



A Message from Cardiology Associates, P.C.



Dear Colleagues,

Our May 2011 Referring Physician Newsletter focuses on Radiation-Induced Heart Disease. This is a medical issue many physicians will likely be faced with as we are now seeing the late cardiac manifestations of radiation therapy which was delivered initially several decades ago. Dr. Scott Katzen discusses an extraordinary case of a man with a prior history of mediastinal radiation therapy who recently survived sudden cardiac death, the cause thought likely secondary to effects from his prior radiation treatment. Dr. Katzen outlines the clinical spectrum of cardiac problems caused by mediastinal radiation therapy, and the consensus recommendations regarding management and surveillance in patients who have been exposed.

About the Author

Dr. Scott M. Katzen completed his post-graduate training from the University of Maryland Medical Center in Baltimore, MD, including an additional year as Chief Medical Resident. He is board-certified in Internal Medicine, Cardiovascular Diseases, and Interventional Cardiology, and is a Fellow of the American College of Cardiology. Dr. Katzen practices consultative cardiology in our Annapolis office, and also practices interventional cardiology at Anne Arundel Medical Center as well as at Washington Hospital Center, in Washington, DC.

Mediastinal Radiation Therapy: No Good Deed Goes Unpunished

PRESENTATION OF CASE

- Mr. DS is a 48-year-old man with a history of hypothyroidism, dyslipidemia, GERD, and Hodgkin's Lymphoma for which he underwent extensive radiation therapy to the chest in the early 1980s, leading to complete remission of his cancer.
- He has been very active, participating in competitive softball for the past several years and had been experiencing progressive exertional dyspnea over the summer, which he attributed to him "getting older."
- After a base hit during a playoff softball game, he was running around third base, and after crossing home plate, he suddenly collapsed. He was unresponsive, cyanotic, and pulseless, and CPR was begun immediately. He was successfully revived after approximately 1 to 2 minutes of chest compressions and mouth-to-mouth resuscitation.
- Upon arrival of Emergency Medical Services, his initial ECG showed sinus tachycardia with a right bundle branch block. There were no ischemic changes, AV block, or arrhythmia noted. The QT interval was normal. Other than a regular tachycardia, his physical exam was unremarkable.
- He was urgently transferred to the hospital and his preliminary work-up consisted of a head CT which was negative, unremarkable bloodwork except for a borderline abnormal troponin of 0.7, and an echocardiogram which demonstrated preserved biventricular systolic function and normal valves without obstructive lesions.
- A cardiac catheterization was performed the following day. Hemodynamic evaluation demonstrated no evidence of constrictive physiology. Coronary angiography showed evidence of severe calcific ostial and proximal disease of the left coronary and right coronary artery systems.
- Why would a man with no traditional coronary artery disease risk factors have such advanced disease at such a young age? Is this considered purely bad luck?

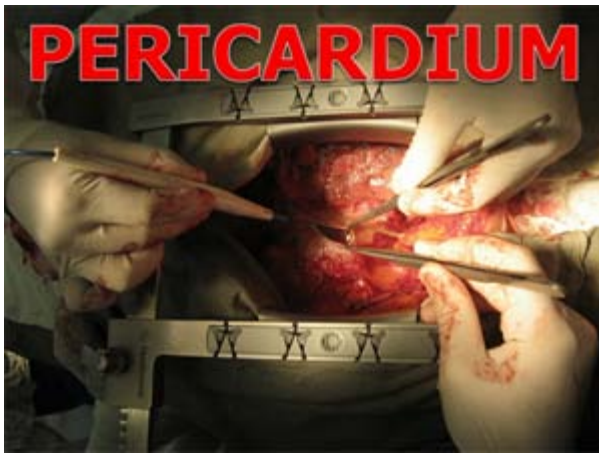


Historical Perspective

In the early days of treatment for malignancies of the chest wall and breast cancer, high doses of radiation were delivered to the thorax, exposing and affecting a substantial volume of the heart. In the 1960's, the heart was actually thought to be radio-resistant, and the long term damaging effects were underappreciated. It was not until the 1990's when a relationship between mediastinal radiation therapy and cardiovascular disease was first understood and recognized. Initial evidence came from a retrospective analysis of ~1,400 breast cancer survivors who underwent mastectomy and were treated in the early 1950's and followed for ~34 years. Those who received immediate radiation therapy after surgery were noted to have had a significantly increased cardiovascular mortality after 15 years compared to those who did not undergo this initial form of treatment. This sparked more research into this issue, and a large meta-analysis reviewed 40 randomized trials comparing radiation therapy versus no radiation therapy in almost 20,000 women; it demonstrated that in those who received radiation therapy, the annual mortality rate from breast cancer significantly declined by 13%, but the annual mortality rate from other cardiovascular causes in these patients significantly increased by 21%. Investigators also recognized that this problem was not just common in breast cancer patients, but was present in other patients who had received mediastinal radiation, including those with Hodgkin's Lymphoma, thymomas, esophageal cancer, and lung cancer. Of these malignancies, patients with Hodgkin's Disease were found to carry the highest risk for future cardiac complications. This was thought secondary to the nature of mantle radiation and its field proximity to the cardiac structures. In a study of ~2,200 Hodgkin's survivors who had received mantle radiation therapy to the chest and who were followed for approximately 10 years, 13% died and 4% of these deaths were due to cardiovascular causes. The relative risk of death from cardiovascular disease in these patients compared to the general population was 3.1 (95% CI 2.4-3.7). This group of individuals experienced significantly more angina and myocardial infarctions compared with age-matched controls in the general population. Because of this causal relationship, technical modifications were instituted to the way in which radiation therapy was delivered to patients, including field shielding, lower doses, and 3D CT planning allowing radiation to be precisely directed towards the malignancy while sparing surrounding structures as much as possible. Not surprisingly, with these changes in radiation delivery came a decrease in the incidence of radiation-induced heart disease. However, although significantly improved, the risk was not completely eliminated; and there will always be some risk to the cardiac structures with this form of cancer treatment.

Pathophysiology

Although the beam of radiation is intended to treat the cancerous cells only, it affects any tissue in its path. Once this form of therapy interacts with tissue (healthy or not), it generates reactive oxygen species and disrupts DNA strands. There are also secondary inflammatory changes observed, including the deposition of fibrin and collagen to these areas which have been damaged by the beam of radiation. Mediastinal radiation can affect virtually ANY component of the heart it comes in contact with, including the pericardium, myocardium, conduction system, valvular structures, and coronary arteries, leading to dysfunction of these tissues.

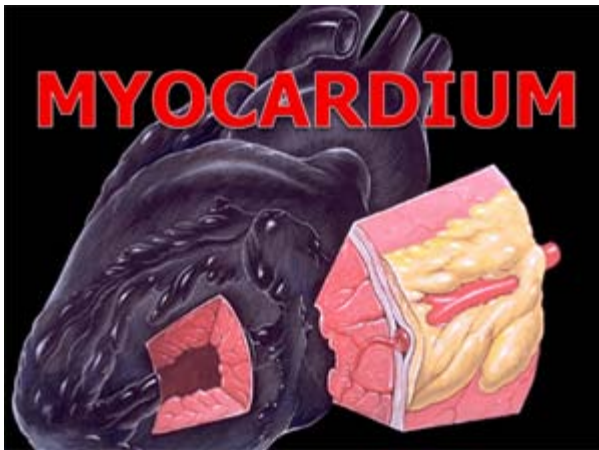


Pericardium

This is the most commonly affected cardiac structure and is affected 4-20% of the time. Pericardial disease is typically dose-dependent and more commonly seen in patients who have not had appropriate shielding in the past.

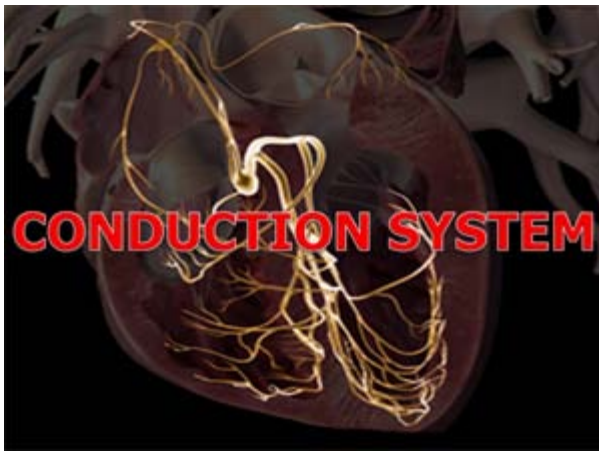
Acute pericarditis usually occurs a few weeks after receiving radiation therapy and is often observed in patients who have mediastinal tumors contiguous with the heart. Radiation therapy to the cancer leads to tumor necrosis and inflammation thereby affecting the pericardium as well, causing fever, chest pain, a friction rub, typical electrocardiographic abnormalities consistent with pericarditis, and possibly a pericardial effusion.

Chronic constrictive pericarditis is recognized more frequently compared with acute pericarditis. This problem usually occurs ~10 years or longer after initial radiation treatment, and is due to direct effects of therapy on the pericardial tissue itself. Histologically, normal pericardial tissue is replaced by collagen and fibrin, and is associated with fibrous adhesions and thickening. Constrictive pericarditis is a difficult clinical diagnosis, and is usually made based on the patient's history along with echocardiographic and invasive hemodynamic findings, including simultaneous left and right ventricular discordance.



Myocardium

The myocardium is relatively resistant to the direct effects of radiation, mostly due to the lack of myocyte cell division. However, toxic effects have been observed with higher doses (>60 Gy). Radiation typically causes injury to the microvasculature endothelium and affects the coronary arteries, arterioles, and capillaries, leading to microvasculature thrombosis, ischemia, and fibrosis. Histology demonstrates normally appearing cardiac myocytes but diffuse patchy fibrosis of the interstitium. It is this interstitial fibrosis which leads to systolic dysfunction (usually involving the right ventricle (more than the left ventricle) due to its anterior location in the chest), as well as diastolic dysfunction causing a restrictive cardiomyopathy. It is the decreased myocardial compliance which is more common (and worse) than the systolic dysfunction seen with radiation to the heart.



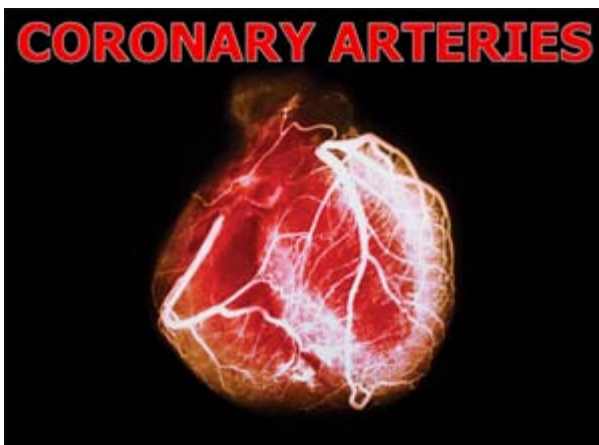
Conduction System

The mechanism of damage is similar to that of the myocardium, involving tissue fibrosis adjacent to the conduction system. Early evidence of conduction disease can be seen approximately 1 year post-radiation therapy, including non-specific ECG abnormalities (which are usually transient and benign) as well as repolarization abnormalities and PVC's which are typically observed in ~50% of patients. More serious and significant problems arise later, greater than 10 years after initial therapy. These include arrhythmias such as ventricular tachycardia and infra-nodal conduction disease including bundle branch blocks (RBBB greater than LBBB due to higher exposure of the right ventricle due to its anterior chest location), as well as various degrees of AV block including complete heart block which can lead to syncope and sudden death.



Valves

The prevalence of radiation-induced valvular disease is 6-40%, and often progresses with time after initial exposure. Radiation directly damages the valves and valvular endocardium, leading to fibrotic thickening, calcification, and retraction of leaflets. Clinically, this may present itself as mixed valvular stenosis and regurgitation.



Coronary Arteries

It is now well recognized that mediastinal radiation significantly increases the risk of death from CAD. This has been observed in children and young adults (without traditional CAD risk factors) who have been treated with radiation to the chest, and have died of fatal myocardial infarctions. In addition, many survivors have been shown to have abnormal nuclear myocardial perfusion scans even within the first 5 years post-cancer treatment. The largest published study in 2007 looked at ~7,000 Hodgkin's disease survivors and demonstrated a significantly increased risk of fatal myocardial infarctions (mortality ratio 2.5 (95% CI 2.1-2.9) compared with age-matched controls in the general population). This was confirmed in multiple supporting studies, which quoted a relative risk of fatal myocardial infarctions in Hodgkin's survivors from 2.2 to 8.8 times higher than that of the general population. With the technical changes in radiation delivery, the incidence of CAD has decreased, but is still present in this population. It is typically seen 5-10 years after initial radiation treatment, and extends beyond 20 years from the start of therapy.

Besides the traditional risk factors for CAD (hypertension, diabetes, hyperlipidemia, and smoking), a history of anterior radiation exposure without shielding, high radiation doses, radiation exposure at young ages, and a prior history of heart disease, confer additional risk for developing radiation-induced CAD. Radiation directly affects the coronary arteries, producing arterial endothelial cell edema and proliferation, which leads to microvascular hyperplasia, fibrointimal thickening, and adventitial scarring, ultimately causing luminal obstruction. There is often a characteristic pattern of CAD in these patients as well, as radiation therapy typically causes regional effects on the coronary ostia or proximal segments (usually involving the proximal RCA, left main coronary artery, and proximal LAD, all of which are more anteriorly located compared with the posterior origin of the left circumflex ostium).

Management

There are no official guidelines regarding the screening, surveillance, and management of radiation induced heart disease at the present time. However, there are recommended suggestions for treatment of this particular patient population. The first involves prevention in regards to radiation therapy planning and treatment delivery methods. Specifically, the emphasis is placed on cardiac shielding from the radiation beams, as well as decreasing the volume and dose of incidental cardiac irradiation and equally weighting anterior and posterior forms of radiation delivery. Secondly, we must keep a high index of suspicion in patients who have a prior history of mediastinal chest radiation. This involves close long-term follow up and observation, including annual histories and physical exams, with attention paid toward signs and symptoms of heart disease (which may otherwise be overlooked in a generally young healthy population). Standard traditional CAD risk factors (hypertension, diabetes, hyperlipidemia, and cigarette smoking) should be treated aggressively.

In asymptomatic individuals, general screening may be performed. A baseline ECG is recommended to assess for conduction disease. There are no guidelines to support outpatient arrhythmia monitoring in asymptomatic patients. As valvular disease is slowly progressive, this often necessitates lifelong follow up and surveillance. A baseline transthoracic echo is recommended with serial studies over time as deemed clinically appropriate. Once valvular disease has been identified, an annual echocardiogram should be considered. The recommendations for CAD screening are somewhat less established. One study examined approximately 300 asymptomatic Hodgkin's disease survivors without a prior history of CAD, who had received radiation therapy (>35 Gy). These patients underwent screening with a stress test, followed by coronary angiography if the non-invasive study was abnormal. The prevalence of severe triple vessel CAD or significant left main coronary artery disease was 2.7%, and the prevalence of a coronary stenosis > 50% was 7.5%. Because of these findings, it is felt reasonable to consider non-invasive stress testing in patients >30 years old who have received high doses of radiation (>35 Gy) and if it has been >5 years from their initial therapy. If this screening evaluation is abnormal, subsequent coronary angiography is recommended given the increased potential for significant left main coronary disease or proximal LAD disease.

In symptomatic patients, the treatment depends on the cardiac structure affected. Acute pericarditis is typically treated with NSAID's. Standard heart failure management is recommended for those with myocardial involvement causing systolic or diastolic dysfunction. For those with conduction disease, permanent pacemakers and ICD's should be implanted per standard practice guidelines. Therapy for valvular disease depends on the severity of a particular stenotic or regurgitant lesion, and in severe cases may require valve replacement surgery. Finally, symptomatic coronary stenoses should be managed with appropriate revascularization strategies (PCI or CABG). Unfortunately, left main coronary artery and ostial LAD lesions are usually not amenable to PCI, and CABG is usually pursued in many of these patients. Although surgical coronary revascularization is more difficult in this patient population because of extensive substernal scarring, mediastinal fibrosis, and friability of the internal mammary arteries and ascending aorta, CABG often provides favorable long-term outcomes.

Conclusions and Recommendations

Mediastinal radiation therapy is associated with a significant risk for the progressive development of cardiovascular disease over time. Despite technical modifications to the delivery method of radiation to the chest, the risk to the heart is not fully eliminated. Any cardiac structure within the treatment beam is at risk for injury, including the pericardium, myocardium, the conduction system, valvular structures, and the coronary arteries (specifically the ostial and proximal vessel segments). Management consists of maintaining a high index of suspicion in this patient population. In addition to treating traditional risk factors, individuals with prior radiation therapy to the chest should have a baseline ECG and echocardiogram. Stress testing may be considered in those who are >30 years old, have received high doses of radiation (>35 Gy), and if it has been >5 years since treatment, followed by coronary angiography if indicated. These patients should be followed closely and long term.

Our patient described in the case presentation had objective involvement of the myocardium (diastolic dysfunction on echocardiogram), conduction system disease (RBBB on ECG), and coronary involvement (severe ostial and proximal disease). He was referred for CABG surgery and did well post-operatively. Prior to discharge home, an ICD was implanted for secondary prevention of sudden cardiac death. He has done remarkably well and continues to follow up regularly in our office.

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