CASE REPORT

Radiation-Induced Coronary Artery Disease Manifested at Very Late Phase

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Summary
We report the case of a 51-year-old female, in whom coronary artery disease such as occlusion of septal perforators was manifested, on the occasion of hospitalization with congestive heart failure. The patient had a history of radiation therapy for a mediastinal tumor 19 years previously. As she had no conventional coronary risk factors, the cause of the coronary artery disease is thought to have been related to the radiation therapy. As survival rates of cancer patients improve as a consequence of therapeutic advances, we should be aware of the possibility of coronary artery disease as a very late complication of radiation therapy, even in patients who have no coronary risk factors.

Key words: Radiation therapy, Very late complication, Cardiovascular complication, Heart failure

Radiation therapy has an important role as a mode of therapy for malignant tumors. When the radiation is performed for lung, breast, or esophageal cancer, or for mediastinal tumors such as malignant lymphoma, other intrathoracic organs including the heart are also exposed to the radiation. This can cause coronary artery disease, constrictive pericarditis, valvular disease, and cardiomyopathy in the late stages. As the survival rates of intrathoracic malignant neoplasms have been improved by recent therapeutic developments, radiation-induced cardiovascular disease may become more common. Here we report a case with coronary artery disease manifested 19 years after radiation therapy for a mediastinal tumor.

Case Report

A 51-year-old female suspected of having congestive heart failure was admitted to our hospital. She had a history of a mediastinal tumor, where information of histopathological diagnosis was absent, but she had received radiation therapy at a total dose of 64.8 Gy (Figure 1A, B), 19 years previously. She had been experiencing palpitations and shortness of breath for six months, during which time the symptoms had gradually worsened. She had also been having attacks of nocturnal dyspnea at increasing frequency for the past month. On admission, her heart failure symptoms corresponded to New York Heart Association (NYHA) Class III. Her temperature, heart rate, and blood pressure were 36.1°C, 120 beats/minute, and 148/94 mmHg, respectively. Jugular venous dilatation and edema of the lower extremities were absent. Blood oximetric oxygen saturation was 92% when breathing room air. A Levine II/VI pansystolic murmur and third heart sound were audible maximally at the apex.

At admission, a chest roentgenogram showed mild pulmonary congestion and elevation of the left diaphragm, but no cardiomegaly (Figure 2A). An electrocardiogram had showed regular sinus rhythm and narrow QRS complex waves 3 years before (Figure 2B), but complete left bundle branch block was present at admission. Figure 2C shows the electrocardiogram 2 days after admission. Blood cell counts and clinical chemistry were within the normal range, including levels of total cholesterol, triglycerides, and hemoglobin A1c (187 mg/dL, 76 mg/dL, and 5.4%, respectively). The serum brain natriuretic peptide (BNP) and high-sensitivity troponin T levels were 95.6 pg/mL (normal < 18.4 pg/mL) and 0.005 ng/mL (normal < 0.014 ng/mL), respectively. The serum noradrenaline and angiotensin converting enzyme (ACE) concentrations were 95.6 pg/mL (normal 100-400 pg/mL) and 12.6 IU/L (normal 8.3-21.4 IU/L), respectively. An echocardiogram showed moderate mitral regurgitation and akinesia in the basal antero-septal wall of the left ventricle, but no evidence of thinning of basal septum or aneurysmal change of the left ventricle. The echocardiogram-based ejection fraction was 41%. The pulmonary function test showed restrictive ventilator impairment as vital capacity of 65.1%.

After admission, intravenous administration of 0.0125 mg of the Department of Cardiovascular Medicine, Dokkyo Medical University, Tochigi, Japan.

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Cardiovascular complications associated with radiation therapy are rare, but can occur at a late stage when the heart has been positioned in the irradiated field. It has been reported to involve heart valves, the pericardium, the conduction system, the coronary arteries, and bypass graft vessels. Coronary artery disease induced by radiation therapy was first reported in 1991. Ng argued that screening for coronary artery disease by coronary computed tomography angiography should be performed in survivors of Hodgkin lymphoma who have undergone mediastinal radiotherapy. It appears that radiation can promote inflammation and fibrous proliferation of the intima, and then cause thinning of the medial vessel wall with extensive adventitial fibrosis in addition to intimal plaque, a process differing from atherogenesis.

In our case, the exercise stress thallium SPECT indicated myocardial ischemia in the basal-septal area, which corresponded to the CAG finding of occlusion of septal perforators. As the patient had no conventional coronary risk factors, the primary cause of the occlusion was probably the past radiation therapy for a mediastinal tumor, although it is uncertain when the septal perforators were occluded and why only septal perforators were occluded. The severity of heart failure as demonstrated by mild pulmonary congestion without cardiomegaly in the chest roentgenogram and a BNP level of only 95.6 pg/mL was inconsistent with the symptoms of NYHA Class III, although the reason for this was not apparent. We first considered that the cause of the heart failure was myocardial ischemia secondary to the septal perforator occlusion. However, septal perforator occlusion alone could not explain the low left ventricular systolic function as 41% ejection fraction. We also considered cardiac sarcoidosis as a cause of heart failure. However, that diagnosis was not supported by the lack of basal septal thinning or left ventricular aneurysmal change on echocardiogram, late gadolinium enhancement on MRI findings, and the normal serum ACE concentration, although these findings alone could not deny the cardiac sarcoidosis. We should have performed gallium scintigraphy and/or positron emission tomography. In addition, another possibility is that radiation therapy could directly produce myocardial injury independently of septal ischemia, which led to impaired left ventricular systolic function and heart failure. This possibility would be supported by the appearance of complete left bundle branch block for 3 years, perfect thallium uptake at rest phase SPECT, and myocardial atrophy with interstitial fibrosis on myocardial biopsy findings. In our case, a catheterization-based cardiac pressure study showed pulmonary hypertension as demonstrated by the elevated pulmonary artery pressure, with normal pulmonary capillary wedge pressure. Although the etiology of pulmonary hypertension cannot be clearly explained, we speculate that it might be caused by a decrease in the pulmonary vascular bed due to lung volume reduction, as demonstrated by an elevated left diaphragm on the chest.

**Discussion**

Figure 1. A: Mediastinal tumor on chest computed tomography (white arrows). B: Chest roentgenogram showing a mediastinal tumor (white arrows) and the field of radiation therapy.

μg/kg/minute carperitide during 3 L/minute of oxygen inhalation through a nasal cannula quickly improved her congestion. Exercise stress thallium-201 chloride single-photon emission computed tomography (SPECT) showed the reduced radio isotope-uptake corresponding to the echocardiographic akinetic area, although it was absent at rest. The akinetic region of the left ventricle was also evident on magnetic resonance imaging (MRI), but late gadolinium enhancement was absent. Cardiac catheterization was performed after the heart failure symptoms were improved. Cardiac pressure study results showed elevated right ventricular systolic pressure (43 mmHg), mean pulmonary artery pressure (29 mmHg), and left ventricular end-diastolic pressure (18 mmHg), while pulmonary capillary wedge pressure (9 mmHg) and other pressure data were normal. The right ventricular diastolic pressure wave did not show a dip and plateau pattern, suggesting that constrictive pericarditis or restrictive cardiomyopathy seemed contradictory. The thermodilution-based cardiac index was 2.48 L/minute/m². A myocardial biopsy showed myocardial atrophy with interstitial fibrosis, no deposit of amyloid or other metabolites, and no non-caseating granuloma. A coronary angiogram (CAG) showed that the proximal septal perforators were occluded, and collateral circulation from the right coronary artery was evident (Figure 3A). Exercise stress thallium-201 myocardial scintigraphy showed the presence of an early perfusion defect and delayed redistribution in the area of the anterior septum of the left ventricle (Figure 3B). The patient left the hospital on the 35th day without any recurrence of heart failure while taking 2.5 mg enalapril, 25 mg spironolactone, 5 mg carvedilol, and 30 mg azosemide daily by mouth.
roentgenogram, which was also possibly associated with quondam radiation therapy. Actually the result of the pulmonary function test showed restrictive ventilator impairment.

As reported by others, the time of onset of cardiovascular complications caused by radiation therapy has varied. In particular, Gamerkeli et al.\(^{13}\) reported that cardiac complications can occur even as late as 40 years after the treatment. To our knowledge, the period of 19 years between radiation therapy and onset of heart failure, in our case, is second only in length to the case of Gamerkeli et al. As survival rates in cancer patients increase as a consequence of therapeutic developments, survivors of radiation therapy are more likely to suffer radiation-associated cardiovascular complications. From our experience with the present case, clinicians should be aware of coronary artery disease as a late complication of radiation therapy of the chest, particularly in patients with no coronary risk factors.

**Conclusion**

We report a case with coronary artery disease, which was manifested 19 years after radiation therapy for a mediastinal tumor. Coronary artery disease should be kept in mind as a possible complication at a very late phase after radiation therapy.
Figure 3.  A: Coronary angiogram showing that the proximal septal perforators were occluded. Collateral circulation from the right coronary artery was also evident. B: Exercise stress thallium-201 myocardial scintigraphy showing the presence of an early perfusion defect, and delayed redistribution in the area of the anterior septum of the left ventricle.

Disclosures

Conflicts of interest: None.

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