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CARDIAC SARCOIDOSIS PRESENTING AS SUSTAINED VENTRICULAR TACHYCARDIA

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ABSTRACT

Introduction: Sarcoidosis has many possible clinical presentations since it can affect any organ, most commonly the lungs. The hallmark of the disease consists of the formation of non-necrotising granulomas. Pathogenesis is thought to rely on the interplay of genetic, environmental and epigenetic factors. This case highlights the importance of a thorough clinical history and physical examination, and the correlation with imaging findings in the diagnostic work-up of the non-ischaemic cardiomyopathy.

Case description: A 57-year-old woman was admitted due to the sudden onset of malaise, dizziness, and chest discomfort. Sustained monomorphic ventricular tachycardia was evidenced and the patient rapidly evolved with haemodynamic instability; she underwent successful electrical cardioversion. The electrocardiogram afterwards showed a high-risk electrocardiographic pattern. Invasive coronary angiography excluded obstructive epicardial coronary lesions. Physical examination revealed skin lesions on the lower limbs which raised suspicion for erythema nodosum and therefore a biopsy was performed. Transthoracic echocardiography and cardiac magnetic resonance imaging revealed features consistent with an inflammatory cardiomyopathy, and an implantable cardioverter-defibrillator was placed. The histologic examination of the cutaneous lesions showed a non-necrotising granulomatous inflammatory process. Radionuclide imaging was inconclusive. The patient underwent an endomyocardial biopsy, which confirmed the diagnosis of systemic sarcoidosis with cardiac involvement.

Conclusions: Systemic sarcoidosis with cardiac involvement is a challenging diagnosis. The role of imaging techniques such as transthoracic echocardiography, cardiac magnetic resonance imaging and radionuclide imaging is essential in raising suspicion and diagnosing this pathology. Endomyocardial biopsy is the 'gold standard' for its diagnosis; however, it has a low diagnostic yield.

KEYWORDS

Ventricular tachycardia, systemic sarcoidosis, cardiac sarcoidosis, endomyocardial biopsy

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LEARNING POINTS

- Systemic sarcoidosis with cardiac involvement is a challenging diagnosis as it may present in many different ways.
- The case presented highlights the importance of a thorough clinical history and physical examination, and the correlation with imaging findings.
- Imaging techniques such as transthoracic echocardiogram, cardiac magnetic resonance and radionuclide imaging are essential in raising suspicion and diagnosing cardiac sarcoidosis.

INTRODUCTION

Sarcoidosis is known as the great mimicker as it may present in a wide variety of ways. It can affect any organ, but most commonly the lungs. The pathogenesis of sarcoidosis has not been completely elucidated; however, there is growing evidence suggesting an immunological response to an unidentified antigenic trigger in individuals with genetic susceptibility. The hallmark of the disease consists of the formation of non-necrotising granulomas. This report relates to a unique clinical case highlighting the importance of a thorough clinical history and physical examination, and the correlation with imaging findings in the diagnostic work-up of the non-ischaemic cardiomyopathy.

CASE DESCRIPTION

We present a 57-year-old woman with no known heart disease and no family history of cardiac disease or sudden death. Past medical history is relevant for type 2 diabetes mellitus, arterial hypertension, dyslipidaemia, hypothyroidism and being submitted to bilateral carpal tunnel syndrome intervention. Her usual therapy was treatment with gliclazide 60 mg once daily (od), dapagliflozin 10 mg od, bisoprolol 5 mg od, telmisartan 80 mg plus hydrochlorothiazide 12.5 mg od, metformin 1,000 mg plus vildagliptin 50 mg od, levothyroxine 0.1 mg od, rosuvastatin 10 mg plus ezetimibe 10 mg od and long-acting insulin adjusted to capillary glycaemia.

The patient was brought to the emergency department due to the sudden onset of generalised fatigue, malaise, dizziness and chest discomfort one hour prior to admission. On monitoring, sustained monomorphic ventricular tachycardia (VT) was evidenced *(Fig. 1)* and the patient rapidly evolved with haemodynamic instability.

She underwent successful electrical cardioversion. The electrocardiogram (ECG) afterwards showed sinus rhythm with slight elevation of the ST-segment in aVR and generalised depression of the ST-segment *(Fig. 2)*.

The transthoracic echocardiogram (TTE) showed diffuse hypokinesia of the septum and anterior wall, and moderate left ventricle (LV) dysfunction. She was referred for emergent coronary angiography, which did not reveal significant epicardial coronary lesions. Subsequently, during hospitalisation, she remained stable under anti-arrhythmic therapy with bisoprolol and amiodarone, and heart failure guideline-based prognostic modifying therapy.

Anamnesis and physical examination were relevant for COVID-19 active immunisation ten days prior and the existence of brownish-coloured skin lesions on the lower limbs *(Fig. 3)*, which had a maximum diameter of 1 cm; non-painful induration was felt under each lesion. The lesions developed approximately one year before this hospitalisation, were initially painful but no apparent cause was found. Although there was low suspicion for erythema nodosum, a biopsy was performed.

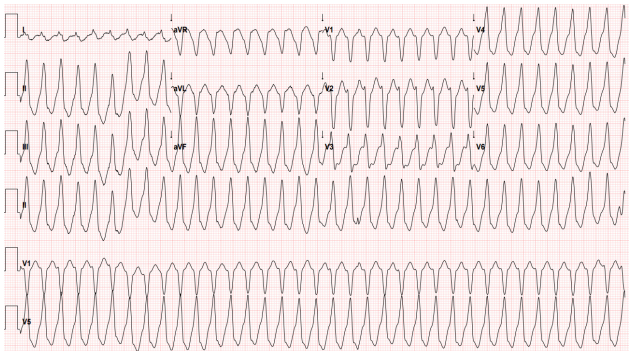


Figure 1. Electrocardiogram at admission; sustained monomorphic VT.

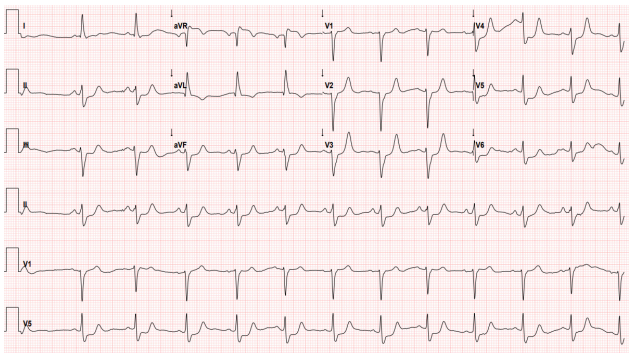


Figure 2. Electrocardiogram post-electrical cardioversion; ST-segment elevation of aVR and diffuse ST-segment depression.

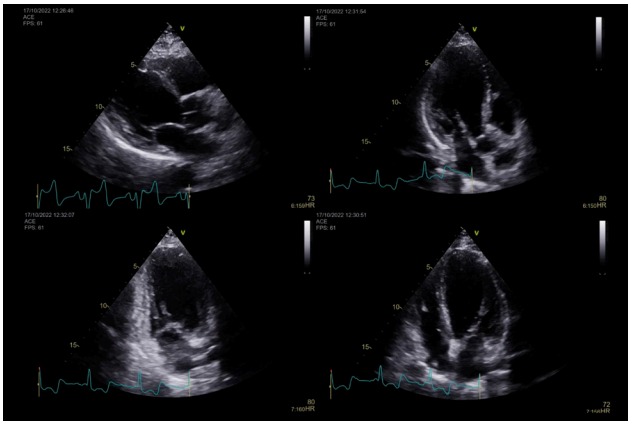
A complete TTE revealed mild systolic dysfunction of the LV and hypokinesia of the basal segments of the interventricular septum (IVS) and inferior wall, also showing basal thinning of the IVS *(Video 1)*. Cardiac magnetic resonance imaging demonstrated the presence of subepicardial late gadolinium enhancement (LGE) in the inferior and inferolateral basal segments and anteroseptal and anterior basal and middle segments, accompanied by changes in segmental kinetics and myocardial oedema *(Fig. 4)*. This non-coronary territory pattern raised suspicion for an inflammatory cardiomyopathy. A thoracic computed tomography showed normal pulmonary parenchyma and excluded hilar adenopathy.

Blood work allowed the exclusion of tuberculosis with an interferon-gamma releasing assay analysis; the angiotensin converting enzyme was 69 U/l (normal range 8–52 U/l), with normal erythrocyte-sedimentation rate velocity. The autoimmunity study showed slight positivity for anti-nuclear antibodies with other parameters being negative, and viral serologies only revealed a positive hepatitis B immunoglobulin E. Hepatitis B viral load was undetectable; no other analytical abnormalities were noted. A genetic cardiomyopathy study was ordered. An implantable cardioverter-defibrillator (ICD-DDD) was placed as secondary prevention and the patient was discharged while awaiting positron emission tomography (FDG-PET), skin biopsy results and a genetic cardiomyopathy study.

The histologic examination of the cutaneous lesions was positive for a non-necrotising granulomatous inflammatory process *(Fig. 5)*. The search for microorganisms in histochemistry stains was negative. This finding supports the diagnosis of systemic sarcoidosis with probable cardiac affection. The FDG-PET revealed increased uptake of ^{18}F-Fluorodeoxyglucose in the basal half of the LV. However, this was reported as possibly corresponding to physiological uptake due to inadequate preparation. The evaluation was also limited by ICD-related artefacts, and therefore the presence of metabolically active sarcoidosis in the heart could not be completely confirmed. The examination excluded other suspicious metabolically active locations. From the inconclusive results of the FDG-PET and high suspicion of cardiac sarcoidosis (CS), the patient was submitted to an endomyocardial biopsy which unveiled small epithelioid non-necrotising granulomas, with multinucleated giant cells confirming the diagnosis *(Fig. 6)*. The thoracic CT was later reviewed and found to have findings in the lung parenchyma consistent with an inflammatory process, most probably secondary to pulmonary sarcoidosis. A cardiomyopathy and autoimmunity consultations were scheduled, and a multidisciplinary meeting took place to decide which therapeutic strategy the patient was going to start. It was decided that the patient would begin immunosuppression with an anti-tumour necrosis factor (TNF) agent.

DISCUSSION

Sarcoidosis is a multisystem, non-caseating granulomatous disease with an unknown aetiology. It is characterised by a dysregulated T cell-driven immunologic response and activation of macrophages that accumulate in the affected organs. Researchers hypothesise that the pathogenesis is related to an exaggerated immune response to an environmental factor, infectious agent or antigen in a genetically susceptible individual[1]. Some clinical cases have been published reporting a correlation of sarcoidosis and COVID-19 vaccination, which may have been the trigger for our patient's exacerbation since she was actively immunised 10 days prior to her presentation[2]. However, further research is required to confirm this correlation. The



Video 1. Transthoracic echocardiogram – mild systolic dysfunction of the left ventricle (LV) and hypokinesia of the basal segments of the interventricular septum (IVS) and inferior wall, also showing basal thinning of the IVS. Apical 4 chamber view – lower right; apical 2 chamber view – lower left; apical 3 chamber view – upper right; parasternal long axis view – upper left.
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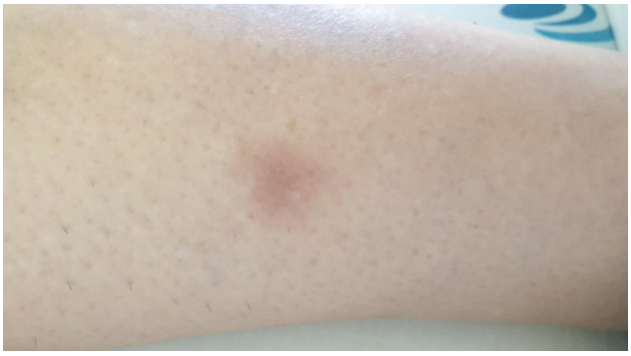

Figure 3. Cutaneous lesions: brownish-coloured skin lesion on the lower limb.

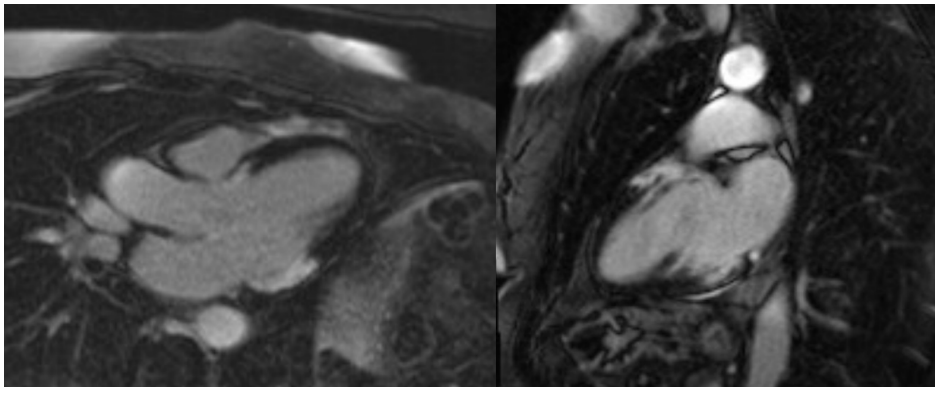

Figure 4. Cardiac magnetic resonance imaging – subepicardial late gadolinium enhancement in the inferior and inferolateral basal segments, and anteroseptal and anterior basal and middle segments.

diagnosis of sarcoidosis is challenging, resting on clinical presentation, display of non-necrotising granulomatous inflammation, exclusion of other granulomatous diseases and evidence of a systemic condition[3].

Sarcoidosis affects approximately 10 out of 100,000 people each year[4]. Cardiac involvement in sarcoidosis has been reported in 25% to 58% of autopsy studies; however, only approximately 5% of patients with sarcoidosis have clinically manifest cardiac affection. Patients most often present with conduction abnormalities, arrhythmias and heart failure; on the other hand, it may have a silent course[5]. Our patient presented with a ventricular tachyarrhythmia, which is the second most common manifestation of CS. Ventricular tachyarrhythmias usually result from re-entry circuits in inflamed and scarred myocardial areas, but automatic and triggered arrhythmias are also possible[3].

The diagnosis of CS is made through an endomyocardial biopsy with tissue confirmation, but the reported yield of unguided biopsy is low. Therefore, clinical guidelines have been proposed for assistance with this entity's diagnosis, based on histological and clinical diagnostic criteria. The Heart Rhythm Society and Japanese Circulation Society Working Group criteria for the diagnosis of CS are used worldwide for diagnosing this pathology. Despite this, it should be remembered that these criteria have not been prospectively validated[6], which was one of the reasons that compelled us to perform the endomyocardial biopsy. Our patient has a confirmed myocardial histological diagnosis; nonetheless, she also fulfilled the criteria for the clinical diagnosis based on the histological diagnosis of extra-cardiac sarcoidosis, left ventricular dysfunction, initially unexplained sustained VT, LGE on cardiovascular magnetic resonance in a pattern consistent with CS and basal thinning of the IVS[7]. Ventricular arrhythmias associated with CS are most likely due to macro re-entry phenomena around areas of fibrosis. Inflammation may also play a role in initiating re-entry with ventricular ectopy in CS patients, or by slowing conduction in diseased tissue[8]. As our patient was already on beta-blocker therapy, it was decided to initiate amiodarone. The implantable cardioverter-defibrillator was placed as a secondary prevention of sudden cardiac death according to the latest recommendations on ventricular arrythmias and sudden cardiac death[9]. Secondly, clinically manifest CS is an indication for anti-inflammatory treatment, preferentially with corticosteroids. However, taking into account our patient's poorly controlled hyperglycaemias, it was decided to initiate an anti-TNF agent. These are not associated with heart failure deterioration in studies of CS patients, making them a safe and effective choice. FDG-PET should be used to serially evaluate cardiac inflammation and response to treatment but unfortunately, the one performed on our patient prior to the initiation of immunosuppression was inconclusive for the reasons already explained. It was decided in a multidisciplinary meeting not to repeat the FDG-PET before starting therapy, as it would lead to a significant delay[10].

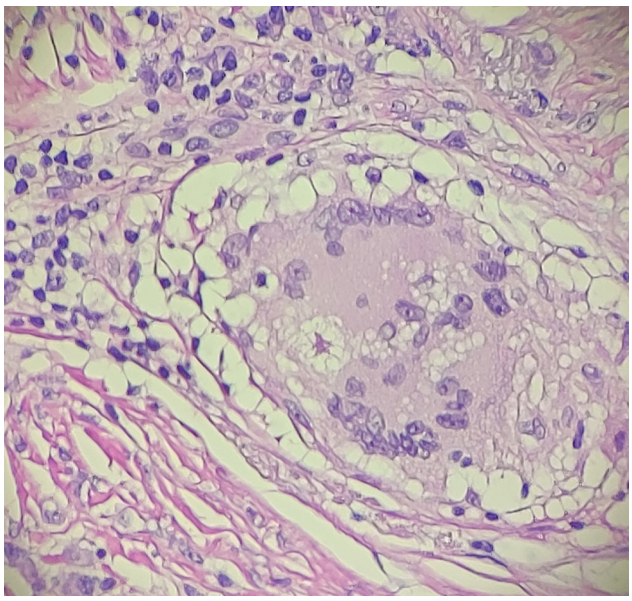

Figure 5. Skin lesion histology – non-necrotising granulomatous inflammatory process.

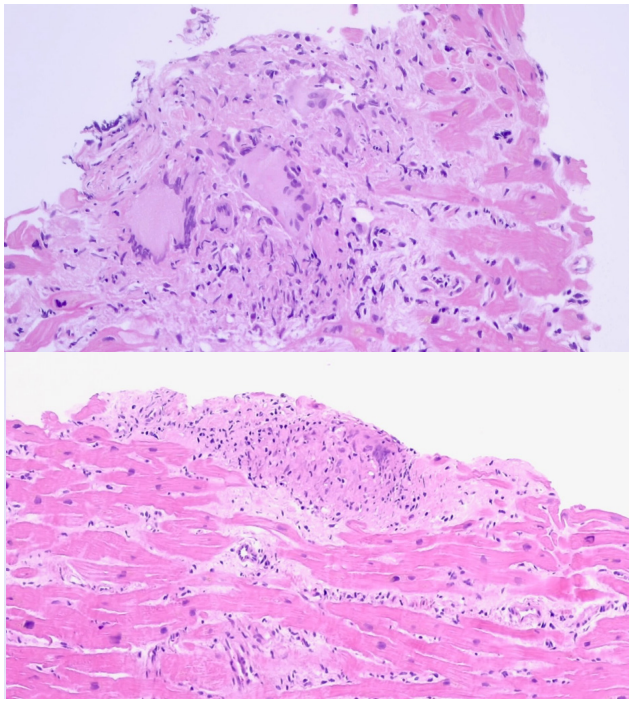

Figure 6. Endomyocardial biopsy specimen – non-necrotising epithelioid granulomas with multinucleated giant cells, some of Langhans type, with minimal peripheral inflammation, compatible with a granulomatous inflammatory process. Minimal interstitial and subendocardial fibrosis. (Left image – magnified 200×; right image – magnified 100×).

This is a case of a sustained VT as the initial presentation of an inflammatory cardiomyopathy, highlighting the difficult differential diagnosis between the various non-ischaemic aetiologies and the rare aetiology of CS. Suspicion for this diagnosis was raised on the pattern of LGE on cardiovascular magnetic resonance and basal thinning of the IVS on TTE, alongside the small asymptomatic cutaneous lesions, which underline the importance of a thorough physical examination and high clinical suspicion after excluding the usual culprits.

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