Irradiation-Induced Pericarditis*

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Three patients with pericarditis following therapeutic irradiation for malignant tumors were studied at autopsy. In one subject, death occurred five days after the last dose of radiation. The pericardial involvement was characterized by fibrinous exudation. This was more marked in degree over the right side of the heart than the left and corresponded with the field of irradiation. In the remaining two patients, two and four courses of radiation had been applied, the interval between the last dose and death being seven weeks in one patient and 1½ years in the other. The lesions were those of organizing pericarditis.

Although the pericardium and myocardium were initially thought to be resistant to damage by radiation, injury may occur.1-3 In the files of the Cardiovascular Registry of the United Hospitals-Miller Division, St. Paul, Minn, there are three cases of irradiation-induced pericarditis (one acute and two chronic). The purpose of this report is to describe both the short-term and long-term changes as observed. To our knowledge, the literature does not describe short-term changes in man following therapeutic doses of irradiation.

Case Reports

Case 1

The patient was a 39-year-old white man who was seen in August 1970 with a right hilar mass. At limited right thoracotomy, the tumor was considered to be unresectable. Biopsy showed a large cell carcinoma. Postoperative treatment consisted of irradiation with 60cobalt. A total of almost 4,700 rads to the mediastinum and right hilum was given on an outpatient basis (Table 1), after which therapy was interrupted when the patient became progressively weak. He was readmitted to the hospital. The patient did not complain of pleuritic pain in the chest or shortness of breath. Physical examination revealed dullness at the right pulmonary base and distant heart sounds. A thoracic roentgenogram showed a wide mediastinum and infiltrates in the middle lobe of the right lung and left costophrenic angle. An electrocardiogram showed sinus tachycardia, right axis deviation, and T-wave inversion in the inferolateral leads. The T-wave inversion was new, compared with a tracing obtained two months earlier. The patient experienced progressive shortness of breath and died five days after admission. The last dose of irradiation was given five days before death.

Autopsy revealed primary bronchogenic carcinoma of the middle lobe of the right lung, with metastases to the brain, mediastinal and retroperitoneal nodes, the adrenal glands, and the kidneys. Additional findings included (1) recurrent pulmonary emboli, with massive acute infarcts of the lower lobes of both lungs, (2) right ventricular congestive heart failure, with mural thrombi in the right ventricle and hepatic congestion, (3) localized pleuritis of the middle lobe of the right lung, and (4) thin fibrinous deposits upon the epicardium over the right atrium (Fig 1a) and a suggestion of granularity of the epicardium over the left ventricle.

Histologic examination of the right atrium showed a thin layer of unorganized fibrin on the epicardial surface (Fig 1b). Occasional macrophages and a few polymorphonuclear leukocytes were present in the epicardium. In one section of the left ventricle, which showed only a small amount of fibrin on its surface (Fig 1c), a clump of tumor cells was seen in a deep lymphatic vessel of the epicardium; however, no tumor was identified in multiple sections of the remaining epicardium.

There was patchy replacement of the myocardial muscular

Table 1—Radiotherapy in Three Patients with Irradiation-Induced Pericarditis

<table>
<thead>
<tr>
<th>Case, Underlying Disease and Time to Death</th>
<th>Total Dose, No. of Sessions</th>
<th>Port</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, Bronchogenic carcinoma 5 days</td>
<td>4,668 25</td>
<td>Anterior mediastinum and right hilum</td>
</tr>
<tr>
<td>2, Hodgkin’s disease 17 mo</td>
<td>4,200 26</td>
<td>Mantle plus left anterior mediastinum</td>
</tr>
<tr>
<td>7 weeks</td>
<td>3,500 27</td>
<td>Anterior left midhemothorax</td>
</tr>
<tr>
<td>3, Hodgkin’s disease 7 yr</td>
<td>3,700 23</td>
<td>Mantle</td>
</tr>
<tr>
<td>3 yr</td>
<td>3,215 20</td>
<td>Anterior left lower hemothorax</td>
</tr>
<tr>
<td>2½ yr</td>
<td>3,000 13</td>
<td>Right axilla</td>
</tr>
<tr>
<td>1½ yr</td>
<td>3,400 16</td>
<td>Left axilla and left side of neck</td>
</tr>
</tbody>
</table>

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fibers by edematous eosinophilic material, with loss of the normal striation and nuclear detail. Occasional macrophages and proliferating fibroblasts were seen. The valves were normal, and the coronary arteries showed atherosclerosis (grade 1 to 2).

CASE 2

The patient was a 22-year-old white man with Hodgkin’s disease, which was diagnosed in April 1970. He was treated with a course of irradiation in May 1970 and another in July 1971 (Table 1). Beginning in October 1970, the patient received two courses of chemotherapy, consisting of two cycles of cyclophosphamide, vinblastine, and prednisone. Beginning in February 1971, he received therapy with six cycles of cyclophosphamide, vinblastine, prednisone, and procarbazine.

In September 1971, the patient experienced an episode of right anterior pleuritic pain associated with shortness of breath and a pleuritic friction rub. At that time, the thoracic roentgenogram and radioisotopic scan of the lungs were normal. An electrocardiogram revealed supraventricular tachycardia, right axis deviation, and, as compared with a study done two months previously, marked new changes in the S-T segment and T wave. The episode resolved without specific therapy, and the patient was discharged with the tentative diagnosis of direct cardiac involvement by Hodgkin’s disease. Chemotherapy with cyclophosphamide, vinblastine, prednisone, and procarbazine was reinstituted. One month later, the patient was readmitted for dizziness associated with hypotension and died within hours of entering the hospital.

Autopsy revealed Hodgkin’s disease, with involvement of the superior mediastinal, celiac, splenic, and periaortic lymph nodes and the left adrenal gland. A left subphrenic abscess was present. Irradiation-induced fibrosis was found to involve the left lung.

The pericardial surfaces, except for sparing of the medial wall of the right ventricle and the left ventricular apex, were covered by adherent fibrin (Fig 2). No free fluid was present in the cavity.

From the areas of most prominent fibrinous deposits, histologic examination revealed thick masses of fibrin (Fig 3). Over the surface of the heart, there were signs of ongoing organization, with a few strands of collagen present. A
she was treated in 1971, 1974, 1975, and 1976 with multiple courses of irradiation (Table 1) and in August 1976 with two cycles of chemotherapy (cyclophosphamide, vincristine, prednisone, and procarbazine). The patient's last admission to the hospital was in August 1977, when she had fever and malaise. At that time, physical examination revealed tachycardia and dullness at the left pulmonary base. The thoracic roentgenogram showed left apical pleural thickening and blunting of the left costophrenic angle. The cardiac shadow was normal. The electrocardiogram showed supraventricular tachycardia, right axis deviation, and nonspecific changes in the S-T segment and T wave. Soon after hospitalization, the patient suffered cardiopulmonary arrest and died, despite efforts at resuscitation.

Autopsy revealed Hodgkin's disease involving the left hilar nodes and left pulmonary apex, with fibrinous pleuritis of the left lung. In general, the epicardial surfaces were shaggy, with sparing over the apices of the ventricles (Fig 4). Histologic examination from areas of obvious involvement showed that fibrinous material was attached to the epicardial surface. This was composed of collagenous fibers, among which were remnants of unorganized fibrin (Fig 5). In the areas of the epicardium that appeared to be spared of abnormality on the gross examination, histologic examination revealed that a thin layer of collagenous fibers was deposited upon the epicardium. No significant cellular infiltrate was observed in any of the sections of the epicardium.

The myocardium was normal. The aortic valve showed mild to moderate spongiosis. The coronary arteries were normal.

**DISCUSSION**

Irradiation-induced pericarditis may be divided into a short-term process occurring days to weeks
Following exposure and a long-term process occurring months to years after exposure, there were few reports on the pathologic abnormalities of short-term irradiation-induced damage to the heart. Most of the latter reports deal with victims of atomic warfare or of accidents involving radiation, who died soon after receiving massive doses of radiation. Liebow and associates described the pathologic abnormalities in casualties of the atomic bomb. These investigators found occasional myocardial perivascular edema and hemorrhage in victims dying less than six weeks after the bomb was dropped. Petechiae of the epicardium were also described.

Reports by Karas and Stanbury and by Fanger and Lushbaugh described a patient who died two days after receiving 8,800 rads of whole-body irradiation. At autopsy, a pericardial effusion of 100 ml was associated with fibrinous deposits over the right atrium and ventricle. Histologically, polymorphonuclear leukocytes were scattered in the epicardium related to the fibrinous deposits.

Hempelmann and associates described a patient who died three weeks after an accident involving radiation. The autopsy showed a serofibrinous pericardial exudate that was most prominent over the left ventricle. Biventricular hypertrophy and right-sided dilatation were also observed. Histologic examination revealed fibrin and mononuclear leukocytes, with a few eosinophils and mast cells deposited over the pericardial surface. Beneath the surface, an inflammatory reaction was present, with scattered hemorrhages and granulation tissue.

Lushbaugh described a patient dying 34 hours after receiving 4,500 rads of whole-body irradiation. Autopsy revealed right atrial and right ventricular dilatation, with pericardial and intramuscular linear petechial hemorrhages localized to the right side of the heart and ventricular septum, with sparing of the left ventricle. Histologically, swollen serosal cells, edema, fibrinoid necrosis, and polymorphonuclear leukocytes that were often localized around small arterioles were found.

Our case 1, in whom death occurred five days after a course of therapeutic irradiation, demonstrated changes similar to those described in the preceding paragraphs. These involved the epicardium over the right atrium and, to a lesser extent, over the left ventricle. Although no tumor was found in the pericardium, one histologic focus of tumor was present in a deep lymphatic vessel of the epicardium over the left ventricle. The question arises as to whether the pericarditis was a reaction to the tumor, rather than to irradiation. This seems unlikely, since the pericardial reaction was most marked in the area that received the radiation (right atrium), compared to the area in which the small focus of tumor cells was found (left ventricle).

In contrast to short-term irradiation-induced damage, the changes occurring months to years after exposure to radiation are well described. The gross changes consist of thickening of the pericardium (up to six times normal), pericardial effusion, and, in about one-half of the cases, a sterile serosanguineous exudate. Occasional myocardial fibrosis is also described. Histologic examination shows replacement of the normal adipose by fibrous tissue, organizing fibrinous exudate, scant mononuclear cells, proliferating capillaries, and usually no deposition of calcium. Our cases 2 and 3 demonstrate similar features, with the exception that no myocardial fibrosis was present. Also, our cases demonstrate the additive effects of repeated courses of radiotherapy, showing more marked changes over the right ventricle than the left. In each case the area of the right ventricle received two courses of radiotherapy, while that over the left ventricle received only one course of therapy. This is in keeping with the reported observation that extensive radiation-induced changes involving the myocardium and the pericardium are much more common with repeated courses of radiotherapy.

In clinical studies, the incidence of irradiation-induced pericarditis is reported to range from 6 to 30 percent, depending on the method used to detect it. Many patients are asymptomatic, and the pericarditis is detected only by cardiomegaly seen in thoracic roentgenograms. The incidence increases with (1) a higher dose, (2) a decreasing number of sessions for a given dose, and (3) the extent of the heart that is irradiated. Clinical signs of pericar-
Pericarditis may appear de novo years after exposure to radiation, although, when present, these usually appear in the first 12 months following irradiation. The clinical manifestations may be those of acute pericarditis, delayed acute pericarditis, pericardial effusion (with or without signs of tamponade), constrictive pericarditis, or myocardial fibrosis. Disturbances in cardiac rhythm and coronary arterial disease have also been claimed as consequences of irradiation. The sudden withdrawal of therapy with steroids has been associated with the activation of pericarditis in patients previously irradiated. The usual methods of detecting pericardial disease apply to irradiation-induced pericarditis, including a history of pleuritic pain in the chest, shortness of breath, fever, and abnormal physical signs, such as a pericardial rub or increased venous pressure with a paradoxical pulse (or both), if tamponade is present. Periodic thoracic roentgenograms have been recommended to detect irradiation-induced pericarditis in asymptomatic patients, and echocardiograms are very sensitive in detecting pericardial effusions. Electrocardiograms may show decreased QRS voltage, changes in the S-T segment and T wave, or tachycardia. Pericardiocentesis of an irradiation-induced pericardial effusion usually demonstrates a serosanguineous exudate with a protein content greater than 5 gm/100 ml.

In subjects with signs of cardiac tamponade and pericardial effusion, cardiac catheterization and simultaneous pericardiocentesis may be necessary to establish whether the tamponade is caused solely by effusion or in part by fibrosis of the pericardium or the myocardium (or both). Some investigators have recommended that a myocardial biopsy be done prior to pericardiectomy to determine whether myocardial fibrosis is present in patients with constrictive irradiation-induced pericarditis.

If irradiation-induced pericarditis becomes evident clinically, it may resolve spontaneously. Symptomatic treatment has included administration of salicylates or indomethacin and, in refractory cases, corticosteroids. Morton and associates have recommended pericardiectomy in all cases with chronic effusion.

References


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CHEST, 75: 5, MAY, 1979