




ORIGINAL RESEARCH

Manifestations and Outcome of Cardiac Sarcoidosis and Idiopathic Giant Cell Myocarditis by 25-Year Nationwide Cohorts

Hanna-Kaisa Nordenswan, MD ; Jukka Lehtonen, MD; Kaj Ekström, MD; Anne Räisänen-Sokolowski , MD; Mikko I. Mäyränpää, MD; Tapani Vihinen, MD; Heikki Miettinen, MD; Kari Kaikkonen, MD; Petri Haataja, MD; Tuomas Kerola, MD; Tuomas T. Rissanen , MD; Jorma Kokkonen, MD; Alekski Alatalo, MD; Päivi Pietilä-Effati, MD; Seppo Utriainen, MD; Markku Kupari, MD

BACKGROUND: Cardiac sarcoidosis (CS) and giant cell myocarditis (GCM) share many histopathologic and clinical features. Whether they are parts of a one-disease continuum has been discussed.

METHODS AND RESULTS: We compared medical record data of 351 CS and 28 GCM cases diagnosed in Finland since the late 1980s and followed until February 2018 for a composite end point of cardiac death, aborted sudden death, and heart transplantation. Heart failure was the presenting manifestation in 50% versus 15% ($P<0.001$), and high-grade atrioventricular block in 21% versus 43% ($P=0.044$), of GCM and CS, respectively. At presentation, left ventricular ejection fraction was $\leq 50\%$ in 81% of cases of GCM versus in 48% of CS ($P=0.004$). The median (interquartile range) of plasma NT-proBNP (N-terminal pro-B-type natriuretic peptide) was 5273 (2782–11309) ng/L on admission in GCM versus 859 (290–1950) ng/L in CS ($P<0.001$), and cardiac troponin T exceeded 50 ng/L in 17 of 19 cases of GCM versus in 48 of 239 cases of CS ($P<0.001$). The 5-year estimate of event-free survival was 77% (95% CI, 72%–82%) in CS versus 27% (95% CI, 10%–45%) in GCM ($P<0.001$). By Cox regression analysis, GCM predicted cardiac events with a hazard ratio of 5.16 (95% CI, 2.82–9.45), which, however, decreased to 1.58 (95% CI, 0.71–3.52) after inclusion of markers of myocardial injury and dysfunction in the model.

CONCLUSIONS: GCM differs from CS in presenting with more extensive myocardial injury and having worse long-term outcome. Yet the key determinant of prognosis appears to be the extent of myocardial injury rather than the histopathologic diagnosis.

Key Words: cardiac sarcoidosis ■ giant cell myocarditis ■ inflammatory heart disease

See Editorial by Birnie et al.

Cardiac sarcoidosis (CS) and idiopathic giant cell myocarditis (GCM) are rare but serious inflammatory cardiomyopathies affecting mainly middle-aged adults.¹ The details of their pathogenesis remain unknown but autoimmune-related myocardial injury mediated by T lymphocytes and triggered by infectious or noninfectious agents has been incriminated in both.^{1–4} They also share clinical manifestations, like high-grade atrioventricular block (AVB), heart failure,

and fatal or life-threatening ventricular tachyarrhythmias,^{1,5–7} although the presentation and course are more aggressive in GCM.⁶ They have resemblances in myocardial histology too, as multinuclear giant cells, necrosis, fibrosis, lymphocytes, macrophages, and eosinophils are seen in both conditions, though their relative proportions differ.⁶ Myocardial granulomas constitute the hallmark of CS, but some experts do not consider their presence exclusive of GCM either.^{6,8}

Correspondence to: Hanna-Kaisa Nordenswan, Division of Cardiology, Heart and Lung Center, Helsinki University Central Hospital, 00029 HUS, Finland. E-mail: hanna-kaisa.nordenswan@helsinki.fi

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CLINICAL PERSPECTIVE

What Is New?

- For the first time, cardiac sarcoidosis and giant cell myocarditis were compared clinically in a large and unselected series of cases.
- Cardiac troponins and natriuretic peptides were available for group comparisons and survival analyses.
- Although prognosis was worse for giant cell myocarditis, the histopathologic diagnosis lost its strong predictive value in an analysis adjusting for markers of myocardial injury and dysfunction.

What Are the Clinical Implications?

- It is possible that cardiac sarcoidosis and giant cell myocarditis either are intimately related conditions or represent opposite ends of the spectrum of a single inflammatory cardiomyopathy.
- A cardiologist approaching a patient with cardiac sarcoidosis or giant cell myocarditis should give more weight to the clinical presentation and signs of cardiac injury and dysfunction than on the histologic diagnosis.

Nonstandard Abbreviations and Acronyms

AVB	atrioventricular block
CS	cardiac sarcoidosis
GCM	giant cell myocarditis
MIDFIN	Myocardial Inflammatory Diseases in Finland

Accordingly, whether CS and GCM are phenotypes of a single T-cell-mediated inflammatory cardiomyopathy has been debated. However, since the reports by Litovsky et al² and Okura et al⁶ at the turn of the millennium, the view of 2 unique and different diseases has prevailed.^{9,10}

We have an ongoing registry of cases of CS or GCM diagnosed in Finland since the late 1980s either during life or only at autopsy.^{7,11,12} The cohorts have been identified and collected by a nationwide research network. Here, we compare the clinical characteristics, cardiac manifestations, and long-term outcomes of cases of CS and GCM identified and included in the registry by the end of 2015. The starting point for our analyses was the view of these being different disease entities. Whether and how our findings align with this concept is discussed at the end of this article.

METHODS

The data cannot be made available to other researchers for purposes of reproducing the results because of restrictions related to the patient consent. Individual-level data cannot be shared openly.

Study Population

We included in the present work a total of 310 patients with a lifetime clinical diagnosis of either CS or GCM and 69 similar cases diagnosed only at autopsy and identified in retrospect from the cause-of-death registry. The clinical case series was based on our nationwide registry of MIDFIN (Myocardial Inflammatory Diseases in Finland) and comprised patients admitted to and diagnosed with the Finnish university and main provincial hospitals from the late 1980s until the end of 2015. The essentials of the MIDFIN registry and of the methods by which the patients were identified and included were detailed in our earlier publications.^{7,12,13} The postmortem cases were identified by screening a total of 820 605 death certificates available in digital form in the national cause-of-death registry from 1998 until the end of 2015. The method of screening and the yield of candidate cases, as well as their further assessment and ultimate inclusions and exclusions, have been reported lately in full detail.^{12,13}

Diagnostic Criteria and Reassessment of the Original GCM Diagnoses

For the diagnosis of CS, histology of sarcoidosis was mandatory, confirmed preferably in a sample of the myocardium or, absent that, in extracardiac organs or lymph nodes. Besides histology, the diagnosis required the presence of clinical signs of myocardial involvement, for example, high-grade AVB, heart failure attributable to left ventricular (LV) dysfunction, or ventricular arrhythmias together with findings compatible with inflammatory cardiomyopathy in either 18F-fluorodeoxyglucose positron emission tomography (PET), cardiac magnetic resonance imaging, or echocardiography. Presence of non-necrotic epithelioid cell granulomas together with multinuclear giant cells, sharply demarcated areas of inflammation and fibrosis, and absence of considerable myocardial necrosis or abundant tissue eosinophilia were required for the histology of sarcoidosis. These criteria conform with the Heart Rhythm Society's recommendations and the World Association of Sarcoidosis and Other Granulomatous Diseases diagnostic instrument.^{14,15}

The diagnosis of GCM required myocardial histology showing myocyte damage, full absence of granulomas, and the presence of multinucleated giant cells amid a mixed inflammatory infiltrate of histiocytes, lymphocytes, eosinophils, and plasma cells. The histologic

features of GCM and CS overlap, and their distinction on microscopy can be difficult, sometimes even a matter of judgment. Our reanalysis of the autopsy material available from cases of the cause-of-death registry showed that many diagnoses of GCM signed by forensic pathologists were likely to represent mistaken CS. As we also came across a parallel clinical case where the diagnosis of GCM was converted to CS at the post-transplant study of the native heart, we decided to re-evaluate each single GCM diagnosis made by the end of 2015. The details of the audit have been reported lately.¹³ As a result of that work, as many as 19 of the 24 cases filed as GCM in the cause-of-death registry were reclassified as CS, as were 25 of the 49 cases included earlier as GCM in the MIDFIN registry.¹³ The main reason for reclassification was finding granulomas that had been missed or misinterpreted on original microscopy.¹³ Ultimately, we had 28 cases of confirmed GCM and 351 cases of CS for our comparative analyses. Histologic confirmation for the final diagnosis of CS was myocardial in 224 cases (150 diagnostic myocardial biopsies, 10 studies of explanted hearts, and 64 autopsies) and made from samples of lymph nodes ($n=102$) or extra-cardiac organs ($n=25$) in the remainder. Studies evaluating coexistent coronary artery disease were reviewed, and significant 3-vessel disease was found in 9 patients with CS and none with GCM.

Data Collection

The information on patients in the MIDFIN registry was collected in retrospect from the hospital charts until the year 2010 and mainly prospectively thereafter. The database includes information on patients' demographics, clinical cardiac manifestations, and associated diseases, as well as results of diagnostic imaging and laboratory studies and details of treatment with drugs and devices. All patients have been followed in the hospitals of the MIDFIN research network and their later treatment modifications, results of imaging and laboratory studies, and the occurrence of cardiac events have been entered into the database. The cases identified from the cause-of-death registry were mainly individuals dying suddenly and unexpectedly and undergoing forensic autopsy. Their medical documents were acquired from the local hospitals and health centers and their past medical history as well as any cardiac symptoms, examinations, and treatment shortly before death were recorded for our analyses.

Definition of Major Adverse Cardiac Events

Cardiac death, aborted sudden cardiac death, and heart transplantation were recorded and analyzed as major adverse events. Aborted cardiac death was a documented episode of ventricular fibrillation terminated successfully

either by an implantable cardioverter-defibrillator or by external defibrillation during resuscitation for a cardiac arrest. The dates and characters of the events were confirmed by review of medical records, 12-lead ECGs, and implantable cardioverter-defibrillator reports until the end of February 2018. The causes of death were determined from medical records and findings at autopsy.

Ethical Approvals

The MIDFIN registry study received the approval of the national ethical review board in 2009 (STM/1219/2009) and all involved centers granted approval to conduct the study. Two Finnish governmental authorities, the National Authority for Medicolegal Affairs (4615/06.01.03.01/2016), and the National Institute for Health and Welfare (THL/691/5.05.00/2016) approved the study of cases from the cause-of-death registry and the review of postmortem autopsy material. Written informed consent was obtained from each patient alive at the time of recruitment into the MIDFIN registry study.

Statistical Analysis

Patient characteristics at presentation are presented as frequencies of categorical variables and as means (\pm SD) or medians (interquartile range) for continuous variables. The groups were compared with ANOVA and Kruskal–Wallis tests for normally distributed and skewed continuous data, respectively, and with Fisher's exact test for categorical variables. Follow-up times were calculated from the disease presentation, defined as the date of the first medical contact for symptoms that led to the diagnosis of CS or GCM during life or were attributable to either condition in cases diagnosed at autopsy. The outcome end point was the composite of cardiac death, aborted sudden cardiac death, or transplantation during follow-up. Sudden cardiac death (fatal or aborted) as the presenting manifestation was not considered an outcome event. The Kaplan–Meier method was used to construct the survival curves with noncardiac deaths coded as censoring events. Factors influencing survival were analyzed by Cox regression models with the proportional hazards assumption tested using log-log survival plots. Cases with sudden cardiac death as the only disease manifestation, that is, having no follow-up time, were excluded from survival analyses. P values <0.05 were considered statistically significant. Analyses were performed using SPSS–24 for Macintosh (SPSS Inc, Chicago, IL) and Xlstat Lifesciences (Addinsoft, Paris, France).

RESULTS

Characteristics of the Study Groups

Tables 1 and 2 summarize the clinical characteristics and selected diagnostic examinations of the study

Table 1. Comparison of Clinical Characteristics Between Patients With GCM and CS

Characteristic	GCM n=28	CS n=351	P Value
Age at disease presentation, y	58±10	51±12	0.002
Female sex	19 (68)	248 (71)	0.830
Main presenting manifestation			
AVB, third degree or Mobitz II 2nd degree	6 (21)	149 (43)	0.044
Heart failure	13 (46)	54 (15)	<0.001
Sudden cardiac death			
Fatal	3 (11)	40 (11)	1.000
Aborted	1 (4)	12 (3)	1.000
Sustained VT	2 (7)	47 (13)	0.557
Frequent VPC or nonsustained VT	1 (4)	20 (6)	1.000
Atrial tachyarrhythmia	0 (0)	4 (1)	1.000
Syndrome mimicking myocardial infarction*	1 (4)	11 (3)	0.607
Miscellaneous symptoms or signs†	1 (4)	14 (4)	1.000
Comorbidities			
Autoimmune disease‡	4 (14)	46 (13)	0.778
Diabetes mellitus	2 (7)	34 (10)	0.755
Hypertension	6 (21)	76 (22)	1.000
Hypercholesterolemia	5 (18)	49 (14)	0.574
Asthma/COPD	3 (11)	36 (10)	1.000
Coronary artery disease§	0 (0)	9 (3)	1.000
Cancer	1 (4)	30 (9)	0.716
Duration of illness, mo¶	0.3 (0.1–1.09)	7.0 (2.0–24.4)	<0.001

Data are numbers (%) of cases, means±standard deviation, or medians (interquartile range). AVB indicates atrioventricular block; COPD, chronic obstructive pulmonary disease; CS, cardiac sarcoidosis; GCM, giant cell myocarditis; VPC, ventricular premature complexes; and VT, ventricular tachycardia.

*Chest pain, ischemic electrocardiographic changes, and normal coronary angiogram.

†One or more of the following: unexplained syncope, elevated cardiac troponin, fatigue, dyspnea, or bundle-branch block on the ECG or anginal-like exertional chest pain.

‡Rheumatoid arthritis, hypo- or hyperthyreosis, celiac disease, Sjögren syndrome, iritis, or ulcerative colitis.

§Significant 3-vessel coronary artery disease.

¶Time from symptom onset to diagnosis in patients with lifetime disease presentation.

groups. The patients with GCM were older, but there was an equal female predominance in either group. The median age at disease presentation in women versus men was 52 (43–58) and 47 (42–57) years, respectively, in the CS group ($P=0.072$) and 60 (52–65) versus 58 (50–67) years in the GCM group ($P=0.156$). The presenting cardiac manifestations consisted of lifetime symptoms or signs in 311 of 351 cases with CS and 25 of 28 cases with GCM. In the rest, the presentation was an unexpected sudden death leading to

Table 2. Summary of Key Imaging and Laboratory Examinations at Presentation or Diagnosis in Patients With GCM and CS

Characteristic	GCM (n=28)	CS (n=351)	P Value
Findings at echocardiography			
Left ventricular ejection fraction			0.004
<30%	7/26 (27)	36/299 (12)	
30%–50%	14/26 (54)	109/299 (36)	
>50%	5/26 (19)	154/299 (52)	
Left ventricular dilatation*	4/26 (15)	100/270 (37)	0.031
Septal thinning	9/19 (47)	89/297 (30)	0.128
Abnormal focal cardiac uptake on ¹⁸ F-FDG PET	2/2 (100)	165/191 (86)	1.000
Myocardial late gadolinium enhancement on MRI	12/12 (100)	151/177 (85)	0.377
NT-proBNP, ng/L	5273 (2782–11309)	859 (290–1950)	<0.001
BNP, ng/L	4114 (1844–9607)	650 (122–1000)	0.006
Cardiac troponin T >50 ng/L†	17/19 (89)	48/239 (20)	<0.001
Cardiac troponin I, ng/L	0 (0)	45 (20–90)	

Data are numbers (%) of cases or medians (interquartile range). BNP indicates plasma brain natriuretic peptide; CS, cardiac sarcoidosis; ¹⁸F-FDG PET, ¹⁸F-fluorodeoxyglucose positron emission tomography; GCM, giant cell myocarditis; MRI, magnetic resonance imaging; and NT-proBNP, plasma N-terminal pro-B-type natriuretic peptide.

*Left ventricular diastolic diameter >55 mm in women or >60 mm in men.

†50 ng/L was used as cutoff level to have comparable cardiac troponin T data from the 2 platforms¹⁶ used over the years covered by our study.

autopsy and postmortem diagnosis. At presentation, patients with GCM more often had heart failure and impaired LV ejection fraction but less LV dilatation, while high-grade AVB was more common in CS. Circulating concentrations of natriuretic peptides and cardiac troponins were much more often elevated in GCM. The frequency of comorbidities, including autoimmune diseases, was nearly identical in the 2 groups. The rate of autoimmune diseases did not vary statistically significantly by sex in either group (data not shown). According to clinical examination, autopsy findings, ¹⁸F-fluorodeoxyglucose PET, and extracardiac biopsies, 225 of the 351 patients with CS had systemic sarcoidosis, while 35 patients had isolated CS. The remaining 91 patients had clinically isolated CS but had not undergone all examinations needed to firmly rule out sarcoidosis outside the heart.

Summary of Treatment in Patients With Lifetime Disease Presentation

From among the 311 patients with an ultimate diagnosis of CS and lifetime disease presentation, 278 received immunosuppressive treatment with prednisolone (n=276),

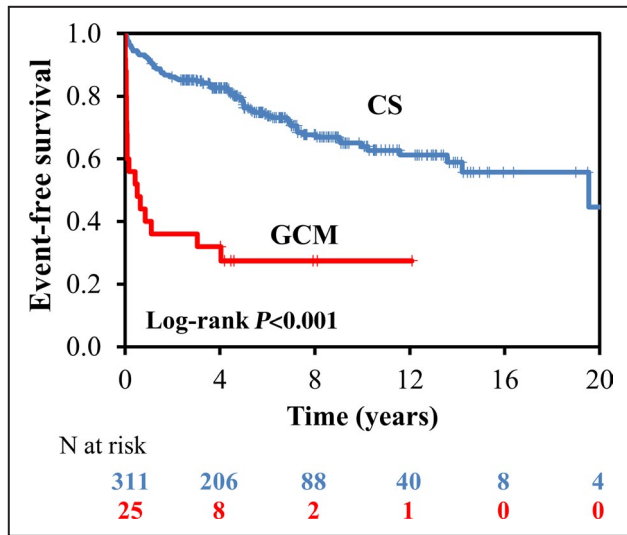


Figure. Kaplan–Meier graphs for cardiac survival free of transplantation and aborted sudden cardiac death in patients with lifetime presentation of cardiac sarcoidosis (CS) or giant cell myocarditis (GCM). Cases with sudden death as the only disease manifestation (n=43) were excluded from the analysis.

azathioprine (n=114), cyclosporine (n=21), methotrexate (n=18), infliximab (n=7), or mycophenolate mofetil (n=21) in various combinations. Of the 25 patients with GCM presenting during life, 7 were administered prednisolone alone and 14 received the triple combination of prednisolone, azathioprine, and cyclosporine. An implantable cardioverter-defibrillator was implanted in 191 patients with CS (61%) and 13 with GCM (50%), while 67 and 6 patients with CS (21%) and GCM (23%), respectively, received a permanent pacemaker.

Long-Term Outcome and Its Predictors

The 311 CS patients with lifetime disease presentation had total follow-up times ranging from 6 months to 29.7 years (median, 6.3 years) from symptom onset to the end of our study. Among them, 39 fatal and 32 sudden aborted cardiac deaths were recorded, the former including 31 fatalities from ventricular arrhythmia, 7 from heart failure, and 1 from extensive coronary artery disease. Nine patients with CS died of a noncardiac cause (5 from cancer and 1 from each of tuberculosis, dementia, terminal lung sarcoidosis, and brain infarction). Among the 25 GCM patients with total follow-up times from 3 days to 19.1 years (median, 3.6 years), 7 fatal and 7 sudden aborted cardiac deaths occurred, the former including 5 deaths from arrhythmia and 2 from heart failure. Altogether, 25 patients with CS and 11 with GCM underwent cardiac transplantation; of them, 9 with CS and 3 with GCM died later following transplantation. The composite end point of fatal or aborted cardiac death or

Table 3. Univariate Cox Regression Analyses of Predictors of Fatal or Aborted Cardiac Death or Transplantation in the Entire Study Population

Predictive Characteristic	e/n	HR (95% CI)	P Value
Age, per 1 y	109/336	1.01 (0.99–1.03)	0.186
Male sex	109/336	1.23 (0.83–1.84)	0.306
Diagnosis of GCM vs CS	109/336	5.72 (3.42–9.55)	<0.001
Main presenting manifestation	109/336		
High-grade AVB (reference)	42/154		
Heart failure	32/68	2.13 (1.34–3.39)	0.001
Aborted sudden death or sustained VT	22/62	1.43 (0.85–2.39)	0.179
Other*	13/52	1.09 (0.58–2.03)	0.790
Duration of illness, per 1 mo [†]	109/336	1.00 (0.99–1.00)	0.115
Left ventricular ejection fraction	99/324		
>50% (reference)	31/158		
30%–50%	49/126	2.26 (1.44–3.54)	<0.001
<30%	19/40	2.92 (1.64–5.23)	<0.001
High BNP or NT-proBNP [‡]	54/204	3.02 (1.63–5.58)	<0.001
High cTnT or cTnI [§]	59/229	2.98 (1.78–4.99)	<0.001

AVB indicates atrioventricular block; BNP, brain natriuretic peptide; CS, cardiac sarcoidosis; cTnI, cardiac troponin I; cTnT, cardiac troponin T; e/n, number of events per number of patients in the model; GCM, giant cell myocarditis; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and VT, ventricular tachycardia.

*Other manifestations include frequent ventricular premature complexes or nonsustained ventricular tachycardia, atrial tachyarrhythmia, syndrome mimicking myocardial infarction, angina-like exertional chest pain, unexplained syncope, elevated cardiac troponin, fatigue, dyspnea, or bundle branch block on the ECG.

[†]Time from symptom onset to diagnosis in patients with lifetime disease presentation.

[‡]Plasma brain natriuretic peptide level at presentation above their respective medians in all patients, ie, BNP >849 ng/L or NT-proBNP >938 ng/L at disease presentation.

[§]Plasma cTnT >50 ng/L or cTnI >45 ng/L at disease presentation.

transplantation was recorded in a total of 91 patients with CS and 18 patients with GCM. The Figure presents the Kaplan–Meier graphs for event-free survival in the 2 groups. The curves show a rapid divergence, with most events in GCM occurring within 1.5 years from disease presentation. Still, at the end of our study, occasional GCM patients had follow-up times beyond 8 to 12 years without events. The Kaplan–Meier estimate (95% CI) of 5-year event-free cardiac survival was 77% (95% CI, 72%–82%) in CS versus 27% (95% CI, 10%–45%) in GCM (P<0.001). The results of 2 additional Kaplan–Meier analyses are given in the supplemental material, one of transplant-free cardiac survival excluding aborted sudden cardiac

Table 4. Multivariate Cox Regression Models for the Prediction of Fatal or Aborted Cardiac Death or Transplantation

Predictor	Model 1	Model 2	Model 3*
	n of Events=99	n of Events=59	n of Events=48
	n of Pts=300+24	n of Pts=209+19	n of Pts=173+17
GCM diagnosis	5.16 (2.82–9.45), $P<0.001$	2.59 (1.27–5.27), $P=0.009$	1.58 (0.71–3.52), $P=0.268$
Presentation with HF	0.86 (0.50–1.46), $P=0.569$
LVEF $\leq 50\%$	2.19 (1.37–3.51), $P=0.001$	2.34 (1.28–4.27), $P=0.006$	2.11 (1.04–4.28), $P=0.039$
High cTnT or cTnI [†]	...	2.18 (1.24–3.86), $P=0.007$	2.83 (1.45–5.51), $P=0.002$
High BNP or NT-proBNP [‡]	1.71 (0.83–3.50), $P=0.145$

Data are hazard ratios (95% CIs). BNP indicates brain natriuretic peptide; cTnT; cardiac troponin T; cTnI, cardiac troponin I; GCM, giant cell myocarditis; HF, heart failure; LVEF, left ventricular ejection fraction; pts, patients with CS+patients with GCM; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

..., not included in the model.

*Correlation coefficients across LVEF, cTnT, and NT-proBNP varied from 0.19 to 0.42 speaking against a significant multicollinearity problem.

[†]Plasma cTnT >50 ng/L or TnI >45 ng/L at disease presentation.

[‡]Plasma BNP >849 ng/L or NT-proBNP >938 ng/L at disease presentation.

deaths (Figure S1) and another of survival with all-cause death as the only outcome event (Figure S2).

To study which patient characteristics aside from the diagnosis were predictive of outcome and whether the diagnosis was an independent prognostic factor, we conducted uni- and multivariate Cox regression analyses in all patients with lifetime disease presentation ($n=336$). The results of the univariate analyses are shown in Table 3. The hazard ratios indicate that, aside from diagnosis, the main presenting manifestation, as well as LV ejection fraction, cardiac troponins, and natriuretic peptides measured at onset of follow-up, were predictive of end point events. Table 4 summarizes the results of multivariate analyses and shows that GCM remained an independent prognostic factor ($P<0.05$) except in a model adjusting for the predictive effects of LV ejection fraction, cardiac troponins, and natriuretic peptides (Model 3 in Table 4). All predictive variables met the proportional hazard assumption by log-log survival plot.

DISCUSSION

We compared the characteristics and outcomes of CS and GCM between 25-year cohorts of cases detected nationwide in Finland. Our observations show a similar end-to-end spectrum of presenting cardiac manifestations with a relative predominance of left-sided heart failure in GCM versus high-grade AVB in CS. In GCM, circulating cardiac troponins and natriuretic peptides were more often strongly elevated and the left ventricle had poorer ejection fraction but less dilatation, suggesting a more extensive and more acute myocardial injury compared with CS. Event-free survival was worse in GCM, but the predictive power of diagnosis diminished conspicuously after adjustment for markers of LV dysfunction and myocardial injury.

Earlier Studies Comparing CS and GCM

Before our work, 3 original studies had compared selected aspects of CS and GCM.^{2,6,17} In a retrospective autopsy study, Litovsky et al² analyzed myocardial histopathology in 8 hearts with GCM and 7 hearts with CS. Both conditions were characterized by histiocytic giant cells the main discriminator being the absence of myocardial granulomas in GCM and necrosis in CS. Eosinophils were frequent in GCM but rare in CS. In another study, Okura et al,⁶ on behalf of the Multicenter Giant Cell Myocarditis Study Group, compared cardiac histopathology and clinical features in 73 cases of GCM and 42 cases of CS collected from nearly 50 institutions worldwide. The groups differed in ethnic background and had a recruitment imbalance, as most centers did not have a single case of CS though all contributed cases of GCM. Worthy of note, myocardial necrosis and granulomas were seen in both conditions, though necrosis was more extensive in GCM and granulomas more common in CS.⁶ Eosinophils were more frequent in GCM, while fibrosis was more extensive in CS. Left-sided heart failure predominated in GCM, whereas syncope and AVB were seen more often in CS. The 5-year transplant-free survival was 61% in CS versus only 10% in GCM. Notwithstanding their disagreement on the presence of granulomas in GCM and necrosis in CS, the above reports^{2,6} have been considered to establish CS and GCM as histopathologically different disease entities.

The third comparative study, focusing on transcriptomics, analyzed the myocardial expression profiles of a selected set of 28 genes in 10 patients with CS and 10 with GCM diagnosed on endomyocardial biopsies.¹⁷ Five genes, 2 coding for cytokines and 3 for mitochondrial energy metabolism, showed differential expression. The authors speculated that measuring the myocardial expression of these genes could help

distinguish GCM from CS and guide treatment.¹⁷ This observation has not been replicated elsewhere.

What Our Study Adds and Suggests

The present findings support the clinical differences between CS and GCM reported by Okura et al,⁶ albeit in a much larger and more homogenous study population. Our comparisons of echocardiographic details add to the literature by showing that septal thinning, considered a hallmark of CS,¹⁸ was even more common in GCM, while LV dilatation at presentation was more frequent in CS. The data on cardiac troponins and natriuretic peptides are also novel and show that both biomarkers were much more frequently elevated in GCM. Together with a shorter duration of illness before diagnosis and with less dilated but more poorly contracting left ventricles, these data fit well with the idea of more acute and more destructive LV injury in GCM. A provocative if merely a statistical observation was that GCM lost much of its prognostic weight to markers of LV injury and dysfunction in multivariate analyses. It appears that the overarching determinant of prognosis is the extent of myocardial injury and not the histopathologic diagnosis per se. Admittedly, this tells little about the pathogenetic relationship of the 2 conditions.

Two Diseases or 1 with Varying Facies?

The prevailing view among today's researchers and clinicians is that CS and GCM constitute different disease entities.^{9,10} Yet they have remarkably much in common. Although the details of their cause and pathogenesis are unknown, T lymphocyte-mediated inflammatory injury appears crucial in both,^{1,2} and the association with thymomas described in GCM¹ holds for sarcoidosis as well.^{19–21} The prevalence of concomitant autoimmune diseases, known to be high in GCM,^{1,5} was equal in both conditions in our study, which is the first comparing CS and GCM in this respect. The preponderance of women was also similar, whereas the GCM case series was on average a few years older. Both the study of Okura et al⁶ and our work show that the end-to-end spectrum of cardiac manifestations is similar in CS and GCM, but heart failure with a rapid clinical deterioration is more prevalent in GCM, while AVB and a slow disease course characterize CS. Still, it is well known that CS, too, can cause an acute and fulminant myocarditis^{22–24} and that a protracted clinical course, in turn, is possible in GCM.^{25,26} It is also undeniable that patients with confirmed systemic sarcoidosis can harbor GCM in their hearts. In the seminal report by Davies et al²⁷ of idiopathic GCM, 1 of 11 patients had sarcoidosis in the lungs, liver, and spleen, and in the study by Davidoff et al,²⁸ 4 of 10 patients with GCM had extracardiac sarcoidosis.

More recently, Nakasuka et al²⁹ described a patient with GCM who had been diagnosed with pulmonary sarcoidosis only a few months earlier. In his treatise of 1956, Tesluk³⁰ described GCM as a condition frequently associated with granulomas in extracardiac organs, and, decades later, Cooper¹ wrote that 5% to 10% of his patients with GCM have granulomas outside the heart. In their autopsy study and review of CS, Roberts et al³¹ concluded that the reported cases of GCM with granulomas outside the heart were likely to be CS. There are no studies comparing CS and GCM for findings on cardiac magnetic resonance imaging or PET. Lamacie et al³² recently reported on serial PET studies in a case of GCM showing uptake of 18-F fluorodeoxyglucose in the heart without any extracardiac activity. Identical findings were seen in our study in the 2 patients with GCM who had undergone PET as part of their diagnostic assessment (Table 1). However, similar findings can be seen in a significant minority of patients with CS as well.^{33,34} Although we started the present work from the concept of 2 unique and different diseases, our findings and scrutiny of the past literature suggest that CS and GCM may rather be either closely related types, “twins,” of T-cell myocarditis, or severity phenotypes of a single disease. In the latter case, GCM would represent an aggressive form of isolated CS. At the same time, fulminant GCM with a rich eosinophilic infiltrate has histologic and clinical resemblance with necrotizing eosinophilic myocarditis. Okura et al⁶ speculated on the possibility of eosinophilic proteins being responsible for the difference between the phenotypes of GCM and CS. In the Lewis rat experimental model of GCM,³⁵ giant cells and necrosis are present, but tissue eosinophilia is missing, as is myocardial granuloma formation even during the late phase of the condition. An experimental model of CS does not exist.

Strengths and Limitations

The major strength of our work resides in the study population. We included cases of CS and GCM diagnosed clinically over 25 years in our country and completed the study groups with cases diagnosed at autopsy and identified from the cause-of-death registry. The study population was considerably large, given the rarity of the diseases, and was composed of White northern Europeans exclusively. Although this is a strength of our comparative analyses, it may limit the generalizability of our data as the susceptibility and manifestations of CS and GCM may vary by the ethnicity of the population under study.¹ All diagnoses of GCM were based on myocardial histology, as were two-thirds of the CS diagnoses. In the remaining third of CS, histology of sarcoidosis was confirmed from extracardiac biopsies in conformity

with the current recommendations.^{14,15} Importantly, each GCM diagnosis was based on a reanalysis of all available myocardial specimens from lifetime biopsies, explanted native hearts, or autopsies.¹³ It should be recognized, however, that our comparative data are specific to the criteria used to distinguish GCM from CS on myocardial microscopy. Our diagnostic criteria differed from the ones used by Okura et al,⁶ as here the presence of myocardial granulomas categorically excluded the diagnosis of GCM. In the work of Okura et al, all diagnoses were based on myocardial histology and the proportion of postmortem and posttransplant case inclusions was higher than in our study. This may have resulted in more severe average disease phenotypes explaining the worse outcomes. A key limitation of our study is that a considerable number of cases were included in retrospect, such as all those diagnosed before the year 2010 or postmortem. Furthermore, the availability and use of diagnostic methods changed over the 25-year study coverage and certain important examinations, like cardiac imaging with PET or magnetic resonance and measurements of cardiac troponins and natriuretic peptides, were, therefore, missing in many cases. Only a minority of patients with GCM had undergone magnetic resonance imaging and we decided not to include the presence of myocardial late gadolinium enhancement in our analyses despite its known predictive value.^{36,37} The Cox regression models adjusting for the effects of cardiac troponins and natriuretic peptides could include less than half of the study population. This needs to be considered in interpreting the respective hazard ratios of Tables 3 and 4. The strength of our survival analyses is, on the other hand, that the composite outcome endpoint only included unequivocally hard cardiac events.

CONCLUSIONS

The present comparison of 25-year cohorts of histopathologically diagnosed CS and GCM shows that these conditions have a similar end-to-end spectrum of clinical manifestations, similar female preponderance, and similar coexistence of autoimmune diseases. They are distinguished by the severity of acute cardiac injury and dysfunction and by the long-term outcome, both being worse in GCM. The case of whether CS and GCM are unique and different entities or subgroups of a single disease cannot be brought to an issue without in-depth basic research settling their pathogenesis.

ARTICLE INFORMATION

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Affiliations

From the Heart and Lung Center (H.N., J.L., K.E., M.K.) and Department of Pathology (A.R., M.I.M.), University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; Heart Center, Turku University Hospital, Turku, Finland (T.V.); Heart Center, Kuopio University Hospital, Kuopio, Finland (H.M.); Medical Research Center Oulu, University and University Hospital of Oulu, Oulu, Finland (K.K.); Heart Hospital, Tampere University Hospital, Tampere, Finland (P.H.); Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland (T.K.); Heart Center, North Karelia Central Hospital, Joensuu, Finland (T.T.R.); Central Finland Central Hospital, Jyväskylä, Finland (J.K.); South Ostrobothnia Central Hospital, Seinäjoki, Finland (A.A.); Vaasa Central Hospital, Vaasa, Finland (P.P.); and South Karelia Central Hospital, Lappeenranta, Finland (S.U.).

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Disclosures

None.

Supplementary Material

Figure S1-S2

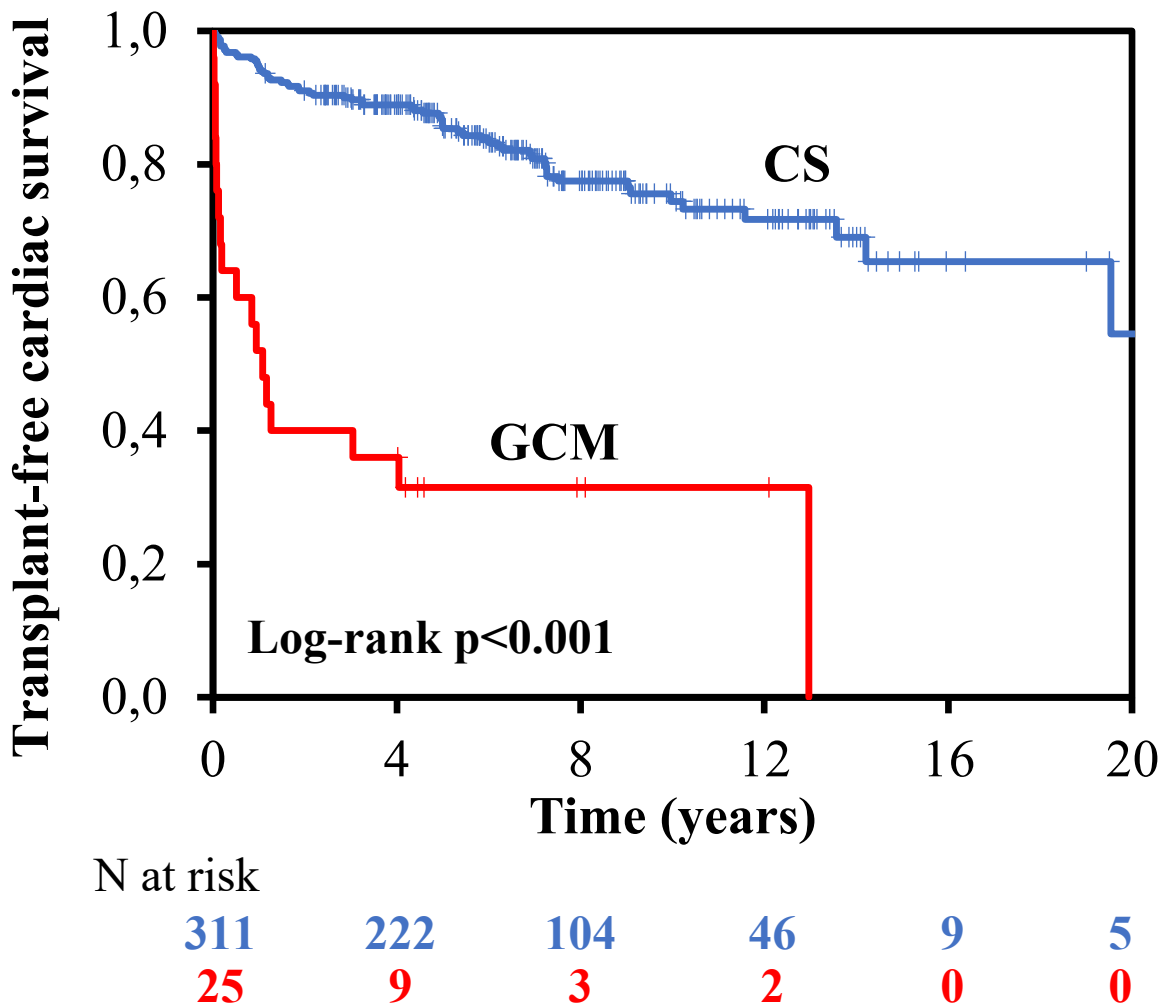
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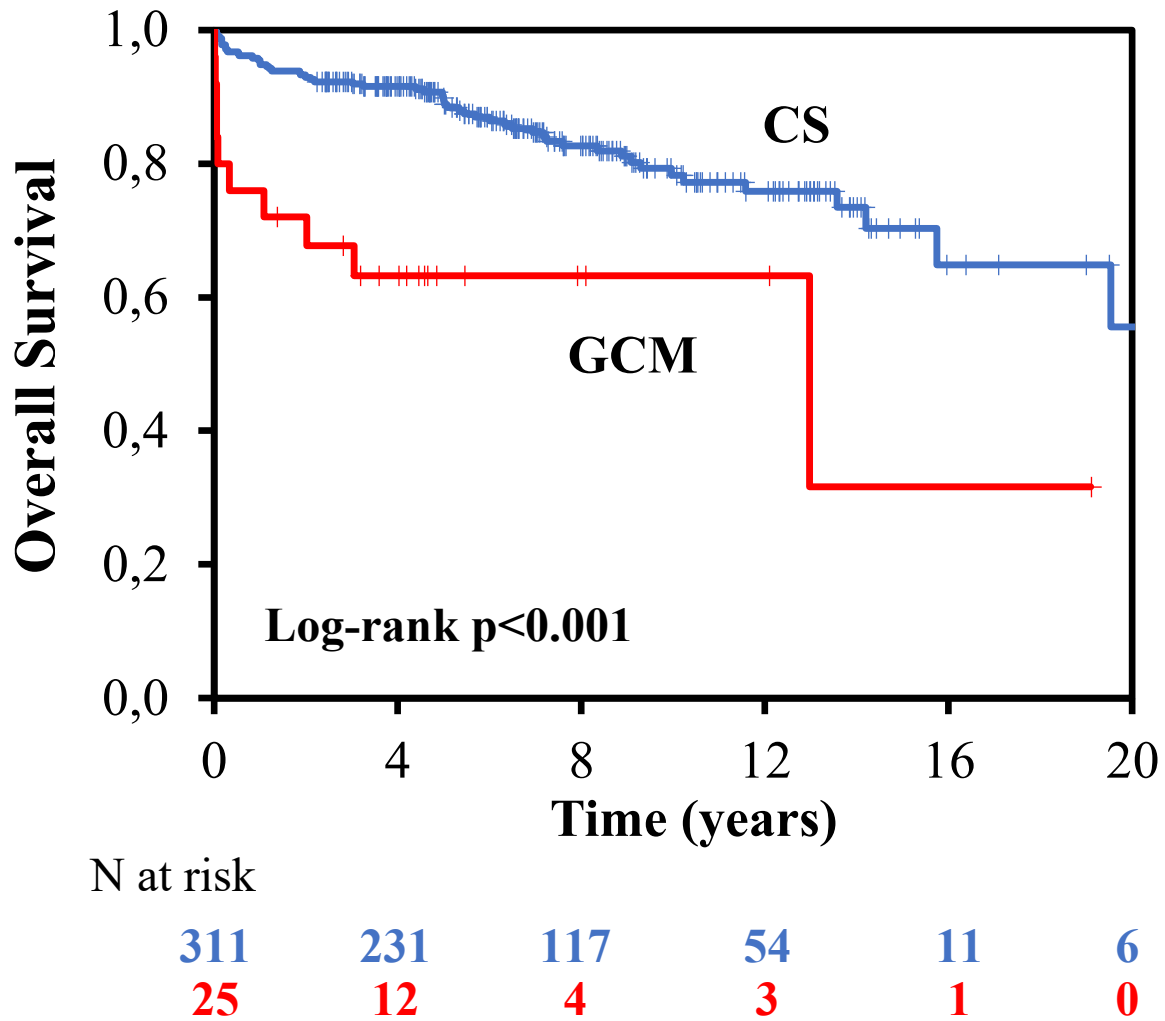
SUPPLEMENTAL MATERIAL

Figure S1. Transplant-free cardiac survival in cardiac sarcoidosis (CS) vs giant cell myocarditis (GCM).



In this analysis, the endpoint was the composite of cardiac death and transplantation; aborted cardiac deaths were not considered events. The 5-year estimate (95 % confidence interval) of event-free survival was 86% (82-90%) in CS and 32% (13-50%) in GCM.

Figure S2. Survival in cardiac sarcoidosis (CS) vs giant cell myocarditis (GCM).



In this analysis, the outcome endpoint was death from any cause thus including non-cardiac and posttransplant fatalities. Transplantations were considered part of therapy. The 5-year estimate of true survival was 89% (86-93%) in CS and 63% (44-82%) in GCM.