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ORIGINAL RESEARCH ARTICLE

Diagnosis of isolated cardiac sarcoidosis based on new guidelines

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Abstract

Aims In the updated guidelines for cardiac sarcoidosis (CS) proposed by the Japanese Circulation Society (JCS), the definition of isolated CS (iCS) was established for the first time. This prompted us to examine the characteristics of patients with CS including iCS according to them by reviewing patients undergoing ^{18}F-fluoro-2-deoxyglucose positron-emission tomography/computerized tomography (FDG-PET/CT), compared with those with CS determined by the conventional international criteria.

Methods and results From 2013 to 2019, 94 patients (61 ± 15 years, 50 female patients) with suspected CS underwent whole-body and cardiac FDG-PET/CT scanning. In contrast to 22 patients with CS based on the international criteria, 34 [27 with systemic sarcoidosis including cardiac involvement (sCS) and 7 with definitive iCS] were diagnosed with CS according to the new JCS guidelines (P = 0.012), and 60 were not (4 suspected iCS, 13 systematic sarcoidosis without cardiac involvement, and 43 no sarcoidosis). In addition to 26 of 34 patients with CS, corticosteroids were also started in 6 of 60 without CS according to clinical need.

Conclusions Diagnostic yield with the new JCS guidelines was higher, with approximately 1.5-fold of the patients diagnosed with CS compared with the previous international criteria and definitive iCS accounting for approximately 20% of the whole CS cohort. In addition to 75% of the patients with sCS or definitive iCS in the updated guidelines, 10% in whom CS was not documented were also started on corticosteroids for clinical indications such as reduced cardiac function or arrhythmia.

Keywords Cardiac sarcoidosis; Fluorine-18-fluorodeoxyglucose positron emission tomography; Isolated cardiac sarcoidosis

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Introduction

Sarcoidosis is a systemic disease associated with non-caseating granulomas. Immunosuppression therapy, usually with corticosteroids, is suggested for the treatment of clinically manifest cardiac sarcoidosis (CS).[1,2] Compared with those with moderately reduced left ventricular ejection fraction (LVEF) (30–54%), immunosuppressive therapy does not improve the left ventricular (LV) function of patients with severely reduced LVEF (≤30%) whose higher scar burden precludes any improvement with immunosuppressive therapy.[3,4] Despite the need for early diagnosis and therapeutic interventions, diagnostic confirmation of CS is difficult because endomyocardial biopsy has low sensitivity (less than 20%) due to the disease's focal nature.[5,6] That is the reason why multimodality cardiac imaging is essential for identification of patients with the early stage of CS. Meanwhile several reports about patients with isolated cardiac sarcoidosis (iCS) have been published.[7–9] The prevalence of iCS among patients with systemic sarcoidosis varies widely (23–54%),[10,11] mainly because of differences in the definitions used.

The guidelines for the diagnosis and treatment of CS from the Japanese Circulation Society (JCS) were recently updated[1] (*Table 1*). Several marked changes are suggested in this guideline. First, abnormally high tracer accumulation in the heart with ^{18}F-fluorodeoxyglucose (FDG) positron emission

Table 1 JCS 2016 Guidelines on Diagnosis and Treatment of Cardiac Sarcoidosis

a. Criteria for cardiac involvement
Cardiac findings should be assessed based on the major criteria and the minor criteria. Clinical findings that satisfy the following 1) or 2) strongly suggest the presence of cardiac involvement.
1) Two or more of the five major criteria (a) to (e) are satisfied
2) One in the five major criteria (a) to (e) and two or more of the three minor criteria (f) to (h) are satisfied.
Major criteria
(a) High-grade atrioventricular block (including complete atrioventricular block) or fatal ventricular arrhythmia (e.g., sustained ventricular tachycardia, and ventricular fibrillation)
(b) Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening)
(c) Left ventricular contractile dysfunction (left ventricular ejection fraction less than 50%) or focal ventricular wall asynergy
(d) ^{67}Ga citrate scintigraphy or ^{18}F-FDG PET reveals abnormally high tracer accumulation in the heart
(e) Gadolinium-enhanced MRI reveals delayed contrast enhancement of the myocardium
Minor criteria
(f) Abnormal ECG findings: Ventricular arrhythmias (non-sustained ventricular tachycardia, multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal Q waves
(g) Perfusion defects on myocardial perfusion scintigraphy
(h) Endomyocardial biopsy: Monocyte infiltration and moderate or severe myocardial interstitial fibrosis
b. Diagnostic guidelines for cardiac sarcoidosis
1) Histological diagnosis group (those with positive myocardial biopsy findings)
Cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas.
2) Clinical diagnosis group (those with negative myocardial biopsy findings or those not undergoing myocardial biopsy)
The patient is clinically diagnosed as cardiac sarcoidosis (1) when epithelioid granulomas are found in organs other than the heart, and clinical findings strongly suggestive of the above-mentioned cardiac involvement are present; or (2) when the patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis; at least two of the following five characteristic laboratory findings of sarcoidosis (bilateral hilar lymphadenopathy: high serum ACE activity or elevated serum lysozyme levels: high serum sIL-2R levels: significant tracer accumulation in ^{67}Ga citrate scintigraphy or ^{18}F-FDG PET: a high percentage of lymphocytes with a CD4/CD8 ratio of $>$3.5 in BAL fluid); and clinical findings strongly suggest the above-mentioned cardiac involvement.
c. Diagnostic guidelines for isolated cardiac sarcoidosis
Prerequisite
1. No clinical findings characteristics of sarcoidosis are observed in any organs other than the heart (The patient should be examined in detail for respiratory, ophthalmic, and skin involvements of sarcoidosis. When the patient is symptomatic, other aetiologies that can affect the corresponding organs must be ruled out.).
2. ^{67}Ga scintigraphy or ^{18}F-FDG PET reveals no abnormal tracer accumulation in any organs other than the heart.
3. A chest CT scan reveals no shadow along the lymphatic tracts in the lungs or no hilar and mediastinal lymphadenopathy (minor axis $>$10 mm).
1) Histological diagnosis group
Isolated cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas.
2) Clinical diagnosis group
Isolated cardiac sarcoidosis is diagnosed clinically when the criterion (d) and at least three other criteria of the major criteria (a) to (e) are satisfied.
When the patient meets at least four criteria for cardiac involvement other than the criterion (d), or when the patient meets the criteria (b) and (d) plus one of the remaining criteria, the patient should be suspected to have isolated cardiac sarcoidosis.

^{67}Ga, gallium-67; ^{18}F-FDG PET, fluorine-18 fluorodeoxyglucose positron emission tomography; ACE, angiotensin converting enzyme; BAL, bronchoalveolar lavage; CT, computed tomography; ECG, electrocardiography; MRI, magnetic resonance imaging; sIL-2R, soluble interleukin 2 receptor.

tomography/computed tomography (FDG-PET/CT), which was categorized in the remarks in the 'Guidelines for the Diagnosis of Cardiac Involvement in Patients with Sarcoidosis' in 2006,[12] was raised to the major criteria as well as late-gadolinium enhancement (LGE) of the myocardium in gadolinium-enhanced magnetic resonance imaging (MRI). Whole-body FDG-PET is useful for the evaluation of inflammatory lesions in patients with suspected CS; it can demonstrate extra-cardiac uptake in some patients who have not been diagnosed with extra-cardiac sarcoidosis. Second, in the guidelines proposed by the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) in 2014[13] or the Heart Rhythm Society (HRS) in the United States in 2014,[14] the histologic evidence of granulomatous inflammation of unknown cause needed to be demonstrated in at least one organ. However, in the JCS guideline, the patient is also clinically diagnosed with CS when he/she shows clinical findings strongly suggestive of cardiac involvement and those of pulmonary or ophthalmic sarcoidosis, and at least two of the five characteristic laboratory findings of sarcoidosis (*Table 1a* and *1b*). Last, the definition of iCS was established for the first time (*Table 1c*). It is also important for the patients with iCS to start appropriate treatment without delay, because iCS is considered not to differ from systemic sarcoidosis with cardiac involvement (sCS) as well as in terms of pathophysiology and prognosis.[11]

Here, we examined retrospectively a group of consecutive patients undergoing FDG-PET/CT for suspected CS to determine the characteristics of CS including iCS according to the new guidelines, as compared with those based on the conventional international criteria.[13,14]

Methods

Study populations

We retrospectively examined all patients with suspected CS who underwent whole-body and cardiac FDG-PET/CT scanning from January of 2013 to August of 2019 after excluding those who were already taking corticosteroid. For the diagnosis of systemic sarcoidosis, the enrolled patients were also examined with electrocardiography, chest X-ray, Holter monitoring, echocardiography, chest CT, and gadolinium-enhanced cardiovascular magnetic resonance (CMR) for those without a pacemaker or with an MRI-compatible pacemaker. The presence or absence of systemic involvement was determined by ophthalmologic, dermatologic, and other examinations in all included patients. For the patients needing a differential diagnosis, coronary CT angiography, invasive coronary angiography, endomyocardial biopsy, or perfusion scintigraphy was added. Cut-off levels of the angiotensin converting enzyme (ACE), soluble interleukin-2 receptors (sIL-2Rs), troponin I, and N-terminal pro-Brain Natriuretic Peptide were decided as 21.4 U/L, 500 U/mL, 0.0473 ng/mL, and 125 pg/mL, respectively. On echocardiography, the presence of any ventricular septal thinning (≤4 mm thick at 10 mm from the aortic annulus in the LV long axis view),[15] ventricular aneurysm, localized wall motion abnormality, and the value of LVEF were determined. High-grade atrioventricular block (including complete atrioventricular block) or fatal ventricular arrhythmia (e.g., sustained ventricular tachycardia and ventricular fibrillation) on Holter monitoring and the presence of LGE of the myocardium in CMR were also examined. According to the updated guidelines for the diagnosis and treatment of CS from JCS,[1] the examined patients were divided into five groups: sCS, definitive iCS, suspected iCS, systemic sarcoidosis without cardiac involvement, and no sarcoidosis (*Table 1*). The patients were also determined as having CS when they met the criteria for the diagnosis of CS on expert consensus recommendations from HRS[14] in accordance with A Case Control Aetiology of Sarcoidosis Study set of criteria published and updated by the WASOG.[13] All examinations were performed before steroid treatment in Fujita Health University. The study was approved by the Institutional Review Board and ethics committee of our university. We applied an opt-out method to obtain consent for this study on the website of our department.

^{18}F-fluoro-2-deoxyglucose positron-emission tomography/computerized tomography procedure and image analysis

^{18}F-fluoro-2-deoxyglucose positron-emission tomography/computerized tomography scans were performed with a dedicated PET/CT scanner (Biograph mCT, Siemens Healthineers AG, Erlangen, Germany). Patients were instructed to ingest a low-carbohydrate, fat-rich, and protein-permitted diet the day before the examination, followed by a fast of at least 18 h immediately before it. The CT data were obtained in 2 mm slices with a 0.35 helical pitch at 120 kV and 82 mA on average that auto exposure control adjusted (CARE Dose 4D, Siemens Healthineers AG, Erlangen, Germany) with a matrix of 512 × 512 pixels. After CT scanning, patients also received a low dose (50 IU/kg) of intravenous unfractionated heparin unless contraindicated. Finally, the patients received a whole-body acquisition 60 min after the intravenous injection of 185 MBq of ^{18}F-FDG, followed immediately by a cardiac acquisition with electrocardiography gating for evaluation of LV function. The FDG-PET data were obtained in three-dimensional mode for 2 min in each bed position. The FDG-PET data consisted of a matrix of 200 × 200 pixels. The CT and FDG-PET images were fused to match a matrix of 512 × 512 pixels.

^{18}F-fluoro-2-deoxyglucose positron-emission tomography/computerized tomography data were analysed by one cardiologist (M.S.) and two radiologists (H.T. and A.W.) blinded to the clinical data. Sites of disease involvement were defined as positive when abnormal FDG uptake in a pattern consistent with sarcoidosis was present. Regarding lymph node involvement, FDG uptake above that of the mediastinal blood pool was considered significant.[16] As a visual assessment for cardiac FDG-PET/CT, 'focal' or 'focal on diffuse' pattern myocardial uptake was defined as positive, and 'diffuse' or 'none' as negative.[17]

Statistical analysis

Variables with a normal distribution are expressed as mean values ± standard deviation, and asymmetrically distributed data are given as the median and interquartile range. Categorical variables were presented as frequency (percentage). Differences among five groups were evaluated using ANOVA or Kruskal–Wallis test for continuous variables, and χ^2-square test for categorical variables. McNemar's test was used to compare the prevalence of each factor in the patients determined as having CS between JCS and WASOG/HRS guidelines. Multiple comparison was also performed by Dunnet's test or Steel's test for contentious variables, and χ^2-square test with Bonferroni correction for categorical variables. All statistical analyses were carried out using JMP version 13 (SAS Institute, Cary, NC, USA).

Results

Study population

Of 94 patients (mean age 61 ± 15 years, 50 female patients), 36 had received a diagnosis of extra-CS before FDG-PET/CT, while the remaining 58 had not. Of the 36 with extra-cardiac sarcoidosis, cardiac FDG was positive (focal or focal on diffuse) in 21 and negative in 15. Finally, 20 of 21 judged as FDG positive and 3 of 15 judged as FDG negative were diagnosed with systemic sarcoidosis including myocardium after all examinations were completed. On the other hand, of 58 in whom extra-CS had not been identified before FDG-PET/CT, extra-cardiac FDG uptake was seen in four; these four were also considered to have sCS. Of the remaining 54, cardiac FDG was positive in 17 and negative in 37. Of the 17 judged cardiac FDG positive, seven were finally diagnosed with definitive iCS and two with suspected iCS. Of the 37 with negative findings in cardiac FDG, 35 were diagnosed as not having sarcoidosis and the remaining two with suspected iCS. Finally, 27 and 7 patients were diagnosed with sarcoidosis with CS and definitive iCS, respectively (*Figures 1* and *2*).

Clinical characteristics of the patients undergoing FDG-PET/CT were shown in *Table 2*. There were significant differences in ACE, sIL-2R, limited thinning of interventricular septum (IVS) or ventricular aneurysms, LV dysfunction (ejection fraction $<$ 50%) or local LV wall motion abnormality, LGE uptake in heart, FDG-PET/CT findings, and the number of major criteria among the five groups. The prevalence of LV wall motion abnormality (100% vs. 44%, P = 0.042) and the number of major criteria (4.0 [4.0–4.0] vs. 2.0 [2.0–4.0], P = 0.028) were higher in the definitive iCS group than sCS group. Similarly, there were differences in the prevalence of LV wall motion abnormality (100% vs. 23%, P = 0.004), IVS thinning or ventricular aneurysms (86% vs. 8%, P = 0.002), cardiac FDG findings (100% vs. 8%, P = 0.004), and the number of major criteria (4.0 [4.0–4.0] vs. 0 [0–1.0], $P < 0.001$) between the definitive iCS group and systemic sarcoidosis without cardiac involvement one. Furthermore, between definitive iCS and no sarcoidosis group, there were significant differences in the prevalence of IVS thinning (86% vs. 26%, P = 0.0148), cardiac FDG findings (100% vs. 19%, $P < 0.001$), and the number of major criteria (4.0 [4.0–4.0] vs. 2.0 [1.0–3.0], $P < 0.001$). Except for the patients with definitive or suspected iCS or sCS, one patient in the sCS without cardiac involvement group and eight in the no sarcoidosis group had positive findings on cardiac FDG. Of them, seven had similarities with CS clinically (but did not fulfil the criteria for it), and the remaining two were finally diagnosed with muscular dystrophy and myocarditis, respectively.

Comparison between Japanese Circulation Society guidelines and international criteria from World Association of Sarcoidosis and Other Granulomatous Disorders/Heart Rhythm Society

Of 94 patients, 34 (27 with sCS and 7 with iCS) were diagnosed with CS based on the new JCS guidelines, and 60 were not. Based on the international criteria from WASOG/HRS, 22

Figure 1 Patient population. AF, atrial fibrillation; AVB, atrioventricular block; CS, cardiac sarcoidosis; ECG, electrocardiogram; e-CS, extra cardiac sarcoidosis; FDG, ^{18}F-fluorodeoxyglucose; HF, heart failure; iCS, isolated cardiac sarcoidosis; LVEF, left ventricular ejection fraction; PVC, premature ventricular contraction; SVT, sustained ventricular tachycardia; UCG, ultrasonic cardiogram.

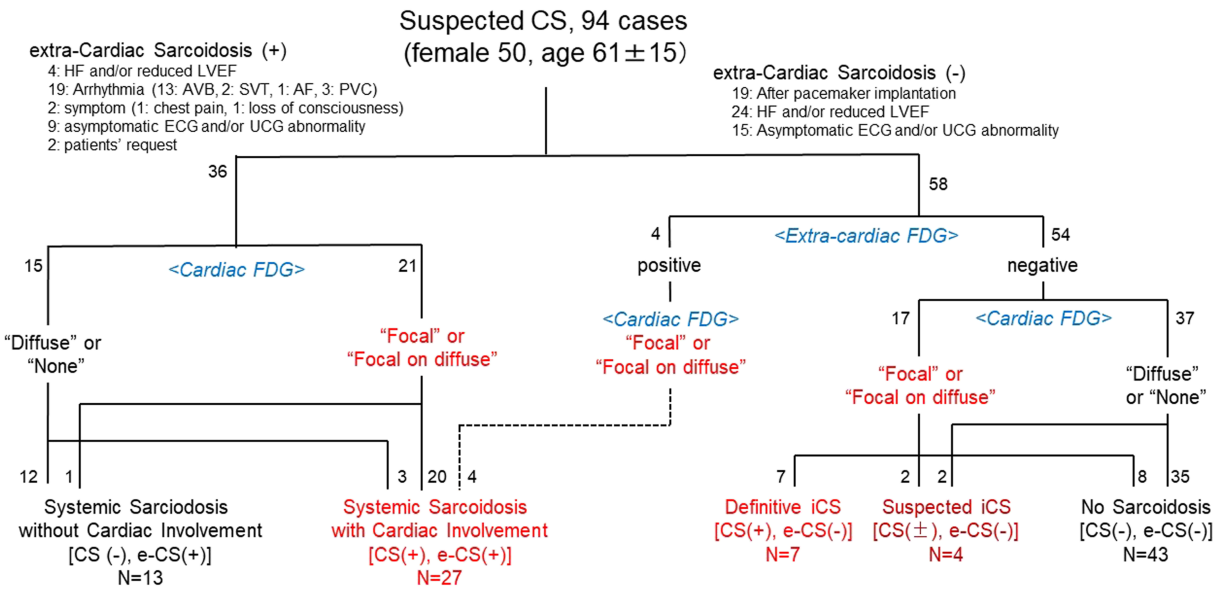

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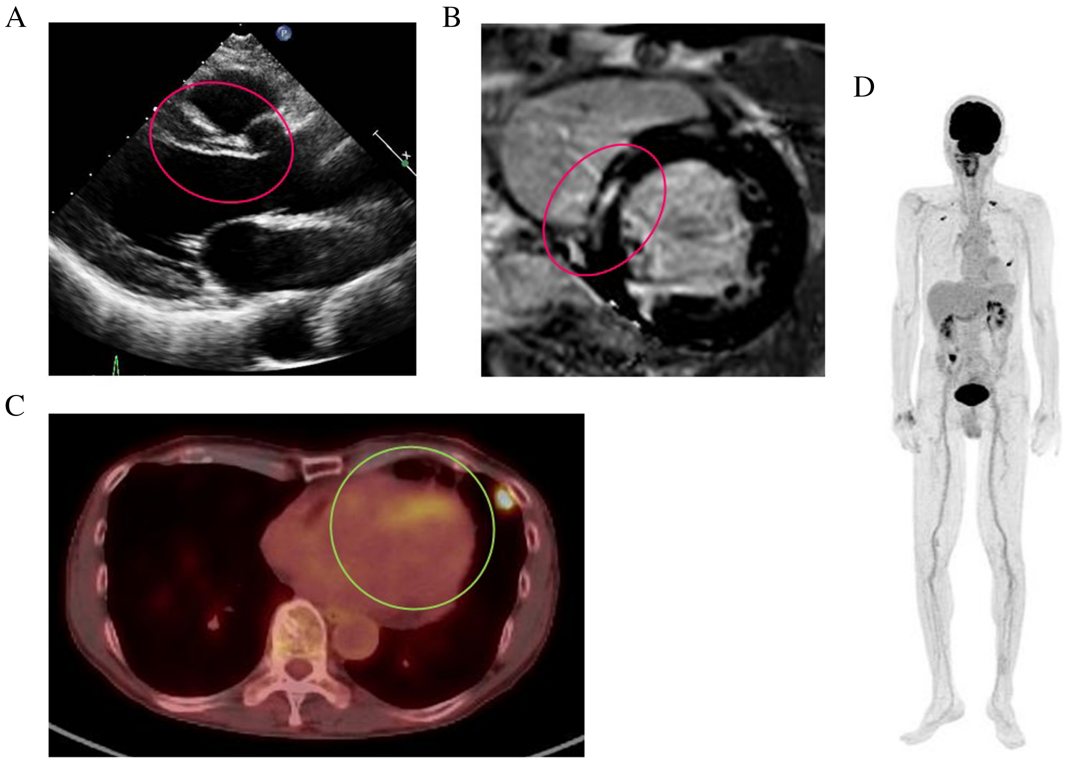
Figure 2 Representative case of isolated cardiac sarcoidosis. Sixty-five-year-old asymptomatic man presented with electrocardiography abnormality. Cardiac ultrasound showed left ventricular ejection fraction of 26% and thinning of interventricular septum (A), and magnetic resonance imaging (MRI) showed late-gadolinium enhancement (LGE) uptake in basal septum (B). ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) revealed focal uptake in septum (C) and no uptake outside the heart (D). No caseating granuloma was found in myocardial tissue.



of 94 patients were determined to have CS, while 72 were not. In the new JCS guidelines, 16 of 72 with negative results according to WASOG/HRS criteria were newly diagnosed with CS, whereas 4 of 22 with positive results on WASOG/HRS criteria did not meet the new criteria (P = 0.012). Between CS from JCS guidelines and WASOG/HRS criteria, there were significant differences in the proportion of females (P = 0.039), ACE negative status (P = 0.022), N-terminal pro-brain natriuretic peptide positive status (P = 0.002), incidences of high-grade atrioventricular block or fatal ventricular arrhythmia (P = 0.021), thinning of IVS or ventricular aneurysms (P = 0.003), LV dysfunction of local LV wall motion abnormality (P = 0.022), LGE in CMR (P = 0.039), and cardiac uptake on FDG-PET/CT ($P < 0.001$).

Clinical characteristics of the patients with isolated cardiac sarcoidosis/suspected isolated cardiac sarcoidosis

Details of the seven definitive iCS and four suspected iCS cases are shown in *Table 4*. All of the seven patients with iCS fulfilled four criteria including positive findings on FDG-PET/CT. Two with suspected iCS (Nr. 8 and 9) met three criteria with positive findings on FDG-PET/CT and the remaining two (Nr. 10 and 11) met four criteria except for it (*Table 4*).

Initiation of corticosteroids

The indication for corticosteroid administration was decided based not only on the guidelines but also other clinical requirements. Corticosteroids were initiated in 5/7 cases with definitive iCS and 1/4 with suspected iCS after the first FDG-PET/CT. Patient Nr. 3 rejected them because of advanced age, and Nr. 6 was not started on them because atypical mycobacterial disease was present. Because Nr. 11 showed high uptake in the heart on the repeated FDG-PET/CT, he was confirmed to have CS and started corticosteroid then. In addition to them, corticosteroids were initiated in 5/56 cases in the no CS group as well as 21/27 in the sCS group. In contrast, in the international criteria, corticosteroids were initiated in 18 of 22 patients with CS and 14 of 72 without it.

Table 2 Patient characteristics

Characteristic	Definitive sarcoidosis with cardiac involvement (n = 7)	Systemic sarcoidosis with cardiac involvement (n = 27)	Suspected sarcoidosis with cardiac involvement (n = 4)	Systemic sarcoidosis without cardiac involvement (n = 13)	No sarcoidosis (n = 43)	P value
Cardiac sarcoidosis	(+)	(+)	(±)	(−)	(−)	
Extra-cardiac sarcoidosis	(−)	(+)	(−)	(+)	(−)	
Age (years mean ± SD)	59.4 ± 14.9	62.7 ± 13.0	51.5 ± 22.1	69.5 ± 9.8	57.5 ± 16.0	0.0938
Female, n (%)	3 (43%)	17 (63%)	2 (50%)	9 (69%)	19 (43%)	0.3932
ACE > 21.4 U/L, n (%)	1/5 (20%)	9/26 (35%)	0/4 (0%)	4/13 (31%)	2/38 (5%)	0.0259
sIL-2R > 500 U/mL, n (%)	2/5 (40%)	13/24 (54%)	1/4 (25%)	6/10 (60%)	4/26 (15%)	0.0346
TnI > 0.0473 ng/mL, n (%)	2/5 (40%)	7/25 (28%)	2/4 (50%)	3/10 (30%)	14/37 (38%)	0.8731
NT-proBNP > 125 pg/mL, n (%)	5/5 (100%)	20/26 (77%)	4/4 (100%)	5/12 (42%)	29/40 (73%)	0.0524
Non-caseating granuloma on myocardial tissue, n (%)	0/5 (0%)	2/12 (16.7%)	0/4 (0%)	0/1 (0%)	0/22 (0%)	0.2322
Sustained VT/VF, Mobitz type II or third degree AVB, n (%)	4 (57%)	15 (56%)	2 (50%)	1 (8%)	19 (44%)	0.0616
Thinning of interventricular septum or ventricular aneurysms, n (%)	6 (86%)	12 (44%)	4 (100%)	1 (8%)*	11 (26%)*	0.0002
LV dysfunction (ejection fraction < 50%) or local LV wall motion abnormality, n (%)	7 (100%)	12 (44%)*	2 (50%)	3 (23%)*	29 (67%)	0.0055
LGE uptake in cardiac MRI, n (%)	4/4 (100%)	12/15 (80.0%)	4/4 (100%)	1/7 (14%)	11/22 (50%)	0.0047
Cardiac uptake in FDG-PET/CT, n (%)	7 (100%)	24 (89%)	2 (50%)	1 (8%)*	8 (19%)*	<0.0001
(Focal)	5 (71%)	19 (70%)	0 (0%)	1 (8%)	6 (14%)	
(Focal on diffuse)	2 (29%)	5 (19%)	2 (50%)	0 (0%)	2 (5%)	
(Diffuse)	0 (0%)	0 (0%)	1 (25%)	1 (8%)	9 (21%)	
(No)	0 (0%)	3 (11%)	1 (25%)	11 (85%)	26 (60%)	
The number of major criteria	4.0 [4.0–4.0]	2.0 [2.0–4.0]*	3.5 [3.0–4.0]	0 [0–1.0]*	2.0 [1.0–3.0]*	<0.0001

ACE, angiotensin converting enzyme; AVB, atrioventricular block; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; LGE, late-gadolinium enhancement; LV, left ventricular; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; sIL-2R, soluble interleukin-2 receptors; TnI, troponin I; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3 Comparison between the updated JCS guidelines and international criteria from WASOG/HRS

Characteristic	JCS Guideline (+)	JCS Guideline (−)	P^{*}	WASOG/HRS Criteria (+)	WASOG/HRS Criteria (−)	P^{*}	P^{**}
	(*N* = 34)	(*N* = 60)		(*N* = 22)	(*N* = 72)		0.012
Age (years, mean ± SD)	62.0 ± 13.2	59.7 ± 16.0	0.5708	60.4 ± 13.2	60.6 ± 15.7	0.8512	
Female, *n* (%)			0.4104			0.5263	
Positive	20 (59%)	30 (50%)		13 (59%)	37 (51%)		0.039
Negative	14 (41%)	30 (50%)		9 (41%)	35 (49%)		0.227
Non-caseating granuloma in any organ, *n* (%)			<0.001			<0.001	
Positive	18 (53%)	10 (17%)		22 (100%)	6 (8%)		0.125
Negative	16 (47%)	50 (83%)		0	66 (92%)		N.A.
ACE > 21.4 U/L, *n* (%)			0.0146			0.001	
Positive	10/31 (32%)	6/55 (11%)		9/21 (43%)	7/65 (11%)		1
Negative	21/31 (68%)	49/55 (89%)		12/21 (57%)	58/65 (89%)		0.022
sIL-2R > 500 U/mL, *n* (%)			0.0484			0.0663	
Positive	15/29 (52%)	11/39 (28%)		11/20 (55%)	15/48 (31%)		0.289
Negative	14/29 (48%)	28/39 (72%)		9/20 (45%)	33/48 (69%)		0.18
TnI > 0.0473 ng/mL, *n* (%)			0.5073			0.1144	
Positive	9/30 (30%)	19/51 (37%)		4/20 (20%)	24/61 (39%)		0.063
Negative	21/30 (70%)	32/51 (63%)		16/20 (80%)	37/61 (61%)		0.227
NT-proBNP > 125 pg/mL, *n* (%)			0.2012			0.3979	
Positive	25/31 (81%)	38/56 (68%)		13/20 (65%)	50/67 (75%)		0.002
Negative	6/31 (19%)	18/56 (32%)		7/20 (35%)	17/67 (25%)		1
Sustained VT/VF, Mobitz type II or third degree AVB, *n* (%)			0.0711			0.4903	
Positive	19 (56%)	22 (37%)		11 (50%)	30 (42%)		0.021
Negative	15 (44%)	38 (63%)		11 (50%)	42 (58%)		0.344
Thinning of interventricular septum or ventricular aneurysms, *n* (%)			0.0109			0.6274	
Positive	18 (53%)	16 (27%)		7 (32%)	27 (38%)		0.003
Negative	16 (47%)	44 (73%)		15 (68%)	45 (63%)		1
LV dysfunction (ejection fraction < 50%) or local LV wall motion abnormality, *n* (%)			0.9413			0.2376	
Positive	19 (56%)	34 (57%)		10 (45%)	43 (60%)		0.022
Negative	15 (44%)	26 (43%)		12 (55%)	29 (40%)		0.453
LGE uptake in cardiac MRI, *n* (%)			0.0108			0.2744	
Positive	16/19 (84%)	16/33 (48%)		9/12 (75%)	23/40 (58%)		0.039
Negative	3/19 (16%)	17/33 (52%)		3/12 (25%)	17/40 (43%)		1
Focal or focal on diffuse type cardiac uptake in FDG-PET/CT, *n* (%)			<0.001			0.0025	
Positive	31 (91%)	11 (18%)		16 (73%)	26 (36%)		<0.001
Negative	3 (9%)	49 (82%)		6 (27%)	46 (64%)		0.375

ACE, angiotensin converting enzyme; AVB, atrioventricular block; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; HRS, Heart Rhythm Society; JCS, Japanese Circulation Society; LGE, late-gadolinium enhancement; LV, left ventricular; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; sIL-2R, soluble interleukin-2 receptors; TnI, troponin I; VF, ventricular fibrillation; VT, ventricular tachycardia; WASOG, World Association of Sarcoidosis and Other Granulomatous Disorders. The updated JCS guidelines[1]; international criteria from WASOG/HRS.[13,14]

$^{*}P$: comparison of positive rate between positive vs. negative in each category.

$^{**}P$: comparison of positive rate between updated JCS guidelines vs. WASOG/HRS criteria in each positive and negative case category.

Table 4 Characteristics of definitive or suspected iCS

No.	Age	Sex	Definitive or suspected	EMB	Clinical Criteria of iCS	FDG-PET/CT	VT/VF	Advanced AVB	Pacemaker	Thinning septal wall or ventricular aneurysms	LVEF < 50 or local LV wall motion abnormality	LGE uptake in heart	Initiation of corticosteroid after FDG examination
1	45	F	D	(−)	4	Focal	(−)	(−)	(−)	(+)	47%, inferior hypokinesis	severe(+)	(+)
2	53	M	D	(−)	4	Focal	(−)	(−)	(−)	(+)	27%	(+)	(+)
3	80	M	D	NA	4	Focal diffuse	on(−)	(+)	PM	(+)	36%	NA	Reject
4	63	F	D	(−)	4	Focal	(−)	(+)	CRTD	(+)	35%	NA	(+)
5	72	F	D	NA	4	Focal	(−)	(+)	PM	(+)	48%	NA	(+)
6	65	M	D	(−)	4	Focal	(−)	(−)	(−)	(+)	26%, inferior hypokinesis	severe(+)	Not possible
7	38	M	D	NA	4	Focal diffuse	on(+)	(−)	CRTD	(−)	28%	(+)	(+)
8	68	M	S	(−)	3	Focal diffuse	on(−)	(−)	(−)	(+)	52%	(+)	(+)
9	31	F	S	NA	3	Focal diffuse	on(−)	(−)	(−)	(+)	59%	(+)	(−)
10	34	F	S	NA	4	None	(+)	(−)	ICD	(+)	32%	(+)	(−)
11	73	M	S	(−)	4	None	(−)	(+)	PM	(+)	59%, anteroseptal hypokinesis	(+)	After second PET

AVB, atrioventricular block; CRTD, Cardiac Resynchronization Therapy with Defibrillator; EMB, endomyocardial biopsy; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; ICD, implantable cardioverter defibrillator; iCS, isolated cardiac sarcoidosis; LGE, late-gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; PM, pacemaker; VF, ventricular fibrillation; VT, ventricular tachycardia.

Discussion

Of the consecutive 94 patients who underwent FDG-PET/CT because of suspicion of cardiac sarcoidosis, 34 were given a definitive diagnosis based on the updated guidelines for the diagnosis and treatment of CS from the JCS.[1] Of the 34 patients with cardiac sarcoidosis, 27 had systemic sarcoidosis with cardiac involvement, and 7 had definitive iCS. Of the remaining 60, 4 were judged to have suspected iCS, 13 systemic sarcoidosis without cardiac involvement, and 43 no sarcoidosis. Among the five groups, there were significant differences in ACE, sIL-2R, LV dysfunction or local wall motion abnormality, any structural changes on echocardiography (limited thinning of IVS or ventricular aneurysms), and LGE uptake in the heart in addition to the FDG-PET/CT findings. In marked contrast, only 22 patients were diagnosed based on the international criteria in which histologic evidence of granulomatous inflammation in at least one organ is indispensable.[13,14] In addition to 75% of the patients with sCS or definitive iCS in the updated guidelines, 10% in whom CS was not documented were also started on corticosteroids for clinical indications such as reduced cardiac function or arrhythmia. In the present study, all of the included patients underwent FDG-PET/CT and had not been taking corticosteroids before the examination. In this way, the present study is the first to focus on the diagnosis of CS based on the updated guidelines, in which notably high uptake in the heart on FDG-PET/CT is set as the major criterion and a definition of iCS provided for the first time.

When the diagnosis according to the updated JCS guideline is regarded as correct, the positive and negative predictive values of FDG-PET/CT were 74% and 94%, respectively. In our study, 11 PET-positive cases were cardiac sarcoidosis-negative based on the new guideline. One of the limiting factors of FDG-PET is the false positives that occur due to physiological uptake. Although we divided all cases into four types and diagnosed the patients with 'diffuse' type indicating physiological uptake as negative, some false positive cases may have been included. Some of them, of course, may meet the criteria of CS at some time in the future, even though they do not now. On the other hand, three PET-negative cases were diagnosed with CS based on the new guideline. We surmise that they likely have CS but without myocardial inflammation at this time.

Because high tracer accumulation in the heart with FDG-PET/CT is emphasized in the new guidelines especially for the diagnosis of iCS, all seven patients showing a positive finding on FDG-PET/CT were determined to have definitive iCS. Although two of four patients with suspected iCS had a negative finding on FDG-PET/CT initially, one obtained a positive finding at the second examination. Furthermore, it is not impossible but still difficult to perform cardiac MRI for patients after pacemaker implantation. So, such

patients need to meet all of the remaining four criteria except for LGE to be diagnosed with definitive iCS. Consequently, several cases after pacemaker implantation have been assigned to the suspected iCS or no sarcoidosis groups, despite being strongly suspected of having had definitive iCS at that time. They did not meet the criteria of CS then but will possibly be diagnosed with CS subsequently with disease progression.

To meet the criteria of CS in WASOG/HRS, histologic evidence of granulomatous inflammation in at least one organ has been needed. However, in the updated JCS guidelines, the diagnosis of CS is made for patients showing clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis, with at least two of the five characteristic laboratory findings of sarcoidosis even in the absence of histological evidence. So 16 of 72 with negative on WASOG/HRS criteria were newly diagnosed as CS, whereas 4 of 22 positive on WASOG/HRS did not meet the criteria on the new JCS guidelines. Because of the respective clinical circumstances, corticosteroids were also initiated in 1 of 4 with suspected iCS and 5 of 56 with no cardiac sarcoidosis, as well as 21 of 27 patients with sCS and 5 of 7 with definitive iCS. Additionally, two cases with initially negative findings on FDG-PET/CT in the suspected iCS or no sarcoidosis group showed high uptake in the heart and were started on these agents. On the other hand, in the international criteria, corticosteroids were initiated in 18 of 22 patients (82%) with CS and 14 of 72 (19%) without CS. In clinical practice, corticosteroids are initiated for patients with severe ventricular arrhythmia (sustained VT/VF) or reduced LVEF who are strongly suspected of having CS even if they do not satisfy the criteria. Careful follow-up is needed for patients highly suspected of having of CS clinically even when the first FDG-PET/CT is negative.

Several papers have quantified the prevalence and proportion of iCS. The reported proportion of iCS varies widely (23% to 54% of CS) due to differences in its definition.[10,11,18–20] Isobe *et al*. describe various possible clinical scenarios in which CS may involve only the heart: (i) lesions of sarcoidosis may arise in the heart but spread to other organs over time, (ii) a subtype of sarcoidosis that is confined to the heart may exist, and (iii) lesions are present also in other organs but remain silent or clinically undetectable because the degree of inflammation is too low or for some other as yet unrecognized reasons.[11] It is important that the manifestation of extra-CS be searched for in patients who are diagnosed with definitive or suspected iCS, and by the same token that those of CS not be overlooked in patients diagnosed as having no sarcoidosis, and their clinical course and outcome carefully followed. This would help to facilitate elucidation of the pathogenetic mechanisms underlying iCS and assess and validate the established criteria in the updated guidelines.

Limitations

The present study was a retrospective investigation of a relatively small sample population from a single centre, although a few similar reports on patients with suspected CS before the initiation of corticosteroids have been published previously. Endomyocardial biopsy was performed in only 44 patients and revealed non-caseating granuloma in only two with sCS. The low sensitivity of biopsy in this condition was consistent with that noted in a past report.[5] Previously, we reported the one patient with pathologically proven iCS[20] but did not include him in the present study because he had already been started on corticosteroid before FDG-PET/CT. It has been reported that the detection rate of non-caseating granulomas can be improved by repetition of endomyocardial biopsy in the same patients,[21] although this is not standard in daily clinical practice.[22,23]

Conclusions

The diagnostic yield of the updated JCS guidelines in which the definition of iCS was established for the first time was high, with more than 1.5-fold of patients diagnosed with CS as compared with the previous international criteria. Approximately 20% of the whole CS population were determined to have definitive iCS. In addition to the 75% of patients with sCS or definitive iCS, 10% of them who were not diagnosed as having CS were also started on corticosteroids based on clinical necessity. Because some cases show a positive finding at subsequent examinations, careful observation is needed especially for those highly suspected of having CS clinically even when their first FDG-PET/CT is negative.

Conflict of interest

None declared.

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