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Tsun-Ho LAM

*Cardiology Division, Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong*

Jeffrey Sum-Lung WONG

*Medical Oncology Division, Department of Medicine, Queen Mary Hospital*

Chun-Ka WONG

*Cardiology Division, Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong*

Gerry Gin Wai KWOK

*Medical Oncology Division, Department of Medicine, Queen Mary Hospital*

Miaochang ZHOU

*Department of Adult Intensive Care Unit, Queen Mary Hospital*

*See next page for additional authors*

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### Recommended Citation

Tsun-Ho LAM, Jeffrey Sum-Lung WONG, Chun-Ka WONG, Gerry Gin Wai KWOK, Miaochang ZHOU, Benjamin Yu-Fai SO, Ian Yu-Hin LEUNG, Hung-Fat TSE, From Bad to Worse: The Clinical Spectrum of Immune Checkpoint Inhibitor Myocarditis and Associated 3M Syndrome with Concomitant Myositis and Myasthenia *Journal of the Hong Kong College of Cardiology* 2022;29(3):135-142 <https://doi.org/10.55503/2790-6744.1484>

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# From Bad to Worse: The Clinical Spectrum of Immune Checkpoint Inhibitor Myocarditis and Associated 3M Syndrome with Concomitant Myositis and Myasthenia

## Authors

Tsun-Ho LAM, Jeffrey Sum-Lung WONG, Chun-Ka WONG, Gerry Gin Wai KWOK, Miaochang ZHOU, Benjamin Yu-Fai SO, Ian Yu-Hin LEUNG, and Hung-Fat TSE

## CASE REPORT

# From Bad to Worse: The Clinical Spectrum of Immune Checkpoint Inhibitor Myocarditis and Associated 3M Syndrome with Concomitant Myositis and Myasthenia

Tsun-Ho Lam <sup>a,1</sup>, Jeffrey Sum-Lung Wong <sup>b,1</sup>, Chun-Ka Wong <sup>a,1</sup>, Gerry Gin-Wai Kwok <sup>b</sup>, Miaochang Zhou <sup>c</sup>, Benjamin Yu-Fai So <sup>d</sup>, Ian Yu-Hin Leung <sup>e</sup>, Hung-Fat Tse <sup>a,\*</sup>

<sup>a</sup> Cardiology Division, Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

<sup>b</sup> Medical Oncology Division, Department of Medicine, Queen Mary Hospital, Hong Kong, China

<sup>c</sup> Department of Adult Intensive Care Unit, Queen Mary Hospital, Hong Kong, China

<sup>d</sup> Nephrology Division, Department of Medicine, Queen Mary Hospital, Hong Kong, China

<sup>e</sup> Neurology Division, Department of Medicine, Queen Mary Hospital, Hong Kong, China

## Abstract

Immune checkpoint inhibitors (ICIs), though revolutionizing cancer care, are well known to cause a diverse array of autoimmune side effects termed immune-related adverse events (IRAEs). ICI Myocarditis is a rare manifestation of IRAE associated with high mortality. We report two cases of fulminant ICI myocarditis refractory to potent immunosuppressants. Our first patient received pembrolizumab for lymphoma, small cell lung cancer and renal cell carcinoma. After 13 doses of ICIs, he developed fulminant myocarditis with concomitant lower-motor neuron type facial nerve palsy. Despite receiving triple immunosuppressive therapies with pulse steroid, mycophenolate mofetil and basiliximab, his cardiac condition progressively worsened and eventually died of heart failure. Our second patient received dual ICIs with pembrolizumab and ipilimumab for inoperable hepatocellular carcinoma. Shortly after first doses of ICIs, he developed 3M syndrome with the classically described triad of Myocarditis, Myositis and bulbar Myasthenia gravis. Despite receiving pulse steroid, mycophenolate mofetil, tacrolimus, plasmapheresis and intravenous immunoglobulin, he had persistent myocardial inflammation with elevated troponin level, and refractory bulbar myasthenia requiring mechanical ventilation and nasogastric tube feeding. Our case series illustrates challenges with managing ICI myocarditis and its associated clinical syndromes including the 3M syndrome. Given the wide application of ICIs, clinical trials as well as preclinical studies are urgently needed to find out the optimal therapy for ICI myocarditis. As early identification of ICI myocarditis allows prompt cessation of ICIs and initiation of immunosuppressants, which may potentially improve cardiovascular outcome of these patients, it is also crucial to determine to optimal strategies for screening ICI myocarditis.

**Keywords:** Immune checkpoint inhibitor, Anti-PD1, Anti-CTLA-4, Myocarditis, Myositis, Myasthenia gravis, 3M syndrome

*Abbreviations:* ASCO, American Society of Clinical Oncology; ECG, Electrocardiogram; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; ICI, Immune checkpoint inhibitor; IRAE, Immune-related adverse events; IVIG, Intravenous immunoglobulin; LGE, Late gadolinium enhancement; LVEF, Left ventricular ejection fraction; MRI, Magnetic resonance imaging; NT-proBNP, N-terminal pro-b-type natriuretic peptide; PD-1, Programmed cell death protein 1; PD-L1, Programmed death ligand 1; PET-CT, Positron emission tomography-computed tomography; PE, Pulmonary embolism; RCC, Renal cell carcinoma; SCLC, Small cell lung cancer; TACE, Transarterial chemoembolization,



Received 7 July 2022; accepted 12 August 2022.  
Available online 23 September 2022

\* Corresponding author at: Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China. Fax: (852) 2818 6304.  
E-mail address: [hftse@hku.hk](mailto:hftse@hku.hk) (H.-F. Tse).

<sup>1</sup> These authors contributed equally.

<https://doi.org/10.55503/2790-6744.1484>

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## Introduction

Immune checkpoint inhibitors (ICIs) have been increasingly utilized in recent years owing to their potent effect against a wide range of malignancies. Immune-related adverse events (IRAEs) may occur as a result of autoimmunity from activated lymphocytes and the immune system. IRAEs may affect virtually any organs such as skin, thyroid, lungs, heart, gut, adrenal glands and nervous systems [1]. ICI myocarditis is a rare complication of immunotherapy associated with high mortality [2]. Prompt initiation of potent immunosuppression is necessary to reduce myocardial injury. We report two cases of fulminant ICI myocarditis that were refractory to potent immunosuppression to illustrate the challenges with managing this newly emerged disease entity.

## Case 1

A 71-year-old Chinese man was diagnosed to have stage 4 cytotoxic T cell lymphoma, gastric cancer, renal cell carcinoma (RCC) and small cell lung cancer (SCLC) within a span of 1.5 years. After he received distal radical gastrectomy for his gastric cancer, systemic therapy for his remaining malignancies was started per a multidisciplinary team decision, with priority given to his lymphoma. Pre-chemotherapy echocardiography in 2021 showed normal left ventricular systolic function with structurally normal valves. He was subsequently given 5 cycles of SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) for his lymphoma from April to December 2020. Reassessment positron emission tomography-computed tomography (PET-CT) showed metabolic response of his lymphoma but disease progression of his RCC and SCLC. He then received the anti-programmed cell death protein 1 (PD-1) antibody pembrolizumab 200 mg every 4 weeks as both maintenance therapy for his lymphoma and first-line treatment for his SCLC and RCC. From March 2021 to January 2022, he was given 13 doses of pembrolizumab, which were well tolerated aside from grade 2 IRAE endocrinopathies (hypothyroidism and adrenal insufficiency) requiring thyroxine and hydrocortisone replacements.

In February 2022, he was admitted for pleuritic chest pain and left lower motor neuron type facial nerve palsy. 12-lead electrocardiogram (ECG) showed ST segment elevation and deep T wave inversion over V2 to V6. Peak troponin T level during hospital stay was 104 ng/L (Figure 3A)

Echocardiography showed impaired left ventricular ejection fraction (LVEF) of 45% with no pericardial effusion. Coronary angiogram and endomyocardial biopsy were offered to the patient to rule out coronary artery disease and to obtain histological diagnosis. Nonetheless, patient declined both procedures in view of advanced malignancy. Empirical treatment with prednisolone 50 mg daily was given for possible ICI related facial nerve palsy and myocarditis. One month later, he was readmitted for atrial fibrillation with rapid ventricular rate and cardiogenic shock requiring inotropic support, with a blood pressure on admission of 90/60 mmHg and pulse rate of 135 beats per minute. ECG showed atrial fibrillation with similar ST segment elevation over leads V2 to V6. Initial troponin T was 2167 ng/L, creatinine kinase was 284 U/L, N-terminal pro-b-type natriuretic peptide (NT-proBNP) was 10,011 ng/L and lactate was 5.8 mmol/L (Figure 3A) Echocardiography showed a LVEF of 15% with global hypokinesia and circumferential pericardial effusion up to 1.7 cm with no tamponade effect. Coronary angiogram and endomyocardial biopsy were again offered but refused by the patient. Cardiac magnetic resonance imaging (MRI) was performed and showed globally hypokinetic left ventricle with LVEF 12% associated with a left ventricular thrombus (Figure 1). In addition, extensive transmural myocardial infiltration involving left and right ventricular apices and interventricular septum with positive late gadolinium enhancement (LGE) of non-ischemic pattern was present, compatible with myocarditis. In view of compatible history and investigation findings, a presumptive diagnosis of ICI peri-myocarditis was made. Ischemic cardiomyopathy was considered less likely in view of the non-ischemic patterns demonstrated on MRI. Alternative etiologies of heart failure such as Takotsubo cardiomyopathy are uncommonly associated with the constellation of thyroiditis, adenitis and neuritis manifested in this patient. He was started on pulse steroid with methylprednisolone 1000 mg daily for 3 days. From day 4 onwards, methylprednisolone 1 mg/kg daily were given with mycophenolate mofetil 1000 mg twice daily was later added on day 6. He initially responded to treatment with partial improvement of troponin T level to 295 ng/L on day 4 of pulse steroid, restoration of sinus rhythm and reduction in pericardial effusion. However, his NT-proBNP remained markedly elevated at > 16,000 ng/L and he remained inotrope-dependent requiring concurrent noradrenaline and dopamine infusions. He declined insertion of mechanical circulatory support and his condition progressively deteriorated. Plasmapheresis was not considered

owing to the unstable hemodynamic status. Since ICI myocarditis is a T cell-driven condition, we administered 2 doses of the interleukin-2 (IL-2) receptor antagonist basiliximab 20 mg IV, given 4 days apart. Although experience with basiliximab is sparse in the management of IRAEs, basiliximab has been successfully used as induction therapy in solid organ transplantation and as salvage therapy for steroid-refractory graft-versus-host disease in haematopoietic stem cell transplantation. IL-2 receptor blockade rapidly and effectively inhibits proliferation of activated T cells. Experience from solid organ and bone marrow transplantation suggests high tolerability and a low risk of infusions reactions or infective complications, especially compared to alternative T-cell specific antibody therapies such as anti-thymocyte globulin or alemtuzumab. Nevertheless, he further deteriorated and eventually succumbed 10 days after initiation of pulse steroid.

## Case 2

A 75-year-old Chinese man, who was an ex-smoker with hypertension, diabetes mellitus, hyperlipidemia, and benign prostatic hypertrophy, had advanced hepatocellular carcinoma (aHCC) presenting with tumor rupture requiring urgent transarterial chemobolization (TACE) and pulmonary embolism in late 2021. Anti-vascular endothelial growth factor antibodies and tyrosine kinase inhibitor were considered extremely high risk in view of his history of ruptured HCC. After discussion, he opted for treatment with the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody ipilimumab 1 mg/kg and pembrolizumab 2 mg/kg, given in combination every 3 weeks. Pre-ICI echocardiography showed normal left ventricular systolic function. After six weeks of treatment with 2 doses of ICIs given, he was admitted for further assessment with complaints of 2 weeks' history of shortness of breath and myalgia. On admission, he was afebrile with a blood pressure of 174/84 mmHg, pulse rate of 116 beats per minute and fully preserved muscle power over all four limbs (Medical Research Council grade 5/5). ECG showed sinus rhythm with no ST segment or T wave changes. Initial blood tests showed elevated creatine kinase 2515 U/L, troponin T 1350 ng/L and NT-proBNP 413 ng/L (Figure 3B). Electromyography demonstrated features suggestive of inflammatory myositis. Echocardiography showed normal left ventricular cavity size and systolic function with no pericardial effusion. Cardiac MRI showed patchy intramural delayed myocardial enhancement at basal septal, inferior and mid inferolateral left ventricular wall. Coronary

angiogram only showed moderate stenosis over left anterior descending artery (Figure 2), which was not accountable for the persistently elevated troponin level and the extensive myocardial involvement in MRI. Endomyocardial biopsy showed diffuse inflammatory infiltration consisting of mostly polymorphs and occasional eosinophils. Expression of programmed death-ligand 1 (PD-L1) was assessed using PD-L1 (E1L3N) XP rabbit monoclonal antibody (Cell Signaling Technology, USA). PD-L1 expression was completely absent in cardiomyocytes, while weak staining was observed in <5% infiltrating lymphoid cells. No viral inclusion bodies, granuloma or giant cells were detected. Microbiological investigations including polymerase chain reaction for enterovirus, parvovirus B19, severe acute respiratory syndrome coronavirus 2, and mycobacterium tuberculosis nucleic acid were negative. Overall histological diagnosis was consistent with polymorphic myocarditis.

With the overall clinical picture being compatible with ICI-related myositis and myocarditis, he was started on methylprednisolone 1000 mg for three days on the second day of admission, followed by methylprednisolone 1 mg/kg and mycophenolate mofetil 1,000 mg twice daily. On day four of admission, he developed severe dysphagia and type 2 respiratory failure requiring emergency intubation, mechanical ventilation and admission into the intensive care unit. Physical examination demonstrated bilateral ptosis and fatigability over eyelids with intact limb power. Despite electromyography of limbs with repetitive nerve stimulation showing no evidence of significant polyneuropathy or neuromuscular junction disorder, the clinical features were highly suspicious of bulbar myasthenia gravis and he was thus given intravenous immunoglobulin (IVIG) for 5 days followed by 3 sessions of plasmapheresis as well.

After commencement of immunosuppressants, his troponin T initially improved to 780 ng/L but subsequent rebounded to 2573 ng/L as steroid was tapered, after which tacrolimus was added on the third week of admission. Reassessment echocardiography one week later showed preserved biventricular systolic function with LVEF of 60%. Nevertheless, he remained dependent on nasogastric tube for feeding and mechanical ventilation for respiratory support. After 2 weeks of intensive care unit stay, the patient opted for comfort care and requested withdrawal of invasive therapies. The patient's autonomy was respected after thorough discussion involving relatives, intensivists, and neurologists. He eventually succumbed 28 days after admission.

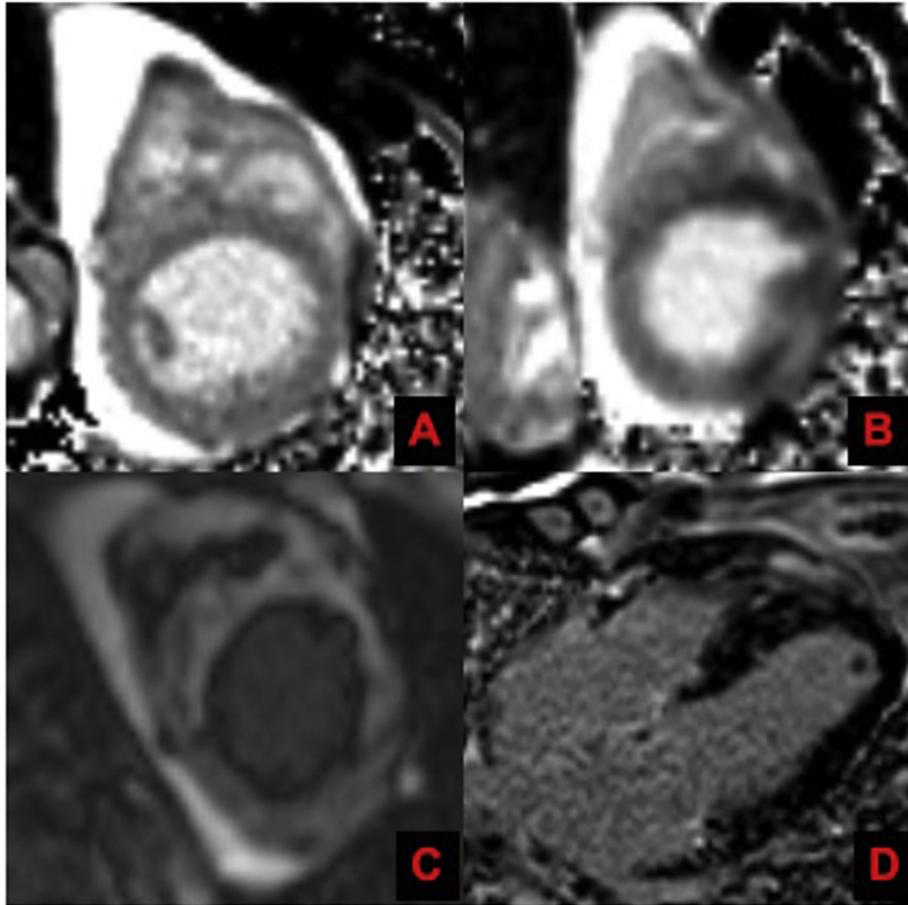


Figure 1. Cardiac magnetic resonance imaging (MRI) of the left ventricle at (A) mid, and (B) apical levels demonstrated patchy non-ischemic infiltrates involving left ventricular apex, right ventricular apex and interventricular septum. (C) Late gadolinium enhancement was seen in the same areas at left ventricular apical level. (D) Pericardial effusion with no tamponade and left ventricular apical thrombus were present.



Figure 2. Coronary angiogram only revealed moderate left anterior descending artery stenosis, which was not accountable for the persistently elevated troponin level and the extensive myocardial involvement in magnetic resonance imaging.

## Discussion

Myocarditis is a rare but highly fatal IRAE, with a reported incidence of 0.06–1.14% but mortality of 25–50% [2,3]. Due to the novelty and rarity of the condition, relevant literature is scant. The majority of ICI myocarditis appears to occur within the first 3 months of ICI treatment, but onset of more than 18 months after ICI commencement has been documented. Patients with ICI myocarditis are more likely to have received combination ICI therapies with anti-CTLA-4 and anti-PD-1/L1 and suffering from diabetes mellitus [2]. Common manifestations include heart failure, complete heart block, ventricular arrhythmia and sudden death [2]. Intriguingly, although IRAEs frequently co-exist with each other, ICI myocarditis seems to have particularly strong associations with myositis and peripheral nervous system disorders, most commonly myasthenia gravis. Our first patient had lower-motor neuron type facial nerve palsy with a similar onset time to myocarditis, and our second patient had 3M

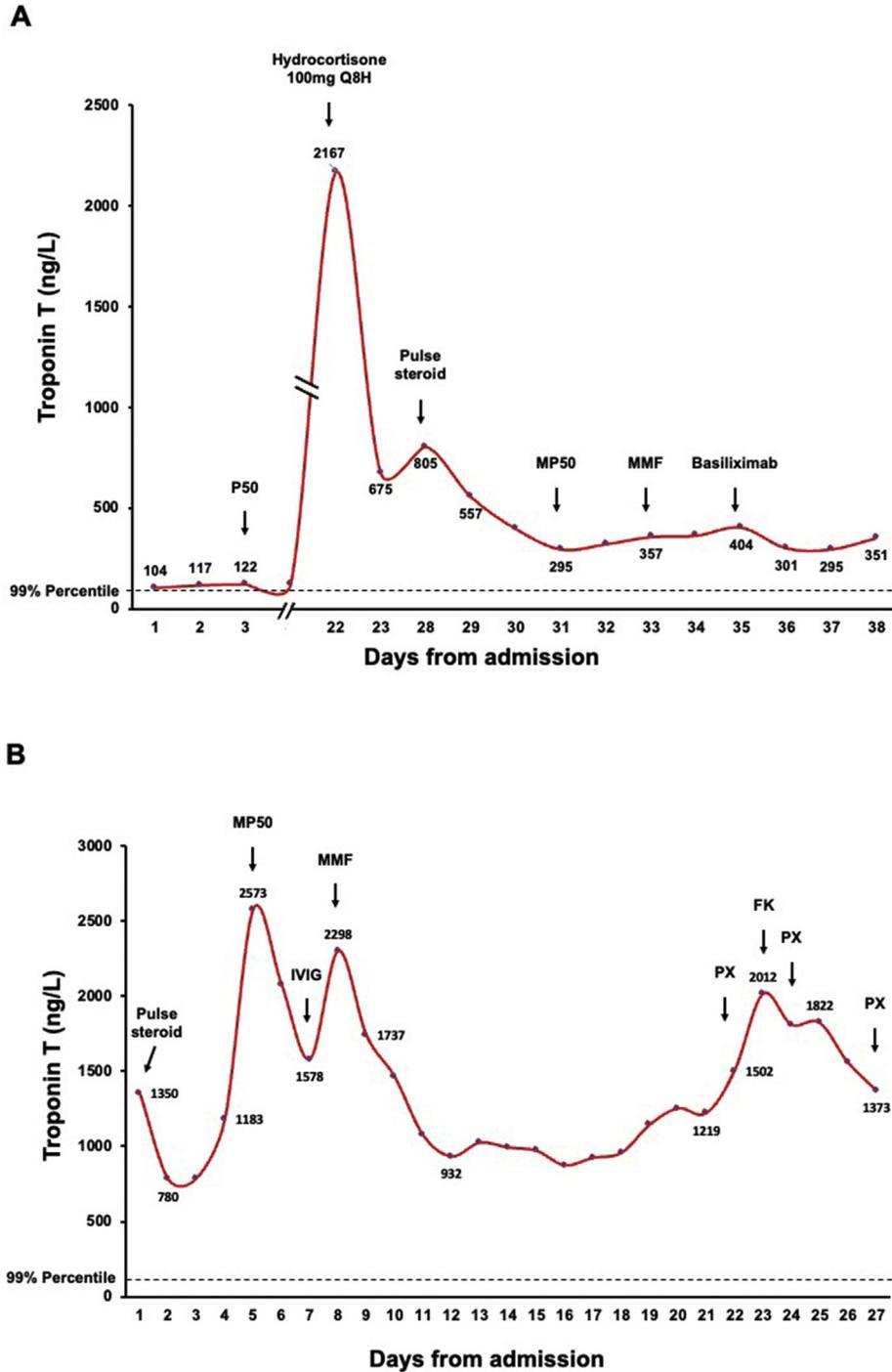


Figure 3. Temporal relationship between immunosuppressive therapy and cardiac enzyme levels of the two patients. (A) Pulse steroid, mycophenolate mofetil and basiliximab were given to the first patient. (B) Pulse steroid, mycophenolate mofetil, tacrolimus and plasmapheresis were given to the second patient. Abbreviations: FK, tacrolimus; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; MP50: methylprednisolone 50 mg daily; P50: Prednisolone 50 mg daily; PX: plasmapheresis.

syndrome, comprising the classically described triad of myocarditis, myositis and bulbar myasthenia gravis [4–10].

To understand the pathophysiology of ICI myocarditis, it is necessary to first revisit the underlying mechanisms that prevent autoimmunity

against the heart [11–14]. T cells that are auto-reactive against cardiomyocyte antigens undergo negative selection during central tolerance induction of thymic development [15]. Nevertheless, some T cells that are reactive against cardiac antigens are not eliminated in the central tolerance phase, and

peripheral tolerance mechanisms in heart draining lymph nodes are responsible for inhibiting these autoreactive T cells, via regulatory T cells and CTLA-4 mediated block in costimulation [16]. In the myocardium, tissue-based tolerance mechanisms are also in place to further prevent autoimmunity against the heart, including expression of PD-L1 by cardiomyocytes. Binding of cardiomyocytes PD-L1 with lymphocyte PD1 blocks antigen and costimulator activation of T cells. Anti-PD1 therapeutics increases risk of autoimmune myocarditis by inhibiting the PD1-PD-L1 axis and activating effector T cells. Interestingly, contrary to the expectation that T cell infiltration leads to increased interferon- $\gamma$  secretion and upregulated PD-L1 expression in cardiomyocytes as a protective measure against autoimmunity [17,18], we observed no PD-L1 expression by cardiomyocytes in immunohistochemistry studies of the second patient. The relative lack of PD-L1 expression may further exacerbate impairment of the PD1-PD-L1 axis. Anti-CTLA-4 therapeutics impairs mechanisms in secondary lymphoid organs that prevent naïve autoreactive T cell activation. Furthermore, as CTLA-4 is essential for regulatory T cell functions [19], blockade of CTLA-4 impairs regulatory T cell and increases risk of autoimmunity.

There is no international consensus regarding the optimal immunosuppressants regimen in ICI myocarditis. The 2018 American Society of Clinical Oncology (ASCO) Guidelines recommends permanent discontinuation of ICI and initiation of steroid at 1–2 mg/kg of prednisolone, and in patients without immediate response, to administer pulse steroid with methylprednisolone 1,000 mg per day [20]. Alternatively, the French Working Group of Cardio-Oncology recommend up-front pulse steroid with methylprednisolone 1000 mg per day [21], as higher dose steroid was associated with lower risk of MACE in a large cohort of patients with ICI myocarditis [2]. A second agent is often required to suppress myocardial inflammation, especially when steroid is being tapered, with commonly recommended choices being mycophenolate, infliximab or anti-thymocyte globulin [20]. Agents including abatacept [22], plasmapheresis [5], and IVIG [6] have also been reported. In both of our patients, despite administration of pulse steroid with methylprednisolone 1000 mg per day and mycophenolate as second agent, normalization of troponin was not achieved, though some response was noted. Available literature suggests that it is indeed not uncommon to have protracted troponin elevation despite potent immunosuppression with 2–3 agents, even amongst patients who survived ICI

myocarditis [23]. As illustrated by our cases, the high fatality of the condition is likely multi-factorial, including difficulties inherent in diagnosing a rare and novel entity, rapid progression to hemodynamic failure, incessant myocardial damage despite potent immunosuppression, the co-existence of debilitating myositis and peripheral nervous system IRAEs and finally side effects of profound immunosuppression. Given the wide application of ICIs, clinical trials are urgently needed to find out the optimal therapy for ICI myocarditis. ATRIUM (NCT05335928) and ACHLYS (NCT05195645) are two on-going prospective studies investigating the use of abatacept for treatment of ICI myocarditis. In addition, animal models have been developed to facilitate pathophysiology studies and drug screening [24–27].

Early identification of ICI myocarditis allows prompt cessation of ICI and initiation of immunosuppressants, which may potentially improve cardiovascular outcome of these patients. Therefore, it is imperative to determine to optimal strategy for screening myocarditis among ICI recipients. Multiple strategies for screening ICI myocarditis have been proposed, although no direct comparisons exist [21]. The first is symptom-driven, with patients receiving cardiac investigations including ECG and blood tests for troponin and BNP if they develop symptoms or signs of heart failure or arrhythmia. The second is systematic screening, by which all patients receive regular ECGs and blood tests for troponin and natriuretic peptide after each cycle of ICI regardless of whether they are symptomatic. In a recent study investigating the use of systematic screening approach in 214 patients receiving ICI alone or in combination, 11.2% had raised troponin I and 1.4% had ICI myocarditis [28]. Nonetheless, systematic screening is yet to be widely adopted as more studies is required to clarify its impact on prognosis and perform cost-benefit analysis. Our center is currently adopting symptom-driven strategy for identifying ICI myocarditis. ECG and cardiac enzymes are performed if patients develop new symptoms suggestive of possible cardiac etiologies. Prompt reaction and joint care by oncologists and cardiologists will be initiated if abnormalities are detected.

It is crucial for clinicians to remain highly vigilant in detection of this rare but lethal complication of ICI. Nevertheless, alternative explanations of a new onset heart failure and cardiogenic shock should always be thoroughly investigated. Risk and benefit of invasive and non-invasive diagnostic modalities must be carefully balanced as patients usually have poor Eastern Cooperative Oncology Group (ECOG) functional status on presentation and have

complicated past medical history. Patient's hemodynamic stability must be taken into consideration before invasive procedure. Conservative approach with noninvasive imaging test was adopted in the first case. Specific attention to pattern of abnormalities on MRI, such as LGE patterns, is key to exclude acute myocardial infarction with territorial abnormalities.

### Limitation

Our case series has several limitations. First, endomyocardial biopsy and histological analysis of the first patient was not available as patient declined the procedure. Diagnosis of myocarditis was established using clinical and MRI criteria. Second, as our second patient passed away owing to type 2 respiratory failure, we could not assess the long-term effect of myocarditis and immunosuppressive therapies he received.

### Conclusion

ICI myocarditis is a rare but highly fatal IRAE, with a disease course potentially refractory to immunosuppression despite early recognition and aggressive treatment. Further research is needed to develop better treatment options and screening strategies.

### Acknowledgement

The authors would like to thank all clinicians who contributed to managing the patients from this case series.

### Ethical statement

Written consent were obtained from both patients for publication of case reports.

### Conflict of Interest

The authors report no conflict of interest.

### Funding

This study was partly supported by Li Shu Fan Medical Fellowship, by Li Ka Shing Faculty of Medicine, The University of Hong Kong, and Hong Kong Sanatorium & Hospital, Hong Kong SAR.

### References

[1] Lui DTW, Lee CH, Tang V, Fong CHY, Lee ACH, Chiu JWY, et al. Thyroid immune-related adverse events in patients with cancer treated with anti-PD1/anti-CTLA4 immune

checkpoint inhibitor combination: clinical course and outcomes. *Endocr Pract* 2021;27:886–93.

[2] Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzlering LM, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;71:1755–64.

[3] Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016;375:1749–55.

[4] Valenti-Azcarate R, Esparragosa Vazquez I, Toledano Illan C, Idoate Gastearena MA, Gallego Perez-Larraya J. Nivolumab and Ipilimumab-induced myositis and myocarditis mimicking a myasthenia gravis presentation. *Neuromuscul Disord* 2020;30:67–9.

[5] Wakefield C, Shultz C, Patel B, Malla M. Life-threatening immune checkpoint inhibitor-induced myocarditis and myasthenia gravis overlap syndrome treated with abatacept: a case report. *BMJ Case Rep* 2021;14.

[6] Yanase T, Moritoki Y, Kondo H, Ueyama D, Akita H, Yasui T. Myocarditis and myasthenia gravis by combined nivolumab and ipilimumab immunotherapy for renal cell carcinoma: a case report of successful management. *Urol Case Rep* 2021;34:101508.

[7] Rajendram P, Torbic H, Duggal A, Campbell J, Hovden M, Dhawan V, et al. Critically ill patients with severe immune checkpoint inhibitor related neurotoxicity: a multi-center case series. *J Crit Care* 2021;65:126–32.

[8] Rhee JY, Torun N, Neilan TG, Guidon AC. Consider myocarditis when patients treated with immune checkpoint inhibitors present with ocular symptoms. *Oncol* 2022;27:e402–5.

[9] Wai Siu DH, O'Neill RS, Harris CA, Wang J, Ardolino L, Downton T, et al. Immune checkpoint inhibitor-induced myocarditis, myositis, myasthenia gravis and transaminitis: a case series and review. *Immunotherapy* 2022;14:511–20.

[10] Bai J, Li D, Yang P, Xu K, Wang Y, Li Q, et al. Camrelizumab-related myocarditis and myositis with myasthenia gravis: a case report and literature review. *Front Oncol* 2021;11:778185.

[11] Dong H, Qi Y, Kong X, Wang Z, Fang Y, Wang J. PD-1/PD-L1 inhibitor-associated myocarditis: epidemiology, characteristics, diagnosis, treatment, and potential mechanism. *Front Pharmacol* 2022;13:835510.

[12] Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A. Immune checkpoint inhibitor myocarditis: pathophysiological characteristics, diagnosis, and treatment. *J Am Heart Assoc* 2020;9:e013757.

[13] Grabie N, Lichtman AH, Padera R. T cell checkpoint regulators in the heart. *Cardiovasc Res* 2019;115:869–77.

[14] Varricchi G, Galdiero MR, Marone G, Criscuolo G, Triassi M, Bonaduce D, et al. Cardiotoxicity of immune checkpoint inhibitors. *ESMO Open* 2017;2:e000247.

[15] Hogquist KA, Baldwin TA, Jameson SC. Central tolerance: learning self-control in the thymus. *Nat Rev Immunol* 2005;5:772–82.

[16] Mueller DL. Mechanisms maintaining peripheral tolerance. *Nat Immunol* 2010;11:21–7.

[17] Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol* 2001;2:261–8.

[18] Hardy T, Yin M, Chavez JA, Ivanov I, Chen W, Nadasdy T, et al. Acute fatal myocarditis after a single dose of anti-PD-1 immunotherapy, autopsy findings: a case report. *Cardiovasc Pathol* 2020;46:107202.

[19] Wing K, Yamaguchi T, Sakaguchi S. Cell-autonomous and -non-autonomous roles of CTLA-4 in immune regulation. *Trends Immunol* 2011;32:428–33.

[20] Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J Clin Oncol* 2018;36:1714–68.

- [21] Thuny F, Alexandre J, Salem JE, Mirabel M, Dolladille C, Cohen-Solal A, et al. Management of immune checkpoint inhibitor-induced myocarditis: the French working group's plea for a pragmatic approach. *JACC CardioOncol* 2021;3:157–61.
- [22] Jespersen MS, Fano S, Stenor C, Moller AK. A case report of immune checkpoint inhibitor-related steroid-refractory myocarditis and myasthenia gravis-like myositis treated with abatacept and mycophenolate mofetil. *Eur Heart J Case Rep* 2021;5:ytab342.
- [23] Miyauchi Y, Naito H, Tsunemori H, Tani R, Hasui Y, Miyake Y, et al. Myocarditis as an immune-related adverse event following treatment with ipilimumab and nivolumab combination therapy for metastatic renal cell carcinoma: a case report. *J Med Case Rep* 2021;15:508.
- [24] Liu SY, Huang WC, Yeh HI, Ko CC, Shieh HR, Hung CL, et al. Sequential blockade of PD-1 and PD-L1 causes fulminant cardiotoxicity-from case report to mouse model validation. *Cancers* 2019;11.
- [25] Wei SC, Meijers WC, Axelrod ML, Anang NAS, Screever EM, Wescott EC, et al. A genetic mouse model recapitulates immune checkpoint inhibitor-associated myocarditis and supports a mechanism-based therapeutic intervention. *Cancer Discov* 2021;11:614–25.
- [26] Wang J, Okazaki IM, Yoshida T, Chikuma S, Kato Y, Nakaki F, et al. PD-1 deficiency results in the development of fatal myocarditis in MRL mice. *Int Immunol* 2010;22:443–52.
- [27] Tay WT, Fang YH, Beh ST, Liu YW, Hsu LW, Yen CJ, et al. Programmed cell death-1: programmed cell death-ligand 1 interaction protects human cardiomyocytes against T-cell mediated inflammation and apoptosis response in vitro. *Int J Mol Sci* 2020;21.
- [28] Waliany S, Neal JW, Reddy S, Wakelee H, Shah SA, Srinivas S, et al. Myocarditis surveillance with high-sensitivity troponin I during cancer treatment with immune checkpoint inhibitors. *JACC CardioOncol* 2021;3:137–9.