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Letter to the Editor
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An Unusual Case of Pericarditis

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INTRODUCTION

With the advent of immune checkpoint inhibitors (ICI) as a novel drug therapy for cancer patients, there is a growing number of patients who present with immune-related adverse events (irAEs). IrAEs can affect any system in the body including cardiologic manifestations. Although cardiac irAEs are rare, it is important to recognise these complications as they are often associated with significant morbidity and mortality. We present a rare case of pericarditis with pericardial effusion in a patient treated with pembrolizumab, which is an ICI for metastatic lung adenocarcinoma.

CASE

A 45 year old gentleman presented to the hospital with a 4 day history of central chest pain and dyspnoea. The pain was pleuritic in nature, worse on lying down and better whilst sitting upright. He could not lie flat due to the pain and had to recline in sleep for the past few days. This was associated with fever episodes of up to 39 °C. He had no respiratory symptoms or myalgia.

The patient had a 30 pack-year smoking history. He was currently being treated with pembrolizumab for metastatic lung adenocarcinoma after having failed two lines of conventional chemotherapy. He received 2 cycles of carboplatin and gemcitabine as first line therapy before proceeding to another 2 cycles of carboplatin and pemetrexed as second line treatment. The patient did not receive any radiotherapy treatment.

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His blood pressure was 120/80 mmHg with a pulse rate of 100 bpm and oxygen saturation of 98% on room air. Physical examination revealed dual heart sounds with no additional heart sounds. Auscultation of the lungs was clear. His abdomen was soft and non-tender and his calves were supple with no oedema.

His electrocardiogram (ECG) showed sinus tachycardia with a ventricular rate of 100 bpm and diffuse ST-segment elevation in most limb and precordial leads. There was PR-segment elevation in lead aVR and PR-segment depression in leads II, aVF, V5 and V6 (Figure 1A). His chest radiograph showed presence of a globular heart and clear lung fields.

Initial blood test results showed a haemoglobin level of 10.1 g/dL (normal 13.1-16.6 g/dL) and a raised total white blood cell count of 14×10^9/L (normal 3.8-10.0 $\times 10^9$/L). Renal and liver function were normal. Serum troponin I level was 15 mg/L (normal 0-39 mg/L). His C-reactive protein level was 210 mg/L (normal < 10 mg/L) while his erythrocyte sedimentation rate was 117 mm/hr (normal 1-7 mm/hr).

Transthoracic echocardiogram revealed a large pericardial effusion, fibrinous strands within the pericardial space and ventricular septal shift (Figure 1B). There was presence of mitral annulus reversus as well as respiratory variation in the mitral inflow, pulmonary venous and hepatic venous flow Doppler signals (Figure 1C-1D). The inferior vena cava was plethoric. These features are consistent with an effusive-constrictive physiology.

The patient underwent cardiac magnetic resonance imaging (MRI) which showed pericardial effusion with diffusely smooth, thickened and enhancing pericardium. There was no enhancing pericardial nodule. No myocardial oedema, fibrosis or infarction was seen (Figure 2A-2D).

Pericardiocentesis yielded heavily blood stained fluid that was negative for bacterial growth, mycobacterium tuberculous and malignant cells. Serum thyroid function test and serum anti-nuclear antibody level were normal.

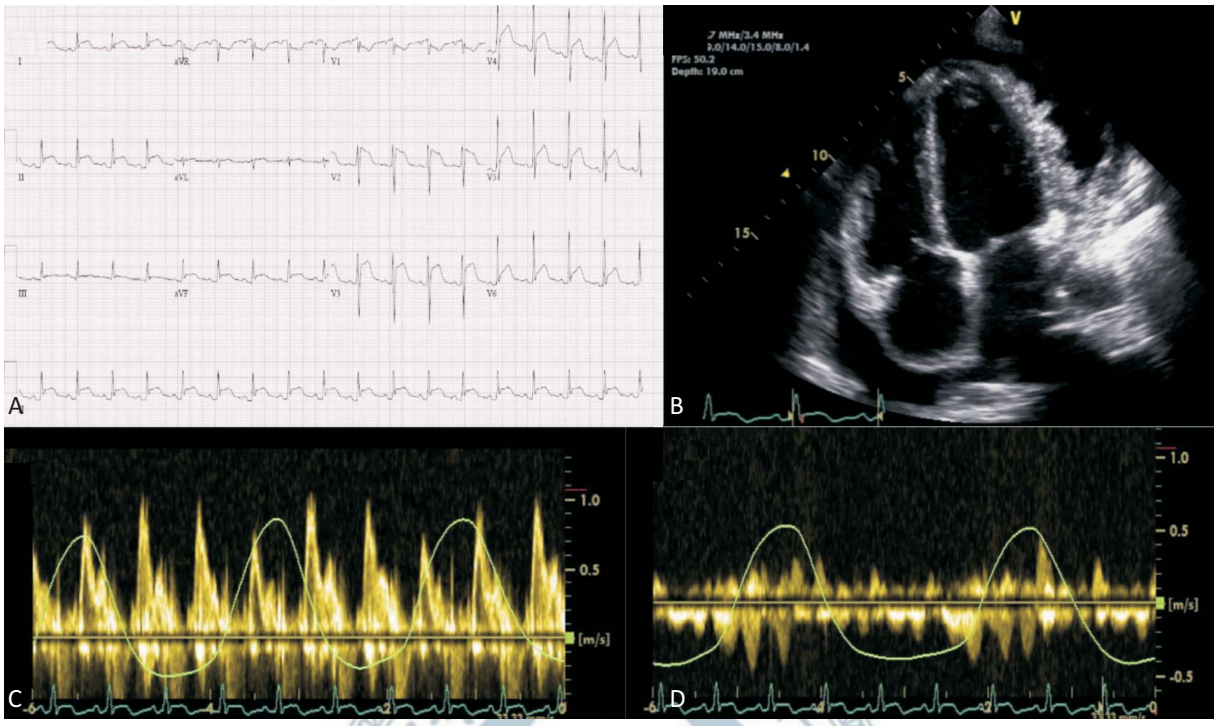

Figure 1. *(A) Electrocardiogram of patient showing PR-segment elevation in lead aVR and PR-segment depression in leads II, aVF, V5 and V6. (B) Apical 4 chamber view of transthoracic echocardiogram of patient showing a large pericardial effusion, fibrinous strands within the pericardial space. (C) Respiratory variation in the mitral inflow Doppler signal. (D) Respiratory variation in the hepatic venous flow Doppler signal.*

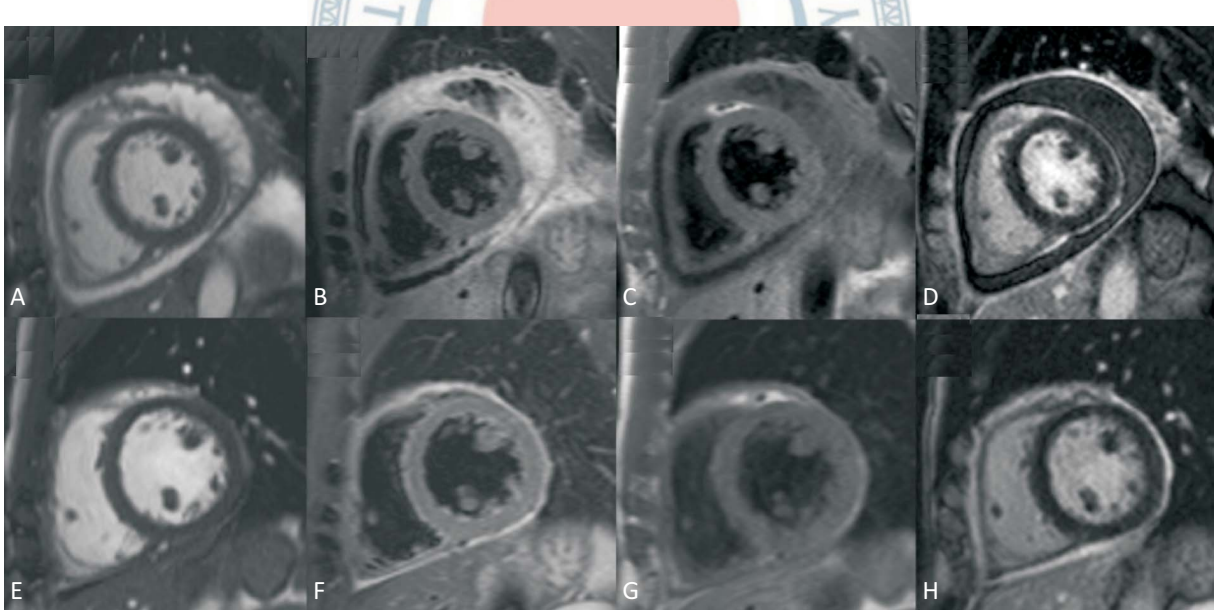

Figure 2. *(A) Still image from cine gradient echo short axis images of the heart show global pericardial effusion with thickened pericardium and fibrinous strands within the pericardial effusion. (B) T2-weighted short tau inversion recovery (STIR) image of the heart in short axis view show pericardial effusion. No myocardial oedema. (C) T1-weighted image of the heart in short axis view show pericardial effusion with thickened pericardium. (D) Late gadolinium enhancement image of the heart in short axis view show global pericardial effusion with diffuse smooth enhancement of the pericardium. (E) Still image from cine gradient echo short axis images of the heart with resolution of the pericardial effusion. (F) T2-weighted STIR image of the heart in short axis view with resolution of the pericardial effusion. (G) T1-weighted image of the heart in short axis view showing resolution of the pericardial effusion and thickened pericardium. (H) Late gadolinium enhancement image of the heart in short axis shows resolution of enhancement of the pericardium.*

The patient was diagnosed with acute pericarditis with pericardial effusion secondary to pembrolizumab. Pembrolizumab was discontinued, and he was prescribed ibuprofen, colchicine and oral prednisolone at 1 mg/kg/day with marked symptom improvement after 2 days. Repeat ECG showed resolution of the initial widespread ST-segment elevations. The patient was discharged with colchicine and a tapering dose of oral prednisolone that was reduced by 10 mg every week.

Repeat cardiac MRI (Figure 2E-2H) after completion of steroid treatment showed resolution of the pericardial effusion and pericardial thickening. Late gadolinium enhancement imaging did not show any pericardial enhancement. There was no myocardial oedema, fibrosis or infarction. He remained well with no complaints of pleuritic chest pain or dyspnoea during outpatient review. ICI was not restarted after discussion between the oncology and cardiology teams.

DISCUSSION

With the advent of ICI as a novel drug therapy for cancer patients, there is a growing number of patients who present with irAEs.[1] ICI work by blocking the immune checkpoint pathways which cancer cells use to disguise themselves as regular components of the human body.[2] As a result of ICI treatment, the body's innate immune system is able to target these foreign cancer cells and eliminate them. However, the body's natural cells are also targeted which result in the development of irAEs.

IrAEs most commonly involve the skin, gastrointestinal tract and endocrine system. Though cardiac manifestations of irAEs are rare (incidence < 1%),[1] they are associated with significant mortality and morbidity. Examples of cardiac irAEs include myocarditis, left ventricular dysfunction, arrhythmias, pericarditis and pericardial effusion.[1] The relationship between cardiac irAEs and the dose of ICI remains to be fully established. Cardiac irAEs typically occur after 3 cycles of ICI[3] but they may occur as early as after the first cycle or have a delayed onset even years after discontinuation of ICI therapy.[4]

ICI-mediated pericarditis predominantly affects men, especially in patients with lung cancer, and is often associated with thyroid dysfunction and pulmonary involvement (predominantly pleural effusion and pneumonitis).[5] Other common causes of pericarditis [such as viruses, bacteria (especially *Mycobacterium tuberculosis*), metabolic and autoimmune conditions, malignancy] need to be ruled out during the work-up of ICI-mediated pericarditis.[6] Patients with ICI-mediated pericarditis may be asymptomatic and present insidiously, and the time to clinical presentation can be variable.[7]

Successful treatment of irAEs depends on early recognition, prompt cessation of ICI and initiation of high-dose immunosuppression. Early collaboration between the cardiologist (preferably a cardio-oncologist) and oncologist is necessary when a patient is suspected to have a cardiac irAE. Permanent discontinuation of ICI is advised in patients with life-threatening cardiac irAEs (such as myocarditis). There are reports of patients with prior history of ICI-mediated pericarditis who underwent successful drug re-challenge with low-dose steroid cover and close cardiac surveillance.[8]

LEARNING POINTS

1. Pembrolizumab, which belongs to the class of ICI, is a rare but important cause of pericarditis and pericardial effusion, especially with its emerging role in the treatment of solid and haematological malignancies.
2. The diagnosis of ICI-mediated pericarditis and pericardial effusion is a diagnosis of exclusion; it requires thorough history taking, physical examination and investigations to rule out other more common aetiologies.
3. The mainstay of management is discontinuation of ICI and high-dose steroid therapy.

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None.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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