**CLINICAL VIGNETTE**

# Radiation-Induced Coronary Artery and Combined Valvular Disease

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***Abstract***

Patients who have received mediastinal radiation or certain chemotherapy regimens are at significantly increased risk of developing cardiovascular complications. This case illustrates a patient who developed systolic heart failure from multivessel coronary artery disease, severe aortic stenosis, and moderate mitral regurgitation twenty years after undergoing chemotherapy and mediastinal radiation for Hodgkin's lymphoma. Given the strong association between chemoradiation and late cardiovascular complications, there might be a role for cardiovascular screening in patients who have undergone mediastinal irradiation or chemotherapy with anthracyclines.

***Background***

Hodgkin's lymphoma is one of the most common cancers in young adults with an incidence of three in 100,000.[1] Current standard therapy for early-stage Hodgkin's lymphoma is chemotherapy followed by consolidation radiation therapy to the involved field.[2] Despite some progress over the last five decades in minimizing the risks of therapy, cardiovascular complications still remain significant adverse effects of combined modality chemoradiation for Hodgkin's lymphoma.

***Case Presentation***

A 42-year-old female presented to cardiology with substernal chest pain and dyspnea with exertion. The patient had a past medical history significant for Hodgkin's lymphoma 20 years prior, status post debulking surgery, with thoracotomy and MOPP chemotherapy followed by radiation. She had remained relatively stable and had been lost to routine follow-up medical care.

Her chest pain, which mostly occurred with exertion, had been gradually increasing over the prior eight months. In the weeks leading up to our initial evaluation, she was increasingly symptomatic, could only ambulate a few steps before feeling dyspneic, and required 3-4 pillows at a 60 degree angle in order to sleep at night.

On physical examination, the patient had a systolic murmur heard at the right upper sternal border without radiation, a jugular venous distention of 10-11 cm above the level of the right atrium, crackles throughout her lung fields, and bilateral pitting edema. A stress test revealed a mild fixed defect in the anterior septum and inferior ventricular walls (Figure 1). An echocardiogram showed severe hypokinesis of the anterior septum and distal 1/3 of the left ventricle and mild hypokinesis in the inferior wall. Her ejection fraction was estimated at 35-40%. The echo also displayed severe aortic stenosis and severe aortic regurgitation as the valve leaflets were thickened and calcified with restricted cusp opening. A mean pressure gradient of 31mmHg was measured (Figure 2A, B, C). Likewise, the mitral valve appeared thickened with severe annular calcifications. These findings were consistent with at least moderate mitral regurgitation (Figure 3). The patient's clinical presentation of worsening decompensated heart failure warranted hospitalization and medical optimization. Given significant segmental wall motion abnormality and moderate cardiomyopathy, cardiac catheterization revealed a 60-70% lesion in the ostium of the right coronary artery with a fractional flow reserve (FFR) of 0.69, as well as a 50-60% lesion in the ostium of the left main coronary artery with FFR of 0.78 (For reference, <0.80 is consistent with significant obstructive coronary artery disease). CT's of the patient's chest, abdomen, and pelvis ruled out a recurrence of malignancy. The patient's cardiomyopathy and heart failure was secondary to combine valvular and coronary artery disease, which were likely complications of prior direct radiation to the heart.

She underwent three vessel coronary artery bypass grafting (CABG) as well as aortic and mitral valves replacement. The patient did well post-operatively except for intermittent episodes of atrial fibrillation and tachycardia-bradycardia syndrome. The patient eventually had a dual chamber pacemaker implanted after developing complete heart block two years post-operatively (Figure 4).

***Discussion***

Cardiovascular disease is the most common non-malignancy cause of death in patients cured of Hodgkin's Lymphoma.[1] Radiation to the heart can damage virtually any of its components, including the pericardium, myocardium, all four heart valves, coronary arteries, and conduction system.[2] A study of 1,400 patients treated for Hodgkin's lymphoma and followed-up for 18 years reported significantly increased incidences in myocardial infarction (2.4 fold), angina (4.9 fold), valvular heart disease (7.0 fold), and congestive heart failure (7.4 fold).[3] Most of the cardiac sequelae became apparent at least 5-10 years after initial treatment, and the cardiovascular risk has been shown to remain elevated as far as 25 years post-chemoradiation.[1,4] The type of valvulopathy seen after chemoradiation is also time-dependent with

regurgitation being the early-stage manifestation and stenosis requiring over twenty years to develop.[1] In 116 patients observed 10 years after treatment, 31% had moderate mitral or aortic regurgitation, while none had stenosis.[1] In the same group of patients, 39% had aortic stenosis 22 years after treatment.[1]

The pathophysiology behind cardiac manifestations of radiation therapy involves damage to blood vessels.[2] Reactive oxygen species generated by radiation damaged DNA strands in endothelial cells lead to inflammation.[2] Nuclear factor-kappa B (NF-kB), a family of transcription factors, becomes activated and induces endothelial cells to secrete E-selectin, VCAM1, and ICAM1, which attracts monocytes.[5] The monocytes then take up low-density lipoprotein (LDL) and form an unstable plaque prone to thrombosis that is the hallmark of coronary artery disease.[5] In coronary artery disease secondary to mediastinal radiation, the left anterior descending artery and right coronary artery are most affected especially at the ostia.[3] Radiotherapy is also believed to directly damage heart valves leading to valve retraction and regurgitation, and later, thickened and calcified valves that lead to stenosis.[1] The aortic and mitral valves are more affected than tricuspid and pulmonary valves because of higher pressures in systemic circulation.[1] Fibrosis of cardiac myocytes reduces the heart's compliance and may cause diastolic heart failure.[6] Heart arrhythmias are also seen because of fibrosed conducting cells.[7]

In addition to standard cardiac disease risk factors, the risk factors for radiation-induced heart disease include younger age at time of therapy, use of anthracyclines, volume of heart irradiated, and radiation dose. The risk of myocardial infarction after mediastinal irradiation for Hodgkin's lymphoma was 2.6-fold increased for patients treated at ages 36-40 compared with a 5.4-fold increase for patients treated at less than 20 years of age.[3] The use of anthracyclines, of which doxorubicin is the most well-known, substantially increases the risk of cardiac events. Doxorubicin is one of the four drugs used in the ABVD regimen that became the first-line treatment regimen for Hodgkin's lymphoma after it was shown that doxorubicin regimens were superior at reducing the burden of disease.[7] This is despite the significant increases in risk of cardiovascular complications, arrhythmias, and valvular disease relative to other chemotherapeutic agents.[7] Two other radiation-associated cardiac disease risk factors, the volume of heart irradiated as well as dose of radiation, have been reduced in recent years.[2] Current guidelines advocate using a combined modality approach where chemotherapy is followed by radiotherapy only to affected lymph nodes. In this way, chemotherapy assures systemic control while radiotherapy can be more localized to only the nodes with active disease.[8] Involved-node radiation therapy (INRT) has gained traction as the preferred form of radiotherapy after it was shown to have the same rate of cure as more extensive forms of radiotherapy.[8]

***Conclusion***

The cardiovascular side effects of chemoradiation have been long known, but recently there has been more discussion about the need for screening individuals who have received mediastinal chemoradiation. Patients who have received mediastinal radiotherapy likely have cardiac dysfunction even if they are asymptomatic. In this patient population, > 75% of asymptomatic patients have coronary artery disease with 30% having severe multivessel disease.[9] It is recommended that before undergoing treatment, a cardiovascular baseline should be established through history, physical, risk factor profiling, and echocardiogram[1,2]. Unfortunately, no formal guidelines exist from the American College of Cardiology or American Heart Association about screening guidelines in asymptomatic post-chemoradiation patients. Some studies suggest that screening should begin five years after mediastinal chemoradiation with CT-angiography, echocardiograms, and electrocardiograms.[10] Strategies for early detection likely make up the best approach for reducing the morbidity and mortality from chemoradiation-induced heart disease.

***Figures***

Figure 1: Nuclear stress imaging in grayscale indicative of ischemia.

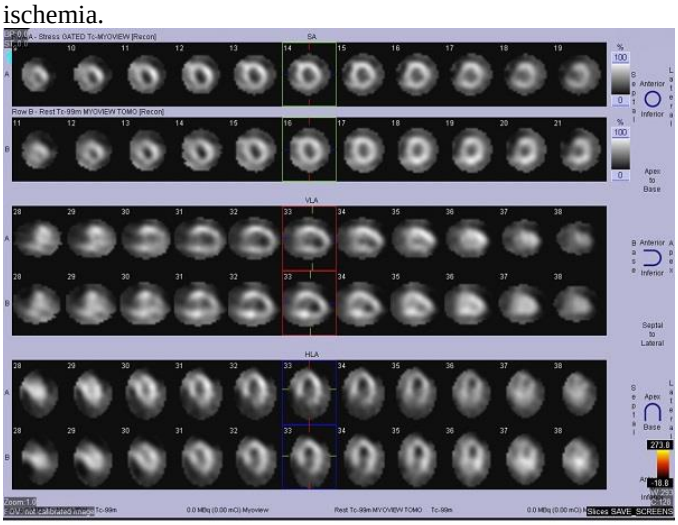


Figure 2A: Transthoracic echocardiogram with color Doppler showing apical three chamber view indicating aortic regurgitation.

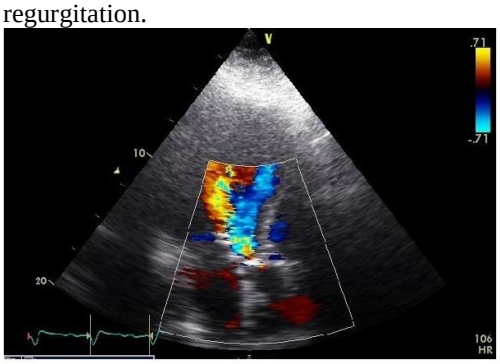


Figure 2B: Transthoracic echocardiogram with color Doppler showing calculated aortic regurgitation PHT= 166 msec (severe at <250 msec).

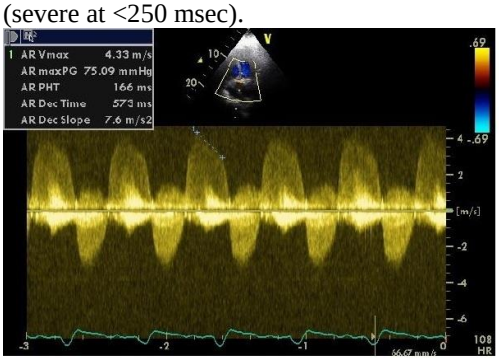



Figure 2C: Transthoracic echocardiogram with color Doppler showing calculated aortic volume mean pressure gradient= 31.1 mmHg (normal= <5 mmHg) and valve area = 0.84 $cm^2$ (less than 1.0 $cm^2$ is indicative of severe aortic stenosis).

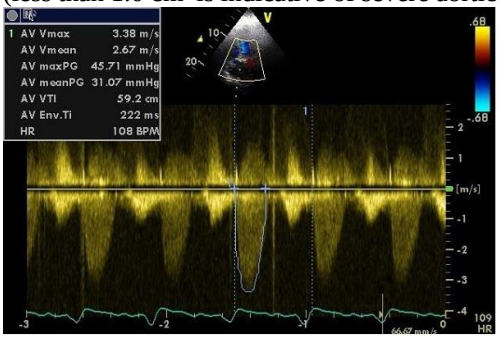



Figure 3: Transthoracic echocardiogram with color Doppler (apical four chamber view) illustrating mitral regurgitation.

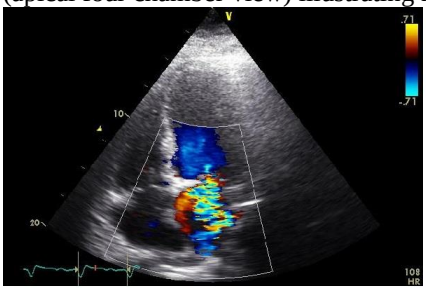
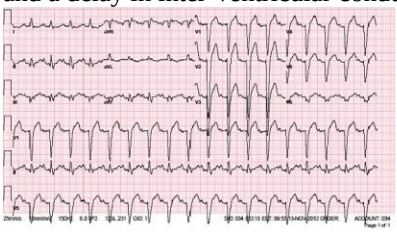


Figure 4: Electrocardiogram reveals rate of 110 beats per minute, sinus tachycardia, atrioventricular block, and a delay in inter-ventricular conduction.



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