Case Report

Coronary Artery Disease Following Mediastinal Irradiation

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Mediastinal irradiation is a known cause of late onset cardiac complications including coronary artery disease. We describe a 58-year-old female patient, without any of the traditional coronary risk factors, who presented with inferior infarction 23 years after radiotherapy for Hodgkin's lymphoma of the mediastinum. Coronary angiography demonstrated severe ostial stenoses of both coronary arteries. The patient underwent coronary artery bypass grafting and is doing well 10 months later. The therapeutic value of mediastinal irradiation is unquestionable. However, it may be associated with late complications from the irradiated tissues, including the heart. Long-term follow up of cancer survivors who have received mediastinal irradiation should therefore include annual cardiac ultrasound examinations, as well as functional testing for the detection of myocardial ischaemia.

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The most common cause of obstructive coronary artery disease is luminal narrowing due to subintimal atheromatous deposits. However, when evaluating a patient with myocardial ischaemia, the cardiologist must keep in mind that there are other, non-atheromatous causes of coronary flow obstruction, with angiitides, emboli, aortic root dissection and coronary artery spasm being the most common.[1] Patients with a history of mediastinal irradiation for the treatment of lymphomas or other malignancies constitute a special group that may manifest radiation-induced heart disease, and specifically coronary artery disease, decades after the index event.[2]

Mediastinal radiation has been associated with pericardial and valvular scarring, coronary artery disease and conduction disease.[3] Coronary lesions tend to be ostial in location, usually involving the right coronary ostium but occasionally also the left coronary ostium, and are more common in women.[4] The mean time period from mediastinal irradiation to the diagnosis of coronary artery disease is 16 years (range 3 to 29).[4] Frequently, these patients have few, if any, of the traditional coronary risk factors, but in a recent registry of 415 patients at least one coronary risk factor was present in all patients who developed radiation-induced coronary artery disease (n=42, 10%).[5]

The pathobiological process leading to radiation-induced coronary stenosis appears to be different from that leading to atheromatous plaque formation. Certain cytokines and growth factors, such as transforming growth factor-beta 1 and interleukin-1 beta, may stimulate radiation-induced endothelial proliferation, fibroblast proliferation, collagen deposition and fibrosis leading to advanced obstructive lesions.[6] Histology of tissue specimens from the ascending aorta and the coronary arteries, obtained during surgery from such patients, has demonstrated intimal thickening due to fibrous proliferation with min-

imal extracellular lipid deposits.[7-9] Here we describe a 58-year-old woman who presented to our hospital with myocardial infarction 23 years after mediastinal radiation therapy for Hodgkin's lymphoma.

Case presentation

A 35-year-old woman was treated with mediastinal radiation and chemotherapy for Hodgkin's lymphoma (records regarding the specifics of the chemotherapeutic regimen are not available). At the age of 52 she developed chronic myelogenous leukemia that was treated with imatinib with stable blood counts and a rather good long-term prognosis. She remained asymptomatic until the age of 58 years, when she presented to our institution with waxing and waning chest pain of two days' duration and syncope a few hours before admission. The patient was haemodynamically stable, but the electrocardiogram demonstrated right bundle branch block with q waves in leads II, III, aVF, as well as associated deep T wave inversions consistent with a recent myocardial infarction. Upon admission her troponin levels were elevated and cardiac ultrasound showed hypokinesis of the inferior wall with an ejection fraction of 55%, normal valvular morphology and function, without significant pericardial thickening or an effusion. Cardiac catheterisation and coronary angiography confirmed a left ventricular ejection fraction of 55% with hypokinesis of the inferior wall and identified significant ostial stenoses of both coronary arteries (Figure 1). Computed tomography of the chest revealed scarring in the right upper and lower lobes with a small left pleuritic effusion and only mild pericardial scarring (Figure 2).

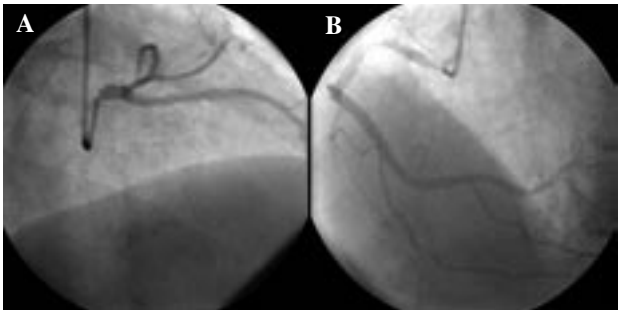

Figure 1. A: Right anterior oblique projection with cranial angulation demonstrating severe stenosis of the left coronary ostium. Note that the small circumflex and large left anterior descending arteries appear angiographically free of atheromatous disease. B: Left anterior oblique projection demonstrating severe stenoses of the ostium and the proximal segment of the right coronary artery. Note that the remainder of the large, dominant right coronary artery appears angiographically free of atheromatous disease.

Coronary artery bypass grafting was performed, with placement of two saphenous vein conduits to the left anterior descending and the right coronary artery. Internal mammary arteries were not used because of extensive post-irradiation intrathoracic scarring. Following surgery, the patient developed persistent tachycardia and hypotension attributed to dysautonomia (possibly related to mediastinal irradiation and chemotherapy)[10] and required intravenous inotropic and mechanical support (IABP) for 48 hours. However, she recovered uneventfully thereafter and is doing well 10 months postoperatively.

Discussion

We believe that prior mediastinal radiation contributed to the development of severe coronary artery disease in this 58-year-old woman. Although intraoperative histology samples were not obtained, there are several important features of the case that support our hypothesis. First, the time course and sex of the patient are compatible with the patient profile reported in the literature. Second, the coexistence of other evidence of radiation-induced tissue injury, such as the unilateral pulmonary fibrosis and the mild pericardial scarring.[11] Third, and probably the most compelling support for the possible causal role of radiation, is the bilateral ostial location of the coronary stenoses, while the remaining coronary tree had a non-atheromatic appearance.[12]

Apart from the above, previous mediastinal radiation may contribute to operative difficulties and postoperative complications in thoracotomy patients. Extensive retrosternal scarring can render the harvesting of internal mammary conduits impossible in these patients. Moreover, pulmonary fibrosis and baroreflex dysfunction may delay weaning from cardiopulmonary bypass and mechanical ventilation and require extensive and prolonged haemodynamic support, thereby lengthening intensive care unit and hospital stay.

In conclusion, over the past decades advances in oncology and radiotherapy have transformed Hodgkin's lymphoma from a frequently fatal to a commonly curable disease. However, some of the late complications of these therapies, as is evident from this case of severe coronary artery disease, can rival the initial neoplastic disease in poor prognosis.[13] Improved radiotherapy techniques have emerged in recent years

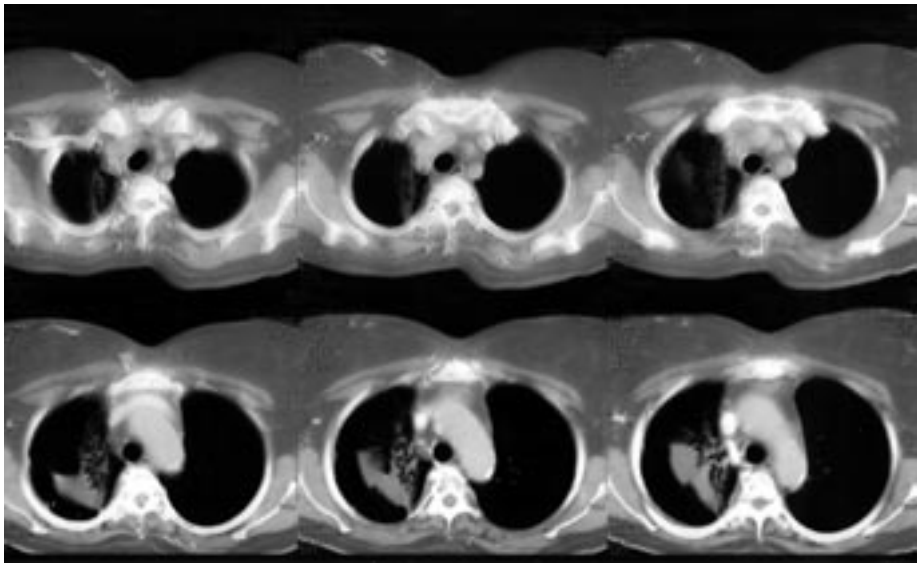

Figure 2. Computed tomography scan of the chest demonstrating scarring of the right upper and lower lobes.

with the purpose of minimising cardiac irradiation, such as cardiac shielding, intensity modulated radiation therapy, and respiratory gating during radiation delivery.[14] However, since radiation-induced heart disease is a late onset complication, the benefits of these new techniques may not be evident for many years. Therefore, we recommend that the long-term follow up of patients who have received mediastinal irradiation in the past should include screening for evidence of cardiac involvement with annual cardiac ultrasounds as well as functional testing for myocardial ischaemia.[15]

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