Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Circ Heart Fail 2013;6;15-22; originally published online November 13, 2012;
DOI: 10.1161/CIRCHEARTFAILURE.112.969261
Circulation: Heart Failure is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-3289. Online ISSN: 1941-3297

Diagnosis, Treatment, and Outcome of Giant-Cell Myocarditis in the Era of Combined Immunosuppression

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Background—Giant-cell myocarditis often escapes diagnosis until autopsy or transplantation and has defied proper treatment trials for its rarity and deadly behavior. Current therapy rests on multiple-drug immunosuppression but its prognostic influence remains poorly known. We set out to analyze (1) our experience in diagnosing giant-cell myocarditis and (2) the outcome of patients on combined immunosuppression.

Methods and Results—We reviewed the histories, diagnostic procedures, details of treatment, and outcome of 32 consecutive patients with histologically verified giant-cell myocarditis treated in our hospital since 1991. Twenty-six patients (81%) were diagnosed by endomyocardial or surgical biopsies and 6 at autopsy or post-transplantation. Twenty-eight (88%) patients underwent endomyocardial biopsy. The sensitivity of transvenous endomyocardial biopsy increased from 68% (19/28 patients) to 93% (26/28) after up to 2 repeat procedures. The 26 biopsy-diagnosed patients were treated with combined immunosuppression (2–4 drugs) including cyclosporine in 20 patients. The Kaplan-Meier estimates of transplant-free survival from symptom onset were 69% at 1 year, 58% at 2 years, and 52% at 5 years. Of the transplant-free survivors, 10/17 (59%) experienced sustained ventricular tachyarrhythmias during follow-up and 3 received intracardiac defibrillator shocks for ventricular tachycardia or fibrillation.

Conclusions—Repeat endomyocardial biopsies are frequently needed to diagnose giant-cell myocarditis. On contemporary immunosuppession, two thirds of patients reach a partial clinical remission characterized by freedom from severe heart failure and need of transplantation but continuing proneness to ventricular tachyarrhythmias. **(*Circ Heart Fail*. 2013;6:15-22.)**

Key Words: cardiac transplant ■ endomyocardial biopsy ■ myocarditis

Giant-cell myocarditis (GCM) is known as a rare, rapidly progressive, and frequently fatal myocardial disease in young and middle-aged adults. It is attributed to a T lymphocyte-mediated inflammation of the heart muscle and associates with systemic autoimmune diseases in ≈20% of cases.[1,2] The most common early manifestations are heart failure, ventricular arrhythmias, and atrioventricular block, but GCM may also disguise as an acute myocardial infarction and rarely presents as an unexpected sudden cardiac death.[1–3] The diagnosis of GCM rests fully on microscopy of the heart muscle and even in experienced centers >4 in 10 cases may escape detection until autopsy or cardiac transplantation.[3]

Aside from nonspecific measures to combat its symptomatic manifestations, the treatment of GCM relies on immunosuppression. Retrospective observations from the Multicenter GCM Registry[1,4] and a small prospective study with repeat biopsies[5] suggest that cyclosporine-based combined immunosuppression may be able to reduce myocardial inflammation[5] and improve clinical outcome.[1,4,5] Yet, these data are uncontrolled and suffer from lack of details about the treatments given[1,4] and the possibility of survivor bias.[1,4,5] The key problem is that the rarity and seriousness of GCM make controlled treatment trials, let alone use of a placebo arm, virtually impossible. The only such attempt, a cooperative endeavor by 17 centers, was terminated after 6 years because of difficulties in recruiting patients.[5] Therefore, carefully studied observational patient series continue to add to the knowledge about GCM. We report here our experience in 32 patients with GCM, of whom 26 received combined immunosuppression. We focus on the diagnosis of GCM and on the outcome of patients with contemporary treatment. Our key observations suggest that repeat and imaging-guided biopsies increase the detection rate of GCM and that combined immunosuppression supported by therapy for heart failure and arrhythmias may result in transplant-free survival in two thirds of patients.

Clinical Perspective on p 22

Methods

Patients

From the year 1991 through 2011, 32 patients with histologically verified GCM were seen at the Division of Cardiology, Helsinki University Central Hospital. The majority of diagnoses (29/32) were made after year 2000, that is, during the latter half of the study period. The medical records, laboratory test, imaging studies, and available biopsy material of all patients were retrospectively reviewed and

Received April 8, 2012; accepted October 22, 2012.

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Circ Heart Fail **is available at http://circheartfailure.ahajournals.org** **DOI: 10.1161/CIRCHEARTFAILURE.112.969261**

analyzed for the present study. Of the 32 cases, 26 were diagnosed by endomyocardial biopsies (EMBs [n=23]) or surgical biopsies (n=3), 4 at autopsy, and 2 from explanted hearts post-transplantation. The median follow-up time calculated from symptom onset was 15.0 months (range, 0.3–90.3 months). Nine patients with ventricular tachycardia (VT) have been reported previously[6] but we provide new clinical and follow-up data of them in the present report.

Diagnostic Practice

From 1991 through 2005, we were routinely using clinical examination, 12-lead ECG, laboratory tests, and echocardiography to explore the pathogenesis of an unknown myocardial disease. Selective coronary angiography and left-ventricular cineangiography were done whenever coronary artery disease was to be excluded. Angiography was not performed if coronary disease was considered unlikely, eg, in women aged <50 years free of risk factors for atherosclerosis. EMBs were taken if a chronic infiltrative or inflammatory myocardial disease or an aggressive myocarditis, like GCM, was considered possible. Biopsies were usually omitted, however, if chronic dilated cardiomyopathy was the likely diagnosis on clinical grounds. Right-ventricular septum was the target area for myocardial sampling. In 2005, we revised our diagnostic strategy and have since been actively using gadolinium-enhanced cardiac MRI and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) combined with resting myocardial perfusion imaging with ^{99m}Tc-tetrofosmin SPECT to identify and localize possible inflammatory myocardial processes. The details of these imaging methods in our hands were recently published.[7] Concomitant with the active use of gadolinium-enhanced cardiac MRI and ^{18}FDG-PET we changed our EMB policy from random right-ventricular septal sampling to targeted biopsies of myocardial areas showing signs of damage or inflammation at MRI or PET. Since then, left-ventricular biopsies were also acquired more often and we started to admit patients for repeat EMBs if the first samples showed nondiagnostic despite other findings suggestive of an inflammatory myocardial disease.[7]

Practice of Immunosuppression

In the early 1990s, patients with biopsy-verified GCM were treated with a combination of prednisone and azathioprine in addition to a general treatment for heart failure and arrhythmias. Since the first report of the Multicenter GCM Study Group,[1] our recommended treatment has been the triple combination of cyclosporine, prednisone, and azathioprine. Exceptionally, other immunosuppressive drugs like mycophenolate mofetil, methotrexate, or the T-cell antibody muromonab could be added or substituted for other agents. Our practice has been to initiate cyclosporine cautiously aiming at trough blood concentrations inside the lower therapeutic range for immunosuppression after cardiac transplantation (80–120 μg/L). Prednisone was started at 60 mg (or ≈0.75–1 mg/kg) per day decreasing the dose thereafter at 1- to 2-month intervals to 10 mg per day after 6 months. In very severe cases, steroids could be introduced with intravenous methylprednisolone, 500 to 1000 mg per day for 2 to 3 days. The duration of prednisone was not predefined, and continuation at a small dose (5–10 mg per day) was possible as long as was clinically considered necessary. Discontinuation of prednisone was considered if the patient had been stable for 6 to 12 months or if the side-effects were intolerable. The target dose of azathioprine was ≈1.5 to 2 mg/kg per day. The dose was adjusted according to blood count and liver enzyme surveillance. Once stabilized, the patients were seen 2 to 4 times a year in our outpatient cardiology service.

Review of Biopsy Material

We initially identified from the medical records 36 patients with GCM, the diagnoses having been made by pathologists in the referring hospitals (n=18) or at our institution (n=18). The diagnosis of GCM was based on the presence of a widespread inflammatory infiltrate including lymphocytes, histiocytes, and multinucleated giant cells in association with myocyte necrosis and eosinophils. We adhered to the early criteria of the Multicenter GCM Registry[1] and, to avoid any mistaking of sarcoidosis for GCM, unequivocal granuloma formation excluded the diagnosis of GCM. Two experienced cardiac pathologists (K.S., A.R.-S.) reanalyzed the tissue samples. By the consensus of the reviewing pathologists, 4 of the initial diagnoses of GCM were converted to cardiac sarcoidosis. In 2 cases, the slides were unavailable for reanalysis. One diagnosis was based on autopsy and the other on EMB. The available histology reports described findings typical for GCM by experienced pathologists and both cases were retained in the study.

Statistical Analyses

We used χ^2 or log-rank tests for comparison. Survival analyses were calculated, first, from the onset of symptoms and, second, from the date of diagnosis. The time point of symptom onset was considered the date of the first medical contact for symptoms compatible with GCM. The former analyses encompassed all patients, even the ones diagnosed at autopsy or after transplantation, whereas the latter ones only included the 26 patients who were identified by cardiac biopsies and underwent GCM-targeted treatment. Including in the analysis cases identified postmortem or post-transplantation assumes that there is no benign form of GCM and that the diagnosed cases are therefore representative of all those who have the disease. In this respect our methods are identical to the strategy used in the prior survival studies in GCM.[1,3] The primary end point for assessing outcome was heart transplantation or death. Transplant-free survival rates were compared using the log-rank test. In all tests, $P<0.05$ were considered statistically significant. All analyses were performed using SPSS-19 for Windows (SPSS Inc, IL).

Results

Demographics and Clinical Presentation

The mean age (±SD) was 52.5±12.7 years (range, 35–69) in patients diagnosed at autopsy or transplantation and 49.5±11.1 years (range, 29–70) in patients diagnosed by lifetime biopsy. Of the 32 patients, 22 (69%) were female and 10 (31%) were male. The main presenting clinical manifestations were congestive heart failure in 10 of the 32 patients (31%), distal atrioventricular block in 10 patients (31%), sustained VT in 7 cases (22%), and a syndrome mimicking acute myocardial infarction with chest pain and ST-segment changes in 4 cases (13%). In 1 case, the first manifestation was an out-of-hospital cardiac arrest and death because of ventricular fibrillation. Six patients (19%) had associated autoimmune disorders: reactive arthritis, iritis, and thyreoiditis (n=1), vitiligo with orbital myositis (n=1), coeliac disease (n=1), psoriasis (n=1), rheumatoid arthritis (n=1), and hypothyroidism (n=1). Among the 32 patients, there were 2 siblings; both had coeliac disease. They had 1 healthy brother and their first-degree relatives did not have evidence of cardiomyopathy or autoimmune diseases.

Findings at Cardiac Imaging

Thirty-one patients underwent echocardiography during the initial diagnostic work-up. The mean ejection fraction was 38±13% with values <50% in 23 patients (74%). The left ventricle was dilated (end-diastolic diameter >55 mm in women or >60 mm in men) in 9 patients (28%). Twenty-one patients (68%) had locally thinned or thickened interventricular septum and 3 (10%) had aneurysms of the left ventricle (Figure 1). Twenty-two patients underwent coronary angiography; none had evidence of coronary artery disease.

Contrast-enhanced cardiac MRI was done in 9 patients and showed areas of late contrast enhancement in each. Twelve

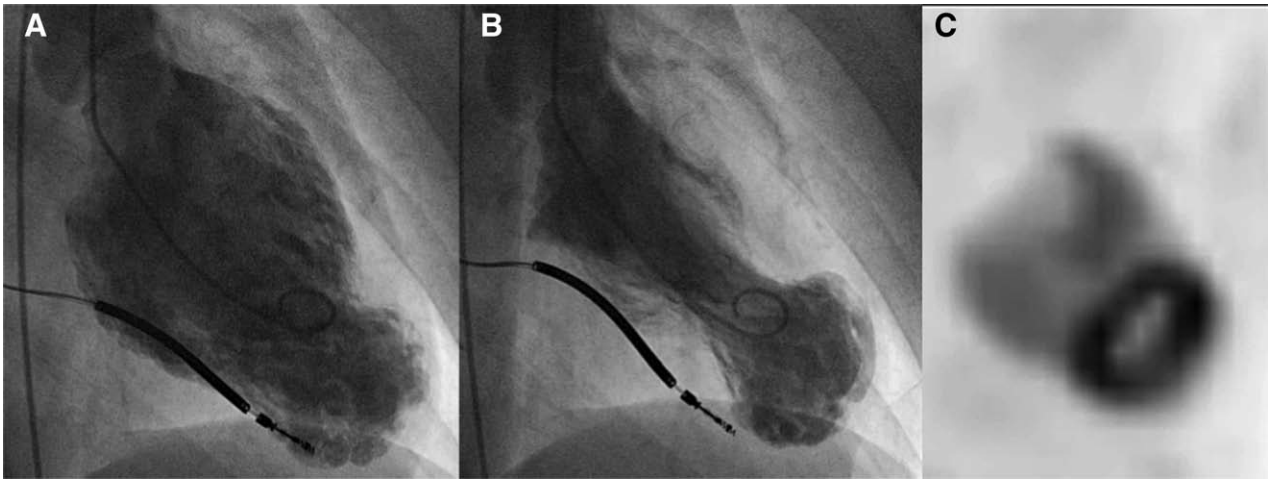

Figure 1. A 47-year-old female with multifocal ventricular premature complexes and left-ventricular aneurysm. In echocardiography, the left-ventricular ejection fraction was >50%. Left-ventricular cineangiography in diastole (**A**) and in systole (**B**) demonstrating an apical aneurysm. **C**, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) image demonstrates an increased FGD uptake suggesting active inflammation at the opening of the left-ventricular aneurysm. Endomyocardial biopsies from this site showed active giant-cell myocarditis.

patients underwent ^{18}FDG-PET combined with a myocardial perfusion study. Of them, 10 patients had focally enhanced ^{18}FDG uptake that was superimposable on a ^{99m}Tc-tetrofosmin perfusion defect in 9 patients and involved the septum in all. Two patients had a perfusion defect without a hot spot at PET.

Confirmation of Diagnosis

A total of 28 (88%) of the 32 patients underwent 1 or more EMB sessions or surgical biopsies (Figure 2). The reported number of samples taken per session varied from 2 to 10 (median, 5.3). One of the procedures was complicated by pericardial tamponade requiring surgical drainage. GCM was diagnosed at the first EMB in 19/28 cases (sensitivity, 68%). Of the 9 patients with nondiagnostic histology initially, 7 underwent a second EMB session, which gave the diagnosis of GCM in 5 patients. Finally, 2 patients had a third EMB that exposed GCM in both. Thus, repeated procedures improved the yield of EMB from 68% to 93% (26/28 patients). In 3 patients, the repeat EMBs were taken from the left ventricle. All surgical biopsies were from the left ventricle. Typically, the first nondiagnostic biopsies showed nonspecific abnormalities such as myocyte degeneration, edema, and nuclear size variation. The surgical biopsies revealing the presence of GCM in 3 patients were done in association with (1) resection of a left-ventricular aneurysm, (2) placement of a left-ventricular assist device, and (3) treatment of cardiac tamponade (see above). The interval from the onset of symptoms to the biopsy diagnosis of GCM varied from 0.3 to 16 months (median, 3 months).

Four of the 32 cases were diagnosed at autopsy (Figures 2 and 3) and 2 from explanted hearts after transplantation. Five of these 6 patients had undergone diagnostic procedures including echocardiography (5/6), coronary and left-ventricular cineangiography (2/6), and EMB (2/6) but none had been studied with MRI or PET. Their diagnoses had been dilated cardiomyopathy (n=3), idiopathic atrioventricular block

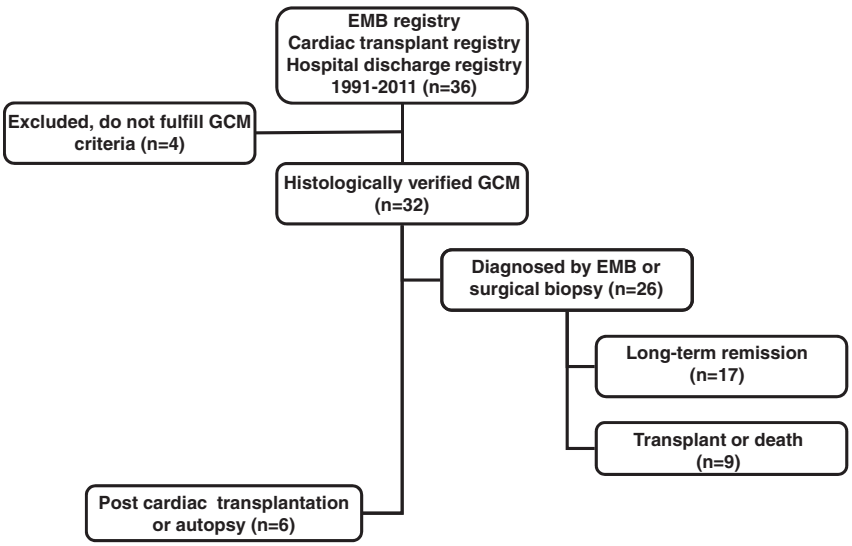

Figure 2. Summary of patient selection and classification. EMB indicates endomyocardial biopsy; and GCM, giant-cell myocarditis.

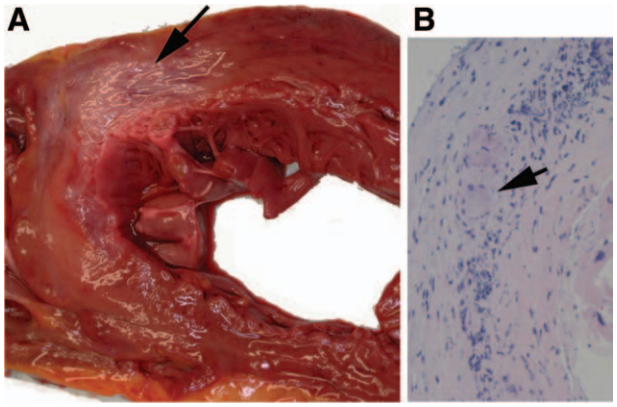

Figure 3. Autopsy samples from a 29-year-old female that presented with complete heart block and normal left-ventricular function in echocardiography. She died 5 years later because of ventricular fibrillation (VF). **A**, Left-ventricular (LV) septum shows macroscopic evidence of scarring. Arrow points to an area of extensive scarring. **B**, Large number of histological samples from the various parts of the myocardium demonstrated that inflammation attributable to giant-cell myocarditis (GCM) was confined to interventricular septum. Arrow points to a giant cell, a hallmark of giant-cell myocarditis. This case demonstrates that GCM can be localized to a specific region in the heart and can be dormant for years.

(n=1), and acute nonspecific myocarditis (n=1). The time from symptom onset to death or transplantation ranged from 1 to 66 months (median, 11 months).

Treatment

The 26 biopsy-diagnosed patients were all treated with combined immunosuppression that included steroids (n=26), azathioprine (n=24), cyclosporine (n=20), mycophenolate mofetil (n=3), muromonab (n=1), gammaglobulin (n=1), and methotrexate (n=1). Table 1 specifies the combinations used and Table 2 summarizes the mean doses of prednisone, azathioprine, and cyclosporine as well as the blood cyclosporine concentrations during treatment. Seven patients received high-dose intravenous methylprednisolone. Twenty-five of the 26 patients were on β-blockers and 19 received antiarrhythmic drugs (mainly amiodarone). Intracardiac defibrillators (ICD) were implanted in 18 patients, and 9 patients received a permanent pacemaker solely for a high-grade atrioventricular block.

The most significant side-effects of treatment included cyclosporine-related elevations of serum creatinine in 10 patients (100–156 μmol/L); elevated liver enzymes, lymphocytopenia or pancreatic irritation attributed to azathioprine in 6 patients; and muscular weakness, marked weight gain, insomnia, or cataract from prednisone in 7 patients.

Survival and Adverse Events

Figure 4 shows Kaplan-Maier curves for survival from the onset of symptoms for all 32 patients. Altogether 15 patients (47%) either died (n=5) or underwent transplantation (n=10), a median of 11.0 months (range, 0.3–66.0 months) from symptom onset. Among the 5 fatalities, GCM was diagnosed postmortem in 4 patients and the fifth patient died 2 weeks after the diagnostic EMB. All 5 deaths were arrhythmic. Of the 10 transplanted patients, 3 died of postoperative complications (large intracardiac thrombus, bleeding, multiple organ failure) within 38 days of surgery. The remaining 7 transplanted patients were alive at the end of our follow-up in December 2011. One patient had a recurrence of GCM in the graft 4.8 years post-transplantation. The Kaplan-Meier estimates of transplant-free survival from symptom onset (95% CI) were 69% (50%–83%) at 1 year, 58% at 2 years (39%–75%), and 52% at 5 years (34%–70%). Age, sex, or symptoms at presentation did not predict outcome.

Figure 5 shows the Kaplan-Meier curves for survival from onset of GCM-targeted therapy (ie, from diagnosis) in the 26 patients diagnosed by EMB or surgical biopsy. Their follow-up times ranged from 0.3 to 90.0 months (median, 14.5 months). One of the 26 patients died and 8 patients (31%) underwent transplantation while on immunosuppressive medication: 6 patients were transplanted for severe heart failure and 2 for life-threatening arrhythmias. All 8 listings for transplantation were made within 9 months of diagnosis, and the transplantations were accomplished within 1 year of diagnosis in 7 of the 8 cases. Three transplanted patients died early of postoperative complications (see above). Thus, at the end of follow-up 22 of 26 patients (85%) having received GCM-targeted treatment were alive. Seventeen (65%) were alive free of transplantation with a median of 35.0 months from diagnosis (range, 4.0–90.0 months). Table 3 compares the characteristics of patients with and without the primary outcome event (death or transplantation) during follow-up. The 1 patient who expired was diagnosed 2 weeks before death and thus received targeted therapy only for 2 weeks; therefore, data concerning her have been excluded from the treatment analysis in Table 3. Patients on cyclosporine had a trend toward a lower likelihood of cardiac transplant or death (4/20 versus 4/6, log rank P=0.086). Patients requiring a cardiac transplant had lower median left-ventricular ejection fraction during follow-up (26±7%) than patients surviving free of transplantation (45±11%, P=0.03).

Table 1. Immunosuppressive Treatment of the 26 Patients With Biopsy-Diagnosed GCM

Corticosteroid + Azathioprine + Cyclosporine 17 (65%)
Corticosteroid + Azathioprine 4 (15%)
Corticosteroid + Azathioprine + Muromonab + Gammaglobulin 1 (4%)
Corticosteroid + Azathioprine + Myocophenolate mofetil 1 (4%)
Corticosteroid + Cyclosporine+ Myocophenolate mofetil 2 (8%)
Corticosteroid + Cyclosporine + Azathioprine/Methotrexate* 1 (4%)

GCM indicates Giant-cell myocarditis.
*Azathioprine was replaced with methotrexate after 3 wk of treatment because of pancreatic irritation.

Table 2. Dosing of the Key Immunosuppressive Drugs From Start to 48 Months of Treatment

	Duration of Treatment, Months							
Drug	Start	3	6	12	18	24	36	48
Prednisone, mg	60 (40,80)	30 (30,60)	20 (10,60)	5 (10,40)	10 (0,10)	5 (0,10)	0 (0,40)	0 (0,30)
n/N	23/23*	20/20	20/20	19/19	14/15	8/12	5/11	2/5
Azathioprine, mg	100 (50,150)	100 (50,150)	100 (0,150)	100 (25,150)	100 (25,150)	100 (25,150)	100 (25,150)	100 (25,150)
n/N	21/23*	17/20	17/20	16/19	12/15	11/12	7/11	5/5
Cyclosporine dose, mg	175 (0,400)	150(125,300)	150(100,250)	150(75,250)	150(0,225)	150 (75,225)	150 (100,150)	125 (100,150)
Cyclosporine plasma†, μg/L	144 (144,216)	132 (80,221)	104 (73,189)	102 (53,183)	86 (68,111)	85 (69,153)	82 (74,124)	87 (81,108)
n/N	19/23*	16/20	15/20	14/19	12/15	7/12	5/11	2/5

The data are median and range. If prednisolone was used it was expressed as equipotent dose of prednisone.
n=number of patients on a drug, N=total number of patients on follow-up.
*Detailed treatment data on 3 patients were unavailable.
†Cyclosporine assay was changed from radioimmunoassay to chemiluminescent microparticle immunoassay (Architect) at the end of 2008. This results in measurement variation <5% in the plasma concentration range of cyclosporine seen in this study.

The treatment delay (time from symptom onset to diagnosis and treatment) did not correlate with poor prognosis (death/transplant) of GCM (P=0.71). The Kaplan-Meier estimate of transplant-free survival from diagnosis (95% CI) was 77% (56%–90%) at 1 year, 63% at 2 years (42%–81%), and 63% at 5 years (42%–81%).

During follow-up, 24 of the 26 patients receiving GCM-targeted treatment (92%) had 1 or more episodes of VT, 17 patients (65%) had sustained VTs, and 1 patient was resuscitated successfully from ventricular fibrillation. Of the 18 patients receiving an ICD, 4 experienced appropriate shocks for sustained VT (n=3) or ventricular fibrillation (n=1), and in another 4 patients VT was terminated with antitachycardia pacing. In the subgroup of transplant-free survivors, 10 of 17 (59%) had sustained VTs during follow-up and 3 received appropriate ICD shocks. During follow-up, 7 of the 26 patients receiving GCM-targeted therapy had The New York Heart Association class II to IV chronic heart failure with ejection fraction between 20% and 40%. Six of these patients required cardiac transplantation and 1 was stabilized with medical treatment only.

Discussion

The key finding of this work is that current immunosuppression appeared able to arrest the disease process in two thirds of patients with GCM resulting in clinical remission sufficient for survival free of transplantation. Yet, the remission was incomplete in the sense that the patients remained subject to ventricular tachyarrhythmias, and our follow-up was too short to tell about prognosis years ahead. Another key lesson is that 1 set of nondiagnostic EMB samples is far from being exclusive of GCM. If clinical presentation and other findings suggest a serious myocardial disease, repeat biopsies are indicated. A clinically worthwhile observation was also the high frequency of atrioventricular block as the first manifestation of the disease, equaling the frequency of heart failure at hospital presentation.

With 32 patients ours is by far the largest series of GCM reported from a single institution. For comparison, the 5 core centers of the Multicenter GCM Study Group were able to collect altogether 28 patients over periods covering 10 to 17 years, and nearly 40 centers worldwide were needed to compose a series of 73 patients.[3] Our hospital is a nationwide

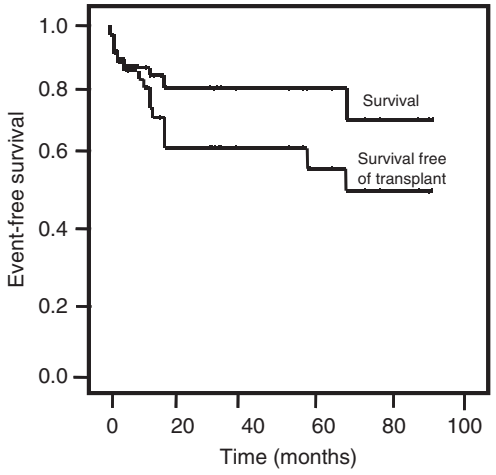

Figure 4. Kaplan-Meier curves for survival free of major adverse cardiac event (death, transplant) in all 32 patients with giant-cell myocarditis (GCM).

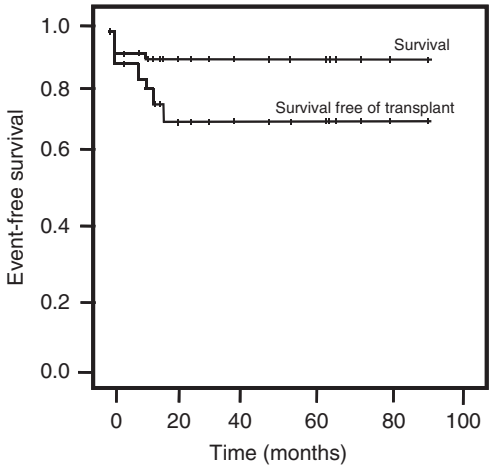

Figure 5. Kaplan-Meier curves for survival free of major adverse cardiac event (death, transplant) from the time of diagnosis in 26 giant-cell myocarditis (GCM) patients diagnosed by endomyocardial or surgical biopsies and treated with immunosuppressive medications.

Table 3. Characteristics of Individuals With and Without an Outcome Event During Treatment (Death, Transplantation) in the Subgroup of GCM Patients Receiving Combined Immunosuppression

Characteristic	Patients With an Event, n=9	Patients Without an Event, n=17
Age, y	50 (29–70)	50 (31–66)
Sex, m/f	2/7	5/12
Mode of presentation		
Heart failure	2	6
VT	2	4
Other	5	7
Symptoms to treatment, mo	1 (0.3–8.0)	5 (0.3–16.0)
LVEF at diagnosis	33 (20–60)	35 (20–61)
LVEF during follow-up	26 (15–36)	45 (26–69)
Lowest pro-BNP, ng/l*	2300 (1687–3063)	854 (128–3528)
Highest pro-BNP, ng/l†	8236 (4945–15519)	4272 (528–16804)
TnT at the time of diagnosis, ng/L	0.64 (0–9.73)	0.1 (0–2.3)
Cya treatment >1 mo	5/8‡	15/17
At 6 months§	107 (99–146)	104 (73–189)
Below median (120)	5/6	7/14
Prednisone, mg		
Starting dose	60 (40–80)	60 (40–80)
At 6 mo‖	10 (10–40)	20 (5–60)
Aza, mg (maintenance dose)¶	100 (50–150)	100 (50–150)
High-dose steroids	2	4

Aza indicates azathioprine; Cya, cyclosporine; GCM, Giant-cell myocarditis; LVEF, left-ventricular ejection fraction; pro-BNP, Brain natriuretic peptide; TnT, troponin T; and VT, ventricular tachycardia. One patient received only 2 weeks of immunosuppressive treatment before an event and was thus excluded from treatment analysis. Data presented as number of patients or median and range. Detailed treatment data on 3 patients were unavailable

*The lowest measured pro-BNP over the follow-up.

†The highest measured pro-BNP over the follow-up.

‡One patient received only 2 wk of immunosuppressive treatment.

§At 6 mo, 15/23 on cyclosporine, detailed data on treatment for 3 patients were unavailable. Data on 3/6 and 12/14 in patients with and without events.

‖At 6 mo, 20/20 on steroids. Data on 6/6 and 14/14 patients with and without events at 6 mo.

¶At 6 mo, 17/20 on azathioprine. Data on 5/6 and 12/14 patients with and without events.

referral center for cardiac transplantation and therefore the present work is likely to cover most of the GCM cases diagnosed in the 5.2 million Finnish population over the 20 years of our study. The finding of increasing number of cases diagnosed over time suggests that the adoption of gadolinium-enhanced cardiac MRI and FDG-PET into clinical routine with an activated biopsy policy improved our detection rate of GCM. It is therefore possible that GCM was underdiagnosed in the 1990s and over the first years after 2000. Kytö et al[8] reported recently that GCM caused 5.6% of the 649 fatalities attributed to myocarditis in death certificates between 1970 and 1988 in Finland. Resulting in an estimate of 35 fatal cases over 18 years in an era of missing premortem recognition of GCM, these data support the representativeness of the present series. The other strengths of our work are access to detailed patient data and the relative uniformity of the therapeutic strategy even though the diagnostic approach changed over time.

In the Multicenter GCM Registry,[1] the main presenting manifestation was heart failure in 75% of cases, VT in 14%, a syndrome mimicking myocardial infarction in 6%, and complete heart block in 5% of the cases. These were the main first manifestations in our series, too, but their frequency spectrum was different in that high-grade atrioventricular block was much more common (31%) and in fact equaled the frequency of heart failure (31%) at presentation. One explanation for the difference could be our particular activity in pursuing the diagnosis of an unexplained distal atrioventricular block in young and middle-aged individuals.[9] GCM as the cause of years of monosymptomatic heart block, until sudden death (see Figure 3 and its legend), has been reported from elsewhere too.[10] Contrary to earlier observations,[3] our present or previous[9] findings do not support heart block as a distinguishing characteristic between cardiac sarcoidosis and GCM.

In the complete series of 73 patients of the Multicenter GCM Registry, 56% of diagnoses were made by EMBs or surgical biopsies and the remaining 44% at autopsy or after cardiac transplantation.[3] In our work the proportion of biopsy diagnoses was as high as 26/32 cases (81%). The relatively high rate of lifetime diagnoses was probably attributable to a proactive biopsy policy in our institution.[7,9] We take patients with unexplained new complete atrioventricular block, ventricular arrhythmias, or left-ventricular dysfunction regularly to either MRI or FDG-PET, and if the imaging suggests inflammation or infiltration, right- or left-ventricular EMB is

done. Severe, rapidly progressive symptoms and persistent release of troponin T also favor early EMB. It is also worthy of recognition that as many as 27% of our biopsy-diagnosed cases (7/26) were detected by repeat procedures. We feel the seriousness of diseases like GCM or cardiac sarcoidosis justifies the risks of repeated biopsies if the imaging studies or other findings strongly suggest these conditions.[7] The diagnostic sensitivity of our EMBs was 68% after the first procedure increasing to 93% after repeat biopsies. In a subgroup of 20 patients from the Multicenter GCM Registry, EMB reached a sensitivity of 80% to 85%, but neither the number of procedures nor the number of samples per procedure was reported.[11] If GCM involves the myocardium only locally (Figure 3) the risks of sampling normal heart muscle increases. The use of contrast-enhanced MRI and PET helps identify the target areas for biopsies.[7]

The differential diagnosis between GCM and isolated cardiac sarcoidosis depends solely on the histopathology of the myocardium. We were careful to exclude patients with any granulomatous changes at microscopy to avoid mixing sarcoid heart disease into our study population. The Multicenter GCM Study Group also initially required absence of granulomas for the diagnosis of GCM[1] but later considered some granuloma formation compatible with GCM provided the extent of myocardial necrosis was out of proportion to the degree of granulomatous changes.[3,5]

The 1997 report by the Multicenter GCM Study Group established the gloomy prognosis of the disease: out of 63 patients, 89% either died or underwent transplantation with a median transplant-free survival of only 5.5 months from symptom onset.[1] On the contrary, combined immunosuppression, but not corticosteroids alone, appeared to prolong survival compared with no immunosuppression.[1] In the present study, all 26 patients with biopsy-diagnosed GCM received double- or triple-drug immunosuppression with prednisone, azathioprine, and cyclosporine as the main components (Table 1). Small as it is, ours is the largest series hitherto pertinent to combined immunosuppression. With 1 death and 8 transplantations over follow-ups from 0.3 to 90.3 months the estimated transplant-free survival was 77% (56%–90%) at 1 year and 63% (42%–81%) at 2 years of diagnosis. Importantly, all patients were listed for a cardiac transplant within 9 months. Of the 8 patients, 7 (88%) were transplanted within 1 year of diagnosis, the median time from diagnosis being 9 months (range 0.3–15 months). This agrees well with findings in the Multicenter GCM Registry where transplantations were done a median of 6 months after onset of symptoms.[1] The potential of combined immunosuppression to alleviate myocardial inflammation in GCM was shown by the prospective Multicenter GCM Treatment Trial[5] where 11 patients received corticosteroids and cyclosporine, and 9 of them also muromonab, in a standard protocol. Though falling short as a controlled trial, the study showed that the treatment reduced myocardial inflammation and necrosis from baseline to 4-week on-treatment EMBs.[5] The actual 1-year transplant-free survival was 73% (8/11 patients) but the patients were old for GCM (mean age 60 years) and represented the milder spectrum of the disease.[5]

There are no good data to guide immunosuppression for long-term maintenance of remission in GCM. Yet, continued treatment appears important because cessation of immunosuppression may lead to a fatal disease relapse.[4] Our practice has been to maintain immunosuppression with cyclosporine and azathioprine with, or preferably without, a small dose of prednisone. Our long-term treatment is in many ways reminiscent of post-transplantation immunosuppression without routine surveillance biopsies.

Serious ventricular tachyarrhythmias were common both as the presenting manifestation (22%) and during follow-up (65%). Further, all 5 fatalities were considered arrhythmic and 2 of the 10 transplantations were done for failure to control recurrent VTs. The high frequency and clinical importance of ventricular tachyarrhythmias was seen also in the Multicenter GCM Registry where sustained, refractory VTs were seen in almost one half of patients during the course of their illness.[1] Still, only 12% of the registry patients had received an ICD, although the rate was not specified for the biopsy-diagnosed subgroup.[3] In our series, 56% (18/32) of the total group and 69% (18/26) of the biopsy-diagnosed patients had an ICD implanted. It may be that arrhythmias respond poorly to immunosuppression in GCM because, as in cardiac sarcoidosis,[12] they are related to myocardial scars rather than to active inflammation.

We have described here the largest series hitherto of patients with GCM on combined immunosuppression. Two thirds of our patients achieved a partial clinical remission characterized by freedom from severe heart failure but continuing susceptibility to ventricular tachyarrhythmias. Although the outlook of GCM on combined immunosuppression thus looks less grim than usually thought the present data are at best suggestive and there remain many deficiencies in our knowledge about GCM. Future challenges include defining the optimal immunosuppressive regimens for early and maintenance treatments, identifying the most informative markers for follow-up of disease activity, and finding the best methods to control and prevent life-threatening tachyarrhythmias.

Acknowledgments

We want to acknowledge the colleagues and staff of the Department of Cardiology at Helsinki University Central Hospital.

Sources of Funding

This study was supported by the Finnish Foundation for Cardiovascular Research and Finnish government grant for medical research (EVO).

Disclosures

None.

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CLINICAL PERSPECTIVE

Giant-cell myocarditis is often rapidly progressive myocardial disease of unknown pathogenesis. The diagnosis is based on endomyocardial biopsy. To select appropriate treatment strategy, differential diagnosis from viral myocarditis and cardiac sarcoidosis is essential. We found that the sensitivity of the first endomyocardial biopsy was 68% and sensitivity was increased to 93% with up to 3 biopsies. Thus repeat endomyocardial biopsies are frequently needed to diagnose giant-cell myocarditis. Earlier reports have shown that if left untreated, giant-cell myocarditis is often fatal. On contemporary immunosuppression, two thirds of patients reach a partial clinical remission characterized by freedom from severe heart failure and need of transplantation.