Multimodality imaging, electrophysiologic, electroanatomic, and histopathologic characterization of atrial sarcoidosis presenting with sinus arrest and reentrant right atrial flutter

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Introduction

Sarcoidosis is a multisystem disorder of unknown etiology characterized by noncaseating granuloma formation in pulmonary tissue and extrapulmonary organs, such as the skin, the lymph nodes, and the heart.[1] Imaging studies have found asymptomatic cardiac involvement in 4% to 55% of patients and symptomatic involvement in 5% of patients with extracardiac sarcoidosis.[2] Owing to heterogeneous involvement of the myocardium, cardiac disease manifestations are highly dependent on the location of inflammation and subsequent scar formation. The 3 principal sequelae of inflammation and scarring are conduction abnormalities, ventricular arrhythmias, and heart failure.[2] Diagnosis of cardiac sarcoidosis may be elusive. Cardiac or extracardiac biopsy and, more recently, positron emission tomography–computed tomography (PET-CT) and magnetic resonance imaging (MRI) play a critical role in diagnosis. Expert consensus guidelines recommend the diagnosis of cardiac sarcoidosis be made through the "histologic pathway" with biopsy-proven myocardial involvement or the "clinical pathway" of extracardiac pathologic involvement with evidence of cardiac phenotypic involvement.[2] Unexplained cardiac conduction abnormalities in young patients are a potential clue for cardiac sarcoidosis; heightened clinical suspicion for cardiac sarcoid in such patients may allow early diagnosis and treatment.

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Atrial involvement in cardiac sarcoid has been recognized; 32% of patients may develop supraventricular arrhythmias, with atrial fibrillation (AF) the most common arrhythmia (18% of patients).[3] Sinus node abnormalities in cardiac sarcoid are rare. In this case report, we describe a nonclassic presentation of sarcoidosis with cardiac involvement manifesting predominantly with atrial involvement, namely severe sinus node dysfunction and reentrant, typical cavotricuspid isthmus (CTI)-dependent flutter. Uniquely, we invoked multimodality imaging with MRI, PET-CT, and high-density electroanatomic mapping and electrophysiologic evaluation combined with histopathologic analysis to (1) confirm the diagnosis of cardiac sarcoid; (2) confirm that the mechanism of sinus node dysfunction and atrial flutter was related to atrial inflammation and scar; and (3) initiate appropriate immunosuppressant therapy for sarcoid and appropriate device therapy to address both sinus node dysfunction and future risk of ventricular arrhythmias.

Case report

A 42-year-old man presented to the emergency department with a 1-month history of dizziness and chest discomfort. Past medical history was notable only for well-controlled type 2 diabetes mellitus managed with metformin alone. Apart from bradycardia, clinical examination was normal. On telemetry, he was noted to be profoundly bradycardic to 40 beats per minute (bpm). An electrocardiogram (ECG) revealed sinus bradycardia without any other abnormalities. His chest radiograph was unremarkable; high-sensitivity troponin I was raised at 240 ng/L (<15 ng/L). Renal, liver, thyroid, and hematologic blood work was unremarkable. Selective coronary angiography showed minor coronary artery disease. Telemetry detected frequent episodes of persistent junctional bradycardia down to 30 bpm with frequent sinus pauses and sinus arrest of up to 8 seconds associated with dizziness (Figure 1A and B).

KEY TEACHING POINTS

- While cardiac sarcoidosis typically presents with atrioventricular conduction block, we describe the rare presentation of sinus node dysfunction, sinus arrest, and reentrant cavotricuspid isthmus–dependent atrial flutter, mediated by atrial inflammation and scar.

- The diagnosis of cardiac sarcoidosis, in addition to late gadolinium enhancement on cardiac magnetic resonance imaging, led to appropriate device therapy selection that aimed at correcting sinus node dysfunction and primary prevention of sudden cardiac death with a dual-chamber defibrillator.

- Unexplained sinus node dysfunction with bradycardia, pauses, and sinus arrest in a young patient should heighten suspicion for secondary causes, in particular cardiac sarcoidosis.

Subsequent ECGs demonstrated junctional bradycardia with aberrantly conducted premature atrial complexes (Figure 1C). He also experienced symptomatic episodes of AF with rapid ventricular rate up to 120 bpm, followed by prolonged conversion pauses. Transthoracic echocardiogram showed a structurally normal heart with normal-sized atria, preserved biventricular systolic function, and no valvular dysfunction. Electrophysiology study demonstrated severe sinus node dysfunction, exemplified by a severely prolonged sinus node recovery time up to 2834 ms at a pacing cycle length of 300 ms (Supplemental Figure 1; corrected sinus node recovery time 2529 ms at 300 ms; 1590 ms at 600 ms). Atrioventricular (AV) nodal function was preserved (AH 102 ms, AV nodal Wenckebach 435 ms), as was His-Purkinje conduction (HV 40 ms). AF was provoked during anterograde study but there was no inducible ventricular tachycardia with programmed ventricular stimulation with a drive train cycle length of 400 ms and up to 4 extrastimuli, in the baseline state and with isoprenaline.

Given his young age and otherwise unexplained sinus node dysfunction, further investigation was done to search for secondary causes. Serum angiotensin converting enzyme level was elevated at 96 U/L (20–70 U/L). Corrected calcium levels were normal; autoimmune screen and Lyme serology were negative. Cardiac magnetic resonance imaging (cMRI) demonstrated significant biventricular T_2 hyperintensity and diffuse late gadolinium enhancement (LGE) involving the posterior right atrial wall, both left and right ventricular free walls, and ventricular septum (Figure 2A). This correlated with the findings of a subsequent 18F-FDG PET-CT scan, which showed avid hypermetabolism in both ventricles and atria (Figure 2B), as well as multiple mediastinal and hilar lymph nodes (Supplemental Figure 2). There were no associated perfusion defects on his technetium-99m sestamibi scan.

Myocardial biopsy from the right ventricular mid and basal septum showed patchy stromal fibrosis (Figure 2C).

An endobronchial ultrasound-guided fine needle aspiration biopsy of a paratracheal lymph node revealed a noncaseating granuloma (Figure 2D). Flow cytometry was negative for malignancy and culture was negative for mycobacteria. A diagnosis of sarcoidosis with cardiac involvement was made. The patient received a dual-chamber defibrillator and was commenced on pulsed methylprednisolone and cyclophosphamide, with normalization of the serum angiotensin converting enzyme level from 90 to 48 U/L.

At 4 months follow-up, the patient complained of intermittent rapid palpitations, reduced exercise tolerance, and exertional dyspnea, without syncope. Device interrogation revealed persistent atrial flutter. His 12-lead ECG was consistent with typical counterclockwise atrial flutter (Figure 3A). No ventricular arrhythmias were detected. High-density activation mapping and entrainment mapping confirmed typical CTI-dependent atrial flutter (cycle length 220 ms), which was successfully terminated with linear radiofrequency ablation at the CTI with confirmation of bidirectional block. When flutter reverted, electrograms also revealed that the patient was now in complete atrial standstill. Voltage mapping demonstrated low-voltage scar (<0.05 mV) along the posterior right atrial wall that correlated with earlier cMRI findings, likely in the anatomic region of the sinoatrial node (Figure 3B). Right heart study showed normal mean right atrial pressure of 2 mm Hg.

A progress radionuclide gallium scan performed after 6 months of immunosuppression with cyclophosphamide demonstrated no abnormal myocardial uptake, indicating a significant response to treatment. Device interrogation also demonstrated a substantial atrial pacing burden at 98.5%.

Discussion

Despite growing awareness and the availability of more advanced imaging, cardiac sarcoidosis remains difficult to diagnose. This is a unique case report of cardiac sarcoid with a clinical presentation *dominated by atrial involvement* with severe sinus node dysfunction, rapidly progressing to sinus arrest, and reentrant CTI-dependent atrial flutter. Unlike typical presenting features of cardiac sarcoid, AV conduction was preserved and there was absence of spontaneous and inducible ventricular arrhythmias, despite ventricular involvement on cMRI and PET-CT. The case highlights comprehensive use of multimodality imaging with cMRI, PET-CT combined with high-density electroanatomic atrial mapping, electrophysiologic evaluation, and tissue histopathology to demonstrate atrial sarcoid infiltration and resultant scar with consequent effect on sinus node function and creation of substrate for reentrant atrial flutter. Further, the case highlights the merit of heightened vigilance to look for secondary causes of unexplained sinus node dysfunction in young patients, especially for treatable conditions with major prognostic implications such as cardiac sarcoidosis.

Cardiac sarcoidosis is typically dominated by clinical presentation with 1 or a combination of 1 or more of the
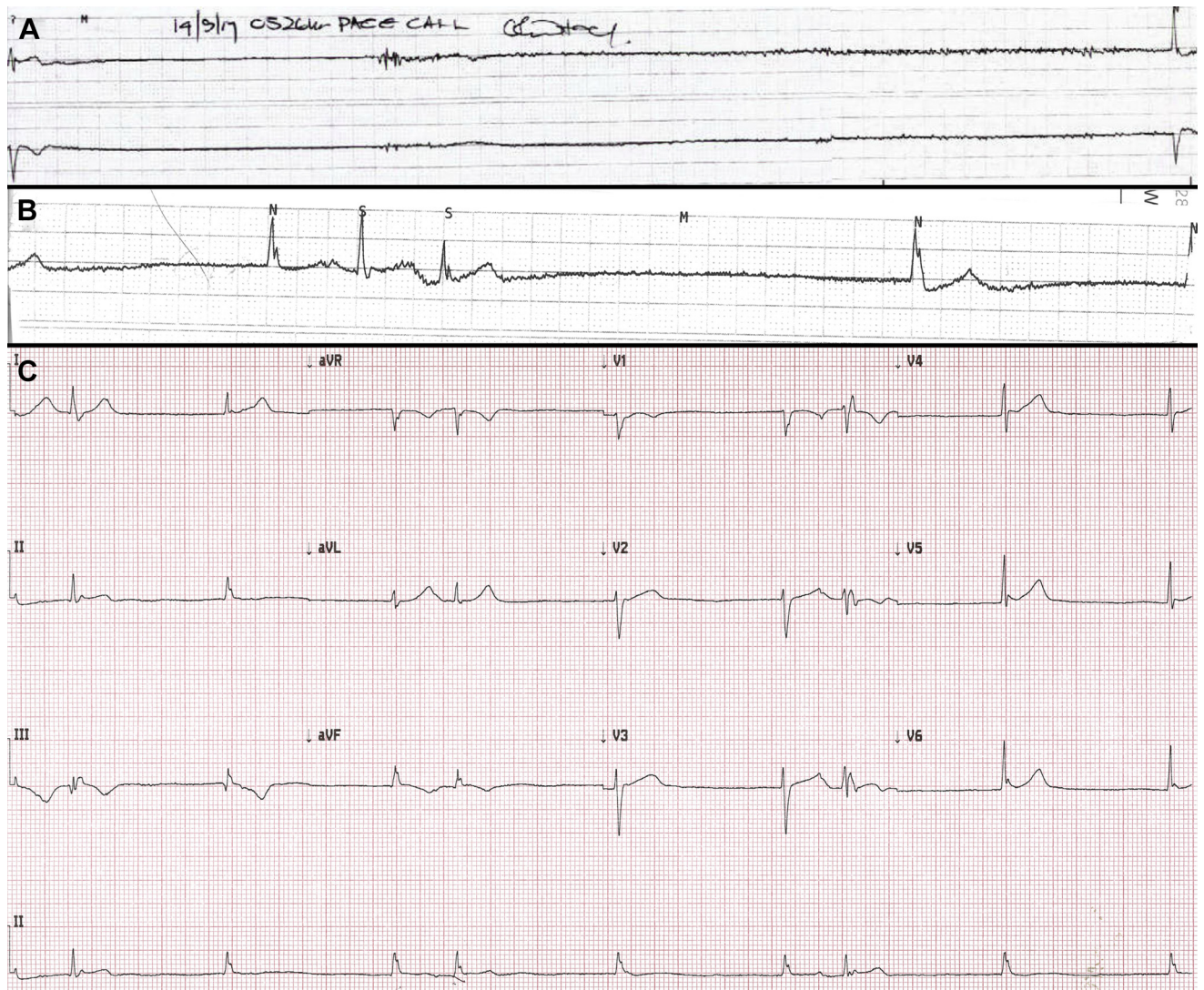
Figure 1   **A:** Telemetry strip demonstrating a prolonged sinus pause. **B:** Junctional bradycardia with frequent prolonged sinus pauses. **C:** A 12-lead electrocardiogram showing junctional bradycardia with aberrantly conducted premature atrial complexes (Ashman phenomenon).

following: conduction abnormalities (varying degrees of AV block), ventricular arrhythmias, and heart failure.[2] Atrial involvement is common but tends to be less extensive than in the ventricles. Viles-Gonzalez and colleagues[3] investigated 100 patients with biopsy-proven systemic sarcoidosis and evidence of cardiac involvement by performing cMRI, PET-CT, or endomyocardial biopsy. After a mean follow-up of 5.8 years, the prevalence of supraventricular arrhythmias was reported to be 32%. AF was the most common form of arrhythmia (18%), followed by atrial tachycardia (7%), atrial flutter (5%), and AV nodal reentrant tachycardia (2%). Willner and colleagues[4] reported that 32% of 100 patients with cardiac sarcoidosis had atrial arrhythmias; 9 underwent catheter ablation. Five of the 9 patients had reentrant atrial flutter, with only 2 patients having reentrant right-sided typical CTI mechanism. Atrial flutter, as in this case, is therefore uncommon in atrial sarcoid.

Reports of sinus node dysfunction are also rare. The first,[5] in which sinus node dysfunction was determined to be the probable cause of death in a patient later found to have extensive granulomatous infiltration of the sinoatrial node on autopsy, dates back to 1979. Sinus node dysfunction was never confirmed on ECG or telemetry in that report. A more recent report described a young patient with sinus bradycardia and progressive conduction disease manifesting as a first-degree AV block and left anterior hemiblock.[6] Neither electrophysiology testing nor high-density electroanatomic mapping were performed to assess sinus nodal function. Our case therefore represents a rare presentation of atrial cardiac sarcoidosis manifesting as *both* sinus node dysfunction and reentrant right atrial flutter, with detailed electroanatomic and electrophysiologic assessment.

The pathogenesis of atrial arrhythmias in cardiac sarcoidosis remains uncertain, but is thought to be attributed to either (1) elevated atrial pressure owing to progressive
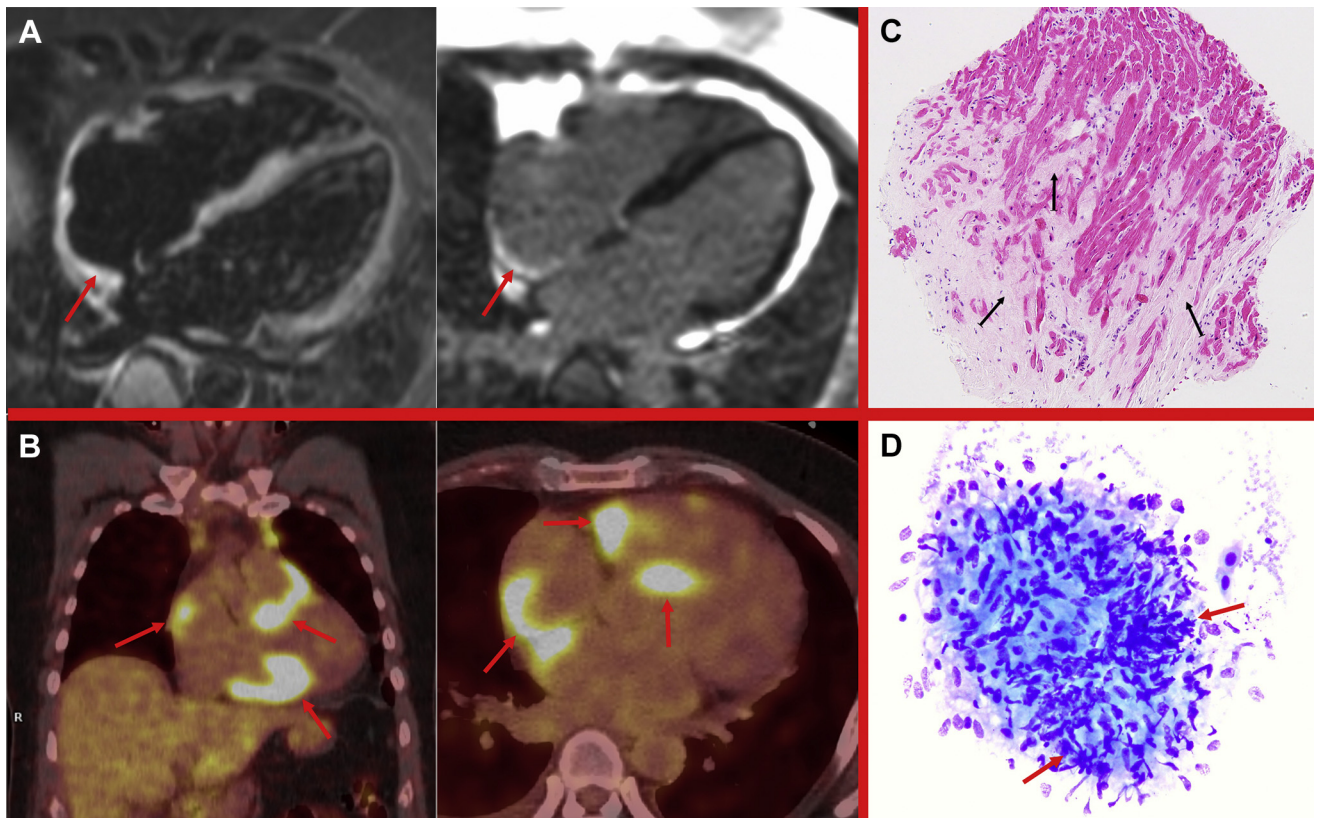
Figure 2   **A:** Cardiac magnetic resonance imaging showing T2 hyperintensity (left) and late gadolinium enhancement (right) of the right atrium (*arrows*). **B:** 18F-FDG positron emission tomography with marked multichamber hypermetabolism in the septal and lateral left ventricular walls, basal inferior right ventricle, and posterior right and left atrium (*red arrows*). **C:** Right ventricle myocardial biopsy demonstrating patchy stromal fibrosis (*black arrows*). **D:** Cytology of fine needle aspiration biopsy of paratracheal lymph node demonstrating epithelioid granuloma (*red arrows* highlighting histiocytes).

ventricular dysfunction and/or pulmonary hypertension, or (2) sarcoid granulomatous deposition causing inflammation, scarring, and substrate heterogeneity. Recently, Hasegawa and colleagues[7] elegantly reported extensive left atrial scar with sparing of only the anterolateral left atrial wall (no recorded electrograms in the posterior left atrial wall and posterior left atrium), creating the substrate for reentrant perimitral flutter. In that report, FDG uptake was increased on the anteroseptal and septal walls, correlating with low-voltage area on mapping, with weak uptake, consistent with scar in the posterior left atrium. In that case, however, there was left atrial dilation and left ventricular dysfunction, which improved with immunosuppression therapy. Although likely scar mediated, atrial stretch may have contributed to the pathogenesis of atrial arrhythmia in that case. In the series by Viles-Gonzalez and colleagues,[3] left atrial enlargement was an independent predictor of supraventricular arrhythmias, suggesting that atrial stretch may have contributed to the pathogenesis of atrial arrhythmia. Indeed, sarcoid patients may have impaired left and right atrial reservoir function (suggesting impaired atrial mechanical function) very early in the disease, before left ventricular dysfunction is seen on conventional echocardiography.[8] In our case, there was absence of biatrial enlargement and ventricular dysfunction, and right-sided pressures were

normal on hemodynamic evaluation, implicating atrial sarcoid infiltration and scar as the predominant mechanism for sinus node dysfunction and reentrant CTI-dependent atrial flutter.

Given the patient's history of type 2 diabetes, it is possible that diabetic atrial remodeling could have contributed to atrial flutter. However, the rapid progression from sinus node dysfunction to atrial flutter and atrial standstill with PET-CT and cMRI evidence of focal right atrial hyperenhancement and low-voltage scar on electroanatomic mapping suggests active inflammation and sarcoid-related scar to be the likely etiology.

The case also highlights the importance of investigating the underlying causes of unexplained sinus node dysfunction in the young. Clearly in this case, the diagnosis of sarcoid had a critical influence on selecting appropriate device therapy. The patient undoubtedly required a dual-chamber pacemaker for sinus node dysfunction. However, the diagnosis of sarcoid, when combined with the finding of LGE on MRI (despite lack of inducible ventricular tachycardia), were critical factors weighing on the decision to upgrade to primary-prevention defibrillator therapy. Notably, presence of LGE has been associated with increased risks of both cardiovascular mortality and ventricular arrhythmias in cardiac sarcoidosis.[9] Indeed, expert consensus does indicate that an ICD
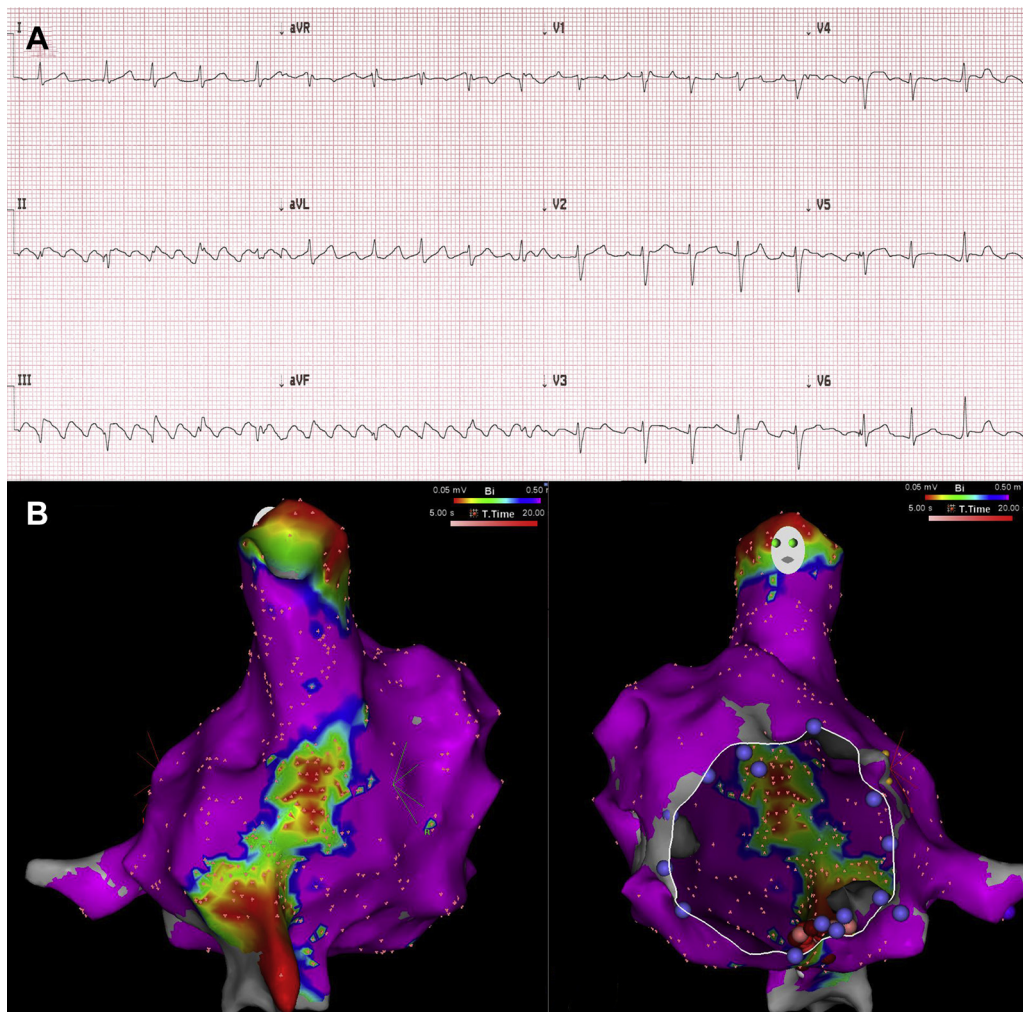
Figure 3   **A:** A 12-lead electrocardiogram showing typical counterclockwise atrial flutter. **B:** Voltage map of the right atrium (posterior-anterior view on the left and anterior-posterior view on the right) demonstrating low-voltage scar (*yellow to red*) along posterior wall extending inferiorly in the probable region of the sinoatrial node. *Purple dots* mark the tricuspid annulus.

should be implanted, if there is an indication for permanent pacemaker placement, independent of ventricular function (class IIa).[2]

Conclusion

This case is a rare manifestation of cardiac sarcoidosis presenting with a clinical picture dominated by atrial involvement in the form of profound sinus node dysfunction, rapidly progressive sinus arrest, and reentrant CTI-dependent atrial flutter. The mechanism was likely attributed to atrial sarcoid infiltration, inflammation, and scar in the sinoatrial node region leading to sinus arrest and creating the relevant electrophysiologic milieu for right-sided atrial flutter. Heightened index of suspicion led to the diagnosis of sarcoid using multimodality imaging and high-density electroanatomic and electrophysiologic testing. This resulted in a major impact on therapy, including initiation of immunosuppression and insertion of a dual-chamber defibrillator to address both sinus node dysfunction and primary prevention of sudden cardiac death.

Appendix
Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2018.06.014.

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