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Sarcoidosis

What is sarcoidosis?

Sarcoidosis is a multisystem chronic inflammatory condition characterised by the formation of non-caseating epithelioid granulomata at various sites in the body.[1] It has a predilection for the lungs and thoracic cavity; however, there are many different manifestations that may cause a great deal of diagnostic difficulty.

Sarcoidosis largely affects patients in their mid-20s to mid-40s but cases do appear infrequently in younger and older patients. After the thorax, the skin and eyes are most commonly affected, followed by the liver (not usually clinically relevant), heart and nervous system.

How common is sarcoidosis?[2] [3]

- The prevalence of sarcoidosis varies greatly depending on region of the world, from 1-5 per 100,000 in South Korea, Taiwan and Japan, to 140-160 per 100,000 in Sweden and Canada.
- Although sarcoidosis may occur at any age, it is usually seen in adults under the age of 50 years.
- Sarcoidosis is usually sporadic but is familial in 3.6-9.6% of cases.

Sarcoidosis symptoms[4] [5] [6]

This is highly variable depending on ethnicity, duration of illness, pattern and degree of inflammatory organ involvement.[7]

Sarcoidosis can affect any organ. Intrathoracic involvement occurs in 90% of patients with symmetrical bilateral hilar adenopathy and/or diffuse lung micronodules, mainly along the lymphatic structures. Of the potential extrapulmonary manifestations, skin lesions, uveitis, liver or splenic involvement, peripheral and abdominal lymphadenopathy and peripheral arthritis are the most frequent with a prevalence of 25-50%. Cardiac and neurological manifestations which can be the initial manifestation of sarcoidosis, as can be bilateral parotitis, nasosinusal or laryngeal signs, hypercalcaemia and renal dysfunction, affect less than 10% of patients.

There may be nonspecific constitutional symptoms or organ-specific symptoms. About a third will have a nonspecific presentation with fever, fatigue, cachexia and lassitude.

An acute presentation is more common in white patients, as is remission of disease about two years after presentation. About 10-30% of patients will have a chronic, progressive pattern of disease.

Black patients have more serious pulmonary involvement with a poorer long-term prognosis and an increased frequency of relapses.

Constitutional upset

- Fever and night sweats, malaise, fatigue, weight loss.
- Heerfordt's syndrome (inflammation of submaxillary/parotid glands with uveitis and facial nerve palsy) may accompany constitutional presentation.[8]

Lung[4]

- The lungs are affected in more than 90% of people with sarcoidosis.
- Pulmonary function studies are abnormal in many patients with sarcoidosis but there is no diagnostic pattern.
- A restrictive pattern is usually seen as a result of diffuse parenchymal lung disease.
- However, airflow obstruction is found in a significant proportion of people with pulmonary sarcoidosis..

- Patients may present with dry cough, fever and dyspnoea accompanied by chest discomfort.

Skin

- This is commonly affected. Sarcoidosis may cause a diverse variety of skin manifestations and may resemble both common and rare cutaneous diseases.[9]
- Papules may be seen on the face and resembling rosacea or maculopapular rashes on the body or extremities. Brownish-red infiltrative plaques on the extremities and trunk may be present (very similar in appearance to plaque psoriasis).
- Erythema nodosum on the legs is a relatively common feature. Löfgren's syndrome refers to the combination of erythema nodosum with arthritis (commonly affecting the ankles) and bilateral hilar or paratracheal adenopathy seen on CXR.
- Lupus pernio is a violaceous, soft infiltration affecting the nose and cheeks that is uncommon but pathognomonic.

The eye

- This is affected in >20% of cases, most frequently as a granulomatous uveitis.
- Anterior uveitis is frequently of limited duration but posterior uveitis tends to be more persistent.
- Dry eyes and glaucoma can appear years after other symptoms have disappeared.
- The optic nerve may be affected but severe sight impairment is rare.

Neurosarcoidosis

- Infiltrative nerve lesions can affect any part of the central or peripheral nervous system, leading to a huge variety of neurological disease.
- Bell's palsy and lymphocytic meningitis are common manifestations of neurological involvement but diabetes insipidus is also seen.

- The following symptoms are encountered relatively commonly as a result of neurological involvement:

    - Facial numbness, dysphagia, hoarseness, headache, visual field defects, polydipsia, hearing impairment, lesions of cranial nerves VII, VIII, IX and X, bitemporal hemianopia due to optic chiasmal involvement, seizures, stroke/transient ischaemic attack (TIA), peripheral neuropathic lesions.

Heart disease

This can (rarely) cause sudden death from arrhythmias or cause symptoms of heart failure in a young patient, due to cardiomyopathy.[10]

Lymphadenopathy

This is commonly picked up on CXR but may be symptomatic and affect the axillary, cervical, and inguinal nodes and those around the salivary glands.

Liver

There may be deranged LFTs but symptoms are rare, causing significant hepatitis in <10% cases.

Hypercalcaemia and hypercalciuria

Caused by humoral effect of granulomata on vitamin D3 metabolism. Can cause nephrolithiasis, neuropsychiatric disturbance, abdominal pain and bone pain.

Joints

It tends to present as an inflammatory arthritis (often oligoarticular initially) with periarticular soft-tissue swelling, tenosynovitis, dactylitis, osteopenia and associated myopathy.

Other organs/systems

Other areas that are more rarely involved and the symptoms they cause are listed here:

- Bone marrow (leading to anaemia, immunosuppression).
- Spleen (causing abdominal discomfort and distension due to splenomegaly).
- Upper respiratory tract (causing nosebleeds, rhinitis, nasal obstruction/masses or tonsillar involvement).
- Salivary glands (causing facial swelling and pain and other symptoms of parotitis).

Signs of sarcoidosis

In a patient who is suspected of having sarcoidosis, the following examination scheme will give a good chance of detecting any relevant signs that may suggest or confirm the diagnosis:

Skin

Carefully examine the skin all over, looking for characteristic rashes. Lupus pernio (chronic raised hardened, often purple lesion) may be seen on the face, and the shins should be looked at to detect erythema nodosum. Old scars or tattoos may show granulomatous infiltrative lesions.

Eyes

Look carefully at the eyes to detect signs of uveitis, dry eyes or conjunctival infiltrates. Consider slit-lamp examination if any abnormalities are found (this usually needs expert input).

Joints and muscles

Examine any painful joints and muscles and characterise the nature of the problem and affected structures.

Head and neck

Check for lymphadenopathy, salivary gland swelling, tonsillar enlargement/inflammation and patency/abnormality of nasal passages if there are any relevant symptoms.

Abdomen

Check for hepatomegaly and splenomegaly.

Cardiorespiratory

Chest signs of sarcoidosis are usually not detected unless advanced interstitial lung disease is present, when there may be scattered crackles. Check the pulse to detect any rhythm disturbance. Look for signs of heart failure.

Nerves/central nervous system (CNS)

Check the function of the VIIth and other cranial nerves and peripheral sensory/motor nerve function to detect peripheral neuropathy. Formal neurological examination is appropriate if there are relevant symptoms.

Differential diagnosis

The differential diagnosis is huge depending on the type of presentation, affected organs, age of the patient and ethnic origin/recent travel history. The diagnoses listed below have frequent, overlapping clinical and investigational features with sarcoidosis and are important to consider or exclude where relevant:

- Rheumatoid arthritis.
- Lymphoma.
- Metastatic malignancy.
- Tuberculosis.
- Multiple sclerosis.
- Lung cancer.
- Systemic lupus erythematosus.
- Other causes of interstitial (parenchymal) lung disease, including idiopathic pulmonary fibrosis.
- Multiple myeloma.
- Eosinophilic granulomatosis with polyangiitis (EGPA).

Investigations

The diagnosis of sarcoidosis can occasionally be made on clinical grounds without a confirmatory biopsy when very specific clinical findings are present. Otherwise the diagnosis requires histological evidence of granulomatous inflammation, exclusion of alternative causes, and evidence of systemic disease.[11]

Isolated involvement of a single organ or organ system is rare in sarcoidosis. Therefore, all patients must be thoroughly assessed for additional disease manifestations.[5]

- Blood tests:
    - FBC may show raised white count/eosinophilia or lymphopenia. Anaemia may be seen.
    - ESR is often raised (~ 65% of cases).
    - Check U&E, creatinine (renal impairment is quite rare) and serum calcium (elevated in 10-15% of cases). Phosphate and alkaline phosphatase may be increased. LFTs may show derangement.
    - If calcium is elevated then 24-hour urinary collection may demonstrate hypercalciuria.
    - Serum angiotensin-converting enzyme (ACE):
        - Levels are elevated in around 60% of patients with acute disease and reduce in response to treatment or resolution of the disease.
        - The serum ACE level has only a limited role in diagnosis and does not contribute to monitoring patients with pulmonary sarcoidosis when added to serial lung function and imaging.[12]
- The tuberculin skin test (Mantoux) is classically negative in patients with sarcoidosis. A positive test result raises the possibility of tuberculosis.[13]

- Plain CXR may show bilateral hilar or paratracheal lymphadenopathy. High-resolution CT scanning is often used to detect interstitial lung disease.
- Lung function tests show restrictive defect in severe, progressive cases (shrinking lung syndrome).
- ECG is important to check for early signs of rhythm disturbance due to conducting system disease or effects of hypercalcaemia. 24-hour ECG may be used to detect paroxysmal rhythm disturbance.
- Pulmonary sarcoidosis:
    - Bronchoalveolar lavage findings: increased lymphocytes, especially raised CD4:CD8 ratio, can help to clinch diagnosis in the correct circumstances.
    - Transbronchial biopsy can demonstrate the presence of non-caseating granulomata, giving a more accurate diagnosis.
    - For patients with suspected stage I or II (see 'Staging', below) pulmonary sarcoidosis undergoing tissue confirmation, the use of endosonographic nodal aspiration has been shown to provide greater diagnostic yield compared with bronchoscopic biopsy. [14]
- Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) can be used to assess inflammatory activity accurately in patients with unexplained, persistent, disabling symptoms without serological inflammatory activity. It can help to predict pulmonary deterioration at one year and the pulmonary improvement expected after treatment. [2]
- Gallium scanning may be used to detect extrapulmonary disease and tends to reveal a 'lambda' pattern.
- Diagnosis may be achieved by biopsy of any suspicious skin lesions or accessible lymph nodes. There will be multiple non-caseating epithelioid granulomata.
- Formal ophthalmological examination is recommended for all newly diagnosed cases.

Kveim's test (intradermal injection of splenic material from a confirmed case of sarcoidosis, and histological examination of any nodule formed) has fallen out of favour due to the risk of transmission of new-variant Creutzfeldt-Jakob disease (nvCJD), and the several weeks it takes to get a diagnosis.

Staging[15]

Traditionally, pulmonary involvement has been classified into five stages based on CXR findings. The prognostic value of this classification in children is uncertain. Note that CXR may also demonstrate pleural involvement, such as a pneumothorax or pleural effusion.

- Stage 0 - normal findings on chest radiograph.
- Stage I - bilateral hilar lymphadenopathy (which may be accompanied by paratracheal adenopathy).
- Stage II - bilateral hilar adenopathy with pulmonary infiltrates (parenchymal involvement or reticular opacities).
- Stage III - parenchymal infiltrates without hilar adenopathy.
- Stage IV - parenchymal involvement turns into volume loss (pulmonary fibrosis) and there may be other features (cavitations, calcifications, hilar retraction, bullae, cysts and emphysema).

Sarcoidosis treatment and management[16] [17]

- About half of patients with sarcoidosis will need systemic therapy for their disease.
- Oral glucocorticoids are the standard first-line treatment for sarcoidosis. With time, patients might develop substantial morbidity from long-term use of high doses of glucocorticoids.
- The antimetabolites (eg, methotrexate, azathioprine, leflunomide and mycophenolate) are considered second-line agents and used as alternatives to steroids.
- For patients who cannot be treated with low-dose glucocorticoids and an antimetabolite, anti-tumour necrosis factor (TNF) monoclonal antibodies have been shown to control disease. Infliximab and adalimumab are considered as third-line agents.

- Unfortunately, anti-TNF drugs are associated with substantial toxic effects and in some cases are ineffective.
- The next step in treatment includes other therapeutic options such as rituximab.

Pulmonary disease

Treatment is mainly symptomatic and the mainstay remains the use of oral corticosteroids.[18]

- Patients with early disease (hilar lymphadenopathy only) often do not require any therapy.
- Consideration of prophylaxis against osteoporosis with bisphosphonate drugs is recommended but calcium and vitamin D are usually avoided due to the risk of hypercalcaemia in sarcoidosis.
- Given the significant morbidity attributable to long-term use of steroids, they should be given with extreme caution and under expert monitoring in patients with pulmonary sarcoidosis.
- There is no current evidence of any efficacy for inhaled corticosteroids.

Surgical intervention may be considered in extreme cases of fibrotic lung disease with life-threatening haemoptysis. Lung transplantation has also (rarely) been used.

Extrapulmonary disease[18]

Corticosteroids are also the initial drug of choice to treat most forms of extrapulmonary sarcoidosis.

Cardiac sarcoidosis[19]

Treatment of cardiac sarcoidosis is often multifactorial, involving a combination of therapy for sarcoidosis with treatment for cardiac arrhythmias and/or heart failure in addition to device placement and cardiac transplantation.

Eye sarcoidosis

- May cause an isolated anterior uveitis confined to the anterior chamber. Topical corticosteroids (eye drops) can then be used without oral corticosteroids.
- If there is an associated intermediate and/or posterior uveitis then oral corticosteroids will be required.
- Intraocular corticosteroid injections may be given when eye sarcoidosis extends deeper than the anterior chamber.
- A shorter course (eg, 3-6 months) of corticosteroids for sarcoid uveitis is usually recommended because both sarcoidosis and corticosteroid therapy can lead to cataracts and glaucoma. Corticosteroid-sparing agents are therefore considered earlier than with other forms of sarcoidosis.
- Sarcoidosis may cause an acute optic neuritis which is vision-threatening. High-dose intravenous corticosteroids should be strongly considered.

Neurosarcoidosis
Neurosarcoidosis is relatively refractory to corticosteroids. It has therefore been recommended by some authorities that the initial corticosteroid dose for neurosarcoidosis should be 40-80 mg of daily prednisolone equivalent.

Skin

- Cutaneous sarcoidosis almost never causes significant medical problems and is, therefore, treated only if it is of cosmetic importance to the patient. The initial corticosteroid dose is 20-40 mg of daily prednisolone equivalent.
- For one or a few small lesions, intralesional injections of triamcinolone acetonide are often effective. Topical corticosteroid creams may also be used but are probably not as effective as intralesional injections.
- Lupus pernio is disfiguring. Although lupus pernio lesions usually improve with corticosteroid therapy, these lesions usually require infliximab therapy for significant resolution.

Joint
Non-steroidal anti-inflammatory agents should be used prior to consideration of corticosteroid or other immunosuppressive therapy.

Complications[4] [15]

Complications occur according to the organ affected but are subject to variability in incidence and severity.

Pulmonary

- Infections.
- Pulmonary embolism.
- Progressive fibrotic lung disease leading to death.
- Pulmonary hypertension.

Cardiac

- Cardiac arrhythmia and sudden death.
- Cardiac failure.

Ocular

- Uveitis and conjunctivitis.
- Severe sight impairment (rare).
- Ocular sicca syndrome.

Skin

Chronic refractory skin disease.

Liver

Commonly involved but rarely clinically significant.

Nervous system

- Cranial and peripheral nerve damage.
- Neuropsychiatric illness.
- Permanent CNS impairment.
- Stroke/TIA.

Ear, nose and throat

- Salivary gland dysfunction.
- Nosebleeds, nasal obstruction.

Others

- Lymphatic (evidence of hypersplenism).
- Sarcoidosis can be associated with increased incidence of lymphoma.[2]
- Hypercalcaemia.
- Nephrolithiasis.
- Arthritis and joint damage.

Prognosis[2] [20]

Although many patients have sarcoidosis which resolves spontaneously, a significant proportion of patients have chronic or progressive disease with resultant morbidity. About 20% of patients have permanent clinical symptoms because of irreversible fibrosis, mainly pulmonary fibrosis.

Patients with sarcoidosis have a lower survival rate than that of the general population. Premature death is most often due to advanced pulmonary fibrosis and less often due to cardiac, CNS and hepatic involvement. However, only approximately 1-5% of patients with sarcoidosis die as a result of complications of sarcoidosis.

Most patients with advanced lung disease die from respiratory failure, pulmonary hypertension or both. Other causes of death include haemoptysis from aspergilloma.

Sarcoidosis prevention

Although sarcoidosis cannot be prevented, some preventative measures may reduce complications. For example:

- Influenza vaccination.
- Osteoporosis prophylaxis (steroid usage).

- Patient education (early treatment of extrapulmonary complications such as uveitis and arrhythmias).
- Smoking cessation advice (although evidence is lacking to show it causes deterioration in pulmonary sarcoidosis).

Further reading

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Last updated by: Dr Colin Tidy, MRCGP 15/08/2022	
Peer reviewed by: Dr Hayley Willacy, FRCGP 15/08/2022	**Next review date:** 14/08/2027

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