

Immune checkpoint inhibitor-related myocarditis: an illustrative case series of applying the updated Cardiovascular Magnetic Resonance Lake Louise Criteria

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Background

Immune checkpoint inhibitors (ICIs) have improved outcomes for many types of cancer. However, ICI therapies are associated with the development of myocarditis, an immune-mediated adverse event associated with a high mortality rate. Therefore, prompt diagnosis and early intervention are of outmost importance. There is limited data on the application of cardiovascular magnetic resonance (CMR)-based modified Lake Louise Criteria (mLLC) with the use of relaxometry techniques for the diagnosis of ICI myocarditis.

Case summary

Four cancer patients undergoing ICI treatment presented with various clinical symptoms and troponin elevation to emergency/ambulatory clinics within 10–21 days after ICI initiation. On the suspicion of possible ICI-related myocarditis all patients underwent CMR within a few days after admission. Applying mLLC including relaxometry techniques, all patients met 'non-ischaeamic injury criteria', while 3/4 patients met 'oedema criteria'. In most patients, quantitative mapping revealed substantially increased T1 values, while T2 values were only mildly increased or normal. In two patients with follow-up, CMR demonstrated improvement in findings after immunosuppressive treatment. However, there was only limited agreement between the degree of high-sensitive troponin levels and T1/T2 levels.

Discussion

The application of mLLC with T1/T2 mapping appears useful in the CMR diagnosis of acute ICI myocarditis with non-ischaeamic myocardial injury criteria being the most common finding. The sensitivity of native T1 appears higher than T2 mapping in the acute diagnosis as well as in the assessment of treatment response. As troponin elevations may persist for some time with ICI myocarditis, CMR may represent an alternate strategy to monitor treatment response.

Keywords

Magnetic resonance imaging • Myocarditis • Immune checkpoint inhibitors • Left ventricular function • Case series

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Learning points

- Application of modified Lake Louise Criteria appears useful in the cardiovascular magnetic resonance diagnosis of immune checkpoint inhibitor (ICI) myocarditis across a wide variety of clinical presentations/lab results.
- Non-ischaemic myocardial injury may be the most common finding in patients with acute ICI myocarditis.

Introduction

Immune checkpoint inhibitor (ICI)-related myocarditis is a rare (incidence ~1%) immune-related adverse event (irAE).¹ While uncommon, it is associated with major adverse cardiac events in 20–40% of patients.^{1–3} Cardiovascular magnetic resonance (CMR) is the reference imaging test for the diagnosis of myocarditis.⁴ The CMR approach has evolved since publication of the initial Lake Louise Criteria (LLC) with added quantitative approaches (e.g. T1/T2 mapping) resulting in improved diagnostic accuracy.^{5–9} Recent work has demonstrated that in patients with ICI myocarditis, abnormalities in T2-weighted imaging and late gadolinium enhancement (LGE) were absent in >50% of the patients.³ However, the diagnostic value of modified LLC (mLLC) for ICI myocarditis is unknown. With the rapidly increasing use of ICI cancer therapy, there is a need for improved diagnosis of ICI myocarditis. Given the non-invasive nature of CMR, its application is attractive.

In this case series, we illustrate four representative patients who underwent CMR with suspected ICI-related myocarditis; Research ethics board (REB) approval and written informed consent was obtained (all patients deceased). We focus on CMR based mLLC for the diagnosis⁹ through illustrating: (i) the value of multi-parametric and quantitative CMR, (ii) the regionality of the myocardial T1/T2 changes, (iii) the relationship between troponin levels and CMR changes, and (iv) the potential role of CMR in assessing recurrence/treatment responsiveness.

Case presentation

Case 1

A 52-year-old male with metastatic melanoma undergoing therapy with an anti-cell death ligand 1 (anti-PD-L1) antibody in combination with an investigational ICI presented with fatigue and marked shortness of breath on exertion 21 days from the first treatment. Oxygen saturation (room air) was 96% and his electrocardiogram (ECG) was normal. Chest computed tomography (CT) identified mild bilateral pleural effusions, compression atelectasis, new moderate pericardial effusion, and minor pulmonary oedema.

The high-sensitivity troponin I (hsTnI) was 19 ng/L [upper limit of normal (ULN) 26 ng/L, pre-treatment <2 ng/L], creatine Kinase (CK) was 14 (ULN ≤240 U/L), and brain natrium peptide (BNP) was 108 pg/mL (ULN <99.9 pg/mL). Echocardiography showed preserved left ventricular ejection fraction (LVEF) without signs of tamponade. CMR (1.5 T) was performed 2 days after symptom onset (hsTnI at time of CMR: 5 ng/L, CK <10 U/L, and BNP 110 pg/mL). The exam demonstrated focal signal abnormalities on T2-weighted imaging (Figure 1A), and regional variability in T2 values on T2 mapping [T2-prep steady state free-precession (SSFP)] slightly exceeding ULN (up to 58 ms; local normal: 45–57 ms) (Figure 1B). Native T1-mapping [modified Look-Locker inversion recovery (MOLLI); 5(3)3] demonstrated significantly elevated T1 (segmental: up to 1153 ms; local normal: 953–1053 ms) (Figure 1C). Post-contrast (0.15 mmol/kg) imaging, identified minor areas of LGE (Figure 1D and E). Cine SSFP demonstrated a moderate pericardial and pleural effusion (Figure 1F) with

Timeline

Age/sex	Cancer diagnosis	Time post-immune checkpoint inhibitor initiation	Symptoms	hsTnI [high-sensitivity troponin I (local upper limit of normal, ULN: 26 ng/L)]	BNP [brain natrium peptide (local ULN: <99.9 pg/mL)]	Treatment	Remarks	
Case 1 52/male	Melanoma (metastatic)	Day 21 (Presentation)	Fatigue, shortness of breath on exertion	19 ng/L	108 pg/mL		endomyocardial biopsy (EMB) confirmation	
		Day 23 (cardiovascular magnetic resonance, CMR)		5 ng/L	110 pg/mL	2 mg/kg IV methylprednisolone (mPRED) (3 days) 150 mg prednisone (PRED)/day		
		Day 37		99 ng/L				
		Day 38 (repeat CMR)				1 g IV mPRED (5 days)	Improved EF, reduced effusions	
		Day 44 (discharge)			36 ng/L			
		Day 100 (readmission)			109 ng/L		2 mg/kg PRED/day	

Continued

Continued

Age/sex	Cancer diagnosis	Time post-immune checkpoint inhibitor initiation	Symptoms	hsTnI [high-sensitivity troponin I (local upper limit of normal, ULN: 26 ng/L)]	BNP [brain natrium peptide (local ULN: <99.9 pg/mL)]	Treatment	Remarks
Case 2 60/female	Gynecological Cancer (metastatic)	Day 13 (presentation)	Generalized weakness, muscle pain, fatigue	168 ng/L	Not available	1 mg/kg IV mPRED	Coronary angiogram due to rapidly rising hsTnI EMB confirmation
		Day 15 (CMR)		12 122 ng/L	Not available	1 g IV mPRED (2 days) 2 mg/kg PRED/day	
		Day 26 (discharge)		26 ng/L			
Case 3 49/female	Breast cancer (metastatic)	Day 13 (presentation)	Fever, cough	1829 ng/L	405 pg/mL		EMB declined
		Day 23 (CMR)		855 ng/L	Not available	50 mg PRED/day 1 g mofetil mycophenolate (MMF) 2× day	
		Day 25 (discharge)					
Case 4 74/female	Gynecological cancer (metastatic)	Day 17 (presentation)	General pain, progressive muscle weakness, diplopia	3744 ng/L	26 pg/mL		Coronary angiogram excluded coronary artery disease No EMB
		Day 20 (CMR)		4717 ng/L	Not available	1 g IV mPRED (5 days) 50–70 mg PRED/day 750 mg MMF 2× day	
		Day 30 (discharge)					

normal LVEF (56%). Due to discrepancy between troponin levels and CMR findings, the patient underwent endomyocardial biopsy (EMB), which demonstrated interstitial infiltration by macrophages (CD68) and lymphocytes (CD3/CD8) consistent with myocarditis. The patient was treated with corticosteroids (3 days of 2 mg/kg IV methylprednisolone, followed by a taper of oral prednisone starting at 150 mg/day). Despite treatment, hsTnI levels rose peaking at 99 ng/L on Day 16 after symptoms onset. Repeat CMR confirmed initial findings with stable LGE, improvement in LVEF (59%), and reduction in pericardial and pleural effusions. However, given the rising troponin, patient received 5 days of 1 g of methylprednisolone followed by oral prednisone (2 mg/kg) and was discharged with declining hsTnI levels (36 ng/L).

On tapering oral steroids, he was readmitted 79 days after initial presentation (hsTnI 84–109 ng/L); repeat CMR confirmed stable LGE/focal elevated signal on T2-weighted imaging, normal LVEF (67%), resolution of pericardial effusion, and no elevation in myocardial T1/T2 values. Patient received 350 mg infliximab IV and mofetil mycophenolate (MMF) (1000 mg twice a day), while oral prednisone was continued; ICI therapy was never re-started.

Patient had routine follow-up CMR 6 months after the initial diagnosis demonstrating normalization of T2 values (slice 50 ± 4 ms, max: 51 ms) and a prominent interval reduction in T1 (slice: 1044 ± 68 ms) (Figure 2A and B). Focal LGE changes were stable (Figure 2C and D); ECG and hsTnI values (9 ng/L) were normal.

Despite initial discordant hsTnI values and CMR findings, T1 mapping demonstrated significant abnormalities that resolved with aggressive immunosuppression. The main T1/T2 criteria of mLLC for diagnosis of myocarditis were met (Table 1).⁹ Nevertheless, there was a larger increase in myocardial T1 vs. T2 values compared to normal ranges.

Case 2

A 60-year-old female undergoing combination treatment including anti-PD-L1 antibody in the setting of metastatic gynaecological cancer presented 13 days after first administration complaining of generalized weakness, muscle pain, and fatigue. She had a fever, elevated creatinine kinase (CK) (2260 U/L), and hsTnI (168 ng/L). Due to progressive hsTnI elevation (peak: 15 463 ng/L), despite normal ECG, a coronary angiogram was performed ruling out obstructive coronary artery disease (CAD).

Cardiovascular magnetic resonance (1.5 T) was performed 2 days after initial presentation and post coronary angiogram. At the time of CMR, hsTnI was 12 122 ng/L and the first methylprednisolone dose (1 mg/kg) was administered 48 h prior. Cardiovascular magnetic resonance identified focal signal elevation on T2-weighted imaging (Figure 3A) and T2 values were increased (up to 58 ms) (Figure 3B). Corresponding T1 was increased (up to 1115 ms) with regional variation (Figure 3C). LGE imaging demonstrated multiple high intensity subepicardial to mid-myocardial areas of enhancement (Figure 3D and

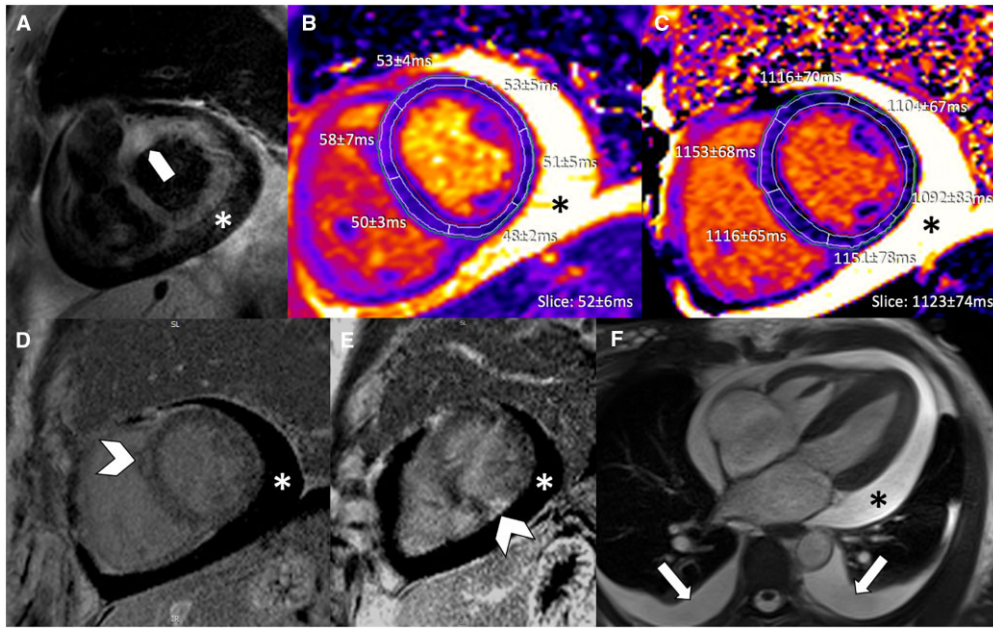


Figure 1 Initial multi-contrast cardiovascular magnetic resonance image panel in patient with immune checkpoint inhibitor myocarditis (high-sensitivity troponin I at time of cardiovascular magnetic resonance: 5 ng/L). (A) T2-weighted SPAIR, (B) T2 mapping, (C) native T1 mapping, (D, E) phase sensitive inversion recovery late gadolinium enhancement imaging, and (F) cine steady state free precession. Focal basal myocardial oedema (block arrow), focal late gadolinium enhancement (arrowheads), moderate pericardial effusion (*), and mild bilateral pleural effusion (arrows) are demonstrated.

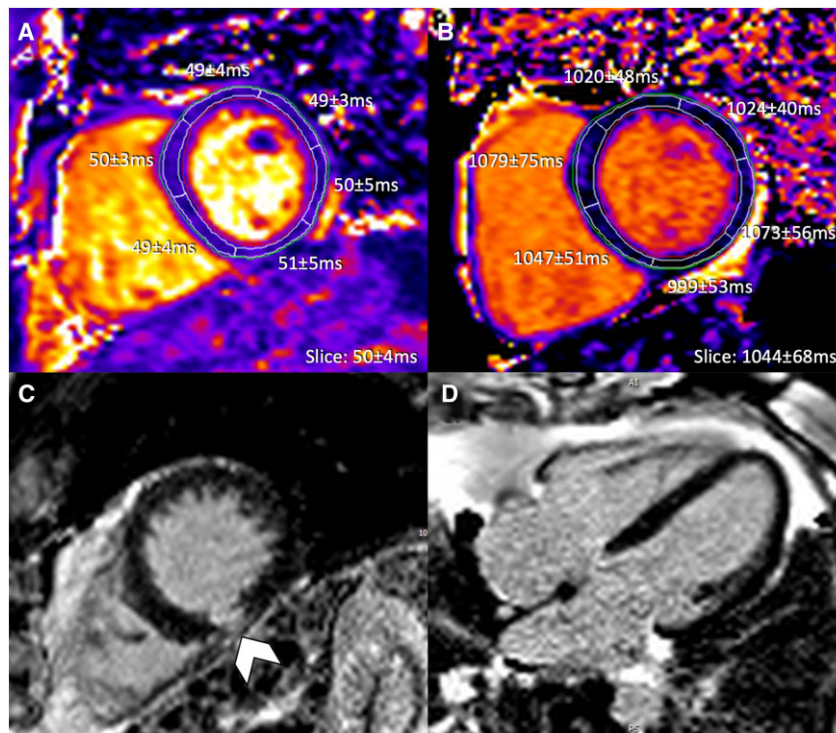


Figure 2 Repeat cardiovascular magnetic resonance of same patient as displayed in [Figure 1](#) after 6 months of steroid treatment demonstrating (A) T2 mapping, (B) native T1 mapping, and (C, D) phase sensitive inversion recovery late gadolinium enhancement imaging. Pericardial effusion has resolved, residual focal late gadolinium enhancement demonstrated (arrowhead).

Table 1 Summary of presence/absence of main and supportive criteria according to modified Lake Louise Criteria in presented cases.

	Main criteria		Supportive criteria	
	T2-based imaging (oedema) ^a	T1-based imaging (non-isoaemic injury)	Pericarditis	Systolic dysfunction
Case 1	Regional high T2 signal intensity + Increase in T2 relaxation time +	Increase in native T1 relaxation time ^b + LGE with non-isoaemic distribution +	Pericardial effusion (cine images) + Abnormal LGE, T2w or T1w imaging -	Regional wall motion abnormalities - Global hypokinesia -
Case 2	Regional high T2 signal intensity + Increase in T2 relaxation time +	Increase in native T1 relaxation time ^b + LGE with non-isoaemic distribution +	Pericardial effusion (cine images) + Abnormal LGE, T2w or T1w imaging +	Regional wall motion abnormalities - Global hypokinesia -
Case 3	Regional high T2 signal intensity - Increase in T2 relaxation time -	Increase in native T1 relaxation time and ECV + LGE with non-isoaemic distribution +	Pericardial effusion (cine images) + Abnormal LGE, T2w or T1w imaging +	Regional wall motion abnormalities - Global hypokinesia -
Case 4	Regional high T2 signal intensity + Increase in T2 relaxation time -	Increase in native T1 relaxation time ^b + LGE with non-isoaemic distribution -	Pericardial effusion (cine images) - Abnormal LGE, T2w or T1w imaging -	Regional wall motion abnormalities - Global hypokinesia -
Total	Cases with ↑T2 SI 3/4 Cases with ↑T2 time 2/4	Cases with non-isoaemic LGE 3/4 Cases with ↑ native T1 4/4	Cases with pericardial effusion 3/4 Abnormal LGE, T2w or T1w imaging 2/4	Cases with abnormal regional wall motion 0/4 Cases with global hypokinesia 0/4

^aPerformed imaging protocols did not include assessment of T2 SI ratios.

^bNo post-contrast T1 mapping performed for ECV calculation.

E). The LVEF was 56% and there was a trivial pericardial effusion (Figure 3F). Endomyocardial biopsy demonstrated interstitial infiltrates of CD3 positive T-lymphocytes. After biopsy confirmation, she received 2 days of 1 g IV methylprednisolone followed by oral prednisone (2 mg/kg daily). She was discharged 13 days after initial presentation with an hsTnI of 26 ng/L. Immune checkpoint inhibitor therapy was never re-started. Follow-up CMR (3 T) performed 8.5 months after initial presentation revealed improvement in LGE and signal elevation on T2-weighted imaging (Figure 4A and B); respective T1/T2 values were normal (Figure 4C and D).

In this patient, CMR demonstrated a clear increase in T1 albeit a smaller increase in T2 in the context of high hsTnI and acute ICI myocarditis.

Case 3

A 49-year-old female with metastatic triple-negative breast cancer presented 13 days after initiation treatment with anti-PD-L1 antibody with fever and cough. A non-contrast-enhanced chest CT excluded underlying pneumonia/-onitis. After fluctuating symptoms and initiation of antibiotics and anti-inflammatory therapy, she was admitted to intensive care unit 6 days later with a clinical picture suspicious of haemophagocytic lymphohistiocytosis/cytokine release syndrome. Her ECG showed small QRS complexes and non-specific ST-T wave abnormalities; hsTnI was 1829 ng/L; BNP was 405 pg/mL. Repeat CT excluded pulmonary embolism but demonstrated bilateral pleural effusions and diffuse pulmonary oedema. Due to the suspicion of myocarditis, MMF was added and titrated to 1000 mg twice daily.

After clinical stabilization (Day 10 post-admission), the patient underwent CMR (1.5T) for further evaluation (hsTnI at CMR: 855 ng/L). While pre-contrast T2-weighted imaging showed no abnormal signal intensity (Figure 5A) and global and regional T2 times (max. 56 ms) were upper normal (Figure 5B), native T1 values reached as high as 1192 ms (Figure 5C). In post-contrast imaging, subtle sub-epicardial basal inferior-lateral wall LGE with adjacent pericardial enhancement (Figure 5D) was identified. The extracellular volume fraction ranged from 33.2% to 40.2% (local volunteer cohort: 19.2–29.2%). Cine SSFP confirmed a small pericardial effusion on two-chamber view (Figure 5E) and small bilateral pleural effusions (Figure 5F); with LVEF of 56%.

Despite lack of EMB confirmation (patient declined), ICI myocarditis was diagnosed based on European Society of Cardiology (ESC) criteria.¹⁰ Patient was discharged on oral prednisone (50 mg/day) and MMF 1000 mg twice per day. Immune checkpoint inhibitor therapy was never re-started. Again, in this patient, we note significantly elevated T1 values with upper normal T2 values in the setting of pre-treatment with steroids 10 days before CMR. In fact, in this case, T2-based criteria for diagnosis of myocarditis according to mLLC were not met (Table 1).

Case 4

A 74-year-old female with metastatic gynaecological cancer presented 17 days after initiation of anti-PD-L1 antibody therapy complaining of general pain, progressive muscle weakness and diplopia. Her hsTnI was 3744 ng/L, BNP 26 pg/mL, and the ECG demonstrated new ST-segment depression in inferolateral leads thus meeting ESC

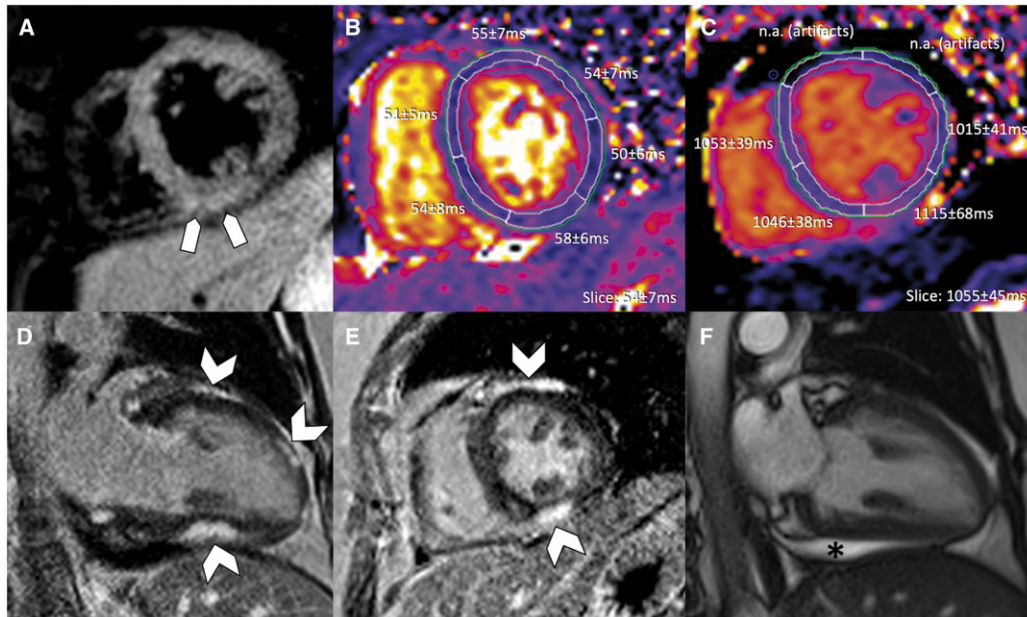


Figure 3 Myocarditis from anti-PD-L1 treatment with a very high-sensitivity troponin I level (12 122 ng/L at time of cardiovascular magnetic resonance). (A) T2-weighted SPAIR, (B) T2 mapping, (C) native T1 mapping, (D, E) phase sensitive inversion recovery late gadolinium enhancement imaging, and (F) cine steady state free precession. Focal mid-ventricular inferior/inferoseptal myocardial oedema (block arrows), high signal intensity focal sub-epicardial late gadolinium enhancement (arrowheads), and mild pericardial effusion (*) are demonstrated.

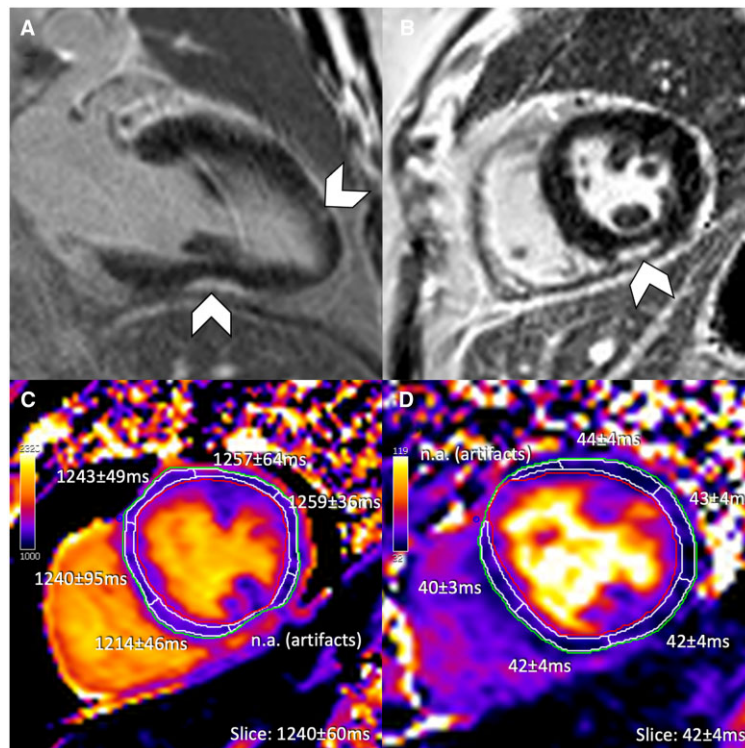


Figure 4 Follow-up cardiovascular magnetic resonance of same patient as displayed in Figure 3, 8.5 months after initial presentation and steroid treatment demonstrating (A, B) phase sensitive inversion recovery late gadolinium enhancement, (C) native T1 mapping, and (D) T2 mapping. Small pericardial effusion has resolved, and focal late gadolinium enhancement has improved (arrowheads). Segmental and global T1 and T2 values are within local normal ranges (Note: Follow-up performed at 3 T).

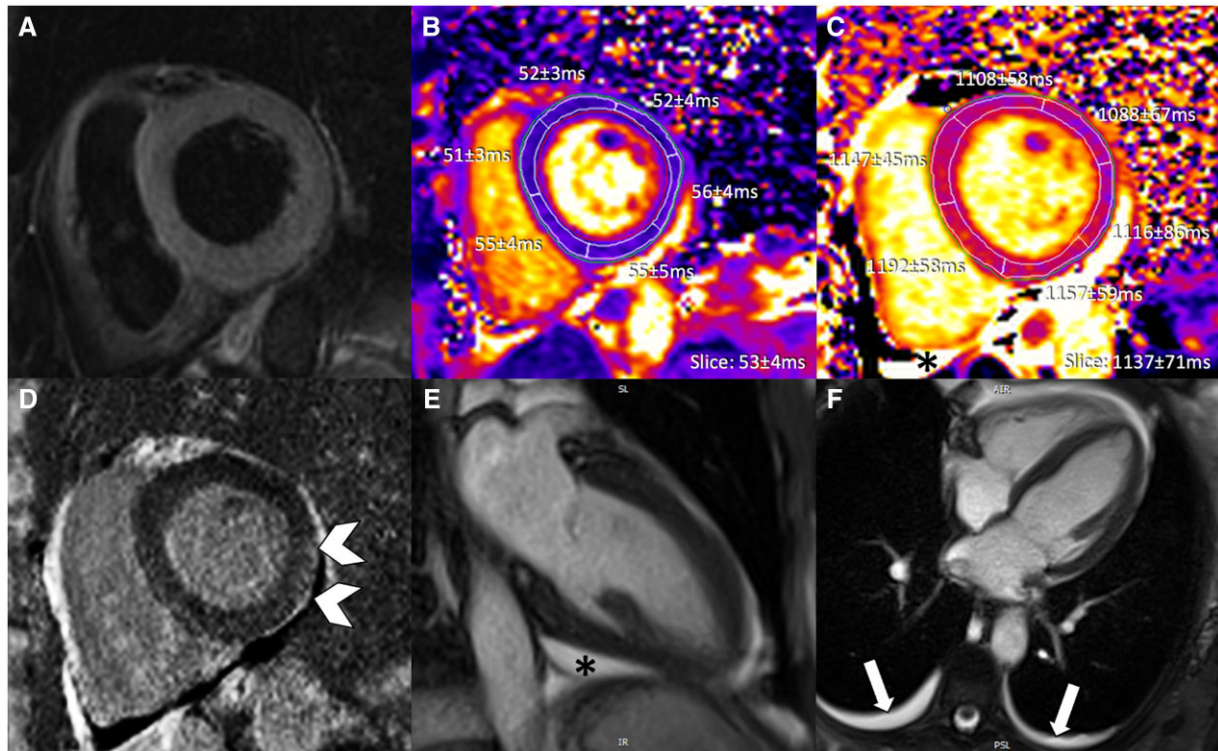


Figure 5 Anti-PD-L1 antibody-induced myocarditis and pericarditis with moderate to high elevations in high-sensitivity troponin I. (855 ng/L at time of cardiovascular magnetic resonance). (A) T2-weighted SPAIR, (B) T2 mapping, (C) native T1 mapping, (D) phase sensitive inversion recovery late gadolinium enhancement imaging, and (E, F) cine steady state free precession. Very subtle subepicardial late gadolinium enhancement with additional pericardial enhancement (arrowheads), mild pericardial effusion (*), and mild pleural effusions are demonstrated.

clinical criteria for myocarditis¹⁰; coronary angiogram excluded obstructive CAD.

For confirmation of possible myocarditis, CMR (1.5 T) was performed 3 days after initial presentation (hsTnI at time of CMR: 4717 ng/L) with patient having been on 1 g methylprednisolone for 3 days prior.

T2-weighted imaging demonstrated subtle high signal intensity within the interventricular septum (Figure 6A) suggesting myocardial oedema. Despite significant regional heterogeneity of T1/T2 values (global and segmental) at various slice positions, overall values were within normal ranges (Figure 6B and C). The highest/lowest segmental T2 and T1 times were 54/49 ms and 1023/938 ms, respectively. There was mild mid-wall LGE at the basal anterior septum (Figure 6F) while LVEF was normal (58%).

After 5 g of methylprednisolone, the patient was switched to oral prednisone (50 mg/day). Due to persistent hsTnI elevation (607 ng/L), she was also started on MMF 750 mg twice per day with further increase of oral prednisone to 70 mg/day. She was discharged 13 days after initial presentation and ICI therapy was never re-started.

While conventional qualitative CMR techniques delineated changes that fulfilled mLLC, both quantitative approaches (T1/T2 mapping) failed to identify regional elevations despite high hsTnI elevation. This case illustrates the fact that using site-based normal

ranges, some patients with clinical diagnosis of myocarditis¹⁰ may not show abnormal quantitative T1/T2 on a single applied slice.

Discussion

This case series illustrates the important CMR contribution in the assessment of ICI myocarditis. Using the mLLC, all patients met the 'non-ischaemic myocardial injury criteria' and 75% met the 'oedema criteria' (Table 1). Although LGE was present in all patients with elevated T1 values, the degree of elevation was higher than expected given the subtle LGE in some of the cases (e.g. Patient 3). While T2 criteria were met in three cases based on elevated signal intensities on T2-weighted techniques, T2 values were only mildly elevated in two cases (Table 1). Our findings are consistent with a recent meta-analysis in patients with non-ICI myocarditis demonstrating the potential advantage of T1 over T2 mapping, especially with respect to sensitivity and negative predictive value.¹¹ While the increase in T1 may illustrate a combined effect of progressive myocardial fibrosis in addition to acute injury, the lack of significant T2 elevations may reflect the fact that imaging was performed after initiation of steroid therapy and a potential greater impact of steroid therapy on T2 changes. Interestingly, there was significant heterogeneity in segmental T1/T2 values in our patients possibly

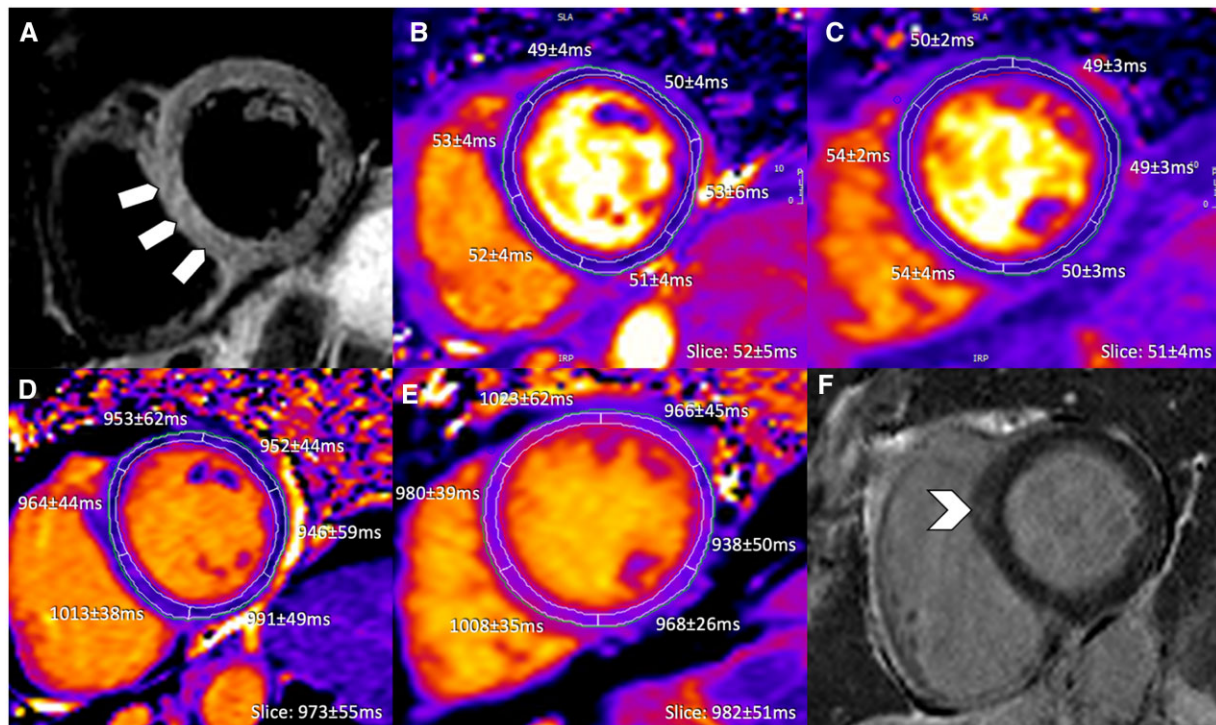


Figure 6 Anti-PD-L1 therapy-mediated myocarditis with moderate increase in high-sensitivity troponin I (4717 ng/L at time of cardiovascular magnetic resonance). (A) T2-weighted SPAIR, (B, C) T2 mapping, (D, E) native T1 mapping, and (F) phase sensitive inversion recovery late gadolinium enhancement imaging. Diffuse septal oedema (block arrows) and only subtle focal septal late gadolinium enhancement (arrowhead) visualized.

reflecting heterogeneous myocardial injury pattern in ICI myocarditis that warrants further exploration. It must be noted that T1/T2 mapping coverage is commonly limited (single slice in 3/4 of our cases) and does not match left ventricular coverage of LGE/T2-weighted imaging thus possibly missing regional abnormalities.

Pericardial abnormalities supportive mLLC were identified in most of our patients; however, none demonstrated LVEF/regional wall motion abnormality. Therefore, this case series, along with published studies,^{1,3} suggests that an optimal CMR protocol should include functional imaging, T2-weighted and LGE imaging (ventricular coverage) enhanced by T1/T2 mapping (ideally with ventricular coverage).

Interestingly, troponin levels at the time of CMR varied widely amongst our patients; significantly elevated T1 values were identified at normal/moderately elevated hsTn levels (5 ng/L, 855 ng/L; ULN <26 ng/L) with normal T1 in a patient with significantly elevated hsTnI (4717 ng/L; Patient 4). This suggests that markedly elevated hsTnI levels alone may not be a useful gatekeeper to CMR in patients with ICI myocarditis, but decision should be driven by clinical suspicion.

Two cases also demonstrate the responsiveness of CMR tissue characteristics to immunosuppression. While native T1 was still elevated despite CMR being performed within 3–10 days after initiation of corticosteroid therapy, prolonged treatment resulted in reduced T1/T2 values. As troponin elevations can persist in some patients with ICI myocarditis,¹² CMR may also be an alternate strategy to monitor treatment response and to decide timing of stopping immunosuppression.

In conclusion, mLLC appear useful in the diagnosis of ICI myocarditis across a wide variety of clinical and laboratory findings. Our case

series suggests that non-ischæmic myocardial injury may be the most common sign in patients with acute ICI myocarditis with greater sensitivity of native T1 compared to T2 mapping; T1 mapping may also have a role in identifying treatment response.

Notice: Only ICI drug classes are provided without specific drug names as per clinical study institutional policy.

Lead author biography



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special emphasis on quantitative methods, quantitative tissue characterization, and innovative accelerated imaging methods. Other aspects involve cardiovascular MRI at high-field strength (3 T) and clinical applications of novel contrast agents. Dr Bernd J. Wintersperger has >180 PubMed listed publications.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case series including images and associated text has been obtained from the patients' next-of-kin in line with COPE guidance.

Conflict of interest: B.J.W. has received research support and speaker's honorarium from Siemens Healthineers and is consulting for Bayer AG. B.J.W. is an inventor of the IG fitting method owned by UHN (US10314548B2). T.G.N. has received grant support from Astra Zeneca. P.T. has received consultancy fees from Amgen, Takeda, and BI. The University Health Network (UHN) has a master research agreement (MRA) with Siemens Healthineers.

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