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【 CASE REPORT 】

A Patient with Cardiac Sarcoidosis in Whom an Abnormal Myocardial Uptake of Fluorine-18 Fluorodeoxyglucose and Sustained Ventricular Tachycardia Recurred 3.5 Years after Discontinuing Oral Corticosteroid Therapy

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Abstract:
We herein report a woman diagnosed with cardiac sarcoidosis (CS) based on the presence of epithelioid granulomas in non-cardiac organs and clinical findings including sustained ventricular tachycardia (VT) and cardiac dysfunction. She stopped oral corticosteroid after 4 years of treatment, and an abnormal myocardial uptake of fluorine-18 fluorodeoxyglucose and sustained VT recurred 3.5 years later. There is no consensus concerning whether or not corticosteroid therapy should be discontinued in the treatment of CS. As a relapse of sarcoidosis-related inflammation may be associated with life-threatening arrhythmia, some patients should continue corticosteroid therapy, even at low doses.

Key words: life-threatening arrhythmias, ventricular dysfunction, disease activity, diagnostic imaging

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Introduction

Pharmacotherapy for cardiac sarcoidosis (CS) mainly consists of immunosuppressants that are used for controlling inflammation, thereby improving clinical symptoms. Corticosteroids are widely used as first-line immunosuppressants for patients with CS. Corticosteroid therapy should be considered for patients with CS who have high-grade atrioventricular block, ventricular arrhythmias, or cardiac dysfunction (1, 2). Although no placebo-controlled, prospective studies have been reported, clinical experience in patients showing improvement in clinical findings after starting corticosteroids has suggested their benefits.

However, there is no consensus on whether or not corticosteroid therapy should be discontinued in the long-term treatment of CS. We herein report the clinical course of a patient with CS who stopped oral corticosteroid after 4 years of treatment and then showed an abnormal myocardial uptake of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) on positron emission tomography (PET) and recurrence of sustained ventricular tachycardia (VT) 3.5 years later. As a relapse of sarcoidosis-related inflammation may be associated with life-threatening arrhythmia, the continuation of corticosteroid therapy should be recommended in some patients.

Case Report

Our patient is a woman in her 60s with a history of hepatitis B. In 2009 (54 years old), left hilar lymphadenopathy was detected during a routine health checkup. Blood chemistry revealed an angiotensin-converting enzyme (ACE) level of 24.3 U/L (reference range: 8.3 to 21.4) and a soluble interleukin-2 receptor (sIL-2R) level of 903 U/mL (reference range: 145 to 519), showing increases in ACE and sIL-2R levels. ^{18}F-FDG PET revealed abnormal tracer accumulation in the bilateral supra-clavicle lymph nodes, mediastinal lymph nodes, bilateral hilar lymph nodes, and the left upper lung lobe. As non-caseating epithelioid cell granuloma was found in biopsy samples from mediastinal lymph nodes and

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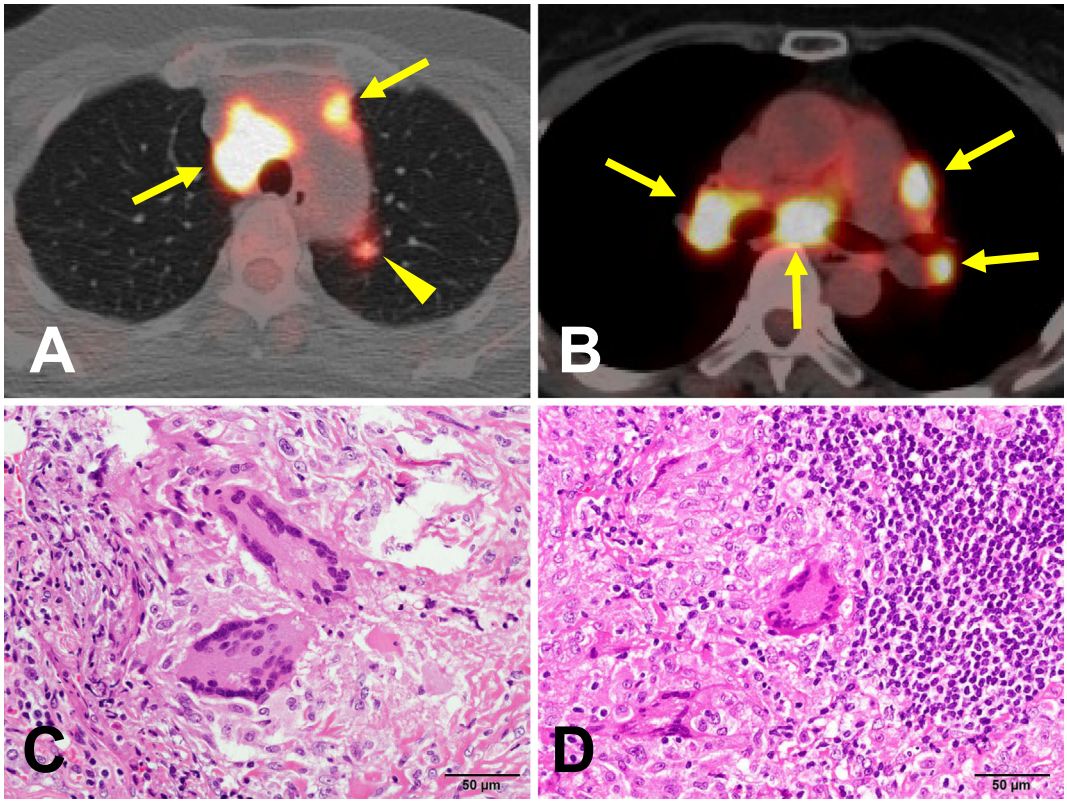

Figure 1. **^{18}F-FDG PET and histopathological findings in 2009. An abnormal FDG uptake is observed in the left upper lung (S1+2) (Arrowhead in A) and mediastinal lymph nodes (Arrows in A and B). Noncaseating epithelioid cell granulomas containing multinucleated giant cells are detected in samples from partial lobectomy of the left upper lung (C) and a mediastinal lymph node biopsy (D). C and D, Hematoxylin and Eosin staining; scale bar=50 μm.**

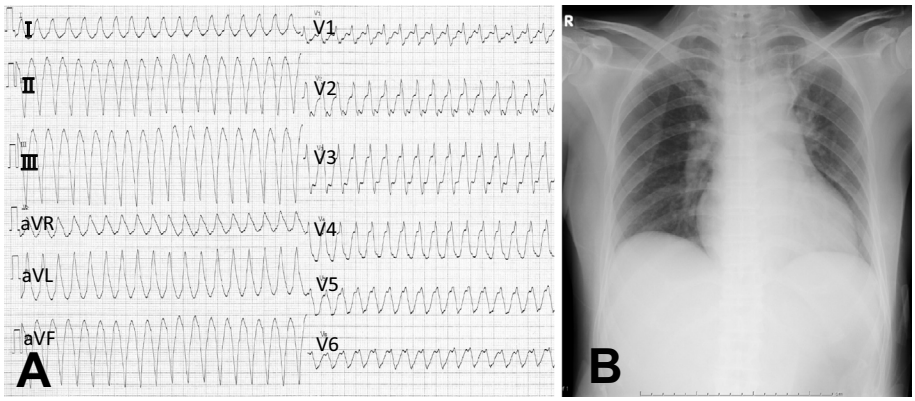

Figure 2. **An electrocardiogram (A) and chest X-ray (B) at the time of emergency admission in 2012. Sustained ventricular tachycardia is documented (A), and cardiomegaly with hilar lymphadenopathy is observed (B).**

pulmonary tissue samples from partial left lung lobectomy (S1+2) (Fig. 1), a definitive histological diagnosis of lung and lymph node sarcoidosis was made. She started visiting a respiratory medicine clinic regularly.

In April 2012, she felt chest tightness while exercising at a gym. She then slipped into a shock status and was transferred to an emergency department. At the emergency department, she was found to have sustained VT (Fig. 2), which returned to sinus rhythm after electrical defibrillation. Cardiac catheterization conducted at the emergency department revealed no significant coronary stenosis. She visited our clinic to undergo a detailed examination to specify the cause of VT and receive treatment.

On an examination, her height was 156 cm, weight 48 kg, body temperature 36.0℃, respiratory rate 18/min, blood pressure 100/60 mmHg, and heart rate 66 bpm. No cardiac murmurs or loud heart sounds were present. No abnormal findings were found in the lungs, abdomen, or nerves. Blood

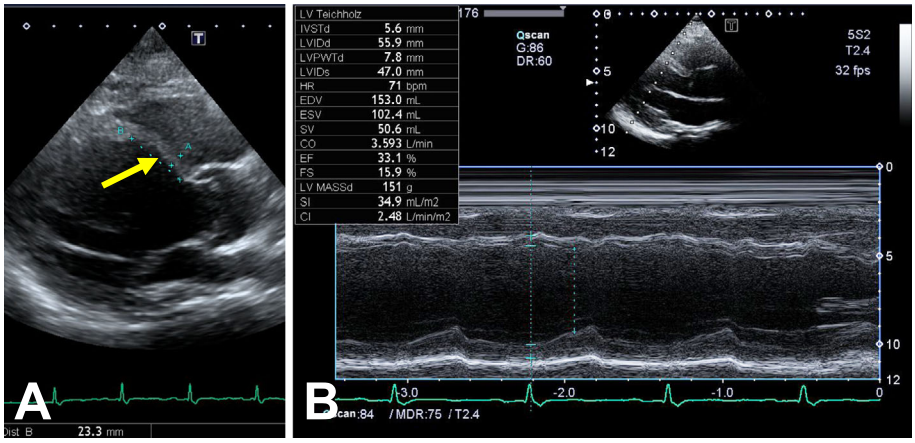

Figure 3. **An echocardiogram on admission in 2012. Left ventricular dilatation with a reduced systolic function (Dd/Ds 56/47 mm; LVEF 33%) is shown. Asynergy with thinning is present on the basal antero-septal wall (arrow). A: Parasternal long-axis view, end-diastole, B: M-mode scan of the left ventricle. Dd: left ventricular dimension in end-diastole, Ds: left ventricular dimension in end-systole, LVEF: left ventricular ejection fraction**

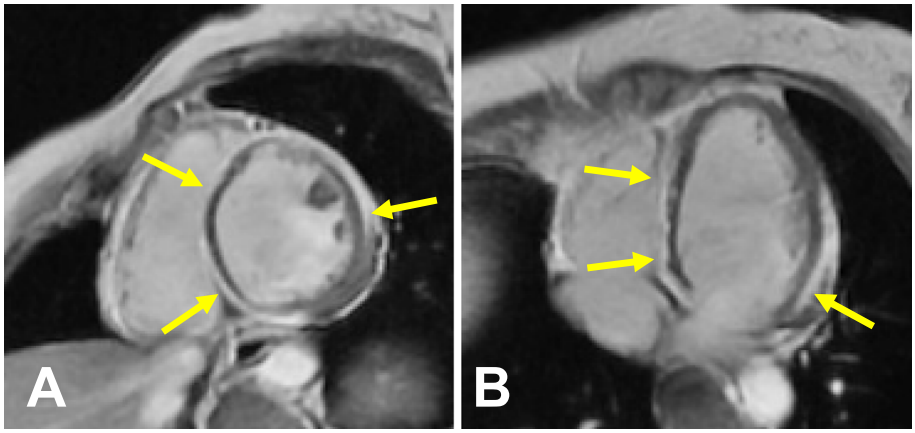

Figure 4. **Cardiac magnetic resonance imaging (MRI) on admission in 2012. Subepicardial to midwall late gadolinium enhancement (LGE) is present in almost the entire part of the left ventricle (arrows). A: short-axis view, B: four-chamber view.**

chemistry revealed a brain natriuretic peptide (BNP) level of 181 pg/mL (reference range: <18.4), and an ACE level of 15.3 U/L, and a sIL-2R of 771 U/mL, showing an increase in BNP and sIL-2R. On chest X-ray, bilateral hilar lymphadenopathy (BHL) was found. An electrocardiogram (ECG) showed sinus rhythm. Echocardiography showed left ventricular enlargement and left ventricular dysfunction, with a left ventricular end-diastolic dimension (Dd)/left ventricular end-systolic dimension (Ds) of 56/47 mm, and left ventricular ejection fraction (LVEF) of 33%, as well as regional asynergy in the antero-septal wall (Fig. 3). Cardiac magnetic resonance imaging (MRI) showed late gadolinium enhancement (LGE) mainly in the epicardial side of almost all parts of the left ventricle (Fig. 4). She did not undergo an endomyocardial biopsy. Based on the presence of sustained VT and findings of echocardiography and cardiac MRI, a diagnosis of cardiac sarcoidosis was made.

She started corticosteroid therapy at an initial dose of 30 mg/day of prednisolone, which was then tapered. She also started taking oral amiodarone 200 mg/day and underwent implantable cardioverter defibrillator (ICD) implantation (Fig. 5). An oral beta-blocker was not introduced at that time because of her relatively low blood pressure and to keep the heart rate with her own heart beats, as much as possible, thereby avoiding the pacing rhythm that could possibly lead to a lower cardiac output due to ventricular dyssynchrony. She continued outpatient treatment with maintenance prednisolone therapy at 5 mg/day and amiodarone 100 mg/day. Four years later, the prednisolone treatment was discontinued at her request and out of consideration of the risk of reactivation of hepatitis B virus. In March 2018, two years after the discontinuation of prednisolone therapy, sustained VT developed again. ^{18}F-FDG PET revealed no abnormal tracer accumulation in the lymph nodes or heart (Fig. 6), but echocardiography showed left ventricular enlargement and left ventricular systolic dysfunction with a

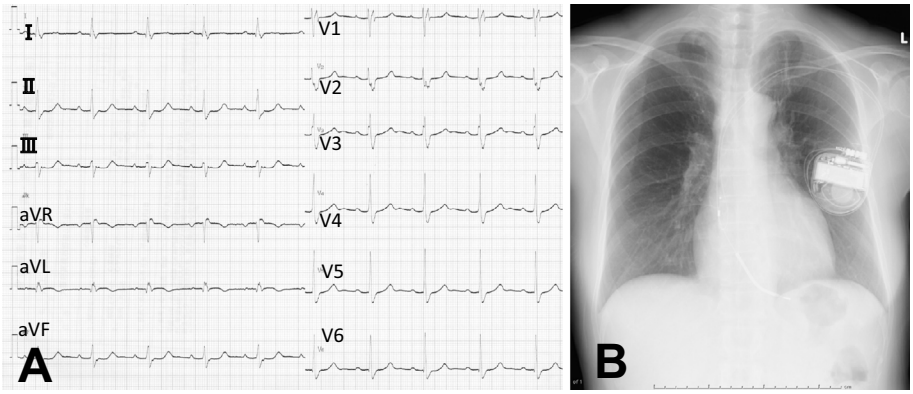

Figure 5. **Electrocardiogram and chest X-ray findings after medical treatment followed by ICD implantation in 2012. Sinus rhythm with complete right bundle branch block is present (A). Cardiomegaly observed on admission is improved (B).**

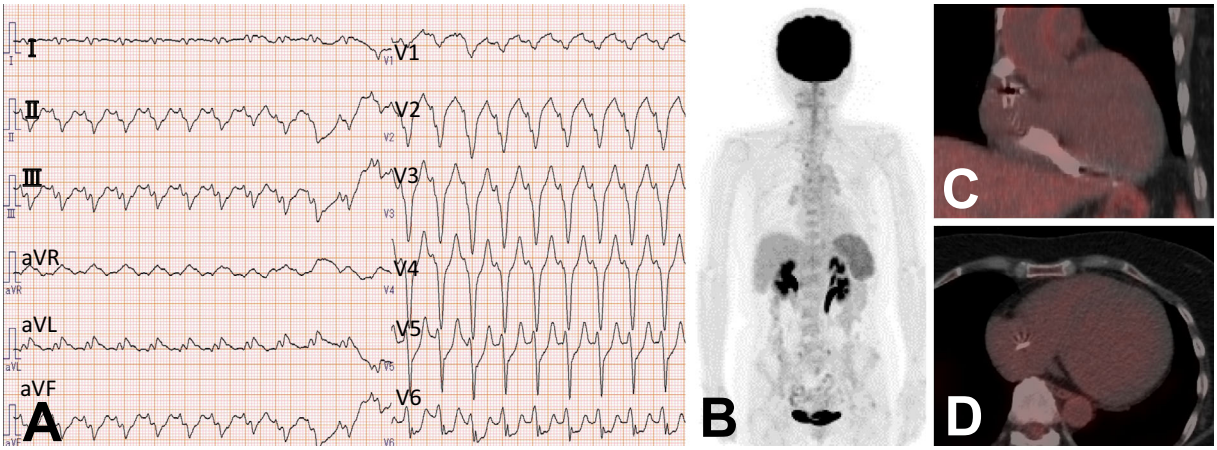

Figure 6. **Electrocardiogram and ^{18}F-FDG PET findings in March 2018. Sustained VT is present (A). After corticosteroid therapy initiated, the abnormal tracer uptake in the heart and lymph nodes disappeared completely by the time of imaging in 2018 (B, C, D). B: maximum intensity projection, C: frontal-axis view, D: horizontal-axis view.**

Dd/ Ds of 66/59 mm and a LVEF of 23%. She started taking oral beta-blocker therapy and was carefully followed up.

In August 2019, after about 1.5 years of beta-blocker therapy, she had an episode of sustained VT again and underwent ^{18}F-FDG PET, which revealed abnormal tracer accumulation (Fig. 7) showing a relapse of inflammation. She restarted corticosteroid therapy. The serial changes in clinical and laboratory findings are presented in the Table.

Discussion

Patients with CS have a high risk of ventricular arrhythmias, which may lead to sudden death. The risk of lethal arrhythmias is particularly high in patients with a history of life-threatening arrhythmias as well as in those with cardiac dysfunction even when they have no history of life-threatening arrhythmias (3-5). ICD implantation is recommended for patients with an LVEF of <35% (6, 7). As the present patient experienced sustained VT, the use of an ICD was a Class I recommendation according to various treatment guidelines for CS (1, 2, 8). As her left ventricular systolic dysfunction progressed during pharmacotherapy, as shown by the reduction in the LVEF to <35%, we should also have considered using cardiac resynchronization therapy (CRT), which is a Class IIb recommendation (1, 2).

When cardiac dysfunction progresses or life-threatening arrhythmias, such as VT, and high-grade atrioventricular block develop in patients receiving corticosteroids for several years for the treatment of CS, it is important to determine whether these issues have resulted from a relapse of inflammation or the progression of myocardial fibrosis that occurs during the healing process, and appropriate treatment strategies should then be implemented. At present, the most useful measures of the activity of sarcoidosis-associated inflammation include the blood levels of ACE and sIL-2R and the findings of ^{18}F-FDG PET.

The present patient experienced another episode of sustained VT two years after discontinuing corticosteroid ther-

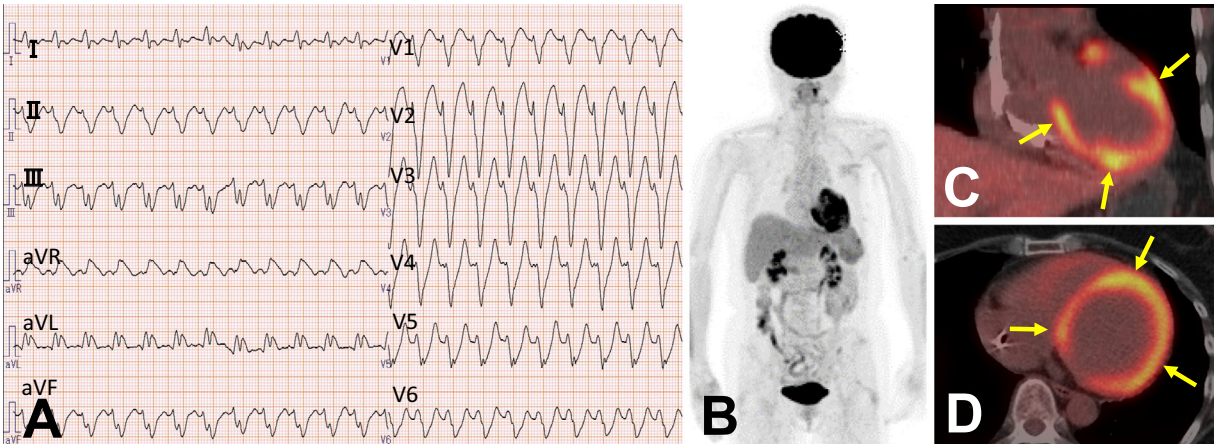

Figure 7. **Electrocardiogram and ^{18}F-FDG PET findings in August 2019. Sustained VT recurred (A). The abnormal focal uptake at the basal lesion of the interventricular septum and antero-lateral wall as well as the inferior wall of the left ventricle is obvious (arrows) (C and D). No abnormal uptake is seen in the lymph nodes (B). B: maximum intensity projection, C: frontal-axis view, D: horizontal-axis view.**

Table. **Serial Changes of Clinical and Laboratory Findings.**

	July/2009	April/2012	January/2016	April/2016	January/2017	March/2018	August/2019	February/2020
VT documentation		first time				second time	third time	
General PET	positive							
Cardiac PET						negative	positive	
Cardiac MRI (LGE)		positive						
Steroid therapy	-	first started	+	discontinued	-	-	second started	+
BNP(pg/mL)	12.2	181	55.5		74.1	103.9	238.7	96.5
LVEF (%)	57	33	34		37	23	30	35
ACE (U/L)	24.3	15.3	25.2		31.9	ND	14.1	ND
sIL-2R (U/mL)	903	771	439		1,030	ND	352	ND

ACE: angiotensin-converting enzyme, BNP: brain natriuretic peptide, LGE: late gadlinium enhancement, LVEF: left ventricular ejection fraction, MRI: magnetic resonance imaging, PET: positron emission tomography, sIL-2R: soluble interleukin-2 receptor, VT: ventricular tachycardia, ND: not done

apy when ^{18}F-FDG PET did not show any abnormal tracer accumulation in the heart or lymph nodes (Fig. 6). However, at 3.5 years after discontinuing corticosteroid therapy, sustained VT recurred, and ^{18}F-FDG PET showed abnormal tracer accumulation (Fig. 7). These findings suggest that a relapse of inflammation associated with sarcoidosis plays a role in inducing VT and accelerating cardiac dysfunction. It has been suggested that corticosteroid therapy may be discontinued in patients with CS (9), but there is no consensus on whether or not corticosteroids should be discontinued. Nagai et al. reported that the discontinuation of steroids was related to the risk of cardiac mortality in association with worsening left ventricular dysfunction in CS (10). The present case suggests the importance of continuing corticosteroid therapy, even at low doses, and we should investigate this matter in detail in the future.

In the present patient, the axis of VT was similar between the episode when no abnormal tracer accumulation was found in ^{18}F-FDG PET and the episode with a relapse of inflammation, suggesting that these VT episodes originated from similar segments of the ventricle (Fig. 6, 7). Accordingly, it is difficult to rule out the possibility that ventricular remodeling due to myocardial fibrosis may have played a role in accelerating the progression of cardiac dysfunction or inducing VT in this patient. The presence of diffuse myocardial fibrosis and progressive left ventricular remodeling (11) may result from repeated episodes of myocardial inflammation and fibrosis. Further studies are needed to clarify the factors associated with the pathological mechanisms. Factors such as (1) the depth of the initial sarcoid granulomatosis lesion; (2) the timing of the start, dose, and duration of corticosteroid therapy; and (3) the genetic background may all play important roles.

Interestingly, our patient's ^{18}F-FDG PET findings at the time of relapse showed abnormal tracer accumulation only in the heart, with no tracer accumulation in lymph nodes or lungs. If her latest ^{18}F-FDG PET findings had been examined by physicians who only had information on her history,

she would have been diagnosed with isolated CS (1, 2, 12). The normal blood levels of ACE and sIL-2R shown at the time of relapse may have been associated with this condition. Circulating ACE is mainly derived from activated alveolar macrophages, and increased levels of sIL-2R have been found to correlate with the activity of T-cells in systemic sarcoidosis patients. It is suggested that sarcoid inflammation restricted to the myocardium does not always dramatically increase the levels of ACE and sIL-2R (13, 14). If the patient had not had corticosteroid therapy reintroduced, an abnormal tracer accumulation would have subsequently appeared in the lymph nodes and lungs as well. Physicians should be aware of the fact that active lesions of sarcoidosis may appear and disappear at different times in different locations and organs, including the heart (15). It is therefore meaningful to follow up patients with CS through periodic ^{18}F-FDG PET scans.

The authors state that they have no Conflict of Interest (COI).

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