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Editorial

Differences in clinical presentation and outcome between immune checkpoint inhibitor-associated myocarditis and classical acute myocarditis: Same disease, distinct challenges to face

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Immune checkpoint inhibitors (ICI) are new cancer drugs that target immune checkpoints, molecules acting as regulators of the immune system, boosting the immune response against cancer cells. Currently approved ICI block cytotoxic T-lymphocyte antigen-4 and programmed death (PD)-1 and PD ligand-1. Since their introduction in cancer therapy, ICI had great impact on treatment and prognosis of different cancers. As highlighted by US estimates, ICI are increasingly being used in cancer population, with the percentage of eligible patients for ICI increasing from 1.5% in 2011 to 43.6% in 2018 [1]. Among the wide range of reported immune-related ICI adverse events, acute myocarditis (AM) was found to be more common than initially appreciated and to have the highest fatality rate, raising the attention toward the topic [2,3]. Of note, the more checkpoints are targeted (i.e. combination therapy), the more adverse events are recorded [4].

In this issue of the Journal, Pradhan et al. performed a literature review identifying a total of 88 cases of ICI-related AM, of whom 53 derived from case reports/series and 35 came from the single available observational study by Mahmood et al. [5], with the aim to better characterize diagnostic approaches, clinical presentation, management and outcome of this important ICI-related cardiac adverse effect [6]. To date, it represents the largest report on the topic based on a series of published cases.

The Authors compared the population derived from the pooled data of case reports with the one derived from observational data. The two populations were similar in terms of age at presentation (mean, 64 years old), female prevalence, time to presentation (between 5 and 7 weeks since ICI initiation), presenting symptoms and remaining baseline characteristics. Focusing on diagnostic investigations, elevated troponin levels and abnormal ECG findings were common in both groups, with a mean incidence of sustained ventricular arrhythmias (VA) of 22% and advanced heart block of 28%. Echocardiography revealed a left ventricular ejection fraction (LVEF) <50% in nearly 50% of patients in both groups. Cardiac magnetic resonance imaging findings were similar, with evidence of late gadolinium enhancement in the majority of patients. A complicated presentation (i.e. LVEF<50% on first echocardiogram, sustained VA or low cardiac output syndrome [LCOS]) was described in 70% of the case reports. Unfortunately, no stratification according to the presence of complicated presentation was available in the single observational cohort study. Histologic findings from endomyocardial biopsy (EMB) and autopsy were reported in 52% in the case reports and 31% in the observational data, with a described predominantly lymphocytic cellular infiltration. Treatment was similar in both groups, with steroids being the most common immunosuppressive treatment (89% in patients from observational data and 91% in those from case reports), with heterogeneous treatment duration and need of second line immunosuppressive therapies. Focusing on prognosis, 40% of the patients from the case reports died of cardiac related complications, mostly during index hospitalization (mean follow-up, 94 days). Approximately one half of the patients from observational data experienced a major cardiovascular event (MACE) with a death rate of 17% (median follow-up, 102 days). Interestingly, 38% of MACE occurred in patients with a normal LVEF in the observational study and 50% of deaths occurred in patients with an uncomplicated presentation when referring to patients collected from case reports. A comparison of the two cohorts with a recent large contemporary population of non-ICI-related AM patients [7], mainly of post-viral etiology or associated with autoimmune disorders, is provided in Table 1.

Conclusion of the review was that ICI-related AM is characterized by elevated cardiac biomarker levels, nonspecific ST and arrhythmic changes on ECG and lack of correlation between preserved systolic function and survival. A claim for a standardized

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Table 1
Focused comparison between immune-checkpoint inhibitor-related myocarditis and data from the multicenter Lombardy registry on acute myocarditis [7].

	Acute myocarditis		
	ICI-related		Data from Multicenter Lombardy Registry [7]
	Pooled data from case reports [6]	Data from Mahmood et al. [5]	
Overall n	53	35	443
Demographics			
Age, years	Mean, 64	Mean, 65	Median, 34
Female	22 (41%)	10 (29%)	86 (19%)
Presenting symptoms			
Dyspnea	49%	25 (71%)	84 (19%)
Chest pain	17%	12 (34%)	379 (86%)
Fulminant presentation	NR	NR	38 (9%)
Complicated presentation	37 (70%)	NR	118 (27%)
Autoimmune disorders	3 cases[a]	NR	31 (7%)
ECG at admission			
Abnormal	91%	89%	382 (86%)
ST segment elevation	15 cases[a]	NR	245 (57%)
Other ST-T segment abnormalities	2 cases[a]	NR	100 (23%)
Life threatening arrhythmias			
Cardiac arrest	NR	4 (11%)	NR
VT/VF	15 cases[a]	14%	NR
Advanced AV block	16 cases[a]	23%	13 (3%)[b]
Admission laboratory tests			
Increased troponin T/I or CK-MB	97%	33 (94%)	434 (99%)
Echocardiography at admission			
LVEF <50%	27 (51%)	49%	111 (25%)
Coronary angiogram performed	31 (58%)	NR	203 (47%)
CMRI performed	14 (26%)	31 (88%)	415 (94%)
LGE	65%	64%	100%
Histological diagnosis	28 (52%)	11 (31%)	61 (14%)
Steroids as immunosuppressive therapy	48 (91%)	31 (89%)	40%
ECMO support	5 (9%)	NR	18 (4%)
Outcome			
Cardiac death	21 (39%)	6 (17%)	12 (3%)
Overall death	27 (51%)	NR	17 (4%)
In patients with complicated presentation	19/37 (51%)	NR	16/118 (8%)
In patients w/o complicated presentation	8/16 (50%)	NR	1/325 (0.3%)
In-hospital death	22 (41%)	NR	10 (2%)

Abbreviations: ICI, immune-checkpoint inhibitor; NR, not reported; VT/VF, ventricular tachycardia/ventricular fibrillation; AV, atrioventricular; LVEF, left ventricular ejection fraction; CMRI, cardiac magnetic resonance imaging; LGE, late gadolinium enhancement; ECMO, extra corporeal membrane oxygenator; w/o without.
[a] Cases were reported without percentage when the overall number of available data was not present.
[b] It refers to AV block of any degree identified on ECG.

surveillance strategy, for an optimal diagnostic/therapeutic approach and for a better risk evaluation of ICI-related AM is advocated by the Authors.

Given the predicted future high prevalence of ICI use in cancer patients, a growing role of this specific subtype in myocarditis etiology has to be expected. Awareness on ICI-associated AM among cardiologists, oncologists and critical care providers should be developed, particularly due to its reported high fatality rate and the fact that it poses different challenges compared to non-ICI-related AM. ICI-related AM affects a by far older population (64 vs. 34 years in non-ICI-related forms), frequently affected by advanced cancer as well as previous comorbidities and prognosis seems poorly defined by stratifying LVEF at presentation, in contrast to non-ICI-related AM [7,8]. Furthermore, limited evidence exists on indications to mechanical circulatory support in cancer population. These factors could explain the high mortality rate in ICI-related compared with non-ICI-related AM. A possible overestimation of mortality in ICI-associated AM can be also due to the known publication bias in case reports. Clinicians and future prospective studies including patients with suspected ICI-related AM should stratify patients not only according to LVEF but taking into consideration the presence of complicated presentation (i.e. VA, LCOS), which has strongly been associated with adverse outcomes in non-ICI-related AM [7–9].

The role of EMB in the specific setting of ICI-related AM is unknown, but it may be reasonable in those with complicated presentations [8]. Histologic findings confirmed the presence of lymphocytic infiltrates in most of cases, but giant cells and eosinophils were also found. This represents relevant information, in fact, ICI or other ongoing drugs may cause hypersensitivity reactions triggering an eosinophilic myocarditis, potentially explaining a different mechanism underlying AM [10]. Furthermore, histologic subtype is an important determinant of outcome, with giant cell myocarditis burdened by the worst prognosis [9]. Histologic subtype can further guide immunosuppressive regimens in terms of immunosuppressant choice and therapy duration.

Finally, thanks to the current review, the perceived role of immunosuppression in ICI-related AM from the medical community is evident, despite the absence of a standardized therapeutic approach. High-dose steroids were used in approximately 90% of the cases, a percentage which is far higher than the one reported for non-ICI-related forms of lymphocytic AM where the role of immunosuppression is still debated [8]. Efforts should be made in defining standardized immunosuppressive regimens in relation to specific histologies defined by EMB, especially in patients presenting with features of complicated AM.

Declaration of competing interest

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