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CASE SERIES
Other

Cardiovascular complications of mantle field radiation: a case series

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Background Mantle field radiotherapy has been known to cause cardiovascular complications even years after therapy. Complications include pericardial disease, coronary artery disease, and conduction abnormalities.

Case summary We present a case series of two patients who developed cardiovascular complications years after receiving mantle radiation. Patient 1 is a 52-year-old man who presented with symptoms of heart failure. He had a neurostimulator which precluded him from cardiac magnetic resonance imaging. Haemodynamic findings on right heart catheterization raised suspicion for constrictive pericarditis and pericardiectomy was performed. Histopathological analysis reported dense, sclerotic fibrous tissue consistent with radiation-related changes. Patient 2 is a 37-year-old man with a 2-month history of chest pain and exertional dyspnoea who was admitted for management of coronary artery disease. Coronary angiography demonstrated bilateral subclavian artery stenosis and an elevated left ventricular end-diastolic pressure (50 mmHg). He had bilateral percutaneous subclavian artery stenting. Both patients had complete resolution of symptoms on follow-up.

Discussion Our case series emphasizes the need for an index of suspicion for radiation-related cardiovascular changes in patients who have a history of mantle radiation, especially in younger patients. This was especially pertinent in the case of our first patient who presented a diagnostic challenge due to certain patient factors. Our second patient is a case of subclavian artery stenosis which is less frequently reported as a complication of mantle radiation in the literature.

Keywords Mantle field radiotherapy • Constrictive pericarditis • Subclavian artery stenosis • Case series

ESC Curriculum 3.1 Coronary artery disease • 6.1 Symptoms and signs of heart failure • 6.9 Cardiac dysfunction in oncology patients • 6.6 Pericardial disease

Learning points

- In patients presenting with abnormal cardiovascular findings with a history of mantle field radiotherapy, radiation-related cardiovascular complications should be suspected as a cause.
- The use of multi-modality imaging is helpful in establishing the diagnosis of constrictive pericarditis.
- Mantle field radiotherapy can also accelerate atherosclerosis in the major vessels of the head and neck.

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Introduction

In recent times, advances have been made in deliverance of radiation therapy to the chest. However, many patients treated in previous decades were subject to mantle field radiation. This form of high-dose therapy has been associated with cardiovascular complications such as pericardial disease, conduction abnormalities and premature coronary atherosclerotic disease. Less commonly, carotid and subclavian artery disease and clinically significant valvular dysfunction have also been reported.[1] At 10 years post-radiotherapy, the incidence of radiation-induced cardiac disease is 10–30%, with up to 88% of patients suffering asymptomatic cardiac abnormalities such as subclinical valvular and myocardial dysfunction.[2] Notably, the increased relative risk of fatal cardiovascular events after mediastinal irradiation for Hodgkin's lymphoma ranged between 2.2 and 7.2 compared to the general population.[1] This risk is greater with high mediastinal doses (>30 Gy), minimal protective cardiac blocking, young age at irradiation, and increasing duration of follow-up.[3] In this case series, we describe cardiovascular complications, such as constrictive pericarditis and subclavian artery stenosis, associated with radiotherapy at young age and causing significant morbidity, requiring invasive surgical intervention.

Timeline

Time	Events
Patient 1	
21 years prior to admission	Non-Hodgkin's lymphoma diagnosed. Treated with chemotherapy and extended mantle field radiotherapy.
5 years prior to admission	Dual-chamber permanent pacemaker insertion due to syncope with complete atrioventricular block.
1 year prior to admission	Coronary artery disease diagnosis with 90% stenosis of the ostial right coronary artery (RCA), treated with drug-eluting stent.
2 months prior to admission	4-day admission due to acute pericarditis.
2 weeks prior to admission	Re-presentation to hospital with worsening exertional dyspnoea, peripheral oedema with a weight gain of 9 kg over the previous month.
Latest admission	5-day admission for worsening exertional dyspnoea, orthopnoea, and peripheral oedema. Comprehensive investigations undertaken to investigate the cause of the right-sided heart failure.
1 month after admission	Elective pericardiectomy and RCA bypass for constrictive pericarditis.
18 weeks after admission	Patient demonstrated complete resolution of right-sided heart failure.
Patient 2	
28 years prior to admission	Diagnosis of MEN 1 and insulinoma removed by partial distal pancreatectomy.
7 years prior to admission	Resection of atypical carcinoid tumour likely thymic in origin followed by radiation to the mediastinum (60 Gy/30 F).
2 months prior to admission	Patient experienced intermittent chest pain and exertional dyspnoea and was referred to Cardiologist.
Day of admission	Patient underwent outpatient cardiac angiogram.
Admission	17-day admission for inpatient coronary artery bypass grafting and bilateral subclavian artery stenting.
1 month after admission	Complete resolution of symptoms and no post-operative complications at follow-up.
6 months after admission	Patient remained well with no cardiac symptoms.

Case presentation

Patient 1

A 52-year-old man was admitted to hospital to investigate a 2-week history of worsening exertional dyspnoea, orthopnoea, and peripheral oedema. He had multiple admissions in the previous few months due to symptomatic right-sided heart failure.

Background medical history includes extended mantle field radiotherapy for non-Hodgkin's lymphoma 21 years earlier and spinal cord stimulator insertion 18 years prior for treatment of chronic back pain. He also had coronary artery disease with drug-eluting stent implantation to an ostial right coronary artery (RCA) stenosis 12 months prior and previous dual-chamber permanent pacemaker insertion due to syncope with complete heart block. Family history was unremarkable for inherited cardiomyopathies.

On examination, the jugular venous pressure (JVP) was elevated 10 cm above the sternal edge with prominent v waves. Heart sounds were dual with a soft pansystolic murmur at the left sternal edge. There was bilateral lower limb pitting oedema to his knees.

Resting electrocardiogram demonstrated sinus rhythm, paced rhythm (*Figure 1*). Transthoracic echocardiogram (TTE) showed normal left ventricular (LV) size and wall thickness with normal systolic function (global longitudinal strain -22%, ejection fraction 65.2%) (*Video 1*). The atria were normal sized and there were no significant valvular abnormalities. The pericardium appeared normal with no evidence of increased thickness. Pulmonary function tests demonstrated no evidence of restriction on spirometry. Positron emission

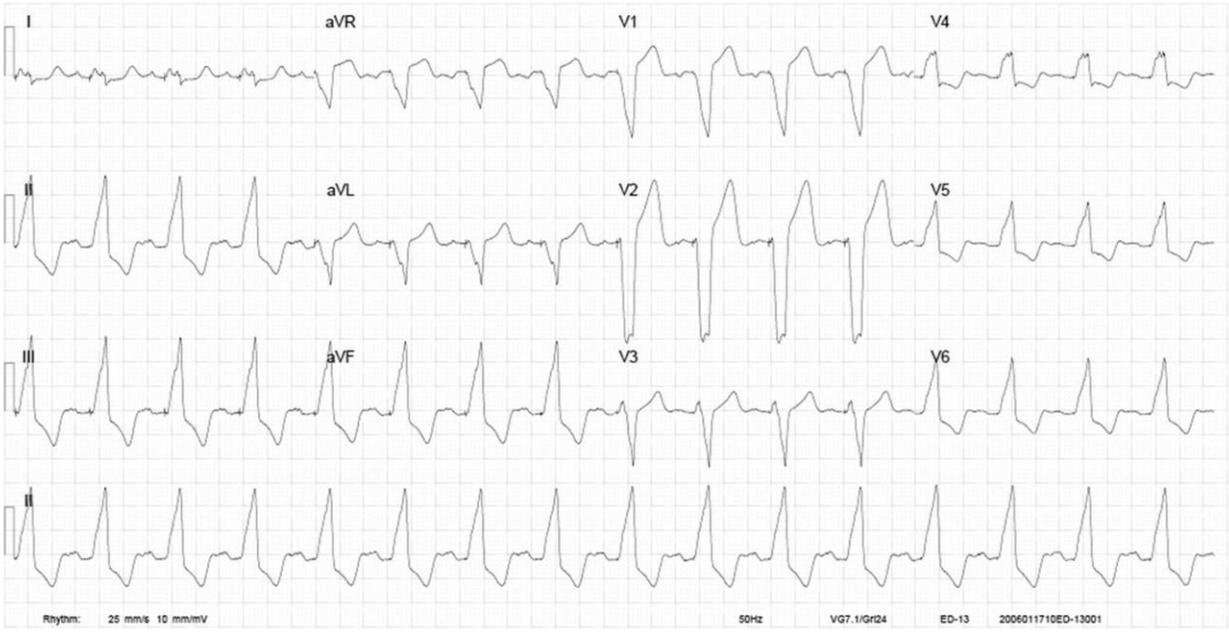
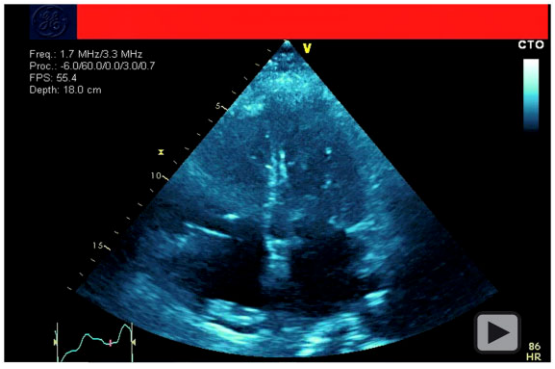


Figure 1 A 12-lead electrocardiogram from the first day of 5-day admission demonstrating sinus rhythm with paced rhythm.



Video 1 Patient 1 - Transthoracic echocardiogram demonstrating normal left ventricular size and wall thickness with normal systolic function.

tomography (PET) scan demonstrated no evidence of lymphoma recurrence.

Right heart catheterization revealed elevated right atrial pressures (16 mmHg), prominent y descent with mildly elevated pulmonary capillary wedge pressure and normal pulmonary artery pressures (*Figure 2*). Coronary angiography revealed in-stent restenosis of the ostial RCA drug-eluting stent with non-obstructive coronary artery disease in the left system (*Figure 3*). A high-resolution computed tomography (CT) of his chest found left deviation of the interventricular cardiac septum, suggestive of increased right heart pressures but no significant enhancement or thickening of the pericardium. Constrictive pericarditis was considered a differential diagnosis due to these haemodynamic findings. At a consequent heart team discussion, the consensus opinion was to proceed with a semi-urgent elective pericardiectomy and simultaneous bypass graft of his RCA. Our patient continued to require increasing loop diuretic titration in community follow-up for 1 month until the surgery due to worsening exertional dyspnoea.

Histopathological analysis of sections of the pericardium showed dense, sclerotic, fibrous tissue consistent with radiation-related changes. Ideally, a cardiac magnetic resonance imaging (MRI) would have been performed to assist in confirming radiation-related myocardial changes; however, the patient had a previous lumbar stimulator insertion which is a major contraindication.

Post-operatively, he was commenced on perindopril 2.5 mg, bisoprolol 2.5 mg, furosemide 40 mg twice daily, and spironolactone 25 mg once daily. At subsequent follow-up consultations with his cardiologist, there was gradual improvement in his symptoms and his neurohormonal-blockading agents and diuretics were able to be weaned. At follow-up 14 weeks after surgery, there was complete resolution of his original symptoms of exertional dyspnoea and no clinical signs of fluid overload. His weight stabilized at 83 kg, compared to 95 kg prior to the procedure.

Patient 2

A 37-year-old man was admitted to hospital for the management of coronary artery disease demonstrated on an outpatient CT coronary angiogram. This was in the context of a 2-month history of intermittent dull chest pain and dyspnoea on exertion.

Background medical history was significant for multiple endocrine neoplasia type 1, which was complicated by an insulinoma removed by partial distal pancreatectomy at age 9 and an atypical carcinoid of probably thymic origin, which was resected and followed by adjuvant

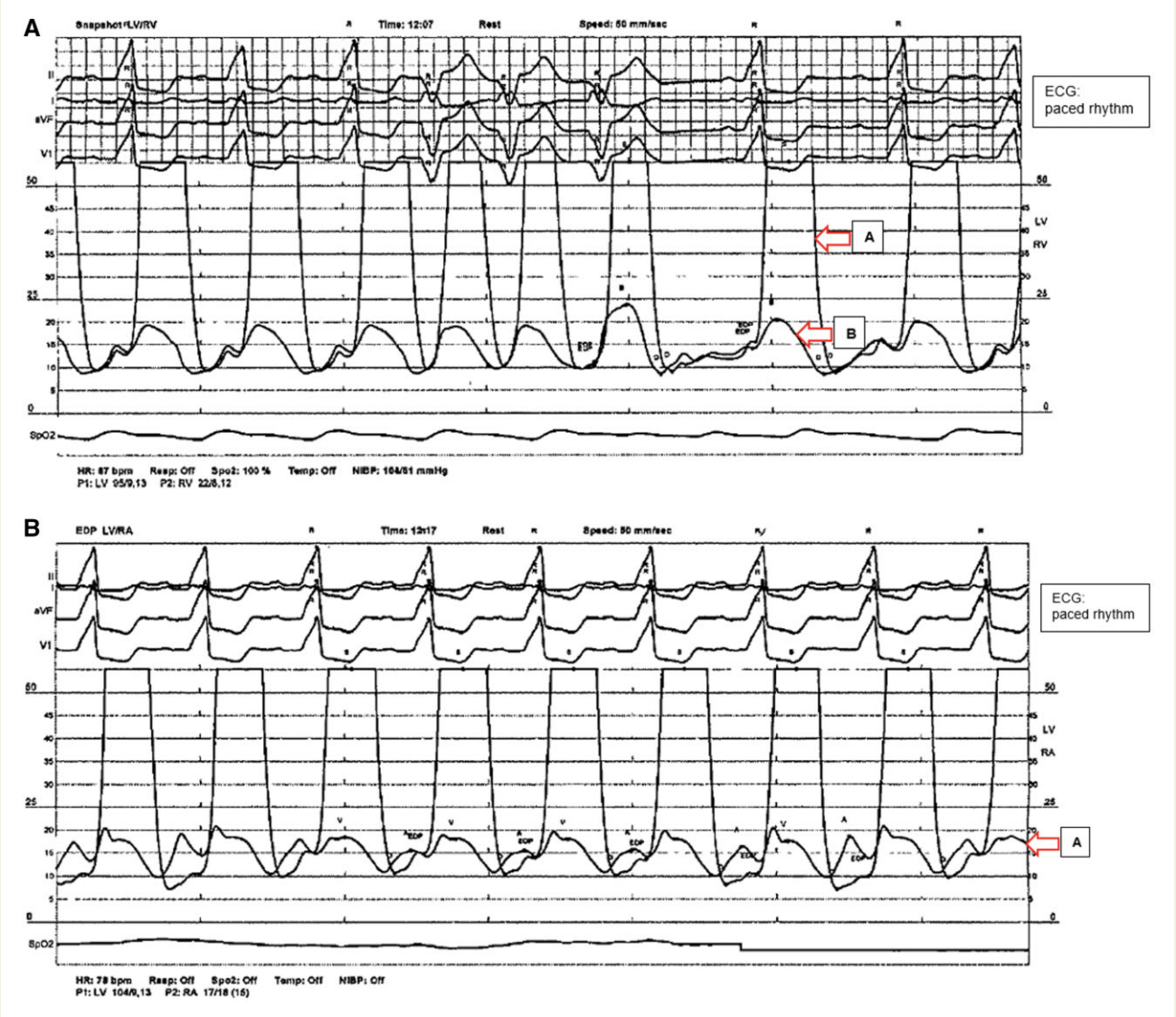


Figure 2 (*A*) Right heart catheterization showing (arrow A) left ventricular end-diastolic pressure compared to (arrow B) right ventricular end-diastolic pressure. (*B*) Right heart catheterization showing (arrow A) left ventricular end-diastolic pressure of 13 mmHg.

radiotherapy 60 Gy/30 F to the mediastinum at age 30. There was no significant family history of ischaemic heart disease. He was a life-long non-smoker, drank minimal alcohol, and had no other known risk factors.

On examination, he was tachycardic to 100 b.p.m. but otherwise haemodynamically stable (blood pressure at left arm 100/80 mmHg, left popliteal 150/80 mmHg). His JVP was not elevated. On auscultation, his chest was clear with dual heart sounds no murmurs. There was no evidence of peripheral oedema.

Resting electrocardiogram demonstrated sinus rhythm (*Figure 4*). Coronary angiography showed significant left main disease (95% stenosis) with 100% chronic total occlusion of the ostial left anterior descending coronary artery with collaterals from the RCA (*Video 2*). He also had proximal 90% stenosis of the circumflex artery. It also revealed bilateral subclavian artery stenosis (90% right and 90% left) (*Figure 5*) and an elevated LV end-diastolic pressure 50 mmHg. Carotid ultrasound showed bilateral vertebral artery flow abnormalities which may reflect the previous radiotherapy to the area. There was no flow limiting stenosis in the carotid arteries bilaterally. Transthoracic echocardiogram reported moderate segmental systolic dysfunction with prominent LV trabeculation (*Video 3*). He had a mildly dilated aortic root, probable bicuspid mildly thickened aortic valve and mild mitral regurgitation. Cardiac MRI was performed to determine myocardial viability and reported mild ischaemic LV dysfunction with apical infarction and near full thickness fibrosis of the apex. Sequential CT scans of his brain, neck, chest, abdomen, and pelvis identified no discrete lesions

or lymphadenopathy. It reported fibrotic changes in the left upper lobe consistent with post-treatment changes following radiotherapy. DOTA-PET scan showed a focus in the head of the pancreas and chromogranin A level was within normal range.

Our patient underwent uncomplicated bilateral percutaneous subclavian artery stenting (*Figure 6*) as he was symptomatic with dizziness. Both stents were Omnilink elite bare metal stent, left subclavian artery stent was 8.0 × 19 mm and right subclavian artery stent was 9.0 × 19 mm. He had return of normal blood pressure measurements to the upper limbs. Three days later, he had an intra-aortic balloon pump inserted and had coronary artery bypass grafting surgery with two grafts using the left long saphenous vein. The left internal mammary artery could not be visualized due to significant mediastinal fibrosis and hence not harvested. There were no pericardial adhesions or evidence of constriction. Post-operative recovery was uncomplicated, and his medications included aspirin 100 mg, rosuvastatin 20 mg, furosemide 40 mg, and metoprolol 25 mg twice daily. Furosemide was ceased 1-week post-discharge with resolution of fluid overload, while the other medications were to be continued long term. At 1-month follow-up, the patient was well and his angina and exertional dyspnoea had resolved with no post-operative complications. At 6-month follow-up with his cardiologist, he remained well with no cardiac symptoms.

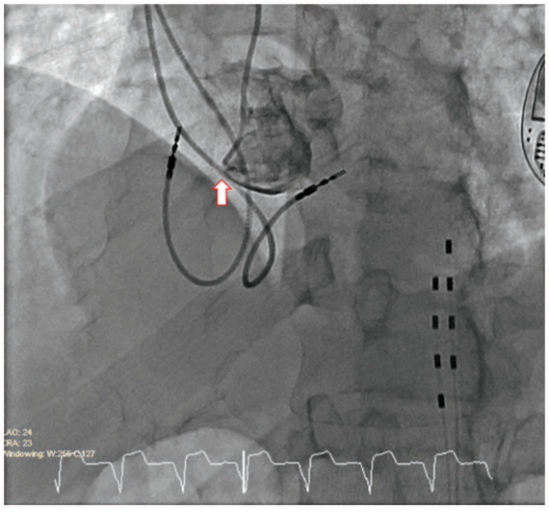
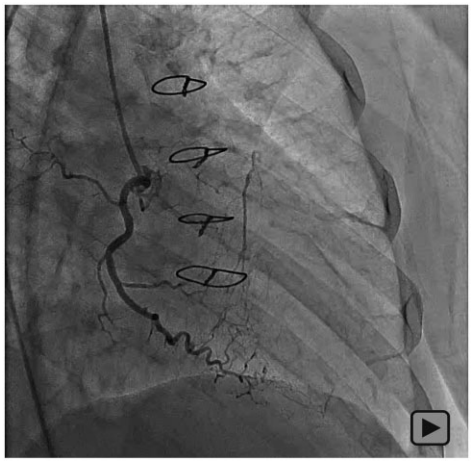


Figure 3 LAO/CRA non-selective shot showing chronic total occlusion of right coronary artery (arrow). *LAO: left anterior oblique; CRA: cranial.*



Video 2 Patient 2 - Right coronary artery and collaterals to chronic total occlusion of the left anterior descending artery.

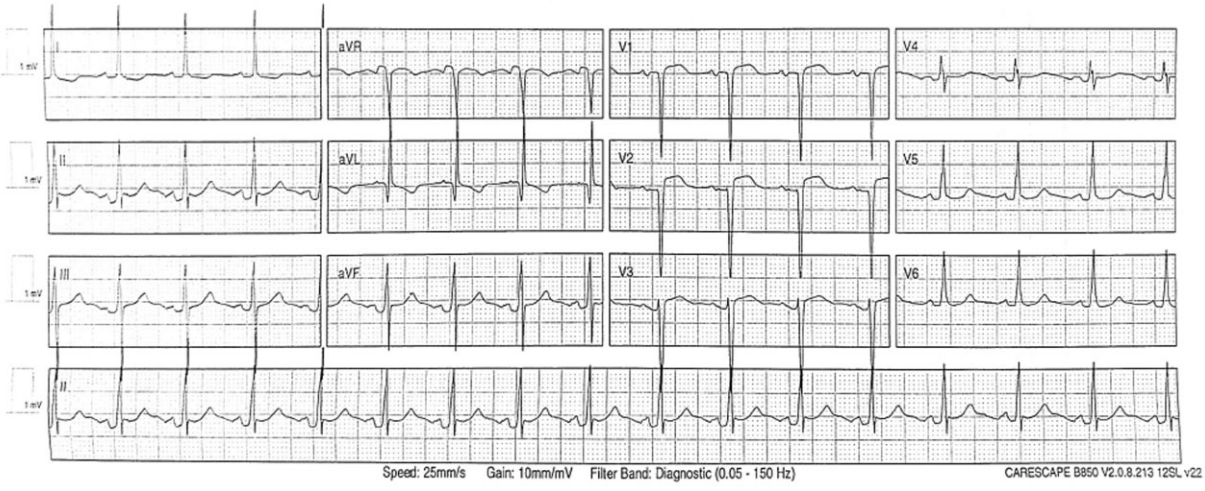


Figure 4 A 12-lead electrocardiogram demonstrating sinus rhythm.

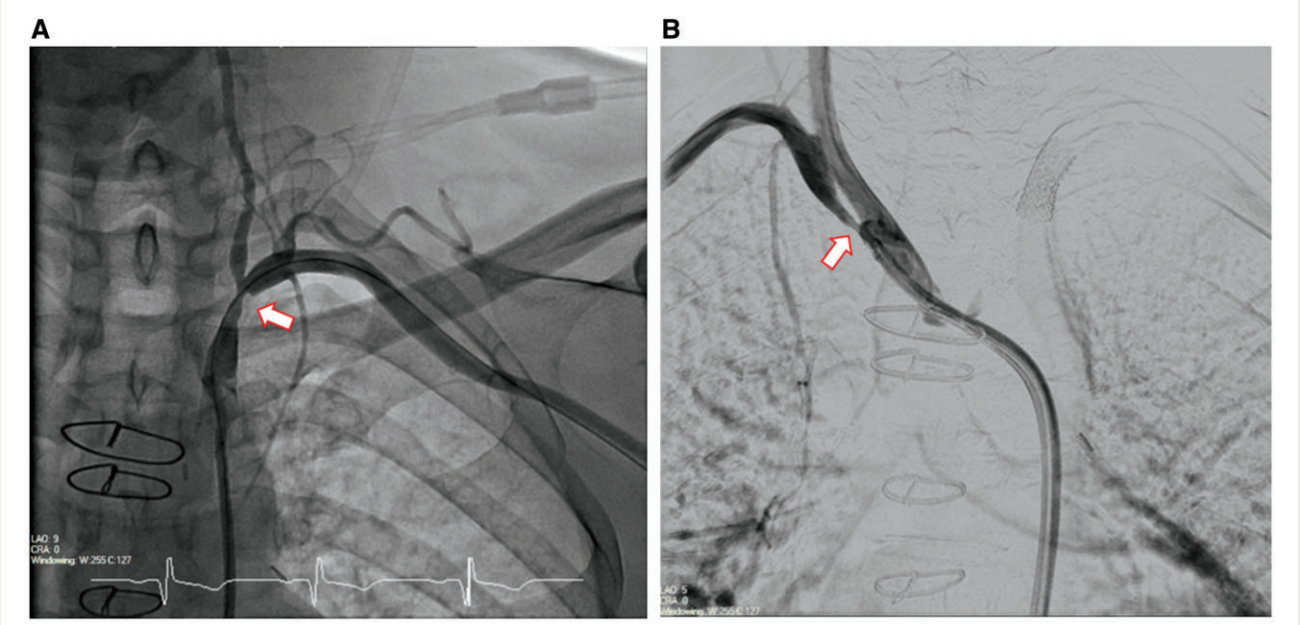
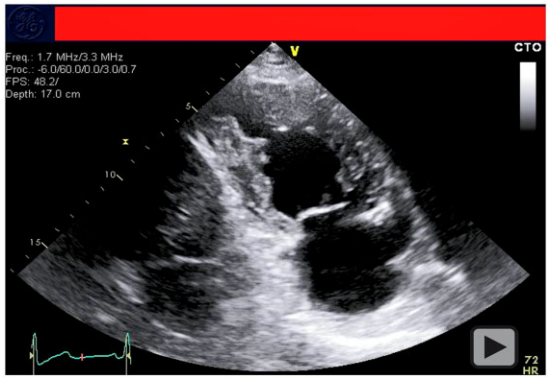


Figure 5 (*A*) Angiogram of Patient 2 demonstrating left subclavian artery stenosis (arrow). There is evidence of previous sternotomy from resection of an atypical carcinoid tumour (likely thymic in origin) in 2013. (*B*) Angiogram demonstrating right subclavian artery stenosis (arrow).



Video 3 Patient 2 - Transthoracic echocardiogram demonstrating moderate segmental systolic dysfunction with prominent left ventricle trabeculation.

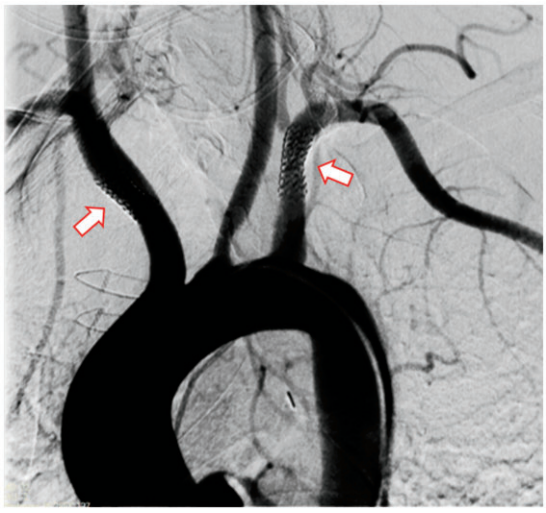


Figure 6 Aortogram post-bilateral percutaneous subclavian artery stenting (arrows).

Discussion

Diagnosing constrictive pericarditis on echocardiography and right heart catheterization

Fibrous thickening of the pericardium in constrictive pericarditis leads to loss of pericardial compliance. Consequently, LV filling is severely impaired, as diastolic filling halts abruptly during, or prior to, mid-diastole. Additionally, due to ventricular interdependence, the right heart volume expands via shifting of the interventricular septum. These features can be appreciated using echocardiography, which along with chest radiograph (CXR) and electrocardiogram, form the essential initial evaluation of constrictive pericarditis.[4,5]

Either M-mode or two-dimensional echocardiography can be used to assess for increased pericardial thickness, which can be seen in ~40% of patients.[6] Rightward movement of the interventricular septum can be seen transiently with septal bounce. Other appreciable features include: moderate biatrial enlargement, hypermobile atrioventricular valves, an abnormal contour between the posterior and LV and left atrial walls, and dilatation of the inferior vena cava and

hepatic veins.[7,8] Doppler echocardiography can be used in conjunction with other modes to visualize abnormal filling of the ventricles during early diastole, notably a sharp halt in early rapid filling.[7,8] It must be noted that no specific sign or combination of signs on M-mode is diagnostic of constrictive pericarditis[9] and pericardial calcifications cannot be assessed with echocardiogram.[10] Thus, a multimodal approach with CXR or CT may be required.

When echocardiography, cardiac CT, and/or MRI are non-diagnostic for constrictive pericarditis, invasive haemodynamic evaluation may be considered. Right atrial pressure is typically elevated, with prominent x and y descents of venous and atrial pressure tracings. Rapid early diastolic filling may be represented by 'square root' signs in the right ventricular (RV) and LV diastolic pressure tracings, and increased RV end-diastolic pressure, usually to a level one-third or more of systolic pressure.[4] As both ventricles are constricted in fibrous pericardium, LV and RV diastolic plateau pressure tracings can be equalized. Kussmaul's sign and a greater inspiratory fall in pulmonary capillary wedge pressure compared with LV diastolic pressure may be observed.[4] Pressure changes in the setting of increased ventricular interdependence can be seen as mirror-image discordance between RV and peak LV systolic pressures during inspiration.[11] In the case of Patient 1, the standard modalities used to assess for constriction on TTE were of limited use due to RV septal pacing (due to his pacemaker) and may also have been confounded by the chronic total occlusion of the RCA, which was causing mild segmental LV dysfunction. Furthermore, a cardiac MRI was not able to be performed to diagnose constriction due to his previous lumbar stimulator insertion.

As these patient factors made diagnosis difficult, right heart catheterization was required to identify the haemodynamic changes indicating possible constrictive pericarditis.

Management of constrictive pericarditis

Constrictive pericarditis is a potentially reversible cause of heart failure and can be treated using medical or surgical methods. Surgical pericardiectomy is the treatment of choice and was used in Patient 1.[12] It involves the complete resection of all fibrotic and calcified parietal pericardial tissue, and ideally the entire posterolateral and diaphragmatic pericardium as incomplete removal entails the risk of recurrence.[13] Surgical pericardiectomy relieves symptoms by restoring diastolic filling capacity and cardiac output, consequently reducing fluid overload. Symptom alleviation is most successful with early intervention before prolonged constriction leads to atrophy of the myocardium.[14]

Alternatively, medical management of constrictive pericarditis may be considered; however, efficacy is dependent on the aetiology. For example, in cases of inflammatory subacute constrictive pericarditis (which are often idiopathic or related to infection), treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is the mainstay of therapy.[12,13] A combination of NSAIDs, corticosteroids and/or colchicine can also minimize pericardial constriction by reducing inflammation.[15] Comparatively, in chronic cases of fibrosis including those induced by radiation, diuretic therapy can palliate symptoms. However, this is usually only partly effective due to progressive fibrosis.[13] Therefore, complete surgical pericardiectomy remains the only definitive treatment for chronic constrictive pericarditis, as seen in Patient 1.[14] Symptomatic cardiac failure may persist after successful pericardiectomy, due to remaining constriction or myocardial atrophy induced by prolonged constriction. In this situation, medical therapy with diuretics may play an important post-surgical role. This was apparent for Patient 1, with diuretics alleviating unresolved systemic and pulmonary fluid congestion post-surgical pericardiectomy.[14]

Coronary artery bypass grafting

Management of coronary artery disease secondary to mantle field radiation therapy generally involves coronary artery bypass grafting or percutaneous coronary intervention (PCI).[16] Given the young age of Patient 2 when he presented with severe coronary artery disease, his previous mantle radiation appears to be the precipitant. Coronary artery bypass grafting was preferred to PCI as it might have reduced the need for unplanned revascularization and, possibly, improved survival compared to PCI in this case.[16,17]

Assessment workflow for suspected cardiovascular complications after mantle field radiation

A multimodal diagnostic workup is suggested for patients presenting with suspected cardiovascular complications after mantle field radiation therapy, as in our two cases. This should include physical examination, electrocardiography and imaging (including echocardiography, cardiac computerized tomography, cardiac MRI, coronary angiography, and left and right heart catheterization).[18]

Lead author biography

Abhisheik Prashar is currently the Interventional Cardiology Fellow at St George Hospital in Sydney, Australia and hopes to continue his commitment to research and clinical excellence.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case series including images and associated text has been obtained from the patients in line with COPE guidance.

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