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Case Report

Heart of the Matter: Reversal of Systolic Heart Failure and Long Term Remission in Primary Cardiac Lymphoma with Multi-Agent Chemotherapy with Continuous Intravenous Administration of Doxorubicin

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Abstract

Primary cardiac lymphoma is rare with diffuse large B cell lymphoma being the most common histology. The main treatment modality is anthracycline based chemotherapy, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus rituximab (anti-CD20 monoclonal antibody). However, regimens containing doxorubicin are often used with caution as heart failure is a common presenting feature of primary cardiac lymphoma. We present a case of a patient with diffuse large B cell lymphoma of the myocardium presenting with cardiogenic shock who achieved long-term remission and reversal of biventricular heart failure after receiving RCHOP with continuous infusion doxorubicin.

Keywords: Diffuse Large B-cell Lymphoma (DLBCL); Cardiac Lymphoma; Systolic Heart Failure

Introduction

Primary Cardiac Lymphomas (PCL) are rare and account for 1% of primary cardiac tumors, with Diffuse Large B-Cell Lymphoma (DLBCL) being the most common histology [1]. While there is no standard of care, patients are often treated with multiagent chemotherapy which can be challenging as heart failure can be the presenting symptom in nearly half of the cases [1]. With the DLBCL subtype, there have been case reports of long-term survival with RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and REPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) chemotherapy, sometimes used in combination with radiation [2-4]. In the largest case series of 197 patients with cardiac lymphoma, the long-term overall survival was 40% [1].

Continuous intravenous administration of doxorubicin has been used as an alternative to bolus administration to reduce incidence of cardiotoxicity by 75% [5, 6]. In the NCCN guidelines, dose adjusted REPOCH is an acceptable alternative to RCHOP for those with poor cardiac function. Herein, we describe a case of primary cardiac lymphoma, DLBCL subtype who presented with cardiogenic shock but achieved complete remission with multiagent chemotherapy containing rituximab and infusional doxorubicin.

Case Report

A 67-year-old HIV-negative, physically active female with hypertension presented with a one week history of fatigue, night sweats, midsternal chest pressure, dyspnea on exertion, nausea and vomiting. Initial ECG showed sinus rhythm with diffuse ST-segment elevation with an elevated troponin of 0.38 ng/dL. Transthoracic Echocardiogram (TTE) revealed a Left Ventricular Ejection Fraction (LVEF) of 30-35%, grade 2 diastolic dysfunction, apical hypokinesis with severe apical hypertrophy and a small pericardial effusion. She underwent left heart catheterization which showed non-obstructive coronary artery disease with concern for an infiltrative cardiomyopathy as multiple coronary arteries appeared stuck in her myocardium. Cardiac MRI revealed a reduction in left and right ventricular volumes and function as well as concentric endocardial thickening and subendocardial hyperenhancement of the apical half of the left and right ventricles suggestive of endomyocardial fibrosis. Subsequent right heart catheterization with cardiac biopsy showed a severely depressed cardiac output of 1.66 with cardiac index of 0.96. Due to low cardiac output from biventricular failure, hypotension, in addition to hepatic and renal failure, she was placed on dopamine and milrinone drips and transferred for higher level of care. Repeat TTE showed a LVEF of 15% with left ventricular contraction preserved in the basal segments and severely reduced contraction in the mid and apical segments. Her hospital course was further complicated by multiple arrhythmias including atrial fibrillation and flutter requiring amiodarone, bilateral pleural effusions negative for lymphoma requiring thoracentesis, and re-expansion pulmonary edema.

Myocardial biopsy ultimately revealed the diagnosis of non-germinal center subtype DLBCL positive for CD10, CD20, CD79a, MUM-1, BCL 6, and BCL-2. Ki-67 with proliferation rate 90% and negative for CD68 and CD43, (Figure 1). PET/CT showed irregular FDG activity along the cardiac apex with no other metabolically active disease consistent with Stage IE disease. She was then initiated on RCVP (Rituximab, Cyclophosphamide, Vincristine, And Prednisone) with rituximab given at 50cc/hr and cyclophosphamide given in a hyperfractionated pattern to avoid ventricular perforation. Notably, doxorubicin was omitted due to a LVEF of 15%. After one cycle, she was weaned off of vasopressor support; repeat cardiac MRI showed improvement in LVEF to 42% (Figure 2). After cycle two, cardiac MRI showed improvement in LVEF to 56%. Given improvement in her cardiac function she continued treatment with curative intent. She was subsequently given RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for cycles 3-5 of treatment. Doxorubicin was given at half the recommended dose in a 25mg/m2 infusion over 48 hours due to her tenuous cardiac status and previous administration of amiodarone. She ultimately completed five cycles of chemotherapy with a total dose of 75mg/m2 of doxorubicin which led to complete remission. PET/CT showed no metabolically active disease and resolution of previous abnormal uptake at the cardiac apex. She remained in remission at 2 years; however, she ultimately passed away from septic shock, unrelated to lymphoma or cancer associated treatment.

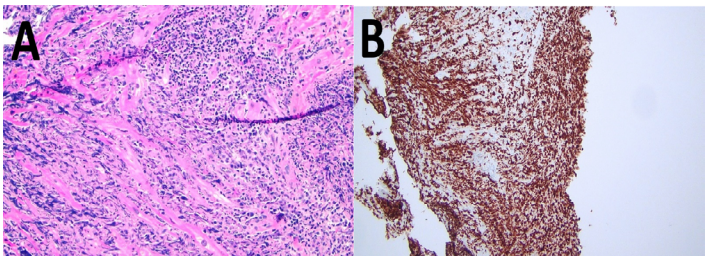

Figure 1: Final pathology consistent with non-germinal center subtype DLBCL. Shown here are the immunohistochemistry features of primary cardiac lymphoma from myocardial biopsy. A. H&E stain B. Ki-67 proliferation activity.

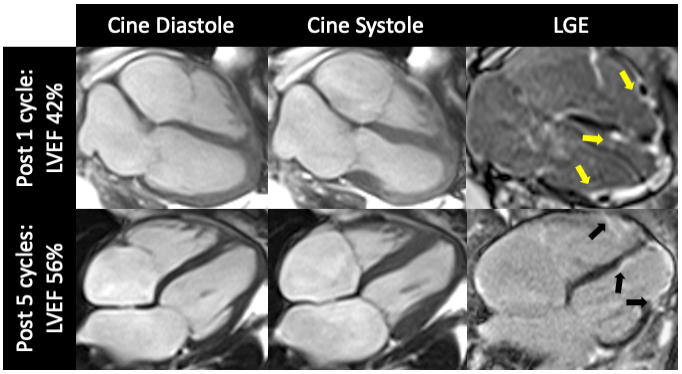

Figure 2: Cardiac Magnetic Resonance Images (Seimens Sola 1.5T) after one cycle and after five cycles of chemotherapy. Significant improvement in Left Ventricular Ejection Fraction (LVEF) from baseline (15% by transthoracic echocardiogram) and resolution of cardiogenic shock to LVEF 42% by cardiac MRI after one cycle of chemotherapy. Additional improvement of LVEF 56% after 5 cycles of chemotherapy.

Late Gadolinium Enhancement (LGE) imaging after one cycle with significant enhancement and thickening of the apical

segments of the left and right ventricle (yellow arrows) consistent with primary cardiac lymphoma with post treatment LGE imaging demonstrating normalized wall thickness of the apical RV and LV walls with persistent enhancement representing extensive residual fibrosis from treated lymphoma (black arrows).

Discussion

Primary cardiac lymphoma (PCL) is defined by the WHO as an extranodal lymphoma involving only the heart and/or pericardium [1, 3]. PCL is rare and accounts for only 1.3% of all cardiac tumors and 0.5% of all extranodal lymphomas with the most common subtype being diffuse large B-cell lymphoma which comprises more than 80% of PCLs [7]. The disease is more common in the elderly with a median age of 63 years old and in females with a female to male ratio of 2:1 [1]. PCL is often difficult to diagnose as the presenting signs and symptoms are nonspecific. Presenting findings include dyspnea (64%), pericardial effusion (58%), Arrhythmia (56%), Congestive Heart Failure (47%), and constitutional symptoms (26%). Less common findings include pericardial mass, cardiac tamponade, peripheral edema, and SVC syndrome [1]. Diagnosis is made by thorough examination and the use of multiple imaging techniques including echocardiogram and cardiac CT or MRI. However, the ultimate diagnosis can only be made following histological evaluation.

Congestive heart failure is a common presenting finding as noted above. It is also the most common cause of death in patients with PCL at 40%, followed by sepsis or other severe infection (26%), and progression of lymphoma (23%) [1]. Petrich, et al., noted four adverse prognostic factors including immunocompromised status, extracardiac disease, left ventricular involvement, and absence of arrhythmia [1]. PCL mainly involves the right atrium and the right ventricle and thus those with left ventricular disease may be a group with higher overall burden of cardiac disease and thus higher overall risk of mortality [1, 2]. Our patient presented with biventricular heart failure and an R-IPI score of 3 indicating a poor prognosis.

Due to late diagnosis and the rapidly progressive nature of DLBCL, prognosis in PCL is usually poor. Since most of the information about PCL comes from case reports or case series, there is no treatment consensus and various treatment modalities such as systemic chemotherapy, surgical resection, radiation therapy, and combined treatments have been attempted [2,3]. The Overall Response Rate (ORR) to chemotherapy is high at 79% with 59% achieving Complete Remission (CR) in one study [1] while another single-center retrospective study demonstrated an ORR of 85% and 62% achieved CR [8]. The main treatment modality is CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus rituximab (anti-CD20 monoclonal antibody) [3]. These regimens containing doxorubicin are used with caution in patients with poor cardiac function due the cardiotoxic effects. Additional treatment above a total cumulative dose to 450-500mg/m2 body surface area, produces a rapidly increasing incidence of clinically significant, and often fatal, cardiomyopathy. This, however, can be reduced by 75-88% by decreasing peak plasma levels with slow intravenous infusions without altering therapeutic efficacy [5,6]. Due to our patient already having significant cardiac dysfunction with an LVEF of 15% prior to treatment, this treatment strategy was taken. Our patient first received RCVP with improvement of cardiac function and reversal of organ failure. She was subsequently given 25mg/m2 infusions of doxorubicin over 48 hours for three cycles for a total dose of 75mg/m2 with curative intent. Another option is dose adjusted R-EPOCH in which doxorubicin is given as an infusion over 72 hours [3]. Recently, one case series showed that renal and hepatic dysfunction due to tumor infiltration with lymphoma or obstruction due to lymphadenopathy can be rapidly reversed with initiation of RCHOP chemotherapy with appropriate dose reductions [9]. These patients attained high rates of complete remission and long-term survival.

This case describes a 67-year-old female who presented with cardiogenic shock found to have Stage IE non-GCB subtype diffuse large B-cell lymphoma exclusively confined to the myocardium who received curative intent therapy. With chemotherapy, cardiogenic shock was resolved, and biventricular systolic failure was reversed. Since prospective clinical trials exclude patients with organ dysfunction, real world evidence is needed to guide treatment for these patients. We have previously demonstrated that patients with DLBCL who present with hepatic and renal dysfunction can have long-term remissions with curative intent chemoimmunotherapy [9]. Our case suggests that multiagent chemotherapy regimens including doxorubicin can be safe and effective for PCL when treated at a center with cardiology and malignant hematology expertise. Doxorubicin can be administered to patients with cardiac lymphoma if there is improvement in cardiac function after debulking with non-anthracycline based chemotherapy. Most importantly, DLBCL patients with organ dysfunction can be rapidly reversed with initiation of chemotherapy and can achieve a long-term remission.

Contributions

A.M. and B.H. wrote and edited the paper. J.S., S.A., N.G., B.H. provided patient care, edited the manuscript and provided important suggestions and contributions to the report. J.B. and J.S. provided the figures for pathology and cardiac MRI. B.H. wrote the case report and designed the original concept of this report. All authors approved the final submission of this report.

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