A rare presentation of primary cardiac diffuse large B-cell lymphoma: A case report

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Abstract. Primary cardiac lymphomas display a low frequency, sudden onset, swift progression of illness and elevated mortality rates. The current study presents a unique instance of primary cardiac diffuse large B-cell lymphoma and examines its clinical manifestations, pathological characteristics and differential diagnosis. A 64-year-old male patient sought medical attention due to cardiac debility and exertional dyspnea persisting for >10 days. Chest enhanced computed tomography revealed a moderately enhancing irregular mass in the ventricular area, exhibiting limited demarcation from the pericardium and left atrium, accompanied by irregular thickening of the interventricular septum. The postoperative specimen showed the presence of yellow fish-like tumor tissue. Immunohistochemical analysis revealed the presence of lymphocytes positive for CD20, BCL-2, BCL-6, c-Myc-binding protein, mutated melanoma-associated antigen 1 and CD79a, along with a high Ki-67 proliferation index of 80%. Conversely, CD10, CD30, CD3, pan cytokeratin, cyclin D1, desmin and vimentin marker results were found to be negative. Additionally, *in situ* hybridization demonstrated a lack of Epstein-Barr virus-encoded small RNA expression. The present case report emphasizes the significance of conducting a thorough analysis of the clinical manifestations of diffuse large B-cell lymphoma to assist clinicians in establishing a diagnosis and determining an effective treatment approach, thereby enhancing the patient's prognosis.

Introduction

Primary cardiac tumors are extremely rare, in a 2023 analysis of suspected factors regarding the rarity of primary cardiac lymphomas, prevalence rates ranged from 0.001 to 0.03%, with cardiac primary lymphomas accounting for only 1.3% of cases and diffuse large B-cell lymphoma (DLBCL) being the most common. A correlation with impaired immune function in the patients was confirmed (1). Primary cardiac lymphomas display a low frequency, sudden onset, swift progression of illness and elevated mortality rates, predominantly associated with DLBCL as the prevailing histological subtype (2). The right atrium is the most frequent site of onset for this condition, and patients commonly present with symptoms such as dyspnea, chest pain, heart failure, lower limb edema, arrhythmias and dizziness (3,4). In cases of DLBCL, microscopic examination reveals a distinct heterogeneity and morphological diversity among the tumor cells. These cells typically exhibit medium to large cellular morphology, large and rounded nuclei, irregular and vacuolated features, fine chromatin, prominent nucleoli, frequent nuclear schizophrenia and inconspicuous cytoplasm (5).

The present study reports the detailed treatment of a rare case of primary cardiac DLBCL in the hope of providing theoretical support and case accumulation for future treatment.

Case report

Case presentation. A 64-year-old male patient was admitted to the Suining Central Hospital (Suining, China) in September 2022 presenting with symptoms consistent with heart failure. The patient reported experiencing unprovoked shortness of breath, which was alleviated by rest. Additionally, the patient exhibited abdominal distension, loss of appetite, occasional nausea and vomiting, malaise after eating and oedema in both lower limbs. The patient had no history of hypertension or diabetes mellitus, and no generalised superficial lymph node enlargement was observed. The patient consented to further evaluation and was subsequently transferred to the Department of Cardiac Surgery. However, the patient was admitted to the hospital with a poor mental health status due to the dyspnoea, nausea and fatigue caused by the heart failure and was unable to tolerate a pericardiocentesis. Therefore, a pericardiocentesis cytological analysis was not performed on this patient.

Pulmonary artery computed tomography angiography (CTA). CTA was performed and irregular filling defects were observed within the region of the right cardiac cavity, encompassing both the ventricular and atrial regions, accompanied

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by a minor constriction of the right ventricular outflow tract (data not shown).

Enhanced CT results. On enhanced CT, the right side of the heart exhibited irregular morphology, with the right auricle, right atrium and ventricular area displaying enhancement. An irregular mass with relatively weak enhancement was observed, measuring ~6.9x6.2 cm on cross-section. The lesion lacked clear demarcation from the pericardium and the left atrium, while the interventricular septum showing irregular thickening (Fig. 1).

Cardiac ultrasound. On cardiac ultrasound, a moderately robust echogenic mass was observed within the right heart cavity, accompanied by an enlarged right atrium. Additionally, mild aortic regurgitation and a small quantity of pericardial effusion were noted. A carotid vascular ultrasound revealed bilateral intima-media thickening of the common carotid arteries, along with the presence of atherosclerotic plaque formation. Notably, the patient experienced arrhythmias during the examination, as depicted in Fig. 2.

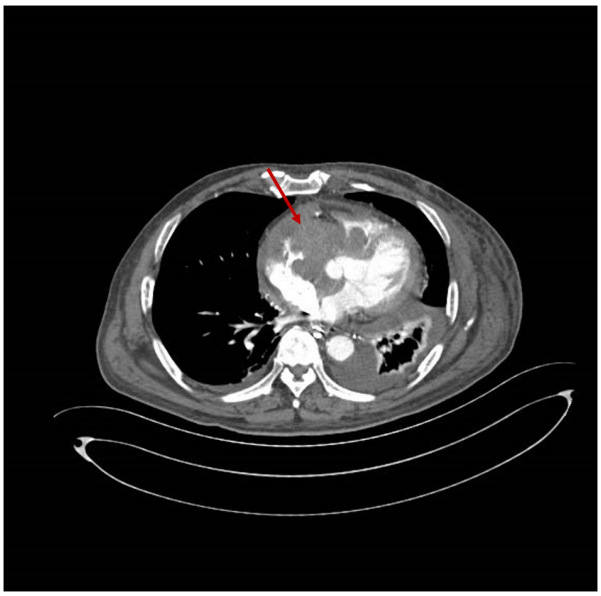

Figure 1. Enhanced CT scan of the right heart. As indicated by the arrows, the CT scan shows an irregular morphology of the right side of the heart with a mass observed and enhancement of the right auricle, right atrium and ventricle regions.. CT, computed tomography.

Pathological findings

Macroscopic examination. Following a meticulous preoperative examination, a surgical procedure was conducted on the third day after admission to alleviate the symptoms and clarify the diagnosis. The surgery included a right atrial tumor resection, right ventricular tumor resection, pericardial mediastinal drainage and internal sternal fixation under general anaesthesia, plus tracheal intubation with extracorporeal circulation. During the operation, the presence of multiple tumors in the right atrium and right ventricle was observed, with the largest tumor measuring ~7x4 cm in size. The tumor was found at the base of the interventricular septum, exhibiting dense growth and adherence to both the interventricular septum and tricuspid valve. Additionally, the tumor was surrounded by a significant amount of adherent thrombus in the right atrium, some of which were embedded in the right atrial comb muscle. Multiple tumors, measuring ~3 cm in diameter, were observed in the right ventricle. These tumors caused severe occlusion of the tricuspid valve as they straddled its orifice. The tumor exhibited a yellow hue and a texture reminiscent of fish meat. After the surgery, upon making an incision into the right heart tumor, it became evident that there was a conglomeration of disfigured tissue in shades of greyish-white and greyish-brown. The tissue measured 7.5x6.5x3.0 cm in total volume and exhibited a solid composition with a soft, fish-like texture on the cut surface. These characteristics served as pathological evidence supporting the diagnosis of diffuse cardiac large B-cell lymphoma (Fig. 3).

Microscopic observation. Tissue specimens were fixed in 10% buffered formalin for 6 h at room temperature and subjected to graded alcohol dehydration (70, 80, 95, 95, 100 and 100%), then made transparent twice using environmentally friendly clearing agent, and dipped in wax after transparency, all in a Leica fully automated dehydrator (Leica Microsystems, Inc.). The following day, after paraffin embedding, the tissues were sectioned at a thickness of 3 μm, and the slices were baked for 30 min and then stained with hematoxylin (10 min at room temperature) and eosin (3 min at room temperature) in a Leica automatic stainer (Leica Microsystems, Inc.). The application of hematoxylin and eosin staining revealed a diffuse distribution of tumor cells with evident heterogeneity. These cells exhibited medium to large cellular morphology, characterized by round or oval nuclei, prominent nucleoli, irregular contours, fine and vesicular chromatin, one to two conspicuous nucleoli, frequent nuclear division and inconspicuous cytoplasm (Fig. 4A and B). Immunohistochemical staining was performed on representative sections of 3 μm in thickness, and immunohistochemistry was performed on a Roche BenchMark ULTRA IHC machine (Roche Diagnostics). Immunohistochemical staining was performed using the following antibodies at 37˚C for 60 min: CD20 (cat. no. L26), BCL-2 (cat. no. OTIR1H2), BCL-6 (cat. no. LN22), c-Myc-binding protein (c-Myc) (cat. no. EP121), mutated melanoma-associated antigen 1 (MUM-1) (cat. no. EP190), CD79a (cat. no. EP82), CD10 (cat. no. UMAB235), CD30 (cat. no. UMAB256), CD3 (cat. no. EP41), pan-cytokeratin (CK-pan) (cat. no. AE1/AE3), cyclin D1 (cat. no. SA38-08), Ki-67 (cat. no. MIB1), desmin (cat. no. OTIR4A8) and vimentin (cat. no. EP21). The primary antibodies were all ready-to-use antibodies from OriGene Technologies, Inc., and were added manually during the run without dilution. The secondary antibody (UV HRP UNIV MULT; 8 min at 37˚C) was detected using the UltraView Universal DAB Detection Kit system [(10)K01773; Roche Tissue Diagnostics]. DAB was used as the color developer (8 min at 37˚C), hematoxylin (37˚C; 8 min) was used for re-staining after color development and Roche Bluing reagent was used for re-bluing. The films were sealed with neutral gum and then read and imaged under an Olympus light microscope. Immunohistochemical staining revealed positive expression of CD20, BCL-2, BCL-6, c-Myc, MUM-1 and CD79a, with a Ki-67 proliferation index of 80% in the lymphoid cells (Fig. 5). Conversely, negative results were found for CD10, CD30, CD3, CK-pan, cyclin D1, desmin and

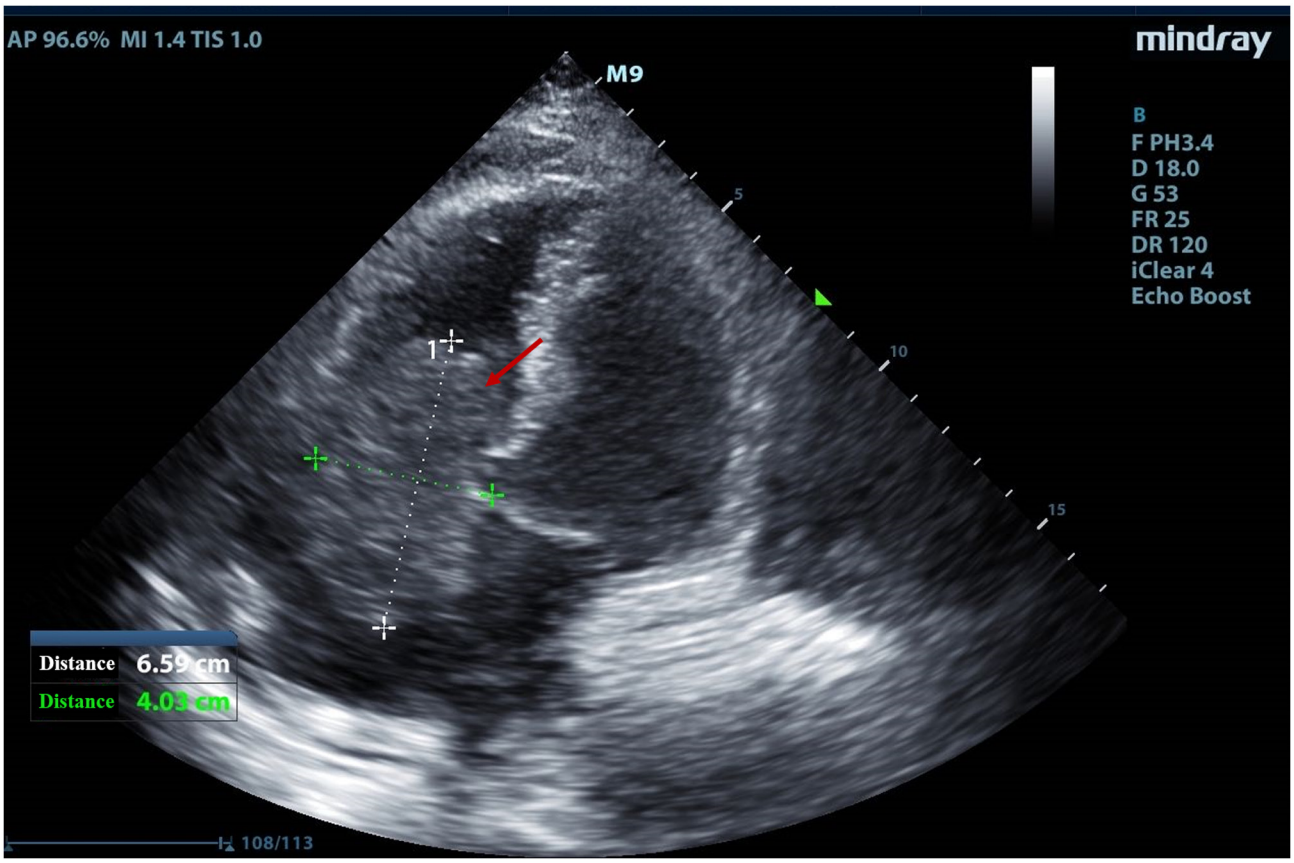

Figure 2. Ultrasound examination of the right heart. An ultrasound examination of the heart revealed the presence of moderate to strong echogenic masses within the right heart cavity, accompanied by an enlargement of the right atrium, as indicated by the arrow.

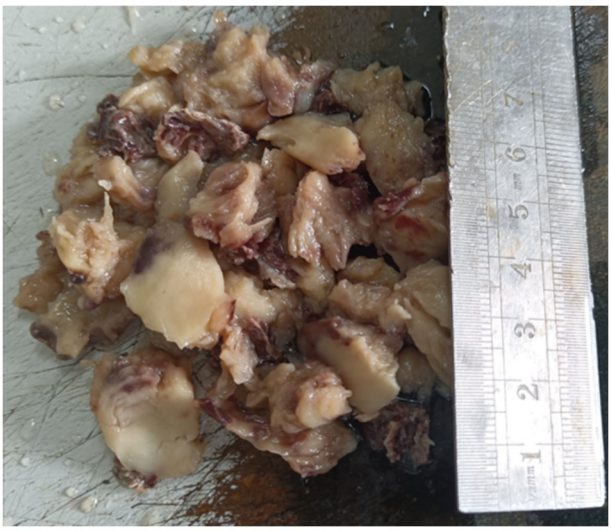

Figure 3. Macroscopic observation of the resected right heart tumor.

vimentin (data not shown). Furthermore, *in situ* hybridization (performed by the West China Hospital of Sichuan University) demonstrated the absence of Epstein-Barr virus-encoded small RNA.

Gene detection. Gene detection, specifically fluorescence *in situ* hybridization (FISH), was performed on specific paraffin-embedded tissue sections at West China Hospital of Sichuan University. The findings revealed the absence of isolated rearrangements of BCL-2 and C-MYC genes (data not shown).

Pathological diagnosis. The patient was diagnosed with DLBCL originating from the right heart, specifically the non-growth center B-cell subtype.

Follow-up. After the surgery, the patient was prescribed chemotherapy employing the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) regimen. The patient was administered combination chemotherapy with the R-CHOP regimen (0.5 g cyclophosphamide on day 1 and 0.9 g on day 8, 40 mg epirubicin on day 1, 40 mg liposomal doxorubicin on day 8, 2 mg vincristine on day 1, 100 mg prednisone on days 1-5 and 700 mg rituximab on day 6) in fractions starting in October 2022. The patient was provided with long-term out-of-hospital oral anticoagulation with rivaroxaban. However, the patient died of heart failure in March 2023 after 6 months of follow-up.

Discussion

Primary cardiac lymphoma typically affects individuals who are immunocompromised, resulting in the targeting of the heart or pericardium. This form of lymphoma, known as DLBCL of the heart, is distinguished by its rapid onset and severe nature,

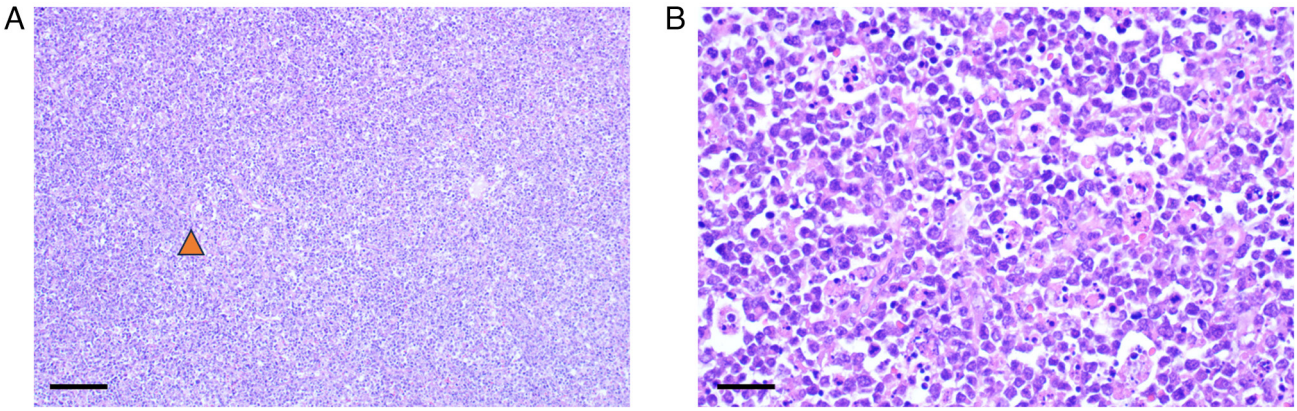

Figure 4. Hematoxylin and eosin staining of DLBCL. The histopathological presentation of DLBCL is characterized by the diffuse distribution of tumor cells, which are larger in size. Under microscopic examination, the tumor cells exhibit circular or elliptical nuclei with prominent and irregularly shaped nucleoli. The cytoplasm is not readily discernible. (A) Magnification, x100 (scale bar, 100 μm). (B) A magnified view of the region indicated by the red triangle in (A), emphasizing the typical characteristics of DLBCL (magnification, x400; scale bar, 30 μm). DLBCL, diffuse large B-cell lymphoma.

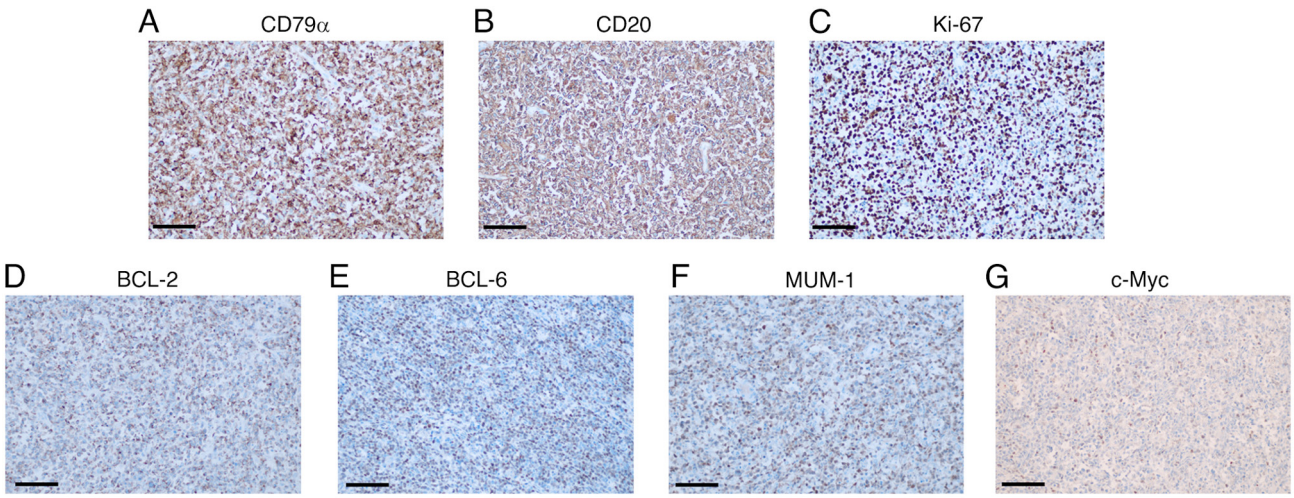

Figure 5. Immunohistochemical staining for markers associated with diffuse large B-cell lymphoma, observed under a microscope. The expression of B-cell markers (A) CD79a and (B) CD20 was strongly positive, the expression of B-cell lymphoma markers (C) MUM-1, (D) BCL-2, (E) BCL-6 and (G) c-Myc (~10%) was positive, and the expression of (F) Ki-67, a marker associated with cellular proliferation, was positive with a proliferation index of 80%. Magnification, x200; scale bar, 60 μm. MUM-1, mutated melanoma-associated antigen 1.

often presenting with symptoms such as cardiac arrhythmia, heart failure, palpitations and dyspnea (4,6). The present study observed a patient who primarily exhibited symptoms of heart fatigue, weakness, nausea, loss of appetite with vomiting and bilateral lower limb edema without identifiable triggers. Notably, the patient did not experience palpitations, cardiac pain, chest pain or detectable enlargement of superficial lymph nodes throughout the body. As a result, cardiac lymphoma is often not considered in emergency treatment evaluations due to the absence of these symptoms. However, this case serves as a reminder for clinicians to consider the possibility of cardiac lymphoma when encountering similar patients. Cardiac DLBCL is characterized by its atypical and infrequent occurrence, with advanced cases exhibiting a dismal prognosis (2). Therefore, it is imperative to prioritize early diagnosis and suitable treatment. Consequently, maintaining a high level of suspicion and conducting appropriate investigations are strongly advised to facilitate prompt intervention and achieve favorable treatment outcomes.

However, the clinical manifestations of cardiac lymphoma lack specificity, necessitating reliance on pathological diagnosis as the definitive method. Hence, the diagnosis of the patient under investigation in this study was conclusively established through the examination of surgically resected specimens. During the surgical procedure, the excision of the tissue occupying the right atrium and the thrombus that adhered to its wall was performed with meticulous care. However, complete removal of these entities proved unattainable due to the dense proliferation of the tumor's base and the interatrial septum. This observation supports the notion that surgical excision of tumor tissue holds significant diagnostic value in confirming the presence of the disease. However, performing surgery on immunocompromised and older patients carries a potential risk of severe complications. In light of this, it has been proposed that pericardial biopsy and cytology of the pericardial effusion may offer some degree of benefit in confirming the diagnosis of cardiac lymphomas, particularly for DLBCL (6). Consequently, it is desirable that

the less invasive cytological examination of pericardial effusion, along with associated genetic tests, be employed in the subsequent clinical practice to mitigate the surgical trauma experienced by these patients.

Certain scholars argue that the prognosis of cardiac lymphoma is unfavorable, with treatment primarily encompassing radiotherapy, surgery, chemotherapy, combined treatment and other modalities (7,8). The administration of chemotherapy has been observed to extend a patient's survival duration, while surgical intervention can effectively alleviate symptoms and facilitate an accurate diagnosis, thereby enhancing the overall survival period (7,8). However, in the present study, following the surgical excision of the tumorous tissue, the patient was prescribed chemotherapy employing the R-CDOP regimen, ultimately succumbing within 6 months of surgery during the postoperative monitoring period. It has been postulated that this outcome may be attributed to the heterogeneity observed in DLBCL, with specific variants identified in the World Health Organization classification constituting a substantial proportion, ~20%, of all cases of SLBCL (9). These variants exhibit distinctive morphological or immunophenotypic characteristics and present with diverse clinical manifestations, thereby posing a significant challenge. One case report in the literature (2) describes the occurrence of a large mass in the right atrium obstructing the tricuspid valve in a 26-year-old immunocompetent female patient. The patient visited a clinic due to symptoms of shortness of breath, facial puffiness and lower limb edema. In order to confirm the diagnosis of DLBCL, prompt surgery was conducted, followed by six cycles of postoperative R-CHOP chemotherapy. As a result of this treatment, the mass completely resolved. This case exhibits certain dissimilarities from the present case, and it is posited that the patient's age greater constituted a significant risk factor. However, it is imperative to acknowledge the potential association with the autoimmune profile in the literature case as well (2).

Cardiac tumors, including cardiac lymphomas, are infrequent occurrences. With regard to cardiac lymphomas, the right atrium is the most frequently affected site of invasion (3). Notably, diffuse cardiac large B-cell lymphoma represents the predominant pathological type, constituting ~75% of reported cases (5). The microscopic examination of diffuse cardiac large B-cell lymphoma reveals a notable heterogeneity among the tumor cells, characterized by a wide range of morphological variations and peculiarities. These include medium to large cellular morphology, large and rounded nuclei with irregular and vacuolated features, fine chromatin, prominent nucleoli, frequent nuclear divisions and inconspicuous cytoplasm. The immunophenotype analysis revealed that the tumor cells exhibited positivity for B-cell-derived markers, including CD20, CD79a and CD19, while showing negativity for T-cell-derived markers, such as CD3 and CD5 (9). It is worth noting that some cases demonstrated positivity for CD5 (10). Additionally, the clinical presentation of positive cases is characterized by aggressiveness (10).

The diagnosis of diffuse cardiac large B-cell lymphoma also needs to be differentiated from other malignancies of the heart (2) such as: i) In metastatic carcinoma, the patient's medical history is clear, the tumor cells have obvious heterogeneity, most of them show large, deeply stained nuclei, the ratio between the nuclei and cytoplasm is out of proportion, and the tumor cells are solid and nested. Tissues are usually positive for CK-pan and negative for lymphocyte markers, such as CD3, CD20 and CD45. In the present case, the auxiliary examination showed that no lesion was present in any organ except the heart, which confirmed that the lymphoma was a primary tumor of the cardiac tissues; cardiac malignancies such as ii) cardiac rhabdomyosarcoma, which occurs in adolescents or young children, microscopically shows astrocytes or small round cells with round or ovoid, deeply stained nuclei, transverse and multinucleated cells, and immunohistochemistry positive for vimentin, myogenin, partially positive for desmin and scattered positive for MyoD1, with a Ki-67 proliferation index of ~20%; and iii) cardiac mucinous fibrosarcoma, a low-grade cardiac tumor with the following immunohistochemical presentation: CD30(-), CD34(-), S100(-), smooth muscle actin(+), desmin(+), CD99(-), vimentin(+++), epithelial membrane antigen(-) and BCL-2(-), with a Ki-67 proliferation index of ~20%.

In summary, DLBCL with cardiac involvement exhibits a markedly unfavorable prognosis. The clinical presentation lacks specificity, necessitating heightened vigilance among cardiovascular practitioners for accurate diagnosis. Patients presenting with unexplained pericardial effusion should be promptly evaluated for potential lymphoma. Timely establishment of an early diagnosis and initiation of treatment are of utmost significance.

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Authors' contributions

HL and LZ managed the patient's cardiac condition, and performed cardiac ultrasound and enhanced CT, as well as contributing to the diagnosis and management of the patient. LY and YZ, as pathologists, helped to clarify the diagnosis. HJ created HE and IHC sections of the patient's pathological samples, and completed relevant experimental operations, which assisted in the diagnosis. All authors participated in the drafting of the manuscript. LY and YZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Availability of data and materials

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

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of anonymized data and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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