Long-Term Risk of Recurrence, Morbidity and Mortality in Giant Cell Myocarditis

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Giant cell myocarditis (GCM) is a rare disorder in which survival beyond 1 year without heart transplantation is uncommon. Long-term follow-up data on those with such survival are lacking. Twenty-six patients with biopsy-proved GCM who survived for >1 year without heart transplantation were identified from a multicenter GCM registry. The incidence of death, transplantation, ventricular assist device placement, and histologically proved disease recurrence was ascertained retrospectively. The rates of recurrent heart failure, ventricular arrhythmias, renal failure, and infectious complications were calculated. The mean age of the cohort was 54.6 ± 13.9 years (65% women). The mean follow-up duration was 5.5 years starting 1 year after diagnosis. There were 3 deaths (12%), 5 heart transplantations (19%), and 1 ventricular assist device placement (4%). Three histologically confirmed recurrences of GCM (12%) occurred between 1.5 and 8 years after diagnosis. Thirteen of 26 patients experienced a total of 30 heart failure episodes ≥1 year after initial diagnosis. There were 23 episodes of elevated creatinine in 12 patients, 41 infectious events in 13 patients, and 19 episodes of ventricular arrhythmias in 6 patients with a total of 144 years of follow-up. Starting 1 year after GCM diagnosis, the combined rate of death, transplantation, ventricular assist device placement, and GCM recurrence was 47% at 5 years. In conclusion, the risk for GCM recurrence continues to ≥8 years after diagnosis. **(Am J Cardiol 2015;■:■−■)**

Giant cell myocarditis (GCM) is an uncommon but frequently fatal form of acute myocarditis that has been shown to respond to cyclosporine-based immunosuppressive therapy.[1] In cases proved by biopsy, the most frequent outcome is death or transplantation within the first year after diagnosis.[2] Even with transplantation, GCM recurrence in the donor heart has been cited as high as 20% to 25%.[3,4] As patients survive longer without transplantation because of efficacious medical therapy, questions of long-term survival and of recurrence risk in the native heart beyond the first year have not been answered. Likewise, the optimal duration and intensity of immunosuppression beyond 1 year are not known. Furthermore, extracardiac morbidity in these patients has not been evaluated. No single center has accumulated experience to catalog the long-term risks for disease recurrence and extracardiac morbidity in patients with GCM. To assess survival and recurrence risk, and to characterize the clinical picture of a prolonged course of GCM, we followed patients from multiple sites in the United States and Germany with biopsy-proved GCM who survived for >1 year on immunosuppression without cardiac allotransplantation.

Methods

Records from Mayo Clinic (Rochester, Minnesota) and Charite Hospital (Berlin, Germany) were systematically searched to gather all cases of histologically confirmed GCM with survival beyond 1 year without heart transplantation. Additional known cases, in our consultative files, were also included if sufficient patient data and research consent were available. Investigators completed a form on each case, requesting historical data on the medical history, presenting symptoms, cardiac rhythm, immunosuppressive regimen during and after year 1 after diagnosis, and heart failure treatment.

Adverse events were followed after the first year. These included new or worsening heart failure, defined as a change in New York Heart Association class of ≥1, a ≥10% decrease in the ejection fraction (by any method) compared with the year 1 value or subsequent peak before measure, or a new hospitalization or emergency department visit for heart failure; new or worsening renal insufficiency, defined as elevated serum creatinine higher than the end of year 1 baseline by 0.3 mg/dl; new or worsening ventricular arrhythmias; and infection. Outcomes including death, heart transplantation, ventricular assist device (VAD) placement, biopsy-proved GCM recurrence, and date of last follow-up were obtained.

Available slides from patients with GCM were retrieved from institutional archives. Three separate biopsies were considered for scoring: initial GCM diagnosis; post-diagnostic biopsy, usually at 1 month after initial diagnosis; and at the time of suspected recurrence. A single cardiovascular pathologist (JJM) reviewed all available material. Histologic features assessed included the presence of giant

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See page 5 for disclosure information.

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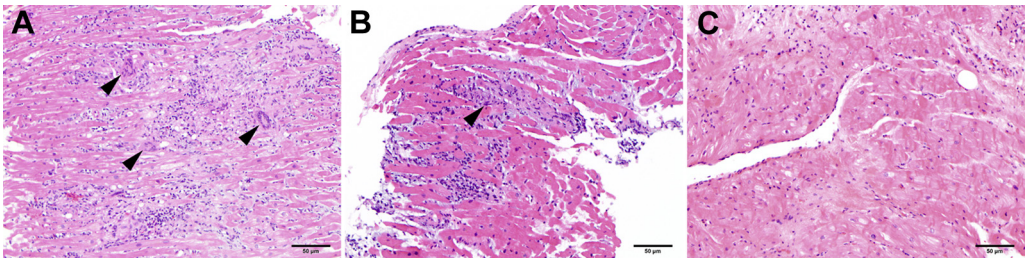

Figure 1. Histopathologic presentation of GCM. *(A)* Active GCM characterized by an intense lymphoplasmacytic and eosinophilic infiltrate with scattered multinucleated giant cells (arrowheads), associated with myocyte injury and necrosis (hematoxylin and eosin staining, 100× original magnification). *(B)* Recurrent GCM, characterized by a lymphoplasmacytic infiltrate with rare multinucleated giant cell (arrowhead) (hematoxylin and eosin staining, 100× original magnification). *(C)* Moderate myocyte hypertrophy with moderate interstitial (replacement-type) fibrosis, likely representing myocarditis-associated injury (hematoxylin and eosin staining, 100× original magnification).

cells, the character of inflammation (lymphocytes, eosinophils, macrophages), the presence of granulomas, the presence of myocyte hypertrophy, and interstitial fibrosis (particularly replacement type). The diagnosis of active GCM (Figure 1) was made by established criteria.[5] Likewise, recurrence was established on the basis of the same criteria (Figure 1). The finding of replacement-type fibrosis, in the absence of coronary artery disease, was interpreted as representing myocarditis-related injury (Figure 1). If histologic features did not allow definitive discrimination among GCM, lymphocytic myocarditis, and/or cardiac sarcoidosis, the case was excluded from the study.

Overall event rates were estimated using the Kaplan-Meier method. These events included overall survival as well as event-free survival for the combined events of infection, heart failure, and ventricular arrhythmia. Comparisons of the cumulative event rates between groups were completed using log-rank tests. Event rates were evaluated starting 1 year after diagnosis.

Results

Twenty-six patients with GCM met the selection criteria of ≥1-year survival without heart transplantation. The demographics, presenting features, and medical treatment for all patients are described in Table 1. The mean age was 54.6 ± 14.1 years at the time of diagnosis. The cohort was 65% female. The mean follow-up duration, starting from 1 year after diagnosis, was 5.5 years (range 1 to 16.6, median 4.8).

Detailed medication and device therapy data were available for 23 patients. Of these, 23 (100%) received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 19 (83%) received β blockers, 19 (83%) received antiarrhythmic medications, and 9 (39%) received digoxin. Fifteen subjects (65%) received implantable cardioverter-defibrillators. One subject (4%) received a pacemaker, and 1 subject (4%) required a temporary VAD for 53 weeks before undergoing heart transplantation but did not survive the transplantation surgery. No patients required permanent VAD support or intra-aortic balloon counterpulsation.

During the first year after diagnosis, all patients received cyclosporine-based immunosuppression. At the time of diagnosis, 11 of the 26 patients (42%) received muromonab-CD3, antithymocyte globulin, equine antithymocyte globulin, or a comparable antilymphocytic agent. One patient received a combination of antilymphocyte therapies. Seven patients (27%) were weaned to corticosteroid therapy only, and the remaining 19 (73%) received a combination of cyclosporine and corticosteroids during the first year. At varying times in the first year, 6 patients (23%) received azathioprine, 6 (23%) received mycophenolate mofetil, and 5 (19%) were switched to a sirolimus-based regimen for cyclosporine intolerance. The average minimum number of immunosuppressive medications used in the first year after diagnosis was 1.91 ± 0.65. The average maximum number of immunosuppressive medications used was 2.7 ± 0.46 (Table 1).

After the first year after diagnosis, the average minimum number of immunosuppressive medications decreased to 1.25 ± 0.85, while the average maximum number of immunosuppressive medications decreased to 2.12 ± 0.90. At any point in time, 26 patients (100%) received corticosteroids, 21 (81%) received cyclosporine, 10 (38%) received mycophenolate mofetil, 8 (31%) received azathioprine, and 8 (31%) received sirolimus. The indications and combinations of these drugs were dictated by clinical course, tolerance of the medications, and episodes of renal insufficiency or heart failure.

In general, the dose of cyclosporine was adjusted to achieve 11-hour trough levels of 150 to 200 μg/L during the first 6 months, 100 to 150 μg/L between 6 and 12 months, and 75 to 100 μg/L after 1 year. Of those with histopathologic recurrence, 2 patients had recently discontinued or decreased immunosuppression. There was no definite correlation between arrhythmia risk and level of immunosuppression.

All patients, as a matter of selection, met histologic criteria for GCM at the time of initial biopsy (Figure 1). Tissue slides were available for review in 17 patients (65%). The remaining 9 patients were all evaluated at outside academic institutions with experienced cardiovascular pathologists rendering unequivocal diagnostic interpretations. Well-formed granulomas were not present in any case.

Throughout follow-up, additional histologic material was available in 13 patients (ranging from 1 to 11 biopsy procedures) beyond their diagnostic biopsies, either for therapeutic monitoring or suspected disease recurrence. Three cases of biopsy-proved recurrence were identified within the cohort (Figure 1), 2 of which were available for histologic review (the third had only a detailed pathology report

Table 1
Study cohort

Case	Age	Sex	Duration of Follow-up (years)	Primary presenting symptoms	Number of Immunosuppressive		Non-Infectious Adverse Outcomes
					First Year	> First Year	
1	32	F	15.0	heart failure	steroid, azathioprine	-	-
2	34	F	16.6	chest pain	cyclosporine, steroid, azathioprine, OKT3	cyclosporine, steroid, azathioprine	renal failure, heart failure
3	35	M	5.9	shortness of breath	cyclosporine, steroid	cyclosporine, steroid	-
4	38	M	9.2	chest pain	cyclosporine, steroid, OKT3	cyclosporine, steroid, azathioprine, sirolimus	heart failure, ventricular arrhythmia
5	42	F	1.4	shortness of breath	cyclosporine, steroid, OKT3	cyclosporine, steroid	-
6	45	F	9.0	presyncope	cyclosporine, steroid, OKT3	cyclosporine, steroid	renal failure, heart failure
7	46	F	1.0	heart failure	cyclosporine, steroid, OKT3	-	death
8	47	F	2.7	chest pain	cyclosporine, steroid, OKT3	cyclosporine, steroid	renal failure
9	47	M	12.5	heart failure	cyclosporine, steroid, azathiprine, OKT3	cyclosporine, steroid, azathioprine	renal failure, heart failure
10	47	M	6.5	heart failure	steroid, sirolimus, mycophenolate mofetil	steroid, mycophenolate mofetil	renal failure
11	50	F	4.1	heart failure	cyclosporine, steroid, sirolimus, mycophenolate mofetil	cyclosporine, steroid, sirolimus, mycophenolate mofetil	renal failure, heart failure, ventricular arrhythmia
12	50	F	6.7	presyncope	steroid, azathioprine	steroid, azathioprine	heart failure, ventricular arrhythmia
13	51	M	1.4	shortness of breath	steroid, azathioprine	azathioprine	-
14	51	F	4.0	shortness of breath	cyclosporine, steroid, azathioprine	cyclosporine, steroid, azathioprine, mycophenolate mofetil	-
15	52	M	1.4	heart failure	steroid	-	-
16	52	M	7.6	presyncope	cyclosporine, steroid, OKT3	cyclosporine, steroid, mycophenolate mofetil	heart failure
17	55	F	1.3	heart failure	cyclosporine, steroid, sirolimus	cyclosporine, steroid, azathioprine, sirolimus	renal failure, heart failure
18	58	F	4.8	heart failure	cyclosporine, steroid, OKT3	steroid, sirolimus, mycophenolate mofetil	renal failure, heart failure
19	60	F	1.7	heart failure	cyclosporine, steroid, sirolimus, mycophenolate mofetil	steroid, sirolimus, mycophenolate mofetil	renal failure, heart failure, ventricular arrhythmia
20	60	M	2.6	heart failure	cyclosporine, steroid, mycophenolate mofetil	steroid, mycophenolate mofetil	renal failure, heart failure, ventricular arrhythmia, death
21	69	F	1.6	heart failure	cyclosporine, steroid, mycophenolate mofetil		heart failure, death
22	72	M	5.7	heart failure	cyclosporine	Cyc, Ster, Siro, MM	heart failure
23	76	F	6.8	heart failure	cyclosporine, steroid	cyclosporine, steroid, mycophenolate mofetil	heart failure
24	78	F	1.2	heart failure	cyclosporine, steroid, mycophenolate mofetil	steroid, sirolimus, mycophenolate mofetil	-
25	78	F	7.9	heart failure	cyclosporine, steroid, sirolimus, mycophenolate mofetil	cyclosporine, steroid	renal failure, heart failure, ventricular arrhythmia
26	80	F	4.4	shortness of breath	cyclosporine, steroid	steroid	-

Table 2
Infectious adverse events by subject in descending order of frequency

Case	Events	Total Events
1	Urinary tract infection with sinusitis, sinus "fullness", herpes, upper respiratory tract infection (5 episodes), fever	9
2	Herpes (labialis and genitalis), pneumonia, sepsis, ventricular assist device infection	5
3	Bronchitis (2 episodes), *Mycobacterium chelonae* infection, shingles	4
4	Urinary tract infection (2 episodes), pyelonephritis, bloody diarrhea	4
5	Pneumonia (lobar), cutaneous fungal infection, nosocomial vancomycin resistant enterococcus	3
6	Urinary tract infection, pyelonephritis, chronic cough	3
7	Pulmonary infiltrate (lobar), sinus congestion, diarrhea + flu-like symptoms, urinary tract infection	3
8	Sore throat, urinary tract infection (2 episodes)	3
9	Sore throat, unproductive cough	2
10	Pacemaker pack infection, recurrent sinus drainage	2
11	Sinus infection	1
12	Epstein-Barr virus reactivation	1
13	Fungal rash	1

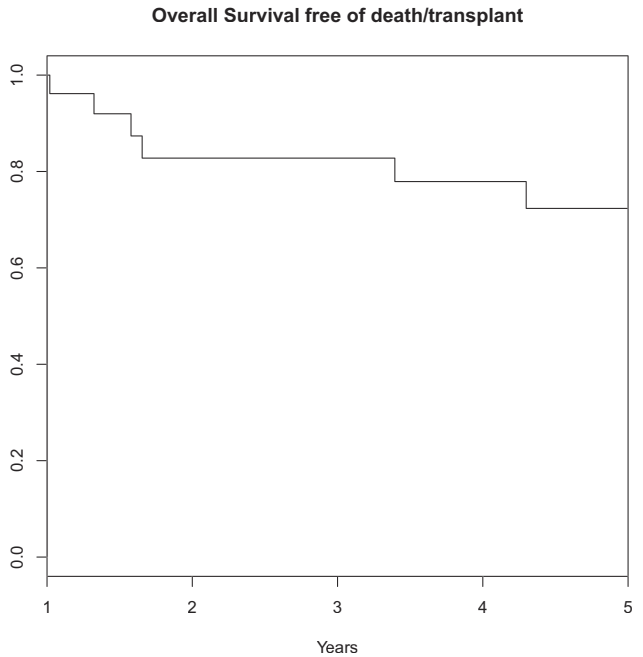

Figure 2. Survival without heart transplantation starting 1 year after initial GCM diagnosis.

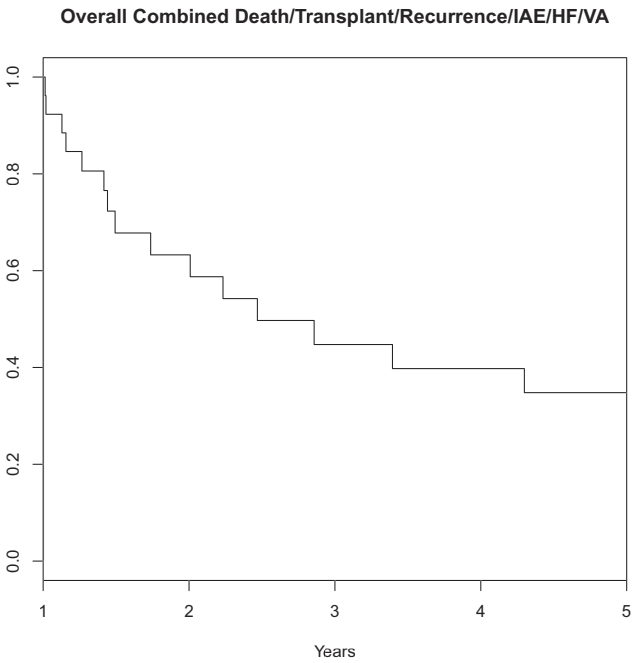

Figure 3. Survival free of death, transplantation, GCM recurrence, heart failure, and ventricular arrhythmias starting 1 year after initial GCM diagnosis.

available). These recurrences occurred 1.5 to 8 years after initial diagnosis.

Changes in myocardial infiltrate were noted in all patients for whom initial and follow-up biopsy samples were available. The 2 cases of recurrence available for review showed increased interstitial (replacement-type) fibrosis (there was no mention of such in the report of the third case, so it is not possible to determine whether such was present or not). Although 2 cases contained giant cells, the third exhibited only a lymphocytic-eosinophilic inflammatory infiltrate with associated myocyte injury. The remaining 10 cases, sampled after the diagnostic biopsy, uniformly lacked giant cells in the subsequent biopsies. The 3 most extensively sampled cases (with 11, 6, and 4 endomyocardial biopsies), showed a stepwise progression from fulminant GCM, to a myocarditis characterized by a lymphocytic-eosinophilic infiltrate, to a smoldering lymphocytic myocarditis, to interstitial (replacement-type) fibrosis over the course of 2 years, 5 months, and 2 years (respectively). Two cases showed unremarkable myocardium on repeat biopsy, and 1 showed only mild interstitial fibrosis. One case showed persistent lymphocytic-eosinophilic myocarditis. The remaining 4 cases all showed borderline lymphocytic myocarditis with associated mild to moderate interstitial (pericellular- and replacement-type) fibrosis.

Adverse events were dichotomized into noninfectious and infectious events. In this sick population, 84 total noninfectious adverse events were noted over 144 patient-years of follow-up after the first year after diagnosis (Table 1). New or worsening renal insufficiency was noted in 12 patients, with an event rate of 20% per year. Ventricular arrhythmias were noted in 6 patients, all of whom presented initially with some form of arrhythmia, for a total of 19 episodes during the

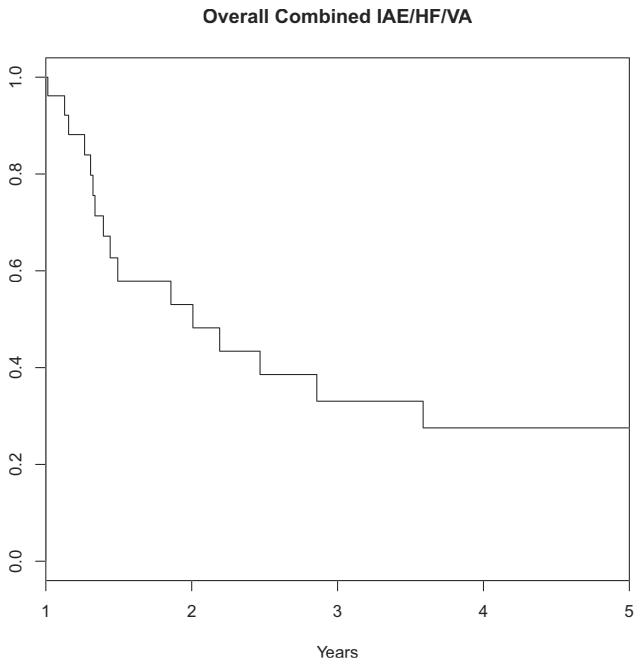

Figure 4. Survival free of infectious adverse events, heart failure, and ventricular arrhythmias starting 1 year after initial GCM diagnosis.

observed follow-up period and an event rate of 17% per year. No new ventricular arrhythmias were noted in patients who did not initially have arrhythmias at presentation. New or worsening heart failure, suggesting possible disease recurrence,[4] was noted in 13 patients, including 30 total distinct events with a 26% event rate per year. There were 23 episodes of elevated creatinine (renal failure) in 12 patients, resulting in an event rate of 20% per year.

Infectious adverse events were observed in 13 patients, totaling 41 separate events (Table 2). These included 2 episodes of pneumonia, 2 cases of herpes (including oral and genital forms), and 1 case each of atypical mycobacterial infection, Epstein-Barr virus, and herpes zoster reactivation. Examples of urinary tract infections, upper respiratory infections, and sinusitis were also noted.

Three patients died, 5 underwent heart transplantation, and 23 of the 26 patients were alive at follow-up. The 5-year survival rate free of transplantation was 72% (Figure 2). No patient underwent permanent VAD placement. Survival free of death, transplantation, GCM recurrence, heart failure, and ventricular arrhythmias was 35% at 5 years (95% confidence interval 20% to 62%; Figure 3). Survival free of infectious adverse events, heart failure, and ventricular arrhythmias was 28% at 5 years (95% confidence interval 14% to 56%; Figure 4). Of those patients with histopathologic recurrence, 2 had recently discontinued or decreased immunosuppression. Degree of immunosuppression during the first year after diagnosis did not predict subsequent risk for death, transplantation, first heart failure recurrence, first ventricular arrhythmia, or GCM recurrence during follow-up after year 1 ($p = 0.19$).

Discussion

This experience, with the longest and most detailed multi-institutional GCM data set, provides several novel observations that add meaningfully to the existing knowledge regarding the disease's long-term morbidity and mortality. Contemporary care that includes long-term immunosuppression appears capable of lengthening transplantation-free survival >19 years beyond initial diagnosis with reasonable safety. Cessation or sometimes reduction of immunosuppression is associated with GCM recurrence as far as 8 years after diagnosis. Eight patients (5 in the first year and 3 in subsequent years) who developed renal failure associated with cyclosporine were switched to a sirolimus-based regimen. However, our data do not provide more specific insight regarding the optimal duration or intensity of immunosuppression in this population. Our data and the recent report by Kandolin et al[6] found that ventricular arrhythmias occur frequently in GCM survivors. We extend those investigators' experience to report that ventricular arrhythmias after the first year occur primarily in patients with GCM who initially present with ventricular arrhythmias.

Despite optimal management of GCM, patients generally remain ill and require close monitoring for heart failure, renal insufficiency, and adverse events related to the underlying disease and immunosuppression. Renal failure likely reflects a combination of cardiac dysfunction and chronic calcineurin inhibitor use. The types of infections affecting chronically immunosuppressed GCM patients are typical of similarly immunosuppressed cohorts and with proper management are rarely life threatening.

Several groups advocate the use of endomyocardial biopsy, repeated if necessary, to confirm suspected GCM.[6–10] Our data support this practice and extend the indication for endomyocardial biopsy to include the diagnosis of recurrent GCM in the native heart. We report for the first time the stepwise, histopathologic improvement of GCM under immunosuppression, whereby giant cells disappear early on, followed by eosinophils, with smoldering lymphocytic myocarditis being the last inflammatory manifestation to disappear. Resolution with replacement-type interstitial fibrosis also appears to be common. In recurrence, giant cell number did not affect immunosuppressive regimen.

Our data are limited in several ways. This retrospective data set lacks standardized serum drug levels for cyclosporine and sirolimus. In the absence of these data, we cannot attribute specific episodes of renal failure or heart failure to the underlying disease, immunosuppressive treatment, or possible undertreatment. Similarly, it is possible that there was difference in outcome by ethnicity, but such data are not universally available in our series. Despite these limitations, this report adds to the largest contemporary series of patients with GCM receiving combined immunosuppression by Kandolin et al.[6] Our follow-up duration was longer (median 57.4 vs 14.5 months) and assessment of noncardiac morbidity greater. Observations on the histologic response to treatment and recurrence of GCM have not been reported with this level of detail.

Disclosures

The authors have no conflicts of interest or funding to disclose.

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