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CASE REPORT
Cardiac imaging

A case report of recovery of sinus node abnormalities associated with right atrial involvement of 'early-stage' cardiac sarcoidosis

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Background Cardiac sarcoidosis (CS) is a chronic inflammatory disease characterized by impaired contractility of the myocardium secondary to cardiac conduction system abnormalities, which result in atrio-ventricular (AV) conduction block and ventricular tachyarrhythmias. Notably, sinus node (SN) abnormalities are rarely associated with CS.

Case summary We herein present a case of CS presenting with SN abnormalities associated with atrial involvement of the CS and describe the utility of cardiac magnetic resonance imaging (cMRI), fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG-PET-CT) scans, and cardiac biopsy, in making an initial early diagnosis of early-stage CS. Fortunately, an initial appropriate immunosuppression therapy with methylprednisolone for the CS thus far can help the SN and AV conduction function recover and has provided a good clinical course without the implantation of a pacemaker or implantable cardio-defibrillator.

Discussion Although the diagnosis of CS may be elusive, the initial clinical suspicion and use of advanced imaging may be important for an early diagnosis of CS. Furthermore, because CS may sometimes rapidly progress, the early diagnosis and treatment of early-stage CS may also be important to help the SN and AV conduction function recover, and avoid implantation of a pacemaker, as in this present case.

Keywords atrio-ventricular conduction • cardiac sarcoidosis • case report • early stage • sinus node abnormalities

ESC Curriculum 5.7 Bradycardia • 6.5 Cardiomyopathy • 2.1 Imaging modalities

Learning Points

- Sinus node abnormalities associated with right atrial involvement in cardiac sarcoidosis (CS) are an uncommon initial presentation of CS.
- In a clinical investigation with a myocardial biopsy, both cardiac magnetic resonance imaging (cMRI) and fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG-PET-CT) scans are required to prove the diagnosis of CS.
- Discrepancies in the findings between cMRI and 18-FDG-PET-CT are possible, and normal findings of cMRI do not exclude the diagnosis of CS.
- In patients with an improvement in the conduction disease under immunosuppressive therapy for CS and normalization of the 18-FDG-PET-CT, an implantable cardioverter defibrillator implantation can be avoided.

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Introduction

Cardiac sarcoidosis (CS) is a chronic inflammatory disease characterized by impaired contractility of the myocardium secondary to cardiac conduction system abnormalities, which result in atrio-ventricular (AV) conduction block and ventricular tachyarrhythmias (VTs).[1] Although common, atrial involvement in CS[2] tends to be less extensive than that of the ventricles.[3] Notably, sinus node (SN) abnormalities are rarely associated with CS.[3–5]

Time line

1-month before admission	Symptoms—dizziness.
1-week before admission	Symptoms—syncope.
On admission	A 12-lead electrocardiogram showed a first-degree atrio-ventricular (AV) block, incomplete right bundle branch block (RBBB), and terminal T inversion in precordial leads V1–V4. Echocardiography revealed preserved left ventricular (LV) and right ventricular (RV) systolic function, normal chamber size, and cardiac hypertrophy, without evidence of myocardial thinning of the basal interventricular septum (IVS).
Day 3	Cardiac magnetic resonance imaging revealed subtle late gadolinium enhancement of the interventricular septum of the myocardium.
Day 7	24-hour Holter monitoring revealed a first-degree AV block and frequent sinus arrest episodes of up to 6 s associated with dizziness.
Day 9	Fluorine-18-fluorodeoxyglucose positron emission tomography/CT (18-FDG-PET-CT) revealed 18-FDG uptake in the mediastinal lymph nodes, the right atrium, RV, and IVS, but not in other organs. Thus, he had a high clinical suspicion of CS.
Day 12	A myocardial biopsy from the RV and IVS was performed.
Day 20	The histological findings revealed an early stage of CS. Thus, the methylprednisolone (30 mg/day) therapy was initiated. The patient had no symptoms including syncope or dizziness thereafter.
Follow-up at 3 months	A 12-lead electrocardiogram continued to show RBBB, although the first-degree AV block was abolished, and 24-hour Holter monitoring showed no findings of AV block or sinus arrest of >2 s and fatal arrhythmias.
Follow-up at 4 months after immunosuppression with methylprednisolone	The methylprednisolone dose was tapered over 4 months, and the patient received maintenance methylprednisolone therapy (5 mg).
Follow-up at 5 months after immunosuppression with methylprednisolone	18-FDG-PET-CT revealed no abnormal 18-FDG myocardial uptake.
Follow-up at 2 years after the diagnosis of CS	He has been asymptomatic and is closely followed up as an outpatient over 2 years after diagnosis of CS.

Case presentation

A 61-year-old man was referred to our hospital for the evaluation of syncope. On admission, his blood pressure was 138/85 mmHg, and the pulse rate was regular at 62 beats per minute. Auscultation revealed normal cardiac and respiratory sounds, and lower extremity examination showed no oedema. His blood test results, including serum angiotensin-converting enzyme activity, were normal. A 12-lead electrocardiogram showed a first-degree AV block, incomplete right bundle branch block (RBBB), and terminal T inversion in precordial leads V1–V4 (*Figure 1A*). Chest radiography findings were unremarkable. Echocardiography revealed preserved left ventricular (LV) and right ventricular (RV) systolic function, normal chamber size, and cardiac hypertrophy, without evidence of myocardial thinning of the basal interventricular septum (IVS). Coronary computed tomography (CT) revealed no evidence of coronary artery stenosis. Cardiac magnetic resonance imaging (cMRI) revealed LV or RV wall motion or chamber size abnormalities and subtle late gadolinium enhancement (LGE) of the interventricular septum of the myocardium (white arrows in *Figure 2G*, *H*). Notably, 24-hour Holter monitoring revealed a first-degree AV block and frequent sinus arrest episodes of up to 6 s (*Figure 1B*) associated with dizziness. Fluorine-18-fluorodeoxyglucose positron emission tomography/CT (18-FDG-PET-CT) revealed 18-FDG uptake in the mediastinal lymph nodes, the right atrium (RA), RV, and IVS (*Figure 3A–H*) but not in other organs. We performed an RV and IVS myocardial biopsy based on a high index of clinical suspicion for CS. Histopathological findings showed multinucleated giant cells (arrow in *Figure 4A*) and a subpleural hyalinized nodule containing abundant dense eosinophilic hypocellular collagen fibrosis surrounding and bridging discrete granulomas (arrow in *Figure 4B*), suggestive of early-stage CS.[1] The patient was diagnosed with CS and methylprednisolone (30 mg/day) therapy was initiated. The methylprednisolone dose was tapered over 4 months, and the patient received maintenance methylprednisolone therapy (5 mg) and had no symptoms such as syncope or dizziness thereafter. A 12-lead electrocardiogram continued to show RBBB at the 3-month follow-up, although the first-degree AV block was abolished (*Figure 1C*), and 24-hour Holter monitoring showed no findings of AV block or sinus arrest of >2 s. Therefore, pacemaker implantation was not indicated. Notably, 18-FDG-PET-CT performed after 5-month methylprednisolone immunosuppressant therapy revealed no abnormal 18-FDG myocardial uptake (*Figure 3I–L*). Considering the evidence of myocardial LGE, we discussed implantable cardioverter defibrillator (ICD) implantation. Based on guidelines of the Heart Rhythm Society,[6] an electrophysiological study was warranted in this patient to evaluate

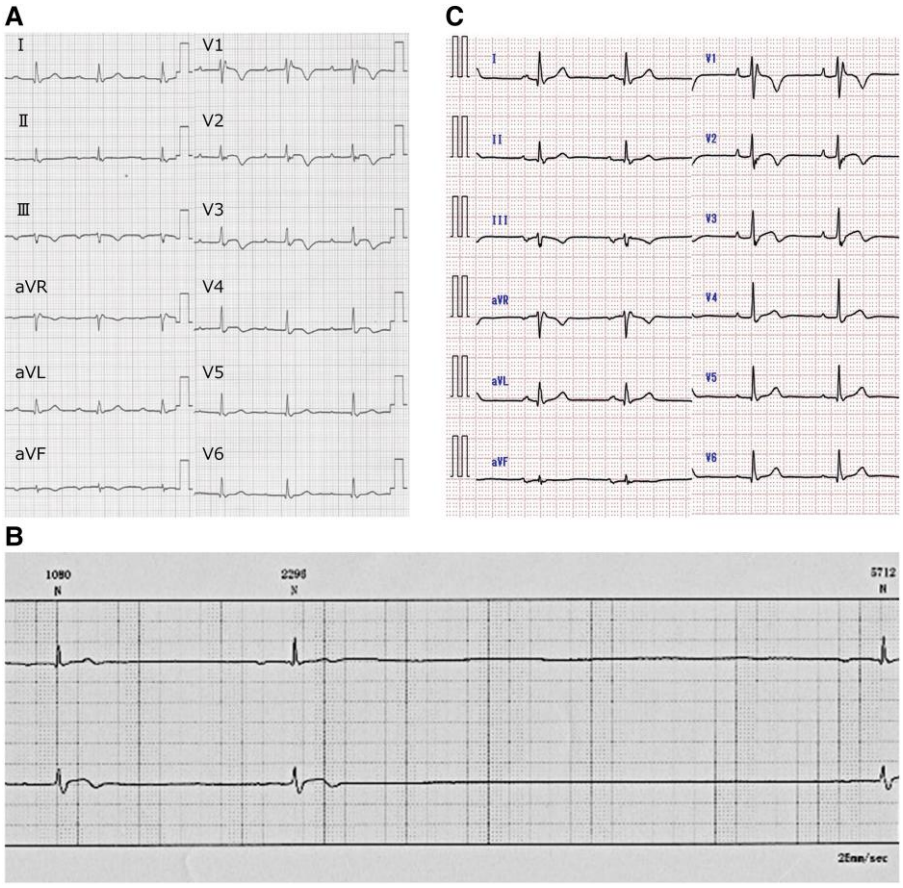


Figure 1 The 12-lead electrocardiograms on admission (*A*) and 3 months after immunosuppression therapy (*C*). The 24-hour Holter monitoring revealed an atrial standstill for 6 s (*B*).

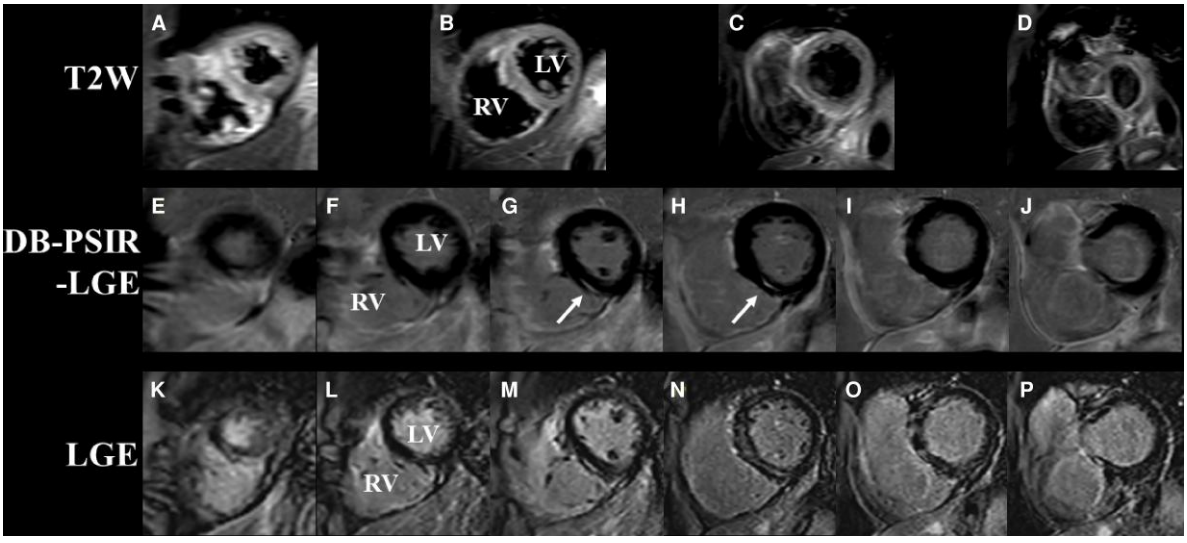


Figure 2 Cardiac magnetic resonance imaging of T2-weightend (T2W) images (*A–D*) using dark blood (DB) phase-sensitive inversion recovery (PSIR) late gadolinium enhancement (LGE) images (*E–J*), and LGE images (*K–P*) of the short-axis views revealed no findings of left (LV) or right ventricular (RV) wall motion or chamber size abnormalities, but the finding of the presence of subtle LGE of the myocardium (white arrows in panel *G*, *H*).

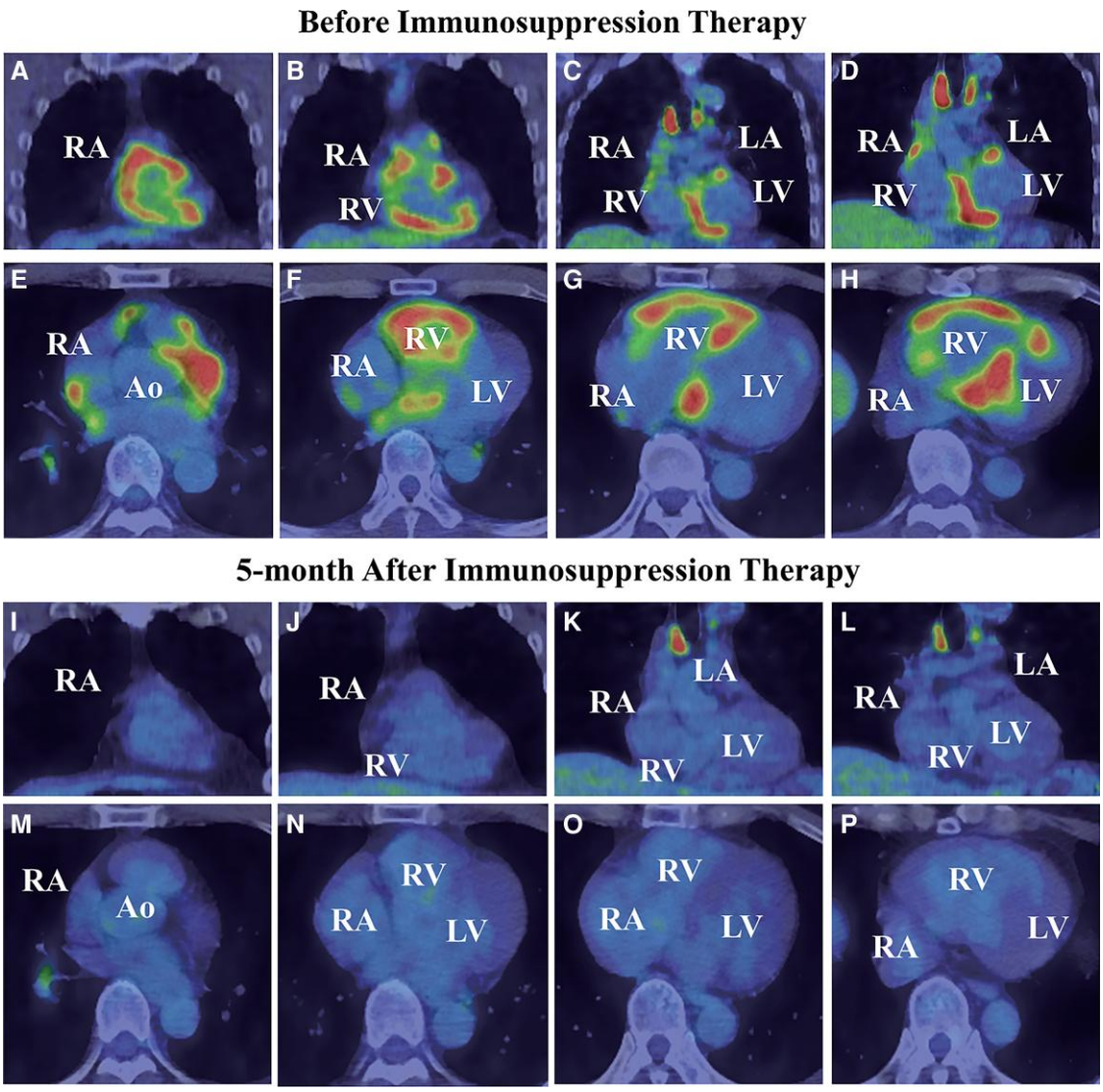


Figure 3 The vertical (*A–D*, *I–L*) and horizontal (*E–H*, *M–P*) images of the fluorine-18-fluorodeoxyglucose (18-FDG) positron emission tomography/computed tomography scan revealed an uptake of the 18-FDG noted in the right atrium and ventricle and interventricular septum (*A–D*, *E–H*), but after 5 months of immunosuppression with methylprednisolone, it demonstrated no abnormal 18-FDG myocardial uptake (*I–L*, *M–P*). RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; Ao, aorta.

fatal arrhythmia. However, the patient refused ICD implantation and has continued to receive maintenance methylprednisolone treatment (5 mg). He has been asymptomatic and is closely followed up as an outpatient over 2 years after the diagnosis of CS.

Discussion

Sarcoidosis, a complex disease with a heterogeneous clinical presentation, may affect any body organ.[1] Cardiac involvement, which has been reported in 5–50% of patients with systemic sarcoidosis, is characterized by myocardial inflammation, conduction system impairment, arrhythmias, and ventricular dysfunction.[7] CS is characterized by granulomas of the IVS, anterior and posterior LV walls, and the anterior RV wall.[8] Although common, atrial involvement is less extensive compared to ventricular disease in patients with CS.[2,3] RBBB and AV blocks (ranging from first- to third-degree blocks) are the most common manifestations[9] of CS, as observed in the present case (*Figure 1A*). However, SN abnormalities associated with RA involvement represent an uncommon initial presentation of CS.[3–5] RA involvement, which causes inflammation, fibrosis, and/or scarring of the SN area[3] and/or an obstructive granulomatous angiitis of the SN artery, is implicated as the mechanism underlying SN abnormalities in CS.[10] Immunosuppressant therapy administered to our patient led to the complete recovery of the first-degree AV block and SN abnormalities as indicated by the lack of 18-FDG myocardial uptake on the 18-FDG-PET-CT scan (*Figure 3A–L*). Therefore, SN abnormalities are attributable to the effects of CS on the SN. Previous studies have reported that SN abnormalities were irreversible even in those who received immunosuppressants and that ICD implantation with significant atrial pacing was necessary for patients with probable late-stage CS.[3–5] Therefore, early diagnosis and prompt initiation of

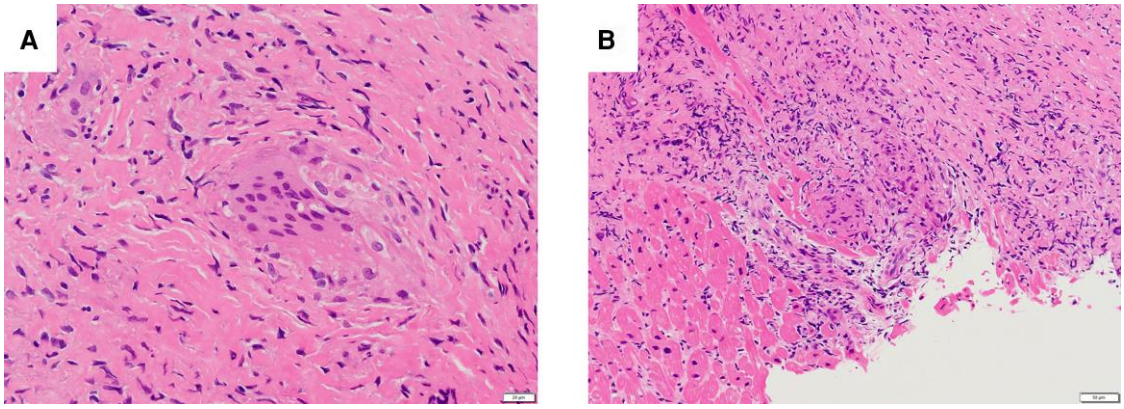


Figure 4 The histological analysis from a right ventricular biopsy revealed multinucleated giant cells (haematoxylin and eosin stain, 40×, in *A*) and a subpleural hyalinized nodule containing abundant dense eosinophilic hypocellular collagen fibrosis surrounding and bridging discrete granulomas (haematoxylin and eosin stain, 20×, in *B*).

treatment are important to prevent the progression of early- to late-stage CS to aid with the recovery of SN and AV conduction[11] and to avoid pacemaker implantation, considering that CS may occasionally be rapidly progressive.[1,5]

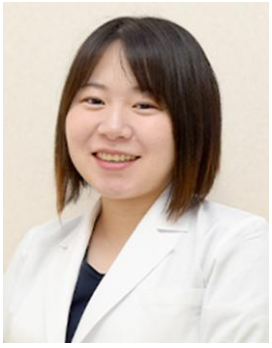
Despite the availability of advanced imaging modalities and prompt evaluation based on a high index of clinical suspicion, CS remains diagnostically challenging, particularly in the early stages. In some cases, cMRI may show insufficient sensitivity for accurate diagnosis of early-stage CS.[1] However, 18-FDG-PET-CT, a more recent innovative technology[1] that accurately reveals extensive RA, RV, and IVS inflammation, was useful in our patient (*Figure 3A–H*). Interestingly, clinical manifestations, including SN abnormalities and AV block, were correlated with areas of inflammation identified on the 18-FDG-PET-CT scan in our patient with CS. These cMRI and 18-FDG-PET-CT documented findings indicated subtle myocardial fibrosis and scarring, which may represent irreversible changes in addition to inflammatory changes, which may suggest reversibility; this presentation indicated early-stage CS in this case.[1] Histopathological evaluation (*Figure 4A, B*) of myocardial biopsy specimens showed changes in early-stage CS, supporting their findings.

Indications for ICD implantation were controversial in this patient. Echocardiography and cMRI revealed preserved LV and RV systolic function. Prognosis is poor in patients with CS who show reduced LV[12] and/or RV[13] systolic function. Although cMRI revealed myocardial LGE in our patient, the findings were subtle (*Figure 2G, H*). Notably, 18-FDG-PET-CT revealed myocardial 18-FDG uptake (*Figure 2A–H*) in this patient. LGE is associated with an increased risk of mortality or significant ventricular arrhythmia even in patients with preserved LV systolic function.[14] Conversely, patients with CS without cardiac manifestations (which may indicate early-stage CS) are known to have a low cardiovascular risk, even with myocardial LGE.[15] Our patient had preserved LV and RV systolic function and denied a history of fatal arrhythmias, as confirmed by close 24-hour Holter monitoring and also denied unexplained syncope. Moreover, the patient's cardiac manifestations (except for RBBB) were completely resolved following immunosuppressant therapy. Therefore, this patient may have had a comparably low risk of cardiovascular mortality or VT. However, further studies are warranted to gain a deeper understanding of the clinical implications of this finding. The patient refused ICD implantation; therefore, close follow-up as an outpatient is important.

Timely diagnosis of early-stage CS facilitated the prompt initiation of appropriate immunosuppressant therapy in our patient who has shown a good clinical course even without a pacemaker or ICD implantation. However, limited data are available regarding the timing of dosage de-escalation and the overall duration of immunosuppressant therapy.[1] The Japan Circulation Society guidelines[16] recommend long-term maintenance immunosuppressant therapy. Our patient received maintenance methylprednisolone therapy (5 mg) and was closely followed up as an outpatient.

Future research is warranted to investigate whether timely diagnosis and initiation of treatment can improve prognosis in patients with early-stage CS, including the potential for prophylactic pacemaker or ICD implantation.

Lead author biography



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Supplementary material

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

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

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