JACC: CASE REPORTS VOL. 1, NO. 3, 2019

CASE REPORT

ADVANCED

CLINICAL CASE

Complete Regression of Primary Cardiac Lymphoma With Dose-Attenuated R-CVP Chemotherapeutic Regimen

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ABSTRACT

An elderly man was found to have a large right atrioventricular mass and pericardial effusion. He was diagnosed and treated as having primary cardiac lymphoma. A dose-attenuated chemotherapy regimen of rituximab, cyclophosphamide, vincristine, and prednisolone, with a cytoreductive pre-phase, afforded complete regression of disease with resolution of the patient's symptoms, and without deterioration in cardiac function or immunosuppression. The patient remains well 12 months after presentation. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2019;1:332–6)

An 83-year-old man presented with a 6-week history of unintentional weight loss, cough, and night sweats. His medical history was significant for percutaneous coronary intervention 3 years previously, with stenting to the proximal and distal left anterior descending artery for symptoms of exertional angina. Examination revealed an underweight male with no palpable organomegaly or lymphadenopathy.

LEARNING OBJECTIVES

- To appreciate the role of multimodality imaging in the diagnosis and characterization of cardiac tumors, particularly PCL.
- To understand the rationale and benefits of tailored, multiagent, dose-attenuated chemotherapy, specifically R-CVP, for the treatment of cardiac lymphoma with curative intent among the elderly and frail populations.

INVESTIGATIONS

Laboratory investigations noted a C-reactive protein level of 117 mg/l and a lactate dehydrogenase (LDH) level of 439 U/l. The patient was immunocompetent. Computed tomography (CT) imaging of the neck, chest, abdomen, and pelvis revealed a 6.2 × 5.2 × 5.5 cm mass arising from the right atrium (RA), extending into the right ventricle (**Figure 1**), and scattered peritoneal nodules suspicious for metastatic disease.

Transthoracic echocardiography (TTE) confirmed a 5.6 × 4.5 cm mass, originating in the RA causing right ventricular (RV) outflow obstruction and a moderate global pericardial effusion without diastolic collapse (**Figures 2A and 2B**). Serial echocardiography over the next 2 weeks showed an enlarging effusion with

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Manuscript received May 9, 2019; revised manuscript received June 16, 2019, accepted June 19, 2019.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2019.06.033

features of cardiac tamponade. Comparatively, a TTE 3 months before admission was normal.

DIFFERENTIAL DIAGNOSIS

Given the patient's cardiovascular instability, we proceeded to CT-guided needle biopsy of a peritoneal node. The initial histological examination with hematoxylin and eosin stain disclosed atypical lymphocytes with prominent cytoplasm and pleomorphic nucleoli, features consistent with lymphoma (Figure 3A). Immunohistochemistry, which uses the antibody-antigen interaction to identify selective antigens, further refined the specific lineage and potential response to chemotherapy of the lymphoma. Expression of CD45 (leukocyte common antigen) indicated a hematopoietic malignancy, and BCL-2 expression with Ki67 80% to 90% confirmed a diagnosis of high-grade B-cell lymphoma of nongerminal center B type. CD20 (B-lymphocyte antigen) positivity suggested potential response to rituximab (a chimeric monoclonal antibody against the protein CD20) (Figures 3B to 3D). A diagnosis of hematological malignancy involving only the peritoneum and the right atrioventricular cavity, in the absence of intermediate nodes of disease, initially raised the suspicion of 2 separate primary malignancies.

SEE PAGE 337

Cardiac magnetic resonance (CMR) characterized a solid right heart mass originating in the RA. It was isointense relative to myocardium on T_1-weighted imaging and hyperintense on T_2-weighted imaging with tissue heterogeneity after gadolinium administration, consistent in appearance with cardiac lymphoma. For further diagnostic clarity, pericardiocentesis and fluoroscopic-guided transvenous endomyocardial biopsy were performed. Pericardial fluid was blood-stained, exudative, and cellular, predominantly consisting of inflammatory cells on the background of atypical epithelioid cells with reactive mesothelial cells on cytology. Biopsy specimens taken from the RA and right ventricle were histologically normal. The authors were conservative in the sampling because of the risk of cardiac perforation; even light sedation, to facilitate transesophageal echocardiography guidance, was believed to be too risky.

A diagnosis of primary cardiac lymphoma (PCL) was assumed given the lack of other organ involvement, absence of intermediate nodes, and the scanty peritoneal nodules appearing typical of metastases on CT imaging, in addition to quantitative assessment by CMR. All imaging modalities confirmed the mass originating from the RA (the most common site for PCL), further supporting the diagnosis. Using the Lugano Modification of the Ann Arbor staging system for lymphoma, this was tumor stage III (advanced), with disease on either side of the diaphragm. The patient was unfit for further open cardiac biopsy or debulking surgery, owing to his rapid physical decline and the size and location of the mass. Given clinical urgency, necessitating treatment initiation, fluorodeoxyglucose-positron emission tomography was not performed, although this test would have further supported the diagnosis by excluding a somewhat occult primary.

MANAGEMENT

A staggered, dose-attenuated regimen of rituximab, cyclophosphamide, vincristine, and prednisolone (R-CVP) cytotoxic chemotherapy was initiated. The first 2 cycles consisted of pulsed prednisolone (1 mg/kg orally) and rituximab (375 mg/m^2 intravenous [IV] infusion) as a cytoreductive pre-phase to minimize risk of cardiac perforation and treatment-related toxicities. Cyclophosphamide (750 mg/m^2 IV bolus) was added to the third cycle, and vincristine (1.0 mg/m^2 IV infusion) was added to the fourth. This protocol was continued for an additional 5 cycles, totaling 8 × 5-day cycles repeated every 21 days.

FOLLOW-UP

After 3 cycles, TTE demonstrated a reduced tumor burden of ~50%, with LDH falling to 180 U/l. Further follow-up staging CT imaging, after completion of chemotherapy, confirmed no residual disease, and disappearance of the right heart mass and pericardial effusion on TTE (Figures 2C and 2D) with good left ventricular function. Twelve months after presentation, the patient has returned to his pre-morbid baseline with an LDH level of 175 U/l and normal TTE appearances.

DISCUSSION

Primary cardiac tumors are incredibly rare. These include atrial myxoma, lipoma, angiosarcoma, and lymphoma. Metastatic cardiac disease is far more recognized, most commonly attributable to bronchial and breast carcinomas, followed by melanoma and lymphoma. PCL represents <1% of primary cardiac tumors, whereas metastatic cardiac involvement from non-Hodgkin lymphoma has a reported incidence of 18% (1). Involvement of the right heart

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CT = computed tomography

IV = intravenous

LDH = lactate dehydrogenase

PCL = primary cardiac lymphoma

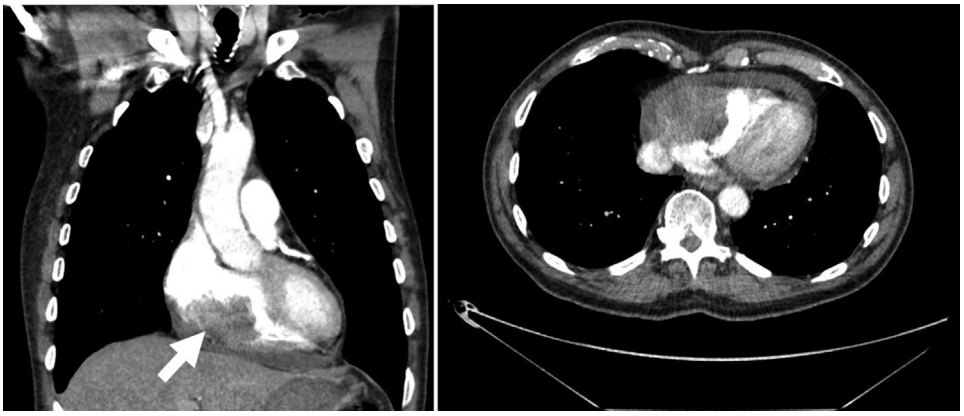
R-CVP = rituximab, cyclophosphamide, vincristine, and prednisolone chemotherapy

RA = right atrium

RV = right ventricular

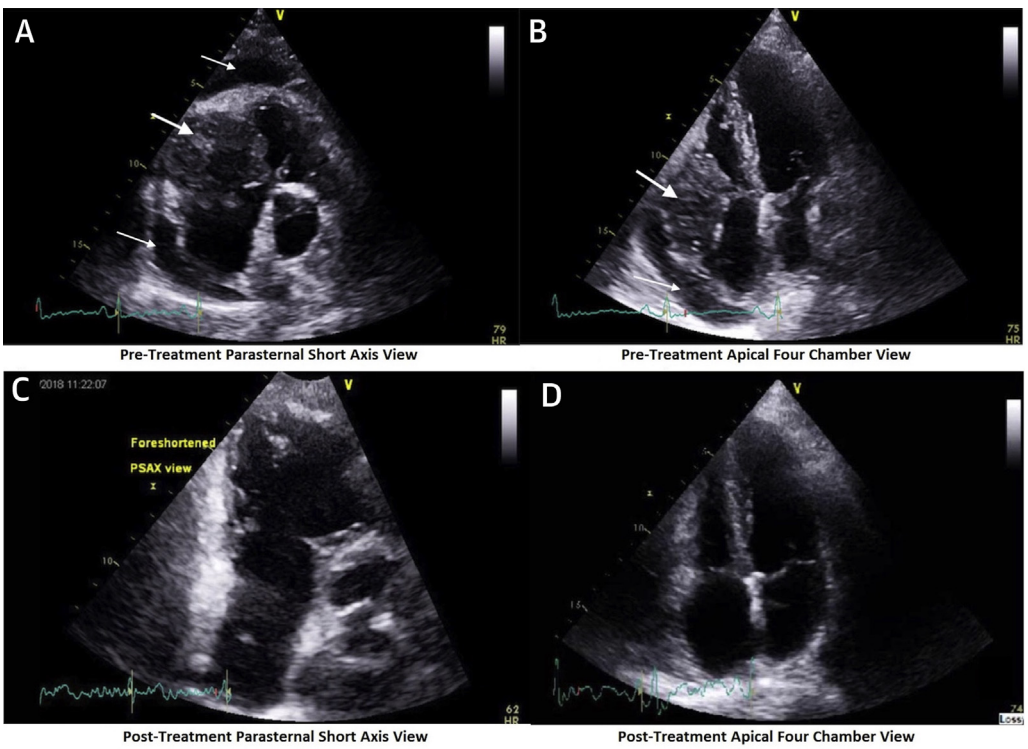
TTE = transthoracic echocardiography

FIGURE 1 Computed Tomography of the Chest



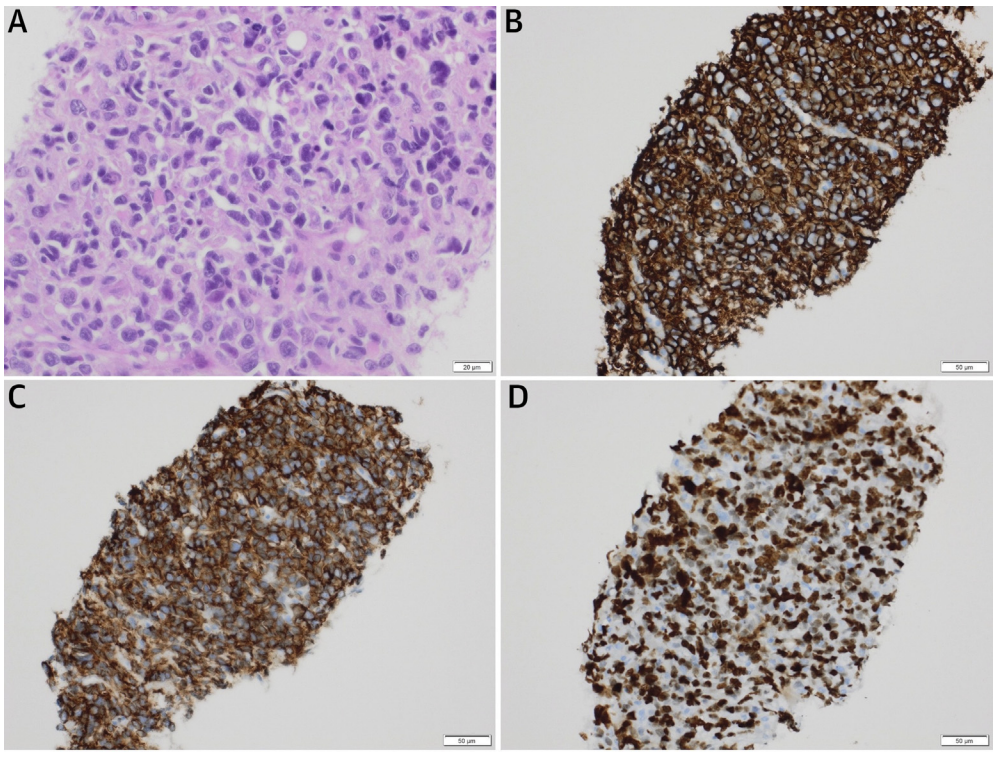
Computed tomography chest imaging with contrast in coronal and sagittal planes showing a large right atrioventricular mass **(arrow)**.

FIGURE 2 Transthoracic Echocardiography Pre- and Post-Treatment



Pre-treatment transthoracic echocardiography showing a 5.6 × 4.5 cm right ventricular mass extending from the free wall causing right ventricular outflow obstruction **(bold arrows)** and moderate global pericardial effusion **(small arrows)** (**A**, parasternal short-axis view; **B**, apical 4-chamber view.) Post-treatment TTE showing right heart mass and pericardial effusion resolution after rituximab, cyclophosphamide, vincristine, and prednisolone chemotherapy (**C**, parasternal short-axis view; **D**, apical 4-chamber view.

FIGURE 3 Histology and Immunohistochemistry of Biopsied Peritoneal Node



(A) Hematoxylin and eosin stain: large lymphocytes with prominent cytoplasm and nucleoli. **(B)** CD20 stain: a B-cell marker retained until B-cell development, which may indicate suitability for treatment with rituximab. **(C)** CD45 or leukocyte common antigen stain: expressed on nucleated hematopoietic cells assisting in tumor classification. **(D)** Ki67 stain: 80% to 90%, a marker of nuclear proteins expressed during phases of cell division and cell proliferation, often associated with a poor prognostic outcome (high percentages reflect a worse prognosis).

predominates, with the RA being the usual site of origination for PCL. It is hypothesized that direct receipt of lymph drainage from the thoracic duct via the superior vena cava renders right chambers, particularly the RA, vulnerable as the primary site. With this model it could also be argued that PCL may, in fact, be an extranodal manifestation of occult systemic lymphoma (2).

Clinical presentation is often nonspecific, owing to variations in tumor site, size, and infiltration. Heart failure from inflow or outflow tract obstruction, cardiomyopathy, arrhythmias from conduction disturbance, and sudden death from cardiac tamponade or rupture have been described (3).

The heterogeneity of radiographic appearance necessitates multimodal imaging techniques capable of tissue characterization, particularly contrast CT imaging and CMR. CMR allows discrimination between benign and malignant cardiac masses and provides functional information in addition to echocardiography regarding hemodynamic significance of inflow/outflow obstruction or pericardial constriction (4).

Definitive diagnosis is histological. Image-guided sampling including endomyocardial biopsy or pericardiocentesis is preferred to open thoracotomy, with biopsy of extranodal disease a less-favored alternative if these methods fail or prove impractical.

Treatment options include minimally invasive surgery for tumor resection and anthracycline-based cytotoxic agents with or without radiotherapy (5). Due to the significant risk of cardiomyopathy and pericarditis, there is no credible indication for radiotherapy in treating PCL. The overall extrapolated survival data indicate only chemotherapy, sole or adjunctive, to be statistically significant. Cumulative data have shown that multiagent chemotherapy seems to be the best therapeutic option, although overall prognosis remains poor. Drug-related cardiotoxicity is reduced by the omission of the

anthracycline agent doxorubicin used in more conventional chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), giving R-CVP, which was used with good effect in this case. Despite anthracycline exclusion, an established risk of cardiotoxicity with high-dose cyclophosphamide administration remains, reported as between 5% and 19% (6,7), with acute heart failure developing within 48 h to 21 days from initiation. This scenario seems to be related to a single-cycle dose rather than cumulative drug dose. Advanced age, coronary artery disease, and lymphoma itself are independent predictors of cyclophosphamide cardiac toxicity (8).

CONCLUSIONS

The authors describe an elderly patient afforded complete remission from advanced inoperable disease after attenuated multiagent chemotherapy, yielding comparatively long-term favorable outcome data. Diagnostically, results of a high-risk cardiac biopsy proved low yield, but an extracardiac nodal biopsy provided adequate histopathological data to initiate guided therapy. After the initial stabilization, the patient was well managed in the community with thorough safety-netting, patient education, monitoring, and facility for urgent admission with TTE for any changes in symptoms. Ambulatory dose-attenuated R-CVP chemotherapy proved a safe and viable alternative to prolonged hospitalization, lending credence to the role of nonsurgical management in specific populations. Throughout treatment, the patient remained immunocompetent with no unplanned admissions and no compromise in cardiac performance.

Although there are no established guidelines for the treatment of de novo primary cardiac diffuse large B-cell lymphoma, in this case, an individual-specific R-CVP regimen provided an optimum outcome for an elderly patient vulnerable to treatment-related death (9). Future research is awaited to guide best practice decision-making. In addition, the potential of a cytoreductive pre-phase in further reducing the risk of cardiac perforation and treatment-related toxicities should be explored.

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KEY WORDS cancer, cardiomyopathy, right ventricle, tamponade, tricuspid valve