Radiation-related Chronic Heart Disease*  
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Three cases of radiation-related chronic heart disease are reported. All three patients had been treated for Hodgkin's disease with a mantle technique six to ten years earlier. Ten years after radiation treatment, a 34-year-old woman had dyspnea during exercise. Her heart was enlarged, and an ECG showed a RBBB. An echocardiogram showed pericardial effusion. Right-sided catheterization revealed an infundibular stenosis. A 31-year-old man had chest pain nine years after radiation. An ECG showed complete RBBB and an exercise stress test signs of ischemia; a coronary angiogram showed three proximal stenoses; and an echocardiogram revealed pericardial effusion. A 12-year-old boy had angina pectoris six years after radiation; one year later, he suffered an acute posterior infarction. Two weeks later he died suddenly. An autopsy showed a severe fibrotic and calcified narrowing of the proximal part of the left main coronary artery. Regardless of the patient's age, radiation-related cardiac complications must be kept in mind. Echocardiograms and, in cases of chest pain, exercise stress tests should be a part of routine postradiation follow-up.

Radiation-related cardiac damage has been reported recently.1-5 This damage can be acute,1 subacute,2-5 or chronic.1 Usually, complications manifest themselves in connection with radiation treatment or during the next two years.1,2,5

Reported heart radiation complications are: pericarditis,6-11 pericardial effusion1,6-9 and tamponade,6,7 constrictive pericarditis,8,10,11 valvulitis,9 myocarditis,4 myocardial fibrosis,11,13 and coronary heart disease.3,10-14 As far as we know, no obstructive myocardial changes have been reported. This kind of complication, combined with RBBB and pericardial fluid, was seen in one of our three patients ten years after radiation. In the two other patients, a boy of 12 and a man of 31, clinical signs of ischemic heart disease were evident. The boy may be the youngest radiation-treated Hodgkin's disease patient with confirmed ischemic heart disease related to therapy.

CASE REPORTS

CASE 1

A 34-year-old woman was referred to the cardiovascular laboratory for evaluation of a systolic murmur and an enlarged heart. In November 1970, Mb Hodgkin stage 2a was confirmed. A chest x-ray film showed the left hilus to be enlarged by a mediastinal mass. The patient received cobalt megavolt therapy, of which 4,032 rad was given to the mediastinum. During an acute attack of cholelithiasis in 1973, a rough systolic murmur was heard by auscultation. Her ECG and a chest x-ray film were both normal. In April 1980 the murmur was still of the same type and intensity as in 1973. Furthermore, a retrospective evaluation of chest x-ray films showed a continuous increase in heart volume since 1977.

Physical examination disclosed a systolic ejection murmur heard on the left second intercostal space, and muffling of the pulmonic component of the second heart sound. An ECG showed sinus rhythm, an abnormal P terminal force (−0.04 mmsec) in V1, and complete RBBB. Her heart was enlarged, with relative heart volume of 610 ml/m². A right-sided heart catheterization showed an increase in ventricular systolic pressure (51 mm Hg), with a peak systolic gradient of 25 to 28 mm Hg in infundibulum. Right ventricular angiogram showed a rigid stenosis of the infundibular region. The echocardiogram showed a large amount of pericardial fluid.

CASE 2

A 31-year-old man was admitted to the cardiovascular laboratory for further investigation of an enlarged heart and chest pain related to exercise.

In January 1970, Mb Hodgkin was confirmed by scalenus node biopsy. A chest x-ray film revealed a mass close to left hilus. During cobalt megavolt treatment, the mediastinum was radiated with 4,200 rad. During the winter of 1980 he first experienced exercise-induced retrosternal chest pain. Chest x-ray film showed an enlarged heart, and a comparison with earlier chest x-ray films revealed that his heart size had increased since 1976. By auscultation, the second heart sound was split, but no murmurs were heard. An ECG showed an abnormal P terminal force (−0.04 mmsec) in V1, and a complete RBBB. An exercise stress test was performed, but the test had to be discontinued after one minute due to chest pain at the workload of 600 kpm/min. ST-segment depression of 2 to 4 mm occurred in precordial leads V4-V6. Catheterization revealed slightly elevated right and left ventricular end-diastolic pressures (10 and 14 mm Hg, respectively) and a peak systolic gradient at the aortic valve of 20 mm Hg.

On coronary angiogram three proximal stenoses were demonstrated. In the left circumflex artery there was a stenosis of more than 50 percent; in the left anterior descending artery the degree of stenosis was 80 percent; and the right main-stem artery was narrowed by 95 percent. An echocardiogram showed pericardial fluid. During partial pericardiectomy, 600 ml of serosanguinous fluid was removed. Cytologic examinations of the fluid and histologic examination of the pericardium showed no signs of infection or malignancy. His angina pectoris is now well controlled by β-blocking therapy.

CASE 3

A six-year-old boy was discovered to have swollen cervical lymph...
nodes. A histologic diagnosis of Mb Hodgkin was made from scalenus node biopsy. A chest x-ray film disclosed a narrow mediastinum, and lymphography results were normal.

After splenectomy, the mediastinum was radiated by a minimum tumor dose of 2,940 rad.

Six years later, at the age of 12 years, he complained of progressive chest pain and dyspnea during exercise. The patient was admitted in June 1981 to a community hospital with severe dyspnea and pulmonary edema. A chest x-ray film showed patchy miliary opacities. Initial laboratory studies showed the following values: WBC, 18,000/dl; SGOT, 67 U/L (normal <40 U/L); SLDH, 750 U/L (normal <450 U/L); and serum creatine kinase, 803 U/L (normal <170 U/L). The patient was digitalized and referred to a University Hospital.

On admission the boy was tired and tachycardic, but not in severe distress. A soft systolic murmur was heard at the apex, and his blood pressure was normal; there were no pulmonary rales, and the liver size was normal. An ECG showed a 2.5-mm high peaked P wave in standard lead 2, and incomplete RBBB. All T waves were normal, and there were no pathologic Q waves. His serum cholesterol level was 4.1 mmol/L, and serum triglycerides were 0.90 mmol/L. An M-mode echocardiogram showed an enlarged left atrium as well as hypokinetic ventricular septum. On an exercise stress test, a 5-mm horizontal ST-segment depression occurred in precordial leads. An aortic root angiogram revealed a normal right coronary artery, but the left main-stem artery was not visible at 3 to 4 mm from the coronary ostium, suggesting a stenosis. The left circumflex branch and the left descending branch both were normal. Before discharge, β-blocker treatment was started. Two days later he was found dead at home.

An autopsy showed severe narrowing of the proximal part of the left main-stem artery and a recent infarction of the posterior wall of the left ventricle. Microscopic examination revealed poorly staining new collagen as a sign of healing infarction in the same area where there was wavy of myocardial fibers. Cross sections of the left main-stem artery showed severe intimal fibrotic thickening and calcification, and the media was markedly fibrotic (Fig 1).

**DISCUSSION**

The heart was formerly considered to be highly radioresistant, but today, when megavolt therapy is used, numerous complications are known to be related to radiation treatment. Mainly pericardial complications, such as pericarditis, pericardial effusion and tamponade, pericardial fibrosis, and constrictive pericarditis, have been reported, and attention has been paid to coronary artery disease.

An immediate effect of radiation is inflammation of different tissues followed by complete healing or replacement with collagen and fibrosis. ECG changes in connection with radiation treatment have been reported by many authors. Changes in T waves and ST segments are usually observed after radiation therapy; these changes may reflect damage to the myocardium. Later, low voltage may occur in patients with large pericardial effusions, but bundle branch block has seldom been reported.

In all of our patients, either incomplete or complete RBBB was demonstrated. In one adult patient (case 1); the pretreatment ECG was normal, and in the other patient (case 2); no pretreatment ECG recording was found. However, because of the low incidence of RBBB at this age, it is obvious that this intraventricular conduction disturbance had occurred in both patients after radiation treatment. One explanation could be the anatomic site of the right bundle, which lies close to the endocardium and on the right side of the septum, with a greater risk of exposure to radiation. The injury may occur directly in the bundle or later in connection with myocardial fibrosis. In the young boy (case 3), an incomplete RBBB was found; however, this is a frequent finding in children. A pretreatment ECG was not available.

In two of our three patients (cases 1 and 2), pericardial fluid was discovered on the basis of angiograms and echocardiogram studies. Retrospective evaluation of chest x-ray films showed large variations in heart size since the radiation treatment ten years earlier. For an unknown reason, this cyclic variation stopped six to seven years later and changed into a continuous growth of heart size in both patients. There was no physical sign of pericardial tamponade in either patient. In a patient (case 2) with partial pericardiectomy and removal of 600 ml of serosanguinous fluid, the pericardium showed degenerative changes, but no evidence of Hodgkin’s disease.

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*Figure 1.* Cross-sections of left main artery (case 3). A (upper): Intima is thick and fibrotic, media severely fibrosed. B (lower): Calcified deposits in the intima.
Usually, pericardial effusion occurs in connection with radiation treatment period or within 12 to 24 months thereafter.1,2,4 The incidence of pericardial effusion reported in the literature varies between 6 and 29.6 percent,1,2,7 but it is possible that it is even more common, because in many studies the diagnosis is based on changes in cardiac size.2,7 It is obvious that a chest x-ray film cannot be the best way to evaluate pericardial effusion, since at least 250 ml of fluid must be present before the cardiac shadow is interpreted as abnormal.24 We can only suggest that prospective studies in which asymptomatic patients are examined with more sensitive procedures, like echocardiography, will reveal pericardial effusion in a higher ratio. Further, patients with enlarged hearts and with a history of mediastinal radiation should always be referred to echocardiography before undergoing other interventions.

Pericardium and the muscular wall of right ventricle are most commonly affected by fibrotic changes.1,3,10,11 Histologic examinations often reveal diffuse fibrotic changes throughout all layers of myocardium but becoming more pronounced toward the epicardial side.5,5,10 Minimal fibrotic changes will probably only increase ventricular wall rigidity and cause decrease in compliance, whereas extensive fibrosis increases the risk for congestive heart failure and death.4,10,11 It is obvious that some extent of myocardial fibrosis had occurred in all our patients. The autopsy findings of the young boy (case 3) showed marked myocardial fibrosis and infarcted areas, whereas in one patient (case 1), a right ventricular cineangioagram showed a rigid infundibulum. Although no myocardial biopsy was performed on this patient, it is most likely that local fibrosis was the reason for the stenotic change. A congenital infundibular stenosis of the right ventricle is very rare.23 The murmur was first noted three years after radiation, and the pretreatment ECGs were normal, whereas the postradiation ECGs disclosed marked abnormalities. Furthermore, in two patients (cases 1 and 2), ECG recordings showed signs of left atrial overload. The cause underlying this change could be a decrease in left ventricular compliance caused by myocardial fibrosis.

In two patients (cases 2 and 3) in whom no hyperlipidemia or other coronary risk factors were present, marked coronary changes were seen in angiography. Both patients suffered clinically from coronary artery disease (CAD), the course of which was fatal in the young boy.

On the basis of experimental animal studies we know that radiation may cause both fibrotic and atherogenic changes in arteries.5,24 Hyperlipidemia increases the rate of the process.25,26 In comparison with the wide use of radiation treatment, ischemic coronary heart disease has relatively seldom been reported. Our knowledge of radiation-related coronary heart disease is mainly based on case reports1,2,4,10,27,28 or autopsy studies.1,2 In published cases of patients younger than 35 years of age, the time interval from radiation to symptoms of CAD varied from two months to 13 years.1,13-15 Even if no symptoms arise, the coronary arteries of the radiated patients are narrowed more than those of unradiated.3 In patients with short survival this kind of complication will seldom occur clinically, whereas in patients with good prognosis, such as those with Hodgkin's disease, the risk for CAD should be increased.

Besides the early heart complications of radiation, late onset of clinical symptoms from radiation-related myocardial, pericardial, and coronary artery complications should be kept in mind. Furthermore, these complications may occur at a young age, because the onset is time-related, not age-related. We suggest that exercise stress testing and echocardiography be a part of a long-term follow-up in patients undergoing radiation treatment to mediastinal areas.

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