

## IDIOPATHIC GIANT-CELL MYOCARDITIS — NATURAL HISTORY AND TREATMENT

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### ABSTRACT

**Background** Idiopathic giant-cell myocarditis is a rare and frequently fatal disorder. We used a multicenter data base to define the natural history of giant-cell myocarditis and the effect of treatment.

**Methods** We identified 63 patients with idiopathic giant-cell myocarditis through journal announcements and direct mailings to cardiovascular centers worldwide.

**Results** The patients consisted of 33 men and 30 women with an average age of 42.6 years; 88 percent were white, 5 percent were black, 5 percent were Southeast Asian or Indian, and 2 percent were Middle Eastern. Most presented with congestive heart failure (47 patients, or 75 percent), ventricular arrhythmia (9 patients, or 14 percent), or heart block (3 patients, or 5 percent), although in some cases the initial symptoms resembled those of acute myocardial infarction (4 patients). Nineteen percent had associated autoimmune disorders. The rate of survival was worse than among 111 patients with lymphocytic myocarditis in the Myocarditis Treatment Trial ( $P < 0.001$ ); among our patients, the rate of death or cardiac transplantation was 89 percent, and median survival was only 5.5 months from the onset of symptoms. The 22 patients treated with corticosteroids and cyclosporine, azathioprine, or both therapies survived for an average of 12.3 months, as compared with an average of 3.0 months for the 30 patients who received no immunosuppressive therapy ( $P = 0.001$ ). Of the 34 patients who underwent heart transplantation, 9 (26 percent) had a giant-cell infiltrate in the transplanted heart and 1 died of recurrent giant-cell myocarditis.

**Conclusions** Giant-cell myocarditis is a disease of relatively young, predominantly healthy adults. Patients usually die of heart failure and ventricular arrhythmia unless cardiac transplantation is performed. Despite the possibility of fatal disease recurrence, transplantation is the treatment of choice for most patients. (N Engl J Med 1997;336:1860-6.)

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IDIOPATHIC giant-cell myocarditis is a frequently fatal type of myocarditis; only approximately 80 isolated cases and two small clinical series have been reported.<sup>1,2</sup> The clinical course, unlike that of lymphocytic myocarditis,<sup>3</sup> is usually characterized by progressive congestive heart failure, frequently associated with refractory ventricular arrhythmia. Most patients die of congestive heart failure, although some have survived for long

periods, often after immunosuppressive treatment.<sup>4,5</sup> Several instances of cardiac transplantation have been reported<sup>6</sup>; however, the efficacy of transplantation has been questioned because the disease can recur in the transplanted heart.<sup>7-11</sup> Until 1984 the diagnosis was uniformly based on histologic findings at autopsy. In the past 13 years, cases have been diagnosed by endomyocardial biopsy, thus permitting the collection of prospective data on survival and the efficacy of treatment. The epidemiology, causes, and natural history of idiopathic giant-cell myocarditis and the effect of treatment, including cardiac transplantation, on the disease have not been systematically investigated.

The Giant Cell Myocarditis Study Group was set up as a multicenter, international effort to gather data on the natural history of and the effect of treatment on this unusual disorder. Journal announcements<sup>12-16</sup> and direct mailings to cardiovascular centers worldwide produced data on 63 cases, most diagnosed by endomyocardial biopsy or apical-wedge section. We describe the results of this observational study, including characteristics and survival of the patients and the effect of immunosuppression and cardiac transplantation on idiopathic giant-cell myocarditis.

### METHODS

#### Study Subjects

Information on patients was solicited through study announcements placed in *Circulation*,<sup>16</sup> the *Journal of the American College of Cardiology*,<sup>14</sup> the *American Heart Journal*,<sup>12</sup> the *American Journal of Cardiology*,<sup>13</sup> and the *Journal of Heart and Lung Transplantation*,<sup>15</sup> as well as through direct mailings to the directors of U.S. heart-transplantation centers participating in the United Network for Organ Sharing and to major cardiovascular centers worldwide. The criterion for enrollment was a definite histologic diagnosis of giant-cell myocarditis obtained by endomyocardial biopsy, examination of the explanted heart, or autopsy. These efforts produced data on 90 patients from 49 medical centers in 16 countries.

A four-page case-report form was sent to investigators at each of the 49 medical centers, requesting anonymous historical data on the patients' medical history, presenting symptoms, ventricular function, hemodynamic measures, cardiac rhythm, and treatment. Respondents were asked to list test results that ruled out other pos-

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sible causes of reactions resembling giant-cell myocarditis and to give detailed data on the post-transplantation course, if applicable.

A single experienced cardiac pathologist who was blinded to the patients' histories reviewed all the histologic slides and detailed photomicrographs and confirmed 54 cases of giant-cell myocarditis. Histologic findings of widespread or multifocal serpiginous necrosis with mixed inflammatory infiltrate composed of lymphocytes and histiocytes were considered diagnostic. The presence of eosinophils was noted in most cases. Admixed with the infiltrate were multinucleated giant cells in the absence of sarcoid-like granuloma (Fig. 1).<sup>1,17</sup> An additional nine patients were included because three investigators who could not supply pathological slides reported histologic findings typical of giant-cell myocarditis that had been confirmed by experienced cardiac pathologists. The remaining 27 of the original 90 reported cases were not included because the patients either did not meet histologic criteria of giant-cell myocarditis (10 patients) or lacked completed case-report forms or slides (17).

Giant-cell myocarditis was diagnosed by endomyocardial biopsy in 33 cases (52 percent), by examination of the explanted heart in 14 (22 percent), at autopsy in 11 (17 percent), and by examination of apical wedge sections obtained at the time of the placement of the ventricular assist device in 5 (8 percent). Patients with multiple tissue samples were considered to have giant-cell myocarditis if one of the submitted samples met the diagnostic criteria.

Data on 17 of the cases included in our series have been published in previous reports.<sup>1,2,5,7,8,11,18,19</sup> In all 17 cases, we were able to include previously unreported data and conducted an independent pathological review.

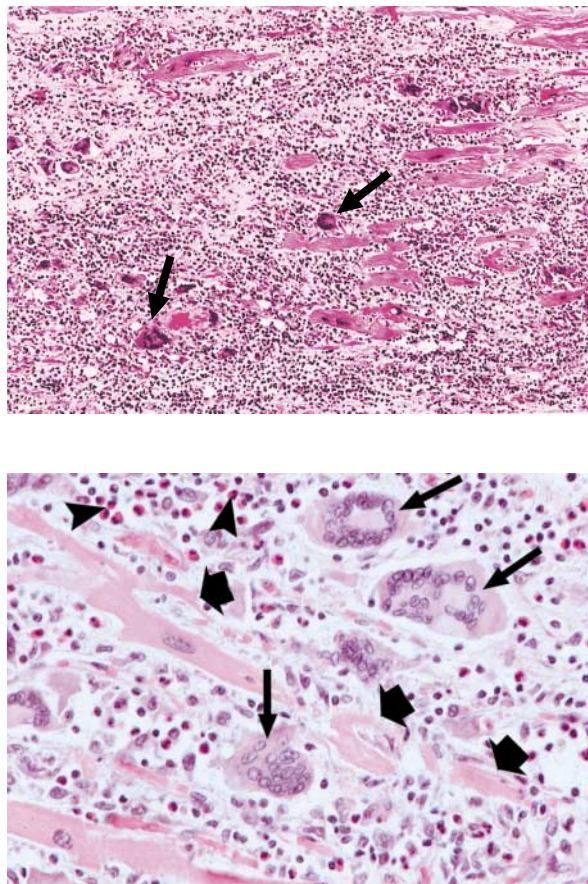
We compared the survival of the 63 patients in our series with that of patients from the Myocarditis Treatment Trial<sup>3</sup> who had biopsy-proved lymphocytic myocarditis. Actuarial survival in the groups with giant-cell myocarditis and lymphocytic myocarditis was determined by the Kaplan-Meier method and compared with use of the log-rank test. Survival data are expressed in terms of the median duration of survival. Patients who died or underwent cardiac transplantation were considered to have reached the combined end point for mortality.

**Statistical Analysis**

Because there was no perfect way to analyze our survival data, we have presented the survival of the patients with giant-cell myocarditis in several ways (Fig. 2). We first calculated Kaplan-Meier survival curves from the time of the onset of symptoms in the group with giant-cell myocarditis (i.e., a leftward shift of the survival curve for the patients with giant-cell myocarditis) (Fig. 2A). Survival in the group with lymphocytic myocarditis was calculated from the time of randomization in the Myocarditis Treatment Trial. A second analysis compared the Kaplan-Meier curves for survival among patients with giant-cell myocarditis from the time of presentation at the referring institution (Fig. 2B) — the time from which we had complete data on the patient. The third analysis considered the survival of the 38 patients in whom giant-cell myocarditis was diagnosed on the basis of endomyocardial biopsy or ventricular-apex sections obtained at the time of the placement of the assist device (i.e., patients in whom the disease was diagnosed before death or cardiac transplantation) (Fig. 2C). This survival analysis excluded patients in whom the disease was diagnosed at autopsy or on examination of an explanted heart. A final survival analysis used left truncation as well as right censoring in a Cox model to accommodate variable times of entry into the risk set.<sup>20</sup>

Because left ventricular ejection fractions were measured variously by echocardiography, radionuclide studies, or ventriculography, data on the ejection fraction were not considered suitable for analysis.

Because of concern about referral bias, we requested that all institutions check their pathology records to ensure that all cases of giant-cell myocarditis were included in this study. Thirty-two medical centers (86 percent) searched pathology logs for additional cases. Only three medical centers identified additional cas-



**Figure 1.** Histologic Findings in Giant-Cell Myocarditis.

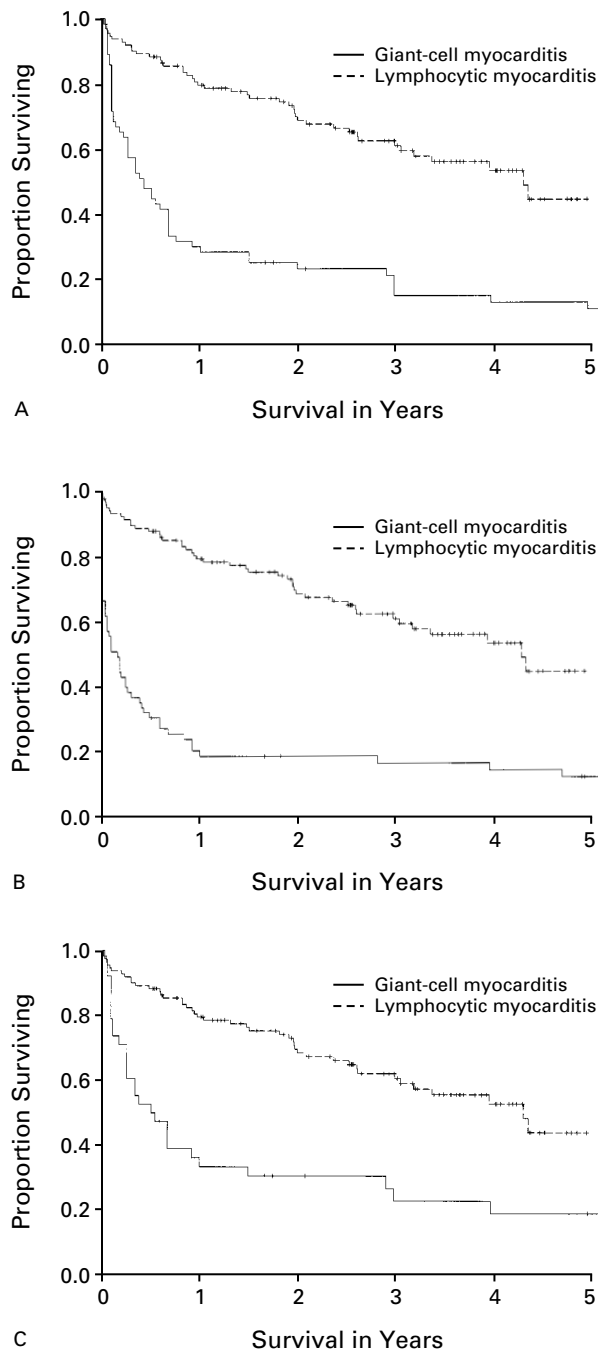
The top panel shows diffuse geographic myocardial necrosis at low-power magnification. Numerous giant cells (arrows) can be identified within the inflammatory infiltrate (hematoxylin and eosin, ×100). In the bottom panel, multinucleated giant cells (long arrows) are seen adjacent to degenerating myocytes (short arrows). The cellular infiltrate contains lymphocytes, histiocytes, and collections of eosinophils (arrowheads) (hematoxylin and eosin, ×400).

es; clinical data could not be obtained for them, so they were not included in this study. All but two institutions had computerized pathology records.

**RESULTS**

**Demographic Characteristics of the Patients**

The mean (±SD) age of the 63 patients with confirmed giant-cell myocarditis was 42.6±12.7 years at the time of the onset of symptoms. There was a bell-shaped age-distribution curve around the average (Fig. 3). The youngest patient was 16 years old, and the oldest was 69 years old at the time of the onset of symptoms. The number of women with giant-cell myocarditis (30 patients) was not significantly different from the number of men (33). We



**Figure 2.** Kaplan–Meier Survival Curves for Patients with Giant-Cell Myocarditis.

Panel A shows the duration of survival from the onset of symptoms; Panel B shows the duration of survival from the time of presentation at the referring institution; and Panel C shows the duration of survival among 38 patients in whom giant-cell myocarditis was diagnosed by endomyocardial biopsy or by examination of a section of ventricular apex. In each case, survival was significantly longer among patients with lymphocytic myocarditis ( $P < 0.001$  by the log-rank test for each comparison).

found no significant difference between the average age of the men (41.6 years) and that of the women (43.7 years). The patient's race or ethnic origin was reported in 57 cases (90 percent): of those 57, 50 patients (88 percent) were white, 3 (5 percent) were black, 3 (5 percent) were Southeast Asian or Indian, and 1 (2 percent) was Middle Eastern.

Autoimmune disorders were reported in 19 percent of the cases (Table 1). Previously published reports cite associations with Hashimoto's thyroiditis,<sup>17,21</sup> rheumatoid arthritis,<sup>22</sup> myasthenia gravis,<sup>23</sup> Takayasu's arteritis,<sup>24</sup> alopecia totalis vitiligo,<sup>25</sup> and pernicious anemia<sup>26</sup> in isolated cases and with Crohn's disease,<sup>1</sup> ulcerative colitis,<sup>18,27</sup> and orbital myositis<sup>28,29</sup> in several reports. In our series, five patients (8 percent) had either Crohn's disease or ulcerative colitis. In all five the diagnosis of idiopathic bowel disease preceded the onset of clinical myocarditis by several years. No other autoimmune disorder occurred in more than a single case.

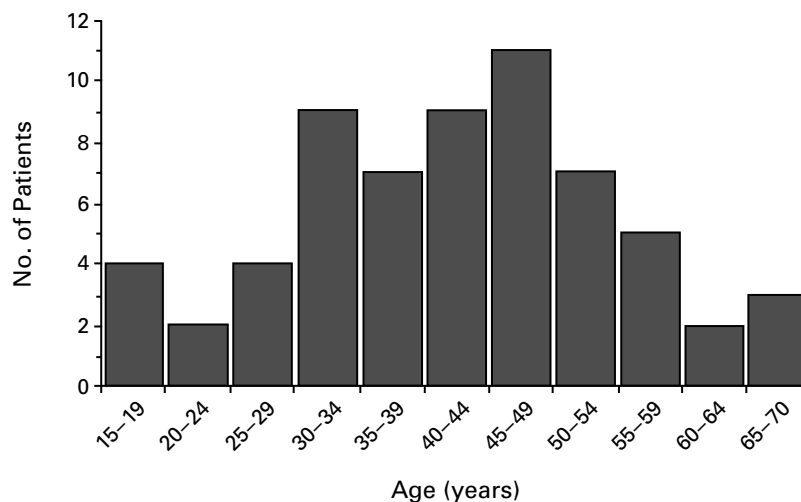
The presenting symptoms in the majority of the patients in our series were those of congestive heart failure (47 patients, or 75 percent). They included dyspnea of recent onset, decreased exercise tolerance, orthopnea, and peripheral edema. In a substantial minority of patients (9 patients, or 14 percent) ventricular tachycardia was present, with symptoms of palpitation or syncope or sudden death. Sustained, refractory ventricular tachycardia developed in almost half the patients during the course of their illness. Four patients (6 percent) presented with a syndrome of chest pain and electrocardiographic findings suggestive of acute myocardial infarction. Three patients (5 percent) presented with complete heart block.

#### Survival

The rate of death or cardiac transplantation was 89 percent, with a median survival of 5.5 months from the onset of symptoms to the time of death or transplantation. There was no significant difference in average survival between men (33 patients, 5.5 months) and women (30 patients, 6.0 months;  $P = 0.52$ ) or between patients younger and older than the median.

Survival among the patients in our series was compared with that among 111 patients randomly assigned to treatment groups in the Myocarditis Treatment Trial (Fig. 2).<sup>3</sup> Cumulative mortality from all causes was greater ( $P < 0.001$ ) among the patients with giant-cell myocarditis, regardless of whether survival was measured from the time of first symptoms (Fig. 2A) or from presentation at the referring institution (Fig. 2B). Survival among the 38 patients in whom giant-cell myocarditis was diagnosed on the basis of endomyocardial biopsy or apical-wedge sampling was also worse than that among the patients with lymphocytic myocarditis ( $P < 0.001$ ) (Fig. 2C).

Because of the possibility of deaths among pa-



**Figure 3.** Age at the Time of Onset of Symptoms in 63 Patients with Giant-Cell Myocarditis.

tients with giant-cell myocarditis before presentation, we analyzed survival using a Cox proportional-hazards model, which allowed left truncation as well as right censoring.<sup>20</sup> In this model, the survival curve for all 63 patients with giant-cell myocarditis started at the time of the onset of symptoms, but patients did not enter the risk set for events until the time of presentation, thus allowing for variable times of entry to as well as exit from the risk set. A score statistic, analogous to a log-rank statistic, comparing the survival of the groups with giant-cell and lymphocytic myocarditis in this model, was less than 0.001, supporting the conclusion that patients with giant-cell myocarditis have worse survival.

The time from the onset of symptoms to the end point of death, transplantation, or the end of follow-up was longer for patients treated with certain combinations of immunosuppressive agents than for those who did not receive such agents (Table 2). The median survival of patients who received no immunosuppressive agents was 3.0 months (30 patients). The 11 treated with corticosteroids as the only immunosuppressive agent survived, on average, 3.8 months ( $P=0.68$ ). The 11 treated with corticosteroids and azathioprine had a longer survival, averaging 11.5 months ( $P=0.025$ ). Those treated with cyclosporine (10 patients) in combination with any other agent (corticosteroids, 3 patients; corticosteroids and azathioprine, 5; and corticosteroids, azathioprine, and muromonab-CD3 [OKT3], 2) survived an average of 12.6 months ( $P=0.003$ ). A final patient was treated with corticosteroids and muromonab-CD3 and was not included in the above analysis. When all patients who received combined immunosuppressive therapy were compared with patients who received no immunosuppressive agents, those in the treatment group lived longer

(22 patients, 12.3 months vs. 30 patients, 3.0 months;  $P=0.001$ ).

The median time from the onset of symptoms until presentation at the referring institution was three weeks (range, 0.01 to 36 months). Analysis of variance for the time to treatment revealed no difference between the treatment groups ( $P=0.59$ ). Age ( $P=0.23$ ), sex ( $P=0.57$ ), and time to presentation ( $P=0.09$ ) were not significant factors in survival (by Cox regression analysis).

**Post-Transplantation Course**

Thirty-four patients underwent cardiac transplantation a median of six months after the onset of symptoms. Nine of them (26 percent) died during an average follow-up of 3.7 years. Five died within 30 days after transplantation. One died of heart failure without evidence of a specific disorder and one

**TABLE 1.** ASSOCIATED DISORDERS IN 63 PATIENTS WITH GIANT-CELL MYOCARDITIS.\*

DISORDER OR STATUS	NO. OF PATIENTS
Disorder	
Ulcerative colitis or Crohn's disease	5
Cryofibrinogenemia	1
Optic neuritis	1
Fibromyalgia	1
Hyperthyroidism	1
Hypothyroidism	1
Status	
After thymoma resection	1
Immediately post partum	1

\*The patients with cryofibrinogenemia or thymoma and two of the patients with ulcerative colitis were included in previously published reports.

**TABLE 2.** THE EFFECT OF IMMUNOSUPPRESSION ON SURVIVAL IN PATIENTS WITH GIANT-CELL MYOCARDITIS.

PATIENT GROUP	NO. OF PATIENTS	MEDIAN SURVIVAL FROM SYMPTOM ONSET (MO)	P VALUE*
No immunosuppression	30	3.0	—
Corticosteroids alone	11	3.8	0.68
Corticosteroids plus azathioprine	11	11.5	0.025
Cyclosporine combination therapy†	10	12.6	0.003
All treatment groups except corticosteroids alone	22‡	12.3	0.001
All treatment groups including corticosteroids alone	33	8.2	0.014

\*P values are for the comparison of median survival with that in the group that received no immunosuppressive therapy, by the log-rank test.

†Cyclosporine was combined with corticosteroids (three patients), with corticosteroids and azathioprine (five patients), or with corticosteroids, azathioprine, and muromonab-CD3 (OKT3, two patients).

‡This group includes one patient treated with corticosteroids and muromonab-CD3 only.

of squamous-cell carcinoma of the lung. One underwent a second transplantation because of transplant rejection but subsequently died, and another died of recurrent giant-cell myocarditis despite aggressive immunosuppressive therapy.

Giant-cell myocarditis is known to recur in the transplanted heart, but the frequency of recurrence is unknown. Giant-cell infiltrate was identified by endomyocardial biopsy in 9 of the 34 patients after transplantation. Eight underwent transplantation for giant-cell myocarditis and one for ischemic cardiomyopathy. Giant-cell infiltrate occurred an average of 3.0 years after transplantation (range, 3 weeks to 9 years). Three of the nine in whom giant-cell infiltrate occurred had symptoms and signs of left ventricular failure. One of these three died despite aggressive immunosuppressive therapy 3.5 years after transplantation. In the remaining two patients, the giant-cell infiltrate and symptoms resolved with heightened immunosuppressive therapy. Five of the six asymptomatic patients in whom recurrent giant-cell myocarditis was diagnosed on routine surveillance biopsy were well an average of 2.1 years after recurrence (the sixth died of squamous-cell carcinoma of the lung).

Giant-cell myocarditis developed in one patient six years after transplantation for ischemic cardiomyopathy. The patient had dependent edema, but the estimated left ventricular ejection fraction was 55 to 60 percent. After he was treated with corticosteroid bolus and an increased dose of cyclosporine, his symptoms improved and there was no recurrence of the disease in six years of regular follow-up.

Survival among patients in whom giant-cell myocarditis was confirmed by independent histologic re-

view was not statistically different from survival among patients classified as having the disease on the basis of an investigator's report ( $P = 0.28$ ).

## DISCUSSION

This report adds to the available knowledge of giant-cell myocarditis by providing demographic information and describing disorders associated with this unusual disorder. We attempted to assess the efficacy of cardiac transplantation and the role of pretransplantation immunosuppression in the treatment of the disease. Our data are limited by the highly selected patient cohort and the potential biases in the observational study design. Our data on survival may be inaccurate because of missing information on early deaths due to this rapidly fatal disease. The strengths of this study are the large number of cases and the interpretation of most of the histologic slides by a single pathologist, which we believe prevented the mistaken inclusion of cases of cardiac sarcoidosis.

The literature supports our finding that giant-cell myocarditis is a disease of young adults. The youngest reported patient was six weeks old<sup>30</sup>; this is the only reported case we are aware of in an infant. Studies of acute myocarditis in children do not describe giant-cell myocarditis in this population.<sup>31</sup> The average ages in two previously reported series were 37 years (five patients)<sup>1</sup> and 48 years (five patients).<sup>2</sup> The oldest reported patient was 88 years old.<sup>17</sup> The paucity of reported cases in the elderly may reflect less frequent diagnosis or a more or less fulminant course of disease in this population.

The occurrence of giant-cell myocarditis in minority populations has not been previously described and cannot be determined from a review of the English-language literature, because information on race or ethnic origin is not included in most published reports. Eighty-eight percent of the patients in this study were white; only three patients were black (all three cases were from U.S. medical centers). Although myocardial sarcoidosis in the United States usually occurs in blacks,<sup>32</sup> conclusions regarding the incidence of idiopathic giant-cell myocarditis in minority groups must be limited because the racial composition of our study population may be largely a reflection of the populations at the participating medical centers.

Numerous autoimmune disorders have been associated with giant-cell myocarditis in case reports, but no data have been available on the incidence of these disorders in a study population with giant-cell myocarditis. Our study suggests that the majority of cases of giant-cell myocarditis occur in otherwise healthy persons (81 percent). Five of the 63 patients in this study (8 percent) had idiopathic bowel disease — either Crohn's disease or ulcerative colitis. This association has previously been reported in sev-

eral isolated cases. We found no other autoimmune disease present in two or more patients (Table 1).

Our data suggest that immunosuppressive therapy with regimens including cyclosporine, azathioprine, or both, but not corticosteroids alone, may prolong the time to transplantation or death in patients with giant-cell myocarditis. Although we used several techniques to minimize bias, bias resulting from the selection of survivors who received a particular treatment remains an important concern in the interpretation of these data.<sup>33</sup> Given the rapidly fatal course of the disease in most patients with giant-cell myocarditis, those who would have survived longer without treatment would have a better chance of obtaining immunosuppressive therapy. A randomized, prospective clinical trial involving a larger number of patients would be necessary to validate our results with respect to survival.

Several lines of evidence suggest that giant-cell myocarditis is an autoimmune disorder dependent on CD4-positive T lymphocytes. Experimental giant-cell myocarditis can be produced in Lewis rats by autoimmunization with myosin.<sup>34,35</sup> Both human and experimental giant-cell myocarditis are characterized by an infiltrate of T lymphocytes and histiocytes. In laboratory experiments therapy with cyclosporine and anti-T-lymphocyte antibodies can prevent giant-cell myocarditis.<sup>36,37</sup> One patient treated with muromonab-CD3 was alive with improved left ventricular function 28 months after the initiation of treatment. However, a second patient underwent transplantation one month after beginning treatment with muromonab-CD3, and a third patient, who received muromonab-CD3 and corticosteroid alone, died shortly after the initiation of treatment. Corticosteroids alone have no benefit in the treatment of experimental giant-cell myocarditis in animals<sup>36</sup> and had none in our observational series. The histologic and survival data from our series suggest that the pathogenesis of human giant-cell myocarditis is quite similar to that of the experimental disease.

The recurrence of giant-cell myocarditis in cardiac transplants has been described in only four isolated cases.<sup>1,7-10</sup> We report a series of patients who received transplants for giant-cell myocarditis. The 30-day postoperative mortality rate of 15 percent may reflect the poor clinical condition of the patients at time of transplantation. The 15 percent mortality at three years is roughly similar to the overall survival rates for patients who undergo transplantation for ischemic or dilated cardiomyopathy. The occurrence of giant-cell myocarditis in the transplanted heart, which is sometimes fatal, is noteworthy in this disease.

The post-transplantation care of patients with giant-cell myocarditis should probably be different from that of patients who receive transplants for other reasons. More frequent follow-up, perhaps ev-

ery three to six months, should be maintained indefinitely to assess signs or symptoms of left ventricular dysfunction, since the disease may recur up to nine years after transplantation. Particularly careful attention is warranted to rule out recurrent giant-cell myocarditis in post-transplantation biopsies. Asymptomatic patients in whom routine biopsy reveals a prominent giant-cell infiltrate seem to do well with short-term heightened immunosuppression or no alteration in therapy. Patients in whom left ventricular dysfunction is accompanied by giant-cell myocarditis may die despite aggressive immunosuppression.

Our findings suggest that giant-cell myocarditis in the native heart is distinct from lymphocytic myocarditis, in that giant-cell myocarditis has a more fulminant clinical course and may respond to treatment with a combination of immunosuppressive drugs. One should consider the diagnosis of giant-cell myocarditis in patients with left ventricular failure of new onset who decline clinically despite usual care, particularly if refractory ventricular tachycardia develops. In these patients, a biopsy-based diagnosis of giant-cell myocarditis will yield prognostic information and allow them to be considered early for transplantation. Immunosuppressive therapy with a combination of cyclosporine, azathioprine, and corticosteroids may be considered, although the applicability of our data on the effect of these drugs is limited by the observational design of our study. Perhaps most important, the possibility of potentially fatal post-transplantation recurrence can be discussed with patients for whom transplantation is being considered.

Supported by a Giannini-Bank of America Biomedical Research Award.

*We are indebted to Vern Hartz, Paul L. Clopton, and Kent Bailey, Ph.D., for help with statistical analysis, to Ana Gil for assistance with the preparation of the manuscript, and to Jay W. Mason, John B. O'Connell, Abvie Herskowitz, Noel R. Rose, Bruce M. McManus, Margaret E. Billingham, Thomas E. Moon, and the Myocarditis Treatment Trial Investigators for providing data for use in our analyses of survival.*

## APPENDIX

The members of the Multicenter Giant Cell Myocarditis Study Group were as follows: *Massachusetts General Hospital, Boston:* G.W. Dec, J.T. Fallon, and J. Southern; *Stanford University Hospital, Stanford, Calif.:* J.S. Schroeder and J. Friedman; *Johns Hopkins Hospital, Baltimore:* J.M. Hare and R.H. Hruban; *Rikshospitalet, Oslo, Norway:* S. Simonsen; *Rush-Presbyterian-St. Luke's Medical Center, Chicago:* M. Johnson; *Hospital of the University of Pennsylvania, Philadelphia:* E. Loh, B. Drachman, C. Reynolds, and M. van de Rijn; *Alfred Hospital, Praban, Australia:* M. Richardson, S.K. Tang, and J.S. Pedersen; *Sahlgrenska University Hospital, Göteborg, Sweden:* C.-H. Bergh, A. Oldfors, and U. Nystrom; *Virginia Commonwealth University/Medical College of Virginia, Richmond:* 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:* D.K.C. Cooper; *Brigham and Women's Hospital, Boston:* S. Davis, M. Givertz, and G. Winters; *Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland:* J.J. Goy and C. Genton; *Elmhurst Hospital Center, Elmhurst, N.Y.:* N.E. Kantrowitz and G. Turi; *Harefield Hospital, London:* M. Yacoub and A. Pomerance; *Hospital Germans Trias I Pujol, Barcelona, Spain:* A. Ariza; *Hospital Henri Mondor, Paris:* D. Tixier; *Herzzentrum Bad*

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