Long-Term Outcome in Probable Versus Absolute Cardiac Sarcoidosis

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Suspicion of cardiac sarcoidosis (CS) arises when a patient has clinical cardiac manifestations and findings on cardiac imaging suggestive of inflammatory cardiomyopathy with or without history of extracardiac sarcoidosis. The additional requirement for diagnosis is proof of sarcoidosis histology. Endomyocardial biopsy (EMB) showing granulomatous inflammation in absence of other explanations confirms an absolute diagnosis of CS while similar histology in an extracardiac biopsy gives a probable diagnosis of CS. Our aim was to study the equivalence of probable to absolute CS in terms of patients' characteristics and outcome. We reviewed the available clinical information, diagnostic procedures, details of treatment and event-free survival of 149 consecutive patients (103 women, mean age 50 y) diagnosed with CS at our institution. The diagnosis was absolute in 68 patients and probable in 81 patients. There was no difference in age or sex distribution between the diagnostic subgroups but left ventricular dysfunction on echocardiography (ejection fraction <50%) was more common in absolute CS (60% vs 36%, p = 0.003) as was abnormal myocardial late gadolinium enhancement on magnetic resonance imaging (96% vs 78%, p = 0.006). Over a median of 54 months of follow-up, 19 of 68 patients with absolute CS versus 15 of 81 with probable CS either died, suffered an aborted sudden cardiac death or underwent cardiac transplantation (log rank p = 0.334). In conclusion, in terms of prognosis, clinical diagnosis of CS supported by extracardiac histology is equivalent to diagnosis confirmed by myocardial histology. No distinction should be made between probable and absolute CS as regards treatment and follow-up. **(Am J Cardiol 2019;123:674−678)**

Sarcoidosis is a granulomatous inflammation that may involve the heart as a subclinical or manifest segment of a multiorgan disease or, more rarely though not exceptionally, as an isolated heart condition.[1−3] Even as a clinically silent or isolated disease, cardiac sarcoidosis (CS) entails significant future morbidity and mortality on the afflicted individuals.[4,5] Its diagnosis is challenging since, to be absolute, it requires histology of sarcoidosis in a sample of myocardium, yet the sensitivity of endomyocardial biopsy (EMB) is no better than 25% to 30% and remains below 60% even after repeated biopsies.[6,7] It is therefore understandable that some diagnostic uncertainty needs to be tolerated in clinical practice. Two experts' recommendations[8,9] have recently defined probable CS as a diagnostic category where clinical manifestations and/or findings on cardiac imaging consistent with inflammatory cardiomyopathy associate with extracardiac documentation of sarcoid histology. Provided alternative causes are excluded the likelihood of true CS is considered high enough for clinical practice.[8,9] The recommendations even go as far as to prefer extracardiac biopsies over EMB in the diagnostic process.[9] Yet, as regards the characteristics, course and prognosis of CS, the equivalence of probable to absolute CS has not been properly studied, let alone proven hitherto. To bridge this gap in knowledge, we identified all patients diagnosed with CS at our institution over the last 3 decades, divided them into the above groups of diagnostic certainty and compared their characteristics, disease manifestations, treatment, and long-term outcome. Our data suggest a more extensive myocardial involvement with absolute diagnosis of CS but no difference in long-term survival free of life-threatening cardiac events.

Methods

Consecutive patients diagnosed alive with CS at Helsinki University Central Hospital since 1988 were considered for the present work. Cases of CS detected only at autopsy were omitted. The diagnostic criteria for CS have been detailed in our earlier reports[5,7] and required either myocardial histology of noncaseating granulomatous inflammation typical for sarcoidosis, representing absolute CS,[8,9] or extracardiac sarcoid histology associated with both clinical manifestations and findings compatible with myocardial disease at either gadolinium-enhanced cardiac magnetic resonance imaging (Gd-MRI) or 18-F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) or echocardiography, representing probable CS.[8,9] Other causes of myocardial disease had to be excluded. Until 2005, patients admitted to our hospital for high-grade atrioventricular block (AVB), sustained ventricular tachycardia

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(VT), or left ventricular (LV) dysfunction, that is, for signs of myocardial disease, underwent routine laboratory tests, 12-lead electrocardiogram, chest X-rays, echocardiography, and coronary angiography if ischemic heart disease could not be otherwise excluded. If the initial studies raised suspicion of inflammatory or other cardiomyopathy amenable to specific treatment, like CS, giant cell or eosinophilic myocarditis or amyloidosis, right ventricular EMB was done. In 2005 to 2006, Gd-MRI and ^{18}F-FDG PET were adopted into routine use at our institution changing our diagnostic practice. Thereafter similar patients regularly also underwent Gd-MRI unless this was contraindicated. Findings suggestive of myocardial inflammation, like myocardial edema or late gadolinium enhancement (LGE), led to EMB from the right or left ventricle depending on the localization of MRI abnormalities. Cardiac or preferably whole-body ^{18}F-FDG-PET combined with resting myocardial perfusion imaging was done if MRI was contraindicated, if the findings on MRI were nonrevealing or if the first MRI-guided EMB was nondiagnostic but a suspicion of CS persisted. Focal myocardial ^{18}F-FDG uptake with or without a superimposable perfusion defect led to EMB. If this was negative and there was ^{18}F-FDG accumulation outside the heart, or if abnormal ^{18}F-FDG uptake was found only outside the heart, extracardiac tissue biopsy was done. In patients with previous histologically proven other organ sarcoidosis, diagnosis of CS was based on cardiac signs and symptoms and findings on MRI and/or PET.

In June 2017, our database included altogether 153 consecutive patients diagnosed with CS during life. Of them, 4 patients were excluded since they had been diagnosed from native hearts removed at transplantation. The remaining 149 patients constitute the present study population with the overwhelming majority of them (n = 143) having been diagnosed after 2005, that is, during the diagnostic era of MRI and ^{18}F-FDG PET. The hospital charts of all patients were scrutinized in retrospect for demographics, cardiac signs and symptoms, laboratory tests, imaging studies, diagnostic biopsies and treatment, and the data pertinent to the present work were collected for analysis. The patients had been followed at our institution and their adverse events including death, aborted sudden cardiac death (SCD), and heart transplantation were updated for the present analyses at the end of December 2017. Aborted SCD was defined as ventricular fibrillation terminated either by an intracardiac cardioverter defibrillator (ICD) or externally during successful resuscitation. The study was performed according to the principles of the Declaration of Helsinki. The Ethics Committee for the Department of Medicine, Helsinki University Central Hospital, approved the study protocol, and the MIDFIN registry study has been approved by the national ethical review board (STM/1219/2009).

All statistical analyses were performed with the SPSS for Windows 24.0 statistics (SPSS, Chicago, IL). Data are presented as mean ± SD for continuous variables and as absolute numbers or percentages for categorical variables, unless otherwise noted. Normal distribution and homogeneity of variance were checked before further analyses. Between group comparisons for continuous variables were made with the Student's *t* test. Comparisons of discrete variables between groups were assessed with χ^2 test or Fisher's exact test. The primary endpoint in outcome analyses was a composite of cardiac death, cardiac transplantation, and aborted SCD. The survival was calculated from the date of diagnosis and analysed and plotted as Kaplan-Meier curves. All statistical tests were 2-tailed, and $p < 0.05$ was regarded as statistically significant.

Results

Among the 149 patients with CS, the diagnosis was absolute in 68 patients and probable in 81 patients. All absolute diagnoses were made from EMBs, 55 at the first procedure and 13 at repeats after a nondiagnostic primary EMB. The median time from the first symptoms to absolute diagnosis of CS was 1 month (range, 0.1 to 38 months). Histologic confirmation of sarcoidosis for the probable CS diagnosis was obtained from mediastinal lymph nodes in 63 patients and from other extrathoracic tissues in 18 patients. Before the confirmatory extracardiac biopsy, 64 of these 81 patients had undergone at least 1 nonrevealing EMB. All patients with probable CS had both history of clinical symptoms and findings on either cardiac MRI (myocardial LGE) or PET (focal cardiac ^{18}F-FDG uptake) compatible with inflammatory cardiomyopathy. The median time from the first symptoms to diagnosis of probable CS was 4 months with a range of 0.1 to 75 months ($p = 0.003$ vs absolute CS). Altogether 167 EMBs were taken during the diagnostic process in the total study population, 152 from the right ventricle and 15 from the left. No serious complications were recorded.

Table 1 summarizes the key characteristics and therapeutic interventions in the diagnostic subpopulations of CS. Age and gender distribution were comparable in the two groups. Heart failure and LV systolic dysfunction at presentation were statistically significantly more common in patients with absolute CS, as was the presence of LGE on cardiac MRI (Table 1). The frequency of focal cardiac ^{18}F-FDG uptake on PET was uniformly high in both groups. Extracardiac ^{18}F-FDG uptake, instead, was less common with absolute than with probable CS (39% vs 93%, $p = 0.001$) but whole-body PET was available for only one-third of patients with absolute CS (Table 1). All patients received basically similar immunosuppressive therapy irrespective of the diagnostic subgroup (see Table 1). As for the device treatment, a higher proportion of patients with absolute CS received an ICD (57 of 68 vs 52 of 81, $p = 0.009$).

In the total CS population, follow-up from diagnosis to the first event of the composite endpoint, or to the end of December 2017, lasted from 2 to 278 months (median, 54 months). In the absolute CS group, 2 patients suffered a cardiac death, 4 patients underwent cardiac transplantation and 13 experienced an aborted SCD with ventricular fibrillation defibrillated by an ICD or externally during resuscitation in 9 and 4 cases, respectively. The events in the probable CS group included 3 cardiac deaths, 1 cardiac transplantation, and 11 aborted SCDs with ventricular fibrillation treated by an ICD in 9 cases and defibrillated externally in 2 cases. Figure 1 shows the Kaplan-Meier

Table 1
Key characteristics and therapeutic interventions in the diagnostic subgroups of CS

Variable	Absolute CS (n = 68)	Probable CS (n = 81)	p*
Male/Female	20/48	26/55	0.724
Age, years (mean ± SD)	51 ± 11	49 ± 11	0.500
Diagnosis of ES before CS	7 (10%)	16 (20%)	0.171
Main presenting manifestation of CS			
High-grade atrioventricular block	27 (40%)	44 (54%)	0.075
Ventricular tachycardia	21 (31%)	18 (22%)	0.231
Heart failure	17 (25%)	10 (12%)	0.046
Other	3 (4%)	9 (11%)	0.134
Echocardiography			
LV dysfunction (EF <50%)	41 (60%)	29 (36%)	0.003
LV dilatation**	26/61 (43%)	19/76 (25%)	0.061
Magnetic resonance imaging			
Myocardial LGE	50/52 (96%)	47/60 (78%)	0.006
^{18}F-FDG PET			
Abnormal cardiac uptake	31/33 (94%)	65/73 (89%)	0.687
Abnormal extracardiac uptake	13/33 (39%)	68/73 (93%)	0.001
Immunosuppressive therapy	68/68	81/81	1.000
Corticosteroids	67	79	
Azathioprine	37	26	
Mycophenolate	9	11	
Methotrexate	3	1	
Infliximab/golimumab	5	2	
Cyclosporine	2	0	
Intracardiac device therapy			
Cardioverter defibrillator	57 (84%)	52 (64%)	0.009
Permanent pacemaker	7 (9%)	20 (22%)	0.032

The data are numbers (%) of patients.
CS = cardiac sarcoidosis; ES = extracardiac sarcoidosis; EF = ejection fraction; LV = left ventricular; LGE = late gadolinium enhancement; ^{18}F-FDG PET = ^{18}F-fluorodeoxyglucose positron emission tomography.
** Left ventricular end-diastolic diameter >60 mm in men and >55 mm in women.
* *p*, difference between groups.

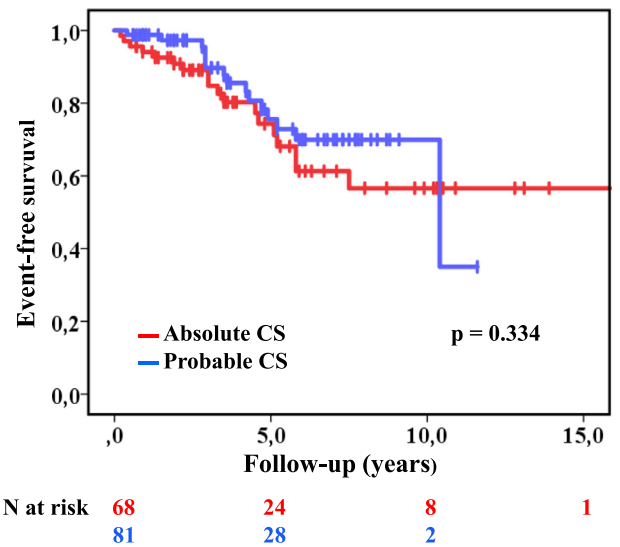

Figure 1. Kaplan-Meier curves for cardiac survival free of the composite of death, aborted sudden cardiac death and heart transplantation in patients with absolute versus probable CS.

curves for event-free cardiac survival. The 5-year survival estimate was 53% (95% CI, 49% to 57%) with absolute CS and 56% (95% CI, 53% to 58%) with probable CS.

Discussion

The main finding of our study was that diagnosis of CS based on the combination of extracardiac sarcoidosis histology with clinical manifestations and cardiac imaging compatible with inflammatory cardiomyopathy has similar prognostic implications as diagnosis confirmed by a study of myocardial histology. This observation bears significantly on daily work as it supports the clinical equivalence of probable to absolute diagnosis of CS as long as the former adheres to the criteria specified in recent recommendations[8,9] and used in our study.

The only earlier study comparing diagnostic subgroups in CS found, unlike us, a worse outcome in probable than in definite CS.[10] However, the subgroups were different from ours since patients with probable CS had neither clinical nor histologic evidence of sarcoidosis but only cardiac manifestations included in the Japanese diagnostic criteria[11] (and seen in many other myocardial diseases as well). They did not receive immunosuppressive treatment either. Further, the majority of patients with definite CS, too (29 of 47), were devoid of any histologic proof of sarcoidosis and would not have qualified even for probable CS in our study. These differences in the definitions of "probable" and "absolute/definite" can be traced to the criteria of the Japanese Ministry of Health and Welfare that do not require histology of sarcoidosis for the diagnosis of CS.[11] The

Japanese criteria have been widely used worldwide but are no longer recommended by experts in the field.[8,9]

Our patients with absolute CS had more often LV dysfunction and heart failure at presentation, as well as more myocardial LGE on cardiac MRI, than patients with probable CS. Since the majority of individuals (80%) with probable diagnosis also had undergone at least one EMB this difference may reflect an increased likelihood of the biopsy hitting granulomas and providing absolute diagnosis with more extensive myocardial involvement. Given the difference in the extent of LV involvement one would have expected a difference in event-free survival, too.[3–5,12] However, our composite endpoint included only hard events (death, aborted SCD, and transplantation) and their total number (34 events in 149 patients over a median of 54 months) may not have been sufficient to expose a subtle but true subgroup difference in prognosis.

The Heart Rhythm Society's expert consensus statement[9] prefers extracardiac biopsies over EMB as the primary way to histologic diagnosis in suspected CS. The recommendation is based on assumptions of higher sensitivity and safety with extracardiac biopsies. The equivalence of our diagnostic subgroups in terms of prognosis gives support to that policy if targets for biopsy outside the heart are identified. EMBs are still needed, however, since isolated CS, that is, sarcoidosis confined to the heart, cannot be identified without a study of myocardial histology. A recent literature review found an approximate rate of 25% for isolated CS among all patients with CS.[13] In our own earlier report, the proportion of isolated cardiac involvement was 31%[14] by whole-body ^{18}F-FDG PET, but clearly smaller rates have also been reported.[15] Giant cell myocarditis is an inflammatory cardiomyopathy that resembles CS in many respects, including clinical manifestations, patients' demographics and adverse events, although its course is frequently more rapid and serious.[1,16] A firm distinction between isolated CS and giant cell myocarditis is impossible without myocardial histology. EMB has the additional advantage over extracardiac biopsy of enabling other than histologic studies, including myocardial gene expression profiling, that may help detect CS and distinguish it from giant cell myocarditis.[17] Recently, the yield of EMB has been improved by using electroanatomic mapping to guide the procedure.[18] We have preferred EMB over extracardiac biopsy in suspected CS whenever cardiac imaging suggests myocardial involvement that is not negligible and looks accessible to biopsy from inside either right or left ventricle. In selected cases of suspected serious focal myocardial inflammation with negative EMBs, we have used core-needle LV biopsies taken through a left minithoracotomy to ascertain the diagnosis and ensure proper therapy.[19] We justify our persevering biopsy policy with the serious and long-lasting consequences that the diagnosis of CS has to the individual involved. It becomes a lifetime companion, brings along an increased risk of premature death and the anxiety thereof, nearly invariably sets off long-term immunosuppressive treatment and constitutes an indication to consider an intracardiac cardioverter-defibrillator.[3] Given the risks of the disease and of its treatments, the diagnosis should, in our view, leave as little room for doubt as possible.

It needs recognition that our work was not a prospective study of 2 diagnostic strategies but a retrospective comparison of subgroups of CS generated by our diagnostic practice that, as described in Methods, aimed at absolute diagnosis from EMB. The subgroup of probable CS therefore represents cases where myocardial histology could not be studied or was nonrevealing, sometimes after repeated biopsies, and where histology was confirmed from tissues outside the heart. We admit that the way our subgroups were formed is a limitation of our data and may explain some of the differences in the characteristics of the subgroups. The other limitations are the single center experience, relatively small sample size, and a relatively short follow-up. However, it should not call in question our main finding, that is, the comparable prognostic significance of probable with absolute diagnosis of CS.

We conclude that a combination of cardiac manifestations suggestive of CS with cardiac imaging compatible with inflammatory cardiomyopathy and extracardiac histology of sarcoidosis represents true CS with a certainty that, though short of absolute, qualifies without restrictions for diagnosis and clinical decision making.

Disclosures

The authors have no conflicts of interest to disclose.

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