Cardiac sarcoidosis presenting with syncope and rapidly progressive atrioventricular block: a case report

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Background
Cardiac sarcoidosis (CS) accounts for a substantial morbidity and mortality. Early recognition of CS is important to prevent such detrimental consequences. A definite diagnosis of cardiac sarcoidosis remains challenging. Even after the diagnosis of CS is established, the appropriate dose and duration of corticosteroids in the treatment of CS have not been well-defined.

Case summary
In this report, we discuss a case of a 50-year-old man who presented with recurrent syncope. Electrocardiogram revealed sinus rhythm with left bundle branch block. Telemetry captured high-grade atrioventricular block. Coronary angiogram showed no coronary artery disease. Left ventriculography revealed left ventricular ejection fraction (LVEF) of 35–40%. A dual-chamber pacemaker was implanted. Cardiac magnetic resonance revealed mid-myocardial scarring suggestive of sarcoidosis. Computed tomography of the chest showed lymphadenopathy. Transbronchial biopsy was unrevealing; however, mediastinoscopy and lymph node biopsy showed non-caseating granulomas diagnostic of sarcoidosis. He became pacemaker dependent as noted in outpatient pacemaker interrogations. A biventricular implantable cardioverter-defibrillator upgrade was performed for primary prevention of sudden cardiac death. He was started on prednisone taper over the course of 6 months. After 1-year, his LVEF improved to 55% and native atrioventricular (AV) conduction had recovered as noted in outpatient device interrogations.

Discussion
This case highlights the importance to include CS in the differential diagnosis of a young patient with conduction system disease and non-ischaemic cardiomyopathy for appropriate treatment. Patients with left ventricular systolic dysfunction and AV nodal disease could potentially benefit from a slow prednisone taper over the course of 6 months.

Keywords
Case report • Cardiac sarcoidosis • High-grade AV block • Syncope • Cardiac magnetic resonance • Prednisone

Learning points
• It is important to consider cardiac sarcoidosis (CS) as a secondary cause of atrioventricular block in a young patient.
• To emphasize the use of cardiac magnetic resonance imaging and extracardiac tissue biopsy to diagnose CS.
• Late initiation of corticosteroid therapy in a patient with CS remained effective in improving left ventricular systolic function and reversing AV block after completing 6 months course of slow prednisone taper.
Introduction

Sarcoidosis is a systemic granulomatous disorder of unknown cause that can virtually affect any organ, most commonly the lungs, skin, lymph nodes, and eyes. Bernstein et al., in 1929, were the first to describe a case of cardiac involvement in a patient with systemic sarcoidosis. A definite diagnosis of cardiac sarcoidosis (CS) is quite challenging as there is no single reliable test to diagnose CS. Nonetheless, early recognition of cardiac involvement in sarcoidosis is imperative as appropriate measures and treatment can be initiated to slow the progression of the disease and prevent death from fatal arrhythmias. In this report, we present an interesting case of CS that was diagnosed after a thorough workup for unheralded syncopal events and non-ischaemic cardiomyopathy.

Timeline

| Day/month       | Event                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|
| 23 November 2016| Developed first episode of syncope while exercising                                                                                  |
|                 | Admission to outside hospital, initial blood test including cardiac enzymes and telemetry monitoring were unremarkable              |
|                 | Discharged for further outpatient investigations                                                                                     |
| 23 December 2016| Seen in the cardiology clinic                                                                                                         |
|                 | Electrocardiogram revealed new left bundle branch block                                                                               |
|                 | Exercise stress test provoked pre-syncopal event and self-limiting bursts of tachycardia                                             |
| 1 January 2017 (a.m.) | Admission to emergency department for four episodes of syncope                                                                       |
|                 | Transthoracic echocardiography (TTE) revealed LVEF of 45–50% with no regional wall abnormalities                                       |
| 1 January 2017 (p.m.) | Coronary angiography revealed no coronary artery disease                                                                             |
|                 | Temporary transvenous pacemaker was inserted                                                                                           |
| 2 January 2017  | Coronary angiography revealed no coronary artery disease                                                                             |
|                 | Left ventriculogram showed LVEF of 35–40%                                                                                             |
|                 | Permanent pacemaker was implanted                                                                                                |
|                 | Started on guideline-directed medical therapy for heart failure                                                                         |
| 28 February 2017| Discharged for further outpatient investigations for progressive AV block and non-ischaemic cardiomyopathy                            |
|                 | Late gadolinium enhancement with cardiac magnetic resonance imaging revealed depressed cardiac function (LVEF of 31% and     |
|                 | right ventricular EF of 23%) with mid-myocardial enhancement in the basal anteroseptal wall                                          |
| 28 March 2017   | Computed tomography chest with intravenous contrast revealed mediastinal and bilateral hilar lymphadenopathy                          |
| 5 April 2017    | Outpatient device interrogation revealed pacemaker dependency                                                                               |
|                 | Biventricular implantable cardioverter-defibrillator upgrade was performed                                                             |
| 12 April 2017   | Transbronchial biopsy of the lymph node was unrevealing                                                                               |
| 28 April 2017   | Mediastinoscopy and lymph node biopsy on histological analysis revealed non-caseating granulomas suggestive of sarcoidosis          |
| 8 May 2017      | Started 60 mg of prednisone three times a day on slow tapering over the course of 6 months                                               |
| 7 December 2017 | Followed-up in the cardiology clinic                                                                                                  |
|                 | TTE revealed LVEF of 55% with no wall motion abnormalities                                                                               |
|                 | Device interrogation revealed recovery of native AV conduction with right bundle branch block                                           |

Case presentation

A 50-year-old man with history of Lyme’s disease, no history of hypertension, hyperlipidaemia or diabetes presented with recurrent episodes of syncope to the emergency department (ED). Approximately 6 weeks prior to presentation, he experienced his first episode of syncope while exercising. He lost consciousness without any prodromal symptoms and was found unconscious on the ground by his wife. He regained consciousness within a few seconds. He was admitted to an outside hospital and workup at that time was unrevealing and was subsequently discharged home with outpatient cardiology follow-up visits. Further outpatient workup at that time revealed new left bundle branch block (LBBB). Given exercise induced syncope, an exercise stress test was performed to evaluate for ischaemia and/or arrhythmia. Unfortunately, it provoked a pre-syncopal event along with a brief episode of atrial tachycardia (AT). A subsequent pharmacological nuclear stress test showed a mild reduced left ventricular ejection fraction (LVEF) of 42% with a moderate size area of ischaemia and scar in the inferior wall segment. He did not experience any angina or congestive heart failure symptoms. In view of the unexplained exertional syncope in a patient with LBBB, a cardiac electrophysiology (EP) study was planned. However, prior to the date of the study, he experienced four episodes of non-exertional syncope in 24 h and he presented to our ED.

At admission, physical examination revealed blood pressure of 140/66 mmHg, heart rate of 54 beats/minute (b.p.m.), respiratory rate of 18 breaths/minute, temperature of 36.2°C, and oxygen saturation of 99% on room air. Cardiovascular examination revealed...
normal heart sounds, no murmurs, no jugular venous distension, and no pitting oedema. Remaining physical examination was unremarkable. A 12-lead electrocardiogram revealed sinus rhythm with a rate of 57 b.p.m., first-degree atrioventricular (AV) block and prolonged QTc interval (Figure 1). He developed a spontaneous brief burst of AT (Figure 2) in the ED which resolved with an intravenous administration of a bolus injection of 5 mg of metoprolol tartrate. Cardiac enzymes, thyroid function test, serum calcium, and serum angiotensin converting enzyme level were normal. Lyme disease antibody test was negative. Chest X-ray was unremarkable. A transthoracic echocardiography showed LVEF of 45–50% with no regional wall abnormalities. Telemetry captured intermittent high-grade AV block (Figure 3) with ventricular escape that was associated with brief lightheadedness. A temporary transvenous pacemaker was placed.

Given AV block and concern for ischaemia on nuclear stress imaging, a coronary angiogram was performed which revealed luminal irregularities with normal coronary vessels and left ventriculography revealed LVEF of 35–40%. Unfortunately, the procedure was complicated by catheter-induced proximal right coronary artery (RCA) dissection which was treated with a 3.5 mm $\times$ 15 mm drug-eluting stent that migrated to mid RCA. The decision was made to imbed the stent into the wall of mid-RCA and lace a second larger stent 4.0 mm $\times$ 15 mm (bare metal stent) in the proximal RCA. A dual-chamber permanent pacemaker (PPM) implantation was then performed given intermittent AV block with syncope. He was subsequently discharged on dual antiplatelet therapy (aspirin 81 mg daily and ticagrelor 90 mg twice daily) and guideline-directed medical therapy (GDMT) for heart failure (lisinopril 2.5 mg daily and metoprolol succinate 25 mg daily) with a close follow-up by his outpatient cardiologist.

Outpatient cardiac magnetic resonance (CMR) was performed to look for infiltrative disease. It revealed focal transmural late gadolinium enhancement (LGE) involving the basal anteroseptal wall (Figure 4), LVEF of 31% and right ventricular (RV) EF of 23%. This was concerning for CS. Therefore, a computed tomography (CT) of the chest (Figure 5) was performed, showing mediastinal and bilateral hilar lymphadenopathy. A transbronchial biopsy was unrevealing, however, mediastinoscopy and lymph node biopsy on histological analysis (Figure 6) showed non-caseating granulomas. The diagnosis of sarcoidosis with cardiac involvement was established. Fungal infection and acid-fast staining for mycobacteria of the tissue specimen were negative. Despite maximally tolerable GDMT (lisinopril 5 mg daily and metoprolol succinate 50 mg daily) for heart failure for over 3 months, the repeated outpatient transthoracic echocardiogram did not show improvement of his LVEF. He progressed to complete heart block and became pacemaker dependent as noted in outpatient PPM interrogations. As per Heart Rhythm Society expert consensus statement on the management of CS (Class IIa recommendation) for primary prevention of sudden cardiac death, an implantable cardioverter-defibrillator (ICD) upgrade was indicated. In addition, based on data from BLOCK-HF trial, a biventricular ICD upgrade was performed.3 An echocardiogram was performed the following day during biventricular pacing which showed LVEF of 40–45%. He was started on prednisone 60 mg orally three times a day with slow tapering (60 mg three times daily for 2 months, 40 mg three times daily for 2 months, 30 mg three times daily for 2 weeks, 30 mg two times daily for 2 weeks, 20 mg two times daily for 2 weeks, 20 mg once daily for 1 week, and 10 mg once daily for 1 week) over a course of 6 months by his pulmonologist. At 1-year follow-up of his CS, his LVEF has normalized to 55% and native AV conduction had recovered with right bundle branch block. There were no further episodes of syncope.

Figure 1 Twelve-lead electrocardiogram showed sinus bradycardia with a rate of 57 b.p.m., prolonged PR (228 ms) likely first-degree atrioventricular block, QRS (114 ms), QTc (526 ms), deep symmetric ST-T waves inversions in V1–V3.
Cardiac sarcoidosis is characterized by granuloma formation within the tissue of the heart. Symptomatic CS is a rare but potentially fatal condition which makes up approximately 5% of patients with sarcoidosis. However, the prevalence of subclinical CS may be higher, which was estimated to be around 25–30%, based on a few autopsy series.

The diagnosis of CS remains a major challenge amongst clinicians for a few main reasons. Firstly, the clinical manifestations of CS can vary widely as they depend on the location and extent of myocardial involvement. Secondly, transvenous endomyocardial biopsy is a diagnostic tool which has a low sensitivity of 20% due to patchy/focal distribution of the granulomas resulting in sampling error and the procedure is not without risk of complications. Finally, although various cardiac imaging modalities have been used to evaluate patient with suspected or known sarcoidosis, their true diagnostic accuracy remain unknown. To date, the two most commonly used diagnostic guidelines for CS were published by the Japan Society of Sarcoidosis and Other Granulomatous Disorders and the Heart Rhythm Society (HRS). Nonetheless, these guidelines were mainly based on expert consensus and lack of prospective trial validation.

The four main clinical manifestations of CS are conduction abnormalities, ventricular arrhythmias, congestive heart failure, and sudden cardiac death. Conduction abnormality can often be the initial manifestation of CS; it may range from first degree heart block to complete heart block which accounts for 23–30% of the patients with CS. Conduction abnormalities develop as a result of the formation of granulomas in the cardiac conduction system, leading to conduction delays and blockages. These abnormalities can progress over time and may require intervention, such as pacemaker placement, to maintain a stable rhythm and prevent complications.

**Figure 2** Twelve-lead electrocardiogram captured a short burst of atrial tachycardia with a rate of 104 b.p.m.

**Figure 3** Telemetry strip shows high-grade atrioventricular block. The sinus P waves (red arrows) follow through but they fail to conduct to the ventricles. Two ventricular escape beats (green arrows) are present followed by conducted sinus beat (blue arrow) at the end of the strip.

**Discussion**

Cardiac sarcoidosis is characterized by granuloma formation within the tissue of the heart. Symptomatic CS is a rare but potentially fatal condition which makes up approximately 5% of patients with sarcoidosis. However, the prevalence of subclinical CS may be higher, which was estimated to be around 25–30%, based on a few autopsy series.

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Cardiac sarcoidosis presenting with syncope

Figure 4 Late gadolinium-enhanced cardiac magnetic resonance (CMR) images showing patchy late gadolinium enhancement within the basal anteroseptal wall. (A, coronal plane; B, sagittal plane).

Figure 5 A contrast-enhanced computed tomography chest showing right paratracheal (A) and bilateral hilar lymphadenopathy (B). Differential includes lymphoma or sarcoidosis.

Figure 6 Patient slides of mediastinal lymph node biopsy. Low- (A) and high-power (B) micrographs showing numerous non-caseating, multinucleated giant cells. (haematoxylin–eosin stain; original magnifications: A, × 100; B, × 200).
of scar tissue or granulomas at the basal septum or near the nodal artery causing ischaemic injury to the conduction pathway. Our patient had exertional syncope initially from worsening infranodal disease that became evident even at rest later. Supraventricular arrhythmias are uncommon (15–17%) and it is usually due to granulomatous formation at the sinus node or atrial dilatation or pulmonary involvement rather than the result of atrial granulomas. Our patient had two brief episodes of atrial tachycardia. This might have been due to any of the above causes.

As seen in our patient, the presence of unexplained conduction abnormalities in young adults less than 60 years of age should prompt further evaluation with non-invasive imaging modalities, such as speckle-tracking echocardiography, CMR, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), or hybrid PET-CMR to look for infiltrative cardiomyopathies. Delayed-enhanced CMR imaging studies have a reported sensitivity between 75–100%, specificity of 78–100%, positive predictive value of 55%, and negative predictive value of 100% in diagnosing CS. Nonetheless, the findings of LGE on CMR can also be present in cardiac amyloidosis, myocarditis, systemic sclerosis, or dilated cardiomyopathy and it does not differentiate an active CS lesion from an inactive CS lesion, which the former is amenable to immunosuppressive therapy. Hence, we take into consideration the clinical presentation of our patient and correlated it to the findings of LGE on CMR to establish the diagnosis of CS. Our patient had a biopsy proven extracardiac sarcoidosis and LGE on CMR. As per the HRS guideline, the diagnosis of ‘probable cardiac sarcoidosis’ was made, and he was started on corticosteroid.

Although corticosteroids have been the mainstay of treatment of CS for many years, the data to prove the effectiveness of this therapy are scare. Observational data have shown that corticosteroid therapy helped in AV conduction recovery and improving heart function, but there is paucity of data to demonstrate its use for survival benefit. More recent studies suggest that FDG-PET may be used to assess and monitor therapeutic response of CS to corticosteroid therapy. Our patient responded to the corticosteroid therapy with partial recovery of AV native conduction and improvement in LVEF. We postulated that the high-dose of prednisone therapy may have decreased the size of granulomas which were infiltrating the conduction system. Heart failure developed when there are widespread of granulomatous infiltration within the myocardium tissue, presence of ventricular aneurysms or valvular regurgitation, rhythm abnormalities, or a combination of any of the above conditions.

Progressive congestive heart failure accounts for 25–75% of all cardiac-related death in patient with CS. Untreated active CS may have progressive granulomatous infiltration of the myocardial tissue leading to the development of fatal arrhythmia or sarcoid myocarditis. As in our patient, he developed exertional syncope but rapidly progressed to unheralded syncope with high-grade AV block and non-ischaeimic cardiomyopathy. His LVEF worsened drastically as reported in the sequential echocardiograms and CMR. This is highly suggestive that the natural course of CS is often unpredictable and can be aggressive at times if left undiagnosed and untreated. Cardiac magnetic resonance is the most useful tool for accurate determination of LVEF as it has high intra-observer, interobserver, and test–retest reproducibility compared to other available reference methods.

Conclusion

This case highlights the importance of including CS in the differential diagnosis in a young patient with conduction system disease to allow for appropriate therapy that can be life-saving. Late initiation of corticosteroid therapy remained effective in our patient with significant improvement of his heart function and recovery of AV conduction.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author’s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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