MINI-FOCUS ISSUE: HEART FAILURE

ADVANCED

CASE REPORT: CLINICAL CASE

Twice Bitten, Thrice Shy

A Case of Recurrent Isolated Cardiac Sarcoidosis in the Transplanted Heart

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ABSTRACT

We present a case of recurrent isolated cardiac sarcoidosis, 3 years post-heart transplantation. The case highlights the scarcity of data on the utility of immunosuppression in cardiac sarcoidosis and, in particular, raises questions about the optimal immunosuppression regimen in transplant recipients. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:427–32) © 2021 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 43-year-old man presented to the heart transplant clinic with palpitations, 3 years post-transplantation for isolated cardiac sarcoidosis. His personal heart rate monitor had detected intermittent bursts of tachycardia exceeding 200 beats/min during exercise. His regular medications included tacrolimus, everolimus, aspirin, trimethoprim-sulfamethoxazole, cholecalciferol, calcium, magnesium, and pravastatin. Hemodynamic parameters and examination were unremarkable.

LEARNING OBJECTIVES

- To make a differential diagnosis of recurrent disease in patients with ventricular arrhythmias post-heart transplantation for cardiac sarcoidosis.
- To understand the complexities of prolonged corticosteroid use in cardiac sarcoidosis.

PAST MEDICAL HISTORY

The patient had undergone heart transplantation 3 years earlier for presumed idiopathic dilated cardiomyopathy with recurrent ventricular tachycardia (VT) necessitating implantation of a secondary prevention cardioverter-defibrillator. He had no other significant medical history and was a nonsmoker with no family history of cardiomyopathy. Only at the time of histological assessment of the explanted heart was the cardiomyopathy determined to be secondary to cardiac sarcoidosis on the basis of the presence of granulomatous inflammation composed of numerous tightly packed, small, non-necrotizing granulomas typical of the disease (**Figure 1A**). In addition, single multinucleated giant cells were found within the myocardium (**Figure 1B**). Rigorous review of the patient's transplantation work-up data, including whole body computed tomography and subsequent screening for extracardiac sarcoidosis, revealed no evidence of other organ involvement.

The patient's early recovery from heart transplantation was relatively unremarkable. He was successfully treated with valganciclovir for cytomegalovirus reactivation and had a single episode of grade 2R cellular rejection requiring a pulse of intravenous methylprednisolone, followed by a weaning regimen of prednisone. Prednisone was successfully weaned to cessation by the 18th month following transplantation, in conjunction with consistently negative surveillance endomyocardial biopsy results and the titration of everolimus and tacrolimus. His smooth recovery enabled him to return to his pre-morbid penchant for mountain bike racing within a year of heart transplantation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis was broad, including electrolyte abnormalities, coronary artery vasculopathy or other disease, structural and conduction abnormalities, and cardiac rejection, as well as medication complications.

INVESTIGATIONS

The patient's electrolyte levels were normal. His electrocardiogram demonstrated sinus rhythm with right-axis deviation and a nonspecific intraventricular conduction delay resulting in a QRS complex duration of 150 ms (Figure 2B). Earlier post-transplant electrocardiograms had shown sinus rhythm without evidence of conduction delay or axis shift (Figure 2A); this change suggested the potential development of conduction system disease. The echocardiogram demonstrated normal left ventricular size and function, despite the presence of a new regional wall motion abnormality at the basal septum. Coronary computed tomography angiography was performed out of concern for coronary artery vasculopathy or

FIGURE 1 Histological Assessments
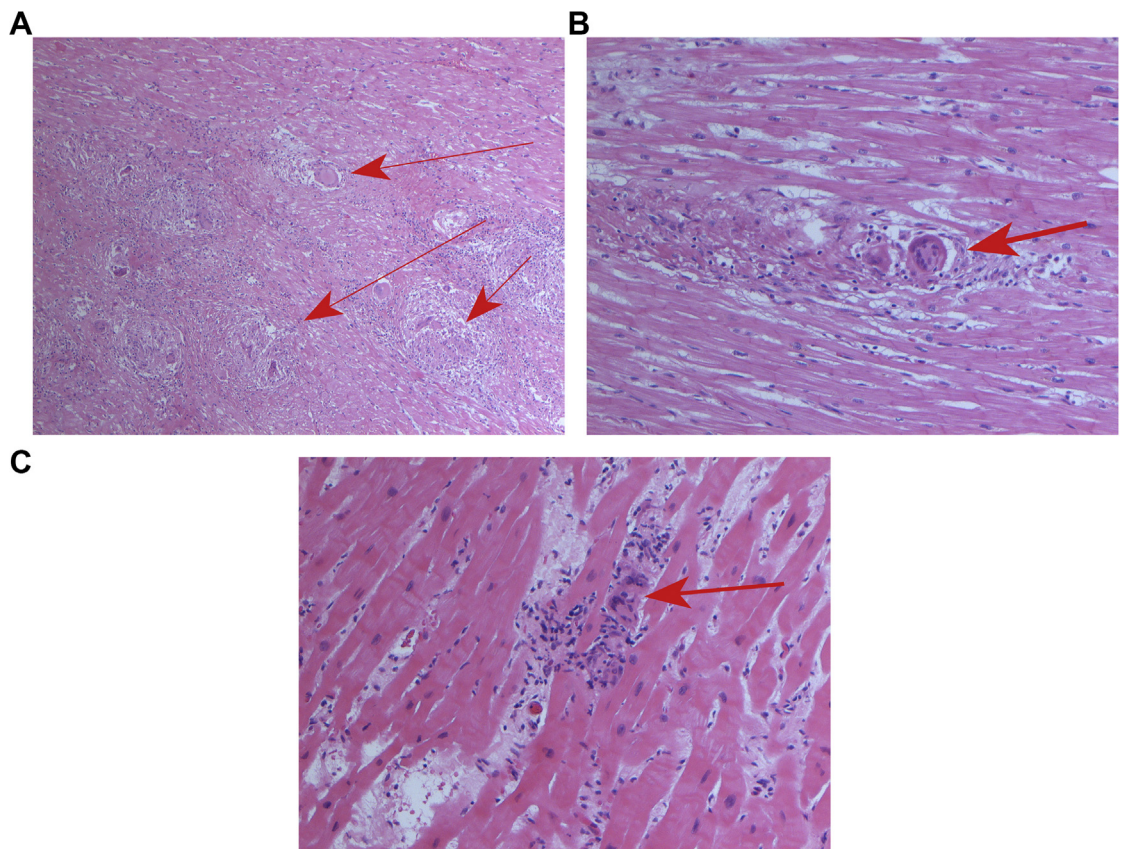
(A) Extensive granulomatous inflammation composed of numerous tightly packed, small, non-necrotizing granulomas **(arrows)** (original magnification ×4) **(B)** Single multinucleated giant cells **(arrow)** within myocardium of the explanted heart (original magnification ×10). **(C)** Endomyocardial biopsy of the transplanted heart showing scattered multinucleated giant cells **(arrow)** within the myocardium (original magnification ×10).
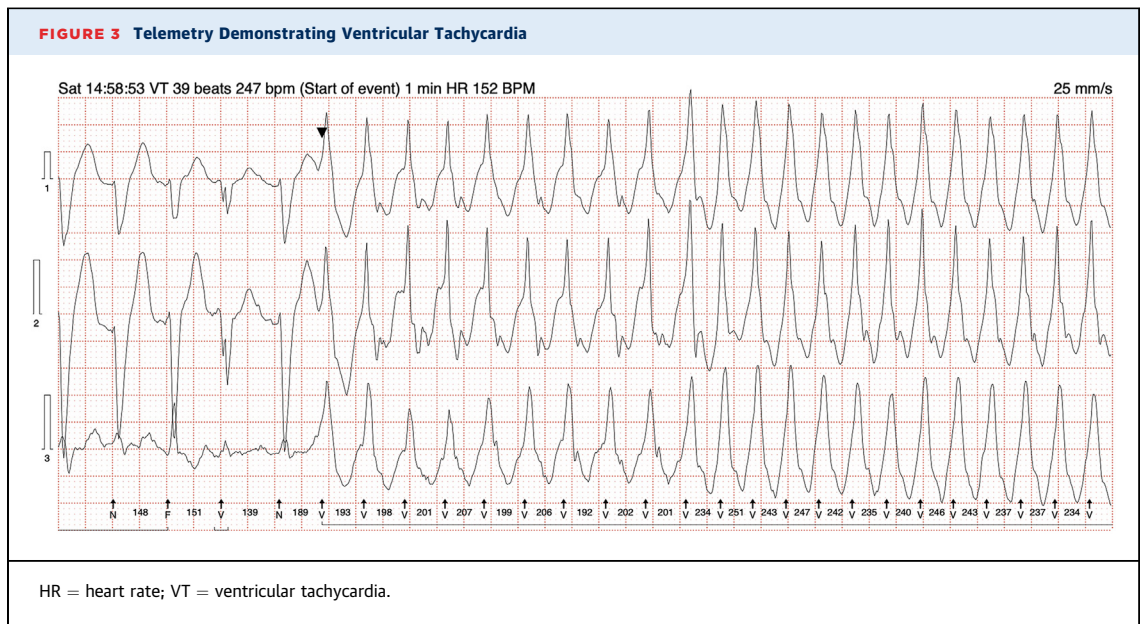
FIGURE 2 Electrocardiograms
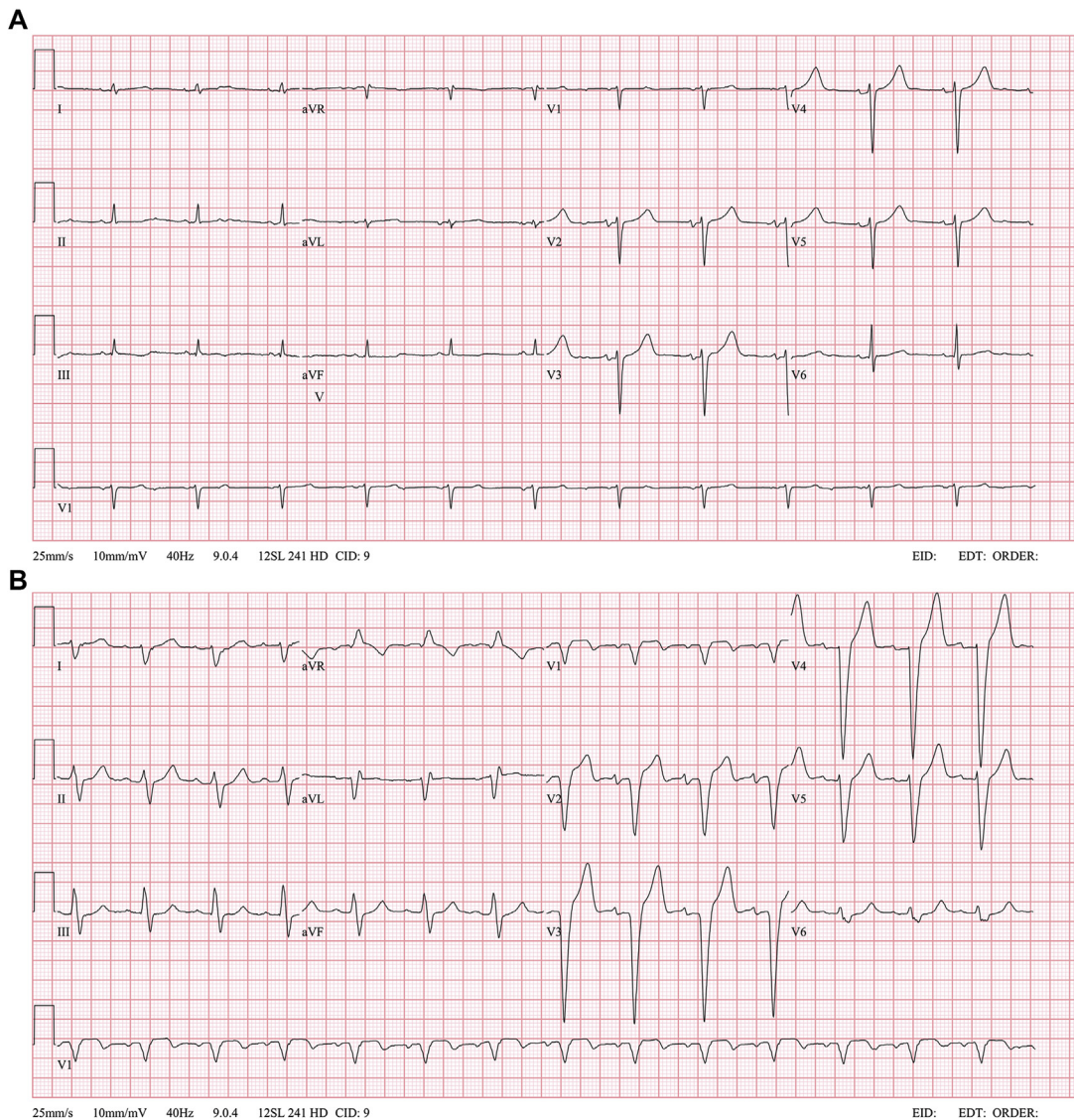
(A) Electrocardiogram recorded 3 years earlier, in the early post-transplantation period, demonstrating no conduction delay. (B) Electro-cardiogram on presentation demonstrating nonspecific intraventricular conduction delay with right-axis deviation.

other disease and identified mixed plaque in the proximal left anterior descending artery with 20% luminal stenosis. A subsequent exercise stress echo-cardiogram showed no evidence of inducible ischemia at a high aerobic capacity. Holter monitoring revealed multiple episodes of symptomatic VT (Figure 3).

The patient subsequently underwent cardiac magnetic resonance (CMR), which demonstrated wall thinning, hypokinesis, and near transmural late gadolinium enhancement of the basal interventric-ular septum without active myocardial inflammation or edema, findings suggestive of sarcoidosis (Figure 4). This diagnosis was then confirmed histo-logically following examination of endomyocardial biopsy specimens (Figure 1C) in which scattered multinucleated giant cells were seen within the myocardium. Repeat screening for extracardiac sarcoidosis again demonstrated no other detectable organ involvement.

FIGURE 3   Telemetry Demonstrating Ventricular Tachycardia

Sat 14:58:53 VT 39 beats 247 bpm (Start of event) 1 min HR 152 BPM   25 mm/s

HR = heart rate; VT = ventricular tachycardia.

MANAGEMENT

Implantable cardiac resynchronization therapy with a defibrillator was inserted in response to the patient's symptomatic VT, his wide left bundle branch block on electrocardiogram, the presence of significant burden of fibrosis on CMR, and the acknowledgment of the patient's clinical course before transplantation, which had resulted in end-stage biventricular heart

FIGURE 4   Cardiac Magnetic Resonance

Basal slice from short-axis stack series of late gadolinium enhancement images (phase-sensitive inversion recovery) showing near transmural late gadolinium enhancement of the basal septum **(arrow)**.

failure. A steroid bolus of methylprednisolone, 1 g daily for 3 days, was commenced, followed by a weaning schedule of prednisone starting at 1 mg/kg in divided doses, weaned by 5 mg/day until a dose of 20 mg daily was reached, after which the patient had a more gradual taper down to a maintenance dose of 7.5 mg daily. The patient continues to take prednisone, in conjunction with other immunosuppressive medications. He was discharged home, with ongoing follow-up in the heart transplant clinic.

DISCUSSION

Sarcoidosis is a relatively rare multisystem disease of unknown etiology, with estimates of 20% to 30% of affected patients demonstrating myocardial granulomas at autopsy [1,2]. The diagnosis of cardiac sarcoidosis is important given its pathological sequelae, including sudden cardiac death (SCD), ventricular tachyarrhythmias, complete heart block, and cardiomyopathy [3].

Heart transplantation resulting from cardiac sarcoidosis is an option for patients with incessant arrhythmias or refractory end-stage heart failure despite optimal medical therapies, although data on outcomes post-transplantation are conflicting [4]. Some data suggest similar or improved outcomes post-transplantation from cardiac sarcoidosis compared with other disorders, whereas a retrospective review by Akashi et al. [4] showed a trend toward higher mortality in patients with cardiac sarcoidosis. Individuals who undergo heart transplantation are pharmacologically immunosuppressed

lifelong, regardless of cause. At our institution (St. Vincent's Hospital, Sydney, Australia), we endeavor to wean patients from corticosteroids in line with endomyocardial biopsy surveillance results because of the widespread deleterious side effects of this therapy (5). This transition often involves commencement of a mammalian target of rapamycin inhibitor such as everolimus, given its anti-proliferative effects and protection from coronary artery vasculopathy (6), in conjunction with myco-phenolate and tacrolimus.

This is one of few reported cases of recurrent iso-lated cardiac sarcoidosis in a transplanted heart, and it raises the question of how to best avoid relapse. Even in the patients who are not transplant re-cipients, data are limited and conflicting when comparing patients with cardiac sarcoidosis who are treated with immunosuppression with patients with cardiac sarcoidosis who are not receiving any immu-nosuppressive agents. In a study by Vignaux et al. (7), the investigators found that patients who had received corticosteroids had improved CMR findings at 12-month follow-up compared with patients who had not received treatment. Similarly, Osborne et al. (8) found with, serial positron-emission tomography imaging, that corticosteroid therapy was associated with an improvement in left ventricular ejection fraction in patients with cardiac sarcoidosis who demonstrated reduction in myocardial inflammation. It has been suggested that such therapies may be of particular benefit if they are started before scar for-mation and irreversible ventricular dysfunction oc-curs (9). However, we have previously found no significant difference in the rate of VT or SCD be-tween patients with CMR detected cardiac sarcoidosis who are receiving corticosteroid therapy and those who are not receiving therapy (1). Therefore, despite some evidence indicating improved cardiac function and imaging parameters, there is a relative deficiency of evidence to suggest that continued systemic corticosteroid use reduces the manifestation and clinical sequelae of cardiac involvement from sarcoidosis. Data pertaining to the transplant recip-ient with sarcoidosis are even more scarce. In a study

by Perkel et al. (10), a few patients with cardiac sarcoidosis who underwent heart transplantation were maintained on low-dose corticosteroids, and none had recurrent disease. These limited data—at least anecdotally—present a case for continued corti-costeroid therapy in this subgroup of heart transplant recipients (10).

FOLLOW-UP

The patient was able to return to normal physical activities soon, with no further palpitations. He has had 3 cardiac device checks, demonstrating 4 epi-sodes of nonsustained VT, but none requiring anti-tachycardia pacing or implantable cardioverter-defibrillator therapy. He has continued on low-dose prednisone, and repeat CMR a year later showed an appearance similar to that of his previous study. Now almost 2 years post-presentation, and 5 years post-initial transplantation, he remains asymptomatic, with preserved allograft function.

CONCLUSIONS

In this case report, we explore the recurrence of cardiac sarcoidosis after heart transplantation. The case was unique by the absence of discernible extracardiac sarcoidosis. There is a scarcity of evi-dence on the optimal treatment regimen to avoid recurrence of cardiac sarcoidosis in heart transplant recipients. This case raises questions about the po-tential utility of lifelong low-dose corticosteroids as part of the immunosuppression regimen in such patients.

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