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LETTER TO THE EDITOR
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Identification and management of severe multiple radiation-induced heart disease: case reports from locally advanced esophageal cancer patient

Yi-Xun GU[1], Xi-Zhi ZHANG[2], Jun LI[2], Yong CHEN[3,✉]

1. Clinical Medical College, Yangzhou University, Jiangsu, China; 2. Department of Oncology, Northern Jiangsu Province People Hospital of Yangzhou University, Jiangsu, China; 3. Department of Oncology, Affiliated Hospital of Yangzhou University, Jiangsu, China

✉ Correspondence to: chenyong_jsyz@sina.com

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Esophageal cancer (EC) is one of the leading causes of cancer-related mortality worldwide. It is a highly malignant tumor with a high local recurrence and distant metastasis. Notably, about half of the world's EC patients occur in China. Smoking, drinking liquor alcohol and eating hot food are the top three risk factors for EC in China.[1] Radiation therapy (RT) plays a pivotal role in the treatment of locally advanced EC patients, and radiation-induced heart diseases (RIHD) has become a clinically concerned problem, which may involve any structure of heart, including coronary heart disease (CHD), atrial fibrillation (AF), valvular heart disease (VHD), pericardial effusion (PE), heart failure (HF), thromboembolic disease (TED) and atrioventricular block (AVB), sick sinus syndrome (SSS), and *etc*; some of which may occur after 10–15 years or even more decades.[2, 3] Herein, we report some cases with severe multiple RIHD after traditional RT and intensity modulated radiotherapy (IMRT) in different ages. To the best of our knowledge, few investigators have focused on relevant similar cases.

Five patients with upper (n = 2) or middle (n = 3) thoracic locally advanced esophageal squamous cell carcinoma who received radiotherapy, combined surgery (n = 4) or concurrent chemotherapy (n = 1) between 1990 and 2018 were retrospectively analyzed. Baseline characteristics and risk factors for cardiovascular disease (CVD) are shown in Table 1. All patients had no clear CVD clinical symptoms prior-RT, but there were some risk factors in three cases. Case 2 had been smoking average 40 cigarettes and drinking 150–250 mL liquor alcohol per day for 27 years prior to RT. Cases 4 & 5 had hypertension and Case 4 had mild diabetes mellitus and did not take hypoglycemic drugs.

EC management and identification of RIHD are presented in Table 2 and Figure1–5. We can't get more details because RT for Cases 1–3 was respectively performed 30, 24 and 20 years ago. Their treatment regiments were similar as follows: Cobalt-60 RT (60 Gy in fractions 5–7 weeks followed surgery). Case 4 was treated with postoperative IMRT in 2014. Due to the patient with advanced age, Case 5 was only treated by chemoradiotherapy, which consisted of Tegio 40 mg/day for the first 14 days, and IMRT at 2 Gy/day for five days per week (total dose: 60 Gy) in 2018. Clinical target volume was defined by referring to EC position plus 1–2 cm. RIHD was mainly detected and evaluated by electrocardiogram (ECG), dynamic ECG (DCG), ultrasonic echocardiography (UCG), CT angiography (CTA), coronary angiography (CAG) and N-terminal pro B-type natriuretic peptide. They were diagnosed with CHD (n = 5), AF (n = 4), VHD (n = 3), PE (n = 5), HF (n = 5), TED (n = 2) and third-degree AVB (n = 1), and SSS (n = 2). RIHD management and prognosis of RIHD are showed in Table 3.

With the continuous progress of esophageal cancer radiotherapy (ECRT) technology, the survival rate of EC patients has been significantly improved. However, RT in the locally advanced stage EC inevitably leads to heart injury. RT mainly results in the

Table 1 Baseline characteristics and risk factors for cardiovascular disease in five patients.

Case	Age/Sex	Tumor location	Clinical stage	Age at radiation therapy	Smoking/ Drinking	Hypertension	Debates mellitus	Hyperlipidemia
1	65/Female	Middle thoracic	IIAcTaNxM0	35				
2	69/Male	Upper thoracic	IIAcTaNxM0	45	√			
3	57/Male	Middle thoracic	IIAcTaNxM0	37				
4	72/Female	Upper thoracic	IIAcTaN0M0	66		√	√	
5	78/Female	Middle thoracic	IIAcTaN0M0	76		√		√

Table 2 Treatment of esophageal cancer and identification of radiation-induced heart disease.

Case	Treatment of esophageal cancer	ECG/DCG	UCG	CTA/CAG	NT-proBNP, pg/mL
1	Traditional RT 60 Gy, 10 weeks, surgery	Persistent AF	Mild VHD, LA 45 mm, Mild PE	70% stenosis in LADm	1,225
2	Traditional RT 60 Gy, 10 weeks, surgery	SSS, Persistent AF	Mild VHD, LVEF 40%, Mile PE	Occlusion in RCAp	1,520
3	Traditional RT 60 Gy, 12 weeks, surgery	Third-degree AVB	Mild VHD, Moderate PE and PC	90% stenosis in LCXp	719
4	IMRT: PTV 59.64 Gy/28 F, 5 weeks, surgery	Sinus bradycardia, Persistent AF, BTS	Mild PE	85% stenosis in LADm	1,084
5	IMRT: GTV 60 Gy/28 F, 5 weeks, concurrent chemotherapy	AP prior to RT, Persistent AF post-RT	Mild PE	70% stenosis in LADm	4,962

AF: atrial fibrillation; AP: atrial premature; AVB: atrioventricular block; BTS: bradycardia-tachycardia syndromome; CAG: coronary angiography; CTA: CT angiography; DCG: dynamic electrocardiogram; ECG: electrocardiogram; F: fractions; GTV: gross tumor volume; IMRT: intensity modulated radiotherapy; LA: left atrium; LADm: the middle segment of the left anterior descending artery; LCXp: the proximal segment of the left circumflex branch; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro B-type natriuretic peptide; PC: pericardial calcification; PE: pericardial effusion; PTV: planning target volume; RCAp: the proximal segment of the right coronary artery; RT: radiation therapy; SSS: sick sinus syndrome; UCG: ultrasonic echocardiography; VHD: valvular heart disease.

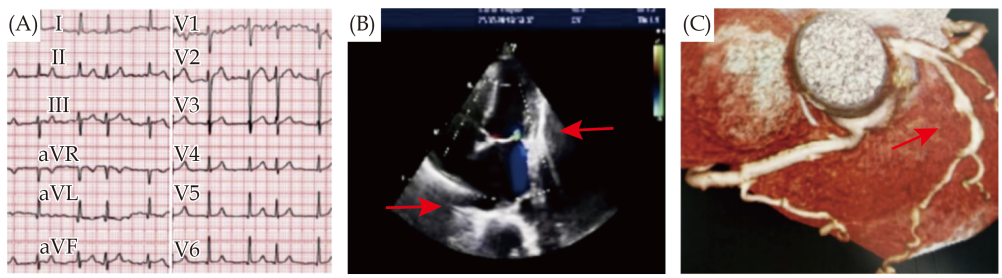

Figure 1 The representative images of Case 1. (A): Electrocardiogram showed atrial fibrillation; (B): ultrasonic echocardiography showed left atrium enlargement, pericardial calcification and pericardial effusion (arrows); and (C): CT angiography showed a 70% stenosis in the middle segment of the left anterior descending artery (arrow).

injury of microvascular endothelial cells, leading to tissue fibrosis and myocardial necrosis, which often affects the coronary arteries, pericardium, conduction system and atrial matrix while the ventricular myocytes have relatively less influence, and there is now no reliable method to reverse it. The production and development of RIHD mostly depend on the total cumulative dose, daily administered dose, radiation site, radiotherapy method, the spatial relationship between the heart and EC, cardiovascular risk factors, heart disease, combined chemotherapy and so on.[4,5] In this group, the Cases 1–3 aged 35–45 years who received high dose of cobalt-60 conventional RT, and the Cases 4 & 5 with some cardiovascular risk factors developed RIHD, which was consistent with the above results. The present study demonstrated that existing RT, even the modern three-dimensional conformal radiotherapy, IMRT and proton beam therapy technologies can't eliminate RIHD, and even some RIHD is severe and multisite due to the close anatomical position between the heart and the esophagus (Figure 6). In other

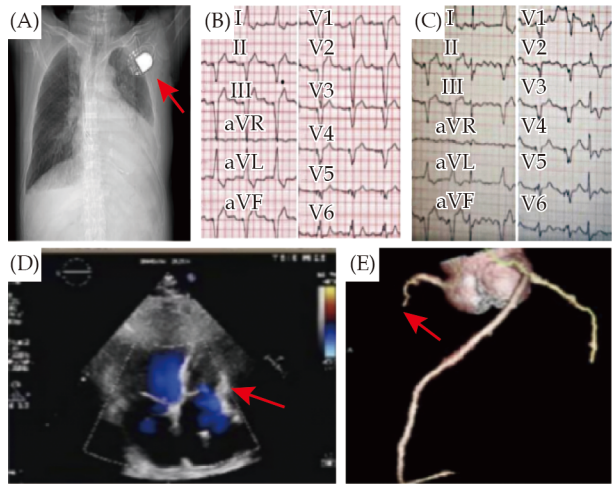

Figure 2 The representative images of Case 2. (A): Chest X-ray showed pacemaker implanted (arrow); (B): electrocardiogram showed pacemaker running well; (C): electrocardiogram showed atrial fibrillation; (D): ultrasonic echocardiography revealed left ventricular ejection fraction 40%, pericardial calcification and pericardial effusion (arrow), aortic valve calcification with light to moderate regurgitation; and (E): CT angiography showed the proximal right coronary artery occlusion (arrow).

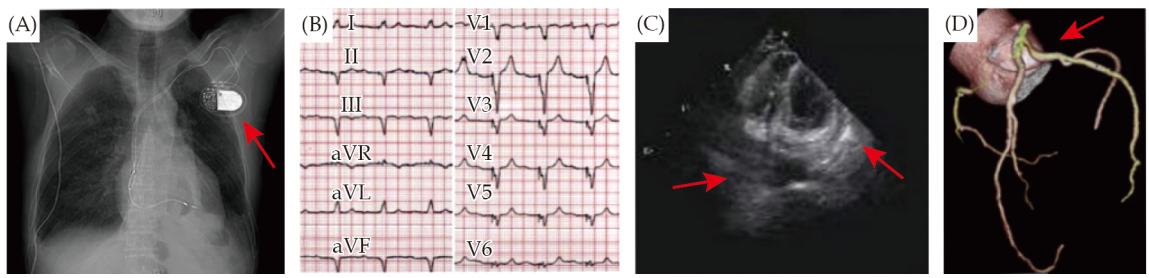

Figure 3 The representative images of Case 3. (A): Chest X-ray showed pacemaker implanted (arrow); (B): electrocardiogram showed pacemaker heart rhythm; (C): ultrasonic echocardiography showed moderate pericardial effusion and pericardial calcification (arrows); and (D): CT angiography showed a 90% stenosis in the proximal segment of the left circumflex branch (arrow).

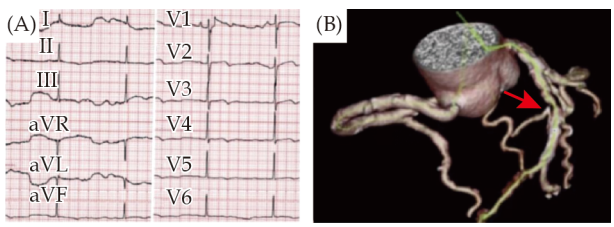

Figure 4 The representative images of Case 4. (A): Electrocardiogram showed sinus bradycardia; and (B): CT angiography showed a 85% stenosis in the middle segment of the left anterior descending artery (arrow).

words, ECRT and RIHD may coexist now and in the future. At a single-center, up to five patients with severe multiple heart disease after ECRT were identified within six months, indicating that the incidence and severity of RIHD in this region were still quite high.

Our results also suggest that RIHD can be accurately identified by routine imaging and laboratory tests. Monitoring and early diagnosis are particularly important to reduce the risk of RIHD. RIHD screening should be started shortly after RT. ECG, DCG, UCG, CTA, CAG, and markers of myocardial injury should be conducted, and active treatment should be coordinated with cardiologists and oncologists. Long-term follow-up with regular screening for RIHD plays an important role in the management of cancer survivors who have undergone RT.[6,7] In addition, remote follow-up and monitoring may also be helpful.

Although the management of RIHD is similar to that of non-RIHD, it has its particularity. In our study, Case 1 had recurrent atrial tachycardia shortly after radiofrequency catheter ablation. Two patients were implanted cardiac pacemaker, and one of them was complicated with left subclavian vein thrombosis. One patient with severe CHD underwent percutaneous coronary intervention, but complicated with coronary artery rupture and tam-

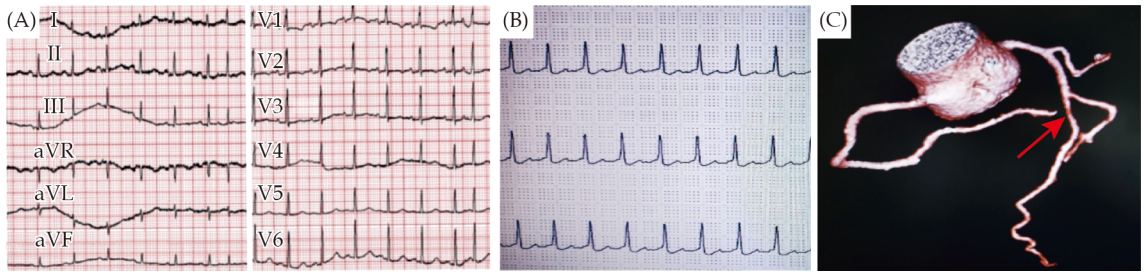

Figure 5 The representative images of Case 5. (A): Electrocardiogram showed sinus tachycardia; (B): dynamic electrocardiogram showed atrial fibrillation; and (C): CT angiography showed a 70% stenosis in the middle segment of the left anterior descending artery (arrow).

Table 3 Treatment and prognosis of radiation-induced heart disease.

Case	Radiation-induced heart diseases	Drugs treatment	Cardiac interventional therapy	Complications	Outcome
1	Persistent AF, VHD, HF, PE, CHD	Warfarin, Valsartan, Diuretics, Metoprolol, Digoxin	RFCA for AT		Stable
2	Persistent AF, VHD, SSS, HF, PE, CHD	Warfarin, Atorvastatin valsartan, Metoprolol	DDD pacemaker implantation for SSS, PCI for CHD	Cardiac tamponade	Stable
3	Third-degree AVB, HF, PE, CHD	Warfarin, Diuretics Metoprolol	DDD pacemaker implantation for third-degree AVB	Subclavian thrombosis	Stable
4	Persistent AF, BTS, VHD, HF, PE, CHD	Warfarin, Isosorbide Rosuvastatin			Stable
5	Persistent AF, HF, PE, CHD	Warfarin, Irbesartan Metoprolol, Diuretics			Stable

AF: atrial fibrillation; AT: paroxymal atrial tachycardia; AVB: atrioventricular block; BTS: bradycardia-tachycardia syndromome; CHD: coronary heart disease; DDD: dual chamber pacemaker; HF: heart failure; PCI: percutaneous coronary intervention; PE: pericardial effusion; RFCA: radiofrequency catheter ablation; SSS: sick sinus syndrome; VHD: valvular heart disease.

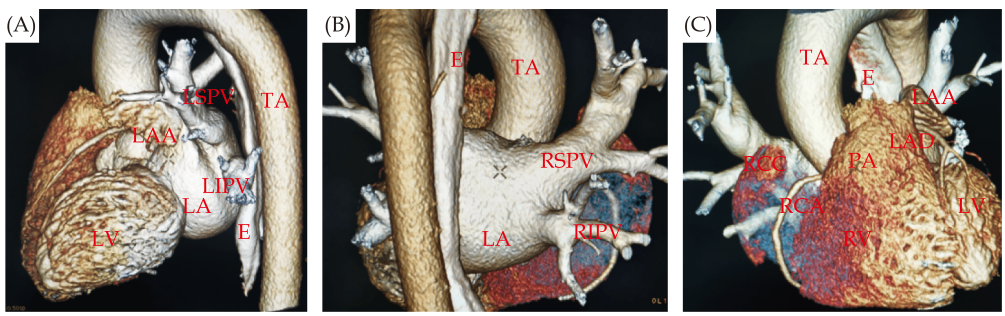

Figure 6 CT angiography and esophageal angiography showed the anatomical relationship between the heart and the esophagus: the esophagus was located behind the left atrium, which was very close to each other, only about 3 mm. (A): Sagittal plane after three-dimensional reconstruction; (B): posterior anterior position: the heart behind the esophagus; and (C): anterior posterior position: the heart in front of the esophagus. E: esophagus; LA: left atrium; LAA: left atrium appendage; LAD: left anterior descending artery; LIPV: left inferior pulmonary vein; LSPV: left superior pulmonary vein; LV: left ventricular; PA: pulmonary artery; RCA: right coronary artery; RCC: right coronary cusp; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein; RV: right ventricular; TA: thoracic aorta.

ponade. The occurrence of serious complications in the above two patients was mainly due to delay in diagnosis and the lack of understanding for the treatment specificity of RIHD. Currently, there is no very effective means to reverse RIHD, thus the primary way to improve its prognosis is through timely identification and accurate treatment. There are no specific drugs applied to RIHD. These drugs included beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin-receptor neprilysin inhibitors, diuretics, statins, antiplatelet drugs, anticoagulants, digitalis, aldosterone antagonists and *etc.* CVD prevention guidelines, including a healthy diet, smoking cessa-

tion, alcohol restriction, weight reduction and aerobic exercise, can be also helpful in improving its prognosis.[8,9] The five patient had a good prognosis after accurate diagnosis and effective treatment, which provides experience for the management of similar RIHD cases.

In conclusion, timely recognition, accurate medication treatment and careful surgical or interventional therapy have an important impact on the long-term stability of patients with ECRT. A multidisciplinary team must make accurate recommendations on the planning and scope of heart screening for early diagnosis and effective treatment of RIHD.

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