Sarcoid heart disease

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To this day the aetiology of sarcoidosis continues to elude definition. Partially as a consequence of this, little in the way of new therapies has evolved. The enigma of this condition is that, unusually for a disease with the potential for devastating consequences, many patients show spontaneous resolution and recover. Cardiac involvement can affect individuals of any age, gender or race and has a predilection for the conduction system of the heart. Heart involvement can also cause a dilated cardiomyopathy with consequent progressive heart failure. The most common presentation of this systemic disease is with pulmonary infiltration, but many cases will be asymptomatic and are detected on routine chest radiography revealing lymphadenopathy. Current advances lie in the newer methods of imaging and diagnosing this unusual heart disease. This review describes the pathology and diagnosis of this condition and the newer imaging techniques that have developed for determining cardiac involvement.

by such clustering,¹¹ and that an as yet unknown stimulus triggers an exaggerated immune response. Sarcoidosis occurs more commonly in monozygotic than dizygotic twins and familial clusters of the disease are described.¹² Takayasu arteritis may be related to sarcoidosis as both diseases are characterised by an immuno-inflammatory abnormality and because several cases have been described that link these two diseases.¹³

PATHOLOGY

Histologically the granulomas are described as non-caseating (non-necrotising) and contain epithelioid cells and large multinucleated giant cells (fig 1). T cell activation is at the centre of the process which pulls in monocytes and allows granulomas to form. B cell activation also occurs and results in immunoglobulin production. In some cases the granulomas will result in a fibrotic reaction that may cause permanent tissue damage (fig 2). At autopsy, heart involvement can range from massive involvement with confluent giant cell granulomas and fibrosis, occupying a majority of the heart, to a microscopic and diffuse pattern.¹⁴

HEART INVOLVEMENT BY SARCOID

Determining if the heart is involved is difficult because granulomas may be present without clinical dysfunction.¹⁵ Sarcoidosis should be suspected in any patient, younger than expected, presenting with complete heart block or heart failure.¹⁴ Sarcoid is an infiltrative disease in character and has a predilection to involve the cardiac conduction system. Patients can develop various degrees of heart block and tachyarrhythmias. They are also liable to sudden death.⁶ A dilated cardiomyopathy can occur, with the left ventricle and the interventricular septum primarily involved. Sarcoid has a predilection for the base of the interventricular septum, which by virtue of the location can cause heart block or an arrhythmia. Mitral valve abnormalities, papillary muscle dysfunction, left ventricular aneurysm formation and pericardial effusions are also seen. Cor pulmonale can develop due to chronic pulmonary fibrotic disease. A resting ECG, 24 hour Holter monitoring and echocardiography are obligatory if cardiac involvement is suspected.

PROGNOSIS

In many cases the granulomas may resolve spontaneously. Cases presenting in an asymptomatic way with bilateral hilar lymphadenopathy

Sarcoidosis is a multisystem disease which is characterised by the formation of granulomas in many tissues. Previously it was thought that the incidence of sarcoidosis was heavily skewed toward the black populations. Now it is recognised worldwide with a high prevalence in Sweden (64 per 100 000), Norway and Denmark. Disease severity is, however, still greater in black patients, both in the USA¹ and in those who have migrated to Europe.^{2,3} In the USA, the incidence for the white population is estimated to be 11 per 100 000.⁴ It predominantly affects 20–30-year-olds and there is a female predominance.^{4,5}

The main organ systems targeted are the lungs and the lymph nodes of the thorax, although virtually no organ systems are spared, including the central nervous system and the skin. The quoted incidence of clinical heart involvement is around 4–5%,⁶ while at autopsy this is a considerably higher figure of 20–25%.⁷

AETIOLOGY OF SARCOIDOSIS

Despite being one of the most common infiltrative cardiac diseases that will be encountered, its aetiology remains unknown, although numerous infective agents (for example, microbial bio-aerosols) and environmental exposures (for example, insecticides and agricultural employment) have been proposed.⁸ Reports of community outbreaks and clustering of cases among working colleagues, including nurses, firefighters, US Navy personnel and neighbours are described.^{9,10} The likelihood is that there is a genetic predisposition as evidenced

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Abbreviations: ACE, angiotensin converting enzyme; CT, computed tomography; FDG, fluoro-2-deoxy-D glucose; MRI, magnetic resonance imaging; PET, positron emission tomography

Figure 1 An endomyocardial biopsy from a patient with active sarcoid who arrived in end-stage heart failure and died shortly thereafter. The slide shows a granuloma with extensive inflammatory cell infiltration. The surrounding myocytes are disrupted in the region below the granuloma with fibrosis and lymphocytes evident.

alone are likely to resolve spontaneously within 2 years. Symptoms at presentation mean the condition is less likely to resolve.

Unlike isolated pulmonary disease, the prognosis with cardiac involvement is much worse. It is estimated that between 5–8% of patients will eventually die of their disease, respiratory failure being the principle cause.³ In Japan, nearly 80% of patients die from cardiac involvement.¹⁶ However, owing to improved rhythm management with pacemakers and implanted defibrillators, the primary cause of death has moved from sudden death to heart failure.¹⁷

LABORATORY INVESTIGATIONS

Blood tests will frequently show anaemia, leucopenia and/or a raised erythrocyte sedimentation rate (ESR). The CD4:CD8 ratio in the blood serum is commonly decreased but the angiotensin converting enzyme (ACE) level is no longer considered reliable as a diagnostic test. This is because the serum ACE is raised in sarcoidosis, but also in other granulomatous diseases, where a local stimulation of macrophages leads to abnormal ACE secretion. A role for ACE measurement remains in providing some indication of the extent and severity of the disease process and response to treatment. Patients with sarcoidosis may be hypercalcaemic due to an activation of vitamin D by macrophages in sarcoid granulomas. In addition, an excess of immunoglobulin may be seen due to the B cell “proliferation” that can occur. The Kveim skin test is no longer performed, largely because of the inherent risk of transfer of an “infective” agent.

IMAGING TECHNIQUES TO IDENTIFY HEART INVOLVEMENT BY SARCOID

Different imaging techniques have been used both for the diagnosis and follow up of patients with suspected cardiac sarcoidosis. These include echocardiography, myocardial perfusion with thallium or Tc-99 nuclear scintigraphy, gallium-67 scintigraphy, positron emission tomography (PET) with ¹⁸FDG (fluoro-2-deoxy-D glucose) and more recently magnetic resonance imaging (MRI) and cardiac computed tomography (CT).

Plain chest radiographs

These provide no particular features for the diagnosis of cardiac sarcoidosis. However, they have been used for presence of

Figure 2 A section from an explanted heart. The transplant was performed for a presumed dilated cardiomyopathy, although granulomas had been seen in node biopsy some 10 years previously. In this case, an acute inflammatory process is less evident. In the centre of the slide a granuloma is evident with extensive fibrosis surrounding it. A margin of lymphocytes, with their dark staining nuclei, separates this area of fibrosis from more normal looking myocardium to the right of the slide.

pulmonary sarcoidosis and staging the disease.¹⁸ Chest radiographs characteristically show bilateral symmetrical hilar with right paratracheal lymphadenopathy with or without pulmonary parenchymal involvement. These findings are generally confirmed with high resolution CT, which is particularly sensitive for detection of pulmonary involvement.^{19–20} Standard contrast enhanced CT may be required for better delineation of mediastinal and hilar lymphadenopathy.

Two dimensional echocardiography

Echocardiography is the first line investigation for evaluation of patients with suspected cardiac sarcoidosis. Echocardiographic appearances are variable and may show regional wall motion abnormalities and thickening of the interventricular septum, with bright shadows consistent with infiltration. Alternatively the ventricles may appear thinned, with global dysfunction and aneurysm formation. Diastolic dysfunction is seen on initial interstitial inflammation, when systolic function may still be normal. Subsequent injury and fibrosis causes systolic abnormalities.^{21–23} As most of these features are also common in ischaemia, coronary artery disease will require exclusion.

Radionuclide scintigraphy studies

²⁰¹Thallium scintigraphy myocardial perfusion studies typically show segmental areas of decreased uptake in the ventricular myocardium that disappear or decrease in size during stress or after intravenous administration of dipyridamole.^{24–25} However, this reverse distribution is not specific for cardiac sarcoidosis as it may also occur in other cardiomyopathies.

In patients in whom the diagnosis of sarcoid is difficult, gallium-67 scintigraphy has also been used to demonstrate both cardiac and extra-cardiac disease.²⁵ The detection of clinically silent extra-thoracic uptake may provide sites for biopsy. It has also been used for follow up of active disease (both cardiac and extra-cardiac) with treatment.²⁶ However, its routine use in the follow up of pulmonary sarcoidosis under treatment has decreased because that is best accomplished by means of serial chest radiographs and pulmonary function tests. Studies in which both ²⁰¹thallium and gallium-67 scintigraphy were performed in patients with suspected sarcoidosis showed that areas of reduced uptake were more common using ²⁰¹thallium than with gallium-67.²⁷ In patients in which both scans were

positive there was more severe cardiac involvement, as indicated by a reduced ejection fraction. More recently, use of ^{99m}Tc sestamibi has been described as the perfusion agent,²⁸ in combination with gallium-67 scintigraphy.²⁹ Like gallium-67 scintigraphy, ^{18}F FDG PET has been shown to be useful for demonstration of both cardiac and extra-cardiac sarcoid disease.²⁵

Magnetic resonance imaging

Due to its high spatial and soft tissue resolution, MRI is now increasingly being shown to be the technique of choice for evaluation and diagnosis of cardiac sarcoidosis.³⁰⁻³³ Acute myocardial inflammation due to sarcoid infiltrates presents as

focal areas of thickening and increased signal intensity on T2 weighted images and early gadolinium enhanced images. Delayed gadolinium enhanced images may show hyperenhancement (fig 3), probably reflecting accumulation of gadolinium chelates in the tissue as a result of differences in contrast distribution volume. Cine MRI may demonstrate focal areas of wall motion abnormality. Focal involvement of the basal septum is most common with occasional involvement of the lateral wall. In severe cardiac involvement, massive infiltration may sometimes lead to diffuse myocardial thickening with diffuse contraction abnormalities and restrictive cardiomyopathy and heart failure.

Figure 3 This patient was a young male who experienced an episode of loss of consciousness and whose ECG demonstrated runs of a broad complex tachycardia. The cardiac magnetic resonance image above shows the presence of abnormal enhancement (arrows) in the epicardium of the anteroseptal wall of the left ventricle on short axis (A) and two chamber (B) delayed post-contrast images. Further enlarged lymph node was noted in the pre-aortic region (arrow in C) on T1 weighted image. Biopsy of an enlarged submandibular gland confirmed this to be sarcoidosis.

Figure 4 This patient had experienced a paroxysmal broad complex tachycardia over a 12 year period, with a dilating left ventricle. The cardiac MRI revealed thinning of the anterior wall, anterior septum and antero-lateral wall with enhancement confined to the epicardium as seen on the short axis delayed post-contrast image (A, arrows). These segments of the left ventricle were severely hypokinetic on cine images. Black blood T1 weighted images demonstrate multiple enlarged lymph nodes in pre-carinal (B, arrow), sub-carinal and hilar (C, arrows) regions. Endomyocardial biopsy confirmed sarcoidosis.

Patients with more advanced post-inflammatory sarcoidosis may show areas of localised thinning of the myocardial wall with contraction abnormality (fig 4) and enhancement on the delayed post-gadolinium images. The latter is believed to represent fibrous replacement of the myocytes with increased interstitial volume. The myocardial enhancement in both active inflammatory and advanced stages show sparing of the subendocardium (figs 3 and 4), unlike the pattern seen in myocardial infarction.^{32–34} In addition, involvement does not conform to a particular coronary vascular territory. Demonstration of myocardial involvement similar to delayed post-gadolinium MRI has been recently shown with delayed post-contrast images with CT.³³ This may be of added benefit in follow up of patients who have implantation of pacemakers or internal cardiorespirators which prevent patients from having MRI examination. It is the pattern of myocardial involvement and delayed enhancement along with associated features like mediastinal and hilar lymphadenopathy and pulmonary involvement that clinches the diagnosis. Histological confirmation is best obtained by biopsy of superficial or mediastinal lymph nodes, or involved lung tissue.

ENDOMYOCARDIAL BIOPSY

Cardiac involvement may be patchy and hence right ventricular biopsy is not a technique of choice. Reports suggest the sensitivity of detecting sarcoid granuloma on endomyocardial biopsy is around 20–30%,¹⁷ hence a negative biopsy does not exclude the disease.

DIAGNOSING SARCOIDOSIS

Making a diagnosis of cardiac sarcoidosis remains one of the main challenges in the management of the disease. As many as 50% of individuals with sarcoidosis will be asymptomatic and are diagnosed from a routine chest radiograph. A further large proportion will present with a non-specific illness of fever, weight loss and malaise. These features, along with erythema nodosum, are of course almost pathognomonic of another granulomatous disease, namely tuberculosis. Overall, erythema nodosum is present in about 50% of patients with sarcoidosis and portends a good prognosis. In the UK, estimates suggest erythema nodosum occurs in 15–20% of patients. Lofgren’s syndrome has been used to describe the combination of erythema nodosum, fevers, bilateral hilar adenopathy and myalgia. Skin sarcoidosis localised to the nose and face with the appearance of violaceous plaques is termed lupus pernio. When sarcoidosis causes swelling of the parotid glands, a fever and uveitis, it is termed Heerfordt’s syndrome or uveoparotid fever.

Diagnosing cardiac involvement by sarcoid

The conclusive diagnosis of cardiac sarcoidosis is made by the demonstration of non-caseating granulomas on myocardial biopsy. This is not always possible and clinically histological proof of sarcoidosis on biopsy of any extra-cardiac tissue (with the exclusion of other causes of granulomatous inflammation such as mycobacterial or fungal infection) and presence of cardiovascular abnormalities for which other possible causes have been excluded is sufficient. Guidelines by Japanese colleagues (table 1) have formed an excellent framework,³⁵ although some revision may now be required in the light of recent imaging developments.

Diagnosis in current clinical practice

A patient, in whom sarcoidosis is a possible diagnosis, with heart block or a tachyarrhythmia confirmed on a 12 lead ECG or on Holter monitoring will initially have an echocardiogram. However, as the findings on the latter are not specific for sarcoid involvement and a normal scan does not exclude the disease, this can be followed by other more specific tests such as

Table 1 A summary of recommendations for the diagnosis of heart involvement with sarcoid

Histologic diagnosis group Endomyocardial biopsy demonstrates epithelioid granulomata without caseating granulomata
Clinical diagnosis group In patients with a histologic diagnosis of extra-cardiac sarcoidosis, cardiac sarcoidosis is suspected when “a” and at least one of criteria “b” to “e” is present, and other aetiologies such as hypertension and coronary artery disease have been excluded (a) Complete RBBB, left-axis deviation, AV block, VT, PVC, or pathological Q or ST-T change on resting or ambulatory electrocardiogram (b) Abnormal wall motion, regional wall thinning, or dilation of the left ventricle (c) Perfusion defect by ²⁰¹ thallium myocardial scintigraphy or abnormal accumulation by ⁶⁷ Ga-citrate or ^{99m} Tc-PYP myocardial scintigraphy (d) Abnormal intracardiac pressure, low cardiac output, or abnormal wall motion or depressed ejection fraction of the left ventricle (e) Interstitial fibrosis or cellular infiltration over moderate grade, even if the findings are non-specific
AV, atrioventricular; LBBB, left bundle branch block; PVC, premature ventricular contraction; RBBB, right bundle branch block; VT, ventricular tachycardia.

gallium-67 scanning and/or cardiac MRI with delayed contrast enhancement to localise the organ involvement in the body and the granulomas and/or fibrosis within the myocardium. MRI itself or a CT scan of the chest can be used to assess extra-cardiac disease, particularly lymphadenopathy for the identification of sites for biopsy.

In addition to establishing features representative of sarcoidosis one needs to rule out several autoimmune, infective and neoplastic conditions. Typically these are other granulomatous diseases (tuberculosis, fungal and parasitic disorders) and in the case of the heart, giant cell myocarditis,³⁶ acute rheumatic fever, lipogranulomatosis and gout. Confusingly, granulomas can also develop as a reaction to implanted foreign bodies and devices in the cardiovascular system.³⁷

Chest radiographic appearances may be classic and diagnostic. Up to 85% of patients will have bilateral hilar lymphadenopathy with right paratracheal adenopathy.³⁸ A diagnostic guideline would be to biopsy easily accessible nodes or to perform a transbronchial biopsy in the context of more than 90% of individuals having pulmonary involvement. Mediastinoscopy can be performed to sample paratracheal lymph nodes. As many as 75% of patients will have asymptomatic liver granulomas, providing an additional biopsy site. Up to 25% will have ocular involvement in the form of an anterior uveitis which can be diagnosed on slit lamp examination. Hypercalcaemia is present in 11–17% of patients due to an excess secretion of 1,25-dihydroxy-vitamin D3 by the alveolar macrophages.³⁹

TREATMENTS

Sarcoidosis is almost unique among potential life threatening diseases in that many patients do not require treatment, largely due to the fact that about two thirds of patients will have spontaneous resolution of their disease. For critical organ involvement (eyes, heart, nervous system), as in pulmonary and extra-pulmonary sarcoid, the treatment of cardiac sarcoid is predominantly with corticosteroids. However, no randomised controlled trials exist to substantiate this. Many patients with major abnormalities on chest radiographs and abnormal lung function tests will do well without treatment.⁴⁰ Heart involvement is life-threatening and hence prompt treatment with steroids, immunosuppressive therapy or both is necessary.⁴¹ In less critical organ involvement, a steroid regimen might typically consist of 40 mg of prednisolone daily for 2 weeks,

Learning points

- Serum angiotensin converting enzyme activity is no longer considered helpful diagnostically, but may be used to monitor disease progression.
- The Kveim test is no longer in use because of the risk of "infective" agent transmission.
- High resolution CT scanning of the thorax may help guide treatment. Potentially reversible conditions indicated by ground glass, nodular and irregular linear opacities. Cystic air spaces and architectural distortion are indicative of irreversible pulmonary disease.
- Magnetic resonance imaging has become the routine image modality of choice due to its high spatial and soft tissue resolution.

falling in stages over a 2 month period to a maintenance dose of 10–15 mg per day. This would be maintained for a minimum of 6 months and then attempts made at reducing this over the following 12 months.⁴² For significant cardiac involvement, high dose steroid treatment with 60–80 mg per day may be indicated. Chloroquine, hydroxychloroquine, methotrexate and azathioprine are also effective treatments. Other agents considered are cyclophosphamide and cyclosporine, although both have limited roles compared to the aforementioned therapies. Treatment may need to be tailored and in some cases lifelong with low dose steroids.⁴³ Amiodarone has proved useful in some cases of resistant arrhythmia.¹⁴ Further options include the use of pacemakers and automated implantable cardioverter-defibrillators for degrees of heart block and tachyarrhythmias, respectively.

Heart transplantation for sarcoid heart disease

With advanced structural involvement, intractable heart failure or refractory rhythm control, some patients will theoretically be eligible for cardiac transplantation. As with other systemic diseases, candidacy for transplantation will depend on the extent and consequences of multisystem involvement. The UK authority on organ transplantation (UK Transplant) report that, to date within the UK, no patient has undergone cardiac transplantation for a pre-transplant diagnosis of sarcoid heart disease (UK transplant data, 2007, personal communication). Up to July of 2006, a total of 24 patients in the UK have undergone either single or bilateral lung transplants and one

patient has had a heart and lung transplant for a pre-transplant diagnosis of end-stage pulmonary sarcoid (UK transplant data, 2007, personal communication). Moreover, despite this surprising fact, in several cases sarcoid granulomas have been found in the ex-planted heart when the assumed pre-transplant diagnosis was an ischaemic or dilated cardiomyopathy. Sarcoid granulomas have also been shown to recur in the transplanted organ whether this be heart, lung or bone marrow,⁴⁴ but can usually be controlled with the immunosuppressive agents used in such patients. Sarcoid has also been demonstrated to have been transmitted via heart transplantation, in this case from a patient with known pulmonary involvement to the recipient of the transplanted heart who subsequently developed pulmonary sarcoid disease.⁴⁵ Isolated cases in the world literature describe recurrence of sarcoidosis in cardiac allografts performed for end-stage sarcoid heart disease, in one case at 6 months after heart transplantation.^{46 47}

CONCLUSION

Sarcoidosis remains something of an enigma. The search for an aetiological agent is ongoing. Heart involvement is on occasions a medical emergency that without treatment can result in sudden and unexpected death due to rhythm disturbance or progressive heart failure from a dilated cardiomyopathy. Advances have been made in diagnostic techniques, largely as a result of new imaging modalities.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. Epidemiology and aetiology of sarcoidosis:

- Sarcoidosis is a disease that is confined to the black and Asian races
- Disease severity appears to be greater in black patients
- The aetiology has been determined to be due to an infective agent
- Clustering of cases suggests an environmental exposure as a trigger for sarcoidosis
- Sarcoidosis has a female preponderance

2. Heart involvement by sarcoidosis:

- A restrictive cardiomyopathy is the most common cardiac feature
- Asymptomatic cardiac involvement by sarcoid is a feature
- Sarcoid has a tendency to involve primarily the atria of the heart
- When the heart is involved the distal interventricular septum is often a target
- Cor pulmonale can occur due to extra-cardiac involvement by the disease

3. Investigations performed in the diagnosis and evaluation of sarcoidosis:

- An elevated serum ACE concentration is necessary to diagnose sarcoidosis
- The Kveim test remains an invaluable diagnostic test for sarcoidosis
- Serum ACE values are elevated in active sarcoid disease
- Hypocalcaemia due to inactivation of vitamin D is a feature of sarcoidosis
- An endomyocardial cardiac biopsy is a reliable diagnostic tool

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4. Features of heart involvement by sarcoid:

- (A) Left ventricular aneurysm formation is a feature seen in cardiac sarcoid disease
- (B) The interventricular septum is frequently thickened on echocardiographic appearances in cardiac sarcoidosis
- (C) The ventricular walls are frequently generally thinned on echocardiography
- (D) Regional ventricular wall motion abnormalities are not a feature of sarcoid heart disease
- (E) The ventricles do not dilate in sarcoidosis due to the fibrotic response to sarcoid granulomas

5. Imaging, management, treatment and prognosis of sarcoidosis:

- (A) Computed tomographic scanning of the heart is the best imaging tool to identify heart involvement
- (B) Corticosteroids are still the main treatment when life threatening organ involvement occurs
- (C) Pacemakers and automatic implantable cardioverter-defibrillators have not had an effect on survival in cardiac sarcoidosis
- (D) The primary cause of cardiac death is now heart failure in sarcoid heart disease
- (E) Heart transplantation for end stage sarcoid heart disease represents a small proportion of transplants performed in the UK

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ANSWERS

1. (A) F (B) T (C) F (D) T (E) T
2. (A) F (B) T (C) F (D) F (E) T
3. (A) F (B) F (C) T (D) F (E) F
4. (A) T (B) T (C) T (D) F (E) F
5. (A) F (B) T (C) F (D) T (E) F