Fulminant myocarditis caused by immune checkpoint inhibitor: a case report and possible treatment inspiration

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Abstract

Immune checkpoint inhibitors (ICIs) have become a new hope for many patients with advanced cancer by blocking tumour immune evasion. However, with the widespread use of ICIs, immune-related adverse events (irAEs) have also been discovered and reported increasingly. Immune-related myocarditis, the most dangerous one of irAEs, still has high mortality in the context of the current treatment. We report the case of a 60-year-old female with fulminant myocarditis induced by ICIs, which caused her to experience frequent ventricular arrhythmias such as ventricular fibrillation and heart failure. She was successfully treated with current mainstream therapies for immune-related myocarditis and additional treatment of sacubitril–valsartan and dapagliflozin. The intriguing observation that the patient condition recovered relatively rapidly in this case shows a possible treatment inspiration, which may be helpful for treating ICIs-associated myocarditis and improving cancer patients’ clinical prognosis.

Keywords
Immune checkpoint inhibitors; Myocarditis; Arrhythmia; Sacubitril/valsartan; SGLT2i

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Introduction

As the basis of self-immune tolerance in normal conditions, immune checkpoints, which mainly include programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen-4 (CTLA-4), enable cancer cells to escape immune-mediated destruction and proliferate under the tumour micro-environment.1 Immune checkpoint inhibitors (ICIs) have become a new hope for many patients with advanced cancer by blocking tumour immune evasion. However, with the widespread use of ICIs, immune-related adverse events (irAEs) have also been discovered and reported increasingly. Immune-related myocarditis with low morbidity and high mortality is considered as the most dangerous one of irAEs.1 Herein, we report a case of fulminant myocarditis caused by ICIs with the innovative proposal of a possible therapy.

Case report

A 60-year-old female patient was treated with camrelizumab after being diagnosed with pancreatic head metastasis from cholangiocarcinoma in June 2021. Her electrocardiogram (ECG) and transthoracic echocardiography (TTE) were normal before treatment (Figure 1A). About 6 weeks later, she suffered from an onset of progressive muscle weakness and shortness of breath for 4 days. ECG showed a short burst of ventricular tachycardia, accelerated idioventricular rhythm, and ST-T segment abnormalities (Figure 1B).
Cardiac troponin I (cTnI) was 2.2 ng/mL (normal value < 0.023 ng/mL). N-terminal pro-brain natriuretic peptide (NT-proBNP) was 3596 ng/L (normal value 300–900 ng/L). The coronary angiography showed 50% stenosis in the proximal right coronary artery (RCA) (Figure 2). With a prior history of diabetes mellitus, the patient’s physical examination showed bilateral ptosis, pulmonary moist rales, and grade 3 muscle strength. The patient later suffered frequently from Adams–Stokes syndrome with the ECG monitor showing ventricular fibrillation or ventricular tachycardia. She recovered consciousness soon after being treated with cardiopulmonary resuscitation, defibrillation/cardioversion, and so on repeatedly. However, she still presented frequent short bursts of ventricular tachycardia, and the blood pressure fluctuated around 80/40 mmHg. In response to that, we supported her with a
continuous intravenous drip of dopamine and administered amiodarone, followed by nifekalant. This elevated the patient’s blood pressure to around 100/70 mmHg but failed to eliminate ventricular arrhythmia. Laboratory tests revealed serum potassium 3.69 mmol/L (normal value 3.5–5.3 mmol/L), CTnI 4.0 ng/mL, pro-BNP 5240 ng/mL, creatine kinase (CK) 24 196 U/L (normal value 26–174 U/L), creatine kinase-myocardial band (CK-MB) 625 U/L (normal value < 25 U/L), alanine transaminase (ALT) 916 U/L (normal value < 40 U/L), and aspartate transaminase (AST) 1295 U/L (normal value < 35 U/L). TTE showed new wall motion abnormality with left ventricular ejection fraction (LVEF) of 34%.

Our diagnoses were fulminant myocarditis, immune myositis, and acute liver injury secondary to PD-1 inhibitor. Intravenous methylprednisolone (1 g/day) was started at once for 3 days (Day 2 to Day 4 of admission). We added intravenous immunoglobulin therapy (10 g/day) and mycophenolate mofetil (0.5 g/day) on Day 3 to Day 5 of admission. After that, the patient showed some improvement, with CTnI 1.2 ng/mL, pro-BNP 5100 ng/mL, CK 3542 U/L, CK-MB 138 U/L, ALT 546 U/L, AST 324 U/L, and still wall motion abnormality with LVEF of 38%. We then adjusted the dose of intravenous methylprednisolone (120 mg/day on Day 5 to Day 9 of admission) and mycophenolate mofetil (1 g/day). Additional treatment of sacubitril/valsartan (25–50 mg/bid) and dapagliflozin (10 mg/day) were given in view of her unresolved symptoms of heart failure (HF) and of her TTE result of the still low LVEF.

Subsequently, marked improvement was observed and her ventricular arrhythmia did not reappear with CTnI 0.072 ng/mL, CK 389 U/L, CK-MB 68 U/L, ALT 156 U/L, and AST 50 U/L. TTE showed wall motion returned to normal and LVEF increased to 61%. Therefore, we reduced the intravenous methylprednisolone dose to 60 mg/day (Day 10 to Day 15 of admission). Cardiac magnetic resonance imaging (CMR) revealed myocardial oedema and myocardial delayed enhancement (Figure 3). Repeat laboratory tests declined further. Intravenous methylprednisolone was changed to oral prednisone acetate tablets (30 mg/day) for patient. Eventually, the patient was discharged with normal laboratory examinations and ECG of sinus bradycardia and complete right bundle branch block (Figure 4D). We prescribed her oral methylprednisolone tablets (20 mg/day) and advised her to come back for a review after 1 week. The adjustment of the corticosteroids regimen and the changes in the serum myocardial markers during the patient’s hospitalization are shown in Figure 4.

Discussion
The presentations of ICIs-related myocarditis range from an asymptomatic elevation of cardiac biomarkers to severe clinical signs and symptoms, including ventricular arrhythmias, cardiogenic shock, and even sudden death.2 ECG was abnormal in 89% of patients, natriuretic peptides

![Cardiac magnetic resonance imaging.](image-url)
were abnormal in 66%, troponin was elevated in 94%, and the LVEF was normal in 51%.\textsuperscript{3} Using tissue characterization techniques such as T1-weighted and T2-weighted imaging along with late gadolinium enhancement imaging to detect myocardial oedema, inflammation, and fibrosis, CMR is the gold-standard non-invasive imaging test for diagnosis in myocarditis of other aetiologies. However, it seems to have decreased sensitivity in the diagnosis of ICIs-related myocarditis.\textsuperscript{4,5} Endomyocardial biopsy (EMB) remains the diagnostic gold standard for myocarditis. Nevertheless, it is underutilized for its invasive nature and interrelated potential complications.\textsuperscript{4} In this case, our patient failed to perform EMB examination due to the refusal from the patient’s family, but we diagnosed her as ICIs-related myocarditis (grade 4) by combining with her clinical data.\textsuperscript{6,7}

With a high mortality, ICIs-related myocarditis is a serious disease. Detecting early ICIs-mediated cardiotoxic effects before severe and life-threatening complications develop is crucially important. Some scholars proposed several surveillance strategies: (i) baseline cardiac assessment before ICIs treatment including clinical history and risk factor assessment, ECG, cardiac troponin, BNP or NT-proBNP, and echocardiogram for all patients; (ii) in higher-risk patients, measurement of ECG, cardiac troponin, and BNP before ICIs Doses 2 to 4; (iii) if normal at Dose 4, then reducing surveillance to alternate doses for 6 to 12 and if still normal, then reducing to every three doses until completion of course.\textsuperscript{8}

Recently, the Society for Immunotherapy of Cancer (SITC) issued the latest clinical practice guideline for the management of ICIs-associated myocarditis indicating that high-dose corticosteroids (intravenous methylprednisolone 1 g/day or equivalent for 3–5 days, until troponin normalizes) should be given to patients with suspected ICIs-induced myocarditis as soon as possible once the diagnosis is considered likely, followed by 4–6 weeks 1–2 mg/kg prednisone taper.
Table 1 Clinical guideline for the immunosuppressive management strategies of immune checkpoint inhibitors-associated myocarditis.\textsuperscript{7,9,10}

| Clinical guideline | Year | Management recommendations |
|--------------------|------|---------------------------|
| SITC\textsuperscript{5} | 2021 | - Patients should receive high-dose corticosteroids (1 g intravenous methylprednisolone or equivalent daily for 3–5 days, until troponin normalizes) as soon as possible once the diagnosis of ICI-induced myocarditis considered likely, followed by 4–6 weeks 1–2 mg/kg prednisone taper.  
- Additional therapies such as ATG, mycophenolate mofetil, abatacept, or alemtuzumab should be considered if signs or symptoms do not respond to corticosteroid therapy within 24 h.  
- Caution is advised against the use of infliximab for steroid-refractory myocarditis.  
- Permanent discontinuation of ICI therapy should be seriously considered.  
- Hold ICIs for patients with grade 1 and recheck troponin 6 h later.  
For patients with grade ≥ 2, discontinuation of ICIs therapy and early (i.e. within 24 h) initiation of corticosteroids (1–2 mg/kg/day of prednisone) should be considered.  
- In patients without an immediate response to above dose corticosteroids, consider early institution of high-dose corticosteroids (methylprednisolone 1 g/day) and the addition of mycophenolate mofetil, ATG, or infliximab (contraindication in patients with moderate–severe heart failure).  
- Consider abatacept or alemtuzumab as additional immunosuppression in life-threatening cases.  
- Treating with high-dose methylprednisolone (1 g/day for 3–5 days) until cardiac function returns to baseline, then dose taper over 4 to 6 weeks.  
- If no improvement is noted within 24 h, the addition of other potent immunosuppressive agents should be considered, such as ATG, intravenous immunoglobulin, mycophenolate mofetil, or infliximab (contraindication for patients who have heart failure).  
- Two additional immunosuppressive agents (alemtuzumab and abatacept) may be used.  
- Immunosuppression should be permanently discontinued for patient with grade ≥ 3. |
| ASCO\textsuperscript{10} | 2021 |  
| NCCN\textsuperscript{7} | 2020 |  

Additional treatment except for infliximab such as mycophenolate mofetil, anti-thymocyte globulin (ATG), abatacept, or alemtuzumab should be taken into account if signs or symptoms are not relieved within 24 h after corticosteroid therapy.\textsuperscript{9} More clinical guideline management recommendations are shown in Table 1.\textsuperscript{7,9,10} In this case, we only treated patient with high-dose intravenous methylprednisolone for 3 days and then reduced its dose (from 1 g/day to 120 mg/day) considering that high-dose corticosteroids are easy to cause gastrointestinal bleeding and increased infection for the patient despite the guidelines indicate that corticosteroids pulse therapy should be maintained until troponin normalizes. Such regimen was potentially disadvantageous because tapering corticosteroids before normalization of troponin levels may cause patient’s myocarditis to worsen. But the side effects of high-dose steroid therapy are also threatening. There is no evidence to prove which is more dangerous. In the situation that our patient’s ventricular arrhythmia did not occur again after high-dose steroid for 3 days, we tried to taper the steroid dose. Meanwhile, in order to consolidate the curative effect, we added the dose of mycophenolate mofetil (from 0.5 to 1 g/day). Finally, the patient was discharged in stable condition.

Significantly, our patient’s clinical symptoms, laboratory examinations, and TTE had almost returned to normal level on about the 10th day after treatment manifesting her condition recovered relatively rapidly. The main reason for that might be the timely adoption of combined therapy of corticosteroids, immunoglobulin and mycophenolate mofetil. But on the other hand, we also considered that it might be related to the simultaneous use of sacubitril/valsartan and dapagliflozin. Previous studies have indicated that sacubitril/valsartan (an angiotensin receptor–neprilysin inhibitor) improved the risk of cardiovascular death or HF hospitalization in patients with heart failure with reduced ejection fraction (HFrEF).\textsuperscript{11} As a sodium-glucose cotransporter 2 inhibitor (SGLT2i), dapagliflozin has shown significant cardiovascular benefits and has been proved to reduce the risk of the primary composite endpoint (i.e. cardiovascular death and HF events) by 26% in HFrEF patients.\textsuperscript{12} Furthermore, a recent study found that SGLT2i was associated with a lower risk of cardiac arrhythmias such as ventricular tachycardia.\textsuperscript{13} So far, no case reports or studies have been found in patients with ICIs-associated myocarditis using the above two drugs simultaneously. Therefore, further prospective studies are needed to prove their efficacy in the treatment of ICIs-associated myocarditis.

Immune checkpoint inhibitors have revolutionized treatment of multiple malignancies, with nearly 50% of patients with cancer eligible for checkpoint inhibitor drugs.\textsuperscript{2} As the widespread use of ICIs, any medical centre may encounter a patient with ICIs-related myocarditis. The management of these patients is not entirely dependent on EMB and is not generally suitable for cardiac transplantation.\textsuperscript{6,14} Hence, non-transplant/non-EMB centres have also the capacity and even an important role to manage these patients. What matters is to identify suspected patients early and treat them with corticosteroid and immunosuppressant as soon as possible once the diagnosis is established likely.
The reports that patients died for ICIs-related myocarditis despite using the core corticosteroids pulse therapy challenge the present treatments of ICIs-related myocarditis. In this case, we innovatively proposed that using sacubitril/valsartan and SGLT2i may be helpful for treating ICIs-associated myocarditis, especially in patients with HF and ventricular arrhythmia. We are looking forward to more studies about that in the future to manage patients with ICIs-associated myocarditis and to improve their clinical prognosis.

Conflict of interest
None declared.

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