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

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Editorial by Kouranos et al.

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Received: May 15, 2022

Accepted: June 21, 2022

Early publication date: June 27, 2022

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 excellent diagnostic accuracy in the detection of heart involvement by sarcoidosis.

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

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

Results: In 3 (6%) patients, the LGE pattern consistent with cardiac sarcoidosis was detected. In all patients, preserved left ventricular systolic regional and 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 assessed by CMR. However, CMR may be considered as part of routine evaluation of patients with extracardiac sarcoidosis due to its higher diagnostic yield in comparison with echocardiography and electrocardiography, respectively.

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

INTRODUCTION

Sarcoidosis is a systemic inflammatory disease of unknown origin characterized by epithelioid non-necrotizing granulomas, which can affect almost any organ. The most common form of the disease is pulmonary sarcoidosis. However, the presence of cardiac involvement determines the prognosis of affected individuals. The heart may be involved as part of the systemic disease or in an isolated form. Approximately only 5% of patients with systemic disease have symptoms of cardiac sarcoidosis [1]. However, the prevalence of heart involvement seems to be more frequent and

WHAT'S NEW?

Our study shows the prevalence of cardiac involvement in patients with newly diagnosed extracardiac sarcoidosis and no symptoms of heart disease. Our data suggest that the prevalence is very low as assessed by cardiac magnetic resonance. Nevertheless, based on the current knowledge the detection of heart involvement has significant impact on the management of these patients.

present in about 25% of patients with systemic sarcoidosis based on autopsy studies [2]. Nevertheless, the frequency of cardiac involvement in living 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 several types of arrhythmias. Conduction 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 the early stages of the disease. Cardiac magnetic resonance (CMR) has 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 to our institution between August 2015 and November 2021 for evaluation of the presence of cardiac sarcoidosis. In all of them, the extracardiac form of sarcoidosis had been confirmed in the previous 12 months. The diagnosis of extracardiac sarcoidosis was based on the positive histology characterized by the presence of epithelioid, 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 for 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, IL, US), and all measurements were done according to the current recommendations of American Society of Echocardiography/European Association of Cardiovascular Imaging [5].

CMR imaging was performed using a 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, and four-chamber views. 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) - from 320 to 440 mm with phase FOV - from 0.75 to 1.0 mm, 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 analyzed. The presence of myocardial edema was evaluated on T2-weighted spectrally selective inversion recovery (SPIR) images. Late gadolinium enhancement (LGE) images were obtained from 5 to 15 minutes after intravenous administration of 0.2 mmol/kg gadoterate 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 the 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 conformed 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 (IQR), or as number and percentage of subjects. The normality of data was tested with the 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 included 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

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)
Active smoking, 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, n (%)	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; ECG, electrocardiogram; NSVT, non-sustained ventricular tachycardia; PAC, premature atrial contraction; PVC, premature ventricular complex

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 ECG Holter monitoring data are presented in Table 2. All patients were in sinus rhythm. The first-degree atrioventricular (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. ECG Holter monitoring did not document sustained or nonsustained ventricular tachycardia or a significant number of premature ventricular extrasystoles 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 ECG Holter monitoring were detected.

Table 3. Echocardiographic parameters

IVS, mm, mean (SD)	9 (2)
LVEDD, mm, mean (SD)	48 (4)
LVEF, %, mean (SD)	63 (5)
LAVi, ml/m², mean (SD)	26 (7)
DD absent/grade I/grade II/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; LAVi, left atrial volume index; 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

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 left ventricular global systolic function, and no regional wall motion abnormality was observed either. No moderate or severe valvulopathy was found in any patient. 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%), the 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 the lateral LV wall were seen (Figure 1). One of these patients had a 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



Figure 1. The presence of subepicardial late gadolinium enhancement (the arrow) in the lateral wall of the left ventricle detected by cardiac magnetic resonance

with the endomyocardial biopsy, is its sensitivity for detection of cardiac sarcoidosis, which is reported to be 90%– -100% [7, 8], whereas the sensitivity of the endomyocardial biopsy is only about 25% [9]. The diagnosis of myocardial involvement based on the CMR study is traditionally based on the presence of LGE of non-ischemic etiology found in the subepicardial or midmyocardial segments of the LV walls, often involving the basal LV segments including the 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 for 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]. Those authors screened only patients without known cardiovascular diseases and no cardiac symptoms, and detected 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 to show the prevalence of clear myocardial involvement in patients with newly diagnosed extracardiac sarcoidosis lacking cardiac symptomatology.

An early diagnosis of cardiac sarcoidosis is of utmost importance because it makes it possible to administer 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 for cardiac involvement in subjects with extracardiac sarcoidosis. However, its sensitivity in the early stages of cardiac sarcoidosis is very low and reaches only about 25% [17]. Following that, we were unable to detect any specific features of cardiac sarcoidosis, such as the presence of thinning of the 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 a small pericardial effusion in 11% of individuals. However, none of these subjects expressed pericardial LGE that would suggest pericardial involvement associated with sarcoidosis.

Twelve-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, which are traditionally considered diagnostic for cardiac sarcoidosis in patients with a confirmed extracardiac form of the disease.

Study limitation

The main limitation of our study is the 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 the early stages of the disease may still be considered for routine evaluation of heart involvement in patients with extracardiac sarcoidosis.

Article information

Acknowledgment: The study was supported by the Charles University Research program Cooperatio Cardiovascular Science. Conflict of interest: None declared. Funding: None. **Open access:** This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially. For commercial use, please contact the journal office at kardiologiapolska@ptkardio.pl.

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