

## Successful Treatment of Cardiac Diffuse Large B-cell Lymphoma : A Report of Two Cases

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Cardiac lymphoma is a rare neoplasm of the heart, defined as an extranodal lymphoma exclusively located in the heart and/or pericardium. Multiple imaging modalities may help to diagnose cardiac tumors ; however, pathological diagnosis is difficult because of the limited approaches for obtaining tissue samples. This report describes two cases of prompt histological diagnosis of cardiac lymphoma as diffuse large B-cell type and their successful treatment with chemotherapy. Immunohistochemical analyses revealed one case as CD5-positive and the other as CD5-negative lymphoma. This report highlights the necessity of histological diagnosis and the importance of clinicopathological characterization of cardiac lymphoma. *Shinshu Med J 59 : 177-183, 2011*

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### I Introduction

Cardiac lymphoma is described as a lymphoma involving only the heart and/or the pericardium, or with the main bulk of the tumor localized intrapericardially. It is a very rare disease in immunocompetent patients, estimated to account for 1-2 % of primary cardiac tumors and for 0.5 % of non-Hodgkin lymphoma cases ; cardiac metastases of malignant lymphoma are more common with an incidence of 9-24 %<sup>1)</sup>. Here, the authors report two cases of cardiac lymphoma with representative images of the tumor. Tissue biopsy specimens revealed both cases as diffuse large B-cell lymphoma (DLBCL), and immunohistochemical analyses for CD5 expression demonstrated that case 1 was CD5-positive, whereas case 2 was CD5-negative. The two patients were successfully treated

with 6 courses of standard chemotherapy. The importance of prompt pathological diagnosis and immunophenotyping is highlighted in this report.

### II Case Reports

#### A Case 1

A 58-year-old man presented with a history of low-grade fever, general fatigue, and palpitation since 2 months before admission. Transthoracic echocardiography indicated the presence of an abnormal mass at the posterior wall of the left ventricle and atrium, and the patient was referred to our hospital. On admission, the patient's body temperature was 36.8 °C, and blood pressure was 132/88 mmHg. Physical examinations were normal and no swelling of the superficial lymph nodes was observed. Standard laboratory examinations disclosed no abnormalities other than elevations in brain natriuretic peptide (147.6 pg/mL), C-reactive protein (6.79 mg/dL), and soluble interleukin-2 receptor (sIL-2R, 1,498 U/mL) levels. The patient tested negative for human immunodeficiency virus infec-

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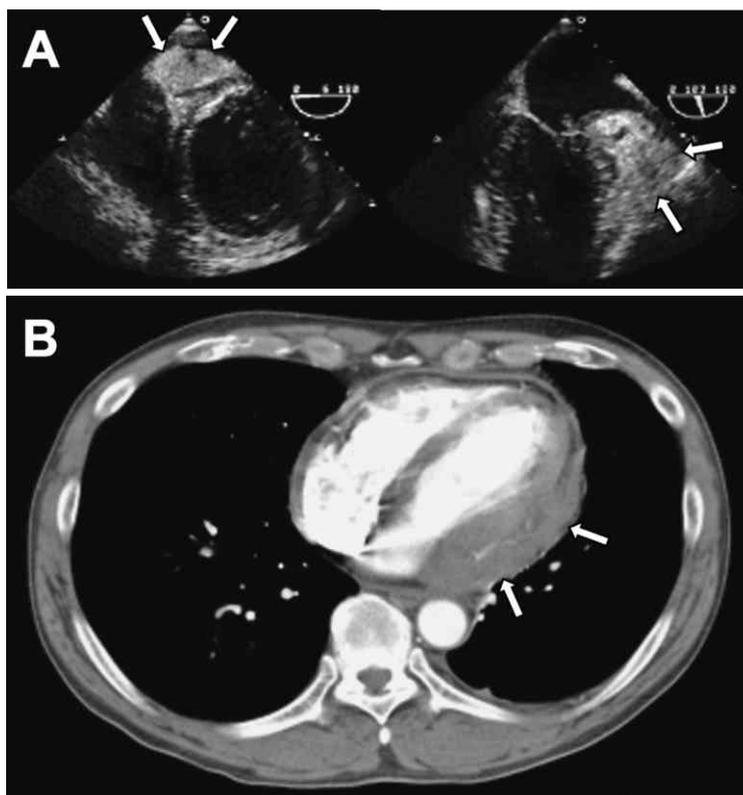


Fig. 1 Images of transesophageal echocardiogram (A) and enhanced CT scan (B) showing bulky, immobile, broad-based mass involving posterior wall of the left myocardium (Case 1). The surface protruded partly into the left atrium.

tion. The cardiothoracic ratio was 52 % with no abnormalities on the chest radiograph. Electrocardiography showed normal sinus rhythm at 99 bpm. Transesophageal echocardiography demonstrated an abnormal mass echo involving the posterior wall of the left ventricle and atrium (Fig. 1A). The surface of the tumor partially protruded and evolved into the left atrium.

A CT scan revealed heterogeneous enhancement of the tumor (Fig. 1B), and cardiac MR showed heterogeneous intensity (Fig. 2A). An enhanced uptake of gallium-67 citrate was observed at the cardiac lesion with no other significant uptake (Fig. 3A). Left ventricular endomyocardial biopsy failed to obtain tissue samples; surgical open biopsy was therefore performed to confirm the pathological diagnosis. Histopathological and immunohistochemical analyses revealed DLBCL (Fig. 3B, left) with positive staining for CD20 and MUM1, but negative for CD3, CD10, and CD5 (Fig. 3B, right).

The patient was treated with cyclophosphamide,

doxorubicin, vincristine, and prednisone combined with rituximab (R-CHOP), and successfully achieved complete remission for 20 months after the end of 6 courses of the chemotherapy.

#### B Case 2

A 63-year-old man presented with a 2-month history of low-grade non-specific fever with elevation of serum C-reactive protein levels. The patient developed dyspnea on effort and had pretibial edema with weight gain of 10 kg over 2 months; he was referred to our hospital with an echocardiographic diagnosis of a space-occupying lesion in the right atrium. On physical examination, blood pressure was 96/69 mmHg and the jugular vein was markedly dilated. Chest auscultation revealed bilateral coarse crackles, while the heart murmur was not significant. Enlargement of the liver and marked pitting edema suggested right-sided heart failure. Laboratory examinations revealed elevations in lactate dehydrogenase (526 IU/L), ferritin (758 ng/mL), brain natriuretic peptide (513.5 pg/mL), C-

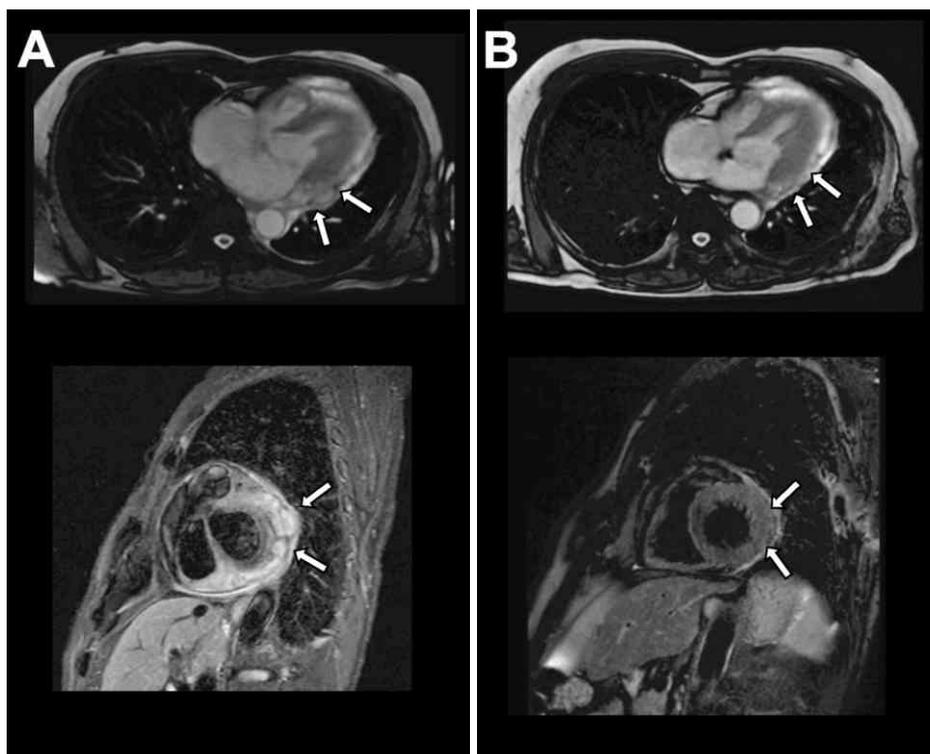


Fig. 2 Cardiac MR images of case 1 before (A) and after (B) a course of R-CHOP chemotherapy showing a significant reduction in tumor size.

reactive protein (6.54 mg/dL), and sIL-2R (6,999 U/mL) levels. The patient developed hepatorenal insufficiency ; none of the findings suggested human immunodeficiency virus infection. Chest radiography showed an increased cardiothoracic ratio (57 %) with bilateral lung congestion. Electrocardiography showed sinus tachycardia at 105 bpm with right bundle-branch block. Transesophageal echocardiography confirmed a large solid tumor in the right cardiac cavity, which almost completely occupied the right atrium and hampered the blood flow across the tricuspid valve (Fig. 4A). CT scan (Fig. 4B) and MR images disclosed the bulk of the cardiac tumor to have heterogeneous enhancement. An enhanced uptake of gallium-67 citrate was observed in the area consistent with the cardiac tumor (Fig. 5A). In addition, increased uptake in the left supraclavicular lymph node was noted ; this provided the opportunity to obtain tissue samples. Histopathological examination of the left supraclavicular lymph node confirmed the diagnosis as DLBCL (Fig. 5B) ; tumor cells were positive for CD20 (Fig. 5C), CD5 (Fig. 5D), and MUM1 but negative for CD10

and BCL6.

The patient was treated with R-CHOP chemotherapy, and after 3 courses, the tumor had decreased in size, right heart failure had disappeared, and the level of sIL-2R had decreased to 612 U/mL. A residual tumor was observed predominantly in the pericardial fat, indicating the origin of the tumor (Fig. 4C). At present, the patient has remained in complete remission for 10 months with no symptoms after the end of 6 courses of the chemotherapy.

### III Discussion

The most common histological type of cardiac lymphoma, accounting for over 90 % of cases, is DLBCL<sup>1)</sup>. Rare diagnoses include T-cell lymphoma<sup>2)</sup>, Burkitt's lymphoma<sup>3)</sup>, anaplastic large-cell lymphoma<sup>4)</sup>, and primary effusion lymphoma of the pericardium. Cardiac lymphoma is located predominantly in the right atrium and right ventricle and less often in the left atrium and left ventricle. Thus, the presentation of cardiac lymphoma at the left posterior wall as shown in case 1 is remark-

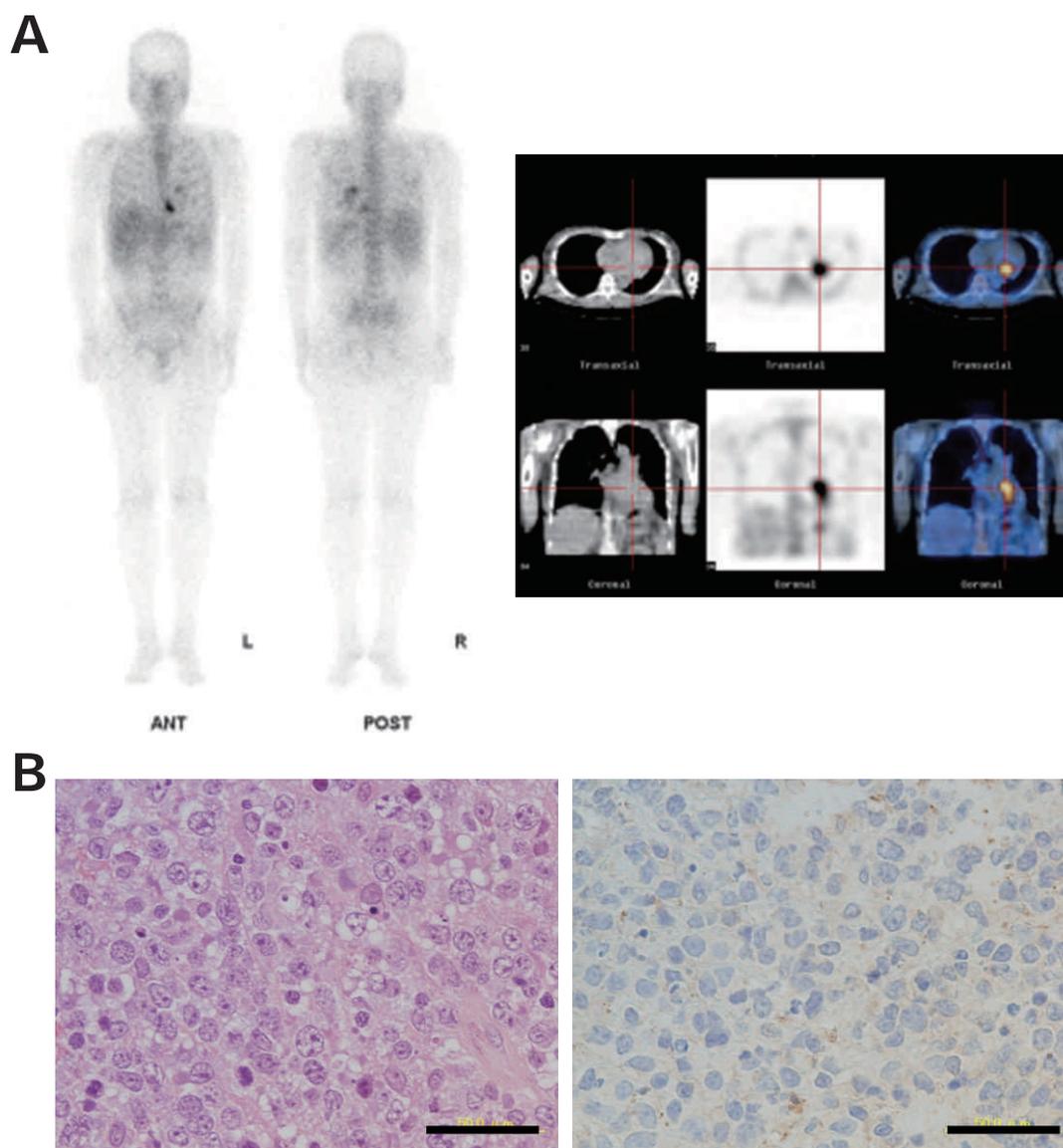


Fig. 3 Gallium-67 scintigram (A) showing an enhanced uptake in the left posterior segment of the heart, which is consistent with the tumor mass. Surgical tissue biopsy specimens (B) showing diffuse large lymphoma cells (left) with negative immunostaining for CD5 (right). Scale bars, 50  $\mu$ m.

ably rare, whereas the extension onto the pericardial surfaces is typical. A rare case of malignant lymphoma arising in a large left atrial myxoma has also been reported<sup>5)6)</sup>.

Common symptoms of cardiac lymphoma include chest pain, low-grade fever, shortness of breath, palpitations, and syncope. Clinical presentations may depend on the location of the tumor and vary as follows: congestive heart failure (mostly right-sided as shown in case 2), pericardial and/or pleural effusion, conduction disturbances, and arrhythmia<sup>17)</sup>. It has been established that the addition of

rituximab to the CHOP regimen (R-CHOP) increases the complete-response rate and prolongs event-free and overall survival in 60-# to 80-year-old patients with DLBCL<sup>8)</sup>. At two years after chemotherapy, 70 percent of patients treated with R-CHOP were alive as compared with 57 percent of those treated with CHOP alone<sup>8)</sup>; therefore, R-CHOP is currently the first-line chemotherapy for DLBCL, especially accompanied with CD20 expression<sup>9)</sup>. Since the tissue samples were CD20-positive, the patients in this report were treated with R-CHOP chemotherapy based on the standard regi-

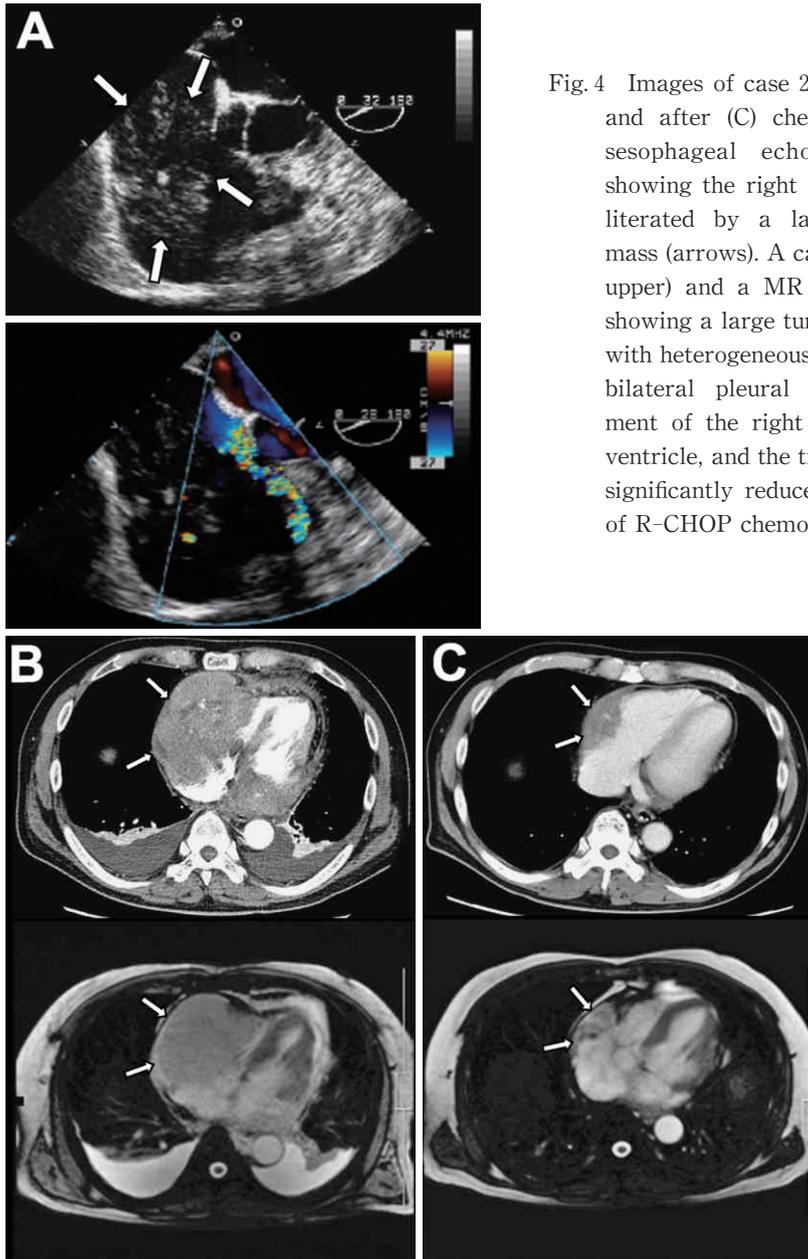


Fig. 4 Images of case 2 before (A and B) and after (C) chemotherapy. Transesophageal echocardiogram (A) showing the right atrium almost obliterated by a large intracavitary mass (arrows). A cardiac CT scan (B, upper) and a MR image (B, lower) showing a large tumor mass (arrows) with heterogeneous enhancement and bilateral pleural effusion. Involvement of the right atrium, the right ventricle, and the tricuspid valve was significantly reduced after 3 courses of R-CHOP chemotherapy (C).

men for focal DLBCL (stage I and II). Radiation therapy protocols for cardiac lymphoma have not been established because of the risk of unexpected local tissue injuries. The first course treatment was administered carefully, because the patients were at risk of death secondary to tissue necrosis causing pulmonary tumor embolisms or cardiac rupture<sup>1)</sup>.

The diagnosis of cardiac lymphoma is often difficult, owing to its rarity, nonspecific clinical presentation, and the limited opportunities for non-invasive tumor biopsy. In addition, identification of lymphoma cells from pericardial fluid is rare,

except in the case of primary effusion lymphoma of the pericardium<sup>10)11)</sup>. Prompt histological diagnosis is essential for successful treatment<sup>7)</sup>; therefore, an open surgical biopsy is sometimes necessary as performed in case 1 in this report.

The importance of CD5 expression has been highlighted in the World Health Organization classification of tumors of lymphoid tissues (2008) and in the National Comprehensive Cancer Network practice guidelines for non-Hodgkin's lymphomas<sup>9)</sup>. Clinically, CD5-positive DLBCL had a poor prognosis and higher staging grades with a

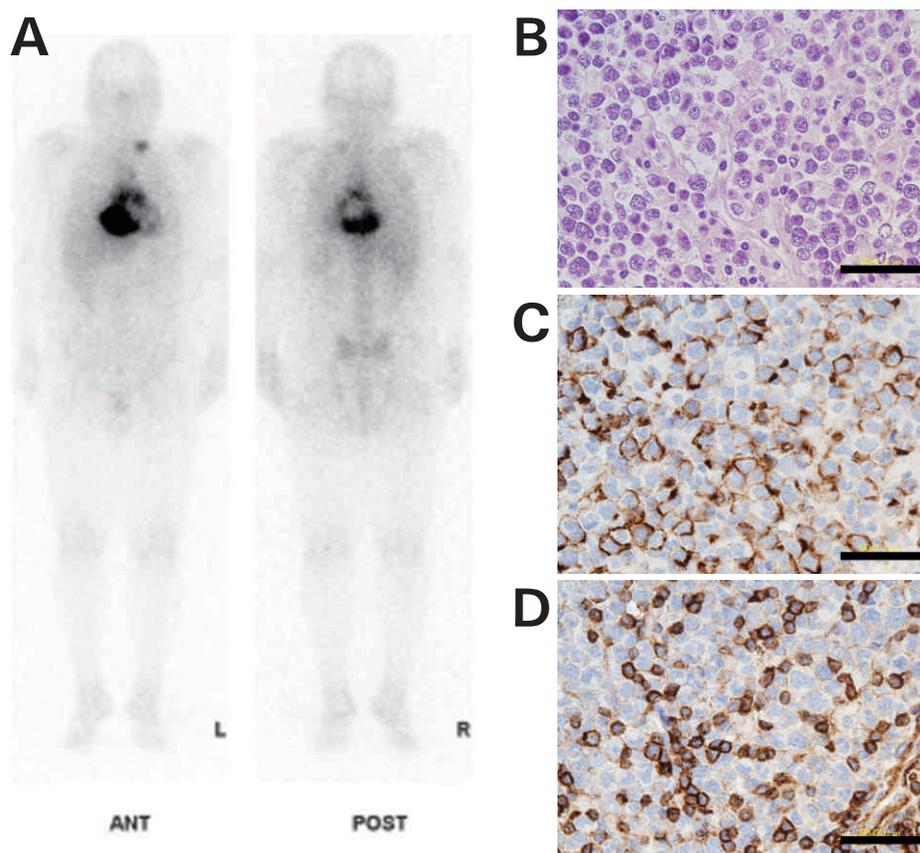


Fig. 5 Gallium-67 scintigram of case 2 (A) demonstrating enhanced uptakes in the right-sided heart and the supraclavicular lymph node. Tissue sections of the supraclavicular lymph node showing diffuse large lymphoma cells (B) with positive immunostaining for CD20 (C) and also positive for CD5 (D). Scale bars, 50  $\mu$ m.

greater number of extranodal sites<sup>12</sup>). In addition, a recent report has demonstrated that the effect of R-CHOP chemotherapy on CD5-negative DLBCL is significant, but this is not true for the CD5-positive group, i.e., 2 year overall survival was significantly poorer in CD5-positive patients as compared with that of CD5-negative patients (45 % versus 91 %)<sup>13</sup>. Although R-CHOP chemotherapy proved effective in both the CD5-positive and CD5-negative patients in this report, further investigation is required to evaluate the impact of CD5 expression on the treatment effectiveness and the prognosis of patients with primary cardiac DLBCL. More importantly, the effect of rituximab combined with chemotherapy is still controversial in patients with CD5-positive DLBCL<sup>14)15</sup>.

The prognosis of primary cardiac lymphoma has not been fully established and may also depend on the profiling of gene expression. In fact, poor prognosis have been reported for patients with CD5-

positive cardiac DLBCL with the tumor chromosome showing t(8; 14)(q24; q32) and c-myc rearrangement<sup>16</sup>. Exploring the importance of CD5 expression and/or cytogenetic analyses are essential for a new clinicopathological characterization of cardiac lymphoma.

#### IV Conclusion

The present cases are didactic for the following points: (1) a prompt histological diagnosis is essential for successful treatment; therefore, surgical open biopsy is valuable and is sometimes necessary to obtain the tissue samples; and (2) the diagnostic and/or prognostic value of the presence or absence of CD5 expression needs to be elucidated in detail.

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