Management of refractory ventricular tachycardia due to cardiac sarcoidosis—A biologic approach

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From the

Introduction
Cardiac sarcoidosis (CS) can present as ventricular tachycardia (VT). Management of VT in CS is difficult and includes disease-specific agents, including steroids, antiarrhythmic drugs (AADs), and implantation of an implantable cardioverter-defibrillator (ICD). In patients with steroid-resistant CS presenting with VT storm / incessant VT, radiofrequency (RF) catheter ablation is usually attempted. Patients with refractory VT and left ventricular (LV) dysfunction are referred for heart transplant. We report a case of steroid-resistant CS presenting with incessant VT and tachycardiomyopathy, in which the patient failed to respond to all the multimodal approaches and was worked up for heart transplantation. Use of a biological agent—adalimumab in this patient—resulted in termination of VT, followed by improvement in cardiac function.

Case report
A 35-year-old man presented with multiple episodes of palpitations, worsening over the past 6 months. He was diagnosed to have right ventricular outflow tract VT, for which RF catheter ablation was performed at another center. However, within a week the patient had a recurrence of VT with multiple morphologies exiting predominantly from the inferoposterior septum. Routine blood investigations were normal except for an elevated erythrocyte sedimentation rate and C-reactive protein. CS was suspected and a cardiac positron emission tomography (PET) scan was performed. It revealed heterogeneous uptake at the septal, apico-anterior, basal inferior, and lateral segments of the left ventricle as well as the left supraclavicular and cervical nodes (Figure 1A). Histopathology of the cervical node revealed multiple noncaseating granulomas suggestive of sarcoidosis, as well as metastatic papillary carcinoma of the thyroid, which was confirmed by immunohistochemistry (Figure 2A and B). A single-chamber ICD was then implanted and AADs were continued with a plan for total thyroidectomy with radical neck dissection for papillary carcinoma of the thyroid. Meanwhile, the patient developed incessant VT, which did not respond to multiple AADs. Immunosuppressive therapy with steroids (0.75 mg/kg methylprednisolone) was initiated for CS, but as the VT remained incessant, therapy was escalated to oral methotrexate (mtx; 20 mg per week), followed by intravenous pulse cyclophosphamide (1 g, single dose), as VT did not terminate with mtx. Conventional immunosuppressive therapy failed to revert the VT.

An electrophysiology study was performed, during which 18 morphologies of VT with varying cycle lengths were induced (Figure 1B). There were low-voltage areas in the LV mid and apical septum but no discrete isolated late potentials. Overdrive pacing as well as endoepicardial ablations of the clinical VT were attempted. There was transient suppression of the arrhythmia. All these features of VT point toward automaticity as a mechanism of arrhythmia. Sympatholysis with a left stellate ganglion blockade using bupivacaine was ineffective as well. Total thyroidectomy with radical neck dissection under general anesthesia was performed under high-risk consent for the thyroid carcinoma, and interestingly the patient remained in VT throughout the procedure. In this setting of refractory VT and severe LV dysfunction (LV ejection fraction of 26%), he was listed for emergent cardiac transplantation.

As an anti–tumor necrosis factor (TNF) agent, adalimumab, has been shown to be effective in sarcoidosis, we administered 40 mg subcutaneous adalimumab at this stage. Within 48 hours, there was a significant reduction of VT (Figure 1C), with a reversion to sinus rhythm by the third dose. During the treatment period there was no change in the PR interval from baseline until the last dose of adalimumab, suggesting sparing of the proximal conduction system. The entire timeline of treatment modalities and VT frequency is depicted in Figure 3. Repeat PET–computed tomography scan demonstrated complete

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At 14 months of follow-up the patient is in functional class I, with improved LV ejection function to 45% and free of VT.

**Discussion**

Our case illustrates the importance of immunosuppression and relative ineffectiveness of conventional antiarrhythmic modalities in the active inflammatory stages of CS.1 This case also illustrates the importance of recognizing steroid-resistant CS, and of intensifying immunosuppression in such cases. Though the use of this individualized approach has been relatively well established, the effectiveness of biological agents, namely adalimumab, in refractory VT has not been reported.

In this young patient, VTs of multiple morphologies and evidence of myocardial inflammation made CS a highly likely diagnosis. Tuberculin skin testing and interferon gamma release assay were negative and biopsy revealed noncaseating granuloma suggestive of CS. However, the newly diagnosed papillary thyroid carcinoma complicated his management. This association of sarcoidosis and papillary carcinoma has been reported in the literature.2,3 Malignancy and sarcoidosis have a complicated and relatively unclear relationship. It appears that presence of malignancy could predispose individuals to sarcoidosis.4 Additionally, there exists the entity of “sarcoid reactions,” which are localized forms of noncaseating granulomas of adjacent lymph nodes. There appears to be a reaction to antigens draining from the malignancy rather than an actual systemic form of sarcoidosis.5,6

Although thyroid metastases to the heart could explain the PET findings, we believed this to be unlikely for 2 reasons. Firstly, papillary carcinomas largely spread through lymphatics, and hematogenous seeding of the heart, though encountered, is extremely rare.7 Secondly, the rapid improvement of VT and complete resolution of cardiac PET findings with adalimumab point strongly toward CS. Adalimumab, in contrast, appears to increase the likelihood as well as severity of papillary cancer, which is very different from what was encountered here.8

VT is a common accompaniment of CS and is often difficult to manage. This difficulty arises from the need for disease-specific approaches along the course of the disease—active inflammatory, scar-related, or both.9 PET imaging is essential to

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**KEY TEACHING POINTS**

- Cardiac sarcoidosis (CS) can present as ventricular tachycardia, the treatment of which involves a multimodal approach including antiarrhythmic drugs, steroids, implantable cardioverter-defibrillator, and radiofrequency catheter ablation.
- It is not uncommon to see steroid-resistant CS in patients in whom other immunosuppressants such as methotrexate are given. Patients who fail to respond to this multimodal approach are subjected to heart transplant.
- It is prudent to try biological agents like adalimumab in such patients, before referring them for cardiac transplant.

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![Figure 1](image-url)

Figure 1  A: Baseline cardiac positron emission tomography and computed tomography (PET-CT) scan showing myocardial and lymph node uptake. B: Eighteen different morphologies of ventricular tachycardia induced in the electrophysiology laboratory. C: 12-lead electrocardiogram of patient showing reversion to sinus rhythm after adalimumab. D: Cardiac PET-CT scan showing myocardial resolution after adalimumab therapy.
make this distinction and guide therapy. Immunosuppression is initiated with corticosteroids while conventional treatment modalities like AADs, ICD implantation, and RF ablation are concurrently employed. We recommend initiating oral prednisolone at 1 mg/kg/day (maximum dose of 60 mg/day) or an equivalent dose of methylprednisolone for 8 weeks. With improvement, steroids are tapered over a period of 3–6 months and stopped. Oral mtx may be used as a steroid-sparing agent and continued for 2 years if there is no VT recurrence.

Steroid-resistant CS is occasionally encountered in clinical practice and is usually managed with an escalation of immunosuppression with agents like mtx and cyclophosphamide. However, disease remained refractory to all these agents and resolved with anti-TNF therapy (adalimumab). TNF-alpha plays an important role in the genesis and perpetuation of granulomas, and its inhibitors have been utilized in the management of refractory sarcoid. To the best of our knowledge this is the first case of refractory VT in CS, successfully managed with anti-TNF therapy. Although it is possible that VT resolution was related to the cumulative effect of immunosuppression and AADs used over the past weeks, we feel that adalimumab is more likely responsible. This is based on the strong temporal association of VT suppression with initiation of adalimumab and the sustained clinical benefit maintained thereafter.
Further studies are needed to validate the dose and duration of these biological agents in CS.

**Conclusion**

Biological agents like adalimumab open up a new avenue in the management of refractory VT in patients with CS unresponsive to conventional immunosuppression.

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