Pembrolizumab induced cardiomyopathy: A Case Report

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Abstract

Background: Pembrolizumab is a humanized IgG4 antibody from the immune-checkpoint inhibitors (ICI) family that has been proven to improve clinical outcomes in many solid organ malignancies. Despite its great therapeutic results, this novel drug has undesirable side effects, including uncommon cardiac and neuromuscular adverse effects. **Case presentation:** The patient, a known case of hypertension, COPD, HFpEF and NSCLC presented with mild chest pain and shortness of breath on exertion for 5 days. His CT scan revealed no pulmonary emboli. His echocardiogram indicated an EF of 10-15%, worldwide hypokinesis, reduced RV function, and a moderately enlarged left atrium. He underwent coronary angiography, which revealed no obstructive lesions. He was managed with IV Lasix, IV methylprednisolone in hospital and prednisone, furosemide, metoprolol succinate, and lisinopril on discharge. He was prescribed spironolactone at his two-week follow-up. **Conclusion:** Pembrolizumab-induced cardiomyopathy is uncommon and should be treated with care because there is no cure.

Introduction:

Pembrolizumab is a humanized IgG4 antibody that disrupts the interaction between programmed cell death protein 1 (PD1) and programmed death-ligand 1 (PDL1)[1]. It belongs to the immune-checkpoint inhibitors (ICI) class, which has been shown to enhance clinical outcomes in a variety of solid organ cancers[2]. Despite positive therapeutic outcomes, this new medicine is associated with a slew of negative side effects. Pembrolizumab-related immune-related side effects include myocarditis and neuromuscular side effects are uncommon. However, there is growing evidence of an increased risk of ICI-related myocarditis. There is no clarity on diagnosis or therapeutic management that we are aware of. Myocarditis, cardiomyopathy, heart failure, and arrhythmias are all associated cardiotoxicities. The offending agent is usually stopped in the majority of cases of immune checkpoint inhibitor cardiotoxicity[3]. We discuss a case of a patient who developed cardiomyopathy as a result of pembrolizumab treatment and was successfully managed.

Case:

A 66-year-old male, a known case of hypertension, diabetes mellitus, heart failure with preserved ejection fraction (HFpEF), chronic obstructive pulmonary disease (COPD), and having metastatic non-small cell lung cancer (NSCLC) (TTF-1 positive, PDL1>50% positive) presented to the emergency department with the complaint of mild chest pain and shortness of breath on exertion for 5 days. The patient was in the usual state of health when he gradually started experiencing mild chest pain, suggesting musculoskeletal pain due to chronic cough predominantly accompanied by shortness of breath. He denied fever, nausea, vomiting, orthopnea, paroxysmal nocturnal dyspnea or leg swelling. The patient was diagnosed with lung cancer 2 months back, for which he was started on pembrolizumab infusion therapy with 3 doses over 6 weeks. He did not have any prior cardiac history. His previous echocardiogram showed a 50-55 percent ejection fraction with grade I diastolic dysfunction 4 months prior to the current presentation.

On examination, the patient was tachycardiac with a heart rate of 134 beats/min and blood pressure of 144/84 mm of Hg with oxygen saturation of 88%, requiring 4 liters of supplemental oxygen. On laboratory evaluation, his NT-proBNP level was 2585 pg/ml, while other vital laboratory parameters (WBC=4.4 B/L, Chloride=98 mmol/L, Co2=30 mmol/L, BUN=21 mg/dL, Anion-gap=13 mmol/L, Calcium=9.6 mg/dL, Magnesium=1.6 mmol/L, Protein Total=7.5 g/dL, Albumin= 4.2 g/dL, Bilirubin=0.7 mg/dL, Hb=8.6 gm/dL, ALT=43 IU/L, AST=37 IU/L, ALP=166 IU/L, Glucose=142 mg/dL, eGFR=67, Cholesterol Total=218 mg/dL, HDL=55 mg/dL, LDL=124 mg/dL, Triglycerides=194 mg/dL and PSA=0.4 ng/mL) were also checked. His EKG revealed sinus tachycardia, Q waves in leads V2 and V3 (anteroseptal infarct), and a low voltage QRS complex that did not differ from the prior one (Figure 1). His CXR showed pulmonary vascular congestion. In addition, his CT scan revealed no pulmonary emboli. His echocardiography revealed an EF of 10-15%, global hypokinesis, reduced RV function, and a moderately enlarged left atrium (Figure 2). He underwent coronary angiography, which revealed no obstructive lesions. A viral etiology of myocarditis was also ruled out in the laboratory workup. Cardiologists and oncologists identified the patient with pembrolizumab-induced cardiomyopathy due to the length of time since starting anti-tumor medication and the reduction in LV function.

The patient was initially treated with, IV methylprednisolone 125 mg daily for 3 days, IV Lasix 40 mg twice daily for 5 days, resulting in an 8-litre diuresis, before being released on oral prednisone 60 mg daily, furosemide 40 mg oral, metoprolol succinate 50 mg daily, and lisinopril 40 mg daily. He was advised to see cardiology and oncology on an outpatient basis. After two weeks of outpatient follow-up, he was started on spironolactone 25mg daily.

DISCUSSION

ICIs have remodeled cancer treatment, and their usage in oncology continues to expand in extent and usage. In this example, we look at a patient with NSCLC treated with pembrolizumab, an ICI that works by blocking the PD-1 receptor on cancer cells. The PD-1 receptor promotes cancer growth by inhibiting anti-tumor T-cell activity. As a result, ICI treatment that targets the PD-1 receptor restores the anti-tumor immune response[4,5]. However, the malignant cells are not the only ones affected by this selective targeting of PD-1 receptor expression. Consequently, it is relatively common for patients receiving immunotherapy to have an ICI-related adverse event (irAE); nonetheless, cardiac myocyte-related irAEs are linked with the highest mortality[6]. Numerous researches have elaborated on the cardio-protective effect of PD-1 in mitigating auto-immune mediated damage targeting cardiac myocytes, and it is thought that PD-1 suppression contributes to ICI-associated myocarditis. Nonetheless, the pathophysiological underpinnings of immunotherapy-related cardiotoxicity are unknown, and further study is needed[7].

Although reports indicate a 0.1–1% incidence rate of ICI-associated myocarditis, real incidence is likely underreported due to imprecise diagnostic tests, varied clinical presentation, and lack of awareness[8]. The difficulty of screening and identifying people at risk for developing an irAE is exacerbated by such obstacles. Despite these obstacles, individuals with ICI-associated myocarditis have reported death rates of 25–50% [8]. As a result, early detection and diagnosis are critical for reversing the potentially deadly effects of cardiotoxicity.

The majority of patients report adverse cardiac events occurring 3–6 months after therapy, while delayed immune effects have been recorded up to 2 years after treatment[9]. Patients with ICI-associated myocarditis may present with cardiac symptoms, although these may be vague and nonspecific[6], as in this case report. While the presenting symptoms of ICI-associated myocarditis vary, recent research found that approximately 25% of patients may exhibit myositis symptoms such as muscular weakness, increased creatine kinase levels, and ptosis[6]. Because patients are not routinely checked for myocarditis while on ICI medication, a diagnosis of ICI-associated myositis necessitates a careful cardiac examination[6]. An EKG, troponin measurements, and echocardiography are proposed as diagnostic tools if anticipated cardiotoxicity. According to a study of 35 patients with ICI-associated myocarditis, 89 percent had abnormal EKG findings such as tachycardia, ST-segment abnormalities, and QT prolongation, among other abnormalities. On echocardiography, 94% had an elevated troponin level, 51% had a preserved left ventricular ejection fraction (LVEF), and 35% had profound LV dysfunction[10].

Studies advocate discontinuing ICI therapy as soon as possible to mitigate the toxicity of ICI-associated myocarditis, starting corticosteroids and immunosuppression[8]. However, due to the low frequency of ICI-associated myocarditis, there is a paucity of relevant research to advise proper treatment. All patients with ICI-associated myocarditis should have their ICI therapy terminated, and steroid therapy instituted, with cardiac stability and treatment response driving further management[8].

In extreme situations, further immunosuppressive medications such infliximab may be required. Mycophenolate mofetil (MMF) or tacrolimus might be used in individuals who have high-grade myocarditis that is not responding to steroids[8]. ICIs may be the only way to improve overall survival in many patients with NSCLC; nevertheless, resuming ICI therapy after a myocarditis episode is contentious. For example, following re-challenge, 55 percent of patients with various IrAEs acquired a new or recurrent IrAE, according to research by Simonaggio et al., and the authors advise avoiding re-challenge in the case of ICI-related myocarditis[2]. In situations of mild myocarditis, Ganatra et al. recommend restarting ICI therapy if no symptoms of recurrence have been seen after one month of monitoring. Patients without signs of left ventricular dysfunction or troponin increase are included in this group[3].

Conclusion

In conclusion, we provide a case of pembrolizumab-induced cardiomyopathy, a rare treatment-associated side effect with no proven cure. Reintroducing ICI treatment after efficient management of myocarditis is under study worldwide as it is one of the most promising medications for improving survival in patients with NSCLC and other solid tumors. However, more research is needed to find the best patient features for reintroducing ICI treatment safely while reducing the risk of recurrent myocarditis.

References:

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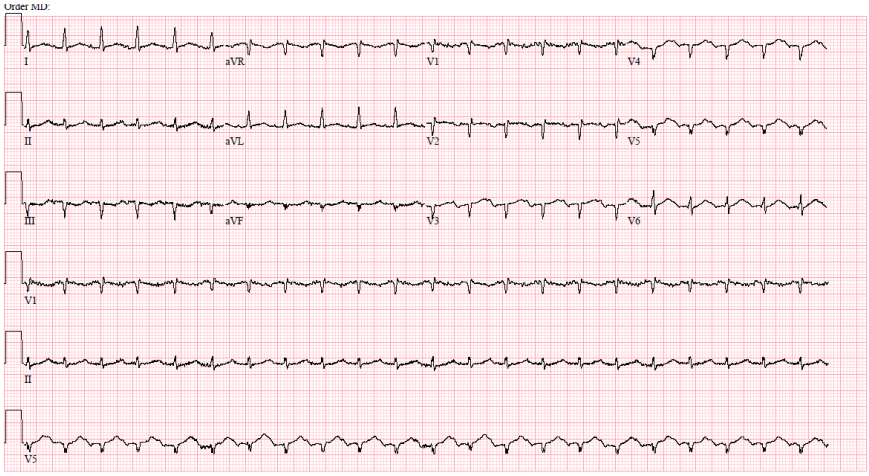
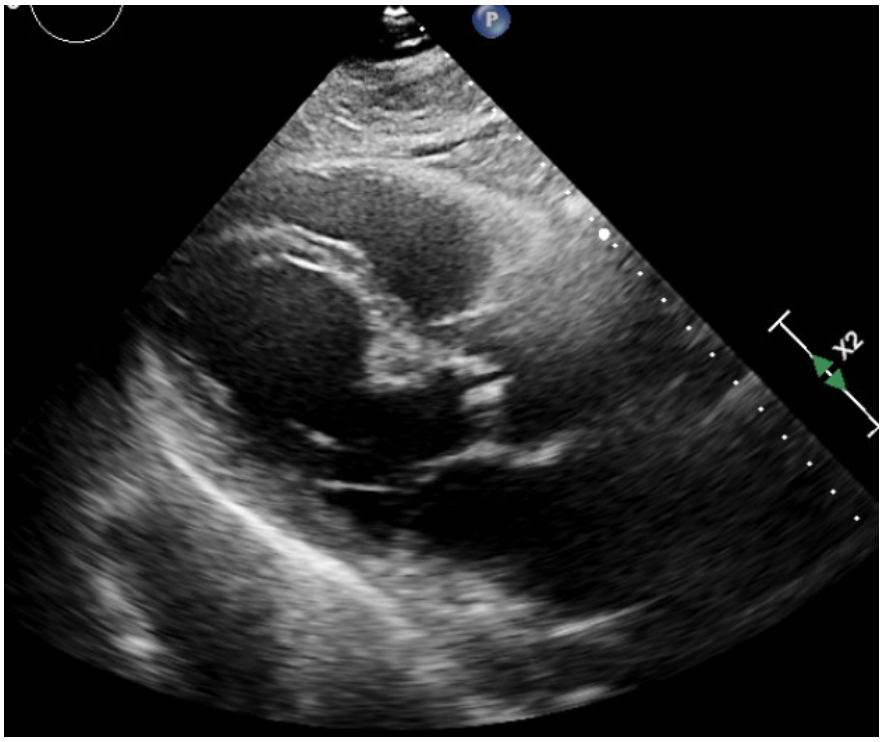
Figure 1



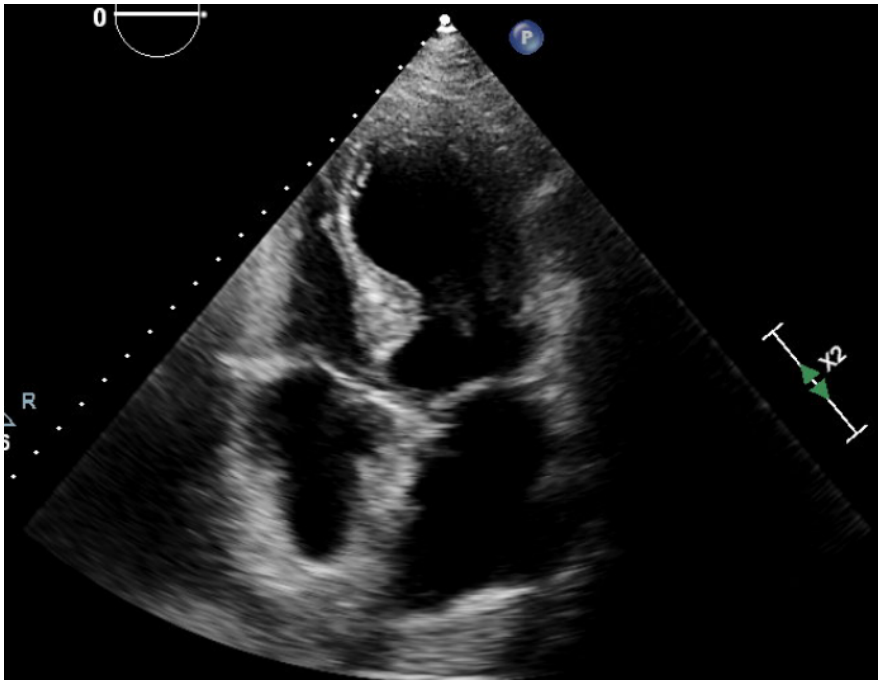
The patient's EKG showing sinus tachycardia, Q waves in leads V2 and V3 (anteroseptal infarct), and a low voltage QRS complex.

Figure 2

2a



2b



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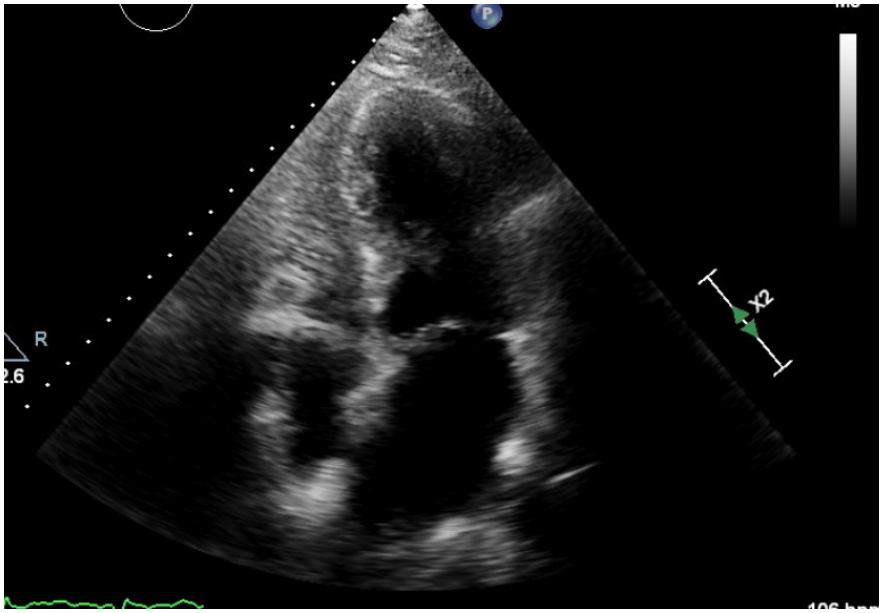
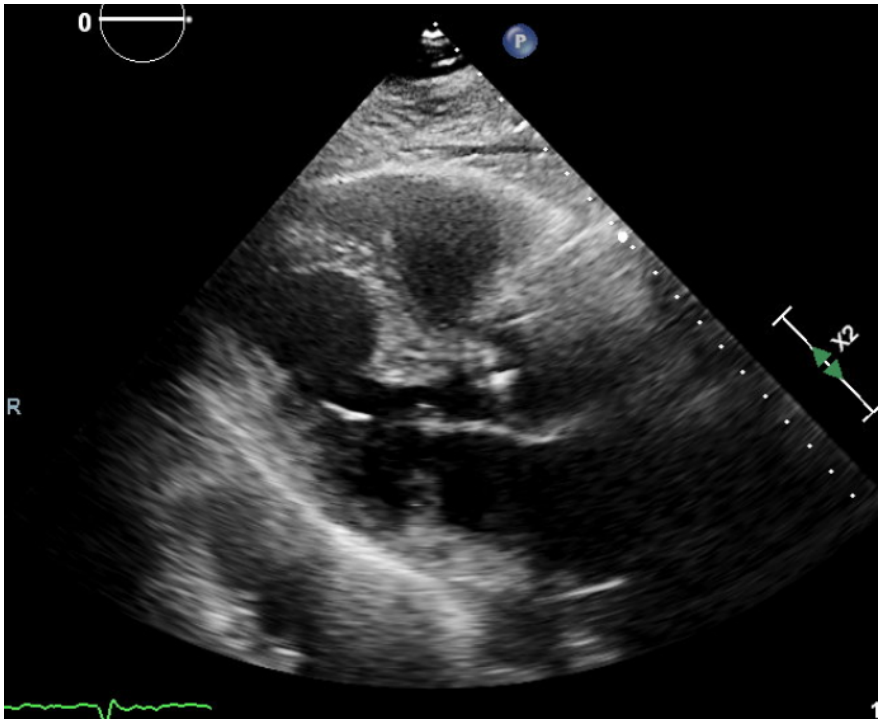


2d



2a and 2b: diastolic echo scan

2c and 2d: systolic echo scan

Echocardiographic scans of patient demonstrating an ejection fraction of 10-15%, global hypokinesis, reduced RV function, and a moderately enlarged left atrium.