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CASE REPORT
Cardiovascular imaging

Cardiac sarcoidosis in a carrier of transthyretin gene mutation: a case report

Silvia Menale [1,2]*, Valentina Scheggi [1,2], Francesco Vanni [1,2], and Carlo Di Mario [2,3]

[1]Division of Cardiovascular and Perioperative Medicine, Florence, Italy; [2]Cardiothoracovascular Department, Clinical and Experimental Medicine, Azienda Ospedaliero-Universitaria Careggi and University of Florence, Largo Brambilla 3, 50134, Italy; and [3]Structural Interventional Cardiology, University Hospital Careggi, Florence, Italy

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Background Sarcoidosis is a rare multiorgan inflammatory disorder of unknown aetiology, characterized by the formation of non-caseating granulomas in the affected organs. Cardiac involvement is underrecognized and observed in up to 25% of cases in autopsy studies, and is associated with a high mortality rate, especially due to sudden cardiac death due to ventricular arrhythmias.

Case summary A 41-year-old man well known to our hospital because of his father's diagnosis of cardiac amyloidosis, and carrier of transthyretin (*TTR*) gene mutation, was hospitalized following a resuscitated cardiac arrest. The patient was hospitalized a month before for a syncopal episode with demonstration of preserved left ventricular ejection fraction (LVEF) with akinetic basal septum at heart ultrasound and normal coronary. Chest computed tomography, performed in the emergency department, was significant for hilar lymphadenopathies and pulmonary nodules highly suggestive of sarcoidosis. A subsequent 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) showed multiorgan phlogistic involvement, including the myocardium. After the diagnosis of cardiac sarcoidosis, the patient was started on steroids therapy and underwent ICD implantation. A follow-up 18-FDG-PET showed a reduction of organs glucose uptake and a follow-up echo an improvement in LVEF. Despite that, he occurs occasional recording of repetitive ventricular arrhythmias and one appropriate ICD shock during the next 12 months.

Discussion Cardiac sarcoidosis is an insidious disease. Its diagnosis can be challenging, with no specific finding in echocardiography. The best strategy would be multi-modality imaging involving both magnetic resonance imaging with late gadolinium enhancement and 18-FDG-PET, followed by biopsy to confirm the diagnosis. Multi-modality imaging should be further used to evaluate the response to treatment and assess prognosis. Since the patient was a known carrier of the *TTR* gene mutation, many efforts were made in order to come up with the correct diagnosis considering that both cardiac amyloidosis and cardiac sarcoidosis are non-ischaemic cardiomyopathy with systemic involvement.

Keywords Cardiac sarcoidosis • Significant ventricular arrhythmias • Sudden death • *TTR* mutation carrier • Cardiac magnetic resonance imaging • Case report

ESC Curriculum 2.3 Cardiac magnetic resonance • 2.5 Nuclear techniques • 5.10 Implantable cardioverter defibrillators • 6.5 Cardiomyopathy • 6.2 Heart failure with reduced ejection fraction

* Corresponding author. Tel: +39 3337336834, Fax: +39 (0)557946316, Email: silvia.menale@unifi.it
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Learning points

- Cardiac sarcoidosis is underrecognized and observed in up to 25% of cases in autopsy studies. An early detection of a potential heart involvement is fundamental to determine the arrhythmic risk and to introduce an adequate therapy.
- Echocardiography often fails to diagnose heart involvement. Cardiac magnetic resonance imaging can guide the diagnosis of cardiac sarcoidosis (multifocal late gadolinium enhancement in a non-infarct pattern, T2 signal alterations). The 18-fluorodeoxyglucose-positron emission tomography examination provides an effective means of assessing myocardial perfusion and inflammation, with high sensitivity.
- The heart muscle involvement is associated with a high mortality rate, especially due to sudden cardiac death because of ventricular arrhythmias.

Introduction

Sarcoidosis is a rare multiorgan inflammatory disorder of unknown aetiology, characterized by the formation of non-caseating granulomas in the affected organs. Cardiac involvement is underrecognized because of a lack of clinical evidence. Here, we present a case of cardiac sarcoidosis in a patient carrier of the transthyretin mutation and its challenging diagnostic workup. Hereditary transthyretin is one of the most frequent forms of amyloidosis, with heart involvement varying from 30–70% depending on the mutation.[1]

Since the patient was a known carrier of the transthyretin (*TTR*) gene mutation, consistent efforts were made in order to come up with the correct diagnosis considering the fact that both cardiac amyloidosis and cardiac sarcoidosis are non-ischaemic cardiomyopathy with systemic involvement.

Timeline

Timeline	Description
−2 Years	The patient was identified as a carrier of the mutation Ile68Leu in the transthyretin (*TTR*) gene and regularly followed in-hospital.
−1 Month	The patient was admitted to the Emergency Department for a syncopal episode while riding a bicycle. The echocardiogram showed an overall preserved systolic function with an akinetic basal septum.
Day 0	A rapid deterioration was observed, with an NT-pro-BNP of 1485 pg/mL, new-onset right bundle branch block and posterior fascicular block, and severe dilatation of the left ventricle, ejection fraction 30%. Coronary angiography showed smooth normal coronary arteries.
Day 3–5	A SPECT with bisphosphonate excluded cardiac amyloidosis. Cardiac MRI was performed and showed patchy areas of late gadolinium enhancement in the left ventricle.
Day 8	The patient was started on a heart failure therapy and was discharged home with a scheduled follow-up visit to evaluate the need for an ICD.
Day 32–36	The patient was hospitalized after a resuscitated cardiac arrest. At the echocardiogram, the ejection fraction dropped to 20%.
	At the abdominal and chest, CT was highly suggestive of sarcoidosis. The 18-FDG-PET examination was significant for multiorgan phlogistic-infiltrative involvement. A hepatic CT-guided biopsy confirmed the diagnosis and immunosuppressive therapy was started. The patient underwent ICD implantation
5–6 Months	At a follow-up, total body FDG-PET observed an important reduction of glucose uptake in all the involved organs, including the myocardium. Progressive improvement of left ventricular systolic function (up to 40%).

Case summary

Following his father's diagnosis of a variant cardiac amyloidosis, a 39-year-old Caucasian male was identified as a carrier of the mutation Ile68Leu in the transthyretin (*TTR*) gene. Engaged in consistent cardiological follow-ups, with no irregularities being found in his blood work, electrocardiogram (EKG), or echocardiograph. No relevant previous health problems were featured in his medical history, except for hyperthyroidism in good control with methimazole, and positive family history for hyperlipidaemia, negative for syncope and sudden cardiac death.

Two years later, at the age of 41 years, the patient was hospitalized after a syncopal episode. At heart examination, no abnormal finding was outlined, heart sounds were rhythmic, and no murmur could be appreciated; lung examination was normal as well as the patient did not exhibit signs of respiratory distress.

An echocardiogram showed an overall preserved systolic function with an akinetic basal septum and a coronary angiography showed normal coronary arteries.

In the hypothesis of an arrhythmic genesis of the syncopal event, the patient was carefully monitored during the hospitalization, and no arrhythmia was observed/outlined all over the 4 days of continuous EKG monitoring, except for rare extrasystolic beats. At discharge, a stress test at cycle ergometer was performed, the patient remained asymptomatic, and only a few supraventricular extrasystolic beats were observed in the cool-down phase.

A rapid deterioration was observed during his follow-up visit a month after hospitalization, with an N-terminal pro B-type natriuretic peptide (NT-pro-BNP) of 1485 pg/mL (normal value (n.v) < 125 pg/mL), new-onset right bundle branch block, posterior fascicular block, and severe dilatation of the left ventricle (ejection fraction 30%) with a restrictive diastolic pattern and mitral tethering causing mild regurgitation (effective regurgitant orifice area 16 mm^2).

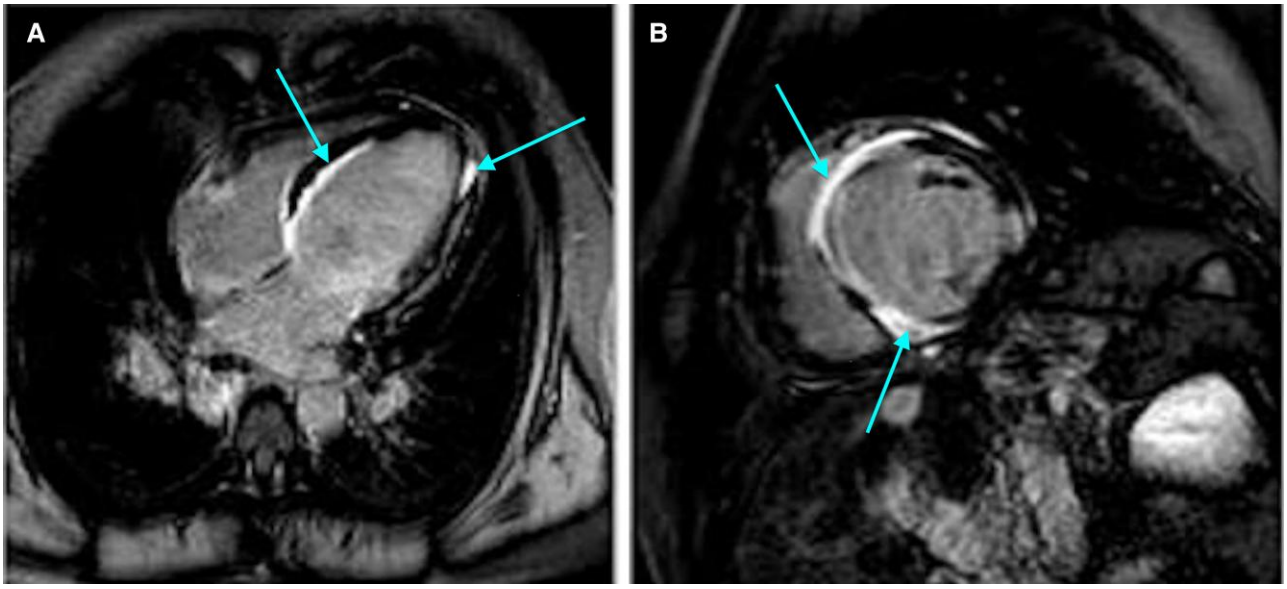


Figure 1 Four chambers CMR image (*A*) and short axis CMR image (*B*) showed patchy areas of LGE, with subendocardial and transmural enhancement, respectively. CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement.

A single-photon emission computed tomography (SPECT) with bisphosphonate unexpectedly excluded cardiac amyloidosis.

Cardiac magnetic resonance imaging (MRI) (*Figure 1*) was performed and showed patchy areas of late gadolinium enhancement in the left ventricle with both transmural (distal tract of the anterolateral wall and basal part of the inferolateral wall) and subendocardial involvement (mid-basal portion of the inferoseptal and posterior walls). The left ventricle had normal wall thickness but was significantly dilated (end-diastolic volume 288 mL and end-systolic volume 194 mL) with diffuse hypokinesia. Overall, a non-ischaemic, non-amyloid pattern was highlighted.

The patient was started on heart failure therapy, including beta-blockers, angiotension converting enzyme inhibitors, furosemide, and spironolactone, and was discharged home with a scheduled follow-up visit to evaluate the need for an ICD after a period of optimal medical therapy.

One month after discharge, an emergency hospitalization was required due to a resuscitated cardiac arrest (CA). EKG tracing during cardiopulmonary resuscitation (CPR) showed ventricular tachycardia and subsequent ventricular fibrillation with the restoration of sinus rhythm after three direct current shocks.

The patient had a full neurological recovery post CPR, without any residual deficit. Blood examinations were performed, showing an almost stable value of NT-pro-BNP (1530 pg/mL) and negative I troponin dosage (0.04, n.v < 0.09 ug/L); calcium, sodium, and potassium levels were normal, and blood count had no significant alteration.

At the emergency department echocardiogram, the ejection fraction had dropped to 20%. An abdominal and chest computed tomography (CT) showed the presence of splenomegaly and hilar lymphadenopathy with bilateral basal parenchymal nodules highly suggestive of sarcoidosis.

A total body 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) examination demonstrated multiorgan phlogistic-infiltrative involvement. (*Figure 2*).

An initial transbronchial biopsy of the mediastinal lymphadenopathies was not diagnostic but a subsequent hepatic CT-guided biopsy eventually confirmed the diagnosis of sarcoidosis, highlighting the presence of typical granulomatous lesions.

So, the patient underwent ICD implantation in secondary prevention and was started on high-dose steroid therapy (25 mg of prednisone two times per day prescribed long term). Cardioactive therapy was strengthened (bisoprolol 7.5 mg, ramipril 2.5 mg, potassium canrenoate 50 mg, and furosemide 25 mg) and 200 mg of mexiletine three times per day was started, with a reduction of the self-limiting persistent episodes of ventricular tachycardia documented by the ICD.

Follow-up

- Five months after the initiation of steroid therapy, a repeated total body 18-FDG-PET showed a crucial reduction of glucose uptake in all the involved organs, including the myocardium (*Figure 3*).
- Repeated echocardiographic controls showed a progressive improvement of left ventricular systolic function (up to 40%), without sign of segmental motion alterations, and persistence of moderate dilatation of the left ventricle (end-diastolic volume 201 mL). NT-pro-BNP blood levels markedly decreased (103 pg/mL) with no symptoms of dyspnoea or palpitations.
- The patient continued to experience occasional ventricular arrhythmias and was again hospitalized 1 year later after an appropriate ICD shock during ventricular tachycardia.
- Unfortunately, the patient had developed iatrogenic Cushing syndrome and thus a gradual reduction of the corticosteroid treatment was required to a dosage of 5 mg per day, with the aim to introduce, after complete tapering, a steroid-sparing immunosuppressive agent.

Discussion

Sarcoidosis is a rare multiorgan inflammatory disorder of unknown aetiology, characterized by the formation of non-caseating granulomas in the affected organs. Cardiac involvement is underrecognized and observed in up to 25% of cases in autopsy studies, with clinical evidence in

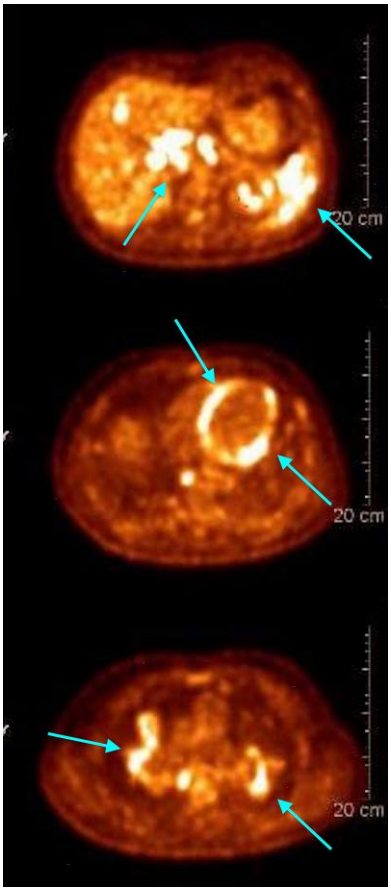


Figure 2 Coronal plane 18-FDG-PET images showing heart, lymph nodes, and spleen uptake of 18-fluorodeoxyglucose.

less than 5% of patients. The presence of cardiac sarcoidosis should always be suspected in the presence of complete atrioventricular (AV) block or ventricular arrhythmias in young patients and is associated with a high mortality rate, especially as a result of sudden cardiac death. Hence, it is important for the early detection of a potential heart involvement to determine the arrhythmic risk and to schedule an adequate follow-up.

Cardiac sarcoidosis is an insidious disease. Its diagnosis can be challenging since myocardial biopsy has high specificity but poor sensitivity due to the patchy nature of the disease. Echocardiography often fails to show typical abnormalities. Cardiac MR may guide the diagnosis of cardiac sarcoidosis (multifocal late gadolinium enhancement (LGE) in a non-infarct pattern, T2 signal alterations) and helps establish the prognosis.[2] 18-FDG-PET effectively assesses myocardial perfusion and inflammation with high sensitivity.

Overall, the best diagnostic strategy is multi-modality imaging, involving both MRI 75 with LGE and 18-FDG-PET. It has been noticed that cardiac magnetic resonance (CMR) may be more sensitive for initial diagnosis, whereas 18-FDG-PET likely has greater utility for serial imaging of inflammation and response to anti-inflammatory therapy.[3]

As a matter of fact, findings of fibrosis by CMR-LGE and increased glucose uptake as an inflammation marker by 18F-FDG-PET should be considered complementary pieces of information for the diagnosis.

Cardiac sarcoidosis diagnostic criteria (*Table 1*) were updated by a recent consensus statement from the Heart Rhythm Society. In the absence of a diagnostic endomyocardial biopsy, diagnosis is likely in the presence of a histological diagnosis of extra-cardiac sarcoidosis and at least one more criterion verified.[4] In this patient, cardiac sarcoidosis was highly probable because we came up with positive extra-cardiac histology + criteria numbers 1, 2, 4, and 5. Despite the confirmed genetic mutation, the imaging findings in this patient were not consistent with the diagnosis of cardiac amyloidosis and pointed in the direction of a dilated cardiomyopathy.

In fact, echocardiographic findings were not suggestive of cardiac amyloidosis, which usually presents with a hypertrophic phenotype

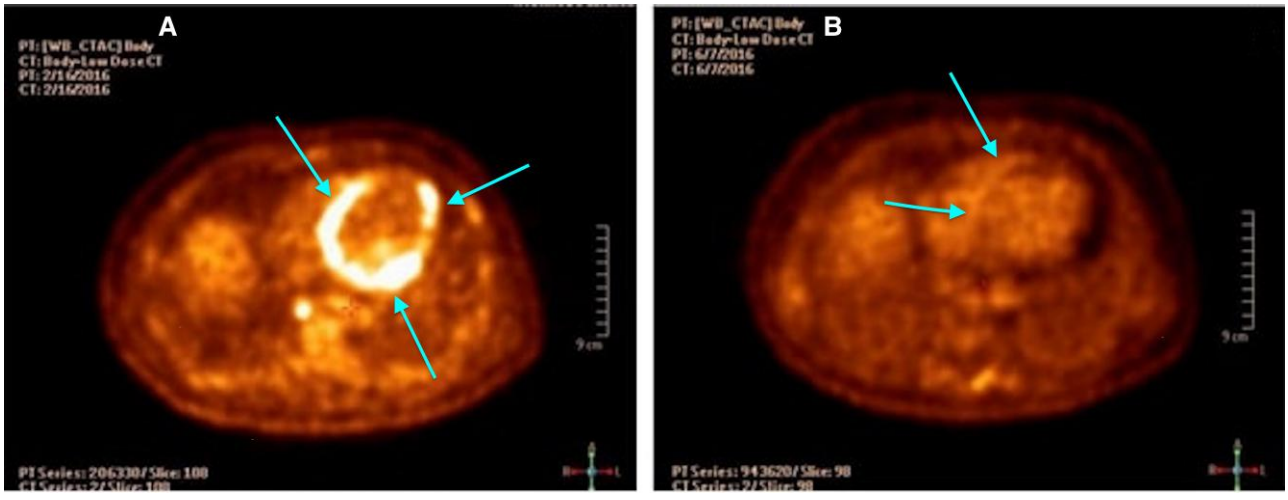


Figure 3 Coronal plane 18-FDG-PET images showing uptake before (*A*) and after (*B*) 5 month of corticosteroid therapy.

Table 1 Diagnostic criteria of cardiac sarcoidosis

A	HISTOLOGICAL DIAGNOSIS OF CARDIAC SARCOIDOSIS: Endomyocardial biopsies positive for non-caseating granulomas without alternative cause
B	CLINICAL DIAGNOSIS OF PROBABLE CARDIAC SARCOIDOSIS: Histological diagnosis of extracardiac involvement +>= 1 of the following
	–1 Corticosteroid or immunosuppressive therapy responsive cardiomyopathy or heart block
	–2 Unexplained reduced LVEF (<40%)
	–3 Mobitz type 2nd degree heart block or 3rd degree heart block
	–4 Patchy uptake on cardiac FDG-PET in a pattern consistent with cardiac sarcoidosis
	–5 LGE on CMR with a pattern consistent with cardiac sarcoidosis

due to myocardial infiltration of amyloid fibrils and a restrictive filling pattern rather than a dilated cardiomyopathy.

Similarly, CMR findings were not typical for amyloidosis, which usually shows global subendocardial late enhancement and abnormal myocardial and blood-pool gadolinium kinetics due to a contrast uptake of amyloid deposits. The gadolinium washout from blood and myocardium is faster than normal, probably due to its distribution into the total body amyloid load.[5] Bone scintigraphy also ruled out the diagnosis of *TTR* amyloidosis with no cardiac uptake of the bone tracer.

The diagnostic workup was extremely challenging, in a previously healthy, young patient, carrier of a known mutation, that initially diverted the physician's attention towards the suspicion of amyloidosis.

The patient had no family history of syncope or sudden cardiac death, and no analogous past events, the syncopal episode was studied to rule out an arrhythmic origin with a continuous 4 days of EKG monitoring and a cycle-ergometer stress test, both of them negative. According to the ESC guidelines, there was no indication for further examinations.[6]

At the 1-month control, given the net cardiac function worsening, and the suspicion of an amyloidosis heart involvement, the patient was again hospitalized; SPECT with bisphosphonate excluded cardiac amyloidosis, whereas CMR outlined a dilatative non-ischaemic pattern.

Only later, after the resuscitated CA, the suspicion of cardiac sarcoidosis was considered, thanks to the systemic involvement that was outlined.

After the diagnosis of cardiac sarcoidosis, electrophysiological study (EPS) was not performed since its role is well codified for arrhythmic burden stratification in patients that have not already experienced a ventricular arrhythmia leading to CA. In fact, according to ESC guidelines,[7] ICD implantation has a class I recommendation in patients with cardiac sarcoidosis who have an left ventricular ejection fraction (LVEF) ≤35% who have documented sustained ventricular tachicardia, or aborted CA. So, regardless of EPS, the patient would have undergone anyway the ICD implantation. Furthermore, the application of EPS for the study and ablation of possible ventricular foci are very unlikely in this case, since the disease involved the myocardium with a patchy and very widespread pattern.

We want to point out that the medical therapy choices made in this case were done before the last HF ESC 2021 guideline updates. For this reason, ARNI and sGLUT 2i would have been considered as second-line treatments/were not considered as first-line treatments.

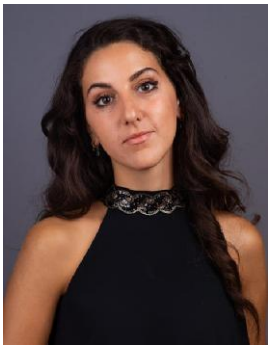
For what concerns immunosuppressive regimen, high-dose corticosteroids represent the mainstay of therapy, but still, prospective clinical trials are needed to determine the optimal dosing and treatment duration.[8,9] Combined immune-depressant therapy is reserved as a second-line treatment or as a steroid-sparing strategy in the long-term treatment. There are still no established guidelines on the use of immunomodulators for steroid sparing and whether to discontinue completely the steroids or not.

For arrhythmic risk reduction, mexiletine was preferred over amiodarone because of the patient's dysthyroidism and considering amiodarone's possible tissue accumulation damages, particularly in a young patient with the need for chronic antiarrhythmic therapy.

Conclusions

Cardiac sarcoidosis is a challenging diagnosis that should always be considered in the presence of complete AV block or ventricular arrhythmias in young individuals, often heralded by extracardiac involvement. Multi-modality imaging is essential to confirm the diagnosis, evaluate the response to treatment, and assess prognosis.

Lead author biography



S.M. is a general cardiology resident at the Università degli Studi di Firenze, Florence, Italy. She has attended the perioperative cardiology unit and currently completing her general cardiology fellowship.

Supplementary material

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

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None.

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 witnessed verbal consent for submission and publication of this case report including images and associated text has been obtained from the patients detailed in this case report. This has been discussed with the editors.

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