Atrial Arrhythmias and Atrial Involvement in Cardiac Sarcoidosis

Short Review with a Case Report

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Summary
Severe ventricular arrhythmias such as high-grade atrioventricular block and ventricular tachycardia may cause lethal conditions or sudden death in patients with cardiac sarcoidosis (CS). Physicians should examine patients carefully for these conditions and treat them appropriately. As arrhythmias are being better diagnosed and treated, physicians are increasingly aware of atrial arrhythmias, which have not been focused upon as CS-related conditions, in patients with CS. This article reports a case of atrial flutter in sarcoidosis, and discusses literature findings on atrial arrhythmias and atrial involvement of CS. It is highly likely that atrial arrhythmia and supraventricular conduction disorder associated with or caused by CS are more common than previously thought. Physicians should pay careful attention for these conditions in the diagnosis and treatment of CS.

Key words: Heart, Atrial flutter, Electrophysiological test, Voltage mapping

Among the major manifestations of cardiac sarcoidosis (CS), conduction disorders such as high-grade atrioventricular block, severe ventricular arrhythmia, and cardiac dysfunction are particularly important as they may be lethal or cause sudden death in some patients.1,2 Patients with CS and these manifestations are treated with immunosuppressive therapy mainly including corticosteroids, and are also indicated for drug therapy for the treatment of arrhythmias and heart failure and/or non-drug therapy such as permanent pacing, catheter ablation, an implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), and heart transplantation.3 Recent advancements in these treatments and devices have significantly improved the prognosis of patients with CS. However, the prognosis is still poor in patients with cardiac dysfunction.

Abnormal electrocardiographic (ECG) findings such as high-grade atrioventricular block and severe ventricular arrhythmias have been and will be important in the diagnosis, treatment, and prognosis of CS. As arrhythmias are being better diagnosed and treated, physicians are increasingly aware of atrial arrhythmias such as atrial fibrillation, which have not been focused upon as CS-related conditions, in patients with CS. Although there are no detailed data on the prevalence and treatment of atrial arrhythmias in CS, these conditions should be investigated in depth to ensure better diagnosis and treatment of CS in the future. The present article describes a case of atrial flutter in a patient with sarcoidosis, and discusses the literature review findings of atrial arrhythmias and atrial involvement in CS.

Case Report
A male patient in his 50s has been monitored since the diagnosis of sarcoidosis after non-caseating epithelioid cell granuloma was found in a mediastinal lymph node biopsy in 2003. In December 2014, he was admitted to Hospital H after he became unconscious due to sick sinus syndrome. Based on the results of detailed examinations, he was considered not to require drug therapy for the treatment of sarcoidosis and was instructed to visit an outpatient clinic regularly to monitor the disease status. In 2015, echocardiography revealed pericardial effusion. Pulmonary hypertension with a transvalvular pressure gradient (TPG) of 40 mmHg was found and progressed gradually. In December 2016 the attending physician concluded that these findings were caused by sarcoidosis, and started to prescribe oral corticosteroid therapy (started with prednisolone 30 mg/day and then tapered the dose to maintain at 9 mg/day). Sarcoid granulomas were found in skin biopsy samples in 2015 and inguinal lymph node biopsy samples in 2016 (Figure 1). In July 2017, dyspnea on exertion developed. Since the pulmonary hypertension (TPG 50 mmHg) worsened as demonstrated by echocardiography and an increased plasma BNP level (112.2 pg/mL),

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his corticosteroid dose was increased. The patient was referred to our clinic to continue ambulatory treatment. Since the pulmonary hypertension improved to a TPG of 26 mmHg, the corticosteroid dose was reduced to prednisolone 10 mg/day. In November 2017, $^{18}$F-FDG PET revealed abnormal tracer accumulation in lymph nodes and vascular wall, but no significant tracer accumulation was found in the heart (Figure 2). Thereafter, the patient complained of palpitations, and underwent 24-hour Holter ECG monitoring, which indicated a frequent occurrence of supraventricular extrasystoles and nonsustained ventricular tachycardia (Figure 3). In May 2018, he complained of chest discomfort, and was hospitalized because an ECG revealed atrial flutter with 2:1 atrioventricular block and premature ventricular contractions (Figure 4).

The patient had no prior history of illness. His mother experienced cerebral infarction and valvular disease with no further detailed information available. He was a non-smoker and occasional drinker. At the time of hospitalization, he was 160 cm tall and weighed 67 kg. He had clear consciousness with a body temperature of 36.3°C, respiratory rate of 18 rpm, pulse rate of 150 bpm with irregularities, and blood pressure of 125/91 mmHg. Chest auscultation revealed no abnormal cardiac or respiratory sounds. No abnormal findings were noted on physical examination of the abdomen. No leg edema or neurological findings were observed. Chest X-rays at the time of hospitalization revealed cardiomegaly (CTR 55%) and pulmonary congestion (Figure 5). Echocardiography revealed left atrial enlargement with a left atrial size of 51 mm (Figure 6). Blood test results showed an ACE of 12.3 U/L (reference range, 8.3 to 21.4), sIL-2R of 711 U/mL (145 to 519), and BNP of 215.9 pg/mL, indicating increases in sIL-2R and BNP levels (Table).

During hospitalization, the atrial flutter ended with a terminal pause of 6.5 seconds. Escaped rhythm with sinus bradycardia was observed. Since paroxysmal atrial fibrillation developed, he underwent electrophysiological tests and catheter ablation for the treatment of atrial arrhythmias. Although the most common ablation technique for the treatment of atrial fibrillation is pulmonary vein elec-
trical isolation that blocks the conduction between the pulmonary vein and the left atrium, this technique was not used as no electric potential was observed in the pulmonary veins indicating no conduction from the left atrium to the pulmonary veins, and in addition, because no conductivity from the pulmonary veins to the left atrium was detected by the pulmonary vein pacing. He was treated only with right atrial isthmus line ablation. Using the CARTO 3D mapping system, a voltage map of the right and left atria was created. The voltage map suggested the presence of substantial fibrosis over an extensive area mainly including the left atrium, as electric potential was observed in almost the entire part of the right atrium and in the septal part and mitral ring in the left atrium, but no

Figure 3. 24-hour ambulatory electrocardiography. Premature atrial contractions and nonsustained ventricular tachycardia were observed.

Figure 4. Electrocardiography. Atrial flutter with 2:1 atrioventricular block and possible decremental conduction (150 bpm), and premature ventricular contractions were observed.
electric potential was found in the pulmonary veins, the posterior and anterior walls of the left atrium, the left atrial appendage, or the posterior wall of the right atrium (Figure 7). During hospitalization, his pulse stopped for 6.8 seconds when tachycardia ended (Figure 8). A permanent pacemaker was implanted in July 2018. Since then he has been in a stable condition with drug therapy consisting of a corticosteroid (prednisolone 10 mg), beta-blocker (bisoprolol fumarate 1.25 mg) and antiarrhythmic drug (flecainide acetate 100 mg). Prior to the pacemaker implantation, cardiac MRI revealed left atrial enlargement. However, there was no late gadolinium enhancement (LGE) in the atria or ventricles (Figure 9).

Prevalence of Atrial Arrhythmias in Cardiac Sarcoidosis

Although an accurate value of the prevalence of atrial arrhythmias in CS is unknown, it has been reported that atrial arrhythmias such as atrial fibrillation and atrial flutter are less prevalent than ventricular arrhythmias in patients with CS. Viles-Gonzalez, et al. have reported that 32 of 100 patients with CS experienced supraventricular arrhythmias, which included atrial fibrillation in 18, atrial tachycardias in 7, atrial flutter in 5, and other types of supraventricular tachycardias in 2. Zipse, et al. have reported that 15 (23%) of 65 patients with CS experienced 28 distinct symptomatic supraventricular arrhythmias, which included 9 atrial fibrillation, 16 atrial tachycardia, and 3 atrial flutter. On the other hand, Cain, et al. ana-
Mechanism of Onset of Atrial Arrhythmias

It has been speculated that atrial arrhythmias in CS are caused by inflammation or scar formation associated with atrial sarcoidosis, or by atrial overload secondary to ventricular dysfunction or pulmonary lesions. Viles-Gonzalez, et al. conducted a multivariate analysis and concluded that left atrial enlargement was the only independent factor associated with atrial arrhythmias in patients with CS. Abeler has described a case of sudden death due to cardiac arrest caused by granulomatous lesions in the sinus node.

Atrial Involvement in Cardiac Sarcoidosis

Roberts, et al. reviewed the autopsy findings of patients with cardiac sarcoidosis and reported that sarcoidosis lesions were found in the left ventricular free wall (96%), the ventricular septum (73%), the right ventricular wall (46%), the right atrium (11%), and the left atrium (7%). Bashour, et al. reviewed the autopsy findings of 45 patients with CS, and reported that lesions were observed in the ventricular wall in 43 patients (95.5%), the ventricular septum in 20 patients (44.4%), the papillary muscle in 7 patients (15.5%), the pericardium in 6 patients (13.3%), and the atrial wall only in 3 patients (6.7%). Atrial lesions of sarcoidosis are similar in nature to ventricular lesions, which represent both inflammation and scar formation (fibrosis) caused by non-caseating epithelioid cell granuloma.

Diagnostic Imaging of Atrial Lesions

Few reports have proved the presence of granuloma lesions in the atria in patients with cardiac sarcoidosis in a direct way. In many cases, atrial involvement of cardiac sarcoidosis has been found on the basis of diagnostic imaging of the atria, histological findings of other organs, and clinical findings. No studies have assessed images of atrial lesions in CS in a systematic manner. Atrial lesions in CS have been described only in case reports, in which atrial involvement was diagnosed based on LGE positivity in the atria on cardiac MRI, tracer accumulation in the atria on 18F-FDG PET, or both, indicating the benefits of imaging techniques. Hasegawa, et al. reported a case of atrial sarcoidosis with abnormal tracer accumulation in the left atrium on 18F-FDG PET disappeared after treatment.

Treatment of Atrial Arrhythmias

Case reports have described that corticosteroid therapy was beneficial in the treatment of atrial arrhythmias in CS, but the efficacy of corticosteroid therapy in this population has not been established. In the treatment of CS, catheter ablation has been mainly used for the treatment of ventricular tachycardia. The use of catheter ablation for the treatment of atrial arrhythmias in CS has been limited, but reported to be beneficial.

Case Discussion

It has been speculated that atrial arrhythmias in CS are caused by inflammation or scar formation associated with atrial sarcoidosis, or by atrial overload secondary to ventricular dysfunction or pulmonary lesions. The patient in the case study presented here had atrial flutter, which was followed by a long pause in the cardiac cycle. We hypothesize that this was caused by the extensive zero-voltage areas that were found in the electrophysiological test. As he had suffered from systemic sarcoidosis that involved mediastinal lymph nodes for more than 10 years, was found to have pericardial effusion in 2015, and had findings suggestive of ascending aortitis, the presence of
atrial inflammation due to sarcoidosis was strongly sus-
pected. More recently, he did not show tracer accumula-
tion in the atria on 18F-FDG PET, which indicates that ar-
rhythmias are caused by extensive fibrosis secondary to
atrial inflammation. Cardiac MRI revealed left atrial en-
largement. No clear LGE was observed in the atrial wall
in the present case, but the significance of LGE in the
atrial wall in patients with atrial dysfunction has recently
been pointed out, and researchers have only just begun to
develop imaging techniques and investigate their repro-

Figure 7. Atrial potential in electrophysiological testing. Voltage maps of the left and right atria were cre-
ated. Areas with normal potential (≥ 0.5 mV) are indicated in violet. Areas indicated in other colors represent
low-potential areas. Red areas represent extremely low or no potential areas (≤ 0.1 mV), which suggest scar
formation or fibrosis. In the left atrium, electric potential is observed only in the septal part and mitral ring,
and no potential is observed in the pulmonary vein or the left auricle. In the right atrium, potential is ob-
served in the right auricle, and atrial septum, but no potential is observed in the posterior wall. A: Left atrial
AP view, B: End-systolic left atrial PA view, C: Right atrial AP view, and D: Right atrial PA view.

Figure 8. ECG finding at the end of atrial tachyarrhythmia. The patient underwent catheter ablation for the treatment of paroxysmal atrial
tachyarrhythmias, which recurred after operation and ended with a terminal pause of 6.8 seconds.
ducibility and sensitivity.\textsuperscript{21,26} We believe that the overall findings of the present patient do not deny the presence of atrial fibrillation. According to the current diagnostic criteria proposed by the Japanese Circulation Society,\textsuperscript{1,2} he does not satisfy the “major criteria” for “clinical findings defining cardiac involvement”, and is only suspected to have cardiac sarcoidosis. Careful follow-up evaluation is needed for this patient.

**Conclusion**
Through our patient case and literature findings, we have learned the following: Recent advancements in the diagnosis and treatment of arrhythmias have significantly improved the diagnosis and treatment of atrial arrhythmias in CS. Atrial fibrillation and atrial tachycardia are the most common types of atrial arrhythmias in CS, and are thus important in the treatment and diagnosis of CS. The advancement of diagnostic imaging techniques such as cardiac MRI and $^{18}$F-FDG PET have allowed physicians to visualize atrial lesions, which has contributed to the better diagnosis and treatment of CS. It is highly likely that atrial arrhythmia and supraventricular conduction disorder associated with or caused by CS are more common than previously thought. Physicians should pay careful attention to these conditions in the diagnosis and treatment of CS.

**Disclosures**

**Conflicts of interest:** None.

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