Cardio-Oncology

CASE REPORT

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Clinical and pathological characteristics of immune checkpoint inhibitor-related fulminant myocarditis

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Abstract

The advent of immune checkpoint inhibitors (ICIs) has significantly improved cancer treatment. With the increasing use of ICIs, ICI-related myocarditis has been recognized. However, an evidence-based therapeutic strategy has not been established because of the limited knowledge on ICI-related myocarditis. Here, we present four cases of ICI-related fulminant myocarditis (FM). Three of the four cases resulted in fatal outcomes despite aggressive treatment with mechanical circulatory support and immunosuppressive therapy with corticosteroids. Given the poor prognosis of ICI-FM, the establishment of rapid and adequate therapeutic interventions on the basis of clinical and pathological evaluation is imperative.

Keywords Immune checkpoint inhibitors,, Immune-related adverse events, Fulminant myocarditis, Mechanical circulatory support, Cardiogenic shock, Ventricular arrhythmia

Background

Advances in cancer treatment have dramatically decreased cancer-related mortality. On the other hand, treatment-related side effects have gained increased importance among cancer survivors [1]. Immune checkpoint inhibitors (ICIs) have emerged as highly effective therapies for many cancers [2, 3]. ICIs are now used not only in advanced or metastatic diseases but also in the early stages of cancers for the prevention of recurrence and improvement of cure rate [2, 4]. Leveraging the immune system by targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death-1 (PD-1), or programmed cell death ligand-1 (PD-L1) leads to side effects, termed immune-related adverse events (irAEs) [5]. These irAEs occur in 50–90% of patients, and all organs can be affected [5, 6]. The frequency of ICI-related myocarditis is reportedly 0.06–1.1%, and its mortality rate is as high as 50% [6–8]. Here, we describe the characteristics and clinical course of four cases of ICI-related fulminant myocarditis (FM) complicated by hemodynamic and electrical instability requiring inotropes and mechanical circulatory support (MCS), three of which resulted in fatal outcomes (Table 1).

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Case presentation

Case 1

A 72-year-old man with renal cell carcinoma with lung and liver metastasis was hospitalized for asymptomatic newly developed trifascicular block with elevated troponin T (TnT) levels. He underwent right nephrectomy 8 years prior and was treated with avelumab (ICI), axitinib (tyrosine kinase inhibitor), and cabozantinib (multikinase inhibitor) for relapse. Although lung metastasis was stable, treatment with nivolumab (ICI) was started 1 month prior because of progressive liver metastasis (Table 2). He had no recent history of antecedent infection, vaccinations, or exposure to new medications other than anticancer drugs. He developed sustained ventricular tachycardia (VT) on day 7 and was subsequently transferred to our hospital. Electrocardiography (ECG) revealed a wide QRS complex and ST elevation in leads V_1-V_3 (Fig. 1). Echocardiography revealed left ventricular (LV) wall motion abnormalities with LV ejection fraction (LVEF) of 40%. Coronary angiography revealed no

Table 1 Patient Characteristics and Clinical Course

	Case 1	Case 2	Case 3	Case 4
Sex	Male	Male	Male	Female
Age	72	69	63	76
Pre-hospital symptom	Presyncope	Fever, Chest pain	Fever, Chest pain	Fatigue, Dyspnea
Cancer	Renal cell carcinoma	Prostate cancer	Lung cancer	Lung cancer
Metastasis	Liver, Lung	Bone	-	-
ICI	Avelumab (anti-PD-L1) Nivolumab (anti-PD-1)	Pembrolizumab (anti-PD-1)	Atezolizumab (anti-PD-L1)	Atezolizumab (anti-PD-L1)
Comorbidities	Hypertension, Diabetes	Hypertension	None	Hypertension, IHD
Time between last ICI administration and onset of myocarditis	18 days	893 days	13 days	11 days
Decompensated heart failure	No	Yes	Yes	Yes
Cardiogenic shock	Yes	Yes	Yes	Yes
Arrythmia	VT	Complete AVB, VT, PAF	Complete AVB	VT, PAF
Associated other irAE	Hepatitis, myositis	None	None	None
QRS width, ms	148	147	172	80
LVEF (on admission)	40	17	10	10
Laboratory data				
CK (on admission), U/L	5724	2450	3859	101
CK (peak), U/L	5724	5103	3859	101
CK-MB (on admission), U/L	96	365	61	5
CK-MB (peak), U/L	141	428	61	7
Troponin T (on admission), ng/mL	1.871	48.118	11	0.226
Troponin T (peak), ng/mL	5.343	48.118	15.561	0.358
BNP (on admission), pg/mL	456.2	921.7	388.9	1357.3
CRP (on admission), mg/dL	1.09	9.32	9.47	0.59
Endomyocardial biopsy	$CD3^+$ T-cells (CD8 > CD4) $CD68^+$ histiocytes A few $CD20^+$ B-cells A few eosinophils High Tenascin C High PD-L1	$CD3^+$ T cell (CD8 > CD4) $CD68^+$ histocytes A few $CD20^+$ B-cells Neutrophils / Eosinophils High Tenascin C High PD-L1	$CD3^+$ T-cells (CD4 = CD8) $CD68^+$ histiocytes A few $CD20^+$ B-cells Moderate Tenascin C Moderate PD-L1	$CD3^+$ T-cells (CD8 > CD4) Rare $CD68^+$ histiocytes Rare $CD20^+$ B-cells Low Tenascin C Low PD-L1
Treatment				
MCS	None	VA-ECMO, IABP	VA-ECMO, Impella CP	VAV-ECMO, Impella CP
Immunosuppressants	Pulse MP (1000 mg, 3 days) Followed by PRD (1 mg/kg)	Pulse MP (1000 mg, 3 days) Followed by PRD (10 mg)	Pulse MP (1000 mg, 3 days)	Pulse MP (1000 mg, 3 days) Followed by PRD (1 mg/kg)
Outcome	Death	Death	Death	Alive
Cause of death	VT	Heart failure / MOF	Intracerebral hemorrhage	-

AVB atrioventricular block, *BNP* B-type natriuretic peptide, *CD* cluster of differentiation, *CK* creatine kinase, *CRP* C-reactive protein, *ECMO* extracorporeal membrane oxygenation, *IABP* intra-aortic balloon pump, *ICI* immune check point inhibitor, *IHD* ischemic heart disease, *irAE* immune-related adverse effect, *LVEF* left ventricular ejection fraction, *MCS* mechanical circulatory support, *MOF* multiple organ failure, *MP* methylprednisolone, *PAF* paroxysmal atrial fibrillation, *PD-L1* programmed cell death ligand 1, *PRD* prednisolone, *VA* veno-arterial, *VAV* veno-arterial-venous, *VT* ventricular tachycardia

Table 2 Detailed treatment history for cancers[a]

Agents	Drug classes	Route of administration	Doses	Courses	First administration to onset of FM [days]	Last administration to onset of FM [days]
Case 1: Renal cell carcinoma						
Avelumab	ICI	IV	600 mg	3	1158	1113
			600 mg	24	1029	679
Axitinib	Tyrosine kinase inhibitor	PO	10 mg/day		1158	1113
			6 mg/day		1085	677
Cabozantinib	Multikinase inhibitor	PO	40 mg/day		676	43
Nivoumab	ICI	IV	240 mg	2	33	18
Case 2: Prostate adenocarcinoma						
Leuprorelin	LH-RH analog	SC	22.5 mg once every 24 weeks		2881	155
Bicalutamide	Androgen receptor antagonist	PO	80 mg/day		2851	1246
IMRT	External beam radiation	Radiation	76 Gy (total)	38	2699	2644
Abiraterone	Androgen synthesis inhibitor	PO	1000 mg/day		1226	1061
Enzalutamide	Androgen receptor antagonist	PO	160 mg/day		1020	886
Pembrolizumab	ICI	IV	200 mg	7	1020	893
Docetaxel	Microtubule inhibitor	IV	70 mg/m^2	9	876	554
Radium-223 chloride	Alpha emitter	IV	55 kBq/kg/month	6	407	267
Ethinylestradiol	estrogen analog	PO	1 mg/day		386	359
			0.5 mg/day		358	211
Cabazitaxel	Microtubule inhibitor	IV	25 mg/m^2	2	50	18
Case 3: Lung cancer (poorly differentiated carcinoma)						
Carboplatin	Platinum compound	IV	540 mg (AUC 6)	4	692	581
Nab-Paclitaxel	Microtubule inhibitor	IV	100 mg/m^2	4	692	581
Atezolizumab	ICI	IV	1200 mg	31	692	13
Case 4: Lung cancer (adenocarcinoma)						
Cisplatin	Platinum compound	IV	60 mg/m^2	3	119	58
Vinorelbine	Microtubule inhibitor	IV	20 mg/m^2	3	119	58
Atezolizumab	ICI	IV	1200 mg	1	11	11

AUC area under the concentration–time curve, *FM* fulminant myocarditis, *ICI* immune checkpoint inhibitor, *IMRT* intensity modulated radiation therapy, *IV* intravenous, *LH-RH* luteinizing hormone-releasing hormone, *NA* not available, *PO* per os, *SC* subcutaneous

[a] The cancer therapeutics were sequenced in early order of start

stenotic lesions. Endomyocardial biopsy (EMB) revealed severe infiltration of lymphocytes, histiocytes, and a few eosinophils with myocardial necrosis. Immunohistochemistry revealed T cells (CD3, CD8 > CD4), CD68$^+$ histiocytes, and a few CD20$^+$ B cells. Tenascin C, a known marker of myocarditis [9], was diffusely expressed, and the myocardium was strongly stained with PD-L1 (Fig. 2A and Fig. 3A). Pulse corticosteroid (CS) therapy with methylprednisolone (MP) followed by high-dose prednisolone (PRD) was started immediately. The TnT level decreased, and VT ceased temporarily; however, the TnT level re-escalated, and VT recurred 6 days later. The implementation of MCS and additional immunosuppressants was considered, but the patient and his family declined further invasive treatments. The patient fell into an electrical storm and died on day 9.

Case 2

A 69-year-old man with prostate cancer (adenocarcinoma) with bone metastasis underwent chemotherapy with docetaxel (microtubule inhibitor), cabazitaxel (microtubule inhibitor) and pembrolizumab (ICI), radiation therapy, and androgen deprivation therapy (Table 2). The last administration of pembrolizumab was 2 years prior, and cabazitaxel was added for progressive bone metastasis 18 days prior. He presented to our hospital for chest pain, vomiting, and fever. He had no recent history of antecedent infection, vaccinations, or exposure to new

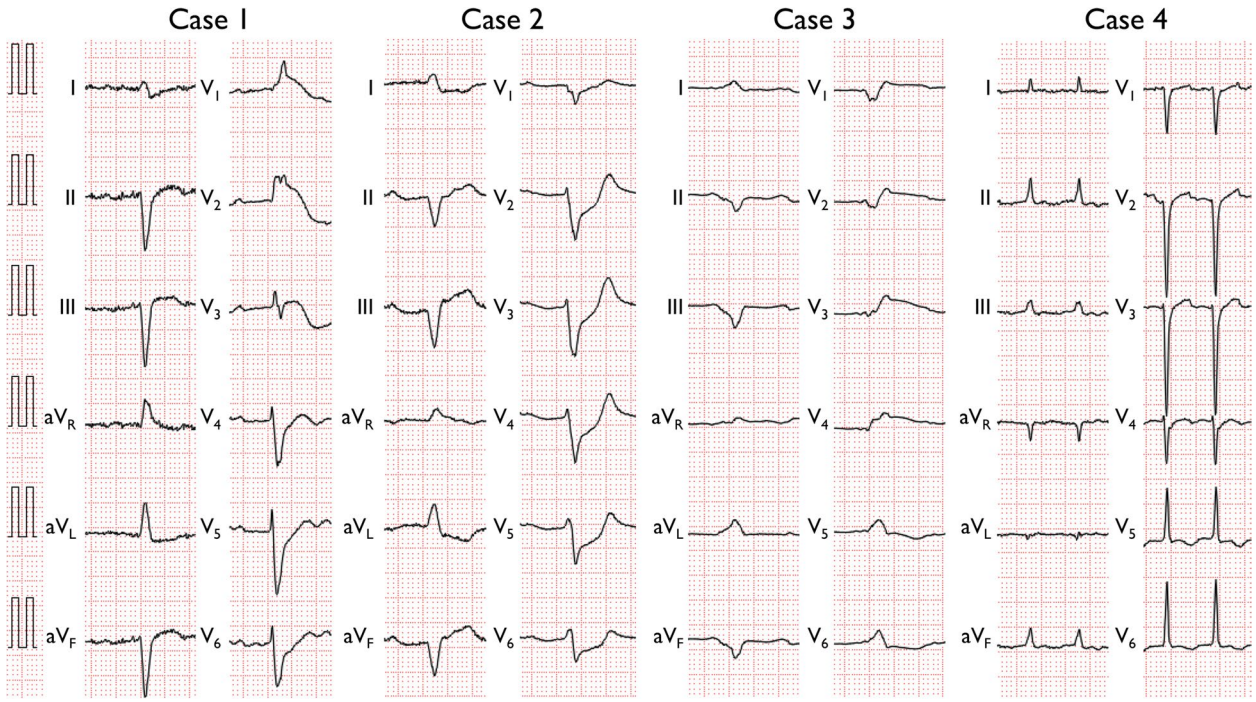

Fig. 1 12-Lead electrocardiography of patients with immune checkpoint inhibitor-related fulminant myocarditis on admission. Note the marked widening of the QRS complex and the deviation of the ST segment in Cases 1–3

other medications. ECG revealed complete atrioventricular block (CAVB), wide QRS, ST depression in the leads I, aV_L, and V_1-V_6, and ST elevation in the aV_R lead. (Fig. 1). Echocardiography revealed diffuse LV hypokinesis with LVEF of 17%. Since the patient was in cardiogenic shock, an intra-aortic balloon pump (IABP) and a temporary transvenous pacemaker were implemented. Coronary angiography was normal. EMB revealed dense infiltration of lymphoplasmacytes, neutrophils and eosinophils associated with myocytic damage and interstitial fibrosis. Immunohistochemistry revealed T cells (CD8 > CD4), $CD68^+$ histiocytes, and a few $CD20^+$ B cells. PD-L1 was highly expressed in the myocardium. (Fig. 2B and Fig. 3B). Pulse CS therapy was initiated immediately. On the same day, the patient experienced a VT storm, and a venoarterial extracorporeal membrane oxygenation (VA-ECMO) was instituted. Since the hemodynamics stabilized, the patient was weaned from VA-ECMO on day 6. Despite the decrease in TnT levels, cardiac function did not improve satisfactorily thereafter, and the patient experienced cardiogenic shock. An IABP was instituted again on day 13. He died on day 47 from multiple organ failure.

Case 3

A 63-year-old man with lung cancer (poorly differentiated carcinoma) had been receiving chemotherapy with carboplatin (platinum compound) plus paclitaxel (microtubule inhibitor), and atezolizumab (ICI) for 2 years (Table 2). The patient showed good response to the treatment and a long survival was anticipated. He was hospitalized for fever and chest pain 2 weeks after the last administration of atezolizumab. He had no recent history of antecedent infection, vaccinations, or exposure to new medications other than anticancer drugs. ECG revealed a wide QRS complex and ST elevation in the leads V_1-V_4 (Fig. 1). Echocardiography revealed diffuse severe LV hypokinesis with LVEF of 10%. Coronary angiography revealed no steno-occlusive lesions. Because of hemodynamic instability, a VA-ECMO and an IABP were instituted, and the patient was transferred to our hospital on day 3. An Impella CP was implemented instead of the IABP. EMB revealed diffuse lymphocytic infiltration associated with myocyte dropout and interstitial fibrosis. Immunohistochemistry revealed numerous T cells (CD4 = CD8) mixed with $CD68^+$ histiocytes and $CD20^+$ B cells. PD-L1 and TNC were moderately expressed in the myocardium (Fig. 2C and Fig. 3C). Pulse CS therapy was started immediately. The following day, dilated pupils were observed, and head computed tomography revealed extensive cerebral hemorrhage in the left frontoparietal lobes associated with ventricular perforation and uncal herniation. Surgery was not indicated because the coma was deemed irreversible. Although cardiac function

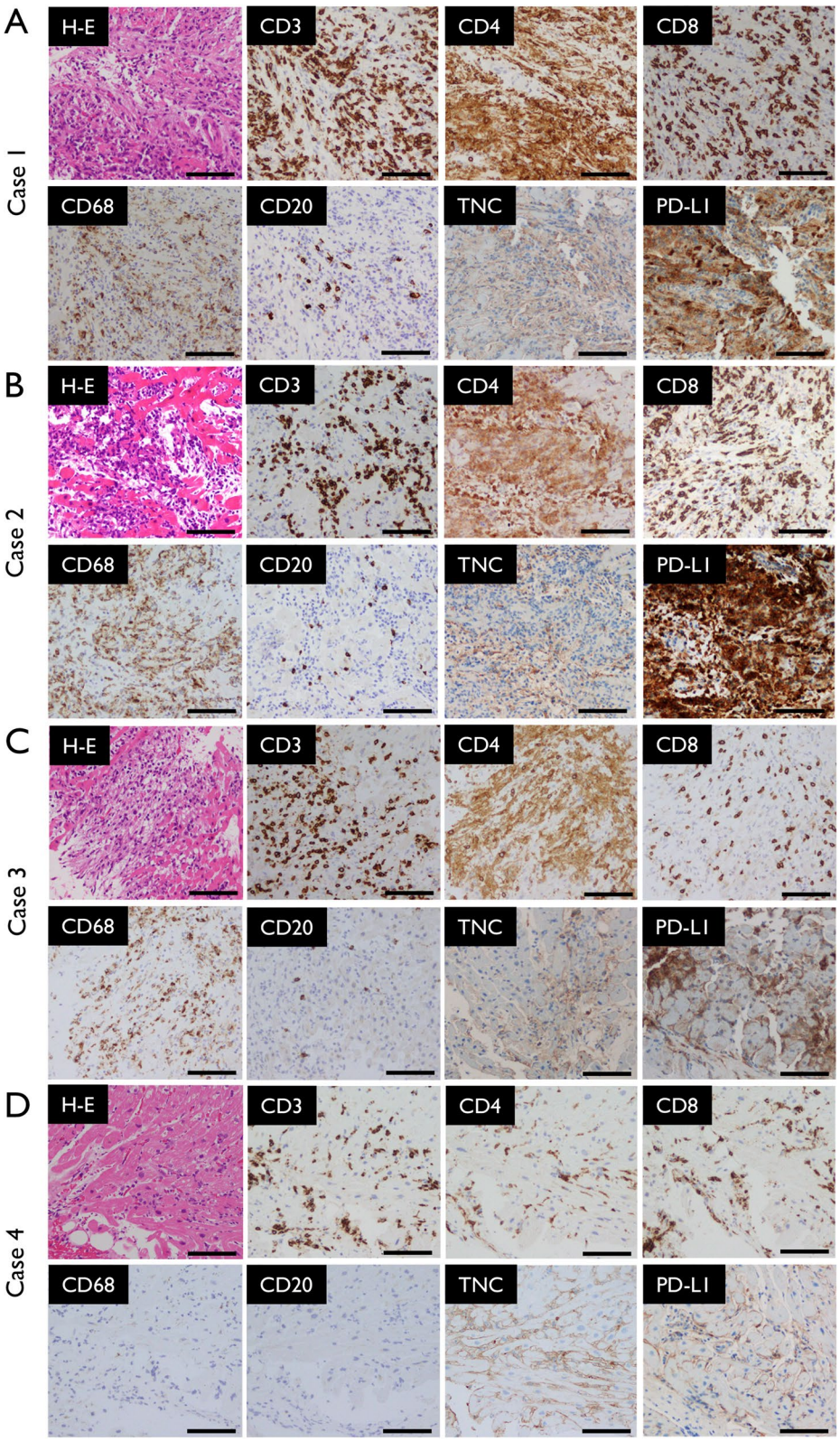

Fig. 2 Histopathology and immunohistochemistry of the endomyocardial biopsy. Hematoxylin–eosin (H-E) staining and immunohistochemistry for the lymphocyte markers, tenascin C (TNC), and programmed cell death ligand 1 (PD-L1) in Cases 1 (**A**), 2 (**B**), 3 (**C**), and 4 (**D**) are shown. The bar indicates 100 μm

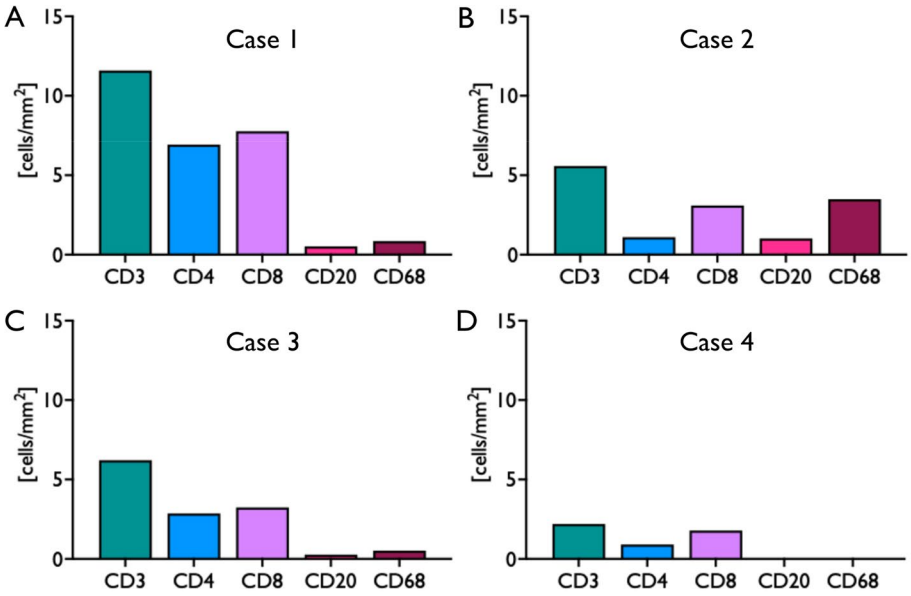

Fig. 3 Quantitative analysis of the infiltrating inflammatory cells including CD3-, CD4-, CD8-, CD20-, and CD68-positive cells in the myocardium of Cases 1 (**A**), 2 (**B**), 3 (**C**), and 4 (**D**) are shown

gradually improved, the patient succumbed to intracerebral hemorrhage complicated with uncal herniation on day 13. The head CT scan of the previous day showed no metastatic lesions or hematomas. The relationship between brain hemorrhage and irAEs is uncertain.

Case 4

A 76-year-old woman underwent left upper lobectomy for lung cancer (adenocarcinoma) and received adjuvant chemotherapy with cisplatin (platinum compound) and vinorelbine (microtubule inhibitor). Atezolizumab was started thereafter for the prevention of recurrence (Table 2). She was hospitalized because of anorexia and fatigue 2 weeks after the start of atezolizumab. She had no recent history of antecedent infection, vaccinations, or exposure to new other medications. The following day, the patient developed pulmonary edema and cardiogenic shock and was transferred to our hospital. ECG revealed poor R-wave progression in leads V_1-V_4 and flat T-waves in all leads, with a normal QRS width (Fig. 1). Echocardiography revealed diffuse LV hypokinesis with LVEF of 10%. The increase in TnT levels was modest. Coronary angiography revealed no significant stenosis. There were no characteristic electrocardiographic or echocardiographic findings characteristic for Takotsubo cardiomyopathy. The patient did not develop giant negative T-waves during the disease course. Sustained VT occurred, but it was terminated by the infusion of amiodarone. EMB confirmed moderate inflammation of inflammatory cells with mild interstitial fibrosis. Immunohistochemically, infiltration of T cells (CD3, CD8 > CD4) was observed, but $CD20^+$ B cells and $CD68^+$ histiocytes were scarce. The myocardial expression of TNC and PD-L1 was weak (Fig. 2D and Fig. 3D). Because of hemodynamic instability, a VA-ECMO and an Impella CP were implemented. Pulse CS therapy followed by high-dose PRD was initiated. Since she developed alveolar hemorrhage, the ECMO configuration was switched to veno-arterial-venous (VAV)-ECMO on day 2. Cardiac function recovered after the treatment with CS, and the circuit configuration was switched to VV-ECMO on day 7. The patient was weaned from ECMO on day 17. LV function recovered to LVEF of 63%. She was transferred to a rehabilitation hospital on day 35 and discharged home 3 months later.

Discussion

Here, we present four cases of ICI-FM. Three of the four resulted in fatal outcomes, indicating a poor prognosis, which is compatible with previous reports. To our knowledge, this is the first case series describing the clinical and histopathological characteristics of ICI-FM. The mortality rate of ICI-related myocarditis is reportedly as high as 50% [6]. Once the disease progresses to the fulminant phenotype, almost all cases are fatal [10–13]. Only one study reported a survival case of an ICI-FM patient treated with VA-ECMO [14]. irAE events start within the

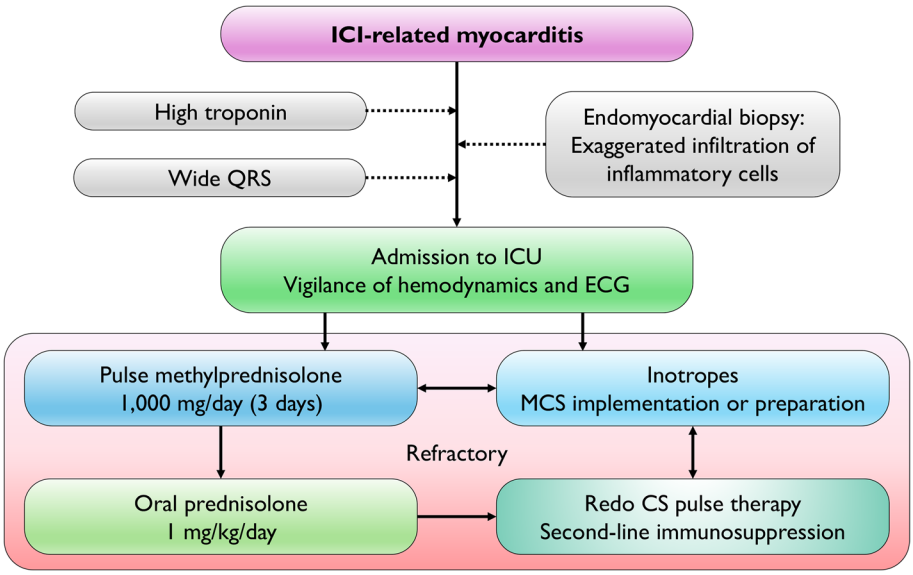

Fig. 4 A proposed management algorithm for immune checkpoint inhibitors-related fulminant myocarditis. CS, corticosteroid; ECG, electrocardiography; ICI, immune checkpoint inhibitor; ICU, intensive care unit; MCS, mechanical circulatory support

first few weeks to months after treatment but can occur anytime, even after discontinuation of the treatment (ranging from 1 to 84 weeks) [3, 15]. In fact, the onset of irAE myocarditis ranged from weeks to years after the first treatment in our patients. In Case 2, the last administration of ICI (pembrolizumab) was 2.4 years prior to the onset of FM, and the patient developed just 18 days after the start of cabazitaxel. Taxoid-related myocarditis is very uncommon, and there is only one case report of paclitaxel-induced myocarditis [16]. In the report, however, the diagnosis of myocarditis was based on cardiac magnetic resonance imaging and the histological evidence was lacking unlike our cases. It is difficult to determine whether pembrolizumab alone provoked late myocarditis, cabazitaxel alone induced myocarditis, or cabazitaxel triggered ICI-related myocarditis in Case 2. In the pooled analysis of ICI-related myositis and myocarditis, patients with early-onset irAEs after the treatment with ICIs showed tenfold higher mortality than those with late-onset irAEs [17]. Interestingly, three fatal cases (Cases 1–3) had late-onset myocarditis, whereas the surviving patient (Case 4) had early-onset myocarditis in the present case series. Different background of the patients and the history of oncological treatment with other drugs may explain this discrepancy.

The American Society of Clinical Oncology guidelines recommend the initiation of CS therapy within 24 h for grade 2 or higher ICI-related myocarditis [15]. Early diagnosis of ICI-related myocarditis is challenging because of mild and nonspecific symptoms at the early stage; in fact, our patinets received CS therapy after developing cardiogenic shock. Interestingly, despite the devastating phenotype with cardiogenic shock and VT requiring ECMO, our only survivor (Case 4) showed mild elevation of TnT, narrow QRS, minimal ST-T change, and mild infiltration of inflammatory cells and low expression of TNC and PD-L1 in the myocardium, whereas three other fatal patients presented high TnT, wide QRS, and dense infiltration of inflammatory cells and high expression of TNC and PD-L1 in the myocardium. We could not conclude whether the high expression of PD-L1 in the myocardium was a cause or consequence (upregulation as a protective negative feedback mechanism) of myocarditis; another possibility is that PD-L1-dependent necroptosis induced by ICIs, at least in part, contributes to cytotoxicity, given the findings of a previous study in hepatocytes [18]. In the above mentioned pooled analysis of irAE myositis and myocarditis, arrhythmia and conduction disturbances were significantly associated with high mortality, consistent with our observation [17]. Power et al. reported that the patients with ICI-myocarditis presented with ECG changes such as new conduction blocks, decreased voltage, and repolarization abnormalities [19]. Another report demonstrated that the cardiac troponin level is associated with major adverse cardiomyotoxic events [20]. Although have been no large studies investigating the determinants for the prognosis of the patients with fulminant form of ICI-myocarditis associated with electrical storm and/or hemodynamic instability requiring MCS, TnT level, QRS width, and EMB findings may predict the outcome of patients.

Although the guidelines suggest the use of second-line immunosuppressants such as mycophenolate, infliximab, anti-thymocyte globulin, tocilizumab, abatacept, alemtuzumab, or tofacitinib in refractory cases [1, 15], the

maximum doses of corticosteroid or the combination with other immunosuppressive therapies did not show the significant difference in mortality [17]. The development of curative therapeutic strategy against refractory ICI-related myocarditis is an urgent issue in addition to the early diagnosis and rapid intervention. Figure 4 illustrates a proposed algorithm for the management of ICI-related fulminant myocarditis based on our observation.

In conclusion, early diagnosis and immediate therapeutic intervention on the basis of clinical and histopathological characteristics are necessary to improve the prognosis of patients with ICI-FM.

Abbreviations

ICI	Immune checkpoint inhibitor
FM	Fulminant myocarditis
CTLA-4	Cytotoxic T-lymphocyte antigen-4
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
irAE	Immune-related adverse event
MCS	Mechanical circulatory support
IHD	Ischemic heart disease
TnT	Troponin T
VT	Ventricular tachycardia
ECG	Electrocardiography
LV	Left ventricle
LVEF	Left ventricular ejection fraction
EMB	Endomyocardial biopsy
CD	Cluster of differentiation
CS	Corticosteroid
MP	Methylprednisolone
PRD	Prednisolone
CAVB	Complete atrioventricular block
IABP	Intra-aortic balloon pump
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
VAV-ECMO	Veno-arterial-venous extracorporeal membrane oxygenation

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Authors' contributions
RI and TH analyzed and interpreted the patient data and provided first draft. TM, MH, YT, TI provided images and revision. TH, HK, KI, WO, SA, SY, KM, TF, KS, SM, KH, SK, and SK provided revisions. YO and KA supervised and provided revisions. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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