Published by Elsevier Science Inc.
ISSN 0735-1097/03/$30.00
PII S0735-1097(02)02715-8

A Clinical and Histopathologic Comparison of Cardiac Sarcoidosis and Idiopathic Giant Cell Myocarditis

Yuji Okura, MD, PHD,* G. William Dec, MD, FACC,§ Joshua M. Hare, MD, FACC,‖ Makoto Kodama, MD,¶ Gerald J. Berry, MD,# Henry D. Tazelaar, MD,† Kent R. Bailey, PHD,‡ Leslie T. Cooper, MD, FACC*

Rochester, Minnesota; Boston, Massachusetts; Baltimore, Maryland; Niigata, Japan; and Stanford, California

OBJECTIVES The goal of this study was to determine the prognostic value of clinical data available at presentation and histology in cardiac sarcoidosis (CS) and idiopathic giant cell myocarditis (IGCM).

BACKGROUND The prognosis of patients with nonischemic cardiomyopathy is partly dependent on the histologic diagnosis. Survival in IGCM is poor. The prognosis of a histologically related entity, cardiac sarcoidosis (CS), is less well established, and the prognostic value of the distinction between CS and IGCM on endomyocardial biopsy (EMB) is unknown.

METHODS We identified 115 patients from the Multicenter IGCM Registry with CS (n = 42) and IGCM (n = 73). We compared the clinical data for these two groups using Cox proportional-hazards models to assess the association between histologic diagnosis and survival. In order to determine whether histologic features could reliably differentiate these two entities, two cardiac pathologists semiquantitatively graded the inflammatory infiltrate components and compared the results between groups.

RESULTS Black race was more frequent in the CS group (31% vs. 4%, $p < 0.0001$). Syncope and atrioventricular block were also more frequently observed in CS than IGCM (31% vs. 5%, $p = 0.0002$ and 50% vs. 15%, $p < 0.0001$, respectively). Left-sided heart failure was more common in IGCM (40% vs. 64%, $p = 0.013$). In CS patients diagnosed by EMB, the five-year transplant-free survival after diagnosis was 69.8% versus 21.9% for IGCM ($p < 0.0001$, log-rank test). In multivariate models, presentation with heart failure predicted IGCM, and presentation with heart block or more than nine weeks of symptoms predicted CS. Eosinophils, myocyte damage, and foci of lymphocytic myocarditis were more frequent in IGCM, while granulomas and fibrosis were more frequent in CS.

CONCLUSIONS Transplant-free survival is better for patients with CS than for IGCM diagnosed by EMB. Presentation with heart failure predicted IGCM, and presentation with heart block or more than nine weeks of symptoms predicted CS. (J Am Coll Cardiol 2003;41:322–8i) © 2003 by the American College of Cardiology Foundation

The prognosis of patients with nonischemic cardiomyopathy is partly dependent on the histologic diagnosis (1). For example, transplant-free survival is much worse for patients with idiopathic giant cell myocarditis (IGCM) than lymphocytic myocarditis (2). An unanswered question is whether IGCM is part of the spectrum of cardiac sarcoidosis (CS) (or idiopathic granulomatous myocarditis) or a distinct clinical and histologic entity (3–5). Reports of IGCM and CS consist of isolated cases and small single-center autopsy series (6). Idiopathic giant cell myocarditis and CS are sometimes grouped together in clinical series (7). Because a systematic clinical and histologic comparison of these entities has not been reported, the value of their distinction remains uncertain.

Idiopathic giant cell myocarditis is a rapidly fatal disorder characterized by the presence of multinucleated giant cells and a lymphocytic inflammatory infiltrate, associated with myocyte necrosis (8). If noncaseating granulomas are present and infectious etiologies are excluded, the diagnosis is idiopathic granulomatous myocarditis or CS (6). This histologic distinction is not based on proven clinical or mechanistic differences between these disorders.

Cardiac sarcoidosis and IGCM are rare and present with similar symptoms. No single center has accumulated a sufficient number of cases diagnosed during life to compare their natural histories (9). Clinical findings of congestive heart failure (CHF), ventricular arrhythmias, and heart block are associated with both CS and IGCM (2,10–12). The relative frequency of cardiac events in these disorders is not known. To assess the value of the histologic distinction of CS and IGCM, we compared the presentation and clinical course of CS and IGCM in 115 patients with histologically confirmed disease.

From the *Division of Cardiovascular Diseases, †Division of Anatomic Pathology, and ‡Department of Biostatistics, Mayo Clinic and Foundation, Rochester, Minnesota; §Cardiovascular Division, Massachusetts General Hospital, Boston, Massachusetts; ‖Cardiovascular Division, Johns Hopkins Hospital, Baltimore, Maryland; ¶First Department of Internal Medicine, Niigata University School of Medicine, Niigata, Japan; and the #Department of Pathology, Stanford University Medical Center, Stanford, California. Supported by Merck-Banyu Fellowship Award (Y.O.) and Leder Family Philanthropic Foundation Grant (L.T.C. and J.M.H.).

Manuscript received March 26, 2002; revised manuscript received August 30, 2002, accepted October 14, 2002.

Abbreviations and Acronyms

CHF = congestive heart failure
CI = confidence interval
CS = cardiac sarcoidosis
EMB = endomyocardial biopsy
IGCM = idiopathic giant cell myocarditis
JHH = Johns Hopkins Hospital
MCR = Mayo Clinic Rochester
MGH = Massachusetts General Hospital
NUH = Niigata University Hospital
SUMC = Stanford University Medical Center

METHODS

Patient selection. Five of the participating centers ("core centers") in the Giant Cell Myocarditis Registry with large referral populations and expertise in CS and IGCM systematically searched the surgical and autopsy pathology records to gather all cases of pathologically confirmed CS and IGCM. These centers are Mayo Clinic Rochester (MCR), Minnesota; Johns Hopkins Hospital (JHH), Baltimore, Maryland; Massachusetts General Hospital (MGH), Boston, Massachusetts; Stanford University Medical Center (SUMC), Stanford, California; and Niigata University Hospital (NUH), Niigata, Japan. The dates of case diagnosis are as follows: MCR (January 1982 to November 1999), JHH (March 1987 to December 1997), MGH (November 1980 to July 1996), SUMC (March 1983 to July 1999), NUH (May 1985 to February 1997).

In addition to the analysis of all cases at these core centers, pathologically confirmed cases of CS and IGCM referred to the registry from other centers were included in a separate analysis. The distribution of cases and method of diagnosis at core and non-core centers is described in Table 1. The "non-core" centers include those participating in the original Giant Cell Myocarditis Registry (see December 18 *JACC* issue on the internet www.cardiosource.com/jacc.html for online Appendix) (2). The cases of idiopathic giant cell myocarditis in the original registry were solicited through study announcements placed in *Circulation* (13), the *Journal of the American College of Cardiology* (14), the *American Heart Journal* (15), the *American Journal of Cardiology* (16), and the *Journal of Heart and Lung Transplantation* (17), as well a thorough direct mailing to the directors of transplantation centers participating in the United Network for Organ Sharing and to other cardiovascular centers worldwide.

Investigators completed a case report form requesting anonymous historical data on the medical history, presenting symptoms, cardiac rhythm, and treatment. Respondents were asked to list test results that excluded other causes of myocarditis. Outcomes including death, heart transplant, and date of last follow-up were obtained. Two patients were excluded from analysis; both had concomitant ischemic cardiomyopathy, and one patient had cor pulmonale that prevented accurate timing of symptom onset.

Pathologic analysis. The initial diagnosis of CS or IGCM was based on review of the tissue at the time of entry into the trial based on published criteria (8) by the local pathologist. Among these, 83 had the diagnosis confirmed by either H.D.T. or G.J.B. The diagnosis of CS required the presence of at least one nonnecrotizing granuloma, with or without foci of lymphocytic myocarditis, necrosis, or the presence of isolated giant cells. The diagnosis of IGCM required the presence of a widespread inflammatory infiltrate with multinucleated giant cells in association with myocyte damage (Fig. 1). The presence of a nonnecrotizing granuloma alone in this background was insufficient to classify a case as CS if the degree of necrosis was judged to be out of proportion of the degree of granulomatous inflammation. Cases that did not fulfill these criteria were excluded from analysis.

At the time of the current study, 74 of the specimens were available for review. Although it was our impression that the previously described criteria were sufficient for separating these two entities histologically, there has been an ongoing debate about whether they are, in fact, two or one disease. Therefore, we thought that a direct comparison of histologic features seen in the pathologic material should be performed. To this end, one of two cardiac pathologists (G.J.B. or H.D.T.) then re-reviewed the available material (endomyocardial, surgical, or autopsy) and scored the specimens on a semiquantitative four-point scale (from 0 to 3+) for multinucleated giant cells, granulomas, necrosis, lymphocytes, eosinophils, fibrosis, and foci of lymphocytic myocarditis.

To assess for consistency of scoring among pathologists, both pathologists scored the same 10 specimens independently. This analysis revealed that there was no significant difference in scoring between pathologists (p values for the

Table 1. Distribution of Cases and Method of Diagnosis

	Idiopathic Giant Cell Myocarditis		
	No. of Cases (%)		
	Core Center (%)	Non-Core Center (%)	All (%)
Biopsy	16 (57)	22 (49)	38 (52)
Explant	4 (14)	11 (24)	15 (21)
Autopsy	8 (29)	9 (20)	17 (23)
Others*	0 (0)	3 (7)	3 (4)
Total	28 (100)	45 (100)	73 (100)
	Cardiac Sarcoidosis		
	No. of Cases (%)		
	Core Center (%)	Non-Core Center (%)	All (%)
Biopsy	25 (71)	4 (57)	29 (69)
Explant	5 (14)	3 (43)	8 (19)
Autopsy	4 (11)	0 (0)	4 (10)
Others*	1 (3)	0 (0)	1 (2)
Total	35 (100)	7 (100)	42 (100)

*Others included three left ventricular apexes during assist device placement in idiopathic giant cell myocarditis and one atrial specimen at maze operation in cardiac sarcoidosis.

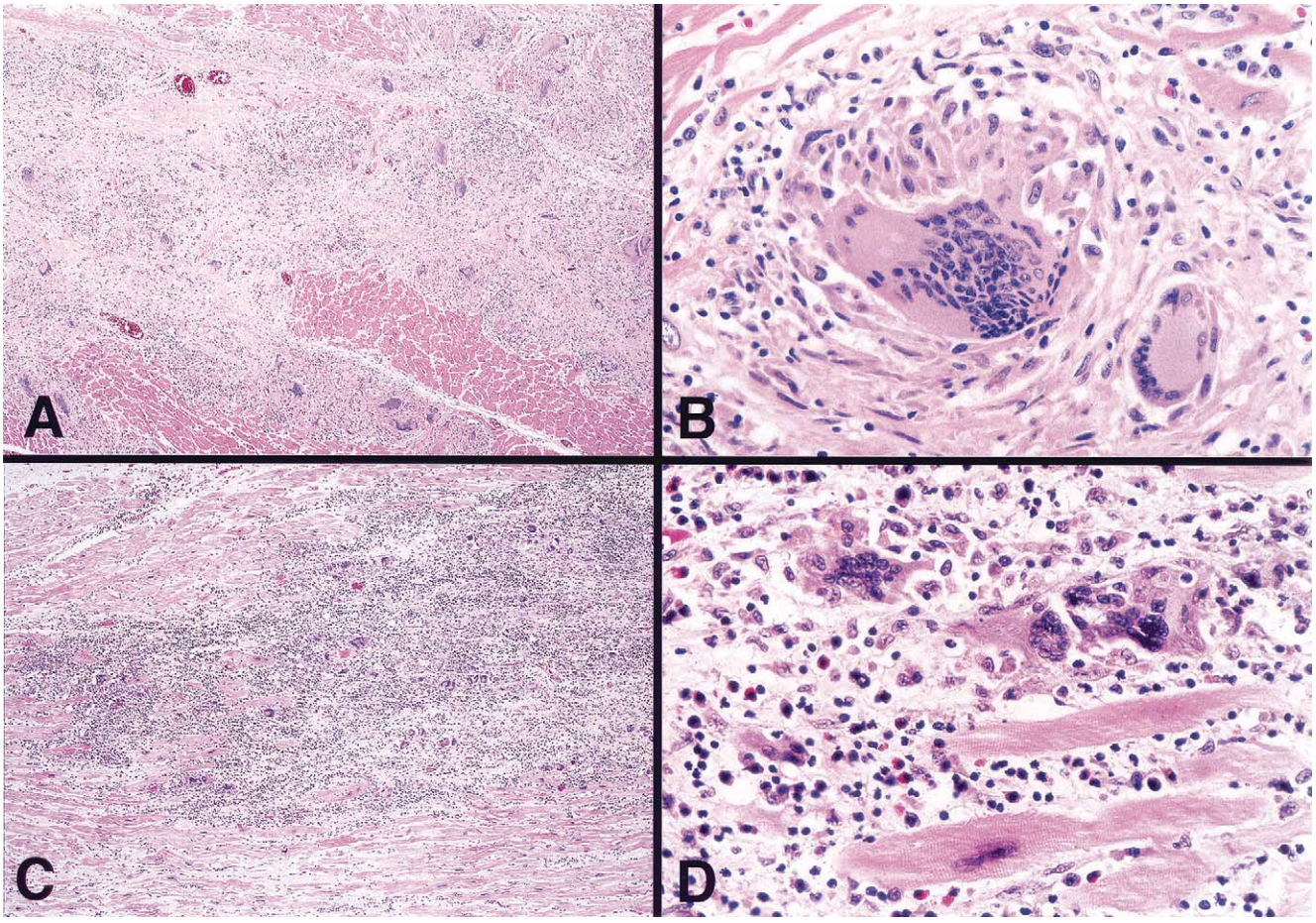

Figure 1. **(A)** Cardiac sarcoidosis characterized by coalescence of granulomatous elements along lymphatic pathways of the myocardial interstitium (H&E × 60). **(B)** High-power magnification showing well-formed nonnecrotizing granulomas composed of epithelioid histiocytes and giant cells embedded in callagenous stroma. Mononuclear inflammatory cells and fibroblasts surround the granulomas (H&E × 400). **(C)** Idiopathic giant cell myocarditis (IGCM) showing widespread necrosis of myocytes by a dense cellular infiltrate (H&E × 100). **(D)** High-power magnification of IGCM displaying giant cells, lymphocytes, histiocytes, eosinophils, and damaged myocytes (H&E × 400).

comparison of scores for each parameter measured ranged from 0.11 to 0.90). The pathologists agreed completely or disagreed by one point (on the four-point scale) for multinucleated giant cells (100%), granulomas (88%), necrosis (100%), lymphocytes (100%), eosinophils (88%), fibrosis (100%), and foci of lymphocytic myocarditis (100%).

Idiopathic giant cell myocarditis and CS had distinct histologic features. Cardiac sarcoidosis specimens had more granulomas ($p < 0.0001$) and fibrosis ($p = 0.0002$), while the IGCM specimens had more necrosis ($p = 0.0217$), foci resembling lymphocytic myocarditis ($p = 0.0427$), and eosinophils ($p < 0.0001$). There were equivalent numbers of giant cells in the CS and IGCM specimens (Fig. 2).

Statistical analysis. The demographics of CS and IGCM cases were compared using the Wilcoxon rank-sum test for continuous variables, and the chi-square or Fisher exact test for dichotomous variables. Fisher exact test was used when the expected count was <5. Multivariate comparison of the two diseases was done by logistic regression modeling. The demographics of cases (within disease category) at the five core and the non-core centers were also compared to assess presence or absence of referral bias in the core center populations. Finally, the patient characteristics, including the presenting symptoms, time from onset of symptoms to presentation, time from onset to diagnosis, and the presence and types of arrhythmia and heart block at presentation for all cases of CS and IGCM from core and non-core centers were compared.

The primary end point for assessing outcome was heart transplantation or death. Transplant-free survival rates in the CS and IGCM cases were compared using the log-rank test. Because of the makeup of cases including cases diagnosed at biopsy, explant, or autopsy, two different comparisons of survival were performed. First, survival from date of endomyocardial biopsy (EMB) diagnosis to death, transplant, or last follow-up was compared in all biopsy-diagnosed cases ($n = 67$). This analysis is mostly free from assumptions, because patients had to have an established diagnosis to enter the study. However, it was also deemed of interest to compare survival from onset of symptoms in all patients ($n = 115$). This latter analysis makes the assumption that patients who were ultimately diagnosed, whether by biopsy, explanted heart, or autopsy were representative of

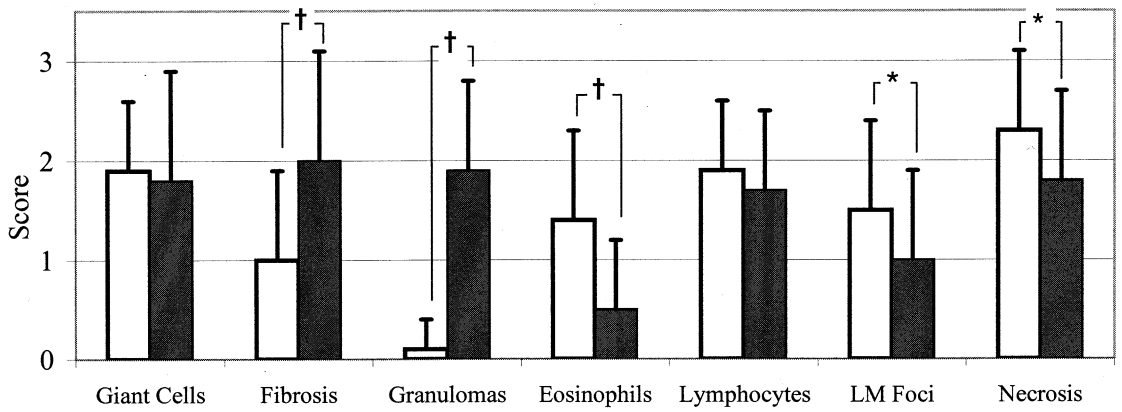

Figure 2. Histologic scores for 75 cases of idiopathic giant cell myocarditis (IGCM) and cardiac sarcoidosis (CS). Scores were compared using the Wilcoxon rank-sum test. *$p < 0.05$; †$p < 0.01$. **Open bar** = IGCM; **solid bar** = CS.

all those who contract each respective disease. Each of these two analyses was repeated on the subset of patients diagnosed at the core centers.

In the comparative survival analysis from biopsy diagnosis, log-rank tests were supplemented by proportional hazards models to adjust for potential confounding variables. Variables considered were age, gender, race, symptoms at presentation, and duration of symptoms. Because of the highly skewed distribution of time from onset of symptoms to diagnosis, this variable was converted into an ordinal scale (≤14 days, 15 to 30, 31 to 179, ≥180 days). In the comparative survival analysis from symptom onset, age, gender, and race were considered as adjusting variables.

RESULTS

Patient characteristics. The demographics for patients from core and non-core centers are described in Table 2. The mean (±SD) age of the 42 patients with CS was 44.7 ± 10.8 years at time of onset of symptoms. This was not significantly different from the age at symptom onset for the 73 patients with IGCM (42.5 ± 13.2). The ages of CS and IGCM patients at core and non-core centers were similar.

The percentage of men was not significantly higher in patients with CS (62%) than in patients with IGCM (52%) in the total cohort ($p = 0.31$) and at the five core centers (CS, 66%; IGCM, 46%, $p = 0.13$). Although the percentage of blacks in CS was higher than in IGCM at the five core centers ($p < 0.001$, Table 2), CS and IGCM were diagnosed most often in whites. The racial composition of our study population may reflect the demographics of the referral populations and not actual differences in the disease prevalence.

Table 2. Patients Characteristics

Characteristics	Idiopathic Giant Cell Myocarditis (n = 73)	Cardiac Sarcoidosis (n = 42)
Age at onset (yr)	42.5 ± 13.2	44.7 ± 10.8
Time; onset to hospital present (mo)	1.2 ± 4.4	5.5 ± 12.1*
Time; onset to diagnosis (mo)	5.0 ± 10.0	29.7 ± 53.3†
Male gender (%)	38 (52)	26 (62)
Ethnicity		
White race (%)	55 (75)	15 (36)‡
Black race (%)	3 (4)	13 (31)‡
Asian race (%)	5 (7)	2 (5)
Other races (%)	4 (6)	2 (5)
Unknown (%)	6 (8)	10 (24)

Plus-minus values are means ± SD. *$p < 0.01$; †$p < 0.005$; ‡$p < 0.001$.

The duration from symptom onset to presentation and symptom onset to diagnosis were greater for CS than IGCM (Table 2; CS, 5.5 ± 12.1 months vs. IGCM, 1.2 ± 4.4 months, $p < 0.01$, and CS, 29.7 ± 53.3 months vs. IGCM, 5.0 ± 10.0 months, $p < 0.005$, respectively). This difference was observed at both core and non-core centers.

Left-sided CHF was more common at presentation in IGCM than in CS (Table 3, $p = 0.0127$), although the left ventricular ejection fraction was similar in the two groups ($n = 85$; IGCM, 29.1% ± 11.2% vs. CS, 30.7% ± 15.5%). Syncope and atrioventricular block were more common in CS (syncope, $p = 0.0002$ and atrioventricular block, $p < 0.0001$). Ventricular tachycardia was commonly observed in both groups at presentation.

The use of pacemakers was more common in the CS group than in the IGCM group (Table 4, 45% vs. 25%, $p < 0.05$); however, the use of intraaortic balloon counterpulsation (2% vs. 34%, $p < 0.001$), ventricular assist devices (0% vs. 16%, $p < 0.05$), and heart transplantation (29% vs. 51%, $p < 0.05$) was more common in the IGCM group. When core and non-core centers treatments for IGCM were compared, the use of intraaortic balloon counterpulsation (18% vs. 44%, $p < 0.05$), ventricular assist devices (4% vs. 24%, $p < 0.05$), and heart transplantation (32% vs. 62%, $p < 0.05$) was more common in the non-core centers.

Survival. The transplant-free survival probability was 10% in the IGCM group ($n = 73$) and 60.5% in the CS group ($n = 42$) at five years after symptom onset ($p < 0.0001$ by log-rank test, Fig. 3A). The survival five years after biopsy diagnosis for the 67 patients diagnosed by EMB (Fig. 3B) was also worse in the IGCM group (21.9%) than the CS group (69.8%, $p < 0.0001$ by log-rank test). When the

Table 3. Symptoms at Hospital Presentation

Characteristics	Idiopathic Giant Cell Myocarditis		Cardiac Sarcoidosis	
	Core Centers (n = 28)	All (n = 73)	Core Centers (n = 35)	All (n = 42)
Symptom at hospital presentation				
Left-sided heart failure (%)	16 (57)	47 (64)	16 (46)	17 (40)*
Right-sided heart failure (%)	1 (4)	2 (3)	2 (6)	2 (5)
Both-sided heart failure (%)	8 (29)	21 (29)	5 (14)	7 (17)
Syncope (%)	1 (4)	4 (5)	8 (23)*	13 (31)†
Palpitation (%)	2 (7)	8 (11)	5 (14)	7 (17)
Chest pain (%)	6 (21)	14 (19)	6 (17)	6 (14)
Sudden death (%)	0 (0)	2 (3)	2 (6)	2 (5)
Arrhythmia				
Sinus bradycardia (%)	1 (4)	2 (3)	3 (9)	4 (10)
Atrioventricular block (%)	5 (18)	11 (15)	17 (49)*	21 (50)†
First degree (%)	3 (11)	5 (7)	8 (23)	9 (21)
Type I second degree (%)	0 (0)	0 (0)	0 (0)	0 (0)
Type II second degree (%)	0 (0)	0 (0)	0 (0)	1 (2)
Complete (%)	2 (7)	6 (8)	9 (26)	11 (26)
Ventricular tachycardia (%)	8 (29)	21 (29)	8 (23)	11 (26)
Ventricular fibrillation (%)	0 (0)	2 (3)	2 (6)	2 (5)

Core centers and all centers in cardiac sarcoidosis were compared with those in idiopathic giant cell myocarditis respectively. *$p < 0.05$; †$p < 0.001$.

latter analysis was further limited to the 41 patients diagnosed by EMB at core centers (Fig. 3C), the same survival difference was observed (35.7% vs. 75.7%, $p = 0.0013$ by log-rank test).

In a Cox proportional hazards model, we analyzed variables that might be independent predictors of transplant-free survival after biopsy diagnosis (at all centers). In a forward stepwise model that included candidate variables of age at diagnosis, gender, white race, presentation with heart failure, duration of symptoms, and IGCM, the selected model variables were IGCM, age, and presentation with heart failure.

In this model, age was negatively associated with risk, that is, younger people had worse transplant-free survival (hazard ratio, 0.755 [confidence interval {CI}, 0.579 to 0.985]; $p = 0.03$). However, when stratified by disease group, age was not significantly associated with worse transplant-free survival (CS, $p = 0.18$; IGCM, $p = 0.11$). The positive effect of CHF symptoms on higher risk was only marginal (hazard ratio, 3.70 [CI, 0.80 to 17.1]; $p = 0.088$). Because IGCM patients tended to be younger and more likely to present with CHF, the adjustment for these variables reduced, but did not eliminate, the significance of IGCM histology (hazard ratio, 3.42 [CI, 1.32, 8.85]; $p = 0.0099$). If all the candidate variables were added into the model whether significant or not, the effect of IGCM was rendered of marginal significance ($p = 0.073$). This was largely because the inclusion of "duration of symptoms" in the model, so dramatically different in the two diseases, inflated the standard error for IGCM as well as reducing the effect somewhat.

In a logistic model, we estimated baseline clinical variables that would predict IGCM among patients diagnosed by biopsy or nontransplant surgical pathology (before transplant or death) diagnosis (Table 5). In this model, heart failure at presentation and white ethnicity predicted IGCM ($p < 0.0001$ and $p < 0.0005$), while atrioventricular block and time from symptom onset of more than nine weeks predicted CS ($p < 0.0002$ and $p = 0.0313$). If the analysis was restricted to those patients who were diagnosed by EMB at core centers, the only variables that predicted IGCM on biopsy were time from symptom onset to biopsy of <9 weeks ($p < 0.004$) and white race ($p < 0.002$).

Table 4. Additional Care to Conventional Therapy

Characteristics	Idiopathic Giant Cell Myocarditis		Cardiac Sarcoidosis	
	Core Centers (n = 28)	All (n = 73)	Core Centers (n = 35)	All (n = 42)
Corticosteroid administration (%)	19 (68)	40 (55)	27 (77)	31 (74)
Pacemaker implantation (%)	8 (29)	18 (25)	15 (43)	19 (45)*
Cardioverter defibrillator implantation (%)	6 (21)	9 (12)	8 (23)	10 (24)
Intraaortic balloon pump insertion (%)	5 (18)	25 (34)	1 (3)*	1 (2)†
Ventricular assist device insertion (%)	1 (4)	12 (16)	0 (0)	0 (0)*
Heart transplantation (%)	9 (32)	37 (51)	8 (23)	12 (29)*

Core centers and all centers in cardiac sarcoidosis were compared with those in idiopathic giant cell myocarditis, respectively. *$p < 0.05$; †$p < 0.001$.

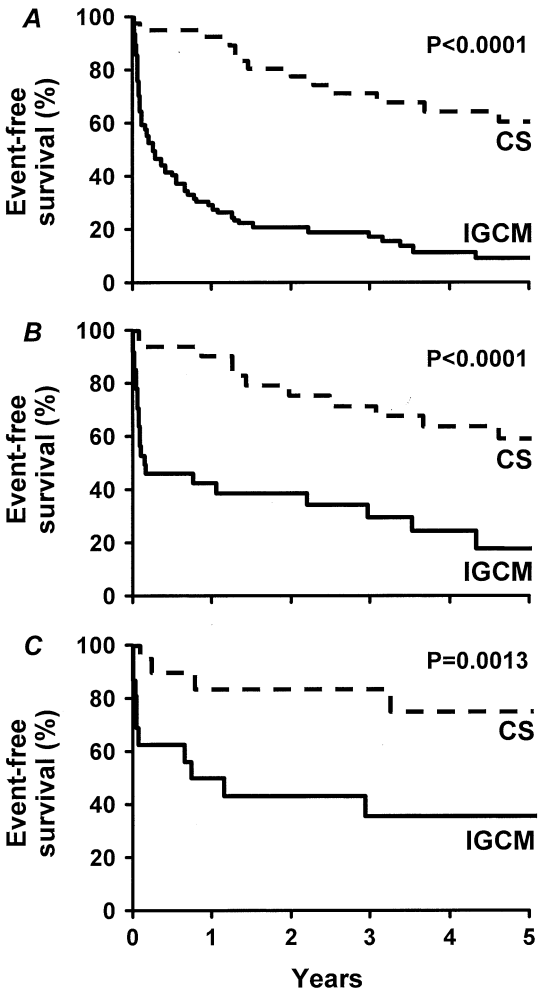

Figure 3. Kaplan-Meier curves illustrating transplant-free survival in cardiac sarcoidosis (CS) and idiopathic giant cell myocarditis (IGCM) patients. **(A)** Time from symptom onset for 115 subjects from all centers. **(B)** Time from endomyocardial biopsy in 67 patients from all centers. **(C)** Time from endomyocardial biopsy in 41 patients at five core centers. All survival comparisons are by log-rank test.

DISCUSSION

The results of this study strongly suggest that CS and IGCM are distinct clinicopathologic entities. The data suggest that despite high rates of heart block, heart failure, and tachyarrhythmias, survival in CS is much better than in IGCM. Presentation with heart failure predicted IGCM, and presentation with heart block or more than nine weeks of symptoms predicted CS.

Our observation that CS and IGCM have distinct natural histories suggests that they may also be pathophysiologically distinct. As the etiology of these disorders is poorly defined, it remains unclear whether the clinical differences relate to different environmental exposures or to variable host immunologic factors. For example, the spatial and familial clustering of sarcoidosis (18) has not been observed in IGCM. Nonetheless, there are gross similarities in immunologic response. Experimental IGCM (19,20) and sarcoidosis are both associated with an early infiltrate of CD4-positive T cells with a T helper type 1 response, secreting interleukin-2 and interferon-γ. At a later stage of lesion evolution, a dominant T helper type 2 response may lead to fibrosis.

Despite a similar reduction in ejection fraction, left-sided CHF and use of ventricular assist devices were more frequent in IGCM than in CS. We speculate that the difference in disease phenotype may be, in part, due to the prominence of eosinophil products in the IGCM lesions. Eosinophil granules contain major basic protein, eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin. Eosinophils are also capable of choemoattractant production, including proteins such as platelet-activating factor and eotaxin, as well as cytokine production. Eosinophilic proteins such as eosinophil peroxidase are also capable of producing cytotoxic substances including hydrogen peroxide and halide acids (21). Idiopathic giant cell myocarditis is also a more acute process than CS in which there is little time for adaptation to myocardial dysfunction. A novel finding from our study is that the number of multinucleated giant cells were similar in CS and IGCM, suggesting that these cells are not primarily involved in the disease phenotype.

Our data are limited by the selected patient cohort and the observational study design. Because sarcoidosis is a multisystem disease with a heterogenous clinical course, our findings may not apply to patients with predominantly lung or other organ involvement. Indeed, only 33% of our CS cohort had evidence of extracardiac involvement. Other studies suggest that there is a gender difference in extrapulmonary sarcoid in Japanese patients (22) that may limit the applicability of our findings to different ethnic groups. However, the relatively large number of cases, the inclusion of all pathologically diagnosed cases at the core centers, and the independent interpretation of histologic slides by cardiac pathologists in most cases strengthen our observations of natural history.

Although cases diagnosed by biopsy yield the most useful clinical data, this analysis is subject to greatest bias due to the low sensitivity of biopsy for sarcoidosis and the exclusion of critically ill patients who might die or undergo transplantation without a biopsy. Realizing the limitations of this analysis, we ascertained all cases of pathologically confirmed CS from the core centers, including autopsy, explanted heart, or other surgical pathology specimens. We estimated

Table 5. Logistic Regression Model for Variables Associated With Independent Predictors of Idiopathic Giant Cell Myocarditis

Variables	Hazard Ratio (95% CI)	p Value
Presenting with heart failure	57.62 (7.94–418.10)	0.0001
White ethnicity	8.90 (2.59–30.56)	0.0005
Atrioventricular blockage	0.20 (0.06–0.70)	0.0121
Time from onset to diagnosis		
More than 26 weeks	0.07 (0.02–0.29)	0.0002
More than 9 weeks	0.12 (0.02–0.83)	0.0313

CI = confidence interval.

transplant-free survival from symptom onset in the entire cohort, as well as from time of diagnosis in the biopsy diagnosed subjects, in order to compare the outcome of patients with granulomas on biopsy to all patients with CS. The additional analyses of patients diagnosed at autopsy or explantation sought to account for survivor selection bias in the biopsy cohort. The differences between CS and IGCM in time to presentation and time to diagnosis may be due to the more indolent natural history of CS.

The question of which, if any, of the variables are legitimately considered as confounding in the multivariate analyses is uncertain. If the question is "which disease has a worse prognosis," then one might consider the unadjusted analysis the preferable one. If the question is "which disease has worse prognosis for a person of a given age, gender, race, with these presenting symptoms, and duration of symptoms," then the adjusted analysis is to be preferred. To equate symptoms and duration of symptoms between groups is perhaps to match patients in a way that is not representative of each disease.

Although there has been debate as to whether IGCM and CS are separate disorders, the results of the pathologic analysis in this study show significant histologic differences between CS and IGCM, which could be clinically useful. Patients with IGCM in our series had a more fulminant clinical course with a shorter time from symptom onset to death or transplantation. Patients with IGCM more frequently required mechanical circulatory support. Despite the aggressive clinical course of IGCM in our series, CS was more frequently associated with high-grade heart block or pacemaker requirement. Further research is required to determine if treatment can favorably alter the natural history of these disorders.

Reprint requests and correspondence: Dr. Leslie T. Cooper, Jr., Cardiovascular Division/Mayo East 16B, Mayo Clinic, Rochester, Minnesota 55905. E-mail: cooper.leslie@mayo.edu.

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APPENDIX

The members of the Multicenter Giant Cell Myocarditis Study Group were as follows:

Massachusetts General Hospital, Boston, Massachusetts: G. W. Dec, J. T. Fallon, and J. Southern; Stanford University Hospital, Stanford, California: J. S. Schroeder and J. Friedman; Johns Hopkins Hospital, Baltimore, Maryland: J. M. Hare and R. H. Hruban; Rikshospitalet, Oslo, Norway: S. Simonsen; Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois: M. Johnson; Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania: E. Loh, B. Drachman, C. Reynolds, and M. van de Rijn; Alfred Hospital, Prahan, Australia: M. Richardson, S. K. Tang, and J. S. Pedersen; Sahlgrenska University Hospital, Goteborg, Sweden: C.-H. Bergh, A. Oldfors, and U. Nystrom; Virginia Commonwealth University/Medical College of Virginia, Richmond, Virginia: M. Flattery, D. E. Tolman, and M. M. Grimes; University of Vienna, Vienna, Austria: R. Ullrich and R. Horvat; Baptist Medical Center of Oklahoma, Oklahoma City, Oklahoma: D. K. C. Cooper; Brigham and Women's Hospital, Boston, Massachusetts: S. Davis, M. Givertz, and G. Winters; Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland: J. J. Goy and C. Genton; Elmhurst Hospital Center, Elmhurst, New York: N. E. Kantrowitz and G. Turi; Harefield Hospital, London, United Kingdom: M. Yacoub and A. Pomerance; Hospital Germans Trias I Pujol, Barcelona, Spain: A. Ariza; Hospital Henri Mondor, Paris,

France: D. Tixier; Herzzentrum Bad Krozingen, Bad Krozingen, Germany: N. Bruns and C. Ihling; Instituto de Cardiologica y Cirugia Cardiovascular-Fundacion Favaloro, Buenos Aires, Argentina: S. V. Perrone and R. R. Favaloro; Mayo Clinic, Rochester, Minnesota: L. J. Olson and W. D. Edwards; Columbia Hospital at Medical City, Dallas, Texas: J. Hunt, J. M. Vidal, and W. J. Esber; Mid America Heart Institute, Kansas City, Missouri: D. R. Bresnahan, N. D. Long, and R. T. O'Kell; Newark Beth Israel Medical Center, Newark, New Jersey: M. J. Zuker and L. T. Boral; Presbyterian Hospital, Albuquerque, New Mexico: D. Sansonetti, C. Moore, and J. H. Spigel; Presbyterian-St. Luke's Hospital, Denver, Colorado: J. Narrod, J. Small, and K. R. Holloman; Prince Charles Hospital, Chermside, Australia: A. Galbraith; Royal National Heart and Lung Institute, London, United Kingdom: M. N. Shepherd; Saint Thomas Hospital, Nashville, Tennessee: K. Biersack and C. M. Davis; Sentara Norfolk General Hospital, Norfolk, Virginia: J. M. Herre and L. Ladaga; Split Clinical Hospital, Split, Croatia: S. Polic; St. Elizabeth Hospital Medical Center, Youngstown, Ohio: P. E. Hill; State University of New York at Buffalo, Buffalo, New York: S. Graham, J. S. Schwartz, and C. F. Celik; Sutter Memorial Hospital, Sacramento, California: S. I. Stark; Honolulu Medical Group, Honolulu, Hawaii: T. Hoffmann and K. Tonaki; University of Alabama at Birmingham, Birmingham, Alabama: R. B. Bourge; Cleveland Clinic Foundation, Cleveland, Ohio: N. B. Ratliff; University of Calgary-Foothills Hospital, Calgary, Alberta, Canada: D. Issac, S. Agarwal, and W. Lester; University of California at San Diego, La Jolla, California: L.T. Cooper; University of Kansas Medical Center, Kansas City, Missouri: S. B. Gollub and O. Tawfik; University of Pittsburgh Medical Center, Pittsburgh, Pennslyvania: S. Murali; University of South Florida College of Medicine, Tampa, Florida: G. B. Cintron and S. Brantley; Washington University School of Medicine, St. Louis, Missouri: M. W. Rich; Hospital, Helsinki, Finland: M. Nieminen; Niigata University of Medicine, Niigata, Japan: Y. Aizawa, A. Shibata; Social Health Insurance Medical Center, Tokyo, Japan: K. Satomi, K. Kondou; Northside Cardiology, P.C., Indianapolis, Indiana: M. N. Walsh; Desert Hospital, Palm Springs, California: W. L. Cooper, R. J. Rosser; South Texas Cardiovascular Consultants, San Antonio, Texas: M. J. Wood.