JACC: CASE REPORTS VOL. 16, 2023

CASE REPORT

INTERMEDIATE

CLINICAL CASE: ACC.23

Cardiac Sarcoidosis and a Likely Pathogenic *TTN* Variant in a Patient Presenting With Ventricular Tachycardia

Zain M. Virk, MD,[a] T. Lee Richardson, Jr, MD,[a] Joseph F. Nowatzke, MD,[a] Asad Ullah, MD,[b] Dawn M. Pedrotty, MD,[a] M. Benjamin Shoemaker, MD, MSCI,[a] Arvindh Kanagasundram, MD,[a] Dan M. Roden, MD,[a] William G. Stevenson, MD[a]

ABSTRACT

Rare variants in *TTN* are the most common monogenic cause of early-onset atrial fibrillation and dilated cardiomyopathy. Whereas cardiac sarcoidosis is very underdiagnosed, a common presentation can be ventricular arrhythmias. This report presents a patient with a likely pathogenic *TTN* variant and cardiac sarcoidosis. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2023;16:101878) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 64-year-old man presented to an outside hospital with dizziness. Examination revealed a regular tachycardia at 148 beats/min with associated hypotension (86/50 mm Hg) and progressive worsening in the patient's mental status. Electrocardiography (ECG) showed a wide complex tachycardia consistent with ventricular tachycardia (VT) (Figure 1). This VT demonstrated a left bundle branch block-like configuration and superior axis consistent with a VT origin from the inferior right ventricle (RV) or septum. Following sedation and successful direct current cardioversion, the patient was placed on a lidocaine infusion and transferred to our facility.

LEARNING OBJECTIVES

- To recognize that the presence of early-onset AF may represent a more serious underlying inherited cardiomyopathy or arrhythmia syndrome and should trigger further investigation.
- To understand presenting clinical features of CS and prioritize studies used for evaluation of suspected cases.

PAST MEDICAL HISTORY

The patient had a history of paroxysmal atrial fibrillation (AF) diagnosed at age 32 years (Figure 2). For over 25 years, he experienced brief, sporadic episodes of AF that did not cause significant symptoms. However, in his early 60s, atrial arrhythmias became more frequent and symptomatic, prompting him to undergo pulmonary vein isolation and cavotricuspid isthmus ablation. The procedure was complicated by intraprocedural monomorphic VT. He was hospitalized and a cardiac magnetic resonance study was

From the [a]Vanderbilt University Medical Center, Department of Medicine Division of Cardiology, Nashville, Tennessee, USA; and the [b]Vanderbilt University Medical Center, Department of Pathology, Nashville, Tennessee, USA.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 5, 2023; revised manuscript received April 12, 2023, accepted April 20, 2023.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2023.101878

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CS = cardiac sarcoidosis

ECG = electrocardiography

LV = left ventricle

PET = positron emission tomography

RV = right ventricle

VT = ventricular tachycardia

suggestive of arrhythmogenic RV cardiomyopathy. His left ventricular (LV) ejection fraction at that time was 50%-55%. Coronary angiography showed mild nonobstructive coronary artery disease. An implantable cardioverter-defibrillator was placed. For arrhythmia suppression, he was started on amiodarone, which he stopped after 6 months because of a rash and fatigue.

At age 64 years, 3 months prior to his presentation at our facility, he experienced recurrent VT and implantable cardioverter-defibrillator shocks. Echocardiogram showed his LV ejection fraction had decreased to 30%-35% with severe global hypokinesis. Amiodarone was again initiated but not tolerated. His medical therapy at the time of transfer to our facility consisted of apixaban, metoprolol, rosuvastatin, and sacubitril-valsartan.

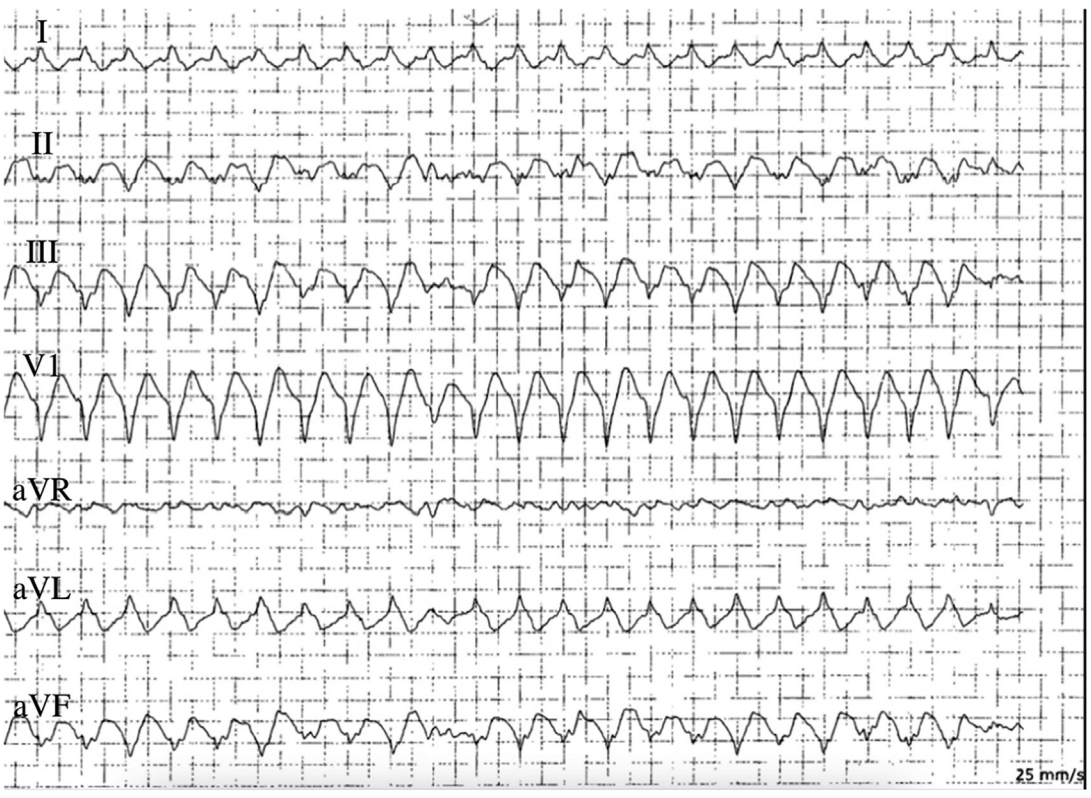
DIFFERENTIAL DIAGNOSIS

The differential diagnosis for his cardiomyopathy and VT at the time of presentation included progression of presumptive genetic arrhythmogenic cardiomyopathy given his history of early-onset AF, development of an infiltrative cardiomyopathy such as cardiac sarcoidosis (CS), arrhythmogenic RV cardiomyopathy, lymphocytic myocarditis, and DSP cardiomyopathy.

INVESTIGATIONS

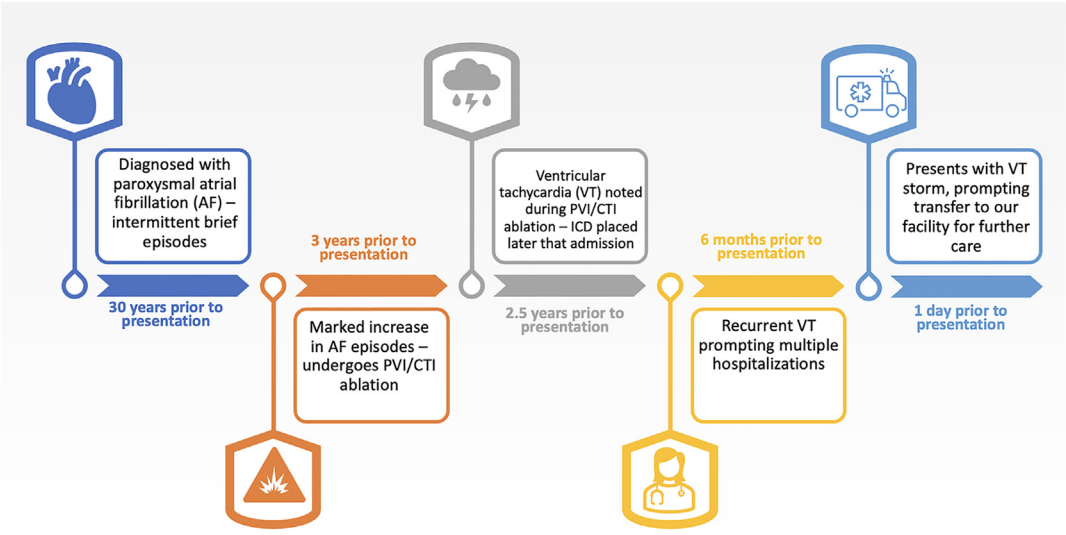
Laboratory data on presentation included troponin-I of 0.07 ng/mL, peaking at 0.08 ng/mL

FIGURE 1 Presenting ECG at an Outside Facility



The rhythm is sustained monomorphic ventricular tachycardia that has a left bundle branch block–like configuration and superior axis consistent with a ventricular tachycardia origin from the inferior right ventricle or septum. **(Top to bottom)** Electrocardiogram (ECG) leads are I, II, III, V_1, aVR, aVL, and aVF.

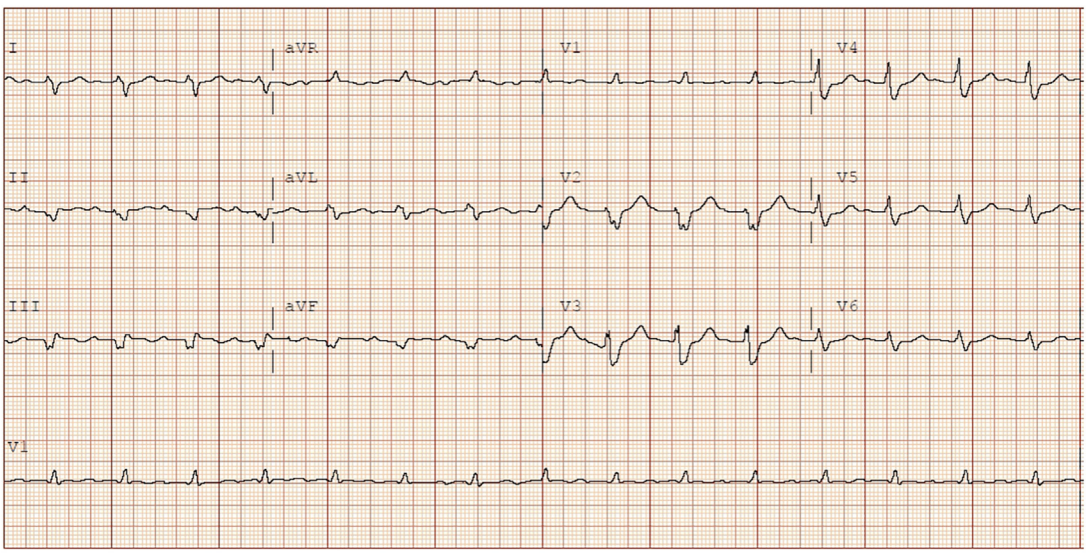
FIGURE 2 **Timeline of Prior Cardiac History**



Details regarding prior cardiovascular events and procedures leading up to his presentation and transfer to our facility. AF = atrial fibrillation; CTI = cavotricuspid isthmus; ICD = implantable cardioverter-defibrillator; PVI = pulmonary vein isolation; VT = ventricular tachycardia.

(normal <0.04 ng/mL). N-terminal pro-B-type natriuretic peptide was elevated at 7,737 pg/mL (normal <124 pg/mL). Initial ECG showed normal sinus rhythm, prolonged PR interval at 219 milliseconds, a QRS interval duration of 170 milliseconds with an unusual right bundle branch block and left anterior fascicular block pattern and Q waves in leads II, III, and aVF (**Figure 3**).

FIGURE 3 **Admission ECG**



Electrocardiogram (ECG) after transfer to our facility shows normal sinus rhythm, prolonged PR interval at 219 milliseconds, a QRS interval duration of 170 milliseconds with an unusual right bundle branch block and left anterior fascicular block pattern and Q waves in leads II, III, and aVF.

MANAGEMENT

An inpatient positron emission tomography (PET) scan was ordered but was unable to be performed. The patient remained on a lidocaine infusion without VT recurrence. On hospital day 5, he underwent an electrophysiological study; programmed stimulation induced VT via single and double extrastimuli from sites at the RV base. The arrhythmia was hemodynamically tolerated, permitting VT mapping. Entrainment of the VT in the inferior RV basal septum demonstrated short stimulation to QRS interval time and a short postpacing interval-tachycardia cycle length that was suggestive of a broad inferobasal RV septal exit. Transeptal access was gained to map the LV, which was then followed with radiofrequency ablation at the inferior basal LV and RV septum (Figure 4). Following ablation, the clinical VT was no longer inducible. However, a ventricular flutter that had not been observed to occur spontaneously was inducible with more aggressive stimulation and was not targeted for ablation. RV septal biopsies were obtained at the time of ablation.

The day after the ablation procedure, he had electrical storm with new VTs at 150-160 beats/min with varying QRS interval morphologies requiring intravenous amiodarone, lidocaine, and esmolol for control. He subsequently developed cardiogenic shock and oliguric renal failure requiring inotropic, vasopressor, and intra-aortic balloon pump support.

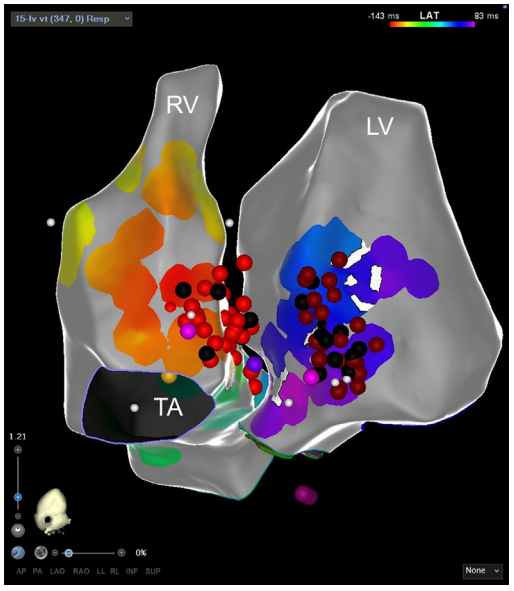
Genetic testing revealed a heterozygous, likely pathogenic truncation alteration in the A-band of the *TTN*. His RV septal biopsy revealed noncaseating granulomas that were consistent with CS (Figure 5). He was started on methylprednisolone 500 mg daily for 3 days, followed by a prolonged steroid taper and mycophenolate mofetil. As he recovered hemodynamically, he was gradually initiated on empagliflozin, sacubitril/valsartan, metoprolol, and spironolactone. VT suppression was achieved with amiodarone and lidocaine infusions; no further electrophysiological studies were performed prior to discharge, and the patient's infusions were transitioned to oral amiodarone and mexiletine.

DISCUSSION

CS is characterized by inflammation and fibrosis of the myocardium, which can lead to cardiomyopathy, conduction abnormalities, and arrhythmias.[1] After establishing the diagnosis, patients should receive guideline-directed medical therapy for heart failure and arrhythmias when appropriate, as well as immunosuppressive therapy if there is evidence of active myocardial inflammation.[1] In our patient, his recurrent ventricular arrhythmias and low output state postablation may have been related to ongoing inflammation from CS that did not improve until starting immunosuppressive therapy.

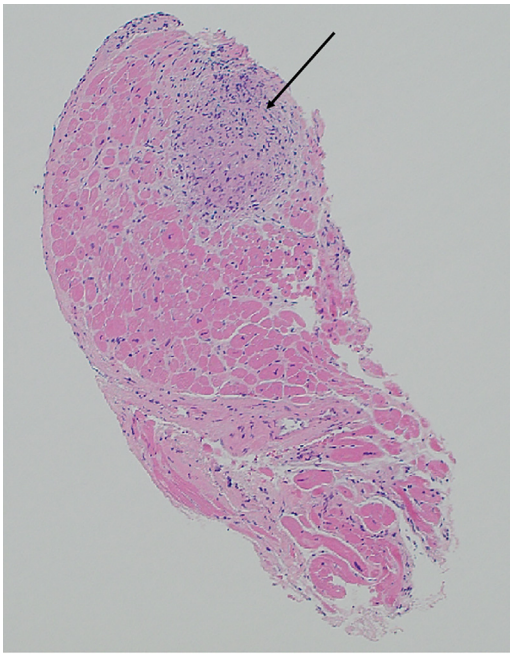
For many patients with suspected CS, a confirmatory diagnosis can be elusive, especially given its phenotypic overlap with other inflammatory and fibrotic myocardial diseases, such as arrhythmogenic RV cardiomyopathy and DSP cardiomyopathy. Evidence of noncaseating granulomas obtained via endomyocardial biopsy remains part of expert consensus diagnostic pathways for CS, although the sensitivity is low at 20%-25% because of the patchy nature of myocardial involvement.[2] Use of noninvasive, multimodal imaging techniques can increase the sensitivity. With cardiac magnetic resonance, T_2 imaging and late gadolinium enhancement can detect areas of scarring, inflammation, and edema, but cardiac magnetic resonance cannot differentiate areas of fibrosis from inflammation.[3] PET imaging following a no-carbohydrate diet to suppress myocardial glucose uptake is used for both diagnosis and surveillance

FIGURE 4 Activation Map of the LV and RV With Ablation Tags



Activation map of the left ventricle (LV) and right ventricle (RV) showing activation times that progress from **red** to **yellow** to **green** to **blue** and **purple**, with **red** signifying the earliest activation. There is a broad area of relatively early activation **(red)** over the inferior RV. **Bright red spheres** indicate ablation sites in the RV and **dark red spheres** indicate ablation sites in the LV. TA = tricuspid annulus.

FIGURE 5 Endomyocardial Biopsy Obtained During Electrophysiology Study



Endomyocardial biopsy specimen that contains a single, subendocardial noncaseating granuloma with tightly packed epithelioid cells **(arrow).** This finding is diagnostic of cardiac sarcoidosis. Acid-fast bacilli and Grocott methenamine silver stains were negative.

given its established prognostic value and ability to discern active disease from quiescent cardiac involvement.[4] PET has sensitivities ranging from 83%-100%, although recent reports highlighting the clinical similarities to DSP cardiomyopathy may reduce the specificity of PET for diagnosing CS.[5]

In addition to the diagnosis of CS, our patient also had a history of early-onset AF. Recently published data demonstrated that 10%-16% of patients with early-onset AF carry disease-associated genetic variants.[6] Interestingly, genes with pathogenic/likely pathogenic alterations were usually associated with cardiomyopathies rather than cardiac ion channel abnormalities, with *TTN* being the most common.[6] These rare genetic variants have prognostic significance—they have been linked to an increased risk of mortality in patients with early-onset AF—highlighting the utility of genetic testing in patients with early-onset AF.[7]

The relationship between the patient's *TTN* sequence variant and the development of CS remains nebulous. It is plausible that the mutant protein expressed by the *TTN* variant may have served as an antigenic stimulus to elicit CS. Different regions of *TTN* have been implicated as potentially immunogenic in an autoimmune neuromuscular disease—autoimmune rippling muscle disease—that can be associated with myasthenia gravis.[8] Additionally, auto-antibodies to the *TTN* have been described in patients with scleroderma.[9] These findings underscore that more work is needed to understand the mechanism by which genetic variants predispose to cardiomyopathies in patients with early-onset AF.

FOLLOW-UP

On 4-month follow-up, the patient remained on mycophenolate mofetil, and prednisone had been titrated to 10 mg daily as part of the prolonged taper. He had not experienced any further VT episodes.

CONCLUSIONS

We present the case of a 64-year-old man with a history of early-onset AF who presented with VT who was found to have CS and a likely pathogenic variant in *TTN*. The link between cardiac sarcoid and *TTN* variants is unclear.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Shoemaker has received sponsored research funds from Roche Diagnostics. Dr Stevenson has received speaker fees from Abbott, Medtronic, Boston Scientific, and Johnson and Johnson. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Tadarro Lee Richardson Jr, Vanderbilt University Medical Center, 2220 Pierce Avenue, 282 Preston Research Building, Nashville, Tennessee 37202, USA. E-mail: Tadarro.l.richardson@vumc.org. Twitter: @tlrichardsonjr.

REFERENCES

1. Markatis E, Afthinos A, Antonakis E, Papanikolaou IC. Cardiac sarcoidosis: diagnosis and management. *Rev Cardiovasc Med*. 2020;21(3):321-338.

2. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;11(7):1305-1323.

3. Patel MR, Cawley PJ, Heitner JF, et al. Detection of myocardial damage in patients with sarcoidosis. *Circulation*. 2009;120(20):1969-1977.

4. Blankstein R, Osborne M, Naya M, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. *J Am Coll Cardiol*. 2014;63(4):329-336.

5. Smith ED, Lakdawala NK, Papoutsidakis N, et al. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2020;141(23):1872-1884.

6. Yoneda ZT, Anderson KC, Quintana JA, et al. Early-onset atrial fibrillation and the prevalence of rare variants in cardiomyopathy and arrhythmia genes. *JAMA Cardiol*. 2021;6(12):1371-1379.

7. Yoneda ZT, Anderson KC, Ye F, et al. Mortality among patients with early-onset atrial fibrillation and rare variants in cardiomyopathy and arrhythmia genes. *JAMA Cardiol*. 2022;7(7):733-741.

8. Zelinka L, McCann S, Budde J, et al. Characterization of the in vitro expressed autoimmune rippling muscle disease immunogenic domain of human titin encoded by TTN exons 248-249. *Biochem Biophys Res Commun*. 2011;411(3):501-505.

9. Machado C, Sunkel CE, Andrew DJ. Human autoantibodies reveal titin as a chromosomal protein. *J Cell Biol*. 1998;141(2):321-333.

KEY WORDS **atrial fibrillation, cardiomyopathy, genetic disorders, imaging, ventricular tachycardia**