Classic diseases revisited

Summary

Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology. The condition commonly affects young adults and frequently presents with bilateral hilar lymphadenopathy with or without pulmonary infiltration, ocular or cutaneous lesions. The clinical presentation can be extremely varied depending upon the organs affected. The diagnosis is firmly established when recognised clinical and radiographic findings are supported by histological evidence of discrete non-necrotising epithelioid cell granulomata in one or more organs. Sarcoidosis is usually self-limiting with spontaneous resolution, although in a few patients there is a progressive downhill course, culminating in irreversible fibrosis and severe impairment of organ function.

Keywords: sarcoidosis, pulmonary granuloma

Sarcoidosis

- more common in developed countries
- prevalence in UK: 10–20/10^5 population
- no clear sex predominance
- median age of presentation: 20 to 40 years
- increased prevalence among blacks where the disease is more aggressive

Box 1

Sarcoidosis: possible aetiology

- infectious agents: eg, mycobacterium, viruses
- hypersensitivity
- organic antigens: eg, pollen, peanut dust, talc
- inorganic antigens: eg, Beryllium, Zirconium
- genetic: eg, HLA-B8, B27, B7
- socioeconomic

Box 2

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Sarcoidosis

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Epidemiology

Sarcoidosis* is a relatively common disease, occurring worldwide with varying incidence and prevalence, although it is more frequently described in developed countries. In Europe, the prevalence ranges between three and 50 cases per 10^5 population, the disease most commonly presenting between the ages of 20 to 40 years.[2] There is no clear sex predominance although some studies have reported a slightly higher prevalence among women.[3] In the UK the overall prevalence of sarcoidosis is approximately 20 in 10^5 population, although there is considerable variation between ethnic groups with a higher prevalence among individuals of West Indian and Indian origin.[5] Similar ethnic differences have been demonstrated in North America where the prevalence of sarcoidosis in the white population is about 5 in 10^5 in contrast to about 40 per 10^5 in the black population.[5] The disease also seems to be more severe, chronic and debilitating in the black population and there is a higher risk of extrathoracic manifestations.

Aetiology

Despite the extensive research into the aetiology of sarcoidosis no identifiable agent has been demonstrated to account for the granulomata which characterise the disease. Infectious agents, chemicals, drugs, allergy, autoimmunity and genetic factors have all been explored as potential causes.

Most studies have focused on an infectious aetiology. A large number of studies have tried to demonstrate that sarcoidosis is an aberrant form of tuberculosis.[6,7] Although there is as yet no convincing evidence for this, the recent finding of mycobacterial nucleic acids (albeit in variable proportions of patients with sarcoidosis) suggest that mycobacterial antigens might play a role in the pathogenesis of sarcoid disease in this small group of patients.[8-10] Sporadic reports have been made of virus isolation, such as mumps, influenza, parainfluenza, Newcastle agent and measles virus particles in patients with sarcoidosis.[11,12] These have been subsequently dismissed as possible laboratory contaminants.[13] High antibody titres to a variety of viruses, eg, Epstein–Barr virus, have also been found in sarcoid patients.[14] On the other hand, it has been suggested that organisms found intermittently in sarcoid tissue are able to survive there because of the altered immunity in such patients.

A positive Kveim–Siltzbach skin test and cutaneous allergy to tuberculoprotein are often present. Immunological features suggest aberrant cell-mediated reactions at the site of inflammation, in the presence of hypergammaglobulinaemia. So far tissue cultures and electron microscopy have failed to uncover any specific infectious agents in sarcoid patients, as has the examination of the suspended sarcoid tissue used in the Kveim test.

In view of the immunological features found in sarcoidosis, it has also been postulated that sarcoidosis may be a form of hypersensitivity to the inhalation of environmental organic antigens. Inhalation of pine pollen, peanut dust, clay soil, talc and secondary oxalosis have all been incriminated as contributory factors in different areas, although their role in the pathogenesis of sarcoidosis remains unclear.[6,15-17] Exhaustive skin testing with metals and other inorganic substances in sarcoid patients and controls have not revealed any peculiar hypersensitivity to chemicals.

The occurrence of sarcoidosis in members of the same family has suggested that genetic factors might be involved but no firm relationship has been demonstrated.[18,19] Sarcoidosis has been reported to be more common in monozygotic than heterozygotic twins while various features of the disease may be associated with specific antigens of major histocompatibility.[20,21] HLA-B8 has been associated with erythema nodosum and arthritis, while HLA-B27 is found more commonly in patients with uveitis.[21,22]

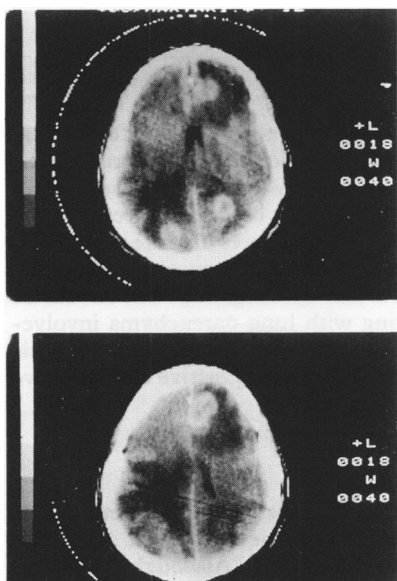---

*Derived from the Greek 'sarkos' meaning 'flesh'

Figure 1   Lupus pernio

Figure 2   Neurosarcoid

There is no definitive evidence to implicate social or occupational elements with sarcoidosis, although some studies have suggested increased prevalence in rural areas.

While the aetiology of sarcoidosis continues to remain elusive, the presence of genetic, environmental, nutritional and socioeconomic factors could play a critical role in the development of sarcoidosis in an immunologically susceptible individual.

Clinical presentation

As sarcoidosis is a multi-system disease and affects most organs, the clinical presentation can be very varied (box 3). Between 20–40% of patients remain symptom free, the disease only being discovered following routine chest radiograph.[23] A significant proportion of patients with acute sarcoid develop erythema nodosum and this is frequently associated with a polyarthralgia, mainly affecting the knees, ankles, wrists and elbows. The course and prognosis of sarcoidosis frequently correlates with the mode of onset. An acute onset with erythema nodosum usually indicates a self-limiting course with spontaneous resolution while an insidious onset may be associated with progressive fibrosis and permanent organ dysfunction.[24] In general, the overall prognosis of sarcoidosis is good, with the majority of patients making full recovery within months or years. In 10–15% of individuals the disease remains progressive, with ensuing chronic disability.[23] In this latter group, extrathoracic features are more frequently prominent. These may range from cutaneous lesions to peripheral lymphadenopathy, parotid enlargement, central nervous system involvement, cardiac syndromes, hepatosplenomegaly, arthralgia, hypercalcaemia, and nephrocalcinosis.

PULMONARY MANIFESTATIONS
The lung is the organ most commonly involved in sarcoidosis. At least 90% of patients have an abnormal chest radiograph showing the classical features of bilateral hilar lymphadenopathy with or without lung involvement.[25] Usually the hilar lymphadenopathy is symmetrical although rarely it may appear unilateral. Patients are commonly asymptomatic or their respiratory symptoms may start insidiously with a dry cough, progressive dyspnoea, exercise intolerance and chest pain.[26] In 10–20% of patients these symptoms progress with concurrent deteriorating lung function.[27] The clinical course of pulmonary sarcoid may be related, at least in part, to the radiological appearance of the disease.[28,29] Patients with sarcoidosis have been divided into clinical groups according to the appearance of the chest film, ranging from the commoner, usually asymptomatic, bilateral hilar lymphadenopathy without parenchymal involvement to diffuse dense progressive and irreversible parenchymal fibrosis.[30-32] Sarcoidosis may also affect the bronchi and rarely the pleura leading to large airway narrowing, pleural thickening and pleural effusions, respectively.

NON-PULMONARY MANIFESTATIONS
Sarcoidosis can affect most organs. Extrathoracic manifestations are common and may present with varied clinical features. At *post mortem*, the organs most frequently affected are the lymph nodes (78%), liver (67%), spleen (50%), heart (20%), skin (16%), central nervous system (8%), kidneys (7%), eyes and parotid glands (6%), thyroid (4%), intestine (3%), stomach (3%) and pituitary (3%).[33] The more common extrathoracic manifestations are given in box 4.

Staging of disease activity

Recent guidelines on the management of sarcoidosis suggest that staging of disease activity can be limited to clinical indices, including worsening respiratory symptoms, deterioration of lung function and chest X-ray (box 5).[34] Several other investigations have also proved useful in the assessment of disease activity. These include biochemical markers such as serum angiotensin converting enzyme, gallium-67 scanning, high resolution computed tomography (CT) and bronchoalveolar lavage cell populations and CD4/CD8 ratio.[34]

RADIOLOGY
Chest X-rays have been used in the clinical staging of pulmonary sarcoidosis and to assess the severity and course of the disease. More recently this has been superseded by standard CT scan and by high resolution and spiral CT, which is a more sensitive tool for detecting early lung fibrosis and assessing functional airway disease. These scans may play a role in detecting the presence of active alveolitis.[35,36] The radiological presence of interstitial fibrosis is usually irreversi-
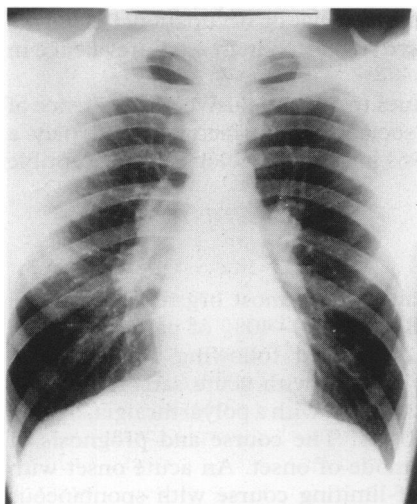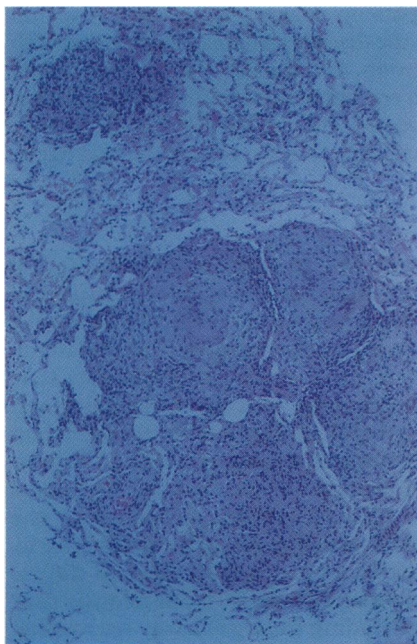
Figure 3 Bilateral hilar lymphadenopathy
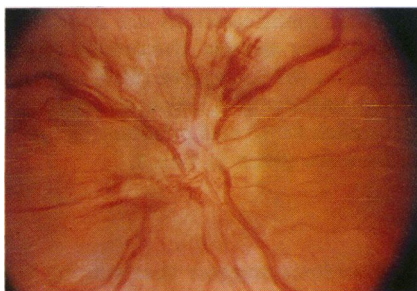
Figure 4 Sarcoid granulomata

Figure 5 Occular sarcoidosis

Figure 6 Cutaneous sarcoidosis

ble and if extensive is often associated with a poor outlook in terms of both morbidity and mortality. While radiography remains an important investigative tool in the diagnosis and management of sarcoidosis, there is not a clear correlation between the radiological appearance, other markers of disease activity and evolution of the disease process over time.[37] Pleural changes are rarely noted on plain chest X-rays. CT scanning of the thorax, however, shows pleural involvement in up to a third of patients and, on occasions, plaque-like or actual calcification may develop in persistently enlarged hilar or mediastinal lymph nodes.[38]

LUNG FUNCTION
The routine measurement of lung function in patients with sarcoidosis remains an important tool in assessing the extent of pulmonary involvement and frequently does not relate to the radiographic changes seen on X-ray. Furthermore, baseline lung function does not appear to relate to the likelihood of disease progression. During the early stages of lung parenchymal involvement a reduction in transfer factor can be measured while with more progressive disease a reduction in lung volumes and decreased lung compliance is seen. The use of serial measurement is extremely useful in assessing disease progression or resolution.

ANGIOTENSIN-CONVERING ENZYME (ACE)
The level of serum ACE is frequently elevated in sarcoidosis and may be helpful in monitoring the course of the disease.[24] The serum levels tend to be higher in clinically active disease although they may be normal at the onset of acute sarcoid. Unfortunately serum ACE cannot be used to detect the level of disease activity and high titres at the onset do not predict the likely course of the disease in any one individual.

BRONCHOALVEOLAR LAVAGE (BAL)
BAL is a simple extension of routine fibre-optic bronchoscopy and permits a repeatable, safe and quantitative evaluation of the cellular and biochemical processes within the lower respiratory tract. Early disease in sarcoid patients is characterised by an alveolitis associated with mononuclear cell infiltration into the lung interstitium, comprised of macrophages and T-lymphocytes.[39-42] This lymphocytic response distinguishes sarcoidosis from other interstitial lung diseases such as fibrosing alveolitis, where polymorphonuclear cells usually predominate in early disease.[39] The lymphocytes associated with granulomata are larger than normal and are mainly of the T-cell type, which express CD-4 surface antigen. As the disease becomes less active these cells decrease and suppressor CD-8 T cells predominate.[43] Such changes within the interstium are accompanied by an increased proportion and total number of lymphocytes in BAL fluid. This increase consists mainly of T-helper cells, the helper/suppressor ratio in active disease being 4–10 times greater than in normal BAL.[44] While BAL is a useful adjunct tool for both the diagnosis of pulmonary sarcoidosis and for assessment of the intensity of inflammatory response (eg, BAL lymphocyte count and CD4/CD8 T cell ratio), it has not been shown to predict the outcome in any individual patient.[24]

Clinical investigations of suspected sarcoidosis

The diagnosis of sarcoidosis should be based on both clinical features at presentation in combination with radiological, biochemical and immunological findings, with tissue samples being obtained if at all possible. Elevated superficial cutaneous lesions or peripheral lymph nodes should be biopsied if present. Any patient presenting with good clinical and laboratory features of acute sarcoidosis but without parenchyma involvement, as measured by high resolution CT and lung function, probably does not warrant further investigations but should be routinely followed-up. In patients presenting with lung parenchyma involvement or with a less characteristic clinical presentation where the diagnosis remains unclear, the diagnosis may only be accepted after positive biopsies have been obtained.

Treatment

The treatment of sarcoidosis remains controversial. As the present aetiology is uncertain there is no curative treatment but most aspects of both acute and chronic sarcoidosis can be ameliorated by glucocorticoids. Although there is no evidence that steroid therapy influences the resolution of radiographic changes in pulmonary sarcoidosis, it is possible that without therapy the number of patients

Stage	Features on chest radiograph	Prevalence
0	normal	5-10%
1	bilateral hilar adenopathy	50%
2	bilateral hilar adenopathy (with or without paratracheal adenopathy) and peripheral pulmonary infiltration	25%
3	parenchyma infiltration alone	15%
4	diffuse progressive fibrosis with upward retraction of hilar areas, honey-combing bullae formation pleural involvement	<10% 5%

Box 5

Sarcoidosis: diagnostic investigations

Chest X-ray: 90% abnormal with variety of appearance (see Clinical staging)

Lung function: may be normal despite extensive radiographic shadows, or may show significant physiological dysfunction with clear radiographical lung fields

Tuberculin skin tests: negative in 2/3 of patients, despite previous bacille Calmette-Guerin immunization

Blood tests: lymphopenia; raised ESR; panhyperglobulinaemia; raised serum ACE in 2/3 of acute patients; abnormal liver function indices in a few may show intrahepatic cholestasis

24-hour urine: hypercalciuria (despite normal serum calcium concentration)

ECG: arrythmias, bundle branch block pattern in some patients

Tissue biopsy: eg, lymph node, lung, skin, liver shows non-caseating epithelioida granuloma

Kveim- Siltzback test: helpful when other histological material unavailable. Positive in up to 75% of patients.

BAL: Many patients with active sarcoidosis show increased percentage of lymphocytes, predominantly of the helper T-cell type. As fibrosis develops, an increase in neutrophils occurs

Others: Gallium scans (often positive in sarcoidosis); radioactive Thallium[201] (taken up by sarcoid tissue and ischaemic myocardium); high resolution CT scan (together with MRI) may be particularly useful in unusual or difficult diagnostic circumstances such as neurosarcoid; slit lamp examination and fluorescein angiography (required in patients with associated ocular symptoms)

Box 6

with chronic persistent disease and its attendant morbidity might be greater. It is generally accepted that corticosteroids improve local and constitutional symptoms and suppress granulomatous infiltration in affected tissues. This is reflected in symptomatic relief from disabling breathlessness, measurable increase in pulmonary function, rapid clearing of radiological infiltration and in improvements in many manifestations of extrathoracic sarcoidosis.

Generally there is now a consensus that patients with bilateral hilar lymphadenopathy alone do not require therapy since the vast majority of cases are associated with spontaneous full recovery. However, the presence of extrathoracic manifestations of sarcoidosis such as uveitis, hypercalcaemia, neurological involvement or, rarely, cardiac involvement are indications for therapy.[45] Patients with arthralgia and erythema nodosum may also warrant symptomatic relief with a short course of steroids if more conventional therapy such as nonsteroidal anti-inflammatory agents is ineffective. The management of patients with stage 2 and 3 disease remains a lot more controversial.[46] Regardless of symptomatology there are some groups who believe that steroid therapy acts as a prophylactic agent in preventing progression of the disease process. Others, however, believe that therapy should only be given when patients become symptomatic or in the absence of clinical improvement. In those patients where steroid therapy is deemed appropriate, it is our practice to give 40 mg a day for 4-6 weeks and then titrate the dose in accordance with clinical status. The aim is to maintain therapy for at least a year and then attempt to stop. In a small group of patients relapse follows the cessation of steroids. In this group a further course of therapy should be given and in a few the use of long-term steroids may be required. In severely ill patients, the use of methyl prednisolone has been used acutely in the form of short courses. In patients where deterioration in pulmonary function occurs despite prednisolone or in the presence of cardiac, neurological or dermatological involvement, adjunct immunosuppressive treatment (eg, methotrexate, chloroquine, cyclophosphamide and cyclosporin) may be needed under specialist supervision. Ocular disease such as uveitis may need local treatment in addition to systemic.

Prognosis

The overall prognosis is good with 60% of patients with thoracic sarcoidosis experiencing spontaneous resolution within two years.[47,48] A further 20% of patients respond to steroid treatment. In the remainder improvement is unlikely despite steroid therapy.

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Sarcoidosis: differential diagnosis

Hilar lymphadenopathy: TB, lymphoma, infectious mononucleosis, leukaemia, metastases, enlarged pulmonary vessels

Hilar lymphadenopathy + lung infiltrate: TB, pneumoconiosis, lymphangitis, idiopathic haemosiderosis, pulmonary eiosinophilia, carcinoma, histiocytosis X

Diffuse pulmonary infiltrate: above and chronic beryllium disease, honeycomb lung, connective tissue disease, cryptogenic and extrinsic fibrosing alveolitis

Non-caseating granuloma: TB, fungal infections, leprosy, syphilis, cat scratch fever, berylliosis, hypersensitivity pneumonitis, extrinsic alveolitis, lymphoma, carcinoma, billiary cirrhosis, Crohns disease

Box 7

Sarcoidosis: indications for steroid therapy

- uveitis
- hypercalcaemia
- neurological involvement
- cardiac involvement
- progressive stage 2/3 pulmonary disease

Box 8

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