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【 CASE REPORT 】

Primary Cardiac Lymphoma: A Lesson Learned from an Unsuccessful Experience

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Abstract:
A 79-year-old man was admitted because of complete heart block. Echocardiograms showed an abnormal mass adjacent to the sinus of Valsalva. Subsequent surgical resection was not successful. Despite chemotherapy, the patient died from multiple organ failure. It is important to recognize that approximately 80% of cases of cardiac lymphoma are diffuse large B-cell lymphoma, which is the only malignant neoplasm that may respond well to chemotherapy with rituximab. In order to save patients' lives, the early implementation of chemotherapy with rituximab is critical and should be considered as a therapeutic diagnostic option in select patients.

Key words: primary cardiac lymphoma, early implementation of treatment, rituximab, therapeutic diagnosis

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Introduction

Malignant primary cardiac tumors constitute approximately 15% of all primary cardiac tumors (1, 2). The most common tissue type of these malignant cardiac tumors is sarcoma. Cardiac lymphoma has been reported to be far less common than sarcoma in postmortem pathological studies (3). However, cardiac lymphoma appears much more frequently in real-world settings than previously thought, constituting one third of all malignant cardiac tumors (1). It is also important to recognize that cardiac lymphoma is the only malignant tumor that may respond well to chemotherapy with rituximab (1, 2, 4, 5) and that without chemotherapy, patients may die relatively soon after the diagnosis of primary cardiac lymphoma.

Case Report

A 79-year-old man was admitted because of increasing dyspnea associated with complete heart block. A physical examination revealed a slow pulse rate of 40 beats/min. There was no lymphadenopathy in the neck, axillae, or groin. His heart sounds were normal without any significant murmur, and his breath sounds were also normal, with no peripheral edema.

An electrocardiogram showed complete heart block (Fig. 1), and chest radiograph showed mild cardiomegaly, while both lung fields were unremarkable. The laboratory data are summarized in Table 1. In brief, the plasma levels of B-type natriuretic peptide (107 pg/mL) and high-sensitivity cardiac troponin T (0.111 ng/mL) were both mildly elevated. Soluble interleukin-2 receptor (2,210 U/mL) was also elevated. Combination of human immunodeficiency virus (HIV) antibody and HIV antigen test was negative.

An emergency temporary pacemaker was introduced via his right internal jugular vein on admission, and a permanent pacemaker was implanted later the same day. Transthoracic echocardiogram revealed an abnormal mass adjacent to the sinus of Valsalva of the aortic root (Fig. 2A). The tricuspid valve appeared intact. Contrast computed tomography (CT) revealed a large, homogenous mass within the right

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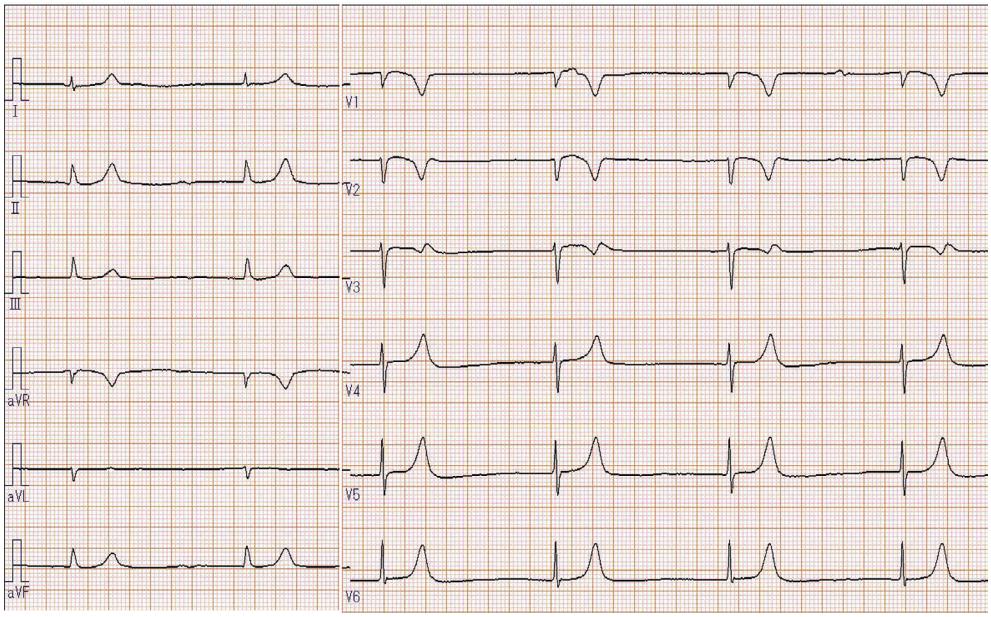

Figure 1. **Electrocardiogram on admission showing complete atrio-ventricular heart block with a heart rate of 40 beats/min.**

Table 1. **Laboratory Data of the Patient.**

RBC	421 $\times 10^4$/μL	TP	6.4 g/dL	BUN	28.2 mg/dL
Hb	13.0 g/dL	ALB	3.3 g/dL	Cr	1.4 mg/dL
Ht	39.0 %	CPK	43 IU/L	UA	10.7 mg/dL
Plt	15.9 $\times 10^4$/μL	LDH	442 IU/L	Na	136 mEq/L
WBC	6,900 /μL	GOT	52 IU/L	K	4.7 mEq/L
Neutro	68.6 %	GPT	29 IU/L	Cl	104 mEq/L
Lymph	20.1 %	ALP	338 IU/L	Ca	9.1 mEq/L
Mono	8.7 %	γ-GTP	135 IU/L	P	4.8 mEq/L
Eoaino	1.0 %	T-Chol	137 mg/dL	BNP	107 pg/mL
Baso	1.6 %	BS	144 mg/dL	hsTnT	0.111 ng/mL
CRP	1.8 mg/dL	HbA1c	6.2 %	sIL-2R	2,210 U/mL

ALB: albumin, ALP: alkaline phosphatase, BNP: B-type natriuretic peptide, BS: blood sugar, BUN: blood urea nitrogen, Ca: serum calcium, Cl: serum chloride, CPK: creatine phosphokinase, Cr: creatinine, CRP: C-reactive protein, GOT: glutamic oxaloacetic transaminase, GPT: glutamic pyruvic transaminase, γ-GTP: gamma-glutamyl transpeptidase, hsTnT: high-sensitivity cardiac troponin T, Ht: hematocrit, K: serum potassium, LDH: lactate dehydrogenase, Na: serum sodium, P: serum phosphorus, Plt: platelet, RBC: red blood cell, sIL-2R: soluble interleukin-2 receptor, T-Chol: total cholesterol, TP: total protein, UA: uric acid, WBC: white blood cell

atrium that extended to the right ventricle as well as the superior great veins (Fig. 3). Gallium-67 scintigraphy showed an excessive accumulation only in the cardiac tumor, with no abnormal accumulation detected in other parts of the body. This abnormal mass rapidly increased in size within two weeks of admission (Fig. 2B and C). An attempt at surgical resection was not successful, but the histological diagnosis of diffuse large B-cell lymphoma was confirmed (Fig. 4).

Despite chemotherapy with rituximab (R-CHOP with no radiation) that markedly reduced the size of the tumor (Fig. 2D), the patient died of multiple organ failure resulting from pyothorax and methicillin-resistant *Staphylococcus aureus* (MRSA) sepsis, probably secondary to chemotherapy-related leucocytopenia, 17 days after the initiation of chemotherapy.

Discussion

It is common clinical practice to first seek a histological diagnosis in order to select the appropriate treatment when a malignant neoplasm is suspected. However, based on our unsuccessful experience in saving the life of this particular patient, we have come to the conclusion that the typical di-

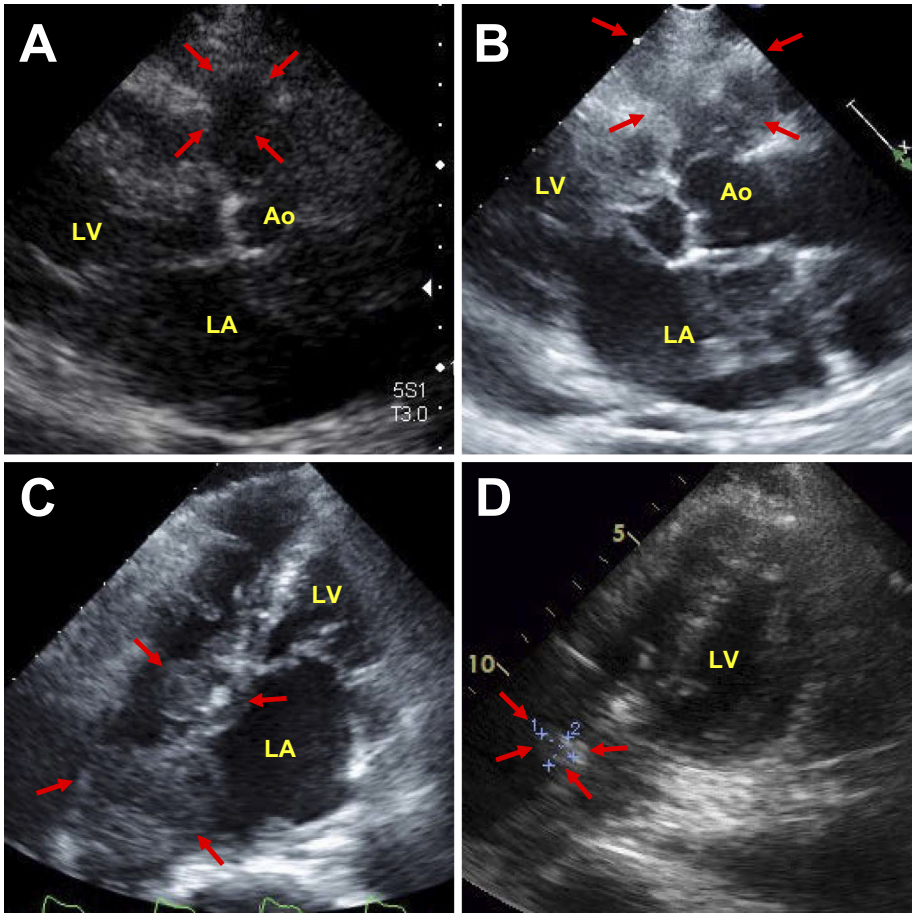

Figure 2. **A) Transthoracic echocardiogram of the long-axis view showing an abnormal mass adjacent to the sinus of Valsalva (arrows). B) The size of the abnormal mass was significantly increased at subsequent echocardiographic examinations (arrows). C) Apical four-chamber view revealing a massive tumor involving the right atrium and the interatrial septum (arrows). D) A significant reduction in the size of the tumor was observed after chemotherapy with rituximab (arrows). Ao: aorta, LA: left atrium, LV: left ventricle**

agnostic approach to malignant cardiac tumors occasionally merits reconsideration in select patients.

Since the most common subtype of cardiac lymphoma in immunocompetent patients is diffuse large B-cell lymphoma, accounting for approximately 80% of all cardiac lymphomas, and given that it is the only malignant cardiac tumor that may respond well to chemotherapy with rituximab (1, 2, 4, 5), the early implementation of this gold-standard chemotherapy should be considered as an alternative diagnostic approach in addition to other therapeutic options in order to save the lives of patients, particularly when cardiac lymphoma is strongly suspected based on a rapidly progressive nature along with imaging findings suggestive of cardiac lymphoma (6-10). Of further note, cardiac lymphoma is known to have a worse survival than extracardiac lymphomas. Therefore, if treatment is delayed, aggressive lymphoma may rapidly progress, leading to serious consequences, as seen in our patient. Although our patient died from multiple organ failure due to a serious infective complication of chemotherapy, we suspect that he may have had a better chance of surviving if chemotherapy had been started earlier, when he was in a much better general condition.

Malignant primary cardiac tumors mainly consist of sarcomas and lymphomas (1, 2, 5). From the standpoint of cardio-oncology, given that a high response rate to rituximab may be expected for diffuse large B-cell lymphoma, the early differentiation of cardiac lymphoma from cardiac sarcoma is important (Table 2). For such differentiation, the difference in the average age at the diagnosis should first be emphasized. Patients with cardiac lymphoma tend to be middle-aged to elderly, making them much older than the average patient with cardiac sarcoma (1). Second, noninvasive cardiac imaging modalities should be used. Although echocardiography is the mainstay in clinical practice for the detection of cardiac tumors, it is inadequate for distinguishing between tumors and thrombi because of its limited tissue characterization. Cardiac CT and magnetic resonance imaging (MRI) are useful for differentiating not only between tumors and thrombi but also between benign and malignant tumors. Furthermore, MRI in particular may be useful for distinguishing cardiac lymphoma from cardiac sar-

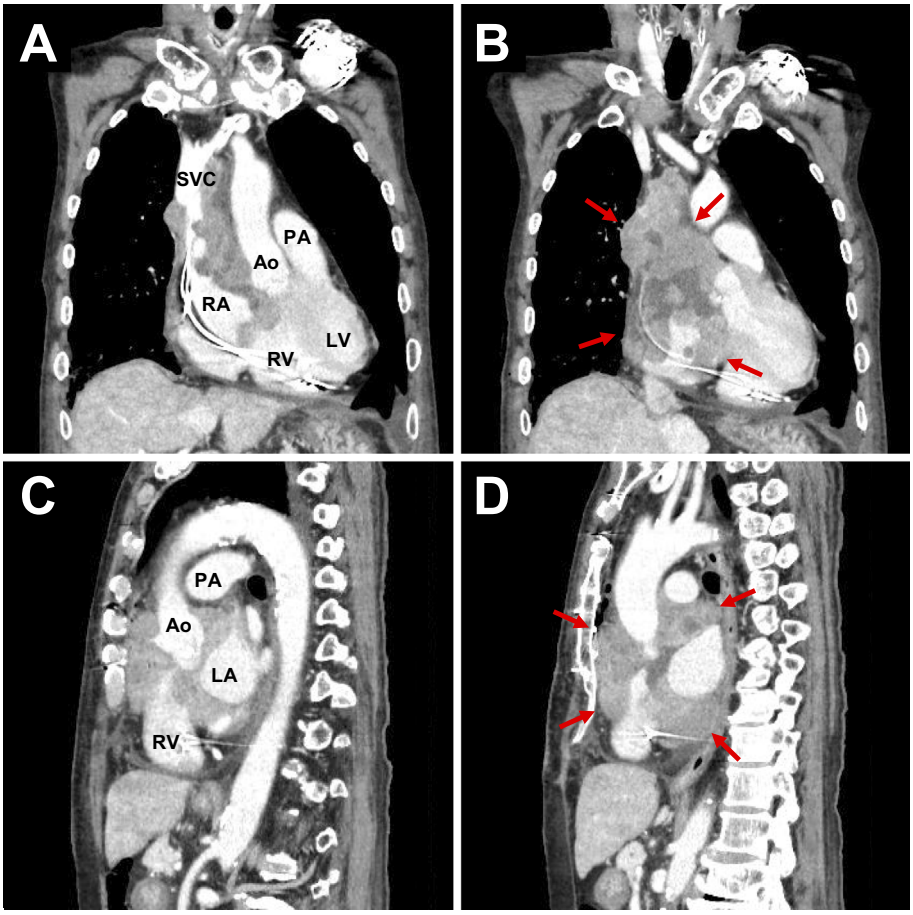

Figure 3. **A) Contrast CT of the frontal plane showing the cardiac anatomy in relation to the tumor. B) A large mass involving the right atrium, the right ventricle, and the superior great veins (arrows). C) Contrast CT of the sagittal plane showing the cardiac anatomy in relation to the tumor. D) A large mass involving the area around the aorta as well as the right atrium and the right ventricle (arrows). Ao: aorta, LA: left atrium, LV: left ventricle, PA: pulmonary artery, RA: right atrium, RV: right ventricle, SVC: superior vena cava**

coma. In their excellent review of many cardiac tumors, Hoey et al. described the MRI differentiation of cardiac lymphoma and cardiac sarcoma (6, 7). The pattern of late gadolinium enhancement (LGE) may also prove useful (8-10).

Several reviews of primary cardiac lymphoma have been published. Most recently, Petrich et al. provided an extremely comprehensive review of 197 cases of primary cardiac lymphoma from a total of 166 articles, analyzing its presentation, treatment, and outcome (5). The male-to-female ratio was 1.94, with a median age of 63, and only 5 cases were ≤17 years of age. Frequent presenting symptoms included dyspnea (64%), constitutional complaints (26%), and chest pain (24%). Clinical findings, such as arrhythmias, including atrioventricular block and atrial arrhythmias (56%) and congestive heart failure (47%), were common. Furthermore, right heart involvement was far more common than left heart involvement, with 92% of cases having either the right atrium or right ventricle involved. Pericardial effusion (58%) and pericardial mass (30%) were also common. For the diagnosis, echocardiography and other imaging modalities were most helpful, as described before. Among the 142 patients treated, the most common therapeutic modality was chemotherapy (89%). Surgical resection (28%) and radiotherapy (20%) were also performed. A total of 23 patients received combined chemoradiation. Of the 142 patients treated, 92 had partial or complete remission, which indicates an overall response rate of 79% (for cases with data available), and a complete response was achieved in 59%. The survival patterns suggest that only chemotherapy made a statistically significant difference in the treatment (30 months vs. 0.3 months, $p<0.0001$, Table 3). The lack of any marked benefit associated with the addition of radiation therapy to chemotherapy was also suggested.

The most important reason for making a definitive diagnosis of cardiac lymphoma and differentiating it from cardiac sarcoma is to determine whether or not the implementation of R-CHOP is necessary. A transesophageal and/or intravascular echo-guided transvenous biopsy has been suggested to obtain a histological diagnosis. However, when it is not possible to perform an echo-guided biopsy or when such a biopsy fails to obtain a sufficiently large specimen

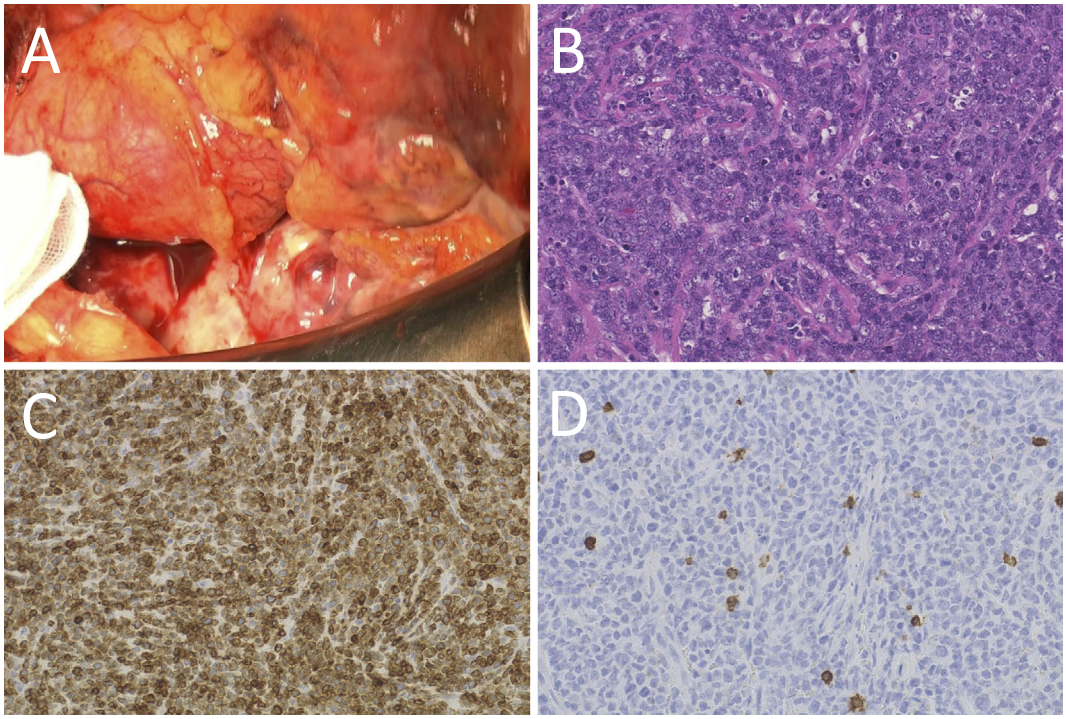

Figure 4. **A) Macroscopic features of the cardiac tumor during surgery. The rigid mass fully covers the SVC and anterior surface of the RV. B, C, D) Microscopic findings of the tumor specimen. Diffuse proliferation of atypical lymphoid cells (B), CD79a-positive (C) and CD3-negative (D), indicative of diffuse large B-cell lymphoma. RV: right ventricle, SVC: superior vena cava**

Table 2. **Difference between Primary Cardiac Lymphoma and Primary Cardiac Sarcoma.**

	Primary cardiac lymphoma	Primary cardiac sarcoma
Age at diagnosis	Middle age-Elderly	Young age-Middle age
Main location	RA, RV	RA
Infiltration	Pericardium, Less frequent valve involvement	Pericardium, TV, RV, Great veins, RCA
Extracardiac involvement	Rare	Lungs, Lymphnodes, Liver, Brain, Bones
MRI features	(1) Multiple solid-appearing myocardium-based mass within the RV T1: isointence, T2: mildly hyperintence	(1) A large infiltrative mass with heterogeneous intensity T1: isointence, Areas of hemorrhage (high T1) and blood flow (signal void)
	(2) Diffuse pericardial soft tissue infiltration with hemorrhagic effusion	(2) A large mixed signial pericardial effusion (blood products)
	(3) Absence of necrosis	(3) Intramural hemorrhage (high T2) and necrosis (low T2)
	(4) Heterogenous LGE	(4) "Sunray" pattern LGE

LGE: late Gadolinium enhancement, MRI: magnetic resonance imaging, RA: right atrium, RCA: right coronary artery, RV: right ventricle, TV: tricuspid valve

Table 3. **Type of Therapy and Overall Survival in Primary Caidiac Lymphoma.**

	Median survival (months)				p
	Therapy (+)		Therapy (-)		
Chemotherapy	30 mo	(n=105)	0.3 mo	(n=23)	<0.0001
Surgery	22 mo	(n=34)	10 mo	(n=92)	0.18
Radiation	NR		10 mo	(n=104)	0.11
Chemotherapy & Radiation	22 mo	(n=19)	22 mo	(n=86)	0.84

Modified from the original report. mo: months, n: number of patients, NR: not reached

for a histological diagnosis, a therapeutic diagnosis must be considered as an alternative, since cardiac lymphoma often shows rapid progression, leading to refractory heart failure and a poor patient outcome. Although it is important to stick to the principle of confirming a histological diagnosis before progressing with any treatment, and while we must be very cautious when starting any particular treatment before a histological diagnosis has been confirmed, the early implementation of R-CHOP may be critical for saving the lives of select patients. To obtain a better and longer patient survival, the importance of an early imaging-guided diagnosis and the early implementation of treatment as a therapeutic diagnostic option should be considered.

The authors state that they have no Conflict of Interest (COI).

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