Netherlands
The Journal of Medicine

REVIEW

Mini-review on cardiac complications after mediastinal irradiation for Hodgkin lymphoma

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ABSTRACT

We present a 62-year-old man who over the years developed almost all the possible cardiac complications of radiation therapy after treatment of a Hodgkin's lymphoma. A review of the literature and a summary of treatment options for cardiac complications after irradiation of the mediastinum for Hodgkin's lymphoma are presented.

KEYWORDS

Cardiac complications, Hodgkin's lymphoma, irradiation

CASE REPORT

A 62-year-old male patient was admitted to our hospital for planned re-re-coronary artery bypass grafting (CABG), as well as mitral and aortic valve replacement.

In 1974, a large mass in the patient's right cervical region and a collection of smaller lymph nodes in the left cervical region were discovered. A biopsy of the mass in the right cervical region was taken. Histological examination showed Hodgkin's lymphoma (HL) of mixed cellularity subtype. Neither involvement of any other lymph node region on either side of the diaphragm, nor involvement of the spleen or of any extralymphatic organ was discovered. The patient was classified as stadium IIA.

The lymphoma was primarily treated with mantle field irradiation (exact dose and duration of treatment unknown), involving the right and left cervical regions, both armpit regions and the mediastinum. In addition, the para-aortic lymph nodes and the spleen were irradiated. After initial irradiation therapy, the patient was treated with vinblastine sulphate injections for two years in the setting of a clinical trial. Treatment was completed after 2.5 years and the patient was declared to be in total remission.

For the patient's medical history until the present admittance we refer to *table 1*.

In April 2006 the patient presented with complaints of progressive dyspnoea, oedema and weight gain. He had never smoked, nor did he have any other risk factors for cardiovascular disease. On physical examination a rough systolic murmur III/VI over the aortic valve, the apex and the carotid area was heard; auscultation of both lungs revealed fine rales. Pretibial oedema was present. The chest X-ray showed an increased heart-thorax ratio and transoesophageal echocardiography (TEE) revealed a moderate decrease in left ventricular function, thickening

Table 1. *Overview of the patient's medical history*

1974	Hodgkin's disease stadium IIA Mantle field irradiation Irradiation of para-aortic lymph nodes and spleen Vinblastine sulphate therapy
1976	Total remission
1993	Unstable angina pectoris Coronary angiography: right-sided one-vessel disease Therapy: CABG (AO-RPL-RPD)
1998	Sick sinus syndrome Therapy: DDD-R pacemaker
2000	Progressive dyspnoea ECG: left bundle branch block (consistent with DDD-R pacemaker) Doppler/TEE: grade 3 mitral valve regurgitation. Coronary angiography: critical stenosis left main coronary artery Therapy: re-CABG (AO-MO-D-LIMA-LAD) + mitral valve repair
2003	Transient ischaemic attack of the brain
2005	Revision of pacemaker system to bi-ventricular pacemaker with one electrode in the right ventricle-outflow tract Admitted to hospital three times with signs and symptoms of right- and left-sided heart failure

CABG = coronary artery bypass grafting; TEE = trans-oesophageal echocardiography.

of the mitral valve with grade 2 mitral valve regurgitation resulting from dilatation of the valve ring and severe calcifications of the aortic valve with an aortic valve area of 0.6 cm^2. Coronary angiography showed a 60% stenosis of the main stem of the left coronary artery (LCA) and severe proximal calcifications of the left anterior descending artery (LAD). The right coronary system showed several sites of severe stenosis of the grafts.

Although aortic valve replacement was indicated this would mean a third, high-risk operation on a patient with previous radiation therapy of the mediastinum, and the intervention was therefore postponed whilst conservative therapy was intensified.

Progressive dyspnoea and four episodes of collapse of cardiac origin led to readmission. Atrial fibrillation secondary to severe right- and left-sided cardiac failure with dilatation of both sides of the heart was diagnosed.

At this point surgery to undergo re-re-CABG, aortic and mitral valve replacement was considered inevitable to improve the patient's condition. The intervention was complicated because of a constrictive pericarditis, showing multiple sites of calcifications and adherence of previously constructed venous grafts. A new grafting procedure was therefore technically impossible. The aortic and mitral valves were replaced and an intra-aortic balloon pump was inserted.

The postoperative period was complicated by acute renal failure for which continuous veno-venous haemodiafiltration (CVVH) was started. During treatment on the ICU the patient developed pneumonia with *Streptococcus pneumoniae* and *Pseudomonas* bacteria. In spite of circulatory support with inotropic agents and treatment of the infectious complications, the patient developed a refractory cardiogenic shock and multiple organ failure. The patient died as a result of this condition.

Histopathology of both the aortic and mitral valves showed fibroid and mucoid degenerative changes and calcifications with sites of chronic infiltrations secondary to these changes.

DISCUSSION

Cardiovascular complications after treatment for Hodgkin's lymphoma can arise due to both radiation therapy and chemotherapy.

Cardiotoxicity following chemotherapy is mainly associated with the use of anthracycline. This drug causes direct damage to the myoepithelium and cardiotoxicity is strongly associated with the cumulative dose.[1]

From the use of vinblastine sulphate alone, no direct toxic effects on the heart have been described.

Radiation injury may develop acutely or over the course of several years after exposure and typically leads to progressive tissue fibrosis, necrosis, atrophy and vascular damage. The spectrum of mediastinal injury is wide, ranging from minor fibrosis to heavy scarring and fusion of mediastinal structures with extensive cardiac and great vessel disease.[2]

Radiation-induced cardiac damage is the next most frequent cause of treatment-related morbidity after second malignancies in HL and accounts for 25% of mortality in cured patients. Cardiovascular complications depend upon the total radiation dose, the percentage of the heart that is being irradiated and the fractionation scheme, dose per fraction and field size.[3-5]

Aleman *et al.* studied the primary cause of death of patients who had been treated for HL before the age of 41, between 1965 and 1987. Increased absolute and relative risks (RRs) of death resulting from cardiovascular disease and myocardial infarction were found. The RRs were especially increased in patients treated before the age of 21. Consistent with other studies, a declining trend of these specific RRs was observed with advancing age. This may be due to the strong increase in baseline risk for cardiovascular disease and myocardial infarction with advancing age in the general population.[5]

This same group studied the risk factors for cardiovascular disease in patients who were treated for HL and who survived at least five years after treatment. Compared with the general population, the incidence of valvular disease, myocardial infarction and congestive heart failure was shown to be three- to five-fold increased after treatment for HL. Mediastinal radiotherapy is associated with a significant two- to seven-fold increase in the risk of myocardial infarction, angina pectoris, congestive heart failure and valvular disorders.[6]

Cardiovascular risk factors in general, such as hypertension, hyperlipidaemia, obesity, diabetes mellitus, (history of) smoking and a positive family history may contribute to the risk of developing cardiac complications. Also, cardiovascular complications can occur indirectly, as irradiation of the renal region whilst treating para-aortic nodes and spleen can cause hypertension.[5]

In the following section the cardiac complications after radiation therapy will be discussed in more detail.

Pericarditis

Approximately 20 to 40% of patients who have received mediastinal radiation therapy develop pericarditis; the incidence is proportional to dose and treatment volume.[3,7]

Acute radiation pericarditis usually develops a few weeks after treatment; chronic pericarditis can occur five to ten years after treatment even if the patient did not suffer from acute pericarditis.

The pericardium becomes thickened as a result of fibroid changes; the vasculature within the pericardium shows characteristic changes leading to increased vascular permeability.[3] Constrictive pericarditis has been reported

to be a marker for greater radiation injury to the heart and is associated with ventricular diastolic dysfunction and high mortality.[2]

Pericarditis is treated with nonsteroidal anti-inflammatory agents and drainage of the pericardial effusion if the patient is severely compromised. For recurrent symptomatic pericardial effusion, pericardial fenestration or pericardiectomy may be indicated. In case of constrictive pericarditis, pericardiectomy seems to be an effective form of therapy.[3,8]

Arrhythmias

A wide variety of arrhythmias either as a result of direct damage to the cardiac conduction system or as a result of dysfunction of the autonomic regulatory functions after chest irradiation have been described: QT-interval prolongation, sick sinus syndrome, all grades of heart block, and loss of circadian and respiratory phasic heart rhythms.[3] Crestanello *et al*. reported a prevalence of 27% of patients requiring a pacemaker as a result of damage to the conduction system after irradiation of the mediastinum.[2]

Coronary vasculature

Cardiovascular calcification is a strong marker of the presence of atherosclerosis and occurs in patients after mediastinal radiotherapy for HL at a relatively young age. Coronary artery disease occurs almost exclusively in patients with other cardiac risk factors.[9] A prevalence of 55% of patients with coronary artery disease after mediastinal irradiation has been reported.[2]

Osteal stenosis is typical for radiation-induced coronary artery disease. Subtle differences from common atherosclerosis are typical for radiation-induced atherosclerosis: subintimal fibrosis, proliferation and paucity of lipid in the atherosclerotic plaque.[8,10]

Usually the right coronary and left anterior descending coronary arteries are included in a common mantle radiation field, typically resulting in stenosis of these vessels.

Percutaneous transluminal coronary angioplasty alone appears to have a high rate of restenosis.[8] Surgical arterial revascularisation using one or both internal thoracic arteries has good long-term results.[11]

In a retrospective analysis, early and late results of coronary artery bypass grafting for the treatment of ischaemic heart disease after mediastinal radiation therapy were studied. The mean interval between mediastinal radiation therapy and CABG was approximately 15 years. A substantial number of the included patients needed concomitant valve surgery. Early results such as operative mortality, sternal wound infection, and one to five year survival were good. Late survival was limited by malignancy, recurrent or new, and by the development of valvular disease (30%) and heart failure. No cases of re-CABG were mentioned in this study.[12]

Noncoronary atherosclerotic vascular disease

The overall estimated incidence of noncoronary atherosclerotic vascular disease in HL survivors after radiation therapy is 7.4%, including carotid artery stenosis and subclavian artery stenosis.

Aortic calcification secondary to atherosclerotic changes typically occurs in patients over 60 years of age, and is characteristically present in the aortic arch. In various studies, aortic calcification after radiation of the mediastinum has been described to occur typically in the ascending aorta, as this site is probably more vulnerable to radiation injury due to its location more anteriorly than the aortic arch.[10]

Valvular dysfunction

Cardiac valve disease develops in approximately 60% of patients with previous radiation therapy of the mediastinum and is an important source of long-term morbidity among HL survivors. This condition is progressive, with clinically important valvular dysfunction increasing with time after radiation and being more severe when radiation has taken place at a younger age. Most patients are asymptomatic with valve regurgitation being more prevalent than valve stenosis. Fibrosis and calcification are typical changes of the cardiac valves that have been reported after radiation therapy, often with progression to heart failure and death.[2,9,10]

Left-sided valvular radiation disease is predominant.[4] Heidenreich *et al*. reported that abnormalities of the aortic valve were more common than abnormalities of the mitral and tricuspid valves after irradiation of the mediastinum. The increased incidence of aortic valve involvement is most probably the result of its location nearer to the mediastinal radiation field than the other valves mentioned.[7]

In patients with cardiac valve disease and no previous radiation therapy of the mediastinum, preservation of the native valve by surgical repair is associated with better outcome in long-term survival, preservation of ventricular function, and freedom from reoperation, thromboembolism and anticoagulant-associated morbidity. Crestanello *et al*. were the first to examine whether these advantages of valve repair were also present in patients with radiation-associated mitral and tricuspid valve disease. They studied 22 patients who had mitral or tricuspid valve repair from 1976 to 2001.[2] Early results at five years after operation showed overall survival of 66%, freedom from cardiac death and from valve reoperation or cardiac valve transplantation of 85 and 88% respectively.

Durability of valve repair in long-term survivors was limited as severe dysfunction of the repaired valve developed in one third of the patients, resulting in reoperation in 16%. Progression of coronary artery disease and myocardial and valve fibrosis may contribute to progressive deterioration of cardiac valve function, irrespective of a successful initial

repair. It was suggested that valve replacement might be preferable over valve repair in this specific group of patients.

Cardiac failure

Diffuse interstitial fibrosis occurring after relatively low doses of radiation alters the compliance of the myocardium. These changes will lead to both systolic and diastolic dysfunction, giving rise to dilated, restrictive or hypertrophic cardiomyopathy.[3]

Systolic function as measured by fractional shortening has been reported to be slightly lower in asymptomatic patients after irradiation compared with community controls.[13] Nearly all patients with systolic dysfunction have some degree of concomitant diastolic dysfunction, specifically, impaired relaxation and variable decreases in ventricular compliance.[14]

In a study by Heindenreich *et al.* the prevalence of diastolic dysfunction in asymptomatic patients after mediastinal radiation was 14%. The authors showed that patients with diastolic dysfunction had decreased cardiac event-free survival and were more likely to have stress-induced ischaemia than patients with normal diastolic function.[13]

Both systolic and diastolic dysfunction may partially be explained by an increase in myocardial fibrosis after irradiation, but also by other factors contributing to cardiac failure such as ischaemic and valvular heart disease after irradiation of the mediastinum.

Heart transplantation for radiation-induced end-stage heart failure was reported in a study done by Handa *et al.* in 2000. The early results of this study were positive with all four patients surviving 48 months after transplantation. At that time all the patients were free from a new second malignancy and recurrence of the original disease as well.[15]

CONCLUSION

In our patient almost all the possible cardiac complications after radiation therapy of the mediastinum are represented.

Mediastinal irradiation for Hodgkin's disease can cause damage to all the different anatomic structures of the mediastinum, such as the chest wall, pleura, and lung, diaphragm, oesophagus and the heart and great vessels. Radiation-induced injury of the heart develops over the course of years and is usually more severe with high mediastinal doses (total dose and dose per fraction), minimal protective cardiac blocking and when radiation is given at younger age.

The attending physician should be aware of the possible acute and late cardiac complications of treatment for HL and distinguish them from cardiac disease with another underlying mechanism. Treatment should be tailored towards the experience given in the medical literature.

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