Ventricular tachyarrhythmia as a primary presentation of sarcoidosis

Paavo Uusimaa¹*, Kari Ylitalo¹, Olli Anttonen², Tuomas Kerola², Vesa Virtanen³, Eija Paäkkö⁴, and Pekka Raatikainen¹

¹Department of Internal Medicine, Division of Cardiology, University of Oulu, PO Box 5000, 90014 Oulu, Finland; ²Päijät-Häme Central Hospital, Lahti, Finland; ³Heart Center, University of Tampere, Tampere, Finland; and ⁴Department of Radiology, University of Oulu, Oulu, Finland

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Aims Sarcoidosis is a multisystem, granulomatous disease with occasional cardiac manifestations. The clinical course of patients with ventricular tachyarrhythmias as a primary presentation of sarcoidosis is mostly unknown.

Methods and results We describe nine patients (four males and five females) in whom sarcoidosis manifested as ventricular tachycardia (VT). The age of the patients was 53 ± 10 years (range 33–68). The disease was diagnosed by endomyocardial biopsy in eight patients and by lymph node biopsy in one patient. The presenting arrhythmia varied from non-sustained VT to incessant VT and ventricular fibrillation. All patients received implantable cardioverter defibrillator (ICD) and anti-arrhythmic medication. High-dose steroid treatment was used in eight cases. During the follow-up (50 ± 34 months), five patients underwent appropriate ICD therapies and non-sustained VT episodes were detected in four patients. Two patients developed incessant VT, which was treated by catheter ablation. One patient was referred for heart transplantation.

Conclusion Our data indicate that sarcoidosis can manifest as VT without any detectable systemic findings. This makes sarcoidosis an important diagnostic consideration in patients with VT of unknown origin. Arrhythmia control in cardiac sarcoidosis is difficult, and all modern treatments including high-dose steroids, anti-arrhythmic drugs, ICD, and catheter ablation are needed to suppress the arrhythmias.

KEYWORDS Catheter ablation; Implantable cardioverter defibrillator; Sarcoidosis; Ventricular tachycardia

Introduction

Sarcoidosis is a multisystem disease of unknown aetiology. Its hallmark histopathological findings are non-caseating granulomas and subsequent tissue scarring.¹,² Clinical course and prognosis of sarcoidosis are highly variable and correlate with the involved organs. It primarily affects the lungs and thoracic lymph nodes. Cardiac manifestations such as conduction abnormalities, congestive heart failure, and ventricular arrhythmias are rare, but potentially fatal.³,⁴ Myocardial involvement is usually associated with widespread multiorgan disease and carries a 40% mortality in 5 years.⁵ The most important causes of death are ventricular tachyarrhythmias and congestive heart failure caused by infiltration of the heart by sarcoïd granulomas.³,⁶–⁸ The granulomas not only diminish the systolic contractile function but also form an anatomical substrate for re-entrant ventricular tachycardia (VT) by creating a slow conduction zone in and around the scar areas.⁸,⁹

Given the findings that in patients with cardiac sarcoidosis, ventricular ectopy and non-sustained and sustained VTs are commonly observed and carry poor prognosis,¹⁰ exclusion of sarcoidosis is clinically important in patients with VT of unknown origin. The diagnostic work-up in patients with presumably idiopathic VT should include careful history and clinical examination, laboratory tests, repeated electrocardiogram (ECG) recording, chest X-ray, and cardiac imaging with modern techniques including cardiovascular magnetic resonance (CMR) and endomyocardial biopsy to exclude cardiac sarcoidosis. The treatment of life-threatening ventricular tachyarrhythmias in patients with myocardial sarcoidosis is challenging, and in many cases, all modern treatments including systemic steroids, anti-arrhythmic drugs, implantable cardioverter defibrillator (ICD), and catheter ablation are needed to control the arrhythmias. Here, we describe nine patients in whom ventricular tachyarrhythmias were the initial manifestation
of sarcoidosis. The diagnostic work-up, treatment, and clinical course of the disease are discussed.

Methods

Patients

The present study comply with the Declaration of Helsinki. The patient population consisted of nine patients (four males and five females) who were admitted to the University Hospital of Oulu (n = 6), the University Hospital of Tampere (n = 1), and the Päijät-Häme Central Hospital (n = 2) during years 1998–2006 for the evaluation of VT. The age of the patients was 53 ± 10 years (range 33–68). The presenting symptoms of the patients varied from occasional palpitations to cardiac arrest. The clinical characteristics of the patients are described in Table 1. All patients gave informed consent for the examinations, and all procedures were performed according to the commonly accepted clinical protocols.

Cardiac sarcoidosis was suspected after coronary artery disease, cardiomyopathies, and other cardiac diseases, which have been commonly associated with life-threatening ventricular tachyarrhythmias, were excluded. The diagnosis was made according to the guidelines of the Japanese Ministry of Health and Welfare. Only patients in whom the clinical presentation was supported by the histological evidence of non-caseating granulomas by endomyocardial biopsy were included in the study. Patients with the possibility of infection (e.g. tuberculosis), or hypersensitivity reaction to medication causing granulomatous inflammation were excluded from the study.

Examinations

All patients underwent thorough non-invasive and invasive cardiological examinations including careful history and clinical examination, laboratory tests, repeated ECG recording, cardiac imaging, programmed electrophysiological testing, and endomyocardial biopsy. Chest X-rays of the patients were evaluated by a radiologist, and all patients were also carefully studied by a specialist of lung biopsy. Cardiovascular magnetic resonance was done using a 1.5 T magnet. Cine images were obtained by using FIESTA sequence in axial, two and four chamber, and short-axis directions. Contrast enhanced images were obtained in one patient by a T1-weighted fast spin echo sequence, whereas in the other patients, a specific delayed enhancement gradient echo sequence was used. In one patient, CMR was hampered by ventricular ectopy, and in another patient, the short-axis images were suboptimal because of technical failure. Cardiovascular magnetic resonance could not be performed in three patients because of previous implantation of the ICD. Coronary angiography was made in all patients and left ventricular (LV) cineangio- graphy in seven patients. Right ventricular endomyocardial biopsies were taken from all patients. In one patient, a lymph node biopsy was taken by mediastinoscopy 3 years after the initial examination.

Inducibility of ventricular tachyarrhythmias was tested by twice-threshold stimulation at right ventricular apex and outflow tract at 600 and 400 ms basic cycle length with up to three extra stimuli. In three patients, endocardial ventricular electrogram voltage maps were obtained using an electroanatomic CARTO mapping system (Biosense Webster, Inc., Diamond Bar, CA, USA). Electrogram amplitude <1.5 mV was considered to be abnormal. In two patients, catheter ablation was performed with a 7 Fr steerable catheter with 3.5-mm saline-irrigated electrode tip (Navi-Star ThermoCool, Biosense Webster, Inc., Diamond Bar, CA, USA). Radiofrequency ablation targeted the potential VT isthmus sites in and around the low-voltage area in the LV.

Results

Diagnostics

Clinical characteristics of the patients are shown in Table 1. Tachyarrhythmias varied from frequent ventricular ectopy and non-sustained VT to incessant VT and ventricular fibrillation (Figure 1). The QRS complex during VT had left bundle branch block morphology in three patients and right bundle branch block (RBBB) pattern in two patients (Table 2). In the rest of the patients, the QRS complex was polymorphic during VT. During normal sinus rhythm, there were no echocardiographic signs of prior myocardial infarction or

<table>
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<th>Patient</th>
<th>Age</th>
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<th>Symptoms</th>
<th>Other diseases</th>
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<th>ACE (9-65 U/L)</th>
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ESR, erythrocyte sedimentation rate; ACE, angiotensin-converting enzyme.

⁴Endomyocardial biopsy contained fat suggesting arrhythmogenic right ventricular dysplasia but biopsy from mediastinal lymph nodes revealed granulomas 3 years afterwards.
ischaemia. The QRS morphology was normal in three patients, one patient had left anterior hemiblock, and five patients had a partial or complete RBBB. The corrected QT interval was 425 ± 47 ms (range 358–485 ms), and the PR interval was 175 ± 36 ms (range 130–260 ms). One patient had a complete atrioventricular (AV) conduction block in the baseline ECG.

Significant coronary artery disease was excluded by angiography in all patients. Left ventricular ejection fraction was >50% in all patients. Echocardiography, LV angiography, or CMR revealed small aneurysms in three cases and slight abnormalities of the left or right ventricular wall in three cases (Figure 2 and Table 2). Electrophysiological study confirmed susceptibility to ventricular arrhythmias in all patients. Sustained monomorphic VT was detected in three patients, and in all others programmed electrophysiological stimulation-induced long runs of non-sustained VT. In a patient with initial diagnosis of arrhythmogenic right ventricular dysplasia (ARVD), detailed electroanatomical mapping of the right ventricle with the CARTO system did not reveal any low-voltage areas.

The diagnosis of myocardial sarcoidosis was confirmed by the analysis of the right ventricular endomyocardial biopsies in eight patients (Table 1). In one patient, right ventricular endomyocardial biopsy revealed fatty infiltration suggesting ARVD. Sarcoidosis was diagnosed 3 years later from lymph node biopsy taken by mediastinoscopy; therefore, VT was regarded as a cardiac manifestation of sarcoidosis also in this patient.

**Treatment and clinical course**

Treatment of the patients was focused both on the arrhythmia and on the underlying sarcoid heart disease (Table 3). All patients received an ICD. Single lead system with VVIR backup pacing was used in seven cases, and two patients with impaired AV nodal conduction received a dual-chamber device. High-dose steroid treatment was used in eight patients. The mean initial daily dose of prednisolon was 58 ± 13 mg (range 40–80 mg). During follow-up, the steroid dose was gradually decreased to a maintenance dose of 10–15 mg/d. The patient with initial diagnosis of ARVD (Patient 3) was asymptomatic during early follow-up, and therefore, no steroid treatment was initiated. Recently, he had hypercalciuria and some episodes of urinary stones, hence initiation of steroid treatment is reconsidered.

Anti-arrhythmic medication included β-blockers (n = 9), amiodarone (n = 2), flecainide (n = 2), mexiletine (n = 1), and quinidine (n = 1) (Table 3). Two patients had incessant VT on admission to the hospital. In one of them, VT was suppressed by a combination of β-blocker and amiodarone. The other one was treated with catheter ablation before ICD implantation. She had multiple episodes of VT requiring anti-tachycardia pacing 3 weeks after the ablation. In the re-ablation, a careful electroanatomic map of the LV was constructed and the local scar area was identified. Radiofrequency ablation targeted the potential VT isthmus sites in and around the low-voltage area. After the re-ablation, no sustained VT was inducible, and she has been free of VT episodes for over 40 months.

The clinical course of cardiac sarcoidosis in this patient group was very variable. Arrhythmia was the initial manifestation of sarcoid heart disease in all patients. One patient (Patient 3) was later diagnosed with pulmonary sarcoidosis, whereas in the other patients, involvement of other organs has not been detected to date. The development of pulmonary sarcoidosis in Patient 3 was not accompanied by the activation of cardiac disease. During follow-up of 51 ± 37 months (range 5–118), five patients had VTs treated by overdrive pacing and/or defibrillation and four patients had several non-sustained VT episodes (Table 3). Moreover, one patient (Patient 6) developed a complete AV block.

**Figure 1** Examples of ventricular tachycardias caused by sarcoidosis. Sarcoidosis caused monomorphic ventricular tachycardia with QRS morphology of right bundle branch block type (A) in two patients and left bundle branch block type (B) in three patients. In the rest of the patients, the presenting arrhythmia was either polymorphic ventricular tachycardia (C) or ventricular fibrillation.
Two patients developed severe LV dysfunction and dilated cardiomyopathy. In one of them (Patient 1), LV function improved during medical treatment, whereas in the other one (Patient 2), the disease was in remission for 6 years after the implantation of ICD but reactivated thereafter, leading to a rapid decline in LV function with non-sustained VT. Despite increased doses of steroid and conventional medical treatment of heart failure, she developed severe rest dyspnoea and incessant VT. Ventricular tachycardia was successfully treated by catheter ablation. During the ablation, large low-voltage areas were identified in the LV, and a long ablation line from the border of the scar area to the mitral annulus was performed (Figure 3). However, 4 months later, VT requiring ICD discharge recurred spontaneously. Heart failure deteriorated despite medical treatment, and the patient was referred for heart transplantation. During early post-operative phase, she developed multiorgan failure leading to death.

**Discussion**

Our data indicate that sarcoidosis can manifest as malignant ventricular tachyarrhythmia without any systemic findings. Given these findings and the poor prognosis of cardiac sarcoidosis, exclusion of sarcoidosis is important in patients with VT of unknown origin. Particularly, patients with VT and conduction abnormalities in resting ECG or even slight abnormalities in cardiac imaging should be suspected as having cardiac sarcoidosis. Systemic steroids and anti-arrhythmic medication alleviate arrhythmic symptoms, but long-term response to these agents is unpredictable. In our patient series, two patients required catheter ablation for incessant VT, and one patient was referred for heart transplantation after being in stable condition for many years.
The main differential diagnostic options in this population with normal LV function were ARVD and giant cell myocarditis. In particular, the clinical and morphological features of ARVD may mimic cardiac sarcoidosis. Here, the diagnostic delay was long in one patient, as clinical features and endomyocardial biopsy suggested ARVD.

**Electrocardiogram findings**

The results of our study showed that the clinical spectrum of ventricular arrhythmias in sarcoidosis is highly variable. In contrast to previous series, all of our patients initially had preserved systolic function and arrhythmias were not associated with LV dilation and dysfunction. It has been suggested that the mechanism of VT in patients with cardiac sarcoidosis is re-entry occurring through surviving myocyte bundles in and around the scar. In keeping with this concept, echocardiography, LV angiography, and CMR revealed small aneurysms and other abnormalities as potential anatomic substrates for re-entrant VT in most of our patients. In Patient 5, the RBBB and axis were consistent with the location of the scar in the LV cineangiography, and CMR. Furthermore, the induction and termination of the VT by pacing and elimination of all VTs by modification of the anatomic substrate are consistent with the re-entrant mechanism.

Many patients in the current (56%) and previous series had a complete or partial RBBB. In autopsy studies, virtually all subjects with advanced AV conduction abnormalities had sarcoid granulomas in the basal ventricular septum. Hence, it was not surprising that the patient with echocardiographic abnormalities in the basal ventricular septum had a complete AV block.

**Treatment of the patients**

The optimal management of cardiac sarcoidosis has not been well defined. In the present series, all modern treatments including steroids, anti-arrhythmic medications, ICD, and catheter ablation were used to control the arrhythmias. High-dose steroid treatment was started in all but one

**Diagnosis of cardiac sarcoidosis**

According to the guidelines of the Japanese Ministry of Health and Welfare, cardiac involvement should be suspected in patients with histological diagnosis of extracardiac sarcoidosis if the patient has abnormalities in the resting or ambulatory ECG (e.g. bundle branch or AV block, pathological Q or ST-T changes or ventricular tachyarrhythmias) and/or in echocardiography or other cardiac imaging (e.g. abnormal wall motion, regional wall thinning, dilation of the LV or depressed LV function in echocardiography, local perfusion defects or other abnormalities in positron emission computed tomography, or CMR). In our series, none of the patients had any findings or symptoms of systemic sarcoidosis. Nevertheless, cardiac sarcoidosis was suspected if coronary artery disease, cardiomyopathies, and other cardiac diseases commonly associated with life-threatening ventricular tachyarrhythmias were excluded and if local wall motion abnormalities were detected by echocardiography, LV cineangiography, or CMR. The diagnosis of sarcoidosis was confirmed by histopathological analysis of right ventricular biopsy in eight patients and mediastinoscopic lung biopsy in one patient.

The diagnosis of cardiac sarcoidosis is elusive in patients with negative endomyocardial biopsy. In these cases, the diagnosis often requires high clinical suspicion with a combination of serial ECG recordings, Holter monitoring, echocardiography, myocardial perfusion studies, and CMR. In our experience, the sarcoid lesions were often limited to relatively small areas and were commonly not detected by transthoracic echocardiography. Among the modern cardiac-imaging techniques, the ability of CMR to provide detailed information on cardiac anatomy and function has made it an attractive tool in the diagnosis of cardiac sarcoidosis. In the current study, CMR provided valuable diagnostic information in five cases. The principal drawback of magnetic resonance imaging in this and previous studies was that it could not be used in patients with a pacemaker or ICD. In these cases, LV cineangiography, single-photon emission computed tomography, or multislice computed tomography might be valuable tools in detecting local wall motion and perfusion abnormalities.
patient immediately after the diagnosis of cardiac sarcoidosis was made. Steroid treatment combined with anti-arrhythmic therapy suppressed ventricular arrhythmias in seven patients, which is in accord with the previous findings. It is also possible that early treatment with steroid may have prevented or decelerated the systemic manifestations of the disease. Cardiac involvement of sarcoidosis is associated with a mortality rate exceeding 40% at 5 years, and many of the deaths are caused by ventricular tachyarrhythmias. Therefore, we feel, like many other investigators, that implanting an ICD is prudent in all patients with cardiac sarcoidosis and VT regardless of the initial response to other therapies. This opinion is supported by the fact that most of the patients in our study had VT requiring ICD therapy and one patient developed incessant VT after being in stable condition for 6 years. The high prevalence of AV nodal conduction disturbances observed here and in previous studies indicates that it may be advisable to implant a dual-chamber device to the patients with cardiac sarcoidosis.

Noda et al. recently performed successful linear catheter ablation to a 33-year-old patient with cardiac sarcoidosis and right ventricular tachycardia. We performed radiofrequency catheter ablation of drug-refractory LV tachycardia in two patients. The first patient had recurrent VT 3 weeks after the ablation, and a more extensive re-ablation with a long linear lesion through the scar area was performed. After the re-ablation, she has been free of VT for 40 months. The other patient had recurrent VT and progressive heart failure after the ablation and was referred

Figure 3  Catheter ablation of incessant ventricular tachycardia in a patient with cardiac sarcoidosis. During the ablation, large low-voltage areas were identified in the left ventricular and long ablation line from the border of the scar area to the mitral annulus (MA) was performed. The symptoms of the patient improved transiently, but 4 months after the ablation she had relapse of ventricular tachycardia associated with deterioration of left ventricular function. In the CARTO™ map, the dense scar is marked with gray and the low voltage by red colour, respectively. Fragmented signals are marked with light pink and the ablation points with red dots, respectively.
for heart transplantation. Hence, our experiences with catheter ablation in patients with sarcoidosis and VT are quite similar to those of Koplan et al.9 In their cohort, four out of eight patients who underwent ablation for medically refractory VT were free of recurrent VT at long-term follow-up. Although sarcoidosis has been reported to recur in the transplanted donor heart, transplantation remains the only option in the most severe situations. In our cohort, one patient was referred for cardiac transplantation, despite steroids, anti-arrhythmic medication, ICD, and catheter ablation. Unfortunately, she died from peripartum multiorgan failure soon after the surgery.

Limitations

Although this study represents the largest series of patients reported with life-threatening ventricular tachyarrhythmia as a primary presentation of sarcoidosis, it has several limitations. First, our study was retrospective and consisted only of patients with histologically proven cardiac sarcoidosis. This may have caused considerable selection bias, because the results of the previous studies indicate that due to the patchy location of the sarcoid granulomas, the diagnostic yield of endomyocardial biopsy is low.10,11 In contrast, by relying on positive endomyocardial biopsies, we were able to reliably exclude wrong positive cases. Secondly, accurate data on the number of patients examined for VT during the study period are not available. Therefore, no conclusion with regard to the prevalence of sarcoidosis among patients with unexplained VT can be made. Likewise, no attempt was made to evaluate the prevalence of VT among patients with systemic sarcoidosis. Previous studies indicate that although cardiac involvement has been described in 20–58% of the patients with sarcoidosis in histopathological studies, <5% of the patients with sarcoidosis have cardiac symptoms and findings.6,12

Clinical implications

In our cohort, none of the subjects had any clinical or radiological evidence of systemic sarcoidosis at the initial examination. This is an interesting finding because previously isolated cardiac sarcoidosis has been reported to be rare.3,4 Given the important role of ventricular tachyarrhythmias as the mechanism of sudden death in patients with cardiac sarcoidosis,7,10 exclusion of sarcoidosis is essential in all patients with VT of unknown origin. In particular, sarcoidosis should be suspected if the patient has a partial or complete RBBB in baseline ECG and local wall motion abnormalities in cardiac imaging. It is concluded that VT can be the first manifestation of sarcoidosis. The clinical spectrum of ventricular tachyarrhythmias in cardiac sarcoidosis is variable. Implantable cardioverter defibrillator and high-dose steroid therapy should be considered in every patient with cardiac sarcoidosis, because anti-arrhythmic medication is insufficient to control arrhythmias in these patients. Catheter ablation is a viable therapeutic option in selected patients with frequent VT episodes. In patients with life-threatening ventricular arrhythmias, despite all other therapies, heart transplantation remains the only choice.

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References