International Journal of Cardiology 296 (2019) 113–121

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Diagnosis of immune checkpoint inhibitor-associated myocarditis: A systematic review☆

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ARTICLE INFO

Article history:
Received 9 March 2019
Received in revised form
14 June 2019
Accepted 8 July 2019

Keywords:
Immune checkpoint inhibitors
Myocarditis
Systematic review
Diagnosis
Prognosis
Investigations

ABSTRACT

Background: Myocarditis is a rare but severe adverse event associated with immune checkpoint inhibitors, its diagnosis depending on a high index of suspicion and appropriate investigations. Our objective was to systematically review the diagnostic approaches to myocarditis associated with immune checkpoint inhibitors.

Methods: The systematic review was conducted according to the PRISMA guidelines (PROSPERO Registration: CRD42018097247). We searched Medline and Embase for case reports, case series, and observational studies published in journal articles or presented as conference abstracts that describe patients who developed myocarditis after immune checkpoint inhibitor therapy.

Results: After a review of 2326 citations, we included 88 cases (53 case reports/series published in journal articles and 35 cases in the observational study). Serum troponin was elevated in 98% of the case reports and 94% of participants in the observational study. ST changes including ST elevation were present in almost a third of case reports. Echocardiography revealed preserved left ventricular ejection fraction in 32% of case reports and 51% of cases in the observational study; however, preserved systolic function did not predict greater survival. Patients who suffered poorer prognosis tended to have major conduction defects or ventricular arrhythmias more frequently than patients who did not. Acute myocardial ischemia was ruled out in all cases (n = 31) when the diagnostic workup included coronary angiography.

Conclusions: Immune checkpoint inhibitor-associated myocarditis is characterized by elevation of cardiac troponin levels and non-specific electrocardiographic changes. Early coronary angiography may distinguish it from myocardial ischemia or myocardial infarction.

1. Introduction

Immune checkpoint inhibitors (ICI) have a wide range of immune-related adverse events affecting different organs of the body. Myocarditis is one such rare yet severe adverse event, with the highest case fatality rate among the immune-related adverse events of ICIs [1].

There have been reports of myocarditis among ICI users in the World Health Organization pharmacovigilance database Vigibase [2] and the US Food and Drug Administration Adverse Event Reporting System (FAERS) [3]. Since ICI-associated myocarditis is rare, occurring at a frequency of 0.09% [4] to 1% [5,6], a high index of clinical suspicion is needed to diagnose and manage this condition. Recent studies [7–9] have identified the clinical features of ICI-associated myocarditis but a full understanding of the diagnostic approaches to evaluate this condition is needed. The objective of this systematic review was to characterize the diagnostic approaches to ICI-associated myocarditis.

2. Methods

2.1. Study design

We conducted a systematic review according to the PRISMA Harms guidelines [10] (Supplementary Material 1). Our protocol was registered in PROSPERO CRD42018097247 (Supplementary Material 2).

☆ Authorship statement: All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2019.07.025
0167-5273/

2.2. Search strategy

We searched Medline and Embase on 10th June 2018 to find studies on heart conditions (searched using terms denoting cardiac diseases involving endocardium, myocardium, or pericardium) associated with ICIs. We limited our search to studies published after the approval of the first ICI in the US in 2011. We did not have any study design or language restrictions. We searched the reference section of included articles for additional reports. Our search strategy is described in Supplementary Material 3.

2.3. Eligibility criteria

We included case reports, case series, and observational studies published in journals or presented in conferences and excluded animal studies, pharmacokinetic/pharmacodynamic studies, and randomized controlled trials. The included reports/studies described patients who received an approved ICI (Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, and Durvalumab) as a mono- or combination therapy for any indication and developed ICI-associated myocarditis, as defined by the authors. The reports/studies had to have an adequate description of relevant investigational approaches used to diagnose myocarditis.

2.4. Study selection

Two reviewers initially screened titles and abstracts for eligibility using Rayyan [11]. Full texts of citations deemed eligible were retrieved and further assessed for eligibility by two team members. A third reviewer adjudicated all disagreements. We achieved full consensus prior to inclusion.

2.5. Data extraction and assessment of reporting standards or risk of bias

One of three reviewers extracted data on the study and patient characteristics, description of the ICI-associated myocarditis, investigative procedures, and outcomes (Supplementary Material 2). A second reviewer checked all entries to ensure accuracy of the extracted data. Patients with left ventricular ejection fraction <50%, sustained ventricular arrhythmias, or low cardiac output syndrome were classified as having complicated myocarditis, while patients without such presentation were considered as having uncomplicated myocarditis [12].

To evaluate the standard of information in the case reports we used the guidelines from the International Society for Pharmacoepidemiology for the reporting of adverse events in case reports [13]. We used the Newcastle-Ottawa scale to assess the risk of bias of the observational study [14].

2.6. Data synthesis

We report aggregated data from the case reports/series. No inferential or predictive statistics were computed.

3. Results

3.1. Study inclusion

After a review of 2326 citations in PubMed and Embase, we included 46 case reports, 4 case series, and one observational study. This resulted in a total of 88 cases of ICI-associated myocarditis, including 53 cases from reports published in journals or conference abstracts and 35 cases from a single observational study. Fig. 1 describes the PRISMA flow sheet.

3.2. Completeness of reporting elements and risk of bias

Of the published case reports, none provided complete demographic description. Only 29% of the cases commented on the presence or absence of autoimmune diseases at baseline. Information on concomitant medications and dosage of ICIs was unavailable in 32% cases. The conference abstracts were of lower quality while the observational study was adequate in quality. The assessments of the risk are shown in Supplementary Material 4.

3.3. Clinical characteristics

The characteristics of the included patients in the case reports are described in Table 1. The average age of the patients was 64 years, and 41.5% of them were women. The most commonly reported symptom was dyspnea (49%). Patients also presented with fatigue/generalized weakness/lethargy (25%), chest pain (17%), edema/weight gain (17%), malaise (9%), nausea (9%), syncope/fainting (9%), palpitation (6%), fever (6%), cough (4%) and anorexia (4%). Myalgia due to myositis was the presenting symptom in three cases with myocarditis being a chance finding [15–17], and myocarditis was only discovered during autopsy in another case [18]. A patient with a history of heart transplant who received ICI therapy presented with symptoms of heart failure as a result of acute transplant rejection [19].

Myocarditis was complicated by the occurrence of a low left ventricular ejection fraction (LVEF < 50%), sustained ventricular arrhythmias, or low cardiac output syndrome [12] in 37/53 (70%) cases, among which death was reported in 19 cases (51%). Conversely, 8 of the 16 cases with an uncomplicated presentation died (50%). Treatment comprised of two strategies: immunosuppression and supportive therapy for heart failure. Corticosteroids were the most commonly used form of immunosuppressive therapy (91%). Details of treatments are shown in Supplementary Material 5.

3.4. Diagnostic markers and investigations

The results of diagnostic markers and investigations are shown in Table 2.

3.4.1. Cardiac biomarkers and other blood tests

3.4.1.1. Serum troponin. Among the 43 cases which reported on this outcome, serum troponin I or T was elevated in 42 cases. The only case where troponin was negative also had normal levels of other serum cardiac biomarkers. The diagnosis of myocarditis was only established during autopsy in this case [20]. Seven of the 42 cases presenting with elevated serum troponin levels reported either lowering or normalization of troponin levels after resolution of myocarditis.

Pre-ICI treatment troponin level was reported in three studies. It was normal in two of the studies [21,22], while in another it was found to be elevated on retrospective evaluation after the patient's death [23]. Serial troponin monitoring correlated with clinical course, with gradual normalization in myocarditis cases that responded to immunosuppressant therapy [21,24]. Conversely, an eventually fatal case was characterized by progressive increase in troponin levels despite oral steroid treatment [25]. Norwood et al. reported a case of smoldering myocarditis where the troponin level declined initially after immunosuppressive treatment of myocarditis, but rose again after two months [22]. This elevation in troponin was accompanied by persistent immune-mediated myocardial injury, and required prolonged immunosuppressive therapy for normalization of the troponin level [22].

The cohort study [6] also reported findings similar to the case reports, in that 94% of the 35 myocarditis cases had elevated troponin T levels. Among the cases, a higher troponin level (>1.5 ng/dl) predicted an adverse myocardial event (Specificity 95%).

3.4.1.2. Serum creatine kinase-muscle/brain (CK-MB) and serum creatine kinase (CK). Serum CK MB was elevated in all 19 cases in which it was reported. In four of the 19 cases, a lowered/normalized CK-MB result was reported during post-treatment follow-up. Pre-ICI treatment CK-MB levels were normal in two prospective studies [21,22]. However, in the case with elevated pre-ICI treatment troponin level and presence of anti-troponin antibodies, pre-treatment CK-MB level was normal [23]. Serial changes in serum CK-MB levels with treatment roughly mirrored troponin levels [21,22,25].

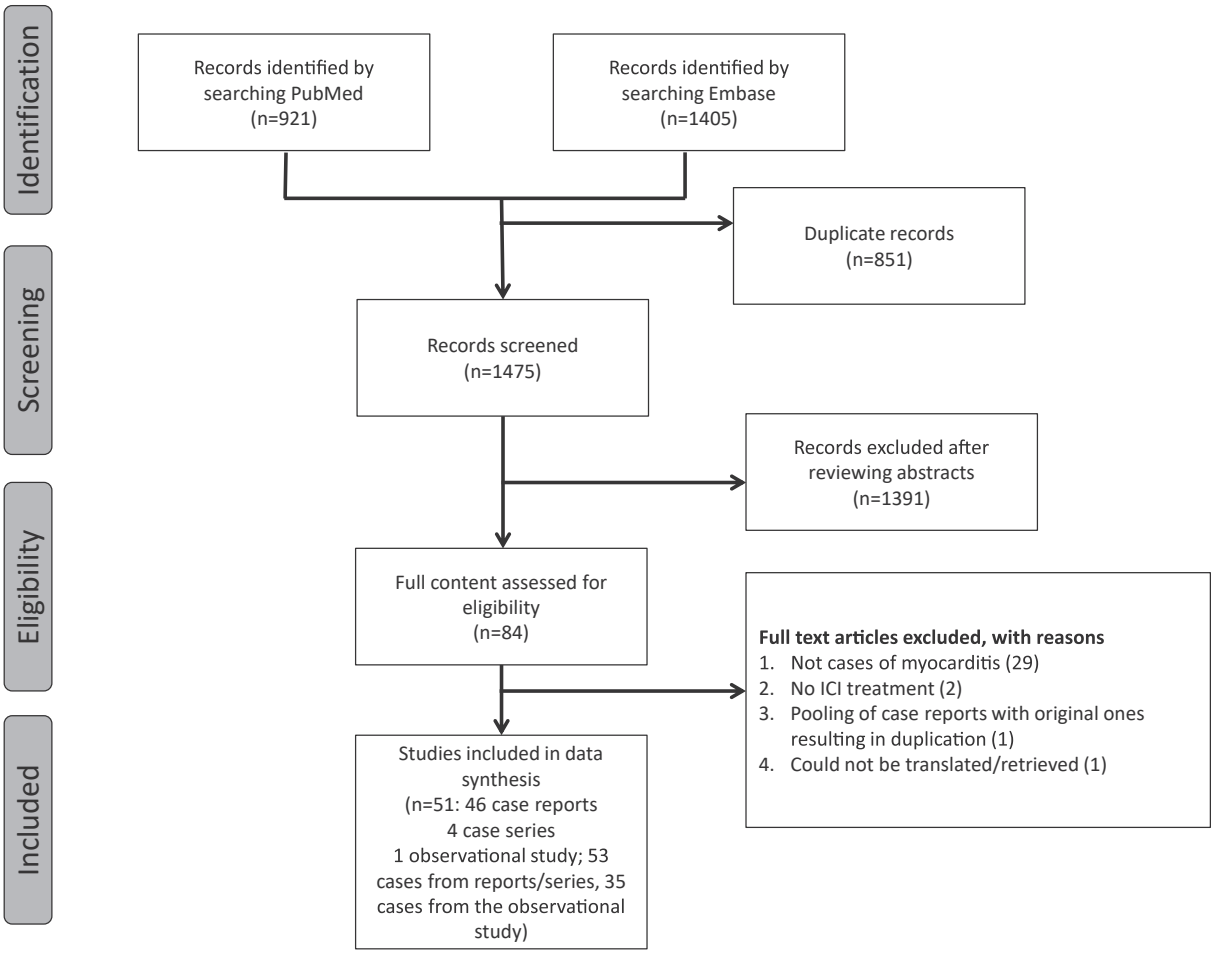

Fig. 1. PRISMA flow diagram of study selection.

Serum CK was elevated in all 24 cases in which it was reported, and myositis was diagnosed as an accompanying immune related adverse event in nine cases.

3.4.1.3. Serum brain natriuretic peptide (BNP). Among the 15 cases of myocarditis in which it was reported, serum BNP was elevated in the majority (13/15). In one case it remained within normal range during initial measurement [26], while in another case of smoldering myocarditis reported by Norwood et al., it remained within normal range during the post-myocarditis treatment phase when an elevated troponin indicated underlying persistence of the disease [22]. On the other hand, it was elevated in only about 66% cases in the cohort study [6]. Body mass index or obesity status, an important factor having an inverse relationship with BNP levels [27], was not reported in any of the 53 cases or the cohort study.

3.4.1.4. Autoimmune antibodies. Among the 18 studies in which post-ICI treatment antibodies were reported, they were positive in 11 cases. However, there was no consistent pattern of elevation. The commonest antibodies elevated were antinuclear antibodies (3 cases) and anti-acetylcholine receptor antibodies (3 cases). Nine of the 11 cases had a concomitant immune related adverse event other than myocarditis.

Pre-ICI treatment autoantibody elevations reported in two cases, one with elevated anti-acetylcholine receptor antibody [28] and another with cardiac anti-troponin antibody [23].

3.4.1.5. Virology. Profiling of serum and/or myocardial tissue for active viral infection yielded negative results in all 25/53 cases where it was reported. Three cases reported finding Herpes virus simplex-1 (HSV-1) [4], Epstein Barr virus (EBV) [4], and parvovirus B19 [29] viral genomic DNA in the myocardial tissue which was detected during autopsy. However, in all three cases the authors concluded that these findings were incidental since these viral particles often have long latency period in tissues [29].

3.4.2. Cardiac electrophysiology and imaging

3.4.2.1. Electrocardiogram (EKG). 47/53 myocarditis cases commented on EKG features, out of which 4 were within normal limits and 43/47 (91%) with abnormal findings. ST changes were reported in 17 cases that included ST elevation (15 cases) and ST depression (2 cases). Conduction abnormalities with various degrees of heart block were noted in 24 cases. Right bundle brunch block (10 cases) was more commonly reported than left sided fascicular block (4 cases); 16/24 cases eventually developed a complete heart block. Cardiac rhythm abnormalities were noted in 16 cases that included ventricular tachycardia or fibrillation in 15 cases. Among those with cardiac rhythm abnormalities, a prior conduction defect was noted in 7 cases.

The cohort study reported that the majority (89%) of EKGs were abnormal among those with ICI-associated myocarditis. The incidence of ventricular fibrillation among their 35 cases of myocarditis was 14% and that of complete heart block was 23% [6].

Table 1
Clinical history of patients described in the case reports/case series.

Parameter	Anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) therapy N = 5	Anti-programmed cell death protein 1 (anti-PD-1) therapy N = 34	Anti- Programmed death-ligand 1 (anti-PDL-1) therapy N = 1	Combination therapy N = 13
Basic information				
Mean age in years	62	67	55	59
Male/female	5/0	21/13	0/1	5/8
Primary cancer indication	80% skin, 20% hematological	38.2% lung, 23.5% skin, 17.6% urinary tract, 8.8% gastrointestinal tract, 2.9% each of brain, eye, hematological, and thymus gland	Lung	100% skin
Case history				
Prior autoimmune disease	Not reported (NR)	2/34	NR	1/13
Preexisting cardiovascular conditions/risk factors	3/5	9/34	NR	5/13
Previous radiotherapy	NR	8/34	NR	1/13
Anthracycline use	NR	NR	NR	1/13
Prior ICI use	NR	3/34	NR	NR
Small molecule use	NR	3/34	NR	1/13
Angiogenic growth inhibitor use	NR	1/34	NR	NR
Previous immunomodulating therapy apart from ICI	NR	7/34	NR	1/13
Clinical features				
Time to development of symptoms (Mean, Range in weeks)	10.04, 2–31 (reported in 5/5 cases)	6.54, 0.71–52 (reported in 25/34 cases)	9	4.54, 1–21 (reported in 10/13 cases)
Concomitant IrAE	3 cases of hepatitis, 1 case each of colitis, uveitis, and rash	8 cases of myositis, 3 cases of myasthenia, 3 cases of hepatitis, 1 case each of type 1 diabetes, pneumonitis	NR	3 cases of thyroid involvement, 5 cases with myositis, 2 cases of hepatitis, 2 cases of hypophysitis, 1 case each of colitis and meningitis
Complicated presentation	5/5	25/34	1/1	7/13
Treatment strategies				
- Immunomodulation				
- Steroids	5/5	30/34	1/1	12/13
- Infliximab	0/5	3/34	0/1	3/13
- Tacrolimus	0/5	2/34	0/1	1/13
- Mycophenolate	0/5	1/34	0/1	2/13
- Cyclophosphamide	0/5	1/34	0/1	1/13
- Infliximab	0/5	3/34	0/1	3/13
- IVIG	0/5	6/34	0/1	4/13
- Plasmapheresis	0/5	4/34	0/1	0/13
- ATG	0/5	4/34	0/1	0/13
- Therapy directed at heart failure				
- Beta blockers	1/5	7/34	1/1	1/13
- ACE-I	1/5	2/34	0/1	2/13
- Anti-arrhythmics	1/5	4/34	1/1	0/13
- Diuretics	1/5	3/34	0/1	0/13
- Inotropes	3/5	4/34	0/1	0/13
- Pacemaker	0/5	4/34	0/1	4/13
- ECMO	0/5	4/34	0/1	1/13
Prognosis				
Deaths				
- Overall death	5/5	16/34	0/1	6/13
- Cardiac death	3/5	14/16	0/1	4/6
- In-hospital death	4/5	13/16	0/1	5/6

IVIG: intravenous immunoglobulin; ATG: antithymocyte globulin; ACE-I: angiotensin-converting-enzyme inhibitor; IrAE: Immune related adverse events; ECMO: extra-corporeal membrane oxygenation; complicated presentation defined by presence of left ventricular ejection fraction <50%, sustained ventricular arrhythmias, or low cardiac output syndrome.

3.4.2.2. Echocardiography. 45/53 myocarditis cases reported on echocardiographic features, of which 11 (23%) were within normal limits. Of the 40 reports that commented on LVEF, systolic function was preserved (LVEF > 50%) in 13 cases in the case reports. Despite a preserved systolic function, however, eight of these 13 cases died, indicating the poor correlation of preserved LVEF with mortality. In the cohort study, 51% of cases had preserved systolic function whereas the average left ventricular internal dimensions in diastole

Table 2
Diagnostic investigations in the pooled case reports and the cohort study.

Parameter	Pooled data from case reports/series (n = 53)	Mahmood et al. 2018 (n = 35)
Cardiac biomarkers		
Troponin	Reported in 43/53; elevated in 42/43	Reported in 100%; elevated in 94%
Creatine kinase-muscle/brain	Reported in 19/53; elevated in 19/19	Not reported (NR)
Brain natriuretic peptide	Reported in 15/53; elevated in 13/15	Reported in 100%; elevated in ~66%
Acute phase reactants		
WBC counts/flow cytometry	Reported in 3/53; elevated in 2/3. In both cases, flow cytometric analysis showed a rise in CD8 T cell counts.	- NR
C-reactive protein	Reported in 5/53; elevated in 4/5.	- NR
Coagulation markers	Reported in 3/53; elevated in 2/3.	- NR
Pathological/ microbiological tests		
Post treatment autoantibodies	Reported in 18/53; elevated in 11/18.	- NR
Virology examinations	Reported in 25/53; negative in 25/25 for active viral infection	- NR
Electrocardiogram features		
Number of cases where reported	47/53	100%
ST changes		
- ST elevation	- 15 cases (four of them had chest pain/discomfort)	- NR
- ST depression	- 2 cases (one with chest pain)	- NR
Average QRS interval	- NR	- 102.45 milliseconds
Average QTc interval	- NR	- 457 milliseconds
Rhythm or rate abnormalities		
- Complete heart block	- 16 cases	- 23%
- Ventricular tachycardia or fibrillation	- 15 cases	- 14%
- Atrial flutter or fibrillation	- 2 cases	- 26%
Echocardiography features		
Number of cases where reported	47/53	100%
Left ventricular ejection fraction (LVEF) <50%	- 27 cases (LVEF reported in 40 cases)	- 49%
Right ventricular systolic dysfunction	- 5 cases	- NR
Motion abnormality		
- Global left ventricular hypokinesis	- 10 cases	- NR
- Septal hypokinesis	- 3 cases	- NR
Anatomical features		
- Average left ventricular internal dimensions in diastole	- NR	- 48 mm (that is, within normal limits)
- Dilatation of the heart	- 5 cases (right ventricle in 2 cases, left ventricle in 1, both in one, and unspecified in 1)	- NR
- Thickened myocardial walls	- 3 cases	- NR
- Valvular regurgitations	- 2 cases (one with aortic and one with tricuspid and mitral insufficiency)	- NR
Cardiac magnetic resonance imaging		
Number of cases where reported	14/53	88%
Late gadolinium enhancement		
- None	- 5 cases	- 26%
- Subepicardial	- 1 case	- 19%
- Mid-myocardial	- 2 cases	- 39%
- Diffuse	- 3 cases	- 29%
Other features		
- T2 hyperintensity	- 3 cases	- NR
- Early enhancement	- 1 case	- NR
- T1 mapping	- NR	- NR
Cardiac catheterization and coronary angiography	Reported in 31/53; all cases negative for acute pathology	- NR
Histological findings (from endomyocardial biopsy, muscle biopsy, or autopsy)	Reported in 28/53; majority reported lymphocytic infiltration, but giant cell, eosinophil and neutrophil infiltrations were also reported.	Reported in 31%; patchy to diffuse T-cell predominant infiltrates without granulomas or giant cells.
Chest X ray	Reported in 8/53; noted cardiomegaly (n = 2), pulmonary effusion (n = 2), pulmonary infiltrates (n = 1), or were within normal limits (n = 3)	- NR
Computed tomographic scan of the chest	Reported in 10/53; excluded lung pathologies like pulmonary embolism (n = 4) pneumonitis (n = 3).	- NR

was within normal limits (about 47–49 mm) [6]. A lack of correlation between preserved LVEF and adverse cardiac events was also noted in the observational study [6].

3.4.2.3. Cardiac magnetic resonance imaging (MRI). 14/53 myocarditis cases commented on cardiac MRI. Location of the late gadolinium enhancement was varied, having subepicardial, mid wall, or diffuse involvement. Predominant involvement of the right ventricle, a finding typical of toxic myocarditis, was reported in two cases [30,31]. Late gadolinium enhancement was absent in five, i.e., one third of the cases where cardiac MRI was reported. Similarly, the observational study reported no enhancement in 26% cases [6].

3.4.2.4. Cardiac catheterization and coronary angiography. Cardiac catheterization and angiography was reported in 31 cases of myocarditis, all negative for acute pathology. Chronic and/or partial occlusions were noted in four cases, but did not fully explain the current symptoms. A low cardiac index was reported in four cases all of whom survived [26,32–34], suggesting that a low cardiac index does not necessarily correlate with mortality, and that these patients recover their cardiac function with adequate immunosuppression.

In two cases with confusing clinical features and investigational findings where presumptive therapy for acute myocardial infarction with aspirin and anticoagulation was started, angiographic exclusion of acute stenosis helped eliminate myocardial infarction as a differential diagnosis and initiate immunosuppressive therapy to treat myocarditis [35,36]. In another case, presumptive heparin therapy was started and although angiography excluded significant stenosis, steroid was not instituted with deterioration of the patient's clinical condition [37].

Table 3
Comparison of reported events between patients who died versus those who survived.[a]

Parameter	Patients who died, N = 27	Patients who survived, N = 23
Clinical features		
Mean age in years	63.1, 23–83	63.6, 35–80
Male/female	17/10	11/12
Mean time to development of symptoms, range in weeks	5.5, 0.71–31 (reported in 23/27)	7.7, 1–52 (reported in 18/23)
Immune checkpoint inhibitor (ICI) used	5 anti-CLA-4 (19%), 16 anti-PD-1 (59%), 6 combination (27%)	16 anti-PD-1 (70%), 1 anti-PDL-1 (4%), 6 combination (26%)
Previous autoimmune diseases	1/27	2/23
Preexisting cardiovascular conditions/risk factors	14/27	3/23
Other ICI-induced immune related adverse events	17/27	8/23
Complicated presentation	19/27	17/23
Investigations		
Troponin	Reported in 21/27; elevated in 20/21	Reported in 19/23; elevated in 19/19
Creatine kinase-muscle/brain	Reported in 11/27; elevated in 11/11	Reported in 6/23; elevated in 6/6
Brain natriuretic peptide	Reported in 4/27; elevated in 4/4	Reported in 9/23; elevated in 7/9
Electrocardiogram features	Reported in 24/27	Reported in 21/23
ST changes		
- ST elevation	- 5 cases	- 9 cases
- ST depression	- 1 case	- 1 case
Rhythm or rate abnormalities		
- Complete heart block	- 12 cases	- 4 cases
- Ventricular tachycardia/fibrillation	- 10 cases	- 4 cases
- Atrial flutter/fibrillation	- 2 case	- NR
Echocardiography features	Reported in 21/27	Reported in 21/23
Left ventricular ejection fraction (LVEF) < 50%	- 10 cases	- 16 cases
Wall-motion abnormality		
- Global left ventricular hypokinesis	- 3 cases	- 6 cases
- Septal hypokinesis	- NR	- 2 cases
Anatomical features		
- Dilatation of the heart	- 2 cases	- 3 cases
- Thickened myocardial walls	- 2 cases	- 1 cases
Cardiac magnetic resonance imaging	Reported in 3/27 (in one, no details about characteristic features provided)	Reported in 10/23
Late gadolinium enhancement		
- None	- 1 case	- 4 cases
- Subepicardial	- NR	- 1 case
- Mid-myocardial	- 1 case	- 1 case
- Diffuse	- NR	- 3 cases
Other features		
- T2 hyperintensity	- NR	- 3 cases
- Early enhancement	- NR	- 1 case
Cardiac catheterization and coronary angiography	Reported in 11/27; all cases negative for acute pathology	Reported in 19/23; all cases negative for acute pathology
Histological findings (from endomyocardial or muscle biopsy or autopsy)	Reported in 18/27; majority showing lymphocytic infiltrate	Reported in 8/23; majority showing lymphocytic infiltrate
Treatment		
Immunomodulators used	Steroids in 22/27, other immunosuppressants in 7/27, IVIG in 4/27, plasmapheresis in 2/27, ATG in 2/27	Steroids in 23/23, other immunosuppressants in 5/23, IVIG in 5/23, plasmapheresis in 2/23, ATG in 2/23

[a] Data for 3 patients in whom outcome was unclear excluded.

3.4.2.5. Histological findings from endomyocardial biopsy or autopsy. Myocardial histological findings after endomyocardial biopsies during angiography (14 cases) or autopsies (12 cases) were reported in 26 cases, while skeletal muscle histology was reported in two cases. The findings ranged from active infiltrative myocarditis to myocardial fibrosis, with some cases showing presence of both features. The cellular infiltration was predominantly lymphocytic (26 cases), but also stained positive for macrophages/histiocytes/giant cells/clusters of differentiation (CD)68+ cells (11 cases), eosinophils (two cases), and neutrophils (one case). The lymphocytic population constituted predominantly of CD8+ T cells, with traces of nonregulatory CD4+ T cells and absence of CD20+ B cells. Similar findings of patchy to diffuse T-cell predominant infiltrates without granulomas or giant cells were reported in the cohort study [6].

Out of the five cases where programmed cell death protein 1 (PD-1) staining was reported, the CD8+ T cells stained negative for PD-1 in three cases (indicating possible engagement of the PD-1 sites by the drug) [23,33,34], while there was expression noted in 50-85% T cells in two cases [18,38]. PD-L1 staining, conversely, was strongly positive in the affected myocardium in all six cases where it was reported [4,15,25,33,38]. None of the cases undergoing anti-PD-L1 therapy (three on anti-PD1 and CTLA4 combination therapy, two on anti-PD1 therapy, and one on anti-CTLA4 therapy). T cell receptor sequencing was conducted in five cases, in four of which the authors reported that the T cells affecting the myocardium [4,39] or the skeletal muscle [28] were of the same strain as the tumor killing T cells presumably generated by the ICI treatment. Conversely, one study reported a heterogeneous T cell repertoire, differing substantially between the tumor and the myocardium [25].

Conflicting findings were reported in the four cases describing human leukocyte antigen (HLA) staining from biopsy samples.

Fukasawa et al. reported the expression of HLA-ABC and HLA-DR antigens on the cardiac muscle cells, providing evidence of immune response on the basis of HLA associations [40]. Similarly, Reuben et al., reported significantly higher expression of HLA-DR1 and HLA-DR3 in the myocardial cells compared to lung and liver tissues from the same person [25]. On the other hand, the only HLA-type that Johnson et al. found common between their two myocarditis cases was HLA-DQB1*03:01, which is a prevalent antigen in the population [4]. They concluded that their cases were not due to HLA-mediated drug hypersensitivity.

3.5. Prognosis and follow-up

Death was reported in 27/53 cases. Of these, 21 were cardiac deaths related to the ICI-associated myocarditis while the remaining deaths were attributed to other immune related adverse events or underlying tumor progression. Twenty-two deaths occurred in-hospital. Conversely, of the 26 cases where the patient were not reported to die within the follow-up period, 23 had partial or complete resolution of myocarditis with an average post-ICI treatment follow-up of 13.7 weeks (range 2–40 weeks), while outcome was unclear in three cases. The follow-up investigations, in decreasing frequency of use, included echocardiography (10 cases, with an improvement in LVEF the commonest parameter reported), biomarkers (7 cases), EKG (4 cases), cardiac MRI (1 case), and biopsy (1 case).

The clinical profile and investigational features of 27 patients who died and 23 patients who survived are listed in Table 3. Those who died had a shorter time to development of symptoms after onset of ICI therapy, had more frequent preexisting cardiovascular conditions, and other concomitant immune related adverse event. While rhythm or rate abnormalities were more commonly reported among patients who died, preserved left ventricular ejection fraction was also more frequently reported among them. Conversely, impairment of ventricular movement and function was more commonly reported in those who survived. Patients who had ICI-associated cardiac deaths and those who had non-cardiac deaths or survived have been compared in Supplementary Material 6.

In the cohort study, six out of 35 ICI-associated myocarditis cases suffered death from cardiovascular causes [6]. The authors compared ICI-associated myocarditis cases that had major adverse cardiovascular events (MACE: cardiovascular death, cardiogenic shock, cardiac arrest, or complete heart block) versus those who did not. Compared to those without MACE in univariate assessments, patients with MACE had received Nivolumab monotherapy more frequently and Pembrolizumab monotherapy less frequently, had greater troponin values, lower diastolic blood pressure levels, required intubation more often but had received lower doses of steroid per kilogram of body weight. Importantly, the average time from admission to steroid administration in those who had MACE outcomes was longer than those who did not have MACE (27. 2 v 18.3 h; $p = 0.12$) [6].

4. Discussion

Our review suggests that ICI-associated myocarditis is accompanied by elevated cardiac biomarker levels, nonspecific ST and arrhythmic changes on EKG, lack of correlation between preserved systolic function and survival, and negative results on coronary angiography.

4.1. Recommendations for early diagnostic workflow

Our review demonstrates that cardiomyocyte damage markers like troponin and CK-MB were more commonly abnormal than BNP. Similarly, while non-specific EKG abnormalities such as ST-related and arrhythmic changes were reported, echocardiography was normal in a substantial number of cases. However, the significance of a positive cardiomyocyte damage marker level and abnormal EKG, both used in diagnosis of acute myocardial infarction, an important differential diagnosis [41,42], remains uncertain. Conversely, in our review coronary angiography was negative for acute coronary obstruction in all cases, suggesting a negative result would further support the diagnosis of ICI-associated myocarditis.

Cardiomyocyte damage markers and EKG should be the first line of investigations, as reflected in previously proposed diagnostic algorithms. [6,26,43,44] The use of invasive coronary angiography is useful in patients with acute presentations to exclude myocardial infarction, an important diagnosis to exclude with a very different management. Cardiac MRI and endomyocardial biopsy can be considered if the diagnosis of ICI-associated myocarditis remains uncertain [45].

4.2. Factors associated with poor prognosis

A high troponin level correlated with adverse cardiovascular outcomes in the cohort study, and EKG abnormalities like complete heart block and ventricular tachyarrhythmias were more frequently reported in the case reports where the patient died. On the other hand, myocardial wall hypokinesis and impaired ejection fraction was more commonly reported in patients who survived, findings which were also seen in the study by Mahmood et al. [6] It is possible that patients with low LVEF present sooner resulting in an earlier diagnosis whereas diagnosis and treatment may be delayed in those with preserved LVEF. These findings are in contrast to findings of myocarditis associated with other causes in which low LVEF (<50%) (as well as sustained arrhythmias and low cardiac output) is associated with significantly higher risk of cardiac death and cardiac transplantation [12].

4.3. Proposed future research

Future studies should evaluate the value of surveillance utilizing serial troponins and EKGs in the first two to three months, particularly among those with preexisting cardiovascular diseases for the diagnosis of -ICI-associated myocarditis among asymptomatic patients. Studies should also determine the diagnostic accuracy of high-sensitivity troponin levels for ICI-associated myocarditis. Among those who exhibit clinical symptoms of myocarditis, studies should examine the accuracy of first line investigations (cardiac biomarkers, EKG) against the gold standard test of endomyocardial biopsy. In patients with ICI-associated myocarditis, the prognostic value of investigations likes serial troponin monitoring and EKG abnormalities and their value in identifying those in need for second or third line therapy in addition to corticosteroids need to be determined. Additionally, while corticosteroid therapy seems to be the standard first-line treatment strategy, appropriate use of second or third line immunosuppressant medications or the use of specific antidotes like abatacept [46] needs to be evaluated.

4.4. Limitations

Our study has some limitations. The reporting of diagnostic tests was incomplete in several case reports, and we were unable to distinguish whether lack of reporting reflected a normal test result or whether it was not conducted. As a result, these numbers do not reflect the true incidence of these complications. Since our sample was potentially non-representative, we did not estimate any accuracy parameters. Our findings are also subject to reporting bias.

5. Conclusion

In summary, immune checkpoint inhibitor-associated myocarditis is characterized by elevation of cardiomyocyte damage biomarker levels and non-specific electrocardiographic changes. Early coronary angiography may distinguish it from myocardial ischemia or myocardial infarction. Cardiac arrhythmias are frequently reported in ICI-associated myocarditis patients with poorer prognosis, while reduction in left ventricular ejection fraction does not correlate with survival. Prospective studies with consistent follow-up to determine the optimal approach to diagnosis of ICI-associated myocarditis are needed.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.07.025.

Funding

None.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgement

The authors would like to acknowledge the help of Dr. Govind Jha in data extraction for this paper.

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