EDITORIALS

Radiation-Induced Coronary Artery Disease

Extensive clinical and experimental work performed in the late 1960s and the early 1970s has shown that the heart of man and other mammals can be damaged by therapeutic doses of ionizing radiation. Contrary to what was believed by many prior to those studies, the possibility of injury to cardiac tissues imposes a limit to the radiotherapy of malignant neoplasms of the lungs, mediastinum, and breast. The most common lesion is exudative pericarditis appearing usually within a year of the initiation of radiotherapy. Although the majority of cases have a benign course, in some the lesion has progressed to cardiac tamponade or pericardial constriction. In addition, individuals receiving high doses of radiation to a large volume of the heart may develop diffuse myocardial fibrosis.

Both pericardial and myocardial lesions have been well reproduced in the New Zealand white rabbit. In the rabbit, it has been established that the myocardial lesion is mediated through injury of capillary endothelial cells, resulting in compromise of the microcirculation of cardiac muscle. Study of a large group of patients who underwent radiotherapy of the mediastinum for Hodgkin's disease at Stanford University and at the University of California (San Francisco) has shown that the lesion is clearly dose-dependent and that the limits of tolerance to radiation can be defined for the pericardium. It is expected that, when a large volume of the heart is included in the field of radiation, the administration of 4,000 rads in 16 fractions over a four-week period will result in an incidence of pericarditis of about 5 percent.

Ordinarily, hearts with severe radiation-induced disease show no more atherosclerosis than that expected for the corresponding age. Since 1957, at least ten reports have been published (and three more are being printed) describing 16 patients with coronary artery disease seemingly related to radiotherapy. In six of these individuals, coronary atherosclerosis developed within the range of ages in which spontaneous atherosclerosis is frequently observed. The other cases are those of young patients (15 to 35 years old) in whom coronary arterial disease was totally unexpected or disproportionate to the condition of the other vessels. These patients often lacked many risk factors for coronary artery disease, such as family history, hypertension, hyperlipidemia, etc. A dramatic example was that of a 14-year-old boy who received 4,000 rads to the mantle for the treatment of Hodgkin's disease. Sixteen months later, he died with very severe coronary atherosclerosis and an extensive myocardial infarct (Fig 1).

In cases such as this, one is tempted to establish a cause-and-effect connection between radiation and coronary artery disease. But this is not appropriate scientific methodology. First, one should be able to prove that ionizing radiation is capable of causing atherosclerosis in general. Several experiments (in monkeys, dogs, rats, mice, birds, etc) have been performed precisely to prove such a point, with varying degrees of success; for instance,

![Figure 1. Transverse section of left anterior coronary artery from 15-year-old boy who died with large, acute, anteroseptal myocardial infarct. Sixteen months earlier, he had received 4,000 rads to mantle for Hodgkin's disease. Notice marked eccentric myointimal proliferation (and atheromatosis) which at this point has reduced lumen to less than one-fourth of its expected diameter (hematoxylin-eosin, original magnification × 27).]
coronary atherosclerosis quite similar to human coronary arterial disease has been produced in rabbits receiving radiation (2,500 rads in five fractions) to the heart and a diet with high concentrations of lipids and cholesterol.7 If the rabbits did not receive the abnormal diet, atherosclerosis did not develop. As far as I know, typical coronary atherosclerosis, of the type seen in man, has not been produced experimentally by the administration of radiation alone.

Secondly, atherosclerosis should appear in irradiated human arteries other than coronary arteries. This seems to occur, particularly in the carotid vessels. There are reports of carotid artery narrowing, sometimes resulting in neurologic deficits, after radiotherapy of tumors of the head and neck;8 however, most of these patients are individuals in whom (again) spontaneous atherosclerosis cannot be ruled out.9 Therefore, there is a suggestion, both experimentally and clinically, that radiation may contribute to premature development of atherosclerosis or may increase the severity of spontaneous atherosclerosis. Furthermore, it is possible that, for the full expression of atherosclerosis, it may be necessary to have a diet rich in lipids and cholesterol. Such a diet is common in the population of the United States, but the number of cases of possible radiation-induced coronary artery disease is apparently very small in relation to the number of irradiated individuals at risk. Therefore, one may speculate that diet and radiotherapy alone are not sufficient and that there may be other factors which, additionally or independently, predispose to atherosclerosis and whose effect is preferentially expressed in areas subjected to some form of physical injury, such as irradiation.

Now, should one try to prevent the possible radiation-induced coronary disease? The answer is that one should try to prevent radiation-induced heart disease in general, but coronary arterial disease in particular should not be an important consideration when planning a course of radiotherapy because the relationship of coronary artery disease to radiation is still questionable; and even if the relationship exists, the incidence of such coronary disease appears to be very low. At Stanford University the overall incidence of radiation-induced heart disease in patients irradiated to the mantle for Hodgkin's disease was reduced by shielding the cardiac apex after a dose of 3,000 rads; however, one should not fail to treat a tumor adjacent to the heart, thereby compromising a valuable form of therapy against a neoplasm that otherwise would kill the patient, because of the possibility of producing a lesion of the heart. In the majority of cases, radiation-induced heart disease will be mild and confined to the pericardium and, therefore, treatable by pericardiocentesis or pericardectomy.

In the event that coronary artery disease does develop after irradiation of the heart, what should be the treatment? Since the distribution of coronary artery disease in irradiated hearts is not different from that in nonirradiated hearts,4 it should be possible to approach the disease surgically as if it were spontaneous coronary atherosclerosis. This type of approach has been exemplified in the case reported in this issue of Chest by Iqbal and associates (see page 694). They describe a patient in whom radiation-induced coronary artery disease was suspected and who was treated by saphenous vein coronary artery bypass with satisfactory results. If the angiogram shows that the distal portions of the major coronary arteries are free of disease, coronary artery bypass should be feasible. Nevertheless, it is important to realize that the technique of bypass probably will not benefit those patients with diffuse myocardial fibrosis secondary to irradiation in whom the microcirculation is compromised.

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