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Original Research

A closer look at immune-mediated myocarditis in the era of combined checkpoint blockade and targeted therapies

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Abstract Immune checkpoint inhibitors (ICI) and tyrosine kinase inhibitors (TKI) have transformed the management of many malignancies. Although rare, immune-mediated myocarditis presents unique clinical challenges due to heterogenous presentation, potential life-threatening consequences, and the time-critical need to differentiate it from other causes of cardiac dysfunction. Increasingly, TKI are being combined with ICI to promote immune modulation and improve efficacy. However, these combinations are associated with more toxicities. This series describes six patients with advanced melanoma who developed immune-mediated myocarditis while receiving an anti-PD-1 antibody or an anti-PD-L1 antibody plus a mitogen-activated protein kinase inhibitor. It provides a review of their heterogenous clinical presentations, investigational findings and treatment outcomes. Presentations ranged from asymptomatic cardiac enzyme elevation to death due to heart failure. We highlight the role of cardiac MRI (CMRI), a sensitive and non-invasive tool for the early detection and subsequent monitoring of myocardial inflammation. Five of the six patients exhibited CMRI changes characteristic of myocarditis, including mid-wall myocardial oedema and late gadolinium enhancement in a non-coronary distribution. Critically, two of these patients had normal findings on echocardiogram. Of the five patients who received immunosuppression, four recovered from myocarditis and one died of cardiac failure. The sixth patient improved with cardiac failure management alone. Three of the four patients responding to ICI derived long-

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term benefit. Clinical vigilance, prompt multimodal diagnosis and multidisciplinary management are paramount for the treatment of immune-mediated myocarditis.

1. Introduction

Immune checkpoint inhibitors (ICI) and molecularly targeted therapies have transformed the management of various malignancies [1,2]. Increasingly, these agents are combined to exploit potential synergistic immune modulation [3–6]. Recent trials of immunotherapy and targeted therapy combinations have demonstrated enhanced efficacy [4,7], thereby fuelling ongoing research to explore tyrosine kinase inhibitors (TKI) and immunotherapy combinations in a wide range of cancers.

Both TKI and ICI are known to cause drug-induced cardiotoxicity. TKI of the mitogen-activated protein kinase pathway can cause reduced ejection fraction (EF), congestive cardiac failure (CCF), prolonged QT interval, hypertension and acute coronary syndrome (ACS). Phase III studies of MEK inhibitor monotherapy and the combination of BRAF and MEK inhibitors reported reduced EF in 7% and 3–8% of patients, respectively [8–10].

The incidence of immune-related myocarditis due to ICI is around 1% with a mortality rate of up to 46% [11–13]. Immune-mediated myocarditis has a heterogeneous clinical presentation including reduced EF, CCF, arrhythmias, dyspnoea, palpitations, nausea, fatigue, weight loss, and/or chest pain [11–18]. Growing interest in combining ICI with TKI may lead to an increase in the incidence of drug-induced myocarditis given their overlapping toxicities and potential interaction [19]. The time-critical need to differentiate myocarditis from other causes of cardiac enzyme rise and/or symptoms present unique management challenges.

The present series reports on six cases of myocarditis due to ICI monotherapy or a combination ICI and MEK inhibitor. Emphasis is placed on the cardiac enzyme kinetics of each case and its relationship with immunosuppressive therapy. We highlight the role of non-invasive diagnostic tools and the current challenges faced in the management of ICI-related myocarditis.

2. Materials and methods

This series included six patients with metastatic melanoma who received ICI or a combination ICI and MEK inhibitor and presented with myocarditis between July 2016 and December 2018 at Peter MacCallum Cancer Centre in Australia. Institutional review board approval was obtained. Medical records were retrospectively reviewed for data on patient demographics, clinical presentation, diagnosis, and cancer and myocarditis treatment outcomes. Tumour responses were assessed using computer tomography and fludeoxyglucose-positron emission tomography (FDG-PET) with responses determined using RECIST version 1.1 and PERCIST, respectively [20,21]. Myocarditis was diagnosed using a combination of cardiac enzyme testing, cardiac MRI (CMRI), and transthoracic echocardiogram (TTE). Descriptive statistics were used for the reporting of clinical outcomes.

3. Results

Four male and two female, with a median age of 72 years (range: 60–88 years), presenting with myocarditis were identified. Four patients were treatment-naïve and two patients received prior anti-PD-1 therapy. The clinical presentation, investigational findings (Appendix B), and treatment (Appendix B) of each case is provided.

3.1. Case 1 and 2: myocarditis in patients receiving anti-PD-L1 antibody plus MEK inhibitor

3.1.1. Case 1

A 74-year-old male with stage IV melanoma with distant skin metastases presented with fatigue, fevers, chills, anorexia, diarrhoea, and an acneiform rash 15 days after starting cobimetinib (60 mg oral daily) and atezolizumab (840 mg intravenous (IV) 3 weekly). This was after disease progression after 34 cycles of pembrolizumab.

Creatinine kinase (CK) was elevated at 1,165 U/L (normal range: 20–200 U/L) and high-sensitivity troponin T (hs-TnT) was elevated at 77 ng/L (upper limit normal [ULN]: 20 ng/L). TTE demonstrated left ventricular ejection fraction (LVEF) of 55%. Electrocardiography (ECG) showed pre-existing left-axis deviation. The patient's presentation and findings on ECG and TTE were not suggestive of ACS. CMRI demonstrated midwall myocardial oedema and late gadolinium enhancement (LGE) of the basal, anterolateral, mid-inferior, and inferior segments in keeping with myocardial inflammation and necrosis (Fig. 1).

Methylprednisolone (2 mg/kg IV daily) was administered for three days and transitioned to prednisolone (2 mg/kg oral daily) which was weaned over eight weeks as the CK and hs-TnT declined (Fig. 2). Repeat TTE and CMRI eight weeks after starting corticosteroids showed preserved LVEF and reduced midwall oedema. The patient developed progressive disease 4.6 months after myocarditis diagnosis.

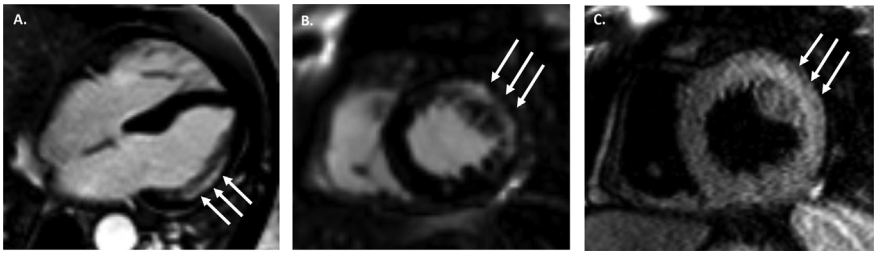

Fig. 1. Characteristic cardiac MRI findings of immune-mediated myocarditis. A. Postcontrast image: four chamber showing normal black myocardium with area of bright late gadolinium enhancement (arrows) in the anterolateral wall sparing the subendocardium, consistent with necrosis or scarring due to myocarditis. B. Postcontrast image: short axis image of left ventricle showing midwall late gadolinium enhancement (arrows) consistent with necrosis or scarring due to myocarditis. C. T2 weighted (STIR) image: left ventricle in short axis showing mid-wall high signal (arrows) indicative of myocardial oedema.

3.1.2. Case 2

A 60-year-old female with stage IV melanoma involving the lung, liver and bone presented with nausea, vomiting, diarrhoea, and mucositis 13 days after commencing cobimetinib (60 mg oral daily) and atezolizumab (840 mg IV 3 weekly). This was after tumour progression after 12 cycles of pembrolizumab. She did not have any cardiac symptom; however, CK (377 U/L) and hs-TnT (455 ng/L) were elevated (Fig. 2). ECG showed new flattened T waves in the inferior leads (II, III, AVF). LVEF was normal on TTE and did not demonstrate any regional wall motion abnormality. Methylprednisolone (1 mg/kg IV daily) was administered for 3 days. hs-TnT and CK normalised on day five and the patient was switched to prednisolone (1 mg/kg oral daily) which was tapered over six weeks. CMRI and coronary angiography performed several weeks after starting corticosteroids were normal. The temporal relationship between cardiac enzyme rise after the commencement of atezolizumab and cobimetinib, the rapid decline in cardiac enzymes on starting corticosteroids, and the normal coronary vessels are suggestive of drug-induced myocarditis. The patient received two cycles of ipilimumab-plus-nivolumab in the context of intracranial progression three months after the resolution of these treatment-related toxicities. Treatment with ipilimumab-plus-nivolumab was ineffective and complicated by immune-related nephritis requiring prednisolone (1 mg/kg oral daily weaned over six weeks).

3.2. Case 3 and 4: myocarditis and myositis

3.2.1. Case 3

A 75-year-old male with stage IV melanoma involving the chest wall, omentum, and distant lymph nodes, and a prior history of ulcerative colitis, presented with fatigue, weight loss, back and neck pain, and truncal and limb girdle weakness 20 days after receiving a single dose of pembrolizumab. Initial CK was 13,025 U/L and hs-TnT was 2,978 ng/L. CMRI showed midwall LGE in the basal septal and inferoseptal segments (Fig. 1). TTE showed preserved LVEF and there was no clinically significant ECG finding. The patient's presentation and findings on ECG and TTE were not suggestive of ACS. Pulmonary function test excluded respiratory muscle involvement.

Pulse methylprednisolone (1 g IV daily) was administered for three days, then at 1 mg/kg, for seven days before transitioning to oral prednisolone. Mycophenolate mofetil (building up 1.5 g oral twice daily [BD]) was introduced three weeks later when hs-TnT and CK remained persistently elevated at 113 ng/L and 513 U/L, respectively. CK and hs-TnT normalized six weeks after myocarditis diagnosis (Fig. 2). Prednisolone was weaned over eight weeks and mycophenolate was stopped after six months.

3.2.2. Case 4

A 74-year-old female with stage IV melanoma with lung and small bowel metastases, medically controlled CCF and type 2 diabetes presented with exertional dyspnoea eight weeks after the commencement of pembrolizumab. CK was 395 U/L and hs-TnT was 106 ng/L (Fig. 2). TTE showed a decrease in LVEF from 57% at baseline to 35% and inferolateral akinesis. ECG showed a pre-existing right bundle branch block, deep Q waves in the inferior leads, and corresponding T wave inversion in the anterolateral leads. The patient declined coronary angiogram or CMRI at the time of diagnosis. Low molecular weight heparin was commenced because myocardial infarction was a possible differential. The patient was already on a beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, and loop diuretic.

A CMRI performed three weeks after initial presentation to investigate persistently elevated levels of hs-TnT (100–200 ng/L) demonstrated epicardial LGE and oedema within the mid-inferolateral, anterior, basal, and lateral myocardial walls (Fig. 1), as well as an old inferolateral partial thickness infarct. Methylprednisolone (2 mg/kg IV daily) was administered for four days and escalated to 1 g daily for three days when cardiac enzymes failed to decline. Mycophenolate mofetil (MMF) (1 g oral BD) was added. After one month of immunosuppression, LVEF improved from 35% to 50%.

Five weeks into the prednisolone wean, while still on 50 mg prednisolone and MMF 1 g BD, the patient presented with bilateral limb girdle weakness and CK had

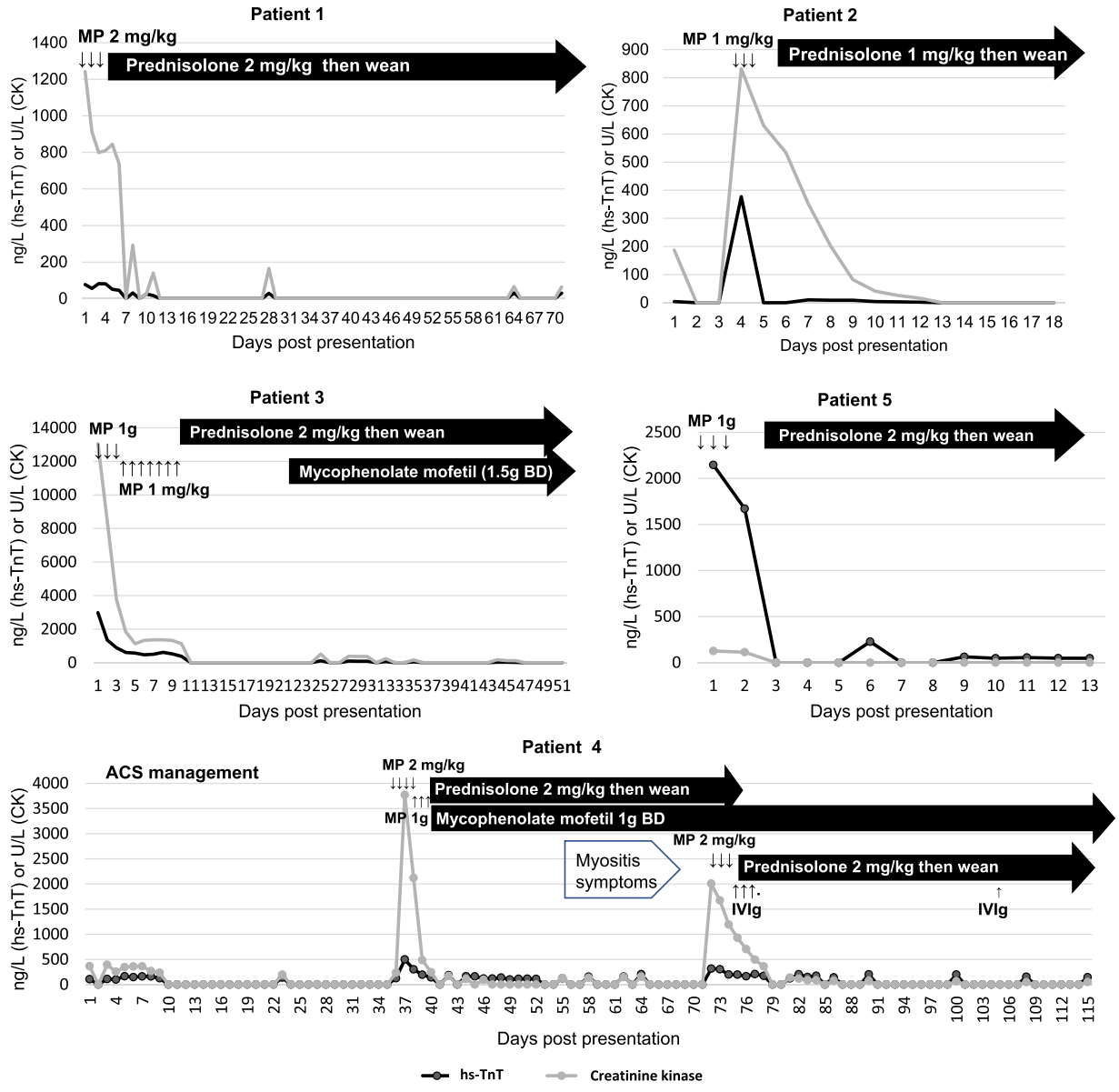

Fig. 2. Cardiac enzyme levels in correlation with treatment in patients with immune-mediated myocarditis. Each panel provides the CK (grey) and hs-TnT (black) levels for each patient from the time of myocarditis diagnosis. Black horizontal arrows represent the timing of immunosuppressive therapies. Black vertical arrows under the letters MP or IVIg represent each dose administered. Patient 4 developed myositis which was diagnosed on day 72. Abbreviations: MP, methylprednisolone; ACS, acute coronary syndrome; IVIg, intravenous immunoglobulin.

risen from 257 U/L to 3,769 U/L. hs-TnT incremented from 159 ng/L to 501 ng/L. An electromyograph confirmed symmetrical proximal myositis. Myositis antibody screen was negative. Muscle biopsy showed CD68+ histocytic infiltrate with a scant CD8+ and CD4+ T cells infiltrate. The patient received methylprednisolone (2 mg/kg IV daily) for three days, followed by oral prednisolone taper as well as intravenous immunoglobulins (IVIg) (2 g/day for three days), resulting in normalisation of CK after nine days and improvement in muscle strength. hs-TnT remained elevated at 100–200 ng/L even though a repeat CMRI showed reduction in LGE. Prednisolone was weaned over 10 weeks. The patient currently continues to receive MMF and maintenance IVIg (0.4 mg/kg IV monthly).

3.3. Case 5: myocarditis

An 88-year-old male with stage IV melanoma with locoregional and distant nodal metastases presented with dyspnoea and a pleural effusion after four doses of pembrolizumab. TTE showed LVEF had decreased from 48% at baseline to 18%. Initial hs-TnT was 2,146 ng/L and CK was within normal limits (Fig. 2).

CMRI demonstrated inferolateral akinesis and subendocardial LGE (consistent with previous infarction) plus scattered foci of mid-wall LGE (Fig. 1). Methylprednisolone (1 g IV daily) was administered for three days followed by oral prednisolone (2 mg/kg oral daily) tapered over six weeks hs-TnT fell to 40 ng/L within eight days of initiating corticosteroids but failed to normalise completely. The patient's symptoms initially improved with corticosteroids and diuresis but he subsequently declined further intervention and opted for best supportive care. He died of progressive CCF two months later. FDG-PET performed at the onset of myocarditis demonstrated a partial metabolic response.

3.4. Case 6: dilated cardiomyopathy and colitis

A 61-year-old man with stage IV melanoma with lung metastases presented with exertional dyspnoea after receiving 11 doses of pembrolizumab. The TTE showed a decrease in LVEF from a baseline of 48% to 31%. ECG showed a pre-existing left bundle branch block. Standard cardiac failure treatments, including a beta-blocker, an ACE inhibitor, and a loop diuretic, were commenced with symptomatic benefit. There was delay in recognising that the patient's CCF was immune-related; hence corticosteroids were not commenced. CMRI performed two months after symptom onset demonstrated midwall LGE in the basal inferolateral wall and septum (Fig. 1) and pembrolizumab was ceased. The LVEF improved from 31% to 45% on a TTE performed six months later and normalised to 51% 18 months later. The patient subsequently developed immune-mediated colitis six months later and received prednisolone (1 mg/kg oral daily).

4. Discussion

ICI-mediated cardiotoxicity is rare but potentially life-threatening. The incidence of immune-mediated myocarditis is possibly underreported in clinical trials given cardiac assessments were not routinely performed and trial patients may have less comorbidities. Emerging evidence suggests that the real-world rates of cardiotoxicity is higher than previously reported [12,22].

There is strong preclinical and clinical rationale for combining TKI and ICI given their complementary response profile and synergy in generating antitumour immunity. TKI including BRAF and MEK inhibitors have been shown to affect the tumour microenvironment and enhance tumour immunogenicity [3,5–7,23,24]. Early clinical trials of ICI in conjunction with BRAF and MEK inhibition have demonstrated enhanced efficacy [7,23,24]. In renal cell carcinoma, axitinib and pembrolizumab is a new standard of care and similar approaches of combining TKI and ICI are being investigated in multiple tumour types [4,25,26].

Both TKI and ICI have cardiac liabilities. However, it is unclear whether TKI and ICI interact to potentiate cardiotoxicity. TKI can cause off-target cardiotoxicities due to the highly conserved nature of the ATP binding pocket of kinases across various organs [27]. In addition, trametinib is highly selective for MEK1/2; the MEK-ERK axis has been shown to be cardioprotective against oxidative stress, myocardial ischaemia-perfusion injury and adaptive hypertrophy [28]. In contrast, immune-mediated myocarditis is postulated to be an exaggerated adaptive immune response against shared epitopes in the myocardium and tumour and is hence characterised by extensive CD4+ T cell, CD8+ T cell and macrophage infiltration [11]. Given inflammation causes oxidative stress, MEK-ERK inhibition may increase the susceptibility of cardiomyocytes to ICI-mediated inflammation. It is therefore possible that a higher rate of cardiotoxicity will be observed with combinatorial approaches.

Our series highlights the clinical heterogeneity of immune-mediated myocarditis. Clinical presentations included asymptomatic cardiac enzyme elevation, dyspnoea and fatigue. Most patients presented within three months (range: day 13–214) of commencing ICI, which is consistent with published literature [12,13]. In a safety review of 211 patients treated with trametinib, the median time to onset for cardiomyopathy was 63 days (range 16–153) [29]. It is possible that the combination of ICI plus MEK inhibition and/or prior PD-1 inhibition contributed to the early onset (within 15 days) of myocarditis in case 1 and 2.

It is common for patients to experience multiple immune-related adverse events (irAE) [12,13]. Four of the six patients developed a second irAE: two developed myositis, one developed colitis and one developed nephritis. Myositis was the most common second irAE (25% of patients) in a series of 101 patients with immune-mediated myocarditis [13]. Another case series of patients with immune-mediated myocarditis showed 11% of patients developed colitis and 20% developed hepatitis [12]. It is critical to maintain vigilance for the emergence of other irAE if the patient's symptoms cannot be explained by one unifying diagnosis.

Immune-mediated myocarditis requires multimodal diagnosis. While the current gold standard for its diagnosis is histological findings of endomyocardial lymphocyte infiltration with myocyte necrosis, myocardial biopsies are rarely performed because of its invasive nature and the risk of false negative findings [30]. Non-invasive investigations are an integral part of the workup of patients with suspected myocarditis. All five of

the patients who underwent cardiac enzyme testing had elevated hs-TnT. A preserved EF, observed in two of the six patients, does not exclude myocarditis [12,31]. In a retrospective series of 35 patients with immune-mediated myocarditis, 38% of major adverse cardiac events (MACE) occurred in patients with preserved EF [12].

Five of the six patients underwent CMRI. Four had characteristic findings of myocarditis, including myocardial oedema on T2-weighted imaging and LGE in a non-coronary distribution (Fig. 1) [32]. Case 2, the only patient with a normal CMRI, may have had partially treated low-grade inflammation given the modest troponin and CK elevations. CMRI is highly specific (91%) and moderately sensitive (67%) for the diagnosis of myocarditis [32]. CMRI may be normal in those with scattered or low-grade inflammation [30,32]. CMRI mitigates issues with sampling error and the risks associated with myocardial biopsy [30,32]. A series of 16 patients showed early gadolinium enhancement at the diagnosis of myocarditis was associated with worse long-term functional recovery and more protracted symptoms [33]. The utility of CMRI in prognostication and follow-up warrants further assessment.

FDG-PET is also emerging as a useful non-invasive tool for the diagnosis of myocarditis. In a study of 65 patients with suspected myocarditis, FDG-PET demonstrated high specificity (97%) and moderate sensitivity (74%) when compared with CMRI [34]. FDG-PET may complement the use of CMRI by improving the detection of scattered or low-grade inflammation which may not be visible on CMRI. The ability of FDG-PET to quantify the degree of inflammation by measuring pathologic glucose uptake may be useful for monitoring myocarditis and guiding immunosuppressive therapy, thus warrants further prospective evaluation [34].

The management of immune-mediated myocarditis has been extrapolated from myocarditis of other aetiologies. The optimal dosing of corticosteroids and timing for the addition of other immunosuppressants is unclear. While the consensus for the initial steroid dose is an equivalent dose of (methyl)prednisolone 1–2 mg/kg [35,36], some experts suggest using methylprednisolone 1 g daily upfront [37]. Higher initial dose of steroids is associated with a lower risk of MACE ((methyl)prednisolone dose: 160 mg versus 72.5 mg; $p = 0.055$) [12]. In our series, prompt initiation of high-dose corticosteroids rapidly normalised cardiac enzyme in three of five patients (Fig. 2). Case 2 and 3 received methylprednisolone 1 g daily upfront in part because of their higher initial hs-TnT. Some patients required the addition of MMF and IVIg in the setting of persistent troponin elevation. Antithymocyte globulin, IVIg, and infliximab have been used in steroid refractory cases of myocarditis, although infliximab is not preferred at higher dosing given its association with cardiac failure [12,15,38]. Tacrolimus and ciclosporin could be considered in refractory cases given their efficacy in treating allograft rejection however this should be done in the setting of a conclusive diagnosis of myocarditis [39]. Importantly, high-dose immunosuppression must be weighed against the risk of reversing desired anti-tumour immunity. In this series, three of the four responders maintained partial or complete metabolic responses. One patient had stable disease at the time of myocarditis diagnosis, but developed tumour progression 4.6 months later. Another patient never responded to ICI.

The long-term sequelae of immune-mediated myocarditis are yet to be characterised. In a retrospective case series of patients with immune-mediated myocarditis, an elevated discharge troponin T (>1.5 ng/ml) was associated with a four fold increased risk of MACE, suggesting prolonged low-grade inflammation is detrimental [12]. There is currently no evidence to guide the need for cardiac monitoring, optimal follow-up strategy or the role of cardioprotective therapies in patients with persistent myocardial inflammation due to ICI and/or TKI.

5. Conclusion

We highlight the challenges in the diagnosis and management of immune-mediated myocarditis. CMRI and FDG-PET are useful diagnostic tools that warrant further evaluation. Immune-mediated myocarditis is an important clinical event requiring prompt diagnosis and multidisciplinary management. Future clinical trials combining ICI and TKI need to prospectively collect biomarkers of toxicity to facilitate the mechanistic dissection of this serious side effect.

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Conflict of interest statement

Shahneen Sandhu reports receiving honoraria from Merck Sharp & Dohme, Merck Serono, Janssen, AstraZeneca, Bristol-Myers Squibb, and Amgen, outside the submitted work; grants from Bristol-Myers Squibb, Merck Sharp & Dohme, and AstraZeneca, outside the submitted work.

Peter K. H. Lau reports receiving honoraria from Bristol-Myers Squibb and Pfizer, outside the submitted work; travel grant from Bristol-Myers Squibb, outside the submitted work.

Other authors do not have any conflict of interest to declare.

Appendix A. Clinical characteristics of six patients with immune-mediated myocarditis.

Case	Age Sex	Mutational status	Stage and site of metastatic disease	LDH (Normal: 120–250 U/L)	Comorbidities	Prior systemic therapy	Treatment resulting in myocarditis	Time of onset	Clinical Present-ation	Other symptoms/ signs	Other irAE(s)
1	74M	BRAF/ NRAS/KIT wild-type	Stage IV (M1a): Distant skin metastases	188 U/L	Hypertension, obesity (BMI 37)	Pembrolizumab x 34 cycles	Cobimetinib (60 mg PO OD) and atezolizumab (840 mg IV 3-weekly)	C1D15 (D15)	CK & troponin rise, fatigue	Fever*, chills*, anorexia*, diarrhoea*, rash*, serous retinopathy*	None
2	60F	BRAF wild-type NRAS Q61K	Stage IV (M1c): Chest wall, greater omentum, neck LN, mediastinal LN	249 U/L	Nil significant	Pembrolizumab x 12 cycles	Cobimetinib (60 mg PO OD) and atezolizumab (840 mg IV 3-weekly)	C1D13 (D13)	CK & troponin rise	Nausea*, vomiting*, diarrhoea*, mucositis*	Immune nephritis after 2 cycles of ipilimumab-plus-nivolumab administered 3 months after the cessation of cobimetinib and atezolizumab
3	75M	BRAF wild-type	Stage IV (M1c): Lung & small bowel	222 U/L	Hypertension, dyslipidaemia, ulcerative colitis, hyperthyroidism, pulmonary embolism, obesity (BMI 36)	None	Pembrolizumab (2 mg/ kg IV 3-weekly)	C1D20 (D20)	Fatigue, weight loss	Back pain, neck pain, truncal weakness, proximal limb weakness	Concurrent myositis
4	74F	NRAS Q61R mutant	Stage IV (M1c): Subcutaneous, adrenal gland	224 U/L	Type 2 diabetes, hypertension, multinodular goitre, non-ST elevation myocardial infarction, congestive cardiac failure (NYHA class I), chronic kidney disease (stage 3), overweight (BMI 29)	None	Pembrolizumab (2 mg/ kg IV 3-weekly)	C2D16 (D37)	Exertional dyspnoea	Proximal limb girdle weakness	Myositis 5 weeks after initiation of corticosteroids for myocarditis
5	88M	BRAF/ NRAS/KIT wild-type	Stage IV (M1a): Parotid LN, facial LN, cervical LN, abdominal LN	Not available	Hypertension, hypercholesterolaemia, transient ischaemic attack, chronic kidney disease (stage 2), hypothyroidism, congestive cardiac failure, obesity (BMI 30)	None	Pembrolizumab (2 mg/ kg IV 3-weekly)	C4D15 (D78))	Exertional dyspnoea	None	None
6	61M	BRAF wild-type	Stage IV (M1b): Lung	225 U/L	Overweight (BMI 26)	None	Pembrolizumab (2 mg/ kg IV 3-weekly)	C11D4 (D214)	Exertional dyspnoea	Diarrhea	Colitis 6 months after cessation of pembrolizumab

BD, twice daily; BMI, body mass index; irAE, immune-related adverse events; IV, intravenous; LN, lymph node; M, metastatic stage; OD, once daily; PO, per oral; *related to MEK inhibitor.

Appendix B. Key investigations and treatments of six patients with immune-mediated myocarditis.

Case	TTE	ECG	CMRI	Cardiac Enzymes hs-TnT (ULN: 20 ng/L) CK (normal range: 20–200 U/L)	Myocarditis management	Treatment discontinuation	Subsequent systemic therapy	Tumour response at the time of myocarditis diagnosis)	Current tumour response OS
1	Pre-treatment TTE: NA TTE at myocarditis onset: LVEF: 55% No valvular abnormality or regional wall motion abnormality TTE 6 weeks post myocarditis onset LVEF: 60%	Left-axis deviation (pre-existing)	Midwall myocardial oedema and LGE in the basal, mid anterolateral, mid-inferior segments	Initial/peak troponin: 77 ng/L Initial/peak CK: 1165 U/L	Methylprednisolone 2 mg/kg IV OD x 3 days → prednisolone 2 mg/kg PO OD weaned over 8 weeks Candesartan 8 mg PO OD	Yes	Limb infusion (melphalan and dactinomycin)	SD	PD 4.6 months after myocarditis diagnosis. OS: 18 months (alive)
2	Pre-treatment TTE: NA TTE at onset of myocarditis: LVEF: 55–60% No significant valvular pathology	Flattened T waves in lead II, III, AVF (new)	Mildly impaired LVEF (48%). No LGE or myocardial oedema	Initial/peak troponin: 377 ng/L Initial CK: 455 U/L Peak CK: 630 U/L	Methylprednisolone 1 mg/kg IV OD x 3 days → prednisolone 1 mg/kg PO OD tapered over 6 weeks.	Yes	Developed intracranial metastases 3 months after the diagnosis of myocarditis and received 2 cycles of ipilimumab and nivolumab	PD	PD OS: 4.9 months (alive)
3	Pre-treatment TTE: NA TTE at myocarditis onset: LVEF: 68% Mild mitral regurgitation and mild tricuspid regurgitation.	Normal	Epicardial LGE in the basal septal and inferoseptal segments without subendocardial enhancement.	Initial/peak troponin: 2978 ng/L Initial/peak CK: 13,025 U/L	Methylprednisolone 1 g IV OD x 3 days → methylprednisolone 1 mg/kg for 7 days → predniso-lone 1 mg/kg weaned over 8 weeks Mycophenolate mofetil (up-titrated to 1.5 g PO BD). All immunosuppression ceased after 6 months. Perindopril 5 mg PO OD Frusemide 40 mg PO OD	Yes	None	PMR	PMR OS: 20.5 months (alive)
4	Pretreatment TTE: LVEF 57%, hypokinesis is of inferior wall, basal to mid-posterior and lateral wall. TTE at myocarditis	Right bundle branch block, deep Q waves in lead II, III, aVF, T wave inversion in V5-6, lead I and AVL (pre-existing)	First MRI: epicardial LGE and oedema in the anterior, basal, mid-inferolateral and lateral myocardial segments as well as inferolateral partial	Initial troponin: 106 ng/L Peak troponin: 501 ng/L Initial CK: 395 U/L Peak CK: 3769 U/L	Methylprednisolone 2 mg/kg IV OD x 4 days → methylprednisolone 1 g IV OD x 3 days → prednisolone 2 mg/kg OD weaned to 50 mg after 5 weeks.	Yes	None	PMR	PMR OS: 4.2 months (alive)

	onset: LVEF 35%. Areas of hypokinesis unchanged from baseline TTE 1 month after myocarditis onset LVEF: 50%		thickness infarct and akinesis. Second MRI 6 weeks later: less pronounced LGE in the same distribution. Inferolateral partial thickness infarct remains unchanged.		Mycophenolate 1 g PO BD added 5 days after initiation of methylprednisolone in the setting of myositis 5 weeks after starting corticosteroids Methylprednisolone increased to 2 mg/kg IV OD x 3 days → prednisolone 2 mg/kg PO OD weaned over 10 weeks. IVIg (2 g/kg/day) for 3 days, then 0.4 g/kg monthly maintenance Frusemide 40 mg PO OD (pre-existing) Spironolactone 25 mg PO OD Perindopril 5 mg PO OD (pre-existing) Bisoprolol 2.5 mg PO OD (pre-existing) Aspirin 100 mg PO OD (pre-existing)				
5	Baseline TTE: NA TTE at myocarditis onset: LVEF: 18% Mild-moderate aortic regurgitation, mild mitral regurgitation	Normal	Subendocardial LGE in the inferolateral wall. Scattered foci of midwall LGE affecting the septum.	Initial/peak troponin: 2146 ng/L Initial/peak CK: 126 U/L	Methylprednisolone 1 g × 3 days →prednisolone 2 mg/kg weaned over 6 weeks. Perindopril 5 mg PO OD (pre-existing) Spironolactone 25 mg PO OD Frusemide 40 mg PO OD	Yes	None	PMR	No further disease-assessment Died of cardiac failure 2.1 months post myocarditis diagnosis
6	Baseline TTE: LVEF 48%, mild aortic and mitral regurgitation, mild LV hypertrophy TTE at myocarditis onset: LVEF: 31% TTE 6 months after myocarditis onset LVEF: 45%. TTE 18 months after myocarditis onset LVEF: 51%.	Left bundle branch block (pre-existing)	Midwall LGE in the basal inferolateral wall and septum	NA	Nebivolol 2.5 mg PO OD Ramipril 2.5 mg PO OD Frusemide 40 mg PO OD	Yes	None	CMR	Ongoing CMR at 28.3 months (alive)

ACE, angiotensin converting enzyme; BD, twice daily; CK, creatine kinase; CMR, complete metabolic response, CMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; hs-TnT, highly-sensitive cardiac troponin T; IV, intravenous; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction, NA, not available; OD, once daily; PMR, partial metabolic response; CMR, complete metabolic response; PO, per oral; TTE, transthoracic echocardiogram.

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