Sarcoidosis

Sarcoidosis is a multisystem disease with an unclear aetiology.

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The term 'sarkoid' was first coined by Caesar Boeck in 1899 while describing skin lesions initially documented by the English physician Jonathan Hutchinson in 1877. Boeck used the term to describe what he presumed were benign 'sarcoma-like' lesions, and more than a century later sarcoidosis remains an enigma. As a result sarcoidosis is still defined vaguely as a disease where granulomas are formed in multiple organ systems, without a recognised cause.

The incidence of sarcoidosis for South Africa is unknown. However, it is likely to be lower than that in northern Europe – which has the highest incidence of 5 - 40 cases per 100 000 people per year. The risk of developing the disease is 3.8 times higher in African Americans compared with white Americans, and additionally appears to be more severe in black people. Women are affected more often than men in all studied population groups, and, typically, sarcoidosis is thought of as a disease of young adults. However, in Scandinavian countries, another peak has been observed between the ages of 65 and 69 years, giving a classic bimodal age distribution.[1,2]

Although sarcoidosis is a multisystem disease, this review will focus primarily on sarcoidosis of the lungs.

Pathogenesis

The characteristic histological feature of sarcoidosis is the presence of non-caseating granulomas in tissues. Although the exact cause and mechanism of disease in sarcoidosis are still not known, it is believed that there are potentially a number of different unknown triggers (antigens) that can result in the granulomatous inflammatory response. Sarcoidosis appears to be five times more common in first-degree relatives,[3] and twin studies also support a degree of genetic predisposition. However, as both HLA and non-HLA gene studies have shown, it is highly unlikely that it is caused by a single gene abnormality.[2,4]

Evidence for antigenic stimulation of the immune system comes from a number of sources. For example, in the years following the World Trade Center disaster, the incidence of sarcoidosis among the involved fire fighters rose noticeably.[5] Additionally, the granulomas formed appear to involve oligoclonal $CD4^+$ T cells, suggesting that these cells have been stimulated by a common antigen.[6] Numerous candidate antigens have been proposed, and more recently mycobacteria and proprionibacteria have been implicated. Mycobacteria are attractive as causal agents as they produce disease histologically very similar to sarcoidosis, with some studies even demonstrating the presence of mycobacterial antigen in sarcoid tissue. However, it is still far too premature to assign mycobacteria as the cause of sarcoidosis, as they may merely represent 'innocent bystanders'.

Clinical presentation

The clinical presentation depends largely on which organs have been affected, with the lungs being the most commonly involved (in up to 95% of patients). The most frequent respiratory symptoms are cough, shortness of breath and chest pain, and these may occasionally be accompanied

Table 1. Organ systems involved in sarcoidosis[2,4,9,15]

Organ system	Frequency of involvement (%)	Comment
Lungs	≤95	Most commonly involved organ
Skin	15 - 25	Erythema nodosum, plaques, subcutaneous nodules, lupus pernio (facial plaques)
Lymph nodes	15 - 30 (hilar in up to 90)	Usually firm and non-tender
Eye	12	Anterior uveitis most common (65% of eye involvement). Also posterior uveitis, keratoconjunctivitis and vasculitis
Liver	12	40 - 70% have granulomas, up to 30% have hepatomegaly, and significant dysfunction is rare
Nervous system	5 - 10	Any part of the nervous system can be involved (most common is unilateral facial nerve palsy and meningitis)
Bone marrow	4 - 20	Anaemia and leukopenia common but not diagnostic
Blood	4 - 11	Hypercalciuria in up to 40%, renal calculi in 10%
Cardiac	5 - 10	Up to 76% have cardiac involvement at autopsy
Bone/joint	0.5	Joint pain in 25 - 40%. Deforming arthritis is rare
Muscle	0.4	
Upper respiratory tract (esp. nasal)	(unknown)	Consider if persistent symptoms in a patient with known sarcoidosis

by constitutional symptoms, e.g. fatigue, fever and weight loss – similar to those of tuberculosis. Fatigue can be distressing and is reported in 30 - 70% of patients.[7] On respiratory examination, the clinical findings vary widely – they are unremarkable in the majority of cases. Some patients may wheeze and/or have crackles, but clubbing is rare.

Because of its multisystemic nature, it is important to assess other organ systems when considering a diagnosis of sarcoidosis, as this may affect treatment decisions. Although almost any system can be involved, the lymph nodes, skin and eyes are most commonly affected (Table 1). It is important to identify Löfgren's syndrome (consisting of erythema nodosum, bilateral hilar adenopathy, migratory polyarthritis and fever), as not only does it have a good prognosis, but it is also made without the need for histological proof.

Making a diagnosis

The diagnosis of sarcoidosis is made on finding non-caseating granulomas on histology, combined with a compatible clinical and radiological picture, with the exclusion of other causes of granuloma formation (most importantly mycobacterial and fungal infections).

Routine work-up for a suspected pulmonary sarcoidosis patient should include a thorough history and examination as well as lung function testing, chest radiographs, an electrocardiogram (ECG), blood tests (see below), and ophthalmological examination (with a slit lamp to exclude posterior uveitis). The lung function test pattern is variable between patients, with airflow obstruction (FEV_1:FVC ratio <70%), restrictive lung disease (normal or increased FEV_1:FVC ratio, with reduced FEV_1 and reduced FVC) or even normal lung functions being observed. The diffusion capacity (TL_CO) is frequently reduced if the lung parenchyma is involved.

Sarcoidosis is a diagnosis of exclusion. Other causes of granuloma (e.g. TB, non-tuberculous mycobacteria and fungi) need to be actively excluded.

On chest X-ray examination, bilateral hilar lymphadenopathy (BHL) is common, as are nodules, which predominantly affect the upper lobes. These can occasionally conglomerate into large masses. The chest X-ray changes are staged from 0 to 4 (Table 2). However, these changes are not necessarily progressive (Figs 1 - 5).

High-resolution CT scanning (HRCT) is not required if the diagnosis is secure, but can be helpful when the diagnosis is uncertain or if complications develop. The characteristic findings include hilar and mediastinal lymphadenopathy, multiple parenchymal nodules (1 - 10 mm in size), bronchial wall thickening with beading and irregularity of the bronchovascular bundles and sub-pleural space (Fig. 6). Unfortunately, none of these features is specific for sarcoidosis, and tissue biopsy is often still needed.[8]

Magnetic resonance imaging (MRI), while important in the diagnosis of neurological and cardiac sarcoidosis, has little role in the diagnosis of the pulmonary form of the disease. Other imaging modalities, such as positron emission tomography (PET) and gallium scanning, remain controversial and should not be used routinely.

Blood investigation may provide supportive evidence, but cannot be used to reliably make a diagnosis, or to monitor disease activity. Serum angiotensin-converting enzyme (SACE) is raised in 60% of sarcoidosis cases.[2] However, the test is not specific for this disease, and may be raised in a variety of other conditions (including tuberculosis, leprosy, silicosis and histoplasmosis as well as HIV). Hypercalcaemia is observed in up to 11% of patients; however, hypercalciuria is more frequent (40% of patients) and renal calculi are not uncommon (10%).[2] A full blood count, creatinine, electrolyte and liver function tests should be performed to screen for involvement of other organs.

An ECG is insensitive but useful to assess for cardiac sarcoidosis. Clinically significant cardiac sarcoidosis is found in only 5 - 10% of subjects, and about 50% of these will have ECG abnormalities.

Table 2. Radiological staging of sarcoidosis

Stage	Finding	Proportion of cases (%)	Expected remittance rates (%)	Treatment
0	Normal chest X-ray	8		
1	Bilateral hilar lymphadenopathy (BHL)	40	60 - 80	Does not require treatment
2	BHL with pulmonary infiltrates	37	50 - 60	Symptomatic disease requires treatment. Asymptomatic disease is controversial
3	Pulmonary infiltrates (without BHL)	10	<30	Symptomatic disease requires treatment Asymptomatic disease is controversial
4	Pulmonary infiltrates with evidence of volume loss (fibrosis)	5	0	Treatment unlikely to be beneficial, but a trial of therapy is warranted
Other	Pleural effusion, cavity formation, lymph node calcification	Rare		

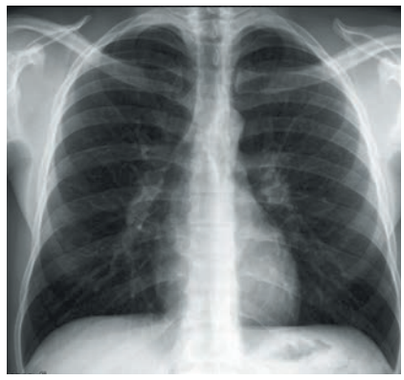

Fig. 1. Stage 0 sarcoidosis – normal chest radiograph.

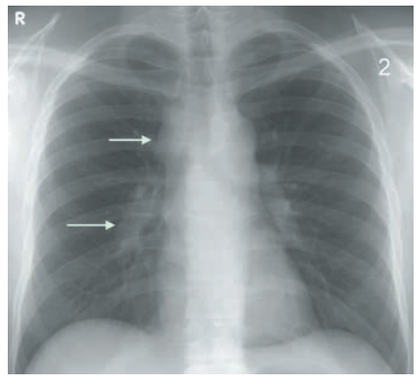

Fig. 2. Stage 1 sarcoidosis – bilateral hilar lymphadenopathy and mediastinal lymphadenopathy (arrows).

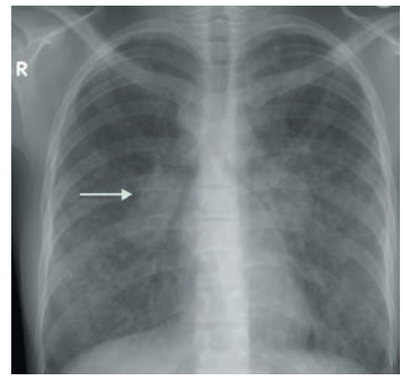

Fig. 3. Stage 2 sarcoidosis – bilateral hilar lymphadenopathy (arrow) with pulmonary infiltrates.

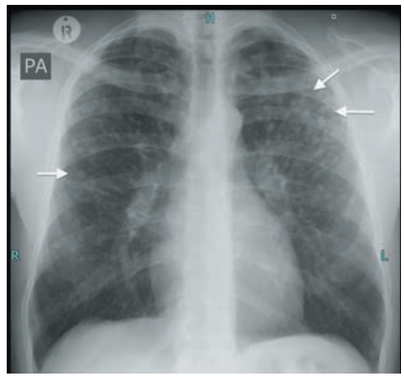

Fig. 4. Stage 3 sarcoidosis – pulmonary infiltrates (arrows) without bilateral hilar lymphadenopathy.

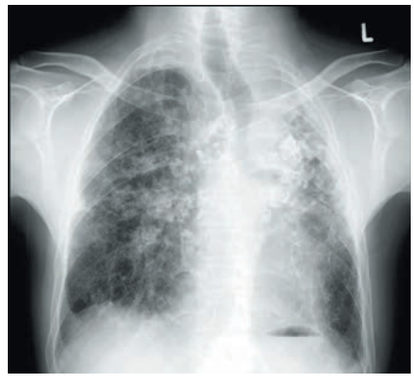

Fig. 5. Stage 4 sarcoidosis – pulmonary infiltrates with evidence of volume loss (fibrosis).

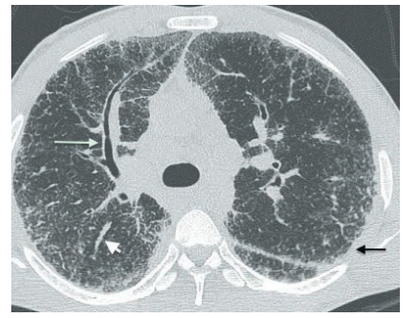

Fig. 6. High-resolution CT scan changes of sarcoidosis – bronchial wall thickening (white arrow), beading of bronchovascular bundles (arrow head), and sub-pleural nodularity (black arrow).

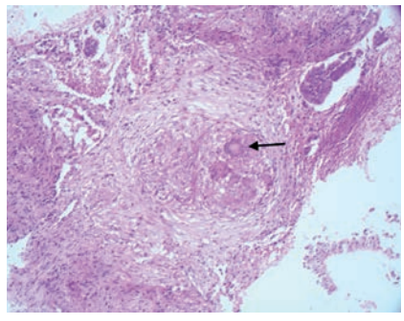

Fig. 7. Non-caseating granuloma of sarcoidosis (giant cell indicated). (Courtesy of Professor H Wainwright, Department of Histopathology, University of Cape Town.)

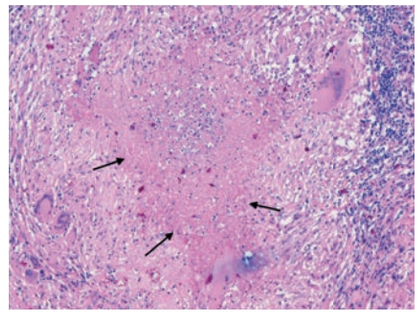

Fig. 8. Caseating granuloma of tuberculosis (caseous material indicated). (Courtesy of Professor H Wainwright, Department of Histopathology, University of Cape Town.)

Histology remains central to the diagnosis, and in most patients a tissue biopsy is needed for confirmation. The one exception is in patients with classic Löfgren's syndrome (see above). The hallmark histological feature of sarcoidosis is the non-caseating granuloma (Fig. 7), which contains epithelioid and multinucleate giant cells. Additionally, asteroid and Schaumann bodies may be seen within the giant cells. Unfortunately, none of these histological features is pathognomonic for sarcoidosis, making it essential to first exclude other causes of granulomatous disease (Table 3). Caseating granuloma of tuberculosis can be seen in Fig. 8.

Tissue should also be sent for microscopy and culture, looking for tuberculosis, non-tuberculous mycobacteria and fungi.

Additionally, beryllium exposure (used in X-ray equipment, nuclear reactors and the aerospace industry), drug use (e.g. methotrexate) and exposure to organic material (e.g. birds) should be excluded on history.

Table 3. Causes of granulomatous disease

Infections	
• Mycobacteria	Tuberculosis, non-tuberculous mycobacteria
• Bacteria	Brucellosis, syphilis
• Fungi	Histoplasmosis, coccidioidomycosis
• Other	Leishmaniasis
Occupational and environmental exposure	
• Organic	Hypersensitivity pneumonitis
• Inorganic	Beryllium, talc, titanium
• Drugs	E.g. methotrexate
Malignancy	Lymphoma
Auto-immune disease	Granulomatosis with polyangiitis (formerly Wegener's), Churg-Strauss syndrome
Other	Sarcoidosis

When acquiring tissue, the most accessible site should be used. For lung lesions, endo- or transbronchial lung biopsy (TBL) is a safe procedure in experienced hands, and has a positive yield of 40 - 90%.[9] If hilar or mediastinal lymph nodes are present, these may be sampled using mediastinoscopy by a cardiothoracic surgeon. More recently, endoscopic needle sampling of mediastinal lymph nodes can be performed during a minimally invasive out-patient procedure using a bronchoscope with ultrasound capabilities (endobronchial ultrasound (EBUS)). This technique is locally available.[10] Larger specimens of lung tissue are very occasionally needed to secure the diagnosis. These can be obtained via either an open lung biopsy or using the less invasive video-assisted thoracoscopy (VATS) procedure.

Need for corticosteroid treatment

It is important to appreciate that the majority of patients do not require treatment, and the true natural history of sarcoidosis is confounded by the frequent use of corticosteroids. The course of sarcoidosis is highly variable, tending to wax and wane. In general, approximately two-thirds of patients have spontaneous remissions (particularly those with Stage 1 chest radiographs), while 10 - 30% may have chronic or progressive disease.[9] In prospective studies, more than 85% of these spontaneous remissions have occurred within 2 years of presentation.[9] Unfortunately, there are no clear predictors of who will resolve and who will progress, which is reflected in differing clinical practice, with some centres treating only one-third of patients and others treating more than two-thirds.[8]

Oral corticosteroids (OCSs) remain the most commonly used therapy. In general, severe systemic disease will require additional treatment (e.g. hypercalcaemia, cardiac, neurological or ocular involvement not responsive to topical drops). For respiratory disease a trial of therapy is indicated if there are prominent symptoms, progression of disease or lack of remission over 6 months follow-up. However, the benefit of long-term corticosteroids needs to be carefully balanced with the risks of therapy (e.g. the development of osteoporosis, hypertension, diabetes, etc.). Table 2 shows the expected frequency of resolution of disease for the various radiographic stages of pulmonary sarcoidosis.

It is recommended that Stage 1 disease is not treated initially, whereas Stage 2 and 3 disease are treated if symptomatic or if there is progressive deterioration. Stage 4 disease is unlikely to respond owing to the irreversible nature of the fibrosis, but a trial of therapy is warranted. Treatment of asymptomatic Stage 2 and 3 disease remains controversial, with at least one randomised trial showing only a small but significant benefit in the use of OCSs.[11] Of those with Stage 2 or 3 disease who respond to OCSs, up to 25% will relapse once therapy is stopped.[4] Relapse is far more frequent in corticosteroid-induced remissions than in patients who remit spontaneously. In the latter group relapse is rare, especially if they are stable and off treatment for more than 1 year, with relapse rates of 2 - 8% expected.[9] Therefore, most clinicians will treat for at least 1 year, with prolonged monitoring for deterioration.

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We recommend that prednisone be initiated at a dose of 20 - 40 mg for 2 - 3 months, which may be extended if the patient continues to improve and there are no significant side-effects. Thereafter, the OCS is weaned over 1 - 3 months to the lowest effective dose (usually about 10 mg daily or alternate daily therapy), which is maintained for a further 6 - 9 months. This gives a total duration of treatment of 12 months.

All patients should be followed up for at least 3 - 5 years, and current guidelines promote indefinite follow-up of Stage 2, 3 or 4 disease regardless of whether treatment is given or not. Symptoms, radiological changes and changes in lung function (FVC and TL_CO) are used to monitor response or disease progression. If a relapse occurs the corticosteroids are increased to the last effective dose for 3 - 6 months.

It is also essential to monitor patients regularly for the side-effects of long-term corticosteroid therapy, the most important being osteoporosis, hypertension and the development of diabetes.

Alternatives to corticosteroids

Inhaled corticosteroids have been used by patients with pulmonary sarcoidosis; however,

a Cochrane review failed to show convincing evidence supporting their use.[12]

There are a number of other agents that can be used in the management of pulmonary sarcoidosis; however, they all have the potential for serious toxicity. The main reasons for their use are to reduce the dose of corticosteroids (and therefore the side-effects) in patients who cannot be weaned, as well as attempting to halt the disease in those who progress despite an adequate trial of corticosteroid therapy. Methotrexate (10 - 20 mg per week) is the most widely used alternative, and two-thirds of patients can be expected to respond after a trial of at least 6 months. Azathioprine (50 - 150 mg per day) is less commonly used, and the available data report lower response rates, ranging from 20% to 80%.[8] Other agents that have been used with variable success include: the antimalarials (chloroquine and hydroxychloroquine), leflunomide (an alternative to methotrexate), and the biologicals (infliximab and adalimumab, TNFα blockers, but not etanercept).

Prognostic features

The prognosis of sarcoidosis is variable, with Löfgren's syndrome having the best prognosis, with a high probability of spontaneous relapse. Poor prognostic features include older age (over 40 years), black race, multi-system disease (more than 3 organ systems involved), respiratory Stage 3 and 4 disease, symptoms of more than 6 months' duration and the absence of erythema nodosum.[4]

Sarcoidosis in South Africa

The high incidence of tuberculosis in South Africa complicates both the diagnosis and ongoing management of sarcoidosis. Because of the similarity in disease presentation, patients are unfortunately often given a 'trial of tuberculosis therapy' prior to seeking an alternative diagnosis. Additionally, before making a definitive diagnosis of sarcoidosis, tuberculosis needs to be aggressively excluded. Furthermore, when a known sarcoidosis patient deteriorates, it is imperative to first exclude active tuberculosis before labelling the deterioration as a 'sarcoidosis flare' (which may require increased immunosuppression). Long-term isoniazid prophylaxis (IPT) to prevent tuberculosis remains controversial, but should be considered in patients requiring ongoing therapy.

The local HIV epidemic further complicates the management of sarcoidosis, which is largely a CD4-driven disease, and therefore appears to be rare in patients with a $CD4^+$ count <200 cells/μl.[13] Opportunistic infections (e.g. mycobacterial and fungal infections) need to be considered in all HIV-positive patients found to have a granulomatous disorder prior to making a diagnosis of sarcoidosis (especially if the $CD4^+$ count is <200 cells/μl) (Table 3). HIV-positive patients may develop sarcoidosis on initiation of antiretroviral therapy. This is attributed to an immune reconstitution inflammatory syndrome (IRIS) of the recovering immune system, and similarly requires the exclusion of active opportunistic infections before therapy is considered.[14]

Conclusion

Sarcoidosis is a far less common cause of respiratory disease than tuberculosis in South Africa, and needs a high index of suspicion to diagnose. The diagnosis requires a combination of clinical, radiological and histological findings, as well as the exclusion of other causes of granulomas, especially mycobacterial and fungal infections. Therapy is not always required, but when given is usually instituted to prevent progressive organ dysfunction. The potential benefits of treatment need to be carefully weighed against the potential risks.

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Summary

- Sarcoidosis is a granulomatous disorder of unknown cause that affects multiple organ systems.
- The lungs are the most frequently affected organ (up to 95%), and the clinical presentation is variable.
- The diagnosis of sarcoidosis requires the demonstration of non-caseating granulomas with a compatible clinical and radiological picture.
- Sarcoidosis is a diagnosis of exclusion. Other causes of granuloma (e.g. TB, non-tuberculous mycobacteria and fungi) need to be actively excluded.
- Many patients with pulmonary sarcoidosis will not require treatment, as spontaneous remission is common.
- Patients should be monitored frequently to assess for relapse or disease progression.
- Treatment is indicated for sarcoidosis with cardiac, neurological or eye involvement (not responding to topical therapy) or for hypercalcaemia.
- If treatment is indicated, oral corticosteroids should be used initially and for at least 1 year at the lowest effective dose.
- Relapse after corticosteroid-induced remission is not uncommon.