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John D. Firth
Christopher P. Conlon
Timothy M. Cox

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Sarcoidosis

Robert P. Baughman and Elyse E. Lower

ESSENTIALS

Sarcoidosis is a disease of unknown cause that is characterized by the presence of noncaseating granulomas in at least two organs. It can present in a wide variety of ways. Differential diagnosis is most commonly from tuberculosis or lymphoma.

Clinical features

Respiratory involvement—described in more than 90% of patients and staged according to the chest radiograph appearance: stage 1, hilar adenopathy alone; stage 2, adenopathy and parenchymal disease; stage 3, parenchymal disease alone; and stage 4, fibrosis. Such staging predicts outcome (resolution in 2–3 years—stage 1, 90%; stage 3, 30%) but not the degree of extrapulmonary disease. Pulmonary function studies typically demonstrate a restrictive pattern.

Skin involvement—the second most commonly affected organ: manifestations include hyperpigmentation; hypopigmentation; keloid reaction; waxy, maculopapular lesions, which when present on face are called lupus pernio and diagnostic of sarcoidosis; erythema nodosum.

Other organ involvement—eye: uveitis and lacrimal glands; neurological: cranial nerves (especially VII), central nervous system (lymphocytic meningitis, hypothalamic involvement) and peripheral nerves; liver: abnormal liver function tests in more than 25%; hypercalcaemia/hypercalciuria; heart: involvement is rare but can be serious with arrhythmic death.

Acute vs. chronic disease—acute disease (which lasts for <2 years) is associated with erythema nodosum, hilar adenopathy, anterior uveitis, and cranial nerve VII paralysis. Chronic disease includes such manifestations as lupus pernio, stage 4 chest radiograph, posterior uveitis, urolithiasis, and bone cysts.

Investigations and management

Investigations—those of particular note include: (1) serum angiotensin converting enzyme levels—elevated in 60% of patients with acute and one-third of those with chronic disease; (2) bronchoalveolar lavage—revealing increased lymphocytes, especially an increased CD4:CD8 ratio; (3) transbronchial biopsy—noncaseating granulomas found in greater than 60% of stage 1 and 80% of stage 2 or 3 disease; (4) gallium scan—uptake in the parotid and conjunctiva (the 'panda' sign) and/or in the hilar nodes (the 'lambda' sign) are fairly characteristic and useful confirmation of diagnosis in difficult cases; (5) characteristic changes on CT scan of chest or positive emission tomography scan.

Management—there is no single treatment for all patients with sarcoidosis. Key issues are to determine (1) whether the patient requires treatment, this usually being based on symptoms, and then (2) the extent of symptomatic disease, and (3) whether this is acute or chronic. First line treatment is usually with corticosteroids, often prednisolone 20–40 mg/day (initial dosage, followed by gradual reduction) if topical administration is not possible, although it is not universally accepted that steroids change the course of the disease. If the dose of steroid cannot be reduced to an acceptable level, or if the patient is not responding, then other agents (e.g. chloroquine/hydroxychloroquine, methotrexate, leflunomide, infliximab) are added.

Prognosis—most patients with sarcoidosis will experience disease resolution within 2–5 years; about 25% will develop residual fibrosis in the lungs or elsewhere; in a few the disease will become chronic and persist for more than 5 years. Most series from referral centres report 5% disease-related mortality, usually from respiratory failure.

Introduction

Sarcoidosis was first recognized in 1869 by Jonathan Hutchinson, who treated a man with skin lesions that appeared unrelated to tuberculosis. Over the next few decades most case reports of sarcoidosis described patients with skin lesions, and pathological information was scarce since the disease is often self-limiting. Schaumann in Sweden was one of the first to recognize the multiorgan features of the disease combined with common pathological feature: his original thesis was written in 1914, but not published until 1936.

After the Second World War, the use of routine screening chest radiographs identified patients with asymptomatic abnormalities. Löfgren described a group with erythema nodosum, uveitis, and hilar adenopathy. Others began to appreciate the unique aspects of sarcoidosis compared to tuberculosis. Interestingly, as tuberculosis becomes less frequent in a country, sarcoidosis becomes more obvious, which may reflect the observation that sarcoidosis is a

disease of industrial nations and temperate climates, although several groups have reported series of patients with sarcoidosis in India, Thailand, and China.

Pulmonary sarcoidosis can be evaluated by chest radiography, with Scadding in Scotland and Wurm in Germany independently developing a staging system based on the chest radiograph pattern that has become a useful method of describing the extent of and characterizing lung involvement, and which also provides prognostic information.

Newer radiological techniques have been evaluated in sarcoidosis. The chest CT scan provides more detailed information regarding adenopathy, but has not replaced the prognostic information available from the chest radiograph. Gallium scanning will reveal increased uptake in areas of inflammation such as lung and mediastinum. MRI and positron emission tomography (PET) scanning have brought new methods for evaluating extrapulmonary disease.

Bronchoalveolar lavage provides a sample of lower airway secretions, with lavage findings from patients with sarcoidosis being distinctly different from those without disease, this window into the lung providing insights into the true inflammatory response of the lung.

Aetiology

The cause of sarcoidosis remains obscure, one hypothesis being that it is an inflammatory response to an environmental agent (including infection) which occurs in a susceptible host, susceptibility being determined by genetic predisposition.

Several potential infectious agents have been proposed as causes of sarcoidosis. The granulomatous reaction reminds many of tuberculosis, and much effort has been made to identify a mycobacterial cause of sarcoidosis. Several studies using polymerase chain reaction and similar molecular biological techniques have been employed, but there is still no convincing evidence that *Mycobacterium tuberculosis* causes most cases of the condition, which may lead to an occasional case of sarcoid-like reaction. Other mycobacteria have been identified in some cases, and cell-wall-deficient mycobacteria have been grown from the blood of patients with sarcoidosis. However, a controlled trial failed to demonstrate a difference in the incidence of cell-wall-deficient mycobacteria between sarcoidosis patients and controls. Another potential pathogen is *Propionibacterium acnes*. There is increasing evidence supporting nontuberculous mycobacteria as the cause if sarcoidosis in at least some patients.

Epidemiology

Sarcoidosis is a worldwide disease. It has been reported to have a higher prevalence in Scandinavian countries and in Ireland. Table 18.12.1 summarizes the relative frequency of sarcoidosis per 100 000 population around the world. In the United States of America, a higher incidence of sarcoidosis has been reported in African-Americans.

The disease presentation differs in different parts of the world, with Table 18.12.1 listing some of the more frequent patterns seen in various ethnic groups. For example, lupus pernio is common among African-Americans and West Indians who have migrated to the United Kingdom, whereas erythema nodosum is common among Scandinavians. Cardiac disease has been reported at a higher frequency in Japanese sarcoidosis patients than for other groups.

There is evidence that there is a link between genetic predisposition and environmental exposure, but genetic studies regarding the cause of sarcoidosis are hindered while the cause remains unknown. However, once a patient has sarcoidosis it is clear that genetic background may affect clinical outcome, for example, most patients who present with Löfgren's syndrome (erythema nodosum and hilar adenopathy) resolve their disease within a few years, and about 10% have chronic disease; resolution occurs in almost everyone with the human leucocyte antigen (HLA) alleles DRB1*0301/DQB1*0201, but only 55% of those without.

Several occupations have been associated with sarcoidosis, including healthcare workers, firefighters, and seamen aboard aircraft carriers. In a detailed study of exposures of over 700 patients with recently diagnosed sarcoidosis compared to unaffected age-, race-, and sex-matched controls from the same geographic area, those with sarcoidosis were more likely to have been exposed to mouldy environments or insecticides, although one-half of them had no known exposure to these factors.

Occupational exposures can lead to reactions mimicking sarcoidosis. Beryllium—a metal used in certain industries (ceramics,

Table 18.12.1 Sarcoidosis around the world

	Scandinavia	Ireland	Japan	USA		West Indies
				African-American	White	
Prevalence per 100 000	1200	213	20	140	50	180
Female predominant	No	Yes	No	Yes	No	No
Erythema nodosum	+3	+3	Rare	Rare	+2	Rare
Lupus pernio	Rare	Rare	Rare	+1	Rare	+1
Hypercalcaemia	+3	+2	Rare	Rare	+2	Rare
Cardiac	Rare	Rare	+3	+1	+1	+1
Neurological	+1	+1	+1	+1	+1	+1
Hypergammaglobulinaemia	+1	+1	+1	+4	Rare	+1

Rare, <1%; +1, 1–5%; +2, 5–10%; +3, 10–30%; +4 >30%.

nuclear processing, dental)—can cause a reaction in the lung and skin indistinguishable from sarcoidosis. Besides clinical history, the distinguishing feature about berylliosis is the lymphocyte's sensitivity to beryllium salts, and the lymphocyte stimulation test of blood, or the more sensitive bronchoalveolar lavage, is a reliable way of detecting which patients are reacting to the metal.

None of the infectious, occupational, and environmental exposures encompass all cases of sarcoidosis, one possible explanation being that the condition is a common reaction to several agents.

Pathogenesis

Sarcoidosis is defined by its immunological reaction, the granuloma. Original immunological studies stressed a lack of systemic immune response by the sarcoidosis patient, including anergy, which is a common feature of active sarcoidosis. A reduction in circulating leucocytes, especially lymphocytes, is an important feature of the disease.

In the 1970s, new techniques helped us understand sarcoidosis better. The most important tool introduced at the time was bronchoalveolar lavage, which provided a sampling of the inflammatory cells in the lower respiratory tract. Alveolar macrophages are the usual resident inflammatory cell retrieved by lavage, with lymphocytes and neutrophils much less frequent in normal lavage fluid. The T lymphocyte is usually increased in the lavage fluid from patients with active sarcoidosis: these are often T helper/inducer lymphocytes (CD-4+), and the ratio of CD4/CD8 lymphocytes is increased from that normally found in the blood, often to greater than 3.5. T lymphocytes can mount either a Th1 or Th2 response, the Th1 response being associated with granuloma formation, whereas Th2 is associated with an eosinophilic response and fibrosis. The initial response of sarcoidosis follows a Th1 pattern, with lymphocytes releasing interleukin (IL)-2 spontaneously, and γ-interferon being released by lymphocytes and macrophages. Increase in IL-12 and reduced levels of IL-10 have also been described, both consistent with a Th1 response. The resolution of sarcoidosis has also been studied with serial lavages: the T lymphocytes remain elevated for some time, but the proportion of CD4 to CD8 decreases to the ratio found in blood (0.8–2.2), and the amount of cytokines released also decreases. This normalization of the inflammatory response has been shown to occur during treatment of sarcoidosis with corticosteroids or methotrexate.

The alveolar macrophage is also activated in sarcoidosis. Increased levels of IL-1, tumour necrosis factor (TNF) and oxygen free radicals are released by macrophages retrieved by bronchoalveolar lavage. For those patients with chronic disease, the macrophages and other resident cells may continue to release proinflammatory cytokines, especially TNF, which has become a target for some therapies. Alveolar macrophages from patients may also begin releasing profibrotic factors such as IL-8 and endothelin.

Clinical features

Patients with sarcoidosis may have a variety of presentations. Commonly affected organs include the lung, skin, and eyes. Less commonly the liver, heart, and brain are affected by the disease. Individual organ involvement can be proven by a biopsy showing noncaseating granuloma; organ involvement is presumed if certain criteria are met. Table 18.12.2 lists some of the criteria suggested for definite or probable organ involvement for some of the more commonly affected organs in sarcoidosis.

Table 18.12.2 Organ involvement in patients with biopsy-confirmed sarcoidosis[a]

Organ	Definite	Probable
Lung	Positive biopsy of lung Chest radiograph characteristic for sarcoidosis (hilar adenopathy. diffuse infiltrates, or upper lobe fibrosis) Pulmonary function tests showing restriction	Lymphocytic alveolitis by bronchoalveolar lavage Any other pulmonary infiltrate Isolated reduction of $D_L$co (carbon monoxide transfer factor)
Skin	Positive biopsy of skin Lupus pernio Erythema nodosum Annular lesion	Macular/papular lesion New nodules (including subcutaneous)
Eyes	Positive biopsy of eye Lacrimal gland swelling Uveitis Optic neuritis	Blindness
Liver	Positive biopsy of liver Liver function tests >3 times normal	Compatible CT scan Elevated alkaline phosphatase
Neurological	Positive biopsy of nerve tissue MRI with gadolinium uptake in meninges, brainstem, or mass lesion Cerebrospinal fluid with increased lymphocytes or protein Diabetes insipidus Cranial nerve VII paralysis Other cranial nerve dysfunction	Other abnormalities on MRI Unexplained neuropathy Positive electromyogram
Cardiac	Positive cardiac biopsy Treatment responsive cardiomyopathy ECG showing intraventricular or nodal block Positive PET, MRI, or gallium scan	Cardiomyopathy or ventricular arrythmias and no other cardiac problems Positive thallium scan

$D_L$co, carbon monoxide transfer factor.

[a] Patients with documented sarcoidosis and no other explanation for organ specific abnormality.

Fig. 18.12.1 Chest radiograph showing stage 2 involvement with sarcoidosis. Enlarged hilar lymph nodes and lung infiltrates are seen.

Commonly affected organs and systems

Respiratory system

Respiratory involvement has been described in more than 90% of patients, including both the lymph nodes and the lung parenchyma. Scadding and Wurm independently described stages of the chest radiograph, the commonly used stages being: stage 1, hilar adenopathy alone; stage 2, adenopathy and parenchymal disease (Fig. 18.12.1); stage 3, parenchymal disease alone; and stage 4, fibrosis. The interstitial disease usually has a diffuse reticulonodular appearance, but confluent patches of disease (alveolar sarcoidosis) have been described. Fibrotic changes due to sarcoidosis are usually in the upper lobe, with retraction. The staging system has proved useful both in standardizing the reports of pulmonary level of involvement, also as a prognostic measure. Patients with stage 1 disease have a 90% rate of resolution within 2 to 3 years, whereas stage 3 patients possess only a 30% chance of resolution. However, 'staging' by chest radiograph appearance does not predict the degree of extrapulmonary disease, hence the choice of the term 'stage' is unfortunate, although it is so standard that it will not be easily replaced.

Table 18.12.3 lists the other diseases to be considered in the differential diagnosis based on the chest radiographic pattern. The presence of mediastinal adenopathy alone (stage 1 disease) is certainly consistent with lymphoma or metastatic cancer, although it has been pointed out that symmetrical bilateral adenopathy with right paratracheal adenopathy in an asymptomatic individual is almost always sarcoidosis. Asymmetrical adenopathy raises the question of lymphoma, and a tissue diagnosis is usually required. For patients with diffuse infiltrates, adenopathy points one toward sarcoidosis. However, several other conditions may have some adenopathy, including hypersensitivity pneumonitis and idiopathic pulmonary fibrosis.

The use of the CT scan has changed the evaluation of many interstitial lung diseases, when the larger the adenopathy, the more likely the patient has sarcoidosis (Fig. 18.12.2). Nodularity may be more obvious on high-resolution CT than on plain chest radiography, and peribronchial thickening is often seen in the upper lobe in sarcoidosis (Fig. 18.12.3). The CT scan is also useful in patients with more advanced disease, since it can identify honeycombing, traction bronchiectasis, and superimposed mycetomas (Fig. 18.12.4). It must, however, be appreciated that increased adenopathy is much more frequently recognized on CT scan than on chest radiographs, making the staging system only applicable for plain radiography. But if the CT scan identifies adenopathy in a patient with possible extrapulmonary sarcoidosis, then this may help in deciding where to proceed to obtain a tissue diagnosis (e.g. brain biopsy vs. mediastinoscopy).

Pulmonary function studies in patients with sarcoidosis classically demonstrate a restrictive pattern, with reduction of lung volumes. The transfer factor is usually reduced out of proportion to the loss of lung volume, as one would expect in an interstitial lung disease. In advanced cases, the oxygen level will be reduced, especially during exercise. Obstructive disease can also occur due to airway involvement by sarcoidosis or associated with cough, a common complaint in sarcoidosis.

Table 18.12.3 Differential diagnosis of sarcoidosis according to the stage on chest radiography

	Stage 1	Stage 2	Stage 3	Stage 4
Pattern	Hilar adenopathy	Adenopathy plus lung infiltrates	Lung infiltrates alone	Fibrosis
Diseases that can commonly cause similar appearances on chest radiography	Tuberculosis Lymphoma Enlarged pulmonary arteries Metastatic carcinoma Histoplasmosis	Lymphangitic carcinoma *Pneumocystis jirovecii* *Pneumoconiosis* Histoplasmosis Berylliosis	Lymphangitic carcinoma *Pneumocystis jirovecii* Pneumoconiosis Histoplasmosis Idiopathic pulmonary fibrosis Berylliosis Hypersensitivity pneumonitis Bronchoalveolar cell carcinoma Pneumonia Congestive heart failure Collagen vascular disease associated lung disease Eosinophilic granuloma	Lymphangitic carcinoma Pneumoconiosis Histoplasmosis Idiopathic pulmonary fibrosis Berylliosis Hypersensitivity pneumonitis Bronchoalveolar cell carcinoma Pneumonia Congestive heart failure Collagen vascular disease associated lung disease Eosinophilic granuloma
Diseases that can rarely cause similar appearances on chest radiography	Leukaemia Infectious mononucleosis	Alveolar proteinosis Idiopathic hemosiderosis α_1-Antitrypsin disease Bronchoalveolar cell carcinoma	Sjögren's syndrome Haemosiderosis Alveolar proteinosis	Sjögren's syndrome Haemosiderosis Alveolar proteinosis

Fig. 18.12.2 High-resolution CT scan of the chest demonstrating both interstitial infiltrate as well as significant hilar adenopathy in sarcoidosis.

Fig. 18.12.3 High-resolution CT scan of the chest demonstrating peribronchial thickening, which is more prominent in the right lung.

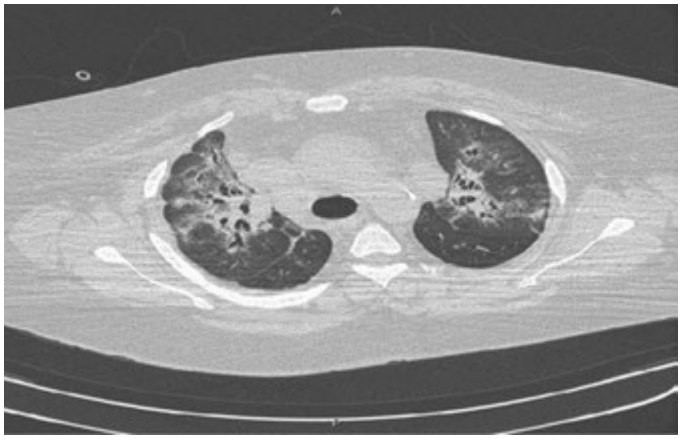

Fig. 18.12.4 High-resolution CT scan of the chest from the upper lobe area, which is more commonly affected in sarcoidosis, demonstrating fibrotic changes including traction bronchiectasis and honeycombing.

The skin

The skin is the second most commonly affected organ in sarcoidosis. Hyperpigmentation, hypopigmentation, and keloid reaction may demonstrate granulomas on biopsy, but their appearance is not always specific. Waxy, maculopapular lesions, which occur on the extremities, back, and face, are usually raised with most less than 2 cm in diameter. When the lesions occur on the face, especially on the cheeks and nose, they are called lupus pernio (Fig. 18.12.5). Erythema nodosum—red nodular lesions on the extremities—usually involves the legs. The constellation of erythema nodosum, arthritis (in the ankles), and hilar adenopathy is referred to as Löfgren's syndrome, which as noted earlier usually has a good prognosis. Interestingly, the skin lesions from erythema nodosum do not contain granulomas, but are thought to be due to circulating immune complexes from the disease.

The eyes

The eye is affected in more than 20% of patients with sarcoidosis. The most common findings are uveitis and lacrimal gland involvement. Anterior uveitis is often self-limiting and can be treated topically, but posterior uveitis is a more chronic form of the disease and may require injections of corticosteroids or systemic therapy. Sicca (dry eyes) and glaucoma are long-term complications which are encountered in patients often years after other sarcoidosis symptoms have resolved. They are consequences of the fibrotic changes in the lacrimal glands and eye and do not respond to anti-inflammatory therapy. Optic nerve involvement can be seen with sarcoidosis, with idiopathic disease and multiple sclerosis being the other major causes of this sight-threatening complication. Retinal disease has also been reported. Blindness from sarcoidosis is fortunately rare, and it is usually a consequence of untreated uveitis, retinitis, or optic neuritis.

Neurological disease from sarcoidosis can affect the cranial nerves, central nervous system (CNS), and peripheral nerves. Cranial nerve involvement, especially of the nerve VII, is a common complaint in neurosarcoidosis. CNS lesions can lead to a lymphocytic meningitis.

Fig. 18.12.5 Lupus pernio due to sarcoidosis. The plaque-like lesions can be seen on forehead and both cheeks; the nasal area is also affected and can be associated with sinusitis, as it was in this case.
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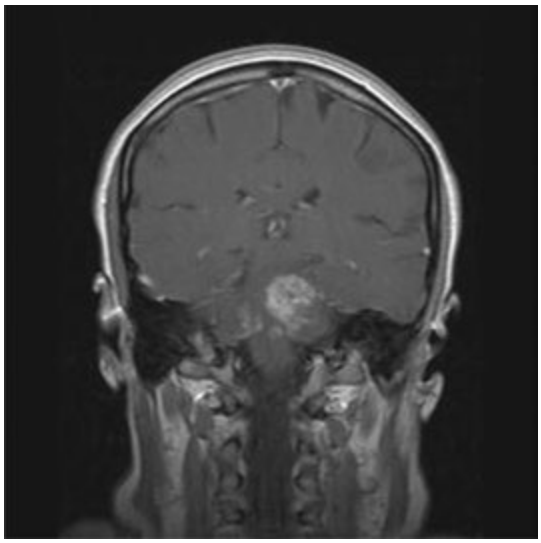

Fig. 18.12.6 Brain MRI with gadolinium contrast. There is uptake in multiple areas (white areas) indicating inflammatory lesions within the brain due to neurosarcoidosis.

Hypothalamic involvement is a characteristic pattern, with diabetes insipidus as a resulting complaint. Contrast-enhanced MRI is the most sensitive method for detecting CNS disease (Fig. 18.12.6). The lumbar puncture is complementary, with increased protein and lymphocytes often seen in active disease. Detection of angiotensin converting enzyme (ACE) in the spinal fluid is suggestive but not diagnostic of neurosarcoidosis.

Liver and spleen

Liver and spleen involvement may be found in over one-half of patients with sarcoidosis, but symptomatic disease occurs in less than 10% of cases. Liver function tests are often elevated, especially the alkaline phosphatase, suggesting an obstructive pattern. Hyperbilirubinemia is relatively rare, but implies extensive disease and is usually an indication for therapy. Massive splenomegaly can occur, and occasionally splenectomy is performed to avoid rupture.

Hypercalcaemia and hypercalciuria can be seen with sarcoidosis. One mechanism is the granuloma converting 25-hydroxyvitamin D_3 to the biologically active form 1,25-dihydroxyvitamin D_3, which is also increased by sunlight exposure. In the Unites States of America, hypercalcaemia is far more common in whites than in African-Americans. Because of the effect of increased calcium absorption, urolithiasis may be also seen in patients with sarcoidosis.

A less common but serious complication of sarcoidosis is cardiac involvement. Direct involvement of the heart can lead to arrythmias such as heart block and ventricular ectopy, which can lead to sudden death. Once the problem is recognized, the use of an implanted defibrillator may reduce the risk of death. Cardiomyopathy is also seen, and cardiac sarcoidosis should be considered in a young patient who presents with unexpected heart failure. Endomyocardial biopsy rarely makes a diagnosis because the granulomas are patchy. Cardiac MRI and PET scanning are the most commonly used imaging techniques to identify cardiac involvement.

Sarcoidosis granulomas can involve virtually any organ of the body. Rare manifestations of sarcoidosis include bone cysts, usually in the distal portion of the fingers, sinus invasion, pleural disease, breast disease, and ovarian or testicular masses.

Fatigue is a major complaint of over half of patients with sarcoidosis. This may be related to sleep apnoea, which occurs in about one-third of patients with the condition, although other factors may also be involved.

The multiorgan involvement of sarcoidosis distinguishes it from other diseases, with lymphoma and tuberculosis the two that are most often considered in the differential diagnosis. Table 18.12.4 summarizes the common features in all three of these diseases and points out features that can be used to separate them.

Pathology

The noncaseating granuloma is the characteristic pathological feature of sarcoidosis. The centre of the granuloma includes macrophages and giant cells which are of the Langerhans' type and can contain more than 10 nuclei. This core of cells is surrounded by

Table 18.12.4 Comparison of features of sarcoidosis, tuberculosis, and lymphoma

Feature	Sarcoidosis	Tuberculosis	Hodgkin's lymphoma
Bilateral hilar adenopathy	Very common	Rare, except in HIV patients	Common
Skin lesions	Common	Rare	Rare
Lupus pernio	Diagnostic	None	None
Erythema nodosum	Common	Rare	Very rare
Hypercalcaemia	Can occur	Very rare	Rare
Eye disease	Common	Rare	Very rare
Pleural disease	Very rare	Common	Common
Cranial nerve VII paralysis	Common	Very rare	Very rare
Elevated ACE	Very common	Rare	None
Tuberculin skin test	Anergic	Positive	Anergic
BAL lymphocytes	Very common	Common	Very rare

ACE, angiotensin converting enzyme; BAL, bronchoalveolar lavage.

lymphocytes. Immunohistochemical studies have shown that the lymphocytes present two rings of cell types: the larger component is the CD4 lymphocyte, while the outer ring usually includes CD8 lymphocytes. The granulomas tend to be well formed, and in lung biopsies they are often well demarcated from normal tissue. The central area will occasionally contain a Schaumann body, which is formed of crystallized material (calcium phosphate) and different in appearance from the foreign bodies or caseation that can be seen in other granulomatous diseases. Occasionally the granuloma will have a necrotic area, but most are bland.

The diagnosis of sarcoidosis is always one of exclusion, but the finding of noncaseating granulomas in two or more organs is—for practical purposes—considered diagnostic. Cultures and special stains for tuberculosis and deep-seated fungal infections should be taken to rule out infection as the cause of granulomas. Close examination should also be made for foreign bodies and malignancy, both of which could lead to a granulomatous reaction.

Investigation

Serum ACE levels

In 1976, Lieberman reported that serum ACE was elevated in the blood of some patients with sarcoidosis, and it has subsequently become clear that this can also occur in a few other conditions. Only 60% of patients with acute sarcoidosis and less than one-third of patients with chronic disease will have elevated levels of ACE. Patients with infectious granulomatous diseases such as tuberculosis, histoplasmosis, and coccidiomycosis occasionally have an elevated ACE level. Mild elevations have also been reported in diabetes mellitus and osteoarthritis, and high levels have been detected in Gaucher's disease, leprosy, and hyperthyroidism. ACE levels are usually lower than normal in patients with Hodgkin's lymphoma, and because ACE is measured using a biological assay, patients on ACE inhibitors have low functional levels. In sarcoidosis the ACE level will decrease in response to treatment or disease resolution with time. It has been proposed as a marker for disease activity, but corticosteroids independently suppress ACE levels, and reducing the dose of corticosteroids may lead to a rise in ACE level without a clinical worsening of disease.

There is a genetic polymorphism for ACE, with an insertion (I) or deletion (D) of a nonsense DNA fragment. ACE levels are higher in DD patients, which needs to be considered when interpreting the serum ACE level, but there appears to be no difference in the distribution of the alleles in patients with sarcoidosis versus the general population.

Serum lysozyme is also elevated in the same way as ACE. Unfortunately, it is elevated in a smaller number of patients with sarcoidosis. Most clinicians will only determine ACE levels.

Tests of the lung

Bronchoalveolar lavage findings have proved to be fairly characteristic in sarcoidosis. The finding of increased lymphocytes, especially an increased CD4:CD8 ratio, has been interpreted by some groups as enough evidence to make a diagnosis of sarcoidosis, and lavage findings may be considered sufficient in a patient with a compatible clinical history and no evidence for infection or malignancy. A more definitive answer from bronchoscopy includes a transbronchial biopsy showing noncaseating granulomas. In over 60% of patients with a stage 1 chest radiograph the biopsy should be positive, rising to 80% in patients with stage 2 or 3 disease. Transbronchial needle aspiration can sample mediastinal and hilar lymph nodes, but unfortunately incomplete sampling of the lymph node in a granulomatous response to malignancy can occur. Endobronchial ultrasound (EBUS) has been shown to be superior to blind transbronchial needle aspiration in identifying granulomas in lymph nodes of sarcoidosis patients. Mediastinoscopy and video assisted thoracoscopy provide minimally invasive methods to obtain more tissue and are usually definitive.

Imaging

Aside from chest radiography and CT scanning, which have already been discussed, gallium and PET scans can demonstrate active inflammation in lymph nodes and other active areas in sarcoidosis. However, the uptake is nonspecific and the level of uptake can be the same as seen with malignancy. This can lead to confusion in patients undergoing PET scan for possible lymphoma, when the activity will be the same for both sarcoidosis and lymphoma. In the gallium scan, which is the older-established procedure, uptake in the parotid and conjunctiva (the 'panda' sign), and uptake in the hilar nodes (the 'lambda' sign), are fairly characteristic for sarcoidosis and are useful confirmation in difficult cases. PET scan, when available, has replaced gallium scan to detect active inflammation. PET scan and MRI have been found particularly helpful in detecting myocardial involvement in sarcoidosis.

Other tests

The Kviem–Siltzbach agent is a suspension of spleen tissue from a patient with confirmed sarcoidosis. Six weeks after an intradermal injection of the agent, the site is inspected for a reaction, which will occur in over 60% of patients with acute sarcoidosis. On biopsy the reaction will show noncaseating granuloma, consistent with sarcoidosis. Properly prepared Kviem–Siltzbach agent has a less than 1 in 500 chance of causing a false positive, however, because of the difficulties in preparing the agent and concerns regarding transmission of an infectious agent, the test is rarely used except in centres with a well-established reagent.

Other laboratory tests may support the diagnosis of sarcoidosis or the level of disease activity. For example, the sedimentation rate and C-reactive protein can be elevated in sarcoidosis and may be useful for disease monitoring, but in over half of patients these inflammatory markers are normal, hence they are neither specific nor sensitive diagnostic tests.

Serum calcium is elevated in 10% of patients with sarcoidosis and is supportive of the diagnosis, but hypercalcaemia can be seen in other conditions which mimic the condition, such as malignancy. Hypercalcaemia due to sarcoidosis should be associated with a normal to low serum phosphate. Renal failure may occur in those with significant hypercalcaemia, which is usually reversible with treatment of the hypercalcaemia.

Hypergammaglobulinemia is also a feature of sarcoidosis, with activated T lymphocytes in the lung capable of stimulating circulating peripheral blood B cells to produce the polyclonal γ- globulin response found in the condition. Serological markers for some diseases may be falsely elevated as a result of this nonspecific reaction, including antifungal and antinuclear antibodies. The

hypergammaglobulinemia is more common in African-Americans than in whites.

As stated previously, liver involvement occurs in over one-half of patients with sarcoidosis, although in some cases there is no serum chemistry test indicating involvement. However, most patients with liver involvement will have elevated serum enzymes, and usually the pattern is obstructive with a rise in the serum alkaline phosphatase. In some patients an elevation of the transaminases is seen. Elevation of the serum bilirubin is less frequent and associated with more extensive liver involvement. Rarely, lymphadenopathy at the porta hepatis can lead to biliary obstruction.

Haematological abnormalities are common in sarcoidosis. Lymphopenia is frequently seen, and is probably due to sequestration of the lymphocytes into the area of inflammation, such as the lung. Anaemia has been reported in about 20% of cases: the mechanism is multifactorial, including a high proportion with iron deficiency. Other causes include direct bone marrow invasion by granulomas and suppression of the bone marrow by cytokines such as IL-2.

Treatment

The natural course of sarcoidosis is unclear because corticosteroids are normally used to treat symptomatic patients. The prognosis is often good for the patient with no symptoms on presentation, with spontaneous resolution of the disease often occurring within a year or two of diagnosis. However, the disease can also take a chronic form, with symptoms for many years.

The concept of acute disease, which lasts for less than 2 years, vs. chronic disease has been a useful method of discussing patients, especially in terms of therapy. Table 18.12.5 lists several factors associated with resolution within 2 to 5 years, as well as those predicting chronic disease. Acute disease is associated with erythema nodosum, hilar adenopathy, anterior uveitis, and paralysis of cranial nerve VII. Chronic disease includes such manifestations as lupus pernio, stage 4 chest radiograph, posterior uveitis, urolithiasis, and bone cysts. Most chronic disease is controllable by therapy, but there are refractory patients. Mortality from sarcoidosis occurs, but is less than 5% in most series, with the most common causes of death being from lung, cardiac, and neurological disease refractory to therapy.

Table 18.12.5 Features predictive of the clinical course of sarcoidosis

Organ	Acute	Chronic
Chest radiograph	Stage 1	Stage 4
Skin	Erythema nodosum	Lupus pernio
Eyes	Anterior uveitis	Posterior uveitis Pars planitis
Joint involvement		Bone cysts
Calcium metabolism	Hypercalcaemia	Urolithiasis
Cardiac		Cardiomyopathy
Neurological	Cranial nerve VII palsy	Central nervous system mass
Sinus		Sinus involvement

The main indication for therapy in sarcoidosis is symptoms, although hypercalcaemia should be treated even if the patient is asymptomatic. An eye examination should be performed in all patients with sarcoidosis: uveitis may be misdiagnosed as sicca (dry eyes), but the former will require anti-inflammatory agents, while the latter will only need a wetting agent.

Corticosteroids

If possible, treatment should be topical. Corticosteroid topical creams and eye drops are effective if the inflammation is superficial. The effectiveness of inhaled steroids is less clear cut. The higher-potency steroids such as budesonide appear to have a role in reducing the dosage of systemic corticosteroids, and randomized trials have indicated a role for this drug as maintenance therapy for a patient who has received systemic therapy for 3 months to induce a remission.

It is not clear whether corticosteroids change the course of the disease. Early randomized trials found no difference in the long-term outcome of patients who received corticosteroids versus controls. A British Thoracic Society randomized study demonstrated a small benefit for corticosteroids over placebo for patients with persistent, but not severe disease. However, in this study—as in most of the early studies—patients with symptomatic disease were excluded and always treated with corticosteroids, which could lead to a limit in the observed response to therapy.

Several groups have looked at the need for treatment and the duration of therapy. The genetic background of these groups varies, from mostly white northern European descent, where 60% never required systemic therapy, to African-Americans, where 70% were treated. In general, about one-half of sarcoidosis patients will require systemic therapy for their disease, and after 2 to 5 years, 18–53% of the patients could not be withdrawn from therapy. In patients who were tapered off corticosteroids, one group found that 80% eventually relapsed and required reinstitution of therapy. The differences in rate of continued therapy and relapse between the centres could be due to either the genetic background of the patients or the bias of the treating physicians. Interestingly, two studies demonstrated that if the patient did not require initial systemic therapy, there was a less than 10% chance that they would require treatment after 2–5 years.

The toxicities of corticosteroids are well known. These include weight gain, diabetes mellitus, hypertension, and mood swings, and with prolonged use avascular necrosis and osteopenia are significant problems. Some patients with sarcoidosis will have lost weight as part of their disease, but the weight gain with treatment often surpasses the amount of weight lost. The longer a patient is on corticosteroids, the more problematic, and unfortunately most patients will require more than a year of treatment.

Several alternatives to systemic corticosteroids have been proposed over the years. These are summarized and compared to corticosteroids in Table 18.12.6, which includes the usual doses, commonly encountered toxicities, an estimate of response rate, and the usual indications for use.

Other agents

The commonly prescribed antimalarial agents chloroquine and hydroxychloroquine possess anti-inflammatory activity, with the major toxicities being eye and gastrointestinal. Hydroxychloroquine has been associated with less eye toxicity and therefore it is more

Table 18.12.6 Treatments for sarcoidosis

Drug	Dosage	Efficacy (%)	Toxicity	Usage
Prednisone/Prednisolone	5–40 mg/day	90	Weight gain Diabetes Hypertension Osteoporosis Psychiatric	Acute Chronic Refractory
Hydroxychloroquine	200–400 mg/day	30–50[a]	Gastrointestinal Retinal	Acute Chronic
Methotrexate	10–25 mg once a week	60–80	Haematological Gastrointestinal Lung Hepatic Mutagenic	Chronic Refractory
Leflunomide	10–20 mg/day	60–80	Haematological Gastrointestinal Hepatic Mutagenic	Chronic Refractory
Azathioprine	50–200 mg/day	50–80	Haematological Gastrointestinal Carcinogenic Mutagenic	Chronic Refractory
Pentoxifylline	400 mg three times a day	50	Gastrointestinal	Acute
Cyclophosphamide	50–150 mg/day orally, 500–2000 mg every 2 weeks IV	80	Gastrointestinal Haematological Carcinogenic Bladder Teratogenic	Chronic Refractory
Thalidomide	50–100 mg/day	80[a]	Teratogenic Somnolence Peripheral neuropathy	Chronic Refractory
Infliximab	3–5 mg/kg IV initially, 2 weeks later, then every 4–8 weeks	90	Allergic reactions Infections Worsening heart failure Probable carcinogen	Refractory
Adalimumab	20–40 mg every week to every other week	80	Infections Worsening heart failure Probable carcinogen	Refractory

IV, intravenous

[a] Refers to efficacy for skin manifestations of sarcoidosis: other manifestations respond less well.

frequently prescribed, although some experts feel chloroquine is a more effective agent. The drugs concentrate in the skin and have been most efficacious for skin disease and hypercalcaemia: they are less successful for treating pulmonary disease.

Methotrexate is an antimetabolite chemotherapy used for various solid tumours. In a double-blind randomized placebo-controlled trial of acute pulmonary sarcoidosis it was found to be steroid sparing, but required 6 months to be effective. The response rate for chronic sarcoidosis is 60–80% and methotrexate is usually used in this context. Most patients who respond can be treated with methotrexate alone, but about 20% of patients will require low-dose corticosteroids in addition. The usual dose is 10 to 15 mg orally each week, which may need to be adjusted for toxicity. We have successfully treated patients with doses as small as 2.5 mg of methotrexate a week. Acute toxicity, including mucositis and nausea, can be minimized with supplements of folic acid at 1 mg/day. Leucopenia can also occur, but is usually insignificant unless the patient is already leucopenic from sarcoidosis or the patient has renal insufficiency. The long-term toxicity of methotrexate can include hypersensitivity pneumonitis and cirrhosis, the latter being a concern because 50% of chronic patients will have sarcoidosis granulomas in a liver biopsy, hence we recommend liver biopsies every 2 years for patients requiring prolonged treatment with methotrexate.

Leflunomide is an antimetabolite similar to methotrexate but with less pulmonary and gastrointestinal toxicity. It appears to be as effective as methotrexate and has also been given in combination with methotrexate, when the two drugs appear to be synergistic.

Azathioprine has been used as an immunosuppressant for solid organ transplant patients and patients with idiopathic pulmonary fibrosis for many years. However, its use in sarcoidosis has been more sporadic, and it is usually reserved for chronic cases.

Other drugs have been used for refractory sarcoidosis. Cyclophosphamide, a cytotoxic agent used in the treatment of many vasculitic diseases, has been reported as very useful in neurological and cardiac sarcoidosis, but it has more gastrointestinal, haematological, and bladder toxicity than methotrexate or azathioprine. Ciclosporin has been used with limited success in some neurological cases, but a randomized trial failed to show additional benefit over corticosteroids alone in patients with pulmonary sarcoidosis.

Persistent release of TNF by alveolar macrophages is a feature of patients with chronic sarcoidosis, hence the effects of drugs that block TNF release or action have been studied. These include corticosteroids, methotrexate, and azathioprine, which have been discussed previously. Others include pentoxifylline, which inhibits alveolar macrophage release of TNF, and can provide benefit in some cases of acute sarcoidosis, although associated with significant gastrointestinal toxicity which has limited its use. Thalidomide also has significant anti-TNF activity and is effective at treating chronic, severe skin lesions including lupus pernio, but the drug has severe teratogenic potential such that close monitoring is required, and it also causes hypersomnolence, constipation, and a peripheral neuropathy. The treatment of eye or pulmonary eye disease often requires high doses of thalidomide, hence the risk–benefit ratio limits use of the drug to skin disease.

Biological agents directed against TNF have been developed for various inflammatory diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis. These include infliximab, which is a monoclonal antibody that binds TNF, and etanercept, a TNF receptor antagonist. Numerous case reports and case series have demonstrated a rapid and sometimes dramatic response to infliximab in refractory cases of sarcoidosis. A double-blind placebo-controlled randomized trial of infliximab for chronic pulmonary sarcoidosis found it to be effective in further improving the vital capacity of those patients already on at least 10 mg prednisone per day and/or cytotoxic agents, with the study demonstrating a larger effect of therapy for those with more severe disease. The TNF receptor antagonist etanercept has been less successful in treating sarcoidosis: in pulmonary and ocular disease less than one-third of patients improved on therapy, and one-third became worse during treatment. The difference in efficacy between infliximab and etanercept has also been noted in Crohn's disease, where infliximab is the biological agent of choice. The differences between agents may be due to mechanism of action or peak dose of the drug; infliximab is given intravenously, etanercept subcutaneously); infliximab binds TNF on the cell surface, whereas etanercept blocks soluble TNF. The interaction on the cell surface can affect the transmembrane TNF effect, and the binding has also been associated with inducing apoptosis that would lead to reduction of the number of inflammatory cells releasing TNF and other proinflammatory cytokines. Experience with the totally humanized monoclonal anti-TNF antibody adalimumab has been increasing: it is effective in refractory sarcoidosis, but may require a large dose, similar to that used for Crohn's disease.

The biological agents are associated with significant toxicities and cost. Among the class toxicities are the allergic reactions, increased rate of infection, worsening of pre-existing congestive heart failure, and potential carcinogenic effects. Compared to etanercept, infliximab is associated with a higher rate of reactivation of tuberculosis, which may be a reflection of its superior antigranulomatous properties. Overall, because of the potential severe toxicities, infliximab use appears limited to refractory cases.

Strategy

There is no single treatment for all patients with sarcoidosis. The first step is to determine whether the patient requires treatment, the decision to treat usually being based on the patient's symptoms. The clinician needs to determine the extent of the symptomatic disease and whether the disease is acute or chronic. Asymptomatic or minimally symptomatic patients with hypercalcaemia, cardiac, or CNS disease may require therapy to prevent life-threatening complications. The use of systemic therapy usually means corticosteroids first. If the patient is able to be successfully treated with corticosteroids, the dose is gradually reduced to minimize toxicity. If the dose cannot be reduced to an acceptable level, or if the patient is not responding to corticosteroids, then steroid sparing agents should be added. For most of these the onset of action is 6 months or more, hence the clinician should not hesitate to add these drugs early into therapy if the patient has evidence for chronic disease (**Table 18.12.5**) or recurrent symptoms whenever steroids are withdrawn.

Prognosis

Most patients with sarcoidosis will experience disease resolution within 2–5 years; about 25% will develop residual fibrosis in the lungs or elsewhere; in a few the disease will become chronic and persist for more than 5 years. For the chronic patient, treatment can usually palliate symptoms, but organ failure—including eye, liver, cardiac, or respiratory—can occur as a result of disease. Most series from referral centres report 5% disease-related mortality, with 1% probably the rate in nonselected patients. The most common cause for sarcoid-related death is respiratory failure, with cardiac, neurological, and liver disease as other causes. Respiratory failure leading to death can be predicted from pulmonary function tests, for example, one study found no patient with a vital capacity of more than 1.5 litres died from respiratory failure, whereas one-third of those with vital capacity persistently less than 1 litre died of this complication. In patients with severe restriction the best predictor of death was presence of pulmonary hypertension and evidence of right heart failure (as associated with an elevated right atrial pressure). Recent studies, including a large retrospective study from the United States, suggest a rise in the mortality from sarcoidosis over the past 20 years. Organ transplantation has been successfully performed in sarcoidosis patients: although sarcoidosis lesions can occur in the new organ, organ failure due to sarcoidosis is unlikely.

Particular complications

As stated earlier, end-stage lung disease is the most common problem for patients with severe sarcoidosis, with fibrotic disease leading to cor pulmonale and respiratory distress. In addition, cavitary lesions can lead to bronchiectasis or become colonized with aspergillus. Aspergillomas can cause haemoptysis, which can be fatal, and treatment is difficult because most patients are not good surgical candidates: embolization has been used for life-threatening bleeding.

In studies of patients who are persistently dyspnoeic due to sarcoidosis, up to 50% have pulmonary hypertension. Factors associated with this are stage 3 or 4 chest radiograph, hypoxia, and reduced D_LCO. A right heart catheterization is an important part of their evaluation because they may have coincident left ventricular disease. Precapillary pulmonary hypertension in sarcoidosis has a higher risk of mortality than patients with similar advanced pulmonary sarcoidosis without pulmonary hypertension. In case reports of

patients with sarcoidosis associated pulmonary arterial hypertension, both epoprostenol and bosentan have been reported as useful, working independently of any anti-inflammatory drugs used to treat the underlying condition.

Steroid-induced osteopenia is a significant problem with long-term corticosteroid therapy. Patients are often not treated initially with calcium supplements because of the risk of hypercalcaemia, but calcium supplementation should be considered if a patient requires long-term systemic steroids, with monitoring serum calcium during therapy usually sufficient to avoid complications. The use of nasal calcitonin or bisphosphonates should also be considered if the patient requires prolonged therapy.

Cardiac sarcoidosis can lead to sudden death, hence arrythmias must be evaluated in patients with sarcoidosis. Continuous electrocardiographic monitoring is useful to identify episodes, and we use electrophysiological studies in patients with symptomatic arrythmias to determine their source. Treatment of the sarcoidosis alone may be insufficient to control rhythm disturbances in patients with ventricular arrythmias: an implanted defibrillator may be required, particularly for those with refractory ventricular tachyarrthymias.

Areas of uncertainty/controversy

Some clinicians have proposed the use of bronchoalveolar lavage as the exclusive diagnostic test for sarcoidosis: this is based on the rationale that, in the appropriate clinical setting, findings of increased lymphocytes and a CD4:CD8 ratio greater than 3.5 represents a granulomatous process. In patients with cultures negative for tuberculosis and fungal infection, sarcoidosis is most likely and no further diagnostic testing may be needed. However, the percentage of patients with increased lymphocytes and CD4:CD8 ratio varies from centre to centre: in our institution at least 50% will meet these criteria, but the use of bronchoalveolar lavage does not provide an absolute diagnosis of sarcoidosis. As previously noted, transbronchial needle aspirate may also be useful in making a diagnosis, but the finding of a granuloma does not assure the diagnosis.

The use of corticosteroids for the treatment of sarcoidosis remains controversial. In the patient with minimal symptoms, treatment can be withheld or topical. If the disease spontaneously resolves, no therapy is indicated. However, if the patient becomes symptomatic, corticosteroids will probably be useful. The best treatment of the patient with persistent, mild disease is unclear: the British Thoracic Society study suggests that these patients should receive corticosteroids; others argue that the differences are small and do not justify treatment.

Possible future developments

The cause of sarcoidosis remains unknown. Newer molecular biological techniques may provide further insight into a causative agent and/or an underlying genetic predisposition for the disease, and study of causality may provide better answers to other questions in the disease process as well.

The patient with chronic disease represents a disproportionate number of cases with increased morbidity and need for medical services, and the use of corticosteroids alone is not adequate for many of these. Research is still required into whether other agents are truly steroid sparing and associated with improved clinical outcome, and pulmonary arterial hypertension and its treatment have to be studied in these chronic cases.

The quality of life of patients with sarcoidosis is affected by both the disease and its treatment. Corticosteroids may cause more problems than benefit, and steroid-sparing drugs also have their toxicity. Fatigue is a major complaint for the patient and not well treated by our current drugs: new agents such as modafinil and methylphenidate are being developed to treat fatigue and may be applicable in sarcoidosis.

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