Sarcoidosis: a pattern of clinical and morphological presentation

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SUMMARY The diagnosis of cardiac sarcoidosis, particularly when there is no overt systemic involvement, is frequently delayed because of its varied manifestations. Focal left ventricular wall motion abnormalities were recognised in five patients with sarcoidosis. Three patients showed abnormal regional wall motion in the basal portion of the ventricular septum and free wall with sparing of the apex. The angiographic appearances supported the echocardiographic findings which were atypical of ischaemic heart disease. The remaining two patients both had diffuse left ventricular hypokinesia, with a focal abnormality that was most pronounced in the anteroapical region; this pattern is often seen with coronary disease.

The recognition by echocardiography or angiography of focal abnormalities of wall motion affecting the basal portion of the ventricular septum should suggest the possibility of myocardial sarcoidosis even in the absence of recognised systemic manifestations.

Focal abnormalities of left ventricular wall motion are uncommon except in coronary artery disease in which the distribution is dependent on coronary artery anatomy. It is therefore unusual to find wall motion abnormalities localised to the basal part of the septum with sparing of the apical portion. This report of five cases shows that although sarcoid granuloma can occur anywhere in the heart a pattern of fibrosis distinct from coronary disease may be recognised by echocardiography and angiography.

Patients and methods

We studied five men aged 29, 36, 37, 45, and 46 years. One was black and the remainder were white. Systemic sarcoidosis had been diagnosed because at least two organ systems were affected and there was either positive lymph node histology or a Kveim test. All patients underwent cardiac catheterisation,

coronary angiography, and cross sectional echocardiography. Three patients shared several clinical characteristics. None of these three had clinical evidence of heart failure. All had normal physical examination, normal laboratory indices of bone marrow, renal, and hepatic function. All had left anterior hemiblock and right bundle branch block. Left ventricular end diastolic and pulmonary artery pressures were normal and there was no disease of the major epicardial coronary arteries. The table summarises the investigations that were performed to assess disease activity and distribution.

In patient 1 systemic sarcoidosis was not diagnosed during life. He presented with a two year history of palpitation and ventricular tachycardia associated with syncope and evidence of a progressive conduction system disturbance. During cross sectional echocardiography from the parasternal long axis view (fig 1a) the basal part of the ventricular septum was thin and akinetic with increased echo reflectivity and paradoxical systolic motion. The same abnormality was seen in serial short axis views at the level of mitral valve and papillary muscle (fig 2). The apical third of the ventricular septum, the posterior wall of the ventricle, and the right ventricular free wall were normal. Left

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Accepted for publication 23 October 1986

Table Investigations to assess activity and extent of sarcoidosis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
ESR	4	10	8	70	10
SACE	ND	33	88	58	ND
Gallium uptake	ND	Normal	Matched uptake in left lung hilum, and paratracheal area	ND	ND
Thallium uptake*	Septum and free wall	ND	Septum	Anteroapical and free wall	ND
Chest x ray	Recurrent pulmonary infiltrates	Normal	Hilar lymphadenopathy, pulmonary infiltrates	Hilar lymphadenopathy	Hilar lymphadenopathy
Cardiothoracic ratio	19/30	15/30	14/28	20/30	18/30
Pulmonary function tests	ND	Normal†	Decreased lung volumes and gas transfer	Decreased lung volumes and gas transfer	Normal

*Thallium scans showed decreased uptake during exercise without recovery in the designated areas.
†At diagnosis chest x ray showed right hilar lymphadenopathy and a right apical infiltrate.
SACE, serum angiotensin I converting enzyme (normal range = 16–53 units/ml); ND, not done; ESR, erythrocyte sedimentation rate.

ventricular angiography in the right anterior oblique projection (fig 3a) showed poor contraction of the anterobasal and posterobasal segments whereas the apical segments contracted normally. Coronary angiography was normal. Endocardial resection for

resistant ventricular tachycardia was complicated by a low output state and the patient died during operation.

At necropsy the heart weighed 583 g. The basal ventricular septum was thick and replaced by fibrous tissue (fig 4) that extended into the basal part of the posterior wall. This mirrored the echocardiographic and angiographic appearances. Histological examination confirmed replacement of this part of the septum by dense fibrous tissue. The remainder of the myocardium showed focal scarring with an occasional giant cell but no granulomas. Typical sarcoid granulomas were, however, present in the lungs, spleen, mediastinal lymph nodes, and liver.

In patient 2 sarcoidosis of the heart had been diagnosed 10 years earlier when he presented with supraventricular and ventricular arrhythmia, progressive conduction disturbance, and pulmonary sarcoidosis (table). He was referred for control of ventricular arrhythmias that had failed to improve on increasing doses of steroids. Cross sectional echocardiography in the parasternal long axis view (fig 5) showed that the basal portion of the ventricular septum was thin, akinetic, and aneurysmal, and clearly protruded into the right ventricle in systole, while the apical part was of normal thickness and contracted normally. This focal ventricular abnormality was also seen in short axis views at the level of mitral valve and papillary muscle (fig 6). The cardiac apex was seen to be contracting normally. Angiographic examination showed that the basal part of the left ventricle was dilated and aneurysmal and the apical portion contracted normally (fig 3b). He was treated with mexiletine and amiodarone. Ventricular arrhythmia was inadequately controlled and he died suddenly. At necropsy the heart weighed 500 g. The basal two thirds of the ventricular septum was thin

Fig 1 Echocardiographic appearances in the parasternal long axis views in patients 1(a) and 3(b) showing thinning of the basal portion of the ventricular septum, which was pronounced in patient 1.

and extensively replaced by fibrous tissue that extended into the basal part of the posterior wall. Elsewhere the myocardium appeared to be normal and no granulomas were found in histological sections of the heart. Examination of the lungs, mediastinum, liver, and spleen showed extensive replacement of the normal tissue by the typical non-caseating granuloma of sarcoidosis.

Patient 3 was known to have had pulmonary sarcoidosis for 14 years before his presentation with

syncope, complete heart block, and a soft systolic murmur at the apex. Echocardiography from the parasternal long axis view (fig 1b) showed that the ventricular septal dimension was within normal limits, but in its basal portion the septum was akinetic and showed increased echo reflectivity. The apical third of the ventricular septum, posterior wall, and right ventricular free wall were normal. The short axis views (fig 7) at the level of the mitral valve also showed the same akinetic and echo-dense ventricular septum which was of normal dimensions at the level of the mitral valve, but at the papillary muscle level the septum was thin and akinetic. Appearances were normal at the level of the apex. Left ventricular angiography showed mild impairment of contraction of the basal portion of the left ventricle with mild mitral regurgitation (fig 3c). A biopsy specimen of the right ventricle contained epithelioid giant cells and fibrous granulomas characteristic of sarcoidosis. The patient has been symptom free after the insertion of a permanent pacemaker.

The clinical features and mode of presentation were different in the remaining two patients. Patient 4 presented with an acute systemic illness characterised by fever, high erythrocyte sedimentation rate (70 ml/h), hilar lymphadenopathy, and congestive cardiac failure. There were Q waves on the electrocardiogram that simulated anterior myocardial infarction. Echocardiography showed septal hypertrophy and mild global hypokinesia and there was a fixed thallium perfusion defect of the anteroapical region of the left ventricle. Angiographic examination of the left ventricle showed a considerable increase in end systolic volume with extensive anteroapical akinesia, and hypokinesia of the remainder of the ventricle. The result of coronary arteriography was normal. A biopsy specimen of the myocardium showed diffuse interstitial fibrosis but no granulomas, and the diagnosis of sarcoidosis was based on a biopsy specimen of the mediastinal lymph nodes.

Patient 5 presented with ventricular tachycardia and no evidence of congestive cardiac failure. An electrocardiogram showed T wave inversion in the inferior and lateral leads and voltage criteria that were characteristic of hypertrophy of the left ventricle but no conduction abnormality. Cross sectional echocardiography showed global hypokinesia, which was confirmed by angiography, with akinesia and calcification of the apex. The haemodynamic function of the right and left heart and the results of coronary arteriography were normal. A biopsy specimen of the myocardium showed diffuse interstitial fibrosis only. Systemic sarcoidosis was diagnosed on the basis of bilateral hilar lymphadenopathy and a positive Kviem test.

Fig 2 Echocardiographic appearances in the short axis views in patient 1 at the level of mitral valve (a), papillary muscle (b), and apex (c). There was no systolic thickening of the septum at the mitral and papillary muscle level. In contrast apical contraction was normal.

Fig 3 Left ventricular angiograms of patients 1, 2, and 3 (a, b, and c respectively) in systole (right) and diastole (left) in the right anterior oblique projection, showing impaired contraction of the base of the heart, which is most pronounced in patient 2.

Fig 4 Echocardiographic and necropsy appearances of the heart in patient 1 as seen from the short axis views at the level of the papillary muscles, showing the thin and akinetic septum, which is replaced by fibrous tissue.

Fig 5 Long axis views of systolic and diastolic frames in patient 2.

Discussion

Sarcoidosis is a multisystem granulomatous disorder of unknown cause. The frequency of clinical cardiac involvement in patients with systemic sarcoidosis is low (1.5%).^{1,2} Most (80%) patients with cardiac sarcoidosis have conduction disturbance or arrhythmia³⁻⁸ and/or impaired cardiac function (31%).⁵⁻⁹ Patients have also presented with mitral stenosis caused by leaflet granuloma¹⁰ or with mitral regurgitation caused by infiltration of the papillary muscle.¹¹ In patients with cardiac sarcoid the risk of sudden death is considerable.³ An additional 23% of patients with systemic sarcoidosis will have isolated sarcoid granulomas that are detectable only by histological examination of the heart¹ but the proportion of positive cases probably varies with the extent to which the myocardium is sampled at necropsy.

The wide range of clinical manifestations of cardiac sarcoidosis evident from this report of five cases

is consistent with the varied distribution and morphological features of the abnormalities. In patients who die in the active phase of myocardial sarcoidosis granulomas may either be distributed evenly throughout the myocardium or occur as a localised mass, commonly in the basal portion of the ventricular septum.^{3,5,12} The frequency of sudden death reflects the high risk that the conduction system will be affected in both the focal and diffuse forms.³

This acute phase of myocardial sarcoidosis will resolve either as diffuse interstitial fibrosis of the myocardium and a generalised hypokinesia of the ventricle or as a localised fibrous scar with focal contraction abnormalities. Diffuse fibrosis is difficult to distinguish from dilated cardiomyopathy. Focal lesions may also be difficult to distinguish in life from ischaemic heart disease but the lesion in the basal portion of the septum in cases 1-3 is in an unusual site for old infarction and is typical of sarcoidosis. For these reasons and because of the presence of normal coronary arteriograms the scars in patients

Fig 6 Short axis views in patient 2. Legend as for fig 2.

Fig 7 Short axis views in patient 3. Legend as for fig 2.

1-3 were taken to indicate healed sarcoidosis though no active granulomas were found in the myocardium.

The acute and more chronic forms of myocardial sarcoid have been linked to four histological patterns.¹³ An exudative type (lymphocytic infiltration with oedema) and a granulomatous type (granulomata with epithelial cells) are associated with systemic disease and characterised by a subacute course

with clear clinical evidence of multi-organ involvement. The chronic fibrous types (with and without giant cells) are associated with the chronic insidious course seen in cases 1-3. The papillary muscles and right ventricle are also commonly found to contain granulomas at necropsy. Case 3 had clinical and echocardiographic evidence of papillary muscle dysfunction as well as right ventricular involvement and typical granulomas were found in

biopsy specimens of the right ventricle.

The use of steroids in cardiac sarcoid has not been systematically evaluated. Retrospective analysis, however, suggests that steroids promote healing of granulomas but the concomitant development of fibrous tissue may be complicated by aneurysm formation⁵; this is an otherwise rare complication. Patients 2 and 3 received long term corticosteroid treatment. Both showed thinning of myocardial segments. In patient 2 there was an intracardiac aneurysm of the basal septum that bulged into the outflow tract of the right ventricle; at necropsy this segment was found to be replaced with fibrous tissue. Though granulomas were detected in other organs they were not found in the heart. Patient 1 also had myocardial thinning caused by fibrous tissue replacement and multiple organ granulomas but no cardiac ones. He had not been given steroids, however. These findings are consistent with published reports which suggest that steroids promote healing, which may be complicated by the development of an aneurysm. They also indicate that steroids are not a prerequisite for such a course and they raise the question of the usefulness of steroids once myocardial thinning and aneurysm have developed.

Patient 2 had refractory ventricular arrhythmia and died suddenly. Patients are usually only referred for transplantation when poor and deteriorating left ventricular function and the ensuing shortness of breath, fatigue, and oedema indicate that they will die soon. Referral for transplantation is much more difficult and therefore less often acted upon when life threatening arrhythmia cannot be controlled. The argument for transplantation is more cogent if the arrhythmia is caused by a process which itself may be advancing, such as cardiac sarcoidosis. We considered transplantation in patient 2 but did not act upon it immediately. His death was sudden but predictable. Hearts have been successfully transplanted into patients with cardiac sarcoidosis¹⁴ but we delayed too long.

Our index patient, patient 1, had conduction disturbance and ventricular tachycardia in the absence of recognised systemic sarcoidosis. The diagnosis of cardiac sarcoid is seldom missed when this constellation of changes coexists with systemic sarcoidosis. In the absence of systemic sarcoid these cardiac abnormalities are not specific and are more likely to

have other causes. The focal abnormality of wall motion localised to the basal portion of the ventricular septum that we described is unusual in coronary artery disease and should suggest the diagnosis of cardiac sarcoid even when there are no systemic changes.

We are grateful to Professor John F Goodwin for permission to publish details of case 1.

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