An unusual case of primary cardiac prosthetic valve-associated lymphoma

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Primary cardiac tumors are extremely rare neoplasms with an incidence of less than 0.4%.[1-3] Primary cardiac lymphoma (PCL), the majority of which is non-Hodgkin lymphoma, accounts for around 2% of cardiac tumors and less than 0.5% of extranodal lymphomas.[1,4-6] Primary lymphoma involving cardiac valves has been described in few case reports and small case series owing to its rarity.[7-10] Most cases of PCL present with manifestations of congestive heart failure or cardiac arrhythmias,[11] whereas primary valve-associated lymphoma (PV-AL) is usually diagnosed incidentally during valve repair or replacement. The pathophysiology remains unclear, but a few cases have been associated with Epstein Barr virus (EBV).[7] Cases previously described in the literature carried an overall poor prognosis and to date there is no standardized treatment approach. We provide here an unusual case of primary prosthetic valve-associated cardiac large B-cell lymphoma, which was successfully treated with adjuvant chemotherapy after valve repair and which resulted in an excellent long-term outcome.

Case presentation and summary

The patient presented in 2012 as a 65-year-old man with a history of ascending aortic aneurysm with secondary aortic insufficiency who in 2004 had undergone composite valve replacement of the aortic valve (AV) root and ascending aorta with a St Jude Toronto root. In June 2011, he was found to have a right parietal intraparenchymal hemorrhage that was thought to be a thromboembolic hemorrhagic ischemic stroke. In March 2012, he had routine follow-up brain magnetic resonance imaging that incidentally showed a left frontal ischemic stroke with hemorrhagic conversion. In June 2012, he was found to have first degree atrioventricular block with episodic runs of supraventricular tachycardia.

In September 2012, transthoracic echocardiography was done for further evaluation of possible recurrent cryptogenic strokes. The results showed a hypo-echogenic mass within the proximal ascending aortic root, but this was not confirmed on transesophageal echocardiography. A chest computed-tomography (CT) scan was therefore performed, and it showed aneurysmal dilatation of the aortic root with an irregular marginal filling defect just above the AV suggestive of intraluminal thrombus. The patient was placed on full anticoagulation with warfarin and referred for cardiothoracic surgery to consider graft and valve replacement. However, 3 weeks later and before the surgery, the patient developed a third thromboembolic ischemic event (transient ischemic attack). The recurrent strokes were attributed to thromboembolic events secondary to prosthetic AV thrombosis.

A repeat transthoracic echocardiography was significant for an abnormal AV bioprosthesis with associated thrombus extending to the ascending aorta. Surgical excision and replacement of the AV conduit explant were performed in November 2012. The final pathology was consistent with EBV-associated large B-cell lymphoma (Figure). The initial staging evaluation, including a CT and positron-emission tomography scan and bone marrow biopsy, was negative for any systemic disease. The patient received 4 cycles of R-CHOP-21 (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 , vincristine 2 mg, and prednisone 100 mg) every 3 weeks in an "adjuvant" setting (because patient had no evidence of disease when given the systemic chemotherapy). The patient tolerated chemotherapy well without significant complications, and he is now over 36 months post-treatment without evidence of recurrent disease.

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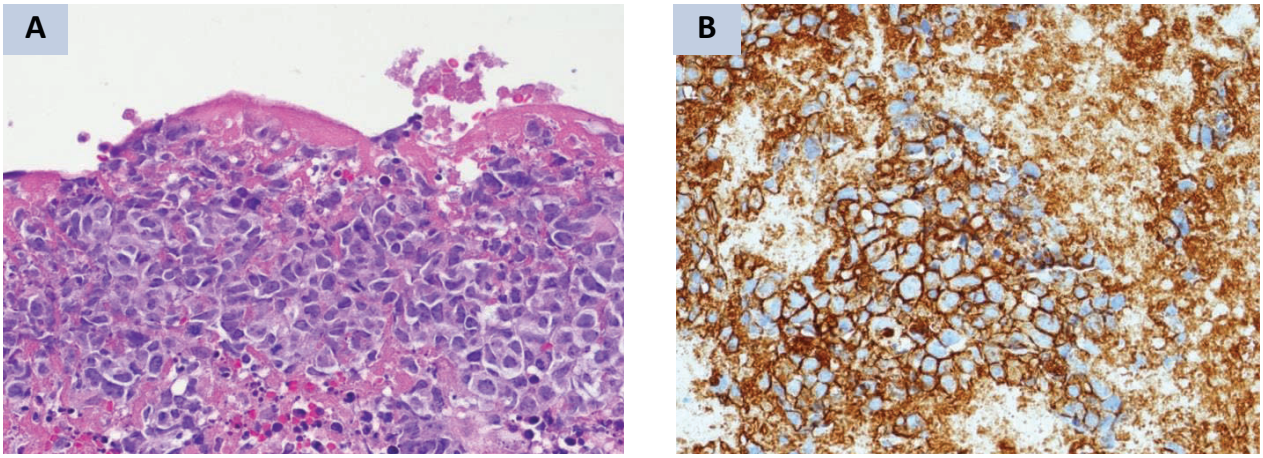

FIGURE The final pathology was consistent with Epstein-Barr-associated large B-cell lymphoma. Shown here are the immunohistochemistry features of resected primary valve-associated lymphoma. **A,** H&E stain, 400x. **B,** CD20 stain, 400x.

Discussion

Cardiac lymphoma limited only to prosthetic valves is rare, but it has been reported increasingly over the past few years. Until 2010, only six cases of PV-AL had been reported in the literature.[7] Including our case, we identified four additional PubMed-indexed cases (using a PubMed search through February 2015). The patient characteristics and treatments received for all identified cases are described in the accompanying Table. The pathology from all of the cases revealed non-Hodgkin lymphoma of large B-cell subtype. PV-AL predominated among men (60%) and older patients with a median age of 62.5 years at diagnosis (range, 48-80 years). Patients had a median duration of 8 years (range, 4-24 years) from date of prosthesis placement to date of lymphoma diagnosis. The three most common presenting manifestations were valvular dysfunction, stroke, and congestive heart failure. All of the patients had surgical intervention on initial presentation. However, management after surgery was not uniform, with only 3 patients reported to have received systemic chemotherapy (Table). None of the patients received adjuvant radiation therapy. Calculated from date of diagnosis, survival duration ranged from less than a month[7] to more than 36 months (as reported in our case).

The pathophysiology of PV-AL is not well understood given the rarity of the condition. Similar to other prosthetic-related neoplasms (metallic implants, breast implants),[12-14] it has been hypothesized that chronic inflammation and EBV infection may play an essential role in the pathogenesis of this entity. Further, it has been suggested that Dacron, which is used in composite cardiac valve replacements, is carcinogenic and may play a role in some cases.[7,15] PV-AL should be highly considered in the differential diagnosis of a suspicious prosthetic valve mass. Various imaging modalities, including echocardiography, CT, and magnetic resonance imaging have been described to have a role in the preoperative evaluation of cardiac tumors by assessing the cardiac function and defining the location and extent of the cardiac tumors.[16-19]

Given the rarity of this disease entity, there is no standardized approach for treatment. Surgical resection along with repair or replacement of primary involved prosthetic valve is essential for initial treatment. However, there is no consensus about the best approach for subsequent therapy. We cannot be conclusive about the optimum treatment, because of the limited number of published cases, but based on our reading of those cases, it would seem that early surgical intervention and "adjuvant" systemic therapy may have influenced prognosis. We speculate that poor outcomes in the first 6 months were most likely related to primary cardiopulmonary deterioration, whereas later poor outcomes were more likely to be attributable to recurrent lymphoma, particularly for patients who received suboptimal systemic chemotherapy treatment after surgery. All 3 patients who received chemotherapy had no evidence of recurrent disease at last follow-up. Of the 4 patients who received no chemotherapy and survived longer than 6 months (all except 1 died; Table), 2 had recurrent valve lymphoma, 1 had secondary systemic lymphoma, and 1 died of metastatic breast cancer. Those outcomes are in contrast to the 2 out of 3 patients who received adjuvant chemotherapy and who were reported to be alive at 16 and 36 months after diagnosis.

In conclusion, cardiac PV-AL is an increasingly recognized entity that warrants greater awareness among health care providers for early diagnosis and timely surgical intervention. Most of the cases are large B-cell lymphoma. Similar to patients with limited-stage DLBCL, fit patients should be highly considered for "adjuvant" systemic chemotherapy to optimize long-term outcomes. Reporting of similar cases is highly encouraged to better define this rare iatrogenic malignancy.

TABLE Patient characteristics, treatments received, and outcomes of reported cases

Case study, y	Patient age, y	Sex	Clinical presentation	Prosthesis type	Prosthesis placement to dx, y	Role of EBV	Subsequent treatment[a]	Treatment outcomes
Albat, 1994[8]	66	F	Syncope, pulmonary edema	St Jude mechanical mitral valve	8	Unknown	None	Alive at 6 mo without evidence of recurrent lymphoma
Durrleman, 2005[10]	65	F	Congestive heart failure	Unspecified mechanical mitral valve (Dacron)	9	Unknown	None	Died at 12 mo from complications of treatment of 'secondary digestive lymphoma' diagnosed at 10 mo from PCL diagnosis
Bagwan, 2009[9]	50	M	Valvular dysfunction	Pocrine stentless freestyle bioprosthesis for aortic valve	Not clearly reported	Negative	Chemotherapy (R-CHOP)	Died at 6 mo after prosthetic valve dehiscence; no evidence of lymphoma at autopsy
Bonnichsen, 2013[20]	48	M	Transient ischemic attack	Bjork-Shiley mechanical aortic valve	24	Positive	None[b]	Alive at 18 mo with evidence of recurrent lymphoma
Miller, 2010[7]	80	F	Dyspnea, congestive heart failure	Bioprosthetic (bovine pericardial) aortic valve	8	Positive	None	Died at 18 mo from metastatic breast cancer
Miller, 2010[7]	79	F	Dyspnea, chest discomfort, pseudo-aneurysm	Synthetic aortic tube graft[c]	5	Positive	None	Died within 24 hours from time of surgery
Berrio, 2010[21]	60	M	Congestive heart failure	Allograft	10	Unknown	Unknown	Died at 24 mo of endocarditis and severe pneumonia
Gruver, 2012[22]	55	M	Stroke	Bicuspid aortic valve and ascending Dacron aortic root graft[c]	4	Positive	Chemotherapy (R-CEOP x 8 cycles)	Alive at 16 mo without evidence of recurrent lymphoma
Farah, 2014[23]	60	M	Valvular dysfunction (fever, weight loss, worsening heart failure)	Allograft	4	Positive	None	Died at 12 mo of acute myocardial infarction; found to have recurrent lymphoma on allograft at autopsy
Current case	65	M	Stroke	St Jude Toronto aortic root	8	Positive	Chemotherapy (R-CHOP x 4 cycles)	Alive at 36 mo without evidence of recurrent lymphoma

EBV, Epstein-Barr virus; dx, diagnosis; F, Female; M, Male; PCL, primary cardiac lymphoma; R-CEOP, rituximab, cyclophosphamide, etoposide, oncovin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

[a]All patients had cardiac surgery on initial presentation. None received radiation therapy. [b]Received chemotherapy upon relapse. [c]Patients with synthetic aortic tube graft; unclear whether valve root was involved.

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