Cardiac sarcoidosis: a diagnostic puzzle

Introduction

With no specific 'biomarker', the diagnosis of sarcoidosis requires histological identification of non-caseating granulomas. Cardiac involvement may be occult, but even when clinically apparent, an endomyocardial biopsy is unreliable because of 'patchy' involvement of the myocardium. In either case, the prognosis and management of this potentially fatal disease requires establishing if the heart is involved. In many circumstances a combination of symptomatology, advanced cardiac imaging and confirmed extra-cardiac histology may be required to satisfy international definitions for heart involvement.

Discussion

Sarcoidosis is a multi-organ disease of uncertain aetiology, most commonly affecting the lungs, CNS, skin, lymph nodes and eyes. Although the majority of cases present with pulmonary manifestations, autopsy studies show cardiac involvement in up to 30% of cases (Ratner et al, 1986). Cardiac sarcoidosis is often underdiagnosed and may be present despite normal routine cardiac investigations.

Heart involvement by sarcoidosis may manifest with conduction disturbances, arrhythmias, ventricular dysfunction and pericardial disease. Complete heart block is the most common finding in patients with cardiac sarcoidosis (30%) (Roberts et al, 1977). Granulomas within the myocardium can form foci for abnormal automaticity producing ventricular tachyarrhythmias (23%) (Silverman et al, 1978), with sudden death a significant risk attributable to complete heart block or ventricular arrhythmias. Supraventricular arrhythmias, including atrial fibrillation, are less common (15%), and are usually the result of atrial dilatation rather than granulomas (Sekiguchi et al, 1980). Up to 75% of cardiac deaths in patients with cardiac sarcoidosis are attributed to progressive cardiac failure, secondary to extensive myocardial infiltration and fibrosis (Yazaki et al, 2001).

Although non-diagnostic, an electrocardiogram forms part of the routine assessment of a patient with sarcoidosis. Echocardiography may show evidence of dilated cardiomyopathy, often with dyskinesia or hypokinesia. A definitive diagnosis of heart involvement is feasible in the presence of clinical features and non-caseating granulomas on endomyocardial biopsy. However, a patchy distribution of sarcoid involvement in the heart results in a low diagnostic yield from endomyocardial biopsy. In some centres, advanced cardiac imaging is used to map deposits and target endomyocardial biopsies, while other units have abandoned cardiac biopsies as part of their work-up.

Dr S Pal is FY1 in Cardiology in the Cardiology Department, The Hillingdon Hospital, Uxbridge, Middlesex

Dr G Karagiannis is Consultant Cardiologist in the Cardiology Department, The Hillingdon Hospital, Uxbridge, Middlesex

Dr SW Dubrey is Consultant Cardiologist in the Cardiology Department, The Hillingdon Hospital, Uxbridge, Middlesex UB8 3NN

Correspondence to: Dr SW Dubrey (simon.dubrey@thh.nhs.uk)

CASE REPORT

A 54-year-old Afro-Caribbean man presented with shortness of breath, cough and lethargy. Both parents died of 'heart disease', his mother suffering a sudden cardiac death at 52 years of age. Two years earlier he had undergone inconclusive investigations for a persistent right pleural effusion. The effusion proved negative for fungi and acid-fast bacilli. A transthoracic thoracoscopic biopsy produced fibrotic tissue with mild inflammatory change and epithelioid cells, of a mesothelial origin, on histological staining.

Clinical examination revealed signs of fluid overload with a raised jugular venous pressure, and marked bilateral peripheral oedema. An electrocardiogram was unremarkable while the chest radiograph showed pulmonary oedema with a right pleural effusion (*Figure 1*).

An echocardiogram indicated moderate concentric left ventricular hypertrophy (wall thickness 18 mm), preserved systolic function (ejection fraction 65%) with no regional wall motion abnormalities and mild diastolic dysfunction. Intravenous diuretics improved his symptoms and he was discharged on a maintenance dose of frusemide.

Over the next year, there were seven further admissions with features of cardiac failure. Both atrial fibrillation and flutter also occurred and required radiofrequency ablation. An episode of non-sustained ventricular tachycardia was controlled with amiodarone.

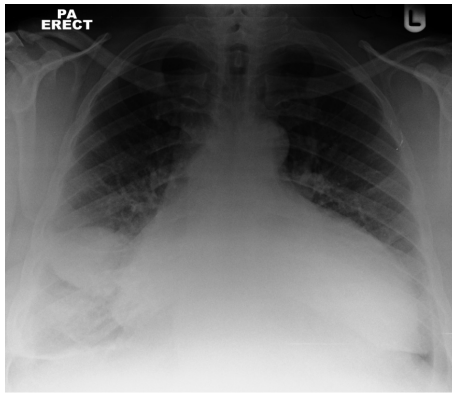
Recurrent admissions, without evidence of significant cardiac dysfunction on echocardiography, raised questions of compliance. Three years after the initial presentation he was again admitted with 'fluid overload' and was observed to also have a unilateral 'red eye', subsequently confirmed as anterior uveitis. This extra-cardiac manifestation suggested a diagnosis of sarcoidosis.

Investigations revealed normal serum and urinary calcium and angiotensin-converting enzyme levels (11 U/litre, reference range 20–90 U/litre). High-resolution computed tomography of the chest showed features of pulmonary sarcoidosis with fibrosis and, as yet unidentified, bilateral hilar and mediastinal lymphadenopathy. A bronchial biopsy identified non-caseating granulomas – a 'hallmark' feature of sarcoidosis.

Cardiac magnetic resonance imaging showed preserved ejection fraction, left ventricular hypertrophy with a maximal septal wall thickness of 22 mm and severe bi-atrial dilatation. There was evidence of patchy mid-wall late gadolinium enhancement throughout the interventricular septum, indicative of fibrosis. Extensive hilar and mediastinal lymphadenopathy and increased parenchymal lung signal intensity were suggestive of sarcoidosis. A 3-day course of intravenous methylprednisolone (1 g/day), followed by oral prednisolone (40 mg/day), resulted in significant clinical improvement.

Now on prednisolone long term (15 mg/day) the patient is being followed up in a specialist sarcoid clinic. He has had few readmissions in subsequent years and has made a reasonable recovery.

Figure 1. Chest radiograph showing cardiomegaly with a suggestion of upper lobe blood diversion. There is a right basal 'lamellar' effusion and a dense 'rugby ball'-shaped opacity in the right lower zone most likely representing encysted pleural fluid in the oblique fissure.



In patients where cardiac sarcoidosis is clinically occult, confined to the heart or diagnostically elusive, extra-cardiac histological evidence combined with clinical cardiac features and advanced imaging techniques may be the only way to confirm prognostically important heart involvement. Cardiac magnetic resonance imaging, nuclear medicine perfusion scans and, increasingly frequently, 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) scans are used to demonstrate both infiltration and disease activity (Kandolin et al, 2011). Typically, algorithms for the diagnosis of cardiac sarcoidosis have required the use of disease exclusion, histology and international guidelines (Judson et al, 2014).

Table 1. Cardiac sarcoidosis – the pieces of the puzzle

Ethnic origin	Afro-Caribbean (an ethnic origin with an increased prevalence of sarcoidosis)
Family history	Sudden cardiac death in first-degree relative
Symptoms	Chronic cough, lethargy and shortness of breath
Signs	Peripheral oedema, pleural effusion, pulmonary oedema
	Cardiomyopathy
	Arrhythmias (atrial fibrillation and atrial flutter or ventricular tachycardia)
	Anterior uveitis (a recognized feature of sarcoidosis)
Advanced imaging	Computed tomography and magnetic resonance imaging of thoracic viscera
Histology	Extra-cardiac (bronchial biopsy) confirmation of sarcoidosis

Conclusions

The 'pieces of the puzzle' (*Table 1*) were present in this patient, but it was only when the patient developed the characteristic extra-cardiac feature of uveitis that sarcoidosis was suspected and eventually substantiated with advanced cardiac imaging techniques. **BJHM**

Judson MA, Costabel U, Drent M et al (2014) The WASOG sarcoidosis organ assessment instrument: an update of a previous clinical tool. *Sarcoidosis Vasc Diffuse Dis* **31**(1): 19–27

LEARNING POINTS

- Sarcoidosis has no specific 'biomarker' to identify the disease.
- Cardiac sarcoidosis may be present but 'occult' with unremarkable routine cardiac investigations.
- Autopsy studies suggest heart involvement in up to 30% of patients diagnosed with sarcoidosis.
- A diagnosis of cardiac sarcoidosis may require a combination of excluding other diseases, histology from an extra-cardiac source, cardiac symptoms and advanced cardiac imaging techniques.

Kandolin R, Lehtonen J, Graner M et al (2011) Diagnosing isolated cardiac sarcoidosis. *J Internal Med* **270**(5): 461–8 (doi: 10.1111/j.1365-2796.2011.02396.x)

Ratner SJ, Fenoglio JJ Jr, Ursell PC (1986) Utility of endomyocardial biopsy in the diagnosis of cardiac sarcoidosis. *Chest* **90**: 528–33 (doi: 10.1378/chest.90.4.528)

Roberts WC, McAllister HA Jr, Ferrans VJ (1977) Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsy patients (group 11). *Am J Med* **63**: 86–108

Sekiguchi M, Numao Y, Imai M, Furuie T, Mikami R (1980) Clinical and histopathological profile of sarcoidosis of the heart and acute idiopathic myocarditis. Concepts through a study employing endomyocardial biopsy. I. Sarcoidosis. *Jpn Circ J* **44**(4): 249–63 (doi: 10.1253/jcj.44.249)

Silverman KJ, Hutchins GM, Buckley BH (1978) Cardiac sarcoid a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation* **58**: 1204–11 (doi: 10.1161/01.CIR.58.6.120)

Yazaki Y, Isobe M, Hiroe M et al (2001) Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol* **88**(9): 1006–10 (doi: 10.1016/S0002-9149(01)01978-6)