CASE REPORT

New drugs and new toxicities: pembrolizumab-induced myocarditis

Faisal Inayat,[1] Muhammad Masab,[2] Sorab Gupta,[2] Waqas Ullah[3]

[1]Allama Iqbal Medical College, Lahore, Pakistan
[2]Einstein Medical Center, Philadelphia, Pennsylvania, USA
[3]University of Arizona, Tucson, Arizona, USA

Correspondence to
Dr Waqas Ullah,
waqasullah.dr@gmail.com

Accepted 3 January 2018

SUMMARY

Pembrolizumab is an immune checkpoint inhibitor that significantly improves clinical outcomes in numerous solid organ malignancies. Despite successful therapeutic responses, this new drug comes with a constellation of adverse reactions. Herein, we chronicle the case of a patient with metastatic non-small-cell lung cancer treated with pembrolizumab. After two cycles, he developed new-onset dyspnoea on exertion. Electrocardiogram showed idioventricular rhythm with diffuse ST-segment elevations. Echocardiography revealed severe biventricular cardiac dysfunction. Based on diagnostic workup and exclusion of probable aetiologies, the patient was diagnosed with pembrolizumab-induced myocarditis. The treatment was initiated with corticosteroids and guideline-conform heart failure therapy. He demonstrated a marked clinical response with resolution of congestive heart failure symptoms. This article summarises the clinical evidence regarding the epidemiology, pathophysiology, clinical features, diagnostic modalities and management of patients with pembrolizumab-associated myocarditis. In addition, it highlights that programmed death receptor-1 inhibition can cause a spectrum of autoimmune adverse events requiring clinical monitoring and periodic screenings.

BACKGROUND

Immune checkpoint inhibitors have significant anti-tumour effects in multiple tumour types.[1] So far, the main checkpoints that have been targeted by immunotherapy are cytotoxic T-lymphocyte activator-4 (CTLA-4) and programmed-death-1 (PD-1) and its ligand programmed death ligand 1 (PD-L1). Nivolumab and pembrolizumab are anti-PD-1 monoclonal antibodies whereas ipilimumab is an anti-CTLA-4 monoclonal antibody.[2] Although a variety of immune-related adverse reactions have been reported following CTLA-4 and PD-1 inhibitors, cardiotoxicity is remarkably rare.[2 3] Therefore, a high degree of awareness is necessary to detect this rare complication in patients on therapy with these agents in order to institute appropriate treatment in a timely manner.

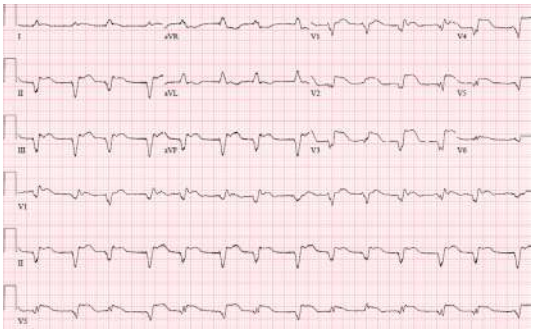

Figure 1 ECG showing idioventricular rhythm with diffuse ST-segment elevations.

CASE PRESENTATION

A 74-year-old man with a medical history of hypertension, cerebrovascular accident, metastatic non-small-cell lung cancer (NSCLC) (stage IV, poorly differentiated adenocarcinoma, EGFR/ROS/ALK-negative and PD-L1 positive) presented to the Emergency Department with dyspnoea on exertion for 3 days. He denied chest pain, orthopnoea or paroxysmal nocturnal dyspnoea. The patient did not have a history of cardiac dysfunction, autoimmune disorders or paraneoplastic syndrome. For stage IV adenocarcinoma, he received four cycles of carboplatin and pemetrexed followed by maintenance pemetrexed, but the patient showed disease progression. He was subsequently started on second-line chemotherapy with intravenous pembrolizumab (Keytruda, Merck, Whitehouse Station, NJ, USA), 2 mg/kg every 3 weeks. However, he developed dyspnoea on exertion and was admitted to our medical centre 19 days after completing the second cycle of pembrolizumab therapy.

INVESTIGATIONS

Physical examination was unremarkable. ECG showed idioventricular rhythm with diffuse ST-segment elevations (figure 1). Bedside echocardiogram was notable for left ventricular ejection fraction (LVEF) of less than 30% with global hypokinesia. Laboratory evaluation revealed brain natriuretic peptide level at 1213 pg/mL (normal, <100 ng/mL) and troponin peaked at 75 ng/mL (normal, <0.01 ng/mL). Serum creatinine 2.4 mg/dL (normal, 0.6–1.2 mg/dL), alanine aminotransferase 153 IU/L (normal, 7–55 IU/L) and aspartate aminotransferase was 332 IU/L (normal, 8–48 IU/L). Plain chest radiograph showed cardiomegaly with clear lung fields. On emergent cardiac catheterisation, left anterior oblique cranial view of left coronary angiography showed coronary vessels without any obstructive disease (figure 2).

Check for updates

To cite: Inayat F, Masab M, Gupta S, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-223252

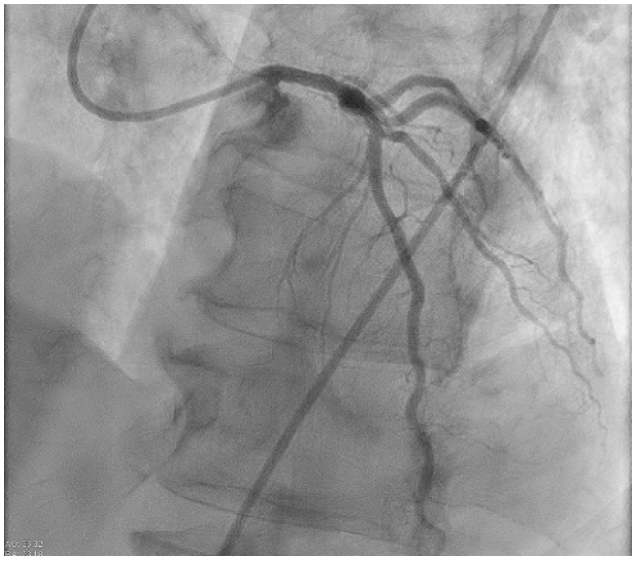

Figure 2 Coronary angiography showing no obstructive disease in the cranial view of left anterior oblique coronary artery.

Similarly, right anterior oblique cranial view of right coronary angiography also showed clean coronary vessels (figure 3).

The patient was then admitted to the coronary care unit. He did not have any symptoms suggestive of enteroviruses, adenoviruses, parvovirus B19, H1N1 influenza and human herpesvirus 6 infections. Subsequently, an official echocardiogram revealed global hypokinesis of right and left ventricles with an LVEF of <30% (figure 4). The troponin peaked at 75 ng/mL on admission continued to drop down to 34 ng/mL. For his severe right ventricular dysfunction, a ventilation–perfusion study was performed, which showed a low probability of pulmonary embolism. For further evaluation of cardiac function, cardiac MRI was planned; however, the patient refused.

DIFFERENTIAL DIAGNOSIS

On presentation, the differentials were broad. ST-segment elevation myocardial infarction, early repolarisation, pericarditis and myocarditis were considered plausible. Based on laboratory, cardiac catheterisation and echocardiography findings, these probable causes of idioventricular rhythm and new-onset biventricular systolic dysfunction were systematically ruled out. Hence, pembrolizumab-induced myocarditis was considered the likely aetiology in our patient.

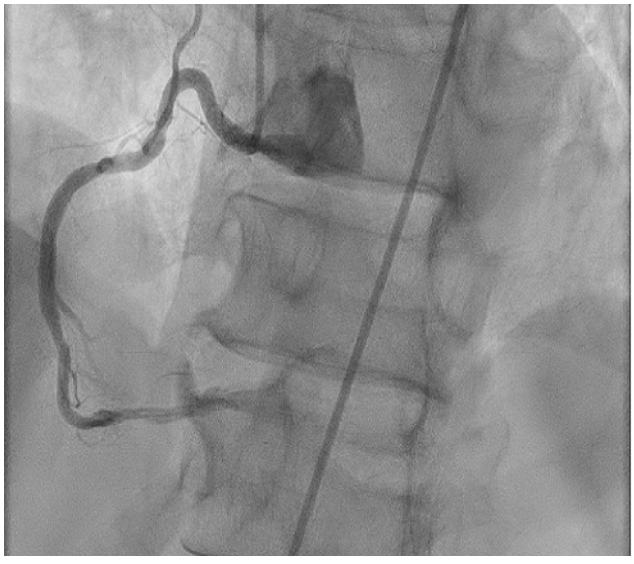

Figure 3 Coronary angiography showing no obstructive disease in the cranial view of right anterior oblique coronary artery.

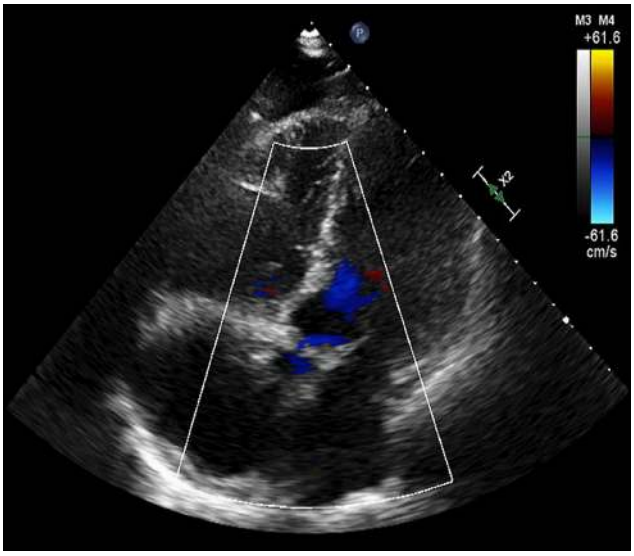

Figure 4 Apical four-chamber view of heart on transthoracic echocardiography showing global hypokinesis of right and left ventricles.

TREATMENT

Aspirin, clopidogrel and 4000 U of heparin were administered in the Emergency Department. The treatment of pembrolizumab-related myocarditis was initiated with 1 mg/kg/day oral prednisone therapy. Acute kidney injury and hepatic transaminitis improved with corticosteroids. While in the coronary care unit, he had occasional runs of non-sustained ventricular tachycardia for which the patient was generally asymptomatic and was started on metoprolol succinate 50 mg/day.

OUTCOME AND FOLLOW-UP

After initiation of steroids, the patient remained haemodynamically stable and his heart failure symptoms resolved. He was discharged on prednisone 80 mg/day (total daily dose: 1 mg/kg). The plan was to taper it down by 10 mg every week. He was educated to follow-up with cardiology and oncology in the outpatient department. No other specific antitumour therapy was initiated at the time. However, after 2 weeks, prednisone therapy was discontinued as he was made comfort care at an in-patient hospice.

DISCUSSION

Pembrolizumab is a PD-1 immune checkpoint inhibitor that has revolutionised cancer therapeutics.[1] This novel drug has significantly increased overall survival rates in patients with melanoma, NSCLC, renal cell cancer, urothelial carcinoma, Hodgkin's lymphoma, head and neck squamous cell carcinoma, Merkel cell carcinoma and microsatellite instability—high or mismatch repair-deficient cancer.[2] Although this medication is overall well tolerated, several immune-mediated adverse events have been documented. We reviewed the pertinent literature for the general toxicity profile of pembrolizumab with a special emphasis on its cardiotoxicity.

Table 1 Literature review on pembrolizumab-associated cardiotoxicity

Authors	Publication year	Age/ gender	Tumour type	Clinical presentation	Dose of pembrolizumab	Cycles of pembrolizumab received	Comorbidity	Echocardiography findings	Diagnosis	Treatment	Clinical outcome
Läubli *et al*[12]	2015	73/F	Metastatic melanoma	Progressive, severe dyspnoea	2 mg/kg every 3 weeks	5	No prior cardiac disease	Severely impaired LVEF of 30% with marked ventricular dys-synchrony	Myocarditis	Candesartan, bisoprolol, spironolactone, torsemide and prednisone 2 mg/kg	Recovered
Heinzerling *et al*[13]	2016	88/M	Metastatic melanoma	Syncope while shopping	NA	9	Coronary artery disease with no culprit stenosis on angiography	Akinesis of the apex, a reduced LVEF of 45% similar to takotsubo cardiomyopathy	Cardiac arrest	High-dose intravenous corticosteroids (125 mg)	Recovered
The present report	2017	74/M	NSCLC	Dyspnoea on exertion	2 mg/kg every 3 weeks	2	No prior cardiac disease	Global hypokinesis of right and left ventricles with LVEF <30%	Myocarditis	Aspirin, clopidogrel, 4000 U of heparin, metoprolol succinate and prednisone 1 mg/kg	Recovered

F, female; LVEF, left ventricular ejection fraction; M, male; NA, not available; NSCLC, non-small-cell lung cancer.

A structured literature search of the medical databases consisting of MEDLINE and PubMed (National Library of Medicine, Bethesda, MD, USA) was conducted. Search criteria consisted of terms, including 'pembrolizumab', 'myocarditis', 'adverse reaction', 'PD-1'', 'immune checkpoint inhibitors' and 'cardiomyopathy', which helped retrieving several accessible articles. A comprehensive review of the relevant publications revealed fatigue, rash, pruritus, arthralgia, amylase elevation and diarrhoea as the most common adverse reactions.[3] These were usually mild and were not considered as treatment limiting in most of the patients. In one study, only 12% of the recruited patients experienced grade 3 or 4 adverse reactions, such as autoimmune hepatitis, maculopapular rash and pancreatitis.[3] In another study on pembrolizumab treatment in patients with NSCLC, adverse events of grade 3 or higher were reported in 9.5% of patients. Significant inflammatory or immune-mediated reactions included infusion-related reactions (3.0%), hypothyroidism (6.9%) and pneumonitis (3.6%).[4] Furthermore, newer reports described notable toxicities, such as type 1 diabetes mellitus,[5] pancytopenia,[6] colitis,[7] keratoacanthomas,[8] scleroderma,[9] myasthenia gravis[10] and uveitis.[11] In terms of cardiotoxicity, two case reports are available in the published literature. One patient developed myocarditis and the other was diagnosed with cardiac arrest.[12 13] It is notable that both of these patients received pembrolizumab for melanoma. To our research, this report represents the first case of NSCLC, treated with pembrolizumab, who developed severe heart failure following pembrolizumab-induced myocarditis. The available data on epidemiology, clinical characteristics, diagnosis and management of patients with pembrolizumab-related myocarditis are presented (table 1).

Läubli *et al*[12] described a 73-year-old Swiss woman with metastatic uveal melanoma treated with pembrolizumab. She developed autoimmune myocarditis that complicated to severe heart failure. Echocardiographic studies revealed a severely impaired left ventricular function. Laboratory evaluation for the cardiotropic viruses was negative. Histopathological analysis of myocardial biopsy was remarkable for lymphocytic infiltration with a predominance of CD8 positive cells and a reduction of FOXP3 positive regulatory T cells. In a report by Heinzerling *et al*,[13] an 88-year-old man with a history of coronary artery disease received pembrolizumab treatment for metastatic melanoma and subsequently developed cardiac arrest. He showed a remarkable response to high-dose systemic corticosteroids. Although the patient was symptom free, pre-existing cardiac disease was present when he was initiated on pembrolizumab. Therefore, this drug possibly resulted in worsening of his cardiac functioning that culminated in cardiac arrest. In our patient, ECG and echocardiography revealed idioventricular rhythm with diffuse ST-segment elevations with an LVEF of less than 30%. Pembrolizumab-associated myocarditis was considered as the most probable diagnosis in the light of diagnostic investigations and exclusion of likely causes. The clinical response to corticosteroid therapy was excellent. However, a myocardial biopsy was not performed.

Although reports on ipilimumab and nivolumab-related cardiologic adverse events are available in the literature, the exact pathogenesis of myocarditis secondary to PD-1 inhibitors is unknown.[13 14] The histopathological examination of tumours and autoimmune lesions following therapy with immune checkpoint inhibitors usually demonstrate effector CD8 T-cell invasion and reduction of regulatory FOXP3 positive T-cells. Similar histopathological findings were noted in the case report by Läubli *et al*.[12] Bench research has shown that fatal myocarditis was developed in the mice who were genetically predisposed to systemic autoimmunity due to PD-1 deficiency.[15] In the cardiac tissue of those mice, infiltration of CD4 and CD8 positive T-cells, and myeloid cells was noted along with a remarkable production of autoantibodies against cardiac myosin. Therefore, evidence suggests a major role of PD-1 in protecting the cardiac tissue from injury related to T-cells.[16] However, the exact pathogenesis of cardiotoxicity in patients under treatment with immune checkpoint inhibitors remains poorly understood and prompts further investigation.

The patients presenting with symptoms suggestive of pembrolizumab-related myocarditis pose a significant diagnostic challenge. In such cases, lymphocytic myocarditis, dilated cardiomyopathy and infections with cardiotropic viruses, including enteroviruses, adenoviruses, parvovirus B19, H1N1 influenza and human herpesvirus 6, should be ruled with the standard set of investigations.[17] Endomyocardial biopsy remains the gold standard for the diagnosis.[18] However, it has low sensitivity and high interobserver variability in interpretation of biopsy samples.[18 19] Hence, immunohistochemistry and PCR analysis of the endomyocardial biopsy specimens may improve the diagnostic accuracy in patients with myocarditis.[18 19]

The management is crucial and demands critical decision-making. In acute management, the initial and most important step should aim to stabilise the cardiac output and tissue perfusion. A careful monitoring of serum electrolytes is also imperative as electrolyte imbalance can lead to other serious arrhythmic complications.[20] Extracorporeal membrane oxygenation (ECMO) can be used in cases of severe cardiogenic shock following fulminant myocarditis.[21] Acute renal failure has been designated as a potential problem with ECMO in such patients

that should not be overlooked.[21] ACE inhibitors can be employed to decrease heart failure-related morbidity and mortality.[22] A rapid recovery is usually observed with the corticosteroid treatment.[23] However, the use of equine antithymocyte globulin may be considered in steroid non-responders.[23] Pembrolizumab therapy should be halted and an alternative antitumour treatment must be sought out to avoid immune-mediated myocarditis in such patients.

Learning points

- Myocarditis is a relatively rare but potentially fatal immune-mediated adverse reaction following pembrolizumab therapy.
- Clinicians should maintain a high index of suspicion for pembrolizumab-induced myocarditis, particularly due to its early onset, non-specific clinical presentation and fulminant progression.
- The cessation of pembrolizumab and corticosteroid administration can be an effective treatment in such patients.
- Future studies employing pembrolizumab as immunostimulatory therapy may undertake risk stratification for cardiac dysfunction.

Acknowledgements The authors would like to thank Dr. Muhammad Wasif Saif and Dr. Hafeez Ul Hassan Virk for their constructive review of this paper and formative feedback.

Contributors FI: designed the study, performed the literature review, drafted the manuscript, formulated the data table, revised the manuscript critically for important intellectual content, and gave the final approval for the version published. MM: wrote the case presentation. SG: contributed to the discussion. WU: reviewed the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1 Khoja L, Butler MO, Kang SP, *et al*. Pembrolizumab. *J Immunother Cancer* 2015;3:36.
2 Davies M, Duffield EA. Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. *Immunotargets Ther* 2017;6:51–71.
3 Robert C, Ribas A, Wolchok JD, *et al*. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet* 2014;384:1109–17.
4 Garon EB, Rizvi NA, Hui R, *et al*. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372:2018–28.
5 Smith-Cohn MA, Gill D, Voorhies BN, *et al*. Case report: pembrolizumab-induced Type 1 diabetes in a patient with metastatic cholangiocarcinoma. *Immunotherapy* 2017;9:797–804.
6 Atwal D, Joshi KP, Ravilla R, *et al*. Pembrolizumab-induced pancytopenia: a case report. *Perm J* 2017;21.
7 Issa M, Milioglou I. Unusual case of immune-related colitis. *BMJ Case Rep* 2017; 2017:bcr-2017-221319.
8 Freites-Martinez A, Kwong BY, Rieger KE, *et al*. Eruptive keratoacanthomas associated with pembrolizumab therapy. *JAMA Dermatol* 2017;153:694–7.
9 Barbosa NS, Wetter DA, Wieland CN, *et al*. Scleroderma induced by pembrolizumab: a case series. *Mayo Clin Proc* 2017;92:1158–63.
10 March KL, Samarin MJ, Sodhi A, *et al*. Pembrolizumab-induced myasthenia gravis: a fatal case report. *J Oncol Pharm Pract* 2017:107815521668738.
11 Hanna KS. A rare case of pembrolizumab-induced uveitis in a patient with metastatic melanoma. *Pharmacotherapy* 2016;36:e183–e188.
12 Läubli H, Balmelli C, Bossard M, *et al*. Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. *J Immunother Cancer* 2015;3:11.
13 Heinzerling L, Ott PA, Hodi FS, *et al*. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. *J Immunother Cancer* 2016;4:50.
14 Johnson DB, Balko JM, Compton ML, *et al*. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med Overseas Ed* 2016;375:1749–55.
15 Wang J, Okazaki I-mi, Yoshida T, *et al*. PD-1 deficiency results in the development of fatal myocarditis in MRL mice. *Int Immunol* 2010;22:443–52.
16 Tarrio ML, Grabie N, Bu D-x, Dx B, *et al*. PD-1 protects against inflammation and myocyte damage in T cell-mediated myocarditis. *J Immunol* 2012;188:4876–84.
17 Sagar S, Liu PP, Cooper LT. Myocarditis. *The Lancet* 2012;379:738–47.
18 Kindermann I, Barth C, Mahfoud F, *et al*. Update on myocarditis. *J Am Coll Cardiol* 2012;59:779–92.
19 Dennert R, Crijns HJ, Heymans S. Acute viral myocarditis. *Eur Heart J* 2008;29:2073–82.
20 Inayat F, Ali NS, Riaz I, *et al*. From the gut to the heart: campylobacter jejuni enteritis leading to myopericarditis. *Cureus* 2017;9:e1326.
21 Liao X, Li B, Cheng Z. Extracorporeal membrane oxygenation in adult patients with acute fulminant myocarditis: clinical outcomes and risk factor analysis. *Herz* 2017. doi: 10.1007/s00059-017-4617-7.[Epub ahead of print 12 Sep 2017].
22 Tai C, Gan T, Zou L, *et al*. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 2017;17:257.
23 Tay RY, Blackley E, McLean C, *et al*. Successful use of equine anti-thymocyte globulin (ATGAM) for fulminant myocarditis secondary to nivolumab therapy. *Br J Cancer* 2017;117:921–4.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit http://group.bmj.com/group/rights-licensing/permissions.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:
- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow