Case Reports

Recurrent Primary Cardiac Lymphoma on Aortic Valve Allograft:

Implications for Therapy

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Primary malignant cardiac lymphomas associated with grafts are extremely rare: to our knowledge, only 6 cases of prosthesis-associated B-cell lymphoma have been reported. Ours is the first report of recurrent diffuse large B-cell lymphoma associated with aortic valve allografts.

We treated a 60-year-old man who presented in early 2007 with aortic valve endocarditis. He underwent aortic valve replacement with an allograft; the resected native valve showed active endocarditis without tumor. In January 2011, the patient underwent repeat aortic valve replacement because of symptomatic aortic regurgitation. The explanted valve specimen displayed diffuse large B-cell lymphoma. In September 2011, the patient presented with fever and a mass around the aortic valve. He died in January 2012. On autopsy, the explanted replacement valve displayed recurrent diffuse large B-cell lymphoma. The recurrent lymphoma on a new graft leads us to believe that this tumor is more aggressive than had been thought. We propose early systemic chemotherapy, in addition to tumor resection, for the possibility of a better prognosis. We discuss our patient's case and review the relevant medical literature. ***(Tex Heart Inst J 2014;41(5):543-6)***

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Primary lymphoma of the heart is rarely reported.[1] Isolated allograft-associated cardiac lymphoma is even more unusual and has a poor prognosis.[2,3] We present the case of a man who had initially presented with endocarditis and was later diagnosed with diffuse large B-cell lymphoma (DLBCL) on his 2 aortic valve allografts. In addition to discussing the patient's case, we review the sparse literature on the topic.

Case Report

In February 2007, a 56-year-old man presented at our institution with *Staphylococcus aureus* endocarditis complicated by multiple septic emboli and severe aortic regurgitation. He underwent aortic valve replacement with an allograft and had concomitant coronary artery bypass grafting. The surgical specimen of his native valve was calcified and showed active endocarditis without tumor. The patient had an uneventful recovery and was managed for heart failure symptoms (New York Heart Association functional class II/III) for approximately 3½ years. In January 2011, at age 60 years, he presented with fever, weight loss, and worsening heart failure. Results of multiple blood cultures were negative; however, echocardiograms revealed an aortic valve mass (Fig. 1A). The patient was treated for presumed culture-negative endocarditis. Because of progressive aortic regurgitation, he underwent repeat aortic valve replacement with a new allograft. The surgical specimen of the explanted valve displayed DLBCL. Biopsy samples were taken from the native tissue surrounding the allograft, and no lymphoma was found (Fig. 2). Computed tomography of the chest, abdomen, and pelvis were performed, as was a bone marrow biopsy. A blood-specimen DNA probe was positive for Epstein-Barr virus (EBV), by means of polymerase chain reaction (PCR). No evidence of systemic lymphoma was found. Because of the patient's poor functional status from debility, prior strokes, and congestive heart failure, no systemic chemotherapy was given. He had a protracted rehabilitation and, in September 2011, was admitted again with fever. Results of blood cultures were negative. Transesophageal echocardiograms revealed a mass around the aortic valve that impinged on the left main coronary artery (Fig. 1B). In January 2012, one year after the initial diagnosis

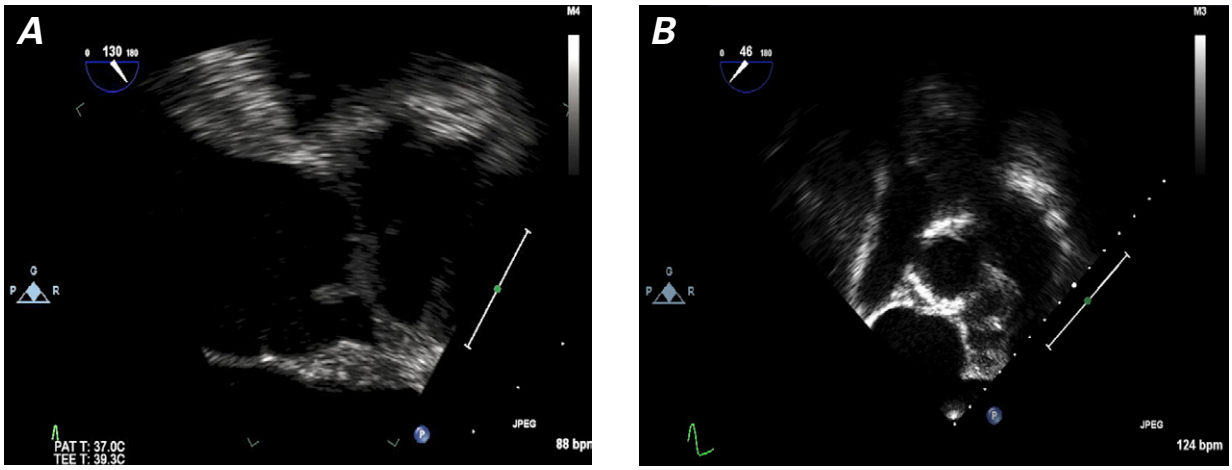

Fig. 1 *Transesophageal echocardiograms show aortic valve involvement with diffuse large B-cell lymphoma.* ***A****) Mass is seen on the first allograft valve before removal in January 2011.* ***B****) In September 2011, after valve replacement with a new allograft, a large mass around the left main coronary artery suggests recurrent lymphoma.*

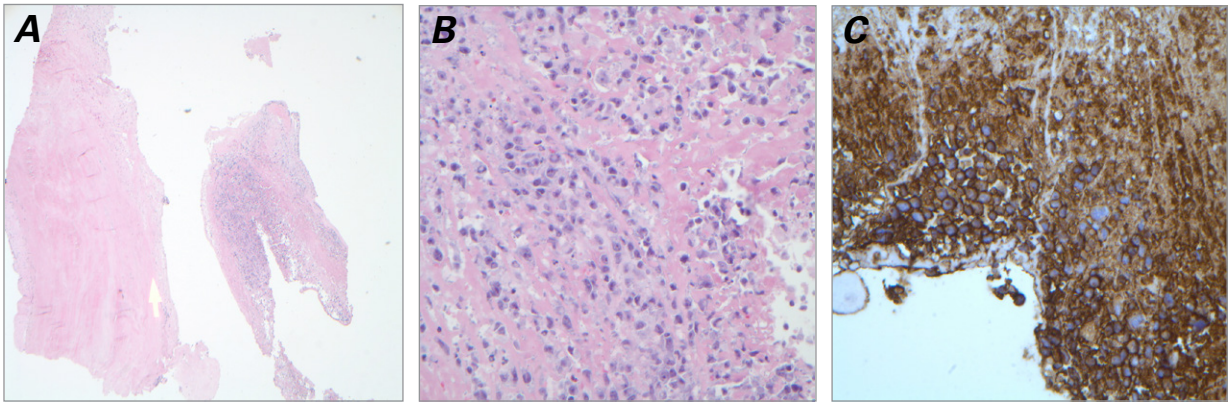

Fig. 2 *Light microscopic photomicrographs of first explanted aortic valve specimen.* ***A****) Native cardiac tissue (at left) displays no atypical cellularity; graft tissue (at right) shows diffuse atypical B-cell lymphocytes (H & E, orig. ×10).* ***B****) Graft tissue shows diffuse B-cell lymphocytes (H & E, orig. ×40).* ***C****) Immunophenotype photomicrograph shows graft tissue highly positive for B-cell lymphocytes (CD20 stain, orig. ×40).*

of DLBCL, the patient died of acute myocardial infarction. On autopsy, recurrent DLBCL was detected on the 2nd aortic valve allograft, and again no lymphoma was found elsewhere (Fig. 3).

Discussion

To our knowledge, ours is the 7th report of B-cell lymphoma that involved valvular prostheses (Table I),[1,4-7] and the first involving recurrent DLBCL on an aortic allograft. All the patients listed in Table I had isolated primary cardiac lymphoma involving a prosthesis, but without disseminated lymphoma. The DLBCL on our patient's first allograft was diagnosed nearly 4 years after that valve was implanted. The diagnosis of recurrent DLBCL of the prosthetic valve was made at autopsy one year after the valve had been replaced. The DLBCL developed much more rapidly on the 2nd occasion—the course was less than one year.

Primary malignant cardiac lymphomas are extremely rare,[1] with a prevalence of 0.002% to 0.3% in an autopsy series.[4,7] Of all primary malignant cardiac tumors, lymphomas comprise 1.5% to 5%.[4]

Chronic inflammation is the probable initiating stimulus that progresses to prosthesis-associated lymphoma. The lymphoma typically associated with chronic inflammation is pyothorax-associated lymphoma. This disease, which results from therapeutic artificial pneumothorax for the treatment of pulmonary tuberculosis, has a latency period of 22 to 67 years.[8-10] Lymphoma associated with mechanical prostheses at other sites, such as the knee, has similarly long latency (7–57 yr).[9] Of the 6 previous patients who had DLBCL in association with a cardiac prosthesis, 3 had mechanical valves (latency periods, 8, 9, and 24 yr), 2 had xenografts (latency periods, 3 and 8 yr), and one had an allograft (latency period unknown).[6] Our patient was given an allograft twice, because of the presence or suspicion of bacterial

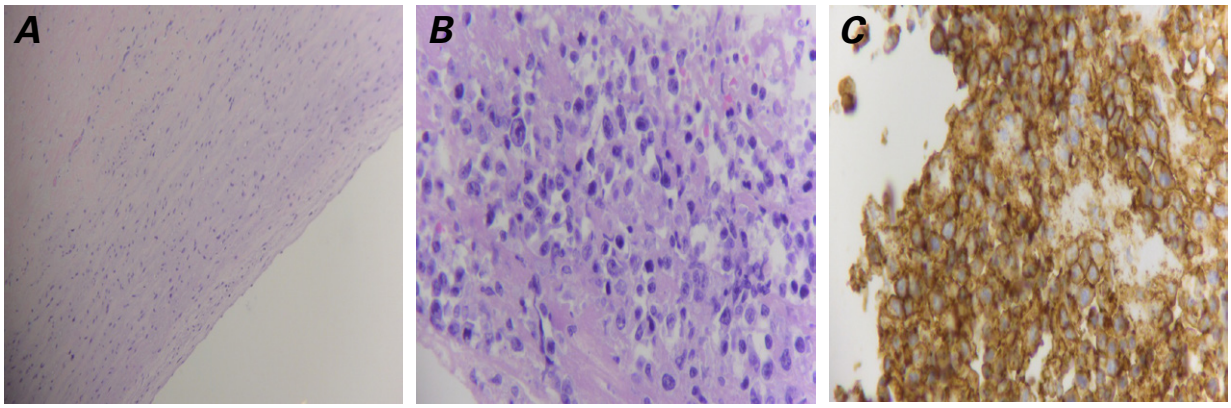

Fig. 3 *Light microscopic photomicrographs of 2nd aortic valve allograft, on autopsy in January 2012.* ***A****) Native cardiac tissue (at left) displays no atypical cellularity; graft tissue (at right) shows diffuse atypical B-cell lymphocytes (H & E, orig. ×10).* ***B****) Graft tissue shows diffuse B-cell lymphocytes (H & E, orig. ×40).* ***C****) Immunophenotype photomicrograph shows graft tissue highly positive for B-cell lymphocytes (CD20 stain, orig. ×40).*

TABLE I. Cases of Cardiac Prosthesis-Associated Diffuse Large B-Cell Lymphoma*

Reference	Age (yr)/ Sex	Prosthesis Type	Interval to Diagnosis (yr)	EBV	Therapy	Outcome
Albat B, et al.[1] (1994)	66/F	St. Jude mitral valve	8	Unknown	None	Alive at 6 mo without evidence of lymphoma
Durrleman N, et al.[4] (2004)	65/F	Unspecified mechanical mitral valve	9	Unknown	None	Died at 10 mo of "secondary digestive lymphoma" (treated with chemotherapy)
Bagwan IN, et al.[5] (2009)	50/M	Freestyle porcine aortic valve	3	LMP-1 on IHC	R-CHOP	Died after prosthetic valve dehiscence at 6 mo, without evidence of lymphoma at autopsy
Miller DV, et al.[6] (2010)	48/M	Björk-Shiley aortic valve	24	Positive	None	Alive at 6 mo without evidence of lymphoma
	80/F	Bovine pericardial aortic valve	8	Positive	None	Died at 18 mo of metastatic breast cancer; no evidence of lymphoma
Berrio G, et al.[7] (2010)	60/M	Allograft	Unknown	Unknown	None	Died of endocarditis and severe pneumonia
Current case	60/M	Allograft	4	Positive	None	Died at 1 yr of acute myocardial infarction; recurrent lymphoma on allograft at autopsy

EBV = Epstein-Barr virus; IHC = immunohistochemistry; LMP-1 = EBV latent membrane protein-1; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone chemotherapy

*All tumors were stage I-E (localized extranodal disease).

endocarditis. His initial lymphoma had a latency period of nearly 4 years, and the 2nd occurrence less than one year. It is possible that the shorter time for recurrence was due to residual tumor from the first allograft.

In the presence of chronic inflammation, DLBCL is a lymphoid neoplasm that shows an association with EBV.[11] Chronic inflammation probably plays a role at the local site in the proliferation of EBV-transformed B cells, enabling them to escape the body's immune mechanisms via the production of interleukin (IL)-10, an immunosuppressive cytokine, and by providing autocrine to paracrine growth via IL-6 and IL-6 receptors.[11] In most instances, tumor markers CD20 and CD79a and possibly CD30 are expressed.[11] The prosthesis type and the donor might also contribute influential factors to graft-associated cardiac lymphoma. Our patient was positive for EBV as determined by means of PCR, and his tumor markers were positive for CD20 and CD30.

In the reported cases of prosthesis-associated DLBCL, the diagnosis was made not long before the patients' deaths (Table I).[12] Two patients were living without evidence of lymphoma at 6 months[1,6]; however, no follow-up information was reported, so their final outcomes

are unknown. Among the others, the longest survival time was 18 months.[6] Only one of the 6 patients had received systemic chemotherapy, and he died 6 months after diagnosis with no recurrent lymphoma detected at autopsy.[5,6]

Miller and colleagues[6] suggested that the resectability of DLBCL in cardiac sites presents a better prognosis than does DLBCL with chronic inflammation at less resectable sites. We agree that the isolated nature of these tumors might enable resection; however, we think that the prognosis is poor regardless of resection, given the outcomes of the published cases. In association with chronic inflammation, DLBCL is an aggressive lymphoma that is typically treated with chemotherapy and radiation therapy.[11] Survival rates in patients with DLBCL at other anatomic sites have improved with use of this therapy. In DLBCL that has involved the pleural cavity, the 5-year overall survival rate has ranged from 20% to 35%; however, with chemotherapy, radiation therapy, or both, complete remission has been achieved in this population (5-year survival rate, 50%).[11] Our patient's recurrent lymphoma on a new graft leads us to believe that this tumor is more aggressive than had been thought. Had our patient's recurrent DLBCL been residual from the first allograft, it would underscore that surgical treatment alone might not be curative. Given the rarity of the disease, a systematic evaluation of potential therapies would be challenging at best. We hypothesize that early systemic chemotherapy, in addition to resecting the tumor, might yield a better prognosis.

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