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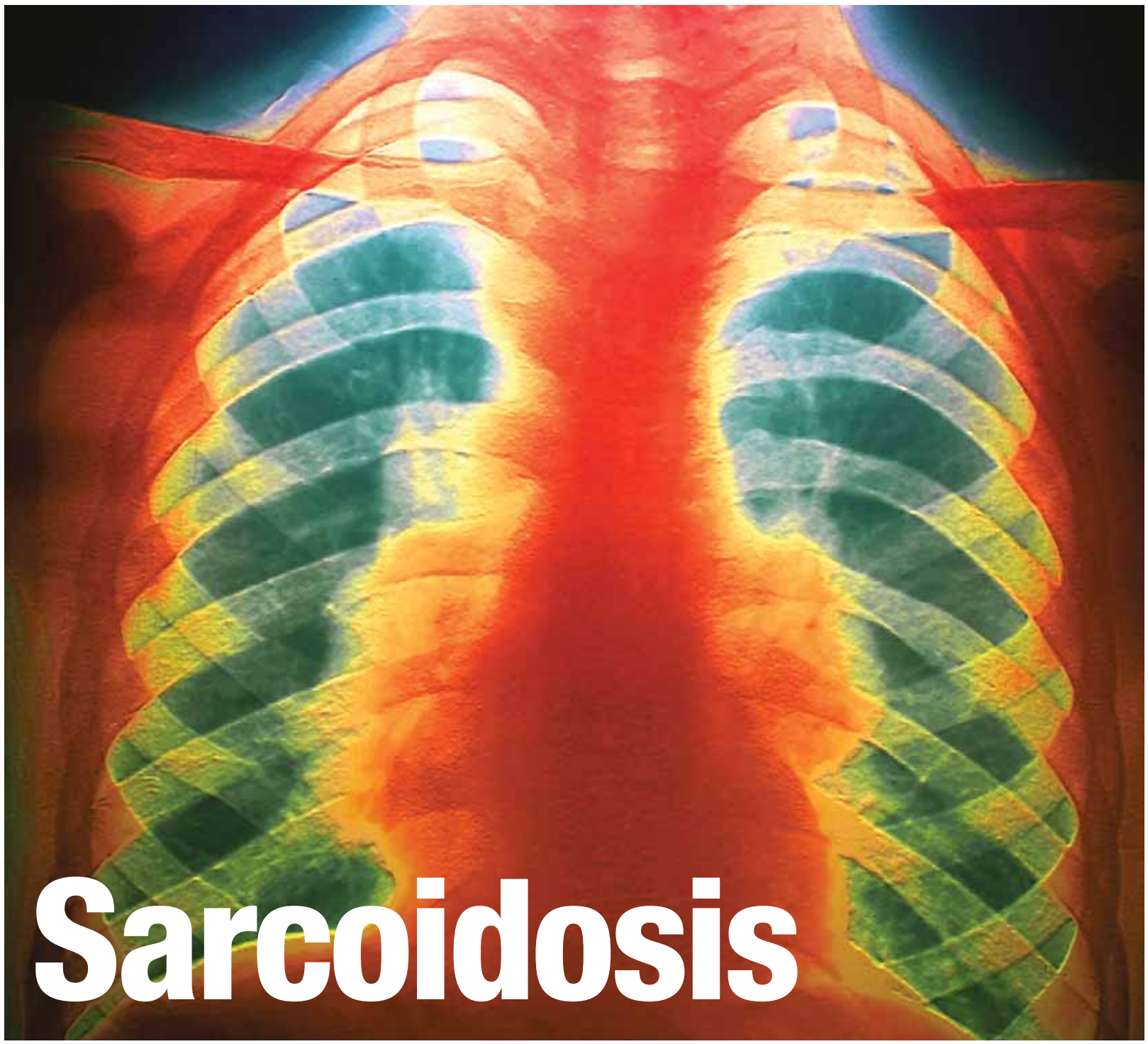

Sarcoidosis

The author

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Background

SARCOIDOSIS is a multisystem disorder of unknown aetiology characterised by non-caseating granulomas in affected organs. As described by Sharma, the granuloma can be thought of as the outcome of a 'battle fought on a genetically vulnerable terrain between an unrecognised antigen(s) and a highly organised team of lymphocytes and macrophages'.[1] It mainly involves the lungs, and it is mainly pulmonary involvement that results in most of the morbidity and mortality.

For most patients the outlook is good; indeed, it is unknown how many patients remain undiagnosed, with the disease remitting spontaneously. For some, however, the disease can be debilitating, with a significant impact on quality of life, or it can be fatal.

GPs are involved in initially recognising the disorder, as patients will present to them with respiratory, ocular or skin symptoms, or with an abnormal chest X-ray in the absence of symptoms. GPs will need to consider referral for both confirming the diagnosis and determining organ involvement and severity. They will be providing ongoing care of patients with mild disease who are being monitored, or patients with significant disease who are taking immunosuppressive drugs. This care is usually provided in conjunction with specialists.

Epidemiology and aetiology

Sarcoidosis was first described in 1887 but the term sarcoidosis was not used until much later. Hutchison (a dermatologist, ophthalmologist, venereologist, physician and surgeon who became president of many of the Royal Societies in these areas) provided the first description of the skin lesions, in a wharf worker. Boeck of Norway published the first case series

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in the late 19th century and used the term 'sarkoid' because the lesion resembled a sarcoma.

Excluding patients with stage I disease, sarcoidosis is the second most common interstitial lung disease. In the UK, general practice data suggest an incidence of about three per 100,000 person-years, with the incidence being higher in Scandinavian countries and in Afro-Caribbean people, and marginally higher in women.

The incidence peaks between the ages of 20 and 50, with a second increase in incidence at age 60. The disease is more common and severe in patients with an Afro-Caribbean background, and uncommon in people of Asian descent.

Despite much research, involving more than 700 patients and almost 30,000 relatives in a US study, no single aetiological factor or genetic locus has been found.[2] It is quite possible there are multiple causes of sarcoidosis, hence the various patterns of presentation. For example, patients presenting with an acute illness, lymphadenopathy and erythema nodosum (see Author's case study — The classic presentation: Löfgren's syndrome, page 31), are usually women and have specific polymorphisms of C-C chemokine receptor 2 and HLA-DQB1*0201. Patients without DQB1*0201 have a poorer prognosis.

Research has looked at infectious agents, such as TB, predisposing genes, cytokines and cellular abnormalities. Despite the cause not being found, there is now a much better understanding of the pathogenesis. A predominately T-lymphocyte alveolitis exists, and activated lymphocytes, along with recruited monocytes and macrophages form non-caseating granulomas in various organs. Calcium metabolism is disturbed, due to extra-renal production of calcitriol by the activated macrophages.

Occupational exposure has always been of interest, as beryllium causes a similar granulomatous process, but no clear link to any agent has been made. Firefighters may have a higher incidence of sarcoidosis than other people. Among firefighters involved in the World Trade Center collapse and cleanup, 26 patients with new-onset sarcoidosis or sarcoid-like granulomatous pulmonary disease were reported, with an estimated incidence of 86/100,000 in the first year after the World Trade Center collapse, and 22/100,000 per year over the next four years, compared with a background incidence of 15/100,000 per year. They also had a high incidence of asthma. This adds to the intrigue as to the cause of sarcoidosis.

Clinical picture

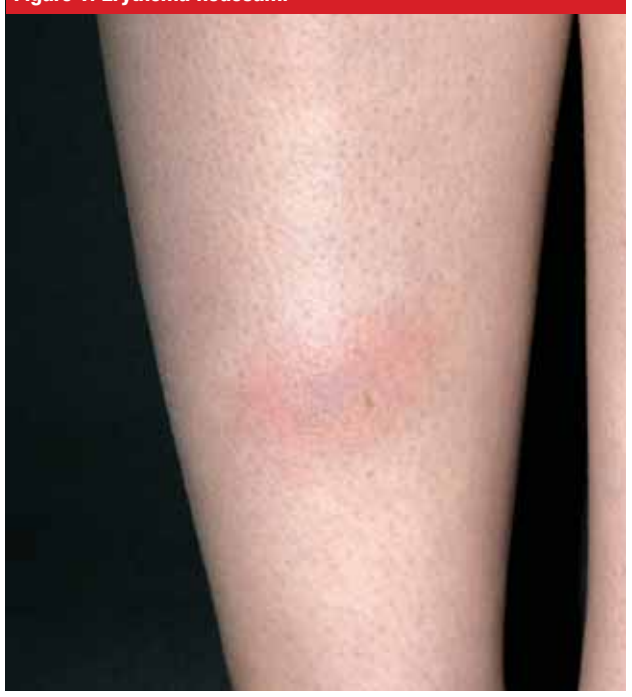
THE lungs are involved in most cases and are affected without other organ involvement in about 50% of patients; 30% of patients have extra-pulmonary involvement, with the skin, liver and eyes the most frequent sites involved (table 1).

Apart from organ-specific symptoms, fatigue, malaise, fever and weight loss are common. Elderly patients are more likely to present with systemic symptoms, including fatigue and anorexia. Occasionally a vasculitic presentation due to sarcoidosis is seen.

Table 1: Clinical features and organ involvement in sarcoidosis

System	Frequency of involvement	Clinical features
Intra-thoracic (lung and lymph nodes)	90% (only system involved in 50%)	Dyspnoea (25%), cough
Liver	50-80%	
Haematological	40% (mild leucopenia)	
Lymphoid system	33% (enlarged peripheral lymph nodes)	
Skin	15% erythema nodosum 5% lupus pernio	Painful nodules, chronic purplish lesions
Musculoskeletal	25-39% arthralgia	
Ocular	5% present with eye disease; significant involvement in up to 20%	Pain or asymptomatic involvement
Heart	5% infiltrate	Arrhythmia, sudden death
Endocrine	50% hypercalciuria 10-20% hypercalcaemia	
Renal, reproductive organs, CNS	Rare	Epilepsy, neuropathy

Figure 1: Erythema nodosum.



Pulmonary disease

The most common pulmonary — indeed overall — presentations are as described in the Author's case studies (page 31), with acute symptoms and signs of fever, malaise, erythema nodosum (painful lumps on the anterior aspects of the lower legs [Figure 1]) and arthralgia, or asymptomatic patients found to have an abnormal chest X-ray when performed for another reason.

Respiratory symptoms of a dry cough and dyspnoea are due to lung involvement. Only a small number of patients present with progressive disease and breathlessness; however, sarcoidosis would be an important differential for patients presenting with breathlessness who are found to have a diffuse process on their chest X-ray.

The site of involvement in the lung is frequently the bronchi (in the absence of symptoms or radiological changes), the interstitium and alveolar spaces but rarely the pleura.

Clinical examination findings in patients with an acute presentation may include fever and erythema nodosum. However, in many patients there is little to find, with clubbing being rare and crackles found in fewer than 20% of patients.

Pulmonary disease is classified on the basis of the chest X-ray. Staging provides insight into the prognosis, with worsening prognosis as the stage increases. Table 2 outlines the radiological stages of pulmonary sarcoidosis.

Table 2: Grading of pulmonary sarcoidosis based on chest X-ray findings

Grade	Chest X-ray findings
Stage 0	Normal
Stage I	Bilateral hilar lymphadenopathy (figure 2)
Stage II	Bilateral hilar lymphadenopathy and pulmonary infiltrates
Stage III	Pulmonary infiltrates alone (figure 3)
Stage IV	Lung fibrosis (figure 4)

The major differential diagnoses include TB, rare fungal infections and, in stage I disease where there is lymphadenopathy alone, lymphoma. With lung involvement, as noted, other forms of interstitial lung disease need to be considered.

Extra-pulmonary disease

Presentation with extra-pulmonary disease is less common but still accounts for up to 30% of presentations and, as with many other disorders, represents a challenge for GPs because they are at the frontline, as the first clinician to see many of these patients.

Skin involvement

Skin involvement is seen in up to 20% of patients and often appears early. Abnormalities include:

- A subacute maculopapular eruption involving the nose, lips, eyelids, forehead, rear hairline, and scars or tattoos.
- Waxy, pink nodular lesions, frequently distributed on the face, trunk, and extensor surfaces of the arms and legs.
- Chronic plaque-like lesions, including lupus pernio (a violet discolouration of the chin, ears, nose and cheeks).
- Erythema nodosum, which is a panniculitis and part of Löfgren's syndrome.

Although lupus pernio (*lupus* [wolf] because it eats away) may be characteristic, many other lesions are not, and an individual doctor's experience is likely to be limited. Therefore one should remain suspicious of lesions that fail to clear in a reasonable period of time, and look for other systemic symptoms or signs.

Eye involvement

Significant eye involvement is the presentation in 5% but actually occurs in up to 20% of patients. Findings include:

- Conjunctival follicles.
- Keratoconjunctivitis.
- Anterior uveitis.
- Posterior uveitis (chorioretinitis).
- Retinal vasculitis.

Secondary glaucoma, cataracts and blindness can be late complications in untreated patients. Sarcoidosis can also affect extra-ocular orbital tissues, including the lacrimal glands, extra-ocular muscles and optic nerve sheath, and may present as a soft-tissue orbital mass.

Liver involvement

Liver involvement is frequent but usually asymptomatic, or an enlarged liver may be noted. LFTs may show a raised alkaline phosphatase level.

Calcium metabolism

Changes to calcium metabolism are frequent and can lead to renal impairment and other problems if not dealt with. As noted previously, activated macrophages produce calcitriol. This leads to increased intestinal calcium absorption and probably increased bone resorption. This can be worsened by sun exposure.

Hypercalciuria occurs in 50% of patients, hypercalcaemia in 10-20% of patients and nephrocalcinosis in a smaller number. Normally the high serum calcium level should suppress parathyroid hormone (PTH) and therefore calcitriol; however, the extra-renal production of calcitriol is not under the control of this pathway. Chronic renal failure and end-stage renal disease can result from renal calcium deposition. Sar-

Figure 2: Stage I pulmonary sarcoidosis on posteroanterior (A) and lateral (B) chest X-ray.

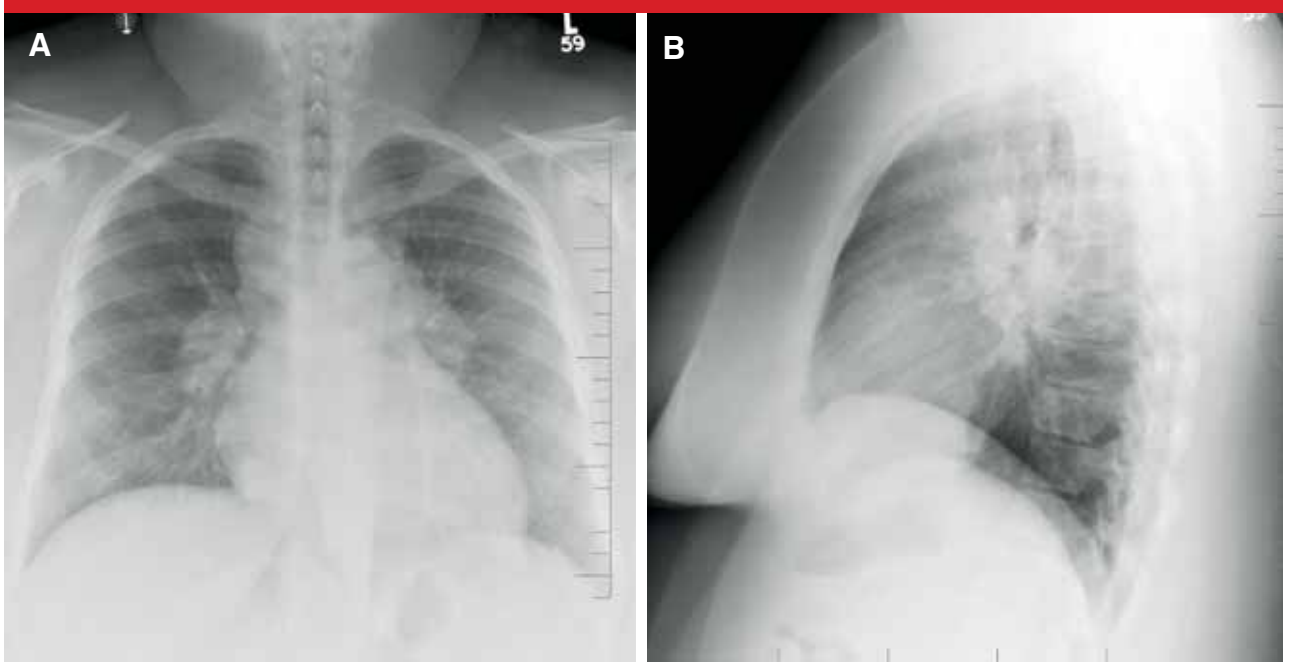
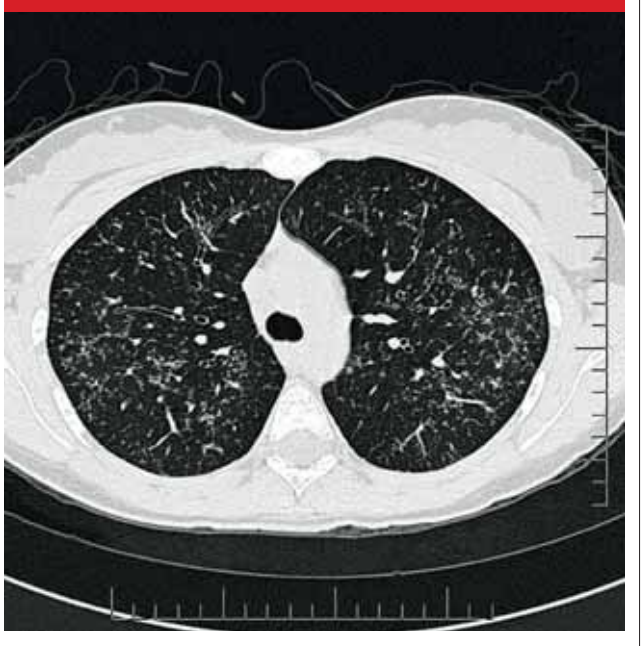


Figure 3: Stage III pulmonary sarcoidosis with nodular infiltrate shown on thoracic CT.



coidosis should be considered when hypercalcaemia is found.

Cardiac involvement

Cardiac involvement can be life threatening and the outcome depends on where the inflammation occurs. Involvement of the ventricular septum and conduction system can result in rhythm disturbances, including complete heart block and sudden death.

Symptoms of palpitations, syncope, dizziness or chest pain may be present. Most patients with cardiac involvement have symptoms. Diagnosis can be difficult, as the ECG is often non-specific, but echocardiography, MRI and endomyocardial biopsy may assist. Prognosis is worse if there is cardiac involvement.

Nervous system involvement

Nervous system involvement is again less common but, as with cardiac involvement, may cause significant morbidity and mortality. Up to 5% of patients have neurological involvement and, as this can be the presenting symptom, sarcoidosis needs to be kept in mind and other symptoms sought, or at least further investigation arranged, for patients with non-resolving problems.

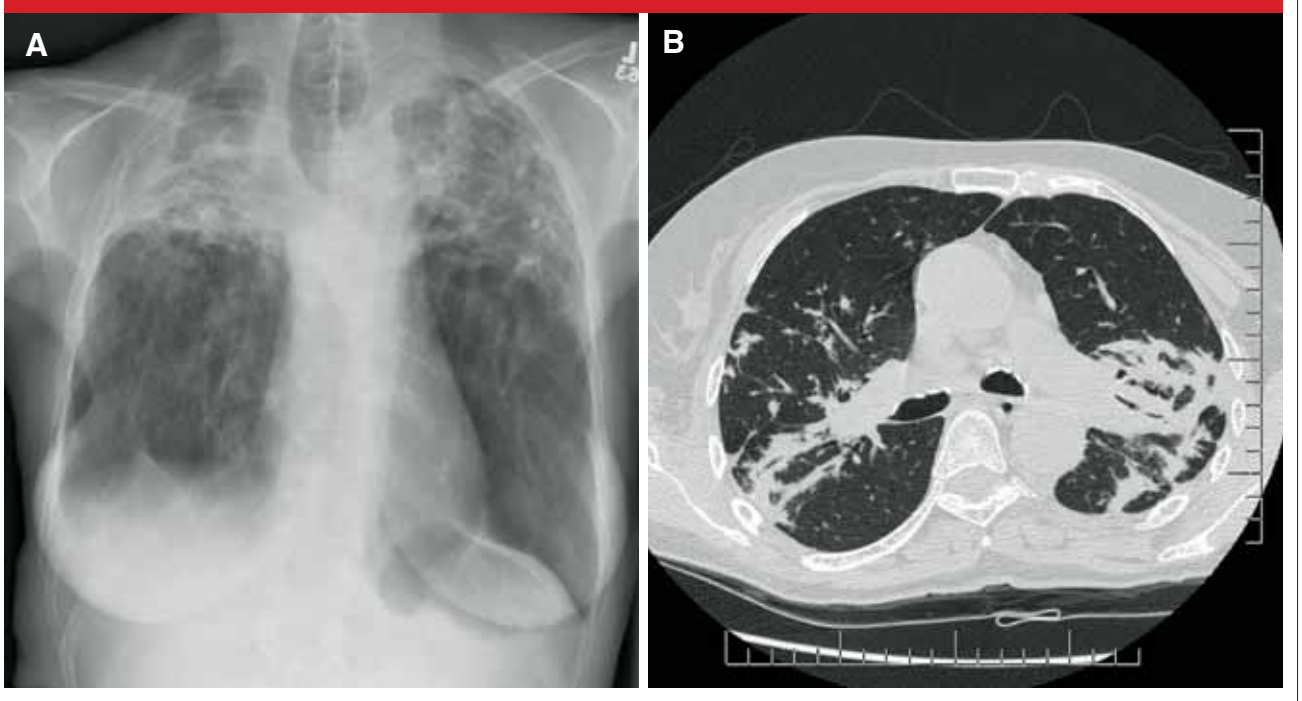
CNS involvement presents early because of the sites involved. It includes basal meningitis, with infiltration of adjacent structures or compression of structures being responsible for the manifestations. These include:

- Hypothalamic hypopituitarism.
- Central diabetes insipidus.
- Hydrocephalus.
- Lymphocytic meningitis.
- Cranial nerve palsies, particularly facial palsy.

Heerfordt's syndrome is characterised by a facial palsy, parotid gland enlargement and anterior uveitis.

Peripheral nerve and skeletal muscle involvement are seen in the later stages of sarcoidosis and can present as acute, subacute, or chronic mononeuropathy, mononeuritis multiplex and polyneuropathies. Occasionally an acute generalised motor neuropathy such as Guillain-Barré syndrome has been seen. Muscle involvement can cause atrophy or a proximal myopathy. An electromyogram (EMG) is useful to diagnose the site of the problem.

Figure 4: Stage IV pulmonary sarcoidosis on chest X-ray (A) and thoracic CT scan (B) with pulmonary fibrosis, predominantly upper lobe, with architectural distortion.



Children

Sarcoidosis is rare in children and, as with adults, is more severe in those of African descent. Children aged 8-15 develop multi-system disease like adults whereas younger children often have a skin rash, arthritis and uveitis, with no lung involvement. The prognosis in general is good but worse in those of African background.

Investigation

DIAGNOSIS of sarcoidosis requires:

- Compatible clinical and radiographic features.
- Exclusion of other diseases that may present with similar features (such as TB).
- Histopathological detection of non-caseating granulomas.

The aims of investigation are to confirm the diagnosis and to determine the extent and severity of tissue involvement. The only situation in which a biopsy can be avoided is when patients present with Löfgren's syndrome (see Author's case study — The classic presentation: Löfgren's syndrome): erythema nodosum, hilar lymphadenopathy, fever and arthralgia, because symptoms and signs in these patients should resolve quickly over a few weeks.

Histopathological diagnosis is most easily made from a biopsy of peripheral nodes if peripheral lymphadenopathy is present, but more commonly from bronchial (yield 41-77%) or trans-bronchial (yield 60-90%) biopsies, even in the absence of obvious radiological or physiological lung involvement.

Biopsies are taken during bronchoscopy, which is a safe procedure performed as a day case under light sedation. The main risk (<5%) is of a pneumothorax caused by a transbronchial biopsy. In the case of a non-diagnostic biopsy, a bronchoalveolar lavage showing elevated lymphocyte levels, in particular, CD4 T lymphocytes, strengthens the diagnosis when the presentation and radiology are classic.

The pathology shows a granuloma that is a focal, chronic inflammatory reaction with an accumulation of epithelial cells, monocytes, lymphocytes, macrophages and fibroblasts. Characteristic are multinucleated giant cells found with the epithelioid cells within the granuloma. Most sarcoid granulomas gradually resolve and leave little residual effect.

Comprehensive lung function tests (spirometry, volumes, transfer factor [see Author's case studies — Side effects of corticosteroids for more severe sarcoidosis, page 31]) should be carried out in all patients and include a six-minute walk test, looking for desaturation. Pulmonary function tests are frequently normal but when abnormal characteristically show a restrictive pattern with:

- Reduced lung volumes (particularly total lung capacity [TLC] and residual volume [RV] consistent with stiff fibrosed lungs).
- Reduced FEV_1.
- Reduced forced vital capacity (FVC).
- Normal FEV_1/FVC ratio.
- Reduced transfer factor (diffusing capacity of the lung for carbon monoxide [DLCO]).

The last of these reflects reduced gas exchange. When corrected for effective alveolar volume (DL/VA), the result may be normal or low.

A significant proportion of patients has airway involvement, which may lead to airway obstruction and a reduced FEV_1/FVC ratio. Oxygen saturation at rest is frequently normal but when there are significant respiratory symptoms or abnormalities of lung function, measurement of SaO_2 during exercise is important. The six-minute walk test is performed by asking patients to walk as far as they can in six minutes, taking as many rests as they need. Dyspnoea is scored on a Borg scale.

Investigations including FBC (leucopenia), LFTs, serum and urinary calcium (elevated) and an ECG should be performed. With cardiac involvement, non-specific ST-T wave abnormalities or conduction problems are seen. Despite its popularity, measurement of serum angiotensin-converting enzyme (ACE) should not be done routinely, as the test has low sensitivity (60%) and poor specificity and does not remove the need for a tissue diagnosis.

A high-resolution CT scan can be very helpful and certain changes are highly diagnostic. Findings include:

- Hilar and mediastinal lymphadenopathy.
- Beading and irregular thickening of the bronchovascular bundles, with nodules along bronchi, vessels, and subpleural regions (figure 3).
- Ground-glass opacification.
- Less commonly, parenchymal masses or consolidation, traction bronchiectasis and fibrosis, with distortion of the lung architecture (figure 4).

Although gallium scans were popular in the past, showing widespread uptake in the lung consistent with underlying inflammation, they are not diagnostic and do not help with monitoring the disease.

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Management

EDUCATION is an important part of management and needs to start early because the public knows little about this condition, and the differential diagnosis of lymphoma will be disturbing. A clear understanding of what sarcoidosis is, the unknown aspects, the prognosis and the need for monitoring should be explained.

Patient information is available from several public websites, including MedLinePlus and UpToDate (see Online resources). Information sheets are published with the recent *Interstitial Lung Disease Guideline* from the British, Irish, and Australian and New Zealand Thoracic Societies.[3]

Treatment

Several important points impact on the decision to treat:

- Spontaneous remission is common, with 55-90% of patients with stage I disease, 40-70% of patients with stage II disease and 10-20% of those with stage III radiological disease remitting. While it is pleasing when they improve with treatment, it is more than likely it had nothing to do with the therapy.
- Remission occurs mainly in the first six months.
- The natural history is variable, so predicting course and prognosis is difficult.

So for many patients, especially those with minimal symptoms and only mild lung dysfunction, the approach will be to watch and wait. If treatment is required for severe lung disease or when there is critical organ involvement, with hypercalcaemia, ocular involvement or neurological or myocardial disease, corticosteroids form the mainstay of therapy (table 3).

Corticosteroid therapy

One could be tempted to use corticosteroids for mild to moderate disease because of the short-term benefits in reducing symptoms and inflammation, but side effects can be considerable and the medium-term (years) benefits are unclear. The long-term effects of treatment on the natural history of disease are unknown.

In a systematic review of oral corticosteroid treatment, four randomised placebo-controlled trials showed improvement in chest X-ray findings in patients with stages II-III but not stage I radiographic disease.[4] There was no or only marginal effect on lung function and the impact on symptoms was not clear. Steroids are essential when there is extra-thoracic disease involving the eye, heart, CNS or when the calcium level is elevated.

Table 3: Indications for treatment in sarcoidosis

No indication

- Asymptomatic stage I disease
- Asymptomatic stage II disease with mildly abnormal lung function and stable disease (measured 3-6-monthly)
- Asymptomatic stage III disease with mildly abnormal lung function and stable disease (measured 3-6-monthly)

Treatment considered

- Worsening lung function over 3-6-month intervals
- Worsening radiological changes
- Significant symptoms of cough, shortness of breath, chest pain or haemoptysis

Treatment given

For extra-thoracic involvement with:

- Ocular, neurological, cardiac or renal disease
- Hypercalcaemia

Side effects of corticosteroids are numerous and almost everyone gets some.

Hypercalcaemia responds well to low-dose corticosteroids, but non-steroid therapy also includes ensuring no calcium or vitamin D supplements are being taken, reducing dietary calcium and reducing sun exposure. As discussed below, osteoporosis is a common side effect of steroids, so use of vitamin D or calcium supplements needs to be tailored to the individual. Referral to an endocrinologist and monitoring calcium metabolism rather than just serum calcium is helpful.

Therapy with prednisolone is usually 30mg per day, with alternate-day therapy as effective as daily therapy. Side effects are significant.

Bisphosphonates have been shown to prevent and treat steroid-induced osteoporosis. Alendronate has been shown in a non-blinded randomised controlled trial of 43 patients to prevent bone loss in steroid-treated patients with sarcoidosis, and a Cochrane review supported the use of bisphosphonates to prevent and treat steroid-induced osteoporosis in general.[5,6]

There is no good evidence for using inhaled corticosteroids, although some find it may help cough in individual patients.

The studies of the long-term benefits of steroids in pulmonary sarcoidosis are inconclusive. In view of the significant rate of spontaneous remission and significant side effects, treatment is not indicated for early-stage disease or when there are few symptoms (table 3).

Side effects of corticosteroids are numerous and almost everyone gets some. They can actually be worse than the disease, and include:

- Skin thinning and purpura.
- Cardiovascular (hypertension and lipid derangement).
- Gastrointestinal (gastritis and peptic ulceration).
- Endocrine:
  - — osteoporosis and avascular necrosis
  - — diabetes mellitus
  - — cushingoid features (moon face, truncal obesity, loss of muscle mass)
  - — obesity.
- Psychiatric (depression, disturbed sleep, psychosis).
- Increased risk of infectious disease.

Whenever using steroids the GP should ask:

- Does my patient really need them?
- Are there alternatives?
- Are there any steroid-sparing drugs that could be used?
- What is the lowest dose that can be used?

Patients should be monitored with symptoms and signs (indigestion, bone pain, psychological state, blood pressure) and tests (calcium studies, bone densitometry, blood glucose levels, lipids), with a healthy lifestyle regarding diet, exercise and no smoking encouraged.

The risk of infection is a major problem, and mortality of patients using immunosuppressives such as steroids and the alternatives noted below is significantly higher than in those not using these medications. Patients must be warned about the risk and advised to try to avoid exposure and to seek help early for infections.

They should have regular vaccination against influenza and pneumococcus and, depending on the maintenance dose of corticosteroids and the severity of lung disease, prophylactic cotrimoxazole should be considered. If an infection occurs, patients should seek help early and culture should be considered, looking for less common organisms. In patients with stage IV disease, bronchiectasis is often present and chronic infection occurs. Again, regular culture with treatment aimed at the resident organisms is required.

Osteoporosis is a (partially) preventable side effect and, as calcium loss begins immediately after the drug is started, so should preventive therapy. As noted previously, calcium metabolism is often deranged, so therapy may need to be individualised and closely monitored.

Bisphosphonates should be considered at the start of steroid therapy and, as previously mentioned, there is evidence that alendronate reduces osteoporosis. In the absence of a fracture, bisphosphonates, apart from risendronate, may not be easily obtained outside of the hospital system. Risedronate is available under PBS authority as the sole PBS-subsidised anti-resorptive agent for corticosteroid-induced osteoporosis in a patient currently on long-term (at least three months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a bone mineral density (BMD) T-score of -1.5 or less.

Alternatives to corticosteroids

Alternatives to corticosteroids or drugs that can act as steroid-sparing agents need to be considered in the small number of patients who:

- Have progressive pulmonary disease despite corticosteroid therapy.
- Do not respond to initial steroid treatment or who do not tolerate them.
- Have severe extra-thoracic (skin or central nervous system) disease.

The drugs that have been tried, both as treatment and as steroid-sparing agents, are chosen because they specifically target the underlying mechanism that promotes inflammation. These include methotrexate, cyclosporin, hydroxychloroquine, pentoxifylline and tumour necrosis factor (TNF) antagonists.

Methotrexate is a folic acid antagonist extensively used in rheumatoid arthritis in low dose. The side effects include pneumonitis (which of course may be hard to differentiate from the sarcoidosis), hepatic fibrosis and infection. Two anti-TNF agents — etanercept, a p75 TNF-receptor fusion protein that binds TNF, and infliximab, a chimeric monoclonal antibody that blocks TNF — have been tried.

There is no evidence for a beneficial effect of most of these drugs in sarcoidosis and they are potentially toxic. Case reports of benefit of infliximab in neurosarcoidosis and lupus pernio have been reported, and infliximab is being further studied. Thalidomide has been reported to be useful, in particular in case series of cutaneous sarcoidosis.

Overall, there are insufficient studies of high quality to clarify the role of immunosuppressive agents in sarcoidosis, with weak evidence for the use of methotrexate as a steroid-sparing agent.

Dilemmas

The challenges in caring for patients with sarcoidosis are:

- Knowing whether a non-specific symptom a patient has is due to the sarcoidosis, steroid therapy or steroid withdrawal, or other conditions, whether physical or psychological. Symptoms such as tiredness are very difficult to assess and manage. Under some circumstances it is tempting to use corticosteroid; however, a trial of therapy needs to be weighed against significant side effects.
- Monitoring the disease, which is usually done with symptoms and 3-6-monthly respiratory function tests — this is especially difficult when patients are asymptomatic and may not be keen to spend the time doing the tests.
- Preventing and managing the side effects of steroids.

Prognosis

The prognosis is generally good, but a few patients die from progressive disease. US data suggest that females and Afro-Caribbean people have increased mortality. The mortality is 1-5% from lung, nervous system or cardiac involvement.

Lung transplantation should be considered for those who are younger and have stage IV disease. Sarcoidosis is a disease that commonly recurs in the transplanted lung, occurring in 35-62% of transplants; however, it rarely causes problems and remains asymptomatic.

Summary

- Sarcoidosis is a multisystem disease in which a diagnosis needs to be made in the setting of consistent clinical features, evidence of non-caseating granulomas and absence of other potential disease.
- Investigation should include measurement of lung function.
- Because of the high rate of spontaneous remission, treatment is not indicated for many patients.
- Observation of symptoms and lung function on a 3-6-monthly basis is recommended.
- Oral corticosteroids are the first line of therapy in patients with progressive disease (radiological, physiological) or significant symptoms or extra-pulmonary disease requiring treatment.
- Prevention of steroid side effects should include use of bisphosphonates to minimise steroid-induced osteoporosis, and vaccination to reduce the risk of infections.
- Inhaled corticosteroids might be considered for symptom control with cough.

Author's case studies

Asymptomatic sarcoidosis

The problem

JB, a 21-year-old man from Scotland, had been on a working holiday in Australia for one year. He applied to have his visa extended and to do so required a chest X-ray. This was abnormal and he was referred for investigation. He was worried the results could affect his visa renewal. In addition he was concerned about costs and could not afford time away from his new job.

He was fit and healthy with no previous illnesses. He had no respiratory symptoms, in particular no cough or dyspnoea. He had not noted fevers, sweats or weight loss. He had smoked 10-15 cigarettes a day since age 17. He worked in a labouring job and had no significant dust exposure.

On examination he looked well but worried. There were no abnormal findings, in particular there was no clubbing or lymphadenopathy; his breath sounds were normal. His chest X-ray showed bilateral hilar lymphadenopathy with normal lung fields.

What next?

The most likely diagnosis is sarcoidosis; however, in the differential diagnosis would be lymphoma. A tissue diagnosis, determination of organs affected and measurement of severity of disease are required for optimal management. How can that be done, taking into account his desire to avoid time off work and the cost?

Approach

JB was accepting of the likely diagnosis and there was no urgency to confirm it. He was counselled about smoking. It was confirmed Australia had reciprocal medical insurance arrangements with the UK.

Simple investigations, which did not take him away from work, were performed and included lung function tests and a six-minute walk test, which were normal. A high-resolution CT scan showed lymphadenopathy that was symmetrical, but no lung abnormality. He eventually agreed to a bronchoscopy. The broncho-alveolar lavage showed an elevated lymphocyte level with a high CD4/CD8 ratio. The transbronchial biopsies were difficult to obtain because of coughing and were non-diagnostic.

Management

The clinical picture and thoracic CT scan were highly suggestive of sarcoidosis, and the diagnostic certainty was increased by the lymphocytic alveolitis with a high CD4/CD8 ratio. In view of the lack of symptoms and normal lung function and the high likelihood of spontaneous remission, he was given no treatment and monitored via symptoms and with a chest X-ray to look for resolution of the hilar lymphadenopathy.

A tissue diagnosis, determination of organs affected and measurement of severity of disease are required for optimal management.

Table 4: Lung function for Mrs RA

	Predicted	Observed	% Predicted
Spirometry			
FVC	4.96L	3.43L	69
FEV_1	3.97L	2.84L	69
FEV_1 /FVC	82%	83%	101
Lung volumes			
RV	1.78L	1.09L	61
TLC	6.75L	4.53L	67
Diffusion			
DLCO corr	32.14	18.6	57
DL/VA	5.06	4.58	90

DLCO corr = diffusing capacity of the lung for carbon monoxide corrected

DL/VA = diffusing capacity of the lung corrected for effective alveolar volume

The classic presentation: Löfgren's syndrome

The problem

LS, a 31-year-old woman, presented with a six-week history of tiredness, mild fevers, swollen glands and a short history of painful red lumps over her shins. In addition she had noted arthralgia in her ankles and wrists. Previously she had been well. She was a non-smoker and was in a long-term relationship.

On examination she was mildly febrile (temperature 37.5°C), with cervical lymphadenopathy. She had painful raised red lesions on her shins and around the knees, consistent with erythema nodosum (figure 1, page 26). Chest examination was normal. Her chest X-ray showed bilateral hilar lymphadenopathy with normal lung fields (figure 2, stage I disease, page 27).

What next?

The most likely diagnosis is sarcoidosis, with this classic presentation of erythema nodosum and hilar lymphadenopathy along with arthralgia and fever (Löfgren's syndrome). The prognosis is very good, with a high rate of early spontaneous remission but a slower resolution of the arthritis. However, if the skin lesions and lymphadenopathy do not clear rapidly, a tissue diagnosis should be made.

Approach

LS was given an NSAID, which controlled her symptoms. The erythema nodosum resolved over a few weeks and the hilar lymphadenopathy over months.

Side effects of corticosteroids for more severe sarcoidosis

The problem

RA, a 62-year-old woman with moderately severe pulmonary sarcoidosis, had been diagnosed eight years before, when she had presented with progressive dyspnoea. Her thoracic CT scan showed evidence of architectural distortion, fibrosis and traction bronchiectasis (figure 4, stage IV disease, page 27).

She had been started on high-dose steroids along with calcium and vitamin D supplements eight years ago. The dose of corticosteroids (prednisolone) was gradually reduced to 12mg/day, which she had remained on for the past two years. Further reduction in her corticosteroid dose caused malaise and some dyspnoea.

Her lung function showed reduced volumes and a low transfer factor, which had stabilised, but had fluctuated when the corticosteroid dose was dropped (table 4). Her exercise capacity was reduced but her oxygenation was normal.

She had had a respiratory tract infection two weeks before, which had resulted in marked coughing and for which she received antibiotics. Subsequently she developed left-sided pleuritic chest pain which made it difficult to breathe and get around.

Clinical findings were of a moderately overweight woman with left-sided chest tenderness. She had no clubbing, but had widespread crackles on chest examination and a moist cough.

Interpretation of lung function tests

RA has reduced ventilator capacity (reduced FEV_1 and FVC) but no airflow obstruction (normal FEV_1/FVC ratio), and reduced gas exchange as measured by low diffusion capacity (DLCO corr). These results are consistent with a fibrosing process causing reduced volumes and impaired gas exchange.

The problem

The chest pain was highly suggestive of a cough-induced fracture, on a background of steroid-induced osteoporosis. Long-term steroid therapy was required for her sarcoidosis, so strategies to counteract the steroid side effects were required.

Patients using steroids are also at risk of infection, not only with the common viruses and bacteria but also atypical infections such as *Pneumocystis jiroveci* pneumonia (PJP). The cause of the current infection needs to be considered and, for the long term, strategies implemented to prevent infections.

Management

Pain relief was prescribed. Bone mineral densitometry showed osteoporosis, and calcium studies hypercalciuria but no hypercalcaemia. She was referred to an endocrinologist and a bisphosphonate was started. Continued monitoring of her calcium balance and osteoporosis was planned.

Her sputum was cultured but no pathogenic organisms grown. She was given yearly influenza vaccination and five-yearly pneumococcal vaccination. Twice-weekly prophylactic cotrimoxazole was started to reduce the risk of *P jiroveci* pneumonia.

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Online resources

- MedLine Plus: www.nlm.nih.gov/medlineplus
- UpToDate: www.uptodate.com/patients

cont'd next page

GP's contribution

DR LINDA MANN
Leichhardt, NSW

A 45-YEAR-old health professional consulted me about individual neck masses on two occasions, which settled with watchful waiting. Her past history was unremarkable, and her only medication was hormone therapy for menorrhagia. She had a striking family history of autoimmune disease, mainly thyroid disease in four first-degree relatives.

She then presented with a left supraclavicular fossa mass, which ultrasound suggested was a lymph node. Concerned that this may be lymphoma, despite normal bloods, no sweats or weight loss, I referred her to a haematologist. His examination found nothing new.

A CT scan revealed lymphadenopathy in her left supraclavicular fossa, upper abdomen, mediastinum and right hilum, and there were nodules in the right lung in a perihilar, peribronchovascular and subpleural distribution. Ultrasound-guided aspiration biopsy indicated granulomatous lymphadenitis. Lung function at this time was normal.

Although a diagnosis of sarcoidosis was likely, this was not made without further information gathered after an overseas trip. There was no abnormality of her eyes or heart, and her ACE level was normal. However, her lung function was now slightly abnormal. Her respiratory physician was much more certain that this combination was consistent with a diagnosis of sarcoidosis.

She has had no active treatment, her clinically palpable nodes have settled, and she is now having annual follow-up by a respiratory consultant with a chest X-ray.

Questions for the author

Despite the widespread nature of her initial presentation, this patient has never been symptomatic. As time goes by, what symptoms should I enquire about, between specialist reviews?

Many patients remain asymptomatic. Symptoms such as cough or breathlessness due to worsening lung function should be looked for. These changes may be subtle, and in fit young people may be a reduction in how far they can run or reduced performance in high level sport.

An open question about anything they have noticed may pick up palpitations suggesting cardiac involvement or visual disturbance with eye involvement. Non-specific symptoms such as tiredness or depression are hard to interpret, but a calcium level should be checked under such circumstances.

She had slightly abnormal lung function, which she did not recognise. Can you explain this (her chest X-ray monitoring indicates that the mediastinal nodes have almost gone away)?

The lungs have substantial reserve, so a mild abnormality in lung function will not cause symptoms. Pulmonary exercise tests may uncover abnormal function, missed on static lung function measurements.

This health professional is exposed to possibly infectious patients every day. Is she at any increase risk from, for example, pertussis and influenza?

Despite mild leucopenia, there is no good evidence for a susceptibility to infectious disease, unless patients are treated with steroids or other immunosuppressive agents. With late-stage lung disease with fibrosis and bronchiectasis, recurrent pulmonary infection can be a problem.

General questions for the author

In preparation for my GP contributor role I searched our database of patients, and found 14 patients out of 23,000 with this diagnosis. This seems much higher than the background rate quoted. Are we getting better at diagnosis?

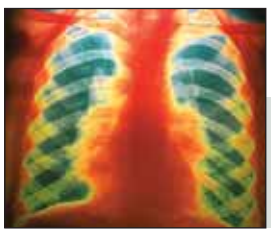
We are uncertain about the true rate in the community, and it can vary depending on racial background and other factors. Many of your patients will have presented because of symptoms or referral because of an abnormal chest X-ray performed for another reason. Could you be seeing more patients with chest X rays for work purposes?

What is the natural history of the erythema nodosum lesions? Do patients continue to have skin discolouration?

The lesions disappear spontaneously in weeks to months. Often NSAIDs are used to reduce the pain, and potassium iodide (300-360mg/day in three divided doses) has been reported in uncontrolled studies to be useful (UpToDate).

Does the presence of sarcoidosis affect vaccination with live vaccines? Will they increase granulomatous immunological response?

It is not clear whether live vaccines present a risk for patients with sarcoidosis and leucopenia, with some physicians recommending avoidance, but not based on good evidence. If there is an alternative, it may be sensible to use it.



How to Treat Quiz

Sarcoidosis — 29 May 2009

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

ONLINE ONLY

www.australiandoctor.com.au/cpd/ for immediate feedback

1. Which THREE statements about the epidemiology and aetiology of sarcoidosis are correct?
a) The incidence of sarcoidosis peaks between the ages of 20 and 50
b) Sarcoidosis is more common and severe in patients of Asian descent
c) No single aetiological factor or genetic locus for sarcoidosis has been found
d) In sarcoidosis, activated lymphocytes form non-caseating granulomas in various organs

2. Which TWO statements about the clinical features of sarcoidosis are correct?
a) Most patients with sarcoidosis will have pulmonary involvement
b) About one-quarter of patients with sarcoidosis have pulmonary involvement alone
c) The most common sites of extra-pulmonary involvement are the skin, liver and eyes
d) Systemic symptoms such as fatigue, malaise, fever and weight loss are uncommon

3. Which THREE statements about the natural history of sarcoidosis are correct?
a) Spontaneous remission occurs in about 10-20% of patients with stage I radiological disease
b) Remission occurs mainly in the first six months
c) The long-term effects of treatment on the natural history of disease are unknown
d) The prognosis of sarcoidosis is generally good; however, the mortality is 1-5%

4. Which TWO statements about pulmonary features of sarcoidosis are correct?
a) Respiratory symptoms may include a dry cough and dyspnoea
b) Most patients will have crackles on auscultation
c) If abnormal, pulmonary function tests characteristically show a restrictive pattern
d) A reduced FEV_1/FVC ratio on pulmonary function testing is inconsistent with a diagnosis of sarcoidosis

5. Which TWO statements about extrapulmonary features of sarcoidosis are correct?
a) The characteristic features of Löfgren's syndrome, with which sarcoidosis may present, are facial palsy, anterior uveitis and parotid gland enlargement
b) Cardiac involvement can result in rhythm disturbances, including complete heart block and sudden death
c) CNS involvement usually presents late in the disease course
d) Ocular involvement in sarcoidosis may include anterior uveitis, chorioretinitis and retinal vasculitis

6. Michelle, 25, presents with a dry cough and mild dyspnoea. Her respiratory examination is normal. Chest X-ray shows bilateral hilar lymphadenopathy and pulmonary infiltrates. Which grade of pulmonary sarcoidosis is this consistent with?
a) Stage I
b) Stage II
c) Stage III
d) Stage IV

7. Which ONE statement about diagnosis and investigation of sarcoidosis are correct?
a) Investigations should include FBC, LFTs, serum and urinary calcium and an ECG
b) A serum angiotensin-converting enzyme (ACE) level should be performed, as this has high sensitivity and specificity for diagnosing sarcoidosis
c) A gallium scan can be very helpful in the assessment and certain changes are highly diagnostic of sarcoidosis
d) A biopsy is not necessary in most cases for the diagnosis of sarcoidosis

8. Which TWO statements about the management of sarcoidosis are correct?
a) Because of the high rate of spontaneous remission, treatment is not indicated for many patients
b) Corticosteroids are essential when there is extra-thoracic disease involving the eye, heart or CNS
c) Alternate-day therapy with prednisolone has been trialled, but is not as effective as daily therapy
d) There is good evidence that using inhaled corticosteroids reduces dyspnoea

9. Which THREE statements about calcium metabolism in sarcoidosis are correct?
a) Hypercalcaemia occurs in 50% of patients with sarcoidosis
b) Corticosteroids are essential for patients with hypercalcaemia
c) Therapy for patients with hypercalcaemia includes reducing sun exposure
d) Referral to an endocrinologist and monitoring calcium metabolism rather than just serum calcium is helpful in patients with hypercalcaemia

10. Which THREE statements about the long-term management of sarcoidosis are correct?
a) Annual monitoring of symptoms and lung function is recommended
b) Patients taking corticosteroids should be monitored for side effects
c) Therapy to minimise osteoporosis should be considered early in patients requiring corticosteroids
d) Vaccination against influenza and pneumococcus should be considered for patients taking corticosteroids for sarcoidosis

CPD QUIZ UPDATE

The RACGP now requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2008-10 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

HOW TO TREAT Editor: **Dr Wendy Morgan**
Co-ordinator: **Julian McAllan**
Quiz: **Dr Wendy Morgan**

NEXT WEEK Acne affects up to 85% of people and can persist for decades. For some patients lesions are painful, scarring may be permanent and the emotional hurt they experience is immense, with the effect on quality of life similar to that of other chronic diseases such as asthma or epilepsy. Safe and effective treatment to avoid later permanent scarring is essential, as well as dispelling the many myths that surround the disease. So clear up any blemishes on your acne treatment with next week's How To Treat on this topic. The author is **Dr Jo-Ann See,** dermatologist in Sydney, chair of the All About Acne group, and a member of the Global Alliance to Improve Outcomes in Acne.