ESC European Society of Cardiology

European Heart Journal - Case Reports (2020) **4**, 1–6
doi:10.1093/ehjcr/ytaa214

CASE REPORT
Other

A different type of acute myocarditis: a case report of acute autoimmune myocarditis mediated by anti-PD-1 T lymphocyte receptor (pembrolizumab)

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Received 28 November 2019; first decision 30 December 2019; accepted 17 June 2020; online publish-ahead-of-print 4 October 2020

Background Pembrolizumab is an immune check-point inhibitor (ICI), which acts by blocking the T lymphocyte PD-1 inhibitor receptor. It has been increasingly used in advanced or non-responsive tumours with promising results. However, acute myocarditis is an infrequent but potentially life-threatening autoimmune adverse effect related to ICIs.

Case summary This case deals with a 69-year-old gentleman on second-line therapy with pembrolizumab for advanced non-small cell lung cancer. Three weeks after first dose, the patient was diagnosed with an autoimmune hepatitis, treated with decreasing corticoid dosage, followed by acute heart failure. On admission, his electrocardiogram (ECG) showed diffuse repolarization changes and a transthoracic echocardiography revealed severe left ventricle impairment (left ventricular ejection fraction 32%). High-sensitivity cardiac troponin was elevated and a coronary angiogram was performed showing non-significant obstructive disease. An autoimmune myocarditis was suspected, and high-dose intravenous corticoid, intravenous vasodilators, and loop diuretics were started with favourable response. Cardiac magnetic resonance (CMR) imaging, performed 2 weeks after clinical onset, revealed extracellular oedema in the anteroseptal-apical left ventricle segments. A new transthoracic echocardiography, performed after 3 months, showed preserved left ventricle ejection fraction. Finally, the patient was readmitted due to an autoimmune myasthenia-like syndrome.

Discussion Acute autoimmune myocarditis related to ICIs is a challenging diagnosis and its incidence has been underestimated in early studies. Endomyocardial biopsy (EMB) is the gold standard test for its diagnosis. Nevertheless, a definite myocarditis diagnosis is possible without EMB when characteristic clinical syndrome, elevated myonecrosis markers, and electrocardiographic, echocardiographic, and CMR changes are present together.

Keywords Acute myocarditis • Immune check-point inhibitor • Anti-PD-1 • Pembrolizumab • Case report

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Handling Editor: Domenico D'Amario

Peer-reviewers: Albert Galyavich and Hajnalka Vágó

Compliance Editor: Mark Philip Cassar

Supplementary Material Editor: Peysh A Patel

Learning points

- Immune-mediated acute myocarditis is an infrequent pembrolizumab side effect that can potentially evolve to fulminant myocarditis which has a mortality up to 50% in published series.
- The diagnosis is challenging due to both low event rate and the lack of well-established diagnostic criteria.
- Definite myocarditis diagnosis is possible when characteristic clinical syndrome, elevated myonecrosis markers, electrocardiographic, echocardiographic, and CMR changes present together.

Introduction

Immunotherapy is an emerging treatment in oncology, widely spread in current clinical practice, which treats advanced or non-responsive tumours to improve their prognosis and survival. Pembrolizumab is a monoclonal antibody that works as an immune check-point inhibitor (ICI). It acts both binding and blocking the T lymphocyte PD-1 inhibitor receptor, providing T cytotoxic lymphocyte activation to attack the malignant cells. However, activating the immune system is not innocuous and it has been related with autoimmune reactions against non-malignant cells, also well known as immune-related adverse effects. Among them, myocarditis is the most frequent and potentially life-threatening cardiovascular side effect, which is potentially life-threatening; therefore, it has become an emergent problem for clinicians in their daily routines.

Timeline

June 2016	Diagnosed with urothelial bladder cancer.Complete remission after treatment with transurethral resection of the prostate and Bacillus Calmette-Guérin therapy for a year.
March 2018	Diagnosed with advanced non-small cell lung cancer. Started on first-line treatment (cisplatin and pemetrexed).
August 2018	No response to treatment. Second-line treatment started with pembrolizumab.
Admission 20 days after first pembrolizumab doses	Autoimmune hepatitis treated with corticoid therapy, and favourable clinical response.
Clinical presentation within 5 days after admission	Switched from intravenous to oral corticoid therapy.Sudden tachypnoea, tachycardia, dyspnoea, and diffuse repolarization ECG changes.Transthoracic echocardiogram showed apical severe left ventricle dysfunction.Coronary angiography did not show significant coronary artery disease.Intravenous corticoid therapy restarted at high doses.
Three days after clinical presentation	Clinical resolution, ECG changes retrogradation and left ventricle ejection fraction recovery.
Fifteen days after clinical presentation	Interstitial oedema in cardiovascular magnetic resonance imaging (CRM).
Three weeks after clinical presentation	Discharge from hospital.
Readmission 4 weeks after clinical presentation	Diagnosed with autoimmune myasthenia-like syndrome.

Case presentation

A 69-year-old gentleman, with a history of urothelial bladder cancer under complete remission 2 years previously, was diagnosed with metastatic advanced non-small cell lung cancer. He was started on first-line therapy without response. He was subsequently treated with pembrolizumab as second-line therapy completing his first cycle of treatment. Approximately 3 weeks after, the patient was hospitalized due to drug-related autoimmune hepatitis which was treated with a slow tapering off corticosteroid regimen with favourable clinical and laboratory markers response.

Five days later, the patient presented a sudden episode of shortness of breath. On physical examination, he was tachypnoeic at 35 breath per minute with intercostal retraction, had a raised jugular venous pulse and bilateral lung crackles. His SpO_2 was 95% on room air, blood pressure was 165/90 mmHg and pulse was regular at 110 b.p.m. His chest X-ray was normal. Electrocardiogram (ECG) (*Figure 1*) showed 1 mm anterolateral ST-segment elevation and anterolateral and inferior negative T waves. Transthoracic echocardiography showed a non-dilated left ventricle, with moderately

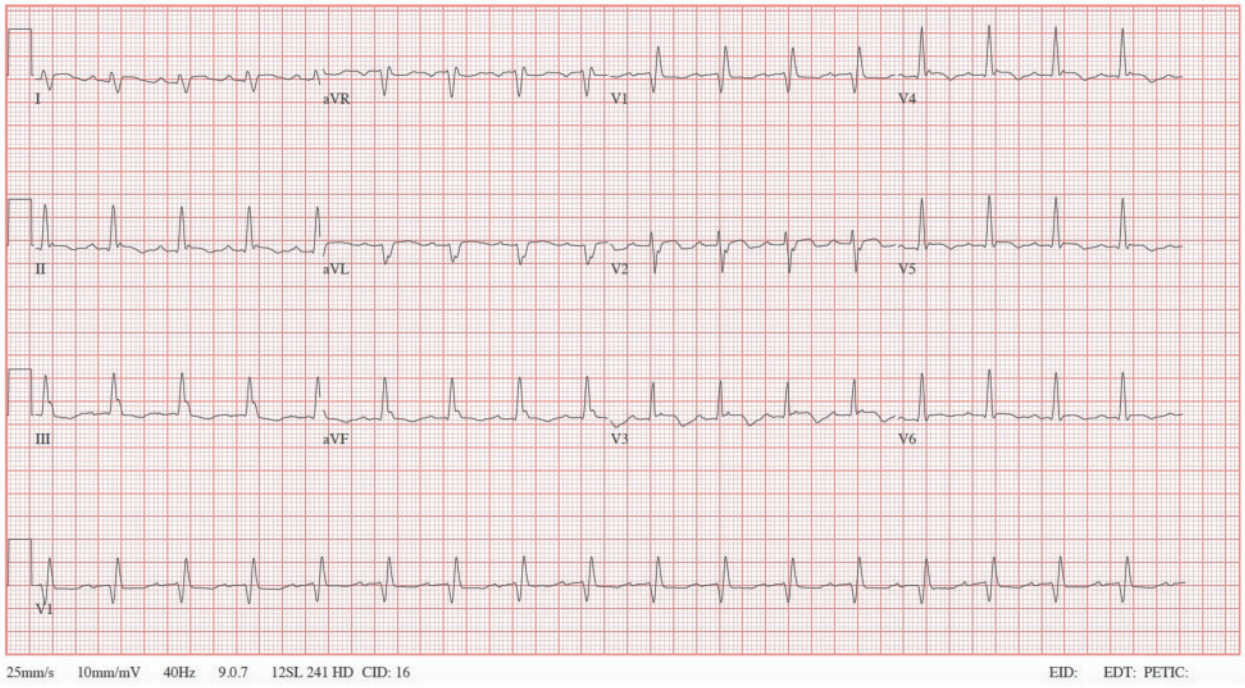

Figure 1 Initial ECG during acute heart failure onset, showing sinus tachycardia and diffuse alteration of repolarization (1 mm anterolateral ST-segment elevation, and anterolateral and inferior negative T waves).

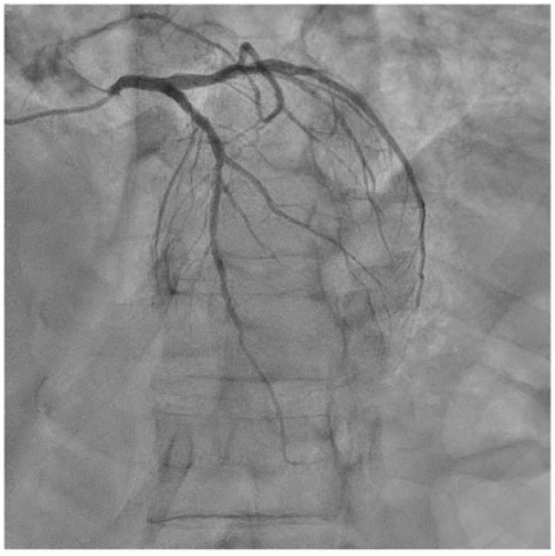

Figure 2 Left coronary circulation. Non-significant obstructive disease shown by coronary angiography.

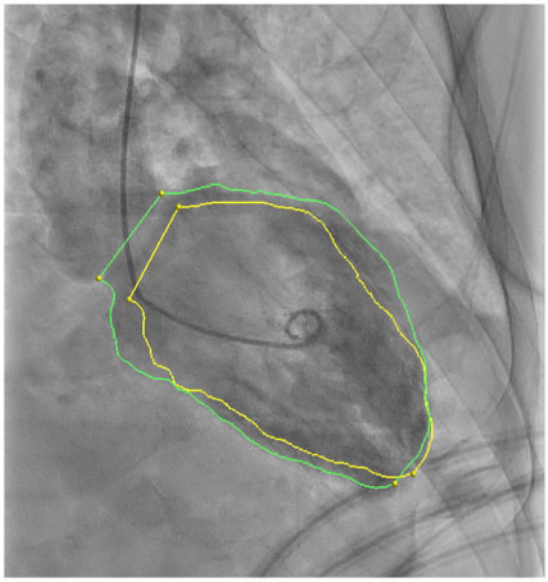

Figure 3 It is shown diastolic left ventricular end-diastolic area in green and left ventricular end-systolic area in yellow by ventriculography.

reduced left ventricular ejection fraction (LVEF) and anterior-septal-inferior apical hypokinaesia (previously normal). Biochemical analyses revealed elevated myocardial injury markers [high-sensitivity cardiac troponin T 1563 ng/L (URL <13 ng/L) and creatine-kinase 1176 UI (nL < 36 UI)].

Oxygen therapy (FiO_2 26%) and intermittent intravenous furosemide were started. An urgent coronary angiography was performed showing normal coronary arteries (*Figure 2*); a left

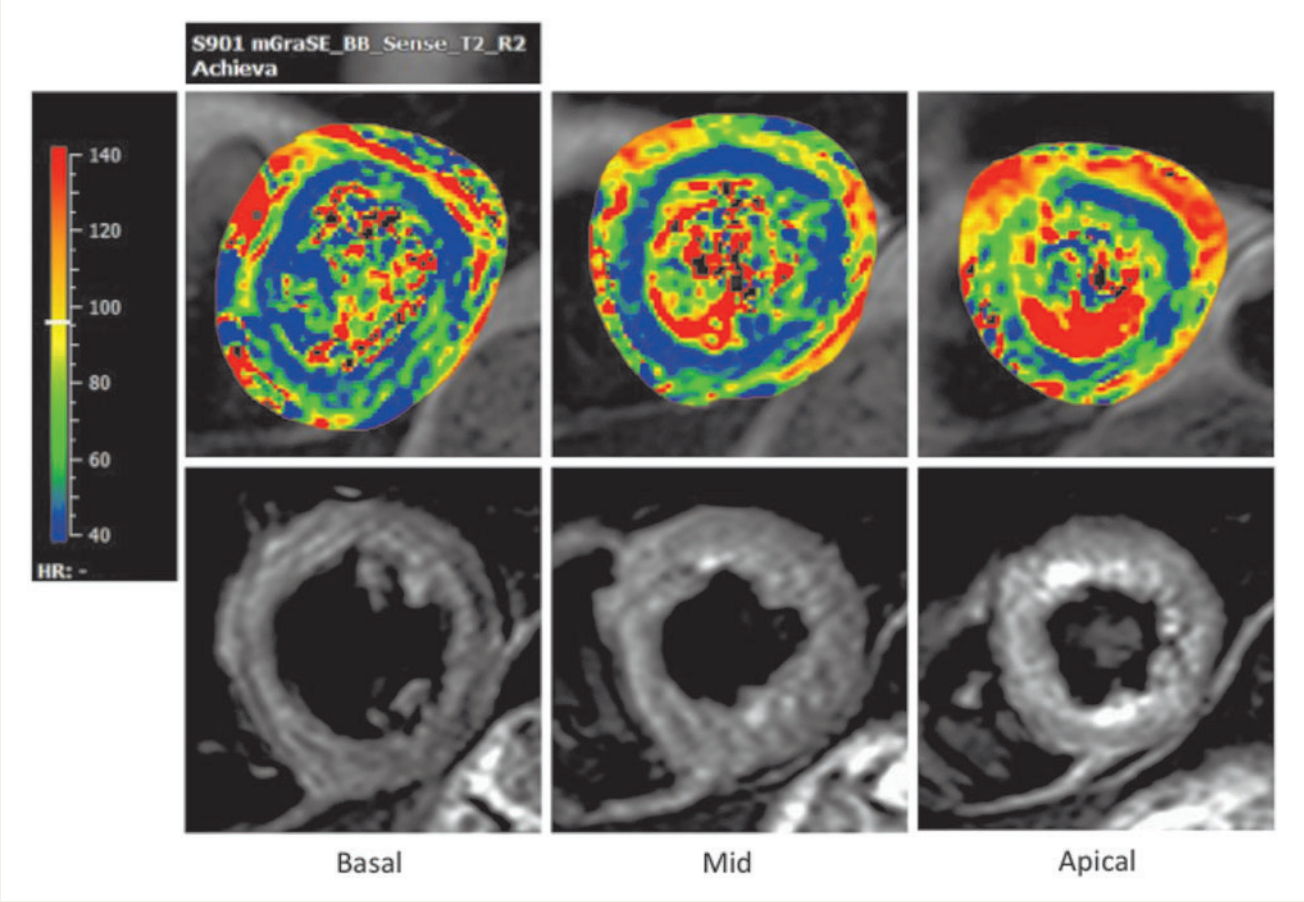

Figure 4 (*A*) Basal, mid, and apical left ventricle cross-sectional images in T2 mapping CMR. Quantitative T2 signal values in milliseconds (ms) with normal values in blue. Apical sector shows increased normal values (>56 ms), mainly in the anteroseptal apical segment consistent with myocardial oedema. (B) T2 STIR RMC images. Semiquantitative evaluation signal, showing a higher signal intensity in the apical segment, concordant with oedema at this level.

ventriculography was performed confirming severe left ventricular function impairment with a left ventricular ejection fraction of 32% (*Figure 3*). Due to clinical instability, a myocardial biopsy was not performed and the patient was transferred to the Intensive Cardiac Care Unit where high-dose boluses of methylprednisolone (1 g/day during 72 h), systemic vasodilators and loop diuretics (continuous infusions of furosemide and sodium nitroprusside) were administered under suspicion of acute pharmacological myocarditis. Oxygen face mask was also needed (FiO_2 30%) without the need for neither ventilatory support nor inotropic treatment. He presented with favourable clinical course, restoring the haemodynamic stability. Corticosteroid dosage (methylprednisolone 1 mg/kg/day), therapy was reduced progressively within 2 weeks without further incidents and enalapril, bisoprolol, and spironolactone were initiated at low doses. An improvement of left ventricular ejection fraction (45%) was evidenced in a control echocardiography before hospital discharge.

Cardiac magnetic resonance with gadolinium contrast, including T1 and T2 mapping and T2-STIR sequences, was performed after 2 weeks of treatment with a 1.5 scanner (Interna CV, Philips Medical System Best, The Netherlands). An LVEF improvement (48%) was confirmed, although slightly reduced due to the overall dyssynchrony of the LV. T1 and extracellular volume values were normal (1044 ms and 26%, respectively) at the mid-septal area and no myocardial late gadolinium enhancement was depicted in the myocardium, but an increase of the myocardial intensity signal in the T2-STIR sequences and T2 values (74 ms, nL <56 ms) in the parametric images were found at the apical LV segments, suggesting the presence of residual myocardial oedema in this region (*Figure 4*). These findings supported the previous clinical diagnosis of acute myocarditis, with no signs of permanent myocardial injury. Three weeks later, the patient was discharged showing regression of the altered repolarization (*Figure 5*) and of the LV regional contractility abnormalities (LVEF 53%).

Four weeks after clinical presentation, the patient was readmitted due to new-onset pharmacological myasthenia-like syndrome.

Discussion

In the last decade, ICIs have shown encouraging outcomes in advanced or metastatic malignancies, where previous prognosis was

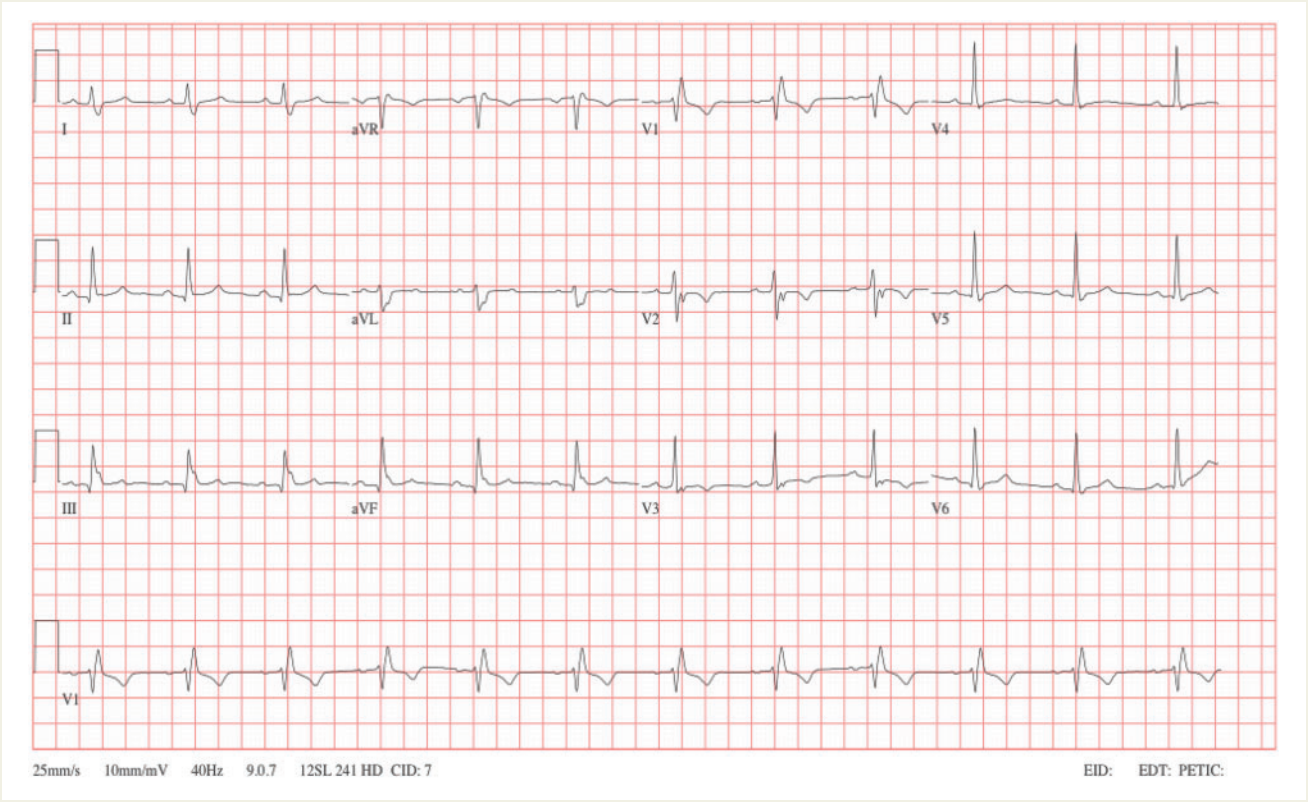

Figure 5 ECG control after 3 weeks of treatment showing regression of the abnormal repolarization pattern.

ominous. Acute myocarditis is the most frequent PD-1 receptor inhibitor (pembrolizumab) induced cardiac toxicity.[1,2]

Cardiomyocytes express PD-L1 at low levels, binding to PD-1 T cell receptor. The interaction leads into suppression of T-cell activation, maintaining self-tolerance and promoting resolution of inflammation. The deletion of gene encoding PD-1 and PD-L1 in mice has been demonstrated to cause dilated cardiomyopathy and lethal autoimmune myocarditis, respectively.[3,4]

Although immune-related cardiotoxicity has been underestimated in initial studies, many cases of myocarditis and fulminant heart failure have been increasingly reported, so the real incidence still remains unknown.[5,6]

Myocarditis frequently presents together with progressive and severe ventricular dysfunction with a high mortality rate up to 50%, although a selection bias may contribute by magnifying its severity.[7] Of note, early diagnosis followed by withdrawal of treatment and early initiation of immunosuppression therapy are the main prognosis and recovery modifiable factors. However, current evidence and clinical recommendations are based on case reports and case series, translating the lack of scientific evidence available concerning this emerging problem.[8–10]

Moreover, myocarditis related to ICIs is a challenging diagnosis as it is a rare event without a specific definition in clinical trials. The low sensitivity and specificity of clinical manifestations, laboratory markers and imaging testing may affect the final diagnosis. Nevertheless, rapid establishment of treatment is only possible when there is a strong clinical suspicion.[11,12]

A confirmatory endomyocardial biopsy (EMB) is generally indicated. Unfortunately, in our case, an EMB could not be performed due to the severe haemodynamic instability. However, in this case, there was a high clinical suspicion with a compatible clinical syndrome, elevated myocardial injury biomarkers, together with electrocardiographic and echocardiographic reversible changes consistent with definite myocarditis according to the diagnostic criteria proposed by Bonaca *et al.*[13,14] This was further substantiated by the results of CRM imaging.

Other autoimmune side effects can frequently present concomitantly. This is the first case report in literature where the patient was first diagnosed with an autoimmune hepatitis, followed by an acute myocarditis and a latter myasthenia-like syndrome. In fact, it has already been described in some case series, where 23–25% of myocarditis associate with myositis; and 10% with myasthenia-like syndrome.[11,15]

Finally, more studies are needed to provide further evidence and to understand underlying mechanisms of ICIs related to cardiac toxicity, as they are not fully understood to date. Also, clinical trials are required to standardize cardiotoxicity treatment.

Lead author biography

Mario Salido Iniesta is a cardiology resident at Sant Pau University Hospital. At present, his work focuses on clinical cardiology. He was graduated in Medicine at Pompeu Fabra University. His favourite place to work and do research is Barcelona where there are both: sea for surfing and mountain for mountain-biking to practice in his spare time.

Supplementary material

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

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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 report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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