ESC European Society of Cardiology

European Heart Journal - Case Reports (2021) **5**(11), 1–6
https://doi.org/10.1093/ehjcr/ytab416

CASE REPORT
Other

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

Silvia Muccioli †, Stefano Albani *†, Barbara Mabritto , and Giuseppe Musumeci

Division of Cardiology, Azienda Ospedaliera Ordine Mauriziano di Torino, Largo Filippo Turati, 62, 10128, Turin, Italy

Received 4 January 2021; first decision 3 February 2021; accepted 11 October 2021; online publish-ahead-of-print 12 October 2021

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 findings 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 oedema detection at the cardiac magnetic resonance. 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.

Keywords Cardiac sarcoidosis • Atrioventricular block • Fluorodeoxyglucose positron emission tomography • Cardiac magnetic resonance • Corticosteroid therapy • Case report

Learning points

- To show one of the first cases of isolated cardiac sarcoidosis affecting a highly active individual.
- To underline the importance of multimodality imaging to perform early diagnosis and to recognize cardiac involvement as a sign of advanced disease phase.
- To highlight the role of the use of electrophysiological study and telemonitoring for the management of arrhythmias and sudden cardiac death prevention.
- 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.

* Corresponding author. Tel: +39 0165543364, Email: albani.aosta@gmail.com
† The first two authors contributed equally to the study.
Handling Editor: Danny van de Sande
Peer-reviewers: Federica Mango
Compliance Editor: Alexander Tindale
Supplementary Material Editor: Ross Thomson

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[1] 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.

Timeline

Day 1	The patient was admitted to the emergency department and 2:1 atrioventricular block (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	Cardiac magnetic resonance 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. High-resolution thoracic computed tomography excluded lung and nodes involvement.
Day 11	Fluorodeoxyglucose positron emission tomography (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 a 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	Electrophysiological study was negative for ventricular arrhythmias induction. Implantable cardioverter-defibrillator implantation was deferred.
Day 21	Loop recorder implantation. Patient was discharged home. Electrocardiogram showed sinus rhythm with normal 1:1 conduction.
Day 178	Treadmill test was performed (heart rate at baseline was 99 b.p.m., heart rate at peak of effort was 144 b.p.m., the total stress test duration was 12 min, 13.6 METS) and no arrhythmias occurred as well as no events was 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 medical treatment).

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 b.p.m. at fitness tracker monitoring during physical activity during the previous week. He used to train 3–4 times/week alternating swimming, running, cycling, callisthenics, and archery for at least 2 h per session. He had no previous medical concerns and he did not 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 haematic 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*).[2]

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 (PVCs) in the recovery phase: exercise-related atrioventricular (AV)-conduction improvement suggested supra-nodal AVB.

Continuous ECG monitoring revealed alternance of 2:1 AVB at 44 b.p.m. 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 b.p.m., 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 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 left ventricular end-diastolic volume 77 mL/m^2, indexed right ventricular end-diastolic volume 80 mL/m^2, left ventricle/right ventricle: 0.96, indexed myocardial mass 63 g/m^2) 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 the basal anterior wall and the second one involving the basal and medium segment of inferior septum and inferior wall. Late gadolinium enhancement quantification was 6.0 g/m^2 (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

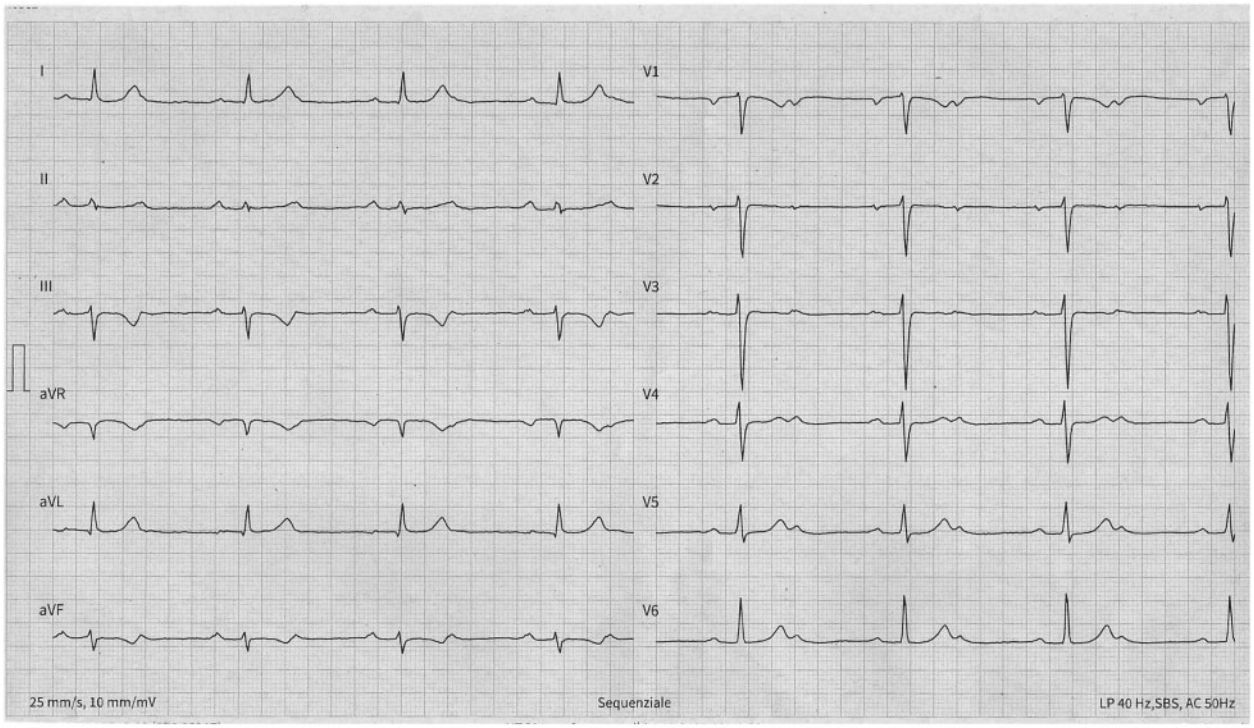

Figure 1 Baseline electrocardiogram showed sinus rhythm, 2:1 atrioventricular block and left axis deviation. Ventricular repolarization was normal.

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 implantable cardioverter-defibrillator (ICD) implantation. However, a loop recorder for continuous arrhythmias monitoring was implanted.

At 3 months, a new CMR was performed and was identical to the previous one, with no significant detection of LGE reduction or increase. In that period, he was allowed to perform mild to moderate training activity (i.e. heart rate < 120 b.p.m.) and competitive archery with close follow-up as suggested by guidelines.[3,4] At 6 months of follow-up, another treadmill test was performed [heart rate at baseline was 99 b.p.m., heart rate at peak of effort was 173 b.p.m., 83% of the maximum heart rate, the total stress test duration was 12 min, 13.6 METS (Metabolic Equivalent of Task)] and no arrhythmias occurred as well as no events were reported at loop recorder monitoring with 17.5 mg of prednisone as specific therapy. A 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.[5] 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[6] suggest CS diagnosis in case of positive endomyocardial biopsy (EMB) or evidence of extra-CS. 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.[7]

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

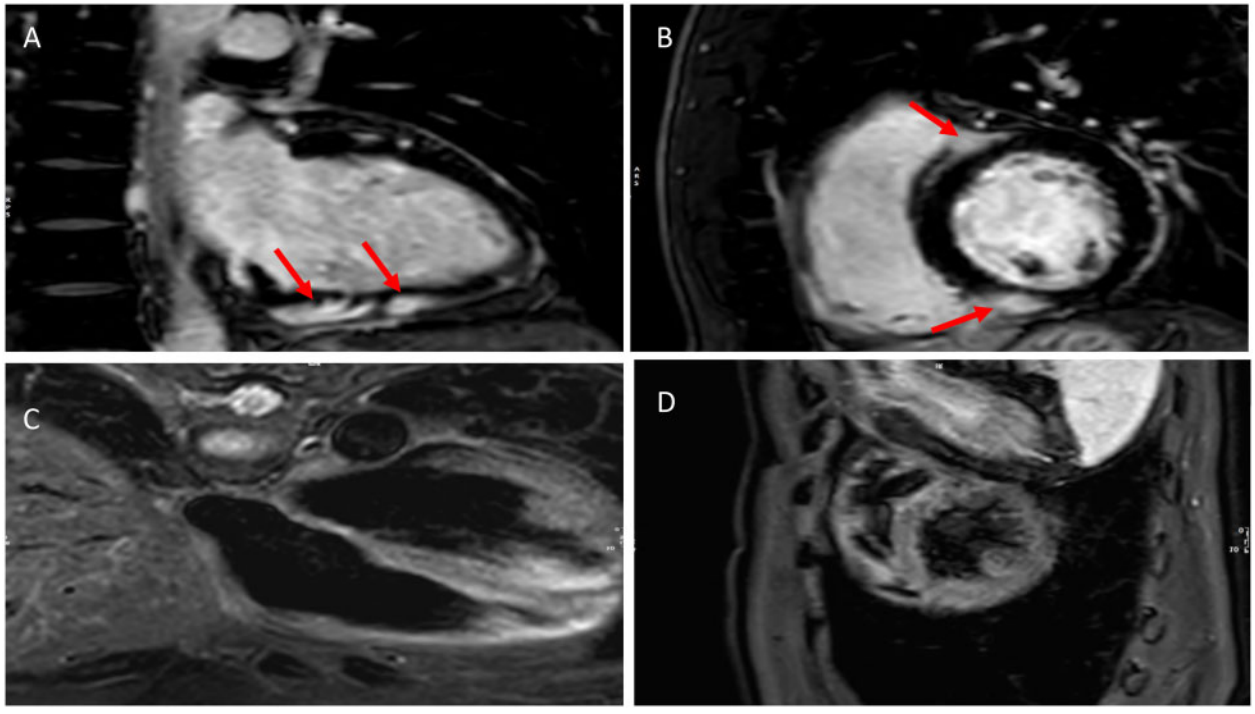

Figure 2 Cardiac magnetic resonance images showing late gadolinium enhancement (red arrows) involving medio-basal region of inferior wall, the base of anterior wall, and antero-septum shown in the two-chamber view (*A*) and short axis (*B*) (late gadolinium enhancement sequences), no oedema was detected in four-chamber view (*C*) and short axis (*D*) (short tau inversion recovery sequences).

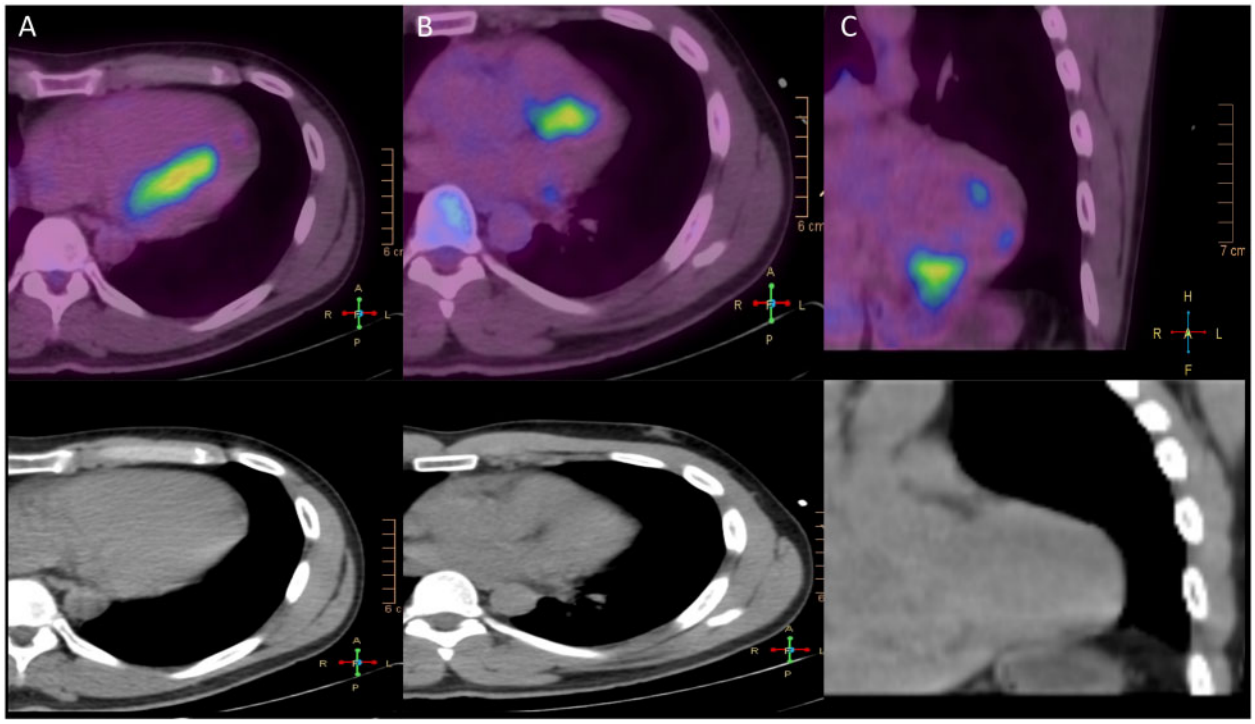

Figure 3 Fluorodeoxyglucose positron emission tomography images showing fluorodeoxyglucose uptake (top) in antero-septum (*A* long axis, *B* short axis) and junctional inferior wall (*C*). Respective computed tomography images are showed at the bottom.

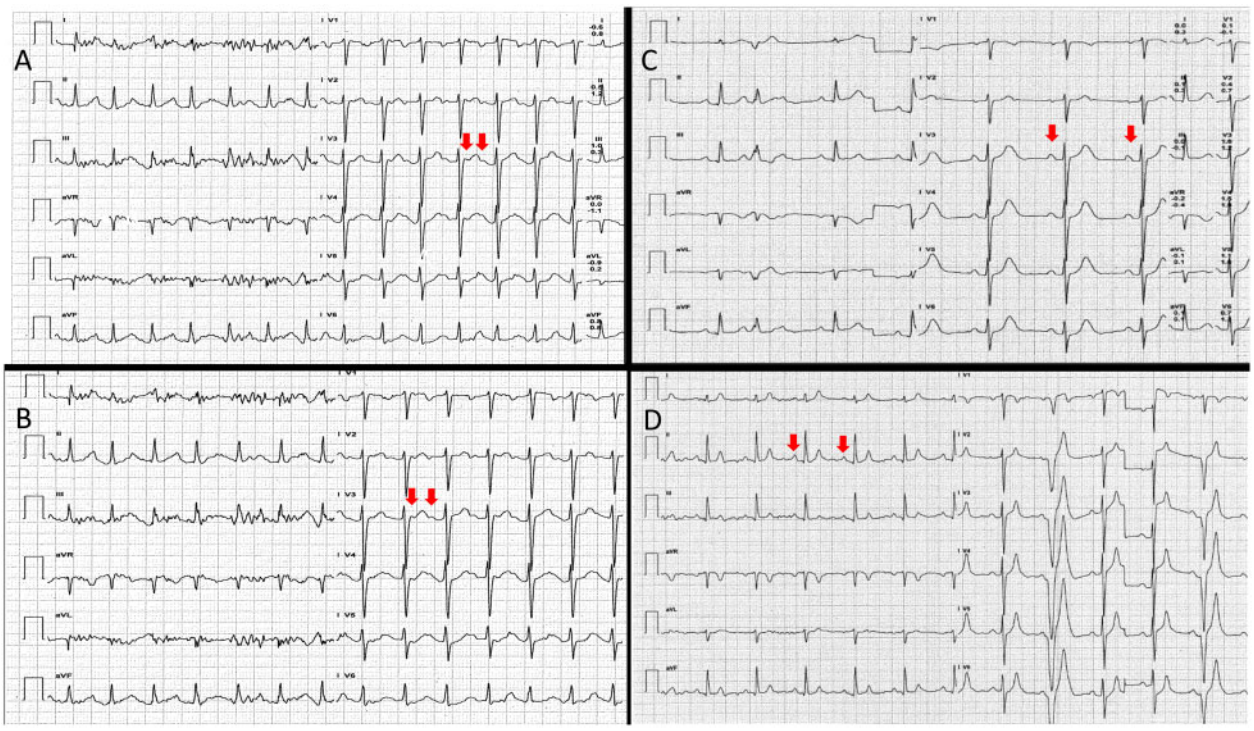

Figure 4 Treadmill exercise test performed before (*A*) and after (*C*) corticosteroid therapy (baseline) and at peak of effort (*B* and *D*), respectively. Before corticosteroid therapy 2:1 atrioventricular block was documented and it was still persistent at peak of effort (heart rate at baseline was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

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 ventricular arrhythmia (VA) burden reduction. A meta-analysis showed reversibility of heart block in 47% of patients treated with prednisone.[8] 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.[9] The immediate response is consistent with previous observations and has been related to better outcome.[8–10] 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 Heart Rhythm Society (HRS) consensus statement suggested that an ICD for CS patient with an indication for PM (Pacemaker) should be considered (class IIA recommendations).[6] Several studies showed that the presence of extensive LGE could suggest elevated sudden cardiac death risk and even worse outcomes.[11–13] The amount of LGE quantification in our patient fell in a 'grey zone' compared to previous studies.[14] However, in a cohort of 112 patients in the primary prevention setting, no patients with normal biventricular function received appropriate ICD therapy.[15] Furthermore, a recent study involving patients with preserved left ventricular ejection fraction showed that a negative EPS identified a population at low arrhythmic risk on 3 years of follow-up.[11] Therefore, we performed an EPS and no arrhythmias were induced. According to the 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 the 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.

Lead author biography

Silvia Muccioli was born in Turin on 14 January 1989 and completed her medical degree at the University of Turin in 2013. She took specialization in Cardiology in 2019 at the University of Insubria, Varese: during these years, she developed an interest in heart failure and followed patients with inotropes depending and refractory heart failure. She is currently working at Mauriziano Hospital in Turin as clinical cardiologist.

Supplementary material

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

Acknowledgements

We thank Dr Stefano Cirillo and Dr Annalisa Macera (Department of Radiology, Azienda Ospedaliera Ordine Mauriziano di Torino), for providing CMR images and Dr Matteo Manfredi (Department of Nuclear Medicine, Azienda Ospedaliera Ordine Mauriziano di Torino) for FDG-PET images.

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

Consent: 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.

Conflict of interest: None declared.

Funding: None declared.

References

1. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation* 1978;**58**:1204–1211.
2. Sharma S, Drezner JA, Baggish A, Papadakis M, Wilson MG, Prutkin JM et al. International recommendations for electrocardiographic interpretation in athletes. *J Am Coll Cardiol* 2017;**69**:1057–1075.
3. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S et al.; ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021;**42**:17–96.
4. Pelliccia A, Solberg EE, Papadakis M, Adami PE, Biffi A, Caselli S et al. Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis: position statement of the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC). *Eur Heart J* 2019;**40**:19–33.
5. Sekhri V, Sanal S, DeLorenzo LJ, Aronow WS, Maguire GP. Cardiac sarcoidosis: a comprehensive review. *Arch Med Sci* 2011;**7**:546–554.
6. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm* 2014;**11**:1304–1323.
7. Sharma A, Okada DR, Yacoub H, Chrispin J, Bokhari S. Diagnosis of cardiac sarcoidosis: an era of paradigm shift. *Ann Nucl Med* 2020;**34**:87–93.
8. Sadek MM, Yung D, Birnie DH, Beanlands RS, Nery PB. Corticosteroid therapy for cardiac sarcoidosis: a systematic review. *Can J Cardiol* 2013;**29**:1034–1041.
9. Orii M, Hirata K, Tanimoto T, Ota S, Shiono Y, Yamano T et al. Comparison of cardiac MRI and 18F-FDG positron emission tomography manifestations and regional response to corticosteroid therapy in newly diagnosed cardiac sarcoidosis with complete heart block. *Heart Rhythm* 2015;**12**:2477–2485.
10. Héno P, Braem L, Mioulet D, Pelloni JM, Bastard E, Paule P et al. Bloc auriculo-ventriculaire complet du sujet jeune. . . Penser à la sarcoïdose. *Ann Cardiol Angeiol (Paris)* 2007;**56**:104–106.
11. Zipse MM, Tzou WS, Schuller JL, Aleong RG, Varosy PD, Tompkins C et al. Electrophysiologic testing for diagnostic evaluation and risk stratification in patients with suspected cardiac sarcoidosis with preserved left and right ventricular systolic function. *J Cardiovasc Electrophysiol* 2019;**30**:1939–1948.
12. Agoston-Coldea L, Kouaho S, Sacre K, Dossier A, Escoubet B, Chillon S et al. High mass (>18 g) of late gadolinium enhancement on CMR imaging is associated with major cardiac events on long-term outcome in patients with biopsy-proven extracardiac sarcoidosis. *Int J Cardiol* 2016;**222**:950–956.
13. Smedema JP, van Geuns RJ, Ector J, Heidbuchel H, Ainslie G, Crijns HJGM. Right ventricular involvement and the extent of left ventricular enhancement with magnetic resonance predict adverse outcome in pulmonary sarcoidosis. *ESC Heart Fail* 2018;**5**:157–171.
14. Murtagh G, Laffin LJ, Beshai JF, Maffessanti F, Bonham CA, Patel AV et al. Prognosis of myocardial damage in sarcoidosis patients with preserved left ventricular ejection fraction: risk stratification using cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 2016;**9**:1–9.
15. Schuller JL, Zipse M, Crawford T, Bogun F, Beshai J, Patel AR et al. Implantable cardioverter defibrillator therapy in patients with cardiac sarcoidosis. *J Cardiovasc Electrophysiol* 2012;**23**:925–929.