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 (¹⁸F-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. ¹⁸F-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...
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°C, 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
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. 18F-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
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 18F-FDG PET.

The present patient experienced another episode of sustained VT two years after discontinuing corticosteroid ther-
In the present patient, the axis of VT was similar between the episode when no abnormal tracer accumulation was found in \( ^{18} \text{F-FDG PET} \) 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 \( ^{18} \text{F-FDG PET} \) 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 \( ^{18} \text{F-FDG PET} \) findings had been examined by physicians who only had information on her history,

**Figure 7.** Electrocardiogram and \( ^{18} \text{F-FDG PET} \) 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.
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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