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AUTHORS' CONTRIBUTIONS

M.L. Peña Peña and M.R. Caballero Valderrama were the clinicians treating the patient presented here, performed the literature review, and wrote the manuscript. S. Navarro Herrero and M.P. Serrano Gotarredona reported the cardiac magnetic resonance images and reviewed the manuscript. J.E. López Haldón contributed to the focus of the article and critically reviewed the manuscript.

CONFLICTS OF INTEREST

No conflicts of interest.

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Cardiac magnetic resonance to detect different patterns of myocardial injury in patients receiving immune checkpoint inhibitors

Resonancia magnética cardiaca para la detección de diferentes mecanismos de daño miocárdico en pacientes que reciben tratamiento con inmunoterapia

To the Editor,

Developments in cancer therapeutics such as immune checkpoint inhibitors (ICIs) have improved outcomes but have also been associated with cardiovascular complications. A variety of mechanisms responsible for cardiovascular damage have been proposed, including acute coronary syndromes, unmasking occult underlying cardiovascular disease, arrhythmias, myocarditis, and pericarditis as part of a systemic immune syndrome as a consequence of ICI treatment. Furthermore, as the clinical use of ICI therapy is increasing rapidly, concern is growing about the long-term sequelae in survivors.

Cardiac magnetic resonance (CMR) is useful to provide a diagnosis in those patients with suspected myocardial injury. To date, all studies in ICI cardiotoxicity have explored the ability of CMR to detect myocarditis exclusively.[1] The aim of this study was to describe the presence, type and extent of myocardial injury in a well-defined cohort of oncological patients receiving treatment with ICIs.

This cross-sectional, observational, cohort study consecutively recruited patients scheduled for therapy with ICIs between April, 2019 and October, 2020 at the University Hospital of Salamanca. The study protocol was approved by the University Hospital of Salamanca ethics committee and participants provided written informed consent. Patients underwent a 1.5-Tesla CMR (Philips Healthcare, Netherlands) including cardiac morphology and function assessment, T_2-weighted short-tau triple inversion-recovery (T2W-STIR) sequence, late gadolinium enhancement (LGE), T_1 modified Look Locker imaging (T_1-MOLLI-with-5(3)3 acquisition scheme) before and 15 minutes after gadolinium, and T_2 (multiecho gradient-spin-echo sequence) mapping according to recommendations.[2] Mapping postprocessing was performed using the Medis 2.1 software, plotting the region-of-interest in the left ventricle midseptum segment in short axis. CMR diagnosis of active myocarditis was based on the published Lake Louise expert recommendations[3]; the main criteria in this document are a positive edema-sensitive T_2-based marker (T_2-weighted images or T_2 mapping) and positive T_1-based tissue characterization markers (abnormal T_1 relaxation time or extracellular volume or LGE).[3] Because myocarditis was diagnosed according to these T_2- and T_1-based CMR markers, we used as controls CMR imaging from 50 sex- and age-matched individuals without cardiac disease from a local population-based sample (NCT03429452).[4]

Categorical variables are described as percentages and continuous variables as median (interquartile range [IQR]). The Fisher exact test was used to compare proportions across groups. Nonparametric tests at the ordinal level were used for independent (Mann-Whitney U-test) samples. Analyses were performed using SPSS Statistics, version 22 (IBM, Armonk, United States).

A total of 53 consecutive patients were enrolled. The median age was 65 [56-71] years, 85% of patients were male, 72% had cardiovascular risk factors, 17% had a history of cardiovascular disease, and 60% were taking concomitant cardiovascular medications. Before treatment with ICI, 11% patients had surgery, 57% received chemotherapy, and 26% thoracic radiation (table 1). The median time since the beginning of ICI was 222 [19-1033] days, with the median number of cycles received being 13 [6.5-23.5]. CMR identified some degree of myocardial injury in 35 (66%) patients (table 2). Decreased left ventricular ejection fraction (LVEF) was

Table 1
Clinical characteristics

	All participants (N = 53)	No myocardial injury (n = 18)	Some degree of myocardial injury (n = 35)	*P*
Age at start ICI, y	65 [56-71]	64 [54-70]	67 [59-73]	.358
Male sex	45 (85)	16 (89)	29 (83)	.701
Cardiovascular risk factors				
Hypertension	15 (28)	6 (33)	9 (26)	.834
Diabetes mellitus	7 (13)	1 (6)	6 (17)	.401
Dyslipidaemia	25 (47)	7 (39)	18 (51)	.562
Smoker	7 (13)	5 (28)	2 (6)	.037
COPD	13 (25)	5 (28)	8 (23)	.743
Prior coronary artery disease	3 (6)	1 (6)	2 (6)	.999
Prior stroke	1 (2)	1 (6)	1 (3)	.340
Prior pulmonary embolism	2 (4)	1 (6)	1 (3)	.416
Prior peripheral artery disease	4 (8)	1 (6)	3 (9)	.999
Prior atrial fibrillation	2 (4)	0	2 (6)	.799
Cardiological treatment prior ICI				
Beta-blocker	8 (15)	1 (6)	7 (20)	.240
ACE inhibitor or ARB	12 (23)	5 (28)	7 (20)	.730
Calcium antagonist	4 (7)	1 (6)	3 (9)	.999
Statin	21 (40)	7 (39)	14 (40)	.999
Aspirin or/and ticagrelor	8 (15)	2 (11)	6 (17)	.864
Anticoagulants	5 (10)	2 (11)	3 (9)	.212
Antidiabetics	7 (13)	1 (6)	6 (17)	.126
Primary cancer type				.272
Nonsmall lung cancer				
Squamous	12 (23)	3 (17)	9 (26)	
Nonsquamous	18 (34)	8 (44)	10 (29)	
Not otherwise specified	9 (17)	4 (22)	5 (14)	
Renal cell cancer	6 (11)	0	6 (17)	
Melanoma	4 (7)	3 (17)	1 (3)	
Urothelial cancer	2 (4)	0	2 (6)	
Head and neck cancer	1 (2)	0	1 (3)	
Endometrial cancer	1 (2)	0	1 (3)	
Prior treatment to ICI				
Surgery	6 (11)	3 (17)	3 (9)	.378
Chemotherapy[a]	30 (57)	9 (50)	21 (60)	.487
Cisplatin	25 (47)	8 (44)	17 (49)	.776
Pemetrexed	7 (13)	4 (22)	3 (9)	.165
5FU/capecitabine	3 (6)	1 (6)	2 (6)	.981
Gemcitabin	3 (6)	0	3 (9)	.201
Taxane	17 (32)	5 (28)	12 (34)	.631
Vinca alcaloids	5 (9)	1 (6)	4 (11)	.488
Somatulin	1 (2)	0	1 (3)	.469
Etoposide	1 (2)	0	1 (3)	.469
Tyrosine kinase inhibitors[b]	6 (11)	1 (6)	5 (14)	.464
Immunotherapy[c]	1 (2)	1 (6)	0	.291
Thoracic radiation	14 (26)	6 (33)	8 (23)	.705
Immunotherapy regimen				.765
Anti-PD1	48 (91)	16 (89)	32 (91)	
Anti-PDL1	5 (9)	2 (11)	3 (9)	
Laboratory measures				
Troponin T, pg/mL	1010 [624-1696]	834 [522-1238]	1071 [726-1713]	.125
NT-proBNP, pg/mL	186 [70-510]	113 [62-415]	197 [84-719]	.512
Glomerular filtration rate, mL/min x 1.73 m^2	79 [60-89]	87 [74-90]	77 [58-85]	.046

5FU, 5 fluorouracil; ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; ICI, immune checkpoint inhibitor; NT-proBNP, N-terminal probrain natriuretic peptide.
Values are expressed as No. (%) or median [interquartile range].
[a] Chemotherapy agents consisted of, in decreasing frequency: carboplatin, pemetrexed, etoposide, cisplatin, capecitabine, 5FU, gemcitabine, somatuline and vinca alcaloids.
[b] Vascular endothelial growth factor inhibitors and tyrosine kinase inhibitors agents consisted of, in decreasing frequency: Sunitinib, pazopanib and cabozantinib.
[c] Previous inmunotherapy consisted on interferon.

Table 2
CMR features

	All participants (N = 53)	No myocardial injury (n = 18)	Some degree of myocardial injury (n = 35)	*P*
LV end-diastolic indexed volume, mL/m²	65 [57-75]	60 [57-73]	65 [57-75]	.487
LV end-systolic indexed volume, mL/m²	23 [19-28]	22 [20-28]	25 [19-29]	.618
Indexed LV mass, g/m²	58 [51-66]	54 [49-65]	59 [52-69]	.272
LV ejection fraction, %	63 [57-66]	63 [59-65]	64 [55-69]	1.000
LV ejection fraction dysfunction, %	10 (19)	0	10 (29)	.011
Wall regional motion abnormalities	8 (15)	0	8 (23)	.776
Global myocardial T_2-relaxation time, msec	56 [52-62]	55 [51-58]	57 [52-63]	.078
Global native myocardial T_1 relaxation time, msec	1005 [965-1035]	1000 [959-1031]	1010 [970-1041]	.260
Global T_1-ECV, %	27 [25-29]	26 [25-29]	27 [25-30]	.425
Any LGE	11 (21)	0	10 (31)	.068
Subendocardial or transmural	6 (11)	0	6 (17)	
Midmyocardial	3 (6)	0	3 (8)	
Subepicardial	2 (4)	0	2 (6)	
Main CMR criteria for myocarditis				
Increase in myocardial T_2-relaxation time	12 (23)	0	12 (34)	.005
T_2-weighted hyperintensity	1 (2)	0	1(3)	1.000
Increase in native myocardial T_1-relaxation time	7 (13)	0	7 (20)	.081
Increase in T_1-extracellular volume	6 (11)	0	6 (19)	.159
T_1-late gadolinium enhancement	10 (19)	0	10 (31)	.068

CMR, cardiac magnetic resonance; LV, left ventricular; ECV, extracellular volume. Values are presented as No. (%) or median [interquartile range].

present in 10 (19%) patients (8 with LVEF between 35% to 55% and 2 with LVEF < 35%), with 3 cases due to myocardial infarction, 2 cases due to aortic regurgitation, and 5 cases without LGE. In total, LGE was present in 11 (21%) patients, with subendocardial or transmural LGE in 6 (11%), subepicardial LGE in 2 (4%), and midwall LGE in 3 (6%) patients. Active myocarditis, fulfilling Lake Louise criteria, was observed in 7 (13%) patients. In patients with myocarditis, compared with those without, values of T_2 mapping (65 ms [63-77] vs 55 ms [51-59]); $P = .005$) were significantly higher, with no differences between both groups on native T_1 mapping (1086 ms [1012-1125] vs 998 ms [959-1032]; $P = .081$) or extracellular volume (34% [29-37] vs 26% [25-28]; $P = .159$). LGE was identified in 3 (43%) of 7 patients with myocarditis criteria and in 8 of 46 (17%) without ($P = .075$). In addition, we found no differences in the presence of regional wall motion abnormalities (14% vs 15%; $P = .937$) between patients with and without myocarditis-like criteria. Finally, we observed mild pericardial effusion in 4 (7%) patients, all without myocarditis. No other complications were detected.

Myocardial injury is common in patients receiving ICI treatment and is not exclusively due to the development of active myocarditis. CMR can frequently reveal occult coronary artery disease, myocarditis-like pathology or other myocardial injury due to (as in our cohort) valvulopathy.[5] In this single-center experience, myocardial injury corresponding to myocarditis-like pathology was observed in 13% of the CMR studies with an additional 11% of patients showing CMR findings consistent with ischemic etiology. The finding of unknown valvular heart disease such as aortic regurgitation could be due to the previous radiotherapy received[6] or could be a casual finding present before the start of ICI. Since CMR is the noninvasive modality most suited to identify the presence, type, and extent of myocardial injury, it should be used to monitor patients receiving ICI treatment to detect pathology occurring before the appearance of regional wall motion abnormalities or LV dysfunction. A longitudinal design, instead of the current cross-sectional design, would be preferable in future studies, in which CMR information before the start of immunotherapy will better establish sequences of cardiac injury.

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AUTHORS' CONTRIBUTIONS

B. Barrio-Collado, A. Martin-Garcia, P.L. Sanchez and Juan Jesús Cruz conceived and designed the study; R. Eiros and A. Martin-Garcia contributed to the literature search; B. Barrio-Collado, A. Martin-Garcia, R. Eiros and C. Sanchez-Pablo contributed by clinically evaluating the participants; B. Barrio-Collado and R. Eiros performed clinical data collection; R. Eiros and P.L. Sanchez contributed to data analysis and interpretation; R. Eiros and P.L. Sanchez contributed to the writing of the report.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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Vector flow mapping analysis in a child with a cardiac resynchronization device

Análisis mediante mapeo de flujo vectorial en un niño con resincronizador cardiaco

To the Editor,

We would like to draw attention to some interesting findings about vortex flow analysis with vector flow mapping in a 14-year-old patient with a triple-chamber epicardial pacemaker, implanted when the child was aged 9 years for intermittent syncopal congenital complete atrioventricular block. The right ventricle (RV) lead and left ventricle (LV) lead were located at the cardiac apex and on the lateral wall, respectively.

Congenital complete atrioventricular block is a rare heart disorder, with an incidence of 1/15 000-20 000 births, that usually requires pacemaker implantation. Although pacemaker implantation has significantly reduced morbidity and mortality in patients with complete atrioventricular block, several studies have

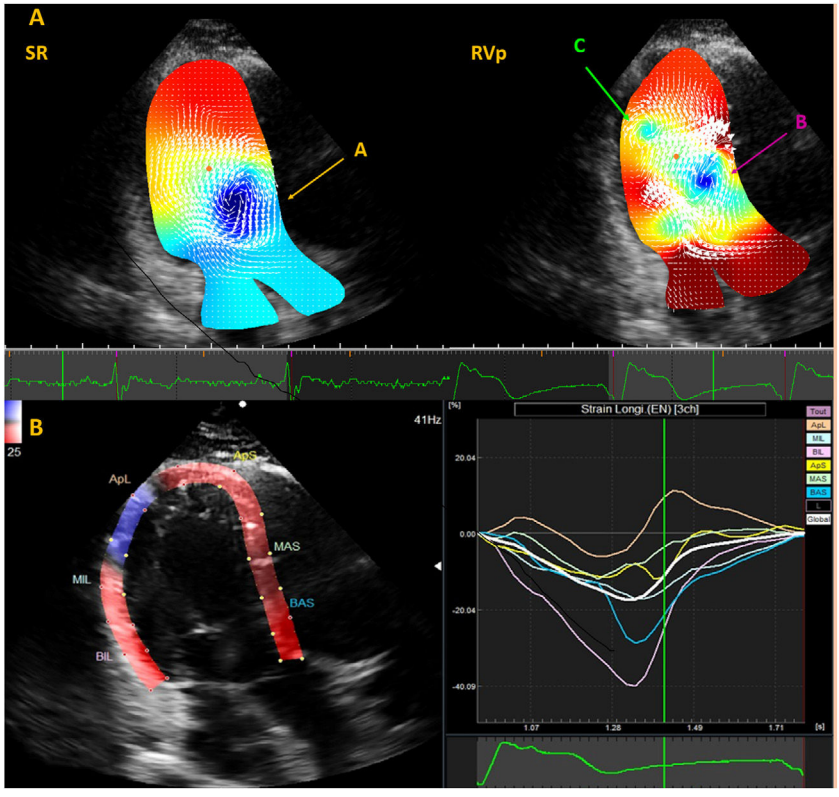

Figure 1. Analysis of vortex formation. A: comparison between SR (left) and RVp (right) during diastole, showing an anterior clockwise vortex (orange arrow, A) during SR and an apical counterclockwise vortex (green arrow, C) in addition to the anterior clockwise vortex (pink arrow, B) during RVp. B: speckle tracking analysis during RVp, showing a prestretch in the apical posterolateral (ApL) segment, as well as an early septal contraction. RVp, right ventricular pacing; SR, sinus rhythm.