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Clinical Case Report

# Primary cardiac diffuse large B-cell lymphoma with concurrent high MYC and BCL2 expression in an immunocompetent Chinese elderly woman☆

Ying Wan [a], Du He [a], Yunxia Ye [a], Wenyan Zhang [a,*], Sha Zhao [a], Yanhong Long [a], Min Chen [a], Can Küçük [b,c]

[a] Department of Pathology, West China Hospital of Sichuan University, Chengdu, China
[b] İzmir International Biomedicine and Genome Institute (iBG-izmir), Dokuz Eylul University, İzmir, Turkey
[c] Department of Medical Biology, Faculty of Medicine, Dokuz Eylul University, İzmir, Turkey;

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ABSTRACT

Primary cardiac lymphoma is a rare type of extranodal lymphoma that involves only heart and/or pericardium. It is usually observed in immunodeficient people. However, immunocompetent patients may also suffer from this disease. Most primary cardiac lymphomas are of B-cell lineage, and they usually present as diffuse large B-cell lymphoma (DLBCL). Diffuse large B-cell lymphoma with concurrently high MYC and BCL2 expression, which is named as double-expressor lymphoma (DEL), is a rare subtype of DLBCL. Here we report a rare case of a primary cardiac DEL in an immunocompetent 65-year old Chinese woman. Echocardiography and magnetic resonance imaging revealed a mass of 6.6 cm×5.6 cm in the right atrium. No tumor formations were observed in other organs. Histopathologic examination showed that the cardiac tumor was diffuse large B-cell lymphoma, non-germinal center B-cell type by Hans algorithm. The tumor cells showed high MYC and BCL2 protein expression by immunohistochemistry, with high proliferative index.



## 1. Introduction

Primary cardiac lymphoma (PCL) has been classified as an extranodal lymphoma, involving only heart and/or pericardium in the latest WHO classification of tumors of the lung, pleura, thymus and heart. Primary cardiac lymphomas are rare tumors that account for <2% of all primary cardiac neoplasms [1]. Here, we report a very rare case of primary cardiac diffuse large B-cell lymphoma of non-germinal center B-cell type with MYC and BCL2 protein co-expression in an immunocompetent patient.

## 2. Case report

A 65-year old woman, who had a 10-year history of hypertension, presented with face swelling, chest discomfort and asthma after physical activity for 4 months. Electrocardiogram showed that the patient has sick sinus syndrome. Echocardiography revealed a low echo mass in the right atrium suggesting the possibility of cardiac myxoma. Magnetic Resonance Imaging (MRI) revealed a soft tissue mass measuring 6.6 cm×5.7 cm in the right atrium which partly extended to the superior vena cava, inferior vena cava, right auricle and right ventricle (Fig. 1). The patient was suspected of cardiac myxoma by MRI too. No tumor formation was observed in other organs. No hepatic or renal dysfunction was identified. The tests for Hepatitis B Virus Surface Antigen (HBsAg) and human immunodeficiency virus (HIV) were all negative. The patient received surgical resection, tricuspid annuloplasty, and temporary pacemaker implantation. The mass was solid, lobulated and soft, 10 cm×7.5 cm×3.5 cm in size, with a complete capsule that attached to the free wall of the right atrium and extended upward to the superior vena cava.

## 3. Materials and methods

The surgically resected specimen was fixed in 10% neutral buffered formalin and embedded in paraffin. Hematoxylin–eosin staining and immunohistochemical analysis were performed on four μM thick paraffin-embedded sections. The following primary antibodies were used: CD20 (clone L26; Dako, Carpentaria, CA, USA), CD3ε (polyclonal),

*Abbreviations:* DLBCL, Diffuse large B-cell lymphoma; PCL, Primary cardiac lymphoma; MRI, Magnetic resonance imaging; HBsAg, Hepatitis B virus surface antigen; HIV, Human immunodeficiency virus; NHL, Non-Hodgkin lymphoma; GCB, Germinal center B-cell-like; ABC, Activated B-cell-like; GEP, Gene expression profile; BL, Burkitt lymphoma; DHL, Double-hit lymphoma; DEL, Double-expressor lymphoma; R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

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* Corresponding author at: Department of Pathology, West China Hospital of Sichuan University, Guoxue Alley No 37, Chengdu, 610041, Sichuan, China. Tel.: +86 28 85423848, +86 18980601864.
*E-mail address:* zhangwenyanpath@163.com (W. Zhang).

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CD10 (clone 56C6; Dako), BCL6 (clone PG-B6p; Dako), MUM1 (cloneMUM1p; Dako), BCL2 (clone 124; Dako), MYC (clone Y69; Epitomics, Burlingame, CA, USA), Ki-67 (clone MIB-1; MaiXin, China), CD5 (clone 4C7; Abcam, Cambridge, UK), CD30 (clone BerH2; Dako, USA), Cyclin D1 (clone SP4; Thermo, USA), CD45 (clone PD7/26; Dako, USA), NF-KB (polyclonal; NeoMarker, USA). In situ hybridization for Epstein–Barr virus (EBV)-encoded RNA (EBER1/2) was performed using a FITC-labeled oligonucleotide probe supplied by DAKO (USA). The FISH probes used in this study are as follows: LSI C-MYC dual-color, break-apart rearrangement probes (Vysis, Des Plaines, IL, USA); LSI BCL2 dual-color, break-apart rearrangement probes (Vysis); and LSI BCL6 dual-color, break-apart rearrangement probes (Vysis).

## 4. Results

### 4.1. Histology

Microscopical examination revealed that the tumor was composed of diffusely infiltrating large lymphoid cells with vesicular chromatin and round or oval nuclei, which show high mitotic activity (Fig. 2A).

### 4.2. Immunohistochemistry

Immunohistochemical staining showed that the tumor cells were positive for CD20, CD45, CD5, MUM-1, and negative for CD3, CD30, BCL6, CD10, Cyclin D1, NF-κB. Approximately 50% and 60% of tumor cells expressed BCL2 and MYC, respectively. Ki-67 index was 85% (Fig. 2B–E).

### 4.3. In situ hybridization

Tumor cells did not show Epstein Barr Virus-encoded small RNA (EBER1/2) expression based on in situ hybridization using a FITC-labeled oligonucleotide probe.

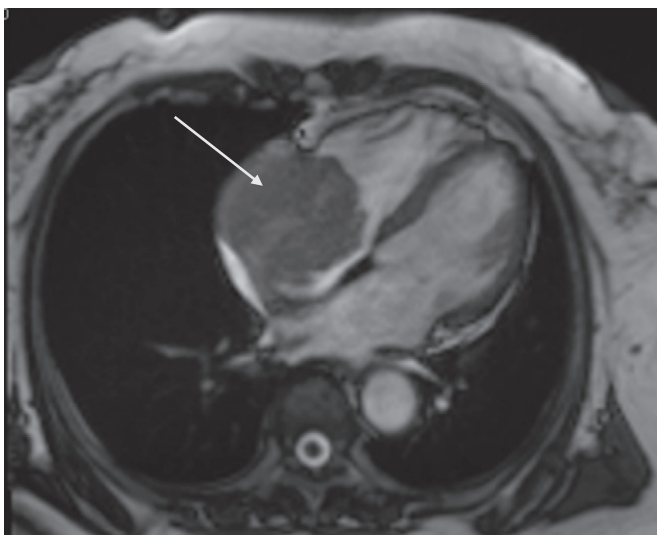

**Fig. 1.** Magnetic resonance imaging of the primary cardiac DLBCL patient tumor. MRI scan revealed heterogeneous soft-tissue density located in the enlarged right atrium with a clear margin. The white arrow shows the tumor mass.

### 4.4. Fluorescence in situ hybridization

Separate red and green signals were detected in more than 50% of tumor cells by a MYC break apart probe, demonstrating the presence of MYC gene rearrangements (Fig. 2F). No BCL2 or BCL6 gene rearrangement has been detected.

### 4.5. Patient treatment and follow up

The patient was treated with 8 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) therapy after surgery. She is alive and in good health condition without tumor recurrence 11 months after initial diagnosis.

## 5. Discussion

Nearly 70–80% of primary heart tumors are benign. Most malignant cardiac tumors are metastatic tumors and only a few are primary cardiac neoplasms. Cardiac myxoma is the most common primary cardiac neoplasm which usually presents in the left atrium. On the other hand, primary cardiac lymphoma (PCL) is a relatively rare malignancy, and it accounts for less than 2% of primary cardiac neoplasms [1]. Primary cardiac lymphoma incidence is slightly higher in male patients, and the elderly are more prone to suffer from this disease [2]. PCL presents mostly in the right atrium of the heart [3].

Diffuse large B-cell lymphoma (DLBCL) is the most common type of

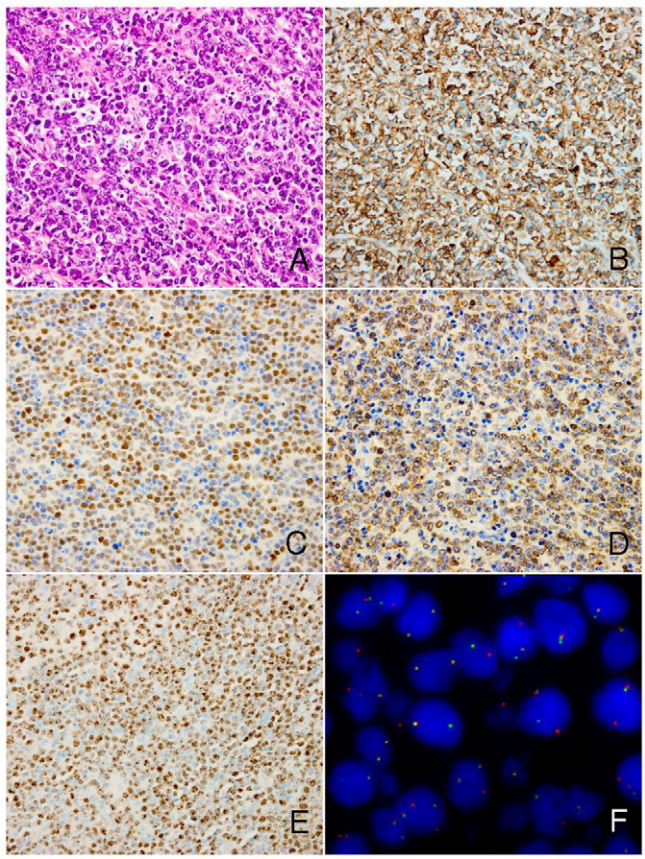


**Fig. 2.** Histopathological and genetic features of the primary cardiac diffuse large lymphoma. (**A**) The tumor cells are large lymphoid cells with round or oval nuclei, vesicular chromatin and mitotic figs. (H&E stain, ×400). They are positive for CD20 (**B**), MYC (**C**), BCL2 (**D**), Ki-67 (**E**) (IHC stain, ×400); (**F**) Interphase FISH study demonstrated separate red and green signals, indicating MYC gene rearrangement (LSIC-MYC dual-color, break-apart rearrangement probes).

non-Hodgkin lymphoma (NHL), which has heterogeneous features implying different biological behavior. DLBCLs have been subclassified into germinal center B-cell like (GCB) and activated B-cell-like (ABC) molecular 'subgroups' based on their gene expression profiles (GEPs) [4,5]. Hans algorithm has been developed to determine the cell-of-origin by immunostaining with CD10, BCL6 and MUM1 antibodies. Generally, non-germinal center B-cell type DLBCL shows worse prognosis than that of germinal center B-cell type [6]. Most of the primary cardiac DLBCLs are classified as non-GCB subtype in the literature [7–9]. The present case is a diffuse large B-cell lymphoma, non-germinal center B-cell type by the Hans algorithm.

*MYC* is a powerful oncogene initially identified as the target of the t(8;14)(q24;q32) chromosome translocation in Burkitt lymphoma (BL). *MYC* gene rearrangements have been identified in many mature B-cell lymphomas that are usually associated with an aggressive clinical behavior [10]. For example, *MYC* rearrangements can be observed in approximately 10% of de novo DLBCL correlating with a worse outcome [10,11].

To the best of our knowledge, only two cases of primary cardiac DLBCL with MYC gene rearrangement and another case with double-hit MYC and BCL2 gene rearrangements were reported by a previous study [7]. Patients with MYC/BCL2 double-hit lymphoma (DHL) have an aggressive clinical course and very poor prognosis with median overall survival of <2 years [12].

DLBCL with concurrent expression of MYC and BCL2 proteins detected by IHC is regarded as double-expressor lymphoma (DEL), which accounts for approximately 20% of DLBCL [13,14]. Previous reports determined the optimum cutoffs for MYC (≥40%) and BCL2 (≥50%) protein expressions to predict survival [14,15]. DEL is predominantly observed in the ABC subtype of DLBCL. A series of studies have shown that DEL patients exhibited a shorter overall survival in response to rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) therapy compared with patients who express only one or neither protein [16,17]. Up to now, very few studies have examined protein expression of MYC and BCL2 with IHC in primary cardiac DLBCL. Only four patients with primary cardiac DLBCL showing co-expression of BCL2 and MYC protein were reported previously by two groups [7,18]. Data are very limited regarding primary cardiac lymphoma with DEL or DHL characteristics. Of course, we should also acknowledge the possibility that cases of primary cardiac DLBCL reported in the past may have included some DEL or DHL cases that were not recognized as such at the time they were published.

As far as we know, this presenting case is a fairly rare case of primary cardiac diffuse large B-cell lymphoma with MYC and BCL2 protein co-expression in addition to MYC gene rearrangement. It can be subclassified as non-germinal center B-cell type by the Hans algorithm. The biological significance of these genetic features as well as protein-expressions in primary cardiac diffuse large B-cell lymphoma should be studied by collecting more cases.

## Conflict of interest

Disclosure statement

All authors disclosed no financial relationships relevant to this publication.

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