Case Reports

Constructive Pericarditis 5 Months after Radiation Therapy

in a 62-Year-Old Woman with Esophageal Cancer

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Most pericardial changes appear within a few weeks in patients who have undergone radiation therapy for thoracic neoplasms. Chronic pericardial constriction typically occurs decades later, consequent to fibrosis. Early constrictive pericarditis after chest irradiation is quite rare. We report the case of a 62-year-old woman who underwent radiation therapy for esophageal cancer and presented with constrictive pericarditis 5 months later.

We searched the English-language medical literature from January 1986 through December 2015 for reports of early constrictive pericarditis after irradiation for thoracic malignancies. We defined "early" as a diagnosis within one year after radiation therapy. Five cases fit our criteria, and we summarize the findings here. To our knowledge, ours is the first definitive report of a patient with esophageal cancer to present with early radiation-induced constrictive pericarditis.

We conclude that constrictive pericarditis can occur early after radiation for thoracic malignancies, albeit rarely. When planning care for cancer patients, awareness of this sequela is helpful. ***(Tex Heart Inst J 2017;44(6):411-5)***

Key words: *Dose-response relationship, radiation; heart/radiation effects; patient care planning; pericarditis, constrictive/diagnosis/etiology/pathology/therapy; radiation injuries/etiology; radiotherapy, high-energy/adverse effects; thoracic neoplasms/radiotherapy; time factors; treatment outcome*

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Heart diseases and malignant neoplasms are major causes of morbidity and death.[1-3] The potential for cardiovascular disease in cancer survivors who have undergone radiation therapy (RT) has long been known, and several risk factors have been identified.[3,4]

Among the numerous sequelae of chest irradiation are coronary artery disease, pericarditis, cardiomyopathy, valvular disease, conduction abnormalities, and other vasculopathies. Classification of cardiovascular injury after RT has been suggested on the basis of the time of occurrence and the structures involved. Such injury appears to be associated with radiation dose and technique, the exposed cardiac volume, the patient's age at the time of RT, and existing cardiovascular risk factors.[1,4] Sequelae can present as subclinical abnormalities during screening or as substantial clinical events, and they can occur despite precautions with respect to procedure, shielding of unintended fields, and dose exposure. Cancer patients' survival rates continue to improve, and RT remains prominent in the treatment of many cancers, so the number of patients with radiation-induced cardiovascular sequelae is expected to rise.[3,4] Pericardial effects are among these, and clinicians should be aware.

Delayed constrictive pericarditis (CP) after RT for thoracic malignancies is well described; conversely, early CP is rare.[5-10] Most pericardial changes are acute and appear within a few weeks after RT. Chronic constriction typically occurs decades later, consequent to fibrosis.[3,4,11,12]

We report what we think is the first definitive case of a patient with squamous esophageal cancer who underwent RT and sustained early CP. Because few investigators have focused on relevant similar occurrences, we searched the medical literature and report our findings.

Case Report

In June 2015, a 62-year-old woman was diagnosed with a stage IIIA T3 N1 M0 G3 esophageal carcinoma, without evident metastasis. She underwent neoadjuvant chemoradiation therapy in accordance with a Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) regimen. The radiation course consisted

of a total dose of 4,140 cGy (41.4 Gy) in 23 fractions. Concurrent chemotherapy included carboplatin and paclitaxel.

The patient completed radiation therapy in July 2015 and then underwent minimally invasive distal esophagectomy and a gastric pull-through procedure in September 2015, after which she felt well. She was referred to the cardio-oncology clinic in December 2015 for evaluation of dyspnea. She reported no chest discomfort, orthopnea, or paroxysmal nocturnal dyspnea. She was not very active physically, but experienced dyspnea when she climbed stairs or talked. Her cardiovascular risk factors included 40 pack-years of tobacco use. There was no family history of premature coronary artery disease. She reported consuming 6 oz of alcohol daily.

On physical examination, she had a blood pressure of 100/60 mmHg, a regular heart rate of 80 beats/min, and evidence of weight loss. Pressures in her neck veins were elevated; however, no Kussmaul sign was detected. Auscultation revealed a normal S_1, normal splitting of S_2, and an intermittent pericardial rub.

Laboratory data included a hemoglobin level of 12.4 mg/dL, a white blood cell count of 7.4 $\times 10^9$/L, and a normal differential and platelet count. The patient's international normalized ratio, partial thromboplastin time, electrolyte results, blood urea nitrogen and creatinine levels, lipid levels, and liver panel were normal. Her erythrocyte sedimentation rate was 42 mm/hr, and her high-sensitivity C-reactive protein level was markedly elevated (87 mg/L).

Transthoracic echocardiograms showed substantial pericardial thickening of 8 mm, which was not present 6 months earlier. The patient's left ventricular (LV) ejection fraction was 0.52, her right ventricular systolic pressure was 42 mmHg, and her inferior vena cava was dilated with no inspiratory collapse. The global average LV strain was an abnormal –15% (normal, lower than –18%). Doppler evaluation with use of a respirometer showed ventricular interdependence (Fig. 1) and diastolic flow reversals in the hepatic veins (Fig. 2), suggesting CP in the presence of thickened pericardium.

Cardiac magnetic resonance (CMR) with gadolinium showed pericardial enhancement compatible with pericarditis, early enhancement consistent with inflammation, and late enhancement suggesting acute and chronic CP. A small volume of pericardial fluid, Ivor Lewis procedure changes, and bilateral pleural effusions were noted. The LV ejection fraction was normal. The pericardium was diffusely thickened (8 mm) along the lateral and posterior walls (Figs. 3, 4, and 5).

Because of the patient's recent surgery and our concern about nonsteroidal anti-inflammatory–induced gastropathy, we prescribed 1.5 mg/kg of steroids tapered over 2 months, together with colchicine (0.6 mg/d). After 30 days, the patient's erythrocyte sedimentation rate and high-sensitivity C-reactive protein level were

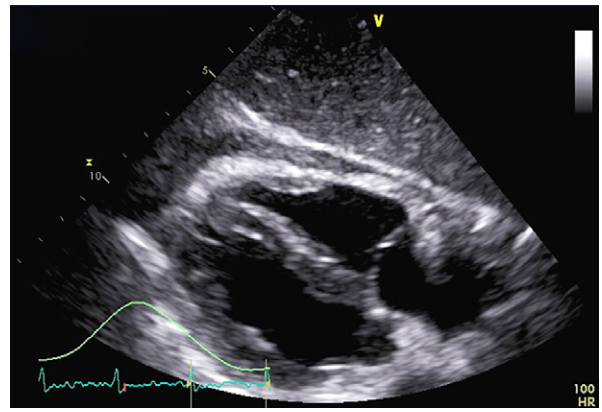

Fig. 1 *Transthoracic echocardiogram (subcostal 4-chamber view) shows thickened pericardium. Ventricular interdependence (septal bounce) was seen on real-time images.*

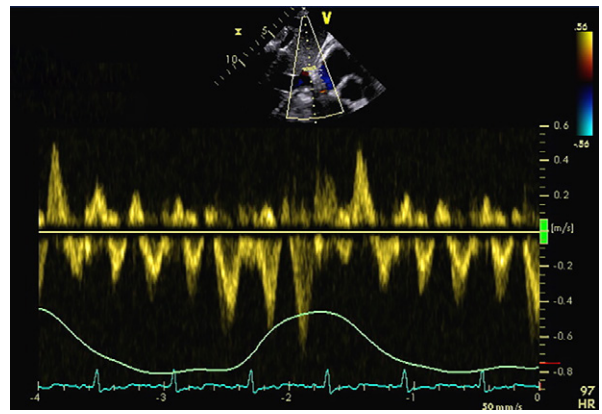

Fig. 2 *Pulsed-wave echocardiogram with color-flow Doppler shows diastolic flow reversal in the hepatic veins.*

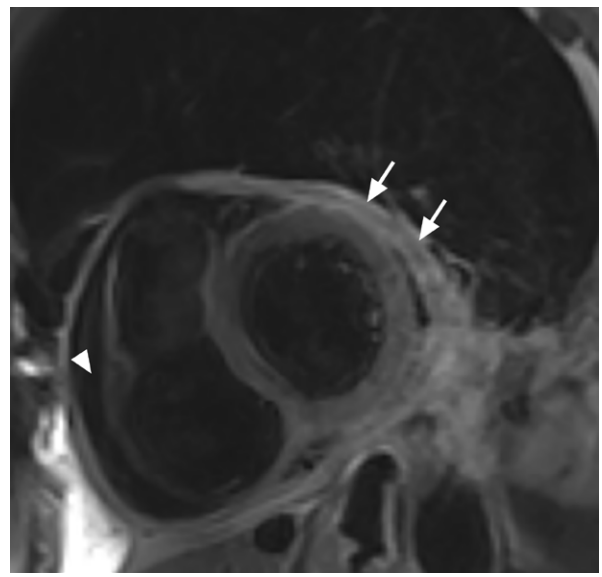

Fig. 3 *Cardiac magnetic resonance (short-axis black-blood image) shows pericardial thickening (arrows) and a small volume of pericardial fluid (arrowhead).*

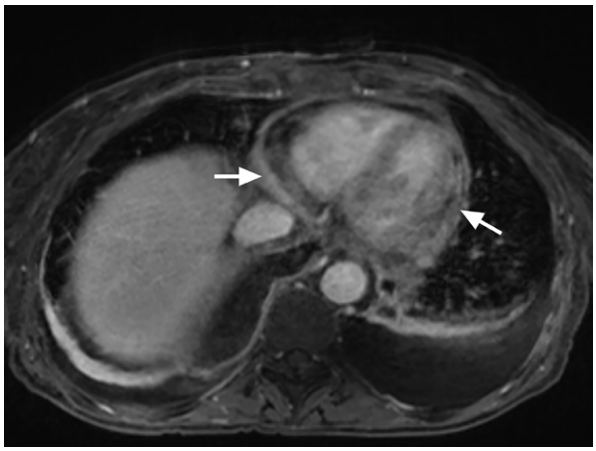

Fig. 4 *Cardiac magnetic resonance (T1-weighted image) shows avid contrast enhancement, suggesting pericardial inflammation (arrows).*

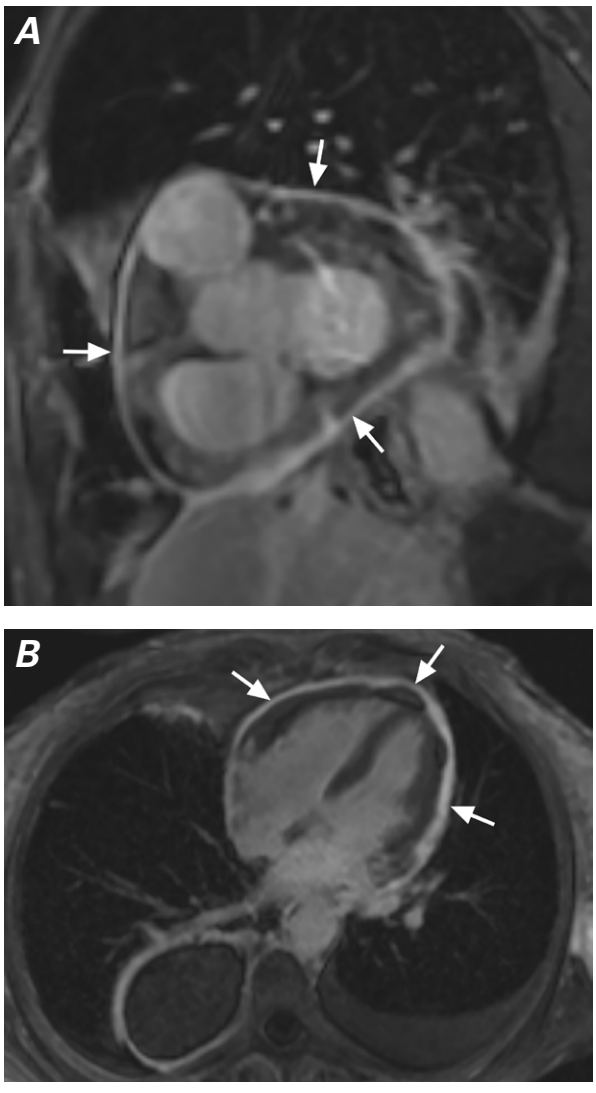

Fig. 5 *Cardiac magnetic resonance in* ***A****) short-axis and* ***B****) 4-chamber views with late gadolinium enhancement show diffuse circumferential pericardial enhancement (arrows).*

normal. Upon completion of therapy, her symptoms improved. An echocardiogram showed no ventricular interdependence or constriction. As of September 2017, she was asymptomatic.

Literature Search

Three of us (BY, SA, and FM) and a librarian independently searched electronic databases for English-language cases of pericarditis in adult patients who had undergone chest irradiation for thoracic malignancies. The search period was January 1986 through December 2015. We used the following key words: acute pericarditis, chronic pericarditis, constrictive pericarditis, effusive-constrictive pericarditis, esophageal cancer, thoracic neoplasms, radiotherapy, and radiation therapy. We also searched these terms from the Medical Subject Headings database: constrictive pericarditis, radiation therapy, esophageal cancer, and thoracic malignancies. We defined early CP, whether effusive or not, as having developed within one year of RT in patients with any thoracic malignancy.

After evaluating 17 full-text articles[5-10,13-23] for eligibility, we analyzed the demographic data, clinical presentations, types of neoplasms irradiated, diagnostic methods, treatments, and outcomes.

Results

In total, we identified 5 instances, including our own case, of early CP that developed consequent to RT for thoracic malignancies (Table I).[5,9,10] Ten articles were excluded for not meeting our definition of early CP,[6-8,13-19] and 4 others because of insufficient data.[20-23]

Demographic Data and Clinical Presentations. The 5 patients ranged in age from 16 to 62 years; 3 were female. Three presented with dyspnea on exertion. Pericardial effusion was present in 2. The prevalent noncardiac finding (in 3) was pleural effusion. Table II shows the malignancies for which the patients underwent RT. Duration from RT to presentation with CP was 5 to 12 months. The total radiation doses ranged from 41.4 to 75 Gy.

Diagnostic Methods and Findings. Diagnostic methods used to identify CP were specified in 3 of the 5 reports. Transthoracic echocardiography was used in all 3. Right-sided heart catheterization, computed tomography, and CMR were used in one patient each. Cardiac involvement included pericardial effusion, right-sided heart failure, and myocardial fibrosis. Noncardiac findings included hepatic congestion or hepatomegaly, pleural fibrosis, and mediastinal fibrosis.

Treatment. Four patients were prescribed medical therapy: steroids alone (2 patients), diuretics (1), and steroids plus colchicine (1). Two underwent pericardiectomy as first-line treatment, and another after failed medical therapy. Four were given neoadjuvant chemotherapy.

TABLE I. Cases of Early Constrictive Pericarditis after Radiation Therapy

Reference	Age (yr), Sex	Presenting Symptom	Time to CP Diagnosis (mo)	Malignancy, Total Radiation Dose (Gy)	Treatment	Outcome
Coltart RS, et al.[5] (1985)	16, M	Cough and fever	12	Hodgkin lymphoma, 46	Medical, then pericardiectomy	Died during surgery
	45, F	Dyspnea on exertion	12	Hodgkin lymphoma, 49	Medical (steroids)	Died after 18 mo
Hickey EJ, et al.[9] (2007)	60, M	Dyspnea on exertion	6	Mesothelioma, 75	Pericardiectomy	Died on post-operative day 4
Hikosaka Y, et al.[10] (2015)	56, F	Nausea and anorexia	7	Thymoma, 50	Pericardiectomy, then medical (diuretics)	Unknown; CP remained
Current case	62, F	Dyspnea on exertion	5	Squamous esophageal cancer, 41.4	Medical (steroids and colchicine)	Alive at 21 mo

CP = constrictive pericarditis

TABLE II. Additional Clinical Characteristics of 5 Patients with Constrictive Pericarditis

Variable	Value
Age (yr)	16–62 (48)
Esophageal cancer	1 (20)
Mesothelioma	1 (20)
Hodgkin lymphoma	2 (40)
Thymoma	1 (20)
Pericardial effusion	2 (40)
Pleural effusion	3 (60)
Time to presentation with constrictive pericarditis (mo)	5–12 (8.4)
Total radiation dose (Gy)	41.4–75 (52.3)

Data are presented as range and average or as number and percentage.

Histologic Diagnoses and Patient Outcomes. Histologic analysis confirmed fibrous pericardium in 4 patients (2 postmortem). Our patient underwent no histologic evaluation, because of her response to primary medical therapy. Among the known outcomes, one patient died during pericardiectomy, one 4 days after pericardiectomy, and one after 18 months.

Discussion

Over the 30-year publication period, we found only 4 other definitive cases of CP that developed early after RT for thoracic malignancies. None clearly occurred after RT for esophageal cancer, apparently making ours the first such case to be definitively reported. In all cases, early CP developed after radiation was delivered across the anterior chest, within the field of the heart. Cardiac damage from RT is related to radiation dose and to the irradiated volume of the heart, in addition to factors such as young age upon exposure.[24]

The average radiation dose in our study was 52.3 Gy. After RT for different thoracic malignancies, the incidence of cardiac sequelae (including pericardial toxicities) increases significantly when the total radiation dose exceeds 30 Gy.[12,25] Similarly, CP is possibly a marker for greater radiation injury to the heart.[25]

In the past, right-sided heart catheterization was usually needed to confirm the diagnosis of CP. Our patient's diagnosis was made early, with use of echocardiography and CMR—methods that enable anatomic, physiologic, and hemodynamic evaluation of the heart and associated structures. In particular, CMR is valuable in tissue characterization. Computed tomography can be used to evaluate calcification in the pericardium.[25]

Our patient did not undergo surgery or a biopsy. In the other patients,[5,9,10] histologic findings suggested thick, fibrous pericardium—the same as in cancer survivors when chronic radiation-induced inflammation leads to fibrotic fusion and thickening of the visceral and parietal pericardium, whether associated with effusion or not.[25,26]

Treatment recommendations for radiation-induced CP continue to evolve; nevertheless, mortality rates remain high. Medical regimens and operative treatments have yielded varying outcomes. Pericardiectomy was once considered to be futile for various reasons, chief among these that the degree of fibrosis from high-dose radiation made surgery difficult.[19] Early stripping of the pericardium in planned cardiac surgery—although still challenging—might improve cardiac physiologic conditions postoperatively.[25,27]

More data on the long-term management outcomes of radiation-induced CP would clarify the therapeutic

options. Detecting pericardial constriction early might enable a response to medical therapy before chronic fibrosis develops and high-risk surgery becomes the only option.

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