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ORIGINAL PAPER

Cardiac magnetic resonance in giant cell myocarditis: a matched comparison with cardiac sarcoidosis

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See the editorial comment for this article 'Two bad actors: can cardiac magnetic resonance distinguish idiopathic granulomatous from giant cell myocarditis?', by P. Reddy and L.T. Cooper, https://doi.org/10.1093/ehjci/jead012.

Aims Giant cell myocarditis (GCM) is an inflammatory cardiomyopathy akin to cardiac sarcoidosis (CS). We decided to study the findings of GCM on cardiac magnetic resonance (CMR) imaging and to compare GCM with CS.

Methods and results CMR studies of 18 GCM patients were analyzed and compared with 18 CS controls matched for age, sex, left ventricular (LV) ejection fraction and presenting cardiac manifestations. The analysts were blinded to clinical data. On admission, the duration of symptoms (median) was 0.2 months in GCM vs. 2.4 months in CS ($P = 0.002$), cardiac troponin T was elevated (>50 ng/L) in 16/17 patients with GCM and in 2/16 with CS ($P < 0.001$), their respective median plasma B-type natriuretic propeptides measuring 4488 ng/L and 1223 ng/L ($P = 0.011$). On CMR imaging, LV diastolic volume was smaller in GCM (177 ± 32 mL vs. 211 ± 58 mL, $P = 0.014$) without other volumetric or wall thickness measurements differing between the groups. Every GCM patient had multifocal late gadolinium enhancement (LGE) in a distribution indistinguishable from CS both longitudinally, circumferentially, and radially across the LV segments. LGE mass averaged $17.4 \pm 6.3\%$ of LV mass in GCM vs $25.0 \pm 13.4\%$ in CS ($P = 0.037$). Involvement of insertion points extending across the septum into the right ventricular wall, the "hook sign" of CS, was present in 53% of GCM and 50% of CS.

Conclusion In GCM, CMR findings are qualitatively indistinguishable from CS despite myocardial inflammation being clinically more acute and injurious. When matched for LV dysfunction and presenting features, LV size and LGE mass are smaller in GCM.

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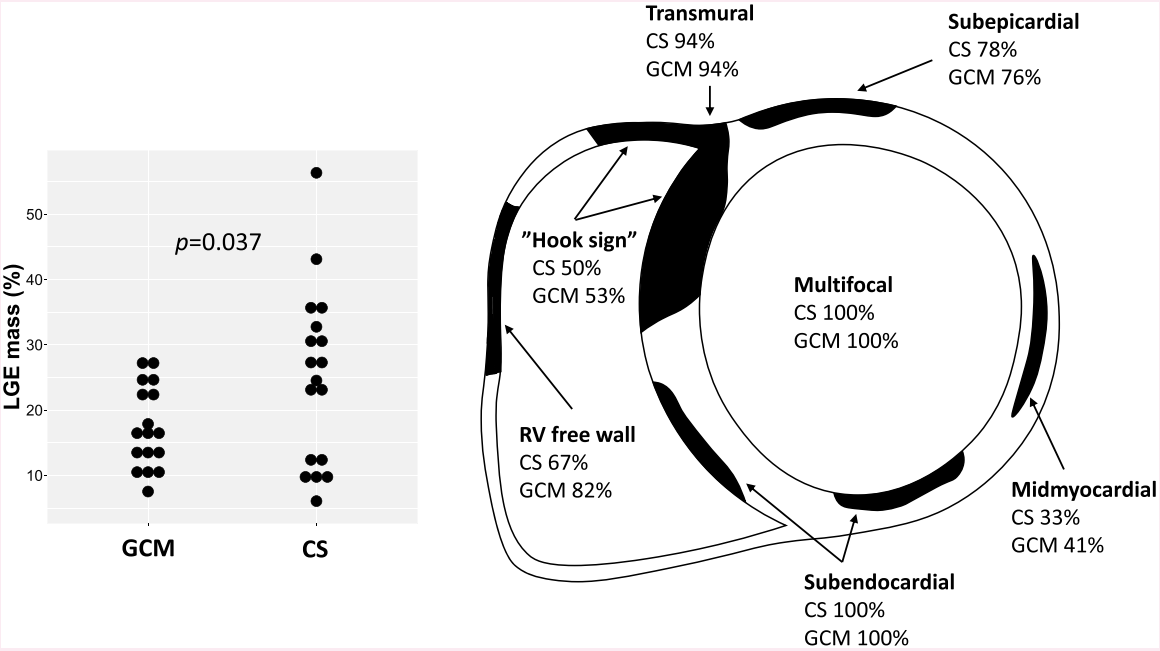
Graphical Abstract



Summary of myocardial late gadolinium enhancement (LGE) by cardiac magnetic resonance in giant cell myocarditis (GCM) and cardiac sarcoidosis (CS). GCM and CS have indistinguishable LGE distribution but, for matched LV dysfunction, the quantity of LGE is lower in GCM.

Keywords giant cell myocarditis • cardiac sarcoidosis • cardiac magnetic resonance

Introduction

Giant cell myocarditis (GCM) is an acute inflammatory cardiomyopathy known for mysterious etiopathogenesis, poor prognosis, and diagnostically challenging overlap with cardiac sarcoidosis (CS). The manifestations common to CS and GCM include high-grade atrioventricular block (AVB), heart failure, and sustained ventricular tachyarrhythmias, of which heart failure predominates in GCM and symptomatic AVB in CS.[1–4] Their differentiation is complicated further by significant issues of histopathology such as lack of consensus of whether cardiac or even extracardiac granulomas can be present in GCM and what extent of myocardial necrosis, if any, is compatible with the diagnosis of CS.[1,2,5–11] The possibility of GCM and CS constituting different severity phenotypes of a single-disease continuum has been debated.[3,5,11]

Contrast-enhanced cardiac magnetic resonance (CMR) holds a key position in the diagnostic work-up of myocardial diseases.[12] There exist many CMR studies on CS, reviewed of late thoroughly by Smedema *et al.*[13] whereas CMR findings in GCM have been described only in two small case series[14,15] and in solitary case reports.[16–24] Myocardial late gadolinium enhancement (LGE) appears ubiquitous in both conditions and preferentially subepicardial in CS[13] and subendocardial in GCM.[14,15,25] Whether CMR can help distinguish between these conditions is unknown, however, as no study has systematically compared GCM with CS. The present work was designed to fill that gap. To that aim, we identified from our nationwide registry of inflammatory cardiomyopathies[3,5] all GCM patients with available diagnostic CMR and selected for each a control patient with CS matched for age, sex, left ventricular (LV) function, and main presenting cardiac manifestation. Here we report results of analyses, blinded to the diagnosis and clinical data, comparing CMR findings between these conditions—and showing their near resemblance.

Methods

Study population

At the end of 2017, the registry of Myocardial Inflammatory Diseases in Finland (MIDFIN)[3] included 33 and 462 cases of GCM and CS, respectively, diagnosed nationwide from the late 1980s onwards. The diagnosis was based on myocardial histology in each case of GCM and in 257 cases of CS. Our criteria for the histopathology of GCM and for its differentiation from CS have been reported recently in full detail.[5] The key point is that the presence of myocardial or extracardiac granulomas is considered exclusive of GCM.[3,5]

Among the 33 GCM patients, 18 individuals had undergone CMR as part of early diagnostic examinations. For each of them, we probed the MIDFIN registry to find a control CS patient matched for (i) availability of diagnostic CMR, (ii) histologic diagnosis from myocardial biopsy, (iii) age (± 10y), (iv) sex, (v) echocardiographic LV ejection fraction on admission (± 5%), and (vi) main initial manifestation which was classified either as arrhythmic presentation (high-grade AVB, sustained ventricular tachycardia, ventricular fibrillation) or heart failure. Ultimately, we were able to identify 17 CS patients fulfilling all the matching criteria but had to accept one control who had histologic confirmation from mediastinal lymph node biopsy but met all the other criteria. The CMR studies of these 18 + 18 patients were re-evaluated for this study at Helsinki University Hospital. Their clinical data and follow-up information until February 2018 were retrieved from the database of the MIDFIN registry.[3] For the present work, death and heart transplantation were recorded as major adverse events. The causes of death were identified from medical records and findings at autopsy.

The characteristics of GCM patients with and without diagnostic CMR; i.e. of those included and excluded here, respectively; were comparable except that larger proportions of patients without CMR had been diagnosed

either at autopsy or in the era (prior to 2010) when CMR imaging for acute cardiac manifestations was done less regularly than in more recent years. The details are shown in the online Supplementary material online, *Table S1*.

CMR protocol

CMR examinations were conducted on 1.5T or 3T scanners using phased-array receiver coils and standard protocols.[26] For LV and right ventricular (RV) anatomical and functional assessment, breath-hold cine studies were performed using electrocardiographically gated steady-state free-precession. Cine images were obtained in long-axis planes (2-, 3-, and 4-chamber view) and short-axis planes covering both ventricles (typical slice thickness 6–8 mm, interslice gap 20%). One patient with GCM had a pacemaker during scanning.

LGE imaging was performed 10–15 min after intravenous injection of contrast agent (Dotarem®, 0.15 mmol/kg) using inversion-recovery gradient echo technique in views identical to cine studies. Inversion time was optimized for each measurement to null the signal intensity of normal myocardium (240–360 ms).

T_2-weighted fat saturation images/short tau inversion recovery images were obtained.

CMR analysis

All images were evaluated by a single CMR-trained cardiologist (P.P.) and read for consensus in a secure video meeting with another experienced CMR cardiologist (C.S.). Image analysis was performed using QMass MR software® (version 8.1, Medis Medical Imaging Systems, Leiden, the Netherlands). The analysts were blinded to the diagnosis and all clinical data.

LV and RV volumes and ejection fractions were evaluated using standard protocols.[27,28] Papillary muscles and outflow tract were included in the LV volume. Ventricular aneurysm was defined as a discrete akinetic or dyskinetic protrusion interrupting the normal ventricular contour during diastole and systole.[29] Maximal and minimal wall thickness were evaluated in each LV segment based on the American Heart Association (AHA) 17-segment model.[30] Maximal thickness of RV free wall was noted. Pericardial effusion was defined as >5 mm pericardial space anterior to the right ventricle.[31]

The presence of LGE was assessed visually and the number of LGE-positive LV segments was counted according to the AHA 17-segment model.[30] LGE pattern was classified as subendocardial (including the RV side of septum),[14] mid-myocardial (only), subepicardial, or transmural in each segment. Regional LGE was scored using a 5-point scale for each segment (0 = no hyperenhancement, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = 76–100%).[32] The total LGE as a percentage of LV mass was calculated by summing the regional scores (each weighted by the midpoint of the range of hyperenhancement) and divided by 17.[33] The CMR criteria for the likelihood of CS developed and reported by Vita *et al.*[34] were applied to all studies. According to these criteria, multifocal LGE without other explanation indicates a 50–90% likelihood of CS ('probable CS') and a prominent involvement of ventricular insertion points with direct and contiguous LGE extension across the septum into the RV wall ('hook sign' or 'hug sign') is considered virtually diagnostic of CS (>90% likelihood, 'highly probable CS').[34] The location of myocardial LGE was also compared with the 4 spatial features of cardiac damage reported to be typical for CS by Okasha *et al.*[35] reviewing gross pathological images of hearts removed at autopsy or transplantation. These types include LV multifocal, LV subepicardial, septal, and RV free wall involvement. In this comparison, but here only, transmural and RV septal involvement were taken to represent LV subepicardial LGE.

Visual and semi-quantitative analysis of T_2-weighted images was performed to detect increased focal or global myocardial free water content (oedema). The presence of oedema was defined by an increased signal intensity ratio of ≥2.0 in the myocardium relative to the reference area in the skeletal muscle within the same slice, preferable *M. serratus* anterior.[36]

The presence of enlarged intrathoracic lymph nodes (>1 cm in the short-axis diameter) was reviewed by a cardiothoracic radiologist (S.S.), blinded to the diagnosis, on scout and cine images, and on gadolinium-enhanced mediastinal images if available.

Table 1 Matched comparison of giant cell myocarditis and cardiac sarcoidosis—patient characteristics

	Giant cell myocarditis *n* = 18	Cardiac sarcoidosis *n* = 18	*P*-value
Age, years	58 ± 9	55 ± 8	0.008
Sex, female	14 (78)	14 (78)	1.000
Disease presentation			
Time from symptom onset to diagnosis, months	0.2 (0.1–0.5)	2.4 (0.5–6.3)	0.002
High-grade atrioventricular block	7 (39)	6 (33)	1.000
Ventricular tachyarrhythmia[a]	3 (17)	4 (22)	1.000
Heart failure[b]	13 (72)	12 (67)	1.000
Chest pain	3 (17)	3 (17)	1.000
LVEF on echocardiography			0.773
≥ 50%	3 (17)	3 (17)	
30–49%	10 (56)	12 (67)	
< 30%	5 (28)	3 (17)	
Cardiac biomarkers at presentation			
Troponin T > 50 ng/L[c]	16 (94)	2 (13)	<0.001
Pro-brain natriuretic peptide, ng/L[d]	4488 (3007–8050)	1223 (840–3146)	0.011

Data are numbers (%) of cases, means ± standard deviation, or medians (interquartile range).
LVEF = left ventricular ejection fraction.
[a]Ventricular fibrillation or sustained ventricular tachycardia.
[b]Heart failure as the only presenting manifestation or impaired impaired LVEF (<40%) in association with other presenting manifestation.
[c]One missing value in giant cell myocarditis and two in cardiac sarcoidosis.
[d]Two missing values in giant cell myocarditis and three in cardiac sarcoidosis.

Ethical approval

This study was performed according to the declaration of Helsinki and covered by local ethical board approval HUS/144/2020, HUS/54/2019, and HUS/27/2012. Written informed consent has been obtained from each patient alive at the time of recruitment into the MIDFIN registry.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) for normally distributed and skewed data, respectively. Matched case–control comparisons (GCM vs. CS) were performed with McNemar's test, Student's paired *t*-test or Wilcoxon signed rank test, as appropriate. The composite of death and heart transplantation was analyzed as the outcome endpoint. Kaplan–Meier plots were used to visualize event-free survival curves. Cox proportional-hazards regression was used to examine the relation of diagnosis (GCM vs. CS) to the composite endpoint-free survival. The analysis was stratified by matched pairs. The proportional-hazards assumption was checked using Schoenfeld residuals. A *P*-value of <0.05 was considered statistically significant and all tests were two-sided. Statistical analysis was performed on R (RStudio, version 4.1.2, The R Foundation; (https://www.r-project.org/)).

Table 2 Matched comparison of giant cell myocarditis and cardiac sarcoidosis—basic CMR characteristics

	Giant cell myocarditis $n = 18$	Cardiac sarcoidosis $n = 18$	*P*-value
Ventricular volumes			
LV EDV, mL	177.4 ± 31.8	211.0 ± 58.0	0.014
LV ESV, mL	117.4 ± 38.9	144.8 ± 53.1	0.061
LV EF, %	34.6 ± 13.8	32.7 ± 10.7	0.583
LV mass, g	123.3 ± 25.7	126.3 ± 33.6	0.713
RV EDV, mL	166.1 ± 47.5	170.4 ± 64.4	0.783
RV ESV, mL	104.3 ± 47.5	103.8 ± 62.2	0.972
RV EF, %	39.0 ± 14.2	43.1 ± 16.3	0.357
Wall thickness			
LV maximal wall thickness, mm	12.0 (10.8–14.0)	11.7 (10.7–14.4)	0.913
RV maximal free wall thickness, mm	3.1 (2.8–3.5)	3.2 (2.9–5.1)	0.446
Basal septal thinning[a]	2 (11)	7 (39)	0.131
Ventricular aneurysm			
LV	2 (11)	7 (39)	0.182
RV	2 (11)	0	0.480
Pericardial effusion[b]	8 (44)	5 (28)	0.547

Data are numbers (%) of cases, means ± standard deviation, or medians (interquartile range).
Abbreviations: CMR = cardiac magnetic resonance, EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, LV = left ventricular, RV = right ventricular.
[a] < 4 mm in the American Heart Association segments 2–3.
[b] > 5 mm effusion anterior to RV wall.

Table 3 LGE in giant cell myocarditis and cardiac sarcoidosis—matched comparison

	Giant cell myocarditis $n = 17$[a]	Cardiac sarcoidosis $n = 18$	*P*-value
LGE presence			
LV	17 (100)	18 (100)	NA
RV free wall	14 (82)	12 (67)	0.371
LV LGE extent			
LGE segments (AHA 1–17), *n*	9 (7–13)	12 (8–16)	0.126
LGE mass, %	17.4 ± 6.3	25.0 ± 13.4	0.037
LGE distribution, LV longitudinal			
Basal	17 (100)	18 (100)	NA
Mid-ventricular	17 (100)	18 (100)	NA
Apical	15 (88)	15 (83)	1.000
LGE distribution, LV circumferential			
Anterior	16 (94)	17 (94)	1.000
Septal	17 (100)	18 (100)	NA
Inferior	13 (76)	15 (83)	1.000
Lateral	14 (82)	17 (94)	0.617
LGE distribution, LV radial			
Subendocardial	17 (100)	18 (100)	NA
Mid-myocardial	7 (41)	6 (33)	1.000
Subepicardial	13 (76)	14 (78)	1.000
Transmural	16 (94)	17 (94)	1.000
Specific sites/modes of LGE involvement			
RV septal	17 (100)	17 (94)	1.000
Anterior ventricular insertion	14 (82)	15 (83)	1.000
Inferior ventricular insertion	15 (88)	16 (89)	1.000
Multifocal	17 (100)	18 (100)	NA
"Hook sign"[b]	9 (53)	9 (50)	1.000

Data are numbers (%) of cases, means ± standard deviation, or medians (interquartile range) AHA = American Heart Association, LGE = late gadolinium enhancement, LV = left ventricular, RV = right ventricular.
[a]One patient with giant cell myocarditis had no LGE data—paired comparison made between 17 pairs.
[b]Prominent involvement of ventricular insertion points with direct and contiguous LGE extension across the septum into the RV wall 34,37.

RESULTS

Clinical characteristics

Table 1 shows that, aside from a slightly higher mean age of the GCM patients, the groups were well-balanced with respect to the applied matching criteria (see Methods). Heart failure was found in ~70% of all patients at presentation. In GCM, the delay from symptom onset to diagnosis was shorter, and the circulating concentrations of biomarkers of cardiac injury and dysfunction were higher, suggesting a more acute and aggressive myocardial involvement on admission. Of the CS patients, six had confirmed extracardiac sarcoidosis, but only four of the 18 patients (and none of those with GCM) had undergone whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) to uncover subclinical extracardiac disease.

CMR studies

All studies had been performed between February 2007 and January 2018 with a similar temporal distribution in the two groups. The heart rate during imaging averaged 77 ± 20 beats/min in patients with GCM and 72 ± 14 beats/min in the CS group ($P = 0.436$).

Basic CMR characteristics

As *Table 2* shows, LV end-diastolic volume was smaller in GCM but there were no other statistically significant differences in LV or RV volumes, ejection fraction, or wall thickness. Basal septal thinning and LV aneurysms, signs of transmural scarring, both had a somewhat higher prevalence in CS (39% vs. 11% in GCM) but the differences did not reach statistical significance (*Table 2*). Pericardial effusion also had a comparable prevalence in the groups. None of the patients had LV or RV intracavitary thrombus.

Presence, extent, and distribution of LGE

All patients in either group had LV LGE and most also had RV free wall LGE (*Table 3*). LGE was multifocal in all patients and the 'hook sign' pattern of LGE (*Figure 1*) was as frequent in GCM as in CS (53% vs. 50%, respectively). The basal and mid-ventricular anteroseptal segments were most involved in both groups (*Figure 2*). The LGE mass was somewhat smaller in GCM (17.4 ± 6.3% vs. 25.0 ± 13.4% of LV mass, $P = 0.037$) but the number of LGE-positive segments was not statistically significantly different (*Table 3*). There were no significant group differences in the segmental distribution of LGE either longitudinally (basal,

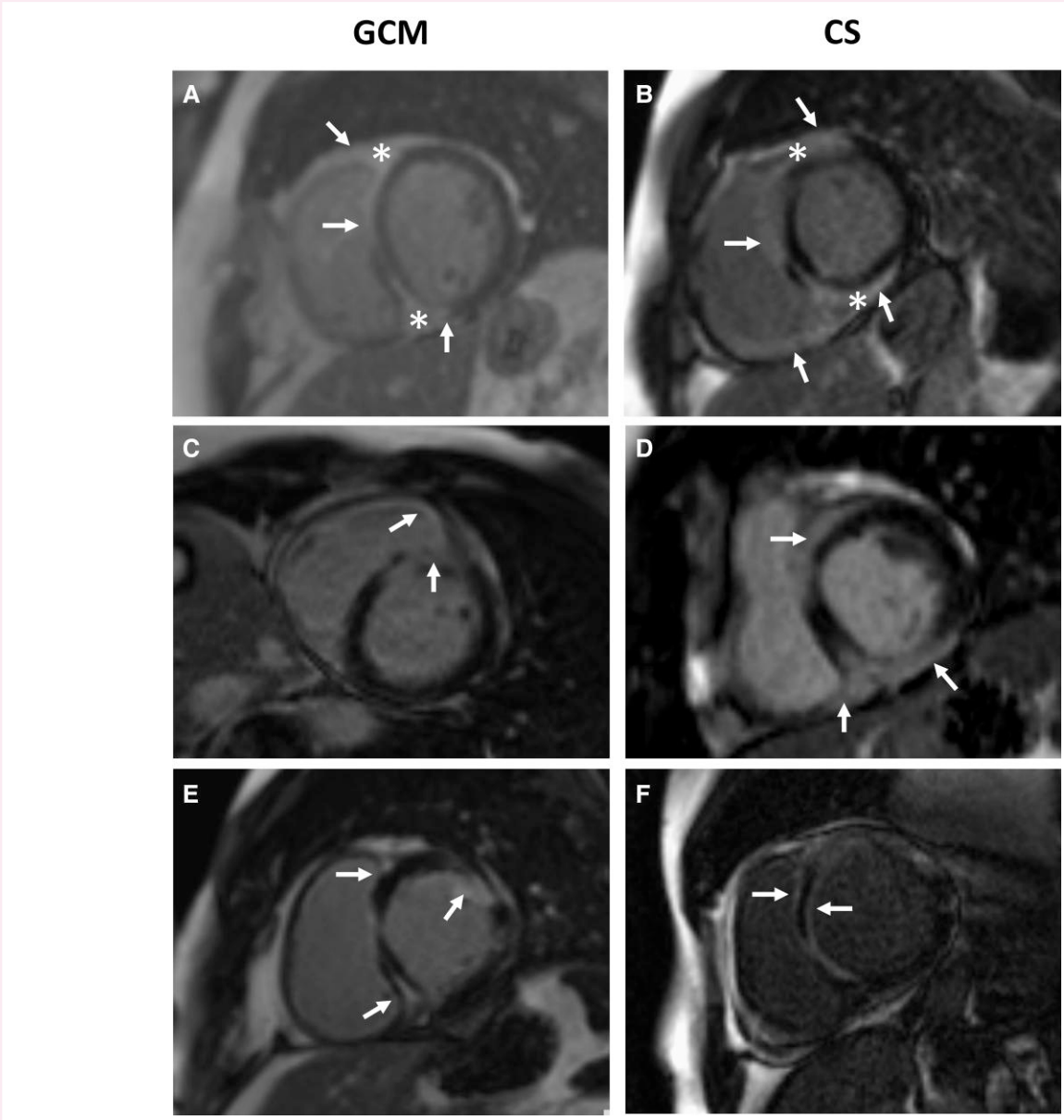


Figure 1 Myocardial late gadolinium enhancement (LGE) in giant cell myocarditis (GCM) and cardiac sarcoidosis (CS). Typical wide-spread and multifocal LGE with a 'hook sign' (or 'hug sign') pattern of involvement of ventricular insertions continuing across the septum into the right ventricle in a patient with GCM (*A*) and another with CS (*B*). Other examples of 'hook sign' patterns of LGE in GCM (*C*) and CS (*D*). Typical subendocardial left- and right-sided LGE in GCM (*E*) and CS (*F*). All myocardial layers may be affected in GCM and CS. Arrows depict ventricular LGE and asterisks insertion point LGE. CS = cardiac sarcoidosis; GCM = giant cell myocarditis; LGE = late gadolinium enhancement.

mid-LV, or apical segments), circumferentially (anterior, septal, inferior, or lateral segments), or radially (subendocardial, mid-myocardial, subepicardial, or transmural layers) across the LV myocardium (*Table 3*, see Supplementary material online, *Figure S1*). Subendocardial LGE was found in all patients (100%) in both groups, the proportions of positive segments being 44% (31–56%) in GCM and 28% (25–48%) in CS ($P = 0.171$). When the analysis was restricted to the LV endocardium, CMR showed subendocardial LGE in 11/17 patients with GCM (65%) and in 12/18 with CS (67%) ($P = 1.000$). Subepicardial LGE was found in 17% (8–31%) and 26% (14–33%) of segments in GCM and CS, respectively, ($P = 0.570$), the corresponding prevalence figures for transmural LGE being 31% (22–39%) in GCM and 39% (26–44%) in CS ($P = 0.548$).

Table 3 shows that of the four features of cardiac involvement considered typical for CS by Okasha *et al.*,[35] multifocal involvement and involvement of the interventricular septum and RV free wall were, by LGE analysis, as common in GCM as in CS. The fourth type, LV epicardial involvement (including transmural and RV septal LGE), also showed an equal prevalence being present in 17/17 patients with GCM and 17/18 with CS ($P = 1.000$).

T_2 imaging

T_2 images were available in 67% and 72% of patients with GCM and CS, respectively. Oedema was present in all (12/12) GCM patients and 12 of 13 (92%) with CS.

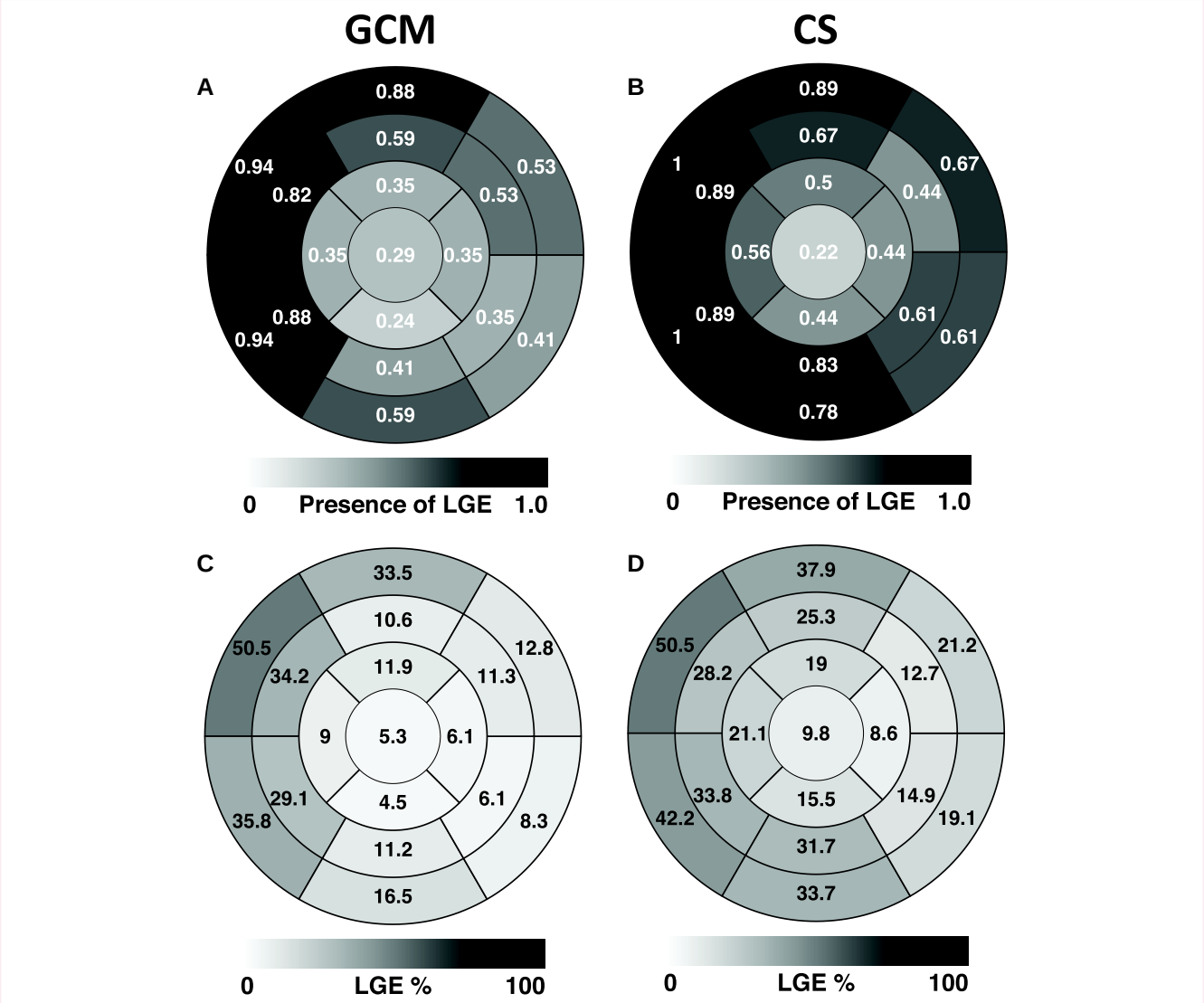


Figure 2 Distribution of late gadolinium enhancement (LGE) in giant cell myocarditis (GCM) and cardiac sarcoidosis (CS) according to AHA 17-segment model. Numbers inside the segments together with the intensity of gray depict the prevalence of LGE (proportion of patients, panels A and B) and its extent as percentage of left ventricular mass (panels C and D). CS = cardiac sarcoidosis; GCM = giant cell myocarditis; LGE = late gadolinium enhancement.

Intrathoracic lymph nodes

One patient with GCM (6%) and three with CS (17%) had enlarged mediastinal or hilar lymph nodes ($P = 0.617$). However, contrast-enhanced images optimal for extracardiac assessment were available in one patient only, the rest of the analyses being made on scout and cine images. Incidentally, abnormal pleural effusion was found in 12 patients with GCM (67%) vs. in three with CS (17%) ($P = 0.027$).

Treatment and outcome in brief

Of the 18 patients with GCM, 15 were treated with a combination of corticosteroid, cyclosporine, and azathioprine, while one patient received corticosteroids only and two underwent an early heart transplantation without preceding immunosuppression. All 18 CS patients received corticosteroids with 7, 3, 2, and 2 of them receiving, respectively, azathioprine, infliximab, methotrexate, or cyclosporine in addition. An implantable cardioverter-defibrillator was inserted in 16/18 patients with CS and in 11/18 with GCM ($P = 0.182$). In all, eight GCM patients underwent heart transplantation and two died suddenly over a median follow-up of 1.1 years (0.6–4.0). In the CS cohort, in turn, one patient underwent transplantation, one suffered a sudden death, and one died of cancer during a median of 3.9 years (2.5–7.9). *Figure 3* shows the graphs for event-free survival in the groups. By Cox regression analysis, GCM predicted a higher event rate with a hazard ratio of 9.0 (95% confidence interval: 1.1–71.0) over CS ($P = 0.037$).

Discussion

Our study shows that, in GCM, diagnostic CMR invariably shows myocardial LGE that is multifocal, can involve any myocardial layer, may associate with local LV wall thinning and aneurysms, and is indistinguishable from CS excepting a smaller LGE quantity for comparable LV dysfunction (*Graphical Abstract*). All GCM patients studied here

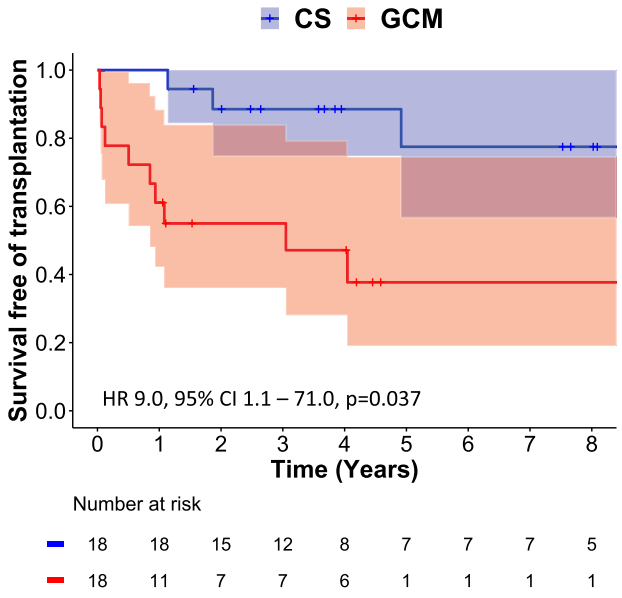


Figure 3 Prognosis of patients with giant cell myocarditis (GCM) and matched patients with cardiac sarcoidosis (CS). Kaplan–Meier plots visualizing survival free of death and transplantation. The hazard ratio is based on Cox proportional-hazards regression stratified by matched pairs.

had CMR findings considered indicative of CS with modest or high likelihood,[34] and the 'hook sign' of LGE (see *Figure 1*), that has been emphasized as a 'signature imaging biomarker' of CS,[37] had an equal prevalence in both groups. The sites of myocardium considered typical, or even unique, for CS-related damage[35] were involved equally in GCM and CS on LGE imaging. Despite its close resemblance with CS on CMR imaging, GCM was distinguished by both clinically and prognostically more aggressive myocardial inflammation.

CMR findings in GCM in the literature

Until two recent original reports from China,[14,15] CMR findings in GCM had been described only in solitary case reports and mostly in passing with results of other diagnostic examinations.[16–24] The studies by Yang *et al.*[14] and Li *et al.*[15] were based on two overlapping case series from the same Chinese centres and apparently involved only seven individual cases of GCM. The authors focused on the myocardial distribution of LGE and showed that all patients had LGE in both ventricles, multilayer LGE was frequent, and the most involved areas were the RV side of the septum, subepicardial LV anterior wall, and subendocardial RV wall.[14,15] Li *et al.* also compared GCM with lymphocytic myocarditis and found that subendocardial and transmural LGE were characteristic of GCM while LGE was predominantly subepicardial or missing in lymphocytic myocarditis.[15] In the previous case reports,[16–24] LV subendocardial LGE in a non-coronary distribution with patchy areas of transmural LGE were typical observations. Our findings are in alignment with these earlier observations.

CMR in GCM versus CS

We analyzed CMR studies in cohorts of GCM and CS matched for presenting manifestations and LV function to enable comparison of their intrinsic CMR characteristics, i.e. findings independent of the current severity of myocardial involvement. No significant differences were found save the somewhat smaller LV size and lesser total LGE mass in GCM. Outside the heart, pleural effusion was more common in GCM suggesting more severe congestive heart failure in alignment with the biomarker data for GCM vs. CS (*Table 1*). Earlier, it had been presented that CMR can distinguish GCM from CS because LV subendocardium is involved in GCM but typically not in CS.[25] Our work disproved this idea in showing that LV subendocardial LGE has a similar prevalence (roughly 65%) in both conditions.

Centres emphasizing imaging-based diagnosis of CS have introduced a diagnostic algorithm based on sequential analysis and interpretation of studies with CMR and 17F-fluorodeoxyglucose-positron emission tomography.[34] According to the algorithm, CMR alone indicates 'probable CS' (50–90% likelihood) when there is multifocal LGE but other explanation cannot be excluded, and 'highly probable CS' (likelihood >90%) when LGE is multifocal without other explanation and has high intensity or forms the 'hook sign' in the septum and RV wall[34] (*Figure 1*). In a recent review of CS,[37] the 'hook sign' on CMR was considered exclusive to CS. Our work shows, however, that both multifocal LGE and the 'hook sign' are equally common in GCM.

Clinical implications

Clinicians need to be aware of the similarities between GCM and CS that, from now on, include their intrinsic characteristics on CMR imaging in addition to T cell-driven pathogenesis, patient demographics, spectrum of cardiac manifestations, and prevalence of associated autoimmune diseases.[3,5] In clinical work, GCM and isolated CS, i.e. sarcoid granulomas confined to the heart, cannot be differentiated with certainty by any means, including CMR, other than a study of myocardial histology. Centres and clinicians applying the current recommendations for a clinical (non-biopsy) diagnosis of isolated CS[38] need to recognize this limitation. In an acute diagnostic and therapeutic dilemma, our practice is to view CS and GCM as a continuum of T cell-mediated inflammatory cardiomyopathies and tailor immunosuppression and other treatment to the severity of myocardial inflammation and its clinical consequences. The exact diagnosis is commonly solved on follow-up.

Strengths and limitations

In addition to the design of our work (see above), its strengths include myocardial histology-based diagnosis in all except one case with CS, and the assessment of CMR images by experts blinded to the diagnosis and

clinical data. The size of our study is small from the viewpoint of statistical power but considerable given the rarity and the frequently fulminant course of GCM. The CMR studies covered a period exceeding 10 years, over which scanners, techniques, and image quality evolved; some early studies had non-optimal though analyzable image quality. Certain novel techniques, such as T_1 and T_2 mapping, assessment of myocardial strain, or hybrid CMR/FDG-PET imaging could not be used here. In theory, simultaneous PET could help as FDG uptake outside the heart would strongly favour CS, although, by some experts,[2,39] not fully excluding GCM. Importantly, due to its matched design, our work does not exclude differences on CMR between GCM and all-comers with CS.

Conclusions

In GCM, myocardial LGE on CMR is ubiquitous and shows a distribution that is indistinguishable from CS. The quantity of LGE may be smaller in GCM for a comparable degree of LV dysfunction. CMR signs considered suggestive of CS, or even exclusive to it, are equally prevalent in GCM. Despite its near resemblance with CS on CMR imaging, GCM is clinically more aggressive and has poorer transplant-free survival.

Supplementary material

Supplementary materials are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data underlying this article cannot be shared publicly due to restrictions by the patient consent.

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