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CLINICAL CASE CHALLENGES

Medical Management of Hemodynamically Unstable Sinoatrial Node Dysfunction in a Patient With Intracardiac Lymphoma

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A 56-year-old woman with no significant previous medical history presented with 1 month of fatigue, chills, night sweats, and 7-pound weight loss in addition to several days of pleuritic chest pain. An electrocardiogram (ECG) showed normal sinus rhythm at a rate of 93 beats/min with normal axis, conduction intervals, and morphologies. Laboratory studies were notable for hemoglobin 9.4 g/dl, D-dimer 674 ng/ml (normal upper limit <230), troponin I 0.099 ng/ml (normal upper limit <0.034), N-terminal pro-B-type natriuretic peptide 2,360 pg/ml (normal upper limit <125 pg/ml), lactate dehydrogenase 1,903 U/l (normal upper limit 618 U/l), and C-reactive protein 191.8 mg/l (normal upper limit 10 mg/l). Human immunodeficiency virus, hepatitis B, and hepatitis C serologies were negative. Computed tomography (CT) revealed no evidence of pulmonary emboli but demonstrated retroperitoneal and right retrocrural adenopathy, omental caking, splenomegaly, and an infiltrative right hilar and mediastinal mass encasing the right pulmonary veins and impinging on the superior vena cava (SVC) (**Figure 1**). Transthoracic echocardiography showed a prominent interatrial septum, normal left and right ventricular function, no significant valvular disease, and a small pericardial effusion. Follow-up transesophageal echocardiography demonstrated an infiltrating mass at the base of the heart involving the right atrium and extending into and involving the interatrial septum and the left atrial wall adjacent to the aortic valve. There was moderate stenosis of the SVC secondary to the mass. Biopsy of a retroperitoneal node revealed high-grade B-cell lymphoma positive for CD10, CD20, BCL2, BCL6, and MYC with negative MUM-1 according to immunohistochemistry and Ki-67 proliferative index of approximately 90%, most consistent with diffuse large B-cell non-Hodgkin lymphoma (DLBCL). With the diagnosis of stage IV DLBCL invading the heart, but without obvious cardiac compromise, the patient was discharged to follow-up urgently in the oncology clinic the next day.

While waiting for her appointment, she experienced a syncopal episode leading to an evaluation in the emergency department. Initial vital signs were notable for a heart rate of 97 beats/min, blood pressure 110/56 mm Hg, and SpO_2 97% on room air. ECG showed an accelerated junction rhythm at a rate of 78 beats/min and nonspecific ST-segment abnormalities. Repeated CT excluded pulmonary embolism. She received 2 liters intravenous fluid but developed progressive bradycardia and hypotension, prompting triage to the intensive care unit for dopamine infusion and potential transvenous pacemaker (TVP) placement for sinus node dysfunction presumed secondary to intracardiac lymphomatous invasion. Her shock was attributed to a decrease in preload secondary to mass effect on the SVC and sinus node dysfunction with resultant bradycardia. She received 1 g intravenous methylprednisolone and laboratory monitoring for tumor lysis syndrome overnight while awaiting more directed anticancer therapy.

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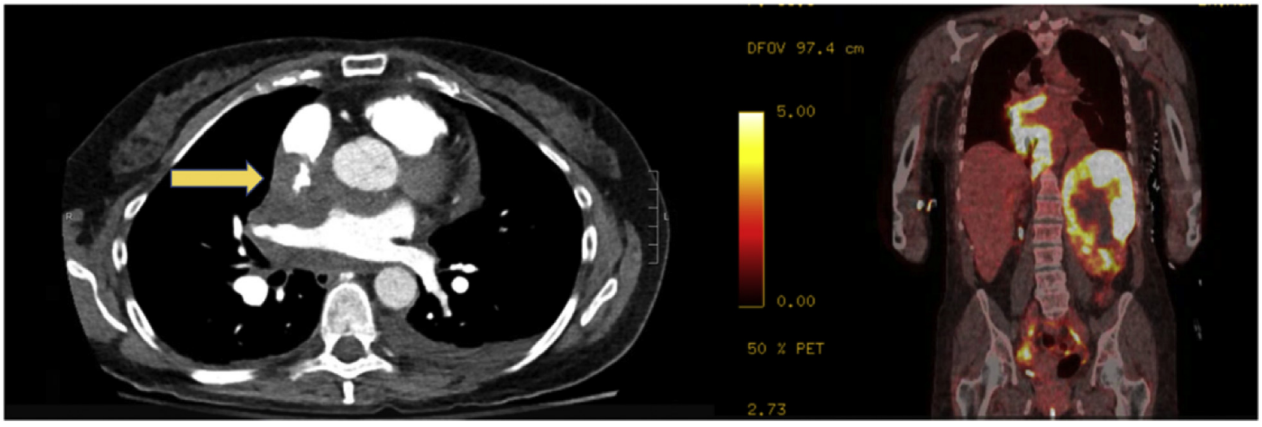
FIGURE 1 Computed Tomographic Pulmonary Angiogram and Positron Emission Tomography



(Left) Axial chest computed tomography, demonstrating stenosis of the superior vena cava secondary to lymphoma-associated mass effect **(arrow)**. **(Right)** Positron emission tomography with extensive fluorodeoxyglucose avidity along the pericardium surrounding the bilateral atria with extension around the suprahepatic inferior vena cava.

Her hemodynamic status stabilized and, given the risk of tumor embolization, TVP placement was deferred. Radiation oncology and medical oncology were consulted. Positron emission tomography demonstrated extensive fluorodeoxyglucose avidity above and below the diaphragm including the regions surrounding both vena cavae (Figure 1). To urgently shrink the mediastinal mass, 2 fractions of radiation (3 Gray each) were delivered on hospital days 2 and 3. She was also started on chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) on hospital day 3. Despite this, the patient continued to have intermittent junctional bradycardia in the 40s (Figure 2). She was supported with additional intravenous fluids to maintain preload, and 1 mg glycopyrrolate 3 times daily and 5 mg methylphenidate twice daily were started to increase her heart rate. Her heart rate gradually improved in the subsequent days, and she was transferred to the step-down unit on hospital day 6 (Figure 2). Her subsequent hospital course was notable for development of hypoxia, and CT pulmonary angiography demonstrated a distal right upper lobe pulmonary artery embolus. She was treated with heparin followed by dalteparin. Her hypoxia resolved by hospital day 10 and she was weaned from methylphenidate and glycopyrrolate by hospital day 11 before discharge on hospital day 12. She was in normal sinus rhythm on discharge and remained so at outpatient follow-up (Figure 2). Unfortunately, her aggressive malignancy progressed through multiple lines of chemotherapy and was refractory to chimeric antigen receptor T cell therapy. She died 9 months after her diagnosis. She had no further significant cardiac complications during the course of her treatment.

DISCUSSION

Cardiac masses can be lethal regardless of their characterization as benign or malignant, given the deleterious effects they can have on cardiac function. Diverse mechanisms result in compromised cardiac output: reduced preload related to space-occupying intracardiac lesions or extrinsic compression, valvular dysfunction, myocardial injury, tachyarrhythmia, or bradyarrhythmia from invasion of the conduction system, pericardial effusion with tamponade physiology, and tumor embolization.

Tumors of the heart can be characterized as primary tumors (with benign and malignant variants) or tumors that arise from noncardiac tissues and invade the heart either by local invasion or metastasis. Primary cardiac tumors are rare, with an incidence of $<$0.1% in a large autopsy series (1). Most primary cardiac tumors are benign (80%); myxomas, lipomatous tumors, and fibroelastomas account for 85% of benign tumors in adult patients. Sarcomas represent the majority of the 20% of primary cardiac tumors that are malignant (2). Metastatic invasion of the heart by tumors arising from other tissues is by far the predominate mechanism of cardiac involvement by cancer, with a 20-fold greater incidence than primary cardiac tumors (1). The most

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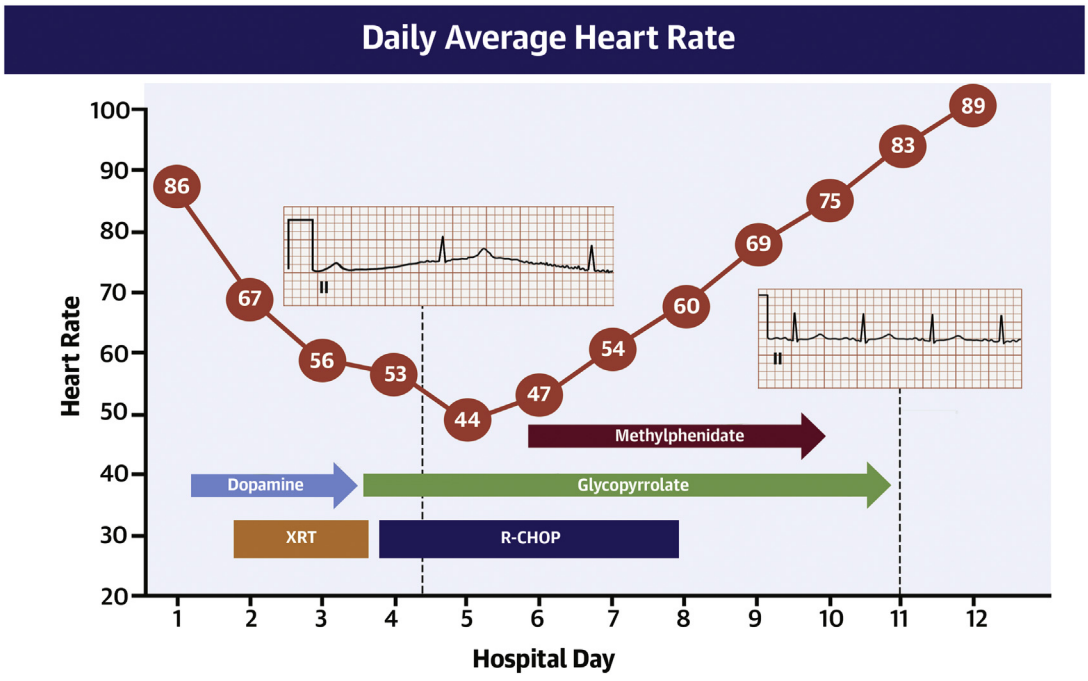
FIGURE 2 Heart Rate and Electrocardiographic Response to Treatments



Daily heart rate (averaged over 3 measurements) over hospitalization course with treatments administered as indicated. Representative lead II electrocardiographic tracings demonstrating junctional bradycardia on hospital day 4 and restoration of normal sinus rhythm before discharge are shown.

common cancers that metastasize to the heart are lung (37%), lymphoma (20%), breast (7%), and esophageal cancers (6%) (3). Lymphoma can present as primary cardiac lymphoma or as metastatic disease. Autopsy studies have demonstrated cardiac involvement in 16% of patients with Hodgkin lymphoma and 18% of patients with non-Hodgkin lymphoma (4).

This case illustrates an approach to the management of cardiogenic shock caused by impaired venous return and bradyarrhythmia resulting from aggressive intracardiac DLBCL. Similar cases of multifactorial cardiac compromise secondary to lymphomatous invasion have been described in the literature (5). Aside from typical considerations in this hematologic emergency, such as monitoring for electrolyte disturbances associated with tumor lysis syndrome, the management of this case relied on noninvasive measures to support hemodynamics and heart rate until anticancer treatment with radiation and chemotherapy took effect. Importantly, TVP placement was avoided and instead treatment of the patient's symptomatic bradycardia focused on medications aimed at manipulating autonomic inputs (parasympathetic and sympathetic) to the cardiac conduction system.

This patient received both radiation therapy and R-CHOP chemotherapy at the outset, given the importance of achieving immediate tumor reduction. A multidisciplinary discussion between medical and radiation oncology concluded that systemic chemotherapy alone might not suffice to rapidly induce a response. In nonemergency settings, DLBCL may be appropriately treated with chemotherapy alone initially. In an emergency such as this, abbreviated radiation therapy can potentially provide a swift local response and serve as a bridge to systemic therapy. Our patient's critical illness indicated the use of both treatment modalities in her initial management strategy.

Similar cases of conduction abnormalities arising from cardiac involvement with lymphoma have been described (6–9). Many of those were managed with temporary TVP, and in some a permanent pacemaker was ultimately placed. It is worth noting that lymphomas tend to be highly responsive to chemotherapy and radiation, and thus potentially offer more opportunities to avoid pacemaker support in this setting than do other

cardiac tumors. Primary or metastatic solid tumors, for example, may be less likely to respond rapidly to anticancer therapies, and thus are more likely to require a pacemaker. The present case with symptomatic junctional bradycardia demonstrates that in patients with noncritical conduction disease (i.e., conduction through the His bundle with no high-degree atrioventricular [AV] block) and disease sensitive to chemoradiation, medical therapy can be an attractive alternative to pacemaker implantation, especially given the risk of tumor embolization with TVP placement.

Glycopyrrolate competitively blocks the effect of acetylcholine at muscarinic receptors within the heart and accelerates the rate of sinus node firing and AV node conduction velocity. It is more potent than atropine but does not cross the blood-brain barrier as effectively and therefore is less likely to cause altered mental status. It is relatively contraindicated in patients who might not tolerate a rapid heart rate after its administration (as in those with known coronary artery disease). Methylphenidate acts on the central nervous system to increase circulating catecholamines that can activate cardiovascular beta-1 adrenoreceptors, resulting in increased heart rate and inotropy. It can also activate alpha-adrenoreceptors on blood vessels, causing vasoconstriction and increased blood pressure. Although these drugs were successful in maintaining adequate heart rate in this patient, it is important to acknowledge that if she demonstrated high-degree AV block or failed medical therapy, TVP placement might have been required. There are reports of increased risk of myocardial infarction, sudden cardiac death, and stroke with the use of stimulants such as methylphenidate, though lack of a dose-response relationship raises questions regarding a causal relationship (10). Therefore, caution should be taken when using these agents in patients with preexisting cardiovascular disease. It is critical to exclude ischemia as a trigger of conduction abnormalities before they are deployed.

In summary, this case provides an interesting example of conduction abnormalities caused by tumor infiltration of the heart and demonstrates a noninvasive medical strategy that allowed maintenance of hemodynamic stability until anticancer therapy could take effect. Similar strategies for support of heart rate and perfusion, avoiding the use of a pacemaker, may be beneficial in other patients presenting without critical conduction disease.

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