Conduction disorders as the first hallmark of isolated cardiac sarcoidosis in a highly active individual: a case report.

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Abstract

Background. Cardiac sarcoidosis (CS) is an inflammatory disease with various clinical presentations depending on the extension of cardiac involvement. The disease is often clinically silent, therefore diagnosis is challenging.

Case summary. We discuss the case of a middle-aged highly active individual presenting with an occasional finding of low heart rate during self-monitoring. The electrocardiogram shows a Mobitz 2 heart block; thanks to multimodality imaging CS was diagnosed and corticosteroid therapy improved cardiac conduction.

Discussion. To our knowledge this is one of the first documented cases of occasional, early finding of CS in a middle-aged highly active individual who presented with cardiac conduction involvement. Despite the very early diagnosis, multimodality imaging suggested an advanced disease with no edema detection at the CMR. Nevertheless, prompt corticosteroid therapy was able to improve clinical conduction. Although non-sustained ventricular arrhythmias were detected, electrophysiological study allowed to discharge the patient safely without implantable cardioverter...
defibrillator implantation. Light-to moderate physical activity was allowed at mid-term follow up. A multidisciplinary evaluation should be considered to resume a high intensity training.

**Abbreviations:**

AVB: atrio-ventricular block  
CMR: cardiac magnetic resonance  
CS: cardiac sarcoidosis  
ECG: electrocardiogram  
ECS: extra-cardiac sarcoidosis  
EMB: endomyocardial biopsy  
EPS: electrophysiological study  
FDG-PET: fluorodeoxyglucose positron emission tomography  
ICD: implantable cardioverter defibrillator  
LGE: late gadolinium enhancement  
LVEF: left ventricular ejection fraction  
PVC: premature ventricular complexes  
SCD: sudden cardiac death  
VA: ventricular arrhythmias

**Keywords:**
Cardiac sarcoidosis, atrio-ventricular block, fluorodeoxyglucose positron emission tomography, cardiac magnetic resonance, corticosteroid therapy, case report
Learning points:

1- To show one of the first cases of isolated cardiac sarcoidosis affecting a highly active individual.

2- To underline the importance of multimodality imaging to perform early diagnosis and to recognize cardiac involvement as a sign of advanced disease phase.

3- To highlight the role of the use of EPS and tele-monitoring for the management of arrhythmias and SCD prevention.

4- To highlight the need for repeated functional and imaging tests in association with a multidisciplinary approach to provide recommendations on sport activity in such patients.
**Timeline**

| Day 1 | The patient was admitted to the emergency department and 2:1 AVB was detected. |
| Day 2 | Transthoracic echocardiogram was normal. Treadmill exercise test revealed persistence of 2:1 AVB at the peak of effort. |
| Day 4 | CMR showed mid-wall and subepicardial areas of late gadolinium enhancement in the basal anterior wall extended to junctional and septal anterior wall and junctional inferior wall. HRCT excluded lung and nodes involvement. |
| Day 11 | FDG-PET confirmed high uptake in the anterolateral wall and in basal and inferior septal areas. Findings are consistent with diagnosis of cardiac sarcoidosis. |
| Day 14 | Corticosteroid therapy was started. |
| Day 17 | Treadmill exercise test showed clear improvement of conduction during effort. At peak of effort and during recovery 1:1 conduction was observed. The test was suspended due to the occurrence of ventricular couples and ventricular bigeminy. |
| Day 18 | EPS was negative for ventricular arrhythmias induction. ICD implantation deferred. |
| Day 21 | Loop recorder implantation. Patient was discharged home. ECG showed sinus rhythm with normal 1:1 conduction. |
| Day 178 | Treadmill test was performed (heart rate at baseline was 99 bpm, heart rate at peak of effort was 144 bpm, the total stress test duration was 12 minutes, 13.6 METS) and no arrhythmias occurred as well as no events reported at loop recorder monitoring. |
| Day 203 | Further FDG-PET study was performed with the detection of the absence of inflammatory activity (optimal response to the medical treatment). |
Introduction

Sarcoidosis is a multiorgan disease characterized by non-caseous granulomas in the affected organs; its prevalence varies from 0.04 to 64 cases per 10,000 inhabitants. Cardiac involvement can occur in up to 25% of cases and is associated with significant morbidity and mortality, so early recognition is mandatory. Cardiac sarcoidosis (CS) management is directed for reduction of inflammation, relief of symptoms and prevention of arrhythmias.

Case presentation

A 45-year-old highly active Caucasian individual was admitted to the emergency department complaining of slightly reduced physical performances: he reported a lack of increase of heart rate beyond 80-100 bpm at fitness tracker monitoring during physical activity during the previous week. He used to train 3-4 times/week alternating swimming, running, cycling, calisthenics and archery for at least 2 hours per session. He had no previous medical concerns and he didn’t take any medication. Clinical examination and standard biochemistry were not noteworthy; no skin lesions were noted, Anti-Borrelia antibodies were negative, while angiotensin converting enzyme hematic levels were elevated. Basal electrocardiogram (ECG) showed 2:1 atrioventricular block (AVB) and left axis deviation, with the exception of his 2:1 AVB, the other features on the ECG are common training related changes (Figure 1).

Transthoracic echocardiogram showed normal left ventricular systolic function and dimension, (septum 10 mm, posterior wall 9 mm, left ventricular mass 136 g), aortic bicuspid valve with trivial regurgitation and no other anomalous findings (mean gradient 12 mmHg, type 1 Sievers classification with right-left coronary cusps fusion). Treadmill exercise test revealed paroxysmal 2:1 AVB and Mobitz I AVB at peak effort, then first degree AVB and isolated and coupled right infundibular premature ventricular complexes (PVC) in the recovery phase: exercise related AV-conduction improvement suggested supra-nodal AVB.
Continuous ECG monitoring revealed alternance of 2:1 AVB at 44 bpm and Mobitz I AVB with narrow QRS complexes and normal repolarization; isolated PVCs and brief runs of non-sustained ventricular tachycardia (VT), the longest of 5 beats at 110 bpm, were recorded. Determination of the origin of the PVC and/or VT was not possible as only a 2-lead ECG was recorded.

High resolution thoracic computed tomography (HRCT) did not show any abnormalities, in specific no pulmonary nodules nor lymphadenopathies with calcifications were found.

Cardiac magnetic resonance (CMR) imaging reported normal biventricular function (indexed LV end diastolic volume 77 ml/m², indexed RV end diastolic volume 80 ml/m², LV/RV: 0.96, indexed myocardial mass 63 g/m²) with no wall motion abnormalities and two areas of late gadolinium enhancement (LGE) with midwall/subepicardial distribution: the first one in the basal anterior septal wall extending to basal anterior wall and the second one involving the basal and medium segment of inferior septum and inferior wall. LGE quantification was 6.0 g/m² (9.5%). Short tau inversion recovery (STIR) acquisitions were negative for oedema (Figure 2).

Subsequent fluorodeoxyglucose positron emission tomography (FDG-PET) imaging confirmed high uptake in the basal anterior septal wall, the anterior wall and in the basal inferior septal area (Figure 3). No other organ involvement was detected.

Considering the FDG-PET, LGE and AV-conduction abnormalities, the patient was clinically diagnosed with symptomatic isolated CS. However, a definitive histologic diagnosis was not possible as no myocardial biopsy was performed. High dose corticosteroid therapy was started (prednisone 1 mg/kg/day) and after few days of treatment ECG monitoring revealed an alternance between normal sinus rhythm with 1:1 conduction and 2:1 AVB. The treadmill test was repeated and showed conduction improvement during effort: normal sinus rhythm with 1:1 conduction was observed, however the test was suspended due to the occurrence of ventricular couples and ventricular bigeminy during effort (Figure 4).

For arrhythmic risk assessment, electrophysiological study (EPS) was performed and no arrhythmias were induced. Considering the good response to corticosteroid therapy and the negative EPS, despite
the presence of LGE, we decided to defer ICD implantation. However, a loop-recorder for continuous
arrhythmias monitoring was implanted.
At three months, a new CMR was performed and was identical to the previous one, with no significant
LGE reduction or increase detected. In that period, he was allowed to perform mild to moderate
training activity (i.e. heart rate < 120 bpm) and competitive archery with close follow-up as suggested
by guidelines. At 6 months follow-up, another treadmill test was performed (heart rate at baseline
was 99 bpm, heart rate at peak of effort was 173 bpm (83% of the maximum heart rate, the total
stress test duration was 12 minutes, 13.6 METS) and no arrhythmias occurred as well as no events
reported at loop recorder monitoring with 17.5 mg of prednisone as specific therapy. Subsequent
FDG-PET study was performed with the detection of no inflammatory activity (optimal response to
the medical treatment).
Finally, with the report of both a maximal treadmill stress test and one more CMR (to assess the
absence of LGE progression), we will discuss with the rheumatologist the possibility to allow to the
patient to perform more than moderate physical activity.

Discussion
This is a case of isolated CS in a highly active individual presenting with cardiac conduction disease.
Sarcoidotic granulomas may involve any area of the heart and clinical presentation varies depending
on the extent, location, and activity of the disease. Atrioventricular dysfunction, related to the
involvement of basal septum or the nodal artery, is the most common clinical presentation; complete
AVB is reported in up to 30% of cardiac sarcoidotic patients. Interestingly, the patient presented
with 2:1 AVB, but he did not experience any fainting nor syncope, probably because of sinus
bradycardia related to physical training.
Currently available diagnostic criteria suggest CS diagnosis in case of positive endomyocardial
biopsy (EMB) or evidence of extra-cardiac sarcoidosis (ECS). The diagnosis of isolated forms of CS
can be challenging due to the suboptimal sensitivity of EMB. Therefore, advanced cardiac imaging techniques play a key role.

The most frequently used diagnostic method is CMR. Although a pathognomonic pattern has not been identified yet, CMR usually demonstrates a patchy and multifocal myocardial involvement. Our patient had a typical antero-septal and infero-septal localization of LGE, commonly related to clinical presentation (Figure 2). In our patient, we observed a close correspondence between LGE and FDG uptake, maybe suggesting a contemporary presence of fibrosis and inflammation, even if STIR sequences were negative for oedema (Figure 2).

Corticosteroids are the mainstay of therapy in sarcoidosis, but standard protocols have not been validated yet. Early corticosteroid therapy might be helpful for AV nodal conduction recovery and for VA burden reduction. A meta-analysis showed reversibility of heart block in 47% of patients treated with prednisone. Interestingly, although the presence of LGE on CMR could suggest an advanced disease, a prompt recovery of conduction with steroid therapy was observed. Indeed, FDG-PET is supposed to be superior to CMR to predict outcome. The immediate response is consistent with previous observations and has been related to better outcome. In our patient, we did not observe an immediate reduction in arrhythmic burden; however, both remote monitoring and treadmill data available at follow-up showed a significant reduction of VA burden (during steroid treatment).

The 2014 HRS consensus statement suggested that an ICD for CS patient with an indication for PM should be considered (class IIA recommendations). Several studies showed that the presence of extensive LGE could suggest elevated SCD risk and even worse outcomes. The amount of LGE quantification in our patient fell in a “grey zone” compared to previous studies. However, in a cohort of 112 patients in primary prevention setting, no patients with normal biventricular function received appropriate ICD therapy. Furthermore, a recent study involving patients with preserved LVEF showed that a negative EPS identified a population at low arrhythmic risk on a 3 years follow-up.
Therefore, we performed an EPS and no arrhythmias were induced. According to HRS consensus statement indication, and after a multidisciplinary meeting, ICD implantation was deferred. Recommendation about exercise training was another critical aspect of the presented case. Bicuspid aortic valve disease is not associated with aortopathy and this condition shares the same exercise recommendation as an individual with normal aortic valve. However, considering that the patient was affected by CS, during the early follow-up phase we allowed the patient to perform mild to moderate training activity as suggested by guidelines\(^3\) (specifically he was allowed to reach 55-74\% of the maximum heart rate). However, even if the patient presented a disappearance of both VAs and inflammatory signs at FDG-PET study during the follow-up, we have to consider that these results were achieved with the concomitant use of steroid therapy. Indeed, CS is characterized by quiescent and relapsing phases\(^5\), therefore we have scheduled a complete re-assessment of the patient (both with stress test and FGD-PET and possibly with CMR) when immunosuppressive regimen is changed by the rheumatologist, in order to hypothesize the possibility for the patient to resume high intensity activity training.

**Conclusion**

We presented a paradigmatic case of CS with AVB as first clinical presentation in a highly active individual. Despite a prompt recognition of conduction abnormalities thanks to careful monitoring of heart rate, cardiac imaging revealed a relatively advanced disease. Nevertheless, corticosteroids treatment induced a recovery of cardiac conduction. Despite VA on ECG monitoring, no major VA were induced during EPS, considering the patient to be at low risk for arrhythmic events. Imaging follow-up is scheduled both for monitoring response to therapy and to help clinicians to provide to the patient the recommendations on the intensity of the physical activity.

The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.
No competing interest or fund are reported.

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Figure legends:

Figure 1. Baseline ECG showed sinus rhythm, 2:1 AVB and left axis deviation. Ventricular repolarization was normal.

Figure 2. Cardiac magnetic resonance images showing LGE (red arrows) involving medio-basal region of inferior wall, the base of anterior wall and antero-septum shown in the 2 chamber view (a) and short axis (b) (LGE sequences), no oedema was detected in 4 chamber view (c) and short axis (d) (Short Tau Inversion Recovery sequences).

Figure 3. FDG-PET images showing FDG uptake (top) in antero-septum (a long axis, - b short axis) and junctional inferior wall (c). Respective CT image are showed at the bottom.

Figure 4. Treadmill exercise test performed before (a) and after (c) corticosteroid therapy (baseline) and at peak of effort (b), (d) respectively. Before corticosteroid therapy 2:1 AVB was documented and it was still persistent at peak of effort (heart rate at baseline was 94 bpm, the patient was very anxious due to the uncertainty of the initial diagnostic phase, heart rate at peak of effort was 135 bpm, the total stress test duration was 17 minutes, 10 METS). After corticosteroid therapy, first degree AVB was documented with 1:1 conduction even at peak of effort (heart rate at baseline was 53 bpm, heart rate at peak of effort was 85 bpm, the total stress test duration was 16 minutes, 8 METS, the test was terminated due to the occurrence of ventricular couples and ventricular bigeminy). Red arrows show P waves.
