Comparison of Outcomes in Patients With Probable Versus Definite Cardiac Sarcoidosis

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Patients with probable cardiac sarcoidosis (CS) who satisfy only clinical cardiac findings for CS are not uncommon. The aim of this study was to compare outcomes between patients with probable CS and those with definite CS treated with steroids. The study population consisted of 101 consecutive patients who satisfied clinical cardiac findings for CS. Patients with definite CS were defined as having histologic or clinical confirmation of CS according to the guidelines and were treated with steroids. Patients with probable CS were defined as having only clinical cardiac findings but not definite CS because of no histologic confirmation or extracardiac sarcoidosis and were not treated with steroids. The end point was major adverse cardiac events. Forty-seven patients had definite CS, and the other 54 had probable CS. Except for serum angiotensin-converting enzyme levels and left ventricular dysfunction, clinical characteristics were similar between the 2 groups. Over a median follow-up period of 15 months, major adverse cardiac events occurred more frequently in patients with probable CS than in those with definite CS (74% vs 53%, p = 0.029). The event-free survival rate was worse in patients with probable CS than in those with definite CS (log-rank test, p = 0.006). Cox proportional-hazards analysis showed that probable CS was an independent predictor of major adverse cardiac events. In conclusion, outcomes were worse in patients with probable CS than in those with definite CS treated with steroids. The initiation of steroid treatment may be considered for patients who satisfy only clinical cardiac findings for CS. **(Am J Cardiol 2015;115:1293−1297)**

Sarcoidosis is a systemic granulomatous disease.[1] Cardiac involvement is associated with adverse outcomes.[2−6] Early diagnosis of cardiac sarcoidosis (CS) is important to initiate steroid treatment before pathologic lesions are irreversible. However, it is difficult to confirm the diagnosis, even in patients who have signs compatible with CS. Endomyocardial biopsy is required for histologic confirmation, but sensitivity is low.[6−8] Clinical confirmation on the basis of the Japanese Ministry of Health and Welfare guidelines revised by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders,[9,10] which is accepted as standard,[11,12] requires the presence of extracardiac sarcoidosis. Therefore, CS cannot be diagnosed in patients who satisfy only the CS diagnostic guidelines' clinical cardiac findings[9,10] without histologic confirmation or extracardiac sarcoidosis. Steroid treatment is the main strategy for CS.[6,13,14] However, patients with probable CS who satisfy only the CS diagnostic guidelines' clinical cardiac findings[9,10] are not treated with steroids, because their prognosis is unknown. We aimed to compare outcomes in patients with probable CS with those in patients with definite CS treated with steroids.

Methods

We enrolled 109 consecutive patients who satisfied the CS diagnostic guidelines' clinical cardiac findings from December 1994 to April 2014. The guidelines for diagnosis of CS[9,10] are listed in Table 1. In brief, CS is diagnosed on the basis of histologic or clinical confirmation. Histologic diagnosis is confirmed when endomyocardial biopsy demonstrates noncaseating epithelioid cell granulomas. Clinical diagnosis is confirmed in the absence of endomyocardial biopsy when extracardiac sarcoidosis is diagnosed and the clinical cardiac findings (>2 of 4 major findings or 1 of 4 major findings and >2 of 5 minor findings) are satisfied. Major findings consist of advanced atrioventricular block, basal thinning of the interventricular septum, positive myocardial uptake of gallium-67 citrate (^{67}Ga) scintigraphy or fluorine-18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET), and a left ventricular ejection fraction <50%. Minor findings consist of abnormal results on electrocardiography, abnormal results on echocardiography, perfusion defect on myocardial scintigraphy, delayed myocardial enhancement on magnetic resonance imaging, and fibrosis or monocyte infiltration on endomyocardial biopsy. All patients gave written informed consent. This study was performed according to the principles of the Declaration of Helsinki and was approved by our institutional ethics committee.

This was a retrospective study. Patients with definite CS were defined as having histologic or clinical confirmation according to the CS diagnostic guidelines.[9,10] Patients with probable CS were defined as having only the CS diagnostic

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Table 1
Japanese Society of Sarcoidosis and Other Granulomatous Disorders guidelines for diagnosis of cardiac sarcoidosis

1. Histological confirmation

Cardiac sarcoidosis is confirmed when endomyocardial biopsy specimens demonstrate non-caseating epithelioid cell granulomas.

2. Clinical confirmation

Cardiac sarcoidosis is confirmed in the absence of endomyocardial biopsy when extracardiac sarcoidosis is diagnosed and the following clinical cardiac findings are satisfied.

Clinical cardiac findings

1) More than two of four major findings are satisfied.
2) One of four major findings and more than two of five minor findings are satisfied.

Major findings

a. Advanced atrioventricular block
b. Basal thinning of the interventricular septum
c. Positive myocardial uptake of ^{67}Ga (^{18}F-FDG)
d. Left ventricular ejection fraction <50%

Minor findings

a. Abnormal electrocardiogram: ventricular tachycardia, multifocal or frequent premature ventricular contractions, complete right bundle branch block, axis deviation, or abnormal Q wave
b. Abnormal echocardiography: regional abnormal wall motion or morphological abnormality (ventricular aneurysm, wall thickening)
c. Nuclear medicine: perfusion defect on thallium-201 or technetium-99m myocardial scintigraphy
d. Gadolinium enhanced cardiac magnetic resonance imaging: delayed myocardial enhancement
e. Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade

FDG = fluoro-2-deoxyglucose; ^{67}Ga = gallium-67 citrate.

guidelines' clinical cardiac findings (>2 of 4 major findings or 1 of 4 major findings and >2 of 5 minor findings),[9,10] but they were not established definite CS because of no histologic confirmation or extracardiac sarcoidosis. Other myocardial diseases, including giant cell myocarditis, arrhythmogenic right ventricular cardiomyopathy, connective tissue disease, and ischemic heart disease, were ruled out by endomyocardial biopsy and clinical examinations. To assess the effect of steroid treatment on outcomes, we excluded 6 patients with definite CS who were not treated with steroids and 2 with probable CS who were treated with steroids. The remaining 47 patients with definite CS and 54 with probable CS were enrolled. In patients with definite CS, steroid treatment with prednisone was initiated at doses of 30 or 40 mg/day. The prednisone doses were tapered over a period of 6 to 12 months to maintenance doses of 5 to 10 mg/day.

The end point was defined as major adverse cardiac events (MACEs), including cardiac death, ventricular fibrillation, sustained ventricular tachycardia, or hospitalization for heart failure. Sustained ventricular tachycardia was defined as spontaneous ventricular tachycardia at a rate of ≥120 beats/min that lasted ≥30 seconds. Patients were followed from the date of diagnosis of definite CS or probable CS until the date of first documentation of MACEs or the end of follow-up, whichever occurred first. The first documentation of MACEs was assessed after the cardiac events at the time of diagnosis had been recovered. Follow-up information was obtained by medical records, contact with the patient's physicians, or telephone interview with the patient or, if deceased, with family members.

Clinical examinations were performed at the time of diagnosis. Echocardiography was evaluated in all patients. The left ventricular ejection fraction was calculated by the disc summation technique. Endomyocardial biopsy was performed in all patients. A minimum of 3 specimens were obtained from the right ventricular septum. Histologic confirmation required the presence of noncaseating epithelioid cell granulomas. All patients underwent ^{67}Ga scintigraphy and/or FDG PET. On FDG PET, patients were instructed to fast for ≥12 hours, blood glucose levels were determined to ensure a level of <150 mg/dl, and unfractionated heparin was preadministrated. Increased uptake of ^{67}Ga or FDG in the myocardium that was higher than background activity was regarded as positive myocardial uptake. After steroid treatment, ^{67}Ga scintigraphy or FDG PET was repeated to evaluate the resolution of active inflammation. Plasma B-type natriuretic peptide levels (normal range ≤18.4 pg/ml) and serum angiotensin-converting enzyme levels (normal range ≤21.4 IU/L) were measured.

Data are presented as mean ± SD for continuous variables and as numbers and percentages for categorical variables. Differences were analyzed using Student's *t* test and the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Event-free survival rate was estimated using Kaplan-Meier analysis, and the difference was analyzed using the log-rank test. Predictors of MACEs were analyzed using Cox proportional-hazards analysis. Variables for univariate analysis included age, gender, New York Heart Association functional class, history of sustained ventricular tachycardia or ventricular fibrillation, the left ventricular ejection fraction, β blockers, and probable CS. Variables with p values <0.10 in the univariate analysis were entered in a multivariate analysis. Hazard ratios are presented with 95% confidence intervals. Statistical analysis was performed with JMP version 8.0 (SAS Institute Inc., Cary, North Carolina), and p values <0.05 were considered to indicate statistical significance.

Results

Among the 47 patients with definite CS, 18 had histologic confirmation and 29 had clinical confirmation. All patients with definite CS were initiated on prednisone at doses of 30 or 40 mg/day. Thirty-eight patients had positive myocardial uptake on ^{67}Ga scintigraphy or FDG PET at baseline, and all of them showed the disappearance of myocardial uptake on repeat ^{67}Ga scintigraphy or FDG PET after steroid treatment. Among the 54 patients with probable CS, 44 satisfied >2 of 4 major findings, and 10 satisfied 1 of 4 major findings and >2 of 5 minor findings. Clinical characteristics were compared between patients with definite CS and those with probable CS (Table 2). Serum angiotensin-converting enzyme levels were lower in patients with probable CS than in those with definite CS. Patients with probable CS more often received β blockers. There were no significant differences in age, New York Heart Association functional class, history of sustained ventricular tachycardia or ventricular fibrillation, and implantation of cardiac resynchronization therapy with defibrillator between