Clinical Outcomes of Radiologic Relapse in Patients With Cardiac Sarcoidosis Under Immunosuppressive Therapies

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Although nuclear imaging can detect cardiac involvement of cardiac sarcoidosis (CS), including subclinical states, little is known about the prevalence and outcomes of radiologic relapse under prednisolone (PSL) therapy. This study aimed to investigate the clinical characteristics and outcomes in patients with radiologic relapse. A total of 80 consecutive patients with CS whose disease activity on nuclear imaging decreased at least once after initiation of immunosuppressive therapy were identified through a retrospective chart review. Radiologic relapse of CS was diagnosed using ^{18}F-fluoro-2-deoxyglucose positron emission tomography or gallium-67 scintigraphy. Composite adverse events were defined as at least 1 of the following: all-cause death, hospitalization for heart failure, or lethal arrhythmia. During the follow-up period (median 2.9 years), radiologic relapse was observed in 31 patients (38.8% of overall patients) at 30 months (median) after immunosuppressive therapy initiation. After radiologic relapse was detected, all patients were treated with intensified immunosuppressive therapies (increasing PSL, n = 26 [83.9%], adding other immunosuppressive therapies to PSL, n = 5 [16.1%]). There were no differences in occurrences of composite adverse events in patients with and patients without radiologic relapse. Radiologic relapse under immunosuppressive therapy was observed in many patients with CS, but it was not associated with clinical outcomes under intensified immunosuppressive therapy. **(Am J Cardiol 2023;188:24−29)**

Patients with cardiac sarcoidosis (CS) often present with fatal ventricular arrhythmias[1,2] and severe heart failure (HF).[3−5] Immunosuppressive therapy, including corticosteroid therapy (CTx), has been accepted as 1 of the standard treatments.[6−9] There is no established protocol for CTx in patients with CS, but as the guideline mentioned,[8] prednisolone (PSL) is usually started at dosages of 30 to 40 mg/day, gradually tapered. Because CS is essentially an inflammatory disease, a risk for relapse remains after immunosuppressants are discontinued. Although nuclear imaging (^{18}F-fluorodeoxyglucose [^{18}F-FDG] and gallium [Ga] scintigraphy) has an essential role in diagnosing CS as the guideline mentioned[8] and as follow-up evaluation in inflammatory activity, the clinical significance in relapse of nuclear imaging has not been determined. To date, there is insufficient evidence on whether relapse evaluated by nuclear imaging, termed radiologic relapse, is associated with poor prognosis. This study aimed to investigate the prevalence, clinical background, and outcomes in patients with radiologic relapse diagnosed by either ^{18}F-FDG positron emission tomography (PET) scans or Ga scintigraphy.

Methods

This study adheres to the principles of the Declaration of Helsinki and was approved by our institutional Ethics Committee (R19079). The study was designed to be carried out without obtaining individual informed consent according to the "opt-out" principle. Instead, we published a summary of the study protocol with the contact information for our office on the institution's website, which provided patients with the ability to refuse enrollment to the study.

In our department, we identified 102 consecutive patients diagnosed with CS (between 2012 and 2019) who met the diagnostic criteria published in the 2016 revised version of the Japanese Circulation Society guidelines for CS.[8] This study focused on the clinical significance of radiologic relapse under CTx. Therefore, we excluded the 22 patients who were not treated with CTx after diagnosis, as shown in Figure 1. The reasons for withholding CTx were patient refusal (n = 4); CTx not recommended by an attending physician because of advanced age (n = 7); severe left

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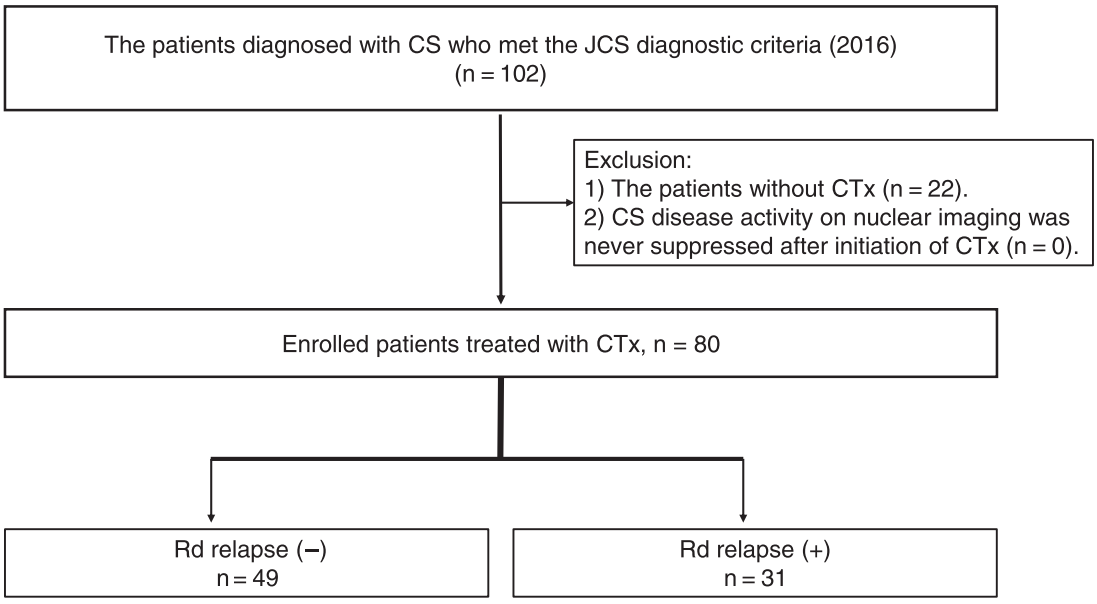

Figure 1. Flowchart of the study. JCS = Japanese Circulation Society; Rd = radiologic.

ventricular (LV) dysfunction (n = 1); and reason not known (n = 10). In addition, this study was designed to exclude the patients whose disease activity in nuclear imaging was never suppressed after initiation of immunosuppressive therapy, but there were no applicable patients. Finally, the remaining 80 patients were enrolled in this study.

Nuclear imaging with either ^{18}F-FDG PET or Ga scintigraphy was performed routinely before CTx initiation and repeated on follow-up. We performed the follow-up nuclear imaging tests at clinically stable phases. All images were assessed by at least 2 experienced nuclear radiologists, and we retrospectively collected data from these reports.

^{18}F-FDG PET images were acquired after >12 hours of fasting to suppress physiologic ^{18}F-FDG uptake in the heart. After evaluating serum glucose levels, patients received an intravenous administration of 2.0 to 2.5 MBq of FDG per kilogram of body weight.[10] All ^{18}F-FDG PET/computed tomography (CT) images were acquired using a 40-slice PET/CT system (Biograph mCT, Siemens Medical Solutions USA Inc., Devault, Pennsylvania) with 3-dimensional acquisition at 60 minutes after ^{18}F-FDG administration. Transmission scanning for low-dose CT as part of PET/CT was performed for attenuation correction.[10] Low-dose noncontrast CT for attenuation correction was performed using spiral mode, 4.0-mm slice thickness, 1.5 pitch, 0.5-second rotation time, 16 × 1.2-mm collimation, 120-kVp tube voltage, and 30 mA tube current. We did not perform heparin injection before ^{18}F-FDG PET/CT as a routine practice. Positive nuclear imaging in ^{18}F-FDG PET was defined as focal on diffuse patterns of ^{18}F-FDG PET, as previously described.[11,12]

Ga scintigraphy was performed 48 hours after intravenous injection of 111 MBq ^{67}Ga-citrate. Anterior and posterior planar images of the whole body and single-photon emission CT of the chest were obtained using a dual-detector single-photon emission CT/6-slice CT scanner (Symbia T6, Siemens Medical Solutions USA Inc.). Positive nuclear imaging in ^{67}Ga scintigraphy was defined as the abnormal uptake of ^{67}Ga in the myocardium.

We retrospectively collected from medical records the results of routine echocardiography performed before the initiation of CTx. LV dimensions were measured according to the American Society of Echocardiography guidelines.[13] LV ejection fraction was measured using either the modified Simpson method or the semiquantitative 2-dimensional visual estimate method.[14]

In this study, radiologic relapse is defined as an increase of the ^{18}F-FDG PET uptake or a positive Ga scintigraphy after a documented resolution or decrease from pretreatment baseline.

Composite adverse events were defined as the presence of at least 1 of the following: all-cause death, hospitalization for HF, or lethal arrhythmia. Lethal arrhythmia was defined as symptomatic ventricular tachyarrhythmias, ventricular fibrillation, and new-onset high-grade atrioventricular block that resulted in death. Follow-up data were collected by the investigators through medical chart review.

Values are expressed as median and interquartile range (IQR). Groups were compared using Wilcoxon test for continuous values, and chi-square test for categorical data, as appropriate. Univariate survival analyses were performed using the Cox proportional hazards model. Long-term event-free survival was estimated using Kaplan−Meier curves with an analysis of a log-rank test. All tests were 2-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed with JMP 12 software (SAS Institute, Inc., Cary, North Carolina).

Results

Clinical characteristics of the 80 patients are summarized in Table 1. There were no significant differences in

demographic data between the enrolled patients and the excluded patients except age (72-year-old vs 60-year-old, the excluded patients vs enrolled patients, respectively, p <0.05). The median age at diagnosis was 60 years (IQR 55 to 67), and 64% were female. In 94% of the enrolled patients, the initial oral dose of PSL was 30 mg (median initial PSL dose: 30 mg). After the initiation of CTx, 1 patient refused to continue with CTx at <1 year. On follow-up (median: 2.9 years from diagnosis, IQR 1.1 to 5.6 years), the remaining patients underwent nuclear imaging tests (^{18}F-FDG PET: n = 69, Ga scintigraphy: n = 10). A total of 31 patients (38.8%) had radiologic relapse. In those with radiologic relapse, 27 patients underwent ^{18}F-FDG PET, and 4 patients underwent Ga scintigraphy (39% and 40% of the patients who underwent each nuclear test, respectively). In the patients with radiologic relapses, no simultaneous clinical events were observed around the time of ^{18}F-FDG PET or Ga scintigraphy. The ^{18}F-FDG PET images in a clinical course of a representative case are shown in Figure 2. The median onset of recurrence after the initiation of CTx was 30 months (IQR 15 to 58 months), and the median dose of CTx during the relapse was 10 mg (IQR 5 to 15 mg). In those without radiologic relapse, the median dose of CTx was reduced to 10 mg (IQR 7.5 to 15 mg) in 17 months (median; IQR 8 to 33 months). No significant differences in patient characteristics at diagnosis were observed in patients with and those without radiologic relapse. No significant differences in LVEF were observed in patients with and those without radiologic relapse (median: 41.0% vs 38.0%, respectively). After the detection of radiologic relapse, all patients received intensified immunosuppressive therapies. In 26 patients, the PSL dose was increased. In the remaining 5 patients, methotrexate was added to the regimen. The frequency of clinical events on follow-up is summarized in Table 2. At approximately 2 years from CS diagnosis, the overall survival rate was 93%. Composite adverse events occurred in 31 patients (all-cause death, n = 8; HF hospitalization, n = 30; lethal

Table 1
Baseline patient characteristics

Variables	Follow-up RI			
	Overall	Rd relapse (−)	Rd relapse (+)	p Value
No of the cases	80	49	31	
Age at diagnosis (y.o.)	60 (55, 67)	63 (57, 69)	59 (49, 65)	0.069
Gender: female, n, (%)	51 (64)	34 (69)	15 (31)	0.235
Clinical history				
Hypertension, N (%)	24 (30)	18 (37)	6 (19)	0.134
Diabetes mellites, N (%)	16 (20)	6 (19)	10 (20)	1.000
Dyslipidemia, N (%)	33 (42)	21 (43)	12 (39)	0.817
Organ involvement				
Lung, N (%)	16 (20)	7 (14)	9 (29)	0.152
Skin, N (%)	7 (9)	4 (8)	3 (10)	0.815
Eye, N (%)	11 (14)	8 (16)	3 (10)	0.515
Systemic sarcoidosis	28 (35)	16 (33)	12 (39)	0.635
Echocardiography at the time of diagnosis				
LVEDD (mm)	55.0 (50.0, 61.0)	54.5 (49.3, 61.8)	56.0 (50.5, 60.0)	0.718
LVEDS (mm)	43.0 (36.5, 51.5)	42.5 (37.3, 53.8)	43.0 (36.0, 50.5)	0.844
LVEF (%)	38.5 (29.8, 46.3)	38.0 (31.0, 49.0)	41.0 (29.0, 46.0)	0.942
IVS (mm)	8.0 (6.8, 10.0)	8.0 (6.0, 10.0)	8.0 (7.3, 9.8)	0.512
LAVi (ml/m^2)	43.0 (36.0, 51.0)	45.0 (36.0, 56.5)	43.0 (38.5, 46.0)	0.496
Other imaging modalities at the time of diagnosis				
Ga scintigram positive, positive / N (%)	33/58 (57)	20/34 (59)	13/24 (54)	0.864
FDG-PET positive, positive / N (%)	68/68 (100)	39/39 (100)	29/29 (100)	0.344
LGE-CMR positive, positive / N (%)	58/59 (98)	38/39 (97)	20/20 (100)	0.308
Laboratory data				
Hemoglobin (g/dl)	13.3 (12.2, 14.6)	13.3 (12.3, 14.4)	13.5 (11.8, 14.9)	0.658
eGFR (ml/min/1.73m^2)	56.0 (45.0, 70.0)	56.1 (46.3, 71.1)	52.8 (44.8, 65.0)	0.525
ACE (IU/l)	16.4 (7.4, 21.6)	14.7 (7.3, 20.7)	16.9 (10.6, 22.8)	0.591
sIL2R (U/ml)	420.0 (282.8, 597.3)	420.0 (269.5, 727.5)	433.0 (313.5, 483.5)	0.854
Lysozyme (μg/ml)	6.6 (5.7, 8.9)	7.1 (5.7, 10.5)	6.5 (5.5, 7.3)	0.280
BNP (pg/ml)	142.0 (53.0, 473.0)	132.0 (76.5, 510.0)	176.5 (36.3, 379.8)	0.633
CRP (mg/dl)	0.06 (0.03, 0.20)	0.06 (0.03, 0.15)	0.12 (0.04, 0.22)	0.324
CRT, N (%)	3/80 (4)	2/49 (4)	1/31 (3)	0.810
Pacemaker and ICD (CRT included), N (%)	24/80 (30)	17/49 (35)	7/31 (23)	0.195

Values are the median (interquartile range: IQR) and patients number, N (%).

ACE = angiotensin converting enzyme; BNP = B-type natriuretic peptide; CMR = cardiac magnetic resonance; CRP = C-reactive protein; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; FDG-PET-PET = fluro-2-deoxyglucose positron emission tomography; Ga = gallium; ICD = implantable cardioverter defibrillator; IVS = interventricular septum; LAVi = left atrial volume index; LGE = late gadolinium enhancement; LVEDD = Left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; Rd = radiologic; sIL-2 = soluble interleukin-2 receptor.

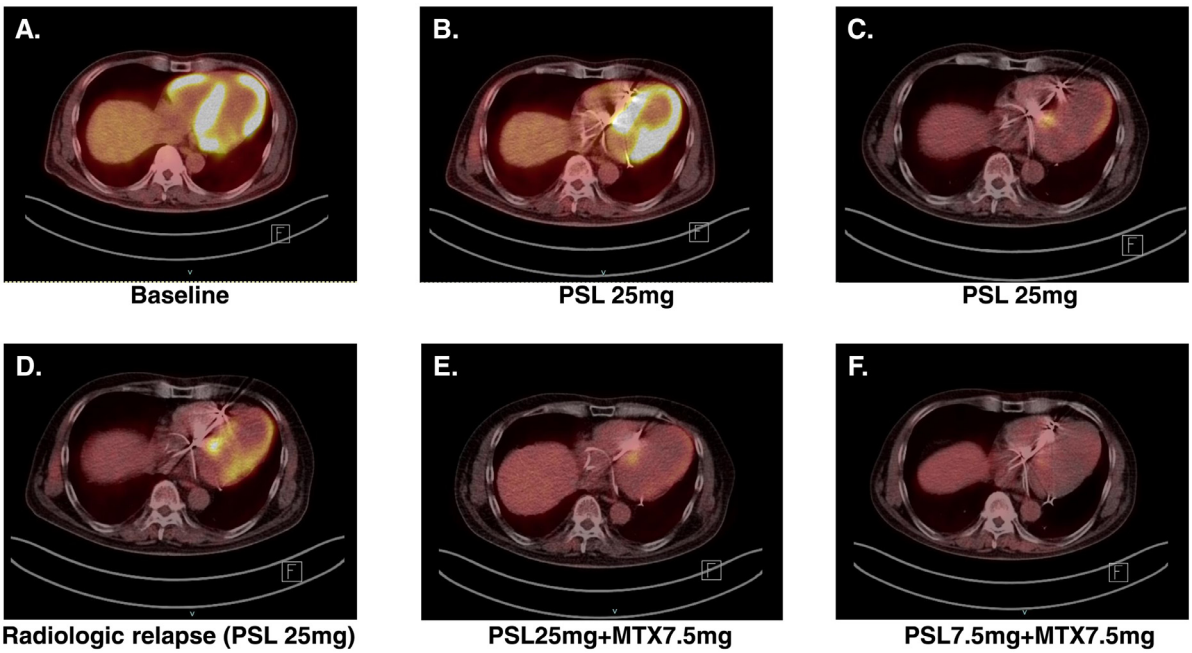

Figure 2. Time course of radiologic relapse in a patient with CS. The ^{18}F-FDG PET images in a representative case (65-year-old man) taken at diagnosis (*A*), and at different periods in the course of follow-up. Three months after initiation of PSL (initial dose 30 mg for 4 weeks, then tapered to 25 mg as maintenance), high uptake of ^{18}F-FDG was observed (*B*). Eight months after starting therapy, uptake was decreased (*C*). After 13 months, radiologic relapse was observed despite continuation of the maintenance dose (PSL 25 mg) (*D*). MTX 7.5 mg was added to the regimen (*E*). Two years after the initiation of the combination therapy, decreased uptake of ^{18}F-FDG was again seen (F: PSL 25 mg plus MTX 7.5 mg). MTX = methotrexate.

arrhythmia, n = 26). There were no significant differences in the incidence of lethal arrhythmia, HF events, and death between the 2 groups. The univariate analysis (Table 3) indicated that the tested laboratory and echocardiographic parameters were not associated with occurrences of a radiologic relapse.

The results of a univariate analysis for composite adverse events are shown in Table 4. LVEF and plasma B-type natriuretic peptide levels were associated with the clinical outcomes ($p < 0.05$). In contrast, radiologic relapse was not associated with the clinical outcomes. Frequency of composite adverse events was not significantly different between the group with radiologic relapse and the group without radiologic relapse, although it tended to be slightly lower in those with radiologic relapse. A Kaplan−Meier analysis of the initial 2 years of follow-up showed that there were no differences in event-free survival rates in the patients with and patients without radiologic relapse (Figure 3).

Discussion

Radiologic relapse was observed in 38.8% of patients in the overall enrolled patients. The median PSL dose at the radiologic relapse was 10 mg, indicating that the onset of relapse occurred during the maintenance phase of CTx. Because CS is essentially an inflammatory disease, the risk of relapse often remains after tapering PSL. A study reported a case of a patient with CS and severe HF who had recurrence of CS during a standard immunosuppressive therapy (including PSL) after heart transplantation.[15] This

Table 2
Clinical outcomes in patients with/without recurrence

	Overall	Rd relapse (−)	Rd relapse (+)	p Value
Advanced AV block, N (%)	5 (6%)	3 (6%)	2 (6%)	1.000
VT/VF, N (%)	22 (28%)	13 (27%)	10 (31%)	0.803
Lethal arrhythmia, N (%)	26 (33%)	15 (19%)	11 (14%)	0.650
HF, N (%)	30 (38%)	20 (41%)	10 (32%)	0.485
Death, N (%)	8 (10%)	5 (10%)	3 (10%)	1.000
Composite adverse events, N (%)	40 (50%)	26 (53%)	14 (45%)	0.647

AV = atrioventricular; HF = heart failure; VF = ventricular fibrillation; VT = ventricular tachycardia.
Other abbreviation as the previous Tables.

Table 3
Univariate analysis for radiologic relapse of CS

	Rd relapse	
	HR (95%CI)	p Value
Age, 1year	0.985 (0.952-1.023)	0.430
Female sex	1.420 (0.689-2.923)	0.347
LVEDD, 1mm	0.991 (0.947-1.035)	0.705
LVEDS, 1mm	0.989 (0.954-1.024)	0.535
LVEF, 1%	1.015 (0.984-1.045)	0.343
BNP	1.000 (0.998-1.001)	0.663
CRP	2.289 (0.548-7.238)	0.234

CI = confidence interval; HR = hazard ratio; LA = left atrial.
Other abbreviation as Table 1.

Table 4
Univariate analysis for composite adverse events

	Composite adverse events	
	HR (95%CI)	p Value
Age, 1year	1.065 (1.019-1.121)	0.005
Female sex	1.007 (0.474-2.140)	0.985
LVEDD, 1mm	1.040 (1.085-0.961)	0.084
LVEDS, 1mm	1.037 (0.999-1.074)	0.059
LVEF, 1%	0.961 (0.923-0.955)	0.025
BNP	1.002 (1.001-1.003)	0.004
CRP	0.812 (0.113-3.121)	0.795
Rd relapse	0.693 (0.336-0.328)	0.336

Abbreviation as the previous Tables.

suggests that immunosuppression may not eliminate the residual risk of recurrence in some patients. In a long-term follow-up study by Cacoub et al,[16] the cumulative incidence of recurrence in 157 patients at 1, 3, 5, and 10 years was 6%, 24%, 32%, and 50%, respectively. However, the relapse was clinically diagnosed without the specific criteria.[16] The diagnostic criteria to determine CS relapse have not yet been established. In our study, CS relapse was diagnosed through nuclear imaging. In addition, we investigated the association of relapse with long-term clinical outcomes. To the best of our knowledge, this is the first detailed report regarding CS radiologic relapse.

No significant differences in clinical outcomes were observed between patients with and patients without radiologic relapse, as shown in Figure 3. This lack of association between radiologic relapse and clinical outcomes needs to be examined in more depth. In previous research,[9] reduction in LVEF was observed in patients not on PSL, suggesting progressive LV remodeling in those without immunosuppressive therapies. Other reports suggested that PSL therapy was associated with lower mortality.[3] To date, the available evidence on the impact of immunosuppression in CS is limited to retrospective studies.

The results of our study suggest that clinical outcomes in patients with radiologic relapse were favorable under intensified immunosuppressive therapies. We noted that LV systolic function, rather than radiologic relapse itself, was significantly associated with long-term clinical outcomes. Immunosuppressive therapy initiated before the onset of cardiac remodeling may be beneficial in preventing or delaying the progression of cardiac remodeling.[17] Furthermore, we noted that patients with radiologic relapse tended to have a lower frequency of composite events (Figure 3), though the difference was not statistically significant. The results suggest that intensified immunosuppressive therapies may be beneficial for patients with a high CS inflammatory activity. From this perspective, a detection of inflammation, which indicates reactivation of CS, is important for the avoidance of further cardiac remodeling. ^{18}F-FDG PET scans or Ga scintigraphy during the follow-up term have a clinical application for early detection of relapse of inflammatory activity.

In our previous study, we observed that substantial cardiac fibrosis, seen as an area of delayed enhancements in the myocardium in magnetic resonance imaging (MRI), is associated with poor clinical outcomes and poor recovery of systolic function after starting CTx. This suggests that patients with advanced cardiac fibrosis might poorly respond to immunosuppressive therapy in terms of systolic recovery.[18] Furthermore, these findings suggest that early pharmacologic intervention may potentially improve the clinical outcomes in patients with CS despite radiologic relapse. MRI is an important tool for early detection of myocardial fibrosis, but the role of MRI for follow-up evaluation in CS has not been established. In the present study, we had no data regarding follow-up MRI. Further investigation is necessary in establishing the role of evaluation for cardiac fibrosis during the follow-up term.

This study has several limitations. This was a single-center investigation with a limited number of patients. Second, the follow-up period varied among cases (IQR 1.1 to 5.9 years). All patients enrolled in this study had been followed

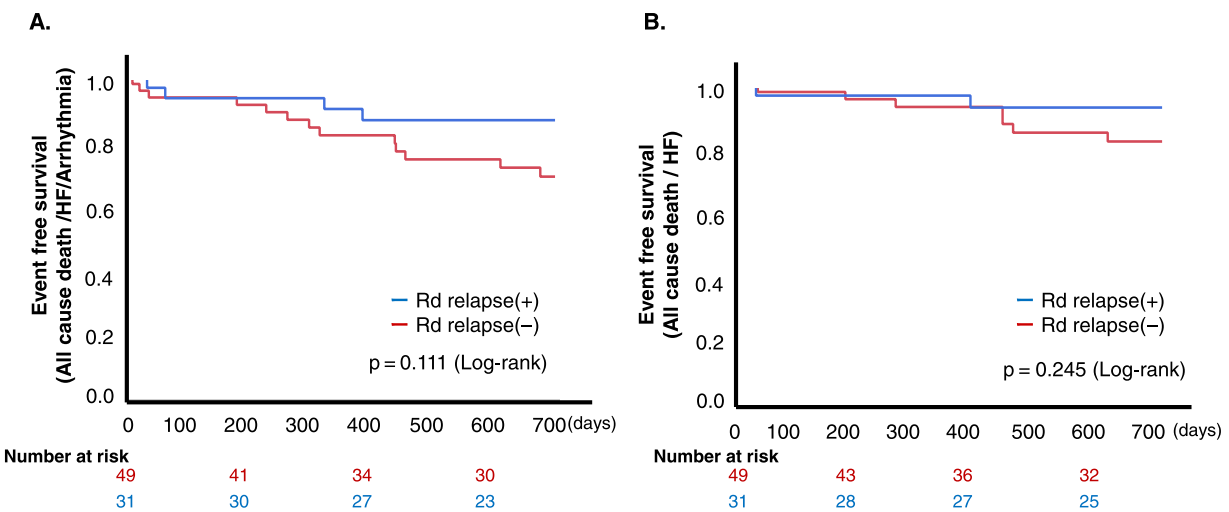

Figure 3. Frequency of composite adverse events in patients with and without radiologic relapse. Kaplan−Meier analysis showed that there were no differences in event-free survival in patients with and without radiologic relapse (blue and red lines, respectively).

up with nuclear imaging; those eligible received intensified immunosuppressive treatments. This underscores the importance of monitoring using imaging modalities that can detect early cardiac inflammation. We recommend further research to address these limitations and to solve the following questions: how often should monitoring of disease activity be done? Will intensified immunosuppression guided by nuclear imaging prevent cardiac remodeling and lead to improved clinical outcomes? Lastly, further investigation is necessary to determine the CTx protocol, including the necessity of long-term treatment as maintenance therapy and the most effective immunosuppressive agent for CS relapse. Methotrexate has been widely used as adjunctive therapy for PSL in sarcoidosis,[19] including our data in this study. One randomized clinical trial comparing low-dose PSL plus methotrexate combination with PSL is ongoing,[20] and is expected to provide important information for this issue.

In conclusion, the radiologic relapse was observed in many patients with CS. Under the monitoring of nuclear imaging tests and appropriate intensification of immunosuppressive therapies, no significant differences in clinical outcomes were observed in the patients with and patients without radiologic relapse.

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Disclosures

The authors have no conflicts of interest to declare.

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