Subclinical myocardial involvement in a cohort of patients with antisynthetase syndrome

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Abstract

Objective

There is an increasing interest in knowing whether patients with antisynthetase syndrome (ASSD) may have silent myocardial interstitial involvement. Mapping techniques in cardiac magnetic resonance (CMR) can detect subclinical myocardial involvement. The purpose of this study was to identify alterations in multiparametric CMR in ASSD patients without overt cardiac involvement.

Methods

Patients diagnosed with ASSD underwent a CMR along with the standard clinical workup, investigation of specific and associated myositis antibodies, and high-resolution chest CT. The CMR protocol includes routine morphologic, functional, and late gadolinium enhancement sequences in standard cardiac planes, as well as native T1 and T2 mapping sequences and extracellular volume (ECV) calculation.

Results

Twenty-five patients were included in this study (56% women; median age 56.3 years). Three patients were considered in the acute phase at the time of inclusion. Eight patients (32%) showed pathological findings in CMR (6 stable disease, 2 acute phase). Elevated T1, T2 and ECV mapping values were found in 20% (5/25), 17% (4/25) and 24% (6/25) of the group, respectively. Two patients in the acute phase had increased values of both T2 and ECV.

Conclusion

Subclinical myocardial involvement in ASSD is not rare (32%) although its clinical significance is uncertain. Myocardial oedema (T2) was the most frequent finding, followed by increased T1 and/or ECV values likely signalling interstitial fibrosis. Of note, patients in the acute phase showed elevated T2 values.

Key words

myositis, antisynthetase syndrome, multiparametric magnetic resonance imaging, cardiac involvement, myocarditis

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Introduction

Antisynthetase syndrome (ASSD) is considered an autoimmune disease characterised by myositis, interstitial lung disease, non-erosive arthritis, mechanical hands, Raynaud's phenomenon, fever and, occasionally, skin rashes. Autoantibodies found in ASSD patients target aminoacyl-transfer RNA synthetases (ARS), a family of cytoplasmic enzymes responsible for the loading of specific amino acids to their cognate tRNA. In humans, 20 different ARS can be found, one for each amino acid of the genetic code. To date, 10 anti-ARS autoantibodies have been reported in myositis: anti-Jo1 (anti-histidyl), the most common, anti-PL7 (anti-analyl), anti-PL12 (anti-threonyl), anti-OJ (anti-isoleucyl), anti-EJ (anti-glycyl), anti-KS (anti-asparaginyl), anti-Ha (or anti-YRS, anti-threonyl), anti-Zo (anti-phenylalanyl) and two recently described against cysteinil-tRNA-synthetase (CARS1) and valyl-tRNA-synthetase (VRS) (1-4).

It is widely known that rheumatic diseases have an increased risk of cardiovascular diseases due to different factors such as genetic compound, traditional cardiovascular risk factors and chronic inflammation (5). The prototype of chronic inflammatory condition is rheumatoid arthritis, but several studies have been published showing an increased risk of cardiovascular events in other rheumatic diseases such as ankylosing spondylitis, psoriatic arthritis, lupus, or systemic sclerosis (5-8). Recent studies have shown that patients with IIM, including ASSD, may develop cardiac involvement, either inflammatory (myocarditis) or ischaemic (coronary artery disease) (5, 9-11). Interestingly, in systemic sclerosis, an autoimmune disease that shares some clinical features with IIM, subclinical cardiac involvement has been described and, subsequently, asymptomatic at early stages of the disease (12), eagerly requesting for new techniques and protocols for its detection.

Although generally asymptomatic and clinically silent for years, cardiac involvement confers higher mortality risk, due to arrhythmia, systolic dysfunction, or heart failure. To evaluate inflammatory cardiac involvement, different biomarkers and techniques have been proposed; enzyme testing, ECG, transthoracic echocardiography (TTE), cardiac magnetic resonance (CMR) and SPECT myocardial perfusion. It seems that troponin T is more related with muscle disease activity whereas high-sensitivity cardiac troponin I correlates with cardiac involvement. ECG findings are non-specific. Despite normal ejection fraction in most IIM patients, the most common finding in TTE found in a systematic review was abnormal ejection fraction, a non-specific finding that could be due to other cardiovascular risk factors (13, 14).

Cardiac magnetic resonance (CMR) has emerged as a non-invasive technique for detailed assessment of cardiac structure, function, and tissue characterisation. CMR parameters include late gadolinium enhancement (LGE), T1 and T2 mapping and extracellular volume (ECV). The LGE technique relies on the visual detection of the retained gadolinium-based contrast agent in the larger extracellular volume fraction of damaged myocardium and require healthy myocardium with a normal extracellular volume and a nulled MR signal. Therefore, it is a suboptimal technique for diffuse myocardial fibrosis since it can only detect focal and macroscopic myocardial abnormalities. In the absence of visible LGE, mapping techniques can detect and quantify subclinical and early diffuse myocardial involvement. T1 mapping and ECV can reflect several alterations in myocardial tissue composition, including oedema, necrosis, and fibrosis, while T2 is a specific marker of myocardial oedema. The ECV is scanner- and site-independent but requires contrast-enhanced T1 mapping in combination with native T1 mapping for its calculation. T1, T2 and ECV mapping allow for more sensitive identification and quantification of diffuse myocardial fibrosis and oedema than LGE (15-17).

Our aim was to describe the presence of myocardial involvement assessed by new CMR techniques in a cohort of patients with antisynthetase syndrome in daily clinical practice.

Table I. Patient characteristics.

ID	Gender	Anti-ARS	Ro52	Acute stage	Treatment	Years of disease	Total cumulative steroid dosage (mg)	ILD	T1 (ms)	T2 (ms)	ECV (%)	LGE
1	Male	Jo1	Yes	No	PDN MMF RTX	9.6	18250	Yes	-	-	-	-
2	Male	Jo1	Yes	No	PDN MMF	3.4	11362.5	Yes	1023	45	26	**Yes**
3	Female	Jo1	Yes	No	PDN MMF RTX LEF	4.6	9000	Yes	**1057**	49	28	No
4	Male	Jo1	Yes	No	PDN LEF	4.3	8212.5	Yes	998	45	24	No
5	Female	Jo1	Yes	No	PDN MTX RTX	4.9	13425	Yes	**1052**	**51**	29	**Yes**
6	Male	PL12	No	No	PFN TAC	13.7	22050	Yes	1011	42	22	No
7	Female	Jo1	Yes	No	PDN TAC RTX CYA	28.6	35075	Yes	1048	56	28	No
8	Male	Jo1	Yes	No	PDN IVIG CYA	12.5	26612.5	No	996	45	22	No
9	Male	Jo1	Yes	No	PDN	8.5	18662.5	Yes	973	42	22	No
10	Male	Jo1	Yes	Yes	PDN MMF IVIG	1.9	14250	Yes	**1060**	**60**	**32**	No
11	Male	EJ	Yes	Yes	PDN TAC RTX IVIG	2.4	14410.5	Yes	1023	**58**	**33**	No
12	Female	Jo1	Yes	No	PDN TAC	2.5	7450	Yes	1005	49	27	No
13	Female	PL12	Yes	No	PDN MMF RTX NIN	2.2	11775	Yes	999	47	22	No
14	Female	Jo1	No	No	PDN TAC CYC	1.9	7715.5	Yes	1025	49	26	No
15	Female	Jo1	No	No	PDN MMF MTX LEF RTX IVIG	1.7	36650	Yes	992	46	26	No
16	Female	Jo1	Yes	No	PDN TAC	2.7	6387.5	Yes	1004	47	27	No
17	Female	PL7	Yes	No	PDN MMF RTX	3.5	5475	Yes	992	49	29	No
18	Female	Jo1	Yes	No	PDN CYA	17.2	41062.5	Yes	**1060**	**52**	**32**	No
19	Female	Jo1	Yes	No	PDN	37.6	13425	Yes	**1060**	**55**	**32**	No
20	Male	Jo1	Yes	No	PDN MMF LEF IVIG CYA	13.0	25050	Yes	962	46	25	No
21	Female	Jo1	Yes	No	PDN MMF IVIG CYC	28.3	73650	Yes	1043	49	27	No
22	Female	Jo1	Yes	No	PDN MTX	6.7	8625	Yes	975	47	-	-
23	Male	Jo1	No	No	-	5.3	0	Yes	1015	44	24	No
24	Male	PL12	Yes	No	PDN TAC	4.6	2737.5	Yes	966	44	26	No
25	Male	OJ	Yes	Yes	PDN MMF TAC IVIG	0.1	1540	Yes	1017	47	29	No
26	Female	PL12	Yes	No	PDN AZA	19.2	2877.5	Yes	1023	45	24	No

In bold, CMR pathological values.
ID: patients' identification; ARS: aminoacyl-transfer RNA synthetases; ILD: interstitial lung disease; ECV: extracellular volume; LGE: late gadolinium enhancement; PDN: prednisone; MMF: mycophenolate; RTX: rituximab; LEF: leflunomide; MTX: methotrexate; TAC: tacrolimus; IVIG: intravenous immunoglobulins; CYA: cyclosporine A; CYC: cyclophosphamide; NIN: nintedanib; AZA: azathioprine.

Methods

This is a retrospective cross-sectional study of a cohort of patients with ASSD visited in a single Myositis Unit.

Study population

From January 2020 to July 2022, we consecutively included all adult patients (>18 years of age at IIM onset) previously diagnosed with ASSD attending the Myositis Unit at the Vall d'Hebron University Hospital, Barcelona, Spain. All patients fulfilled a score of at least 90% ("definite IIM") calculated using the International Myositis Classification Criteria (18) or Connors criteria for ASSD (19). All patients underwent a CMR along with the standard clinical workup, investigation of specific and associated myositis antibodies, high-resolution chest CT (HRCT) and the standard of care with corticoids and immunosuppressive drugs (Table I). Cumulative steroid dosage was calculated as described in Montero-Pastor *et al*. (20). Two of the patients were enrolled in the study at the time of diagnosis, with CMR performed during the first month. Additionally, another patient was included at the onset of a disease flare-up, presenting with fever, weakness, elevated CK levels, and joint symptoms. These three patients were considered as the acute phase subgroup. The remaining 22 patients were deemed stable, as there were no reported disease flare-ups or medication changes in the 6 months leading up to their inclusion. This study was approved by the Clinical Research Ethics Committee of the Vall d'Hebron Research Institute.

CMR acquisition protocol

All CMR studies were performed at a Siemens Magnetom Avanto Fit 1.5 Tesla (Siemens Healthineers, Erlangen, Germany) according to current clinical recommendations (21). Briefly, the protocol included localisers, retrospectively gated steady state free precession cine images (SSFP) in vertical and horizontal long-, and cardiac short-axes (repetition time: 3.1 ms, echo time: 2.3 ms, flip angle: 83°, FOV 350-400 mm), T1 and T2 images in horizontal long-axis and basal, midventricular and apical short-axis (T1: single slice breath hold, modified Look-Locker inversion-recovery (MOLLI) sequences, repetition time: 2.7 ms, echo time 1,1 ms, 5(3)3 grouping, flip angle 35º, FOV 300-360 mm; T2: T2-prepared steady state free precession sequences, repetition time: 2.5 ms, echo time 1,1 ms, 3 echos, flip angle 70º, FOV 300–360 mm), a and late gadolinium enhancement (spoiled gradient-echo sequence, repetition time 9.8 ms, echo time 4.6 ms, inversion time 280–240 ms, flip angle 20º, FOV 230–340 mm) was acquired in long- and short- axes 7 minutes after intravenous injection of 0,15 mmol/Kg of a gadolinium-based contrast media agent (Gadovist, Bayer

Healthcare, Leverkusen, Germany), followed by postcontrast T1 mapping images (with 4(1)3(1)2 grouping).

CMR image analysis

The CMR analysis was performed according to current recommendations (22) using a commercially available solution (Syngo.via, version VB60; Siemens Healthineers, Erlangen, Germany). We performed functional analysis for biventricular volumes and function. For all mapping analyses, a single region of interest (ROI) was drawn in the central part of the septal myocardium on mid-ventricular short axis images. ECV was derived from the native and postcontrast T1 values with hematocrit correction according to the standard method (22). Finally, location and extent of LGE was recorded using the 17-segment model. Upper scanner-specific reference values for T1, T2 and ECV were 1050 ms, 50 ms and 30%, respectively.

Statistical analysis

Continuous variables are presented as mean (SD) or median (inter quartile range). Categorical variables are presented as counts (percentage). The paired sample t-test or Wilcoxon matched-pairs sign-rank test were used to compare continuous variables, as appropriate. Fisher's exact test was used to compare categorical variables. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using STATA 16.1 (StataCorp, College Station, Texas, USA).

Results

Population characteristics

We initially included twenty-six patients in this study, but one did not complete the CMR test because of claustrophobia. Thus, twenty-five patients were included in this study (56% women; median age 56.9 years). The overall population had a median disease evolution time from diagnosis of 4,6 years (IQR 2.5–13.0). Three patients were in the acute phase at the time of inclusion (12%). All patients included presented MSA, with an autoimmune profile as described in Table I. Ninety-six percent of patients associated interstitial lung disease as reported by a thoracic radiologist on HRCT. Only 9 of the 25 patients included (36%) had cardiovascular risk factors (smoking habits, hypertension, diabetes, or dyslipidaemia) (Table II). None of the study patients had developed any type of clinically symptomatic cardiac event in terms of ischaemic cardiopathy or heart failure.

Table II. Population characteristics.

Variable	Value
Sex, n women (%)	14 (56%)
Age, median (IQR), years	56.9 (49.8-67.5)
CV risk factor, n (%)	9 (36%)
Smoking habits, n (%)	
Smoker	1 (4%)
Former smoker	7 (28%)
Non-smoker	17 (68%)
Years of disease, median (IQR), years	4.6 (2.5-13.0)
ILD, n (%)	24 (96%)
MSA	
Jo1, n (%)	18 (72%)
PL7, n (%)	1 (4%)
PL12, n (%)	4 (16%)
OJ, n (%)	1 (4%)
EJ, n (%)	1 (4%)
Ro52, n (%)	21 (84%)
Acute stage, n (%)	3 (12%)

CV: cardiovascular; IQR: interquartile range; MSA: myositis specific antibodies; ILD: interstitial lung disease.

Table III. CMR values.

Variable	Value
IVS thickness, mean (SD), mm	10.4 (2.2)
LV volume, mean (SD), mL	120.9 (34.0)
LV function, mean (SD), %	63.6 (5.4)
RV volume, mean (SD), mL	131.8 (36.8)
RV function, mean (SD), %	59.5 (5.5)
Cardiac involvement, n (%)	8 (32%)
LGE (n=24), n (%)	2 (8.3%)
T1, mean (SD), ms	1015.1 (30.4)
Elevated T1 (>1050 ms), n (%)	5 (20%)
ECV (n=24), mean (SD), %	26.8 (3.4)
Elevated ECV (>30%), n (%)	4 (16.7%)
T2, mean (SD), ms	48.4 (4.7)
Elevated T2 (>50 ms), n (%)	6 (24%)

CMR: cardiac magnetic resonance; IVS: interventricular septum; LV: left ventricle; RV: right ventricle; LGE: Late gadolinium enhancement; ECV: extracellular volume.

CMR imaging

ECV was not available in a single patient with renal injury in which contrast media was not injected.

The rest of the population successfully underwent the CMR protocol. Elevated T1, T2 and ECV mapping values were found in 20% (5/25), 17% (4/25) and 24% (6/25) of the group, respectively. Two stable stage patients had a single elevated parameter (one T1, the other T2). One stable patient had elevated T1 and T2 values, two patients had elevated T2 and ECV values, and another two had elevation of all three parameters. Two acute phase patients showed myocardial involvement, with two (T2 and ECV) and all three parameters elevated, respectively. All patients with elevated ECV values also had T2 elevation. Of note, a single patient in the stable stage had isolated non-ischaemic LGE. The other stable patient found with LGE had also elevated T1 and T2. Overall, multiparametric involvement was more frequent (5/7, 71,4%) than elevation of a single mapping parameter (2/7, 28.6%). Overall mean CMR values are shown in Table III.

We did not identify segmental contraction alterations or ischaemic LGE patterns suggestive of ischaemic injury. Nevertheless, two patients with stable disease showed a mild reduction of left ventricular ejection fraction (both 55%) due to global hypokinesia. Additionally, two patients with stable disease presented a mild non-ischaemic intramyocardial septal LGE. No differences were found among CMR values according to the disease duration or cumulative steroid dosage.

Four patients showed a thick interventricular septum (range: 12–16 mm), and the patient with the thickest septum was clinically interpreted as a case of hypertensive myocardiopathy. Finally, eight patients (32%) presented additional cardiac findings, such as mild aortic dilatation, mitral regurgitation and myocardial hyper trabeculation.

Acute phase CMR

There were no differences in baseline characteristics between patients with stable or acute phase disease (Table IV). Regarding CMR, statistical differences were found in both left and right ventricular volumes that disappeared after adjustment by total body surface area. Non-ischaemic LGE was not present in any of the three patients in the acute phase.

Although no significant differences were found between acute and stable disease stages in T1 mapping values (mean values and proportion of elevated values), both parameters were higher in the acute phase. Mean T2 (55ms *vs*. 47.5ms, $p<0.05$) and ECV values (31.3% *vs*. 26.1%, $p<0.05$) were higher in the acute phase since both parameters were simultaneously elevated in 67% of the group (2/3) (Table IV, Fig. 1).

Table IV. Population characteristics and CMR values in stable disease and early stage.

Variable	Stable disease (n=22)	Acute phase (n=3)	*p*-value (univariate)
Age, median (IQR), years	56.9 (50.8-67.5)	49.7 (48.1-70.5)	0.723
CV risk factor, n (%)	8 (36.4)	1 (33.3)	1.000
Years of disease, median (IQR), years	5.1 (3.4-13.7)	1.9 (0.1-2.44)	**0.010**
ILD, n (%)	21 (95.5%)	3 (100%)	1.000
Ro52, n (%)	18 (81.8)	3 (100%)	1.000
IVS thickness, mean (SD), mm	10.3 (0.5)	11.0 (1.0)	0.604
LV volume, mean (SD), mL	116.0 (7.0)	157.0 (6.8)	**0.047**
LV volume/TBSA, mean (SD), mL/m^2	65.4 (4.2)	80.0 (1.7)	0.218
LV function, mean (SD), %	64.1 (1.1)	59.3 (3.0)	0.151
RV volume, mean (SD), mL	125.2 (7.3)	179.7 (7.4)	0.013
RV volume/TBSA, mean (SD), mL/m^2	70.6 (4.2)	91.7 (2.0)	0.085
RV function, mean (SD), %	59.2 (1.0)	61.3 (7.7)	0.547
LGE (n=24), n (%)	2 (9.5%)	0 (0%)	1.000
T1, mean (SD), ms	1012.7 (6.6)	1033.3 (13.4)	0.279
Elevated T1 (>1050 ms), n (%)	4 (18.2%)	1 (33.3%)	0.504
ECV (n=24), mean (SD), %	26.1 (0.7)	31,3 (1.2)	**0.008**
Elevated ECV (>30%), n (%)	2 (9.5%)	2 (66.7%)	0.061
T2, mean (SD), ms	47.5 (0.8)	55 (4.0)	**0.007**
Elevated T2 (>50 ms), n (%)	4 (18.2%)	2 (66.7%)	0.133

In bold: statistically significant
CMR: cardiac magnetic resonance; CV: cardiovascular; ILD: interstitial lung disease; IQR: interquartile range; IVS: interventricular septum; LV: left ventricle; RV: right ventricle; LGE: late gadolinium enhancement; ECV: extracellular volume.

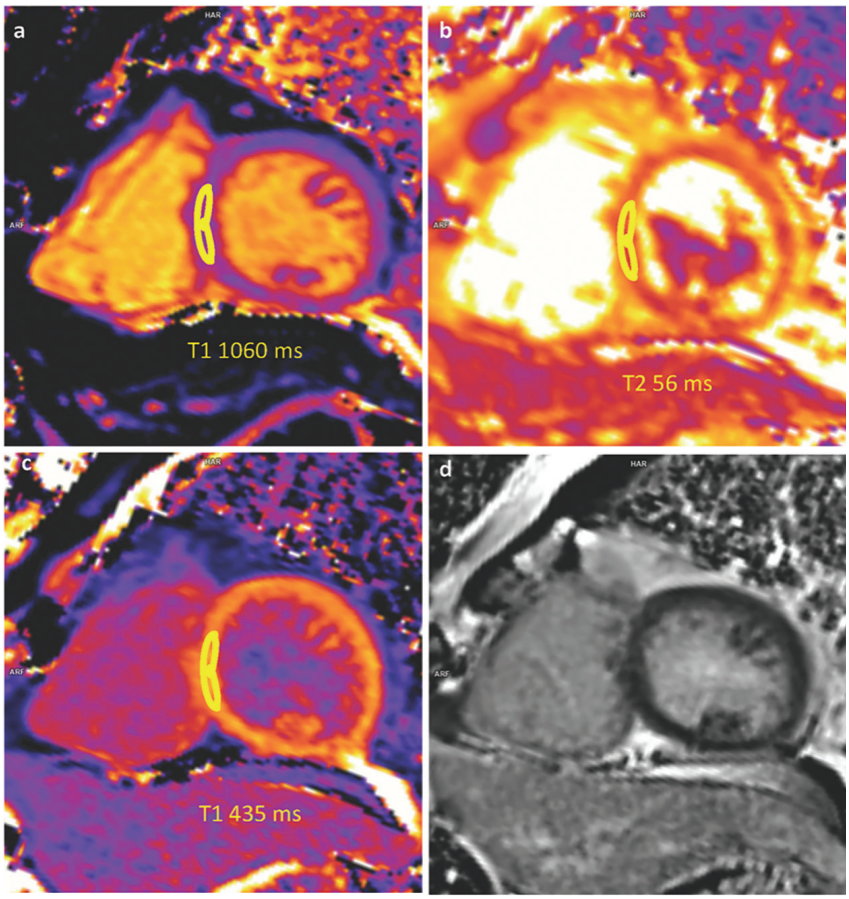

Fig. 1. Midventricular short axis native T1 (**a**) and T2 (**b**) maps of an early-stage patient. The yellow region of interest in the septum showed increased values of 1060 ms and 56 ms, respectively, attributable to myocardial oedema. Changes in T1 values in the septal region and the blood pool in the postcontrast T1 map (**c**) allowed calculation of a pathologic extracellular volume fraction (32%). There were no macroscopic regional alterations in the late enhancement image (**d**).

Discussion

In this article, we present the results of cardiac involvement detected by CMR in patients diagnosed with ASSD in our daily clinical practice. Our study shows that subclinical myocardial involvement in patients with ASSD is not uncommon. CMR mapping techniques detect left ventricular myocardial oedema in patients with ASSD. Of note, two acute patients (2/3, 66.7%) showed myocardial oedema, while two stable patients (2/6, 33.3%) showed no oedema but an isolated non-ischaemic LGE and T1 mapping elevation respectively, suggesting focal or interstitial fibrosis as a possible sequel from silent myocardial oedema at earlier stages.

Until recently, myocardial involvement has not been associated with ASSD. A study from the French National Registry found that 3.4% of patients diagnosed with ASSD develop myocarditis, most revealed by acute or subacute heart failure and half of them requiring intensive care. Similar results were reported by the researchers from John Hopkins who found myocarditis in less than 1% of IIM patients, being the most frequent phenotype the ASSD, with a bad outcome and an 85% 5-year overall survival (23). However, myocardial involvement in other cohorts or studies on inflammatory myopathy typically remains subclinical (13, 16). Our results are in agreement, since all patients studied were asymptomatic. These differences may be due to differences in the diagnostic strategy. The use of CMR with mapping techniques will be able to detect subclinical myocarditis more frequently. Ethnic characteristics may also require consideration.

Thus, it seems that a double scenario may arise from the reported series and

from our own study: on the one hand some patients develop a severe disease that may end in heart failure or even death, and at the other hand asymptomatic myocardial involvement detected by means of CMR is the main picture. Whether these two scenarios are the different expression of the same process or intensive therapy received by the ASSD patients may account for these differences is currently not known.

In this study we found a total 32% of abnormal results in CMR as an expression of myocardial involvement in ASSD patients. Most of these results are pathological values of T2 mapping with or without elevated T1 and / or ECV, a finding that indicates mild myocardial oedema. Interestingly, it has recently been reported that myocardial oedema may correlate with serological findings such as levels of NT-proBNP but may surprisingly remain inconspicuous at echocardiography, highlighting the importance of CMR in detecting subclinical myocardial involvement in these patients (24, 25).

Another interesting finding is the presence of LGE in some patients. LGE technique is an accurate method to detect focal interstitial alterations including fibrosis with gadolinium-based contrast, and it has significant prognostic implications in non-ischaemic cardiomyopathies (26). In our study we found LGE in two patients considered as stable in terms of disease activity. Of note, a single patient had isolated non-ischaemic LGE, while the other one had also elevated T1 and T2 values. The isolated LGE patient may have only focal sequelae from a previous flare without current inflammation, whereas the latter may have current oedema. Although we have only included 3 patients in the acute phase group, none of them exhibited LGE, which could imply that the fibrosis phase occurs in more advanced stages of the disease. In our cohort, 92% of the patients received corticosteroids with another immunosuppressive drug for disease control. Despite cardiac involvement being silent, the identification of only two patients with LGE could underscore the potential significance of early detection and treatment (27).

Myocardial involvement has also been described in other inflammatory myopathies and autoimmune disorders, with a wide range of clinical manifestations from subclinical involvement to fulminant myocarditis (28-30). In a retrospective study, early myocardial involvement in DM and PM was also detected by CMR (16). Poor outcomes despite intense treatment in IIM patients with clinical myocarditis were observed, potentially reflecting late detection of myocarditis and treatment refractoriness (23). Altered T2 values are found in lupus patients, even at preclinical stage, as in our ASSD cohort. Moreover, these abnormal T2 values normalized after clinical improvement in disease activity, reinforcing the need for early detection and treatment of cardiac involvement (7, 31). In systemic sclerosis (SSc), myocarditis is associated with a poor prognosis, and the use of new CMR techniques, especially T2 mapping, increases diagnostic accuracy for the detection of myocardial inflammation in SSc. Additionally, CMR could distinguish between reversible inflammatory and irreversible fibrotic lesions in SSc patients with active myocarditis (32, 33). Taken all together, there is no doubt that CMR emerges as an early diagnostic tool for myocardial involvement in systemic diseases.

There are several limitations in the present study. First, this is a retrospective study with all data recorded through clinical history, although all the patients have been attended during all these years by the same team of physicians. Lack of prospective analysis has led to the absence of certain clinical data collected at the time of inclusion, such as cardiac enzymes (highly sensitive troponin (hsTNI) or NT-proBNP) or echocardiographic data. The lack of cardiac enzymes data at the time of inclusion has not allowed for establishing a correlation with clinical or image findings. Furthermore, this is a single centre study with a small study population and no control group. A prospective multicentre study with a control group would ensure an increase in the subjects included in the study and allow for a more in-depth investigation of the differences observed in our study.

In conclusion, this study illustrates how subclinical myocardial involvement in ASSD is not uncommon. Although its clinical significance is not clear, other autoimmune diseases reveal that myocardial involvement led to a poor prognosis. Our results may suggest that immunosuppressive therapy, administered for the main manifestations of the disease such as myositis or ILD, may also benefit the patients by pre-emptively treating the interstitial myocarditis that might be present in some cases, preventing its clinical manifestation. Whether CMR should be used to screen and monitor ASSD patients warrants further study.

References

1. LEGA JC, FABIEN N, REYNAUD Q *et al*.: The clinical phenotype associated with myositis-specific and associated autoantibodies: A meta-analysis revisiting the so-called antisynthetase syndrome. *Autoimmun Rev* 2014; 13(9): 883-9. https://doi.org/10.1016/j.autrev.2014.03.004
2. MURO Y, YAMASHITA Y, KOIZUMI H *et al*.: Two novel anti-aminoacyl tRNA synthetase antibodies: Autoantibodies against cysteinyl-tRNA synthetase and valyl-tRNA synthetase. *Autoimmun Rev* 2022; 21(12): 103204. https://doi.org/10.1016/j.autrev.2022.103204
3. VULSTEKE JB, DERUA R, DUBUCQUOI S *et al*.: Mass spectrometry-based identification of new anti-Ly and known antisynthetase autoantibodies. *Ann Rheum Dis* 2023; 82(4): 546-55. https://doi.org/10.1136/ard-2022-222686
4. SASAI T, NAKASHIMA R, SHIRAKASHI M *et al*.: A new autoantibody to valyl transfer RNA synthetase associated with anti-synthetase syndrome. *Rheumatology* (Oxford) 2023; 62(5): e155-7. https://doi.org/10.1093/rheumatology/keac569
5. ORESKA S, STORKANOVA H, PEKACOVA A *et al*.: Cardiovascular risk in myositis patients compared with the general population. *Rheumatology* (Oxford) 2023; kead271. https://doi.org/10.1093/rheumatology/kead271
6. CASTAÑEDA S, MARTÍN-MARTÍNEZ MA, GONZÁLEZ-JUANATEY C *et al*.: Cardiovascular morbidity and associated risk factors in Spanish patients with chronic inflammatory rheumatic diseases attending rheumatology clinics: Baseline data of the CARMA Project. *Semin Arthritis Rheum* 2015; 44(6): 618-26. https://doi.org/10.1016/j.semarthrit.2014.12.002
7. TINCANI A, REBAIOLI CB, TAGLIETTI M, SHOENFELD Y: Heart involvement in systemic lupus erythematosus, anti-phospholipid syndrome and neonatal lupus. *Rheumatology* (Oxford) 2006; 45 Suppl 4: iv8-13. https://doi.org/10.1093/rheumatology/kel308
8. MAVROGENI S, PEPE A, GARGANI L *et al*.: Cardiac inflammation and fibrosis patterns in systemic sclerosis, evaluated by magnetic

resonance imaging: An update. *Semin Arthritis Rheum* 2023; 58: 152126. https://doi.org/10.1016/j.semarthrit.2022.152126
9. DIEVAL C, DELIGNY C, MEYER A *et al*.: Myocarditis in patients with antisynthetase syndrome: Prevalence, presentation, and outcomes. *Medicine* (Baltimore) 2015; 94(26): e798. htpps://doi.org/10.1097/md.0000000000000798
10. BANDEIRA M, DOURADO E, MELO AT *et al*.: Predictors of cardiac involvement in idiopathic inflammatory myopathies. *Front Immunol* 2023; 14: 1146817. https://doi.org/10.3389/fimmu.2023.1146817
11. BARSOTTI S, SAPONARO C, GAGGINI M *et al*.: Cardiometabolic risk and subclinical vascular damage assessment in idiopathic inflammatory myopathies: a challenge for the clinician. *Clin Exp Rheumatol* 2019; 37(6): 1036-43.
12. GALEA N, ROSATO E, GIGANTE A *et al*.: Early myocardial damage and microvascular dysfunction in asymptomatic patients with systemic sclerosis: A cardiovascular magnetic resonance study with cold pressor test. *PLoS One* 2020; 15(12): e0244282. https://doi.org/10.1371/journal.pone.0244282
13. FAIRLEY JL, WICKS I, PETERS S, DAY J: Defining cardiac involvement in idiopathic inflammatory myopathies: a systematic review. *Rheumatology* (Oxford) 2021; 61(1): 103-20. https://doi.org/10.1093/rheumatology/keab573
14. ZHANG H, CHI H, XIE L *et al*.: The use of high-sensitivity cardiac troponin I in assessing cardiac involvement and Disease prognosis in idiopathic inflammatory myopathy. *Adv Rheumatol* 2023; 63(1): 52. https://doi.org/doi: 10.1186/s42358-023-00332-0
15. HAAF P, GARG P, MESSROGHLI DR, BROADBENT DA, GREENWOOD JP, PLEIN S: Cardiac T1 mapping and extracellular volume (ECV) in clinical practice: a comprehensive review. *J Cardiovasc Magn Reson* 2016; 18(1): 89. https://doi.org/10.1186/s12968-016-0308-4
16. FENG C, LIU W, SUN X *et al*.: Myocardial involvement characteristics by cardiac MR imaging in patients with polymyositis and dermatomyositis. *Rheumatology* (Oxford) 2022; 61(2): 572-80. https://doi.org/10.1093/rheumatology/keab271
17. MESSROGHLI DR, MOON JC, FERREIRA VM *et al*.: Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2 and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson* 2017; 19(1): 75. https://doi.org/ 10.1186/s12968-017-0389-8
18. LUNDBERG IE, TJÄRNLUND A, BOTTAI M *et al*.: 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis* 2017; 76(12): 1955-64. https://doi.org/10.1136/annrheumdis-2017-211468
19. CONNORS GR, CHRISTOPHER-STINE L, ODDIS C V, DANOFF SK: Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? *Chest* 2010; 138(6): 1464-74. https://doi.org/10.1378/chest.10-0180
20. MONTERO-PASTOR N, SÁNCHEZ-COSTA JT, GUERRA-RODRÍGUEZ M *et al*.: Development of a web tool to calculate the cumulative dose of glucocorticoids. *Reumatol Clin* 2023; 19(1): 1-5. https://doi.org/10.1016/j.reumae.2022.11.001
21. KRAMER CM, BARKHAUSEN J, BUCCIARELLI-DUCCI C, FLAMM SD, KIM RJ, NAGEL E: Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. *J Cardiovasc Magn Reson* 2020; 22(1): 17. https://doi.org/10.1186/s12968-020-00607-1
22. SCHULZ-MENGER J, BLUEMKE DA, BREMERICH J *et al*.: Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update: Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing. *J Cardiovasc Magn Reson* 2020; 22(1): 19. https://doi.org/10.1186/s12968-020-00610-6
23. CHUNG MP, LOVELL J, KELLY W *et al*.: Myocarditis in patients with idiopathic inflammatory myopathies: clinical presentation and outcomes. *J Rheumatol* 2023; 50(8): 1039-46. https://doi.org/10.3899/jrheum.220989
24. HUANG L, TAO Q, ZHAO P *et al*.: Using multi-parametric quantitative MRI to screen for cardiac involvement in patients with idiopathic inflammatory myopathy. *Sci Rep* 2022; 12(1): 9819. https://doi.org/10.1038/s41598-022-13858-y
25. YU L, SUN J, SUN J *et al*.: Early detection of myocardial involvement by T 1 mapping of cardiac MRI in idiopathic inflammatory myopathy. *J Magn Reson Imaging* 2018; 48(2): 415-22. https://doi.org/10.1002/jmri.25945
26. KURUVILLA S, ADENAW N, KATWAL AB, LIPINSKI MJ, KRAMER CM, SALERNO M: Late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiovascular outcomes in nonischemic cardiomyopathy: A systematic review and meta-analysis. *Circ Cardiovasc Imaging* 2014; 7(2): 250-7. https://doi.org/10.1161/circimaging.113.001144
27. XU Y, SUN J, WAN K *et al*.: Multiparametric cardiovascular magnetic resonance characteristics and dynamic changes in myocardial and skeletal muscles in idiopathic inflammatory cardiomyopathy. *J Cardiovasc Magn Reson* 2020; 22(1): 22. https://doi.org/10.1186/s12968-020-00616-0
28. BRADY S, MELATH S, SCALCO RS, PENN H: Fatal cardiac involvement complicating antisynthetase syndrome. *BMJ Case Rep* 2014; 2014:bcr2014204409. https://doi.org/10.1136/bcr-2014-204409
29. STOUGIANNOS PN, MYTAS DZ, KATSAROS AA *et al*.: Chest pain and ST-segment elevation in a patient with polymyositis: a case report. *Cases J* 2009; 2(1): 84. https://doi.org/10.1186/1757-1626-2-84
30. AZZAM M, AWAD A, ABUGHARBYEH A, KAHALEH B: Myocarditis in connective tissue diseases: an often-overlooked clinical manifestation. *Rheumatol Int* 2023; 43(11): 1983-92. https://doi.org/10.1007/s00296-023-05428-w
31. SINGH JA, WOODARD PK, DÁVILA-ROMÁN VG *et al*.: Cardiac magnetic resonance imaging abnormalities in systemic lupus erythematosus: a preliminary report. *Lupus* 2005; 14(2): 137-44. https://doi.org/10.1191/0961203305lu2050oa
32. DE LUCA G, PALMISANO A, CAMPOCHIARO C *et al*.: Cardiac magnetic resonance in systemic sclerosis myocarditis: the value of T2 mapping to detect myocardial inflammation. *Rheumatology* (Oxford) 2022; 61(11): 4409-19. https://doi.org/10.1093/rheumatology/keac098
33. PANOPOULOS S, MAVROGENI S, VLACHOPOULOS C, SFIKAKIS PP: Cardiac magnetic resonance imaging before and after therapeutic interventions for systemic sclerosis-associated myocarditis. *Rheumatology* (Oxford) 2023; 62(4): 1535-42. https://doi.org/10.1093/rheumatology/keac504