

Primary cardiac CD5-positive diffuse large B-cell lymphoma: A case report and review of literature

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Case Report

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Abstract

Background Primary cardiac CD5 positive diffuse large B-cell lymphoma (CD5+ DLBCL) is a rare subtype of DLBCL with many diagnostic challenges. The case is reported, along with a review of several characteristics of the disease.

Case presentation We described a 64-year-old female who presented with a 12-month history of cough, and a mass in the right atrium observed on imaging studies that extended into the right ventricle.

Conclusions CD5+ DLBCL was confirmed finally by pathological examination of the cardiac biopsy. The patient responded well to the modified R-CHOP regime. The poor prognosis factors include CD5 positive, non-GCB immunophenotype, *myc*, *bcl-2* and *bcl-6* gene rearrangements etc. Early diagnosis and aggressive treatment play a key role on improving the prognosis of primary cardiac CD5+ DLBCL.

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common type of Non-Hodgkin's lymphoma (NHL), and representing 30%~40% of all NHLs with a high aggressiveness and poor prognosis, and occurring mostly in immune compromised patients. Primary cardiac CD5 positive diffuse large B-cell lymphoma (CD5 + DLBCL) is extremely rare subtype of DLBCL that involves only the heart and/or pericardium, accounting for < 2% of all primary cardiac tumors^[1, 2]. Gene expression studies support the idea that CD5 + DLBCL is distinct from other DLBCL. The prognosis is poorer due to stronger invasive ability. However, the diagnostic criteria and molecular features are still unclear. Herein, we report a patient who suffered primary cardiac CD5 + DLBCL and summary its clinical characteristics by reviewing literature.

Patient Information

Clinical history

A 64-year-old female presented with 12-month history of cough. No facial puffiness, exertional chest tightness, and dyspnoea, absent lower limb oedema and no lymphadenopathy. Magnetic resonance imaging (MRI) revealed a mass in the right atrium, infiltrating into the right wall of the right ventricle. The bicuspid valve was squeezed. MRI enhanced Scan demonstrated asymmetrical intensification in mass, while showed a low density in the foci compared with the cardiac cavity (Figure 1A-C). Transesophageal echocardiography with color Doppler imaging (TECDI) demonstrated the bicuspid valve was squeezed and cardiac insufficiency with abundant blood flow signal in the lesions (Figure 1D-E). Electrocardiogram (ECG) showed ST Segment and T-wave alternated. In that case, Malignant tumor from right atrial wall was considered. The patient had a history of renal amyloidosis for 5 years and multiple myeloma IgG type for 4 years. No space occupying lesions were found in the lung, liver, spleen and kidney. It showed that Lactate dehydrogenase (LDH), creatine phosphokinase, hydroxybutyrate dehydrogenase and troponin were significantly increased to test the level of serum myocardial enzymogram before biopsy operation.

Pathological findings

The macroscopy pathology showed that the total size of gray and broken tough tissue was about 0.5×0.5×0.2cm. Histopathological examinations revealed the neoplastic proliferation of large lymphoid cells with round to irregular nuclear contours, vesicular nuclei, and single to multiple nucleoli (centroblastic and immunoblastic morphology)(Figure 2A). Immunohistochemical staining were performed and showed that the large neoplastic lymphoid cells positive for CD20 (Figure 2B), CD5 (Figure 2C), Bcl-2 (Figure 2D), Bcl-6 (Figure 2E), MuM-1 (Figure 2F), C-myc (Figure 2G) with a high Ki-67 proliferative rate (85%)(Figure 2H), while were negative for CD3, CD10, CyclinD1. No EBV infection was confirmed by (EBER)-in situ hybridization (Figure 3A). Fluorescence in situ hybridization (FISH) studies were carried to detect myc, bcl-2, bcl-6 gene rearrangement and showed positive for bcl-6 gene rearrangement (Figure 3D) and negative for myc, bcl-2 gene rearrangement (Figure 3B, Figure 3C). Thus, a final diagnosis of primary cardiac CD5-positive diffuse large B-cell lymphoma (CD5+ DLBCL) expressing bcl-6 rearrangement was made.

After diagnosis, the patient underwent comprehensive physical examination prior to rituximab, 600mg mono-therapy. Considering the deterioration of renal amyloidosis during treatment, she received PC chemotherapy regimen▯bortezomib 2mg, day 1; cyclophosphamide 0.3mg, day 1. Then, she received following four cycles of R-CHOP chemotherapy regimen: rituximab, 600mg, day 0; cyclophosphamide, 0.5g, days 1-2; doxorubicin hydrochloride liposome, 40mg, day 1-2; vincristine, 4mg, day 1; prednisone, 15mg, days 1–5. The patient was in remission after 7 months treatment courses. PET/CT showed no obvious morphological changes in the right atrium, and FDG metabolism was normal in the right atrium and the whole body (including brain tissue). However, pancytopenia and suppression of cellular immunity were observed. The patient is receiving further treatment for increasing white cells currently. The further following up is performing.

Discussion And Conclusions

DLBCL is the most common subtype of non-Hodgkin's lymphoma. Many studies showed that the heterogeneity were apparent in clinical features, morphological characteristics, immunophenotype, genetics, therapeutic response and prognosis. As a transmembrane receptor that mainly regulates T cell functions and development, CD5 is also expressed by a small subset of normal B cells. It contributes to the progression of tumor by inhibiting the T cell response and protecting B cells from B cell receptor (BCR) signaling-mediated apoptosis^[3]. Generally, CD5 is expressed in the B cell lymphoma such as chronic lymphocytic leukemia (CLL) and Mantle cell lymphoma (MCL)^[4]. In addition, a number of CD5 positive hairy cell leukemia cases have been reported^[5]. Recent years, Increasing CD5 + DLBCL cases, especially primary occurred in cardiac, have been reported with the imaging examination and technological progress.

As a matter of fact, there were no specific clinical symptoms, which further led to misdiagnosis or missed diagnosis. The most common symptoms are dyspnea, chest pain, and constitutional complaints such as

fever, night sweats, loss of appetite, and weight loss. It usually involves the right heart, in particular the right atrium. Only less than 10% of cases show isolated left heart involvement. Yang Xiao et al^[6] reported a 64 years old female patient with primary CD5 + DLBCL in the right atrium. The patient's main clinical manifestations were facial edema, tiring chest tightness and dyspnea, with jugular vein filling, and no edema of lower limbs. All 3 of cases reported by Gwyneth Soon, MBBS et al^[2] had right heart involvement. Only 1 case involved all 4 chambers of the heart. In our case, the mass occupied the right atrium, infiltrating into the right wall of the right ventricle.

Primary cardiac lymphomas were uncommon and accounted for only 1–2% of all primary cardiac tumors. Over 90% primary cardiac lymphomas are of B-cell type, eg. Burkitt lymphoma (BL) and plasmablastic lymphoma, while the most of those are DLBCL^[7, 8]. Generally, molecular classification was according to the WHO classification for tumors of hematopoietic and lymphoid tissue (2017), which emphasizes that DLBCL is classified according to different gene expression profiling (GEP), i.e. germinal center B-cell (GCB) type, activated B-cell (ABC) type and unclassified DLBCL. Most of CD5 + DLBCL were ABC type^[9]. Immunophenotypic subtyping of primary cardiac CD5 + DLBCL into cell-of-origin GCB and non-GCB subgroups is less commonly reported in the literature compared with DLBCL originating from other sites. In our study, the diagnosis of the case is belonged to non-GCB immunophenotype using the Hans IHC algorithm method.

Patients with DLBCL demonstrating high myc and bcl-2 protein expression by IHC, regardless of status of myc or bcl-2 gene rearrangements, have been shown to have a poorer prognosis. High-grade B-cell lymphomas with both myc and bcl-2 gene rearrangements or double-hit lymphomas are known to have an extremely poor prognosis^[10, 11]. The median survival time was less than 2 years^[12]. Primary cardiac CD5 + DLBCL with myc gene rearrangement and primary cardiac double-hit B-cell CD5 + lymphoma with myc and bcl-2 gene rearrangements are rarely previously reported in the literature. A case of cardiac CD5 + DLBCL co-expressing c-myc and bcl-2 was reported by Yang Xiao et al^[6]. In our case, bcl-6 gene rearrangement was detected positive but no detectable myc and bcl-2 gene rearrangements. Primary studies have shown that compared with CD5- DLBCL, the prognosis of patients with CD5 + DLBCL is characterized by poor prognosis and a high frequency of central nervous system relapse, and there is no significant correlation between CD5 expression and myc, bcl-2 and / or bcl-6 gene rearrangement^[4, 13]. Further studies would be helpful to evaluate the prognostic significance of MYC, BCL-2 and BCL-6 protein co-expression as well as those gene rearrangements with specific reference to primary cardiac CD5 + DLBCL.

There is still no standard and unified scheme for the treatment of CD5 + DLBCL by the now. Early diagnosis and aggressive treatment play a key role on improving the prognosis of primary cardiac CD5 + DLBCL. R-CHOP is still recommended in the current standard first-line therapy. In our case, R-CHOP chemotherapy is adopted and symptoms of the patient have been significantly relieved. However, CD5 + DLBCL occurs frequently in elderly patients who cannot tolerate high-dose chemotherapy and combination therapy. That will be a problem we must face in the future. A phase II study conducted by

Kana Miyazaki et al ^[14] showed that dose-adjusted (DA)-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) combined with high-dose methotrexate (HD-MTX) might be a first-line therapy option for stage II-IV CD5 + DLBCL.

In conclusion, primary cardiac CD5 + DLBCL is an uncommon and aggressive subtype lymphoma with higher risk of central nervous system (CNS) relapse. The factors of poor prognosis include CD5 positive, non-GCB immunophenotype, myc, bcl-2 and bcl-6 gene rearrangements or double/three-hit, Ki-67 positive rate no less than 90% or a higher LDH value (more than 3 times compared with normal value). Earlier detection and diagnosis contribute to promote patient's prognosis. Advanced radiological techniques and confirmatory histologic and / or cytologic diagnosis via periodic fluid drainage or variable endocardial biopsy techniques are the main diagnostic procedures.

Abbreviations

CD5+/- DLBCL ☐ CD5 positive/negative diffuse large B-cell lymphoma

NHL ☐ Non-Hodgkin's lymphoma

MRI ☐ Magnetic resonance imaging

TECDI ☐ Transesophageal echocardiography with color Doppler imaging

ECG ☐ Electrocardiogram

LDH ☐ Lactate dehydrogenase

FISH ☐ Fluorescence in situ hybridization

CLL ☐ Chronic lymphocytic leukemia

MCL ☐ Mantle cell lymphoma

BL ☐ Burkitt lymphoma

GEP ☐ Gene expression profiling

GCB ☐ Germinal center B-cell

ABC ☐ Activated B-cell

IHC ☐ Immunohistochemistry

R-CHOP ☐ rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

DA ☐ Dose-adjusted

EPOCH-R☐etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab

HD-MTX☐High-dose Methotrexate

CNS☐Central nervous system

Declarations

Ethics approval and consent to participate

The study was approved by the Human Ethics Committee of The First Affiliated Hospital Zhejiang University School of Medicine.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

QQ-G collected data. X-Y was involved in the analysis and interpretation of the data. HJ-Y wrote the paper. MD-ZM-W reviewed and edited the manuscript. The final version of the manuscript has been read and approved by all authors.

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References

- [1] Cioc A M, Jessurun J, Vercellotti G M, Pambuccian S E. De novo CD5-positive primary cardiac diffuse large B-cell lymphoma diagnosed by pleural fluid cytology [J]. *Diagnostic Cytopathology*, 2014, 42(3): 259-267.
- [2] Soon G, Ow G W, Chan H L, Ng S B, Wang S. Primary cardiac diffuse large B-cell lymphoma in immunocompetent patients: clinical, histologic, immunophenotypic, and genotypic features of 3 cases [J]. *Annals of Diagnostic Pathology*, 2016, 24(40-46).
- [3] Voisinne G, Gonzalez de Peredo A, Roncagalli R. CD5, an Undercover Regulator of TCR Signaling [J]. *Front Immunol*, 2018, 9(2900-2900).
- [4] Zhang Y, Wang X, Liu Y, Sun C, Shi W, Huang H. Lenalidomide combined with R-GDP in a patient with refractory CD5-positive diffuse large B-cell lymphoma: A promising response and review [J]. *Cancer Biol Ther*, 2018, 19(7): 549-553.
- [5] Jain D, Dorwal P, Gajendra S, Pande A, Mehra S, Sachdev R. CD5 positive hairy cell leukemia: A rare case report with brief review of literature [J]. *Cytometry Part B: Clinical Cytometry*, 2016, 90(5): 467-472.
- [6] Xiao Y, Cai Y, Tang H, Xiao X. De novo CD5-positive primary cardiac diffuse large B-cell lymphoma coexpressing C-myc and BCL2 in an immunocompetent adult [J]. *European Heart Journal*, 2016, 38(24): 1937-1937.
- [7] Miguel C E, Bestetti R B. Primary cardiac lymphoma [J]. *International Journal of Cardiology*, 2011, 149(3): 358-363.
- [8] Chen X, Lin Y, Wang Z. Primary cardiac lymphoma: a case report and review of literature [J]. *International journal of clinical and experimental pathology*, 2020, 13(7): 1745-1749.
- [9] Jain P, Fayad L E, Rosenwald A, Young K H, O'Brien S. Recent advances in de novo CD5+ diffuse large B cell lymphoma [J]. *Am J Hematol*, 2013, 88(9): 798-802.
- [10] Ma Z, Niu J, Cao Y, Pang X, Cui W, Zhang W, Li X. Clinical significance of 'double-hit' and 'double-expression' lymphomas [J]. *Journal of Clinical Pathology*, 2020, 73(3): 126.
- [11] Cucco F, Barrans S, Sha C, Clipson A, Crouch S, Dobson R, Chen Z, Thompson J S, Care M A, Cummin T, Caddy J, Liu H, Robinson A, Schuh A, Fitzgibbon J, Painter D, Smith A, Roman E, Tooze R, Burton C, Davies A J, Westhead D R, Johnson P W M, Du M-Q. Distinct genetic changes reveal evolutionary history and heterogeneous molecular grade of DLBCL with MYC/BCL2 double-hit [J]. *Leukemia*, 2020, 34(5): 1329-1341.
- [12] Li S, Lin P, Young K H, Kanagal-Shamanna R, Yin C C, Medeiros L J. MYC/BCL2 Double-Hit High-Grade B-Cell Lymphoma [J]. *Advances in Anatomic Pathology*, 2013, 20(5): 315-326.

[13] Thakral B, Medeiros L J, Desai P, Lin P, Yin C C, Tang G, Khoury J D, Hu S, Xu J, Loghavi S, Hu B, Oki Y, Li S. Prognostic impact of CD5 expression in diffuse large B-cell lymphoma in patients treated with rituximab-EPOCH [J]. *European Journal of Haematology*, 2017, 98(4): 415-421.

[14] Miyazaki K, Asano N, Yamada T, Miyawaki K, Sakai R, Igarashi T, Nishikori M, Ohata K, Sunami K, Yoshida I, Yamamoto G, Takahashi N, Okamoto M, Yano H, Nishimura Y, Tamaru S, Nishikawa M, Izutsu K, Kinoshita T, Suzumiya J, Ohshima K, Kato K, Katayama N, Yamaguchi M. DA-EPOCH-R combined with high-dose methotrexate in patients with newly diagnosed stage II-IV CD5-positive diffuse large B-cell lymphoma: a single-arm, open-label, phase II study [J]. *Haematologica*, 2020, 105(9): 2308-2315.

Figures

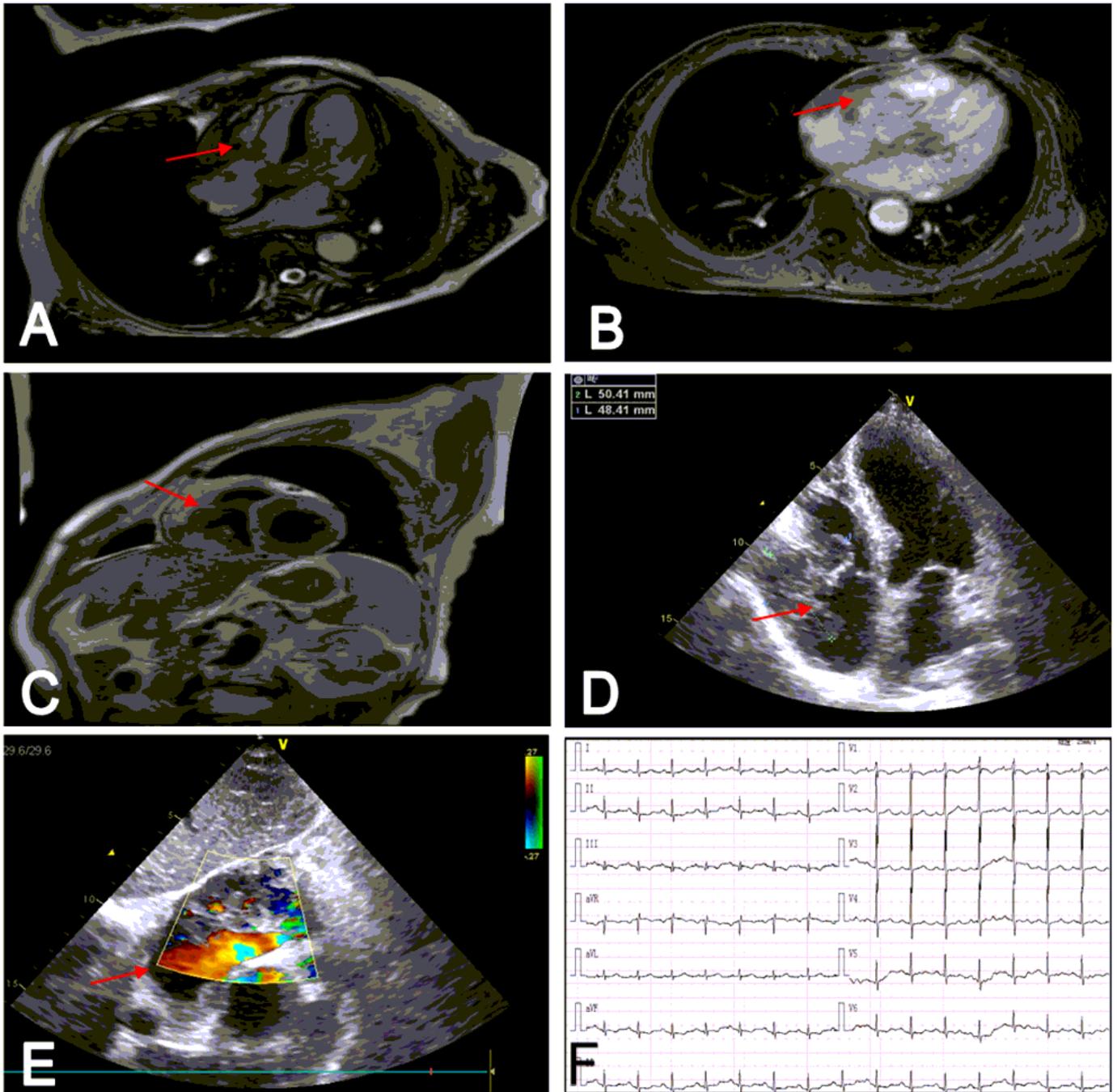


Figure 1

Malignant tumor from right atrial wall was considered by Image analysis and ECG A. Cardiac MRI FIESTA CINE showed the tumor raised in the right atrium, infiltrating into the right wall of the right ventricle (red arrows). B and C. Cardiac MRI LAVA showed the tumor had the same signal strength as adjacent normal cardiac muscle on T1-weighted imaging (red arrows). D. TECDI demonstrated the bicuspid valve was squeezed and cardiac insufficiency (red arrows). E. TECDI showed abundant blood flow signal in the lesions (red arrows). F. Electrocardiogram: ST Segment and T -wave alternans.

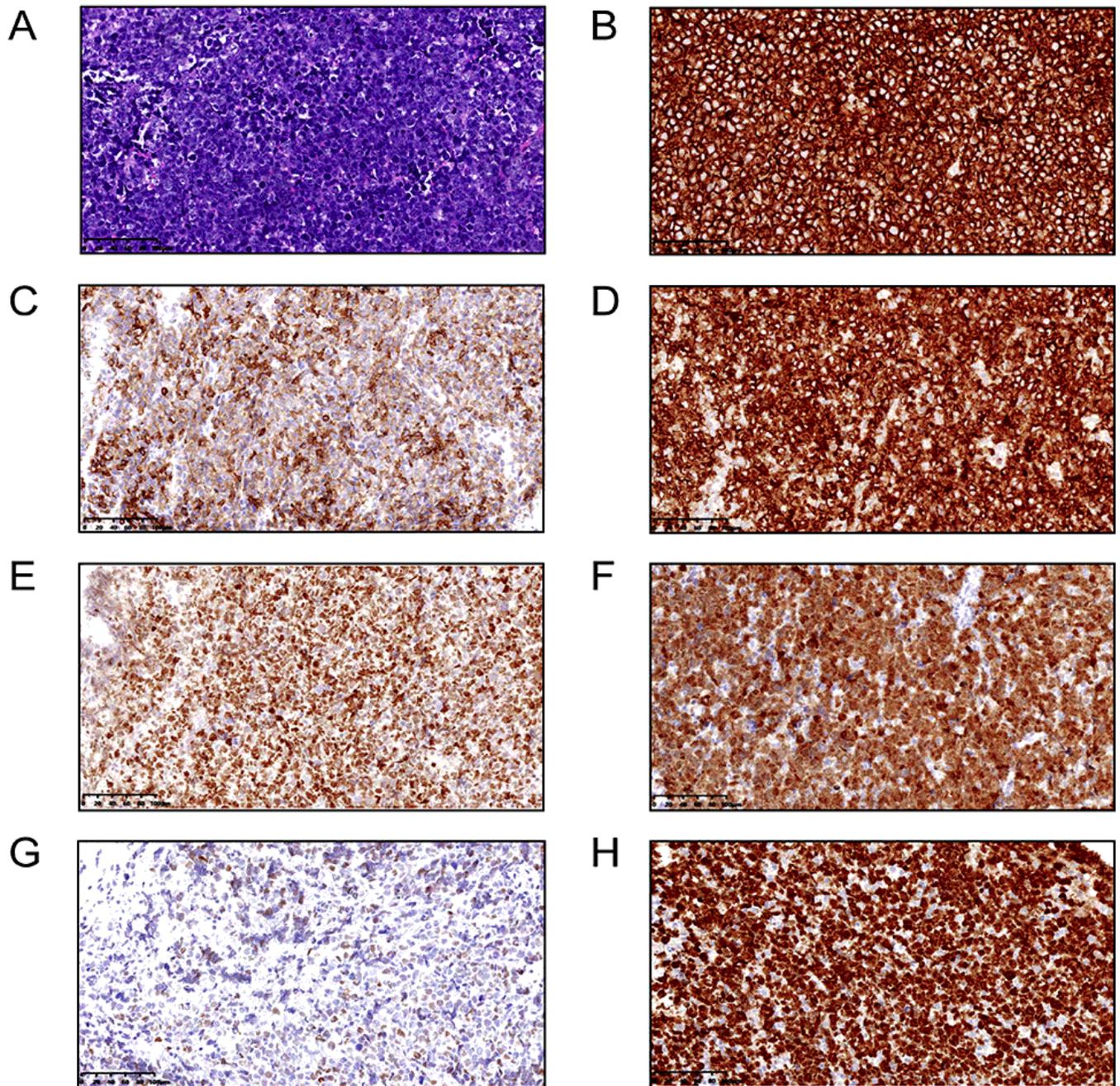


Figure 2

Histomorphology and Immunohistochemical test results of primary cardiac CD5+ DLBCL. A. Cardiac biopsy, hematoxylin-eosin staining (original magnification, $\times 200$). B. Cardiac biopsy, CD20 immunostain (original magnification, $\times 200$). C. Cardiac biopsy, CD5 immunostain (original magnification, $\times 200$). D. Cardiac biopsy, Bcl-2 immunostain (original magnification, $\times 200$). E. Cardiac biopsy, BCL-6 immunostain (original magnification, $\times 200$). F. Cardiac biopsy, MUM-1 immunostain (original magnification, $\times 200$). G.

Cardiac biopsy, c-myc immunostain (original magnification, ×200). H. Cardiac biopsy, Ki-67 immunostain (original magnification, ×200).

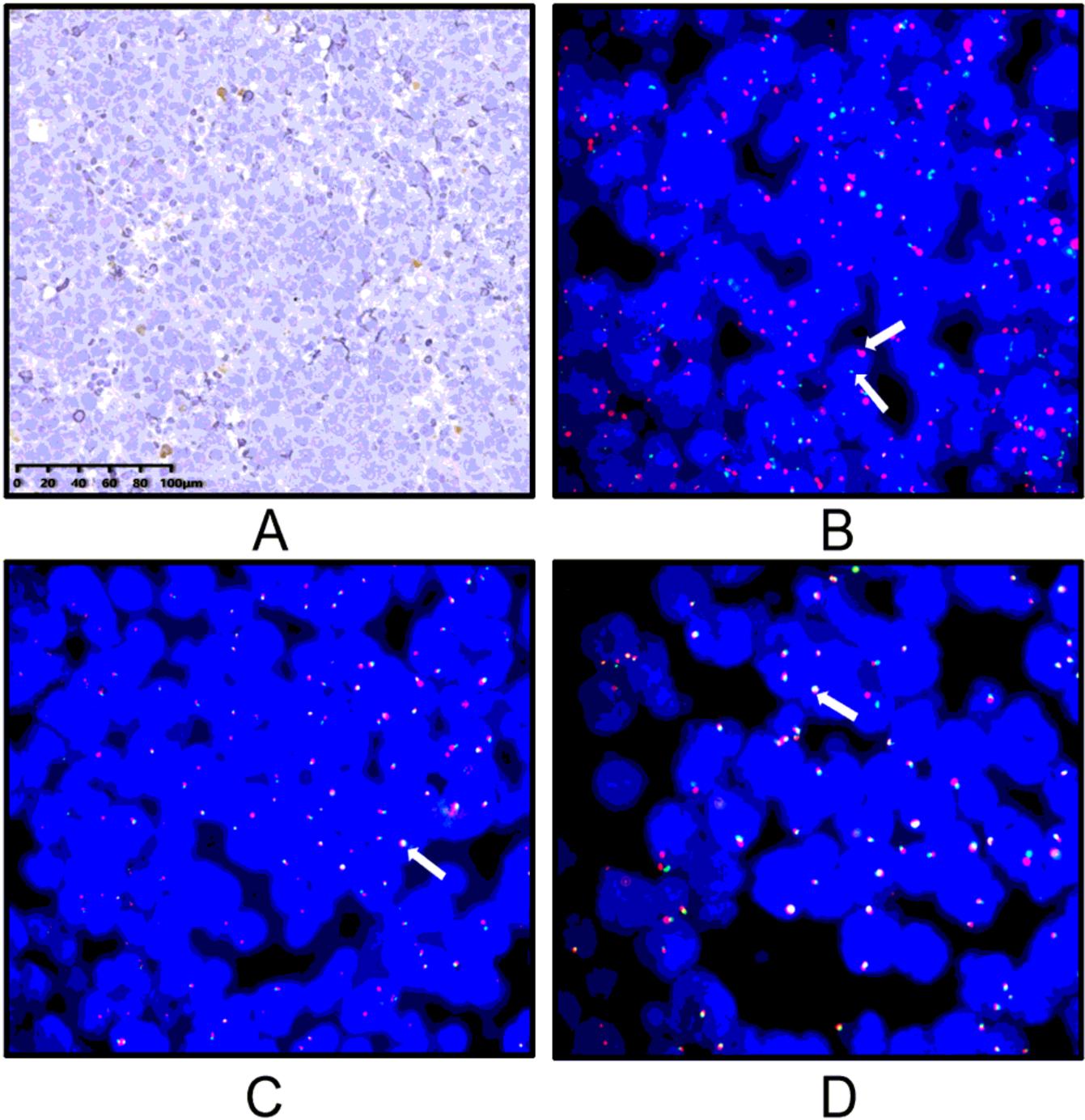


Figure 3

EBV infection test and FISH results of primary cardiac CD5+ DLBCL. A. EBV-negative in situ hybridization (original magnification, ×200). B. Interphase FISH study (dual-color break-apart probe for the bcl-6 locus) demonstrating separate red and green signals (white arrows), indicating positive bcl-6 gene rearrangement or a break at the bcl-6 locus. C and D. Interphase FISH study (dual-color break-apart probe

for the bcl-2 and myc locus) demonstrating fused yellow signals (white arrows), indicating absence of bcl-2 and myc gene rearrangement.

Supplementary Files

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