Giant Cell Versus Lymphocytic Myocarditis

A Comparison of Their Clinical Features and Long-term Outcomes

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Background. Giant cell myocarditis has rarely been diagnosed premortem, and little is known about its natural history. In addition, no comparative studies with lymphocytic myocarditis exist.

Methods and Results. The clinical features, serial change in left ventricular fraction (LVEF), and outcomes of all patients with histologically verified myocarditis were retrospectively evaluated. Ten patients (22%) were found to have giant cell myocarditis (group 1), whereas the remaining 36 (78%) had lymphocytic myocarditis (group 2). Age at presentation, gender distribution, duration of symptoms, initial LVEF, and resting hemodynamics did not differ between groups. Ventricular tachycardia was detected in 90% of group 1 patients compared with only 25% of group 2 (p=0.0007). Atrioventricular block that required pacemaker insertion was also more common in group 1 (60%) than in group 2 (8.3%) (p=0.001). Left ventricular systolic function declined during follow-up in group 1 patients (LVEF, 0.43±0.07–0.26±0.05, p=0.11) but increased in group 2 patients (LVEF, 0.33±0.03–0.41±0.03, p=0.02). When the net change between initial and final LVEF was assessed, a significant difference was evident (giant cell group, −0.17±0.06; lymphocytic group, +0.07±0.03; p=0.0008). Although a greater proportion of patients in group 1 died or required transplantation (seven of 10 versus 11 of 36, p=0.03), actuarial survival over 4 years was not different for the giant cell group (50%) than for the lymphocytic group (62%).

Conclusion. Giant cell myocarditis was more prevalent than previously recognized and highly associated with both ventricular tachycardia and pacemaker requirement. The likelihood of an adverse event, either cardiovascular mortality or cardiac transplantation, was significantly greater for patients with giant cell myocarditis than for those with lymphocytic myocarditis, perhaps because of the progressive decline in left ventricular systolic function that was observed in those with giant cell myocarditis. (Circulation 1991;83:953–961)

The introduction of right ventricular endomyocardial biopsy has facilitated the diagnosis of myocarditis in patients presenting with left ventricular dilatation. Although a prominent lymphocytic infiltrate histologically characterizes the majority of cases of biopsy-verified myocarditis, a smaller subset of patients demonstrates giant cells on biopsy. The term "giant cell myocarditis" was first used in 1905 by Saltikow (McFalls et al) to describe a myocarditis of unknown cause characterized by widespread degeneration of myocardial fibers and formation of multinucleated giant cells. Granulomatous involvement of the myocardium has rarely been diagnosed premortem; there are only two case reports of detection by endomyocardial biopsy. A wide variety of systemic illnesses has been associated with giant cell myocarditis, including sarcoidosis, infective endocarditis, rheumatoid arthritis, Wegener's granulomatosis, Takayasu's arteritis, tuberculosis, fungal infections such as coccidiodomycosis and cryptococcosis, syphilis, foreign body reaction, and drug hypersensitivity. An idiopathic form of giant cell myocarditis that often coexists with autoimmune diseases has been described as rapidly fatal. The natural history of giant cell myocarditis, both idiopathic and secondary, is largely unknown, and no comparative studies with lymphocytic myocarditis exist.

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The purpose of this study was to establish the incidence of giant cell myocarditis on endomyocardial biopsy in cardiomyopathy patients, assess the association of this entity with other systemic diseases, and compare the clinical features and outcomes of patients with giant cell myocarditis with those of patients with lymphocytic myocarditis.

Methods

Patient Population

Between January 1, 1975, and June 30, 1988, 424 patients (excluding cardiac transplant recipients) underwent right ventricular endomyocardial biopsy at the Massachusetts General Hospital, Boston. The vast majority (95%) had dilated cardiomyopathy of less than 2 years' duration, heart failure symptoms, and clinically suspected myocarditis. Additional indications for endomyocardial biopsy included unexplained ventricular tachyarrhythmias (2%), acute chest pain mimicking myocardial infarction with normal coronary arteries (1%), restrictive or constrictive hemodynamics (1%), and suspected cardiac tumors or infiltrative diseases of the myocardium (1%). Coronary angiography had been performed in more than 90% of patients; all had normal coronary arteries. All patients who underwent endomyocardial biopsy without coronary angiography were less than 35 years old.

Technique of Transvenous Endomyocardial Biopsy and Pathological Evaluation

Right heart catheterization was performed in all patients using a triple-lumen thermocatheter. At the conclusion of the procedure, right ventricular endomyocardial biopsy was performed. The technique was similar to that reported by Mason.17 Multiple biopsy specimens (usually four to six, each measuring 2–3 mm in diameter) were obtained from the right ventricular septum using either a Caves-Schultz-Stanford or Cordis Bypal bioptome and were immediately fixed by immersion into buffered 10% formalin.17 Paraffin sections were then stained with hematoxylin and eosin, Masson trichrome, Congo red, Prussian blue, periodic acid–Schiff, and elastic von Gieson's stains as previously described.17 The Dallas criteria were used to diagnose myocarditis and the type and degree of inflammatory cellular infiltrate as well as the extent of myocardial necrosis and fibrosis, and the presence or absence of multinucleated giant cells was carefully detailed in each specimen.18 For all biopsies in which giant cells were seen, special stains for fungi and acid-fast bacilli were performed and were negative. Pathological specimens were reviewed without prior knowledge of the patient's clinical findings.

Fifty-six patients were found to have histologically verified myocarditis; they formed the basis of this study. Ten patients had giant cell myocarditis, and the remaining individuals had lymphocytic myocarditis.

Clinical Evaluation and Assessment of Ventricular Function

The medical records of all 46 myocarditis patients were carefully reviewed. Each patient's clinical presentation, duration of illness, degree of left ventricular dysfunction, concomitant medication, and electrocardiographic abnormalities were carefully detailed. Ambulatory 24-hour electrocardiographic monitoring was performed in a subgroup (50%) of patients when clinically indicated, which was generally by the presence of ventricular tachyarrhythmias or second- or third-degree atrioventricular block on routine 12-lead electrocardiography or in-hospital telemetric monitoring. Temporary or permanent pacemaker insertion was undertaken when high-grade atrioventricular block (Mobitz-type II) or third-degree heart block was evident.

From a review of the medical records and patient interviews, we scored the number (from none to three) of clinical features of the presenting illness that suggested a diagnosis of myocarditis: a febrile, viral-like illness occurring just before the development of cardiac symptoms, pericarditis, or laboratory abnormalities (elevation in serum creatine phosphokinase, erythrocyte sedimentation rate, or white blood cell count). We diagnosed pericarditis if a pericardial friction rub or pleuritic substernal chest pain was present during the initial evaluation. We also noted the duration of illness from the onset of symptoms to the time of right ventricular endomyocardial biopsy, the patient's clinical course, the type of therapy (if any), and whether ventricular tachycardia (three or more consecutive ventricular beats at a rate of more than 100 min⁻¹) was recorded during ambulatory or in-hospital monitoring.

The patients' initial ejection fraction was determined by either contrast ventriculography or radionuclide study using the multigated equilibrium technique after optimization of medical therapy, which included digoxin, diuretic drugs, and an afterload-reducing agent (captopril, hydralazine, or prazosin) for patients with systolic dysfunction. Left ventricular ejection fraction (LVEF) was followed serially by radionuclide angiography, and the most recent value was used to establish a patient's final ejection fraction. Clinical outcome was established from a review of the patients' medical records and via a telephone survey with all surviving patients or their families, which was conducted in August 1988. All available autopsies were reviewed for cardiac pathology.

Immunosuppressive Treatment

Twenty-nine of the 46 myocarditis patients received immunosuppressive therapy—20 in the lymphocytic group and nine in the giant cell group. The decision to institute immunosuppressive therapy was that of the individual referring cardiologist, and no attempt at randomization was undertaken. Seven patients received prednisone alone for 6 months at dosages ranging from 20 to 40 mg/day orally. Twenty-
one patients received combination therapy with azathioprine and prednisone for 6 months per institutional protocol. Azathioprine was administered at a rate of 2 mg/kg/day, and the dosage was decreased if leukopenia (white blood cell count of less than 5,000) developed. Prednisone was administered at a rate of 1.0–1.5 mg/kg/day in divided doses and tapered to 0.3 mg/kg/day by week 12. This dose was continued for the entire 6 months and then tapered off during the final 4 weeks. All treated patients underwent repeat assessment of ventricular function and repeat biopsy after completion of therapy. In addition, three patients received prednisone and cyclosporine therapy. Two of the three cyclosporine-treated patients had failed a previous course of prednisone and azathioprine–based immunosuppression and demonstrated ongoing myocarditis on repeat endomyocardial biopsy. The third patient was randomized to prednisone and cyclosporine as part of the Multicenter Myocarditis Trial. Cyclosporine was administered to all three patients at an initial dosage of 10 mg/kg/day in divided doses. The dosage was then adjusted to maintain a trough cyclosporine level by radioimmunoassay of 50 ng/ml.

**Statistical Analysis**

Whenever appropriate, group means were compared by Student’s t test, and comparisons of proportions were made with the two-tailed Fisher’s exact test. Group data are given as the mean±SEM. Actuarial analyses of survival were performed using Kaplan-Meier analysis. Multivariate analysis of determinants of survival was performed using the Cox proportional hazards model. A probability of less than 0.05 was considered statistically significant.

**Results**

**Giant Cell Histology**

A total of 46 of the 424 patients (11%) who underwent biopsy had histological confirmation of myocarditis. Ten of these 46 patients had giant cell myocarditis on biopsy (22%). Myocardial involvement was diffuse in this group, with nine of 10 patients demonstrating inflammation, myocyte necrosis, and giant cells in multiple biopsy fragments. Eosinophilia was seen in only one of the giant cell biopsies. In contrast, a focal or multifocal pattern that involved only one or two biopsy specimens was characteristic of the lymphocytic myocarditis group. Of the 10 patients with giant cell myocarditis, five had no underlying systemic illness known to be associated with giant cell formation, and four had extracardiac manifestations of sarcoidosis in addition to their giant cell histology on endomyocardial biopsy. The remaining patient had evidence of multisystem involvement with Whipple’s disease. The demographic, clinical, and hemodynamic profiles of the five patients with idiopathic giant cell myocarditis are compared with the profiles of the four patients with cardiac sarcoidosis (Table 1). The apparent difference in gender distribution was not statistically significant, and no parameter was identified that differentiated the idiopathic group from the remaining patients with giant cell histology on biopsy. Because the clinical and hemodynamic profiles at presentation, durations of follow-up, and clinical outcomes for the two subsets of patients with giant cell myocarditis were similar, these two groups were combined for the remainder of this analysis. The demographic findings, initial clinical presentations, ejection fractions, electrocardiographic findings, and outcomes for the 10 patients with giant cell myocarditis are given in Table 2.

**Giant Cell Versus Lymphocytic Myocarditis**

The demographic features of the entire myocarditis group are given in Table 3. Mean patient age was 46±2 years, with 30 men and 16 women. The duration of symptoms averaged 4.0±1.1 months, and clinical follow-up averaged 862±88 days. Patients were divided into two groups based on their histology: giant cell myocarditis (group 1) and lymphocytic myocarditis (group 2). The demographic features of the two groups as well as their ventricular functions and hemodynamics at initial cardiac catheterization are given in Table 3. There was no significant difference in the ages of the two groups (41.9±5.2 years for group 1 versus 48.1±2.5 years for group 2). The gender distribution was similar with seven men and three women in group 1 and 23 men and 13 women in group 2. Duration of symptoms before biopsy was also similar in the two groups (6.8±3.3 versus 3.0±1.0 months, p=NS). There was a trend toward a higher baseline LVEF in the giant cell myocarditis group, but this did not reach statistical significance (LVEF=0.43±0.07 versus 0.33±0.03, p=0.07).

Four of the 10 patients with giant cell myocarditis had an LVEF of 0.45 or more at presentation. Two of

| Table 1. Comparison of Demographics, Ventricular Functions, and Resting Hemodynamics for the Two Groups of Giant Cell Myocarditis at Presentation |
|-------------------|-------------------|---|
| n                 | Cardiac sarcoaidosis | Giant cell (idiopathic group) |
| Age (yr)          | 35±3              | 48±10              | NS |
| Male:female       | 4:0               | 2:3                | NS |
| Duration of symptoms (mo) | 2±1.0           | 6.3±4.3            | NS |
| LVEF (initial)    | 0.45±0.16         | 0.37±0.07          | NS |
| LVEF (final)      | 0.24±0.06         | 0.20±0.04          | NS |
| RA (mm Hg)        | 13±6              | 5±4                | NS |
| PAM (mm Hg)       | 4±4               | 25±1               | NS |
| PCWP (mm Hg)      | 13±5              | 13±3               | NS |
| CO (l/min)        | 5.0±0.5           | 5.5±0.6            | NS |
| VT (%)            | 75                 | 60                 | NS |
| Pacer (%)         | 75                 | 60                 | NS |
| LVEF, left ventricular ejection fraction; RA, right atrial pressure; PAM, pulmonary artery mean pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; VT, ventricular tachycardia. |
TABLE 2. Clinical and Electrophysiologic Findings for the 10 Giant Cell Myocarditis Patients

<table>
<thead>
<tr>
<th>Base</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Presentation</th>
<th>LVEF</th>
<th>Electrocardiography</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>M</td>
<td>5 mo dyspnea, palpitations</td>
<td>0.46</td>
<td>3° AVB, VT</td>
<td>Permanent pacer, sarcoidosis, died—congestive heart failure</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>M</td>
<td>1 mo dyspnea, palpitations, syncope</td>
<td>0.25</td>
<td>Afib, VT, 2:1 AVB, RBBB</td>
<td>Temporary pacer, sarcoidosis, died—cardiogenic shock</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>F</td>
<td>1 mo palpitations, fatigue, dyspnea</td>
<td>0.40</td>
<td>3° AVB, VT</td>
<td>Permanent pacer, progressive congestive heart failure, cardiac transplant</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>M</td>
<td>1 mo dyspnea, syncope, palpitations</td>
<td>0.35</td>
<td>1° AVB, RBBB, VT</td>
<td>Recurrent VT, AICD, temporary pacer, cardiac transplant</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>M</td>
<td>2 wk dyspnea, palpitations, cardiac arrest</td>
<td>0.19</td>
<td>3° AVB, RBBB, VT</td>
<td>IABP for shock, sarcoidosis, temporary pacer, died—congestive heart failure</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>F</td>
<td>3 mo palpitations, night sweats</td>
<td>0.22</td>
<td>VT</td>
<td>Alive, NYHA class III</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>M</td>
<td>2 wk dyspnea, cough</td>
<td>0.61</td>
<td>LBBB, VT</td>
<td>Died—progressive congestive heart failure</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>F</td>
<td>6 mo dyspnea, chest pain, palpitations</td>
<td>0.27</td>
<td>2° AVB, VT</td>
<td>Alive, NYHA class III</td>
</tr>
<tr>
<td>9</td>
<td>39</td>
<td>M</td>
<td>1 mo dyspnea</td>
<td>0.90</td>
<td></td>
<td>Sarcoïdosis, lost to follow-up</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>M</td>
<td>2½ yr dyspnea, syncope</td>
<td>0.67</td>
<td>3° AVB, VT</td>
<td>Whipple’s disease at autopsy, permanent pacer</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; 3°, 2°, and 1° third-, second-, and first-degree; AVB, atrioventricular block; CHF, congestive heart failure; VT, ventricular tachycardia; Afib, atrial fibrillation; RBBB, right bundle branch block; LBBB, left bundle branch block; AICD, automated implantable defibrillator; IABP, intra-aortic balloon pump; NYHA, New York Heart Association.

these four patients underwent biopsy for chest pain mimicking acute myocardial infarction, and the remaining two patients underwent biopsy for heart failure due to diastolic dysfunction. The remaining six patients in the giant cell myocarditis group had an LVEF of less than 0.45 and clinical heart failure. Rather surprisingly, 10 of 36 lymphocytic myocarditis patients had normal systolic function and either heart failure or chest pain; the remainder had symptomatic heart failure and an LVEF of less than 0.45. The resting hemodynamics for the two groups are given in Table 3. No differences were observed in mean right atrial pressure, pulmonary capillary wedge pressure, pulmonary artery pressure, or cardiac output. Duration of clinical follow-up also did not differ between the two groups (609±169 versus 916±103 days, p=0.09).

**Clinical Features**

Neither group 1 (giant cell) nor group 2 (lymphocytic) populations exhibited a high incidence of "clas-

**TABLE 3. Comparison of Demographic, Ventriculographic, and Hemodynamic Findings for the Entire Group, the Giant Cell Group, and the Lymphocytic Group**

<table>
<thead>
<tr>
<th></th>
<th>Entire group</th>
<th>Giant cell (group 1)</th>
<th>Lymphocytic (group 2)</th>
<th>p (group 1 versus 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>46</td>
<td>10</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46.5±2.3</td>
<td>41.9±5.2</td>
<td>48.1±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of symptoms (mo)</td>
<td>4.0±1.1</td>
<td>6.8±3.3</td>
<td>3.0±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical score</td>
<td>0.8±0.1</td>
<td>0.8±0.2</td>
<td>0.9±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Initial LVEF</td>
<td>0.35±0.3</td>
<td>0.43±0.07*</td>
<td>0.33±0.03†</td>
<td>0.07</td>
</tr>
<tr>
<td>Final LVEF</td>
<td>0.37±0.06</td>
<td>0.26±0.05*</td>
<td>0.41±0.03†</td>
<td>0.05</td>
</tr>
<tr>
<td>Change in LVEF</td>
<td>0.02±0.07</td>
<td>-0.17±0.09</td>
<td>0.08±0.04</td>
<td>0.015</td>
</tr>
<tr>
<td>M:F</td>
<td>30:16</td>
<td>7:3</td>
<td>23:13</td>
<td>NS</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>8.5±1.2</td>
<td>8.5±2.9</td>
<td>8.5±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>PAS (mm Hg)</td>
<td>33±2.7</td>
<td>30±5.9</td>
<td>34.2±3.1</td>
<td>NS</td>
</tr>
<tr>
<td>PAo (mm Hg)</td>
<td>15±1.6</td>
<td>13.6±2.9</td>
<td>16.2±1.8</td>
<td>NS</td>
</tr>
<tr>
<td>PAM (mm Hg)</td>
<td>22.3±2.5</td>
<td>18.8±3.3</td>
<td>23.1±2.9</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>14±1</td>
<td>12.3±2.3</td>
<td>14.9±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.9±0.2</td>
<td>5.5±0.4</td>
<td>4.7±0.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Follow-up (days)</td>
<td>862±88</td>
<td>609±168.5</td>
<td>916.2±103.2</td>
<td>0.09</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; RA, mean right atrial pressure; PAS, pulmonary artery systolic pressure; PAo, pulmonary artery diastolic pressure; PAM, pulmonary artery mean pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output.

*p=0.11 (initial versus final LVEF for group 1); †p=0.02 (initial versus final LVEF for group 2).
sic” clinical features of myocarditis. Fewer than 10% had evidence for pericarditis or supportive laboratory abnormalities that suggested myocardial inflammation. The clinical score of the entire group averaged only 0.8±0.1. The clinical score for group 1 patients was 0.8±0.2; for group 2 patients, it was 0.9±0.2. The most striking clinical feature in the giant cell group was the presence of palpitations, which was a complaint on initial presentation in seven of 10 group 1 patients compared with only six of 36 group 2 patients (p=0.002). Ventricular tachycardia was detected on 12-lead electrocardiography or 24-hour ambulatory monitoring in nine of the 10 giant cell patients and nine of 36 (25%) of the lymphocytic group (p=0.00035). If only the cases diagnosed on routine electrocardiography were considered, the difference in the incidence of ventricular tachycardia between the giant cell (seven of 10) and lymphocytic groups (four of 36) was still evident (p=0.0006). Holter monitoring was performed before discharge in approximately 50% of each group and detected the remaining cases of ventricular tachycardia. All five patients with idiopathic giant cell myocarditis had ventricular tachycardia; the only group 1 patient without ventricular tachycardia had sarcoidosis.

High-grade atrioventricular block requiring temporary or permanent pacemaker insertion was diagnosed on routine 12-lead electrocardiography or telemetric monitoring in six of 10 group 1 patients (60%) and three of 36 group 2 patients (8.3%) (p=0.001). Among the group 1 patients, two patients with idiopathic giant cell myocarditis did not require pacemaker insertion; one patient with cardiac sarcoidosis experienced neither ventricular tachycardia nor high-grade atrioventricular block. Multivariate analysis indicated that the presence of atrioventricular block requiring pacemaker insertion was predictive of a subsequent fatal outcome in both group 1 and group 2 patients (p=0.05).

Changes in Ventricular Function

Figure 1 illustrates the change in LVEF that occurred for group 1 patients during treatment. Nine of the 10 individuals received 6 months of immunosuppressive therapy. The mean group 1 ejection fraction decreased during treatment from 0.43±0.07 to 0.26±0.05 (p=0.11). Only one patient (11%) showed improvement in LVEF during treatment. Ejection fraction declined in five patients and remained unchanged in two patients; one patient died before repeat radionuclide angiography, and another did not return for follow-up study.

Figure 2 illustrates the change in LVEF for group 2 patients. Of the 36 group 2 patients, three died before a repeat radionuclide study could be performed, and four did not return for follow-up study. The mean group 2 ejection fraction increased from 0.33±0.03 to 0.41±0.03 (p=0.02). Twenty of the 26 group 2 patients with dilated cardiomyopathy (LVEF of less than 0.45) received 6 months of immunosuppression, whereas none of the 10 patients with normal systolic function were immunosuppressed. Calculation of the change in ejection fraction between initial and repeat radionuclide studies demonstrated a modest but statistically significant increase of 0.07±0.03 in the lymphocytic group, whereas the giant cell group demonstrated a net decrease in ejection fraction of 0.17±0.06. When net change in ejection fraction over time was compared between the two groups, a significant difference was observed (p=0.0008). Ventricular function remained unchanged in six of the 26 patients and decreased in six; two patients did not return for follow-up study. Of the 10 group 2 patients with normal systolic function, ejection fraction remained unchanged in seven and decreased to less than 0.45 in one; two patients did not return for follow-up.

Histological Findings on Repeat Biopsy

Repeat right ventricular biopsy was performed in eight of nine group 1 (giant cell) patients after 6
months of immunosuppression. Histological findings included resolved myocarditis (n=5), resolving myocarditis (n=2), and ongoing myocarditis (n=1). No increase in left ventricular function was noted in any of these patients despite histological improvement in the majority on repeat study.

Twenty-six of the 36 group 2 (lymphocytic) patients underwent repeat biopsy at 6 months; 20 patients were receiving immunosuppression at the time of repeat biopsy. Histological findings were similar to those of group 1: resolved myocarditis (n=20), resolving myocarditis (n=4), and ongoing myocarditis (n=2). Change in LVEF was not predicted by repeat histological findings. The influence of immunosuppression in histological resolution or ventricular function could not be assessed because the majority of patients in each group were immunosuppressed.

**Patient Survival**

Mortality was high in both groups of patients with myocarditis as might be expected because the majority of patients in each group presented with heart failure and impaired ventricular function. Although there was a tendency for higher mortality in the giant cell group, the cumulative group 1 mortality rate of 50% did not differ significantly from the 28% (10 of 36 patients) group 2 mortality rate, possibly because of the small sample size in the giant cell group. However, if patients requiring cardiac transplantation were included with those who died and considered together as having experienced an adverse outcome during follow-up, a significant difference was apparent. In group 1, seven of 10 patients (70%) had an adverse outcome compared with 11 of 36 of group 2 patients (30%) (p=0.04). Figure 3 illustrates adverse event-free survival for both histological groups over time. The giant cell group experienced a higher rate of adverse events, which became statistically significant during the third year of follow-up.

Figure 4 compares actuarial survival for all patients by histological grouping. Mantel-Cox analysis did not detect a statistically significant difference in early or late survival between the two groups. Subgroup analysis also did not detect any difference in survival between the idiopathic giant cell (n=5) and the sarcoid (n=4) patients at 6 months (80±2% versus 100%) and at 2 years (80±8% versus 33±7%, p=0.07). The small sample size in the giant cell population may have accounted for the lack of survival differences between the giant cell and lymphocytic groups. Over time, the likelihood of survival for the two groups tended to converge as additional late deaths occurred in the lymphocytic group. The cumulative survival at 1,600 days was 50% for group 1 patients and 62% for group 2 patients.

**Discussion**

Giant cell myocarditis has been described under a variety of names, including “idiopathic giant cell myocarditis,” “myocarditis of the giant cell type,” and “granulomatous myocarditis.” Tesluk first proposed the term “giant cell myocarditis” to describe the histological pattern of widespread circumscribed areas of myocardial necrosis associated with a prominent infiltrate of lymphocytes, a few eosinophils and plasma cells, and a large number of multinucleated giant cells. The adjacent myocardium is often normal, as are the endocardium and pericardium. Clinical presentations have been reported to include sudden death, progressive cardiac failure, and arrhythmias. There have been approximately 60 cases reported in the literature, all but four of them from pathological series. Based on previous reports, this rare condition has been described as inevitably fatal with a rapidly downhill course resulting in death, usually within 1–3 months. This series represents the first study of the natural history of giant cell myocarditis diagnosed by endomyocardial biopsy. Surprisingly, giant cell myocarditis accounted for 22% of all cases of myocarditis diagnosed at our institution. This may be explained in part by a high
referral rate to our institution and the severity of illness of many of the myocarditis patients. Nonetheless, this incidence suggests that giant cell myocarditis may be more common than previously believed. Whitehead,22 in an autopsy series of 18 cases of fatal myocarditis, reported a similar incidence of 20%.

The etiology of giant cell myocarditis is usually unknown. Specific causes of giant cell formation such as tuberculosis, syphilis, or fungal infection23 may account for a small number of cases but were excluded in this series. Its existence as an entity distinct from myocardial sarcoidosis continues to be debated, and differentiation of the two disorders has been blurred by several reported cases of idiopathic giant cell myocarditis coexisting with associated sarcoidosis or extracardiac granulomatous myocarditis.3 Myocarditis may be the only manifestation of cardiac sarcoidosis during life, and its differentiation from idiopathic giant cell myocarditis may be difficult or impossible when pulmonary involvement is absent. The cardiac manifestations of myocardial sarcoidosis are myriad and include arrhythmias, conduction disturbances, sudden death, congestive heart failure, pathological Q waves simulating myocardial infarction, papillary muscle dysfunction, ventricular aneurysm formation, and pericardial effusion.1–3,15,23,24 Congestive heart failure is a manifestation of cardiac sarcoidosis in 20–30% of reported cases with a fatal outcome.3,4,25 In this series, four of our 10 giant cell patients had histology and clinical findings consistent with cardiac sarcoidosis, and a fifth patient had evidence for widespread Whipple’s disease at autopsy. We chose for several reasons to combine patients with idiopathic giant cell myocarditis and those having a known etiology for myocardial giant cell formation. First, the two groups did not differ in clinical features at presentation, demographics, ventricular functions, or resting hemodynamics. Second, we wanted to examine whether the clinical features and natural history of myocarditis patients varied based solely on the histology observed on endomyocardial biopsy. Finally, the groups were combined because the natural history of giant cell myocarditis as a result of sarcoidosis and Whipple’s disease was no better defined than that of idiopathic giant cell disease. In fact, this study confirms that the clinical features, incidence of ventricular arrhythmias and atrioventricular block, and survival of patients with both idiopathic and known causes for giant cell myocarditis are similar.

Conduction System Abnormalities and Ventricular Arrhythmias in Giant Cell Myocarditis

Davies et al15 reported little clinical difference in the presentation of giant cell and lymphocytic myocarditis, except for its rapidity of onset. Clinical presentations may include progressive heart failure and sudden death in as many as 50% of cases.1,15,19 A variety of electrocardiographic abnormalities have been reported, including nonspecific ST and T wave changes,15,19 Q wave development in the absence of coronary artery disease, conduction system abnormalities, and, rarely, complete heart block.2,20,26 Ventricular tachycardia has also been reported.1,15 Conduction system abnormalities, high-grade atrioventricular block, and ventricular tachyarrhythmias were seen in the majority of giant cell patients in this series. Both ventricular tachycardia and the need for temporary or permanent ventricular pacing were more often observed in this series than in previous case reports and served to differentiate this group of patients from those with lymphocytic histology. Whether the giant cell group had more advanced disease or a predilection for inflammatory involvement of the conduction system remains unknown. The high frequency of complete heart block suggests that patients with giant cell myocarditis must be closely followed for the development of bradycardia. Three of the patients in this series required permanent pacemaker insertion for persistent complete heart block. Rather surprisingly, although 90% of the giant cell patients had evidence for ventricular tachycardia and six required antiarrhythmic suppression, no sudden deaths were encountered in this group. All deaths were due to progressive congestive heart failure.

Influence of Initial and Repeat Histology on Outcome

Survival was similar in the lymphocytic and giant cell groups. Fifty percent of the giant cell patients were alive at 1 year, and despite a deterioration in ventricular function in eight of nine patients during the first 6 months of follow-up, no additional deaths were encountered after the first year. However, two patients required cardiac transplantation for progressive heart failure. Although survival in the lymphocytic group appeared to be slightly better during the first year, this may have resulted from the large number of patients (10/36) whose ejection fraction was normal at presentation. Additional deaths during the subsequent 3 years resulted in a similar survival rate by the end of the study. As have been reported in two other series,27,28 histological findings on repeat biopsy did not predict changes in ventricular function. Despite partial or complete histological resolution of myocarditis in all but one giant cell patient, ventricular function decreased in all individuals. Similarly, the majority of patients with lymphocytic myocarditis (77%) demonstrated resolution of myocarditis on repeat biopsy, but no correlation was evident between histology and improvement in ventricular performance.

The length of survival for the giant cell group in this endomyocardial biopsy series was significantly longer than those of patients in previous autopsy series, which range from 10 days15 to 18 months.29 The higher survival rate may have been the result of earlier diagnosis, use of antiarrhythmic agents, or treatment with immunosuppressive agents. The absence of sudden deaths suggests that either antiarrhythmic therapy or pacemaker insertion may have contributed to the improved survival. The similarity in long-term survival between patients with giant cell and those with lym-
phocytic histology was unexpected because previous series have described uniform fatality rates for giant cell disease compared with significant survival rates and spontaneous improvement in patients with lymphocytic myocarditis. Management of congestive heart failure, ventricular arrhythmias, and bradyarrhythmias was identical in the two groups because patients were treated over the same time period at a single institution. These findings suggest that patient outcome may be more dependent on the degree of left ventricular dysfunction and associated rhythm or conduction system disturbance than on the histological type of myocarditis seen on biopsy.

**Role of Immunosuppressive Therapy**

Corticosteroid therapy alone or in combination with other immunosuppressive agents such as azathioprine or cyclosporine remains of unproven benefit for giant cell myocarditis with little available data in the literature. In an autopsy series of patients with cardiac sarcoidosis, Roberts et al reported that corticosteroid therapy was effective in resolving the myocardial granulomatous inflammation but was associated with an increased likelihood of significant myocardial fibrosis. Stein et al reported improvement in electrocardiographic abnormalities in patients with cardiac sarcoidosis receiving corticosteroids, but no histological correlation was available. Lorell et al reported a single case of biopsy-proven cardiac sarcoid in which improvement in congestive heart failure was noted during treatment with corticosteroids. Nonetheless, Fanta has recently stated that “the ability of steroids to modify the natural history of the disease has never been demonstrated convincingly in a controlled clinical trial.” Likewise, almost no information exists regarding the use of corticosteroids in the treatment of idiopathic giant cell myocarditis. McFalls et al treated two patients with prednisone alone for giant cell myocarditis and reported resolution of granulomas and increase in interstitial fibrosis during treatment. One patient in their series remained alive, although requiring antiarrhythmic therapy, whereas the second patient died suddenly during steroid taper. Postmortem examination of the heart showed mild fibrosis but no active granulomatous disease. In this series, no attempt to control for immunosuppressive therapy was undertaken. The choice of therapy was made by the referring cardiologist and in most instances consisted of corticosteroid-based immunosuppression. Although the short- and long-term survival rates in the treated giant cell group were higher than anticipated, the lack of improvement in ventricular function in eight of the nine treated patients despite histological evidence of partial or complete resolution argues against a significant role for immunosuppression in determining long-term outcome. The patients who succumbed to progressive heart failure or underwent cardiac transplantation had no evidence for granulomas at necropsy or in the explanted heart after completion of immunosuppressive therapy.

Immunosuppression with prednisone and cyclosporine will result in improved ventricular function or outcome in patients with either lymphocytic or giant cell myocarditis awaits completion of the Multicenter Myocarditis Trial. 

**Limitations of the Study**

Any study of giant cell myocarditis at a single institution is limited by the small population size. Although these 10 patients represent the largest single institution series, it is difficult to conclusively define natural history based on such a small sample size. Furthermore, although the majority of both giant cell and lymphocytic myocarditis patients presented with heart failure, the extent of left ventricular dilatation and impairment was quite heterogeneous. A third limitation was the lack of a uniform treatment protocol. Initiation of anticoagulant therapy, antiarrhythmic agents, and immunosuppression was left to the referring physician and, therefore, nonuniform in application. In addition, there was no attempt at randomization or prospective analysis of the effects of immunosuppressive therapy on the giant cell population. Finally, the assessment of ventricular arrhythmias was not performed using 24-hour ambulatory monitoring in all patients, particularly the lymphocytic myocarditis group. It is possible that a significantly higher incidence of ventricular tachycardia may have been present in this group had the entire population undergone 24-hour ambulatory monitoring. Nonetheless, the incidence of ventricular tachycardia was higher in the giant cell group during routine in-hospital telemetric monitoring.

**Conclusion**

Giant cell myocarditis represented 22% of all cases of biopsy-verified myocarditis seen at this institution during a 13.5-year period. The incidence of ventricular tachycardia as well as of high-grade atrioventricular block was significantly higher in the giant cell myocarditis group than in the lymphocytic myocarditis group. Despite a progressive decline in left ventricular function during immunosuppressive treatment in the majority of the giant cell patients, actuarial survival was higher than previously reported, averaging 50% at 4 years. However, the likelihood of an adverse event, either death or cardiac transplantation, was greater in giant cell than in lymphocytic patients. The long-term survival in patients with biopsy-verified myocarditis appears more dependent on the degree of left ventricular dysfunction and the presence of associated conduction system disease or ventricular arrhythmias than on the type of histological inflammation on endomyocardial biopsy. The optimum treatment for giant cell myocarditis remains unknown at this time.

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