Journal of Cancer Research and Clinical Oncology (2019) 145:1527–1557
https://doi.org/10.1007/s00432-019-02927-x

REVIEW – CLINICAL ONCOLOGY

Immune checkpoint inhibitor therapy and myocarditis: a systematic review of reported cases

Suheil Albert Atallah-Yunes[1] · Anis John Kadado[1] · Gregory P. Kaufman[2] · Jaime Hernandez-Montfort[3]

Received: 7 February 2019 / Accepted: 23 April 2019 / Published online: 26 April 2019

Abstract

Introduction The advent of immune checkpoint inhibitors in the treatment of certain types of cancers has revolutionized cancer therapy. In general, these novel agents are more tolerable and have better safety profiles than conventional chemotherapy agents. Although a low incidence of myocarditis was noted as a side effect of immune checkpoint inhibitors in clinical trials, it is being increasingly cited in the literature as their use also increases.

Methods Using a combination of search terms in the PubMed/Medline database and manual searches on Google Scholar and the bibliographies of articles identified, we reviewed all cases reported in the English language citing myocarditis associated with either pembrolizumab, nivolumab, ipilimumab, or any combination of these agents.

Results A total of 42 cases were included in the study. Mean age was 65.5 years; 64% were male, 36% were female. One or two doses preceded the onset of myocarditis in 33% and 29% of cases, respectively. Steroids were used as the first-line therapy in 90% of cases. Complete heart block occurred in 36% of cases. Fourteen (33%) deaths were reported, with 64% and 29% of deaths occurring after one or two doses, respectively.

Conclusion Most cases and fatalities of myocarditis occurred shortly after initiation of immune checkpoint inhibitor therapy. Arrhythmias, particularly complete heart block, appear to be related to the occurrence of more severe and fatal cases. The use of serial electrocardiograms or biomarkers of myocardial injury may be crucial in detecting early stages of the disease process. Further research establishing more specific guidelines is necessary in dealing with this potentially fatal side effect.

Keywords Myocarditis · Immune checkpoint inhibitors · Immunotherapy

Introduction

The recent advent of immune check inhibitors (ICIs) has revolutionized cancer treatment. The FDA has approved the use of ICIs as a first-line agent in metastatic melanoma and non-small cell lung cancer, and as a second-line agent in Hodgkin's lymphoma, head and neck, bladder, renal cancers, and others (Simsek et al. 2019; Hargadon et al. 2018). Various ICIs are now available, acting on different target sites. Ipilimumab targets cytotoxic T-lymphocyte-associated antigen 4(CTLA-4) receptors, while nivolumab and pembrolizumab target programmed cell death 1 (PD-1) receptors (Collin 2016; Hargadon et al. 2018). Despite the benefits, these novel agents have provided; increased autoimmune side effects have been noted, likely attributed to the lack of T cell specificity.

The incidence of patients developing autoimmune side effects with ICIs is approximately 30% with CTLA-4 inhibitors, 20% with anti-PD-1 inhibitors, and 55% in patients receiving a combination of nivolumab and ipilimumab (Norwood et al. 2017). The cardiovascular system is among the least systems affected by immunotoxicity. Pericarditis, myocardial fibrosis, pericardial effusion, and myocarditis are some of possible side effects (Varricchi et al. 2017), with myocarditis being increasingly reported with the use of ICIs. Although very rare, it has been estimated to occur in 0.06–1% of clinical trial patients receiving ICIs (Ganatra and Neilan 2018). However, the incidence of myocarditis as

✉ Suheil Albert Atallah-Yunes
suheil-albert.atallah-yunesmd@baystatehealth.org

[1] Department of Medicine, Baystate Medical Center, University of Massachusetts, Springfield, MA 01103, USA

[2] Department of Hematology/Oncology, MD Anderson Cancer Center, University of Texas, Houston, TX, USA

[3] Department of Cardiology, University of Texas Medical Branch at Galveston, Galveston, TX, USA

a side effect of ICIs might be underestimated as most cases identified had fulminant myocarditis or developed severe side effects; while those with silent or smoldering myocarditis may have not been reported (Ganatra and Neilan 2018; Varricchi et al. 2017).

Patients developing myocarditis related to ICIs commonly present with congestive heart failure, cardiogenic shock, and fatal arrhythmias (Frigeri et al. 2018). No guidelines currently exist for the diagnosis and management of myocarditis caused by ICIs. Early recognition is often challenging due to the lack of specific signs and symptoms at its onset. In addition, the lack of routine cardiovascular testing such as obtaining electrocardiograms or routine bloodwork may explain why many cases are possibly under-reported, thus underestimating the frequency of myocarditis related to ICI use (Ganatra and Neilan 2018).

In this paper, we present a review of the reported cases of myocarditis that developed as a side effect of ICIs. In it, we aim to analyze whether incidence and fatalities were associated with any particular risk factors such as the number of ICI doses administered, class of ICIs used, type of cancer being treated, or other comorbidities. We also aim to investigate the most common electrocardiogram (ECG), laboratory testing, imaging, and biopsy findings in the reported cases with the aim of identifying patterns to aid in the early diagnosis and management of this potentially fatal condition.

Methods

A combination of the following search terms was used to identify articles in the PubMed database up until 12/23/2018: myocarditis, checkpoint or check point, ipilimumab, nivolumab, and pembrolizumab. Case reports on myocarditis caused by immune checkpoint inhibitors nivolumab, pembrolizumab, ipilimumab, or any combination of these agents were selected. More recently, FDA approved agents, durvalumab, avelumab and atezolizumab, were not included in our analysis, given the relatively recent introduction of these agents into the market. In addition, trends and conclusions regarding the reported side effects of these novel agents are less likely to be derived given their relatively infrequent use and rarity of reported adverse outcomes in the literature to date. Fifty records in the PubMed database were identified. Nineteen records did not involve case reports and were excluded (of these 19 records, some were used for literature review). Of the remaining 31 records, 27 were found to be eligible and comprised of a total of 29 cases. Four case reports were excluded as one reported on a case of myocarditis due to combination of pembrolizumab and epacadostat, another was a repetition of a case that was also reported by the same institute in another paper that we had accounted for, a third reported on a case of myocarditis due to a combination of tremelimumab and durvalumab and a fourth was in the German language and, therefore, excluded. Another 10 eligible records involving a total of 13 cases were identified following a manual search on Google scholar, Google search engine, and the bibliographies of articles identified through PubMed. In total, 37 records with 42 case reports were included in the study. Figure 1 represents a PRISMA flowchart showing study screening and selection process.

Results

Forty-two cases citing myocarditis as a side effect of ICI use were identified, with the majority (43%) having been reported in year 2018. Nivolumab was most commonly used (43%), followed by combination therapy of both nivolumab and ipilimumab (24%), pembrolizumab (19%), and, finally, ipilimumab (14%). The cancers being treated were primarily melanoma and non-small cell lung cancer in 45% and 31% of cases, respectively. Thirty-three percent of the reported cases of myocarditis occurred after a single dose of ICI therapy, with 29% occurring after two doses. Presenting symptoms were variable and non-specific with dyspnea, fatigue, and myalgia being most common. Twenty-four percent of patients had a history of hypertension, while 7% reported a history of heart failure, arrhythmias, and peripheral vascular disease, respectively. The most common autoimmune toxicities cited in addition to myocarditis were myositis (29%) and hepatitis (21%), followed by thyroiditis (12%). Table 1 describes the characteristics and presenting features of individual case reports.

Echocardiogram findings at time of presentation revealed a normal ejection fraction and reduced ejection fraction (< 40%) in 36% of reported cases, respectively. Ten-percent of cases showed a borderline preserved ejection fraction between 40 and 50%. ECG findings at presentation were variable with ST elevations, bundle branch blocks, and sinus tachycardia being the most common findings. Complete heart block was noted in 36% of cases. Elevated biomarkers (troponin and creatinine kinase levels) were identified in 33 cases. Normal biomarker levels were reported in three cases and six cases did not comment on biomarker levels. Of those with elevated troponin/creatinine kinase levels, 21 underwent cardiac catheterization with normal coronaries identified. The remaining cases with elevated biomarkers have no reports of coronary angiography taking place. MRI was performed in 26% of cases, the majority of which showed results suggestive of myocarditis. Biopsy to confirm or rule out myocarditis was performed in 52% of reported cases. In 90% of patients, steroids were initiated upon diagnosis. In those clinically unstable or refractory to steroids, various different therapeutic options were utilized including

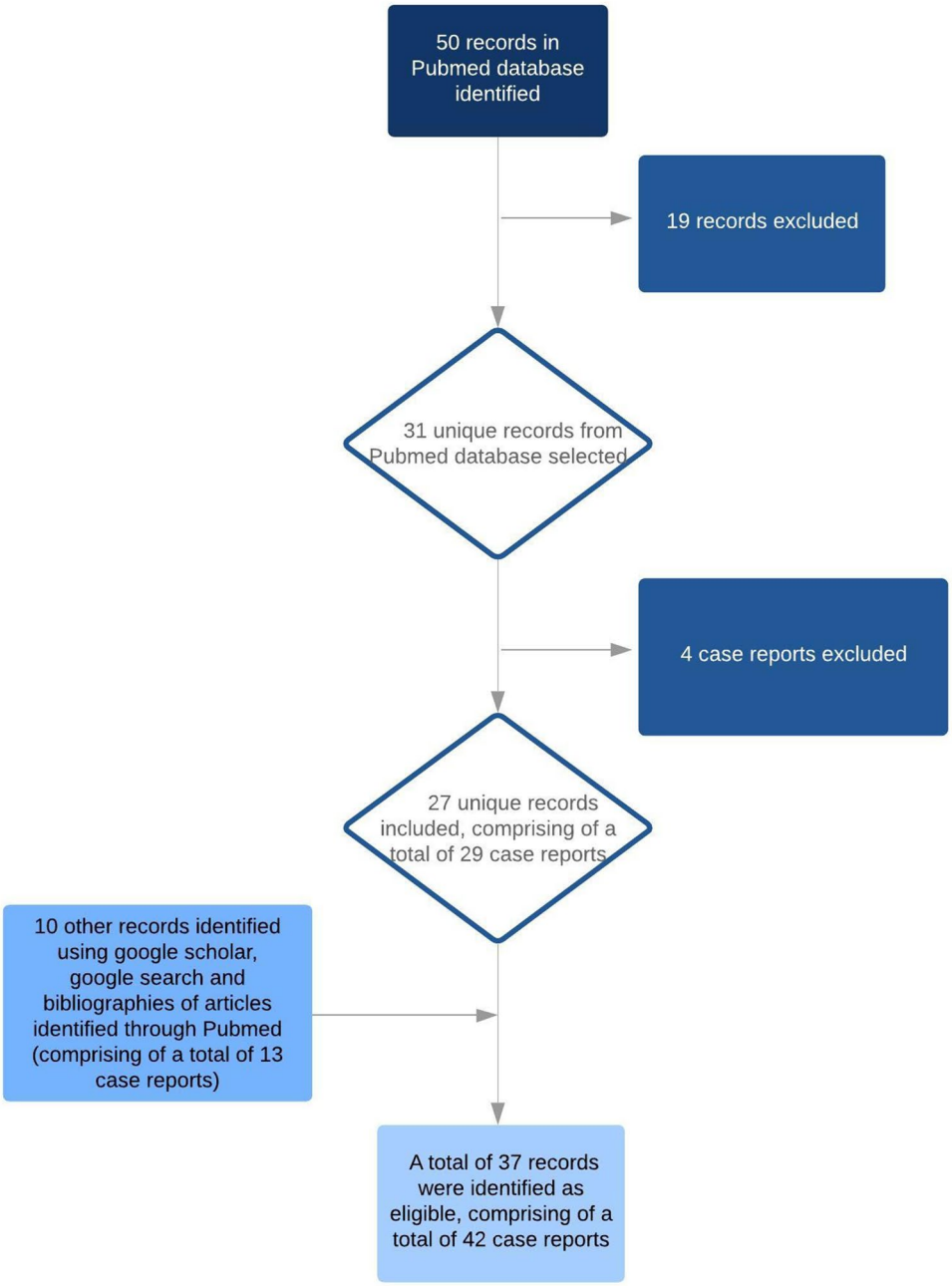

Fig. 1 PRISMA flowchart showing study screening and selection process

plasmapheresis, infliximab, anti-thymocyte globulin, IV immunoglobulins, tacrolimus, and methotrexate. Tables 2 and 3 list the diagnostic tests, therapies, and outcomes of individual case reports. Table 4 lists the cardiovascular outcomes and management in identified cases.

Death was defined as dying as a direct consequence of myocarditis (lethal arrhythmia, cardiogenic shock, cardiac arrest, and multi-organ failure) or patients transitioned to comfort care only following no improvement with therapy. Thirteen patients (93%) who died developed fulminant myocarditis after 1–2 doses with 64% occurring after the first dose and 29% after the second dose (Table 5). Once case reported by Gallegos et al., who describe the course of a patient that ultimately died, does not specify the number of doses received prior to presentation (Gallegos et al. 2019). Fifty percent of patients who died had normal echocardiogram findings (Table 5). Two patients had an ejection fraction below 40% and 21% of those that died had unlisted echocardiogram findings. Complete heart block occurred in 64% of patients that died. In addition, 60% of those with complete heart block died.

Table 1 Characteristics and presenting features of individual case reports

Case	Age and sex	Immune checkpoint inhibitor	Malignancy	Number of doses or days preceding presentation	Documented history of heart failure?	Documented comorbidities?	Presenting symptom (s)	Other autoimmune toxicities
Arangalage et al. (2017)	35 F	Ipilimumab and nivolumab	Stage IIIC melanoma	1 dose; 15 days after initiation	No	No	Dyspnea	Thyroiditis and myositis
Baldetti et al. (2018)	68 M	Nivolumab	Squamous cell carcinoma of the lung (stage unspecified)	6 doses	No	No	Dyspnea, hypotension, and edema	Pulmonary vasculitis
Behling et al. (2017)	63 M	Nivolumab	Metastatic melanoma	1 dose; 3 days after initiation	No	Hypertension, hypolipoproteinemia, diabetes mellitus, and COPD	Dyspnea, dysphagia, and muscle pain	Myositis
Berg et al. (2017)	66 M	Ipilimumab	CMML	1 dose; 2 weeks after initiation	No	No	Dyspnea, myalgia, orthopnea, and increased pedal edema	Colitis, mild hepatitis, and myositis
Chen et al. (2018)	43 M	Nivolumab	Metastatic B3 thymoma	1 dose; 10 days after initiation	No	No	Dyspnea, chest pain, myalgia, and fatigue	Rhabdomyolysis
Cristina et al. (2017)	78 M	Nivolumab and ipilimumab	Metastatic squamous cell carcinoma of the lung	1 dose; 2 weeks after initiation	Ischemic heart disease with preserved ejection fraction	Not listed	Dyspnea	Thyroiditis, polyneuropathy and possible pneumonitis.
Copeland-Halperin and Sahni (2018)	81 M	Pembrolizumab	Stage IV lung adenocarcinoma	2 doses; 6 weeks after initiation	No	Unknown	Dyspnea and fatigue	No
Frigeri et al. (2018)	76 F	Nivolumab	Metastatic lung adenocarcinoma	7 biweekly doses	No	No	Dyspnea	No
Fukasawa et al. (2017)	69 F	Nivolumab	Metastatic lung adenocarcinoma	3 doses; 1 week after third dose	No	Not listed	Malaise and double vision. Dyspnea on second day	Myasthenia gravis
Gallegos et al. (2019)	47 F	Nivolumab	Metastatic melanoma	4 months after starting nivolumab (# of doses not specified)	No	Carotid artery dissection	Hypotension, tachycardia, tachypnea. pulmonary edema, lower extremity edema, JVD	No
Ganatra et al. (2018)	41 F	Ipilimumab and nivolumab	Metastatic melanoma	4 doses; 6 days after 4th dose	No	No	Dyspnea	Hashimoto thyroiditis
Geisler et al. (2015)	83 F	Ipilimumab	Melanoma (invasive locoregional disease)	4 doses	No	Hypertension	Dyspnea and chest pain	No
Gibson et al. (2016)	68 F	Nivolumab	Stage IV adenocarcinoma of the lung	2 doses; 1 week after second dose	No	Pulmonary embolism, DVT, and WPW status post ablation	Altered mental status, nausea, and vomiting	Hepatitis and pneumonitis

Table 1 (continued)

Case	Age and sex	Immune checkpoint inhibitor	Malignancy	Number of doses or days preceding presentation	Documented history of heart failure?	Documented comorbidities?	Presenting symptom (s)	Other autoimmune toxicities
Heinzerling et al. (2016)	23 M	Ipilimumab	Melanoma (stage unspecified)	4 doses; 7 months after 4th dose	No	No	Chest pain and cough	Uveitis
Heinzerling et al. (2016)	64 M	Ipilimumab	Metastatic melanoma	2 doses	No	Peripheral vascular disease	Fatigue, abdominal pain, and seizures	No
Heinzerling et al. (2016)	72 M	Ipilimumab and nivolumab	Metastatic melanoma	22 weeks after initiation of immunotherapy and 3 weeks after starting combination therapy	History of MI with preserved EF 50%	Hypertension, diabetes mellitus, hyperuricemia, and peripheral vascular disease	Dyspnea and anasarca	Thyroiditis and hypophysitis
Heinzerling et al. (2016)	80 M	Ipilimumab	Metastatic melanoma	2 doses; 5 weeks after second dose	No	Non-Hodgkin lymphoma, atrial fibrillation, prosate cancer, hypertension, CAD s/p CABG	Dyspnea	Hepatitis
Imai et al. (2018)	70 M	Pembrolizumab	Metastatic squamous cell carcinoma of the lung	2 doses; 2 weeks after second dose	No	No	Fever, fainting, and weakness	Myositis
Inayat et al. (2018)	74 M	Pembrolizumab	Stage IV lung adenocarcinoma	2 doses; 19 days following second dose	No	Hypertension, cerebrovascular event	Dyspnea	Hepatitis
Jain et al. (2018)	67 M	Ipilimumab and nivolumab	Metastatic melanoma	1 dose; 16 days after first dose	No	No	Dyspnea	Possible dermatitis due to rash, hepatitis
Johnson et al. (2016)	63 M	Nivolumab and ipilimumab	Metastatic melanoma	1 dose; 15 days after first dose	No	Hypertension	Fatigue and myalgia	Myositis
Johnson et al. (2016)	65 F	Nivolumab and ipilimumab	Metastatic melanoma	1 dose; 12 days after first dose	No	Hypertension	Dyspnea, atypical chest pain, and fatigue	Autoimmune myositis and rhabdomyolysis
Katsume et al. (2018)	73 F	Pembrolizumab	Metastatic NSCLC	1 dose; 1 day after first dose	No	No	Fainting and weakness	Hepatitis
Laubli et al. (2015)	73 F	Pembrolizumab	Metastatic melanoma	5 doses	No	No	Dyspnea	No
Lopez et al. (2018)	51 M	Nivolumab	Metastatic renal cell carcinoma	2 doses	No	No	Shortness of breath and dyspnea with exertion	No
Lopez et al. (2018)	79 M	Pembrolizumab	Metastatic melanoma	2 doses	No	No	Near syncope	No

Table 1 (continued)

Case	Age and sex	Immune checkpoint inhibitor	Malignancy	Number of doses or days preceding presentation	Documented history of heart failure?	Documented comorbidities?	Presenting symptom (s)	Other autoimmune toxicities
Martinez-Calle et al. (2018)	67 F	Pembrolizumab	Multiple myeloma	1 dose; 16 days after first dose	No	Bilateral breast cancer treated with radiation and surgery	Dyspnea and malaise	Hepatitis
Matson et al. (2018)	55 M	Nivolumab	Lung adenocarcinoma (stage unspecified)	2 doses; 46–57 days of initiation	No	Hypertension and COPD	Dyspnea and lethargy	Autoimmune type 1 diabetes mellitus
Mehta et al. (2016)	79 M	Nivolumab	Non-small cell lung cancer	Unspecified	No	No	Weakness, back pain, and dyspnea	Myositis and hepatitis
Monge et al. (2018)	79 M	Nivolumab	Metastatic prostate cancer	1–2 doses; after 8 weeks of initiation	No	Atrial fibrillation	Blurry Vision	No
Nasr et al. (2018)	79 M	Pembrolizumab	Metastatic gastric adenocarcinoma	2 doses; 2 weeks after second dose	No	No	Diplopia, blurry vision and ptosis	Myositis (orbital muscles)
Norwood et al. (2017)	49 F	Ipilimumab and nivolumab	Stage III metastatic melanoma	1 dose; 2 weeks after initiation	No	Mild hyperlipidemia	Intractable nausea	Thyroiditis and myositis
Rota et al. (2019)	71 M	Nivolumab	Renal cell carcinoma (stage unspecified)	1 dose	No	No	Dropped head, limb weakness	No
Rota et al. (2019)	72 F	Nivolumab	Renal cell carcinoma (stage unspecified)	1 dose	No	No	Dropped head, limb weakness	No
Sakai et al. (2017)	71 M	Nivolumab	Lung adenocarcinoma (stage unspecified)	2 doses	No	No	Anorexia	No
Samara et al. (2018)	77 M	Ipilimumab	Stage III metastatic melanoma	4 doses	No	Hypertension and mild kidney dysfunction	Malaise and nausea	Hepatitis
Semper et al. (2016)	75 M	Nivolumab	Metastatic squamous cell carcinoma of the lung	9 doses; 3 days after 9th dose	No	No	Dyspnea and chest pain	No
Tadokoro et al. (2016)	69 F	Nivolumab	Metastatic melanoma	3 doses	No	No	Palpitations and malaise	No
Tajmir-Riahi et al. (2018)	72 M	Nivolumab and ipilimumab	Metastatic melanoma	10 doses	History of myocardial infarction with preserved EF.	History of MI, Diabetes mellitus, hypertension, peripheral vascular disease and hyperuricemia	Dyspnea, lower limb edema, ascites, and weight gain	Thyroiditis and hypophysitis

Table 1 (continued)

Case	Age and sex	Immune checkpoint inhibitor	Malignancy	Number of doses or days preceding presentation	Documented history of heart failure?	Documented comorbidities?	Presenting symptom (s)	Other autoimmune toxicities
Tay et al. (2017)	64 F	Nivolumab	Glioblastoma	2 doses; 9 days after second dose	No	No	Myalgia, diplopia and weakness	Myositis
Thibault et al. (2018)	52 M	Ipilimumab and nivolumab	Stage IV renal cell carcinoma	3 doses	No	No	Asymptomatic; diagnosed based on serial follow-up of cardiac enzymes	Possible dermatitis (skin rash)
Yamaguchi et al. (2018)	60 M	Nivolumab	Metastatic melanoma	13 doses	No	No	Fatigue, fever	No

Discussion

Our study reveals several trends and outcomes across all cited cases. Only one or two doses preceded the onset of myocarditis in the majority of cases (62% of cases) and in 93% of fatalities. In addition, complete heart block was the most common arrhythmia that developed as a complication of myocarditis, and was also associated with a higher mortality rate. Steroids were used in 90% of cases and are recommended as initial therapy; however, if this therapy should fail, multiple second-line agents are available yet without strong evidence for support.

The pathophysiology of myocarditis caused by ICIs is still unclear. However, the theory of a shared antigen or high frequency of T-cell receptor sequences between myocardium, skeletal muscle, and tumors has been highlighted in the literature (Reuben et al. 2017). Mouse models for T-cell-mediated myocarditis exist. Fulminant myocarditis has been observed after the CTLA-4 receptor was knocked out in mice, while knocking out the PD-1 receptor led to spontaneous myocarditis and dilated cardiomyopathy (Love et al. 2007). In addition, it was demonstrated that the level of IL-10, an anti-inflammatory cytokine, decreases when PD-1 is knocked out (Frigeri et al. 2018; Tarrio et al. 2012). Recent mice models also suggest that knocking out PD-1 in CD-4 cells enhance T-cell-mediated myocarditis. The rapid onset of myocarditis after initiation of ICIs suggests the role of preexisting autoimmunity (T-memory cells) that is boosted once PD-1 receptors are blocked by ICIs (Martinez-Calle et al. 2018; Okazaki et al. 2003).

Guidelines for the diagnosis of myocarditis related to ICIs have not been established. However, a workup including cardiac biomarkers and electrocardiogram are initially recommended (Lauer et al. 1997; Moslehi et al. 2018). Our results revealed that ECG changes were non-specific and highly variable, and may include ST and PR segment changes, sinus tachycardia, AV block, and malignant arrhythmias. This is consistent with non-specific ECG findings in myocarditis cited in the literature (Fung et al. 2016). However, a trend was noted in our study in which complete heart block was associated in 36% of cases and in 64% of those that died (Tables 4 and 5). Seven patients with complete heart block underwent endomyocardial biopsy, all of which revealed predominantly lymphocytic infiltration and macrophages. This is likely related to inflammatory changes of the conduction system secondary to myocarditis. As such, serial ECGs at the start of therapy and at follow-up visits may be recommended, providing a relatively quick, cost-effective, and non-invasive potential at intervening in early stages of the disease process. This finding also suggests that conduction disturbance may be more predictive of increased mortality, necessitating more aggressive therapy early on.

Table 2 Diagnostic tests, treatments, and outcomes of individual case reports

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Arangalage et al. (2017)	EF 50%	Sinus tachycardia, right bundle branch block and ST elevations in anteroseptal and inferolateral leads	Yes; suggestive of myocarditis	Not performed	Troponin-I: 210 pg/ml, Total CK: 187.6 units/L	Steroids and immunoglobulins started immediately. 4 days later patient developed sustained ventricular tachycardia and had a cardiac arrest. Ultimately started on ECMO. EF dropped to 10%. He then received plasmapheresis for 3 days and later started on tacrolimus	1000 mg methylprednisone daily	IV immunoglobulins, plasmapheresis, and tacrolimus	Echocardiogram improved after tacrolimus initiation. EF 35% on day 18 of admission and then 60% 3 months later
Baldetti et al. (2018)	Severely dilated RV with dysfunction and severe pulmonary HTN	EKG revealing right ventricular strain pattern; 'S1Q3T3′ sign	Yes; suggestive of myocarditis	Not performed	Troponin-T: 459 ng/L	Unknown course	Not described	No	Not described

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Behling et al. (2017)	Not listed	Normal	No	Not performed	Troponin-I: 8464 pg/ml 210, Total CK: 5148 units/L	Steroid therapy initiated. Course complicated by complete heart block requiring temporary pacemaker placement. Intubated for respiratory insufficiency and ultimately died of complications	1.5 mg/kg IV prednisone	No	Patient died 26 days after starting nivolumab
Berg et al. (2017)	Preserved EF and grade 1 diastolic dysfunction	New right bundle branch block and low-voltage sinus rhythm	No	Not performed	Troponin-T: 1.99 ng/ml, Total CK: 1172 unit/L, CK-MB level: 168.5 ng/mL	Started on diuretics. Ultimately required dopamine for blood pressure support. Later developed complete heart block and transitioned to "comfort measures only"	1000 mg methylprednisone	No	Transitioned to comfort care and ultimately died

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Chen et al. (2018)	EF 49%, thickened interventricular septum	Sinus rhythm with prolonged PR interval and right bundle branch block	No	T-lymphocytes	Troponin-I: 16.9 ng/ml, Total CK: 43,130 units/L, CK-MB: 1270 units/L	Cardiac arrest within first 24 h of admission. Cardiogenic shock requiring IABP. Started on IV immunoglobulins for 3 days in addition to steroids. Later developed second-degree AV block with widened QRS and ST elevations in leads I, AVL, AVR and V1–V5. Repeat echocardiogram showed EF now reduced to 40%. 10 days later complete heart block requiring temporary pacer. Patient died due to hypotension and multi-organ failure	1000 mg IV methylprednisone for 3 days followed by 500 mg for 4 days and 60 mg per day with no improvement	IV immunoglobulin	Patient died 40 days later

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Cristina et al. (2017)	Normal	Complete heart block	No	Not performed	Troponin-I: 3–4 mcg/L	Pacemaker inserted for complete heart block. Steroid therapy initiated	Corticosteroids at 1 mg/kg	No	Patient died of cardiac arrest 5 days later
Copeland-Halperin and Sahni (2018)	EF 40%, new diffuse biventricular dysfunction	High degree AV block	No	Not performed	Troponin-I: 9.37 ng/ml, CK-MB: 102.7 ng/ml	Steroids initiated with improvement in EF noted. Permanent pacemaker placed given heart block	High-dose corticosteroids	No	EF improved to 48% after 4 weeks. Later was under hospice care and ultimately perished
Frigeri et al. (2018)	EF 15%, multiple apical thrombi	EKG findings not listed	Yes, findings suggestive of myocarditis	Not performed	High-sensitivity troponin: 2674 ng/L	Cardiogenic shock requiring inotropic support, mechanical circulatory support and ECMO initiation. Steroids and plsamapheresis started on day 4. Infliximab given due to no improvement. Complete heart block requiring pacemaker after first dose of Infliximab. Improvement following multiple doses of Infliximab	Methylprednisolone 5 mg/kg/day	Plasmapheresis, IV immunoglobulins and 5 mg/kg Infliximab days 6, 27 and 39	EF improved to 30% after 5 months

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Fukasawa et al. (2017)	Normal echocardiogram	Diffuse ST elevations	No	Lymphocytic and neutrophilic infiltration with CD8 + > CD 4 + cells	Total CK: 1165 units/L with elevated CK-MB and troponin-I levels (values not mentioned)	Steroids started on day 1. Complete heart block on day 2 requiring pacemaker. Pacemaker removed on day 7 following clinical improvement	1000 mg methlprednisone for 3 days followed by 1 mg/kg/day	No	Significant clinical improvement
Gallegos et al. (2019)	EF 26%, severely dilated left ventricle, and a trivial pericardial effusion	Regular, narrow-complex atrial tachycardia without ischaemic changes	Yes; findings suggestive of myocarditis	Moderate lymphocytic myocarditis; infiltrate composed almost exclusively of T-cells, with an admixture of CD4 + and CD8 + T-cells (postmortem autopsy)	Troponin and CK levels normal	Clinical course complicated by cardiogenic shock refractory to inotropic support, died in hospital	Methylprednisolone 500 mg intravenous BID for 5 days	Infliximab 10 mg/kg/day for 2 days	Death
Ganatra et al. (2018)	EF 15%, global dysfunction	Sinus tachycardia	Yes; findings suggestive of myocarditis	Lymphocytic infiltrates with interstitial fibrosis and CD8 + cells	Troponin-I level normal	Improvement after steroid therapy	1000 mg of methylprednisone for 3 days followed by a PO taper	No	After the steroid course, repeat MRI showed no signs of myocarditis and EF improved to 54% 4 months later

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Geisler et al. (2015)	EF 50%, akinetic apex, and hyperdynamic base/septum. Left ventricular outflow tract obstruction and systolic anterior motion of mitral valve leaflet noted	Sinus tachycardia and 1 mm ST elevations in leads I, V2 and V3	No	Not performed	Troponin-I: 0.98 ng/ml	Transient supraventricular tachycardia and ventricular tachycardia events treated with beta blockade	Not mentioned	No	Asymptomatic on hospital day 3 and transferred to acute cardiac rehabilitation
Gibson et al. (2016)	Normal echocardiogram	Tachycardia, new RBBB with left posterior fascicular block	No	Not performed	Troponin: 3.08 ng/mL, Total CK: 1832 units/L, CK-MB: 112.4 units/L	Steroid therapy initiated. Course complicated by sustained ventricular tachycardia. Ultimately transitioned to palliative care due to brain metastasis	One dose of 250 mg methylprednisone followed by 80 mg methylprednisone daily	No	Patient died following bradycardia and hypotension
Heinzerling et al. (2016)	EF 20%, severe global hypokinesis	ST elevations	Yes, findings suggestive of myocarditis	Lymphohistocytic infiltration	Troponin-T and CK levels elevated (values not mentioned)	Cardiogenic shock requiring pressor support and diuresis. New onset paroxysmal atrial fibrillation	2 mg/kg methylprednisone followed by PO prednisone taper for 6 weeks	No	EF returned to baseline with resolution of akinesis after 1 month
Heinzerling et al. (2016)	No	Normal EKG	No	Hypertrophy and fibrosis with scattered lymphocytes and eosinophils (postmortem autopsy)	Normal	Cardiogenic shock requiring dopamine	Not mentioned	No	Patient died 5 days after admission

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Heinzerling et al. (2016)	EF 15%	Normal EKG	No	Lymphocytic infiltration and interstitial fibrosis	Not reported	Diuresis and steroid therapy	1 mg/kg PO corticosteroids	No	EF improved to 30% in 10 days and to 40% in 2 months
Heinzerling et al. (2016)	EF 40–45% with grade III diastolic dysfunction	Atrial fibrillation, RBBB	No	Lymphocytes, multinucleated giant cells and eosinophils	Troponin level 11.6, CK 97, CK-MB 59.9 (units not mentioned)	Decompensated shortly after admission, EF decreased to 31% requiring pressor support. Also started on steroids but ultimately developed ventricular tachycardia/fibrillation	10 mg dexamethasone followed by 4 mg q 6 h	No	Patient died following cardiac arrest

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Imai et al. (2018)	EF 29%, global hypokinesia	No findings listed on presentation	No	First biopsy: Lymphocytic infiltrates. Second biopsy (day 27): replacement of inflammation with granulation tissue	Troponin-T 17.6 ng/mL, Total CK: 9786 U/L, CK-MB: 154 U/L	Cardiogenic shock necessitating IABP placement. V-fib arrest 1 day later and started on ECMO. EF dropped to 5%. He received 1000 mg methylprednisone for 3 days and IV immunoglobulins for 2 days. IABP removed on day 13; ECMO withdrawn on day 7. Did not tolerate weaning off pressor support and was then started on tacrolimus on day 14. Steroids later tapered	1000 mg methylprednisolone	IV immunoglobulins and tacrolimus	Died on the 69th day due to progression of malignancy

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Inayat et al. (2018)	EF 30%, global hypokinesia	Diffuse ST elevations and idioventricular rhythm	No	Not performed	Troponin: 75 ng/ml	Started on Metoprolol following an event of non-sustained ventricular tachycardia. Later started on steroids with significant improvement. Steroids ultimately discontinued as patient opted for hospice care	1 mg/kg PO prednisone	No	Hospice care

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Jain et al. (2018)	EF 20%, severe global hypokinesis	New interventricular conduction delay	No	Diffuse cardiomyocyte necrosis with lymphocytic infiltrates; mainly CD3/CD8	Troponin 27.9; total CK: 605	Episodes of non-sustained ventricular tachycardia. After 48 h, patient developed complete heart block and required permanent pacemaker implant. Despite IV steroids, she went into cardiogenic shock requiring pressor support. Anti-thymocyte globulin then started; six doses were given with improvement in shock	Already on prednisone. On admission, changed to methylprednisone 500 mg BID	Anti-thymocyte globulin	EF improved to 40% after 2 weeks of receiving anti-thymocyte globulin. Later died due to progression of cancer
Johnson et al. (2016)	EF 50%	ST depressions with new interventricular conduction delay	No	Patchy lymphocytic cells and macrophages in myocardium and conduction system. Minimal eosinophils. (postmortem autopsy)	Troponin-I: 47 ng/ml, CK-MB: 451 ng/ml	Despite receiving steroids and infliximab, complete heart block developed requiring temporary pacemaker. Patient later suffered from cardiac arrest which leads to his demise	1 g/kg methylprednisone for 4 days	Infliximab 5 mg/kg	Patient death due to cardiac arrest

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Johnson et al. (2016)	EF 73%	Prolonged PR interval followed by new interventricular conduction delay and complete heart block	No	Predominant lymphocytic cells with abundant CD 8 T-cells and macrophages also involving the conduction system (postmortem autopsy)	Troponin-I: 51.3 ng/ml, CK-MB > 600 ng/ml	Complete heart block. Refractory ventricular tachycardia ultimately leads to patient demise	1 mg/kg IV methylprednisone	No	Patient death due to ventricular arrhythmia
Katsume et al. (2018)	EF 70%	Complete AV block with wide QRS	No	No	Troponin-T and CK levels elevated (values not mentioned)	Required permanent pacemaker for complete heart block	1000 mg methylprednisone for 3 days then switched to oral steroids	No	Not listed
Laubli et al. (2015)	EF 30%, marked ventricular desynchrony	Sinus tachycardia and ventricular bigeminy	Yes, no signs of myocarditis	Predominantly CD8 lymphocytic cells	High-sensitivity troponin-T elevated: 0.63 mcg/L	Diuretics, ARBs, B-blockers and spironolactone started. Improvement noted with steroids	2 mg/kg prednisone	No	EF improved to 52% after 2 weeks. EKG normalized
Lopez et al. (2018)	EF 30%	Not listed	Yes	Inflammatory infiltrate of lymphocytes and macrophages with myocyte destruction	Not reported	Clinical course complicated by VT storm	High-dose IV steroids	No	Discharged with prednisone taper. 6 months later NYHA class II and normal echocardiogram

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Lopez et al. (2018)	EF 55%	Complete AV block	No	No	Not reported	Patient underwent emergent pacemaker placement and started on high-dose steroids in addition to anti-thymocyte globulin and cyclophosphamides	High-dose IV steroids	Anti-thymocyte globulin and cyclophosphamide	Course complicated by upper GI bleed and pulmonary embolism. Discharged to hospice and died 2 weeks later
Martinez-Calle et al. (2018)	EF 30%, depressed ventricular contractility and focal hypokinesis	New anterolateral ST elevations and new RBBB	No	Predominantly lymphocytic infiltration and macrophages (postmortem autopsy)	High-sensitivity troponin-T: 9.71 ng/mL, Total CK: 3689 U/L; CK-MB 300 ng/mL	EKG progressed to flares of V-tach and complete heart block. Despite steroids, in 24 h he was started on ECMO. No improvement with ECMO, then started on infliximab	1.5 mg/kg methyl prednisone	Infliximab 5 mg/kg	Patient died after 10 days
Matson et al. (2018)	Dilated right ventricle and right atrium	Wide complex tachycardia, successfully cardioverted	No	Diffuse lymphocytic infiltration and focal necrosis. Minimal eosinophils. Predominant CD8 cells, macrophages present. (postmortem autopsy)	Troponin-I: 14.43 ng/mL	Presented with cardiogenic shock. Died 1 day after admission	Steroids not given	No	Patient died 1 day postadmission

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Mehta et al. (2016)	EF 15%	None	MRI done—no results	No	Troponin-T: 0.12 ng/mL; CK-MB 25.1 ng/mL	Ventricular arrhythmias requiring amiodarone and lidocaine, ultimately requiring inotropic support	Corticosteroids initiated	No	Unspecified
Monge et al. (2018)	EF 65% with enlarged left atria and dilated right ventricle	Atrial fibrillation and prolonged QT interval with anterior fascicular block similar to baseline	MRI Findings consistent with myocarditis	No	Troponin-I: 0.209 ng/mL, Total CK: 3200 U/L, CK-MB 65.7 mcg/L	Steroid therapy initiated with clinical improvement noted	1 mg/kg Methylprednisone followed by taper course	No	Not done

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Nasr et al. (2018)	Normal	Normal	No	No	Total CK: 4893 ng/L, CK-MB: 128 U/L troponin-I: 3476 ng/mL	No improvement despite 2 mg/kg prednisone IV for 5 days. Plasmapheresis started for 3 days but also with no improvement. Required external pacing as he developed a complete heart block. Later received prednisone and 2 mg/kg immunoglobulin therapy for 4 days and methotrexate 25 mg/m^2 SC once weekly. Heart block was later reversed	Initially prednisone 1 mg/kg IV was given for ophthalmoplegia, later increased to 2 mg/kg	Plasmapheresis, IV immunoglobulins, and methotrexate	Cardiac function remained normal throughout hospital course
Norwood et al. (2017)	Normal echocardiogram	No EKG changes	Yes; no evidence of myocarditis	Predominantly CD8 lymphocytic infiltration with macrophages and CD4 cells. Minimal CD 20 cells	Troponin-I: 0.44 ng/mL, total CK: 335 U/L, CK-MB: 6.3 ng/mL (normal < 5 ng/mL)	Steroids started. However, due to uprising troponins after tapering of steroids, steroids were reinitiated and were followed by IV immunoglobulin therapy	Initially 125 mg methylprednisone for 3 days follower by prednisone taper. Later prednisone reinitiated at higher doses	IV Immunoglobulin	Normal EKG and echocardiography throughout course

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Rota et al. (2019)	Not listed	Not listed	No	No	Not reported	Course complicated by cardiovascular instability and AV block requiring pacemaker implant. Despite a second immunoglobulin cycle and IV steroid bolus, the patient died	High-dose IV steroids	2 cycles of IVIG	Patient died
Rota et al. (2019)	Not listed	Not listed	No	No	Not reported	Rapid treatment response following initiation of steroids (1 g/kg) and IVIG (0.4 g/kg for 5 days) administration	High-dose IV steroids	IVIG	Complete recovery
Sakai et al. (2017)	Not listed	ST elevations in V2-V5	No	Myocardial hypertrophy and fibrosis	Troponin-I: 400 pg/mL	EKG and symptoms improved after initiating steroids	Hydrocortisone (dose unknown)	No	Improvement following steroid therapy
Samara et al. (2018)	EF 45%, global hypokinesia	Global low voltage and junctional bradycardia	No	No	Elevated troponin level (number not specified)	Steroid therapy initiated with clinical improvement noted	Methylprednisone 60 mg q 6 h daily	No	EF improved to 55% after several days
Semper et al. (2016)	Minor degree of LV impairment and discrete septal hypokinesis	Sinus tachycardia, incomplete RBBB and denovo minor ST depressions in V4-V6	Findings consistent with myocarditis	No	High-sensitive troponin: 101.3 pg/ml	Steroids, diuretics, ACE inhibitor, and B-blockers initiated	Prednisolone 1 mg/kg	No	Repeat echocardiogram with resolution of prior abnormal findings

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Tadokoro et al. (2016)	EF 30%, diffuse hypokinesis of the left ventricle	Sinus tachycardia with ST elevations in leads II, III, and AVF	No	Predominantly CD 8 lymphocytic cells	Troponin-T positive (value not mentioned), total CK: 728 U/L, CK-MB 48.7 U/L	Dobutamine for inotropic support (CI 1.9). Steroids started on day 5	2 mg/kg prednisone	No	EF improved to 55%
Tajmir-Riahi et al. (2018)	EF 15%	Not listed	No	Hypertrophic myocarditis with interstitial lymphocytes and fibrosis. FOXP3 cells were absent	Not reported	Clinical and echocardiographic improvement noted after steroid initiation. Patient was started later on Pembrolizumab after improvement which then resulted in a flare of myocarditis	1 mg/kg Prednisolone followed by taper course	No	EF improved to 24% after 2 weeks of steroid therapy. Later improved to 35–40%

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Tay et al. (2017)	EF 37%	Ventricular bigeminy and frequent ectopy	No	CD8 > CD4 lymphocytes with macrophages.	Troponin-I: 8375 ng/L, total CK: 3538 U/L	Despite receiving steroids and infliximab, course complicated by non-sustained ventricular tachycardia requiring metoprolol and amiodarone. On day 8, sustained V-tach necessitating cardioversion. He later developed complete heart block later requiring pacemaker implant. Anti-thymocyte globulin was started for 5 days followed by initiation of mycophenolate. Clinical improvement noted	500 mg methylprednisone for 3 days then PO prednisone	Infliximab, anti-thymocyte globulins, and mycophenolate	EF improved to 43%. Repeat biopsy showed improvement

Table 2 (continued)

Case	Echocardiogram findings at time of diagnosis	EKG findings	MRI performed?	Results of biopsy (if performed)	Cardiac biomarkers	Clinical course	Dose of steroids (if given)	Use of infliximab/immunoglobulin/anti-thymocyte globulin/tacrolimus/plasmapheresis	Outcome and follow-up
Thibault et al. (2018)	Normal	No EKG changes	No	No	Troponin-I: 0.61 mcg/L	Patient was continued only on Nivolumab and a B-blocker was started. Troponin levels improved thereafter	No	No	No
Yamaguchi et al. (2018)	EF 70%	ST elevations in leads V4–V6 and II, III, and aVF	No	Extensive lymphocytic infiltration, interstitial edema, and myocardial necrosis and with predominant CD4þ+CD8+, CD20-, and PD-1- markers	Troponin-T: 38.81 ng/mL, total CK: 2526 U/L	Course complicated by cardiogenic shock. Repeat echocardiogram showed an EF of 15%. Continued to decline despite inotropic agents; later required ECMO and IABP placement for support. Prednisolone and IVIG initiated	Prednisolone pulse therapy at 1000 mg/d for 3 days	Intravenous immunoglobulin therapy at 50 g/d for 2 days.	LVEF gradually improved. ECMO withdrawn on day 8, IABP withdrawn on day 9. LVEF improved to 56% and patient discharged on day 34

Table 3 Grouped characteristics and outcomes identified across cases

$N=42$ cases; 3 published in 2019 (7%), 18 in 2018 (43%), 9 in 2017 (21%), 10 in 2016 (24%), 2 in 2015 (5%); mean age 65.5 years; males 64%, females 36%	*N* (%)
Immune check inhibitor	
Nivolumab	18 (43)
Ipilimumab and nivolumab	10 (24)
Pembrolizumab	8 (19)
Ipilimumab	6 (14)
Malignancy	
Melanoma	19 (45)
Non-small cell lung cancer	13 (31)
Others	10 (24)
Presenting symptoms	
Dyspnea (Tachypnea)	23 (55)
Myalgia, fatigue, weakness, lethargy anorexia, near syncope, or malaise	19 (45)
Diplopia, ptosis or blurry vision, and head drop	6 (14)
Palpitations	1 (2)
Chest pain	5 (12)
Number of doses preceding myocarditis[a]	
1 dose	14 (33)
2 doses	12 (29)
3–6 doses	12 (29)
>6 doses	3 (7)
Other listed autoimmune toxicities	
Myositis	12 (29)
Hepatitis	9 (21)
Thyroiditis	5 (12)
Hypophysitis	2 (5)
Myasthenia graves	2 (5)
Autoimmune diabetes	1 (2)
Colitis	1 (2)
Uveitis	1 (2)
Comorbidities or past medical history if listed	
HTN	10 (24)
Cardiac[a]	3 (7)
Arrythmias[b]	3 (7)
Diabetes mellitus type II	3 (7)
Dyslipidemia	2 (5)
COPD	2 (5)
Thromboembolic disease[c]	2 (5)
Malignancy[d]	2 (5)
Cerebrovascular incidence	1 (2)
Autoimmune diseases[e]	1 (2)
Kidney dysfunction	1 (2)
Management	
Steroids	38 (90)
IV Immunoglobulins	9 (21)
Infliximab	5 (12)
Anti-thymocyte globulin	3 (7)
Plasmapheresis	3 (7)
Tacrolimus	2 (5)
Methotrexate	1 (2)

Table 3 (continued)

[a]Case report by Gallegos et al. does not specify the number of doses received prior to presentation

[b]Four patients had a history of ischemic heart disease/prior MRI with normal or borderline EF

[c]Two patients had atrial fibrillation and one patient had history of WPW treated with ablation

[d]Same patient had both PE and DVT

[e]Non-Hodgkin's lymphoma and prostate cancer in one patient and bilateral breast cancer in another patient

[f]History of Hashimoto thyroiditis

Cardiac troponins are well established as sensitive and specific markers of myocardial injury (Janardhanan 2016). In patients with a clinical presentation concerning for underlying acute coronary syndrome, coronary angiography may be necessary to help differentiate ischemic heart disease from myocarditis (Caforio et al. 2017). In our study, 33 patients were identified to have elevated troponin/creatinine kinase levels. Sixty-three percent of these patients underwent cardiac catheterization to rule out ischemia as an underlying cause of presentation. The remaining cases with elevated biomarkers have no reports of coronary angiography taking place. No obstructive coronary disease was identified in any of the cases. Given the sensitivity and specificity of cardiac troponins/creatinine kinase levels as markers of myocardial injury, they may be of potential use in certain clinical scenarios where suspicion of myocarditis may arise. However, it is well established that negative troponin and/or creatinine kinase levels does not exclude the diagnosis of myocarditis (Janardhanan 2016). This may be true in patients developing late autoimmune myocarditis after initiating ICIs, which was noted in three cases where normal biomarker levels were reported (Heinzerling et al. 2016; Gallegos et al. 2019; Ganatra and Neilan 2018).

Echocardiography is an important tool in evaluating structural and functional changes secondary to myocarditis (Nieminen et al. 1984; Felker et al. 2000). However, no specific echocardiographic features of myocarditis exist, but it allows the physician to exclude other causes of heart failure, pericardial effusion, and intracavitary thrombi (Kindermann et al. 2012). Patterns consistent with dilated, hypertrophic, and ischemic cardiomyopathies have all described in biopsy-proven myocarditis (Blauwet and Cooper 2010). In our study, no trend was appreciated with regards to echocardiogram findings on presentation, with 36% showing preserved ejection fraction and reduced ejection fraction, respectively (Table 4). However, 50% of patients that died had normal cardiac function on presentation (Table 5). It is important to note that death may have occurred prior to the development of cardiac dysfunction in these cases. While viral

Table 4 Cardiovascular outcomes and management in identified cases

Biomarker levels (troponin/creatinine kinase)	
Elevated (above normal laboratory reference range)	33 (79)
Normal	3 (7)
Not reported	6 (14)
Coronary angiography	
Normal	21 (100)
Most common EKG findings at presentation	
ST elevations	9 (21)
Sinus tachycardia	8 (19)
Complete or incomplete right bundle branch block	7 (17)
Prolonged PR interval	3 (7)
Ventricular bigeminy	2 (5)
Cardiac arrhythmias	
Complete heart block	15 (36)
Ventricular arrhythmias[a]	8 (19)
Non-sustained ventricular tachycardia	3 (7)
Atrial fibrillation	1 (2)
LVEF % at presentation	
LVEF ≥ 50% or echocardiogram listed as normal	15 (36)
LVEF ≥ 40% and < 50%	4 (10)
LVEF < 40%	15 (36)
LVEF not listed	8 (19)
Diagnostic modality if listed or performed	
Biopsy/Autopsy	16 (38)
MRI	6 (14)
Both MRI and Biopsy/Autopsy	6 (14)
Mechanical support	
ECMO	5 (12)
IABP	4 (10)

[a]One of the reported ventricular arrhythmias was ventricular fibrillation, another was unspecified and the 6 remaining cases were ventricular tachycardia

Table 5 Reported deaths related directly to complications of myocarditis or those who were transitioned to comfort care due to no improvement despite treatment

Total number of deaths	14 (33%)
Number of preceding doses	
1	9 (64)
2	4 (29)
≥ 3	0 (0)
Number of doses not reported[a]	1
Echocardiogram findings	
LVEF ≥ 50% or echocardiogram listed as normal	7 (50)
LVEF ≥ 40% and < 50%	2 (14)
LVEF < 40%	2 (14)
LVEF not listed	3 (21)
Arrhythmias	
Complete heart block	9 (64)
Ventricular arrhythmias	4 (29)

[a]Case report by Gallegos et al. does not specify the number of doses received prior to presentation

and autoimmune myocarditis commonly result in dilated cardiomyopathy, no current data exist with regards to the pattern of cardiomyopathy seen in ICI-induced myocarditis (Bracamonte-Baran and Cihakova 2017; Caforio et al. 2007). A study by Caforio et al. showed that biventricular dysfunction at time of diagnosis is the main predictor of death/transplantation in biopsy-proven myocarditis (Caforio et al. 2007); however, our data reveal that echocardiography may be of little utility in predicting mortality and outcomes when assessing for ICI related myocarditis (Table 5).

MRI is the gold standard non-invasive diagnostic modality for myocarditis. Findings consistent with myocarditis include: (a) increased signal activity on T1 and T2 images reflecting edema, (b) myocardia having more contrast enhancement than the skeletal muscle reflecting hyperemia, and c) late contrast enhancement with gadolinium reflecting scar. If any of two out of the three MRI findings are present; the sensitivity and specificity of having myocarditis is 76% and 96%, respectively (Farhad et al. 2016; Ganatra and Neilan 2018; Gibson et al. 2016; Mahrholdt et al. 2004). In our study, MRI and biopsy were both performed in six patients and only MRI was performed (without cardiac biopsy) in six other patients. In the 14 patients who neither had cardiac biopsy nor MRI, diagnosis of myocarditis was done by meeting clinical criteria of myocarditis. Clinically suspected myocarditis involves a combination of: (1) clinical presentations such as acute chest pain, new or worsening dyspnea, or unexplained arrhythmias, (2) diagnostic criteria such as ECG, troponin elevation, and abnormalities on cardiac imaging, and (3) ancillary features such as fever, history of extra-cardiac autoimmune disease, or prior history of myocarditis (Cooper et al. 2007). The low rate of non-invasive imaging in the diagnosis of myocarditis which we report is likely multifactorial and related to patient death prior to diagnosis (postmortem biopsies later proving myocarditis), rapid improvement with steroid therapy, comorbid complications, and clinical instability precluding imaging. In addition, information is limited by what is provided by the case reports with occasional reports not mentioning details nor providing additional information regarding MRI findings.

Cardiac biopsy is the gold standard diagnostic modality; however, it is rarely performed as the first step in diagnosis due to its invasiveness (Guglin and Nallamshetty 2012). Current guidelines recommend endomyocardial biopsy only in cases that do not include common presentations of myocarditis (Cooper et al. 2007). Biopsy usually reveals predominant lymphocytic infiltrates in the myocardium and conduction system. Immunohistochemistry usually shows predominant CD3 + /CD8 + cells with a few CD4 + cells, in addition to CD68 + cells representing histiocytes

(macrophages). Eosinophils are less often seen as compared to levels in drug-mediated myocarditis (Ganatra and Neilan 2018; Hauck et al. 1989). These findings are consistent with results from the 22 patients that underwent cardiac biopsy in our study, in which the majority of results revealed predominant lymphocytic infiltrates in the myocardium and conduction system, in addition to CD68+ cells representing macrophages. Only 52% of reported cases underwent endomyocardial biopsy for diagnosis of myocarditis; the remainder of cases were diagnosed on the basis of clinical criteria or non-invasive imaging. Patients that did not undergo biopsy had other causes of myocarditis ruled out after testing for viral serologies and on the basis of symptom onset following ICI initiation and improvement with steroid therapy.

The majority of cases of myocarditis occurred shortly after initiation of ICI therapy. Thirty-three percent of the reported cases of myocarditis occurred after a single dose and 29% occurred after two doses (Table 3). Ninety-three patients that died developed fulminant myocarditis after 1–2 doses with 64% occurring after the first dose and 29% after the second dose (Table 5). These findings are supported in a study by Moslehi et al. who studied 101 patients that developed severe myocarditis after ICI treatment. In their study, 64% of patients received only one or two doses before onset of myocarditis (Moslehi et al. 2018). In addition, Mahmood et al. identified 35 patients who developed myocarditis while on ICIs and reported the development of myocarditis shortly after the first doses of ICI therapy (Mahmood et al. 2018). The rapid onset of myocarditis after initiation of ICIs may suggest the role of preexisting autoimmunity (T-memory cells) that is boosted once PD-1 receptors are blocked by ICIs (Martinez-Calle et al. 2018; Okazaki et al. 2003). This theory is supported in a study by Okazaki et al. where they identified the development of antibodies against troponin-I, a protein expressed by cardiomyocytes, resulting in increased influx of calcium into cardiomyocytes and, in turn, leading to cardiac dysfunction (Okazaki et al. 2003). Martinez-Calle et al. described a case of myocarditis in a patient receiving pembrolizumab for multiple myeloma as part of a clinical trial. They also highlighted the theory of preexisting autoantibodies to troponin-I and myosin due to the rapid development of myocarditis after starting ICI therapy. This is further supported by the possibility of a shared epitope between myeloma cells and cardiomyocytes (Martinez-Calle et al. 2018). These findings suggest that cases of myocarditis with more serious and detrimental outcomes tend to occur very early after initiation of immunotherapy, while myocarditis occurring later may be more indolent. As such, physicians should be more vigilant in closely examining for signs and symptoms suggestive of myocarditis early in the course of therapy and may utilize ECGs or biomarkers to aid in diagnosing myocarditis early in the course of the disease.

Our findings did not reveal a higher incidence of myocarditis or fatalities when a combination of ICIs was used, which is in contrast to what has been reported in the literature thus far. In our study, 43% of cases of myocarditis occurred with the use of nivolumab as monotherapy, followed by 24% of cases where combination therapy of ipilimumab and nivolumab were used. In a paper by Johnson et al., the cohort included patients either taking nivolumab or nivolumab plus ipilimumab. A significant difference in the incidence of myocarditis was noted among the two groups; with 0.27% of patients taking both nivolumab and ipilimumab developing myocarditis as compared to an incidence of 0.06% in those only on nivolumab. In addition, among the 18 patients found to have myocarditis, 5 deaths were from those on combination therapy, while only one fatality was recorded among those on a single ICI (Johnson et al. 2016). Moslehi et al. also concluded that death was more common when combination therapy was used (Moslehi et al. 2018). In our analysis of case reports, it is likely that only unique and special cases of ICI-induced myocarditis have been reported on. This may explain why a difference in the incidence of myocarditis when using a combination of ICIs was noted in our study as compared to larger cohort studies.

There are limited data with regards to the management of myocarditis secondary to ICI toxicity. No data currently exist regarding the management of myocarditis caused by ICIs exists. However, the American Society of Clinical Oncology (ASCO) provides guidelines with moderate evidence regarding the management of cardiovascular toxicity caused by ICIs (Brahmer et al. 2018; Weber 2012). Once myocarditis is suspected; ICI therapy should be stopped and the patient should be referred to a multidisciplinary team of oncologists and cardiologists for further evaluation and management. Antiarrhythmics should be considered if arrhythmias arise (Ganatra and Neilan 2018). If myocarditis is confirmed, then 1 mg/kg methylprednisone should be administered immediately (Brahmer et al. 2018). Two registry databases show that steroids are effective in improving ejection fraction and decreasing cardiac events in myocarditis (Escudier et al. 2017; Mahmood et al. 2018). However, there are no data with regards to the next steps if steroids fail (Ganatra and Neilan 2018). If the degree of myocarditis is severe enough, such that the patient is unstable, then it is recommended to give anti-thymocyte globulin, IV immunoglobulins, or plasmapheresis. Administration of tacrolimus or mycophenolate is recommended in the event that the patient is clinically stable, but has not responded to steroid therapy (Kobashigawa et al. 2011; Kobashigawa et al. 2006; Rodriguez et al. 2005). However, the lack of guidelines may leave room for error as noted in five cases where infliximab was used despite the patients having a history of moderate to severe HF (Table 1). This may exacerbate the underlying illness and lead to higher mortality rates, as studies have shown

that infliximab itself could precipitate heart failure (Curtis et al. 2007). The lack of knowledge of such contraindications necessitates more awareness about management options in cases refractory to steroid use.

Limitations

The limitations of this study are characteristic to studies based on case reports. The use of case reports imparts a potential selection bias of rather unusual and unique cases of myocarditis secondary to ICI use. In addition, publication bias on the part of authors reporting these cases is another factor to account for. As such, true prevalence and management of this side effect is difficult to deduce from an analysis of reported cases. It is also difficult to establish a cause–effect relationship between ICI use and myocarditis and difficult to ascertain whether cause of death is related directly to myocarditis. Despite these limitations, the use of case reports is fundamental in detecting novelties, generating hypotheses, and laying the groundwork for further research.

Conclusion

Given the increasing use of ICI therapy in the treatment of various types of cancers, an increase in the incidence of detrimental side effects is expected. Very little data currently exist with regards to the evaluation and management of myocarditis in patients on ICI therapy. Despite the availability of limited guidelines in dealing with cardiac immune-related adverse events, further research establishing more specific guidelines is necessary in dealing with myocarditis specifically, given an increase in the incidence of reported cases. Our study reveals several trends and outcomes across all cited cases. In particular, one or two doses preceded the onset of myocarditis in the majority of cases (62% of cases) and in 93% of fatalities. This should make physicians more vigilant of this potential side effect at the start of ICI therapy. Complete heart block was the most common arrhythmia that developed as a complication of myocarditis, and was also associated with a higher mortality rate. Thus, the utility of ECGs should be further analyzed as a potential tool in the monitoring of these patients and early therapy with steroids be considered should such a complication arise. Steroids are recommended as the initial therapy; however, if this therapy should fail, multiple second-line agents are available yet without strong evidence for support. Further research establishing more specific guidelines is necessary in dealing with this increasingly reported side effect.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

References

Arangalage D, Delyon J, Lermuzeaux M, Ekpe K, Ederhy S, Pages C, Lebbe C (2017) Survival after fulminant myocarditis induced by immune-checkpoint inhibitors. Ann Intern Med 167:683–684. https://doi.org/10.7326/L17-0396

Baldetti L, Melillo F, Beneduce A, Camici PG (2018) Combined checkpoint inhibitor-associated myocarditis and pulmonary vasculitis mimicking acute pulmonary embolism. Eur Heart J Cardiovasc Imaging. https://doi.org/10.1093/ehjci/jey191

Behling J, Kaes J, Munzel T, Grabbe S, Loquai C (2017) New-onset third-degree atrioventricular block because of autoimmune-induced myositis under treatment with anti-programmed cell death-1 (nivolumab) for metastatic melanoma. Melanoma Res 27:155–158. https://doi.org/10.1097/cmr.0000000000000314

Berg DD, Vaduganathan M, Nohria A, Davids MS, Alyea EP, Torre M, Padera RF Jr (2017) Immune-related fulminant myocarditis in a patient receiving ipilimumab therapy for relapsed chronic myelomonocytic leukaemia. Eur J Heart Fail 19:682–685. https://doi.org/10.1002/ejhf.806

Blauwet LA, Cooper LT (2010) Myocarditis. Prog Cardiovasc Dis 52:274–288. https://doi.org/10.1016/j.pcad.2009.11.006

Bracamonte-Baran W, Cihakova D (2017) Cardiac autoimmunity: myocarditis. Adv Exp Med Biol 1003:187–221. https://doi.org/10.1007/978-3-319-57613-8_10

Brahmer JR, Lacchetti C, Thompson JA (2018) Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: american Society of Clinical Oncology Clinical Practice Guideline Summary. J Oncol Pract 14:247–249. https://doi.org/10.1200/JOP.18.00005

Caforio AL et al (2007) A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. Eur Heart J 28:1326–1333. https://doi.org/10.1093/eurheartj/ehm076

Caforio ALP, Malipiero G, Marcolongo R, Iliceto S (2017) Myocarditis: a clinical overview. Curr Cardiol Rep 19:63. https://doi.org/10.1007/s11886-017-0870-x

Chen Q, Huang DS, Zhang LW, Li YQ, Wang HW, Liu HB (2018) Fatal myocarditis and rhabdomyolysis induced by nivolumab during the treatment of type B3 thymoma. Clin Toxicol (Phila) 56:667–671. https://doi.org/10.1080/15563650.2017.1401079

Collin M (2016) Immune checkpoint inhibitors: a patent review (2010-2015). Expert Opin Ther Pat 26:555–564. https://doi.org/10.1080/13543776.2016.1176150

Cooper LT et al (2007) The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 50:1914–1931. https://doi.org/10.1016/j.jacc.2007.09.008

Copeland-Halperin R, Sahni GD (2018) Autoimmune Myocarditis With AV Block: Too Much of a Good Thing? JACC

Cristina AADLA, Escudier-Villa JM, Ortega Marcos J, Silva-Melchor L (2017) Progressive exertional dyspnea and fatigue in an oncology-patient. Austin J Clin Cardiolog 4(2):1058

Curtis JR et al (2007) Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology (Oxford) 46:1688–1693. https://doi.org/10.1093/rheumatology/kem212

Escudier M et al (2017) Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity. Circulation 136:2085–2087. https://doi.org/10.1161/CIRCULATIONAHA.117.030571

Farhad H et al (2016) Characterization of the changes in cardiac structure and function in mice treated with anthracyclines using serial cardiac magnetic resonance imaging. Circ Cardiovasc Imaging 9:15. https://doi.org/10.1161/circimaging.115.003584

Felker GM, Boehmer JP, Hruban RH, Hutchins GM, Kasper EK, Baughman KL, Hare JM (2000) Echocardiographic findings in fulminant and acute myocarditis. J Am Coll Cardiol 36:227–232

Frigeri M et al (2018) Immune checkpoint inhibitor-associated myocarditis: a new challenge for cardiologists. Can J Cardiol 34:92 e91–92 e93. https://doi.org/10.1016/j.cjca.2017.09.025

Fukasawa Y et al (2017) Nivolumab-induced myocarditis concomitant with myasthenia gravis. Case Rep Oncol 10:809–812. https://doi.org/10.1159/000479958

Fung G, Luo H, Qiu Y, Yang D, McManus B (2016) Myocarditis. Circ Res 118:496–514. https://doi.org/10.1161/CIRCRESAHA.115.306573

Gallegos C, Rottmann D, Nguyen VQ, Baldassarre LA (2019) Myocarditis with checkpoint inhibitor immunotherapy: case report of late gadolinium enhancement on cardiac magnetic resonance with pathology correlate. Eur Heart J Case Rep. https://doi.org/10.1093/ehjcr/yty149

Ganatra S, Neilan TG (2018) Immune checkpoint inhibitor-associated myocarditis. Oncologist 23:879–886. https://doi.org/10.1634/theoncologist.2018-0130

Geisler BP, Raad RA, Esaian D, Sharon E, Schwartz DR (2015) Apical ballooning and cardiomyopathy in a melanoma patient treated with ipilimumab: a case of takotsubo-like syndrome. J Immunother Cancer 3:4. https://doi.org/10.1186/s40425-015-0048-2

Gibson R, Delaune J, Szady A, Markham M (2016) Suspected autoimmune myocarditis and cardiac conduction abnormalities with nivolumab therapy for non-small cell lung cancer. BMJ Case Rep. https://doi.org/10.1136/bcr-2016-216228

Guglin M, Nallamshetty L (2012) Myocarditis: diagnosis and treatment. Curr Treat Options Cardiovasc Med 14:637–651. https://doi.org/10.1007/s11936-012-0204-7

Hargadon KM, Johnson CE, Williams CJ (2018) Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors. Int Immunopharmacol 62:29–39. https://doi.org/10.1016/j.intimp.2018.06.001

Hauck AJ, Kearney DL, Edwards WD (1989) Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. Mayo Clin Proc 64:1235–1245

Heinzerling L et al (2016) Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer 4:50. https://doi.org/10.1186/s40425-016-0152-y

Imai R, Ono M, Nishimura N, Suzuki K, Komiyama N, Tamura T (2018) Fulminant myocarditis caused by an immune checkpoint inhibitor: a case report with pathological findings. J Thorac Oncol 15:15. https://doi.org/10.1016/j.jtho.2018.10.156

Inayat F, Masab M, Gupta S, Ullah W (2018) New drugs and new toxicities: pembrolizumab-induced myocarditis. BMJ Case Rep. https://doi.org/10.1136/bcr-2017-223252

Jain V, Mohebtash M, Rodrigo ME, Ruiz G, Atkins MB, Barac A (2018) Autoimmune myocarditis caused by immune checkpoint inhibitors treated with antithymocyte globulin. J Immunother 41:332–335. https://doi.org/10.1097/CJI.0000000000000239

Janardhanan R (2016) Myocarditis with very high troponins: risk stratification by cardiac magnetic resonance. J Thorac Dis 8:E1333–E1336. https://doi.org/10.21037/jtd.2016.10.60

Johnson DB et al (2016) Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 375:1749–1755. https://doi.org/10.1056/NEJMoa1609214

Katsume Y, Isawa T, Toi Y, Fukuda R, Kondo Y, Sugawara S, Ootomo T (2018) Complete atrioventricular block associated with pembrolizumab-induced acute myocarditis: the need for close cardiac monitoring. Intern Med 57:3157–3162. https://doi.org/10.2169/internalmedicine.0255-17

Kindermann I et al (2012) Update on myocarditis. J Am Coll Cardiol 59:779–792. https://doi.org/10.1016/j.jacc.2011.09.074

Kobashigawa JA et al (2006) Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. Am J Transpl 6:1377–1386. https://doi.org/10.1111/j.1600-6143.2006.01290.x

Kobashigawa J et al (2011) Report from a consensus conference on antibody-mediated rejection in heart transplantation. J Heart Lung Transpl 30:252–269. https://doi.org/10.1016/j.healun.2010.11.003

Laubli H, Balmelli C, Bossard M, Pfister O, Glatz K, Zippelius A (2015) Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. J Immunother Cancer 3:11. https://doi.org/10.1186/s40425-015-0057-1

Lauer B, Niederau C, Kuhl U, Schannwell M, Pauschinger M, Strauer BE, Schultheiss HP (1997) Cardiac troponin T in patients with clinically suspected myocarditis. J Am Coll Cardiol 30:1354–1359

Lopez EM, Dunn S, Mazimba S (2018) Malignant arrhythmias in autoimmune myocarditis secondary to immune checkpoint blockade treatment. J Am College Cardiol 71:A2375. https://doi.org/10.1016/S0735-1097(18)32916-4

Love VA, Grabie N, Duramad P, Stavrakis G, Sharpe A, Lichtman A (2007) CTLA-4 ablation and interleukin-12 driven differentiation synergistically augment cardiac pathogenicity of cytotoxic T lymphocytes. Circ Res 101:248–257. https://doi.org/10.1161/circresaha.106.147124

Mahmood SS et al (2018) Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol 71:1755–1764. https://doi.org/10.1016/j.jacc.2018.02.037

Mahrholdt H et al (2004) Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation 109:1250–1258. https://doi.org/10.1161/01.CIR.0000118493.13323.81

Martinez-Calle N et al (2018) Anti-PD1 associated fulminant myocarditis after a single pembrolizumab dose: the role of occult pre-existing autoimmunity. Haematologica 103:318–321. https://doi.org/10.3324/haematol.2017.185777

Matson DR, Accola MA, Rehrauer WM, Corliss RF (2018) Fatal myocarditis following treatment with the PD-1 inhibitor nivolumab. J Forensic Sci 63:954–957. https://doi.org/10.1111/1556-4029.13633

Mehta A, Gupta A, Hannallah F, Koshy T, Reimold S (2016) Myocarditis as an immune-related adverse event with ipilimumab/nivolumab combination therapy for metastatic melanoma. Melanoma Res 26:319–320. https://doi.org/10.1097/CMR.0000000000000251

Monge C et al (2018) Myocarditis in a patient treated with Nivolumab and PROSTVAC: a case report. J Immunother Cancer 6:150. https://doi.org/10.1186/s40425-018-0473-0

Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB (2018) Increased reporting of fatal immune checkpoint

inhibitor-associated myocarditis. Lancet 391:933. https://doi.org/10.1016/S0140-6736(18)30533-6

Nasr F, El Rassy E, Maalouf G, Azar C, Haddad F, Helou J, Robert C (2018) Severe ophthalmoplegia and myocarditis following the administration of pembrolizumab. Eur J Cancer 91:171–173. https://doi.org/10.1016/j.ejca.2017.11.026

Nieminen MS, Heikkila J, Karjalainen J (1984) Echocardiography in acute infectious myocarditis: relation to clinical and electrocardiographic findings. Am J Cardiol 53:1331–1337

Norwood TG et al (2017) Smoldering myocarditis following immune checkpoint blockade. J Immunother Cancer 5:91. https://doi.org/10.1186/s40425-017-0296-4

Okazaki T et al (2003) Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. Nat Med 9:1477–1483. https://doi.org/10.1038/nm955

Reuben A et al (2017) Comparative immunologic characterization of autoimmune giant cell myocarditis with ipilimumab. Oncoimmunology 6:e1361097. https://doi.org/10.1080/2162402X.2017.1361097

Rodriguez ER, Skojec DV, Tan CD, Zachary AA, Kasper EK, Conte JV, Baldwin WM 3rd (2005) Antibody-mediated rejection in human cardiac allografts: evaluation of immunoglobulins and complement activation products C4d and C3d as markers. Am J Transpl 5:2778–2785. https://doi.org/10.1111/j.1600-6143.2005.01074.x

Rota E et al (2019) Concomitant myasthenia gravis, myositis, myocarditis and polyneuropathy, induced by immune-checkpoint inhibitors: a life-threatening continuum of neuromuscular and cardiac toxicity. eNeurological Sci 14:4–5. https://doi.org/10.1016/j.ensci.2018.11.023

Sakai T, Sasada S, Jyo C, Ishioka K, Takahashi S, Nakamura M (2017) Acute myocarditis and pericarditis after nivolumab treatment in patients with non-small cell lung cancer. Ann Oncol 28:mdx697.072–mdx697.072. https://doi.org/10.1093/annonc/mdx697.072

Samara Y, Yu CL, Dasanu CA (2018) Acute autoimmune myocarditis and hepatitis due to ipilimumab monotherapy for malignant melanoma. J Oncol Pharm Pract 15:1078155218755868. https://doi.org/10.1177/1078155218755868

Semper H, Muehlberg F, Schulz-Menger J, Allewelt M, Grohe C (2016) Drug-induced myocarditis after nivolumab treatment in a patient with PDL1- negative squamous cell carcinoma of the lung. Lung Cancer 99:117–119. https://doi.org/10.1016/j.lungcan.2016.06.025

Simsek M, Tekin SB, Bilici M (2019) Immunological agents used in cancer treatment. Eurasian J Med 51:90–94. https://doi.org/10.5152/eurasianjmed.2018.18194

Tadokoro T, Keshino E, Mohri M (2016) A case of acute myocarditis during treatment with anti-PD-1 antibody nivolumab in a melanoma patient. J Cardiac Fail 22:220. https://doi.org/10.1016/j.cardfail.2016.07.355

Tajmir-Riahi A, Bergmann T, Schmid M, Agaimy A, Schuler G, Heinzerling L (2018) Life-threatening autoimmune cardiomyopathy reproducibly induced in a patient by checkpoint inhibitor therapy. J Immunother 41:35–38. https://doi.org/10.1097/CJI.0000000000000190

Tarrio ML, Grabie N, Bu DX, Sharpe AH, Lichtman AH (2012) PD-1 protects against inflammation and myocyte damage in T cell-mediated myocarditis. J Immunol 188:4876–4884. https://doi.org/10.4049/jimmunol.1200389

Tay RY, Blackley E, McLean C, Moore M, Bergin P, Gill S, Haydon A (2017) Successful use of equine anti-thymocyte globulin (ATGAM) for fulminant myocarditis secondary to nivolumab therapy. Br J Cancer 117:921–924. https://doi.org/10.1038/bjc.2017.253

Thibault C, Vano Y, Soulat G, Mirabel M (2018) Immune checkpoint inhibitors myocarditis: not all cases are clinically patent. Eur Heart J 39:3553. https://doi.org/10.1093/eurheartj/ehy485

Varricchi G et al (2017) Cardiotoxicity of immune checkpoint inhibitors ESMO Open 2:e000247. https://doi.org/10.1136/esmoopen-2017-000247

Weber JS (2012) Practical management of immune-related adverse events from immune checkpoint protein antibodies for the oncologist. Am Soc Clin Oncol Educ 15:174–177. https://doi.org/10.14694/edbook_am.2012.32.174

Yamaguchi S et al (2018) Late-onset fulminant myocarditis with immune checkpoint inhibitor nivolumab. Can J Cardiol 34:812.e811–812.e813. https://doi.org/10.1016/j.cjca.2018.03.007