

Primary Cardiac Lymphoma

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Primary cardiac lymphoma (PCL) has rarely been reported in Chinese populations. PCL mostly occurs in the right atrium. The clinical manifestations may be variable and are attributed to its location, the presence of congestive heart failure, pericardial effusion, arrhythmia, and cardiomegaly. The prognosis is usually poor because it is usually found too late and therefore, clinicians should be aware of PCL. Imaging examinations are the best methods for initial diagnosis and include echocardiography, computed tomography (CT) scan, magnetic resonance imaging (MRI), and radioisotope scan. However, the final diagnosis is made by pathology, such as cytologic examination of the effusive fluid and tissue biopsy. Because the tumors are difficult to resect, the main treatment for the disease is chemotherapy, which can be successful. Here, we report a 58-year-old man who had a tumor measuring 8 × 5 cm in the right atrium. By clinical staging, including chest X-ray, echocardiography, CT scan of the abdomen, MRI of the heart, whole body tumor Gallium scan, and gastrointestinal series, no metastatic lesion or involvement was found in other parts of the body. Pathologic findings including cytology of pericardial effusion and heart tumor biopsy revealed the case as a diffuse large B-cell lymphoma. After chemotherapy with COP (cyclophosphamide + vincristine + prednisone) and CHOPBE (COP + doxorubicin + bleomycin + etoposide) regimens, the intracardiac tumor had disappeared, but the patient survived for 12 months in total, despite additional radiotherapy over the pericardial lesions. It was presumed that because the tumor was very large and involved all 3 layers of the heart, it did not respond as well to the therapy as expected. [*J Chin Med Assoc* 2006;69(4):169–174]

Key Words: chemotherapy, echocardiography, primary cardiac lymphoma

Introduction

Primary cardiac tumor is rare, with most heart tumors having metastasized from other parts of the body. The prevalence rate of metastatic cardiac tumor is 100–1,000 times higher than primary tumors in the heart.¹ Approximately one-quarter of primary cardiac tumors are malignant, with the majority of such malignant tumors in adults being sarcomas. By order of prevalence, the most common is hemangiosarcoma, then myosarcoma, fibrosarcoma, and so forth. The primary lymphoma in the heart is called primary cardiac lymphoma (PCL). It is a rare tumor, comprising about 0.5% of all lymphomas,² and is difficult to find.² PCL constitutes about 1.3–2% of all heart tumors.³

A tumor found with most of its mass located in the heart including the pericardium is identified as PCL. By definition, those patients with small secondary lesions of the same disease in other parts of the body are included in the PCL group.² Usually, PCL occurs in the right atrium and right ventricle of the heart. Its clinical manifestations are found when the presence of heart failure, pericardial effusion, cardiomegaly, and arrhythmia are noted. The prognosis of PCL is typically quite poor because of delayed diagnosis. The diagnostic instruments and methods for PCL include chest X-ray, echocardiography, computed tomography (CT) scan, magnetic resonance imaging (MRI), and radioisotope scan. The final confirmative diagnosis is made from the cytology of pericardial

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effusive and/or tumor tissue biopsy. The diagnosis depends on the correct specimen having been obtained, including the aspiration of pericardial effusive fluid and biopsy through cardiac catheterization or surgery. The diagnostic procedures should be done rapidly and accurately. Chemotherapy is quite effective for PCL. Usually, the tumor cannot be resected with surgery. The prognosis for PCL is generally poor.²

Case Report

We report on a 58-year-old man who was transferred from another hospital in June 2002 because of chronic cough for 4 months and chest pain with shortness of breath for 1 week. On admission, there were no remarkable physical findings. Hemogram revealed hemoglobin (Hb) 13.19 g/dL, white blood cells (WBC) $10,100/\text{mm}^3$, platelets $280,000/\text{mm}^3$, neutrophils 66.5%, lymphocytes 24.9%, and monocytes 6.0%. Blood biochemistry examinations showed albumin 3.3 g/dL, globulin 3.8 g/dL, and lactic acid dehydrogenase 2,151 MU/L. Liver and renal functions, and blood sugar were all within normal limits. Tests for HBsAg, anti-HCV, and anti-HIV were negative. Chest X-ray showed an enlarged heart. Electrocardiogram showed a low voltage wave indicative of 2nd degree A-V block. Echocardiography revealed a tumor from the free wall of the right atrium entering the right ventricle (Figure 1). The tumor was about 8×5 cm in size. Besides a thickened pericardium, there was a large amount of fluid accumulated inside. On the day of admission, pericardiotomy with drainage was performed. A total of 300 mL of straw-colored fluid was drained. The pathologic examination of the fluid revealed many large lymphoid cells, which were proven B cells, with positive immunocytochemical stains for CD20. Involvement of lymphoma in the pericardium was suspected. Biopsy of the pericardium also revealed the presence of large lymphoid cells. On the 10th day after admission, a biopsy of the heart tumor was performed using catheterization. The pathologic examination showed a picture of large B-cell lymphoma, diffuse type (Figure 2). Immunocytochemical stains of the sections of tumor exhibited large lymphoid cells positive for leukocyte common antigen and CD20, and negative for chromogranin-A, S-100, and T cells. A series of whole-body examinations for the staging of cancer were performed, including CT scan of the heart and whole abdomen, MRI of the heart, gastrointestinal series, and whole-body tumor Gallium scan. A tumor 8×5 cm in size with variable lobes located in the atrium and

ventricle of the right side was noted (Figure 3). There were no tumors found in other parts of the body. The patient was initially treated with chemotherapy, i.e. 2 courses of COP (cyclophosphamide + vincristine + prednisone). The tumor shrank to 2.7 cm in size. This treatment was then followed by 4 courses of COP and 2 courses of CHOPBE (COP + doxorubicin + bleomycin + etoposide), after which the intracardiac tumor disappeared (Figure 4). However, the pericardial tumor was persistent. After a pause following chemotherapy, a dose of 4,160 cGy radiotherapy was applied. The patient developed pneumonia, pulmonary edema, and sepsis. He died 12 months after the diagnosis of PCL was established.

Discussion

This case featured lymphoma with the biggest mass found inside the heart and was compatible with the diagnostic basis for PCL. The tumor was found in the patient's right atrium and right ventricle. There were no tumors found in other parts of his body. In a previous similar reported case (Table 1),⁴ also from this hospital, there was perforation of the ileum with peritonitis about 1.5 months before the diagnosis of PCL was established. Both cases were male, one aged 58 years and one 68 years, which is compatible with the observation that most patients are aged males. However, the disease has also recently been found in a few cases of children.¹⁵ The location of PCL reflects its pathophysiology and clinical symptoms and signs. A tumor in the heart may develop embolism, A-V block, thrombosis, and even strokes. Disturbance of hemodynamics may result.¹⁶ Most frequently, the tumor is found to be located partly in the right atrium. It may disturb the tricuspid and aortic valves, cause heart failure, pulmonary hypertension, and aortic valvular obstruction. In this reported case, the tumor was located mostly in the right atrium. It was found, by echocardiography, CT scan, and MRI of the heart, that the tumor had extended to the right ventricle. However, embolism, thrombosis, and heart failure were not evident. Heart failure and arrhythmia may be caused by tumor extension to the myocardium. In the 68-year-old patient with complete A-V block mentioned earlier, the condition was so serious that a cardiac pacemaker had to be implanted urgently.⁴ In our case, 2nd-degree A-V block developed. After effective chemotherapy, the cardiac arrhythmias of both these cases returned to normal. If the disease involves the pericardium, effusion or hemorrhage may develop and be followed by A-V block, constrictive

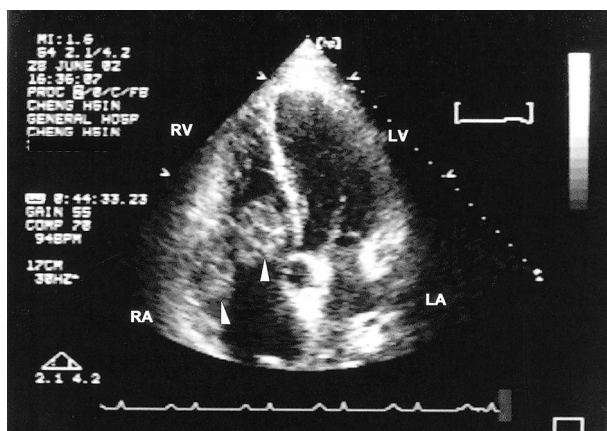


Figure 1. Echocardiography reveals a mass lesion over the right atrium and right ventricle, as indicated by the arrow.

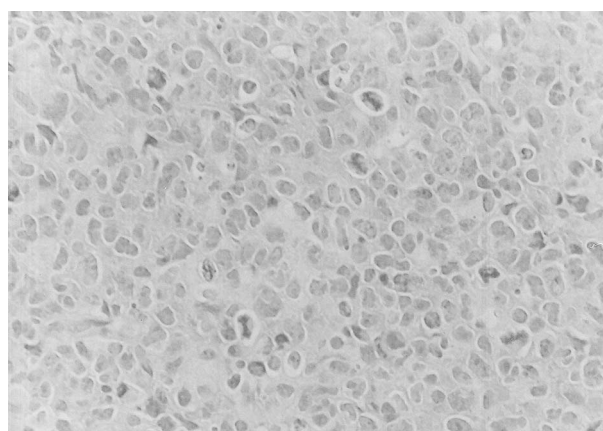


Figure 2. Photomicrograph shows a microscopic view of the cardiac tumor (hematoxylin and eosin stain, $\times 400$) revealing the cytologic characteristics of large lymphocytes with abundant cytoplasm vesicular nuclei and prominent nucleoli.

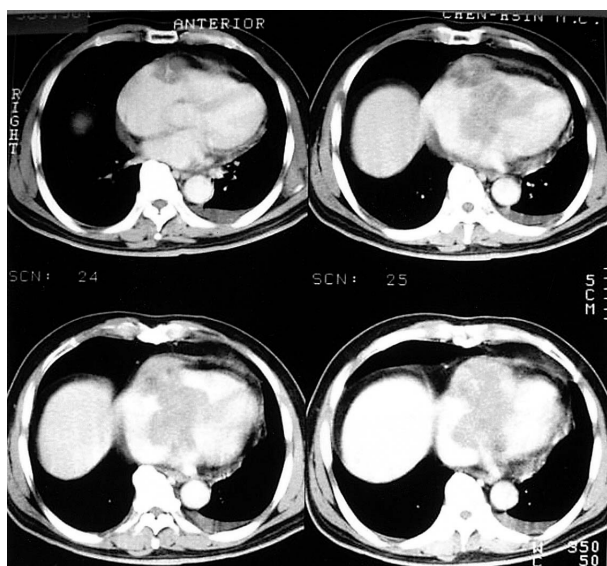


Figure 3. Intracardiac mass of 8 \times 5 cm with lobulation in the right atrium and right ventricle, as indicated by a filling defect within the heart chamber.

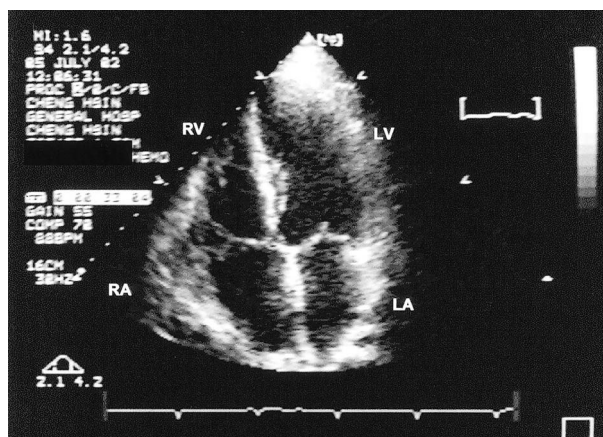


Figure 4. Echocardiography reveals the mass lesion over the right atrium and right ventricle eradicated after chemotherapy.

pericarditis, or symptoms and signs of great vessel obstruction. In this case, there was a large amount of accumulated pericardial effusive fluid, which caused shortness of breath and chest oppression. In the effusive fluid, cancer cells indicative of PCL were identified. It was found that the disease involved the patient's pericardium, resulting in common clinical manifestations such as palpitation, shortness of breath, chest oppression, and cough related to heart failure, pleural irritation, A-V block, arrhythmia, and pleural effusion. However, thromboembolism, myocardial infarction, rupture of the heart, coma, or sudden death were not observed in this case. Intestinal perforation before the diagnosis of PCL has been reported.⁴

Tumor-associated cardiac wall rupture has been described in PCL.¹⁵ The 3 most commonly encountered clinical manifestations of PCL are pericardial effusion, heart failure, and A-V block (Table 1).

PCL is a variant of non-Hodgkin's lymphoma (NHL). Its prevalence has increased in the USA, which is probably related to AIDS or drug abuse in which acquired immune deficiency is observed. Fifteen to 25% of NHLs in adults are extranodal lymphomas, but in AIDS patients they constitute about 90%.¹⁶ Extranodal lymphoma is usually found in the stomach and intestines, nasopharynx, skin, bones, thyroid gland, breasts, lungs, testes, and brain. This reported case had no AIDS, proven by a negative anti-HIV test.

Table 1. Summary of selected cases of primary cardiac lymphoma reported in the recent literature

Reference	Sex	Age (yr)	Presentation	Location of tumor	Tumor type	Treatment response and survival time
Saotome et al ⁵	M	69	Pericardial effusion	Right atrium extending to other chambers	Lymphoma, large cell	C/T with CHOP; survived for 18 days; died of low-output syndrome and multiple organ failure
Rolla et al ⁶	M	72	Moderate AS, pericardial effusion, heart failure, syncope	Right atrium and right ventricle wall	Lymphoma, large B cell	Died after 1st course of C/T; died of fatal ventricular arrhythmia
Tai et al ⁴	M	70	Complete AV block, peritonitis	Pericardium, right atrium	Diffuse large B cell	3 C/T with COP + 3 CHOP; survived > 2 years
Cordel et al ⁷	M	83	Hepatosplenomegaly, acute body weight loss	Right ventricle	Diffuse large B cell, lymphoma	Complete recovery after C/T with cyclophosphamide, prednimustine etoposide; survived > 1 year
Canellos et al ⁸	F	Adult	Heart failure, chest pain, complete AV block	Right atrium, right ventricle	Diffuse large B cell, lymphoma	C/T with complete regression
Nakayama et al ⁹	F	61	Complete AV block, pericardial effusion	Right atrium	Lymphoma	C/T with recovery
Chim et al ²	M	32	Palpitation, heart failure	Right atrium, right ventricle	NHL, diffuse large B cell	C/T with CHOP+R/T; survived > 18 months
Carfagna et al ¹⁰	F	78	Pleural effusion, heart failure, pericardial effusion	Right atrium	High-grade B cell lymphoma, Burkitt's type	Exploratory thoracotomy, but inoperable; died 2 days later
Nakchbandi and Day ¹¹	F	77	GI symptoms, heart failure, pericardial effusion, CHF, AF	RV, epicardium	Diffuse large B cell, lymphoma	C/T with CHOP; survived > 18 months
Anghel et al ¹²	M	52	Dyspnea, pericardial effusion, obstruction of IVC	Right atrium, interatrial septum	Large B cell, lymphoma	High-dose C/T + autologous PBS transplantation + Ruximab ; CR > 24 months
Anghel et al ¹²	F	70	Pericardial tamponade, low-output cardiac failure	Right atrium	Large B cell, lymphoma	Pericardiocentesis; C/T with COP; died 2 weeks later
Beckwith et al ¹³	M	61	Dyspnea, hepatomegaly, heart failure	Right atrium	Diffuse large B cell, lymphoma	Partially resected with bovine pericardial patch over LA wall; C/T with CHOP × 3 courses; died of CNS involvement; survived 2 months
Mejhert et al ¹⁴	M	59	Heart failure, AF	Right atrium, inferior vena cava	B-cell lymphoma	CHOP (cisplatin + hydroxyurea + oncovin + prednisolone) × 8 cycles; survived 10 months; died of septic shock
Hsueh et al, this report	M	58	SOB, chest distress, second-degree AV block	Right atrium	Diffuse large lymphoma	C/T with COP + CHOPBE; survived 11 months; died of sepsis

CR = complete remission; C/T = chemotherapy; COP = cyclophosphamide + vincristine + prednisolone; CHOPBE = cyclophosphamide + doxorubicin + vincristine + prednisolone + bleomycin + etoposide; CHOP = cyclophosphamide + doxorubicin + vincristine + prednisone; AS = aortic stenosis; AV = atrioventricle; GI = gastrointestinal; CHF = congestive heart failure; AF = atrial fibrillation; IVC = inferior vena cava; PBS = peripheral stem cell; LA = left atrium; CNS = central nervous system; RT = radiotherapy; RV = right ventricle; SOB = shortness of breath; NHL = non-Hodgkin's lymphoma.

PCL is rare clinically, although reports on the frequency of secondary lymphoma spreading to the heart state a range of 16–28%.¹⁻⁴ Curtsinger et al¹⁷ reported 15 cases in 1989, and Nakchbandi and Day¹¹ reviewed 29 more cases in 1995. In the latter report, there were 6 cases related to AIDS. In the report of 15 cases by Curtsinger et al,¹⁷ only 2 cases were diagnosed with PCL before death. It was indicated that most PCL cases were diagnosed at autopsy. However, because of advances in diagnostic methods, such cases reported in the period 1989–2002 were mostly diagnosed before death.¹⁸

Echocardiography is a more convenient diagnostic method that can detect pericardial effusion and the presence of tumors in the heart. It may be followed by CT and MRI scans to detect the extent of involvement and the size of the tumor.¹⁹ In this case, we found that echocardiography was more convenient. The diagnosis of PCL in this case was further confirmed through cardiac catheterization and tumor biopsy during hospitalization. Initially, lymphoid cells were also found in the patient's pericardial effusive fluids. It has been reported that biopsy through cardiac catheterization and chest surgery can confirm the diagnosis of PCL.^{18,20} As in this case, the diagnosis of PCL was made by tissue biopsy through exploratory sternotomy and cardiac catheterization.

More than 80% of PCLs are noted as diffuse B-cell lymphomas, mostly with a large cell type (Table 1), but other cell types also present, e.g. T-cell lymphoma.²¹ In recent years, PCL related to immune deficiency has been found as small noncleaved or immunoblastic lymphoma pathologically.¹⁵ Immunoblastic lymphoma is more invasive. In this case, the cells were medium-to-large sized cells.

The therapeutic effect in PCL is usually not promising.^{18,19,22-24} It is difficult to resect by surgery. Because the tumors are mostly large B-cell lymphomas, they are therefore sensitive to chemotherapy. The main chemotherapy regimens are COP and CHOP (cyclophosphamide, doxorubicin + vincristine + prednisone) (Table 1).^{4,22} Patients treated with CHOP may survive for up to 18 months.^{4,24} It has been reported that patients treated with the BACOP protocol (bleomycin + doxorubicin + cyclophosphamide + vincristine + prednisone) might survive for up to 49 months.²³ With surgical resection, the patients might survive for more than 18 months,^{18,20} and with radiotherapy for up to 15 months. Heart transplantation²² or combination therapies have also been tried.²⁴ In recent years, stem-cell transplantation has been used in combination with other chemotherapies in association with Rituximab, to

achieve complete remission in some cases.¹² This patient received chemotherapy associated with radiotherapy, and survived for only 1 year. The causes of death in this case of PCL may be related to refractory control of the disease itself^{2,13,14} and/or therapeutic complications, such as neutropenia with sepsis, cardiotoxicity-related fatal arrhythmia, or rupture of the heart¹² (Table 1). It is still possible to treat this rare disease with high doses of chemotherapy in the status of long-term remission.^{4,7,12,15} To avoid the marrow suppression complications of intensive therapy, stem-cell transplantation may be considered, especially in cases with clinically aggressive PCL. We think that therapeutic efficacy was less than expected in this patient because the diagnosis was made too late and the tumor was large and had extended into the pericardium, myocardium, and endocardium.

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