KARDIOLOGIA POLSKA

Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957

Online first
This is a provisional PDF only. Copyedited and fully formatted version will be made available soon

ISSN 0022–9032 e-ISSN 1897–4279

Role of magnetic resonance in the detection of cardiac involvement in patients with newly diagnosed extracardiac sarcoidosis: Single center experience

Authors: Kristyna Kysperska, Petr Kuchynka, Alena Slovakova, Lenka Roblova, Stepan Havranek, Zdenka Fingrova, Jan Habasko, Martin Masek, Lukas Lambert, Lenka Navratova, Tomas Palecek

Article type: Original article

Received: May 15, 2022

Accepted: June 21, 2022

Early publication date: June 27, 2022

Role of magnetic resonance in the detection of cardiac involvement in patients with newly diagnosed extracardiac sarcoidosis: Single center experience

Short title: Cardiac magnetic resonance in detection of cardiac sarcoidosis

Kristyna Kysperska[1], Petr Kuchynka[1], Alena Slovakova[2], Lenka Roblova[1], Stepan Havranek[1], Zdenka Fingrova[1], Jan Habasko[1], Martin Masek[3], Lukas Lambert[3], Lenka Navratova[2], Tomas Palecek[1]

[1]2nd Department of Medicine, Department of Cardiovascular Medicine, 1st Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic
[2]1st Department of Tuberculosis and Respiratory Diseases, 1st Faculty of Medicine and General University Hospital in Prague, Prague, Czech Republic
[3]Department of Radiology, 1st Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic

Correspondence to:
Petr Kuchynka, MD, PhD,
2nd Department of Medicine, Department of Cardiovascular Medicine,
General University Hospital in Prague,
1st Faculty of Medicine, Charles University in Prague,
U Nemocnice 2, 128 08 Prague 2, Czech Republic,
phone: + 42 022 496 26 34,
e-mail: petr.kuchynka@vfn.cz

Conflict of interest: None declared.

WHAT´S NEW?

Our study shows the prevalence of cardiac involvement in patients with newly diagnosed extracardiac sarcoidosis and no symptoms of heart disease.

ABSTRACT

Background: Sarcoidosis is a systemic inflammatory disease of unknown etiology, which can affect almost any organ. Cardiac involvement determines the prognosis of the affected individuals. Its prevalence in patients with extracardiac sarcoidosis with the absence of cardiac symptoms remains unclear. Cardiac magnetic resonance (CMR) provides an excellent diagnostic accuracy in the detection of the heart involvement by sarcoidosis.

Aim: We sought to determine the prevalence of cardiac sarcoidosis in asymptomatic individuals with newly diagnoses extracardiac sarcoidosis using CMR.

Methods: We prospectively evaluated 55 consecutive patients mean (SD) aged 43 (11) years, including 23 women with newly diagnosed extracardiac sarcoidosis who underwent contrast-enhanced CMR and had no symptoms of heart disease. The presence of myocardial late gadolinium enhancement (LGE) of non-ischemic etiology on CMR examination was considered diagnostic for the presence of cardiac sarcoidosis.

Results: In 3 (6%) patients LGE pattern consistent with cardiac sarcoidosis was detected. In all these patients, preserved left ventricular systolic regional a well as global function was present and in none of them the elevation of blood biomarkers of myocardial injury or overload was found.

Conclusions: Our study suggests that the prevalence of cardiac involvement in patients with newly diagnosed extracardiac sarcoidosis and no symptoms of heart disease is very low as assesed by CMR. However, CMR may be considered as a part of routine evaluation of patients with extracardiac sarcoidosis due its higher diagnostic yield in comparison with echocardiography and ECG, respectively.

Key words: cardiac sarcoidosis, cardiac magnetic resonance, late gadolinium enhancement

INTRODUCTION

Sarcoidosis is a systemic inflammatory disease of unknown origin characterized by epitheloid non-necrosing granulomas, which can affect almost any organ. The most common form of the disease represents pulmonary sarcoidosis. However, the presence of cardiac involvement determines the prognosis of the affected individuals. The heart may be involved as a part of the systemic disease

or in an isolated form. Approximately only 5% of patients with the systemic disease have symptoms reflecting the presence of cardiac sarcoidosis [1]. However, the prevalence of heart involvement seems to be more frequent and present in about 25% of patients with systemic sarcoidosis based on autopsy studies [2]. Nevertheless, the frequence of cardiac involvement in alive subjects diagnosed primarily with extracardiac sarcoidosis remains unclear.

Cardiac sarcoidosis may remain asymptomatic or present as dilated or less frequently restrictive cardiomyopathy with symptoms of heart failure, or in the form of a number of types of arrhythmias. Conduction system disorders, especially atrioventricular blocks, and ventricular arrhythmias are of great clinical importance. Furthermore, these life-threatening arrhythmias may be the first manifestation of the disease and lead to sudden cardiac death [3]. Echocardiography is typically used as a first-line method for the detection of cardiac sarcoidosis. However, its sensitivity is low for detection of early stages of the disease. Cardiac magnetic resonance (CMR) has an excellent diagnostic accuracy in the diagnosis of cardiac sarcoidosis including its subclinical forms [4]. Therefore, we aimed to prospectively assess the presence of cardiac involvement using contrast-enhanced CMR in patients with newly diagnosed extracardiac sarcoidosis and no symptoms of heart disease.

METHODS

In this prospective study, we included 55 consecutive patients with no symptoms of heart disease who were referred between August 2015 and November 2021 to our institution for evaluation of the presence of cardiac sarcoidosis. In all of them, the extracardiac form of sarcoidosis was confirmed within the 12 months. The diagnosis of extracardiac sarcoidosis was based on the positive histology characterized by the presence of epitheloid, non-caseating, non-necrotizing granulomas with varying degrees of lymphocytic inflammation.

The diagnostic evaluation included physical examination, assessment of heart failure symptoms according to the New York Heart Association (NYHA) classification, standard 12 lead electrocardiogram (ECG), 24 hour ECG Holter monitoring, transthoracic echocardiography, blood analysis of biomarkers of myocardial injury and overload, creatinine and serum levels of angiotensin converting enzyme (sACE), and performing CMR.

Transthoracic echocardiography imaging was performed using the GE Vivid 9 or GE Vivid E95 system (GE Healthcare, Chicago, Illinois, USA) and all measurements were done according to the current recommendations of ASE/EACVI [5].

CMR imaging was performed using 1.5 T system Philips Achieva (Philips Healthcare, Eindhoven, The Netherlands). Our protocol included a series of steady-state free precession images in the vertical, horizontal, short axis view, and four-chamber view. The sequence parameters were echo time (TE) 1.46 ms, repetition time (TR) 2.9 ms, flip angle 60 degrees, matrix 204 × 192, field of view (FOV) 320 to 440 mm with phase FOV 0.75 to 1.0-, and 8-mm slice thickness without any interslice gap. Left ventricular (LV) end-diastolic and end-systolic volumes, LV ejection fraction, right ventricular end-diastolic and end-systolic volumes, right ventricular ejection fraction, and cardiac output were analysed. The presence of myocardial edema was evaluated on T2-weighted spectrally selective inversion recovery (SPIR) images. Late gadolinium enhancement (LGE) images were obtained between 5 to 15 minutes after intravenous administration of 0.2 mmol/kg gadoderate meglumine (Dotarem®, Guerbet, France) with segmented inversion recovery fast gradient echo sequences (TE, 1.19 ms; TR, 3.7 ms, flip angle 15 degrees, matrix 209 × 164, FOV 310 mm). The presence of myocardial LGE of non-ischemic etiology on CMR examination was considered diagnostic for the presence of cardiac sarcoidosis as stated in Heart Rhythm Society 2014 Criteria for the Diagnosis of Cardiac Sarcoidosis.

Signed informed consent was obtained from all patients in a format standardized by our institution. The study conforms to the principles outlined in the Declaration of Helsinki.

Statistical analysis

Data are expressed as mean and standard deviation (SD) or median and interquartile range, or as number and percentage of subjects. The normality of data was tested with Shapiro–Wilk test. All analyses were performed using the STATISTICA version 12 software (Statsoft, Inc., Tulsa, OK, US).

RESULTS

The baseline characteristics of the study population are summarized in Table 1. The study cohort consisted of 55 subjects, 23 (42%) were women. The mean age of the patients was 43 (11) years.

Fifty four (98%) patients had pulmonary sarcoidosis, and 34 (62%) patients had multiple organ involvement.

The elevated values of natriuretic peptides (brain natriuretic peptide BNP or N terminal pro-BNP) were found in 4 patients. In all subjects, normal values of troponin I were present. None of the patients had renal insufficiency. sACE levels were increased in 17 (31%).

The 12-lead ECG and 24-hour Holter ECG monitoring data are presented in Table 2. All patients were in sinus rhythm. The first-degree atrioventricular block (AV block) was found in 2 (4%) patients and second-degree AV block Wenckebach type was detected in other 2 (4%) patients. None of the individuals had second-degree AV block Mobitz type or third-degree AV block. Sustained or nonsustained ventricular tachycardia or a significant number of premature ventricle extrasystoles during ECG Holter monitoring were not documented in any subject.

In patients who were subsequently diagnosed with CMR signs of cardiac sarcoidosis, no ECG changes including conduction defects or any significant arrhythmia on Holter ECG monitoring were detected.

Echocardiographic and CMR data are shown in Tables 3 and 4, respectively. The LV was not dilated in any subject based on either echocardiographic or CMR measurements. The right ventricle was of a borderline size in one patient. None of the patients had reduced right or LV global systolic function and no regional wall motion abnormality was observed as well. In any patient, moderate or severe valvulopathy was not found. The values of estimated pulmonary artery systolic pressure were within the normal range in all individuals. A small pericardial effusion was found in 6 patients (11%). LGE of the pericardium was found in none of these 6 patients. Myocardial edema was not present in any patient on CMR examination. In 3 patients (6%), non-ischemic pattern of LGE was found, always involving basal segments of the LV. In more detail, isolated midmyocardial LGE in the basal segment of the interventricular septum was present in one subject, and in two individuals midmyocardial LGE in the interventricular septum together with subepicardial LGE in lateral LV wall were seen (Figure 1). One of these patients had very small pericardial effusion. The sACE level was increased in one subject with LGE positivity. In all LGE positive patients, the levels of cardiac biomarkers were within the normal range.

DISCUSSION

CMR represents currently the preferred non-invasive method for the initial evaluation of patients with suspected cardiac sarcoidosis [6]. Its major advantage in comparison with the endomyocardial biopsy relies on the fact that its sensitivity for detection of cardiac sarcoidosis is reported to be 90%–100% [7, 8] and the sensitivity of the endomyocardial biopsy is only about 25% [9]. The presence of myocardial involvement based on the CMR study is traditionally based on the proof of LGE of non-ischemic etiology found in subepicardial or midmyocardial segments of the LV walls, often involving basal LV segments including interventricular septum [10].

Based on the so far published studies using CMR in patients with known extracardiac sarcoidosis, the presence of myocardial involvement varies between 20% and 35% [11–14]. In our study, we detected clinically probable cardiac sarcoidosis based on the presence of LGE in only 6% of the study cohort. This lower prevalence could be explained by the fact that we screened patients with newly diagnosed extracardiac sarcoidosis who did not have any cardiac symptoms including those that are suggestive of cardiac sarcoidosis such as syncope, light-headedness, palpitations, or chest pain. In all the above-mentioned studies, the authors performed screening in mixed cohorts of individuals regarding the presence or absence of cardiac symptoms. On the other hand, our results are in concordance with a recently published study by Panovsky et al. [15]. These authors screened only patients without known cardiovascular diseases and no cardiac symptoms, respectively, and detected the possible myocardial involvement based on the presence of LGE in 7% of their study population. In contrast to our study, they found only questionable small LGE which did not have the expected pattern of cardiac involvement in all cases. To our best knowledge, our study is the first showing the prevalence of clear myocardial involvement in patients with newly diagnosed extracardiac sarcoidosis lacking cardiac symptomatology.

Early diagnosis of cardiac sarcoidosis is of utmost importance for the possibility of the administration of immunosuppressive therapy. Moreover, the presence of LGE is well known to be associated with worse clinical outcomes including heart failure, arrhythmias, and sudden cardiac death [16].

Echocardiography due to its wide availability, safety, and relatively low cost still represents the first-line imaging method for screening of cardiac involvement in subjects with extracardiac sarcoidosis. However, its sensitivity in early stages of cardiac sarcoidosis is very low and reaches only about 25% [17]. In accordance with that, we were unable to detect any specific features of cardiac sarcoidosis such as the presence of thinning of basal segment of the interventricular septum

or the presence of the phenotype of dilated or restrictive cardiomyopathy in our study subjects. We documented the presence of small pericardial effusion in 11% individuals. However, none of these subjects expressed pericardial LGE that would suggest pericardial involvement associated sarcoidosis.

12-lead ECG and ECG Holter monitoring are often used as screening tools in patients with extracardiac sarcoidosis. Unfortunately, none of these methods has satisfying accuracy in the detection of cardiac sarcoidosis [18]. In our study we did not detect any second-degree AV block Mobitz type, third-degree atrioventricular block or sustained ventricular tachycardia, respectively, which are traditionally considered diagnostic for cardiac sarcoidosis in patients with a proven extracardiac form of the disease.

Study limitation

The main limitation of our study is a relatively small number of patients. Furthermore, newer CMR parametric techniques such as T1 or T2 mapping were not performed.

CONCLUSIONS

The prevalence of myocardial involvement in patients with newly diagnosed extracardiac sarcoidosis and the absence of obvious signs or symptoms suggesting cardiac disease seems to be very low as assessed by CMR. Nevertheless, we believe that CMR with its ability to detect early stages of the disease may still be considered for routine evaluation of heart involvement in patients with extracardiac sarcoidosis.

Acknwledegement: The study was supported by the Charles University Research program Cooperatio Cardiovascular Science.

REFERENCES

1. Mankad P, Mitchell B, Birnie D, et al. Cardiac sarcoidosis. Curr Cardiol Rep. 2019; 21(12): 152, doi: 10.1007/s11886-019-1238-1, indexed in Pubmed: 31768666.
2. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation. 1978; 58(6): 1204–1211, doi: 10.1161/01.cir.58.6.1204, indexed in Pubmed: 709777.

3. Grunewald J, Grutters JC, Arkema EV, et al. High-Density genetic mapping identifies new susceptibility variants in sarcoidosis phenotypes and shows genomic-driven phenotypic differences. Am J Respir Crit Care Med. 2016; 193(9): 1008–1022, doi: 10.1164/rccm.201507-1372OC, indexed in Pubmed: 26651848.
4. Ribeiro Neto ML, Jellis CL, Joyce E, et al. Update in cardiac sarcoidosis. Ann Am Thorac Soc. 2019; 16(11): 1341–1350, doi: 10.1513/AnnalsATS.201902-119CME, indexed in Pubmed: 31322914.
5. Galderisi M, Cosyns B, Edvardsen T, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2017; 18(12): 1301–1310, doi: 10.1093/ehjci/jex244, indexed in Pubmed: 29045589.
6. Slart RH, Glaudemans AW, Lancellotti P, et al. A joint procedural position statement on imaging in cardiac sarcoidosis: from the Cardiovascular and Inflammation & Infection Committees of the European Association of Nuclear Medicine, the European Association of Cardiovascular Imaging, and the American Society of Nuclear Cardiology. J Nucl Cardiol. 2018; 25(1): 298–319, doi: 10.1007/s12350-017-1043-4, indexed in Pubmed: 29043557.
7. Smedema JP, Snoep G, van Kroonenburgh MPG, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol. 2005; 45(10): 1683–1690, doi: 10.1016/j.jacc.2005.01.047, indexed in Pubmed: 15893188.
8. Aitken M, Chan MV, Urzua Fresno C, et al. Diagnostic accuracy of cardiac MRI versus FDG PET for cardiac sarcoidosis: a systematic review and meta-analysis. Radiology. 2022 [Epub ahead of print]: 213170, doi: 10.1148/radiol.213170, indexed in Pubmed: 35579526.
9. Vaidya VR, Abudan AA, Vasudevan K, et al. The efficacy and safety of electroanatomic mapping-guided endomyocardial biopsy: a systematic review. J Interv Card Electrophysiol. 2018; 53(1): 63–71, doi: 10.1007/s10840-018-0410-7, indexed in Pubmed: 30003460.
10. Orii M, Tanimoto T, Ota S, et al. Diagnostic accuracy of cardiac magnetic resonance imaging for cardiac sarcoidosis in complete heart block patients implanted with magnetic

resonance-conditional pacemaker. J Cardiol. 2020; 76(2): 191–197, doi: 10.1016/j.jjcc.2020.02.014, indexed in Pubmed: 32184028.

11. Murtagh G, Laffin LJ, Beshai JF, et al. Prognosis of myocardial damage in sarcoidosis patients with preserved left ventricular ejection fraction: risk stratification using cardiovascular magnetic resonance. Circ Cardiovasc Imaging. 2016; 9(1): e003738, doi: 10.1161/CIRCIMAGING.115.003738, indexed in Pubmed: 26763280.
12. Greulich S, Deluigi CC, Gloekler S, et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. JACC Cardiovasc Imaging. 2013; 6(4): 501–511, doi: 10.1016/j.jcmg.2012.10.021, indexed in Pubmed: 23498675.
13. Flamée L, Symons R, Degtiarova G, et al. Prognostic value of cardiovascular magnetic resonance in patients with biopsy-proven systemic sarcoidosis. Eur Radiol. 2020; 30(7): 3702–3710, doi: 10.1007/s00330-020-06765-1, indexed in Pubmed: 32166494.
14. Cegła P, Ciepłucha A, Pachowicz M, et al. Nuclear cardiology: an overview of radioisotope techniques used in the diagnostic workup of cardiovascular disorders. Kardiol Pol. 2020; 78(6): 520–528, doi: 10.33963/KP.15396, indexed in Pubmed: 32469191.
15. Panovský R, Doubková M, Mojica-Pisciotti ML, et al. Left ventricular myocardial deformation assessment in asymptomatic patients with recently diagnosed sarcoidosis of the respiratory tract and/or extrapulmonary sarcoidosis. Orphanet J Rare Dis. 2021; 16(1): 405, doi: 10.1186/s13023-021-02038-2, indexed in Pubmed: 34587975.
16. Kagioka Y, Yasuda M, Okune M, et al. Right ventricular involvement is an important prognostic factor and risk stratification tool in suspected cardiac sarcoidosis: analysis by cardiac magnetic resonance imaging. Clin Res Cardiol. 2020; 109(8): 988–998, doi: 10.1007/s00392-019-01591-y, indexed in Pubmed: 31872264.
17. Kouranos V, Tzelepis GE, Rapti A, et al. Complementary role of CMR to conventional screening in the diagnosis and prognosis of cardiac sarcoidosis. JACC Cardiovasc Imaging. 2017; 10(12): 1437–1447, doi: 10.1016/j.jcmg.2016.11.019, indexed in Pubmed: 28330653.
18. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and detection of sarcoidosis. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020; 201(8): e26–e51, doi: 10.1164/rccm.202002-0251ST, indexed in Pubmed: 32293205.

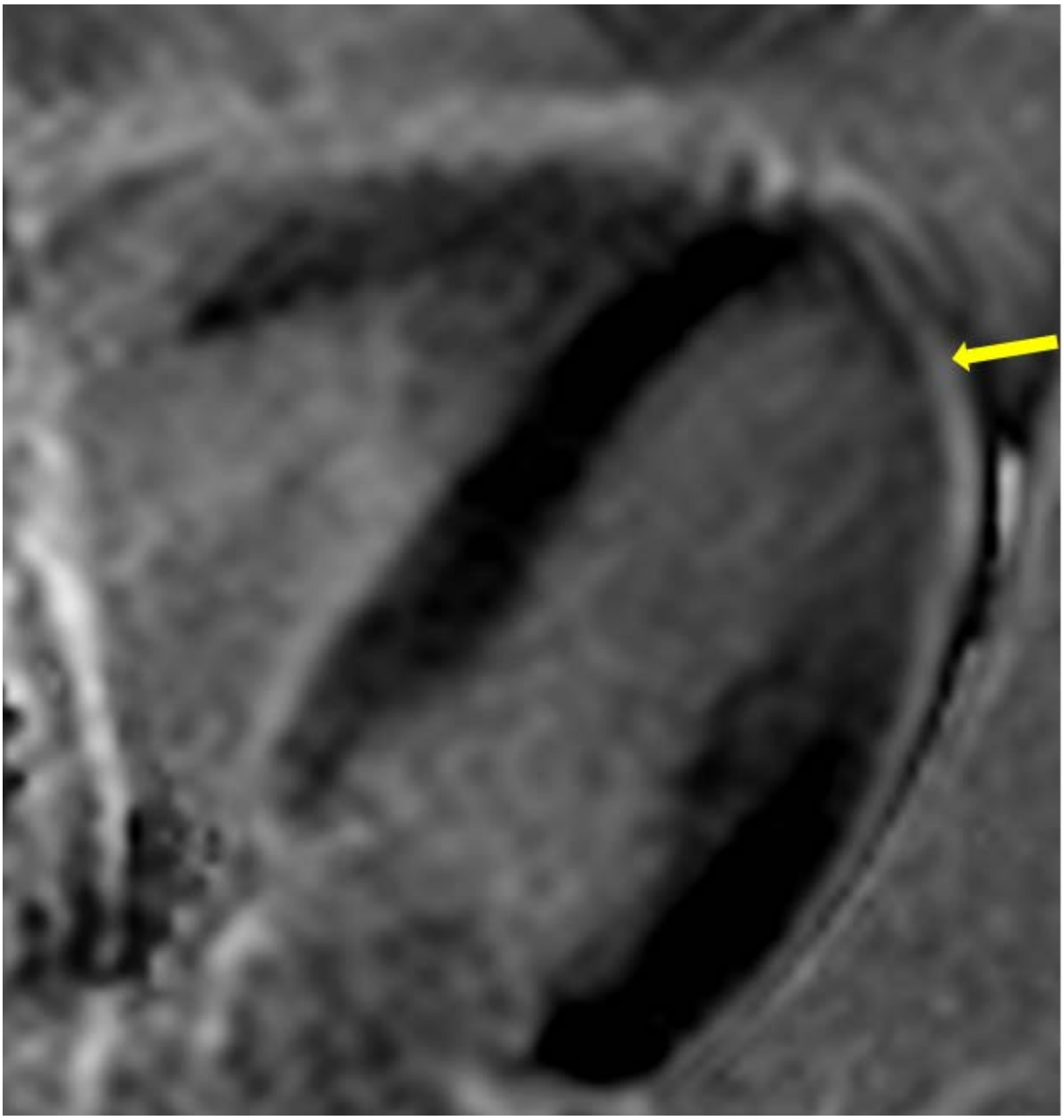

Figure 1. Presence of subepicardial late gadolinium enhancement in lateral wall of the left ventricle detected by cardiac magnetic resonance

Table 1. Clinical characteristics of patients

Number of subjects	55
Age, years, mean (SD)	43 (11)
Females, n (%)	23 (42)
Height, cm, mean (SD)	176 (11)
Weight, kg, mean (SD)	86 (19)

SBP, mm Hg, mean (SD)	129 (18)
DBP, mm Hg, mean (SD)	75 (14)
Arterial hypertension, n (%)	14 (25)
Diabetes mellitus, n (%)	5 (9)
Smokers, n (%)	11 (20)
Dyslipidemia, n (%)	8 (15)
Coronary artery disease	0
Chronic renal insufficiency	0
Bronchial asthma, n (%)	6 (11)
Pulmonary sarcoidosis, n (%)	54 (98)
Cutaneous sarcoidosis, n (%)	5 (9)
Gastrointestinal sarcoidosis, n (%)	4 (7)
Ocular sarcoidosis, n (%)	6 (11)
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure	

Table 2. Electrocardiographic and 24 hour Holter ECG monitoring parameters

Heart rate, min^{-1}, mean (SD)	77 (12)
Sinus rhythm, (%)	55 (100)
PQ, ms, mean (SD)	150 (11)
QRS, ms, mean (SD)	88 (6)
QTc, ms, mean (SD)	414 (23)
PACs, median (IQR)	4 (0–13)
PVCs, median (IQR)	2 (0–14)
Interventricular conduction delay, n (%)	2 (4)
NSVT	0
PVC over 10% QRS	0
AV block first-degree, n (%)	2 (4)
AV block second-degree Wenckebach, n (%)	2 (4)
AV block second-degree Mobitz	0
AV block third-degree	0
Abbreviations: AV, atrioventricular; NSVT, non-sustained ventricular tachycardia; PAC, premature atrial contraction; PVC, premature ventricle complex	

Table 3. Echocardiographic parameters

IVS, mm, mean (SD)	9 (2)
LVEDD, mm, mean (SD)	48 (4)
LVEF, %, mean (SD)	63 (5)
LAVi, ml/m^2, mean (SD)	26 (7)
DD absent/grade I/gradeII/grade III, n (%)	35 (63)/20 (37)/0/0
MR absent/mild/moderate/severe	3 (5)/52 (95)/0/0
RVEDD, mm, mean (SD)	33 (5)
PASP, mm Hg, mean (SD)	25 (5)

TAPSE, mm, mean (SD)	25 (3)
PEEF, n (%)	6 (11)
Abbreviations: DD, diastolic dysfunction; IVS, interventricular septum; LAV, left atrial volume; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR mitral regurgitation; PASP, pulmonary artery systolic pressure; PEEF, pericardial effusion; RVEDD, right ventricular end-diastolic diameter; TAPSE, tricuspid annular plane systolic excursion	

Table 4. Cardiac magnetic resonance parameters

LVEDV, ml, mean (SD)	146 (32)
LVEF, %, mean (SD)	63 (4)
CO, l/min, mean (SD)	7 (2)
RVEDV, ml, mean (SD)	133 (37)
RVEF, %, mean (SD)	58 (7)
Myocardial edema	0
LGE, n (%)	3 (6)
Abbreviations: CO, cardiac output; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; other — see Table 3	