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Electrocardiographic Features of Immune Checkpoint Inhibitor-Associated Myocarditis

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Abstract: Immune checkpoint inhibitors (ICIs) are associated with immune-related adverse events including myocarditis, whilst improving cancer-related outcomes. There is thus a clinical need to identify electrocardiographic manifestations of ICI-related myocarditis to guide clinical management. PubMed was searched for clinical studies and case reports describing electrocardiographic changes in patients with ICI-related myocarditis. A total of 6 clinical studies and 79 case reports were included. This revealed a range of presentations for patients on ICIs, including supraventricular arrhythmias, ventricular arrhythmias and heart block, and new changes of ST-T

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segment unrelated to coronary artery disease, ST-segment elevation or depression and T-wave abnormalities. Several patients showed low voltages in multiple leads and new onset Q-wave development. Patients with ICI-related myocarditis may develop new arrhythmia and ST-T changes, and infrequently low voltages in multiple leads. (Curr Probl Cardiol 2022;48:101478.)

Background

The development of immune checkpoint inhibitors (ICIs) represents a significant breakthrough in tumor therapy. Despite showing better efficacy than traditional anticancer agents, the use of ICIs can lead to potentially life-threatening immune-related adverse events, including cardiovascular complications such as myocarditis.^{7,70,72,103} ICI-induced myocarditis is rare, with an estimated incidence ranging from 0.1% to 1%. Previous findings have showed that ICI-related myocarditis usually occurs in the early stage of ICI treatment and could deteriorate rapidly with a fatality rate up to 30-50%.³¹ Therefore, it is necessary to ensure early identification and diagnosis of myocarditis in patients receiving ICIs.

Recent reports have demonstrated the involvement of the cardiac conduction system, which can lead to cardiac arrhythmias⁷² and have a negative impact on the prognosis of the patients. Since electrocardiogram (ECG) is a simple, noninvasive and cheap investigation, it could be used as a first line screen tool for cardiovascular abnormalities in ICI users. Therefore, in this systematic review, we will summarize the electrocardiographic characteristics of patients with ICI-related myocarditis and hope to provide early recognition to this potentially fatal complication.

Methods

Data sources and searches

PubMed was systematically searched by two cardiologists using the keywords “(immune checkpoint inhibitor) AND (myocarditis)” for articles published on or before October 8, 2022. By reading the full texts, clinical studies and case reports that meet the following conditions were included. The inclusion criteria were as follows: (1) ICI-associated myocarditis was clearly diagnosed by the patient’s ICI medication,

comprehensive clinical manifestations and laboratory tests, etc.; (2) standard

12-lead electrocardiogram was provided; (3) for clinical studies, patients were identified as suffering from ICI-related myocarditis with the provision of ECG findings; (4) publication in English language. References which were in line with the criteria were also included. The following details were extracted from each study: age, sex, type of malignant tumor and ICIs.

A total of 79 case series or reports^{1-6,8-12,15-18,20-23,25-30,32-39,41,42,44,45,47-49,52-54,56,58,60-66,68,69,71,73-75,77-86,88,89,91-98,100} and 6 clinical studies^{13,18,50,67,88,103} were included. The demographic characteristics (such as age, sex), type of tumor and ICI prescribed, symptoms, clinical examinations, cardiological measures and the outcome of patients during hospitalization were obtained.

Electrocardiographic evaluation

For clinical studies, the ECG findings and characteristic changes in patients with ICI myocarditis were extracted by 2 cardiologists, and cross-validated. Similarly, for case reports, the standard 12-lead ECG provided were analyzed by 2 cardiologists independently, with any disagreements resolved by a third cardiologist.

Statistical analysis

The baseline characteristics and ECG findings were expressed as frequency and proportion. Continuous variables were provided as median or mean values.

Results

Case report

A total of 418 cases were found in the literature. Of these, 252 cases were excluded because they provided no descriptions on the relationship between myocarditis and ECG findings, and another 81 cases were also excluded as no ECGs were shown. Finally, 79 studies were included. Nine studies were case series, 70 were case reports, with a total of 91 patients included (Fig 1). Of these, 31% were women (28/91), with a median age of 68 years. The commonest indication for ICI use was lung cancer (n = 23, 25.27%), followed by melanoma (n = 16, 17.58%) and cancers affecting the urogenital and digestive tract (n = 14, 15.38%, respectively). Amongst the included cohort, 38.46% and 31.87% were

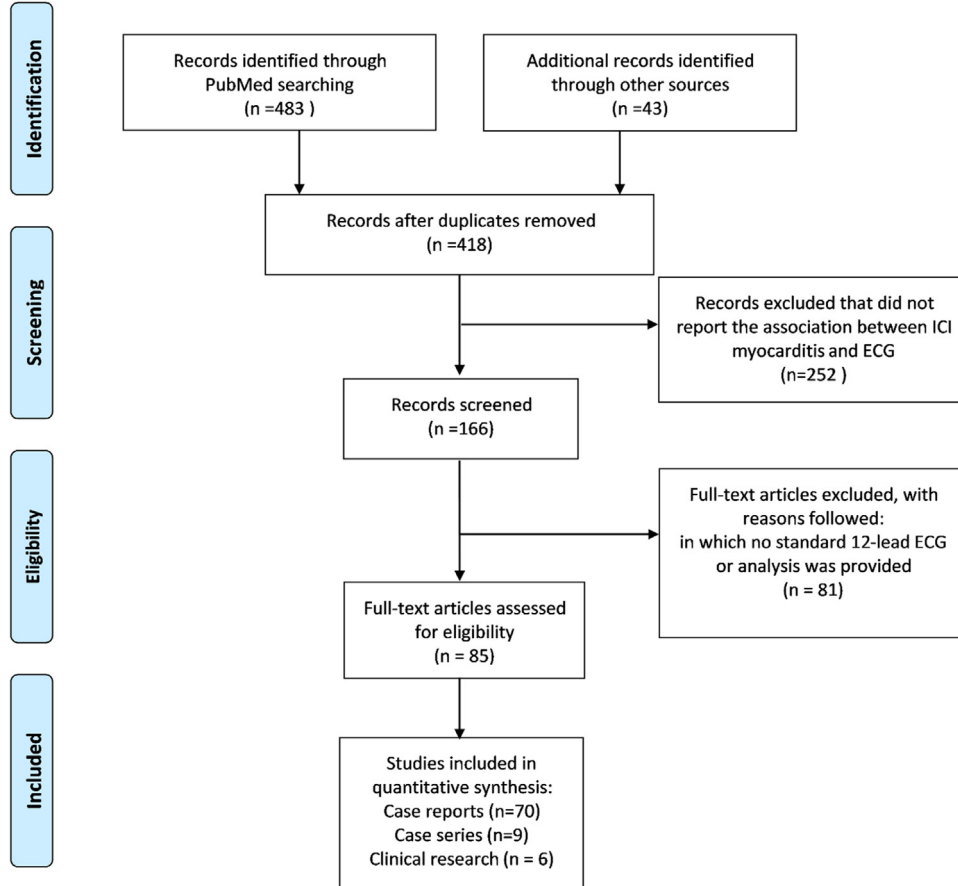


FIG 1. Flow diagram of the study selection process.

treated with nivolumab and pembrolizumab, respectively, followed by ipilimumab (18.68%), camrelizumab (7.69%), bevacizumab (5.49%), sintilimab (4.40%), and durvalumab (3.30%). The commonest symptoms reported were dyspnea (42.86%) and fatigue (41.76%). The others included fever (10.99%), palpitation (12.09%), and chest pain (9.89%). Seven patients (7.69%) were asymptomatic and were diagnosed during

TABLE 1. Clinical characteristics of the patients included in this meta-analysis

Clinical characteristics	N(%)
Age(year)	68 (60.00,74.00)
Female(%)	28 (30.77%)
Tumor	
Gastrointestinal tumor(%)	14 (15.38%)
Urinary tumor(%)	14 (15.38%)
Lung tumor(%)	23 (25.27%)
Thymoma(%)	9 (9.89%)
Melanoma (%)	16 (17.58%)
Hematologic malignancy (%)	5 (5.49%)
Other solid tumors (%)	10 (10.99%)
ICI	
Camrelizumab (%)	7 (7.69%)
Nivolumab (%)	35 (38.46%)
Ipilimumab (%)	17 (18.68%)
Pembrolizumab (%)	29 (31.87%)
Sintilimab (%)	4 (4.40%)
Durvalumab (%)	3 (3.30%)
Bevacizumab (%)	5 (5.49%)
Others(%)	9 (9.89%)
Duration of ICI therapy(days)*	21 (16,42)
Presenting signs/symptom	
Fever (%)	10 (10.99%)
Fatigue/ shortness of breath (%)	38 (41.76%)
Dyspnea (%)	39 (42.86%)
Chest pain (%)	9 (9.89%)
Palpitations (%)	11 (12.09%)
Asymptomatic (%)	7 (7.69%)
Cardiac intervention	
Pacemaker (%)	32 (35.16%)
ICD(%)	2 (2.20%)
IABP(%)	3 (3.30%)
ECMO(%)	1 (1.10%)
Outcome	
Dead(%)	40 (43.96%)
Alive(%)	50 (54.94%)
NA(%)	1 (1.10%)

ICI, immune checkpoint inhibitor; ICD, implantable cardioverter defibrillator; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; NA, not available.

*Two cases did not report the time from the administration of ICI to the date of diagnosis of ICI myocarditis, n = 89.

their pretreatment preparation for ICI treatment (Table 1). The median time from when the first initiation of ICI to myocarditis occurred is 21 days. During hospitalization, in addition to hormone therapy, a total of 32 (35.16%) patients received temporary or permanent pacemaker implantation, and a small number of patients received advanced life support therapy with intra-aortic balloon pumps (3/91) or extracorporeal membrane oxygenation (1/91). The all-cause mortality was 43.96% (40/91) (Table 1).

The electrocardiogram findings are shown in Table 2. A total of 86 patients had new changes in ECG compared to the baseline. The manifestations described were arrhythmias, conduction block, ST-T changes, T-wave abnormalities, new onset Q-wave, and low voltages in multiple leads. Arrhythmias were more common in patients with ICI-related myocarditis and can be manifested as supraventricular and ventricular arrhythmias. For supraventricular arrhythmias, the commonest type was sinus tachycardia (12.09%), of which one patient had transient atrial fibrillation during hospitalization. In addition, there were 5 cases of atrial fibrillation or flutter and one case of sinus arrest followed by atrial fibrillation. It should be noted that among the case studies included, 6 patients developed ventricular tachycardia (Fig 2). Of these, one patient was in critical condition, developing atrial fibrillation and high-degree atrioventricular block. In addition, premature atrial contractions (n = 3) and

TABLE 2. Electrocardiographic findings of patients included in this meta-analysis

Electrocardiographic findings		N(%)
Sinus arrhythmia	Sinus arrest	1 (1.10%)
	Sinus tachycardia	11 (12.09%)
	Sinus bradycardia	1 (1.10%)
Atrial arrhythmia	Premature atrial contractions	3 (3.30%)
	Atrial flutter	2 (2.20%)
	Atrial fibrillation	3 (3.30%)
Ventricular arrhythmia	Premature ventricular contractions	6 (6.59%)
	Ventricular tachycardia	6 (6.59%)
Atrioventricular block	First-degree atrioventricular block	6 (6.59%)
	Second-degree atrioventricular block	2 (2.20%)
	Third-degree atrioventricular block	19 (20.88%)
Bundle branch block	Left bundle branch block	8 (8.79%)
	Right bundle branch block	18 (19.78%)
ST-T segment changes	ST-segment elevation	19 (20.88%)
	ST segment depression	5 (5.49%)
	T wave inversion	6 (6.59%)
Others	New Q wave	1 (1.10%)
	Low voltage	3 (3.30%)
	No change	5 (5.49%)

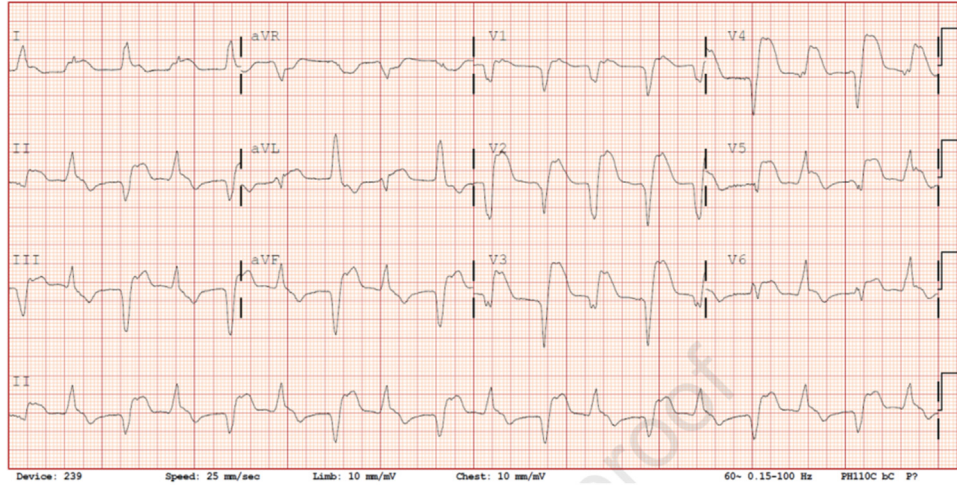


FIG 2. ECG reproduced from Yogasundaram et al. with permission.⁹⁵ A 69-year-old man with metastatic castration-resistant prostate cancer admitted to hospital 74 days after treatment with pembrolizumab, and the electrocardiogram demonstrated bidirectional accelerated idioventricular rhythm with the alternating QRS axis. Retrograde p waves are best visualized in lead V1.

premature ventricular contractions (n = 6) were also observed. For conduction abnormalities, atrioventricular block and bundle branch block were reported. Twenty-seven patients (27/91, 29.67%) had atrioventricular block, of which the commonest type was complete atrioventricular block (19/27, 70.37%) (Fig 3). Patients with complete atrioventricular block often suffered from severe conditions, with complications such as ventricular tachycardia (n = 2) and left bundle branch or right bundle branch block. The number of patients had first-degree atrioventricular block and second-degree atrioventricular block were 6 (22.22%) and 2 (7.41%), respectively. Bundle branch block included left bundle branch block (n = 8) and right bundle branch block (n = 18). Patients also developed left anterior hemiblock block (n = 2) or left posterior hemiblock (n = 1), or complete atrioventricular block (n = 1). Interestingly, one patient had a first electrocardiogram showed left bundle branch block, followed by right bundle branch block several days later. Finally, ST-T changes unrelated to coronary artery disease were reported in ICI-related myocarditis, with ST segment elevation found in 19 cases, ST segment depression in five patients and T-wave inversion in 6 patients. In addition, new onset Q-wave was observed in one patient in an absence of coronary artery lesions from coronary angiography. Rarely, low voltages in multiple leads were observed (n = 3), which was infrequently associated with pericardial effusion. Only 5 patients showed no significant dynamic changes in their ECG when compared to their baseline ECG (Table 2).

Clinical studies

A total of 6 clinical studies were included, all of which were retrospective studies. No prospective clinical studies were identified. One study was published in 2018, two studies in 2020 and three studies in 2021. Two studies were retrospectively analyzed and reported by a single center, with a relatively small sample size. Of the other four studies, the largest consisted of 140 patients with ICI-related myocarditis matched with 179 ICI users without myocarditis. In this study, the type of tumor was not limited, and it was found that the duration of QRS was closely related to MACE development. Another study suggests that patients with ICI-related myocarditis had a faster heart rate, longer QRS and QTc durations on the ECG compared to those without myocarditis. One case-control study including patients with ICI-related myocarditis explored the effects of intensified immunosuppressive therapy (IIST) on the clinical outcome of patients. Previous studies have found that patients who need IIST tend

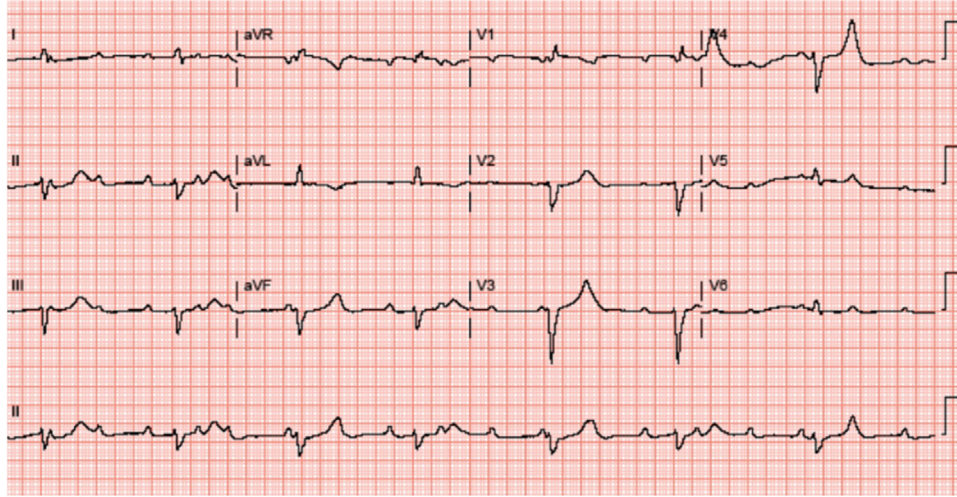


FIG 3. ECG reproduced from Bukamur et al. with permission.¹¹ An 88-year-old woman with squamous cell carcinoma of the lung admitted to hospital 2 cycles after treatment with nivolumab, and during her hospital stay, she developed complete atrioventricular block as seen in the electrocardiogram.

TABLE 3. Summary of clinical studies included in this review

Author	Year	Study Design	No. of Patients	Cancer Type	ICI type	ECG features	Major findings
Chen R et al.	2021	retrospective	10 myocarditis cases	Solid tumors	anti- PD1 anti- PDL1	Heart block	Cardiac conduction disorders including atrioventricular block (AVB) and bundle branch block were found in seven (70%) patients. One patient presented III°AVB, which eventually progressed to complete AVB. In total, three (30.0%) patients experienced more than one type of life-threatening complication. Two (20.0%) patients were admitted to ICU, three (30.0%) patients were put on mechanical ventilation, two (20.0%) patients received the plasma exchange therapy, and one patient was implanted with a pacemaker. Two (20.0%) of the patients succumbed and died, with a median duration of 7.5 days from diagnosis of cardiac immune-related adverse effects to death.
Zlotoff DA et al.	2021	retrospective	140 myocarditis cases and 179 controls treated with ICI	Various	anti- PD1 anti- PDL1 anti- CTLA4	QRS duration	The QRS duration is increased in ICI myocarditis and is associated with increased MACE risk. After adjustment, each 10 ms increase in the QRS duration conferred a 1.3-fold increase in the odds of MACE.
Power JR et al.	2021	retrospective	147 myocarditis cases	NA	NA	heart rate; QRS and QT corrected for heart rate; SokolowLyon Index	Presenting ECG showed elevated heart rate, prolonged QRS and prolonged QT corrected for heart rate compared with baseline ECG. SokolowLyon Index (sum of S wave in V1 and R wave in V5 or V6) showed a significant decrease in voltage from baseline. The incidence of left bundle-branch block and sinus tachycardia was increased versus baseline. In aggregate, conduction disorders

(continued on next page)

Mahmood SS et al.	2018	retrospective	35 myocarditis cases and 105 controls treated with ICI	Various	anti- PD1 anti- PDL1 anti- CTLA4	Heart block	and repolarization abnormalities were significantly increased. Patients with ICI-myocarditis were more likely to experience all-cause mortality within 30 days if they developed complete heart block or life-threatening ventricular arrhythmias. Nearly one-half of all myocarditis cases experienced a MACE: cardiovascular death (n = 6), cardiogenic shock (n = 3), cardiac arrest (4), or CHB (n = 3). Causes of death included 2 sudden deaths, 1 witnessed and 1 unwitnessed, 2 documented ventricular arrhythmias, and 2 of progressive cardiogenic shock.
Cautela J et al.	2020	case-control study	60(36 were treated with intensified immunosuppressive therapy and 24 were not)	Various	anti- PD1 anti- PDL1 anti- CTLA4	Heart block; arrhythmia	Patients requiring intensified immunosuppressive therapy (IIST) had a significantly higher prevalence of sustained ventricular arrhythmia, complete atrioventricular block, cardiogenic shock and troponin elevation. Moreover, they were more likely to have other immune-related adverse events simultaneously, especially myositis and myasthenia gravis. Patients who required IIST were more likely to die from any cause.
Wang F et al.	2020	retrospective	3 myocarditis cases	Solid tumors	anti-PD1 anti-PDL1	Heart block; arrhythmia	One case died on day 56 because of heart and respiratory failure, and the other died on day 34 because of tumor progression. The third case recovered after treatment. The typical clinical manifestations are palpitations, dyspnea, and fatigue. One patient had no clear symptoms. Electrocardiograms showed grade 3 of atrioventricular block and frequent ventricular premature contraction in one case, and frequent ventricular and atrial premature contraction in the other case.

ECG, electrocardiography. ICI, immune checkpoint inhibitor. MACE, major adverse cardiac events.

to have worse overall condition and higher incidence of arrhythmias and malignant cardiovascular events (Table 3).

Discussion

ICIs restore the immune response of CD8+ and CD4+T cells to cancerous tissues by blocking the inhibitory effects of ligand-receptor interactions and have improved the quality of life and survival of patients with many different cancers. However, their immune-related adverse events (IrAEs) affecting different organ systems cannot be neglected.^{19,76,90,101} ICI-related cardiovascular toxicity includes myocarditis, pericarditis, arrhythmia, heart failure, vasculitis and venous thromboembolism.^{14,24,43,51,55,87,99,102} ICI-associated myocarditis is characterized by acute inflammation of the myocardium and may show electrophysiological abnormalities such as ventricular arrhythmias, pulseless electrical activity or complete atrioventricular block, which can progress to acute heart failure or sudden death.^{50,72}

The underlying mechanism may be related to T-cell-mediated cytotoxicity involving the cardiac conduction system. Histological studies have shown that ICI-mediated cardiomyocyte necrosis is characterized by infiltration of CD4+ and CD8+T cells, similar to the development of acute cardiac rejection after transplantation.^{31,46} Lymphocyte infiltration can involve sinoatrial node and atrioventricular node, especially in patients with new-onset bifascicular block and first degree heart block during ICI treatment, reflecting conduction abnormalities across the atrioventricular node or at more distal parts of the conduction system, with a high risk of progression into complete atrioventricular block.⁹² Clinically, patients with complete atrioventricular block and ventricular arrhythmias are often in critical condition with increased mortality. Indeed, ICI-related myocarditis is associated with a fatality rate of 30%-50%,³¹ and thus continuous monitoring of vital signs, cardiac status and ECGs for such patients is needed.

In this study, previously reported cases of ICI-related myocarditis were systematically searched and the ECG findings were summarized. Amongst the 91 patients included, sinus arrhythmias (mostly sinus tachycardia, about 12.09%), atrial fibrillation/atrial flutter, ventricular arrhythmias (including ventricular extrasystole and ventricular tachycardia), heart conduction block, new ST-T abnormalities, T-wave changes, low voltages and new onset Q-waves were detected. Previous clinical studies have reported that ICI-related myocarditis may be associated with ECG changes, mostly arrhythmias. The incidence of ICI-related atrial

arrhythmias is about 1%-3%, of which atrial fibrillation is more common; the incidence of ventricular arrhythmias is about 5%-10%, and is associated with 40% mortality.^{40,57} However, the incidence of complete atrioventricular block is unclear. Power et al. found that nearly 7.5% of patients with ICI-related myocarditis have second degree atrioventricular block and 17% have complete atrioventricular block.⁶⁷ Of the above ECG changes, the incidence of heart block was the highest (about 58.24%), where complete atrioventricular block accounted for 20.88%, followed by right bundle branch block (19.78%).

In addition, we found that ICI-related myocarditis may present with ST-T segment changes unrelated related to coronary artery disease. In this study, 32.97% of the patients had new ST-T changes, excluding vascular lesions after coronary angiography, which could return to normal after high-dose hormone immunosuppressive therapy. Furthermore, some non-specific changes can also be seen in patients with ICI myocarditis, such as multilead low voltage, which may be associated with large pericardial effusion or cardiomyopathy; In addition, there was another patient whose electrocardiogram showed new Q-waves, which ruled out coronary artery disease after coronary angiography. Maybe the appearance of Q-waves was also related to the involvement of ICI related conduction system.

Finally, it is reported that ICI myocarditis usually occurs in the early stage of ICI treatment. Moslehi et al. retrospectively analyzed 101 cases of ICI-associated myocarditis in Vigibase, a pharmacovigilance database by WHO designed to identify drug-associated adverse events. 64% of the patients developed myocarditis after the first or second administration of ICI. The average onset time of myocarditis was 27 days (5-155 days), and 76% occurred in the first six weeks of treatment. Another prospective study of 35 cases of ICI-associated myocarditis from eight centers found that 81% of ICI-associated myocarditis occurred within the first 4 cycles (from the median of 34 days at the beginning of treatment).^{50,59} In their study, the median time from when the first initiation of ICI to myocarditis occurred was 21 days, which was consistent with the previous findings. Patients may have asymptomatic or develop nonspecific symptoms such as progressive fatigue, muscle soreness or weakness, palpitations, chest pain, presyncope, or syncope, shortness of breath and edema. In severe cases, cardiogenic shock or sudden death may occur. Cardiovascular symptoms may be masked or co-present by other irAEs (such as myositis, pneumonia, and hypothyroidism) or lung symptoms associated with malignant tumors or complications.

Limitations and future directions

Some limitations of this study should be recognized. First of all, the case reports included in this study are all from PubMed, and the clinical information available is limited, and the ECG quality of some cases was variable. Second, this study is a retrospective collection of published case reports and clinical studies, there is a specific selection bias. Finally, publication time and attending institutions are different, especially the case reports, diagnosis and treatment programs are different.

By searching the previously published case reports and clinical studies on the changes of ECG in patients with ICI myocarditis, this study emphasizes the feasibility of early identification of ICI-myocarditis using the ECG, which may allow early treatment to improve prognosis. However, the specific physiological mechanism of the disease is not clear and needs to be further explored. Second, most of the clinical reports published are retrospective, and the sample size is relatively small. In the future, clinical studies with a larger sample size are needed to further clarify the ECG manifestations of patients with ICI-related myocarditis.

Conclusion

Myocarditis is a common cardiovascular complication in patients treated with ICIs. The electrocardiogram of patients with ICI-related myocarditis may show new arrhythmias and ST-T changes, and a few patients may show low voltages on multiple leads. A small number of patients had no symptoms and no apparent ECG abnormalities. Monitoring is essential because of its high mortality, with early identification potentially allowing prompt treatment to improve patients' prognosis.

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