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CASE REPORT
Cardiac imaging

Effectiveness of methotrexate as a second-line treatment for cardiac sarcoidosis assessed via ^{18}F-FDG PET: a case report

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Background Although methotrexate has been widely used as a second-line therapy for cardiac sarcoidosis (CS), it is not clear if it has a direct anti-inflammatory effect.

Case summary A 65-year-old man presented to our hospital with symptomatic ventricular tachycardia (VT). After cardioversion, electrocardiography showed a first-degree atrioventricular block with a right bundle branch block, and transthoracic echocardiography revealed left ventricular dilatation. After extensive investigations, including fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), the patient was diagnosed with CS according to the Japanese Circulation Society guidelines. After the implantation of a transvenous implantable cardioverter defibrillator, corticosteroid therapy was introduced at a starting dose of 30 mg/day. After corticosteroid therapy was tapered to a maintenance dose of 10 mg/day, he had an uneventful clinical course without symptoms for the 1st year after hospital discharge. However, symptomatic VT recurred and ^{18}F-FDG PET showed abnormal patterns of cardiac FDG uptake. Although he was treated with corticosteroid therapy once more, which was gradually up-titrated to a dose of 20 mg/day over a 1-month period, myocardial uptake of ^{18}F-FDG PET remained unchanged. As the patient was considered steroid refractory, second-line treatment with 6 mg/week of methotrexate was introduced, whereas maintaining the dose of corticosteroid therapy at 20 mg/day. After 1 month, ^{18}F-FDG PET showed remarkable reduction in FDG uptake, and the patient had a good clinical course without further episodes of arrhythmia or other symptoms during an 8-month follow-up.

Discussion Methotrexate may have a direct anti-inflammatory effect in patients with CS refractory to regular corticosteroid therapy.

Keywords Cardiac sarcoidosis • Methotrexate • ^{18}F-fluorodeoxyglucose positron emission tomography • Immunosuppressive therapy

ESC Curriculum 2.1 Imaging modalities • 6.5 Cardiomyopathy • 5.6 Ventricular arrhythmia

Learning points

- In patients with cardiac sarcoidosis, if corticosteroid therapy alone is insufficient to control disease activity, methotrexate is a potentially effective second-line treatment option.
- Serial fluorine-18 fluorodeoxyglucose positron emission tomography examination is a potentially useful method to evaluate the therapeutic effects of immunosuppressive agents in patients with cardiac sarcoidosis.

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Introduction

Sarcoidosis is a complicated disease with heterogeneous clinical presentations that can affect virtually any organ, including the heart, with non-caseating granulomas that account for most of the morbidity and mortality associated with this disease.[1,2]

For patients with cardiac sarcoidosis (CS), corticosteroids are generally considered as a first-line therapy, and methotrexate is an accepted corticosteroid-sparing second-line agent in patients refractory to corticosteroids.[3] However, whether the addition of methotrexate can directly improve inflammation is unclear. Fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is recommended not only for the diagnosis of CS but also for the assessment of the efficacy of immunosuppressive therapies, including corticosteroids or methotrexate.[3,4] Herein, we report a case of CS showing remarkable reduction in FDG uptake after the addition of methotrexate to corticosteroid therapy.

Timeline

Time period	Event
February 2020	• Patient was admitted with ventricular tachycardia (VT) with cardiac dysfunction • Transthoracic echocardiography showed left ventricular dilatation with a reduced left ventricular ejection fraction of 25% • Coronary angiography revealed no significant stenosis • Cardiac magnetic resonance imaging revealed increased late gadolinium enhancement extending from the basal anteroseptal and inferoseptal areas to the anteroapex and inferoapex of the left ventricle • Patient was diagnosed with cardiac sarcoidosis based on fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) findings • Corticosteroid therapy (30 mg/day, oral) was started and tapered to 20 mg/day at discharge
May 2020	• Corticosteroid therapy was tapered to 10 mg/day in the outpatient setting • A satisfactory clinical course was observed
February 2021	• Symptomatic VT recurred • ^{18}F-FDG PET showed increased FDG uptake • Corticosteroid therapy was up-titrated to 20 mg/day
May 2021	• ^{18}F-FDG PET showed increased FDG uptake • Methotrexate (6 mg per os weekly) was prescribed
June 2021	• ^{18}F-FDG PET revealed a remarkable improvement in FDG uptake
January 2022	• No arrythmia has been observed, and the patient is currently symptom free

Case presentation

A 65-year-old man with no past medical history presented to our hospital with general fatigue and loss of appetite. His vital signs were as follows: blood pressure, 145/119 mm Hg; heart rate, 138 bpm; body temperature, 35.7°C; respiratory rate, 14 breaths/min; and oxygen saturation, 98% on room air on arrival. Physical examination demonstrated tachycardia with regular rhythm and no signs of cardiac congestion such as jugular vein distension or lower leg oedema. Heart auscultation revealed no murmurs or ventricular gallop. Initial laboratory evaluation revealed hyponatremia (Na: 121 mmol/L; normal, 135–145 mmol/L), an elevated high-sensitivity cardiac troponin T level at 0.374 ng/mL (normal, <0.013 ng/mL), an NT-proBNP level of 13 604 pg/mL (normal, <125 pg/mL), elevated liver enzyme levels (aspartate aminotransferase: 1391 U/L, normal, 5–37 U/L; alanine aminotransferase: 2092 U/L, normal, 6–43 U/L), and a C-reactive protein level of 3.98 mg/dL (normal <0.3 mg/dL).

Chest radiography showed cardiac dilatation and no active lung lesions. On admission, electrocardiography revealed ventricular tachycardia (VT) (*Figure 1*). Cardioversion was performed and subsequent electrocardiography showed a first-degree atrioventricular block with a right bundle branch block, and transthoracic echocardiography revealed left ventricular dilatation (end-diastolic dimension,

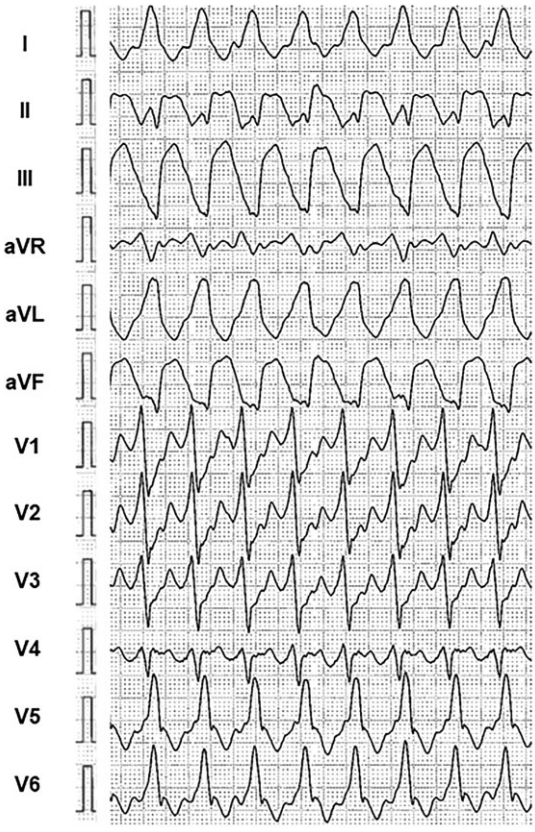

Figure 1 Initial electrocardiography showing wide QRS tachycardia with a heart rate of 134 bpm.

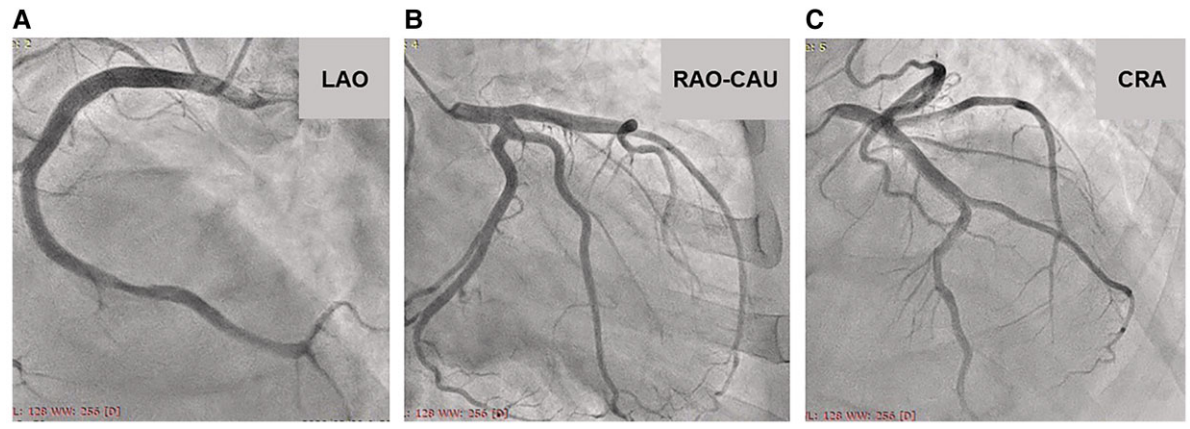

Figure 2 Coronary angiography showing no significant stenosis of the coronary arteries. (*A*) shows the left anterior oblique view of the right coronary artery; (*B*) and (*C*) show the (*B*) caudal right anterior oblique view and (*C*) cranial view of the left coronary artery. LAO, left anterior oblique view; RAO-CAU, caudal right anterior oblique view; CRA, cranial view.

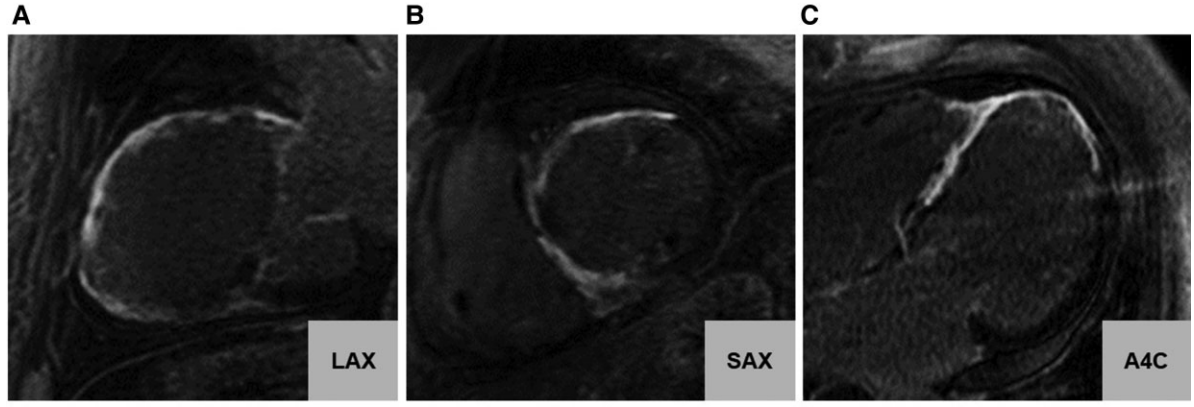

Figure 3 Cardiac magnetic resonance imaging displaying increased late gadolinium enhancement extending from the basal anteroseptal and inferoseptal areas to the anteroapex and inferoapex of the left ventricle. (*A*), (*B*), and (*C*) show the long-axis, short-axis, and apical four-chamber views, respectively. LAX, long-axis view; SAX, short-axis view; A4C, apical four-chamber view.

68 mm) with a reduced left ventricular ejection fraction (LVEF) of 25% (see Supplementary material online, Video S1). Left ventricular hypertrophy was not observed.

After cardioversion, the patient's vital signs improved gradually, and his symptoms resolved. Oral medication, including amiodarone, renin-angiotensin system inhibitors, and beta blockers, was administered gradually. Coronary angiography revealed no significant stenosis (*Figure 2*). Although endomyocardial biopsy was performed from the right ventricle, histological findings were non-specific. As we suspected non-ischaemic cardiomyopathy, including dilated cardiomyopathy or CS, cardiac magnetic resonance (CMR) imaging and ^{18}F-FDG PET were performed as further investigations. Cardiac magnetic resonance imaging revealed increased transmural late gadolinium enhancement extending from the basal anteroseptal and inferoseptal areas to the anteroapex and inferoapex of the left ventricle (*Figure 3*). ^{18}F-FDG PET showed abnormal heterogeneous FDG uptake in the left ventricle without significant uptake in the right ventricle (*Figure 4A*).

According to the results of these investigations, the patient was diagnosed with CS based on the Japanese Circulation Society 2016 Guideline on Diagnosis and Treatment of Cardiac Sarcoidosis.[4] He underwent a transvenous implantable cardioverter defibrillator implantation, after which corticosteroid therapy was commenced at a starting dose of 30 mg/day. The prescribed medications at discharge comprised carvedilol (12.5 mg), enalapril (2.5 mg), spironolactone (25 mg), and amiodarone (200 mg). During the 6-week admission, corticosteroid therapy was tapered, with a dose of 20 mg prescribed at discharge.

After corticosteroid therapy was tapered to a maintenance dose of 10 mg/day during outpatient follow-up, the patient had an

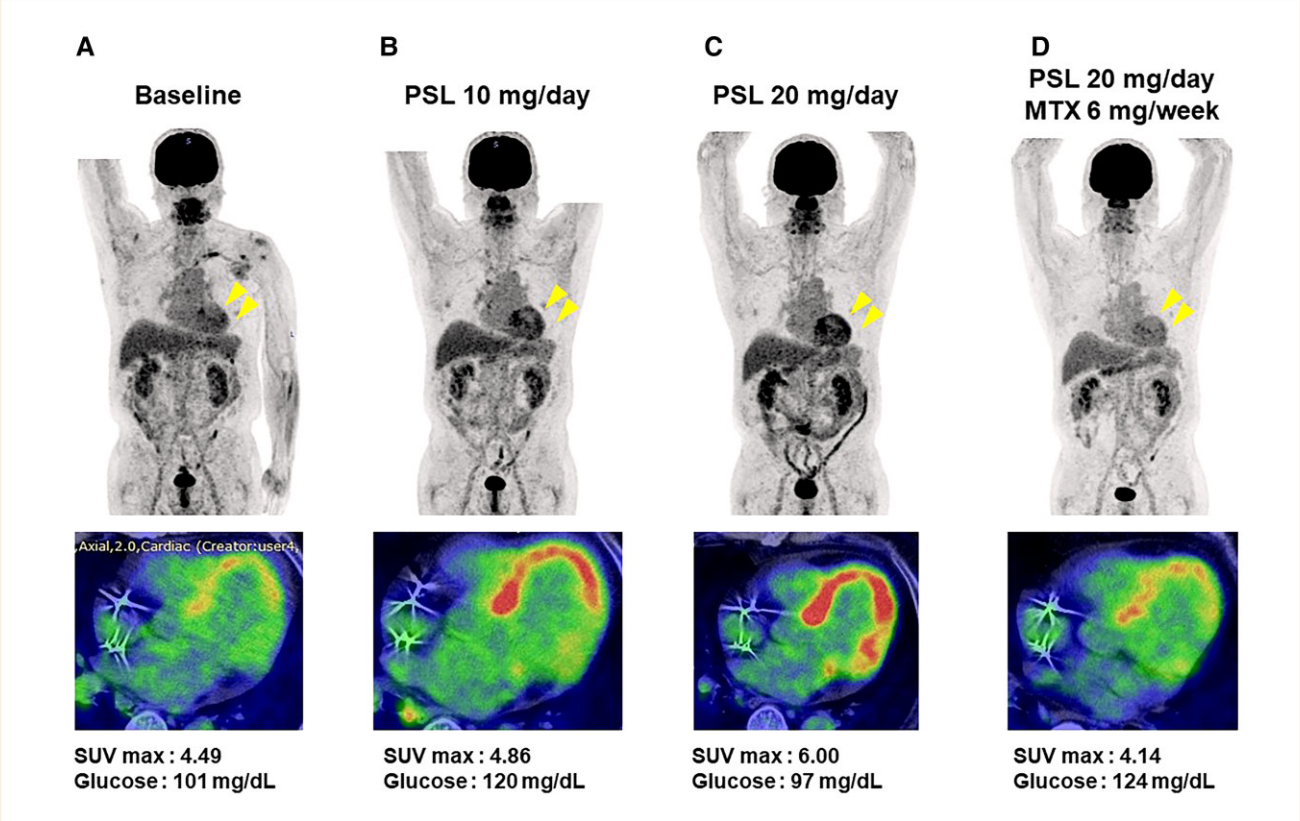

Figure 4 Serial changes in ^{18}F-fluorodeoxyglucose (FDG) uptake. (*A*) shows the baseline FDG uptake without corticosteroid treatment; (*B*) shows increased FDG uptake with a corticosteroid dose of 10 mg/day; (*C*) displays increased FDG uptake despite up-titration of the corticosteroid dose to 20 mg/day; and (*D*) shows significantly decreased FDG uptake with the addition of methotrexate to a stable corticosteroid dose. FDG, ^{18}F-fluorodeoxyglucose; MTX, methotrexate; PSL, prednisolone; SUV, standardized uptake value.

uneventful clinical course without any symptoms. Transthoracic echocardiography revealed no significant change in structure (left ventricular end-diastolic dimension: 66 mm) or function (LVEF: 24%). A year after discharge, symptomatic VT recurred and ^{18}F-FDG PET revealed increased FDG uptake from the cardiac basal anteroseptal region to the apex of the left ventricle without significant uptake in the right ventricle (*Figure 4B*). Initially, corticosteroid therapy was gradually up-titrated to a dose of 20 mg/day over a 1-month period. However, 2 months after corticosteroid therapy was up-titrated, the patient reported general fatigue, and ^{18}F-FDG PET was performed, showing increased FDG uptake (*Figure 4C*). His LVEF remained unchanged (25%).

As the patient was now considered steroid refractory, second-line treatment was introduced with methotrexate 6 mg per os weekly without changing the dose of the corticosteroid and heart failure medications, including carvedilol (17.5 mg/day), sacubitril/valsartan (100 mg/day), eplerenone (50 mg/day), dapagliflozin (10 mg/day), and azosemide (15 mg/day). At 1 month follow-up, although transthoracic echocardiography showed that the LVEF remained unchanged, ^{18}F-FDG PET demonstrated a remarkable reduction in myocardial uptake (*Figure 4D*). The patient's laboratory tests revealed normal levels of high-sensitivity cardiac troponin T, NT-proBNP, and C-reactive protein. His clinical course was uneventful with no reported symptoms or arrythmia for the following 8 months.

Discussion

Although methotrexate is an accepted second-line therapy option for CS, there is currently very limited evidence of its efficacy. A clinical study involving 36 participants with CS revealed that patients receiving a combination of corticosteroid and immunosuppressive agents, including methotrexate, had a lower incidence of relapse than those receiving corticosteroid therapy alone.[5] Another study including 17 patients with CS found that patients who were treated with a combination of low-dose corticosteroid therapy and methotrexate had improved LVEF and NT-proBNP levels compared with those treated with corticosteroid therapy alone.[6] Although these studies highlight the potential benefits of methotrexate therapy, they included small numbers of patients with CS, and no randomised controlled studies have been performed. A multicentre randomized controlled trial evaluating the optimal regimen for CS (a standard dose of corticosteroid therapy vs. a low dose of corticosteroid and methotrexate administration) is ongoing.[7]

Imaging modalities, such as CMR imaging or ^{18}F-FDG PET, may be useful for assessing the efficacy of methotrexate in patients with CS. In a case report, after the addition of methotrexate as a second-line therapy for a patient with refractory CS, CMR imaging revealed significant improvements in cardiac function and late gadolinium enhancement.[8] Regarding ^{18}F-FDG PET, a study involving 23 patients

with CS reported a reduction in FDG uptake that was significantly associated with improvement in the LVEF.[9] However, there are currently no studies showing that methotrexate directly suppresses inflammation, even though its main mechanism of action in the treatment of CS is considered to be its anti-inflammatory properties.[10] To the best of our knowledge, this is the first report to clearly demonstrate the positive effect of methotrexate on inflammation of the myocardium based on ^{18}F-FDG PET examination.

Although the treatment for CS has not been fully elucidated, methotrexate may be a promising option. Serial ^{18}F-FDG PET examination is a potential tool for assessing the therapeutic efficacy of treatments used in patients with refractory CS. Only one case report has documented the efficacy of methotrexate in patients with steroid resistant CS using CMR imaging.[8] However, the clinical value of ^{18}F-FDG PET for this patient group remains unclear. We recommend careful observation with routine follow-up ^{18}F-FDG PET 3–4 months after initiating immunosuppressive therapy, especially for patients with heterogenous FDG uptake, which is associated with worse clinical outcomes.[11] Whilst we have demonstrated an improvement in our patient, larger clinical trials are required to validate these results.

Lead author biography

Taishi Dotare received the MD degree from Juntendo University, Tokyo, Japan in 2016. At present, he works as Cardiologist at the Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine in Japan. His research interest is mainly focused on heart failure and cardiomyopathy. Outside of work, he enjoys playing tennis. He loves his wife 'minori' and daughter 'sayumi.'

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for the submission and publication of this case report, including images and associated text, has been obtained from the patient in line with COPE guidelines.

Conflict of interest: None declared.

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