kaposi’s sarcoma can involve pericardium, myocardium and epicardium, but generally occur in the setting of widespread mucocutaneous disease which was not presented in this patient. And when including all of the clinical setting of the patient, the diagnosis of intracardiac lymphoma was more pronounced.

As referred previously, the incidence of cardiac lymphomas has considerably increased, mainly in HIV-infected patients, with autopsy series documenting cardiac involvement in nearly 20 to 25% of NHL. However, this is the first case report from Thailand.

The clinical presentation of cardiac lymphoma can be varied: chest pain, heart failure, pericardial effusion, arrhythmias, or on the opposite, no cardiac manifestations. The present patient suffered from progressive dyspnea maybe from the moderate amount of pericardial effusion and multiple intracardiac masses which caused left ventricular diastolic dysfunction. Though the cardiac complications in AIDS-related NHL appear late in the course of illness, it seemed that this case was first presented by the cardiac involvement of NHL. This patient also showed the frequently extranodal involvement of AIDS-related NHL: pulmonary, hepatic and central nervous system, in addition to the hallmark primary cardiac lymphoma.

Primary cardiac lymphoma is defined as a lymphoma that predominately involves the heart, although it may involves other sites as well. Most cardiac lymphomas are typically aggressive B-cell lymphoma, as are the majority of AIDS-related lymphoma. Primary cardiac lymphoma typically involves the right atrium; involvement of the other chambers is less common. Most patients have pericardial involvement, but extension into the valve is rare. Secondary cardiac lymphoma may also be pericardial, epicardial, or diffusely infiltrating. In HIV-infected patients, the occurrence of cardiac NHL does not correlate closely with an advanced stage of immunosuppression. In our patient, his CD4 count was rather low (158 cells/mm³ or 4%) and histology showed B-cell lymphoma in origin as previously reported, but the cardiac involvement was notably diffused through pericardium, myocardium and endocardium (involving the tricuspid valve and both atria).

Historically, the prognosis of HIV-associated cardiac NHL has been poor due to the difficulty in diagnosing and early post-chemotherapy death in consequence of massive pulmonary emboli, refractory heart failure and cardiac arrhythmias. Chemotherapy is the main treatment option. Reported median survival in patients treated with chemotherapy is 7 months (range 0-48 months). However, a review of more recent literature reveals a better outcome with clinical remission with chemotherapy. Surgical resection may be considered in large tumors which may be causing hemodynamic obstruction. Fortunately, this patient was treated with CHOP regimen plus intrathecal methotrexate and had no early post chemotherapy complications from rapid regression of cardiac tumors as seen from transthoracic echocardiography and CT scan of chest. Clinical remission has yet to be observed. Nonetheless, with poor prognostic factors, from the international prognostic index (IPI): Ann Arbor staging IV, more than 1 extranodal site, serum LDH level above normal and Eastern Cooperative Oncology Group (ECOG) performance status more than 2, made the complete
response rate 44% and the 5-year survival was 26%.19

In conclusion, 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 non specific and can lead to initial misdiagnosis. Besides tissue diagnosis, Echocardiography is the diagnostic mainstay in cases of cardiac NHL. Although the prognosis is not good, especially with poor prognostic factors, patients could have longer survival with early diagnosis from clinical suspicions and systemic chemotherapy.

References