Myocarditis with checkpoint inhibitor immunotherapy: case report of late gadolinium enhancement on cardiac magnetic resonance with pathology correlate

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Received 24 July 2018; accepted 6 November 2018; online publish-ahead-of-print 7 January 2019

Background

Nivolumab is a human IgG4 anti-programmed cell death protein-1 (PD-1) monoclonal antibody that works by augmenting the immune response against tumour cells. It has the potential of causing multiple autoimmune-related events, including cardiac. However, the real incidence and diagnosis of cardiac complications remains unclear.

Case summary

A 47-year-old woman with a history of carotid artery dissection and metastatic melanoma presented with acute heart failure. One year prior to presentation, she had received one cycle only of checkpoint inhibitor therapy with both ipilimumab and nivolumab, and nivolumab only was restarted 4 months prior to presentation. On admission, she was hypotensive, tachycardic due to atrial tachycardia and with pulmonary oedema. An echocardiogram revealed a left ventricular ejection fraction of 26%. Cardiovascular magnetic resonance (CMR) demonstrated a non-ischaemic pattern of late gadolinium enhancement (LGE), most consistent with myocarditis. The diagnosis of immunotherapy-mediated cardiac toxicity was highly considered and immunosuppressive therapy was initiated. However, she went into refractory cardiogenic shock and did not survive. An autopsy performed with samples from areas of myocardium with and without LGE on the CMR, found correlation.

Discussion

According to the literature, cardiac complications develop in less than 1% of patients treated with checkpoint inhibitors, with a 0.06% incidence reported in nivolumab specifically. However, it may be higher, given the lack of cardiac monitoring during treatment. We present the first case demonstrating direct histological correlation of T-lymphocytic infiltration with areas of LGE on CMR. Future investigation using CMR for early detection of inflammation and left ventricular dysfunction may help to diagnosis disease earlier.

Keywords

Case report • Myocarditis • Cardiac magnetic resonance • Cardiogenic shock • Immunotherapy

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Introduction

Nivolumab is a recently approved human IgG4 anti-programmed cell death protein-1 (PD-1) monoclonal antibody that works as a checkpoint inhibitor, augmenting the immune response against tumour cells. Hence, Nivolumab has the potential to affect many organs, including the heart, resulting in an adverse reaction.

There is not enough data to direct the diagnosis and treatment of patients presenting with myocarditis from checkpoint inhibitors, as the reported incidence of cardiac complications using these agents has likely been underestimated. To highlight the utility of cardiac imaging in this disease state, we present a case of immunotherapy-induced myocarditis with findings on cardiac MRI correlating with areas of myocardial lymphocytic infiltrate and fibrosis on post-mortem pathology.

Timeline

| One year prior to presentation | Patient was diagnosed with melanoma
|                              | Started treatment with nivolumab/ipilimumab (1 cycle)
|                              | No response to treatment. Nivolumab and ipilimumab stopped
|                              | Started on dabrafenib and trametinib
|                              | Some response to treatment. Nivolumab restarted
| 4 months prior to presentation | Dyspnoea, lung oedema, acute decompensated heart failure with shock and biventricular failure in echocardiogram
| Upon presentation to emergency room | Echocardiogram with biventricular failure
|                              | Did not tolerate neurohormonal blockade for heart failure and remained on pressors
|                              | MRI with late-gadolinium enhancement suggestive of checkpoint inhibitor induced myocarditis
| After 1 day                     | Started on infliximab and intravenous steroids
| After 1 week                    | Refractory cardiogenic shock
|                              | Patient and family declined advanced haemodynamic support
| After 1 week                    | Decision was made to palliate patient who passed peacefully surrounded by family
|                              | Autopsy was performed

Learning points

- Nivolumab is a recently approved human IgG4 anti-programmed cell death protein-1 (PD-1) monoclonal antibody that works as a checkpoint inhibitor, augmenting the immune response against tumour cells. Hence, Nivolumab has the potential to affect many organs, including the heart, resulting in an adverse reaction.
- There is not enough data to direct the diagnosis and treatment of patients presenting with myocarditis from checkpoint inhibitors, as the reported incidence of cardiac complications using these agents has likely been underestimated. To highlight the utility of cardiac imaging in this disease state, we present a case of immunotherapy-induced myocarditis with findings on cardiac MRI correlating with areas of myocardial lymphocytic infiltrate and fibrosis on post-mortem pathology.

Case presentation

A 47-year-old woman with a history of carotid artery dissection and metastatic melanoma presented with acute decompensated heart failure. One year prior to presentation, she had received one cycle of combination CPI therapy with ipilimumab and nivolumab. Due to rapidly progressive disease, these medications were discontinued and she was started on dabrafenib and trametinib, BRAF inhibitors. She had initial improvement on this new regimen, and then nivolumab was restarted four months prior to her heart failure presentation. One month prior to presentation, she developed asymptomatic supraventricular tachycardia and subsequent dyspnoea before hospitalization. On admission, she was afebrile, hypotensive, and tachycardic, tachypnoeic, with pulmonary oedema, jugular venous distension, ascites, and lower extremity oedema. Initial ECG demonstrated a regular, narrow-complex rhythm, concerning for atrial tachycardia and without ischaemic changes. Serum troponins were negative, CK was negative, and serum proBNP was 3797 pg/mL (normal reference <300 pg/mL). A transthoracic echocardiogram revealed global dysfunction with biventricular failure.

Figure 1 Short axis image of the mid-ventricle demonstrating late gadolinium enhancement of the mid-wall and epicardial regions of the myocardium, as well as the inferior right ventricular insertion site.
biventricular failure with a left ventricular ejection fraction (LVEF) of 26%, severely dilated left ventricle, and a trivial pericardial effusion. Cardiovascular magnetic resonance (CMR) was performed and demonstrated a non-ischaemic pattern of late gadolinium enhancement (LGE), most consistent with a myocarditis. Given the recent use of nivolumab and the cardiac imaging findings, the diagnosis of immunotherapy-mediated cardiac toxicity was highly considered, and immunosuppressive therapy with steroids (methylprednisolone 500 mg intravenous BID for 5 days) and infliximab (10 mg/kg/day for 2 days) was initiated. Her clinical course was complicated by cardiogenic shock refractory to inotropic support. Due to her poor prognosis, left and right heart catheterization with endomyocardial biopsy and advanced mechanical circulatory support were not pursued. She was palliated and died in the hospital. An autopsy was performed and tissue samples were obtained from areas of myocardium with and without LGE on the CMR.

Cardiovascular magnetic resonance imaging was performed on a Siemens 1.5 T scanner. Cine images were acquired with steady state free precession sequences and revealed four-chamber dilation with severe biventricular dysfunction [LVEF 16%; and right ventricular (RV) ejection fraction 12%] (Supplementary material online, Videos S1 and S2). Late gadolinium enhancement-cardiovascular magnetic resonance was performed using 2D single-shot and segmented inversion-recovery sequences, demonstrating mid-wall and epicardial enhancement of the basal to mid-inferior and inferolateral segments, with a focal area of increased signal intensity at the inferior RV insertion site (Figure 1), involving 15% of the total LV myocardium upon quantitative analysis. Due to the patient's difficulty with breath holds, diagnostic T2 imaging could not be obtained. On microscopy, haematoxylin and eosin (H&E) stains showed evidence of moderate lymphocytic myocarditis in the regions with LGE (Figure 2), with a mild infiltrate throughout other regions of the heart. The infiltrate
was composed almost exclusively of T-cells, with an admixture of CD4+ (helper) and CD8+ (cytotoxic) T-cells. Trichrome stain showed moderate fibrosis in the areas of LGE (Figure 3). Programmed cell death protein ligand-1 (PD-L1) stain showed focal membrane positivity in the areas of LGE (Figure 4). No significant coronary artery disease was seen on autopsy.

Discussion

Nivolumab is a recently approved human IgG4 PD-1 monoclonal antibody that works as a CPI, augmenting the immune response against tumour cells. Although these CPIs have revolutionized the treatment of many cancers, they have also been associated with a spectrum of immune-related adverse events, as they also can affect normal cells. It has been described that cardiac complications develop in less than 1% of patients treated with CPIs, with a 0.06% incidence reported in nivolumab specifically, and more recent data have suggested the prevalence of myocarditis was higher at 1.14%. However, the incidence may actually be higher, given the lack of cardiac monitoring during treatment. One possible pathophysiologic mechanism is that cardiac myocytes may share targeted antigens with the tumour, consequently becoming targets of activated T-cells, resulting in lymphocytic infiltration with downstream heart failure and conduction abnormalities. Although not fully understood nor investigated why the troponin was negative in this case, anti-troponin autoantibodies, had they been present, may result in a falsely low serum troponin level. Although the patient did receive other potentially cardiotoxic therapy with BRAF inhibitors, it was felt that the timing of the presentation in regards to initiation of nivolumab and the histology, which was consistent with other published reports of CPI-associated myocarditis, most supported nivolumab as the underlying cause. When clinically suspected, echocardiography is usually the initial test for cardiac function. However, CMR offers the additional benefit of tissue characterization for diagnosis of inflammation and fibrosis. The value of CMR for diagnosis and prognosis in myocarditis and other non-ischaemic cardiomyopathies has been well established. The role of CMR in this particular cohort of patients has not yet been elucidated, although it holds great potential for the diagnosis and management of adverse cardiac effects from immunotherapy.

Here, we present a case of immunotherapy-induced myocarditis with LGE on CMR correlating with areas of myocardial lymphocytic infiltrate and fibrosis on post-mortem pathology. Although published cases have reported the use of CMR in suspected immunotherapy-induced myocarditis, this is the first case demonstrating direct histological correlation of T-lymphocytic infiltration with areas of LGE on CMR. Interestingly, although the lymphocytic infiltration was most significant in the areas of LGE, there was still evidence of less severe lymphocytic infiltration in areas without LGE, suggesting a more diffuse inflammatory process. Additionally, the presence of fibrosis in the areas of LGE also raises the possibility of a more subacute component to the cardiotoxicity as well. Future investigation with more sensitive techniques using CMR for early detection of inflammation and left ventricular dysfunction may help to diagnosis disease earlier and guide therapy in these patients.

Acknowledgements

Ahmad Charifa, MD, Department of Pathology, Yale University School of Medicine, New Haven, CT, USA; Ashley Brogan, MD, Department of Cardiology, Yale University School of Medicine, New Haven, CT, USA; Ryan T. Sowell, PhD, Brian West, MD, Guoping Cai, MD, Department of Pathology, Yale University School of Medicine, New Haven, CT, USA; Hamid R. Mojibian, MD, Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, CT, USA; Harriet M. Kluger, MD, Department of Medical Oncology, Yale University School of Medicine, New Haven, CT, USA; Forrester Lee, MD, Department of Cardiology, Yale University School of Medicine, New Haven, CT, USA; David L. Rimm, MD, Department of Pathology, Yale University School of Medicine, New Haven, CT, USA; Ralph J. Kiello, PharmD, Department of Pharmacy, Yale University School of Medicine, New Haven, CT, USA; Imran Hafeez, MD; Mariana L. Henry, BS, Judith Meadows, MD, Department of Cardiology, Yale University School of Medicine, New Haven, CT, USA; Isabel Cortopassi, MD, Anna Bader, MD, Jonathan Killam, MD, Stephen Huber, MD, Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, CT, USA.

Supplementary material

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

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s 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 withCOPE guidance.

Conflict of interest: none declared.

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