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Prognosis of immune checkpoint inhibitors-induced myocarditis: a case series

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ABSTRACT

Background Immune checkpoint inhibitors (ICI) have transformed cancer treatment over the last decade. Alongside this therapeutic improvement, a new variety of side effects has emerged, called immune-related adverse events (irAEs), potentially affecting any organ. Among these irAEs, myocarditis is rare but life-threatening.

Methods We conducted a multicenter cross-sectional retrospective study with the aim of better characterizing ICI-related myocarditis. Myocarditis diagnosis was based on the recent consensus statement of the International Cardio-Oncology Society.

Results Twenty-nine patients were identified, from six different referral centers. Most patients (55%) were treated using anti-programmed-death 1, rather than ICI combination (35%) or anti-programmed-death-ligand 1 (10%). Transthoracic echocardiography was abnormal in 52% of them, and cardiac magnetic resonance showed abnormal features in 14/24 patients (58%). Eleven patients (38%) were classified as severe. Compared with other patients, they had more frequently pre-existing systemic autoimmune disease (45% vs 6%, p=0.018), higher troponin level on admission (42-fold the upper limit vs 3.55-fold, p=0.001), and exhibited anti-acetylcholine receptor autoantibodies (p=0.001). Seven patients (24%) had myocarditis-related death, and eight more patients died from cancer progression during follow-up. Twenty-eight patients received glucocorticoids, 10 underwent plasma exchanges, 8 received intravenous immunoglobulins, and 5 other immunosuppressants. ICI rechallenge was performed in six patients, with only one myocarditis relapse.

Discussion The management of ICI-related myocarditis may be challenging and requires a multidisciplinary approach. Prognostic features are herein described and may help to allow ICI rechallenge for some patients with smoldering presentation, after an accurate evaluation of benefit–risk balance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immune checkpoint inhibitors (ICI)-related myocarditis is a rare and life-threatening adverse event, with little data about predictors of outcome.

WHAT THIS STUDY ADDS

⇒ Through a series of 29 ICI-related myocarditis we report an overall lower mortality than initially described and evidence of some prognostic factors for worse outcome, such as a pre-existing autoimmune disease or a higher troponin level on admission. For the first time, we also report safe ICI rechallenge after myocarditis in six patients with a long follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Early detection of ICI-related myocarditis through a multidisciplinary approach may improve the management of oncology patients. Identification of prognostic factors for severity may also allow ICI rechallenge in some cases, after an accurate evaluation of benefit–risk balance.

BACKGROUND

Cancer therapy has profoundly evolved over the past decades, with harnessing of antitumor immunity as a new tool in the treatment landscape. Ipilimumab was the first approved immune checkpoint inhibitor (ICI) in 2011, and since, seven drugs have been Food and Drug Administration approved, targeting cytotoxic T-lymphocyte-associated antigen-4 or programmed-cell death (ligand)-1 (PD(L)−1).[1] Outcomes of patients improved in different types of cancer, and the indications for these drugs are extending fast.[1 2] Yet, they are responsible for multiple side effects, driven by unregulated immune system activation, commonly termed as 'immune-related adverse events' (irAEs). Some are frequent and have been well characterized such as colitis, hepatitis, or thyroiditis.[3 4] In that context, cardiovascular

adverse events are rare, but of rising concern, especially myocarditis.[5 6] More and more cases are described in the literature, with a mortality rate up to 50%.[6] The difficulties are numerous, including the diagnosis of such irAE, as the gold-standard is still endomyocardial biopsy, which may be difficult to perform. Moreover, international guidelines on ICI-related myocarditis management remain vague: beyond ICI discontinuation and the use of steroids, data are limited. Plus, ICI discontinuation can be a loss of chance for the patient, and we lack data about ICI rechallenge.[7] This multicenter case series describes the clinical manifestations, management, and outcomes of patients with ICI-related myocarditis

PATIENTS AND METHODS

We conducted a multicenter retrospective cross-sectional study. We identified consecutive patients in Montpellier University Hospital and Montpellier Institute of Cancer from July 2019 to November 2020 through a regional specific network dedicated to ICI-related toxicities (ToxImmun referral center), led by internists, oncologists, and pharmacovigilance department. This network allows a rather comprehensive identification of cases together with accurate data collection. We also identified cases from four other reference centers (ie, Gustave Roussy Institute, Kremlin-Bicêtre University Hospital, Bordeaux University Hospital and Poitiers University Hospital) by a call for observations through national networks. In the context of ICI therapy, myocarditis definition was based on the recent consensus statement published by the International Cardio-Oncology Society (IC-OS)[8] (online supplemental table S1). Patients were further classified as possible/probable/confirmed myocarditis like proposed by Bonaca *et al*[9] (online supplemental table S1). Alternate diagnosis for troponin elevation (pulmonary embolism, myocardial infarction, pericarditis, …) were excluded. Medical records were reviewed for demographic data, personal medical history, previous oncologic and non-oncologic treatments, clinical data (signs and symptoms, time to myocarditis occurrence), laboratory and imaging data (ECG, high-sensitivity (HS) troponin (T or I), transthoracic echocardiography (TTE), cardiac magnetic resonance (CMR) and endomyocardial biopsies (EMB)). For the sake of standardization, HS-troponin values were normalized according to each laboratory upper limit reference. CMR diagnosis was based on modified Lake Louise criteria.[10] Day 0 was assigned as the day when the myocarditis was suspected (first clinical or paraclinical sign). Myocarditis severity was graded according to Common Toxicity Criteria for Adverse Events (CTCAE V.5.0) and IC-OS consensus statement on cardiovascular toxicities of cancer therapies (online supplemental table S1).

Quantitative variables were reported as medians (range) and compared using Mann-Whitney non-parametric tests. Qualitative variables were expressed as percentage and compared with Fisher's exact test. A receiver operating characteristic (ROC) curve was performed to assess troponin diagnostic abilities to distinguish severe presentations. Statistical differences were considered significant if $p<0.05$. All statistical analysis was made using Prism 8.0.2 (GraphPad Software, San Diego, California, USA).

RESULTS

We included 29 patients from six different care referral centers including 12 definite, 10 probable, and 7 possible myocarditis, with a median age of 68 (32–83) years (see online supplemental figure S1: flow-chart, table 1, and online supplemental table S2 for individual details) . Twenty-four patients (83%) had at least one cardiovascular risk factor, and 13 (45%) had pre-existing underlying autoimmunity (defined autoimmune condition or isolated autoantibodies). Ten patients (34%) received ICI for the treatment of non-small cell lung cancer, 8 (28%) for melanoma, 4 (14%) for renal or bladder carcinoma. Twenty-four out of 29 patients (83%) were at metastatic stage and 26 out of 29 (90%) had previous cancer treatment. Nineteen patients (65%) were treated with anti-PD-(L)1 monotherapy, others with combi-therapy. Myocarditis occurred in a median time of 39 days (IQR 39.5 days) (figure 1). Patients presented with cardiac symptoms most of the time (83%), mainly dyspnea (table 1). Median admission troponin was 5.35-fold (range: 1.57–456) the upper limit. The ECG was abnormal in 20 (69%) patients (nine arrhythmia; nine repolarization abnormalities; six conduction trouble). TTE showed decreased left ventricular ejection fraction (LVEF) in 10 out of 27 (37%) patients. Global longitudinal strain was assessed in eight patients with normal LVEF and altered in four of them (50%). Twenty-five patients underwent CMR, 16 (55%) of them showing late gadolinium enhancement. T2 Short Tau Inversion Recovery (STIR) edema was positive in 7/22 (32%), whereas T1-mapping and T2-mapping were positive in respectively 8/13 (62%) and 6/10 (60%) patients. Eighteen patients had suggestive CMR (ie, isolated T1 or T2 criterion, wall motion abnormality and/or pericarditis) and 10 out of 25 fulfilled modified Lake Louise criteria for myocarditis (table 1, online supplemental table S2 and figure 2 for CMR illustration). Fourteen (48%) patients underwent coronarography for initial alternative diagnosis. EMB was obtained in six patients and showed lymphocyte infiltration in five of them, all with prominent T CD8 cells, and PD(L)-1 expression. Among associated toxicities, there was a median of two other irAE (range: 0–5), with the most frequent being musculoskeletal myositis (13 of 29, 45%). Eleven patients (38%) had sicca syndrome, including two cases fulfilling Sjögren's syndrome criteria.

Twenty-six patients were screened for autoantibodies at the time of myocarditis occurrence, 10 (38%) revealing antinuclear antibodies (ANA), including two patients who had pre-existing ANA. Specific autoantibodies included anti-myocardium in one patient, anti-acetylcholine receptor autoantibodies (AChRAb) in 5 out of 15 patients

Table 1 Description of 29 patients with ICI-induced myocarditis according to the classification by Bonaca *et al*[9]

Characteristics	Total (n=29)	Definite (n=12)	Probable (n=10)	Possible (n=7)
Male	**20 (69)**	7 (58)	8 (80)	5 (71)
Age—median (range), years	**69 (33–84)**	68 (33–84)	69 (54–80)	72 (53–83)
History of autoimmunity				
Definite disease	**9 (31)**	5 (42)	3 (30)	1 (14)
Auto-antibodies alone	**4 (14)**	0	2 (20)	2 (29)
Type of cancer				
Lung carcinoma	**10 (34)**	5 (42)	3 (30)	2 (29)
Melanoma	**8 (28)**	2 (16)	5 (50)	1 (14)
Others*	**11 (38)**	5 (42)	2 (20)	4 (57)
Metastatic	**24 (83)**	10 (83)	8 (80)	6 (86)
Previous cancer treatment				
Radiotherapy	**12 (42)**	6 (50)	3 (30)	3 (43)
Chemotherapy	**8 (28)**	5 (42)	1 (10)	2 (29)
Targeted therapy†	**6 (21)**	3 (25)	3 (30)	0 (0)
Type of ICI				
Anti-PD(L)-1	**19 (66)**	8 (67)	7 (70)	4 (57)
Combi-therapy	**10 (35)**	4 (33)	3 (30)	3 (43)
Time to myocarditis—median (range), days	**39 (2–181)**	33.5 (15–126)	56.5 (2–181)	44 (16–63)
Cardiac clinical symptoms‡	**24 (83)**	12 (100)	8 (80)	4 (57)
HS-troponin fold increase—median (range), UPL	**5.35 (1.57–456)**	6 (1.86–456)	2.89 (1.57–91.6)	25.7 (1.71–56.5)
Abnormal ECG	**20 (69)**	9 (75)	6 (60)	5 (71)
Abnormal TTE	**14/27 (52)**	6 (50)	6/9 (67)	2/6 (33)
Abnormal CMR suggestive of myocarditis	**18/25 (72)**	9/11 (82)	7/8 (87,5)	2/6 (33)
Modified Lake Louise criteria fulfilled	**10/25 (40)**	6 (50)	4 (40)	0 (0)
Myocarditis severity				
Severe	**11 (38)**	7 (58)	2 (20)	2 (29)
Clinically significant	**14 (48)**	5 (42)	6 (60)	3 (42)
Smoldering	**4 (14)**	0 (0)	2 (20)	2 (29)
Treatment modalities				
Glucocorticoids	**28 (97)**	12 (100)	10 (100)	6 (86)
Plasmapheresis	**10 (34)**	4 (33)	2 (20)	4 (57)
IVIg	**8 (28)**	2 (17)	2 (20)	4 (57)
Other immunosuppressants§	**5 (17)**	1 (8)	2 (20)	2 (29)
Follow-up—median (range), days	**123 (19–832)**	133 (8–832)	200 (49–830)	183 (22–333)
Deaths	**7 (24)**	4 (33)	1 (10)	2 (29)

Continued

Table 1 Continued

Characteristics	Total (n=29)	Definite (n=12)	Probable (n=10)	Possible (n=7)

Data are shown as n (%) unless further specified. No statistical difference was found between groups.
*Renal/bladder carcinoma (4), hepatocellular carcinoma (3), cholangiocarcinoma (1), cutaneous squamous cell carcinoma (1), gastric adenocarcinoma (1), mesothelioma (1).
†Regorafenib, sorafenib, pazopanib, everolimus, sunitinib, cabozantinib, nintedanib, bevacizumab.
‡Dyspnea, chest pain, lower limbs edema, palpitations.
§Methotrexate (3), mycophenolate mofetil (1), ciclosporin (1).
CMR, cardiac magnetic resonance; HS, high-sensitivity; ICI, immune checkpoint inhibitor; IVIg, intravenous immunoglobulins; PD(L)-1, programmed-cell death (ligand)-1; TTE, transthoracic echocardiography; UPL, upper limit.

tested (all presenting myasthenia gravis (MG) symptoms), anti-striated muscle in two patients, anti-PL7 and anti-Scl70 for one patient each.

When we compared the most severe patients (n=11) versus non-severe patients (n=18) (table 2), they presented more pre-existent systemic autoimmune disease (45% vs 6%, p=0.018), lower exposure to anti-vascular endothelial growth factor (VEGF) (0/11 vs 7/18, p=0.025), higher heart rate (median of 113/min vs 79.5/min, p=0.001)), more conduction trouble on ECG (45% vs 6%, p=0.018), a higher incidence of AChRAb positivity (5/6 vs 0/9, p=0.001), and higher troponin levels on admission (median of 42-fold the upper limit vs 3.55-fold, p=0.001). There was no difference between the two groups in terms of age, renal clearance, creatine kinase and C-reactive protein levels. Concerning troponin values among these two groups, the ROC analysis showed an area under curve (AUC) of 0.84 (95% CI: 0.69 to 0.98, p=0.002) (figure 3). When choosing a cut-off value of 4.89-fold the laboratory upper limit, we found a sensitivity of 90.9% and a specificity of 66.7%, with a likelihood ratio of 2.727.

Concerning myocarditis management (table 1), almost all patients (28 of 29, 97%) received glucocorticoids, mainly with initial intravenous pulses of 500–1000 mg (19 of 28, 68%). Other modalities of treatment included plasmapheresis, intravenous immunoglobulins, and immunosuppressants, with seven patients receiving combined treatments beyond glucocorticoids. Ten patients were admitted in the resuscitation ward, and six were admitted in cardiac intensive care unit.

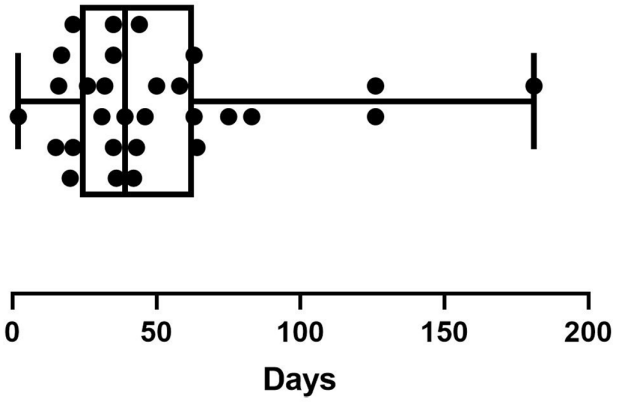

Figure 1 Time from immune checkpoint inhibitor initiation to myocarditis occurrence (days, median, IQR and min–max).

An assessment of cancer response at the time of myocarditis occurrence was available for 21 patients, with only 1 patient exhibiting disease progression, others presenting partial response (13 of 21, 61%), complete response (6 of 21, 29%), or stable disease (1 patient). We had a median treatment-free interval of 3.4 (range: 0–22) months, with a median follow-up of 4 (range: 0–28, IQR=8.6) months. Throughout the follow-up, eight additional patients died of cancer progression.

Six patients (four initially treated with combi-therapy) underwent rechallenge with an ICI in monotherapy (table 3). Initial myocarditis was classified as possible in three, probable in two, and definite in one (the latter with severe presentation, the other considered as clinically significant). After rechallenge, and a median follow-up of 566 (183–830) days, only one patient (first classified as CTCAE grade 3 possible myocarditis) suffered from grade 3 myocarditis relapse requiring ICI discontinuation

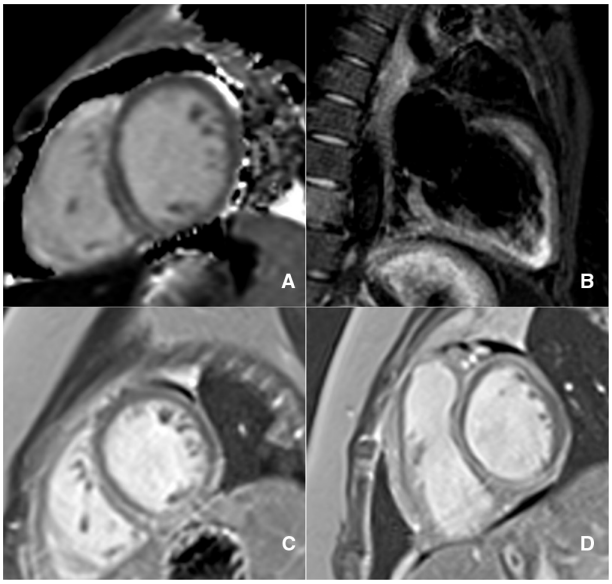

Figure 2 Cardiac MRI demonstrating myocardial inflammation in a 33-year-old woman. (A) Short-axis-native T1 map showing elevated signal (1246±108 ms) consistent with hyperemia and/or fibrosis. (B) Vertical-long-axis Short Tau Inversion Recovery (STIR) image showing midventricular and basal edema. (C, D) Short-axis late enhancement images showing subepicardial late gadolinium enhancement consistent with fibrosis and necrosis in mid and basal left ventricular cardiac wall.

Table 2 Comparison between severe patients versus non-severe patients

Characteristics	Severe patients (n=11)	Non-severe patients (n=18)	P value
Age—median, years	68	68.5	0.321
Previous autoimmune disease			
All	5 (45)	4 (22)	0.237
Systemic	5 (45)	1 (6)	**0.018**
Previous cancer treatments			
Radiotherapy	6 (55)	8 (44)	0.710
Anti-VEGF	0	7 (39)	**0.025**
Chemotherapy	4 (36)	4 (22)	0.432
Combi-therapy	1 (9)	9 (50)	**0.043**
Clinical features			
Heart rate, bpm	113	79,5	**0.001**
Median blood pressure, mm Hg	105	104	0.889
Biologic features			
Troponin—median, UPL	42	3,55	**0.001**
Elevated BNP	6/8 (75)	11/18 (61)	0.667
Conduction trouble on ECG	5 (45)	1/17 (6)	**0.022**
TTE LVEF <50%	4/10 (40)	6/17 (35)	1
Associated toxicities			
Myositis	6 (55)	6 (33)	0.438
Sicca syndrome	3 (27)	8 (44)	0.448
AChRAb	5/6 (83)	0/9	**0.001**
Treatment-free interval—median, months	6.7	2.9	0.428

Data are shown as n (%) unless specified. Severity was defined according to the IC-OS consensus statement by Hermann *et al*.[8] Quantitative variables were compared using Mann-Whitney non-parametric tests, and qualitative variables were compared with Fisher's exact test. P values that reached significance appear in bold.

AChRAb, acetylcholine receptor antibodies; BNP, brain natriuretic peptide; IC-OS, International Cardio-Oncology Society; LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiography; UPL, upper limit; VEGF, vascular endothelial growth factor.

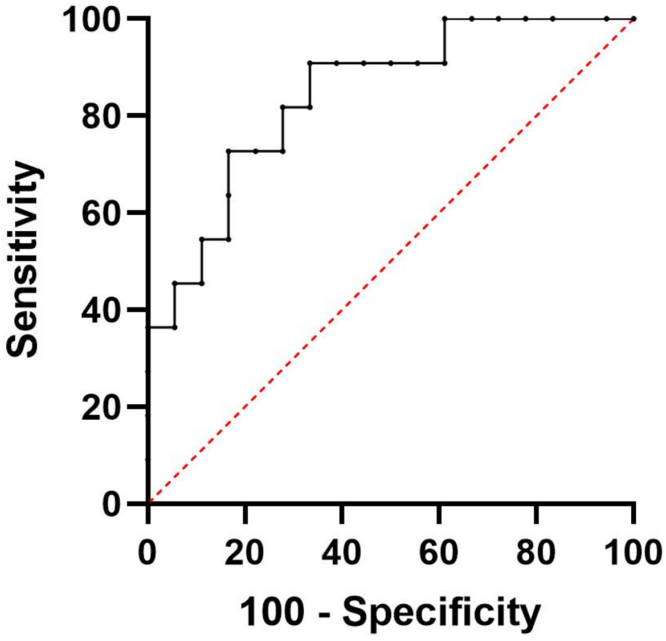

Figure 3 Receiver operating characteristic curve for admission troponin between severe and non-severe patients.

and glucocorticoids, and eventually died of cancer progression.

DISCUSSION

Here we reported on a novel series of 29 cases of myocarditis in patients treated by ICI, with a lower mortality rate than initially described.[6] This may stem from earlier detection using systematic screening on ECG and troponin, as recently reported.[11 12]

If EMB is considered as the gold-standard technique for myocarditis diagnosis, it may be difficult to proceed outside referral centers, it is not free of adverse events, and may be false negative. In five of our patients, EMB showed pre-eminent CD8 T-lymphocyte infiltration within the myocardium, like cellular rejection following heart transplantation. The latter patient did not have lymphocytic infiltration, although it may be important to bear in mind that 10–20% of cardiac allograft rejection are biopsy-negative.[13] In the absence of histology, new CMR procedures such as T1-mapping or T2-mapping seem promising.[14]

One challenge in this analysis is the assessment of myocarditis severity, since clinical presentation may vary from smoldering to fulminant events.[5 15] We found some prognostic factors, such as higher heart rate and troponin values on admission, that were correlated with severity (according to the recent definition of the IC-OS[8] or by CTCAE classification grade 4–5), congruent with literature.[16] We also found in the most severe group a higher proportion of pre-existing systemic autoimmune disease, patients that had been first excluded from clinical trials, but now treated when the benefit/risk balance seems positive. In the same way, our findings confirm that AChRAb positivity is related to the severity of myocarditis, which was previously described ('3M syndrome': MG

Table 3 Outcome of the six patients ICI-rechallenged after myocarditis occurrence

				Myocarditis					ICI rechallenge		Outcome after ICI rechallenge				
	Sex / age	Cancer	Initial ICI	Time to onset (d)	Bonaca	Diagnosis	Severity	Treat-ment	Time (d)	ICI	Myocarditis relapse	New irAEs	TTP (d)	Follow-up (d)	Death*
1	M / 54	Melanoma	CTLA-4+PD-1	63	Pro	Elevation of troponin + clinical syndrome + ECG + decline in systolic function	Clinically significant	GC	112	PD-1	–	–	720	830	0
2	M / 71	NSCLC	PD-1	64	Def	Pathology	Severe	GC	14	PD-1	–	–	180	325	1
3	F / 53	Melanoma	CTLA-4+PD-1	46	Pos	Elevation of troponin + clinical syndrome + concomitant myositis	Clinically significant	GC; IVIg; MTX; PLEx	140	PD-1	–	–	90	288	1
4	F / 69	Melanoma	CTLA-4+PD-1	21	Pos	Elevation of troponin + clinical syndrome + ECG + negative angiography	Clinically significant	GC	42	PD-1	–	–	45	807	0
5	M / 71	Melanoma	CTLA-4+PD-1	39	Pro	Elevation of troponin + clinical syndrome + ECG + elevated T2m on CMR	Clinically significant	GC	28	PD-1	–	–	56	811	0
6	M / 72	NSCLC	PD-1	58	Pos	Elevation of troponin + clinical syndrome + ECG + negative angiography	Clinically significant	–	150	PD-1	+†	–	28	183	1

*All deaths were caused by cancer progression.
†Clinically significant, treated with glucocorticoids with favorable outcome.
CMR, cardiac magnetic resonance; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; d, days; Def, definite; GC, glucocorticoids; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; IVIg, intravenous immunoglobulins; MTX, methotrexate; NSCLC, non-small-cell lung cancer; PD-1, programmed-death 1; PLEx, plasma exchange; Pos, possible; Pro, probable; TTP, time to progression.

associated with myocarditis and myositis).[6 17] Concerning associated toxicities, Sjögren-like syndromes under ICI have been described before, and the onset of sicca syndrome in patients treated with ICI may be a signal for multi-toxicity or severe toxicities.[18] We did not find any correlation either between combi-therapy and myocarditis severity, or with shorter delay for myocarditis (35 days vs 43 for monotherapy, p=0232), although literature seems to identify higher fatality rate during ICI combi-therapy.[6] However, this discrepancy may be linked with the strengthened monitoring of patients under combi-therapy. Unexpectedly, patients previously treated with anti-VEGF were more frequently in the non-severe group, suggesting an unintuitive protective role, although VEGF have been identified to have immunomodulatory effect by reducing CD8 recruitment.[19] Ongoing studies with VEGF-directed therapies and ICI should be examined to validate—or not—the protective role seen in this case series.

Concerning myocarditis management itself, some patients underwent plasma exchanges (four severe cases and six non-severe cases). We did not find any significant difference in outcomes in terms of cardiac function or troponin measurements (data not shown), but we demonstrate the feasibility of this approach. Although studies have to be conducted, we may suggest to propose early plasmapheresis on a case-by-case basis in patients who may be considered at risk for grade 4–5 myocarditis (ie, previous autoimmunity, high troponin level, concomitant myositis or MG). Plasma exchange may also aim at withdrawing the monoclonal antibody when myocarditis occurrence is close to the last infusion. Herein, admission troponin cut-off value of 4.89-fold the upper limit may be used as an early screening tool. It emphasizes the need for early management, supported by a trained network.

Eventually, once the irAE is efficiently managed, current guidelines recommend definitive contraindication if the grade is $\geq 2^4$, which is quite always the case. However, immunotherapy may be the last option for these patients, leading to a predicament. Detection of smoldering presentations of myocarditis with better outcome outlines the need to reconsider definitive contraindication especially in those that had been first treated by combi-therapy. A pharmacovigilance study found a recurrence rate of 28.8% of the same irAE after ICI rechallenge,[7] with no relapse for the three myocarditis cases described, and only one in our series. In our study, rechallenge was also associated with further oncological response although half of the patients finally died from cancer progression with a median follow-up of 566 days.

There are some limitations to our work, mainly the retrospective and declarative design. CMR was performed locally, with heterogeneous protocols. Half of our patients did not undergo coronarography, and EMB was performed in only six of them, while reflecting a real life framework with often unstable patients.

CONCLUSION

Myocarditis may exhibit various clinical presentations from smoldering to fulminant forms. We found that life-threatening events more frequently occurred in patients with underlying autoimmunity and were associated with a higher heart rate and troponin level at admission, and the presence of anti-acetylcholine receptor autoantibodies. Apart from ICI discontinuation and early steroid administration, plasma exchanges are feasible in this context, while their benefits remain to be demonstrated. In smoldering myocarditis with initial favorable course, ICI rechallenge may be considered after an accurate evaluation of the benefit/risk balance. Further studies are needed to evaluate the value of troponin follow-up, specific risk factors and assess the benefit/risk balance of ICI rechallenge.

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Supplementary Table 1: Definitions for ICI-induced myocarditis (*adapted from Herrmann et al.*[8])

IC-OS 2021 Consensus[8]

1/ Either pathohistological diagnosis:
Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples

2/ Or clinical diagnosis:
A troponin elevation (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline) with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion

Major Criterion
CMR diagnostic for acute myocarditis (modified Lake Louise criteria)

Minor Criteria
- **Clinical** syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock)
- Ventricular **arrhythmia** and/or new **conduction system disease**
- **Decline in cardiac (systolic) function**, with or without regional WMA in a non-Takotsubo pattern
- **Other immune-related adverse events**, particularly myositis, myopathy, myasthenia gravis
- **Suggestive CMR** (meeting some -but not all- of the modified Lake Louise citeria)

Modifiers

Severity of Myocarditis	
Severe	Hemodynamic instability, heart failure requiring non-invasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia
Non-Severe (clinically significant)	Symptomatic but hemodynamically and electrically stable, may have reduced LVEF, no features of severe disease
Smoldering (sub-clinical)	Incidentally diagnosed myocarditis without any clinical signs or symptoms
Recovery from Myocarditis	
Complete Recovery	Patients with complete resolution of acute symptoms, normalization of biomarkers and recovery of LVEF after discontinuation of immunosuppressants
Recovering	Ongoing improvement in patient clinical symptoms, signs, biomarkers and imaging parameters, but not yet normalized, while on tapering doses of immunosuppressants

Bonaca et al.[9]

Definitive	Pathology OR Diagnostic CMR + syndrome + biomarker or ECG OR Echo WMA + syndrome + biomarker + ECG + negative angiography
Probable	Diagnostic CMR (no syndrome, ECG, biomarker) OR Suggestive CMR with either syndrome, ECG or biomarker OR Echo WMA and syndrome (with either biomarker or ECG) OR Syndrome with PET scan evidence and no alternative diagnosis
Possible	Suggestive CMR with no syndrome, ECG or biomarker OR Echo WMA with syndrome or ECG only OR Elevated biomarker with syndrome or ECG and no alternative diagnosis

Supplementary table S1: Individual description of clinical and paraclinical features, treatment modalities and outcomes according to Bonaca[9] and Hermann[8].

	Sex	Age (years)	CV risk factors	Previous AI	Cancer type	Stage	ICI	Time to onset (d)	Clinical symptoms	High Tn/ BNP (y/n)	ECG	TTE	CMR	Angio graphy / EMB	Associated irAEs	Bonaca grading	Severity*	Treatment	Outcome *	Follow -up (days)
1	M	69	D; S	Ps	HCC	III	PD1	181	-	+ / +	n	n	LGE; ↑T1m	- / -	Th	Pro	Sm / 2	GC	R; CRD	87
2	F	71	Dl; HBP; S	-	NSCLC	IV	PD1	2	CP; Dy; M; Pa	+ / +	LAFB	DSF	DSF; LGE	- / -	SS	Pro	CS / 3	GC	R; CRD	49
3	M	54	S	Vi	Me	IV	CTL4 + PD1	63	CP; M; Pa	+ / -	n	DSF	LGE	- / -	CNS; De; He; My; Th	Pro	CS / 3	GC	CR; NIC	830
4	M	64	D; HBP; S	ILD	NSCLC	III	PDL1	43	Dy; LLO; M; Pa	+ / -	n	n	LGE; ↑T1m; ↑T2m; T2O	- / -	He; MG; My; SS; Th	Def	Se (HF) / 4	GC; IVIg; MMF; MTX; PLEx	R	486
5	F	70	HBP	-	UTC	IV	PD1	26	CP; Dy; LLO	+ / +	DNTW	DSF; ↓GLS	DSF; LGE; T2O	+ / -	SS	Def	CS / 3	GC; PLEx	R; CRD	69
6	F	33	S	-	NSCLC	IV	PD1	20	LLO	+ / +	DNTW; PVC	WMA; ↓GLS	LGE; ↑T1m; T2O	- / -	SS; Th	Def	CS / 3	GC; PLEx	R; CRD	144
7	M	71	S	My; Ne	NSCLC	IV	PD1	64	Sy	+ / -	HGHB	↓GLS	LGE; ↑T2m; T2O	+ / +	SS	Def	Se / 4	GC	CR; NIC	325
8	F	53	-	ANA	Me	IV	CTL4 + PD1	46	Dy; M; Pa	+ / +	n	n	n	- / -	He; My; Pn; SS	Po	CS / 3	GC; IVIg; MTX; PLEx	R; NIC; CRD	288
9	M	80	HBP; S	-	UTC	IV	PD1	50	LLO	+ / +	PVC	WMA	LGE; T2O	- / -	SS	Pro	CS / 3	GC; PLEx	R	299
10	F	84	D	MG	Me	IV	PD1	17	Dy	+ / +	DNTW; LBBB	n	LGE; T2O	+ / +	He; MG exacerbation; My	Def	Se (HF) / 5	GC; PLEx	MRD	19
11	M	70	Dl; HBP; S	-	GAc	IV	CTL4 + PD1	63	-	+ / +	DNTW	DSF	DSF	- / -	CNS; He; Th	Po	Sm / 2	GC	CR	287

	Sex	Age (years)	CV risk factors	Previous AI	Cancer type	Stage	ICI	Time to onset (d)	Clinical symptoms	High Tn/ BNP (y/n)	ECG	TTE	CMR	Angiography / EMB	Associated irAEs	Bonaca grading	Severity*	Treatment	Outcome*	Follow-up (days)
12	F	50	S	HT; CL	UTC	IV	PD1+ Ox40	35	CP; Dy	+ / +	DNTW	DSF	LGE	+ / -	He; My; Pn; PNS	Def	CS / 3	GC; IVIg	CR	832
13	M	75	Dl; HBP; S	My	UTC	IV	PD1+ Ox40	15	Dy; M	+ / NS	AF	n	LGE	+ / -	My exacerbation	Def	Se (HF) / 5	GC	MRD	123
14	M	83	S	-	NSCLC	IV	PD1	44	-	+ / -	n	DSF	n	+ / -	My	Po	Sm / 2	GC	CR; CRD	333
15	M	61	-	-	Me	IV	PD1	83	Dy	+ / +	HGHB	DSF	LGE; ↑T1m	- / -	Co; Th	Pro	Se / 4	Cy; GC; IVIg	CR	252
16	M	69	D; S	-	NSCLC	IV	PD1	35	Dy	+ / +	n	DSF	NS	- / -	MG	Pro	CS / 3	GC; IVIg; MTX	R	665
17	M	74	Dl; S	-	NSCLC	IV	PD1	126	Dy; Pa	+ / NS	AF	DSF	n	+ / -	-	Def	Se (HF) / 4	GC	R	474
18	M	83	-	PMR	CEC	IIIb	PD1	36	F; M	+ / NS	HGHB	NS	NS	- / -	He; MG; My; SS	Po	Se / 5	GC; IVIg; PLEx	MRD	22
19	M	76	-	ANA; Ps	Me	IV	CTL4 + PD1	31	M	+ / +	n	NS	LGE; ↑T1m; ↑T2m	- / -	PNS; SS	Pro	Sm / 2	GC; PLEx	CR	148
20	F	69	S	ANA	Me	IV	CTL4 + PD1	21	CP	+ / -	SVT	n	↑T1m; ↑T2m	+ / -	Pn	Pro	CS / 2	GC	R; NIC	807
21	M	71	D; HBP	-	Me	IV	CTL4 + PD1	39	Dy	+ / -	DNTW	n	↑ LGE; ↑T1m; ↑T2m; T2O	- / -	Th	Def	CS / 2	GC	CR; NIC	811
22	M	56	-	-	Me	III	PD1	75	CP	+ / -	DNTW	n	LGE; ↑T2m	+ / +(†)	De; Hy; SS	Pro	CS / 2	GC	R	101

	Sex	Age (years)	CV risk factors	Previous AI	Cancer type	Stage	ICI	Time to onset (d)	Clinical symptoms	High Tn/ BNP (y/n)	ECG	TTE	CMR	Angiography / EMB	Associated irAEs	Bonaca grading	Severity*	Treatment	Outcome*	Follow-up (d)
23	M	64	Dl; HBP; S	-	NSCLC	IV	PD1	126	Dy	+ / +	LBBB	DSF	NS	- / -	-	Pro	Se (HF) / 5	GC	MRD	50
24	M	62	S	-	NSCLC	IV	PDL1	21	CP; Dy	+ / +	AF	DSF	NS	+ / +	-	Def	Se (HF) / 5	GC	MRD	40
25	F	69	S	ANA	HCC	IV	CTL4 + PD1	16	Dy; M	+ / -	AIVR	n	LGE	+ / -	My; Th	Po	CS / 3	GC; IVIg; PLEx	R	70
26	F	52	S	-	CC	IV	CTL4 + PDL1	35	F; LLO	+ / -	n	n	†T1m	+ / +	My; SS; Th	Def	CS / 3	GC	R	32
27	M	66	S	-	HCC	III	PDL1	32	Dy; LLO; M	+ / +	n	WMA	n	+ / +	De; MG; My	Def	Se (HF) / 5	GC	MRD	8
28	M	78	S	-	NSCLC	IV	PD1	42	CP; Dy; LLO	+ / +	RBB	n	n	- / -	My	Po	Se (HF) / 5	GC; IVIg; MMF; PLEx	MRD	37
29	M	72	-	-	NSCLC	IV	PD1	58	Dy	+ / +	AF	n	n	+ / -	-	Po	CS / 3	-	NIC; CRD	183

AF: atrial fibrillation; AI: autoimmunity; AIVR: Accelerated idioventricular rhythm; ANA: antinuclear antibodies; CC: cholangiocarcinoma; CEC: cutaneous epidermoid carcinoma; CL: cutaneous lupus; CNS: central nervous system; Co: colitis; CP: chest pain; CR: complete recovery; CRD: cancer-related death; CS: clinically significant; CV: cardiovascular; Cy: cyclosporin; D: diabetes; De: dermatitis; Def: definite; Dl: dyslipidaemia; DNTW: diffuse negative T waves; DSF: decline in systolic function; Dy: dyspnoea; EMB: endomyocardial biopsy; F: fatigue; GAc: gastric adenocarcinoma; GC: glucocorticoids; GLS: global longitudinal strain; HBP: high blood pressure; HCC: hepatocellular carcinoma; He: hepatitis; HF: heart failure; HGHB: high grade heart block; HT: Hashimoto thyroiditis; Hy: hypophysitis; ICI: immune checkpoint inhibitor; ILD: interstitial lung disease; IVIg: intravenous immunoglobulins; LAFB: left anterior fascicular block; LBBB: left bundle branch block; LC: lung cancer; LGE: late gadolinium enhancement; LLE: lower limbs oedema; M: myalgia; Me: melanoma; MG: myasthenia gravis; MMF: mycophenolate mofetil; MRD: myocarditis-related death; MTX: methotrexate; My: myositis; n: normal; Ne: neuropathy; NIC: new ICI challenge; NS: not specified; NSCLC: non-small cell lung cancer; Pa: palpitations; PLEx: plasma exchange; PMR: Polymyalgia rheumatica; Pn: pneumonitis; PNS: peripheral nervous system; Po: possible; Pro: probable; Ps: psoriasis; PVC: premature ventricular contractions; R: recovering; RBB: right bundle block; S: smoking; Se: severe; Sm: smoldering; SS: sicca syndrome; SVT: supra-ventricular tachycardia; Sy: syncope; T1m: T1 mapping; T2O: T2 oedema; Th: thyroiditis; UTC: urinary tract carcinoma; Vi: vitiligo; WMA: wall motion abnormality.

* Severity is assessed according to IC-OS consensus statement (severe, clinically significant, smoldering) and CTCAE v5 (grade 1-5), and recovery is assessed according to IC-OS consensus statement.

† T lymphocytes infiltrate with insufficient density for myocarditis diagnosis.

Supplementary figure 1: Flow chart