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# Sarcoidosis and anaesthesia

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### Key points

- Sarcoidosis is a multisystem inflammatory disease with variable presentation occurring with an incidence of 3000 new cases per year in the UK. The pulmonary system is involved in over 90% of cases.
- The supraglottic region is commonly the site of sarcoid infiltration, and hilar lymphadenopathy can cause vocal cord palsy. Careful airway assessment is advised.
- Hypercalcaemia is the result of activated macrophages producing excess 1,25-dihydroxyvitamin D3, and can cause nephrocalcinosis. Renal function should be checked before operation.
- There is no definitive treatment but patients will often be receiving high-dose steroids or immunosuppressant drugs with concomitant side-effects.
- Preoperative assessment should focus on the airway, pulmonary, cardiac, and renal systems.

Mr D, a 65-yr-old gentleman, presented with a hoarse voice in July 2008. Computerized tomography (CT) scan of his head, neck, and thorax confirmed right vocal cord palsy, but no cause was identified. Blood chemistry was normal. Over the next 2 yr, ENT repeatedly reviewed Mr D and found no cause for the vocal cord palsy.

In June 2010 he was booked for a right vocal cord fat augmentation and presented to the anaesthetic pre-assessment clinic. Blood tests at this appointment revealed a raised urea (12.3 mmol litre$^{-1}$) and a raised creatinine (170 μmol litre$^{-1}$). ECG showed a right bundle branch block (RBBB). No action was taken. He was admitted for surgery in October 2010 and seen before operation by a consultant anaesthetist who made no record of his blood results. Surgery was uneventful and Mr D was discharged home the same day. No GP follow-up of the abnormal renal function was arranged.

Four months later Mr D was admitted with severe malaise, complaining of itch, cramps, and dizziness. Blood chemistry was grossly abnormal (creatinine 391 μmol litre$^{-1}$, urea 17.3 mmol litre$^{-1}$, $Ca^{2+}$ 3.48 mmol litre$^{-1}$). After treatment with i.v. fluids and bisphosphonates, he underwent multiple investigations to elicit the cause of his hypercalcaemic renal failure.

Renal biopsy showed severe scarring with microcalculi in the interstitium and CT scanning identified significant mediastinal and upper abdominal lymphadenopathy. These were sampled at endobronchial ultrasound and confirmed non-necrotizing granuloma consistent with a diagnosis of sarcoidosis.

Mr D was commenced on prednisolone, which normalized the calcium levels with concomitant improvement in renal function and was referred to the chest physicians for ongoing care. Pulmonary function testing elicited respiratory involvement with TLCO (transfer factor for carbon monoxide) reduced to 67% of predicted. Echocardiogram was normal.

### Key learning points

- Anaesthetists have a responsibility to check and document blood results before operation
- New deterioration in renal function always warrants further investigation of the cause
- Prolonged hypercalcaemia can cause nephrocalcinosis and irreversible renal scarring
- Vocal cord palsy can be caused by mediastinal lymphadenopathy

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## Introduction

Sarcoidosis, a term originally coined by Boeck in 1899, is a multisystem inflammatory disease characterized by tissue infiltration with T lymphocytes, mononuclear phagocytes, and non-caseating granulomas. Pulmonary involvement is almost universal. Sarcoid is subject to ethnic, geographic, seasonal, and immunogenetic variability, which confers a variable prevalence of 4.7–64/100 000.[1] The highest incidence is seen in northern European and African-American individuals.[1] In the UK, each year there are about 3000 new diagnoses of sarcoid. Despite extensive research, the exact cause of sarcoidosis remains unknown but the generally accepted view is that it results from the exposure of a genetically susceptible individual to an environmental trigger that produces a Th1-type inflammatory response. A variety of triggering agents have been suggested including inorganic dusts and infectious agents such as mycobacterium.

An interesting case is the higher incidence of sarcoidosis observed in New York firefighters after the World Trade Centre was destroyed in 2001,[2] supporting the suggestion that dust exposure may be a factor.[1]

Patients with sarcoidosis may require anaesthesia for diagnostic procedures (e.g. mediastinoscopy or lung biopsy), for treatment of airway complications of the disease, such as bronchial stenosis, or, as the disease course is long, they may require incidental surgery.

The aim of this article was to outline the pathophysiological and clinical features of sarcoid and highlight the implications for the anaesthetic management of these patients.

### Pathogenesis

The key immunopathogenic process in sarcoid is an excessive host immune response to an antigen with the subsequent formation of non-caseating granulomas. The antigen may be microbial or an organic or inorganic substance. Granulomas contain a central core composed of epithelioid cells, macrophages and multinucleated giant cells, surrounded by fibroblasts, B-cells and CD8 T-cells.[3] $CD4^+$ T-cells and epithelioid cells subsequently interact and drive the formation and maintenance of granulomas through secretion of interleukin-2, interferon-$\gamma$ and TNF-$\alpha$, which all serve to amplify the local immune response. Granulomas may persist, resolve without sequelae or lead to irreversible fibrosis.

### Genetics

Major histocompatibility class II alleles affect the course of the disease. HLA DR3 carries a better prognosis with spontaneous resolution, whereas HLA DR14 and HLA DR15 carry a worse prognosis. Genome-wide association studies have shown other loci that are associated with increased risk, for example, butyrophyllin-like 2 (BTNL2) and ANXA11[1] genes. Thus genetic susceptibility to sarcoidosis depends on multiple genes, the presence of which in combination can substantially enhance risk.

### Clinical presentation and diagnosis

The presentation of sarcoidosis is very variable and dependent on the pattern of organ involvement. A significant proportion of patients are asymptomatic and sarcoidosis is detected as an incidental finding, often when a chest radiograph is performed for other reasons. Constitutional symptoms such as malaise, fever, and weight loss are common. When symptomatic, pulmonary involvement usually causes cough and dyspnoea. There are a number of 'classic' presentations such as Löfgren's syndrome (hilar lymphadenopathy, erythema nodosum, fever and arthralgias), and Heerfordt's syndrome (parotits, uveitis, fever and facial palsy). Organ specific features will be reviewed below. Initial investigation will include a full blood screen, urinalysis, ECG, lung function tests and CT scanning.

Three quarters of patients have an elevated serum angiotensin-converting enzyme concentration.[4] This is neither specific nor sensitive and therefore of little value in diagnosis or disease severity marking. Chitotriosidase is a more useful marker. It is an enzyme produced by activated macrophages, which degrades chitin and is elevated in sarcoidosis.[5]

Where the clinical and radiographic features are characteristic further investigation may not be pursued, but otherwise a biopsy from the relevant site is obtained to look for evidence of non-caseating granuloma, and to exclude other conditions such as tuberculosis or lymphoma. Endobronchial ultrasound-guided mediastinal lymph node biopsy is widely used for diagnosis and has a diagnostic yield of 85%.[3]

Further imaging such as nuclear medicine gallium scanning, positron emission tomography (PET) scanning, and contrast-enhanced magnetic resonance imaging (MRI) may be required occasionally, the latter particularly where neurosarcoid is considered.

The prognosis of sarcoidosis is very variable. The condition will resolve spontaneously in many patients, but in up to one-third of patients a more protracted course may occur and require specific treatment. Lofgren's syndrome often remits rapidly and spontaneously but more chronic presentations are more likely to require treatment and longer term monitoring. If the disease persists beyond 5 yr, remission is unlikely. Disability and death are most likely to result from pulmonary, cardiac, or neurological disease.

## Systems involvement

### Upper respiratory tract

Mucosal infiltration of the nose, nasopharynx, tonsils, or larynx occurs in ~5% of cases.[6] The epiglottis and ary-epiglottic folds are the most common site of infiltration. Interestingly the cords are often spared. Patients may present with dyspnoea, stridor, dysphagia, or with obstructive sleep apnoea (OSA).[7] Occasionally laryngeal involvement may be severe enough to necessitate emergency tracheostomy.[8]

The incidence of bronchospasm is increased and 38% of those with sarcoid granulomata in the bronchial tree demonstrate airway hyper-reactivity to methacholine.[9]

### Pulmonary

Pulmonary involvement is seen in over 90% of cases.[3] The radiographic pattern is often used to stage the disease although this staging does not describe the course of disease in any individual patient: Stage I disease describes isolated hilar and mediastinal adenopathy, stage II adenopathy and parenchymal involvement, stage III parenchymal involvement without adenopathy, and stage IV lung fibrosis. The parenchymal changes are distributed in a peribronchovascular and perilymphatic pattern and include reticulonodular and nodular opacities, ground glass opacities, and sometimes larger nodules. Typically they show a mid- and upper zone predominance. These changes may resolve or progress to irreversible scarring. Pleural inflammation may occur but complications such as effusion are uncommon.

Lung function tests may show a restrictive or an obstructive pattern and often correlate poorly with radiological evidence of disease. There is a reduced diffusing capacity and a reduction in

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lung compliance which progresses with the time course of the disease.

Pulmonary hypertension is not uncommon in advanced sarcoidosis and is largely the result of fibrosis of the distal capillary bed, chronic hypoxaemia, or both. Compression of the pulmonary arteries by adenopathy and left ventricular diastolic dysfunction also contribute to the development of pulmonary hypertension. Its presence significantly worsens prognosis (Figs 1 and 2).

### Cardiac

Cardiac sarcoidosis is related to granulomatous infiltration of the myocardium and conducting tissue, and is much more common than clinically appreciated. In Japan, it is found in 50% of cases of sarcoidosis at post-mortem examination.[3] Clinical presentation varies from asymptomatic to palpitations to sudden death. Supraventricular arrhythmias occur in about a third of patients[10] with atrial fibrillation being the commonest rhythm disturbance. The QT interval is prolonged[11] and may cause ventricular arrhythmias, particularly premature ventricular contractions (PVCs). Degrees of atrioventricular block are also common and implantable pacemakers or an internal cardioverter defibrillator may be required. Cardiomyopathy may lead to congestive cardiac failure and be life-threatening.

### Renal

Renal sarcoid takes two main forms. The first is an acute granulomatous interstitial nephritis. The second, seen in 10% of patients with sarcoid[12] is nephrolithiasis and nephrocalcinosis caused by abnormal calcium metabolism. Activated macrophages within the granulomas produce large amounts of 1,25-dihydroxyvitamin D3. The excess 1,25-dihydroxyvitamin D3 increases absorption of dietary calcium, which is then partially excreted in the urine. The hypercalciuria and hypercalcaemia eventually cause nephrolithiasis and nephrocalcinosis. If untreated, renal calcium deposition may lead to chronic renal failure.

### Liver and spleen

Liver involvement is often asymptomatic but occasionally presents as cholestasis, hepatic failure or portal hypertension. Fifteen per cent of patients have splenic lesions on CT.[13]

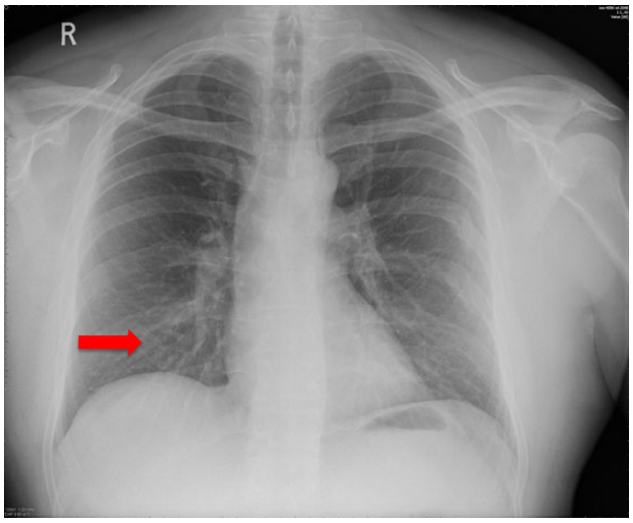


Fig 1 Plain AP chest radiograph showing typical reticulonodular shadowing.

### Haematological

Forty per cent of patients have anaemia, leukopenia, or both, and lymphopenia. Thrombocytopenia is rare unless there is gross splenic involvement.

### Ocular

Twenty-five to 80% of patients with sarcoid have eye involvement[13] often preceding the diagnosis of sarcoidosis by many years. Chronic anterior uveitis is more common than its more painful acute counterpart.

### Neurosarcoidosis

Neurosarcoidosis is often asymptomatic but is detected in a quarter of post-mortem cases and can affect any part of the nervous system.[3] Cranial nerve involvement is the commonest presentation with the optic and facial nerves most affected. Pituitary sarcoid can lead to decreased antidiuretic hormone production and disordered thirst. Small fibre neuropathy can affect all nerves including the autonomic system.

## Treatment

There is no cure for sarcoidosis; treatment modifies only the course of the granulomatous process. Patients who are asymptomatic can be monitored in the hope of spontaneous remission; otherwise, steroids remain the first-line treatment option. Moderate doses are used in most cases (20–40 mg day$^{-1}$ for an adult), but high doses are given when there is life-threatening disease such as acute respiratory failure, neurological deficit, or cardiac disease. The dose is maintained until disease activity is controlled, and then reduced. Maintenance treatment is often continued for 12 months in the first instance. Patients may experience side-effects such as weight gain, diabetes, osteoporosis and increased susceptibility to infection.

Where there is evidence of disease progression despite glucocorticoid therapy, or where the dose cannot be weaned to a low

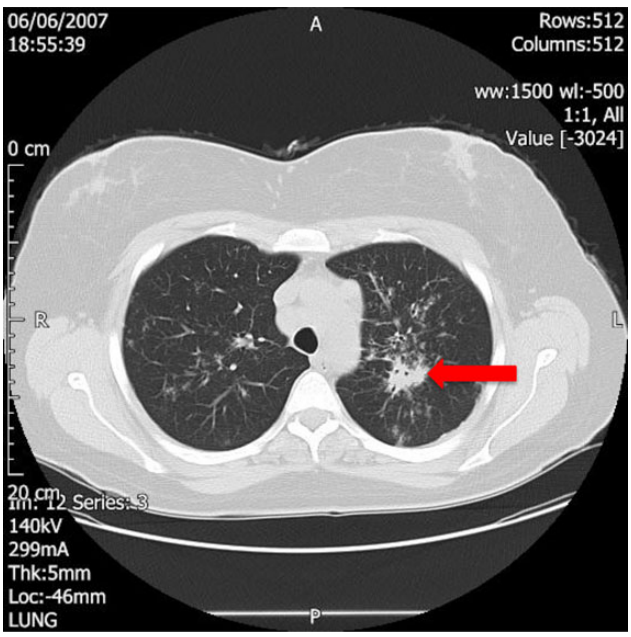


Fig 2 CT thorax showing the 'galaxy sign' particularly evident in the left lung.

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Table 1 Common Drug Therapy for sarcoidosis. CXR, chest X-Ray; LFT, liver function test; LMWH, low molecular weight heparin; NDMRs, non depolarising muscle relaxants; PFTs, pulmonary function tests; RSI, rapid sequence induction; U&E, urea & electrolytes

| Drug | Side-effects | Anaesthetic considerations |
|---|---|---|
| Prednisolone | Weight gain<br>Hypertension<br>Osteoporosis<br>Fragile skin<br>Impaired glucose tolerance<br>Immunosuppression<br>Electrolyte abnormalities<br>Reflux | Preoperative electrolyte correction<br>Impaired stress response-steroid replacement required<br>Sliding scale if diabeticRSI if significant reflux<br>Careful intra operative positioning |
| Methotrexate | Liver and renal toxicity<br>Interstitial pneumonitis<br>Myelosuppression<br>Immunosuppression | Preoperative assessment of respiratory function including PFTs and CXR<br>Preoperative FBC/U &E, LFT<br>Avoid nephrotoxic drugs<br>Low threshold for prophylactic antibiotics |
| Leflunomide | GI side-effects<br>Liver toxicity<br>Neutropenia<br>Hypertension<br>Neuropathy | Preoperative FBC, U&E, LFTs<br>Avoid hepatotoxic drugs<br>Baseline BP before operation<br>Preoperative documentation of any neurological deficit |
| Azathioprine | GI side-effects<br>Liver toxicity<br>Myelosuppression | Preoperative FBC, U&E, LFTs<br>Avoid hepatotoxic drugs<br>Antagonists of NDMRs may require higher doses<br>Low threshold for prophylactic antibiotics |
| Thalidomide | Teratogenicity<br>Venous thrombosis<br>Neuropathy<br>Drowsiness<br>Bradycardias<br>Hypotension | Use of LMWH<br>Cautious use of anaesthetic anti-thromboembolism stockings agents as may have an increased tendency to bradycardias, hypotension, and a slower recovery from anaesthesia. |
| Infliximab | Myelosuppression<br>Increased risk of malignancy and serious infections | Preoperative FBC, U&E, LFTs<br>Low threshold for prophylactic antibiotics |

level, alternative immunosuppressant agents are considered. The evidence base for many of these is poor with the literature mainly being case series. Methotrexate is the most commonly prescribed second-line therapy. It can cause interstitial pneumonitis compounding sarcoid lung disease. Other cytotoxic agents are sometimes used: azathioprine, leflunomide, cyclophosphamide, and mycophenolate, for example. These agents cause neutropenia, liver toxicity, renal toxicity, and GI side-effects. The concomitant use of NSAIDs requires caution.

If these fail to control the disease, then cytokine modulators can be added. Pentoxyphyllin is a phosphodiesterase type 4 inhibitor used as an anti-inflammatory and T-cell inhibitor. Its use is steroid sparing. Thalidomide is used for severe skin sarcoidosis, and infliximab for central nervous system, skin, and eye lesions. Occasionally, anti-malarials are prescribed for mild hypercalcaemia or skin involvement in preference to corticosteroids (Table 1).

## Perioperative management

### *Preoperative assessment*

Given the multisystem nature of sarcoidosis, a meticulous work up is essential and this is best done at a scheduled visit to an anaesthetic pre-assessment clinic. Thorough history, examination, and notes review will elucidate the main systems involved.

History taking should follow a systems approach. Dysphagia, dysphonia, stridor, and noisy breathing may suggest airway involvement and the Stop-Bang scoring system can provide a useful measure of severity of OSA.[14] Symptoms of exertional dyspnoea, chest pain, or palpitations should be sought and investigated. An assessment of functional status is vital and is very representative of respiratory and cardiovascular functioning.

A detailed drug history is important. Steroids can suppress the hypothalamic–pituitary–axis, and many patients with active sarcoidosis will be taking moderate to high doses of glucocorticoids. An early morning cortisol assay or ACTH stimulation test can be useful in determining the extent of suppression.

Routine examination should include the respiratory and cardiovascular systems but if regional anaesthesia is planned pre-existing neurological deficit should be sought and carefully mapped.

Simple investigations can be very informative. Routine blood tests should include FBC, urea & electrolytes (U&E), liver function test (LFT), and serum calcium. Particular attention should be paid to the kidney in order to avoid postoperative renal complications. The serum calcium should be brought into the normal range before anaesthesia. Methods available to achieve this are ketoconazole, bisphosphonates, and calcitonin infusion. LFTs are important because many of the drug treatments cause hepatic inflammation or toxicity.

An ECG will act both as a baseline and serve to highlight any conduction disturbance. If suspected, a period of Holter monitoring can be used before elective surgery. Frequent PVCs are associated with a prolonged $QT_c$ interval. ECG changes of right ventricular hypertrophy with strain should alert the anaesthetist to the possibility of pulmonary hypertension and an

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echocardiogram is mandatory if any degree of pulmonary hypertension or cardiomyopathy is suspected. Specialist review by a cardiologist may be sought with a view to MRI, PET scan, or angiography. Higher degrees of heart block may require pacing before operation.

Symptomatic pulmonary involvement is best assessed formally with pulmonary function tests rather than chest X-Ray alone as radiological signs and functional status may be disparate. Cardio-pulmonary exercise testing may be useful in this group, especially if there is cardiac involvement, to assess perioperative risk and plan postoperative care.

For patients presenting with laryngeal involvement preoperative flexible nasendoscopy and CT of the neck and thorax will help delineate the level of involvement and guide airway planning.

### Intraoperative

#### *Conduct of anaesthesia*

Routine use of AAGBI monitoring is recommended. The need for additional invasive monitoring will depend on the patient and the operation, and the usual considerations apply. If cardiac sarcoid is suspected or diagnosed, then the CM5 ECG configuration (right arm lead on manubrium, left arm lead on V5, and indifferent lead on left shoulder) can aid the identification of ischaemia intraoperatively. Arrhythmias need to be recognized promptly and treated according to ALS guidelines. If severe pulmonary hypertension is present, right heart catheterization can be useful to guide specific treatment especially if the use of specific pulmonary artery vasodilators is planned.

For patients with laryngeal involvement, a strategy for airway management should be decided in conjunction with the ENT surgeons based on the results of preoperative investigations. A selection of airway equipment should be available. Microlaryngoscopy tubes and jet ventilation catheters may be particularly helpful. A short course of dexamethasone can help minimize postoperative oedema and postoperative observation in a high dependency area may be indicated.

Choice of anaesthetic agent is wide but should take into consideration the multisystem nature of the disease. For example patients with cardiac sarcoid may be sensitive to the negatively inotropic effect of induction agents and their dose should be tempered. Patients with pulmonary involvement may have reactive airways and benefit from avoidance of thiopental- and histamine-releasing agents such as morphine and atracurium. Drug dosing and choice may need to be altered if there is renal or liver involvement. Antibiotics should be given according to local guidelines especially as many patients will be taking steroids and other immunosuppressants. For patients on long-term steroids, hydrocortisone cover will need to be considered and dosed according to the grade of surgery.

Cutaneous sarcoid and the prolonged use of steroids accentuate the need for skin protection. Careful positioning is required too, partly owing to steroid thinned skin and partly owing to the potential presence of distal neuropathy.

Local, regional, or axial anaesthesia should be considered in those patients in whom general anaesthesia may exacerbate poor lung or cardiac function.

### Postoperative

Postoperative care depends upon the nature and site of the surgery and the disease pattern of the sarcoidosis. Potential difficulties include respiratory difficulty, arrhythmias, and renal impairment. High dependency or intensive care may be required.

For those with significant pulmonary disease, early involvement of the respiratory team and chest physiotherapy is advisable and postoperative oxygen therapy should be prescribed. Multi-disciplinary care is appropriate and desirable.

## Declaration of interest

None declared.

## MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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