

Clinical Case Report

Large B-cell lymphoma arising in cardiac myxoma or intracardiac fibrinous mass: a localized lymphoma usually associated with Epstein–Barr virus?



Cristian Aguilar ^{a,*}, Brady Beltran ^b, Pilar Quiñones ^a, Tomas Carbajal ^a, Jorge Vilcapaza ^a, Alejandro Yabar ^a, Pedro Segura ^c, Leticia Quintanilla-Martinez ^d, Roberto N. Miranda ^e, Jorge J. Castillo ^f

^a Department of Pathology, Edgardo Rebagliati Hospital, Lima, Peru

^b Department of Oncology and Radiotherapy, Edgardo Rebagliati Hospital, Lima, Peru

^c Department of Cardiology, Edgardo Rebagliati Hospital, Lima, Peru

^d Institute of Pathology and Comprehensive Cancer Center, University of Tübingen, Germany

^e Department of Hematopathology, MD Anderson Cancer Center, Houston, TX, USA

^f Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA

ARTICLE INFO

Article history:

Received 25 July 2014

Received in revised form 26 August 2014

Accepted 27 August 2014

Keywords:

Cardiac myxoma

B-cell lymphoma

Epstein–Barr virus

EBER

Chronic inflammation

ABSTRACT

Primary cardiac neoplasms are rare. However, among them, cardiac myxoma is the most common tumor. In contrast, primary cardiac lymphoma within a cardiac myxoma is extremely rare and might be difficult to diagnose because of non-specific clinical manifestations. We report the case of a previously healthy 52-year-old man who presented with acute onset of transient dysarthria and left hemiplegia. A transthoracic echocardiography showed a 6×2.5-cm solid mass in the left atrium, which was subsequently resected. Histological, immunohistochemical, and molecular analyses revealed an EBV-associated CD30-positive large B-cell lymphoma with anaplastic morphology within a cardiac myxoma and fibrinous material. Staging studies showed no evidence of lymphoma elsewhere. The patient achieved complete remission and is alive 42 months after diagnosis, and did not receive chemotherapy. We discuss the clinical and pathologic features of lymphoma arising in cardiac myxoma or in intra-atrial fibrinoid mass and the potential role of IL-6 in its pathogenesis.

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1. Introduction

Primary cardiac neoplasms are rare. About 80%–90% of primary cardiac tumors are benign [1,2], and of these the most common are cardiac myxomas, which usually arise in the left atrium [1–3]. Most patients present with one or more symptoms of the classic triad of embolic events, intracardiac flow obstruction and constitutional symptoms [2–4], and about 10% of patients are asymptomatic [3].

Primary cardiac lymphoma is a rare neoplasm, accounting for 2% of all primary cardiac tumors, and affects mainly the right chambers of the heart [5]. During the last decade, isolated cases of lymphoproliferative neoplasms within a cardiac myxoma [6–12], or intracardiac fibrinoid masses [13–19], occasionally have been reported in the medical literature; most of these reports show an association with Epstein–Barr virus (EBV) infection and show a local production of inflammatory cytokines.

We report the clinical, histologic, phenotypic, and molecular findings of a patient with large B-cell lymphoma associated with EBV

infection, discovered incidentally within a myxomatous and fibrinoid cardiac mass.

2. Case presentation

A 52-year-old man without any significant past medical history was admitted to our hospital with acute onset of transient dysarthria and left hemiplegia, after a soccer game. On cardiac examination, he had regular rate and rhythm. No murmurs or gallops were audible on auscultation. Laboratory tests showed increased C-reactive protein (4.3 mg/dl) and lactate dehydrogenase levels (538 U/l). Complete blood counts and metabolic panel were normal. Computed tomography (CT) scan of the head suggested focal brain ischemia. A transthoracic echocardiography (Fig. 1A) revealed a 6 × 2.5 cm mass in the left atrium, attached at the interatrial septum and prolapsing through the mitral valve. The patient underwent open heart surgery because of the clinical suspicion of myxoma, and the left atrial tumor was resected.

Histopathological analyses revealed a myxoma with extensive central fibrinous zone surrounded by sparse cellular areas composed of spindle or stellate cells with strong expression of calretinin (Fig. 1B). However, a large peripheral zone of the tumor showed solid sheets and nests of large pleomorphic lymphoid cells (Fig. 1C) with many atypical mitotic figures (Fig. 1D). Immunohistochemical analyses

Funding: Authors disclose no funding sources.

* Corresponding author. Departamento de Patología, Hospital Edgardo Rebagliati, Avenida Salaverry, Jesús María, Lima, Perú.

E-mail address: dr.cris85@yahoo.com (C. Aguilar).

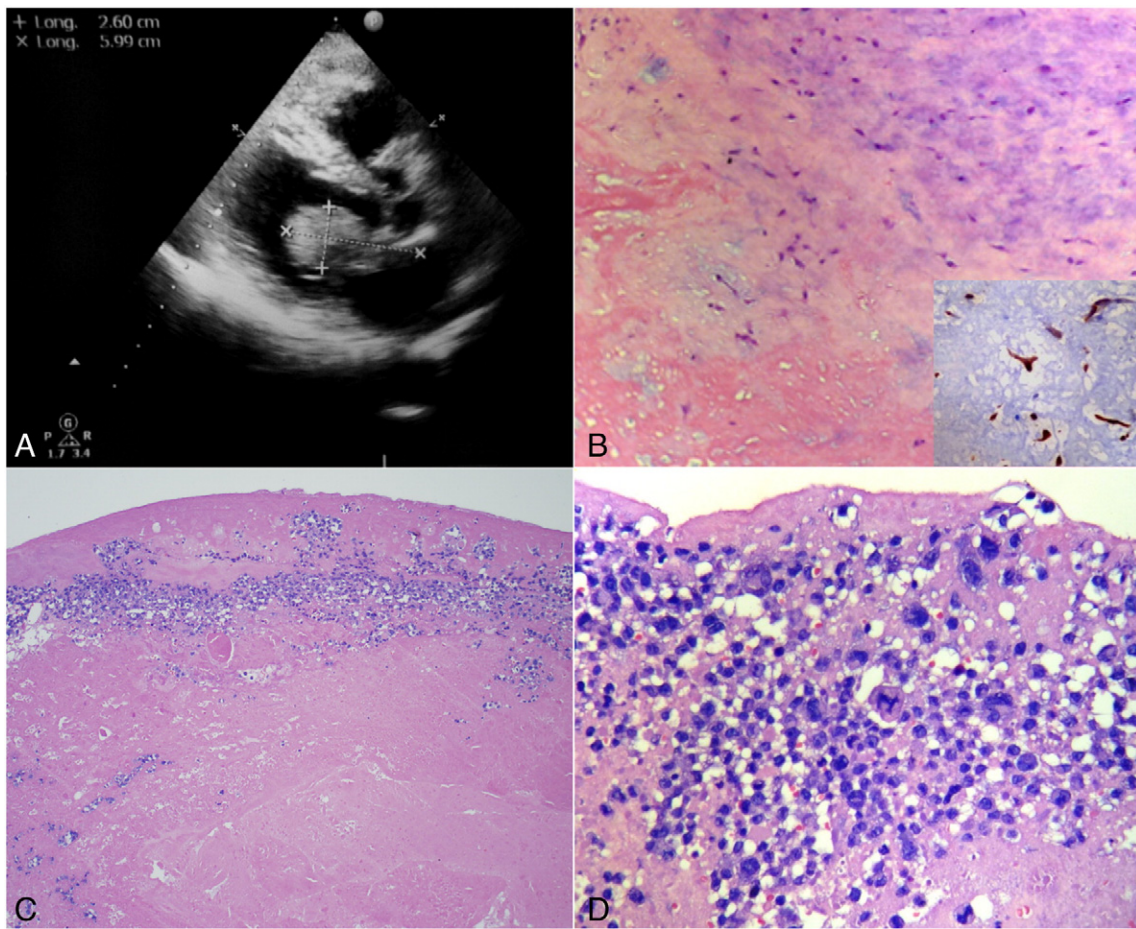


Fig. 1. A) Transthoracic echocardiography showed a mass originating from the interatrial septum. B) Left atrial tumor with central sparse hypocellular area with myxoma cells. These tumor cells were strongly immunoreactive for calretinin (inset). Superficial zone of the tumor showed multiple solid sheets of large pleomorphic lymphoid cells (C) with many atypical mitotic figures (D).

revealed a non-germinal center B-cell large lymphoma with strong expression of CD20 (Fig. 2A), CD79a, PAX5, CD30 (Fig. 2B), and MUM-1, but negative for ALK-1, CD10, CD43, cyclin-D1, and CD3. The proliferation rate was approximately 90%, as shown in the Mib1 stain. The *in situ* hybridization for Epstein-Barr virus latency-associated RNA (EBER) was positive in the majority of the tumor cells. The malignant cells expressed, in addition, LMP-1 and EBNA-2 confirming an EBV infection with a latency type III pattern (Fig. 2C–D). Strong IL-6 expression was demonstrated in both myxoma cells and the atypical lymphoid cells (Fig. 3). The PCR for *IGH* gene rearrangement using BIOMED 2 probes showed two monoclonal peaks in the framework region 2 (FR2) analysis, suggesting a biallelic rearrangement pattern in the tumor clone (Fig. 4).

Staging with whole body CT scan did not reveal evidence of disease in the post-operative period. Bone marrow biopsy was negative for lymphoma, thus the lymphoma was considered as stage IE. The patient refused the recommended chemotherapeutic regimen, and is in complete remission 42 months after diagnosis.

3. Discussion

We report an immunocompetent patient who presented with an incidental CD30-positive diffuse large B-cell lymphoma (DLBCL) arising within a left heart atrium myxomatous and fibrinoid mass. The patient had surgical removal of the mass, and did not need chemotherapy; patient has no evidence of disease 42 months after diagnosis. The association of the DLBCL with EBV type III latency without an associated

underlying immunosuppression of the patient, suggests that unknown mechanisms of local immunosuppression occur in this DLBCL associated with atrial myxoma.

Myxoma is the most common intracardiac tumor, and has an incidence of 0.002% in the general population [2]. Numerous studies have confirmed the constitutive production of interleukin-6 (IL-6) in cardiac myxomas, and a positive correlation between serum levels of IL-6 and susceptibility to cause embolic phenomena as well as constitutional symptoms [20]. IL-6 is a proinflammatory cytokine required for orchestrating the immune-inflammatory response and it is also a key factor during B-cell maturation [21]. IL-6 promotes the survival of maturing B-lymphoma cells in response to cellular stress, highlighting the ability of tumor cells to co-opt pathways used for stem cell protection [21]. In addition, EBV-immortalized B cells can produce IL-6 that it is used as an autocrine growth factor by these cells [22]. In this context, chronic IL-6 exposure within cardiac myxomas might favor the selection of a population of EBV-infected B cells.

Primary cardiac lymphoma (PCL) involving only the heart and/or pericardium without evidence of nodal and extra-nodal involvement [5,23], is a rare and poorly defined entity, estimated to constitute <2% of all cardiac tumors [5,13]. On the other hand, secondary cardiac involvement by malignant lymphoma has been observed in as many as 24% of autopsy patients [13]. DLBCL is the most common histologic subtype (~80% of cases) of PCL independent of immune status [4,23]. DLBCL is a neoplasm of large lymphoid B-cells, and a heterogeneous entity according to the 2008 World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues,

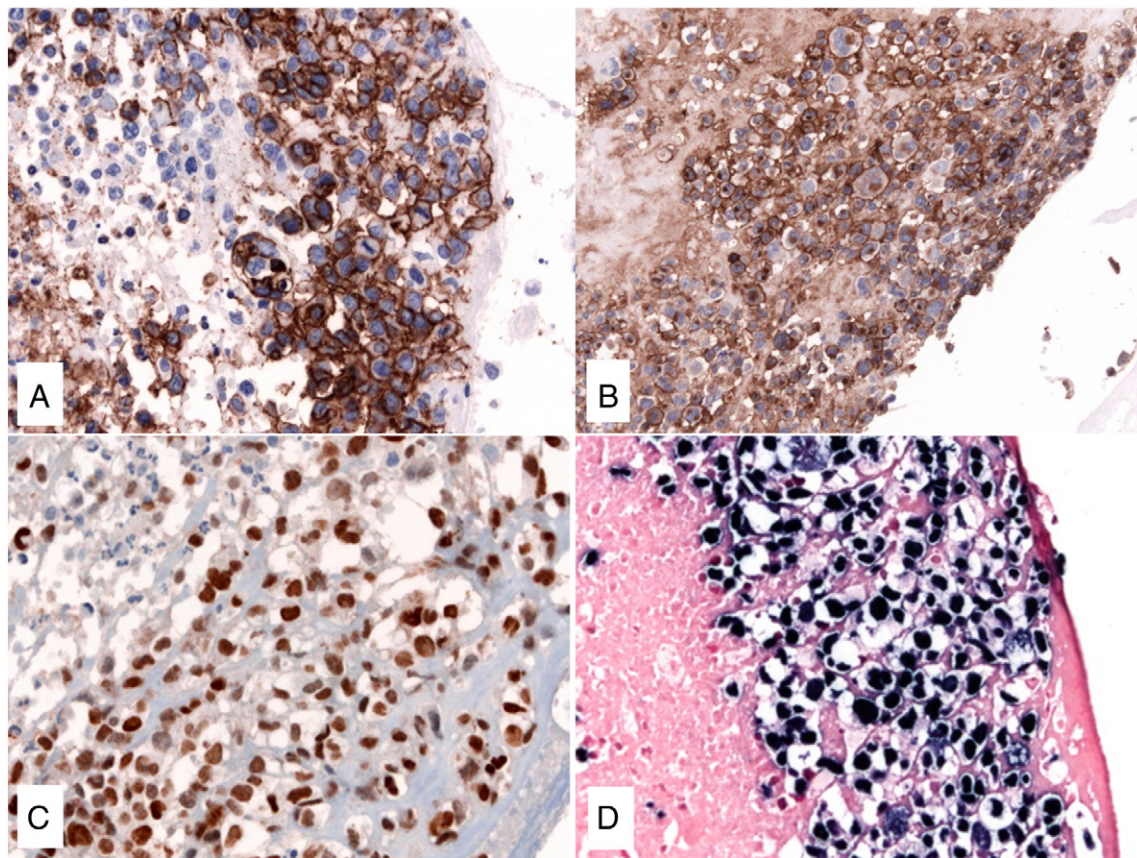


Fig. 2. The atypical lymphoid cells in the periphery of the myxoma are positive with CD20 (A) and CD30 (B). Note the uniform staining of tumor cells for EBNA2 (C) (a–c: Immunoperoxidase, original magnification 400 $\times$), and EBER (D). (*in situ* hybridization, original magnification 400 $\times$).

where three common morphological variants are recognized: centroblastic, immunoblastic, and anaplastic. The anaplastic variant is rare and it shows large pleomorphic cells as well as CD30 expression, reminiscent of anaplastic large cell lymphoma (ALCL) of T-cell lineage [24].

The proportion of EBV-positivity increases with age among patients with DLBCL, and it manifests as a highly aggressive lymphoma in patients older than 50 years, consistent with decreased immunity in

the elderly [25]. However, geographical differences may also play a role. In fact, Beltran et al. [26] have reported the highest frequency of EBV-positive DLBCL in a Peruvian population (15%), including patients younger than 50 years old. The oncogenic mechanisms of EBV are attributed to the expression of LMP1, which activates NF-kappa B and increases expression of Bcl-2 to prevent latently EBV-infected cells from undergoing apoptosis [27].

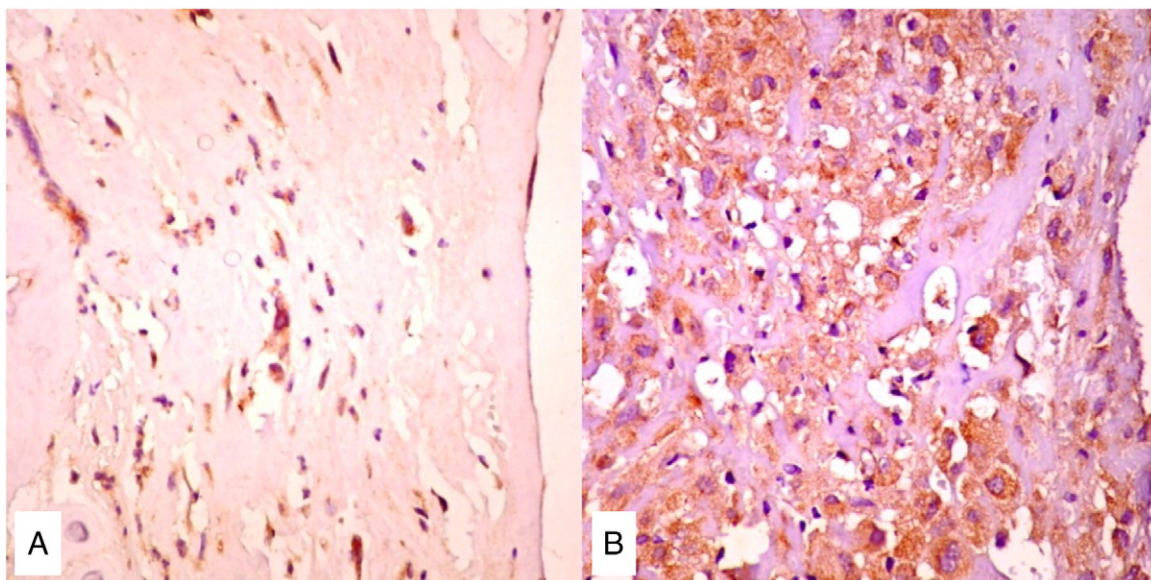


Fig. 3. Expression of interleukin-6 in both myxoma cells (A) and atypical lymphoid cells (B).

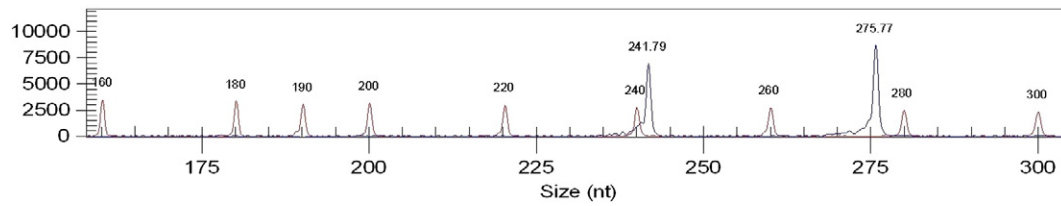


Fig. 4. IGH gene rearrangement shows a biallelic monoclonal peak of 241 and 275 base pairs by FR2 analysis.

DLBCL occurring in cardiac myxomas is commonly associated with EBV infection, suggesting that an underlying inflammatory process predisposes to the development of lymphoma [8–12]. Similar mechanisms have been postulated for DLBCL associated with cardiac prosthesis devices or for lymphomatous-like lesions arising in fibrinous chronic inflammatory processes that also associate with EBV infection [13,14,16]. The patient we report shows a pattern of type III latency of EBV infection, which is the hallmark of EBV lymphoproliferations, arising in the setting of severe immunodeficiency. Since the expression of EBNA-2 is highly immunogenic, the survival of EBV infected cells expressing EBNA-2 is a surrogate evidence of immunodeficiency, and does not occur in immunocompetent patients, where EBV specific cytotoxic T-lymphocytes target infected cells.

According to Loong et al. [8], we believe that type III latency may reflect local rather than systemic immunosuppression. The mechanisms for this pattern of localized immunosuppression in cardiac myxoma are unknown, and local mechanisms in the cardiac myxoma may provide an enclosed environment permitting the EBV-infected B-cells to evade T-cell surveillance. It is possible that cytokines derived from EBV-infected B-cells can build up to high levels in the enclosed space, consistent with our observation that both the myxomatous lesion and lymphoma cells showed strong expression of IL-6 (Fig. 4). In this context, chronic IL-6 exposure within cardiac myxomas might favor the selection of a population of EBV-infected B-cells that grow under privileged conditions enabling them to escape from immune surveillance within the atrial cavity, as suggested by the type III latency pattern.

The clinical presentation of PCL tends to be nonspecific, thus diagnosis is usually made late in the disease course [5,23]. Beyond the

CNS sequelae of tumor embolization or dyspnea, these patients are characterized by the absence of systemic disease [10]. Our search of the literature disclosed several case reports of intracardiac myxoma and EBV-positive DLBCL (Table 1) [7–13]. Five patients were women and two were men. All patients except one were older than 50 years old. All patients had a stage I disease with primary location in the left atrium. Three of four cases had type III EBV latency, as in our case, suggesting local immunosuppression as the pathophysiological substrate in this entity. It is important to note that two patients, as the case we report, did not receive chemotherapy and had more than 3 years without evidence of disease.

Similar results were found in the 11 cases reported of DLBCL in cardiovascular prosthetic devices and fibrin-associated DLBCL (Table 2) [13–19]. All patients except two were older than 50 years old. Eight of eleven cases had cardiovascular prosthetic devices. Six of eight patients had EBV associated DLBCL and two cases evaluated for EBV latency pattern displayed findings consistent with latency pattern type III. Five of eleven cases died of other complications (surgery, infections or a second neoplasm) and only one case showed local recurrence of the same neoplasm. Based on these findings, we suggested that EBV-positive DLBCL occurring in cardiac myxoma, prosthetic devices or fibrin-associated could be distinguished for their better prognosis, in order to avoid unnecessary treatments.

In summary, we report an immunocompetent patient who presented with a left heart atrium myxomatous and fibrinoid mass with incidental DLBCL associated with type III latency, who achieved complete remission after surgical removal of the mass. The association with EBV positive DLBCL with and EBV type III latency without an associated underlying immunosuppression, suggests that several mechanisms of

Table 1
Review of primary cardiac lymphomas arising within cardiac myxoma

Case	Year	Age/Sex	Location (size)	Symptoms	Lymphoma	EBV	Chemotherapy	Follow-up
Bagwan et al.	2009	81/F	Left atrium (4×2 cm)	Multiple strokes	DLBCL (GC)	NA	R-CHOP	24 months NED
Dimitrova et al.	2010	51/M	Left atrium (7.5×4.5 cm)	Chest pain	DLBCL (GC)	NA	R-CHOP	None
White et al.	2010	75/F	Left atrium (6×5 cm)	Dyspnea, atrial fibrillation	LPL	NA	None	24 months NED
Loong et al.	2010	70/F	Left atrium (6.5×4 cm)	Cardiogenic shock, Ischemic stroke	DLBCL (nGC)	Type III Latency EBER +, LMP1 +, EBNA2 +	R-COEP	Died 5 months
Svec et al.	2012	60/F	Left atrium (3.7×1.5 cm)	Ischemic stroke	DLBCL (nGC)	Type III Latency EBER +, LMP1 +, EBNA2 +	R-CHOP	7 months NED
Bartoloni et al.	2013	55/F	Left atrium (5.5×4.5 cm)	Fever and progressive fatigue	Atypical lymphoid B-cell proliferation	Type II Latency EBER +, LMP1 +, EBNA2 -	None	72 months NED
Tapan et al.	2014	49/M	Left atrium (4.2×3.6 cm)	Palpitations	DLBCL (nGC)	Type III Latency EBER +, LMP1 +, EBNA2 +	R-CHOP	12 months NED
Present case	2014	52/M	Left atrium (6×2.5 cm)	Transient ischemic attack	DLBCL, anaplastic morphology (nGC)	Type III Latency EBER +, LMP1 +, EBNA2 +, monoclonal	None	42 months NED

EBV: Epstein–Barr virus; DLBCL: diffuse large B-cell lymphoma; NA: not available; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-COEP: rituximab, cyclophosphamide, vincristine, etoposide, prednisone; NED: no evidence disease; GC: germinal center; nGC: non-germinal center; EBER: EBV-encoded RNA; LMP1: latent membrane protein; EBNA: EBV nuclear antigen; LPL: lymphoplasmacytic lymphoma.

Table 2

Review of DLBCL in cardiovascular prosthetic devices and fibrin-associated mass arising from the heart

Case	Year	Age/ Sex	Location (size)	Symptoms	Lymphoma	EBV	Chemotherapy	Follow-up
Albat et al.	1994	66/F	Mitral valve prosthesis (Mechanical)	Syncope and pulmonary edema	Large cell lymphoma	NA	None	6 months NED
Quigley et al.	2003	29/M	Left atrium “Fibrin thrombus”	Embolitic stroke	DLBCL	EBV +	CHOP	24 months NED
Durrleman et al.	2005	65/F	Mitral valve prosthesis (Mechanical)	Left heart failure	Large cell centroblastic Lymphoma	NA	None (refused)	Died 10 months, surgery complication from secondary digestive lymphoma
Bagwan et al.	2009	81/F	Aortic valve prosthesis (Porcine)	Endocarditis	DLBCL (GC)	EBV –	R-CHOP	Died 6 months, rupture of the bioprosthesis
Berio et al.	2010	60/M	Aortic valve prosthesis (Allograft)	Left ventricular failure	DLBCL	NA	None	Died 24 months, endocarditis and severe pneumonia
Miller et al. Bonnichsen et al.	2010 2013	48/M	Aortic valve prosthesis (Mechanical)	Transient ischemic attacks	DLBCL	EBV +	None	12 months, local recurrence (R-CHOP)
Miller et al.	2010	80/F	Aortic valve prosthesis (Bovine)	Dyspnea and heart failure	DLBCL	EBV +	None	Died 18 months, breast cancer
Miller et al.	2010	79/F	Aortic tube graft (Synthetic)	Dyspnea and chest discomfort	DLBCL	EBV +	None	Early postoperative death
Gruver et al.	2012	55/M	Aortic root graft (Synthetic)	Stroke symptoms	DLBCL (nGC)	Type III Latency EBER +, LMP1 +, EBNA2 +,	R-COEP	16 months NED
Gruver et al.	2012	56/M	Left atrium “Myxomatous mass”	Dyspnea	DLBCL (nGC)	Type III Latency EBER +, LMP1 +, EBNA2 +	R-CHOP	8 months NED
Gruver et al.	2012	75/M	Mitral valve “Myxomatous lesion”	Dyspnea on exertion	DLBCL (nGC)	EBV –	R-CHOP	39 months NED

EBV: Epstein–Barr virus; DLBCL: diffuse large B-cell lymphoma; NA: not available; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-COEP: rituximab, cyclophosphamide, vincristine, etoposide, prednisone; NED: no evidence disease, GC: germinal center; nGC: non-germinal center; EBER: EBV-encoded RNA; LMP1: latent membrane protein; EBNA: EBV nuclear antigen.

local immunosuppression, mediated at least in part by IL-6 expression, occur in cardiac myxomatous or fibrinoid masses, which may predispose to DLBCL.

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