CASE REPORT

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Primary cardiac lymphoma: autopsy case report and literature review

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Abstract

Primary cardiac lymphoma (PCL), defined as extranodal non-Hodgkin's lymphoma involving exclusively the heart and/or pericardium, is a neoplasm with an extremely low incidence, a high degree of malignancy, and a poor prognosis. It comprises 0.5% of all extranodal lymphomas and 1–2% of all primary cardiac tumors, while the most commonly reported subtype is diffuse large B-cell lymphoma (DLBCL). The tumor is more common in immunocompromised patients compared with those who are immunocompetent. Modern imaging methods now allow for earlier detection of these tumors, despite their variable clinical manifestation, which is often a cause of misdiagnosis. We present an autopsy case of undiagnosed PCL in an immunocompetent 72-year-old man, where postmortem examination revealed massive tumor infiltration of the right-sided heart chambers extending to the left ventricle. Histological analysis showed microscopic tumor infiltration within the left atrium as well. A diagnosis of DLBCL of non-germinal subtype was made based on immunohistochemistry.

Keywords: primary cardiac lymphoma, diffuse large B-cell lymphoma, non-germinal center B-cell-like, autopsy.

Introduction

Primary cardiac lymphoma (PCL) is defined as extranodal non-Hodgkin's lymphoma involving exclusively the heart and/or pericardium. The latest available *World Health Organization* (WHO) classification includes under the definition of PCL also tumors located primarily in the heart or presenting with primarily cardiac manifestation while there is limited extracardiac involvement [1–4]. PCL is a neoplasm with an extremely low incidence, a high degree of malignancy, and a poor prognosis. It comprises 0.5% of all extranodal lymphomas and 1–2% of all primary cardiac tumors [5–7]. Majority of PCL are of B-cell lineage, especially diffuse large B-cell lymphoma (DLBCL) [8]. Due to advances of modern-day medicine, reports of autopsy cases presenting undiagnosed or untreated PCL are few.

Aim

The aim of this article was to report a case of a unique autopsy finding of PCL, and to provide a literature review on this rare neoplasm.

Case presentation

We present a case of a 72-year-old man who was hospitalized for acute decompensated heart failure and generalized edema. His medical record included arterial hypertension, type 2 diabetes, and repeated pericarditis. He was initially diagnosed with restrictive cardiomyopathy, affecting primarily the right ventricle (RV) and resulting in diastolic dysfunction. Based on positive blood cultures of *Staphylococcus aureus*, he was treated with antibiotics. Upon the worsening of his condition, he was transported to a medical facility specializing in cardiovascular disease. Transthoracic echocardiography (TTE) revealed right ventricular hypertrophy with diastolic dysfunction and borderline left ventricular ejection fraction with restrictive filling function. Due to the sudden worsening of his health condition, presenting with hypotension and oliguria, a second TTE was performed, which revealed tricuspid stenosis produced by an unknown mass within the RV compressing the tricuspid ostium. Surgical treatment was contraindicated for the patient due to a very high risk, and it was decided that he would be placed on extracorporeal membrane oxygenation (ECMO). During the procedure, the patient underwent cardiac arrest with successful cardiopulmonary resuscitation. He remained hemodynamically unstable, with progression into shock; he later underwent another cardiac arrest and died that same day.

An autopsy was carried out 14 hours after the patient's death. Postmortem external examination of the dead body with a length of 169 cm and weight of 93 kg showed obesity, with a body mass index (BMI) of 32.56 kg/m^2, and generalized edema. Autopsy revealed diffuse pericardial adhesions, with obliteration of pericardial space, an electrode lead was

entering the superior vena cava (SVC). The heart weighed 910 g. Examination of the heart showed massive infiltration replacing myocardium within the right atrium (RA) and RV (Figure 1A), resulting in a thickening of the walls and narrowing of the tricuspid ostium (Figure 1B). The left ventricle (LV) presented with only sporadic small tumor infiltration and insignificant thickening. On gross appearance, the tumor was absent in the left atrium (LA). Although, subsequent histological analysis confirmed microscopic tumor infiltration within the LA as well.

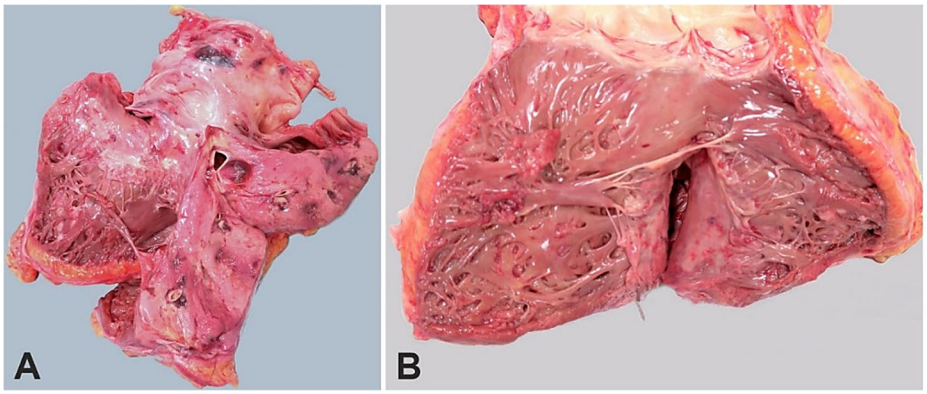

Figure 1 – ***The photographs taken at autopsy: (A) Cut surface of the right ventricle showing tumor infiltration; (B) Significant narrowing of the tricuspid ostium.***

Morphologically, the tumor was composed of large lymphoid cells infiltrating between the bundles of cardiomyocytes (Figure 2, A and B). Immunohistochemistry was positive for cluster of differentiation (CD)20 and multiple myeloma oncogene 1 (MUM1) (Figure 2, C and D), and negative for B-cell lymphoma 6 (Bcl6), CD10 (Figure 2E), and CD138 (Figure 2F). Based on histological findings and immunophenotype, the tumor was diagnosed as DLBCL of non-germinal center subtype.

Discussions

Primary cardiac tumors are rarely encountered in clinical as well as autopsy practice, with PCL being even rarer. The most common type of PCL subtype reported in the literature is DLCBL [9].

Although secondary cardiac involvement of the heart is relatively often encountered in the spectrum of systemic manifestations of aggressive hematological-oncological diseases, primary lymphomas of the heart make up only 0.5% of all extranodal lymphomas [7, 10].

Primary cardiac DLBCL is mostly a hematological-oncological disease of the older age, with a reported median incidence in persons of age 63 years [3, 9]. An unusual case of a 9-year-old child with primarily DLBCL occurring in the heart has been reported [11]. Considering gender predilection, a male-to-female ratio of 2:1 has been noted [9].

The etiology and pathogenesis of cardiac DLBCL are not fully understood yet. A higher proportion of large cell lymphoma types associated with an immunocompromised state has been noted, of which a significant proportion is Ebstein–Barr virus (EBV) positive [12–14]. Fibrin-associated large B-cell lymphomas and DLBCL associated with chronic inflammation are also relatively often encountered [15, 16]. Considering other lymphoma types, rare cases of Burkitt lymphoma and plasmablastic lymphoma have been reported [17, 18].

Primary cardiac DLBCL most often manifests as neoplastic involvement of the right atrial wall and is significantly less commonly encountered in the left-sided anatomical structures of the heart [19]. Multifocal tumor burden, characterized by multiple lesions present in the right-sided heart chambers, is often the case in patients with this oncological disease [20]. Involvement of the pericardium is seen in approximately one third of cases. Infiltration of the right heart valve structures is reported to be very rare [21]. In our presented case, the patient demonstrated substantial tumorous involvement of the RA as well as the RV, which resulted in critical narrowing of the tricuspid ostium. Gross inspection of the heart also confirmed focal tumor infiltration in the LV, and histological analysis proved involvement of the LA.

The reason for the predominantly right-sided localization of DLBCL in the heart is not fully elucidated yet. A possible anatomical-based explanation was suggested by Petrich *et al.*: because the thoracic ducts gather lymph and drain it into the SVC and eventually into the RA as well as the RV, the right-sided heart anatomical structures are more prone to be secondary involved by any pre-existing nodal lymphoma in the body. This could also explain why approximately one quarter of primary cardiac DLBCL patients have SVC involvement. If this hypothesis is correct, it would suggest that what is thought to be primary DLBCL of the heart is just a manifestation of clinically silent systemic (nodal) lymphoma [9]. Further studies are warranted to confirm this hypothesis.

Clinical symptoms of primary cardiac DLBCLC vary depending on the tumor size and degree of involvement of anatomical structures of the heart. The signs of primary DLBCL of the heart are often non-specific or less serious, which can lead to misdiagnosis or underestimation of the condition [3]. The most commonly reported clinical manifestations of DLBCL of the heart included dyspnea, dysrhythmias, and congestive heart failure. Classical systemic B symptoms encountered in Hodgkin's lymphoma (*i.e.*, night sweats, fever, and weight loss) are not so common in primary cardiac DLBCLC, reported to be present in only 7% to 26% of cases [10, 22]. Pulmonary embolism in patients with primary cardiac DLBCL was also reported [23, 24].

In the past, PCL was basically an autopsy diagnosis [3]. Earlier diagnosis of this condition is nowadays possible thanks to the implementation of novel imaging

techniques. Considering the non-invasive methods available, echocardiography is most often utilized. When echocardiography is performed, PCL usually has the appearance of hypoechogenic infiltration of the heart wall, which is often accompanied by pericardial effusion [20]. More advanced methods of magnetic resonance imaging (MRI) are nowadays used in cardiology, which, in some cases, allow the differentiation of DLBCL from other tumors, including cardiac myxoma and angiosarcoma [25, 26]. Despite these recent advances, the diagnostic characteristics of tumors determined by imaging methods seem to overlap in many instances. A biopsy is therefore necessary to conclude a definitive diagnosis. Minimally invasive endomyocardial biopsies are usually performed to obtain tissue for histological evaluation [3]. Because endomyocardial biopsy represents a high-risk procedure for the patient and many anatomical structures of the heart are not readily accessible, it is often difficult to obtain the necessary amount of tissue for detailed histopathological, immunohistochemical (IHC), and molecular-genetic evaluation, which are necessary for adequate diagnostic classification and prognostic characterization [3, 20].

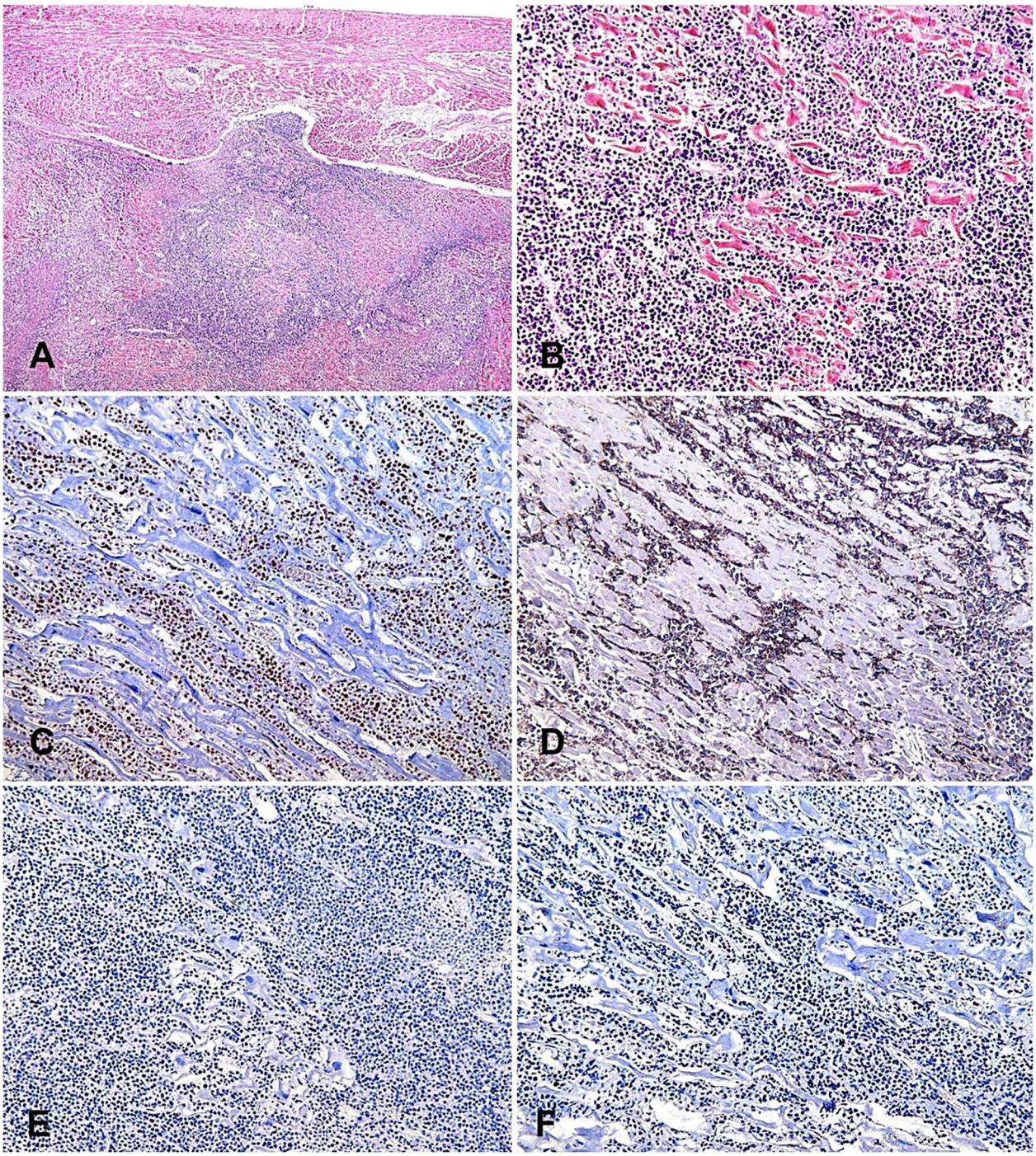

Figure 2 – ***The microscopic aspects of the tumor: (A and B) Diffuse myocardial infiltration with large lymphoid cells; (C) IHC positive for MUM1; (D) IHC positive for CD20; (E) IHC negative for CD10; (F) IHC negative for CD138. HE staining: (A) ×40; (B) ×200. Anti-MUM1 antibody immunomarking: (C) ×200. Anti-CD20 antibody immunomarking: (D) ×200. Anti-CD10 antibody immunomarking: (E) ×200. Anti-CD138 antibody immunomarking: (F) ×200. CD: Cluster of differentiation; HE: Hematoxylin–Eosin; IHC: Immunohistochemistry; MUM1: Multiple myeloma oncogene 1.***

Since the era of precise medicine, it has been recognized that DLBCL does not represent a single entity. Analyses of gene expression profiling (GEP) have evidenced that DLBCL can be further classified based on its constellation of genes. At least two molecular subtypes have been recognized: the germinal center B-cell-like (GCB) subtype, and the non-GCB subtype. The latter encompasses DLBCL with activated B-cell-like (ABC) characteristics and cases unclassifiable by GEP [27, 28]. Evidence points to differences between the GCB subtype and the non-GCB subtype in terms of prognosis and response to therapy. Considering patients treated with the CHOP [Cyclophosphamide, Hydroxydaunorubicin (Doxorubicin, Adriamycin), Oncovin (Vincristine), Prednisone or Prednisolone] combinational chemotherapy regimen, those having the GCB subtype tend to have a more favorable outcome compared to the non-GCB subgroup, despite differences in the International Prognostic Index score [29]. In the clinical study conducted by Fu *et al.*, differences in response to Rituximab treatment between subgroups of DLBCL patients were noted. It was shown that the 3-year overall survival was significantly better in the subgroup of patients having GCB characteristics of DLBCL compared to patients with the non-GCB subtype (85% *vs.* 69%, p=0.032) [30]. Determination of genetic alterations like rearrangements in MYC and B-cell lymphoma 2 (BCL2) has also been shown to be of prognostic and therapeutic significance [31, 32]. There is a general consensus among hematologists-oncologists that the concurrent presence of MYC and BCL2 translocations in lymphoma cells (the so-called double-hit lymphomas) portends an extremely poor prognosis for DLBCL patients [31, 33, 34].

Many laboratories do not have access to GEP. Because of this, various IHC algorithms have been implemented into daily practice that are used as a surrogate for GEP. The most widely used IHC algorithm, used as an approximation to the GEP analysis, was proposed by Hans *et al.* [35]. It is based on the evaluation of CD10, Bcl6, and interferon regulatory factor 4 (IRF4)/MUM1 expression. IHC analysis of the tumor biopsy samples obtained from our presented case showed a CD10 negative and Bcl6 negative immunophenotype, which is consistent with the non-GCB subtype according to the Hans classifier. Positivity of Bcl6 and IRF4/MUM1 in the absence of CD10 expression is also consistent with the non-GCB immunophenotype. On the other hand, isolated CD10 positivity or an immunophenotype characterized by CD10 and IRF4/MUM1 negativity but Blc6 positivity defines the GCB subtype. Most published cases of primary cardiac DLBCL are considered to be of the non-GCB subtype [15, 36–39]. Patients with GCB characteristics of DLBCL have a significantly better 5-year overall survival than the non-GCB subgroup (76% *vs.* 34%; p<0.001) [35]. Considering other IHC characteristics, aberrant positivity of CD5 is present in approximately 5% to 10% of DLBCL and is associated with aggressive tumor behavior [40].

In the past, primary DLBCL of the heart conferred a dismal prognosis. Earlier detection and the addition of Rituximab to standard-of-care therapy ameliorated to some degree the dire outcome of DLBCL patients [41]. The role of surgical tumor debulking before administering chemotherapy is still a matter of dispute [6]. Urgent surgical management is usually reserved for patients with signs of rapidly progressive heart failure or SVC syndrome [42]. Generally, the overall survival of patients with primary cardiac DLBCL varies widely within three to 63 months [10, 22]. Patients with signs of congestive heart failure and those without appropriate chemotherapy management have a poor median survival expectancy of less than two months [22, 43].

Conclusions

PCL is a very rare disease. Despite modern-day medicine allowing for earlier than postmortem diagnosis of the tumor, its nonspecific clinical presentation and rapid progression may still result in late diagnosis and poor prognosis. The presented case is nowadays one of the few reports of PCL diagnosed at the autopsy which presents with an uncommon involvement of all four cardiac chambers.

Conflict of interests

The authors declare that they have no conflict of interests.

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