Precocious Myocardial Infarction after Radiation Treatment for Hodgkin's Disease

David Leigh Rodgers, M.D.*

A 26-year-old man received extensive cardiac radiation in the course of treatment of mediastinal Hodgkin's disease, and six years later, he experienced an acute myocardial infarction. Angiographic studies demonstrated extensive atherosclerotic abnormalities in the coronary arterial system. It is suggested that radiation-induced injury was a provocation of these precocious arterial abnormalities.

A cute myocardial infarction in a 33-year-old man may occur as a result of the same etiologic factors which provoke the event in older persons; however, our patient suffered coronary thrombosis and myocardial infarction six years after intense radiation to the mediastinum. Radiation-induced injury to the heart and coronary vessels, therefore, must be considered as a possible provocation of the disease process in this man.

CASE REPORT

The patient was 26 years old in February 1967, when he was found to have a large mediastinal mass and adenopathy in the neck. This was proven through thoracotomy and biopsy to be Hodgkin's granuloma (mixed lymphocytic and histiocytic), stage 2A.

From March 16, 1967 to May 16, 1967, the patient received therapy with megavoltage radiation in the following amounts: mantle-mediastinum, 4,310 rads; para-aortic nodes, 4,300 rads; and spleen, 4,535 rads.

When the immediate effects of radiation therapy subsided, the patient returned to full vigorous activity. Routine examination on May 23, 1972 demonstrated blood pressure of 128/94 mm Hg and a serum cholesterol level of 271 mg/100 ml (normal, 140 to 270 mg/100 ml).

On Aug 26, 1973, while camping and canoeing, the patient noted dyspnea and upper subternal gaseousness, with radiation of discomfort to the upper pectoral regions. Serial electrocardiograms, cardiac enzyme studies, and the clinical course proved that the patient had suffered an acute anterolateral myocardial infarction. During convalescence, a glucose tolerance test gave normal results, the serum cholesterol level was 228 mg/100 ml, the serum triglyceride level was 159 mg/100 ml (normal, 10 to 150 mg/100 ml), and lipoprotein electrophoresis showed a slight increase in the level of pre-β-lipoproteins.

After recovery the patient was enrolled in a cardiac rehabilitation program. Initial exercise testing showed ischemic changes (without symptoms) in the fourth stage of exercise of the Bruce treadmill procedure. The patient faithfully carried out his exercise and diet program, and he abstained from smoking; yet after several months, stress testing showed ischemic changes at an even lower workload than in the earlier study.

Because of this deterioration in performance, coronary angiographic studies were performed on June 24, 1974. These showed a markedly dominant left coronary arterial system. There was atherosclerotic irregularity and probably significant narrowing in the distal descending portion of the small right coronary artery. The proximal end of the anterior interventricular extension of the left anterior descending artery was completely occluded, with good collateral filling of a normal lumen beyond the proximal occlusion. A left ventriculogram demonstrated a small left ventricle with generally satisfactory contractions; however, there was severe focal hypokinesia about the apex and lateral portion of the septum.

Since the angiographic study of June 1974, the patient has not followed any formal medical regimen, but he has continued to be physically active, free of complaints, and fully engaged in his regular business activities.

DISCUSSION

Cohn et al1 classified their 21 cases of radiation-induced cardiac injury as follows: acute pericarditis, chronic pericardial effusion, chronic constrictive pericarditis (with or without active inflammation and effusion), myocardial disease with mitral insufficiency, and myocardial infarction due to coronary artery disease. Their description of the last of these was the report of a 15-year-old boy who died of an acute myocardial infarction 16 months after 4,000 rads of therapy to the "mantle" (mediastinal area, etc.). Autopsy showed severe intimal proliferation and atheromatous deposits in all of the major coronary arteries, a recent thrombosis of the left anterior descending artery, and a large acute anteroseptal myocardial infarction. No significant atherosclerosis was found elsewhere in the body. Cohn and associates1 speculated that the premature coronary atherosclerosis seen in this patient might represent a particular type of radiation-induced vascular injury with secondary deposition of lipids.

Huff and Sanders2 described a 21-year-old man who died in cardiogenic shock from an acute anteroseptal myocardial infarction occurring nine months after treatment with 3,500 rads to the mantle. Tracy et al3 presented the case of a 35-year-old woman who developed symptoms of ischemic heart disease 19 months after 5,075 rads were delivered to the mediastinum by the mantle technique. Extensive coronary artery disease was demonstrated by coronary angiographic studies. Pearson4 presented two cases of myocardial infarction occurring six months after irradiation for mediastinal neoplasm, and Dollinger et al5 described a 31-year-old patient with an acute inferior myocardial infarction which occurred two months after 1,440 rads to the lower esophageal region. Findings on autopsy nine years after the event caused these investigators4 to conclude: "In the present case it appears that the fibromuscular proliferation of the right coronary artery was due to radiation." They observed that this fibrous occlusion of the right coronary artery was similar to the process observed clinically and experimentally in medium and small arteries exposed to radiation. Finally, Rubin et al6 pre-

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Table 1—Data from Literature on Radiation-Induced Cardiac Injury

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient’s Age (yr), Sex</th>
<th>Type of Neoplasm</th>
<th>Radiation Dose, rads</th>
<th>Interval to Ischemic Attack*</th>
<th>Cardiac Morphologic Findings**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present report</td>
<td>33, M</td>
<td>Hodgkin’s, stage 2A</td>
<td>4,310</td>
<td>6 yr</td>
<td>Arteriographic atherosclerosis of distal descending RCA, probable significant narrowing of RCA, and proximal occlusion of anterior interventricular extension of LAD</td>
</tr>
<tr>
<td>Cohn et al¹</td>
<td>15, M</td>
<td>Hodgkin’s</td>
<td>4,000</td>
<td>16 mo</td>
<td>Autopsy evidence of severe atherosclerosis in all major coronary arteries, recent LAD occlusion, and large acute anterosetal MI</td>
</tr>
<tr>
<td>Huff and Sanders²</td>
<td>21, M</td>
<td>Hodgkin’s, stage 1A</td>
<td>3,500</td>
<td>9 mo</td>
<td>Autopsy evidence of microscopic atherosclerosis, proximal LAD occlusion, organizing thrombosis, adhesive pericarditis, and fociolated pericardial effusion</td>
</tr>
<tr>
<td>Tracy et al³</td>
<td>35, F</td>
<td>Hodgkin’s</td>
<td>5,075</td>
<td>19 mo (angina)</td>
<td>Arteriographic 90 percent narrowing of LAD and two 90 percent lesions in circumflex artery</td>
</tr>
<tr>
<td>Pearson⁴ (2 patients)</td>
<td>&lt;50, F</td>
<td>Mediastinal neoplasm</td>
<td>...</td>
<td>6 mo</td>
<td>...</td>
</tr>
<tr>
<td>Dollinger et al⁴</td>
<td>31, M</td>
<td>Hodgkin’s</td>
<td>1,440</td>
<td>2 mo</td>
<td>Autopsy evidence of narrowing with RCA fibromuscular proliferation, myocardial fibrosis with RV largely replaced, and MI 10 yr before autopsy</td>
</tr>
<tr>
<td>Rubin et al⁵ (3 patients)</td>
<td>67, F</td>
<td>Carcinoma of breast</td>
<td>...</td>
<td>23 yr</td>
<td>Autopsy evidence of atherosclerosis (few raised plaques) and myocardial fibrosis with RA thickened and wrinkled</td>
</tr>
<tr>
<td></td>
<td>48, F</td>
<td>Medullary adenocarcinoma of breast</td>
<td>2,920</td>
<td>14 mo</td>
<td>Autopsy evidence of minimal atherosclerosis, thick fibrotic pericarditis, widespread myocardial fibrosis, and MI</td>
</tr>
<tr>
<td></td>
<td>56, F</td>
<td>Scirrhous carcinoma of breast</td>
<td>4,455</td>
<td>3 yr</td>
<td>Autopsy evidence of moderate atherosclerosis, stenotic LAD and RCA, and patchy myocardial fibrosis</td>
</tr>
<tr>
<td>Prentice⁷</td>
<td>19, M</td>
<td>Lymphoma (Hodgkin’s-group)</td>
<td>3,250</td>
<td>4 yr</td>
<td>Autopsy evidence of atherosclerosis in all 3 main coronary arteries, narrowing of LAD due to extensive fibrin, and recent MI of LV and septum</td>
</tr>
<tr>
<td>Fehér⁸</td>
<td>69, M</td>
<td>Carcinoma of lung</td>
<td>1,200+</td>
<td>3 wk-3 mo</td>
<td>...</td>
</tr>
</tbody>
</table>

*Interval from radiation to onset of ischemic attack.
**RCA, Right coronary artery; LAD, left anterior descending coronary artery; MI, myocardial infarction; RV, right ventricle; RA, right atrium; LV, left ventricle.

sentenced three cases of cardiac fibrosis in which irradiation was suggested as the cause, and studies by Prentice⁷ and by Fehér⁸ added two further cases of myocardial infarction following radiation. These data are summarized in Table 1.

Kirkpatrick⁵ approached the issue experimentally and irradiated rabbit’s ears. He administered 500 to 4,000 rads (doses over 2,000 rads were divided over two to three days) and found that lipid plaques developed in rabbits that were not made to be hyperlipemic animals. Foam cell lesions were well developed in a matter of weeks. Also, Kirkpatrick⁵ found that irradiated ears in rabbits that were not made to be hyperlipemic did not develop foam cell lesions; but after several months, some fibrous plaques appeared. He concluded that radiation-induced injury may work through foam cell (hyperlipid) or fibrotic change.

Fajardo and Stewart¹⁰ irradiated the hearts of rabbits, and when the animals were killed and studied months later, these investigators found that the late lesions were pericardial fibrosis, pericardial effusion, and diffuse myocardial fibrosis. These lesions were identical to those found in humans.¹¹ These investigators noted that connective tissue proliferation is the hallmark of these late radiation-induced lesions wherever they are located in the heart, and endocardial and vascular...
changes are much less frequent.

Thus, experimental, autopsy, and coronary angiographic data suggest that substantial cardiac injury may be a consequence of cardiac irradiation. The mantle technique by which our patient was treated protected the apex of his heart with lead shields, but the remainder of the heart was within the radiation field.

It is suggested that radiation-induced injury was a provocation of the myocardial infarction that our patient suffered when he was 33 years old, six years after treatment for Hodgkin's disease. If this is so, it would be worthwhile to consider modification of the mantle technique of administering radiation to provide better protection of the coronary vessels while not reducing the effect of the radiation on neoplastic disease. 10

REFERENCES

Unusually High Pacemaker Threshold in Severe Myxedema*

Decrease with Thyroid Hormone Therapy

Debal Banu, M.D., and Kanu Chatterjee, M.B.

In a patient with myxedema and complete heart block, an unusually high pacemaker threshold was observed initially during transvenous right ventricular endocardial pacing. The pacemaker threshold gradually decreased with thyroid replacement therapy, suggesting that the lack of thyroid hormone in some patients might increase the pacemaker threshold.

Although minor changes in pacemaker threshold might occur due to various causes, including electrolytic disturbance and catecholamine infusion, a marked increase in pacemaker threshold in the absence of right ventricular perforation, electrode displacement, or breakage is uncommon. We report the case of a patient with severe myxedema and complete heart block, in whom an unusually high pacemaker threshold was observed initially, which gradually decreased coincident with thyroid replacement therapy.

CASE REPORT

A 78-year-old white man was admitted with at least a six-month history of repeated blackout spells and was found to have extreme bradycardia, with a pulse rate of 35 beats per minute. The patient's history and the findings from clinical examination were consistent with myxedema and complete atrioventricular block. An electrocardiogram revealed complete atrioventricular block with bilateral bundle-branch block (Fig 1).

Since the patient had classic symptoms of Stokes-Adams syndrome and profound bradycardia, a temporary transvenous pacemaker was inserted through the right subclavian vein and was positioned in the apex of the right ventricle. A unipolar electrogram recorded from the distal electrode demonstrated the characteristic pattern of a right ventricular intracardiac electrogram with very small amplitude of the P wave and large QRS complexes. 4 The right ventricular endocardial potential was 9 mv (Fig 2) which was within range. 5 The right ventricular electrogram also showed good contact with the endocardium, as evidenced from the magnitude of ST-segment elevation, which exceeded 4 mv; however, ventricular capture could not be obtained below a current of 8 ma. Several different positions near the apex and outflow tract were explored in an attempt to achieve a lower pacing threshold; however, in each position, ventricular capture could only be obtained with a pacing threshold of 8 ma or more. The position of the catheter was verified by a lateral chest x-ray film and also by measuring the right ventricular endocardial potential and the ST-segment elevation due to endocardial contact, which on each occasion were about 9 mv and 4 mv, respectively.

It was believed that such a high pacemaker threshold may be related to myxedema, and it may decrease with thyroid hormone therapy. The patient's serum electrolytic levels, particularly the serum potassium level, were within normal limits at the time of insertion of the temporary transvenous pacemaker. Laboratory study at this time confirmed the diagnosis of myxedema (thyroxine iodine [T4] level, 0.55 μg/100 ml; thyrotropin [TSH] level, 90 MU/ml by radioimmunoassay). On the seventh day of hospitalization, after initiation of thyroid hormone therapy, the patient's pacemaker threshold decreased from 8 ma to 2.5 ma. Because of the persistence of complete atrioventricular block, a permanent pacing system was installed on the 12th day of hospitalization. The pacing threshold at the time of permanent pacemaker insertion was 0.8 ma.

DISCUSSION

A very high initial pacemaker threshold during transvenous endocardial pacing is uncommon in the absence of malposition of the electrode, electrode breakage, a displaced electrode, or perforation of the right ventricle.