

Successful treatment of recurrent cardiac sarcoidosis with the combination of corticosteroid and methotrexate monitored by ^{18}F -fluoro-2-deoxyglucose positron emission tomography: case series

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Background

The standard treatment for cardiac sarcoidosis (CS) is corticosteroids, including prednisolone (PSL). Previous studies have shown that the addition of methotrexate (MTX) to PSL is effective for steroid-refractory and recurrent cases. ^{18}F -fluoro-2-deoxyglucose positron emission tomography (FDG-PET) is an essential tool for the diagnosis of CS. However, it is unclear whether FDG-PET is useful for detecting recurrence of CS and monitoring the effectiveness of PSL and MTX combination therapy.

Case summary

We detected CS recurrence during PSL treatment using FDG-PET. Patient 1 was accompanied by increased FDG uptake in other organs, Patient 2 was complicated with a decrease in left ventricular ejection fraction, and Patient 3 showed enlargement of the late gadolinium enhancement area, which was compatible with the recurrence of CS. We successfully monitored the inflammation activity by FDG-PET and treated recurrent CS by increasing the PSL dose and adding MTX to suppress inflammation.

Discussion

FDG-PET is useful for detecting CS recurrence and monitoring the effectiveness of PSL and MTX combination therapy. Serial FDG-PET scans indicated that it might be more difficult to suppress inflammation in recurrent CS than in the initial treatment. The use of FDG-PET is necessary to monitor long-term disease activity.

Keywords

Case report • Cardiac sarcoidosis • Recurrence • Prednisolone • Methotrexate • Positron emission tomography

ESC Curriculum 2.3 Cardiac magnetic resonance • 2.5 Nuclear techniques • 6.5 Cardiomyopathy

Learning points

- ^{18}F -fluoro-2-deoxyglucose positron emission tomography is useful for detecting the relapse of cardiac sarcoidosis (CS) and monitoring of the therapy response.
- The combination of prednisolone and methotrexate is effective for recurrent CS.
- There is a reluctance to suppress the inflammation in CS recurrence cases.

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Introduction

Cardiac sarcoidosis (CS) is a serious life-threatening disease. CS leads to conduction disorders, ventricular arrhythmias, and heart failure and accounts for 47% of deaths in patients with sarcoidosis of all organs.^{1,2} The 10-year survival rate for CS is reported to be 44%.³

Timeline

	Patient 1	Patient 2	Patient 3
Age	62	54	59
Gender	Female	Male	Male
Onset (date: X)			
ACE (U/L, normal: 8.3–21.4 U/L)	15.1	6.9	20.5
sIL-2R (U/mL, normal: 127–582 U/mL)	367	324	352
BNP (pg/mL, normal: 0.0–18.4 pg/mL)	129.1	117.2	4.3
TTE-LVEF (%)	45	44	86
FDG-PET accumulation	Heart, lung, spleen, lymph nodes	Heart, lymph nodes	Heart, lymph nodes
FDG-PET SUV _{max}	8.8	11.2	8.4
Follow-up	X+1 month	X+1 month	X+6 months
sIL-2R (U/mL)	154	...	279
FDG-PET SUV _{max}	u.d.	u.d.	7.8
Recurrence (date: Y)	X+24 months	X+14 months	X+12 months
ACE (U/L)	7.4	5.4	12.9
sIL-2R (U/mL)	277	259	293
BNP (pg/mL)	75.7	175.5	7.7
TTE-LVEF (%)	54	30	77
FDG-PET accumulation	Heart, spleen, lymph nodes	Heart, lymph nodes	Heart, lymph nodes
FDG-PET SUV _{max}	6.7	5.9	12.8
Follow-up after recurrence	Y+1 month	Y+1 month	Y+1 month
sIL-2R (U/mL)	187	202	266
FDG-PET SUV _{max}	u.d.	5.5	5.1
2nd follow-up after recurrence	Y+9 months	Y+8 months	Y+4 months
sIL-2R (U/mL)	156	154	194
FDG-PET SUV _{max}	u.d.	u.d.	u.d.

The standard treatment for CS is corticosteroids, including prednisolone (PSL).¹ In one study, patients who received steroid therapy had a higher survival rate than patients who did not receive steroid therapy.³ However, there have been several patients with steroid-refractory form or recurrence of CS during tapering down of PSL.⁴ Previous studies have shown that the addition of methotrexate (MTX),⁵ azathioprine,⁶ and infliximab⁷ to PSL is effective for steroid-refractory and

recurrent cases of CS. In particular, the combination therapy of PSL and MTX reportedly improved the left ventricular ejection fraction (LVEF) compared with steroid therapy alone.⁵ Nevertheless, the appropriate criteria and time course of MTX combination therapy have not been fully investigated in recurrent CS.

In recent years, there have been an increasing number of reports that ¹⁸F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) is useful for the diagnosis of CS.⁸ An 18 h fasting can effectively reduce physiological FDG uptake in the heart.⁹ The Heart Rhythm Society and the Japanese Circulation Society have identified FDG-PET as a diagnostic criterion for CS.^{1,10} However, it is unclear whether FDG-PET is useful for detecting recurrence of CS and monitoring the effectiveness of PSL and MTX combination therapy.

In this article, we report three cases in which FDG-PET successfully detected recurrence of CS, and in which the combination therapy of PSL and MTX effectively suppressed inflammation.

Case presentations

Patient 1

A 62-year-old woman with no past medical history presented to the emergency department with syncope. Four years ago, an incomplete right bundle branch block was noted on a check-up electrocardiogram (ECG). One year prior, echocardiography showed decreased wall motion in the basal interventricular septum. On admission, her pulse rate was 200 bpm, and her systolic blood pressure was 80 mmHg. Her height was 162 cm and weight was 62.7 kg. No abnormal heart or breath sounds were observed. Her brain natriuretic peptide (BNP) level was mildly elevated to 129.1 pg/mL (normal: 0.0–18.4 pg/mL). Her angiotensin converting enzyme (ACE) level was 15.1 U/L (normal: 8.3–21.4 U/L), and soluble interleukin-2 receptor (sIL-2R) level was 367 U/mL (normal: 127–582 U/mL). ECG revealed ventricular tachycardia (Figure 1A). After defibrillation, the patient recovered sinus rhythm with a first-degree atrioventricular block, complete right bundle branch block (CRBBB), and left posterior fascicular block (Figure 1B). Transthoracic echocardiography (TTE) revealed hypokinesis in the basal-anterior and basal-to-mid-septal walls of the left ventricle (LV), with an LVEF of 45%. Cardiac magnetic resonance imaging (MRI) revealed late gadolinium enhancement (LGE) and increased T₂-weighted signals in the basal-anterior and anterolateral segments and mid anteroseptum, inferoseptum and inferior segments of the LV (Figure 1C–F). LV biopsy revealed no abnormalities. Chest computed tomography revealed granular shadows in the right upper and middle lobes. The FDG-PET scan demonstrated increased FDG uptake in the heart (Figure 2A), right lung, spleen, bilateral hilar, and abdominal lymph nodes. Spleen biopsy revealed epithelioid cell granuloma, and the patient was diagnosed with sarcoidosis with spleen, lung, and heart involvement.

After implantation of an implantable cardioverter defibrillator (ICD), the patient was started on PSL at 30 mg/day. One month later, FDG-PET scan showed no FDG uptake in the heart, and the patient was discharged (Figure 2B). Her sIL-2R level decreased to 154 U/mL. The PSL dose was tapered in the outpatient setting. Subsequently, radiofrequency catheter ablation (RFCA) was performed for ventricular tachycardia due to repetitive ICD shocks.

One year later, the PSL dose was tapered to 6 mg/day without CS recurrence, as confirmed by FDG-PET. Two years later, the PSL dose was tapered to 5 mg/day. FDG-PET showed significant recurrence of FDG uptake in the heart, spleen, and bilateral hilar, abdominal, and inguinal lymph nodes (Figure 2C), although echocardiography showed no significant changes. Her sIL-2R level increased to 277 U/mL. To exclude malignant lymphoma, an inguinal lymph node biopsy was performed, which showed epithelioid cell granuloma consistent with sarcoidosis. The PSL dose was again increased to 30 mg/day with the addition of MTX 6 mg/week for recurrent CS. One month later, an

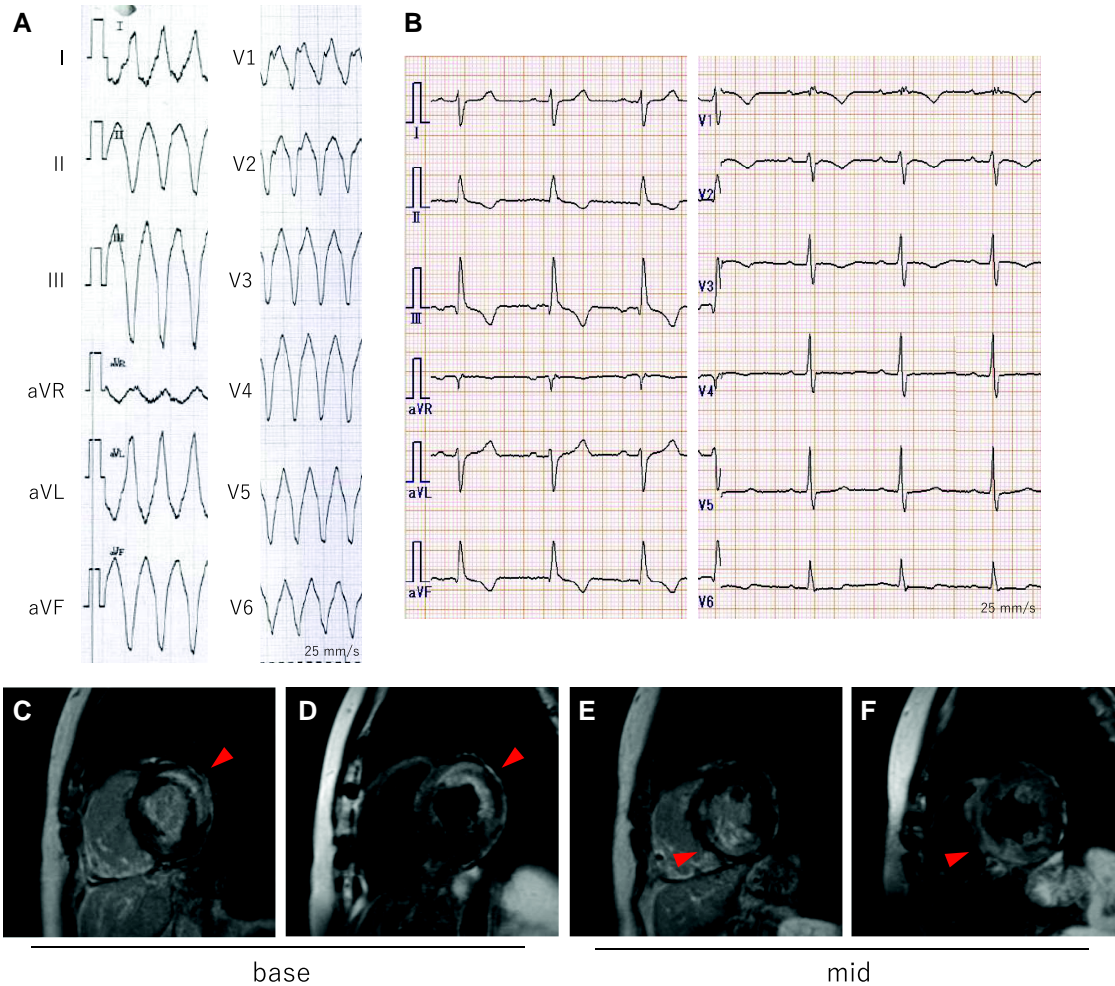


Figure 1 (Patient 1) (A) electrocardiogram (ECG) showed ventricular tachycardia at admission. (B) ECG after defibrillation. (C–F) Cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement (LGE) (C, E) and T_2 -weighted image (D, F). (C, D) was the base and (E, F) was the mid of the left ventricle (LV).

FDG-PET scan showed no FDG uptake (*Figure 2D*). Her sIL-2R level decreased to 187 U/mL. Nine months later, the PSL dose was tapered to 15 mg/day with MTX 6 mg/week, and an FDG-PET scan still showed no FDG uptake (*Figure 2E*). Her sIL-2R level decreased to 156 U/mL. Fifteen months later, the PSL dose was tapered to 12 mg with MTX at 6 mg/week, without FDG uptake in the heart.

Patient 2

A 54-year-old man with hypertension and dyslipidemia presented with shortness of breath. Two years ago, a first-degree atrioventricular block was noted on an ECG check-up. On admission, his pulse rate was 75 bpm, and his blood pressure was 118/70 mmHg. His height and weight were 167 cm and 64 kg, respectively. No abnormal heart or breath sounds were observed. His BNP level was mildly elevated to 117.2 pg/mL. His ACE and sIL-2R levels were 6.9 U/L and 324 U/mL, respectively. ECG showed sinus rhythm with first-degree atrioventricular block, CRBBB, and left anterior fascicular block (*Figure 3A*). TTE showed wall thinning of the basal interventricular septum, and LVEF was reduced to 44%. Cardiac MRI showed wall thinning of the basal septum and LGE and increased T_2 -weighted signal in the mid-anterior and lateral walls of the LV (*Figure 3C–F*). Chest computed tomography

revealed no abnormalities. FDG-PET scan demonstrated increased FDG uptake in the heart and bilateral hilar lymph nodes (*Figure 4A*). During hospitalization, intermittent complete atrioventricular block with presyncope was observed and for which a permanent pacemaker was implanted (*Figure 3B*). The patient was clinically diagnosed with CS based on a progressive conduction disorder, thinning of the basal septum, LGE, increased T_2 -weighted signal, and FDG uptake in the heart and bilateral hilar lymph nodes.

The patient was started on PSL 30 mg/day for CS. One month later, the FDG uptake disappeared (*Figure 4B*), and the patient was discharged. Eight months later, he developed frequent non-sustained ventricular tachycardia (NSVT) with palpitations, for which RFCA was performed.

Fourteen months later, under PSL 10 mg/day, the LVEF decreased to 30%, and an FDG-PET scan showed increased FDG uptake in the heart and bilateral hilar lymph nodes (*Figure 4C*). His sIL-2R level was 259 U/mL. The patient was diagnosed with recurrent CS. Seventeen months later, the pacemaker was upgraded to a cardiac resynchronization therapy defibrillator, the PSL dose was increased to 30 mg/day, and MTX 8 mg/week was added. One month after the intensification of immunosuppressive treatment, FDG uptake persisted (*Figure 4D*). The patient's sIL-2R level decreased to 202 U/mL. After 5 months, the PSL dose was tapered to 15 mg/day, and MTX was titrated to

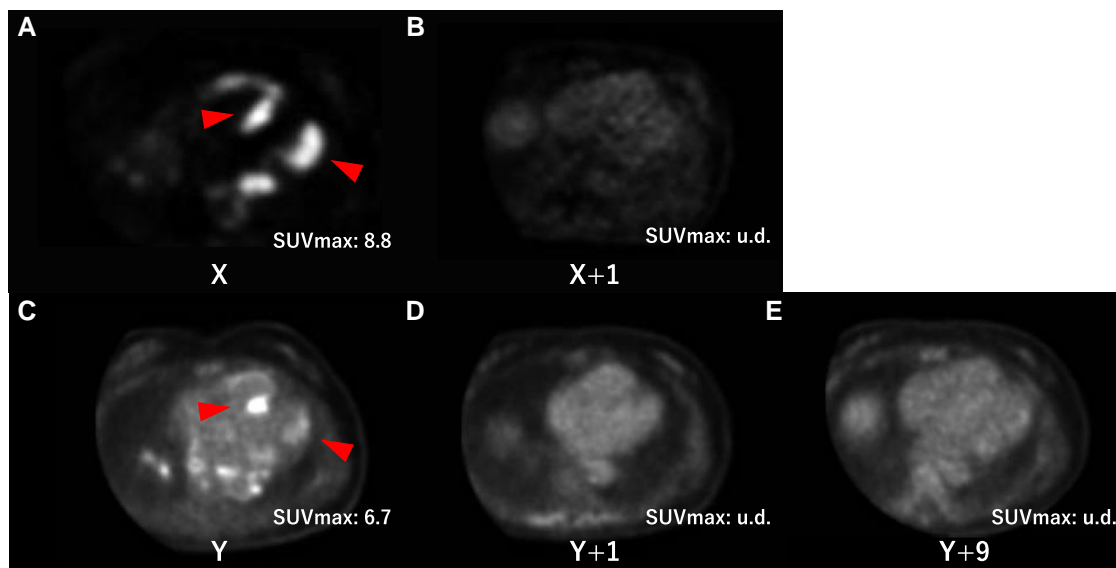


Figure 2 (Patient 1) (A) ^{18}F -fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) image in an axial plane before the initial treatment showed increased uptake in basal-septal and lateral walls of the left ventricle (LV) (arrowheads). (B) One month after the initial treatment it showed no FDG uptake. (C) Twenty-four months after the treatment it showed FDG uptake again in the same region. (D, E) One month after the intensification of immunosuppressive treatment (D), and 9 months after the treatment (E) it showed no FDG uptake. SUVmax standardized uptake value maximum. u.d. undetected.

10 mg/week. The patient's sIL-2R level decreased to 163 U/mL, but FDG uptake remained unchanged. After 8 months, throughout which PSL (15 mg/day) and MTX (10 mg/week) were continued, FDG uptake disappeared (Figure 4E). The patient's sIL-2R level was 154 U/mL.

Patient 3

A 59-year-old man with a history of uveitis presented with an abnormality in the chest radiographs, which indicated bilateral hilar lymphadenopathy (BHL), and was admitted to another hospital for thorough examination. At admission, his height and weight were 168 cm and 72 kg, respectively. No abnormal heart or breath sounds were observed. His BNP level was 7.7 pg/mL. His ACE and sIL-2R levels were 20.5 U/L and 352 U/mL, respectively. ECG showed a normal sinus rhythm (Figure 5A). TTE revealed no abnormalities. Cardiac MRI showed LGE and increased T_2 -weighted signal in the basal-anterior and lateral walls of the LV (Figure 5B, C). Chest computed tomography revealed BHL. An FDG-PET scan demonstrated increased FDG uptake in the heart and bilateral hilar lymph nodes (Figure 6A). The patient was clinically diagnosed with ocular, pulmonary and CS.

The patient was started on PSL 30 mg/day. NSVT was documented during a 1-month hospitalization. Six months later, the PSL dose was tapered to 5 mg/day, and an FDG-PET scan showed increased FDG uptake in the heart and bilateral hilar, abdominal, and left inguinal lymph nodes (Figure 6B). Cardiac MRI showed enlargement of the LGE area (Figure 5D, E). The patient's sIL-2R level decreased to 279 U/mL. Biopsy of the left inguinal lymph node showed epithelioid cell granuloma, and increased FDG uptake was confirmed as a sarcoidosis lesion. The PSL dose was increased to 10 mg/day to treat residual inflammation.

After 6 months of treatment with PSL (10 mg/day), FDG-PET scan showed additional increased FDG uptake in the same area (Figure 6C), and cardiac MRI showed further enlargement of the LGE area (Figure 5F, G) with increased T_2 -weighted signal intensity. The patient's sIL-2R level increased to 293 U/mL. The patient was diagnosed with a recurrent CS. The PSL dose was increased to 35 mg/day, and

MTX 6 mg/week was administered. One month later, the FDG uptake in the heart was mildly attenuated (Figure 6D). His sIL-2R level decreased to 266 U/mL. Four months later, the PSL dose was tapered to 20 mg/day, and MTX was titrated to 8 mg/day. An FDG-PET scan showed no FDG uptake in the heart, indicating the suppression of CS recurrence (Figure 6E). The patient's sIL-2R level further decreased to 194 U/mL. Sixteen months later, PSL was successfully tapered to 5 mg/day with MTX at 8 mg/day, without FDG uptake in the heart.

Discussion

There are no laboratory findings or imaging techniques other than FDG-PET to adequately monitor the inflammation activity in CS. In our cases, disease activity was monitored by FDG-PET during PSL treatment, and recurrence was successfully detected. FDG-PET is a useful modality for the diagnosis of CS.¹¹ However, physiological FDG uptake is one of the reasons for variation in specificity among institutions. In our hospital, physiological uptake was suppressed by fasting for 18 h, as previously reported,⁹ and pathological focal uptake was observed. In Patient 1, FDG uptake also increased in other organs and lymph nodes when CS recurrence was indicated. Patient 2 showed progression of a decreased LVEF and ventricular arrhythmia when CS recurrence was suspected. Patient 3 had LGE enlargement when FDG uptake increased during PSL treatment. These findings suggest that additional FDG uptake during PSL treatment in our three cases was not physiological uptake but CS recurrence. In contrast, the sIL-2R levels were within the normal range in these cases. However, compared to baseline, sIL-2R levels tended to decrease with treatment and increase at recurrence. The sIL-2R levels were not always consistent with the FDG-PET findings. It might be elevated during inflammation due to other diseases, infections, and haematologic malignancies. Moreover, high sIL-2R levels might be observed in patients with sarcoidosis in other organs, such as the lymph nodes, which is not a target of treatment. While using sIL-2R as a guide, FDG-PET was used to determine CS recurrence.

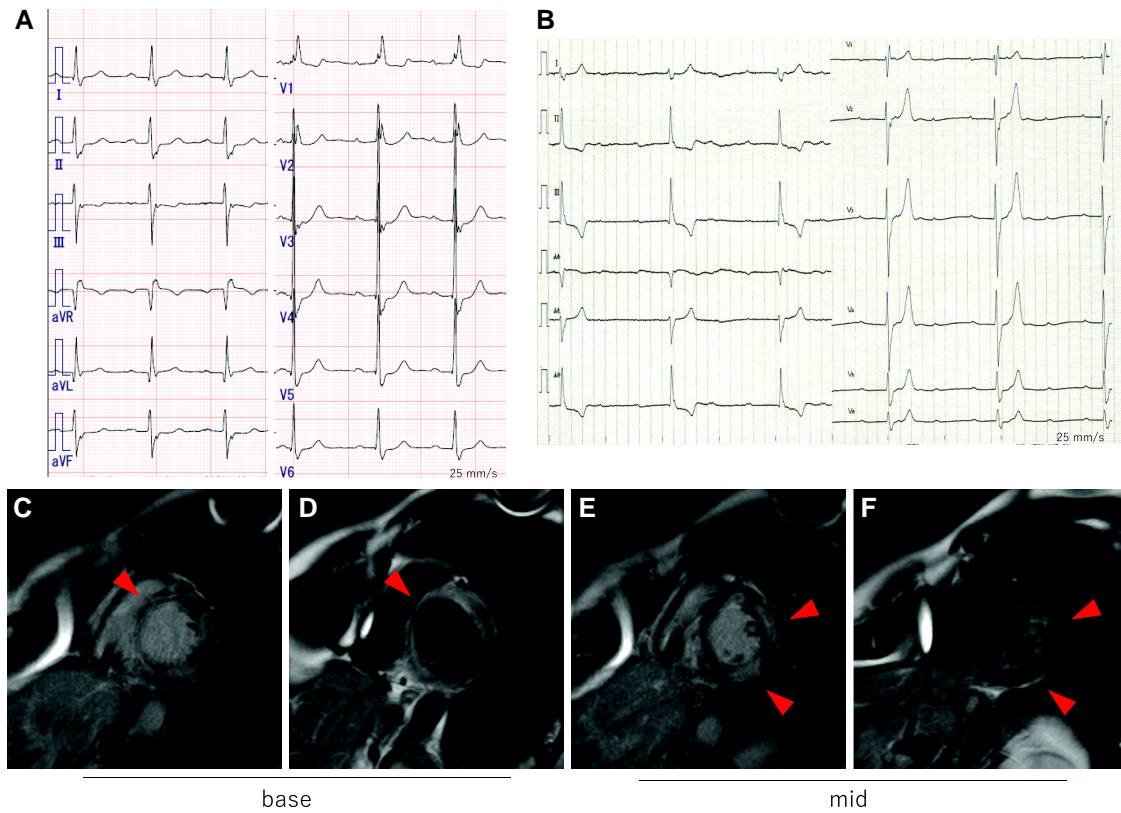


Figure 3 (Patient 2) (A) ECG at admission. (B) ECG showing complete atrioventricular block. (C–F) Cardiac MRI with LGE (C, E) and T₂-weighted image (D, F). (C, D) was the base and (E, F) was the mid of the left ventricle.

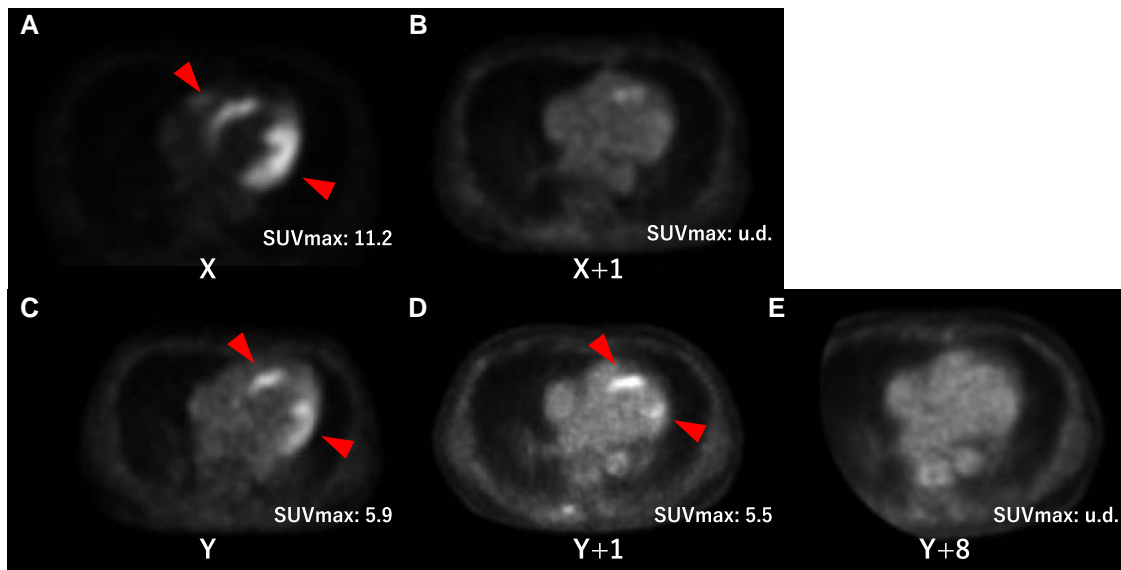


Figure 4 (Patient 2) (A) FDG-PET image in an axial plane before initial treatment showed increased uptake in basal-septal and lateral walls of the left ventricle (arrowheads). (B) One month after the initial treatment it showed no FDG uptake. (C) Fourteen months after the treatment it showed FDG uptake again in the same region. (D) One month after the intensification of immunosuppressive treatment FDG uptake remained. (E) Eight months after the treatment it showed no FDG uptake. SUVmax standardized uptake value maximum. u.d. undetected.

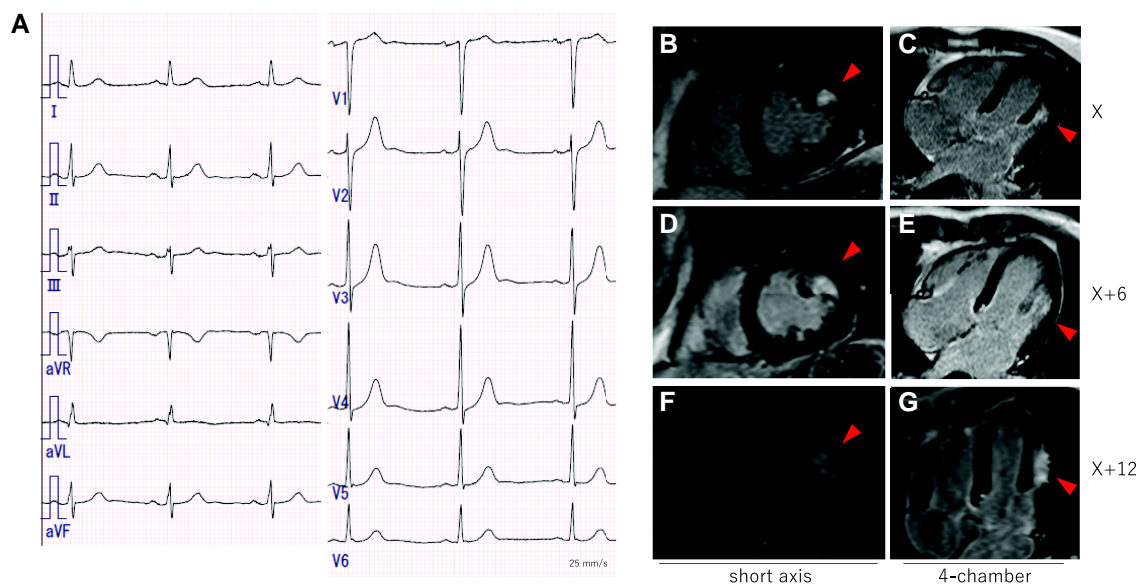


Figure 5 (Patient 3) (A) ECG at admission. (B–G) Cardiac MRI with LGE before initial treatment (B, C), 6 months after initial treatment (D, E), and at recurrence (F, G). Short axis (B, D, F) and 4-chamber view (C, E, G).

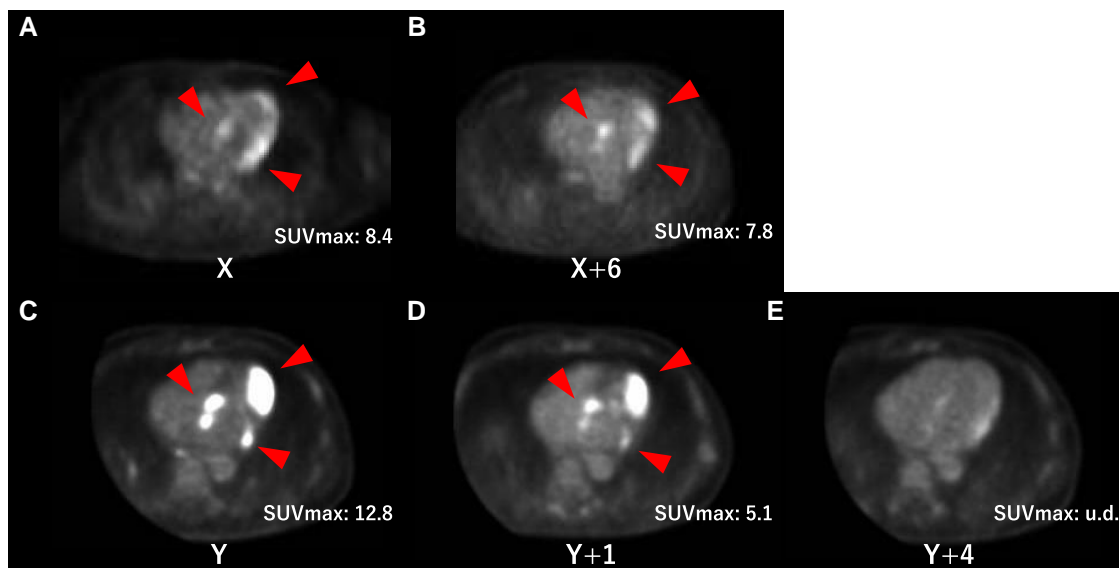
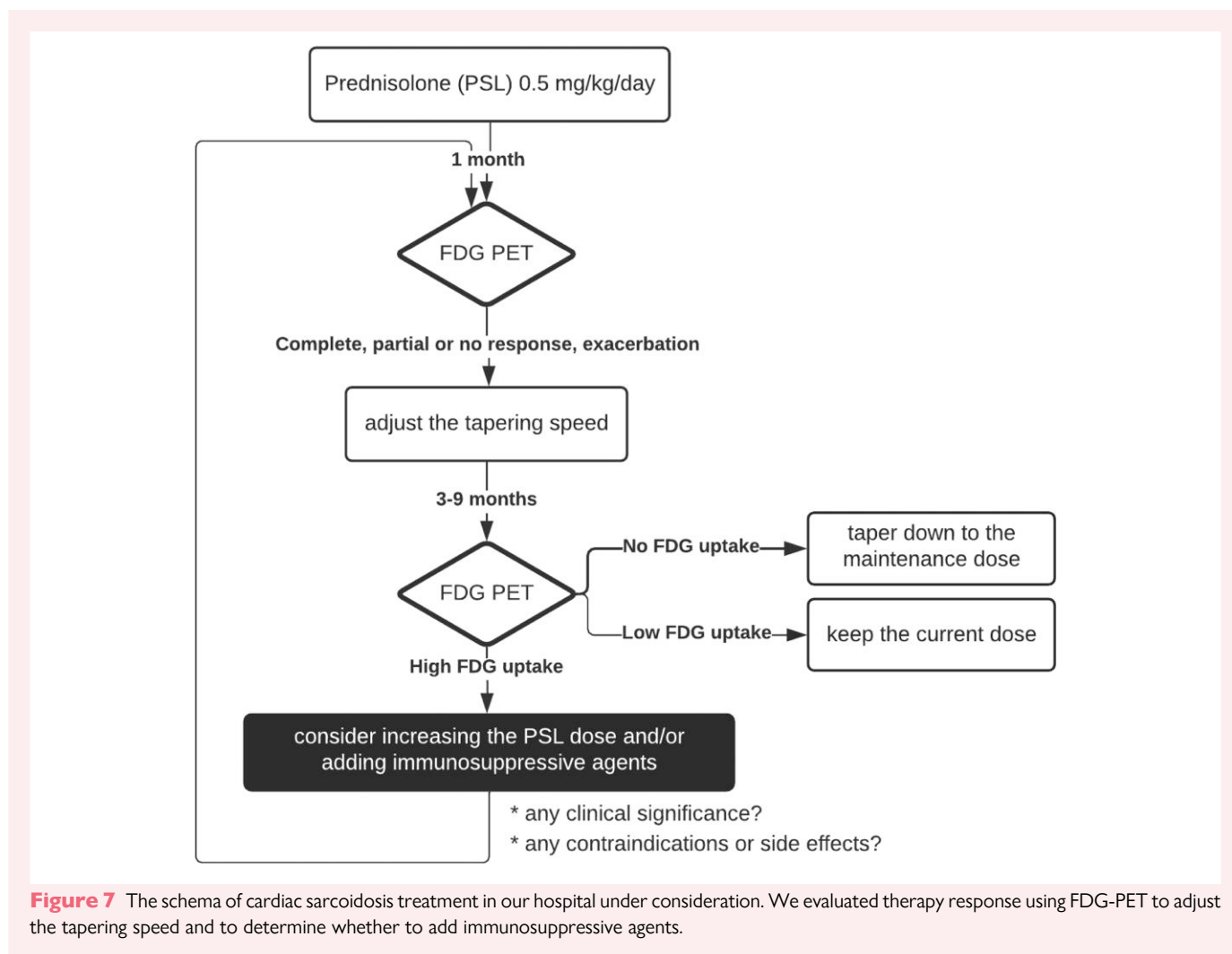


Figure 6 (Patient 3) (A) FDG-PET images in an axial plane before the initial treatment showed increased uptake in basal-septal, lateral and apical walls of the left ventricle. (B) Six months after the initial treatment FDG uptake remained. (C) Twelve months after the treatment FDG uptake exacerbated in the same region. (D) One month after the intensification of immunosuppressive treatment FDG uptake remained. (E) Four months after the treatment it showed no FDG uptake. SUVmax standardized uptake value maximum. u.d. undetected.

Nevertheless, it is unclear whether relapse of FDG uptake indicates poor prognosis and requires therapeutic intervention. A previous study reported that cardiac function improved in patients in whom FDG uptake disappeared with treatment, whereas residual FDG uptake was presumed to have a negative impact on cardiac function.¹² In our cases, Patient 2 had a decrease in LVEF and Patient 3 had an increase in the LGE area at the time of recurrence. If activity is not sufficiently

suppressed, myocardial fibrosis will be exacerbated and cardiac function will decline. Therefore, we increased the PSL dose and administered MTX as an immunosuppressive agent. We used MTX because there have been many reports including clinical studies.⁵ There have been no clinical studies of azathioprine alone in CS. Infliximab has the common side effect of infection and has been used in MTX-intolerant patients.^{7,13} Therefore, we considered the use of



azathioprine and infliximab when MTX could not be used because of renal impairment or side effects.

An FDG-PET scan was performed one month after the first PSL induction in patients 1 and 2. FDG uptake completely disappeared in these two cases, indicating that PSL would take effect in a short time. In contrast, FDG uptake disappeared 1 month after PSL re-induction in Patient 1 but remained in Patients 2 and 3. In cases of CS recurrence, PSL alone may be insufficient to fully suppress the inflammation. FDG uptake disappeared 9 months after PSL re-induction and MTX combination therapy in Patient 2 and 4 months after the same treatments in Patient 3. Based on our cases, we hypothesized that there is a reluctance to suppress inflammation in patients with CS recurrence.

In recent years, there have been many reports of MTX for CS, especially on the effects of sparing the PSL dose.^{5,6,13,14} However, there are concerns about side effects, such as pancytopenia, hepatic dysfunction, and interstitial pneumonia.¹⁵ Fortunately, we experienced no side effects of MTX in these cases. Currently, PSL is used alone to suppress inflammation in most cases.¹⁴ However, when we observed recurrent CS, we found that treatment was sometimes more difficult during recurrence than during initial treatment. Therefore, we believe that a combination of PSL and other immunosuppressive agents should be considered, at least in cases of recurrence. The FDG accumulation

and the LGE region increased under PSL 5 mg/day alone in Patient 3. However, the PSL dose could be reduced to a maintenance dose of 5 mg/day without recurrence by adding MTX 8 mg/week. This result may indicate the steroid-sparing effect of MTX. In contrast, the PSL dose was still high, even after the addition of MTX, for fear of relapse in Patient 1 and 2.

Finally, we proposed the model to adjust the PSL dose and to determine whether to add immunosuppressive agents by monitoring the therapy response with FDG-PET (Figure 7). FDG-PET was used to evaluate therapy response 1 month after PSL introduction, if possible, to adjust the tapering speed. Approximately 3–9 months later, FDG-PET was performed again to assess therapeutic efficacy and to determine whether to taper down to the maintenance PSL dose, keep the current PSL dose, or increase the PSL dose and add immunosuppressive agents. It is better to balance the clinical significance with the side effects of immunosuppressive agents.

Conclusions

FDG-PET is a useful modality for detecting CS recurrences. We successfully treated recurrent CS with PSL and MTX combination therapy and adequately monitored the inflammation using FDG-PET. Serial

FDG-PET scans indicated that it might be more difficult to suppress inflammation during recurrence than during the initial treatment.

Lead author biography



Masato Ishizuka is a physician in the Department of Cardiovascular Medicine, The University of Tokyo Hospital. He is a post-doc researcher and engaged in clinical and basic research of heart failure, especially about cardiac magnetic resonance imaging and cardiac sarcoidosis.

Supplementary material

[Supplementary material](#) is available at *European Heart Journal – Case Reports* online. We provided the initial and follow-up echocardiography images in Patient 1 (videos 1 and 2) and Patient 2 (videos 3 and 4), and cine images of cardiac MRI in Patient 3 (videos 5 and 6) in the [Supplementary materials](#).

Slide sets: A fully edited slide set detailing this case and suitable for local presentations is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report was obtained from the patients in line with the COPE guidance.

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