

Lyme disease and cardiac sarcoidosis: Management of associated ventricular arrhythmias



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Introduction

Cardiovascular involvement in Lyme disease is a rarely occurring manifestation. Following infection with *Borrelia burgdorferi*, Lyme carditis typically presents as atrioventricular (AV) block during the early disseminated stage of the disease ranging from PR interval prolongation to complete heart block, typically resolving after proper antibiotic treatment. Interestingly, AV block is also common in patients with cardiac sarcoidosis (CS), and CS has been linked to Lyme disease. We report a patient who was diagnosed with Lyme carditis and ultimately developed CS.

Case report

A 42-year-old woman without any past medical history from upstate New York presented to our institution after being treated in 3 other tertiary medical centers for an interesting course of heart disease beginning in 2013. A prior marathon runner, the patient first noted symptoms of fatigue, hair loss, paresthesia, and light sensitivity; she was initially misdiagnosed with depression and anxiety for almost 4 to 6 weeks. Owing to worsening symptoms, she consulted at another institution where a 12-lead electrocardiogram revealed complete heart block with a junctional escape rhythm. An enzyme-linked immunosorbent assay and subsequent confirmatory Western blot analysis for IgG and IgM antibodies against *B. burgdorferi* were positive, and a diagnosis of Lyme disease with carditis was made. Following several cycles of antibiotic treatment, the heart block persisted and the patient underwent placement of a dual-chamber pacemaker. Cardiac magnetic resonance imaging (MRI) performed in 2013 was unremarkable. In 2015, the patient developed

progressive heart failure symptoms associated with pacemaker syndrome requiring upgrade to a cardiac resynchronization therapy pacemaker with His-bundle lead placement. In the following months she was noted to have rising His-bundle lead pacing thresholds. Subsequently, the patient manifested palpitations, and in 2015 underwent an electrophysiology study during which typical cavotricuspid isthmus-dependent atrial flutter was induced; a cavotricuspid isthmus ablation was performed successfully.

The patient first presented at our institution early in 2017 with a chief complaint of 1 year of palpitations on exertion and a rapid decline in exercise tolerance. A 12-lead electrocardiogram revealed frequent premature ventricular contractions (PVCs) suggesting an origin in the basal portion of the right ventricle (RV) (Figure 1A). She subsequently underwent a stress test, during which she developed sustained monomorphic ventricular tachycardia (VT) (Figure 1B). A transesophageal echocardiogram revealed a moderately dilated RV with moderate hypokinesis; mild left ventricular dilation with normal left ventricular ejection fraction of 55%. The patient did not respond to beta-blockers (PVC burden 33%) and was referred for catheter ablation, during which 2 distinct PVC/VT morphologies were demonstrated. Using the Carto-Sound system, an electroanatomical endocardial activation map (approximately 400 points for each map) of PVC 1 was created, which was observed in the anterior wall of the right ventricular outflow tract (-37 ms pre-QRS). Radiofrequency energy (power 25 W, temperature < 42°C) was delivered at the right ventricular outflow tract at these sites. Following successful ablation of PVC 1, PVC 2 was no longer seen. Owing to the observed dilation of the RV on transesophageal echocardiogram, an electroanatomic map of the RV was also created, revealing extensive fibrosis in the anterolateral and inferolateral RV wall; unipolar voltage map suggested a larger epicardial substrate (Figure 1C).

The patient was referred for a positron emission tomographic (PET) computed tomography scan with ¹⁸F-fluorodeoxyglucose (PET-CT ¹⁸FDG) and nitrogen-13 ammonia (¹³NH₃) to assess for potential active CS (Figure 2A). Discrete perfusion defects suggestive of scar/fibrosis of the basal anterior wall, the septum, and the basal inferoseptal and distal inferior walls were seen, with areas of

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KEY TEACHING POINTS

- Cardiac sarcoidosis is associated with a high risk of ventricular arrhythmias and worsening left ventricular ejection fraction. Prompt diagnosis (using ^{18}F FDG positron emission tomographic computed tomography scan/ $^{13}\text{NH}_3$ imaging and endomyocardial biopsy) and treatment reduce disease progression and arrhythmia severity.
- Lyme carditis is associated with varying degrees of atrioventricular (AV) conduction anomalies. These usually resolve with appropriate antibiotic therapy.
- Several reports have associated *Borrelia burgdorferi* infection with sarcoidosis, based on detection of “Borrelia-like” organisms in biopsy samples and positive antibodies. Nonetheless, a causative role of *B. burgdorferi* in sarcoidosis has not been clearly established.
- Cardiac sarcoidosis should be included in the differential diagnosis of AV conduction anomalies.

inflammation involving the anterior, septal, and inferior walls consistent with active CS. Additionally, focal FDG uptake was also seen bilaterally in the hilar and subcarinal regions. Genetic testing was negative for any known mutation for arrhythmogenic right ventricular cardiomyopathy and

endomyocardial biopsy (EMB) (Figure 2B) confirmed CS. The patient was started on a 12-week course of high-dose prednisone (ie, 50 mg). A follow-up PET-CT ^{18}F FDG showed a decrease in myocardial ^{18}F FDG uptake (Figure 2C). For the septum, maximum standard uptake value (SUV max) decreased from 6.85 to 4.56, and SUV mean decreased from 2.71 to 2.47. The right ventricular SUV max decreased from 5.99 to 2.71, and the SUV mean decreased from 2.36 to 1.56. The patient was treated for another 3 months with high-dose prednisone, and PET-CT was repeated. There was minimal to no RV FDG uptake, but septal uptake was visually increased (SUV max increased from 4.56 to 7.55).

The patient continued to have frequent symptomatic PVC (burden: 21%) with daily episodes of sustained and nonsustained VT and was referred for a repeat catheter ablation. Frequent PVC was observed spontaneously every 3 sinus beats; an endocardial activation map of the RV was created, revealing an earliest activation site in the distal inferolateral wall of the RV (Figure 3A) and ablation was delivered at this site (35 W). Voltage mapping of the RV revealed a less extensive area of fibrosis/scar tissue in the anterolateral and inferolateral wall when compared to the previous voltage map. This area of low voltage extended from the base to the apex of the RV. The unipolar voltage map of the RV suggested a slightly larger area of fibrosis in the epicardial surface, which also improved from prior voltage maps (Figure 3B).

After ablation and during continued steroid use, the patient has had significant symptomatic improvement, with a decrease in His bundle pacing thresholds from 5 to 3 mV

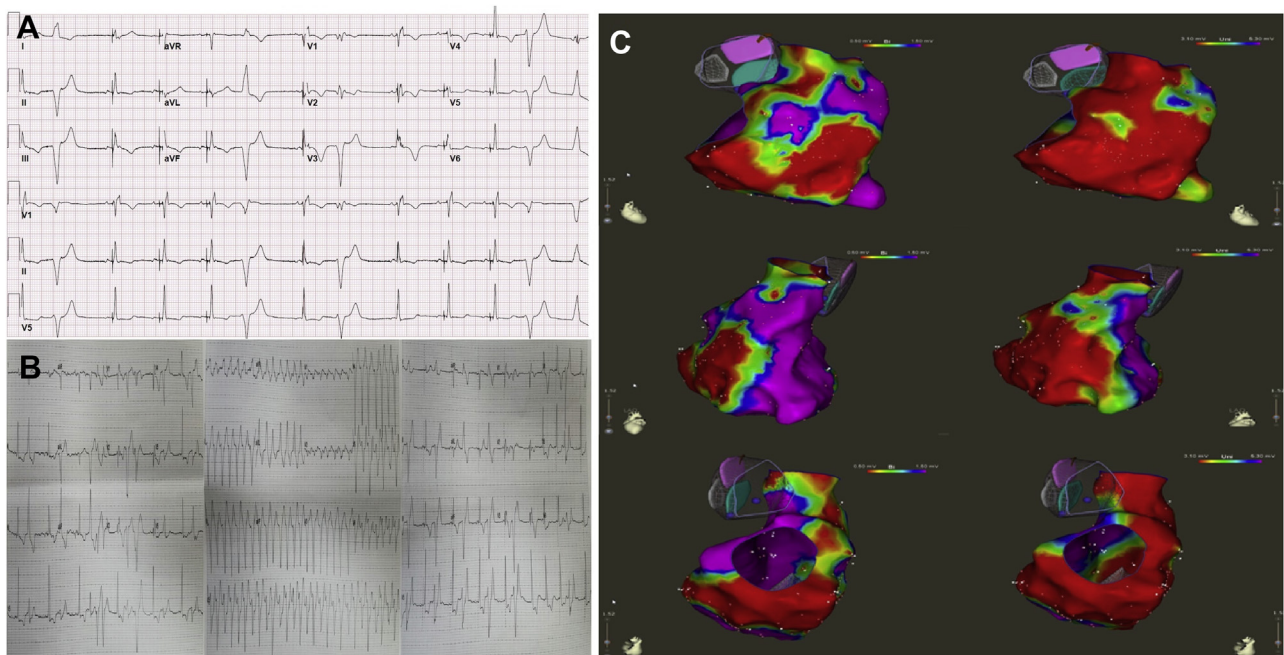


Figure 1 **A:** A 12-lead electrocardiogram showing a premature ventricular contraction with left bundle branch block (LBBB) morphology inferior axis and transition in V6 suggesting right ventricular outflow tract origin. **B:** Sustained monomorphic ventricular tachycardia with LBBB morphology, left superior axis probably originating in the basal portion of the right ventricle (RV) free wall. **C:** Electroanatomical map of the RV revealing extensive fibrosis in the anterolateral and inferolateral RV wall with areas of low voltage extending from the base to the apex of the RV. Unipolar voltage map suggested a larger epicardial substrate (right column).

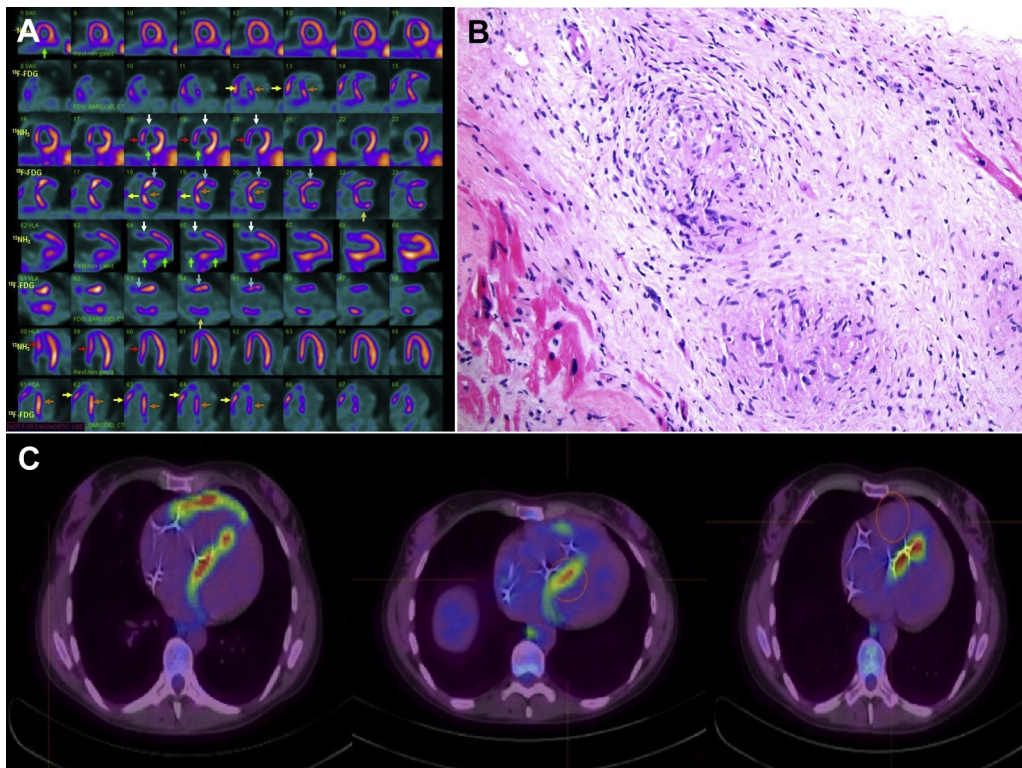


Figure 2 A: $^{13}\text{NH}_3$ perfusion (top rows) and ^{18}F -FDG metabolic (bottom rows) positron emission tomographic (PET) slices. $^{13}\text{NH}_3$ perfusion defects are present in the basal anterior (white arrows), septal (red arrows), and basal and distal inferior (bright green arrows) walls, consistent with scarred regions. Focal ^{18}F -FDG uptake, indicative of inflammation, is present in the anterior wall (turquoise arrows), inferior wall (gold arrows), and septum (orange arrows), as well as the right ventricle (yellow arrows) (note: only selected perfusion defects and focal uptake regions are highlighted). Inflammation in areas of scar, ie, metabolic/perfusion mismatch, is present in the basal anterior (turquoise/white) and septal walls (orange/red arrows). B: Endomyocardial biopsy demonstrating granulomas consistent with cardiac sarcoidosis. C: Transverse PET ^{18}F FDG metabolic / computed tomography (CT) fusion images shows focal tracer uptake in the septum and the right ventricle indicative of inflammation, consistent with active cardiac sarcoidosis (left panel). At 3 months (middle panel) after immunosuppressive therapy shows lessening of septal ^{18}F FDG PET-CT uptake and near-total resolution of right ventricular uptake, but at 6 months (right panel) shows increased septal tracer uptake and total resolution of right ventricular uptake.

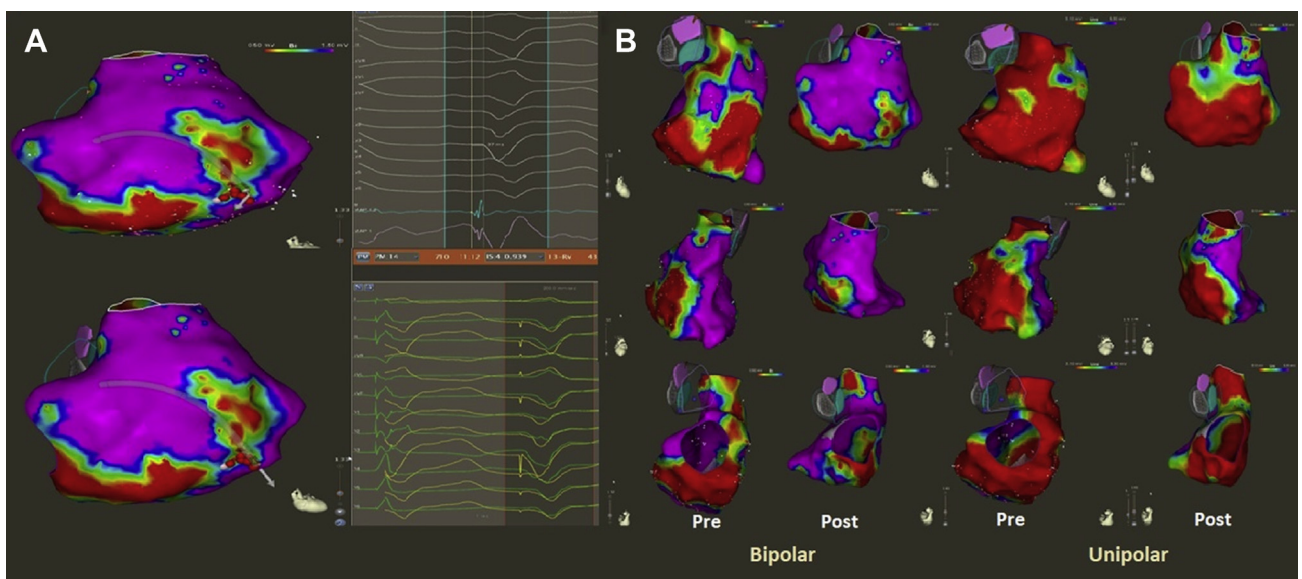


Figure 3 A: Premature ventricular contraction observed spontaneously at the beginning of the second procedure (left bundle branch block pattern, left superior axis and transition in V_6). Epicardial features were not present (maximum deflection index < 55%, intrinsic deflection time 85 ms, and pseudo delta wave < 34 ms). B: Voltage bipolar and unipolar maps of the right ventricle before (pre) and after (post) steroid therapy demonstrating a reduction in the area of fibrosis/scar tissue in the anterolateral and inferolateral right ventricular wall.

and a decrease on PVC burden to 2% and no more episodes of VT seen on device interrogation. Finally, the patient underwent RV lead extraction and upgrade to a Boston Scientific Dynagen cardiac resynchronization therapy defibrillator (His bundle lead) for secondary prevention of sudden cardiac death owing to previously demonstrated sustained VT despite initial ablation.

Discussion

Cardiac involvement is estimated to occur in 20%–30% of individuals with sarcoidosis, yet as few as 5% of total patients present with clinical cardiac manifestations. Complete heart block is the most common finding, occurring in up to 30% of these patients, with ventricular arrhythmias accounting for 23% of cases.¹ When clinical manifestations are limited to conduction system disease, as was the case for our patient at initial diagnosis, age-related conduction diseases such as Lyme disease, Brugada syndrome, myocarditis, and sarcoidosis should be considered.² The etiology remains poorly understood; current knowledge suggests an aberrant immune response in genetically predisposed individuals. Interestingly, multiple pathogens including *Borrelia*, *Mycobacteria*, and herpesvirus have been linked to sarcoidosis.³

Diagnostic criteria for CS have relied on evidence of extracardiac sarcoidosis or positive EMB, even though EMB has demonstrated low sensitivity, making the diagnosis of CS often difficult.^{1,4,5} Importantly, ¹⁸F-FDG PET has emerged as a useful quantitative tool in the diagnosis of CS, given its ability to diagnose active inflammation and monitor response to treatment.^{1,6}

In our case, following a negative cardiac MRI, Lyme carditis was diagnosed based on complete heart block in a young patient, residence in an endemic region, and serologic analysis. Following a delayed diagnosis of Lyme myocarditis, our patient was started on intravenous antibiotics with an unfavorable course. Among patients treated in a timely fashion, heart block is typically resolved, with only a few rare cases describing persistent conduction disturbances.^{7,8} The persistence of heart block in our patient and subsequent development of RV dilation and hypokinesia mandated ruling out sarcoidosis and arrhythmogenic right ventricular cardiomyopathy. Cases of predominant RV dilation have been described in sarcoidosis, helping our team reach our final diagnosis.⁹ Interestingly, only a small reduction in PVC burden with steroid therapy and initial ablation was observed, probably reflecting a reduced effect in patients with more advanced disease.

Several possible explanations can be found regarding the association of previous Lyme disease and sarcoidosis: (1) a “2-hit” scenario, in which the patient developed CS (either preceding or following Lyme disease) and Lyme carditis without any relation between them; (2) increased susceptibility to the development of Lyme disease owing to the immune response of underlying sarcoidosis; or (3) Lyme disease triggering an immune response, which leads to the

development of sarcoidosis. Although initial MRI ruled out sarcoidosis, it is possible that further evaluation with ¹⁸F-FDG-PET could have demonstrated the presence of active inflammation, as both tests are complementary in the diagnosis of sarcoidosis. Sarcoidosis has been demonstrated to occur in areas of intense inflammatory activity, including scars, tattoos, and cutaneous infections. As such, it is possible that intense inflammatory activity during Lyme carditis could have resulted in the patient developing CS. Indeed, *B. burgdorferi* has been hypothesized as a possible etiologic trigger in sarcoidosis, demonstrated by increased seroprevalence of antibodies to *B. burgdorferi* in patients with a confirmed diagnosis of sarcoidosis.^{1,3,10,11} In fact, serum angiotensin-converting enzyme levels (which have been described to be elevated in patients with sarcoidosis) have been reported to return to normal levels after initiation of antibiotic treatment in patients with biopsy-confirmed sarcoidosis and *B. burgdorferi* infection.¹² As such, it is possible that an early diagnosis and initiation of appropriate antibiotic therapy could have changed the disease course, without development of CS. Additionally, “Borrelia-like” organisms have been described within biopsy specimens in patients with cutaneous sarcoidosis.¹³ Nonetheless, other studies using specific immunologic analysis have not found similar results¹⁴ and, as such, a definitive connection between sarcoidosis and Lyme disease has not been established.

Conclusion

Regardless of whether or not an association between Lyme disease and sarcoidosis exists, this case demonstrates the need to include CS in the differential diagnosis of heart block, even in the presence of other confirmed etiologic entities such as Lyme disease.

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