Cardiac Tamponade Associated with Pembrolizumab Therapy in Patient with Pneumonectomy for Lung Cancer

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ABSTRACT

A 57-year-old man with a history of right pneumonectomy for squamous cell lung cancer who presented with dyspnea and hypotension, was found to have pericardial effusion complicated by cardiac tamponade, associated with pembrolizumab therapy. Pericardiocentesis could not be safely attempted due to presence of right-sided mediastinal tissue shift in the setting of previous right pneumonectomy. The patient improved significantly with surgical placement of pericardial window. Analysis of the pericardial fluid was negative for malignancy and was consistent with acute inflammation. Pembrolizumab and other immune checkpoint inhibitors are associated with cardiovascular toxicity, including pericardial effusion and in rare cases, cardiac tamponade. Treatment of cardiac tamponade in post-pneumonectomy patients may be subject to anatomical limitations precluding percutaneous pericardiocentesis and requires early recognition as well as availability of surgical intervention.

KEYWORDS: immunotherapy-related adverse events, pembrolizumab, cardiac tamponade, post-pneumonectomy

INTRODUCTION

As immune checkpoint inhibitors (ICIs) such as pembrolizumab have become commonplace in oncology care, immunotherapy-related adverse events (irAE) in various organ systems have been described. Cardiovascular toxicity including pericardial effusion complicated by cardiac tamponade is one such immunotherapy-related adverse event.

CASE PRESENTATION

A 57-year-old man with chronic obstructive pulmonary disease, heavy tobacco use, and Stage IVB squamous cell lung cancer requiring right pneumonectomy, with metastatic spread to left lung and left femur, currently undergoing carboplatin, paclitaxel and pembrolizumab combination chemotherapy as well as radiation therapy presented to hospital complaining of one day of chest pain and shortness of breath. The patient reported pleuritic substernal chest pain, shortness of breath, and tachypnea. He reported low-grade temperatures and chills at home over two days. He endorsed mild nausea and decreased oral intake. He denied cough, sputum production, hemoptysis, and asymmetric lower-extremity swelling.

The patient was diagnosed with stage IVB squamous cell lung cancer three years prior to presentation and underwent right-sided pneumonectomy for his primary tumor followed by adjuvant chemotherapy which was aborted due to neuropathy. Two years later a recurrence of squamous cell carcinoma was diagnosed in the left lingula and left hip. Immediately prior to presentation the patient was initiated on radiation therapy to left lingula and left hip in addition to four cycles of carboplatin, paclitaxel, and pembrolizumab combination therapy followed by weekly pembrolizumab maintenance therapy.

On admission the patient's blood pressure was 116/53 mm Hg, heart rate was 128 beats/min, respiratory rate was 35, and oral temperature was 36.2°C. He was in moderate discomfort due to pleuritic chest pain and increased respiratory effort. Clinical examination revealed distant heart sounds without cardiac rub, and absent breath sounds on the right side. Bilateral pitting lower extremity edema was noted.

Initial laboratory and ECG results are noted in **Table 1**. Bilateral lower extremity dopplers were negative for deep vein thrombosis. CT angiography of the chest with pulmonary embolism protocol revealed lingular airspace disease at the site of known malignancy, circumferential pericardial effusion, and no evidence of pulmonary embolism.

Several hours after admission, the patient's blood pressure rapidly decreased to 82/38 mmHg. The patient was noted

Table 1. Initial Laboratory and ECG Results

Testing	Results
Basic metabolic panel	BUN 17mg/dl and creatinine 1.7 mg/dl
Complete blood count	White blood cell count 4.5 x10exp9/L, 72% neutrophils, 17.2% lymphocytes
Troponin	0.029 ng/mL (normal range: 0.006-0.060 ng/mL)
D dimer	773 ng/mL (normal range: 0-300 ng/mL).
SARS-CoV-2 and Respiratory pathogen panel	Negative for all viruses
Electrocardiogram	Normal sinus rhythm with normal QRS voltage, absence of electrical alternans

Figure 1. Plain radiograph of the chest demonstrating rightward shift of mediastinal structures.

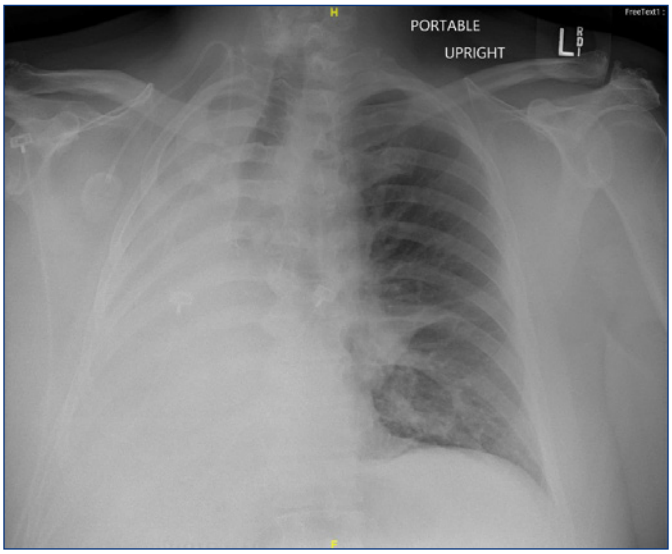


Figure 2. Echocardiogram image demonstrating moderate-large pericardial effusion (arrowhead) and right ventricle (arrow).

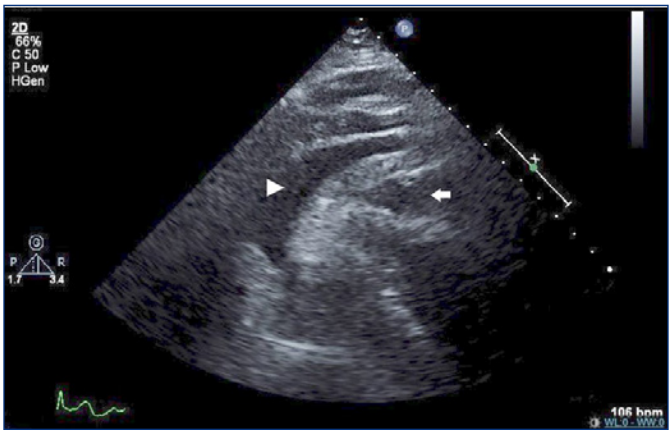


Figure 3. Echocardiogram image demonstrating right ventricular collapse in diastole consistent with presence of cardiac tamponade (arrow).

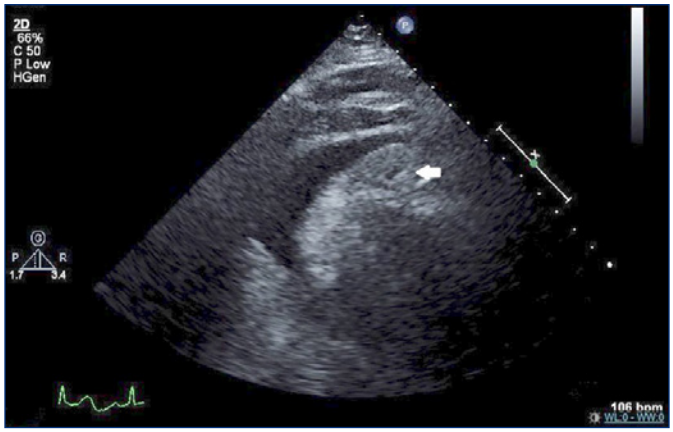
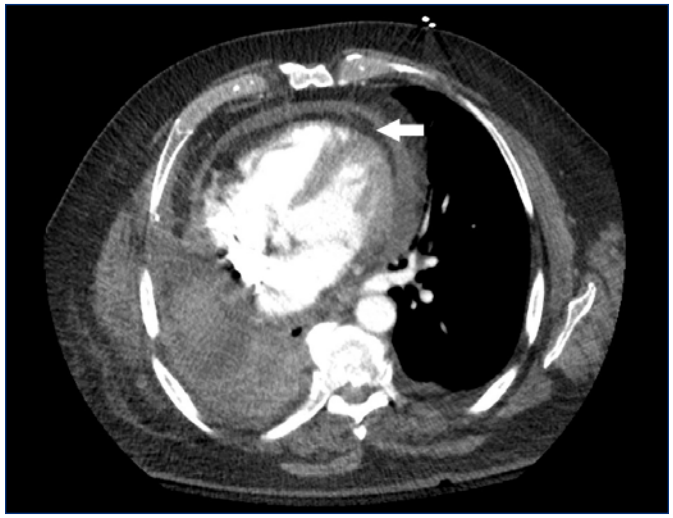


Figure 4. CT image of chest demonstrating pericardial effusion (arrow) and rightward shift of cardiac structures toward side of previous pneumonectomy.



to have pulsus paradoxus with a decrease in cuff pressure of 15mmHg with respirophasic variation. Urgent bedside echocardiography was performed. Despite the difficulty of obtaining echocardiographic windows due to the patient's displaced cardiac anatomy (**Figure 1**), the study revealed a moderate-large sized circumferential pericardial effusion with diastolic right ventricular collapse indicative of tamponade physiology (**Figure 2 and 3**).

The patient was initially considered for percutaneous pericardiocentesis and drain placement. However, due to the volume loss of the right lung with rightward mediastinal shift (**Figure 4**) there was no safe path to the pericardial space. The patient's liver lay between all peri-xiphoid approaches and the pericardium.

The patient underwent surgical placement of a pericardial window without complications. Two hundred mL of pericardial fluid was drained with normalization of blood pressure and improvement of symptoms. Pericardial fluid cytology revealed acute inflammation without presence of malignant cells on smear analysis. He was discharged from the hospital four days later in stable condition. Pembrolizumab therapy was discontinued, and the patient subsequently completed a course of radiation therapy. Follow up echocardiogram five weeks after pericardial window placement revealed only trace posterior pericardial effusion and preserved left ventricular function. The patient never developed recurrence of pericardial effusion on follow-up echocardiograms or CT after discontinuation of Pembrolizumab, reducing the likelihood that pericardial effusion was secondary to radiation or malignancy. The patient passed away one year later due to progression of his squamous cell lung cancer.

DISCUSSION

Immune checkpoint inhibitors (ICI), such as nivolumab and pembrolizumab, have garnered widespread use in oncology and are commonly associated with a variety of immune-related adverse effects including colitis, pneumonitis, hepatitis and endocrinopathies.[1] Pericardial effusions are also common in oncological care and, in lung cancer, where they may be related to pericardial metastases, chest radiation and ICI treatment immune related adverse effects.[1-4] In this case, a patient with Stage IVB squamous cell lung cancer undergoing pembrolizumab therapy presented with pericardial effusion and cardiac tamponade after four cycles of treatment. Pembrolizumab, a member of the class of ICIs, is a monoclonal antibody against programmed cell death protein 1, utilized in the treatment of advanced non-small cell lung cancer.[5,6] Cardiovascular complications of ICI therapy are a rare but important clinical presentation which must be promptly recognized by clinicians.

Immune checkpoint inhibitors have been reported to affect the cardiovascular system, leading to a variety of complications including pericardial effusion and cardiac tamponade, myocarditis, vasculitis and arrhythmia.[1-3] Pericardial effusions are likely to be observed within four months of ICI therapy initiation.[7,8] Oristrell et al described the first described case of cytology negative cardiac tamponade with pembrolizumab in 2018, which was treated with pericardiocentesis and corticosteroids.[4] Atallah-Yunes et al described a case of cytology negative pericardial effusion with pembrolizumab, which was also treated with pericardiocentesis and corticosteroids.[5] Pericardial fluid analysis tends to contain acute inflammatory cells and up to 20% may contain malignant cells.[9,10] Although the incidence of pericardial effusion in patients receiving ICIs is unknown, the reported rate of pericardiocentesis was 0.4% suggesting that hemodynamically significant pericardial effusion is an uncommon complication of ICI therapy.[3] There are 25 reported cases of pericardial effusion associated with ICIs, with at least three complicated by cardiac tamponade, since 2016.[2-12]

Clinical presentation for pericardial effusion complicated by tamponade includes pleuritic chest pain, dyspnea, hypotension and tachycardia followed by circulatory collapse.[13] Physical examination for presence of pulsus paradoxus, a fall in a patient's blood pressure during inspiration by greater than 10 mm Hg, provides a clinical clue to the presence of tamponade.[14-16] Echocardiographic examination may reveal pericardiac effusion, diastolic right ventricular collapse and systolic right atrial collapse.[16]

Pericardial effusions related to ICI use do not have an established mechanism of origin.[2] Immune checkpoint inhibitors may lead to immune system activation against micrometastases within the pericardium leading to T-cell infiltration as observed on biopsy samples of endocardial tissue, a concept known as pseudoprogression.[2,3] Other reports suggest an immune-mediated serositis, due to the presence of PD-1 and PD-L1 proteins on cardiomyocytes, manifest with lymphocytic predominance in tissue biopsy without evidence of malignancy.[3,7,9] It is suspected that ICI driven T cell deregulation leads to production of auto-antibodies by B lymphocytes and further T cell infiltration into affected tissues creating feedback loops of immune system activation and clinically significant presentations of cardiovascular toxicity.[2,4-5,11]

In cancer patients, who develop pericardial effusion while receiving ICI therapy, determining the likely cause is an essential component of prognosis and treatment. Malignancy and radiation therapy can be directly associated with pericardial effusion.[1,17] Neoplastic spread or direct extension of the tumor to the pericardium resulting in pericardial effusion despite ICI therapy carries a grim prognosis.[1-3,7] Radiation therapy has been largely associated with delayed pericardial manifestations, with most cases of pericardial effusion reported within 12 months of therapy completion.[1,17]

Guidelines from The American Society of Clinical Oncology recommend cautious continuation of checkpoint inhibitor therapy for most mild (Grade 1) organ system toxicities. Grade 4 immune related cardiovascular toxicities (such as cardiac tamponade) with severe decompensation call for discontinuation of ICI therapy and treatment with high-dose corticosteroids (1-2mg/kg of prednisone).[18] It should be noted that most reported cases avoided corticosteroids opting for instead for temporary or permanent ICI therapy discontinuation only.[2-3,6] Prognosis likely depends on the severity of cardiovascular toxicity, functional status and cancer stage. Survival at 600 days was reported as 29% in patients with pericardial effusion associated with ICI therapy.[3]

The patient's history of pneumonectomy and alteration of normal anatomy due to right-sided and superior displacement of the patient's intrathoracic and intrabdominal contents prevented the use of percutaneous pericardiocentesis and drain placement. The patient required surgical pericardial window creation with relief of tamponade symptoms. In one other reported case of pericardial tamponade in a patient who had undergone pneumonectomy, the sub-xiphoid approach to pericardiocentesis was abandoned due to risk of hepatic injury, and instead utilized an apex approach under echocardiographic guidance.[19]

Increased awareness of potential cardiovascular toxicities of immune checkpoint inhibitor therapy may lead to quicker recognition and initiation of appropriate management including pericardial drainage, cessation of the offending agent and consideration of corticosteroid use.

CONCLUSION

Pembrolizumab therapy is associated with cardiovascular toxicity including pericardial effusion and cardiac tamponade. It is important to consider cardiac effusions as a cause of chest pain or dyspnea in patients with a history of malignancy, radiation, or immunotherapy. Additionally, patients with a history of pneumonectomy are at risk of intrathoracic rearrangements of normal anatomy. This can make diagnosis and treatment of cardiac tamponade difficult as usual approaches to periocardiocentesis may be difficult to obtain.

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Disclosures

No conflicts of interest to report

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